ORIGINAL ARTICLE

Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants

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ABSTRACT

BACKGROUND

The safety of the monoclonal antibody nirsevimab and the effect of nirsevimab on hospitalizations for respiratory syncytial virus (RSV)–associated lower respiratory tract infection when administered in healthy infants are unclear.

METHODS

In a pragmatic trial, we randomly assigned, in a 1:1 ratio, infants who were 12 months of age or younger, had been born at a gestational age of at least 29 weeks, and were entering their first RSV season in France, Germany, or the United Kingdom to receive either a single intramuscular injection of nirsevimab or standard care (no intervention) before or during the RSV season. The primary end point was hospitalization for RSV-associated lower respiratory tract infection, defined as hospital admission and an RSV-positive test result. A key secondary end point was very severe RSV-associated lower respiratory tract infection, defined as hospitalization for RSV-associated lower respiratory tract infection with an oxygen saturation of less than 90% and the need for supplemental oxygen.

RESULTS

A total of 8058 infants were randomly assigned to receive nirsevimab (4037 infants) or standard care (4021 infants). Eleven infants (0.3%) in the nirsevimab group and 60 (1.5%) in the standard-care group were hospitalized for RSV-associated lower respiratory tract infection, which corresponded to a nirsevimab efficacy of 83.2% (95% confidence interval [CI], 67.8 to 92.0; P<0.001). Very severe RSV-associated lower respiratory tract infection occurred in 5 infants (0.1%) in the nirsevimab group and in 19 (0.5%) in the standard-care group, which represented a nirsevimab efficacy of 75.7% (95% CI, 32.8 to 92.9; P=0.004). The efficacy of nirsevimab against hospitalization for RSV-associated lower respiratory tract infection was 89.6% (adjusted 95% CI, 58.8 to 98.7; multiplicity-adjusted P<0.001) in France, 74.2% (adjusted 95% CI, 27.9 to 92.5; multiplicity-adjusted P=0.006) in Germany, and 83.4% (adjusted 95% CI, 34.3 to 97.6; multiplicity-adjusted P=0.003) in the United Kingdom. Treatment-related adverse events occurred in 86 infants (2.1%) in the nirsevimab group.

CONCLUSIONS

Nirsevimab protected infants against hospitalization for RSV-associated lower respiratory tract infection and against very severe RSV-associated lower respiratory tract infection in conditions that approximated real-world settings. (Funded by Sanofi and AstraZeneca; HARMONIE ClinicalTrials.gov number, NCT05437510).

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A list of the investigators in the HARMONIE Study Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Drysdale, Cathie, Flamein, Knuf, and Collins and Dr. Tissières, Dr. Royal, and Prof. Faust contributed equally to this article.

N Engl J Med 2023;389:2425-35.
DOI: 10.1056/NEJMoa2309189

A Quick Take is available at NEJM.org

Respiratory syncytial virus (RSV) is a common seasonal cause of acute lower respiratory tract infection in young children[1] and a leading cause of hospitalization in infants.[2-5] Nirsevimab, a monoclonal antibody that neutralizes RSV, was recently approved in the European Union (in 2022), the United Kingdom (in 2022), Canada (in 2023), and the United States (in 2023)[6-9] for the prevention of RSV-associated lower respiratory tract disease in neonates and infants during their first RSV season. A placebo-controlled phase 2b trial[10] and the phase 3 MELODY trial[11,12] showed that nirsevimab was safe and effective against medically attended RSV-associated lower respiratory tract infections in healthy preterm and term infants (i.e., infants who are not currently eligible for RSV prophylaxis with palivizumab) in their first RSV season.

Nirsevimab has an extended half-life of approximately 71 days.[13] It therefore has the potential to provide protection to all infants if it is administered in a program similar to programs used for vaccines.[14-16] HARMONIE is an ongoing phase 3b, open-label, two-group, randomized trial that is being conducted in France, Germany, and the United Kingdom, in conditions similar to those in routine clinical practice, to determine the efficacy and safety of a single intramuscular injection of nirsevimab as compared with standard care in preventing RSV-associated hospitalizations in infants 12 months of age or younger who are not eligible to receive palivizumab.

Methods

Participants

Healthy infants who were 12 months of age or younger, had been born at a gestational age of 29 weeks or more, and were entering their first RSV season were eligible for inclusion. Infants could be born before or during the RSV season, which began on September 11, 2022 (week 37), in France; on October 9, 2022 (week 41), in Germany; and on September 4, 2022 (week 36), in the United Kingdom. The RSV season ended on February 28, 2023, in each country.[17-19]

In order to minimize the interference of the trial with routine practice, one of the exclusion criteria was eligibility to receive palivizumab, since the intention was to recruit a wide range of infants who were not currently eligible for RSV prophylaxis with palivizumab. Other inclusion and exclusion criteria are described in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Design and Oversight

Infants were recruited into the HARMONIE trial at 235 sites in France, Germany, and the United Kingdom from August 8, 2022, through February 28, 2023. Interactive response technology was used to randomly assign eligible infants centrally, in a 1:1 ratio, to receive a single intramuscular injection of nirsevimab (50 mg for infants weighing <5 kg and 100 mg for those weighing ≥5 kg) or standard care (no intervention), with stratification according to country and age group (≤3.0 months, >3.0 to 6.0 months, and >6.0 months) at randomization. Beginning on day 1 (the day of randomization and nirsevimab injection) (Fig. S1 in the Supplementary Appendix, available at NEJM.org), all the infants were monitored remotely for safety events (including hospitalization for lower respiratory tract infection) by assessment of reports entered by their parents or legally acceptable representatives into electronic diaries and by digital assessment of infant health records. During the first 6 months after randomization, parents or legally acceptable representatives received monthly automated reminders to enter reports into the electronic diaries. The investigators at the trial sites reviewed the reports and interviewed the parents or legally acceptable representatives for further information if necessary. The parents or legally acceptable representatives of all the infants will be followed up by telephone on day 366 (the trial is ongoing) to collect information about safety events that may have occurred since day 181, when parents and legally acceptable representatives last entered information in the electronic diary.

Infants with lower respiratory tract infection whose treating physician admitted them to the hospital for inpatient care underwent diagnostic testing for RSV (with the use of a test that accorded with hospital policy) as part of routine practice. Parents and legally acceptable representatives were provided with a card to give to the treating physician to encourage RSV testing if testing had not been performed and to facilitate the transfer of data to the trial sites.

This trial was designed by the last author with input from other authors and from Sanofi,

a trial sponsor. The trial was performed in compliance with the International Council for Harmonisation guidelines for Good Clinical Practice and with the principles of the Declaration of Helsinki. We obtained informed consent from the parents or legally acceptable representatives of all the infants before any trial procedures were performed. Information about data privacy is provided in the Supplementary Appendix.

The trial protocol (available at NEJM.org) and any amendments were approved by the appropriate independent ethics committee or institutional review board at each participating site and by the relevant regulatory agencies in each country in accordance with local regulations. Data were collected by the HARMONIE Study Group and were analyzed by Sanofi in collaboration with the authors. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. A medical writer funded by Sanofi wrote the first draft of the manuscript, which was then edited by all the authors. All the authors approved the decision to submit the manuscript for publication. The trial was funded by AstraZeneca and Sanofi. There were no prior agreements concerning confidentiality of the data between the sponsor and the authors or the authors' institutions.

END POINTS

The trial end points accorded with the European Medicines Agency guidelines on the clinical evaluation of medicinal products indicated for RSV prophylaxis.[20] The primary end point was hospitalization for RSV-associated lower respiratory tract infection, defined as admission to the hospital on the basis of the treating physician's decision and confirmation of RSV by means of a positive result of a test performed in accordance with routine practice, during the RSV season in France, Germany, and the United Kingdom. Secondary end points included very severe RSV-associated lower respiratory tract infection (defined as hospitalization for RSV-associated lower respiratory tract infection with an oxygen saturation <90% [in accordance with the World Health Organization case definition[21]] at any time during hospitalization and the need for supplemental oxygen), hospitalization for RSV-associated lower respiratory tract infection in each country, and hospitalization for lower respiratory tract infection from any cause.

Adverse events were assessed throughout the trial. Nonserious adverse events were assessed through day 31, and adverse events of special interest, medically attended adverse events, and serious adverse events were assessed for up to 12 months after randomization. Adverse events of special interest were hypersensitivity reactions, including anaphylaxis, immune complex disease, and thrombocytopenia. Medically attended adverse events were events that prompted the infant's parents or legally acceptable representatives to seek unplanned in-person medical advice in any clinical setting.

MITIGATION OF BIAS

Several steps were taken to mitigate bias associated with the open-label design of the trial. These steps included the use of strictly defined end points (i.e., hospitalization for RSV-associated lower respiratory tract infection and very severe RSV-associated lower respiratory tract infection), the use of standardized electronic diary questions, the training of parents and legally acceptable representatives about how to report efficacy and safety data in the electronic diary and about the importance of reporting every relevant event, and the use of systematic procedures to report efficacy and safety data to the sponsor during follow-up.

The treating physician was rarely an investigator, and although an unknown number of parents and legally acceptable representatives may have made the treating physician aware of the trial, we believe that the risk of bias was low with respect to the primary end-point analysis because the treating physician's decision to hospitalize an infant for lower respiratory tract infection was made solely on clinical grounds. Since the end of the coronavirus disease 2019 (Covid-19) pandemic, testing for respiratory viruses, including RSV, with the use of molecular tests such as the polymerase-chain-reaction assay has been the standard of care for children hospitalized for lower respiratory tract infection in the United Kingdom, France, and Germany. In our trial, the decision to hospitalize an infant was made before the treating physician knew the result of the RSV test. Point-of-care RSV tests, where available, were used to aid in patient care but were administered only after the decision to hospitalize the infant had been made.

STATISTICAL ANALYSIS

On the basis of the reported incidence of hospitalization for RSV-associated lower respiratory tract infection in France, Germany, and the United Kingdom,[22-24] and assuming a mean overall incidence of 1.1% in the standard-care group, we calculated that enrollment of 9620 infants in each of the three countries (28,860 infants overall) would provide the trial with 90% power to detect a nirsevimab efficacy of 60% in each country, at a two-sided alpha level of 1.66% and with the use of Bonferroni correction for multiple comparisons. However, the primary end point was prespecified to be assessed as an event-driven analysis when at least 61 infants had been hospitalized for RSV-associated lower respiratory tract infection in the three countries combined, but no later than April 30, 2023. The trial was closed to recruitment on February 28, 2023; 71 primary end-point events had occurred by this date, which was used as the data-cutoff date for the initial event-driven primary analysis.

The primary and key secondary efficacy end points were assessed in a hierarchical procedure. If the superiority of nirsevimab was shown for the primary end point, we calculated P values for the first secondary end point (very severe RSV-associated lower respiratory tract infection), controlling for family-wise type 1 error. If superiority for the first secondary end point was shown, we calculated P values for the second secondary end point (hospitalization for RSV-associated lower respiratory tract infection in each country), controlling for family-wise type 1 error and adjusting for multiple testing with the use of the Bonferroni–Holm procedure. Statistical analysis of other secondary end points were not adjusted for multiplicity, so the widths of the 95% confidence intervals should not be used in place of hypothesis testing.

The final analysis will be performed when all the enrolled infants complete the scheduled 12-month safety follow-up, which is ongoing. Additional details are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

By February 28, 2023, we had randomly assigned 8058 infants to receive nirsevimab (4037 infants) or standard care (4021 infants) (Fig. S2). At the time of randomization, 946 infants (23.4%) in the nirsevimab group and 963 (23.9%) in the standard-care group were neonates (≤28 days of age). A total of 2177 of the infants (27.0%) were enrolled in France, 1789 (22.2%) were enrolled in Germany, and 4092 (50.8%) were enrolled in the United Kingdom. In the nirsevimab group, 23 infants (0.6%) did not receive the assigned drug, and 16 (0.4%) discontinued the trial, most of whom (15 infants) were withdrawn voluntarily. Nearly all the infants who received nirsevimab (3998 [99.6%]) received it during the RSV season. In the standard-care group, 1 infant (<0.1%) received nirsevimab because of an error in reading the randomization notification, and 16 (0.4%) discontinued the trial, most of whom (11 infants) were withdrawn voluntarily.

The characteristics of the infants at randomization were similar in the two trial groups (Table 1). The sample included a slightly higher percentage of preterm infants (<37 weeks of gestational age) than would otherwise be expected globally and in countries in Europe or other regions with social development goals similar to those in France, Germany, and the United Kingdom (Table S1). Nonetheless, 85.2% of the infants had a gestational age of 37 weeks or more at birth, which makes our findings generalizable to the wider infant birth cohort.

EFFICACY

Hospitalization for RSV-associated lower respiratory tract infection occurred in 11 infants (0.3%) in the nirsevimab group (1 event per 1000 person-months) and in 60 (1.5%) who received standard care (6 events per 1000 person-months), which corresponded to an efficacy of 83.2% (95% confidence interval [CI], 67.8 to 92.0; P<0.001) for nirsevimab during the 2022–2023 RSV season. The superior efficacy of nirsevimab over standard care (83.3%; 95% CI, 68.2 to 91.2) as assessed in a time-to-first-event analysis with the use of a Cox proportional-hazards regression model was consistent with that of the primary efficacy analysis (Fig. 1). Analyses of subgroups defined according to age group at randomization (≤3.0 months, >3.0 to 6.0 months, or >6.0 months), weight at randomization, gestational age, sex, and the timing of randomization (before or during the RSV season) showed efficacy estimates similar to that of the primary efficacy analysis (Fig. 2).

Very severe RSV-associated lower respiratory tract infection occurred in 5 infants (0.1%) in the nirsevimab group (<1 event per 1000 person-months) and in 19 (0.5%) who received standard care (2 events per 1000 person-months), which corresponded to an efficacy of 75.7% (95% CI, 32.8 to 92.9; P=0.004) for nirsevimab during the RSV season. Two of the 5 infants in the nirsevimab group were admitted to an intensive care unit, but neither infant received mechanical ventilation; 4 of the 5 infants had bronchiolitis; no further information other than lower respiratory tract infection was available for 1 infant. Five of the 19 infants in the standard-care group were admitted to the intensive care unit, and in 1 of the 5 infants the trachea was intubated and the infant received mechanically ventilated support; 15 of the 19 infants had bronchiolitis; no further information other than lower respiratory tract infection was available for the remaining 4 infants. The superior efficacy of nirsevimab over standard care (75.4%; 95% CI, 34.0 to 90.8) when assessed in a time-to-first-event analysis with the use of a Cox proportional-hazards regression model was consistent with that of the primary efficacy analysis of very severe RSV-associated lower respiratory tract infection (Fig. 3).

The efficacy of nirsevimab in preventing hospitalization for RSV-associated lower respiratory tract infection was also shown independently in France (89.6% [adjusted 95% CI, 58.8 to 98.7]; multiplicity-adjusted P<0.001), Germany (74.2% [adjusted 95% CI, 27.9 to 92.5]; multiplicity-adjusted P=0.006), and the United Kingdom (83.4% [adjusted 95% CI, 34.3 to 97.6]; multiplicity-adjusted P=0.003). The superior efficacy of nirsevimab over standard care in France (89.4%; adjusted 95% CI, 54.1 to 97.5), Germany (74.2%; adjusted 95% CI, 30.6 to 90.4), and the United Kingdom (83.5%; adjusted 95% CI, 32.9 to 96.0) as assessed in a time-to-first-event analysis with the use of a Cox proportional-hazards regression model was consistent with that in the primary efficacy analysis for each country (Fig. S3).

Hospitalization for lower respiratory tract infection from any cause during the RSV season occurred in 45 infants (1.1%) in the nirsevimab group (4 events per 1000 person-months) and in 98 (2.4%) in the standard-care group (10 events per 1000 person-months). These findings corresponded to a nirsevimab efficacy of 58.0% (nominal 95% CI, 39.7 to 71.2).

Table 1. Demographic Characteristics of the Infants at Randomization.*

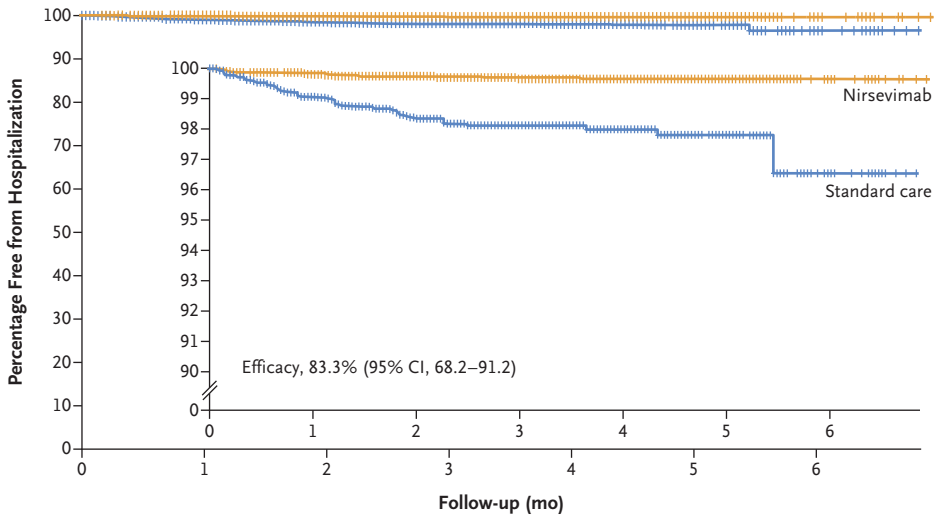
Characteristic	Nirsevimab (N=4037)	Standard Care (N=4021)
Age		
Mean — mo.	4.53±3.34	4.48±3.30
Distribution — no. (%)		
≤3.0 mo	1962 (48.6)†	1954 (48.6)
>3.0 to 6.0 mo	959 (23.8)	953 (23.7)
>6.0 mo	1116 (27.6)	1114 (27.7)
Sex — no. (%)		
Male	2087 (51.7)	2108 (52.4)
Female	1950 (48.3)	1913 (47.6)
Gestational age at birth		
Mean — wk	38.84±2.28	38.93±5.35
Distribution — no. (%)		
<37 wk	567 (14.0)	541 (13.5)
≥37 wk	3434 (85.1)	3434 (85.4)
Data missing	36 (0.9)	46 (1.1)
Weight		
Mean — kg	5.97±2.30	5.92±2.27
Distribution — no. (%)		
<5 kg	1537 (38.1)	1524 (37.9)
≥5 kg	2500 (61.9)	2497 (62.1)
Neonate — no. (%)‡		
Yes	946 (23.4)	963 (23.9)
No	3091 (76.6)	3058 (76.1)
Born during the RSV season — no. (%)§	2001 (49.6)	2025 (50.4)
In France	725	727
In Germany	392	411
In the United Kingdom	884	887
Born before the RSV season — no. (%)§	2036 (50.4)	1996 (49.6)
In France	365	360
In Germany	503	483
In the United Kingdom	1168	1153
Country — no. (%)		
France	1090 (27.0)	1087 (27.0)
Germany	895 (22.2)	894 (22.2)
United Kingdom	2052 (50.8)	2040 (50.7)

* Plus–minus values are means ±SD. Data are from all the infants randomly assigned to receive nirsevimab or standard care. A total of 2147 infants had at least one event documented in their medical history. Nearly half these infants were assessed as having infection, infestation, or both. Notable coexisting conditions that were recorded at randomization included endocrine, cardiovascular, respiratory, gastroenterologic, musculoskeletal, and congenital, familial, or genetic disorders.

† A total of 500 infants were 7 days of age or younger at randomization.

‡ Infants who were 28 days of age or younger at randomization were considered to be neonates.

§ The RSV season began on September 11, 2022 (week 37), in France; on October 9, 2022 (week 41), in Germany; and on September 4, 2022 (week 36), in the United Kingdom. The RSV season ended on February 28, 2023, in each country.[17-19]



No. at Risk							
Nirsevimab	4037	3559	2713	1695	698	190	24
Standard care	4021	3345	2456	1491	601	175	22

Figure 1. Hospitalization for RSV-Associated Lower Respiratory Tract Infection.

Shown are Kaplan–Meier curves of the time to hospitalization for respiratory syncytial virus (RSV)–associated lower respiratory tract infection, defined as hospital admission and an RSV-positive test result, in all the infants randomly assigned to receive nirsevimab or standard care. The efficacy was calculated as 1 minus the hazard ratio (expressed as a percentage) from a Cox proportional-hazards model, with stratification according to age group and country at randomization. The inset shows the same data on an expanded y axis.

SAFETY

Adverse events and serious adverse events that occurred through the data-cutoff date are summarized in Table 2. Most adverse events in the two trial groups were grade 1 or 2 in severity.

DISCUSSION

The HARMONIE trial showed that the incidence of hospitalization for confirmed RSV-associated lower respiratory tract infection (primary end point) and for very severe RSV lower respiratory tract infection during the 2022–2023 RSV season was significantly lower with administration of one dose of nirsevimab than with standard care. This trial enrolled infants in France, Germany, and the United Kingdom and was performed in conditions that approximated real-world settings. No substantial safety concerns were identified in this trial, nor have they been identified across the growing clinical experience with nirsevimab, which now includes more than 7500 infants.[10,12,27]

In this pragmatic trial, which was designed to assess the safety and efficacy of nirsevimab in conditions approximating real-world settings, the efficacy of nirsevimab in reducing hospitalizations for RSV-associated lower respiratory tract infection (83.2%) was similar to that reported in the previous trials that assessed nirsevimab efficacy, which had only included previously uninfected infants.[10,12] Although the infants in our trial were randomly assigned to receive nirsevimab or standard care (no intervention), the trial procedures were limited in scope, and the method of data collection minimized the effect of the trial on the infants and their parents or legally acceptable representatives, in order to mimic real-world settings. The trial settings included maternity wards, community pediatrician offices, and general practices. We encouraged the administration of routine vaccinations simultaneously with nirsevimab when the infants' age and clinical context were appropriate (no vaccine–drug interactions were expected[28]), including during the RSV season, a practice that differed from

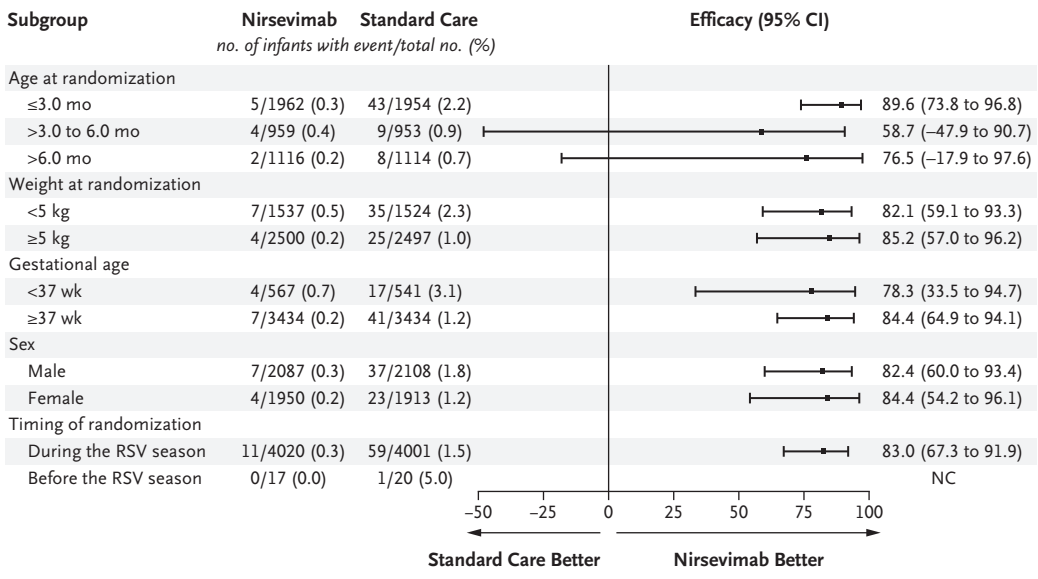


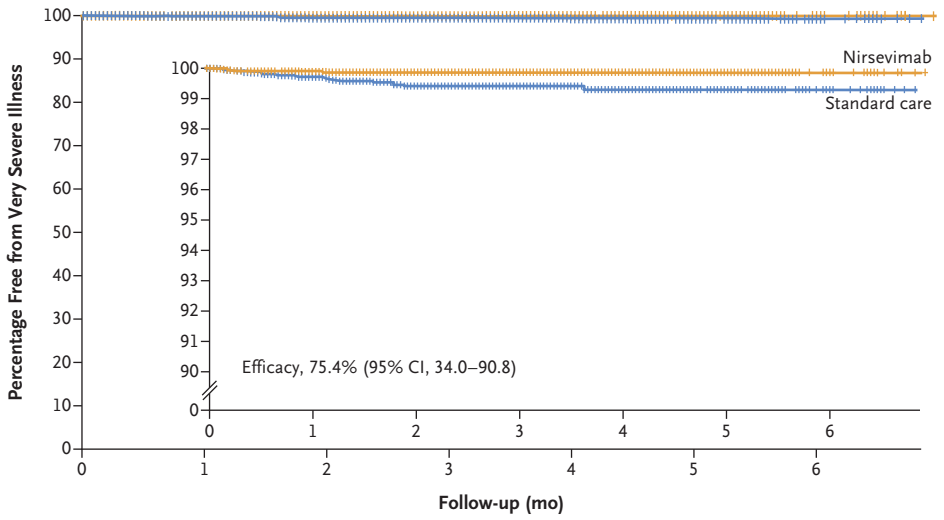
Figure 2. Hospitalization for RSV-Associated Lower Respiratory Tract Infection According to Subgroup.

Shown are subgroup analyses of the incidence of hospitalization for RSV-associated lower respiratory tract infection in all the infants randomly assigned to receive nirsevimab or standard care. The efficacy of nirsevimab in preventing hospitalization for RSV-associated lower respiratory tract infection during the RSV season was calculated as 1 minus the incidence rate ratio and is expressed as a percentage. Of the 2036 infants born before the 2022–2023 RSV season who were randomly assigned to receive nirsevimab, 8 did not receive the treatment, 17 were treated before the season, and 2011 were treated during the season. The two-sided 95% confidence intervals for efficacy were calculated by an exact method described by Breslow and Day[25] and accounted for the follow-up time after randomization. The efficacy analysis was not computed (NC) if there were fewer than five events in the nirsevimab and standard-care groups combined and no events in the standard-care group alone.

that in the previous efficacy trials, in which nirsevimab was administered before or at the beginning of the RSV season.[10-12]

Analyses of subgroups defined according to the age at randomization of 3.0 months or younger, weight at randomization, gestational age, and sex showed consistent efficacy favoring nirsevimab, findings similar to those in the previous efficacy trials.[10,11] The wider variability in the efficacy estimates in the two older age groups (>3.0 to 6.0 months and >6.0 months) is probably a reflection of the low number of primary end-point events in those two age groups. However, the lower incidence of hospitalization for RSV-associated lower respiratory tract infection among children older than 6 months of age in the nirsevimab and standard-care groups will be an important cost-effectiveness consideration. The efficacy of nirsevimab was also consistent in the three participating countries, which suggests that the benefits of nirsevimab are maintained irrespective of differences in clinical practice settings. Thus, the findings of our pragmatic trial should be applicable in other countries.

The HARMONIE trial was designed to be an event-driven trial. The initial plan was to enroll 28,860 infants, a sample that was based on a number of factors, including country-specific epidemiologic data from previous RSV seasons, the use of a conservative incidence estimate (1.1%) for the primary end-point event, and an expected nirsevimab efficacy that would provide sufficient power for the assessment of hospitalization for RSV-associated lower respiratory tract infection at the country level.[22-24] The attack rate of RSV-associated lower respiratory tract infection during the trial period (2022–2023 RSV season), which occurred after the relaxation of nonpharmaceutical interventions to prevent respiratory infection that were imposed during the Covid-19 pandemic, was higher than we expected. Owing to the attack rate and to the expected



No. at Risk							
Nirsevimab	4037	3561	2716	1699	701	192	24
Standard care	4021	3364	2484	1518	613	177	23

Figure 3. Very Severe RSV-Associated Lower Respiratory Tract Infection.

Shown are Kaplan–Meier curves of the time to very severe RSV-associated lower respiratory tract infection, defined as hospitalization for RSV-associated lower respiratory tract infection with an oxygen saturation of less than 90% at any time during hospitalization and the need for supplemental oxygen, in all the infants randomly assigned to receive nirsevimab or standard care. The efficacy was calculated as 1 minus the hazard ratio (expressed as a percentage) from a Cox proportional-hazards model, with stratification according to age group and country at randomization. The inset shows the same data on an expanded y axis.

nirsevimab efficacy prespecified in the protocol, the minimum number of primary end-point events needed to perform the primary analysis was reached by February 2023 (with enrollment paused so that the primary analysis could be conducted), when 8058 infants had undergone randomization. The HARMONIE trial also provided confirmation that RSV contributes to a sizable percentage of hospitalizations for lower respiratory tract infections from any cause, as shown in the standard-care group (61% of hospitalizations [60 of 98]). In addition, the HARMONIE trial built on data from previous trials, which showed the efficacy and safety of nirsevimab with respect to medically attended RSV-associated lower respiratory tract infection,[10-12] by showing the efficacy of nirsevimab in reducing hospitalization for RSV-associated lower respiratory tract infection, which is a key driver of health care resource utilization associated with this disease.

The limitations of the HARMONIE trial and the primary-analysis data presented here include the short duration (approximately 3 months for the majority of infants) of the efficacy assessment and safety follow-up; the trial is ongoing, with a planned follow-up period of at least 12 months after randomization, during which additional data will be collected. The trial design did not include blinding of the group assignments; the parents and legally acceptable representatives knew whether their infant had received nirsevimab or standard care. Whether this affected health care–seeking behavior or RSV testing behavior is not known; however, as described above, we took several steps to mitigate bias associated with the open-label design of the trial. The same number of infants in the nirsevimab and standard-care groups discontinued the trial, and the adverse event profile as reported by the parents and legally acceptable representatives was similar in the two trial groups, which suggests that bias was minimal. Finally, infants without lower respiratory tract infection may have been hospitalized for reasons related to RSV infection, such as dehydration, and among 158 infants hospitalized for lower respiratory tract infection for any cause, 16 did not undergo RSV testing.

Table 2. Adverse Events through the Data-Cutoff Date (Safety Analysis Population).

Adverse Events	Nirsevimab (N=4015)	Standard Care (N=4020)
	number of infants (percent)	
Any event	1479 (36.8)	1326 (33.0)
Immediate event: ≤30 min after injection	26 (0.6)	0
Treatment-related event	86 (2.1)	0
Grade 3 event	48 (1.2)	46 (1.1)
Event of special interest*	3 (0.1)	1 (<0.1)
Serious event†	89 (2.2)	67 (1.7)
Serious treatment-related event	1 (<0.1)	0
Medically attended event‡		
Any	1185 (29.5)	1102 (27.4)
Skin and subcutaneous tissue disorders	94 (2.3)	89 (2.2)
General disorders and administration site conditions		
Overall	119 (3.0)	88 (2.2)
Pyrexia	101 (2.5)	77 (1.9)
Infections and infestations		
Overall	863 (21.5)	799 (19.9)
Nasopharyngitis	192 (4.8)	173 (4.3)
Bronchiolitis	98 (2.4)	143 (3.6)
Conjunctivitis	114 (2.8)	92 (2.3)
Viral infection	96 (2.4)	75 (1.9)
Ear infection	82 (2.0)	79 (2.0)
Upper respiratory tract infection	55 (1.4)	60 (1.5)
Rhinitis	53 (1.3)	39 (1.0)
Bronchitis	43 (1.1)	46 (1.1)
Respiratory, thoracic, and mediastinal disorders		
Overall	184 (4.6)	196 (4.9)
Cough	94 (2.3)	107 (2.7)
Rhinorrhea	58 (1.4)	69 (1.7)
Nasal congestion	43 (1.1)	32 (0.8)
Gastrointestinal disorders		
Overall	168 (4.2)	151 (3.8)
Diarrhea	48 (1.2)	42 (1.0)
Gastroesophageal reflux disease	46 (1.1)	41 (1.0)

* Four infants had at least one adverse event of special interest (drug reaction [reported as fever and rash], maculopapular rash, and allergic dermatitis in 1 infant each in the nirsevimab group and food allergy in 1 infant in the standard-care group), all of which were assessed to be grade 1 or 2 in severity.

† One infant had a grade 3 serious adverse event (infantile spasms [West syndrome]) 23 days after the receipt of nirsevimab that was considered to be related to the trial treatment because the relationship to nirsevimab could not be excluded; however, the occurrence of this event was within the expected background rate for a trial of this size.[26] Two infants discontinued the trial because of safety events: 1 infant in the nirsevimab group had a serious adverse event (facial bruising, considered by the treating physician to be a nonaccidental injury) that was not related to the trial treatment, and 1 infant in the standard-care group had a nonserious adverse event (grade 2 bronchiolitis, for which the infant received palivizumab and was therefore withdrawn from the trial) within 30 days after randomization. All the medically attended adverse events occurred in a similar percentage of infants in each trial group. No deaths were reported.

‡ Medically attended events are listed according to system organ classes and preferred terms in the *Medical Dictionary for Regulatory Activities*, version 25.0, and include those that occurred in at least 1% of infants in at least one of the two trial groups.

The HARMONIE trial showed that nirsevimab prevented hospitalization for RSV-associated lower respiratory tract infection and very severe RSV-associated lower respiratory tract infection in a broad population of healthy preterm and term infants under conditions as similar as possible to real-world settings. The trial also showed that the safety profile of nirsevimab was favorable. These findings suggest that nirsevimab has the potential to reduce the burden of hospitalization for RSV-associated lower respiratory tract infection among infants.

Supported by Sanofi and AstraZeneca.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the infants in the trial and their families; the personnel at the trial sites; Richard Glover (inScience Communications, Springer Healthcare) for editorial assistance with the preparation of an earlier version of the manuscript; Hanson Geevarghese (Sanofi) for editorial assistance with an earlier version of the manuscript and for guidance in coordinating the development of the manuscript; François Beckers (Sanofi) for providing statistical support during the trial and for ensuring the clarity of statistical content in the manuscript; the staff of the National Institute for Health Research (NIHR) Clinical Research Network, the clinical research facilities at NIHR Southampton and NIHR St. George's, and the NIHR Southampton Biomedical Research Centre (in the United Kingdom); the PEDSTART network of pediatric clinical investigation centers and the ACTIV pediatric ambulatory and hospital surveillance network (in France); and the NETSTAP network of pediatricians for clinical studies in ambulatory pediatrics (in Germany). Prof. Faust is a U.K. NIHR Senior Investigator.

APPENDIX

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