Nirsevimab (secondary prophylaxis of RSV lower respiratory tract disease, 2nd RSV season)

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

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

IQWiG thanks the respondent and the Federal Association for Children with Heart Diseases (Bundesverband Herzkranke Kinder e. V.) for participating in the written exchange and for their support. The respondent and the Federal Association for Children with Heart Diseases were not involved in the actual preparation of the 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
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)
RCT	randomized controlled trial
RSV	respiratory syncytial virus
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 15 August 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 up to 24 months of age during their 2nd respiratory syncytial virus (RSV) season with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV.

The research questions presented 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 up to 24 months of age during their 2nd 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 up to 24 months of age during their 2nd RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated[d, e]	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 children during their 2nd 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, or
- Children with haemodynamically significant congenital heart defect (e.g. significant left-to-right and right-to-left shunt diseases, and children with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21

d. The therapeutic advice on RSV antibodies (AM-RL Appendix IV - Therapeutic advice in accordance with §92 [para. 2, sentence 7] SGB V) must be taken into account.
e. With regard to research question 2, the G-BA specified that currently only children with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically significant congenital heart defects) are included in this patient group.

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 their 2nd year of life in whom secondary prophylaxis with palivizumab is indicated
- Research question 2: children in their 2nd year of life in whom secondary prophylaxis with palivizumab is not indicated

The company followed the specification of the ACT for both research questions.

In accordance with the G-BA, the therapeutic advice on RSV antibodies (Pharmaceutical Directive Appendix IV – therapeutic advice according to §92 [para. 2, sentence 7] SGB V) must also be taken into account for the allocation of the patient populations to research questions 1 and 2. According to this therapeutic advice, the use of nirsevimab is indicated at the onset of the 2nd RSV season for the following children ≤ 24 months of age at increased risk of a severe course of infection:

- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia (BPD) 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. significant left-to-right and right-to-left shunt diseases, and patients with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21

According to the above-mentioned therapeutic advice and the approval of palivizumab, secondary prophylaxis with palivizumab is suitable for children up to 24 months of age who required accompanying therapeutic measures for BPD within the last 6 months before the onset of the RSV season, and for children with haemodynamically significant CHD. 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 children with trisomy 21 (without BPD, without haemodynamically significant CHD) are included in research question 2. This concurs with the company's allocation.

In addition, however, the company also allocated children with immunodeficiency, underlying neuromuscular diseases or severe chronic lung diseases to research question 2, citing the justification for the therapeutic advice and the approval of palivizumab. The general allocation of children with these underlying diseases to research question 2 is not appropriate. The justification for the therapeutic advice on RSV antibodies described that, in individual cases, the risk of a severe course of RSV infection can also be increased if other underlying diseases

are present. These underlying diseases according to the G-BA include severe immunosuppression, congenital immunodeficiencies, underlying syndromic diseases with increased susceptibility to infections, neuromuscular diseases with impaired expectoration or impaired lung function, and individual severe lung diseases. In the presence of these diseases, if there is an increased risk of a severe course of RSV infection, an RSV antibody may be prescribed in individual cases and justified in the patient file. Thus, the suitability of children with these underlying diseases for secondary prophylaxis with an RSV antibody is an individual decision in each case, so that a general allocation of this patient group to research question 2 is not possible. However, the company's deviation regarding 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 the company did not present any suitable data for research question 2.

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 their 2nd year of life in whom secondary prophylaxis with palivizumab is indicated

Results

Evidence provided by the company

The MEDLEY study is a completed double-blind RCT comparing nirsevimab with palivizumab in children in their 1st and 2nd RSV seasons. In general, only the period of the 2nd RSV season is of interest for the present research question 1.

The MEDLEY study comprises 2 cohorts in which the children were included during screening before the start of the 1st RSV season: a preterm cohort and a cohort with children with either BPD or haemodynamically significant CHD (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. The BPD/CHD cohort included children with BPD requiring medical intervention within the 6 months prior to randomization, such as supplemental oxygen, bronchodilators, or diuretics, as well as children with haemodynamically significant CHD that was unoperated or partially corrected.

In principle, only the BPD/CHD cohort is of interest for the present research question; the preterm cohort is therefore not considered further.

In the BPD/CHD cohort, 209 children were randomized to the nirsevimab arm and 101 children to the palivizumab arm at the onset of the 1st RSV season. All 262 children of the originally 310 children originally randomized in the BPD/CHD cohort (84.5%) who completed the follow-

up observation during the 1st RSV season transitioned to the 2nd RSV season. These children were treated with nirsevimab or palivizumab also in the 2nd RSV season as part of the study. There were 3 study arms in the 2nd RSV season. Children in the BPD/CHD cohort who received nirsevimab in the 1st RSV season were reassigned to the nirsevimab arm for the 2nd RSV season (nirsevimab/nirsevimab; N = 180). Children who received palivizumab in the 1st RSV season were rerandomized in a 1:1 ratio to treatment with nirsevimab (palivizumab/nirsevimab; N = 40) or palivizumab (palivizumab/palivizumab; N = 42) for the 2nd RSV season.

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 (on Day 1), 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 outcome of the study was the assessment of safety and tolerability based on outcomes in the side effects category. Patient-relevant secondary outcomes were recorded in the category of morbidity.

Suitability of the BPD/CHD cohort presented by the company for research question 1 is unclear

Patient population requirements for suitability for secondary prophylaxis with an RSV antibody

According to the therapeutic advice on RSV antibodies (Pharmaceutical Directive Appendix IV – Therapeutic advice in accordance with §92 [para. 2, sentence 7] SGB V), research question 1 includes children up to 24 months of age who required accompanying therapeutic measures for BPD within the last 6 months before the onset of the 2nd RSV season, as well as children with haemodynamically significant CHD. These criteria must be present at the onset of the children's 2nd RSV season so that there is an increased risk of a severe course of RSV disease of the lower respiratory tract according to G-BA and thus an indication for secondary prophylaxis with an RSV antibody.

Approach of the company

For the present research question 1, the company's Module 4 B presented results of all children in the BPD/CHD cohort of the MEDLEY study who were treated with nirsevimab or palivizumab in their 2nd RSV season. At the time of randomization before the 1st RSV season, the inclusion criteria of the study ensured that children in the BPD/CHD cohort had BPD requiring medical intervention within the 6 months prior to randomization, such as supplemental oxygen, bronchodilators, or diuretics, and/or haemodynamically significant CHD that was unoperated or partially corrected. Of the children in the BPD/CHD cohort who were

treated with nirsevimab or palivizumab in their 2nd RSV season, 189 children had BPD requiring medical intervention within the last 6 months, and 81 children had a haemodynamically significant CHD at the time of randomization before the 1st RSV season. In the MEDLEY study, the inclusion criteria were not re-examined at the onset of the 2nd RSV season. In Module 4 B, the company provided no information on the extent to which children in the BPD/CHD cohort still had an increased risk of a severe course of RSV infection of the lower respiratory tract and thus an indication for secondary prophylaxis with an RSV antibody also in their 2nd year of life. The suitability of the BPD/CHD cohort of the MEDLEY study for answering research question 1 is therefore unclear.

Unclear suitability of children with bronchopulmonary dysplasia

In the MEDLEY study, it was not re-examined at the onset of the 2nd RSV season whether the children with BPD required medical intervention within the last 6 months because of this. The need for medical intervention to treat BPD in the last 6 months is decisive for a continued increased risk of a severe course of RSV infection in the 2nd RSV season. However, no corresponding information is available. It is therefore not guaranteed that the included children with BPD requiring medical intervention within the last 6 months before the onset of the 1st RSV season, continued to have an indication for secondary prophylaxis with an RSV antibody also in their 2nd RSV season. Without further information, the subpopulation of children with BPD from the MEDLEY study is therefore unsuitable for answering research question 1.

Unclear suitability of children with haemodynamically significant congenital heart defect

The BPD/CHD cohort of the MEDLEY study exclusively included children with haemodynamically significant CHD that was unoperated or partially corrected at the time point of randomization before the 1st RSV season. No disease history or information on existing medication or surgical interventions is available for the subpopulation of children with haemodynamically significant CHD on Day 1 of the 2nd RSV season. It can therefore not be ruled out for these children that at least for some of them, the haemodynamically significant changes had completely regressed or had been surgically corrected between their 1st and 2nd RSV season. In these cases, there would no longer be an increased risk of a severe course of RSV infection of the lower respiratory tract for the 2nd RSV season and therefore no longer an indication for secondary prophylaxis with an RSV antibody.

Without further information, the subpopulation of children with haemodynamically significant CHD from the MEDLEY study cannot be used for the benefit assessment.

Summary

The analyses presented by the company on the BPD/CHD cohort during their 2nd RSV season are unsuitable for the benefit assessment, as it is unclear whether or how many of these

children in their 2nd RSV season still had an increased risk of a severe course of RSV infection of the lower respiratory tract and thus an indication for secondary prophylaxis with nirsevimab or palivizumab. Thus, no suitable data are available for the benefit assessment.

Results on added benefit

As no suitable data are available for the assessment of the added benefit of nirsevimab compared with the ACT in children up to 24 months of age during their 2nd RSV season with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV in whom palivizumab is indicated, an added benefit of nirsevimab is not proven for this patient group.

Research question 2: children in their 2nd year of life in whom secondary prophylaxis with palivizumab is not indicated

Results

Although the company did not identify any RCTs for research question 2, it cited the single-arm MUSIC study in Module 4 B, Section 4.4.2, which it used as supplementary information in its reasoning to derive added benefit. The MUSIC study included immunocompromised children in their 1st or 2nd year of life who were entering their 1st or 2nd RSV season when they received their 1st dose of nirsevimab. The MUSIC study is a single-arm study and does not allow for comparison with the ACT specified by the G-BA. In addition, the MUSIC study presented by the company does not represent the population according to research question 2 (children with trisomy 21 without BPD and/or haemodynamically significant heart defects).

The company therefore presented no suitable data for deriving an added benefit in comparison with the ACT for research question 2.

Results on added benefit

As no suitable data are available for the assessment of the added benefit of nirsevimab compared with the ACT in children up to 24 months of age during their 2nd RSV season 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, patient groups with therapeutically important added benefit[3]

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

[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

Table 3: Nirsevimab – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a, b]**	**Probability and extent of added benefit**
1	Children up to 24 months of age during their 2nd 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 up to 24 months of age during their 2nd RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated[d, e]	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 children during their 2nd 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, or
- Children with haemodynamically significant congenital heart defect (e.g. significant left-to-right and right-to-left shunt diseases, and children with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21

d. The therapeutic advice on RSV antibodies (AM-RL Appendix IV - Therapeutic advice in accordance with §92 [para. 2, sentence 7] SGB V) must be taken into account.
e. With regard to research question 2, the G-BA specified that currently only children with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically significant congenital heart defects) are included in this patient group.

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

The G-BA decides on the added benefit.

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].

I 2 Research question

The aim of this report is to assess the added benefit of nirsevimab compared with the ACT in children up to 24 months of age during their 2nd RSV season with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV.

The research questions presented 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 up to 24 months of age during their 2nd 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 up to 24 months of age during their 2nd RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated[d, e]	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 children during their 2nd 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, or
- Children with haemodynamically significant congenital heart defect (e.g. significant left-to-right and right-to-left shunt diseases, and children with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21

d. The therapeutic advice on RSV antibodies (AM-RL Appendix IV - Therapeutic advice in accordance with §92 [para. 2, sentence 7] SGB V) Gemeinsamer Bundesausschuss, 2024 #31} must be taken into account.
e. With regard to research question 2, the G-BA specified that currently only children with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically significant congenital heart defects) are included in this patient group.

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 their 2nd year of life in whom secondary prophylaxis with palivizumab is indicated
- Research question 2: children in their 2nd year of life in whom secondary prophylaxis with palivizumab is not indicated

The company followed the specification of the ACT for both research questions.

In accordance with the G-BA, the therapeutic advice on RSV antibodies (Pharmaceutical Directive Appendix IV – therapeutic advice according to §92 [para. 2, sentence 7] SGB V) [3] must also be taken into account for the allocation of the patient populations to research questions 1 and 2. According to this therapeutic advice, the use of nirsevimab is indicated at the onset of the 2nd RSV season for the following children ≤ 24 months of age at increased risk of a severe course of infection:

- Children who required accompanying therapeutic measures for BPD 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. significant left-to-right and right-to-left shunt diseases, and patients with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21

According to the above-mentioned therapeutic advice and the approval of palivizumab [4], secondary prophylaxis with palivizumab is suitable for children up to 24 months of age who required accompanying therapeutic measures for BPD within the last 6 months before the onset of the RSV season, and for children with haemodynamically significant CHD. 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 children with trisomy 21 (without BPD, without haemodynamically significant CHD) are included in research question 2. This concurs with the company's allocation.

In addition, however, the company also allocated children with immunodeficiency, underlying neuromuscular diseases or severe chronic lung diseases to research question 2, citing the justification for the therapeutic advice [5] and the approval of palivizumab [4]. The general allocation of children with these underlying diseases to research question 2 is not appropriate. The justification for the therapeutic advice on RSV antibodies [5] described that, in individual cases, the risk of a severe course of RSV infection can also be increased if other underlying diseases are present. These underlying diseases according to the G-BA include severe immunosuppression, congenital immunodeficiencies, underlying syndromic diseases with increased susceptibility to infections, neuromuscular diseases with impaired expectoration or impaired lung function, and individual severe lung diseases. In the presence of these diseases, if there is an increased risk of a severe course of RSV infection, an RSV antibody may be prescribed in individual cases and justified in the patient file. Thus, the suitability of children with these underlying diseases for secondary prophylaxis with an RSV antibody is an individual decision in each case, so that a general allocation of this patient group to research question 2 is not possible. However, the company's deviation regarding 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 the company did not present any suitable data for research question 2; see Section I 4.1.

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 their 2nd year of life 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:

Sources of the company in the dossier:

- study list on nirsevimab (status: 8 July 2024)
- bibliographical literature search on nirsevimab (last search on 9 July 2024)
- search in trial registries/trial results databases for studies on nirsevimab (last search on 9 July 2024)
- search on the G-BA website for nirsevimab (last search on 8 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on nirsevimab (last search on 22 August 2024); for search strategies, see I Appendix A of the full dossier assessment

In agreement with the company, the MEDLEY study [6-9] was identified for the direct comparison of nirsevimab versus palivizumab. The study is already known from a previous benefit assessment procedure [10,11]. It potentially contains a relevant subpopulation for the benefit assessment.

The company presented analyses for the subpopulation of children included in the MEDLEY study who were treated with nirsevimab or palivizumab in the 2nd RSV season. The subpopulation includes children with BPD and/or haemodynamically significant CHD. However, it is not clear from the information provided by the company whether or how many children in the subpopulation presented by the company continued to have an increased risk of a severe course of RSV lower respiratory tract infection in their 2nd RSV season and are thus covered by the present research question 1. The analyses presented by the company were therefore excluded from the present benefit assessment. The MEDLEY study is characterized below, and the unsuitability of the presented subpopulation is justified. Further information on the characteristics of the MEDLEY study can be found in Table 6 and Table 7 in I Appendix B of the full dossier assessment.

Evidence provided by the company

The MEDLEY study is a completed double-blind RCT comparing nirsevimab with palivizumab in children in their 1st and 2nd RSV seasons. The benefit assessment of nirsevimab for secondary prophylaxis in children in their 1st RSV season was already conducted in a previous

procedure [10,11]. Only the period of the 2nd RSV season is of interest for the present research question 1.

The MEDLEY study comprises 2 cohorts in which the children were included during screening before the start of the 1st RSV season: a preterm cohort and a cohort with children with either BPD or haemodynamically significant CHD (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. The BPD/CHD cohort included children with BPD requiring medical intervention within the 6 months prior to randomization, such as supplemental oxygen, bronchodilators, or diuretics, as well as children with haemodynamically significant CHD that was unoperated or partially corrected.

At the onset of the 1st RSV season, 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 assigned to the treatment arms in a 2:1 ratio at the onset of the 1st RSV season. 616 children were randomized to the intervention arm and 309 to the comparator arm. In the BPD/CHD cohort, 209 children were randomized to the nirsevimab arm and 101 children to the palivizumab arm. The planned follow-up observation in each of both RSV seasons was 360 days after the 1st dose of the study medication (i.e. until Day 361). In the BPD/CHD cohort, 180 children in the nirsevimab arm and 82 children in the palivizumab arm completed the follow-up observation for the 1st RSV season (Day 361). For the preterm cohort, the observation period ended after Day 361 of the 1st RSV season. The preterm cohort of the MEDLEY study is not relevant for the present benefit assessment, as according to the therapeutic advice, preterm infants without BPD and/or haemodynamically significant CHD generally have no increased risk of a severe course of RSV infection in their 2nd year of life [3]. This cohort is therefore not considered further.

The study population in the 2nd RSV season comprises exclusively children in the BPD/CHD cohort. Of the 310 children originally randomized in the BPD/CHD cohort, all 262 children (84.5%) who completed follow-up observation for the 1st RSV season remained in the study and transitioned to the 2nd RSV season. These children were treated with nirsevimab or palivizumab also in the 2nd RSV season as part of the study. Children in the BPD/CHD cohort who received nirsevimab in the 1st RSV season were reassigned to the nirsevimab arm for the 2nd RSV season. Children who received palivizumab in the 1st RSV season were re-randomized in a 1:1 ratio to treatment with nirsevimab or palivizumab for the 2nd RSV season.

Within the BPD/CHD cohort, there were thus 3 study arms for the 2nd RSV season:

- Nirsevimab/nirsevimab: children in the BPD/CHD cohort who received nirsevimab in the 1st RSV season and in the 2nd RSV season (N = 180)

- Palivizumab/nirsevimab: children in the BPD/CHD cohort who received palivizumab in the 1st RSV season and nirsevimab in the 2nd RSV season (N = 40)
- Palivizumab/palivizumab: children in the BPD/CHD cohort who received palivizumab in the 1st RSV season and in the 2nd RSV season (N = 42)

By participating in the study in their 1st RSV season, all children in the BPD/CHD cohort were pretreated with nirsevimab or palivizumab before the start of the 2nd RSV season.

Nirsevimab and palivizumab were each dosed in compliance with the SPC [4,12]. 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 (on Day 1), 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 there were signs of RSV lower respiratory tract infection, continuous positive airway pressure (CPAP) ventilation or supplemental oxygen was possible, as well as new or increased dose of bronchodilators, steroids, diuretics, or cardiac medication.

The primary outcome of the study was the assessment of safety and tolerability based on outcomes in the side effects category. Patient-relevant secondary outcomes were recorded in the category of morbidity.

Analyses presented by the company

In Module 4 B, the company presented results of the final analysis of the 2nd RSV season (data cut-off from 20 January 2023) for the BPD/CHD cohort. It used analyses on Day 151 of the 2nd RSV season for the benefit outcomes, and analyses on Day 361 of the 2nd RSV season for the safety outcomes.

In Module 4 B, the company presented analyses of all children in the BPD/CHD cohort who received nirsevimab or palivizumab in their 2nd year of life. The company presented 2 analyses for all side effects outcomes:

- Main analysis: exclusive consideration of the study arms with palivizumab treatment in the 1st RSV season: palivizumab/nirsevimab versus palivizumab/palivizumab. This analysis was prespecified.

- Sensitivity analysis: pooling the arms with nirsevimab treatment in the 2nd RSV season: nirsevimab/nirsevimab and palivizumab/nirsevimab versus palivizumab/palivizumab.

The company used the main analysis to derive added benefit.

Suitability of the BPD/CHD cohort presented by the company for research question 1 is unclear

Patient population requirements for suitability for secondary prophylaxis with an RSV antibody

The patient population relevant for the present benefit assessment includes children up to 24 months of age who already had an indication for secondary prophylaxis of RSV lower respiratory tract infection during their 1st RSV season and who still had this indication during their 2nd RSV season. According to the therapeutic advice on RSV antibodies (Pharmaceutical Directive Appendix IV – Therapeutic advice in accordance with §92 [para. 2, sentence 7] SGB V) [3], research question 1 includes children up to 24 months of age who required accompanying therapeutic measures for BPD within the last 6 months before the onset of the 2nd RSV season, as well as children with haemodynamically significant CHD. These criteria must be present at the onset of the children's 2nd RSV season so that there is an increased risk of a severe course of RSV disease of the lower respiratory tract according to G-BA.

Approach of the company

For the present research question 1, the company's Module 4 B presented results of all children in the BPD/CHD cohort of the MEDLEY study who were treated with nirsevimab or palivizumab in their 2nd RSV season. In the MEDLEY study, children in the BPD/CHD cohort received secondary prophylaxis with either nirsevimab or palivizumab in both their 1st and 2nd year of life. At the time of randomization before the 1st RSV season, the inclusion criteria of the study ensured that children in the BPD/CHD cohort had BPD requiring medical intervention within the 6 months prior to randomization, such as supplemental oxygen, bronchodilators, or diuretics, and/or haemodynamically significant CHD that was unoperated or partially corrected. This means that these children had an indication for secondary prophylaxis of RSV lower respiratory tract infection in their 1st year of life in accordance with the therapeutic advice on RSV antibodies (see also A24-27 [10]). Of the children in the BPD/CHD cohort who were treated with nirsevimab or palivizumab in their 2nd RSV season, 189 children had BPD requiring medical intervention within the last 6 months, and 81 children had a haemodynamically significant CHD at the time of randomization before the 1st RSV season. Nine children had both BPD and haemodynamically significant CHD. In the MEDLEY study, the inclusion criteria were not re-examined at the onset of the 2nd RSV season.

In Module 4 B, the company provided no information on the extent to which children in the BPD/CHD cohort still had an increased risk of a severe course of RSV infection of the lower

respiratory tract and thus an indication for secondary prophylaxis with an RSV antibody also in their 2nd year of life. For the 2nd RSV season, it generally included all children in the BPD/CHD cohort of the MEDLEY study who again received an RSV antibody in their 2nd year of life. However, the company described in Module 3 B that health status in children with the risk factors BPD and haemodynamically significant CHD in their 1st year of life may improve as they develop, which means that their risk of a severe course of RSV lower respiratory tract infection is no longer increased in the 2nd RSV season. For example, a haemodynamically significant CHD can be surgically corrected.

Unclear suitability of children with bronchopulmonary dysplasia

In the MEDLEY study, it was not re-examined at the onset of the 2nd RSV season whether the children with BPD required medical intervention within the last 6 months because of this. The need for medical intervention to treat BPD in the last 6 months is decisive for a continued increased risk of a severe course of RSV infection in the 2nd RSV season. In principle, information on treatment of BPD within the 6 months prior to the start of the 2nd RSV season is therefore necessary to assess whether children with BPD in the MEDLEY study had an indication for secondary prophylaxis of RSV lower respiratory tract infections with an RSV antibody also in their 2nd RSV season. According to the study protocol, an update on disease history and existing medication had to be carried out on Day 1 of the 2nd RSV season. However, there is no information available for the update on either disease history or existing medication. It is therefore not guaranteed that the included children with BPD requiring medical intervention within the last 6 months before the onset of the 1st RSV season, continued to have an indication for secondary prophylaxis with an RSV antibody also in their 2nd RSV season. Without further information, the subpopulation of children with BPD from the MEDLEY study is therefore unsuitable for answering research question 1.

Unclear suitability of children with haemodynamically significant congenital heart defect

In general, children with haemodynamically significant CHD are a heterogeneous group with various malformations and functional disorders. The BPD/CHD cohort of the MEDLEY study exclusively included children with haemodynamically significant CHD that was unoperated or partially corrected at the time point of randomization before the 1st RSV season. Children with uncomplicated small atrial or ventricular septal defects or patent ductus arteriosus, or aortic stenosis, pulmonic stenosis, or coarctation of the aorta alone were not included in the BPD/CHD cohort.

No update of disease history or information on existing medication or surgical interventions is available for the subpopulation of children with haemodynamically significant CHD on Day 1 of the 2nd RSV season. It can therefore not be ruled out for these children that at least for some of them, the haemodynamically significant changes had completely regressed or had been surgically corrected between their 1st and 2nd RSV season. In these cases, there would

no longer be an increased risk of a severe course of RSV infection of the lower respiratory tract for the 2nd RSV season and therefore no longer an indication for secondary prophylaxis with an RSV antibody.

Without further information, the subpopulation of children with haemodynamically significant CHD from the MEDLEY study cannot be used for the benefit assessment.

Summary

The analyses presented by the company on the BPD/CHD cohort during their 2nd RSV season are unsuitable for the benefit assessment, as it is unclear whether or how many of these children in their 2nd RSV season still had an increased risk of a severe course of RSV infection of the lower respiratory tract and thus an indication for secondary prophylaxis with nirsevimab or palivizumab. Thus, no suitable data are available for research question 1 of the benefit assessment.

I 3.2 Results on added benefit

No suitable data are available for the assessment of the added benefit of nirsevimab compared with the ACT in children up to 24 months of age during their 2nd RSV season with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV in whom palivizumab is indicated. There is no hint of an added benefit of nirsevimab in comparison with the ACT; an added benefit is therefore not proven.

I 3.3 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 up to 24 months of age during their 2nd RSV season with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV in whom palivizumab is indicated, an added benefit of nirsevimab is not proven for this patient group.

I 4 Research question 2: children in their 2nd year of life 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:

Sources of the company in the dossier:

- study list on nirsevimab (status: 8 July 2024)
- bibliographical literature search on nirsevimab (last search on 9 July 2024)
- search in trial registries/trial results databases for studies on nirsevimab (last search on 9 July 2024)
- search on the G-BA website for nirsevimab (last search on 8 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on nirsevimab (last search on 22 August 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any relevant study for assessing the added benefit of nirsevimab in comparison with watchful waiting.

Although the company did not identify any RCTs for answering research question 2, it cited the single-arm MUSIC study in Module 4 B, Section 4.4.2, which it used as supplementary information in its reasoning to derive added benefit [13]. The company conducted no information retrieval for other study types. The MUSIC study included immunocompromised children in their 1st or 2nd year of life who were entering their 1st or 2nd RSV season when they received their 1st dose of nirsevimab. Children with trisomy 21, who are generally to be allocated to research question 2 of the benefit assessment according to the G-BA, were excluded from participation in the study. The MUSIC study is a single-arm study and does not allow for comparison with the ACT specified by the G-BA. In addition, the MUSIC study presented by the company does not represent the population according to research question 2 (children with trisomy 21 without BPD and/or haemodynamically significant heart defects). A general allocation of immunosuppressed children in the MUSIC study to research question 2 is not appropriate (see Chapter I 2 for justification).

The company concluded from investigations on the 1st RSV season that nirsevimab has very good efficacy and tolerability in all children at increased risk of a severe course of RSV infection regardless of palivizumab suitability and thus that there is an added benefit compared with the ACT watchful waiting. Without suitable data for the present research question 2, the derivation of an added benefit is not appropriate, however.

Overall, the company therefore presented no suitable data for deriving an added benefit in comparison with the ACT for research question 2.

I 4.2 Results on added benefit

No suitable data are available for the assessment of the added benefit of nirsevimab compared with the ACT in children up to 24 months of age during their 2nd RSV season 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.

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 up to 24 months of age during their 2nd RSV season 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.

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 5.

Table 5: Nirsevimab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
1	Children up to 24 months of age during their 2nd 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 up to 24 months of age during their 2nd RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated[d, e]	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 children during their 2nd 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, or
- Children with haemodynamically significant congenital heart defect (e.g. significant left-to-right and right-to-left shunt diseases, and children with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21

d. The therapeutic advice on RSV antibodies (AM-RL Appendix IV - Therapeutic advice in accordance with §92 [para. 2, sentence 7] SGB V) Gemeinsamer Bundesausschuss, 2024 #31} must be taken into account.
e. With regard to research question 2, the G-BA specified that currently only children with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically significant congenital heart defects) are included in this patient group.

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

For both research questions, the assessment described above deviates from that of the company. It derived an indication of a non-quantifiable added benefit for research question 1, and a hint of a non-quantifiable added benefit for research question 2.

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a24-82.html.