The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 30, 2020 VOL. 383 NO. 5

Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

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ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection in infants, and a need exists for prevention of RSV in healthy infants. Nirsevimab is a monoclonal antibody with an extended half-life that is being developed to protect infants for an entire RSV season with a single intramuscular dose.

METHODS

In this trial conducted in both northern and southern hemispheres, we evaluated nirsevimab for the prevention of RSV-associated lower respiratory tract infection in healthy infants who had been born preterm (29 weeks 0 days to 34 weeks 6 days of gestation). We randomly assigned the infants in a 2:1 ratio to receive nirsevimab, at a dose of 50 mg in a single intramuscular injection, or placebo at the start of an RSV season. The primary end point was medically attended RSV-associated lower respiratory tract infection through 150 days after administration of the dose. The secondary efficacy end point was hospitalization for RSV-associated lower respiratory tract infection through 150 days after administration of the dose.

RESULTS

From November 2016 through November 2017, a total of 1453 infants were randomly assigned to receive nirsevimab (969 infants) or placebo (484 infants) at the start of the RSV season. The incidence of medically attended RSV-associated lower respiratory tract infection was 70.1% lower (95% confidence interval [CI], 52.3 to 81.2) with nirsevimab prophylaxis than with placebo (2.6% [25 infants] vs. 9.5% [46 infants]; P<0.001) and the incidence of hospitalization for RSV-associated lower respiratory tract infection was 78.4% lower (95% CI, 51.9 to 90.3) with nirsevimab than with placebo (0.8% [8 infants] vs. 4.1% [20 infants]; P<0.001). These differences were consistent throughout the 150-day period after the dose was administered and across geographic locations and RSV subtypes. Adverse events were similar in the two trial groups, with no notable hypersensitivity reactions.

CONCLUSIONS

A single injection of nirsevimab resulted in fewer medically attended RSV-associated lower respiratory tract infections and hospitalizations than placebo throughout the RSV season in healthy preterm infants. (Funded by AstraZeneca and Sanofi Pasteur; ClinicalTrials.gov number, NCT02878330.)

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This article was updated on July 30, 2020, at NEJM.org.

N Engl J Med 2020;383:415-25.
DOI: 10.1056/NEJMoa1913556

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Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract disease and hospitalizations for respiratory illness among infants and young children, resulting in largely predictable annual epidemics worldwide.[1-3] RSV is a leading cause of infant deaths, primarily in low-income and middle-income countries.[1] During the first year of life, infants with a primary RSV infection are at risk for a severe lower respiratory tract infection.[4] Preterm infants, as well as young children with chronic lung disease of prematurity or congenital heart disease, are at particularly high risk.[5-10]

Preventing RSV illnesses in all infants is a major public health priority,[11] but despite more than 50 years of attempts at vaccine development[12,13] and extensive ongoing clinical research, there is no safe and effective RSV vaccine.[13] Passive RSV antibody approaches have been effective in clinical studies.[14-19] RSV prophylaxis is currently available as a specific RSV immune globulin G (palivizumab [Synagis]), administered in five monthly injections, that is licensed for infants who are at highest risk for serious RSV sequelae.[20] Further restrictive recommendations have been issued by local and national bodies,[21,22] limiting prophylaxis to less than 2% of the annual U.S. birth cohort.[23] Currently, there is no approved RSV prophylaxis for healthy infants. Because the only approved treatment for RSV infection (ribavirin) is difficult to deliver and has limited efficacy,[24] the standard of care for patients with serious RSV illness is supportive management of the condition. There is a need for RSV prophylaxis in healthy infants.

Nirsevimab, a recombinant human immune globulin G1 kappa monoclonal antibody, binds the highly conserved site 0 epitope present on the prefusion conformation of the RSV fusion protein.[25] The enhanced neutralizing activity of nirsevimab as compared with palivizumab[25] and a modification of the Fc region to promote extension of the half-life[26,27] support a vaccine-like strategy to protect infants from RSV with doses administered once per RSV season (which typically spans 5 months of the fall and winter). We evaluated a single dose of nirsevimab prophylaxis in healthy preterm infants entering their first RSV season.

Methods

Participants

Participants were healthy infants who had been born preterm (gestational age of 29 weeks 0 days through 34 weeks 6 days) and who were 1 year of age or younger and entering their first full RSV season. European Union participants had to be 8 months of age or younger. Participants were excluded if they met local, national, or American Academy of Pediatrics[21] recommended guidelines to receive RSV prophylaxis, had an acute illness at the time of randomization, had previously had an RSV infection, or had received palivizumab or any other investigational RSV monoclonal antibody or vaccine, including maternal vaccines (i.e., a vaccine administered to the mother during pregnancy). (Full criteria for inclusion and exclusion are provided in Section S2 in the Supplementary Appendix and in the protocol, both available with the full text of this article at NEJM.org.)

Trial Design and Oversight

Participants were randomly assigned, in a 2:1 ratio, to receive one intramuscular injection of 50 mg of nirsevimab or normal saline placebo during a 2-month period immediately before the RSV season. Randomization was stratified by hemisphere (northern or southern) and by age (≤3 months, >3 months to ≤6 months, or >6 months). Participants were monitored for medically attended respiratory illnesses for 150 days after nirsevimab or placebo was administered: by telephone every 2 weeks and in person during trial site visits on days 8, 31, 91, and 151, as well as on day 361 after administration of the dose (Fig. S1). Monitoring was performed by site investigators, or if the children were treated elsewhere, their medical records were reviewed by site investigators. If a participant received medical attention at a location other than the trial site, the parents were instructed to take the participant to the trial site for an evaluation of the respiratory illness.

This trial was conducted at 164 sites in 23 countries and was performed in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation. Enrollment

by trial site is shown in Table S1. Each site had approval from an institutional review board or ethics committee, and appropriate written informed consent was obtained for each participant. The trial was designed by MedImmune/AstraZeneca, and funding was provided by MedImmune/AstraZeneca and Sanofi Pasteur. Data were collected by clinical investigators and analyzed by AstraZeneca employees. Agreements requiring authors to maintain data confidentiality were in place between AstraZeneca and the authors. The authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first author wrote the first draft with assistance from professional medical writers funded by AstraZeneca.

END POINTS

The primary end point was medically attended RSV-associated lower respiratory tract infection (inpatient or outpatient) through 150 days after nirsevimab or placebo was administered, and the secondary efficacy end point was hospitalization due to this condition during the same period. The incidence of lower respiratory tract infection of any cause and of respiratory-related hospitalization for any cause was also captured.

Participants who were brought to a health care provider for a respiratory illness (inpatient or outpatient) were evaluated for the occurrence of RSV-associated lower respiratory tract infection. All incidents of medically attended lower respiratory tract infection were evaluated by site investigators, who were unaware of the group assignments, who examined the participants or reviewed their medical reports (if a child had been seen by a provider who was not a trial investigator), and the evaluations were reviewed by trial monitors for completeness and accuracy. According to the prespecified case definition, a lower respiratory tract infection was included in our analysis if an RSV test performed at the central laboratory (Viracor Eurofins Clinical Diagnostics) was positive, a physical examination indicated involvement of the lower respiratory tract, and there was at least one indicator of clinical severity (see Table S2).[28] A nasopharyngeal sample from participants who had a lower respiratory tract infection or who were hospitalized for any respiratory infection was obtained for testing at the central laboratory. The test was a real-time, reverse-transcriptase–polymerase-chain-reaction (RT-PCR) in vitro diagnostic assay (Lyra RSV + hMPV, Quidel) that had received U.S. Food and Drug Administration clearance and a European Certificate of Conformity (known as the CE mark). After RSV detection by real-time RT-PCR, RSV A and RSV B subtypes were determined by nucleotide sequencing of a 270 bp region of the RSV G gene second hypervariable region and comparison of the sequence to A and B reference strains (Section S3). Results were included in the analysis if the sample was obtained between 7 days before and 14 days after the participant's initial visit to a health care provider.

Prespecified analyses of the primary and secondary end points were performed in subgroups defined according to hemisphere, age, sex, race, gestational age, and siblings (twins or triplets) enrolled in the trial. The burden on utilization of health care resources, which included the severity of illness during hospitalization, was an exploratory end point.

Data on adverse events that occurred during the trial period were collected. The adverse events were graded by severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events and assessed for association with the investigational product throughout the trial.

To determine the pharmacokinetics of nirsevimab and the incidence of antidrug antibodies, as described previously,[29] serum samples were collected before nirsevimab or placebo was administered; on days 91, 151, and 361 after doses were administered; and when participants were hospitalized for respiratory illnesses. A positive titer for antinirsevimab antibody was defined as a titer of 1:50 or more. The effect of antidrug antibodies on the pharmacokinetics and efficacy of nirsevimab and their association with adverse events that occurred during treatment were assessed.

STATISTICAL ANALYSES

Efficacy analyses were performed in the intention-to-treat population (all participants who

Table 1. Characteristics of the Participants at Baseline.*

Variable	Nirsevimab (N=969)	Placebo (N=484)
Hemisphere — no. (%)		
Northern	659 (68)	329 (68)
Southern	310 (32)	155 (32)
Age		
Mean — mo	3.29±2.22	3.28±2.31
Distribution — no. (%)		
≤3 mo	516 (53.3)	257 (53.1)
>3 to ≤6 mo	320 (33.0)	153 (31.6)
>6 mo	133 (13.7)	74 (15.3)
Gestational age		
Mean — wk	32.7±1.4	32.7±1.5
Distribution — no. (%)		
≥29 to ≤32 wk	363 (37.5)	185 (38.2)
>32 wk	606 (62.5)	299 (61.8)
Female sex — no. (%)	468 (48.3)	224 (46.3)
Weight — kg	4.60±1.92	4.51±1.96
Race or ethnic group — no./total no. (%)†		
American Indian or Alaska Native	0	1/484 (0.2)
Asian	5/968 (0.5)	10/484 (2.1)
Black	189/968 (19.5)	67/484 (13.8)
Native Hawaiian or other Pacific Islander	8/968 (0.8)	3/484 (0.6)
White	693/968 (71.6)	355/484 (73.3)
Other	61/968 (6.3)	43/484 (8.9)
Multiple categories	12/968 (1.2)	5/484 (1.0)
Sibling enrolled in trial — no. (%)	336 (34.7)	172 (35.5)

* Plus–minus values are means ±SD. Data are for the intention-to-treat population. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the participants' parents or guardians. Race or ethnic group was not reported by one participant in the nirsevimab group.

underwent randomization) according to the randomized treatment assignment. Safety analyses were based on the as-treated population (participants who received any investigational product) according to the investigational product received. The sample size, which we selected to evaluate safety and benefit in the population of preterm infants before proceeding to term infants, had more than 99% power to detect a 70% lower relative risk of medically attended RSV-associated lower respiratory tract infection with nirsevimab than with placebo, at a two-sided significance level of 0.05, under the assumption of an 8% event rate in the placebo group.

Primary and secondary efficacy end points were analyzed with the use of a Poisson regression model with robust variance[30] as the primary analysis model. The primary end-point analysis included two randomization stratification factors: hemisphere and age. To control for the overall type I error at a significance level of 0.05, a hierarchical approach was used; the secondary end point would be tested only if statistical significance for the primary end point was shown. For participants who did not have an RSV-associated lower respiratory tract infection and were not followed through 150 days after administration of the dose, their event status was considered missing and was imputed with the observed event rate in the placebo group, with repeated imputation. (Details about handling of missing data are provided in Section S4, and details of additional analyses for the primary and secondary end points, all-cause medically attended lower respiratory tract infections, and all-cause respiratory-related hospitalizations are provided in Section S5.)

Data analyses were conducted with SAS software, version 9.4 (SAS Institute). Pharmacokinetic end points were estimated by noncompartmental analysis with Phoenix 64 WinNonlin, version 6.3 (Pharsight).

RESULTS

PARTICIPANTS

Between November 3, 2016, and December 1, 2017, a total of 1453 participants underwent randomization (969 to the nirsevimab group and 484 to the placebo group), and 1447 (966 in the nirsevimab group and 481 in the placebo group) received injections (Fig. S2). In the two groups combined, 97.5% of the participants (1417 participants) who underwent randomization completed the 150-day efficacy period; 94.2% (913) of those randomly assigned to nirsevimab and 93.8% (454) of those randomly assigned to placebo completed the entire 360-day follow-up (Fig. S2). Baseline characteristics were similar in the two groups (Table 1).

EFFICACY

Medically attended RSV-associated lower respiratory tract infection occurred in 2.6% of the par-

Table 2. Medically Attended Lower Respiratory Tract Infection and Hospitalization Associated with Respiratory Syncytial Virus (RSV) through 150 Days after Dose.*

End Points and Analyses	Nirsevimab (N=969)	Placebo (N=484)	Relative Difference (95% CI)	P Value
	number (percent)		%	
Medically attended RSV-associated lower respiratory tract infection				
Poisson regression with robust variance			70.1 (52.3–81.2)	<0.001
Observed events	25 (2.6)	46 (9.5)		
Participants with imputation of data†	24 (2.5)	11 (2.3)		
Cochran–Mantel–Haenszel test: observed events	25 (2.6)	46 (9.5)	72.9 (56.5–83.1)	<0.001
Hospitalization for RSV-associated lower respiratory tract infection				
Poisson regression with robust variance			78.4 (51.9–90.3)	<0.001
Observed events	8 (0.8)	20 (4.1)		
Participants with imputation of data†	24 (2.5)	11 (2.3)		
Cochran–Mantel–Haenszel test: observed events	8 (0.8)	20 (4.1)	80.0 (55.0–91.1)	<0.001

* Data are for the intention-to-treat population. The case definition for inclusion of the lower respiratory tract infection in the analysis of the end point required a positive result for RSV in a real-time, reverse-transcriptase–polymerase-chain-reaction assay performed at a central laboratory, a physical examination finding indicating involvement of the lower respiratory tract, and at least one indicator of clinical severity. CI denotes confidence interval.

† Data were imputed for participants who had no events and were not followed through 150 days after administration of the dose of nirsevimab or placebo.

ticipants (25 participants) in the nirsevimab group and in 9.5% (46) in the placebo group. Hospitalization for this condition occurred in 0.8% of those in the nirsevimab group (8 participants) and in 4.1% (20) in the placebo group. The incidence of medically attended RSV-associated lower respiratory tract infection was 70.1% lower (95% confidence interval [CI], 52.3 to 81.2) with nirsevimab than with placebo (P<0.001). The incidence of hospitalization for this condition was 78.4% lower (95% CI, 51.9 to 90.3) with nirsevimab than with placebo (P<0.001) (Table 2). Over the entire 150-day efficacy period after administration of the dose, infants who received nirsevimab had a lower risk of medically attended RSV-associated lower respiratory tract infection than infants who received placebo (hazard ratio, 0.26; 95% CI, 0.16 to 0.43), as well as a lower risk of hospitalization for this condition (hazard ratio, 0.19; 95% CI, 0.08 to 0.44) (Fig. 1). RSV-associated lower respiratory tract infections occurred with placebo throughout the 150 days after administration of the dose, but the incidence decreased as the RSV season ended. The separation in event rates between nirsevimab and placebo recipients expanded throughout the 150 days after administration of the dose (Fig. 1). Subgroup analyses according to hemisphere, age at randomization, sex, race, gestational age, and enrolled siblings showed consistent efficacy favoring nirsevimab (Fig. S3 and Table S3, with primary and secondary efficacy end points shown by country in Tables S4 and S5).

Of participants hospitalized because of RSV infection, all those who were admitted to the intensive care unit (5 participants) or received assisted ventilation (4 participants) were in the placebo group. Among participants who had medically attended RSV-associated lower respiratory tract infection, fewer nirsevimab recipients (4 [16%]) than placebo recipients (15 [32.6%]) received supplemental oxygen (Table S6).

In 86.3% of the cases of lower respiratory tract infection (391 of 453 incidents) and 86.0%

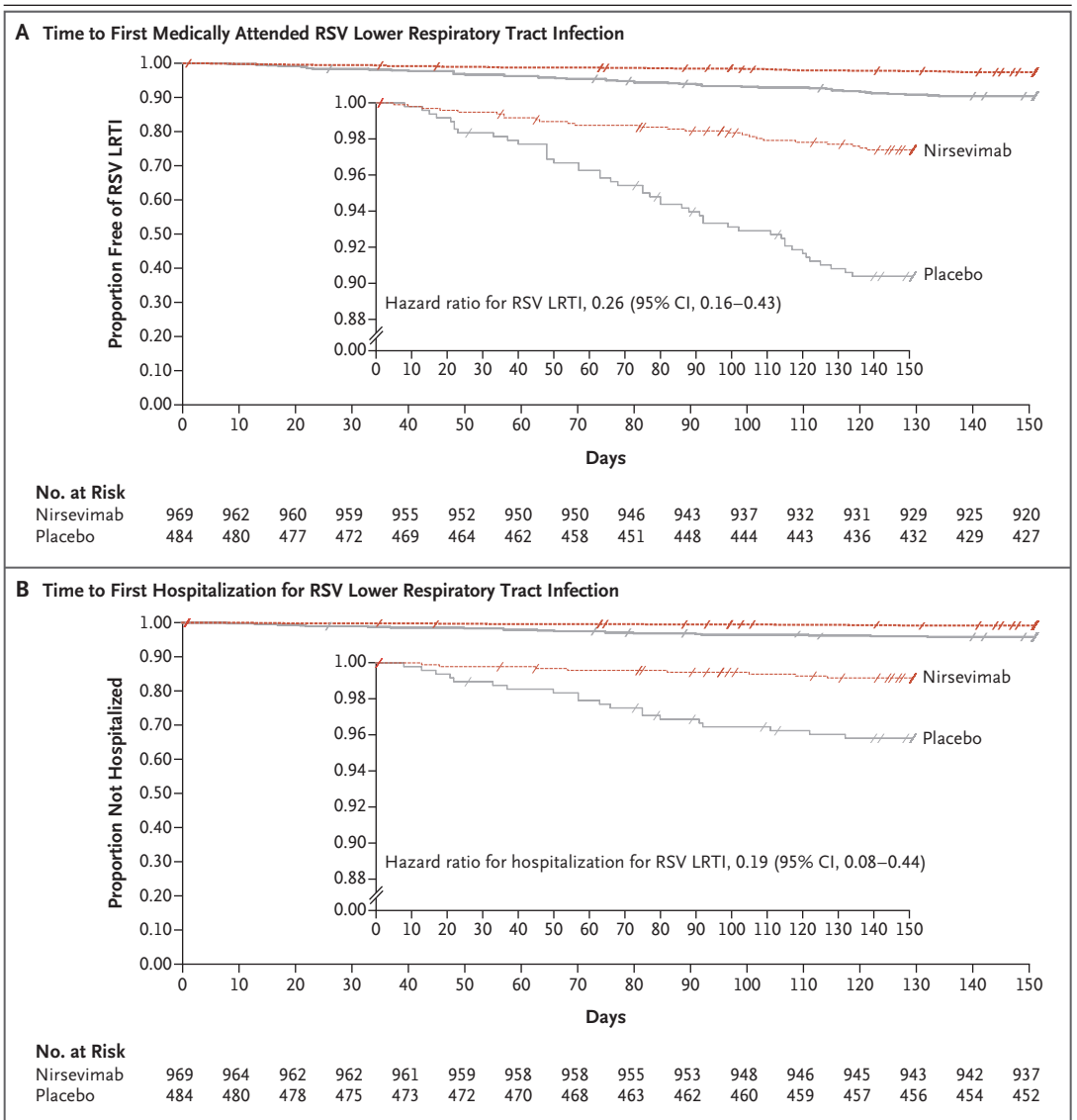

Figure 1. Lower Respiratory Tract Infections (LRTIs) and Hospitalizations Associated with Respiratory Syncytial Virus (RSV).

Kaplan–Meier curves from a time-to-event analysis show estimates of the proportion of participants who were free from a medically attended RSV-associated LRTI (Panel A) and the proportion who were not hospitalized for that infection (Panel B). The hazard ratio was obtained from a stratified proportional-hazards model with two stratification factors (age at time of random assignment and northern or southern hemisphere). In each panel, the inset shows the same data on an enlarged y axis. Tick marks indicate censored data.

of the hospitalizations (104 of 121 incidents), samples were collected for central RT-PCR testing between 7 days before and 14 days after the initial visit to a health care provider. RSV A and B subtypes were responsible for similar proportions of medically attended RSV-associated lower respiratory tract infections. The incidence of either subtype was lower with nirsevimab than with placebo (RSV A, 1.1% [11 participants] vs. 5.0% [24 participants]; RSV B, 1.4% [14 participants] vs. 4.5% [22 participants]). Two clinical isolates identified from nirsevimab recipients, both RSV B, had decreased susceptibility to nirsevimab (Section S3 and Table S7).

Medically attended lower respiratory tract infection from any cause through 150 days after

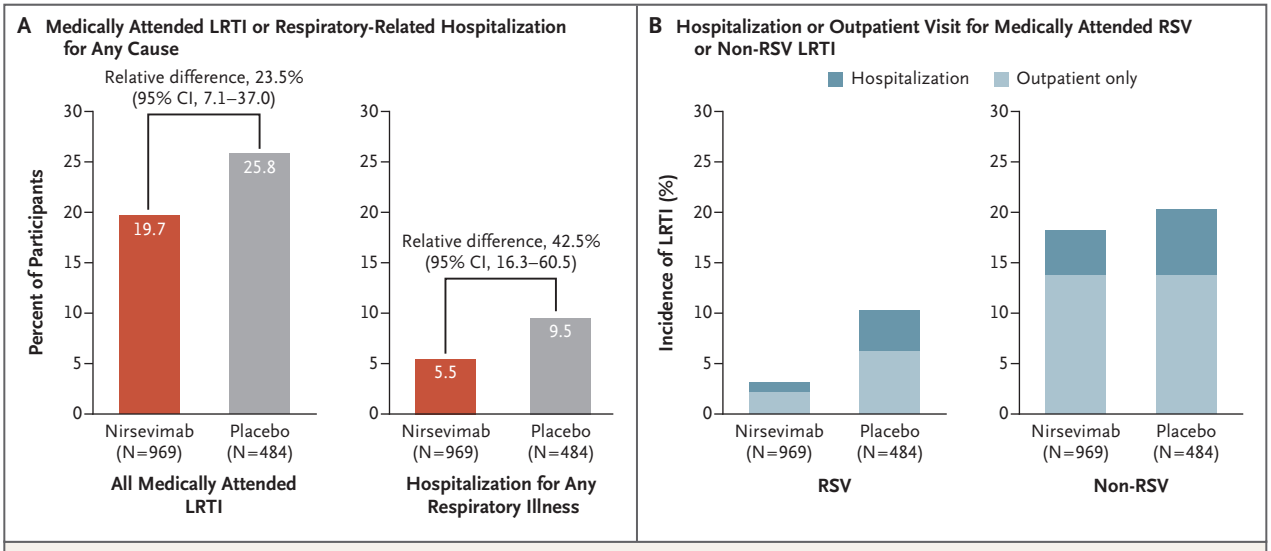

Figure 2. Effect of Nirsevimab on All-Cause Respiratory Events in the Intention-to-Treat Population.

Panel A shows the percentage of participants who had any medically attended lower respiratory tract infection or respiratory-related hospitalization (caused by RSV or non-RSV pathogens) through 150 days after administration of nirsevimab or placebo. Panel B shows the percentage of participants with any medically attended RSV- or non-RSV–associated lower respiratory tract infection who had an outpatient visit or hospitalization through 150 days after administration of nirsevimab or placebo.

the dose occurred in 25.8% of the participants (125 participants) in the placebo group and in 19.7% (191) in the nirsevimab group, representing a 23.5% lower incidence (95% CI, 7.1 to 37.0) in the nirsevimab group (Fig. 2A). Similarly, a lower rate of hospitalization due to any respiratory illness was observed with nirsevimab than with placebo (5.5% [53 participants] vs. 9.5% [46 participants]), representing a 42.5% lower incidence (95% CI, 16.3 to 60.5) in the nirsevimab group (Fig. 2A). Post hoc time-to-event analyses (Fig. S4) further supported the benefit of nirsevimab over placebo in preventing medically attended lower respiratory tract infection from any cause and respiratory-related hospitalization for any cause. Occurrence of non-RSV lower respiratory tract infection was similar in the two groups (Fig. 2B), which suggests that infection due to other respiratory pathogens was not affected by nirsevimab.

SAFETY

The types and frequencies of adverse events that occurred during the trial were similar in the nirsevimab and placebo groups (Table 3 and Table S8). Serious adverse events were reported in 11.2% (108 of 968) of the participants who received nirsevimab and in 16.9% (81 of 479) of those who received placebo; the investigator considered none to be related to the investigational product.

Most adverse events that occurred during treatment were grade 1 or 2 in severity. Adverse events of grade 3 or higher were reported in 8.0% (77 of 968) of those who received nirsevimab and in 12.5% (60 of 479) of those who received placebo. Occurrences of adverse events relative to dose administration within 1 day after the dose or at 7 days after the dose were similar in the two groups.

Adverse events of special interest were reported in 0.5% (5 of 968) of the participants who received nirsevimab and in 0.6% (3 of 479) of those who received placebo. No anaphylaxis or other notable hypersensitivity reactions were reported. All adverse events of special interest were grade 1 in severity and were considered by the investigator to be related to nirsevimab or placebo; these adverse events were rash (4 participants) and petechiae (1 participant) in the nirsevimab group and rash (3 participants) in the placebo group.

Five deaths occurred through day 361 (two deaths in the nirsevimab group and three in the placebo group); one death in the placebo group occurred after the trial period (day 367). No

Table 3. Safety and Adverse Events during the Trial That Occurred in at Least 10% of Participants in Either Group.*

Variable	Nirsevimab (N=968)	Placebo (N=479)
	number (percent)	
Adverse event during the trial period	834 (86.2)	416 (86.8)
Considered related to trial drug†	22 (2.3)	10 (2.1)
≥Grade 3	77 (8.0)	60 (12.5)
Occurred ≤1 day after the dose	24 (2.5)	12 (2.5)
Occurred ≤7 days after the dose	121 (12.5)	73 (15.2)
Death‡	2 (0.2)	3 (0.6)
Serious adverse event during the trial period		
Any	108 (11.2)	81 (16.9)
Considered related to trial drug†	0	0
Adverse event of special interest§		
Any	5 (0.5)	3 (0.6)
Considered related to trial drug†	5 (0.5)	3 (0.6)
Adverse events during the trial period, according to system organ class and preferred term		
Gastrointestinal disorders		
Any	263 (27.2)	146 (30.5)
Diarrhea	100 (10.3)	50 (10.4)
General and administration site disorders		
Any	127 (13.1)	70 (14.6)
Pyrexia	111 (11.5)	64 (13.4)
Infections and infestations		
Any	747 (77.2)	377 (78.7)
Bronchiolitis	96 (9.9)	55 (11.5)
Bronchitis	96 (9.9)	55 (11.5)
Gastroenteritis	122 (12.6)	46 (9.6)
Lower respiratory tract infection	86 (8.9)	53 (11.1)
Nasopharyngitis	164 (16.9)	94 (19.6)
Rhinitis	111 (11.5)	50 (10.4)
Upper respiratory tract infection	395 (40.8)	170 (35.5)
Respiratory, thoracic, and mediastinal disorders	203 (21.0)	91 (19.0)
Skin and subcutaneous tissue disorders	237 (24.5)	110 (23.0)

* Data are for the as-treated population.

† Relation to the trial drug was determined by the investigator, who at the time of assessment of relatedness was unaware of the trial assignment.

‡ In the nirsevimab group, 1 death on day 97 was caused by previously undiagnosed pulmonary vein stenosis, and 1 death of unknown cause occurred on day 123 (infant was well when put to bed). In the placebo group, 1 death on day 343 was caused by pericardial effusion, and 2 deaths (on days 26 and 109) were caused by pneumonia. The participant who died on day 26 was hospitalized for apnea on day 9 (RSV-negative), received a diagnosis of *Escherichia coli* and *Morganella morganii* meningitis at that time, and remained hospitalized until death, which was attributed to pneumonia. In the infant who died on day 109, RSV-associated lower respiratory tract infection had been diagnosed previously, with resolution on day 84; subsequent RSV testing was not performed. A death on day 367 in the placebo group was attributed to pneumonia caused by *Haemophilus influenzae* and *Streptococcus pneumoniae*, which were found in blood and lung tissue on postmortem examination. RSV testing was not performed.

§ Adverse events of special interest were hypersensitivity, immune complex disease, and thrombocytopenia. A case of petechiae was of 1 day in duration, occurred approximately 4 months after receipt of nirsevimab, and was considered related to the trial drug by the investigator. However, this participant was not seen by a health care provider for the petechiae, no laboratory assessments for petechiae were performed, and the adverse event was reported on the basis of parental description.

deaths were known to be due to RSV or were considered by the investigator to be related to nirsevimab or placebo.

PHARMACOKINETICS

The mean (±SD) half-life of nirsevimab was 59.3±9.6 days. On day 151, serum concentrations in 97.9% (833 of 851 infants for whom day-151 serum concentrations were available) of the nirsevimab recipients were above the targeted 90% effective concentration threshold of 6.8 μg per milliliter.[25,29] Mean serum concentrations of nirsevimab decayed in proportion to the concentration beyond 91 days without signs of nonlinearity (Table S9 and Fig. S5A).

ANTIDRUG ANTIBODIES

Postbaseline antidrug antibodies were detected in 5.6% of the participants who received nirsevimab (52 of 929 participants with postbaseline antidrug antibodies that could be evaluated) and in 3.8% of those who received placebo (18 of 469 participants with postbaseline antidrug antibodies that could be evaluated). Serum concentrations of nirsevimab over time were similar in participants who were positive and those who were negative for antidrug antibodies (Fig. S5B). During the 150-day period after administration of the dose, one nirsevimab recipient who had a medically attended RSV-associated lower respiratory tract infection had antidrug antibodies detected by laboratory testing. The respiratory tract infection occurred on day 46; the only positive antidrug antibody titer (1:100) was noted on day 91. There was no notable difference between groups when adverse events occurring during the trial period were analyzed by positive or negative antidrug antibody status.

DISCUSSION

This trial of a monoclonal antibody with an extended half-life showed that a single intramuscular dose of RSV immunoprophylaxis could protect infants against RSV-associated lower respiratory tract infection requiring medical attention. A single intramuscular injection of nirsevimab at a dose of 50 mg resulted in a lower incidence of medically attended RSV-associated lower respiratory tract infections and hospitalizations (approximately 70% and 80% lower, respectively) than placebo in healthy preterm infants entering their first RSV season. Subgroup analyses of the primary and secondary efficacy end points showed results similar to those of the overall analysis, consistently favoring nirsevimab.

Different definitions of lower respiratory tract infection have been used in RSV immunization studies.[31] We used a prespecified objective case definition of this condition to allow transnational standardization of the efficacy end point for lower respiratory tract infection.[28] Of 79 participants who received a confirmed diagnosis of RSV-positive lower respiratory tract infection, 71 (90%) met our case definition. All participants hospitalized with RSV-associated lower respiratory tract infections met the case definition. We observed a lower incidence of medically attended lower respiratory tract infection from any cause and respiratory-related hospitalization for any cause in the nirsevimab group than in the placebo group, with no corresponding increase in non–RSV-associated lower respiratory tract infections, which suggests that preventing RSV infection did not promote emergence of these respiratory infections caused by other respiratory pathogens.

Nirsevimab has greater neutralizing activity and a longer serum half-life than palivizumab. One injection of nirsevimab provided protection for a typical RSV season, whereas monthly injections of palivizumab are required to provide sustained protection during the RSV season.[20] Palivizumab is indicated and recommended only for the highest-risk infants.[1,21] Given the unique characteristics of nirsevimab, including our finding that season-long protection from RSV can be achieved with a single dose, it is currently being evaluated in healthy late-preterm and full-term infants.

Nirsevimab was effective at neutralizing both RSV A and RSV B subtypes. This finding is important because a recent trial of suptavumab (ClinicalTrials.org number, NCT02325791), an investigational RSV F site-V specific monoclonal antibody, failed to meet its primary efficacy end point and was not effective in neutralizing the main circulating strain of RSV B.

In this population of healthy infants who had been born preterm, nirsevimab had a safety profile similar to that of placebo. Administering nirsevimab to larger numbers of infants will be necessary to detect possible less-common adverse events. The incidence of suspected hyper-

sensitivity reactions was similar in the nirsevimab group and the placebo group, and there were no cases of anaphylaxis or other notable hypersensitivity reactions. Antidrug antibodies did not appear to have an effect on efficacy or nirsevimab serum concentrations through day 151, nor did they arouse an obvious safety concern through day 361.

A direct comparison of the results of this trial with those involving other anti-RSV monoclonal antibodies and maternal vaccines (vaccines administered during pregnancy) is difficult because of differences in antibody and functional antibody measurement techniques, end points, trial populations, and dosing regimens. Previous studies have shown that an RSV-specific monoclonal antibody, at an effective concentration provided in advance of the RSV season, can reliably reduce the incidence of serious RSV disease in preterm infants, children 24 months of age or younger with chronic lung disease of prematurity or congenital heart disease,[14-18] and healthy Native American full-term infants.[19] Nirsevimab provided protection with a single intramuscular dose, probably owing to its increased potency and extended half-life of 63 to 73 days[29] as compared with the shorter 19-to-27-day half-life of palivizumab.[32] On day 151 after a single dose of nirsevimab, most infants had serum concentrations above the target threshold. Although prophylaxis with RSV-specific monoclonal antibodies has been shown to be protective, that has not been the case with maternal RSV antibodies. Efficient transfer of maternal RSV antibodies to infants occurs, but it has failed to confer protection from severe RSV disease.[33-35]

In this trial of RSV prophylaxis in healthy preterm infants, a single dose of nirsevimab resulted in a lower incidence of medically attended RSV-associated lower respiratory tract infection and of hospitalization than placebo for 150 days — the length of a typical RSV season — after administration of the dose. Nirsevimab had a favorable safety profile, with no notable hypersensitivity reactions.

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

Presented in part at IDWeek, Washington, D.C., October 2–6, 2019.

Supported by AstraZeneca and Sanofi Pasteur.

Dr. Griffin reports being employed by and owning stock in AstraZeneca; Dr. Yuan, being employed by and owning stock in AstraZeneca; Ms. Takas, being employed by and owning stock in AstraZeneca; Dr. Domachowske, receiving fees for clinical trial activities, paid to his institution, from Regeneron, GlaxoSmithKline, and Merck; Dr. Madhi, receiving grant support, paid to his institution, and advisory board fees from the Bill & Melinda Gates Foundation, and grant support, paid to his institution, from Pfizer, GlaxoSmithKline, Minervax, and Sanofi; Dr. Manzoni, receiving advisory board fees from AstraZeneca; Dr. Simões, receiving grant support, paid to his institution, consulting fees, and travel support from AstraZeneca, Merck, Regeneron, Pfizer, and Roche, consulting fees, lecture fees, fees for serving on a data and safety monitoring board, and travel support from AbbVie, consulting fees from Alere, fees for serving on a data and safety monitoring board from GlaxoSmithKline, grant support, paid to his institution, from Johnson & Johnson, and grant support, paid to his institution, and travel support from Novavax; Dr. Esser, being employed by and owning stock in AstraZeneca; Dr. Khan, being employed by and owning stock in AstraZeneca and holding pending patent US 62/840,701 on dosage regimens for and compositions including Anti-RSV Antibodies, licensed to Sanofi, for which royalties are received; Dr. Dubovsky, being employed by and owning stock in AstraZeneca; Dr. Villafana, being employed by and owning stock options in AstraZeneca; and Dr. DeVincenzo, receiving advisory fees from Vir Biotechnology, Gilead, Adma Biologics, Pfizer, Enanta, GlaxoSmithKline, and Janssen, grant support, paid to the University of Tennessee, and advisory fees from ArkBio, owning stock options in ArkBio, and receiving grant support, paid to the University of Tennessee, and advisory fees from Reviral and Pulmocide. No other potential conflict of interest relevant to this article was reported.

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

We thank the trial investigators, trial participants, participants' families, and the nirsevimab study team; Vadryn Pierre, Ph.D., for conducting the noncompartmental analysis of the pharmacokinetic data; Michael McCarthy, Ph.D., for assistance with manuscript preparation; and Ruvini Jayasinghe, Ph.D., of Oxford PharmaGenesis, for medical writing support of an earlier version of the manuscript, funded by AstraZeneca. JK Associates, a member of the Fishawack Group of Companies, provided additional medical writing assistance, which was funded by AstraZeneca. Nirsevimab is being developed in partnership between AstraZeneca and Sanofi Pasteur.

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