EMADOC-1700519818-2500371
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Beyfortus

Nirsevimab

Procedure no: EMA/PAM/0000303330

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	30 September 2025	30 September 2025	☐
☐	CHMP Rapporteur AR	17 November 2025	17 November 2025	☐
☐	CHMP members comments	1 December 2025	N/A	☐
☐	Updated CHMP Rapporteur AR	4 December 2025	N/A	☐
☐	Request for Supplementary Information	11 December 2025	11 December 2025	☐
☐	Submission of responses	27 January 2026	20 January 2026	☐
☐	Restart	28 January 2026	28 January 2026	☐
☐	CHMP Rapporteur AR	11 February 2026	5 February 2026	☐
☐	CHMP Comments	16 February 2026	N/A	☐
☐	Updated CHMP Rapporteur AR	19 February 2026	18 February 2026	☐
☒	Opinion	26 February 2026	26 February 2026	☐

Table of contents

1. Introduction

On 29 September 2025, the MAH submitted a completed paediatric study for Beyfortus, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure requested by the United States Food and Drug Administration (FDA).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

HARMONIE Study VAS00006 is part of the clinical development program. The current Article 46 procedure does not include suggestions to change the wording in the SmPC or the current conditions of the MA.

A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation is decided on and from the initial phase planned for the use in children.

Table 1

Type	Extended half-life monoclonal antibody
Dose Form	Sterile solution for injection
Unit Dose Strength(s)	100 mg/mL
Excipients/Diluent	• 30 mM histidine/histidine-HCl • 80 mM arginine-HCl • 120 mM sucrose • 0.02% (w/v) polysorbate 80 • pH 6.0 water for injection
Dosage Levels	0.5 mL presentation corresponding to 50 mg (if weight < 5 kg) or 1.0 mL presentation corresponding to 100 mg (if weight ≥ 5 kg)
Number of Doses / Dosing Interval	1 dose
Route of Administration	IM
Site of Administration	Anterolateral aspect of the thigh according to standard practice procedures for IM injections in infants

One intramuscular injection in the anterolateral aspect of the thigh at Day 01.

The injected volume is maximum one mL, which is the usual maximum volume recommended for the use in children.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- VAS00006 HARMONIE Study; Second-year analysis results from the HARMONIE Study.

2.3.2. Clinical study

VAS00006 HARMONIE Study

Description

A Phase IIIb, open-label, randomised, parallel 2-arm, multicentre study to determine the efficacy and safety of a single intramuscular (IM) dose of nirsevimab, compared to no intervention, for the prevention of hospitalisations due to lower respiratory tract infection (LRTI) caused by confirmed RSV infection in healthy infants under 12 months, born ≥ 29 weeks gestational age entering their first RSV season (born either in-season or out-of-season) and not eligible for palivizumab, in France, Germany, and the UK.

As a result of a post-marketing commitment to the United States Food and Drug Administration (FDA), the HARMONIE study was extended to 24 months to collect data during the second RSV season. In order to minimise the burden on sites, families and participants, this study extension was only proposed to UK participants, who represent around 50% of the study population, with a reconsent from parents/ legally acceptable representatives (LARs).

The efficacy results presented by the applicant are from the HARMONIE First-Year and Second-Year Analyses except the primary endpoint which was evaluated at the time of the Primary Analysis.

- Study initiation date: 08 August 2022 (first participant first visit)
- First-Year Analyses report date: 27 March 2024 (last participant last 12-month phone call) The study is completed for France, Germany, and UK non-reconsented participants (i.e., final 12-month safety follow-up completed)
- Second-Year Analyses report date: 9 April 2025 (last participant last 24-month phone call) The study is completed for UK reconsented participants, who were followed up to 24 months post-dosing/randomisation.

The analyses presented in this report are based on a database lock date of 27 May 2025.

Methods

Study participants

This study is being conducted in heathy infants (aged 0 to 12 months; calendar age) born at ≥ 29 WGA, who are entering their first RSV season and who are not eligible for palivizumab on the day of randomisation in the study (D01).

Parents/LARs of participants should be able to attend the scheduled visit and to comply with all study procedures, including their willingness to install the study's dedicated application on their smartphone.

Treatments

Nirsevimab administration (dose of 50 mg for participants weighing < 5kg at dosing/randomisation and 100 mg for participants ≥ 5kg) on D01.

Participants were randomized 1:1 to receive a single IM injection of nirsevimab or no RSV preventive intervention at Day (D) 01 and are planned to be followed up as follows:

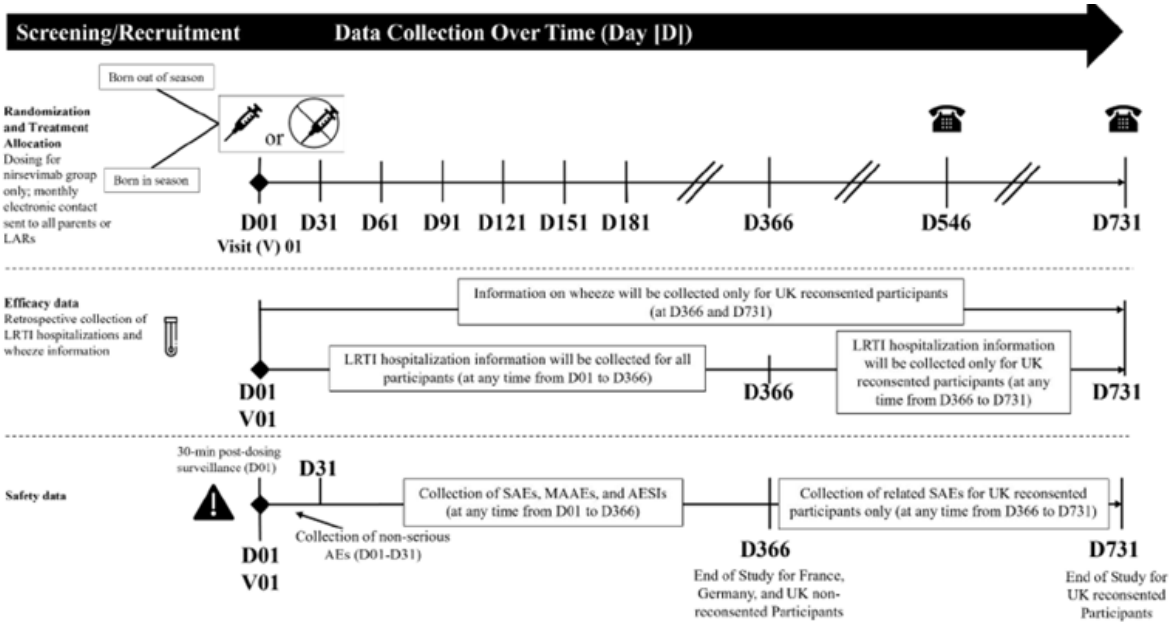
• 1 in-person visit at D01 for randomization and/or immunization • Monthly safety follow-up electronic contacts through 6 months post-dosing/randomization • 12-month (D366) follow-up telephone call (final for France, Germany and UK non-reconsented participants)	For all participants
• 18-month (D546) follow-up telephone call • 24-month (D731) final follow-up telephone call	For UK reconsented participants only

The following start dates were defined for the study (1-3):

- Week 36 2022 for the UK
- Week 37 2022 for France
- Week 41 2022 for Germany

The end date of the RSV season was defined as the data cut-off date for the Primary Analysis (ie, 28 February 2023) and was supported by the low number of RSV cases in the 3 participating countries (3-5).

Figure 1. Graphical Study Design



Abbreviations: AESI, adverse event of special interest; D, day; LAR, legally acceptable representative; LRTI, lower respiratory tract infection; MAAE, medically attended adverse event; SAE, serious adverse event; UK, United Kingdom; V, visit

Objective(s)

Primary objectives:

To assess the efficacy of nirsevimab in preventing RSV LRTI hospitalisation through RSV season.

Secondary objectives:

To assess the efficacy of nirsevimab in preventing:

i) RSV LRTI hospitalisation through 150 and 180 days.

ii) Very severe RSV LRTI through RSV season and through 150 days.

iii) Hospitalisation for all-cause LRTI through RSV season and through 150 and 180 days.

Objectives of the two-year study:

To assess the incidence of:

i) RSV LRTI hospitalisation and hospitalisation for all-cause LRTI from D181 until D366.

ii) RSV LRTI hospitalisation and all-cause LRTI hospitalisation from D366 until D731.

To assess the incidence of recurrent wheeze from D01 until D731.

To further characterize the safety profile of nirsevimab.

Overview of objectives and endpoints:

Table 2. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization compared to no intervention*	• Overall incidence of RSV LRTI hospitalization through the RSV season
Secondary	
• To assess the efficacy of nirsevimab in preventing very severe RSV LRTI compared to no intervention*	• Incidence of very severe RSV LRTI defined as RSV LRTI hospitalization with oxygen saturation < 90% (at any time during hospitalization) and oxygen supplementation, through the RSV season
• To assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization compared to no intervention in each country*	• Incidence of RSV LRTI hospitalization through the RSV season in each country
• To assess the efficacy of nirsevimab in preventing hospitalizations for all-cause LRTI compared to no intervention	• Incidence of hospitalizations for all-cause LRTI through the RSV season
• To assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization through 150 days post-dosing/randomization (overall and in each country)	• Incidence of RSV LRTI hospitalization through 150 days post-dosing/randomization (overall and in each country)
• To assess the efficacy of nirsevimab in preventing very severe RSV LRTI through 150 days post-dosing/randomization	• Incidence of very severe RSV LRTI defined as RSV LRTI hospitalization with oxygen saturation < 90% (at any time during hospitalization) and oxygen supplementation, through 150 days post-dosing/randomization
• To assess the efficacy of nirsevimab in preventing hospitalizations for all-cause LRTI through 150 days post-dosing/randomization	• Incidence of hospitalizations for all-cause LRTI through 150 days post-dosing/randomization

Cont.

Table 3

Objectives	Endpoints
• To further characterize the safety profile of nirsevimab	• Any immediate adverse events (AEs) reported in the 30 minutes after immunization • Non-serious AEs from D01 (post-dosing/randomization) to D31 • Adverse events of special interest (AESIs) from D01 visit through 1-year post-dosing/randomization or D366 • Medically attended adverse events (MAAEs) from D01 visit through 1-year post-dosing/randomization or D366 • Serious adverse events (SAEs) from D01 visit through 1-year post-dosing/randomization or D366 • Related SAEs from D366 to D731 for UK reconsented participants
• To assess the efficacy of nirsevimab in preventing RSV LRTI hospitalization through 180 days post-dosing/randomization (overall and in each country)	• Incidence of RSV LRTI hospitalization through 180 days post-dosing/randomization (overall and in each country)
• To assess the efficacy of nirsevimab in preventing hospitalizations for all-cause LRTI through 180 days post-dosing/randomization	• Incidence of hospitalizations for all-cause LRTI through 180 days post-dosing/randomization
• To assess the incidence of RSV LRTI hospitalization from 181 days post-dosing/randomization until D366 (overall and in each country)	• Incidence of RSV LRTI hospitalization from 181 days post-dosing/randomization until D366 (overall and in each country)
• To assess the incidence of hospitalizations for all-cause LRTI from 181 days post-dosing/randomization until D366	• Incidence of hospitalizations for all-cause LRTI from 181 days post-dosing/randomization until D366
• To describe in each study group the incidence of RSV LRTI hospitalization and all-cause LRTI hospitalization in UK reconsented participants from D366 to D731	• Incidence of RSV LRTI hospitalization in UK reconsented participants from D366 post-dosing/randomization until D731 • Incidence of hospitalization for all-cause LRTI in UK reconsented participants from D366 post-dosing/randomization until D731
• To assess the incidence of recurrent wheeze in UK reconsented participants from D01 to D731	• Incidence of recurrent wheeze in UK reconsented participants through D366 and D731 post-dosing/randomization, from D366 to D731 post-dosing/randomization
Exploratory	
• To assess the efficacy of nirsevimab in preventing of very severe RSV LRTI	• Incidence of very severe RSV LRTI defined as RSV LRTI hospitalization with oxygen saturation < 90% (at any time during

Cont.

Table 4

Objectives	Endpoints
through 180 days post-dosing/randomization	hospitalization) and oxygen supplementation, through 180 days post-dosing/randomization
• To assess health care utilization	• Duration of hospitalization • Admission to the intensive care unit and duration of stay • Number of participants who require oxygen supplementation • Number of participants who require intravenous fluid administration
* These objectives and associated endpoints were evaluated as part of the study Primary Analysis in 2023 (results described in the study Primary CSR dated 26 June 2023). These efficacy analyses served the purpose of evaluating the efficacy of nirsevimab in the study population. These endpoints were re-analysed as part of the First-Year Analysis for descriptive purposes only – without the intention of a confirmatory conclusion – to consider potential new data collected after the Primary Analysis cut-off date.	

Additional objectives and the corresponding endpoints were generated after the First-Year Analysis database lock and therefore considered as post-hoc analyses.

Table 5. Post-hoc Objectives and Endpoints

Objectives	Endpoints
• To assess the efficacy in all-cause hospitalizations associated with nirsevimab compared to no intervention (overall and in each country)	• Incidence of all-cause hospitalization through the RSV season, 150 days and 180 days post-dosing/randomization, from 181 days to 366 days post-dosing/randomization, through the end of the year 2022*
• To describe in each treatment group the incidence of RSV LRTI hospitalization and all-cause LRTI hospitalization in UK reconsented participants during the study	• Incidence of RSV LRTI hospitalization from 366 days to 511 days post-dosing/randomization, from 512 days to 731 days post-dosing/randomization, though 511 days and 731 days post-dosing/randomization • Incidence of all-cause LRTI hospitalization from 366 days to 511 days post-dosing/randomization, from 512 days to 731 days post-dosing/randomization, though 511 days and 731 days post-dosing/randomization
* Analyses for the all-cause hospitalization endpoints were performed at the time of the First-Year Analysis, except through the end of the year 2022 endpoints that was performed at the time of the Second-Year Analysis	

Outcomes/endpoints

Please see table above.

First-Year data collection

Efficacy data were collected through the participant's medical records and reported in the electronic Case Report Form (eCRF) by the site personnel or designee. Adverse events (AEs; including

hospitalisations) were reported by parents or LARs of participants through an electronic diary (eDiary) at any time during the 12-month follow-up period. Each time a health event was captured in the eDiary, a medical call centre contacted parents or LARs to collect and report the health events information in the eCRF.

Second-Year data collection:

Two additional follow-up phone calls at D546 and D731 post-dosing/randomisation were made to the parents or LARs of the UK reconsented participants by the site personnel to collect any LRTI hospitalisations or related SAEs that might occur from D366 to D731 post-dosing/randomisation and to ask if the participants had experienced any medically attended cough, chest or breathing problems throughout the study period.

Sample size

First-Year Analysis (previous):

From 08 August 2022 to 28 February 2023, a total of 8057 participants were randomised at 235 sites in the 3 participating countries (UK, France and Germany): 4038 were assigned to the nirsevimab group and 4019 to the no intervention group.

Second-Year Analysis:

Of 2226 UK reconsented participants, 2111 (94.8%) completed the 24-month follow-up: 1095 (95.9%) participants in the nirsevimab group and 1016 (93.7%) participants in no intervention group.
A total of 115 (5.2%) UK reconsented participants discontinued the study, mainly for lost to follow-up.

Data from the tabular listing of clinical studies:
Participants randomised: 2226
- Nirsevimab group: 1142
- No intervention group: 1084

First visit first patient (FVFP): 08 August 2022:
LCLP First Year Analysis: 27 March 2024 (last participant last 12-month phone call)
LCLP Second Year Analysis: 09 April 2025 (last participant last 24-month phone call)

Randomisation and blinding (masking)

All participants were centrally assigned to randomised study intervention using an Interactive Response Technology (IRT).

This was an open-label study.

Statistical Methods

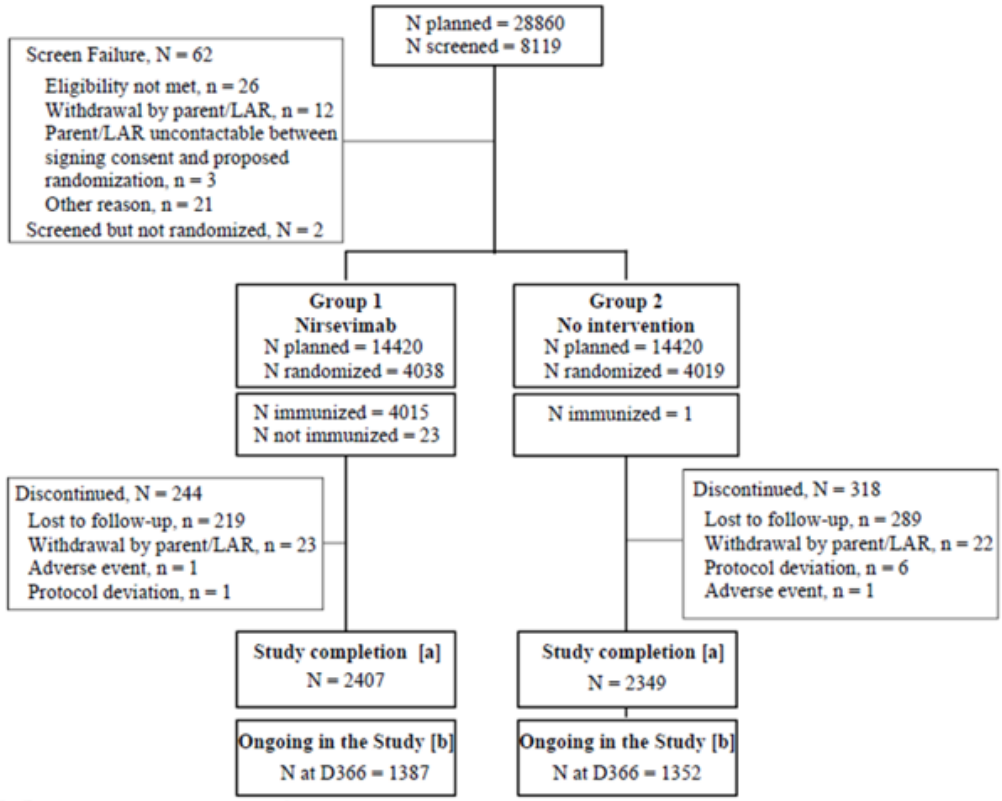
As per HARMONIE's statistical analysis plan, the primary and key secondary efficacy objectives were assessed in the Primary Analysis.

Additional objectives and the corresponding endpoints were generated after the First-Year Analysis database lock and therefore considered as post-hoc analyses.

Results

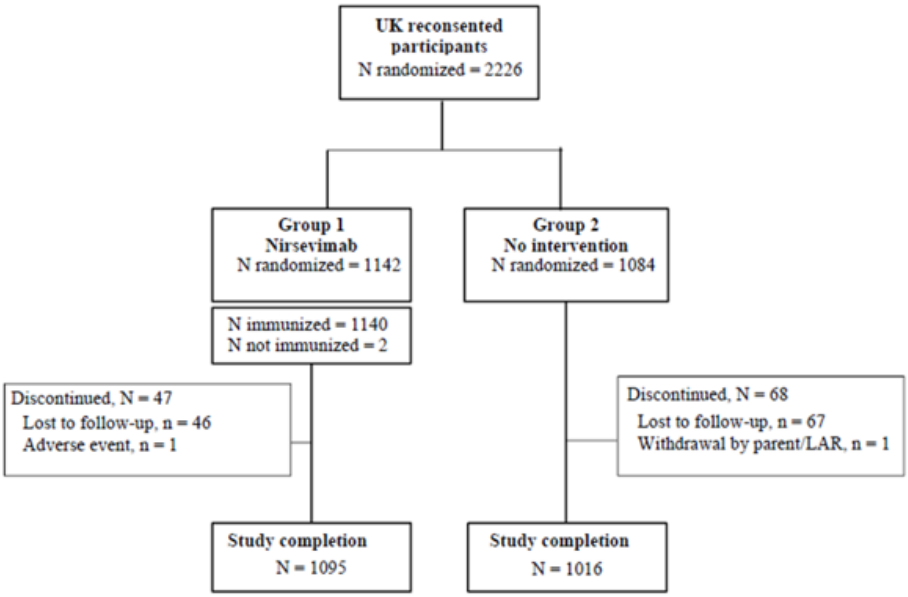
Participant flow

Figure 2. Participant disposition flow chart - First-Year Analysis



LAR = legally acceptable representative
[a] Study was completed for France, Germany, and UK non-reconsented participants.
[b] Study was ongoing for UK reconsented participants and those for whom the reconsent was pending at the time of the data cut-off date for the First-Year Analysis.

Figure 3. Participants disposition flow chart in UK reconsented participants - Second-Year Analysis



Recruitment First Year

From 08 August 2022 to 28 February 2023, a total of 8057 participants were randomised at 235 sites in the 3 participating countries. The first participant was enrolled on 08 August 2022 in the UK, on 08 September 2022 in France, and on 09 September 2022 in Germany. The number of randomised participants in the UK, France and Germany were 4091 (50.8%), 2177 (27.0%) and 1789 (22.2%), respectively.

Recruitment second year (UK only):

Participants randomised: 2226
- Nirsevimab group: 1142
- No intervention group: 1084

Baseline data

Table 6. Summary of Demographic Characteristics (All Randomised Set) - First-Year Analysis

Characteristic Statistic	Nirsevimab (N = 4038)	No Intervention (N = 4019)	Total (N = 8057)
Age (months)			
n	4038	4019	8057
Mean (SD)	4.53 (3.342)	4.48 (3.294)	4.51 (3.318)
Median	4.00	4.00	4.00
Min, Max	0.0, 12.0	0.0, 12.0	0.0, 12.0
Age Group (months), n (%)			
≤ 3.0	1962 (48.6)	1953 (48.6)	3915 (48.6)
> 3.0 to ≤ 6.0	959 (23.7)	954 (23.7)	1913 (23.7)
> 6.0	1117 (27.7)	1112 (27.7)	2229 (27.7)
Sex, n (%)			
Male	2088 (51.7)	2107 (52.4)	4195 (52.1)
Female	1950 (48.3)	1912 (47.6)	3862 (47.9)
Gestational Age at Birth (weeks)			
n	4005	3973	7978
Mean (SD)	38.84 (2.280)	38.85 (2.242)	38.84 (2.261)
Median	39.29	39.29	39.29
Min, Max	28.4, 42.4	28.4, 43.0	28.4, 43.0
Gestational Age at Birth (weeks), n (%)			
< 37	567 (14.0)	543 (13.5)	1110 (13.8)
≥ 37	3438 (85.1)	3430 (85.3)	6868 (85.2)
Missing	33 (0.8)	46 (1.1)	79 (1.0)
Weight (kg) at baseline			
n	4038	4019	8057
Mean (SD)	5.97 (2.299)	5.93 (2.261)	5.95 (2.280)
Median	5.80	5.80	5.80
Min, Max	1.5, 14.4	1.2, 15.0	1.2, 15.0
Weight (kg) at baseline, n (%)			
< 2.5	146 (3.6)	164 (4.1)	310 (3.8)
≥ 2.5	3892 (96.4)	3855 (95.9)	7747 (96.2)
Weight (kg) at baseline, n (%)			
< 5	1537 (38.1)	1521 (37.8)	3058 (38.0)
≥ 5	2501 (61.9)	2498 (62.2)	4999 (62.0)
Neonates [a], n (%)			
Yes	946 (23.4)	963 (24.0)	1909 (23.7)
No	3092 (76.6)	3056 (76.0)	6148 (76.3)
Country, n (%)			
France	1090 (27.0)	1087 (27.0)	2177 (27.0)
Germany	896 (22.2)	893 (22.2)	1789 (22.2)
United Kingdom	2052 (50.8)	2039 (50.7)	4091 (50.8)
Birth Categories, n (%)			
Born in Season [b]	2001 (49.6)	2026 (50.4)	4027 (50.0)
Born out of Season [b]	2037 (50.4)	1993 (49.6)	4030 (50.0)

Max = maximum; Min = minimum; N = number of participants in analysis set; n = number of participants with data available; SD = standard deviation; % = percentages are calculated based on N as the denominator.

[a] Neonates defined as ≤ 28 days of age.

[b] The following start dates were defined for the respiratory syncytial season: week 36 2022 for the UK, week 37 2022 for France and week 41 2022 for Germany. The end date was defined as the data cut-off date for the Primary Analysis, ie 28 February 2023, for the 3 participating countries.

Table 7. Summary of Demographic Characteristics in the UK for Reconsented Participants (All Randomised Participants) - Second-Year Analysis

Characteristic Statistic	Nirsevimab (N = 1142)	No Intervention (N = 1084)	Total (N = 2226)
Age (months)			
n	1142	1084	2226
Mean (SD)	5.92 (3.448)	5.68 (3.350)	5.80 (3.402)
Median	5.00	5.00	5.00
Min, Max	1.0, 12.0	0.0, 12.0	0.0, 12.0
Age Group (months), n (%)			
≤ 3.0	353 (30.9)	347 (32.0)	700 (31.4)
> 3.0 to ≤ 6.0	316 (27.7)	311 (28.7)	627 (28.2)
> 6.0	473 (41.4)	426 (39.3)	899 (40.4)
Sex, n (%)			
Male	588 (51.5)	580 (53.5)	1168 (52.5)
Female	554 (48.5)	504 (46.5)	1058 (47.5)
Gestational Age at Birth (weeks)			
n	1128	1069	2197
Mean (SD)	38.84 (2.318)	38.80 (2.300)	38.82 (2.309)
Median	39.29	39.29	39.29
Min, Max	29.1, 42.4	29.1, 42.9	29.1, 42.9
Gestational Age at Birth (weeks), n (%)			
< 37	156 (13.7)	139 (12.8)	295 (13.3)
≥ 37	972 (85.1)	930 (85.8)	1902 (85.4)
Missing	14 (1.2)	15 (1.4)	29 (1.3)
Weight (kg) at baseline			
n	1142	1084	2226
Mean (SD)	6.86 (2.205)	6.72 (2.143)	6.79 (2.175)
Median	6.90	6.80	6.90
Min, Max	1.6, 14.4	1.4, 15.0	1.4, 15.0
Weight (kg) at baseline, n (%)			
< 2.5	23 (2.0)	19 (1.8)	42 (1.9)
≥ 2.5	1119 (98.0)	1065 (98.2)	2184 (98.1)
Weight (kg) at baseline, n (%)			
< 5	241 (21.1)	252 (23.2)	493 (22.1)
≥ 5	901 (78.9)	832 (76.8)	1733 (77.9)
Neonates [a], n (%)			
Yes	83 (7.3)	114 (10.5)	197 (8.8)
No	1059 (92.7)	970 (89.5)	2029 (91.2)
Country, n (%)			
United Kingdom	1142 (100.0)	1084 (100.0)	2226 (100.0)
Birth Categories, n (%)			
Born in Season	467 (40.9)	455 (42.0)	922 (41.4)
Born out of Season	675 (59.1)	629 (58.0)	1304 (58.6)

N = number of participants in analysis set; n = number of participants with data available; % = percentages are calculated based on N as the denominator
SD = Standard deviation; Min = Minimum; Max = Maximum
Neonates defined as ≤ 28 days of age

Number analysed

Table 8. Reasons for Exclusion from the Analysis Sets (All Randomised Set) - First-Year Analysis

Analysis Set Reason for Exclusion	Nirsevimab (N = 4038) n (%)	No Intervention (N = 4019) n (%)	Total (N = 8057) n (%)
All Randomized Set [a]	4038 (100.0)	4019 (100.0)	8057 (100.0)
Participants Excluded from All Randomized Set			62
Reason for Exclusion			
Screen Failure			62
Per-Protocol Analysis Set (PPAS) [b]	3768 (93.3)	3701 (92.1)	7469 (92.7)
Participants Excluded from PPAS	270 (6.7)	318 (7.9)	588 (7.3)
Reason for Exclusion			
Participant did not meet all protocol-specified inclusion criteria or	7 (0.2)	6 (0.1)	13 (0.2)
Participant met at least one of the protocol-specified exclusion criteria	3 (< 0.1)	1 (< 0.1)	4 (< 0.1)
Participant did not receive nirsevimab or the correct dose of nirsevimab if randomized to nirsevimab	31 (0.8)	0	31 (0.4)
Participant received nirsevimab if randomized to no intervention	0	1 (< 0.1)	1 (< 0.1)
Administration of nirsevimab was not done as per-protocol	15 (0.4)	0	15 (0.2)
Participant did not have at least one contact for efficacy follow-up after dosing/randomization	219 (5.4)	296 (7.4)	515 (6.4)
Participant who received Beyfortus (nirsevimab) as a routine medication during the study	4 (< 0.1)	12 (0.3)	16 (0.2)
Any other protocol deviations identified during the study conduct as relevant to the exclusion from the PPAS	50 (1.2)	50 (1.2)	100 (1.2)
Safety Analysis Set (SafAS) [c]	4016 (99.5) [d]	4018 (> 99.9)	8034 (99.7)
Participants Excluded from SafAS	23 (0.6)	0	23 (0.3)
Reason for Exclusion			
Randomized participant to nirsevimab group and didn't receive nirsevimab in the study	23 (0.6)		23 (0.3)

N = number of participants in analysis set; n = number of participants with data available; PPAS = Per Protocol Analysis Set; SafAS = Safety Analysis Set; % = percentages are calculated based on the number of screened participants as the denominator.
[a] The All Randomized Set consists of all participants randomly assigned to either the nirsevimab group or the no intervention group. All Randomized Set participants were analyzed according to their randomized study intervention group.
[b] The PPAS consists of all randomized participants who did not have any important protocol deviations leading to exclusion from the PPAS. PPAS participants were analyzed according to their randomized study intervention group.
[c] The SafAS consists of all participants who received nirsevimab in the study and all randomized participants who were randomized to the no intervention group and did not receive nirsevimab inadvertently. SafAS participants were analyzed according to the study intervention they actually received.
[d] One Participant was randomized into the no intervention group but was wrongly immunized with nirsevimab. Thus, this participant was included in the nirsevimab group of the SafAS.

Table 9. Reasons for Exclusion from the Analysis Sets in the UK Reconsented Participants (All Randomised Set) - Second-Year Analysis

Analysis Set Reason for Exclusion	Nirsevimab (N=1142) n (%)	No Intervention (N=1084) n (%)	Total (N=2226) n (%)
All Randomized Set [a]	1142 (100.0)	1084 (100.0)	2226 (100.0)
Participants Excluded from All Randomized Set	0	0	0
Per Protocol Analysis Set [b]	1139 (99.7)	1082 (99.8)	2221 (99.8)
Participants Excluded from Per Protocol Analysis Set	3 (0.3)	2 (0.2)	5 (0.2)
Reason for Exclusion			
Participant did not receive nirsevimab or the correct dose of nirsevimab if randomized to nirsevimab	2 (0.2)	0	2 (< 0.1)
Administration of nirsevimab was not done as per-protocol	1 (< 0.1)	0	1 (< 0.1)
Any other protocol deviations identified during the study conduct as relevant to the exclusion from the PPAS	3 (0.3)	2 (0.2)	5 (0.2)
Safety Analysis Set [c]	1140 (99.8)	1084 (100.0)	2224 (> 99.9)
Participants Excluded from Safety Analysis Set	2 (0.2)	0	2 (< 0.1)
Reason for Exclusion			
Randomized participant to nirsevimab group and didn't receive nirsevimab in the study	2 (0.2)		2 (< 0.1)

N = number of participants in analysis set; n = number of participants with data available; % = percentages are calculated based on the number of participants as the denominator.
SafAS = Safety Analysis Set; PPAS = Per Protocol Analysis Set;
[a] All Randomized Set will consist of all participants randomly assigned to either the nirsevimab group or the no intervention group.
[b] The PPAS will consist of all randomized participants who do not have any important protocol deviations leading to exclusion from the PPAS.
[c] SafAS will consist of all Participants who received nirsevimab in the study and all randomized participants who were randomized to the no intervention group and did not receive nirsevimab inadvertently.

Table 10. Reasons for Exclusion from the Analysis Sets in the UK Reconsented Participants (All Randomised Set) - Second-Year Analysis

Analysis Set Reason for Exclusion	Nirsevimab (N=1142) n (%)	No Intervention (N=1084) n (%)	Total (N=2226) n (%)
All Randomized Set [a]	1142 (100.0)	1084 (100.0)	2226 (100.0)
Participants Excluded from All Randomized Set	0	0	0
Per Protocol Analysis Set [b]	1139 (99.7)	1082 (99.8)	2221 (99.8)
Participants Excluded from Per Protocol Analysis Set	3 (0.3)	2 (0.2)	5 (0.2)
Reason for Exclusion			
Participant did not receive nirsevimab or the correct dose of nirsevimab if randomized to nirsevimab	2 (0.2)	0	2 (< 0.1)
Administration of nirsevimab was not done as per-protocol	1 (< 0.1)	0	1 (< 0.1)
Any other protocol deviations identified during the study conduct as relevant to the exclusion from the PPAS	3 (0.3)	2 (0.2)	5 (0.2)
Safety Analysis Set [c]	1140 (99.8)	1084 (100.0)	2224 (> 99.9)
Participants Excluded from Safety Analysis Set	2 (0.2)	0	2 (< 0.1)
Reason for Exclusion			
Randomized participant to nirsevimab group and didn't receive nirsevimab in the study	2 (0.2)		2 (< 0.1)

N = number of participants in analysis set; n = number of participants with data available; % = percentages are calculated based on the number of participants as the denominator.
SafAS = Safety Analysis Set; PPAS = Per Protocol Analysis Set;
[a] All Randomized Set will consist of all participants randomly assigned to either the nirsevimab group or the no intervention group.
[b] The PPAS will consist of all randomized participants who do not have any important protocol deviations leading to exclusion from the PPAS.
[c] SafAS will consist of all Participants who received nirsevimab in the study and all randomized participants who were randomized to the no intervention group and did not receive nirsevimab inadvertently.

Efficacy results

First-year analysis:

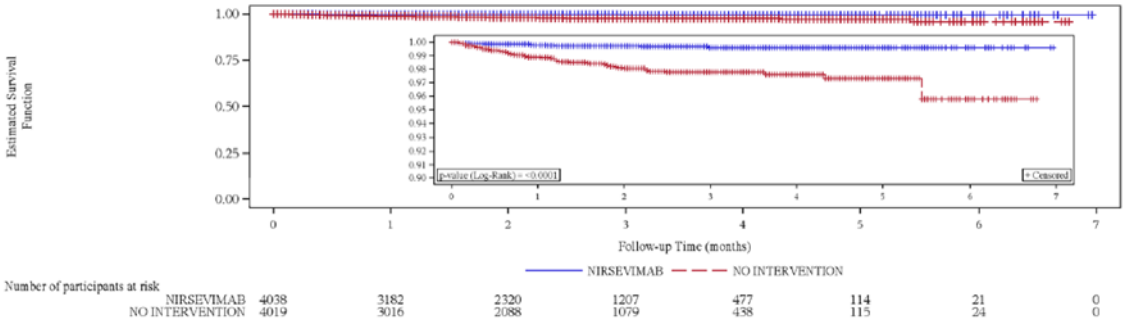
Table 11. Overall Incidence of RSV LRTI Hospitalisation through the RSV Season - Exact Method Using Binomial Distribution (All Randomised Set) - First-Year Analysis

Variable Statistic	Nirsevimab (N = 4038)	No Intervention (N = 4019)
RSV LRTI Hospitalization through the RSV Season, n (%)		
Yes	11 (0.3)	64 (1.6)
No	4027 (99.7)	3955 (98.4)
Total Follow-up Time (Person Months)	8869.979	8236.353
Incidence Rates	0.001	0.008
Efficacy	84.04	
95% Confidence Interval based on Exact Method [a]	69.493 ; 92.411	
p-value	<0.0001	

LRTI = Lower Respiratory Tract Infection; N = number of participants in analysis set; n = number of participants with data available; RSV = Respiratory Syncytial Virus; % = percentages are calculated based on N as the denominator.
"Through the RSV" season is defined as from dosing/randomization to cut-off date (28FEB2023).
The efficacy of nirsevimab in preventing RSV LRTI hospitalization through the RSV Season is defined as (1 minus the incidence rate ratio) × 100%.
[a] The 2-sided 95% CI for the efficacy is calculated by an exact method assuming a binomial distribution of the number of RSV LRTI hospitalizations in the nirsevimab group conditional on the total number in both groups (described by Breslow and Day) accounting for the follow-up time post-dosing/randomization.

Figure 4. Kaplan-Meier Plot for Overall Incidence of RSV LRTI Hospitalisation through

Figure 4 – Kaplan-Meier Plot for Overall Incidence of RSV LRTI Hospitalization through the RSV Season (All Randomized Set) – First Year Analysis



LRTI = Lower Respiratory Tract Infection; RSV = Respiratory Syncytial Virus.
The inset shows the same data on an enlarged y axis.
Follow-up time (month) = (Event or Censored date - Immunization/Randomization date +1)/30.4375.
Reference: Table 8.6.1.5
Reference: First-Year Analysis, Listing 6.1.
Source: First-Year Analysis, Section 8, Figure 8.6.1.5.1.

Second-year analysis:

Table 12. Incidence of RSV LRTI Hospitalisation from 366 Days Post-Dosing/Randomisation to 731 Days Post-Dosing/Randomisation in UK Reconsented Participants (All Randomised Set) - Second-Year Analysis

Variable Statistic	Nirsevimab (N = 1132) [a]	No Intervention (N = 1062) [a]
Overall		
RSV LRTI Hospitalization from Day 366 Post-Dosing/Randomization to Day 731/Post-Dosing Randomization, n (%)		
Yes	7 (0.6)	2 (0.2)
No	1125 (99.4)	1060 (99.8)
Total Follow-up Time (Person Months)	26830.620	25029.520
Incidence Rates	<0.001	<0.001

N = number of participants in analysis set; n = number of participants with data available; % = percentages are calculated based on N as the denominator
RSV = Respiratory Syncytial Virus; LRTI = Lower Respiratory Tract Infection
[a] In participants with no RSV LRTI Hospitalization before Day 366

Table 13. Incidence of Hospitalisation for All-Cause LRTI from 366 Days Post-Dosing/Randomisation to 731 Days Post-Dosing/Randomisation in UK Reconsented Participants (All Randomised Set) - Second-Year Analysis

Variable Statistic	Nirsevimab (N = 1096) [a]	No Intervention (N = 1025) [a]
Overall		
All-Cause LRTI Hospitalization from Day 366 Post-Dosing/Randomization to Day 731/Post-Dosing Randomization, n (%)		
Yes	18 (1.6)	10 (1.0)
No	1078 (98.4)	1015 (99.0)
Total Follow-up Time (Person Months)	25900.090	24108.945
Incidence Rates	<0.001	<0.001

N = number of participants in analysis set; n = number of participants with data available; % = percentages are calculated based on N as the denominator
LRTI = Lower Respiratory Tract Infection
[a] In participants with no Hospitalization for All-Cause LRTI before Day 366

Table 14. Incidence of RSV LRTI Hospitalisation throughout the study in UK reconsented participants (All Randomised Set) - Second-Year Analysis

Variable Statistic	Nirsevimab	No Intervention
RSV LRTI Hospitalization from 366 Days Post-Dosing/Randomization to 511 Days Post-Dosing/Randomization, n (%) [a]	**(N=1132)**	**(N=1062)**
Yes	2 (0.2)	1 (<0.1)
No	1130 (99.8)	1061 (>99.9)
RSV LRTI Hospitalization from 512 Days Post-Dosing/Randomization to 731 Days Post-Dosing/Randomization, n (%) [b]	**(N=1130)**	**(N=1061)**
Yes	5 (0.4)	1 (<0.1)
No	1125 (99.6)	1060 (>99.9)
RSV LRTI Hospitalization through 511 Days Post-Dosing/Randomization, n (%)	**(N=1142)**	**(N=1084)**
Yes	12 (1.1)	23 (2.1)
No	1130 (98.9)	1061 (97.9)
RSV LRTI Hospitalization through 731 Days Post-Dosing/Randomization, n (%)	**(N=1142)**	**(N=1084)**
Yes	17 (1.5)	24 (2.2)
No	1125 (98.5)	1060 (97.8)

N = number of participants in analysis set; n = number of participants with data available; % = percentages are calculated based on N as the denominator.
RSV = Respiratory Syncytial Virus; LRTI = Lower Respiratory Tract Infection.
[a] In participants with no hospitalization before Day 366.
[b] In participants with no hospitalization before Day 512.

The overall incidence rate of recurrent wheeze throughout the study in UK reconsented participants (All Randomised Set) were comparable between treatment groups across all time periods.

Table 15. Incidence of Recurrent Wheeze Events from D01 to D731 Post-Dosing/Randomisation in the UK reconsented Participants (All Randomised Set) -Second-Year Analysis

Variable Statistic	Nirsevimab (N=928)	No Intervention (N=888)
Recurrent Wheeze Event through Day 366 Post-Dosing/Randomization, n (%)		
Yes	52 (5.6)	48 (5.4)
No	876 (94.4)	840 (94.6)
Recurrent Wheeze Event from Day 366 Post-Dosing/Randomization to Day 731 Post-Dosing/Randomization, n (%)		
Yes	40 (4.3)	44 (5.0)
No	888 (95.7)	844 (95.0)
Recurrent Wheeze Event through Day 731 Post-Dosing/Randomization, n (%)		
Yes	101 (10.9)	96 (10.8)
No	827 (89.1)	792 (89.2)

N = number of participants in analysis set; n = number of participants with data available; % = percentages are calculated based on N as the denominator.
Recurrent wheeze event is defined as two or more protocol-defined wheeze episodes throughout follow-up period
In participants for which the medical records were retrospectively reviewed after 24 months to determine if medical event(s) meet the definition of wheeze, i.e., "Was retrospective collection of wheeze data performed in participant medical record?" = Yes.

Safety results

Post-marketing surveillance

The Marketing Authorisation Holders are required to carry out pharmacovigilance (PV) on a routine basis according to the legislation. Routine PV activities are described in the PV system master file. However, a summary of signal identification is provided below.

The sources routinely screened to identifying relevant new safety information include:

- Sanofi Global PV database, to identify signals from individual case safety reports (ICSRs) and clusters of cases as well as from aggregate reports

- Scientific literature to identify signals from case reports or case series, published studies, meta-analyses
- Data mining in publicly available databases of adverse events (AEs) (the US FDA Adverse Event Reporting System, the World Health Organization VigiBase, and the EudraVigilance Data Analysis System databases)
- Product complaints (PCs) database
- Regulatory Authority websites

The following sources of routine safety surveillance are also taken into consideration, as applicable:

- Safety queries and requests from Regulatory Authorities
- Clinical trials and other studies in human (individual study data and integrated study data), Independent Data Monitoring Committee reports
- Non-clinical safety information (i.e., toxicology, safety pharmacology, pharmacokinetics data, in vitro studies)
- Pharmacoepidemiology studies, registries or other observational studies, analysis of pre-existing data
- Manufacturing site quality systems review
- Competitive intelligence
- Signals identified by partners
- Queries and requests from Ethics Committees, Institutional Review Boards
- Media (e.g., press, television, internet including social media)

During the second year of the study, UK reconsented participants' parents/LARs were provided with a memory aid to record any hospitalisations and emergency room visits that occurred. During the 18- and 24-month phone calls, the investigator or site staff interviewed the parents/LARs to collect information reported in the memory aid to assess the SAE relationship. Only SAEs considered related by the investigator or site staff were collected in the eCRF.

Collection of data

1. Non-serious AEs were collected from dosing/randomisation (D01) until 30 days after immunisation, i.e., D31.
2. MAAEs were collected from dosing/randomisation until D366
3. SAEs were collected from dosing/randomisation throughout the study (D366 for France, Germany, and UK non-reconsented participants, and D731 for UK reconsented participants)
4. AESIs were collected from dosing/randomisation until D366

Treatment exposure

The participants were not exposed to additional study treatment in addition to the one initial dose.

Table 16. Summary of Exposure (Safety Analysis Set) - First-Year Analysis

Exposure Statistic	Nirsevimab 50 mg (N = 1524)	Nirsevimab 100 mg (N = 2491)	Nirsevimab Overall (N = 4016) [a]
During the study			
Actual Dose (mL), n (%)			
0.25	2 (0.1)	0	2 (< 0.1)
0.4	1 (< 0.1)	0	1 (< 0.1)
0.5	1519 (99.7)	4 (0.2)	1523 (37.9)
1	1 (< 0.1)	2486 (99.8)	2488 (62.0) [a]
Missing	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Full Dose Received, n (%)			
Yes	1519 (99.7)	2486 (99.8)	4006 (99.8)
No	5 (0.3)	5 (0.2)	10 (0.2)
Side, n (%)			
Left	913 (59.9)	1455 (58.4)	2369 (59.0)
Right	593 (38.9)	1031 (41.4)	1624 (40.4)
Missing	18 (1.2)	5 (0.2)	23 (0.6)
Timing of Dosing, n (%)			
In Season [b]	1523 (> 99.9)	2475 (99.4)	3999 (99.6)
Before RSV Season	1 (< 0.1)	16 (0.6)	17 (0.4)
Infants Dosed In Season [b]			
Actual Dose (mL), n (%)			
0.25	2 (0.1)	0	2 (< 0.1)
0.4	1 (< 0.1)	0	1 (< 0.1)
0.5	1518 (99.6)	4 (0.2)	1522 (37.9)
1	1 (< 0.1)	2470 (99.2)	2472 (61.6) [a]
Missing	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Full Dose Received, n (%)			
Yes	1518 (99.6)	2470 (99.2)	3989 (99.3)
No	5 (0.3)	5 (0.2)	10 (0.2)
Side, n (%)			
Left	912 (59.8)	1444 (58.0)	2357 (58.7)
Right	593 (38.9)	1026 (41.2)	1619 (40.3)
Missing	18 (1.2)	5 (0.2)	23 (0.6)
Infants Dosed Before the Start of the RSV Season			
Actual Dose (mL), n (%)			
0.5	1 (< 0.1)	0	1 (< 0.1)
1	0	16 (0.6)	16 (0.4)
Full Dose Received, n (%)			
Yes	1 (< 0.1)	16 (0.6)	17 (0.4)
No	0	0	0
Side, n (%)			
Left	1 (< 0.1)	11 (0.4)	12 (0.3)
Right	0	5 (0.2)	5 (0.1)

mL = milliliter; N = number of participants in analysis set; n = number of participants with data available; RSV = Respiratory Syncytial Virus; % = percentages are calculated based on N as the denominator.
[a] Participant 8260008-00093 was randomized into the no intervention group but was wrongly immunized in season with nirsevimab, without details about planned dose and actual dose. Thus, this participant appears only in the "nirsevimab overall" group, for which the number of participants is 4016.
[b] In season means dosed on or after the start date of RSV season.

A summary of AEs reported from D01 visit to the data cut-off date for the First-Year Analysis is presented by treatment group in the SafAS (n = 8034):

First-year analysis:

Table 17. HARMONIE - Summary of TEAEs - Safety Analysis Set - First-Year Analysis

Adverse Events Category Adverse Events Type [a]	Nirsevimab (N = 4016) n (%) 95% CI	No Intervention (N = 4018) n (%) 95% CI	Total (N = 8034) n (%) 95% CI
Any TEAE	3212 (80.0) (78.7; 81.2)	3192 (79.4) (78.2; 80.7)	6404 (79.7) (78.8; 80.6)
Leading to discontinuation of study	1 (< 0.1) (< 0.1; 0.1)	1 (< 0.1) (< 0.1; 0.1)	2 (< 0.1) (< 0.1; < 0.1)
Leading to death	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)
Grade 1 severity	2759 (68.7) (67.2; 70.1)	2696 (67.1) (65.6; 68.6)	5455 (67.9) (66.9; 68.9)
Grade 2 severity	1447 (36.0) (34.5; 37.5)	1436 (35.7) (34.3; 37.2)	2883 (35.9) (34.8; 36.9)
Grade 3 severity	151 (3.8) (3.2; 4.4)	143 (3.6) (3.0; 4.2)	294 (3.7) (3.3; 4.1)
Unknown [b]	116 (2.9) (2.4; 3.5)	109 (2.7) (2.2; 3.3)	225 (2.8) (2.5; 3.2)
Any study treatment-related TEAE [c]	102 (2.5) (2.1; 3.1)	0 (0.0) (0.0; < 0.1)	102 (1.3) (1.0; 1.5)
Any serious TEAE	262 (6.5) (5.8; 7.3)	222 (5.5) (4.8; 6.3)	484 (6.0) (5.5; 6.6)
Leading to discontinuation of study	1 (< 0.1) (< 0.1; 0.1)	0 (0.0) (0.0; < 0.1)	1 (< 0.1) (< 0.1; < 0.1)
Leading to death	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)
Any serious study treatment-related TEAE	1 (< 0.1) (< 0.1; 0.1)	0 (0.0) (0.0; < 0.1)	1 (< 0.1) (< 0.1; < 0.1)
Leading to discontinuation of study	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)
Leading to death	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)
Any immediate TEAEs reported in the 30 minutes post-dosing/randomization	27 (0.7) (0.4; 1.0)	0 (0.0) (0.0; < 0.1)	27 (0.3) (0.2; 0.5)
Leading to discontinuation of study	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)
Leading to death	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)	0 (0.0) (0.0; < 0.1)
Non-serious TEAEs until 30 days after Day 1	1316 (32.8) (31.3; 34.2)	1265 (31.5) (30.0; 32.9)	2581 (32.1) (31.1; 33.2)
Medically attended TEAEs	3106 (77.3) (76.0; 78.6)	3100 (77.2) (75.8; 78.4)	6206 (77.2) (76.3; 78.2)
TEAEs of Special Interest	11 (0.3) (0.1; 0.5)	3 (< 0.1) (< 0.1; 0.2)	14 (0.2) (< 0.1; 0.3)

CI = Confidence Interval based on Clopper-Pearson; N = number of participants in analysis set; n = number of participants with data available; TEAE = treatment-emergent adverse event; % = percentages are calculated based on N as the denominator.
[a] Assessment of AE severity was based on the AEs severity grading scales adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007".
[b] AEs for which the severity was unknown at the time of the data cut-off for this First-Year Analysis, as per investigator's judgment.
[c] The relationship between a TEAE and treatment was assessed as related, or not related. A treatment-related TEAE was defined as a TEAE considered by the investigator as related or with unknown / missing relationship to treatment for participants who received nirsevimab on Day 1. An unknown / missing relationship between a TEAE and treatment for participants who received no intervention was considered as not related.
MedDRA version 25.0.
Source: Modified from 5.3.5.1, HARMONIE Final CSR, First-Year Analysis Section 8, Table 8.8.1.

The majority of treatment related AE's (n = 134 out of 136, 98.5%) were resolved at the time of the data cut off for the First-Year Analysis. The most frequent AEs described as related to nirsevimab by investigator judgment were pyrexia (n = 16, 0.4%), injection site erythema (n = 15, 0.4%), nasopharyngitis (n = 12, 0.3%), injection site swelling (n = 6, 0.1%), cough (n = 5, 0.1%) and vomiting (n = 5, 0.1%)

Only one treatment-related SAE was reported 3 weeks after immunisation (West syndrome; PT: infantile spasms). These data are included in previous evaluation of data. The event of West syndrome was reported by the investigator as serious with the following seriousness criterion: involved or prolonged inpatient hospitalisation. The event of West syndrome was reported by the investigator as related to the investigational product or trial procedures as it was not clear at whether there was a causal relationship.

The prespecified AESIs were hypersensitivity (including anaphylaxis), immune complex disease, and thrombocytopenia. Eleven participants (0.3%) in the nirsevimab group experienced 12 AESIs (based on investigator's assessment), all of grade 1 or grade 2 in severity.

Generally, the safety profile of nirsevimab was favourable with no apparent safety concerns identified during the study period. No emerging safety signals were observed, supporting the overall tolerability of nirsevimab in the studied population.

Second-year analysis:

Table 18. Summary of Treatment-Emergent Adverse Events (TEAEs) from Day 1 to 731 Days Post-Dosing/Randomisation in UK reconsented Participants (Safety Analysis Set - Second-Year Analysis)

Adverse Events Category Adverse Events type [a]	Nirsevimab (N=1140) n (%) 95% CI	No Intervention (N=1084) n (%) 95% CI	Total (N=2224) n (%) 95% CI
Any TEAE	975 (85.5) (83.3 ; 87.5)	913 (84.2) (81.9 ; 86.3)	1888 (84.9) (83.3 ; 86.4)
Leading to discontinuation of study	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Leading to death	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Grade 1 severity	834 (73.2) (70.5 ; 75.7)	784 (72.3) (69.6 ; 75.0)	1618 (72.8) (70.8 ; 74.6)
Grade 2 severity	439 (38.5) (35.7 ; 41.4)	396 (36.5) (33.7 ; 39.5)	835 (37.5) (35.5 ; 39.6)
Grade 3 severity	37 (3.2) (2.3 ; 4.4)	24 (2.2) (1.4 ; 3.3)	61 (2.7) (2.1 ; 3.5)
Unknown	40 (3.5) (2.5 ; 4.7)	42 (3.9) (2.8 ; 5.2)	82 (3.7) (2.9 ; 4.6)
Any study treatment related TEAE [b]	34 (3.0) (2.1 ; 4.1)	0 (0.0) (0.0 ; 0.3)	34 (1.5) (1.1 ; 2.1)
Leading to discontinuation of study	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Leading to death	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Grade 1 severity	29 (2.5) (1.7 ; 3.6)	0 (0.0) (0.0 ; 0.3)	29 (1.3) (0.9 ; 1.9)
Grade 2 severity	8 (0.7) (0.3 ; 1.4)	0 (0.0) (0.0 ; 0.3)	8 (0.4) (0.2 ; 0.7)
Grade 3 severity	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Unknown	1 (< 0.1) (< 0.1 ; 0.5)	0 (0.0) (0.0 ; 0.3)	1 (< 0.1) (< 0.1 ; 0.3)
Any serious TEAE	70 (6.1) (4.8 ; 7.7)	56 (5.2) (3.9 ; 6.7)	126 (5.7) (4.7 ; 6.7)
Leading to discontinuation of study	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Leading to death	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Any serious study treatment related TEAE	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Leading to discontinuation of study	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Leading to death	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Non-serious TEAEs until 30 days after Day 1	468 (41.1) (38.2 ; 44.0)	388 (35.8) (32.9 ; 38.7)	856 (38.5) (36.5 ; 40.5)
Leading to discontinuation of study	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Grade 1 severity	371 (32.5) (29.8 ; 35.3)	299 (27.6) (24.9 ; 30.3)	670 (30.1) (28.2 ; 32.1)
Grade 2 severity	115 (10.1) (8.4 ; 12.0)	105 (9.7) (8.0 ; 11.6)	220 (9.9) (8.7 ; 11.2)
Grade 3 severity	2 (0.2) (< 0.1 ; 0.6)	2 (0.2) (< 0.1 ; 0.7)	4 (0.2) (< 0.1 ; 0.5)
Unknown	20 (1.8) (1.1 ; 2.7)	14 (1.3) (0.7 ; 2.2)	34 (1.5) (1.1 ; 2.1)
Any immediate TEAEs reported in the 30 minutes post-dosing/randomization	7 (0.6) (0.2 ; 1.3)	0 (0.0) (0.0 ; 0.3)	7 (0.3) (0.1 ; 0.6)
Leading to discontinuation of study	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)

Adverse Events Category Adverse Events type [a]	Nirsevimab (N=1140) n (%) 95% CI	No Intervention (N=1084) n (%) 95% CI	Total (N=2224) n (%) 95% CI
Leading to death	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Grade 1 severity	7 (0.6) (0.2 ; 1.3)	0 (0.0) (0.0 ; 0.3)	7 (0.3) (0.1 ; 0.6)
Grade 2 severity	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Grade 3 severity	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Unknown	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Medically attended TEAEs	925 (81.1) (78.7 ; 83.4)	878 (81.0) (78.5 ; 83.3)	1803 (81.1) (79.4 ; 82.7)
Leading to discontinuation of study	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Leading to death	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Grade 1 severity	768 (67.4) (64.6 ; 70.1)	740 (68.3) (65.4 ; 71.0)	1508 (67.8) (65.8 ; 69.7)
Grade 2 severity	428 (37.5) (34.7 ; 40.4)	391 (36.1) (33.2 ; 39.0)	819 (36.8) (34.8 ; 38.9)
Grade 3 severity	37 (3.2) (2.3 ; 4.4)	24 (2.2) (1.4 ; 3.3)	61 (2.7) (2.1 ; 3.5)
Unknown	31 (2.7) (1.9 ; 3.8)	35 (3.2) (2.3 ; 4.5)	66 (3.0) (2.3 ; 3.8)
TEAEs of Special Interest	6 (0.5) (0.2 ; 1.1)	2 (0.2) (< 0.1 ; 0.7)	8 (0.4) (0.2 ; 0.7)
Leading to discontinuation of study	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Leading to death	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)
Grade 1 severity	2 (0.2) (< 0.1 ; 0.6)	1 (< 0.1) (< 0.1 ; 0.5)	3 (0.1) (< 0.1 ; 0.4)
Grade 2 severity	4 (0.4) (< 0.1 ; 0.9)	0 (0.0) (0.0 ; 0.3)	4 (0.2) (< 0.1 ; 0.5)
Grade 3 severity	0 (0.0) (0.0 ; 0.3)	1 (< 0.1) (< 0.1 ; 0.5)	1 (< 0.1) (< 0.1 ; 0.3)
Unknown	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.3)	0 (0.0) (0.0 ; 0.2)

N = number of participants in analysis set; n = number of participants with data available; % = percentages are calculated based on N as the denominator.
TEAE = Treatment Emergent Adverse Event; CI=Confidence Interval based on Clopper-Pearson.
[a] Assessment of AE intensity will be based on the AEs intensity grading scales adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007".
[b] The relationship between a TEAE and treatment is assessed as related, or not related. A treatment-related TEAE will be defined as a TEAE considered by the investigator as related or with unknown / missing relationship to treatment for participants who received nirsevimab on Day 1. An unknown / missing relationship between a TEAE and treatment for participants who received no intervention will be considered as not related.
MedDRA version 25.0

The safety objective for the second year was the assessment of the occurrence of related SAEs from D366 through D731 in UK reconsented participants.

At the time of the Second-Year Analysis, AE rates were comparable between the nirsevimab group and the no intervention group, consistent with the AEs profile observed in the overall population during the First-Year Analysis.

One death (see below), but no other related SAEs were reported during the second year of the study.

Death

The participant was an infant who received nirsevimab during the first RSV season.

The participant subsequently experienced intercurrent illnesses and was pronounced dead approximately 16 months after administration of the investigational product. The primary cause of death was reported as complication of influenza A.

Post-marketing

The first marketing authorisation for nirsevimab was obtained in European Economic Area on 31 October 2022. As of 30 April 2025 (the data lock point [DLP] of the last PBRER) nirsevimab was approved in 56 countries worldwide.
As of the DLP of the last PBRER, a substantial number of units of nirsevimab have been distributed worldwide. Based on the cumulative marketing experience, no unanticipated safety findings have been identified that would impact the established safety profile of nirsevimab. There are no important identified or potential risks for nirsevimab.
Since product launch, serious hypersensitivity reactions have been reclassified from a potential to an identified risk
There are no ongoing safety concerns that require further evaluation via additional pharmacovigilance activities for nirsevimab.

2.3.3. Discussion on clinical aspects

The HARMONIE study was one of the pivotal studies for the initial marketing authorisation, including healthy term and preterm infants.

The above data submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 is data provided from an extension of the follow-up period for part of the cohort (UK population) in the VAS00006 HARMONIE Study from the initially planned 12 months to 24 months. No additional exposure to study medication, no additional visits were part of the follow-up program. Follow-up data are obtained from e-Diary registrations and telephone calls.

There are no requests from the applicant for changes in the SmPC or EPAR.

Efficacy

Of the reconsented UK participants (total N=2226; nirsevimab N=1142; no intervention N=1084) data collection was achieved in a large proportion (total N=2194; nirsevimab N=1132; no intervention N=1062). Baseline data were similar between the nirsevimab and the no intervention group. Only few events of '**RSV LRTI** Hospitalisation from 366 Days Post-Dosing/Randomisation to 731 Days Post-Dosing/Randomisation' were recorded (nirsevimab N=7; no intervention N=2). Despite the imbalance disfavouring nirsevimab, number of events are small, likely a chance finding and not considered concerning. Hence, no changes to the SmPC or EPAR is warranted.

As a secondary endpoint was included 'Incidence of Hospitalisation for **All-Cause LRTI** from 366 Days Post-Dosing/Randomisation to 731 Days Post-Dosing/Randomisation in UK reconsented participants', and also here the number of incidents were low (nirsevimab N=18; no intervention N=10). An imbalance disfavouring nirsevimab hospitalisations with RSV and All-cause LRTI infections in year two in children exposed to nirsevimab in their previous and first RSV season (year one) was observed but this finding is most likely a chance finding due to low numbers and this is considered a reasonable explanation.

Prior RSV LRTI as a risk factor for recurrent wheeze is part of the clinical discussion and 'Incidence of Recurrent Wheeze Events from D01 to D731 Post-Dosing/Randomisation in the UK reconsented Participants' was included as secondary endpoint. The overall incidence rate was comparable between the nirsevimab group and the no intervention group.

Safety

The participants were not exposed to additional study treatment after the initial nirsevimab dose (or no exposure) was administered prior to or during the first RSV season, within the first 12 months of the study period.

Only one treatment-related SAE was reported 3 weeks after immunisation (West syndrome; PT: infantile spasms). These data are included in the initial evaluation of data.

One death was reported in second year analysis after administration of investigational product. The death was reported by a healthcare professional as a complication of influenza A and was reported by the investigator as unrelated to the investigational product or trial procedures. This is agreed with.

In conclusion, the above findings do not impact the B/R evaluation and a revision of the SmPC is not considered necessary.

3. CHMP's overall conclusion and recommendation

In conclusion, the above findings do not impact the B/R evaluation and a revision of the SmPC is not considered necessary.

☒ **Fulfilled:**

No regulatory action required.