Nirsevimab for prevention of hospitalizations due to RSV in infants

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Abstract

Background: This pragmatic trial assessed the safety and impact of the monoclonal antibody nirsevimab on hospitalizations associated with RSV lower respiratory tract infection (LRTI) in healthy infants.

Methods: Infants ≤12 months old, born ≥29 weeks gestational age entering their first RSV season in France, Germany and the UK were randomized 1:1 to receive a single intramuscular injection of nirsevimab or no intervention (standard-of-care) before/during the RSV season. Participants were monitored remotely for RSV LRTI hospitalization (defined as in-patient care with confirmed RSV) and very severe RSV LRTI (defined as RSV LRTI hospitalization with oxygen saturation <90% and requiring oxygen supplementation) through the RSV season.

Results: 8,058 participants were randomized: 4,037 to the nirsevimab group and 4,021 to no intervention. Eleven (0.3%) RSV LRTI hospitalizations occurred in the nirsevimab group and 60 (1.5%) in the no intervention group, giving an efficacy of 83.2% (95% CI: 67.8 to 92.0; P<0.001). Very severe RSV LRTI occurred in five (0.1%) participants in the nirsevimab group and 19 (0.5%) in the no intervention group, giving an efficacy of 75.7% (95% CI: 32.8 to 92.9; P=0.004). Efficacy against RSV LRTI hospitalization in each of the countries, France, Germany, and the UK were 89.6% (adjusted 95% CI, 58.8 to 98.7; multiplicity-adjusted P<0.001), 74.2% (adjusted 95% CI, 27.9 to 92.5; multiplicity-adjusted P=0.006), and 83.4% (adjusted 95% CI, 34.3 to 97.6; multiplicity-adjusted P=0.003), respectively. No safety concerns were identified.

Conclusions: Nirsevimab protects infants against RSV LRTI hospitalization and very severe RSV LRTI in near real-world settings.

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Introduction

Respiratory syncytial virus (RSV) is a common seasonal cause of acute lower respiratory tract infection (LRTI) in young children,[1] and a leading cause of infant hospitalizations.[2-5]

A novel RSV-neutralizing monoclonal antibody, nirsevimab, has recently been approved in the EU (2022), UK (2022), Canada (2023), and the USA (2023),[6-9] to prevent RSV lower respiratory tract disease in neonates and infants during their first RSV season. The safety and efficacy of nirsevimab in protecting against medically attended RSV LRTIs was demonstrated in a placebo-controlled phase IIb study[10] and phase III (MELODY) study[11,12] in healthy preterm and term infants (i.e., those not currently eligible for RSV prophylaxis with palivizumab) in their first RSV season.

Nirsevimab has an extended half-life (approximately 71 days[13]) so has the potential to be used for all infants in a 'vaccine-like' program since the extended half-life enables coverage for an entire RSV season.[14-16] HARMONIE is a large ongoing phase IIIb, open-label, randomized, parallel two-arm, multi-center study undertaken in conditions similar to clinical practice in France, Germany and the UK, to determine the efficacy and safety of a single intramuscular dose of nirsevimab in preventing RSV-associated hospitalizations compared with no intervention in infants ≤12 months old who are not eligible for palivizumab.

Methods

Participants

Healthy infants ≤12 months old, born ≥29 weeks gestational age entering their first RSV season (born either in-season or out-of-season [see footnote to Table 1][17-19]) were eligible for inclusion. Exclusion criteria included eligibility to receive palivizumab to minimize interference with routine practice; the intention was to recruit a wide range of infants not currently eligible for RSV prophylaxis with palivizumab. Other inclusion and exclusion criteria are described in the supplementary appendix.

Trial design and oversight

HARMONIE recruited participants at 235 sites (details on the study group are available in the supplementary appendix) in France, Germany and the UK between August 8, 2022and February 28, 2023.

Eligible participants were randomized centrally using interactive response technology in a 1:1 ratio to receive a single intramuscular injection of nirsevimab (50 mg if weight <5 kg or 100 mg if weight ≥5 kg) or no intervention (standard-of-care), stratified by country and age group (≤3.0 months, >3.0 to ≤6.0 months, and >6.0 months). The study started with a visit on day 1 (randomization/treatment allocation) (supplementary appendix Figure S1). Then, participants were monitored remotely for safety events (including LRTI hospitalizations) through reports in electronic diaries entered by their parents/legally acceptable representatives (LARs) and via digital assessment of patient health records. Parents/LARs were sent monthly automated reminders to complete the electronic diaries in the first six months. The study site teams reviewed the information reported and interviewed the parents/LARs for further

information as required. A follow-up phone call to the participants' parents/LARs will be made at day 366 after dosing/randomization (trial on going) to collect information on safety events that occurred after the last electronic contact.

In cases of LRTI where the treating physician admitted the participant for in-patient care, testing for RSV (with whatever diagnostic test was used as per local hospital policy) was performed as part of routine practice. Parents/LARs were also provided a card to give to the treating physician to encourage RSV testing if this had not been done and to facilitate the transfer of data to the study sites.

The trial was designed by the corresponding author with input from other authors and Sanofi, the trial sponsor, and was performed in compliance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. Informed consent was obtained from parents/LARs before any study procedures were performed (see note on data privacy in the supplementary appendix). The protocol and any amendments were approved by applicable independent ethics committees or institutional review boards at each participating site and/or respective country regulatory agencies as per local regulations. Data were collected by the HARMONIE Study Group and analyzed by the sponsor in collaboration with the authors. The authors vouch for the accuracy and completeness of the data and for adherence with the trial protocol. A medical writer funded by Sanofi assisted with drafting the manuscript for submission following guidance from authors. All authors gave approval to submit the manuscript for publication. The trial was funded jointly by AstraZeneca and Sanofi.

Endpoints

The study endpoints were in accordance with those proposed by the European Medicines Agency guidelines on the clinical evaluation of medicinal products indicated for the prophylaxis of RSV.[20] The primary endpoint was the occurrence of RSV LRTI hospitalizations (defined as the decision to admit to in-patient care by the treating physician and RSV confirmed with a positive test as per routine practice) through the RSV season (see footnote to Table 1) in all three countries. Secondary endpoints included: incident cases of very severe RSV LRTI (defined as RSV LRTI hospitalization with <90% oxygen saturation [WHO case definition][21] at any time during hospitalization and need for oxygen supplementation); incident cases of RSV LRTI hospitalization in each country; and incident cases of all-cause LRTI hospitalization. Adverse events (AEs) were assessed throughout the trial: non-serious adverse events were assessed until day 31 post-dose/randomization; adverse events of special interest (AESIs), medically attended adverse events (MAAEs) and serious adverse events (SAEs) were assessed for up to 12 months post-dosing/randomization. AESIs were hypersensitivity, including anaphylaxis, immune complex disease and thrombocytopenia. A MAAE was an AE that prompted the participant's parent/LARs to seek unplanned in-person medical advice in any clinical setting.

Mitigation of bias due to open label design

Several methods were used to mitigate bias and included: use of objective, physician-oriented endpoints (i.e., RSV LRTI hospitalization and very severe RSV); use of standardized electronic diary questions; training of parents/LARs regarding the importance of efficacy and safety data reporting; and robust reporting follow-up procedures. Regarding the primary endpoint of hospital admission, the treating physician was rarely an investigator, and while an unknown small number of

parents/LARs may have made the treating physician aware of the trial, the risk of bias was low as LRTI admission decisions were made solely on clinical grounds. In the post-pandemic period, respiratory virus testing, including for RSV, using molecular testing (e.g. PCR) was the standard-of-care for children being admitted for LRTI management in hospitals in the UK, France and Germany. The decision to admit children to hospital was taken prior to RSV test results being known by treating clinicians. Where available, RSV point-of-care tests were only used for in patient management after a decision to admit the child had already been taken.

Statistical analyses

Based on the reported incidence rates of RSV LRTI hospitalization in France, Germany, and the UK,[22-24] and assuming an average 1.1% incidence rate in the no intervention group, 9,620 participants needed to be enrolled in each of the three countries to ensure 90% power to detect 60% efficacy in each country with a 2-sided α of 1.66% using Bonferroni multiplicity adjustment. A total of 28,860 participants were therefore planned to be enrolled. However, the primary objective was planned to be assessed as an event-driven analysis when at least 61 events of RSV LRTI hospitalization were observed in all three countries combined, but no later than April 30, 2023. The study closed to recruitment on 28th February 2023 at which timepoint 71 events had occurred and which was the cut-off date for this initial event driven primary analysis. The final analysis will be conducted when all enrolled participants complete the scheduled 12-month safety follow-up which is currently ongoing. Additional details are provided in the supplementary file.

Results

Participants

By February 28, 2023, there were 8,058 participants randomized: 4,037 to the nirsevimab group and 4,021 to the no intervention group (supplementary appendix Figure S2). Of these, 946 (23.4%) and 963 (23.9%) in the two groups, respectively, were neonates (≤28 days of age). The number of randomized participants in France, Germany and the UK were 2,177 (27.0%), 1,789 (22.2%), and 4,092 (50.8%), respectively. Among the participants in the nirsevimab group, 23 (0.6%) did not receive the study intervention and 16 (0.4%) discontinued from the study, mainly due to voluntary withdrawal (n=15). Nearly all participants who received nirsevimab (3,998 [99.6%]) did so during the RSV season. In the no intervention group, one infant wrongly received nirsevimab (error in reading randomization notification) and 16 (0.4%) discontinued from the study, mainly due to voluntary withdrawal (n=11). Baseline participant characteristics were similar in the two groups (Table 1). The participant sample included a slightly higher proportion of preterm (<37 weeks' gestational age) infants than would otherwise be expected in European or other countries with similar social development goals, and globally (supplementary appendix Table S1). Nonetheless, infants born ≥37 weeks gestational age represented 86.2% of the participants recruited making the study results generalizable to the wider infant birth cohort.

Efficacy

RSV LRTI hospitalizations occurred in 11 (0.3%) infants in the nirsevimab group (1 per 1,000 person-months) and 60 (1.5%) infants in the no intervention group (6 per 1,000 person-months), corresponding to an efficacy of 83.2% (95% CI 67.8 to 92.0; P<0.001) for nirsevimab through the RSV season. The superior RSV LRTI

hospitalization efficacy of nirsevimab versus no intervention was consistent when computed based on the Cox regression model (83.3%; 95% CI based on Cox Model, 68.2 to 91.2) (Figure 1). Subgroup analyses according to age (≤3.0 months age group, >3.0 to ≤6.0 months and >6.0 months groups), weight at randomization, gestational age, sex and timing of dosing showed similar efficacy estimates favoring nirsevimab (Figure 2).

Very severe RSV LRTI occurred in five (0.1%) infants in the nirsevimab group (<1 per 1,000 person-months) and 19 (0.5%) infants in the no intervention group (2 per 1,000 person-months), corresponding to an efficacy of 75.7% (95% CI 32.8 to 92.9; P=0.004) for nirsevimab through the RSV season. Of the five infants randomized to the nirsevimab group, two required intensive care but none were mechanically ventilated. Four of five had bronchiolitis and one had no further information. The superior very severe RSV LRTI efficacy of nirsevimab versus no intervention was consistent when computed based on Cox regression model by analysis of time-to-first very severe RSV LRTI (75.4%; 95% CI based on Cox Model, 34.0 to 90.8) (Figure 3).

The efficacy of nirsevimab was also demonstrated independently for each participating country. Efficacy in preventing RSV LRTI hospitalization was 89.6% (adjusted 95% CI 58.8 to 98.7; multiplicity-adjusted P<0.001), 74.2 % (adjusted 95% CI 27.9 to 92.5; multiplicity-adjusted P=0.006), and 83.4% (adjusted 95% CI 34.3 to 97.6; multiplicity-adjusted P=0.003) in France, Germany and the UK, respectively. The superior RSV LRTI hospitalization efficacy of nirsevimab versus no intervention through the RSV season was consistent in each country when computed by means of Cox regression model (France: 89.4%, adjusted 95% CI 54.1 to 97.5; Germany:

74.2%, adjusted 95% CI 30.6 to 90.4; UK: 83.5%, adjusted 95% CI 32.9 to 96.0) (Figure S3 in supplementary appendix).

All-cause LRTI hospitalizations occurred in 45 (1.1%) infants in the nirsevimab group (4 per 1,000 person-months) and 98 (2.4%) infants in the no intervention group (10 per 1,000 person-months) through the RSV season, corresponding to an efficacy of 58.0% (nominal 95% CI, 39.7 to 71.2) for nirsevimab.

Safety

AEs and SAEs during the study are summarized in Table 2. Most AEs were grade 1 or 2 in severity across both groups.

Discussion

HARMONIE demonstrated that one dose of nirsevimab significantly reduces confirmed RSV LRTI hospitalization and very severe RSV LRTI through the RSV season in an infant cohort in near real-life settings across all three participating countries. There were no safety concerns in this study (the largest study with nirsevimab to date), and collectively, across all clinical experience with nirsevimab, which now exceeds 7,500 infants.[10,12,25]

In this pragmatic study, designed to assess the impact of nirsevimab in a near "real-world population," the efficacy of nirsevimab in reducing RSV LRTI hospitalizations (83.2%) was at least as high as that reported in the previous efficacy trials (78.4% and 76.8%)[10,12] despite a broader range of recruitment settings. While participants were randomized to receive either nirsevimab or no intervention (i.e., standard-of-care), study procedures were limited in scope, and data collection was done in such a way to minimize the study impact on participants and their parents/LARs, to mimic real world settings. Study settings included maternity wards, community pediatrician offices, and general practices. It was encouraged that participants received their routine vaccinations simultaneously with nirsevimab (no interaction expected[26]), including during the RSV season (unlike the previous efficacy trials where nirsevimab was administered before or at the beginning of the RSV season),[10-12] where age and situation allowed.

Subgroup analyses according to age (≤3.0 months), weight at randomization, gestational age, and sex, showed consistent efficacy favoring nirsevimab, similar to the previous efficacy trials.[10,11] The wider variability in efficacy estimates in the older age groups (>3.0 to ≤6.0 and >6.0 months) likely reflects the low number of cases.

However, the low hospitalization rate due to RSV of children older than 6 months in both the nirsevimab and no intervention groups will be an important cost-effectiveness consideration. The consistent efficacy favoring nirsevimab was also shown across the participating countries, suggesting the benefits are maintained, irrespective of differences in clinical practice settings. Thus, the results of this pragmatic study should be applicable to other country settings.

The HARMONIE study was designed to be event driven. It was initially planned to enrol 28,860 participants based on a number of factors, including country-specific epidemiological data from previous RSV seasons, using conservative estimates for the incidence (1.1%), and efficacy to ensure sufficient power for the primary hospitalization endpoint at country level.[22-24] The attack rate during the study (2022/2023 RSV season), after relaxation of non-pharmaceutical interventions imposed by the COVID-19 pandemic, was higher than assumed. Together with the expected vaccine efficacy in the protocol, this meant that the required minimum number of events to perform the primary analysis was reached by February 2023 (with enrolment paused to conduct the primary analysis), when 8,058 participants had been randomized. Of note, HARMONIE also confirms that RSV contributes to a sizable burden of all-cause LRTI hospitalizations as demonstrated in the no intervention group (61%; 60/98). In addition, HARMONIE built on the existing data from previous studies, which demonstrated the efficacy and safety of nirsevimab with respect to medically attended RSV-associated LRTI,[10-12] by demonstrating its efficacy in reducing RSV LRTI hospitalizations, a key driver of healthcare resource utilization associated with this disease.

The limitations of the HARMONIE trial and its primary analysis data presented here include the short duration of the efficacy and safety follow-up; the trial is ongoing with planned follow-up for a minimum of 12 months after immunization/randomization for additional data collection. The study design did not include blinding: the parents/LARs knew whether their infant had received the study intervention or not. Mitigations taken to reduce bias with adherence to study protocols are detailed in the methods. Finally, it remains possible that some children were admitted to hospital with no lower respiratory tract disease but for other reasons related to RSV infection such as dehydration; and among 158 all-cause LRTI hospitalizations, there were 16 hospitalizations for which RSV testing was not done.

The HARMONIE trial demonstrated that nirsevimab is efficacious in preventing RSV LRTI hospitalizations and very severe RSV LRTI in a broad infant population that included healthy pre-term and term infants from birth, under conditions as similar as possible to real-world settings. The safety profile of nirsevimab was favorable. These results suggest that nirsevimab has the potential to substantially reduce the RSV LRTI hospitalization burden, a key driver of healthcare resources utilization. Overall, the data support the potential use of nirsevimab in a 'vaccine-like' program, as it confirms that a single dose protects infant against RSV LRTI hospitalization through the RSV season in near real-world settings.

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Author contributions

SNF conceived the trial design with RC, MB, CTF, and NCV. SNF, KC, MB, SBD, SR, NCV, and JJ co-wrote the protocol. SNF, KC, SBD, SR, AMC, HCH, SW, and NCV took part in weekly study management meetings in the UK, and FF, RC, DP, PT, SW, and RN took part in *ad-hoc* meetings as required in France as did MK, FK, and MB in Germany to manage trial delivery. KM, RN, MR, CTF, NCV, JJ, PT, SBD, and SNF contributed to data analysis or interpretation of data for the work reported in this article. All authors contributed to the drafting of the article and revisions for important intellectual content, approved the final manuscript, and who are accountable for the accuracy and integrity of the manuscript.

Conflict of interest

CF, NCV, JJ, MB, KM, RN, SW, and MR are employees of Sanofi and may hold shares and/or stock options in the company.

SBD has received honoraria from MSD and Sanofi for taking part in RSV advisory boards and has acted as a consultant and/or investigator in relation to product development for Janssen, AstraZeneca, Pfizer, Moderna, Valneva, MSD, iLiAD and Sanofi, with fees paid to St George's, University of London. SBD is a member of the UK Department of Health and Social Care's (DHSC) Joint Committee on Vaccination and Immunisation (JCVI) RSV subcommittee and Medicines and Healthcare products/Regulatory Agency's (MHRA) Paediatric Medicine Expert Advisory Group (PMEAG), but the views expressed herein do not necessarily represent those of DHSC, JCVI, MHRA or PMEAG.

KC acts on behalf of University Hospital Southampton as an investigator on studies funded or sponsored by vaccine manufacturers including Sanofi (including HARMONIE), AstraZeneca, GlaxoSmithKline, Janssen, Medimmune, Merck, Pfizer, Sanofi and Valneva. She receives no personal financial payment for this work.

FF acts on behalf of Lille University Hospital and the PEDSTART network as an investigator on studies funded or sponsored by vaccine manufacturers including Sanofi (including HARMONIE), GlaxoSmithKline, MSD, AstraZeneca, Janssen and Pfizer. She receives no personal financial payment for this work

MK reports receiving fees for lectures and has acted as a consultant and/or investigator in relation to product development for GSK, Pfizer, Astra Zeneca, Sanofi, MSD and others. He receives no personal financial payment for this work.

AMC reports receiving fees from Sanofi for consultancy on their influenza global advisory panel and has acted as a consultant and/or investigator in relation to product development for Sanofi. She has received grants from Pfizer, MSD and Sanofi, and financial support from Pfizer and Sanofi to attend medical congresses. She is also a member of the data monitoring and safety committee at the University of Oxford.

HCH and FK have nothing relevant to disclose.

RC has received honoraria from Sanofi and Pfizer for participating in RSV advisory boards and has acted as a consultant and/or investigator in relation to product development for GSK, MSD, Pfizer, and Sanofi.

DP reports receiving fees for lectures on RSV from Sanofi for participation in advisory boards on RSV conducted by Sanofi, and fees from AstraZeneca, GSK, and Merck. As investigator, he receives no personal financial payment for this work.

PT has received honoraria from Sanofi for participating in RSV advisory boards and has acted as a consultant and/or investigator in relation to product development for Sedana, Paion, Baxter, ThermoFisher, bioMerieux.

SR acts on behalf of the University of Nottingham Health Service and the National Institute of Health Research as an investigator and adviser on the design and conduct of clinical trials set in UK primary care including studies of vaccines funded or sponsored by vaccine manufacturers including Sanofi (including HARMONIE), AstraZeneca, GlaxoSmithKline and Moderna. He receives no personal financial payment for this work.

SNF acts on behalf of University Hospital Southampton NHS Foundation Trust as an Investigator and/or providing consultative advice on clinical trials and studies of

vaccines funded or sponsored by vaccine manufacturers including Sanofi (including HARMONIE), Janssen, Pfizer, AstraZeneca, GlaxoSmithKline, Novavax, Seqirus, Medimmune, Merck and Valneva vaccines and antimicrobials. He receives no personal financial payment for this work.

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The trial was funded jointly by Sanofi and AstraZeneca. Nirsevimab is being developed and commercialized in partnership between AstraZeneca and Sanofi. There were no prior agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines.

Availability of data and materials

The datasets generated and/or analyzed during the current study, including the raw data, are not publicly available in order to safeguard the privacy of participants and the confidentiality and protection of their data, as well as protect commercially sensitive information. Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, including required permissions to access the data, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

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531

532 Table 1. Summary of participants demographic characteristics at baseline (all
533 randomized set).

Characteristic	**Nirsevimab (N=4,037)[§]**	**No intervention (N=4,021)**
Age, months; mean (SD)	4.53 (3.34)	4.48 (3.30)
Age group, months; n (%)		
≤3.0	1,962 (48.6)	1,954 (48.6)
>3.0 to ≤6.0	959 (23.8)	953 (23.7)
>6.0	1,116 (27.6)	1,114 (27.7)
Sex; n (%)		
Male	2,087 (51.7)	2,108 (52.4)
Female	1,950 (48.3)	1,913 (47.6)
Gestational age at birth, weeks; mean SD	38.84 (2.28)	38.93 (5.35)
Gestational age at birth, weeks; n (%)		
<37	567 (14.0)	541 (13.5)
≥37	3,434 (85.1)	3,434 (85.4)
missing	36 (0.9)	46 (1.1)
Weight at baseline, kg; mean (SD)	5.97 (2.30)	5.92 (2.27)
Weight at baseline, kg; mean (%)		
<5	1,537 (38.1)	1,524 (37.9)
≥5	2,500 (61.9)	2,497 (62.1)
Neonate (≤28 days of age); n (%)		
Yes	946 (23.4)	963 (23.9)
No	3,091 (76.6)	3,058 (76.1)
Birth category; n (%)		
Born in season[#]	2,001 (49.6)	2,025 (50.4)
France	725	727
Germany	392	411
UK	884	887
Born out of season[#]	2,036 (50.4)[⸸]	1,996 (49.6)
France	365	360
Germany	503	483
UK	1168	1153

Country; n (%)		
France	1,090 (27.0)	1,087 (27.0)
Germany	895 (22.2)	894 (22.2)
UK	2,052 (50.8)	2,040 (50.7)

[‡]2147 participants had at least one medical history recorded. Nearly half of these (877) were categorized as infections and infestations. Notable comorbidities including endocrine (n=3), cardiovascular (n=8), respiratory (n=21), gastroenterological (n=2), musculoskeletal (n=2) and congenital, familial, or genetic disorders (n=179) were recorded for 215 participants

[§]500 participants randomized to nirsevimab who were 7 days old or less at time of randomization.

[#]The following start dates were defined for in and out of the RSV season. In France the RSV season ("in season") was defined as September 11, 2022 (week 37) until February 28, 2023, and infants born prior to September 11, 2022 were "out of season".[17] In Germany the RSV season ("in season") was defined as October 9, 2022 (week 41) until February 28, 2023, and infants born prior to October 9, 2022 were "out of season".[18] In the UK the RSV season ("in season") was defined as September 4, 2022 (week 36) until February 28, 2023, and infants born prior to September 4, 2022 were "out of season".[19]

[ɻ]Among the 2036 participants born out of season randomized to nirsevimab, 17 were dosed before the start of the RSV season and 2019 were dosed in season.

552 Table 2. Summary of adverse events up to the data cut-off date (safety analysis set).

Adverse Events Category	**Nirsevimab (N=4,015) n (%)**	**No intervention (N=4,020) n (%)**
Any adverse event (AE)	1479 (36.8)	1326 (33.0)
Immediate (within 30 minutes)	26 (0.6)	0 (0.0)
Treatment-related	86 (2.1)	0 (0.0)
Grade 3	48 (1.2)	46 (1.1)
Adverse events of special interest (AESI)[‡]	3 (< 0.1)	1 (< 0.1)
Serious AE[*]	89 (2.2)	67 (1.7)
Serious treatment-related	1 (< 0.1)	0 (0.0)
Medically attended AEs by system organ class and preferred term[#]	1185 (29.5)	1102 (27.4)
Skin and subcutaneous tissue disorders	94 (2.3)	89 (2.2)
General disorders and administration site conditions	119 (3.0)	88 (2.2)
Pyrexia	101 (2.5)	77 (1.9)
Infections and infestations	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	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	168 (4.2)	151 (3.8)
Diarrhea	48 (1.2)	42 (1.0)
Gastroesophageal reflux disease	46 (1.1)	41 (1.0)

553 [#]In at least 1% of participants in either group

[‡]Four participants (three in the nirsevimab group and one in the no intervention group) experienced at least one AESI (immunization reaction [reported as fever and rash], maculopapular rash, allergic dermatitis in the nirsevimab group and food allergy in the no intervention group), all of grade 1 or 2 severity.

[*]One participant experienced a grade 3 SAE (infantile spasms [West syndrome]) 23 days after receipt of nirsevimab, considered "related" because the relationship to nirsevimab could not be excluded; however, this was within the expected background rate for the study size.[27] Two participants discontinued the study due to safety events: one in the nirsevimab group experienced a SAE not related to nirsevimab (facial bruising, considered non-accidental injury), and one participant in the no intervention group experienced a non-serious AE (grade 2 bronchiolitis; the participant received palivizumab and was therefore withdrawn) in the 30 days after randomization. MAAEs occurred at similar rates in both groups. There were no deaths reported.

Figure Legends

Figure 1. Kaplan-Meier curves for RSV LRTI hospitalization through the RSV season in all three countries combined (all randomized set). The efficacy was calculated as 1 minus the hazard ratio (expressed as a percentage) obtained from a stratified proportional hazards model with the stratification factors of age group at randomization and country. The inset shows the same data on an enlarged axis. Note, three participants (included in the ITT analysis) in the no intervention group received palivizumab recorded as concomitant medication. The number of participants at risk (time from recruitment) increases from none (August 2023 prior to study recruitment but after first site open) to maximum at the end of the recruitment period.

Figure 2. Incidence of RSV LRTI hospitalization through the RSV season by subgroup (all randomized set). The efficacy of nirsevimab in preventing RSV LRTI hospitalization through the RSV season was defined as 1 minus the incidence rate ratio and expressed as a percentage. The 2-sided 95% CIs for the efficacy were calculated by an exact method (described by Breslow and Day) accounting for the follow-up time post-dosing/randomization. NC, not computed (computation done if n in the nirsevimab group + n in no intervention group were ≥5 and n for the no intervention group ≥1).

Figure 3. Kaplan-Meier curves for very severe RSV LRTI hospitalization through the RSV season in all three countries combined (all randomized set). The efficacy was calculated as 1 minus the hazard ratio (expressed as a percentage) obtained from a stratified proportional hazards model with the stratification factor of age group at randomization and country. The inset shows the same data on an enlarged axis.

Note three participants (included in the ITT analysis) in the no intervention group received palivizumab recorded as concomitant medication. The number of participants at risk (time from recruitment) increases from none (August 2023 prior to study recruitment but after first site open) to maximum at the end of the recruitment period.