ORIGINAL ARTICLE

Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

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ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infection and hospitalization in infants. Nirsevimab is a monoclonal antibody to the RSV fusion protein that has an extended half-life. The efficacy and safety of nirsevimab in healthy late-preterm and term infants are uncertain.

METHODS

We randomly assigned, in a 2:1 ratio, infants who had been born at a gestational age of at least 35 weeks to receive a single intramuscular injection of nirsevimab or placebo before the start of an RSV season. The primary efficacy end point was medically attended RSV-associated lower respiratory tract infection through 150 days after the injection. The secondary efficacy end point was hospitalization for RSV-associated lower respiratory tract infection through 150 days after the injection.

RESULTS

A total of 1490 infants underwent randomization: 994 were assigned to the nirsevimab group and 496 to the placebo group. Medically attended RSV-associated lower respiratory tract infection occurred in 12 infants (1.2%) in the nirsevimab group and in 25 infants (5.0%) in the placebo group; these findings correspond to an efficacy of 74.5% (95% confidence interval [CI], 49.6 to 87.1; P<0.001) for nirsevimab. Hospitalization for RSV-associated lower respiratory tract infection occurred in 6 infants (0.6%) in the nirsevimab group and in 8 infants (1.6%) in the placebo group (efficacy, 62.1%; 95% CI, −8.6 to 86.8; P=0.07). Among infants with data available to day 361, antidrug antibodies after baseline were detected in 58 of 951 (6.1%) in the nirsevimab group and in 5 of 473 (1.1%) in the placebo group. Serious adverse events were reported in 67 of 987 infants (6.8%) who received nirsevimab and in 36 of 491 infants (7.3%) who received placebo.

CONCLUSIONS

A single injection of nirsevimab administered before the RSV season protected healthy late-preterm and term infants from medically attended RSV-associated lower respiratory tract infection. (Funded by MedImmune/AstraZeneca and Sanofi; MELODY ClinicalTrials.gov number, NCT03979313.)

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*A list of the MELODY Study Group members is provided in the Supplementary Appendix, available at NEJM.org.

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Respiratory syncytial virus (RSV) is a leading cause of childhood acute lower respiratory tract infection and a major cause of hospital admissions among young children across high-income, middle-income, and low-income countries, resulting in a substantial global burden on health care services.[1] Although premature infants and those with underlying lung or heart disease are among those at highest risk for severe illness,[2-4] most hospitalizations due to RSV occur in healthy infants born at term.[5]

Nirsevimab is a recombinant human IgG1 kappa monoclonal antibody that binds the F1 and F2 subunits of the RSV fusion (F) protein at a highly conserved epitope and locks the RSV F protein in the prefusion conformation to block viral entry into the host cell. Nirsevimab shows greater potency at inhibiting RSV than palivizumab in cell-culture and animal models and has an Fc region engineered to have an extended half-life in vivo.[6] A single dose of nirsevimab administered before the RSV season protected healthy preterm infants (born at a gestational age of 29 weeks to <35 weeks) against RSV-associated lower respiratory tract infection with 70.1% efficacy and had a favorable safety profile.[7] However, interventions to prevent the high burden of RSV-associated lower respiratory tract infection in healthy, term infants are needed. This phase 3 trial evaluated the efficacy and safety of nirsevimab in healthy late-preterm and term infants entering their first RSV season.

METHODS

PARTICIPANTS

Healthy infants who had been born at a gestational age of at least 35 weeks 0 days, were 1 year of age or younger, and were entering their first RSV season were eligible for participation. Potential participants were excluded if they met national or local criteria to receive commercial palivizumab, had any fever or acute illness within 7 days before randomization, or had RSV infection before or at the time of randomization. Palivizumab is licensed for use in infants who are at highest risk for severe RSV disease, including infants who were born preterm (at a gestational age of ≤35 weeks) and are younger than 6 months age at the start of the RSV season and in children younger than 2 years of age with chronic lung disease of prematurity or hemodynamically significant congenital heart disease. National or local recommendations for use are more restrictive.[8,9] Full inclusion and exclusion criteria are listed 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 nirsevimab (at a dose of 50 mg if they weighed <5 kg or at a dose of 100 mg if they weighed ≥5 kg) or placebo. Randomization was stratified according to hemisphere of residence (northern or southern) and age (≤3.0 months, >3.0 to 6.0 months, or >6.0 months). Medically attended respiratory illnesses were captured with the use of standardized methods through day 511 after the injection. (The trial design is described in Section S3 and Fig. S1 in the Supplementary Appendix.) The primary cohort included participants enrolled in 2019 at 150 sites (in 20 countries) in the northern hemisphere and in 2020 at 10 sites (in 1 country) in the southern hemisphere. Enrollment and follow-up for an additional safety cohort of 1500 infants were ongoing at the time of the primary analysis.

The trial was performed in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. Each site had approval from an institutional ethics review board or ethics committee, and appropriate written informed consent was obtained for each participant. Data were collected by clinical investigators and analyzed by ClinChoice (a contract research organization). Neither the investigators nor the parents or guardians were aware of the trial-group assignments, and all authors had access to the results of the aggregated analysis. The authors reviewed the manuscript, 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. Medimmune/AstraZeneca was involved in the trial design; the collection, analysis, and interpretation of the data; and the writing of the manuscript. The trial was funded by MedImmune/AstraZeneca and Sanofi. Medical writing support was funded by AstraZeneca and Sanofi.

END POINTS, ADVERSE EVENTS, AND PHARMACOKINETICS

The primary efficacy end point was medically attended RSV-associated lower respiratory tract infection through 150 days after the injection, and the secondary efficacy end point was hospitalization due to this condition during the same period. The case definition used for the primary end point required detection of RSV by means of polymerase-chain-reaction assay, the presence of signs of lower respiratory tract disease, and the presence of clinical signs of severe respiratory disease (Table S1). Before unblinding of the data, additional exploratory efficacy analyses were added to allow assessment of the efficacy and effect (the number needed to treat to avert one case of RSV-associated lower respiratory tract infection) with the use of more inclusive case definitions. All RSV cases were confirmed by central laboratory testing (Lyra RSV+hMPV, Quidel) (Section S4). Prespecified subgroup analyses of the primary end point were stratified according to hemisphere of residence, age at randomization, sex, race, weight, and gestational age.

The adverse events were graded by severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, and were coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.1. Hypersensitivity (including anaphylaxis), immune-complex disease, and thrombocytopenia were designated as adverse events of special interest.

The pharmacokinetics of nirsevimab were determined as described previously.[10] Serum samples were collected before the injection; on days 31, 151, and 361 after the injection; and at the time participants were hospitalized for respiratory illnesses (the procedures in Japan and Europe were different from those used in other countries and are described in the legend of Fig. S1). Antidrug antibodies to nirsevimab were assessed, and a positive antibody response was defined as a titer of 1:50 or more.[7,10]

STATISTICAL ANALYSIS

All analyses were performed in the primary cohort. Efficacy analyses were performed in the intention-to-treat population (all participants who underwent randomization) according to the assigned regimen. Safety analyses were performed in the as-treated population (participants who received either product) according to the investigational product received. The World Health Organization declared the Covid-19 pandemic on March 11, 2020, at the end of the first season of observation in the northern hemisphere. In consultation with health authorities, the protocol was amended to enable the primary analysis to be performed with the accumulated efficacy and safety data. For the primary analysis, we calculated that a sample size of approximately 1500 participants would give the trial at least 99% power to detect a 70% lower relative risk of a primary end-point event with nirsevimab than with placebo, at a two-sided significance level of 0.05, under the assumption of an 8% incidence of medically attended RSV-associated lower respiratory tract infection among participants in the placebo group. Enrollment continued to the full trial size of 3000 participants, which was selected to support the evaluation of safety in this population.

Analysis of the primary end point was performed with the use of a Poisson regression model with robust variance. Efficacy was calculated as 1 minus the relative risk (with the relative risk estimated with the use of the aforementioned Poisson model) and is expressed as a percentage. The original model included the stratification factors that were used at randomization (age and hemisphere of residence) as covariates. Before unblinding, hemisphere was removed as a covariate because of the absence of observed events in the southern hemisphere. Therefore, a reduced model was used, with age at randomization (≤3.0 months, >3.0 to 6.0 months, or >6.0 months) as a covariate. A hierarchical approach was used to control for the overall type I error; the secondary efficacy end point was tested only if statistical significance with respect to the primary end point was shown. Data from participants who did not have an RSV-associated lower respiratory tract infection and were not followed through 150 days after the injection were considered to be missing and were imputed with the observed incidence for RSV-associated lower respiratory tract infection in the placebo group by means of multiple imputation. A time-to-event analysis through day 361 for participants from South Africa was conducted post hoc.

A pooled analysis of efficacy against hospitalization for RSV-associated lower respiratory tract

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Nirsevimab (N=994)	Placebo (N=496)	Total (N=1490)
	no. of participants/total no. (%)		
Age			
≤3.0 mo	577/994 (58.0)	285/496 (57.5)	862/1490 (57.9)
>3.0 to ≤6.0 mo	317/994 (31.9)	162/496 (32.7)	479/1490 (32.1)
>6.0 mo	100/994 (10.1)	49/496 (9.9)	149/1490 (10.0)
Gestational age			
≥35 to <37 wk	132/993 (13.3)	76/495 (15.4)	208/1488 (14.0)
≥37 wk	861/993 (86.7)	419/495 (84.6)	1280/1488 (86.0)
Female sex	464/994 (46.8)	257/496 (51.8)	721/1490 (48.4)
Weight			
<5 kg	403/992 (40.6)	192/496 (38.7)	595/1488 (40.0)
≥5 kg	589/992 (59.4)	304/496 (61.3)	893/1488 (60.0)
Race or ethnic group†			
American Indian or Alaska Native	57/991 (5.8)	26/496 (5.2)	83/1487 (5.6)
Asian	36/991 (3.6)	18/496 (3.6)	54/1487 (3.6)
Black	286/991 (28.9)	136/496 (27.4)	422/1487 (28.4)
Native Hawaiian or other Pacific Islander	6/991 (0.6)	5/496 (1.0)	11/1487 (0.7)
White	524/991 (52.9)	272/496 (54.8)	796/1487 (53.5)
Other or multiple categories	82/991 (8.3)	39/496 (7.9)	121/1487 (8.1)
Hemisphere of residence			
Northern	686/994 (69.0)	342/496 (69.0)	1028/1490 (69.0)
Southern	308/994 (31.0)	154/496 (31.0)	462/1490 (31.0)

* Data are for the intention-to-treat population.
† Race or ethnic group was reported by the parents or guardians. Each category includes participants whose parents or guardians selected only that category. "Other or multiple categories" includes participants whose parents or guardians indicated a category other than those listed or for whom more than one category was checked.

infection in the previous phase 2b trial[7] involving preterm infants was prespecified and was performed according to a multiplicity-protected hierarchical testing strategy (details are provided in the Supplementary Appendix and the protocol). Similar analytical methods were used for the secondary and exploratory efficacy end points. Confidence intervals for exploratory and post hoc analyses were not adjusted for multiplicity. The methods used for analyses of efficacy, the pooled analysis, the number needed to treat, and the handling of missing data are detailed in Sections S3 and S5.

RESULTS

POPULATION

Between July 23, 2019, and November 30, 2019, a total of 1027 participants were enrolled in the northern hemisphere and were followed through the 2019–2020 RSV season (Table S2). Between January 8, 2020, and March 15, 2020, a total of 462 participants were enrolled in South Africa and were followed through the expected 2020 season. One participant was enrolled in Japan on July 2, 2020, before enrollment was paused as a result of the coronavirus disease 2019 (Covid-19) pandemic. In total, 1490 participants underwent randomization in the primary cohort, and 1478 (99.2%) received an injection (987 received nirsevimab and 491 received placebo). Overall, 1465 participants (98.3%) completed 150 days of follow-up, and 1367 participants (91.7%) completed 360 days of follow-up (Fig. S2).

The trial population included predominantly healthy infants who were born at term (86.0%); the median age was 2.60 months (range, 0.03 to 11.10 months). Four infants (0.3%) had serious

Table 2. Medically Attended Lower Respiratory Tract Infections and Hospitalizations Associated with Respiratory Syncytial Virus (RSV) through 150 Days after the Injection.*

End Point and Analysis	Nirsevimab (N=994)	Placebo (N=496)	Efficacy (95% CI)†	P Value
	no. (%)			
Medically attended RSV-associated lower respiratory tract infection			74.5 (49.6 to 87.1)	<0.001
Poisson regression with robust variance				
Observed events	12 (1.2)	25 (5.0)		
Participants with imputation of data‡	15 (1.5)	6 (1.2)		
Hospitalization for RSV-associated lower respiratory tract infection			62.1 (−8.6 to 86.8)	0.07
Poisson regression with robust variance				
Observed events	6 (0.6)	8 (1.6)		
Participants with imputation of data‡	15 (1.5)	6 (1.2)		

* Data are for the intention-to-treat population.
† Efficacy was defined as the relative risk reduction (calculated as 1 minus the relative risk, where the relative risk was estimated with the use of a Poisson regression model with robust variance) in the nirsevimab group as compared with the placebo group and is expressed as a percentage.
‡ Data were imputed for participants who had no events and were not followed through 150 days after the injection.

and stable underlying diseases: one had cystic fibrosis, and three had Down's syndrome. Baseline characteristics were similar in the two groups (Table 1). The participants were representative of the global RSV patient population (Table S3).

EFFICACY AND END POINTS

Medically attended RSV-associated lower respiratory tract infection occurred in 12 of 994 infants (1.2%) in the nirsevimab group and in 25 of 496 infants (5.0%) in the placebo group. These findings correspond to an efficacy of 74.5% (95% confidence interval [CI], 49.6 to 87.1; P<0.001 by Poisson regression) for nirsevimab; therefore, significance with respect to the primary end point was shown (Table 2). Signs of clinical severity in cases that met the criteria for the primary end point are summarized in Table S4. The results of a time-to-event analysis showed that infants who received nirsevimab had a lower risk of medically attended RSV-associated lower respiratory tract infection than those who received placebo (hazard ratio, 0.23; 95% CI, 0.12 to 0.47) (Fig. 1). Of the 37 infants with RSV-associated lower respiratory tract infection, 33 (12 in the nirsevimab group and 21 in the placebo group) were infected with RSV A, and 4 infants (all in the placebo group) were infected with RSV B. No clinical RSV isolates identified in either group had decreased in vitro susceptibility to nirsevimab (Table S5). Participants from South Africa contributed no events to the primary efficacy estimate because of a low incidence of RSV during the Covid-19 pandemic[11]; howev-

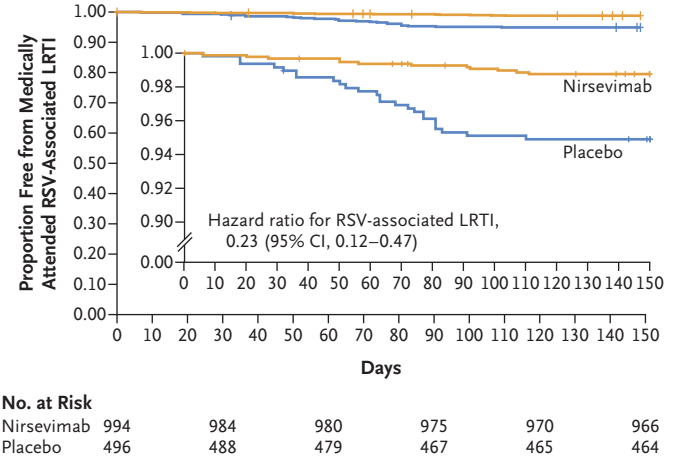

Figure 1. Lower Respiratory Tract Infections (LRTIs) Associated with Respiratory Syncytial Virus (RSV).

Shown are Kaplan–Meier curves from a time-to-event analysis of the proportion of participants in the intention-to-treat population who were free from a medically attended RSV-associated LRTI. The hazard ratio and corresponding 95% confidence interval were obtained from a stratified proportional-hazards model with the stratification factor of age at randomization. The confidence interval was not adjusted for multiplicity. Tick marks indicate censored data. The inset shows the same data on an enlarged y axis.

Table 3. Outcomes through 150 Days after the Injection.*

Outcome	Nirsevimab (N=686)	Placebo (N=342)	Efficacy (95% CI)†	Cases Averted per 1000 Infants Treated (95% CI)‡	Number Needed to Treat (95% CI)§
	no. (%)				
Medically attended RSV-associated lower respiratory tract infection on any test result¶	17 (2.5)	37 (10.8)	77.0 (59.8 to 86.8)	83.4 (62.0 to 105.0)	12 (10 to 17)
Medically attended RSV-associated lower respiratory tract infection on central test result¶	15 (2.2)	33 (9.6)	77.2 (58.7 to 87.5)	74.7 (53.0 to 95.0)	14 (11 to 19)
Medically attended lower respiratory tract infection of any cause¶	60 (8.7)	62 (18.1)	51.5 (32.6 to 65.2)	93.6 (63.0 to 124.0)	11 (9 to 16)
Hospitalization for any respiratory illness due to RSV on any test result	9 (1.3)	11 (3.2)	59.0 (2.1 to 82.9)	19.0 (5.5 to 32.0)	53 (32 to 182)
Hospitalization for any respiratory illness due to RSV on central test result	7 (1.0)	9 (2.6)	61.1 (–3.7 to 85.4)	16.1 (4.5 to 28.0)	62 (36 to 223)
Hospitalization for any respiratory illness of any cause	16 (2.3)	14 (4.1)	42.8 (–15.8 to 71.7)	17.7 (2.0 to 33.0)	57 (31 to 500)

* Data are for participants in the northern hemisphere in the intention-to-treat population. Any test result refers to either the central reference test for the trial or a local test performed in the context of clinical care. Any respiratory illness included both upper and lower respiratory tract infections.

† Efficacy was defined as the relative risk reduction (calculated as 1 minus the relative risk, where the relative risk was estimated with the use of a Poisson regression model) in the nirsevimab group as compared with the placebo group and is expressed as a percentage. The efficacy and 95% confidence intervals were estimated on the basis of Poisson regression with robust variance with the use of only the term of trial-group assignment.

‡ The number of cases averted was calculated as the difference in the estimated number of cases between nirsevimab and placebo and expressed per 1000 infants treated. The 95% confidence intervals were estimated with the use of bootstrapping, with the 2.5 and 97.5 percentiles of 1000 replicates obtained by sampling participants, and were not adjusted for multiplicity.

§ The number needed to treat to avert one case of RSV-associated lower respiratory tract infection was calculated as the reciprocal of the difference in risk between the nirsevimab group and the placebo group.

¶ Included are medically attended lower respiratory tract infections, regardless of whether they met the criteria for the definition used for the primary end point.

er, unseasonal RSV transmission began after day 151, with 12 cases occurring up to day 361 (in 6 of 308 infants [1.9%] in the nirsevimab group and in 6 of 154 [3.9%] in the placebo group) (Fig. S3). One case (in the nirsevimab group) occurred in the northern hemisphere on day 165.

Through 150 days after the injection, 6 of 994 infants (0.6%) in the nirsevimab group and 8 of 496 (1.6%) in the placebo group were hospitalized for RSV-associated lower respiratory tract infection (estimated efficacy, 62.1%; 95% CI, –8.6 to 86.8; P=0.07 by Poisson regression) (Table 2). Hospitalization for any respiratory illness due to RSV (including cases detected by local testing sites) occurred in 9 of 994 infants (0.9%) in the nirsevimab group and in 11 of 496 (2.2%) in the placebo group (estimated efficacy, 59.0%; 95% CI, 1.8 to 82.9). Data on health care use associated with hospitalization are provided in Table S6. The results of a prespecified pooled analysis that compared data from preterm infants who received the assigned regimen in the previous trial[7] with data from the infants in the intention-to-treat population in this trial showed an efficacy of 77.3% (95% CI, 50.3 to 89.7; P<0.001) for nirsevimab against hospitalization for RSV-associated lower respiratory tract infection through 150 days after the injection (Table S7).

Subgroup analyses according to age at randomization, sex, race, weight, and gestational age showed consistent efficacy favoring nirsevimab. However, relatively lower estimates of efficacy were observed among infants who were younger (≤3.0 months vs. >3.0 months of age) and weighed less (<5 kg vs. ≥5 kg) (Fig. S4).

A typical RSV season was seen in the north-

ern hemisphere before the Covid-19 pandemic became established, which allowed a prespecified exploration of the effect of nirsevimab (the number needed to treat). With respect to the primary end point of medically attended RSV-associated lower respiratory tract infection, 55.8 cases (95% CI, 38.0 to 73.0) were averted for every 1000 infants treated. With respect to the secondary end point of hospitalization for RSV-associated lower respiratory tract infection, 14.7 cases (95% CI, 4.0 to 25.0) were averted for every 1000 infants treated. In a post hoc analysis, the number of cases of lower respiratory tract infection of any cause that were averted was estimated to be 93.6 (95% CI, 63.0 to 124.0), and the number of hospitalizations for respiratory illness of any cause that were averted was estimated to be 17.7 (95% CI, 2.0 to 33.0). The results for the end points of efficacy and the corresponding numbers needed to treat are provided in Table 3.

PHARMACOKINETICS

Serum concentrations of nirsevimab decreased linearly over time (Fig. S5). The mean (±SD) half-life of nirsevimab was 68.7±10.9 days. On day 151, mean nirsevimab serum concentrations were 19.6±7.7 μg per milliliter among infants who weighed less than 5 kg and 31.2±13.7 μg per milliliter among infants who weighed 5 kg or more. Four infants in the nirsevimab group had no quantifiable serum concentrations at any time point, of which one had a medically attended RSV-associated lower respiratory tract infection that resulted in hospitalization. The reasons for the absence of detectable nirsevimab in these infants are unclear; however, errors in administration of the injection cannot be ruled out.

ANTIDRUG ANTIBODIES

Among infants with data available to day 361, antidrug antibodies were detected after baseline in 58 of 951 infants (6.1%) in the nirsevimab group and in 5 of 473 (1.1%) in the placebo group. When antidrug antibodies to nirsevimab were present, the first detection was most frequently on day 361; however, sampling was infrequent. There was no evidence of an effect of antidrug antibodies on nirsevimab pharmacokinetics through day 151, since observed serum nirsevimab concentrations were similar between participants who tested positive for antidrug antibodies and those who tested negative. On day 361, serum nirsevimab concentrations were generally lower among infants with antidrug antibodies than among those who tested negative for antidrug antibodies, and more infants who had antidrug antibodies had a nirsevimab concentration below the limit of quantification than those in whom antibodies were not detected. This finding indicates that antidrug antibodies had an influence on nirsevimab pharmacokinetics between days 151 and 361. Antidrug antibodies were detected in 2 of 12 infants in the nirsevimab group who had a medically attended RSV-associated lower respiratory tract infection during the 150-day period after the injection (both infants had a titer of 1:400 on day 151).

SAFETY AND ADVERSE-EVENT PROFILE

The types and frequencies of adverse events that occurred during the trial were similar in the two groups (Tables 4 and S8). Most adverse events were grade 1 or 2 in severity. Adverse events of grade 3 or higher severity were reported in 36 of the 987 infants (3.6%) who received nirsevimab and in 21 of the 491 infants (4.3%) who received placebo. The incidence of adverse events that occurred within 1 day after the injection was low (1.8% among nirsevimab recipients and 0.6% among placebo recipients); all events were of grade 1 severity and were managed with over-the-counter treatments by the parents or guardians. The incidence of adverse events within 7 days after the injection was similar in the two groups (13.4% in the nirsevimab group and 12.8% in the placebo group) (Table 4). Within 7 days after the injection, adverse events in the MedDRA system organ class of general disorders and administration-site conditions occurred in 0.6% of nirsevimab recipients (6 infants) and in 0.4% of placebo recipients (2 infants) and included pyrexia (in 1 infant who received nirsevimab and in 2 infants who received placebo [all events were nonserious and were of grade 1 severity]), discomfort (in 2 infants), and local injection-site pain or swelling (in 3 infants).

Serious adverse events were reported in 6.8% of nirsevimab recipients (67 infants) and in 7.3% of placebo recipients (36 infants). Three deaths occurred through day 361 (all among nirsevimab recipients on or after day 140) (Section S6). One death of unknown cause occurred on day 140 in an infant with failure to thrive. On the basis of reported adverse events of re-

Table 4. Adverse Events That Occurred through 360 Days after the Injection.*

Variable	Nirsevimab (N=987)	Placebo (N=491)	Total (N=1478)
		no. of participants (%)	
Any adverse event	863 (87.4)	426 (86.8)	1289 (87.2)
Considered to be related to the trial regimen	10 (1.0)	7 (1.4)	17 (1.2)
Occurred ≤1 day after the injection	18 (1.8)	3 (0.6)	21 (1.4)
Occurred ≤3 days after the injection	56 (5.7)	23 (4.7)	79 (5.3)
Occurred ≤7 days after the injection	132 (13.4)	63 (12.8)	195 (13.2)
Adverse event of grade ≥3 severity	36 (3.6)	21 (4.3)	57 (3.9)
Adverse event that resulted in death	3 (0.3)	0	3 (0.2)
Serious adverse event†	67 (6.8)	36 (7.3)	103 (7.0)
Considered to be related to the trial regimen	0	0	0
Adverse event of special interest‡	1 (0.1)	0	1 (0.1)
Adverse event related to Covid-19	7 (0.7)	7 (1.4)	14 (0.9)
Confirmed case of Covid-19§	6 (0.6)	6 (1.2)	12 (0.8)
Adverse event suspected to be related to Covid-19¶	1 (0.1)	1 (0.2)	2 (0.1)

* Data are for the as-treated population. Events that occurred 361 days or more after the injection were excluded. Follow-up for one participant was ongoing and had not reached day 361 at the time of data cutoff. Participants with multiple events in the same category are counted once in that category. Participants with events in more than one category are counted once in each of those categories. Grade 3 events were considered severe, grade 4 events life-threatening, and grade 5 events fatal. Causality was determined by investigator assessment. Covid-19 denotes coronavirus disease 2019.
† Serious adverse events were those that resulted in death, were life-threatening, led to hospitalization or prolongation of hospitalization, caused persistent or clinically significant disability or incapacity, or were deemed to be an important medical event.
‡ Adverse events of special interest were hypersensitivity, immune-complex disease, and thrombocytopenia and were reported on the basis of investigator assessment.
§ Confirmed cases of Covid-19 included positive asymptomatic or symptomatic cases.
¶ Suspected cases of Covid-19 included those for which signs and symptoms were judged by the investigator to be highly suggestive of Covid-19 but for which results from a confirmatory diagnostic test were unavailable or were negative.

current vomiting, hypoglycemia, and anemia, the investigator suspected an underlying chronic illness that was undiagnosed before death. Two deaths (on days 143 and 338) were attributed to gastroenteritis in infants who did not have a health care visit for the illness. None of the serious adverse events, including the deaths, were considered by the investigators to be related to nirsevimab or placebo. A single adverse event of special interest was reported: one nirsevimab recipient had a grade 3 generalized macular rash without any systemic features 6 days after the injection, which required no treatment and resolved after 20 days; the investigator considered this event to be related to nirsevimab (Section S6). No anaphylaxis or other serious hypersensitivity reactions were reported. The safety profile of nirsevimab among recipients who were positive for antidrug antibodies after baseline was similar to that among recipients without antidrug antibodies.

DISCUSSION

In this phase 3 trial, a single fixed dose of the monoclonal antibody nirsevimab provided protection against medically attended RSV-associated lower respiratory tract infection when given to healthy late-preterm and term infants before an RSV season. The results were consistent with those from a trial involving preterm infants that showed that the incidence of medically attended RSV-associated lower respiratory tract infection was 70.1% lower (95% CI, 52.3 to 81.2) with nirsevimab prophylaxis than with placebo.[7] No safety concerns were identified, and an adverse event thought to be related to nirsevimab or placebo occurred in 1% of infants.

We assessed efficacy against RSV-associated hospitalization using complementary case definitions — one corresponded to the cases that met the criteria for the primary end point of medically attended RSV-associated lower respiratory tract infection and another included cases of upper and lower respiratory tract infection and RSV, confirmed by local or central testing sites (Table S9). The efficacy point estimates from the two definitions were similar, but the additional cases identified with the use of the more inclusive definition increased the precision of the estimate. The results of a prespecified pooled analysis of the current trial and the previous trial[7] that assessed the efficacy of nirsevimab against hospitalization for RSV in preterm infants and used a multiplicity-protected hierarchical testing strategy showed an efficacy of 77.3%.

Pharmacokinetic data show that nirsevimab levels associated with protection in preclinical studies[6] are maintained through 150 days after administration across age and weight subgroups. Furthermore, the case differential in RSV-associated lower respiratory tract infection after day 151 in South African participants — who remained unexposed to RSV until day 151 because of the Covid-19 pandemic — supports the hypothesis that efficacy extends beyond 5 months.[11] Antidrug antibodies tended to develop later and did not affect nirsevimab pharmacokinetics over the RSV season; however, their influence on subsequent administration is unknown. The MEDLEY trial (ClinicalTrials.gov number, NCT03959488) involves cohorts receiving nirsevimab in consecutive RSV seasons and may provide insights into this important question.

We observed relatively lower efficacy among infants who were 3.0 months of age or younger or who weighed less than 5 kg at the time of the injection. This finding may reflect variability associated with small numbers, as suggested by overlapping confidence intervals. Because body weight correlates with age, it is also possible that shared factors may explain the lower observed efficacy among these infants. Although there was a tendency for higher mean serum nirsevimab levels among infants who received 100 mg, there was a large overlap in serum levels with infants who received 50 mg. Nirsevimab levels among participants with breakthrough cases before day 151 were similar to those among other participants, except for one participant who had undetectable levels at all time points. We intend to further explore the dose–response relationship by pooling data across studies.

The results of the post hoc analysis of medically attended lower respiratory tract infections of any cause suggested potential efficacy. The additional cases of averted medically attended lower respiratory tract infection beyond those ascribed to RSV may be explained by the underdetection of RSV cases because of missing samples. In addition, prevention of RSV may have an add-on effect, since RSV-associated lower respiratory tract infection in infancy has been associated with the occurrence of subsequent non–RSV-associated lower respiratory tract infection.[12,13]

In the northern hemisphere, in a post hoc analysis of lower respiratory tract infection of any cause, the number needed to treat to prevent one case of lower respiratory tract infection of any cause was 11 (95% CI, 9 to 16), and the number needed to treat to prevent one hospitalization for respiratory illness of any cause was 57 (95% CI, 31 to 500). This result is consistent with projected estimates for RSV monoclonal antibodies with extended half-lives[14] and compares favorably with routinely recommended pediatric vaccines.[15-17] Although the number needed to treat is subject to limitations, it provides perspective for public health decision making.[18,19]

Because of the Covid-19 pandemic,[20] a lockdown in South Africa in late March coincided with abrupt termination of RSV circulation until November 2020.[11,21] MedImmune/AstraZeneca paused enrollment globally and amended the protocol in consultation with health authorities to enable the primary analysis to be performed with the accumulated efficacy and safety data. Given that the target enrollment was not reached, the trial had less power than originally planned to evaluate the efficacy of nirsevimab with respect to preventing hospitalizations or the difference in efficacy in subgroups. Although Covid-19 and associated control measures and behavioral alterations appear to have affected the observed RSV disease rates in the northern hemisphere toward the end of the 2019–2020 season, the overall incidence was within the expected range.[22]

There is a serious unmet medical need for RSV protection in healthy infants born at term.

There are currently three approaches at various stages of clinical development: direct administration of antibodies to the infant, passive antibody acquired from maternal vaccination in pregnancy, and active vaccination of infants.[23] A recent phase 3 trial that evaluated maternal vaccination using an RSV F protein nanoparticle did not show significance with respect to the primary end point; the reported efficacy against medically significant RSV-associated lower respiratory tract infection was 39.4% (97.52% CI, –1.0 to 63.7).[24]

Nirsevimab, a monoclonal antibody against RSV with an extended half-life, is efficacious in preventing medically attended RSV-associated lower respiratory tract infection in healthy late-preterm and term infants.

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