ORIGINAL ARTICLE

Clesrovimab for Prevention of RSV Disease in Healthy Infants

Heather J. Zar, M.D., Ph.D.,[1] Eric A.F. Simões, M.B., B.S., M.D., D.C.H.,[2] Shabir A. Madhi, M.B., B.Ch., Ph.D.,[3] Octavio Ramilo, M.D.,[4] Shelly D. Senders, M.D.,[5] Julie S. Shepard, M.D., M.P.H.,[6] Kamolwish Laoprasopwattana, M.D.,[7] Jorge Piedrahita, M.D.,[8] Jose M. Novoa, M.D.,[9] Sergio L. Vargas, M.D.,[10] Marc Dionne, M.D.,[11] Teresa Jackowska, M.D.,[12] Enmei Liu, M.D.,[13] Yasunori Ishihara, M.D., Ph.D.,[14] Kazushige Ikeda, M.D.,[15] Ying Zhang, Ph.D.,[16] Radha A. Railkar, Ph.D.,[16] Jeannine Lutkiewicz, B.S.,[16] Kalpit A. Vora, Ph.D.,[16] Xiaowei Zang, Ph.D.,[16] Brian M. Maas, Pharm.D.,[16] Andrew W. Lee, M.D.,[16] Andrea Guerra, M.D.,[17] and Anushua Sinha, M.D., M.P.H.,[16] for the CLEVER (MK-1654-004) Study Group*

ABSTRACT

BACKGROUND

Clesrovimab is a long-acting investigational monoclonal antibody against site IV of the respiratory syncytial virus (RSV) fusion protein. Data regarding the safety and efficacy of clesrovimab in healthy infants are needed.

METHODS

We randomly assigned healthy preterm and full-term infants entering their first RSV season in a 2:1 ratio to receive one intramuscular 105-mg dose of clesrovimab or placebo. The primary efficacy end point was RSV-associated medically attended lower respiratory infection (including at least one indicator of lower respiratory infection or disease severity) through 150 days after injection. A key secondary efficacy end point was RSV-associated hospitalization during the same period.

RESULTS

A total of 3614 infants received an injection: 2412 infants received clesrovimab, and 1202 infants received placebo. Through day 150 after injection, RSV-associated medically attended lower respiratory infection occurred in 60 of 2398 infants in the clesrovimab group (incidence rate over 5-month period, 2.6%) and in 74 of 1201 infants in the placebo group (incidence rate over 5-month period, 6.5%), for an efficacy of 60.4% (95% confidence interval [CI], 44.1 to 71.9; P<0.001). RSV-associated hospitalization within 150 days was reported in 9 of 2398 infants in the clesrovimab group and in 28 of 1201 infants in the placebo group, for an efficacy of 84.2% (95% CI, 66.6 to 92.6; P<0.001). Serious adverse events were reported in 278 of 2409 infants (11.5%) in the clesrovimab group and 149 of 1202 infants (12.4%) in the placebo group.

CONCLUSIONS

In healthy preterm and full-term infants, a single dose of clesrovimab reduced the incidence of RSV-associated medically attended lower respiratory infection and RSV-associated hospitalization, with a safety profile similar to that of placebo. (Funded by Merck Sharp and Dohme; CLEVER ClinicalTrials.gov number, NCT04767373.)

Author affiliations are listed at the end of the article. Anushua Sinha can be contacted at anushua.sinha@merck.com or at Clinical Research, Merck, 126 E. Lincoln Ave., Rahway, NJ 07065.

*The investigators in the CLEVER (MK-1654-004) study group are listed in the Supplementary Appendix, available at NEJM.org.

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Among infants younger than 1 year of age, respiratory syncytial virus (RSV) causes an estimated 12.9 million lower respiratory infections and approximately 2.2 million hospitalizations per year worldwide.[1] RSV is a leading cause of infant hospitalization in high-income countries and is a frequent cause of infant deaths in low- and middle-income countries.[1] Preterm infants and those with underlying medical conditions are predisposed to severe RSV infection,[2] but the majority of RSV hospitalizations occur in full-term healthy infants.[3] The burden of severe RSV infection is highest during the first 6 months after birth,[1] when prevention is needed. Recently, two RSV preventive therapies — the monoclonal antibody nirsevimab (Beyfortus, Sanofi)[4,5] and the maternal bivalent prefusion F vaccine (ABRYSVO, Pfizer)[6] — have been licensed for use in infants.

Clesrovimab is a human RSV monoclonal antibody with three amino acid substitutions (M252Y, S254T, and T256E, collectively referred to as YTE)[7] in the Fc portion. Clesrovimab binds site IV of the RSV fusion (F) protein,[8] which differs from the RSV antibodies palivizumab (site II) and nirsevimab (site Ф). Site IV is present on prefusion and postfusion conformations of the F protein, whereas site Ф is present on the prefusion conformation only.[9] The availability of RSV antibodies with different binding sites may mitigate the risk of viral resistance. Surveillance studies have shown that site IV is highly conserved,[10-14] which makes it an attractive prophylactic target because this conservation reduces the potential of viral escape. An analysis of more than 15,000 A and B sequences of RSV in GenBank showed that the binding epitope for clesrovimab was conserved with 99.8% identity.[15] Clesrovimab also has high tissue distribution and concentration in the nasal compartment.[16]

In a phase 1b–2a ascending-dose study involving infants, investigators found that clesrovimab had a safety profile similar to that of placebo and a half-life of approximately 45 days, which is amenable to administration once per RSV season.[17] We performed the phase 2b–3 CLEVER (Efficacy and Safety of Clesrovimab in Infants [MK-1654-004]) trial to evaluate the efficacy and safety of one 105-mg dose of clesrovimab in healthy preterm and full-term infants entering their first RSV season.

METHODS

TRIAL DESIGN AND PARTICIPANTS

We conducted this double-blind, randomized, placebo-controlled trial in 22 countries (Section S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The participants were healthy infants under the chronologic age of 1 year who had been born either early or moderately preterm (gestational age, 29 weeks to 34 weeks 6 days) or late preterm or full-term (gestational age, ≥35 weeks), as shown in Figure S1 and described in the protocol (available at NEJM.org).

A Quick Take is available at NEJM.org

Key exclusion criteria were a recommendation that the infant receive palivizumab, a recent history of febrile illness, and any previous preventive RSV treatment. Palivizumab is licensed in many countries for infants at increased risk for severe RSV disease, including those born at a gestational age of less than 35 weeks and those with coexisting conditions such as chronic lung disease of prematurity and hemodynamically significant congenital heart disease. Infants who were eligible to receive palivizumab according to local guidelines were excluded from the current trial but were evaluated in the separate phase 3 SMART (MK-1654-007) trial, as described in a report now published in the *Journal*.[18] A full list of the inclusion and exclusion criteria is provided in Section S2 and the protocol.

The infants were randomly assigned in a 2:1 ratio to receive a 105-mg intramuscular injection of clesrovimab or placebo. All the infants were stratified according to gestational age, chronologic age, and geographic hemisphere. We conducted surveillance for respiratory infection during RSV season 1 (through day 180 after injection) and season 2 (days 365 to 515 in infants who were followed to day 515) (Section S3). This report includes complete efficacy data for the trial; safety follow-up is reported through at least 240 days after injection for all the infants.

OVERSIGHT

The trial was designed by representatives of Merck Sharp and Dohme, a subsidiary of Merck, with input from a scientific advisory committee composed of external experts. The trial was approved by the appropriate institutional review boards and regulatory agencies for each trial center. Written

informed consent was provided by each infant's parent or guardian. An independent external data monitoring committee provided safety oversight for the trial, including two planned interim analyses (Section S4). The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

END POINTS AND ADVERSE EVENTS

The primary efficacy end point was RSV-associated medically attended (inpatient or outpatient) lower respiratory infection that included at least one indicator of lower respiratory infection or one indicator of disease severity from days 1 to 150 after injection. The case definition that was used for the primary end point required confirmation of RSV infection on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay from a sample obtained within 7 days before or 12 days after symptom onset or worsening of symptoms, along with cough or difficulty breathing and at least one the following indicators of lower respiratory infection or disease severity: wheezing, chest-wall retractions, rales or crackles, hypoxemia, tachypnea, or dehydration caused by respiratory symptoms.[19-21]

The secondary efficacy end points were RSV-associated hospitalization from days 1 to 150 after injection and RSV-associated medically attended lower respiratory infection requiring at least one indicator of lower respiratory infection or disease severity from days 1 to 180 after injection. Tertiary end points are detailed in the trial protocol. A definition of RSV-associated medically attended lower respiratory infection that included at least one indicator of lower respiratory infection and at least one indicator of disease severity (i.e., two or more indicators in total), which was similar to the definition used in clinical trials of nirsevimab, was assessed post hoc (Section S5). Diagnostic criteria for each RSV-associated end point are described in detail in Table S2.

Safety and adverse events were primary trial end points. Anaphylaxis or hypersensitivity and rash were prespecified adverse events of special interest. Details regarding adverse-event reporting are provided in Section S3. Pharmacokinetics, serum neutralizing antibodies, and antidrug antibodies were analyzed by means of methods described previously[17] according to the blood-draw schedule outlined in Section S6.

STATISTICAL ANALYSIS

For the primary efficacy analysis, we estimated that a sample size of approximately 3300 participants would provide the trial with at least 95% power to show at least 25% greater efficacy with clesrovimab than with placebo (a significant difference) for the prevention of RSV-associated medically attended lower respiratory infection through day 150 (the primary efficacy end point). For the key secondary end point, the trial had more than 93% power to show significantly greater efficacy of clesrovimab than of placebo for the prevention of RSV-associated hospitalization through day 150. Both the primary and secondary analyses assumed an underlying efficacy of 70% at a one-sided type I error of 2.5%. The overall one-sided type I error in testing the efficacy hypotheses was controlled at 2.5%, given that the secondary hypothesis would be tested only if the primary hypothesis was successfully shown.

Efficacy analyses were performed in the full analysis population, which was defined as all the participants who had undergone randomization and received an injection of clesrovimab or placebo and were not excluded for certain protocol deviations. The estimated efficacy and 95% confidence intervals were calculated on the basis of modified Poisson regression with robust variance proposed by Zou,[22] including gestational age, geographic hemisphere, and chronologic age as covariates. For tertiary end points and subgroups, the model included only the trial-group assignment. If the model did not converge or if a confidence interval could not be estimated with the use of the modified Poisson method, an exact binomial method proposed by Chan and Bohidar,[23] along with Blaker's confidence interval,[24] was used.

Efficacy was calculated as 1 minus the relative risk (as estimated with the Poisson model) and is expressed as a percentage. Incidence rates were calculated as the number of cases during the follow-up period divided by the total follow-up time, multiplied by 5 to obtain the 5-month rate and by 6 to obtain the 6-month rate. The primary and secondary efficacy hypotheses were considered to have been met if the lower boundary of the two-sided 95% confidence interval was greater than 25% and 0%, respectively. The methods used for the calculation of the number needed to immunize and the handling of missing data are detailed in Sections S7 and S8.

Pharmacokinetic, antidrug antibody, and serum neutralizing antibody analyses were conducted in the per-protocol population, which consisted of participants who underwent randomization and received an injection of the correct clinical material (clesrovimab or placebo) corresponding to the assigned trial group. Participants with deviations from the protocol that could substantially affect the pharmacokinetic, antidrug antibody, or serum neutralizing antibody end points were excluded, or their specific data values after the deviation were excluded, from the per-protocol population.

Safety analyses were performed in the as-treated population, which included all the participants who had undergone randomization and received an injection of clesrovimab or placebo and were assessed according to the injection they actually received. Estimated differences and 95% confidence intervals for between-group differences in the percentage of participants with events were calculated with the Miettinen and Nurminen method.[25]

RESULTS

PARTICIPANTS

Of the 3632 infants who underwent randomization, 2421 were assigned to receive clesrovimab and 1211 to receive placebo. Of these infants, 3614 (99.5%) received an injection (Fig. S2). A total of 2412 infants received clesrovimab, including 1 who had been assigned to the placebo group but received clesrovimab, and 1202 infants received placebo. Three infants underwent randomization and received an injection at two different trial sites; they were counted each time in the assessment for eligibility and were given a unique randomization number at each site. These 3 infants were excluded from the efficacy, pharmacokinetic, antidrug antibody, serum neutralizing antibody, and safety analyses. Included in the primary efficacy analyses were 2398 infants (99.0%) in the clesrovimab group and 1201 infants (99.2%) in the placebo group (Table S3). The median age at enrollment was 3.1 months, with most of the infants (79.9%) under 6 months of age; 82.5% were late preterm or full-term infants. The characteristics of the infants were generally similar in the two trial groups (Table 1) and were representative of healthy infants at risk for RSV disease (Table S4).

EFFICACY

The efficacy of clesrovimab, as compared with placebo, against RSV-associated end points ranging from mild to severe disease through 150 days and 180 days after injection are shown in Figure 1A and 1B, respectively. In the first 150 days, RSV-associated medically attended lower respiratory infection (the primary end point) was diagnosed in 60 of 2398 infants in the clesrovimab group and in 74 of 1201 infants in the placebo group (efficacy, 60.4%; 95% confidence interval [CI], 44.1 to 71.9; P<0.001). During the same time period, RSV-associated hospitalization was reported in 9 of 2398 infants in the clesrovimab group and in 28 of 1201 infants in the placebo group (efficacy, 84.2%; 95% CI, 66.6 to 92.6; P<0.001).

In a post hoc analysis of RSV-associated medically attended lower respiratory infection that required at least one indicator of lower respiratory infection plus at least one indicator of disease severity from days 1 to 150, the estimate of efficacy was 88.0% (95% CI, 76.1 to 94.0).

The efficacy of clesrovimab increased across end points of increasing RSV disease severity and persisted through 180 days (Fig. 1). Kaplan–Meier graphs show a separation of clesrovimab and placebo groups through this period (Fig. 2 and Fig. S3). Through 180 days, the efficacy of clesrovimab was 91.7% (95% CI, 62.9 to 98.1) against RSV-associated severe medically attended lower respiratory infection and 91.2% (95% CI, 77.2 to 96.6) against hospitalization for RSV-associated lower respiratory infection.

The number of infants who would need to be immunized to prevent one case of RSV infection through day 150 ranged from 15 (95% CI, 11 to 21) for RSV-associated acute respiratory infection to 108 (95% CI, 60 to 226) for RSV-associated severe medically attended lower respiratory infection (Fig. 1).

Through day 150, hospitalization for lower respiratory infection of any cause was reported in 60 of 2398 infants in the clesrovimab group and in 58 of 1201 infants in the placebo group (efficacy, 49.0%; 95% CI, 26.7 to 64.5). During the same time period, inpatient or outpatient cases of medically attended lower respiratory infection of any cause were reported in 526 of 2398 infants in the clesrovimab group and in 296 of 1201 infants in the placebo group (vaccine efficacy, 13.1%; 95% CI, −0.6 to 24.8).

Table 1. Characteristics of the Infants at Baseline.*

Characteristic	Clesrovimab (N=2411)	Placebo (N=1203)	Total (N=3614)
Sex — no. (%)			
Male	1228 (50.9)	617 (51.3)	1845 (51.1)
Female	1183 (49.1)	586 (48.7)	1769 (48.9)
Age			
Mean — mo	3.7±2.6	3.7±2.6	3.7±2.6
Distribution — no. (%)			
<6 mo	1923 (79.8)	964 (80.1)	2887 (79.9)
6 to <9 mo	383 (15.9)	192 (16.0)	575 (15.9)
≥9 mo	105 (4.4)	47 (3.9)	152 (4.2)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	50 (2.1)	18 (1.5)	68 (1.9)
Asian	641 (26.6)	320 (26.6)	961 (26.6)
Black	326 (13.5)	171 (14.2)	497 (13.8)
Multiple	302 (12.5)	138 (11.5)	440 (12.2)
Native Hawaiian or other Pacific Islander	1 (<0.1)	1 (0.1)	2 (0.1)
White	1082 (44.9)	550 (45.7)	1632 (45.2)
Missing data	9 (0.4)	5 (0.4)	14 (0.4)
Hispanic or Latino ethnic group — no. (%)			
Yes	682 (28.3)	335 (27.8)	1017 (28.1)
No	1660 (68.9)	834 (69.3)	2494 (69.0)
Not reported, unknown, or missing data	69 (2.9)	34 (2.8)	103 (2.9)
Gestational age — no. (%)			
≥29 to <35 wk	422 (17.5)	209 (17.4)	631 (17.5)
≥35 wk	1989 (82.5)	994 (82.6)	2983 (82.5)
Geographic region			
Northern Hemisphere	1650 (68.4)	814 (67.7)	2464 (68.2)
Southern Hemisphere	761 (31.6)	389 (32.3)	1150 (31.8)
Climate in region			
Tropical or subtropical	459 (19.0)	233 (19.4)	692 (19.1)
Temperate	1952 (81.0)	970 (80.6)	2922 (80.9)
Body weight — kg	5.8±2.0	5.9±2.0	5.8±2.0
Body length — cm	59.2±7.6	59.3±7.5	59.2±7.5

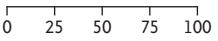
* Plus–minus values are means ±SD.
† Race and ethnic group were reported by the infants' parents or guardians. Data were reported as missing if a race or ethnic group that is not a standard category was reported on the health-report form.

RSV infections caused by RSV A and B subtypes were detected during the trial. The efficacy of clesrovimab across subtypes was consistent with the overall efficacy (Fig. S4).

The observed efficacy of clesrovimab relative to placebo was generally similar across subgroups according to gestational age, body weight, chronological age, and geographic hemisphere and was consistent with the efficacy for the overall population, as evidenced by the overlapping 95% confidence intervals (Fig. 3, Figs. S5 and S6, and Table S5). Although a few of the confidence intervals in this analysis had negative lower boundaries, these findings were due to the limited number of cases

A Efficacy through 150 Days (5 mo) after Injection

RSV-Associated End Point	End-Point Designation	Clesrovimab (N=2398)			Placebo (N=1201)			No. Needed to Immunize (95% CI)	Efficacy (95% CI)
		No. of cases	Total follow-up time	Incidence rate	No. of cases	Total follow-up time	Incidence rate		
			mo	*percent*		*mo*	*percent*		*percent*
Severe medically attended LRI	Tertiary	2	11,882.0	0.1	12	5906.4	1.0	108 (60–226)	91.7 (62.9–98.1)
Hospitalization for LRI	Tertiary	5	11,874.1	0.2	27	5862.8	2.3	48 (32–76)	90.9 (76.2–96.5)
Hospitalization	Secondary	9	11,864.8	0.4	28	5859.0	2.4	50 (33–84)	84.2 (66.6–92.6)
Medically attended LRI with ≥2 indicators of LRI or disease severity	Post hoc	10	11,855.2	0.4	41	5810.8	3.5	33 (24–48)	88.0 (76.1–94.0)
Medically attended LRI with ≥1 indicator of LRI or disease severity	Primary	60	11,685.6	2.6	74	5710.5	6.5	26 (18–42)	60.4 (44.1–71.9)
Acute respiratory infection	Tertiary	148	11,387.7	6.5	148	5467.3	13.5	15 (11–21)	52.0 (39.5–61.9)



B Efficacy through 180 Days (6 mo) after Injection

RSV-Associated End Point	End-Point Designation	Clesrovimab (N=2398)			Placebo (N=1201)			No. Needed to Immunize (95% CI)	Efficacy (95% CI)
		No. of cases	Total follow-up time	Incidence rate	No. of cases	Total follow-up time	Incidence rate		
			mo	*percent*		*mo*	*percent*		*percent*
Severe medically attended LRI	Tertiary	2	14,226.1	0.1	12	7072.2	1.0	108 (60–225)	91.7 (62.9–98.1)
Hospitalization for LRI	Tertiary	5	14,215.2	0.2	28	7012.7	2.4	46 (31–72)	91.2 (77.2–96.6)
Hospitalization	Tertiary	11	14,201.1	0.5	29	7007.8	2.5	50 (33–85)	81.3 (62.5–90.7)
Medically attended LRI with ≥2 indicators of LRI or disease severity	Post hoc	11	14,190.9	0.5	42	6947.5	3.6	32 (23–47)	87.2 (75.1–93.4)
Medically attended LRI with ≥1 indicator of LRI or disease severity	Secondary	64	13,970.8	2.7	77	6813.6	6.8	25 (18–40)	59.5 (43.3–71.1)
Acute respiratory infection	Tertiary	161	13,580.4	7.1	154	6495.0	14.2	15 (11–21)	50.0 (37.4–60.1)

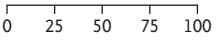


Figure 1. Efficacy of Clesrovimab for RSV-Associated End Points, According to Disease Severity.

The efficacy of clesrovimab is shown through 150 days (Panel A) and 180 days (Panel B) after injection. The primary efficacy end point was respiratory syncytial virus (RSV)–associated medically attended lower respiratory infection (LRI) that resulted in at least one indicator of LRI or disease severity from days 1 to 150 after injection. Secondary efficacy end points were RSV-associated hospitalization from days 1 to 150 after injection and RSV-associated medically attended LRI with at least one indicator of LRI or disease severity from days 1 to 180 after injection. For the primary, secondary, and post hoc end points for RSV-associated medically attended LRI, the model included the following prespecified covariates: geographic hemisphere at randomization, gestational age group, and age group at randomization. For tertiary end points of hospitalization for LRI, severe medically attended LRI, and acute respiratory infection, the model included only the trial-group assignment as a covariate. Incidence rates were calculated as the number of cases during the follow-up period divided by the total follow-up time, multiplied by 5 to obtain the 5-month rate and by 6 to obtain the 6-month rate. The number needed to immunize was defined as the number of infants who would need to be immunized to prevent one end-point event, calculated as the inverse of the product of efficacy and incidence rates. In Panel A, $P<0.001$ for the primary end point (RSV-associated medically attended LRI with ≥1 indicator of LRI or disease severity from days 1 to 150 after injection; lower boundary of the 95% CI, >25%) and the key secondary end point (RSV-associated hospitalization from days 1 to 150 after injection; lower boundary of the 95% CI, >0%).

in those subgroups, which led to large variability and thus to wide confidence intervals spanning 0.

The percentages of infants with non-RSV community respiratory infections from days 1 to 180 were similar in the two trial groups. The most common infections were human rhinovirus or enterovirus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Table S6).

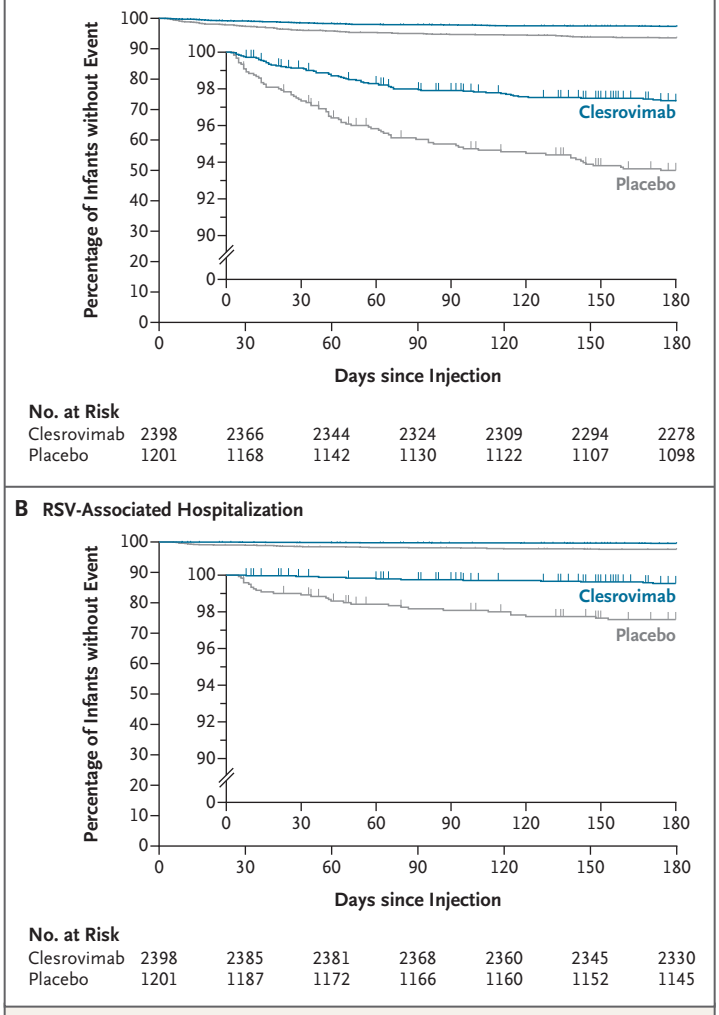


Figure 2. Time-to-Event Analyses.

Kaplan–Meier curves are shown for time-to-event analyses of the percentage of infants in the full-analysis population who were free from RSV-associated medically attended LRI with at least one indicator of LRI or disease severity through day 180 (Panel A) or RSV-associated hospitalization through day 180 (Panel B). Tick marks indicate censored data. The inset in each panel shows the same data on an expanded y axis.

In the absence of RSV prophylaxis in season 2, the incidence of RSV disease was similar across trial groups in that season (Section S9). The 5-month incidence rates of RSV-associated medically attended lower respiratory infection were 5.5% (95% CI, 4.1 to 7.1) for clesrovimab and 5.4% (96% CI, 3.5 to 7.9) for placebo.

PHARMACOKINETICS

Of the time points tested, the peak serum level of clesrovimab occurred on day 7 and declined over time (Fig. S7). At day 150, the geometric mean level of clesrovimab was 10.2 μg per milliliter (95% CI, 10.0 to 10.4) in the per-protocol population consisting of 2107 infants. The geometric mean level at day 150 was 11.7 μg per milliliter (95% CI, 11.3 to 12.0) among the 759 infants who weighed less than 5 kg and 9.4 μg per milliliter (95% CI, 9.2 to 9.7) among the 1348 infants who weighed 5 kg or more at the time of injection (Table S7).

ANTIDRUG ANTIBODIES

At day 150, positive results for antidrug antibodies were reported in 120 of 2112 evaluable infants (5.7%) in the clesrovimab group. Antidrug antibodies were not evaluated in the placebo group. The percentage of infants with positive results for antidrug antibodies increased over time (10.6% at 240 days, 36.0% at 365 days, and 55.3% at 515 days). Antidrug antibodies had no effect on the pharmacokinetics of clesrovimab or on serum neutralizing antibody titers during the efficacy follow-up period. Serum levels of clesrovimab and serum neutralizing antibody titers were similar across subgroups defined according to the presence or absence of antidrug antibodies on the basis of antibody status at day 150 (Figs. S8 and S9).

RSV F SEQUENCES

The RSV F protein was sequenced in samples obtained from infants with RSV infections. Through day 180, RSV with amino acid substitutions in the clesrovimab binding site with a variant allele frequency of at least 10% were identified in seven infants in the clesrovimab group and in one infant in the placebo group. Of those in the clesrovimab group, all the variants were at amino acid position 446 (three G446R, three G446E, and one G446W). One of these infants met the criteria for RSV-associated hospitalization; all the others had mild infections that did not meet the end-point criteria for RSV-associated medically attended lower respiratory infection or RSV-associated hospitalization.

SAFETY

The percentages of infants with adverse events were generally similar in the two trial groups (Table 2). The most common solicited injection-site adverse event was injection-site pain, and the most common solicited systemic adverse event was irritability. Most adverse events were grade 1 or 2

(Table S8). A low percentage (≤1.2%) of infants had a fever (≥102.2°F rectal or ≥101.7°F axillary) during the first 5 days.

The percentage of infants who had adverse events of special interest was less than 0.5% in each trial group (Table 2). All these events were nonserious and grade 1 or 2, except for one infant in the clesrovimab group who had a grade 3 event of urticaria on day 9 after injection, which resolved after 4 days. The infant also had a respiratory infection on day 7; neither the urticaria nor the respiratory infection was considered by the investigator to be related to clesrovimab. One adverse event of special interest — anaphylaxis or hypersensitivity (grade 2 bronchospasm) — occurred on day 3 after injection in the clesrovimab group, an event that was not considered by the investigator to be related to clesrovimab.

One serious adverse event that was considered by the investigator to be related to clesrovimab or placebo occurred in each trial group. An infant who received clesrovimab had an increased body temperature (maximum, 100.4°F) for less than 11 hours on day 4 after injection, for which the infant was hospitalized. In the placebo group, B-cell precursor acute lymphoblastic leukemia was diagnosed in an infant on day 3 after injection.

No adverse events of special interest were reported in infants who were positive for antidrug antibodies. The percentage of infants who had serious adverse events was similar among those with positive antidrug-antibody status (11.7%), those with negative antidrug-antibody status (11.9%), and those in the placebo group (12.4%) through day 365 in season 1, as were the percentages of patients with serious adverse events from days 365 to 515 in season 2 (2.9%, 3.4%, and 4.0%, respectively).

The incidence of death was similar in the two groups, in 7 of 2409 infants (0.3%) in the clesrovimab group and in 3 of 1202 infants (0.2%) in the placebo group. None of the deaths were considered by the investigator to be related to clesrovi-

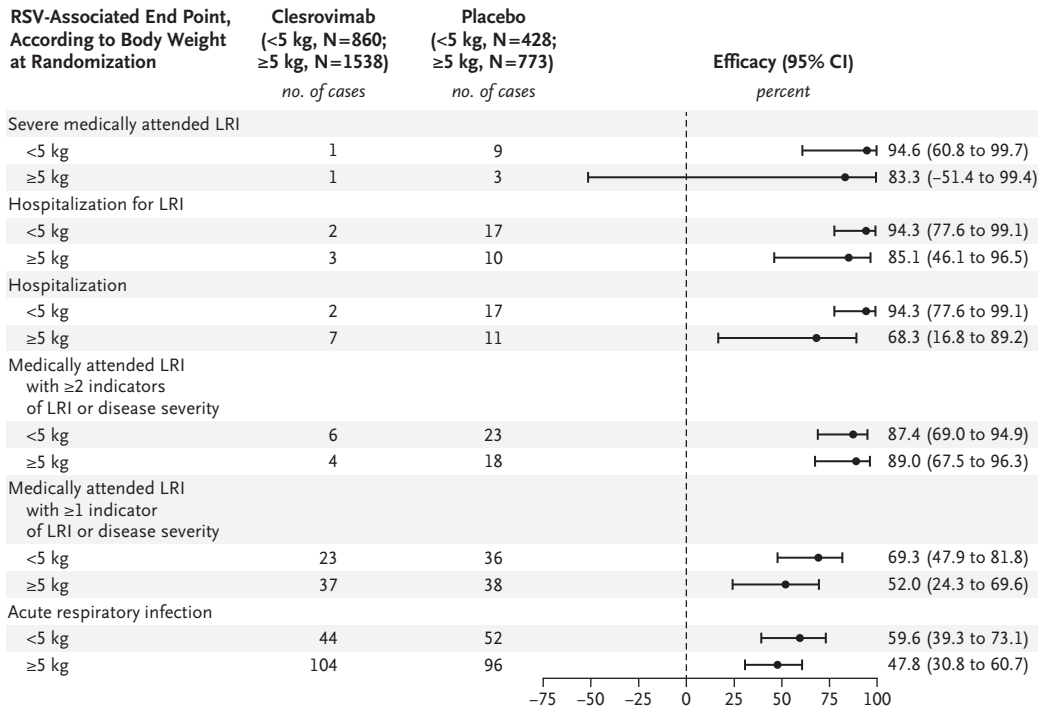


Figure 3. Efficacy of Clesrovimab through 150 Days after Injection for RSV-Associated End Points, According to Body Weight at Randomization.

The efficacy of clesrovimab is shown according to body-weight subgroups in the full analysis population. The model included only the trial-group assignment. If the model did not converge or if a confidence interval could not be estimated with the use of the modified Poisson method, an exact binomial method proposed by Chan and Bohidar,[23] along with Blaker's confidence interval,[24] was used.

Table 2. Adverse Events (Safety Population).*

Adverse Event	Clesrovimab (N = 2409)	Placebo (N = 1202)	Estimated Difference (95% CI)†
	no. of infants (%)		*percentage points*
Overall adverse events‡			
Any adverse event			
≥1 Adverse event	1816 (75.4)	918 (76.4)	−1.0 (−3.9 to 2.0)
Related to clesrovimab or placebo	587 (24.4)	296 (24.6)	−0.3 (−3.3 to 2.7)
Any serious adverse event	278 (11.5)	149 (12.4)	−0.9 (−3.2 to 1.3)
Related to clesrovimab or placebo	1 (<0.1)	1 (0.1)	0.0 (−0.4 to 0.2)
Death§	7 (0.3)	3 (0.2)	0.0 (−0.5 to 0.4)
Solicited adverse event or fever on days 1–5 after injection			
Injection-site reaction	223 (9.3)	117 (9.7)	−0.5 (−2.6 to 1.5)
Erythema	90 (3.7)	40 (3.3)	0.4 (−0.9 to 1.6)
Pain	122 (5.1)	77 (6.4)	−1.3 (−3.1 to 0.2)
Swelling	65 (2.7)	31 (2.6)	0.1 (−1.1 to 1.2)
Solicited systemic adverse event	631 (26.2)	337 (28.0)	−1.8 (−5.0 to 1.2)
Decreased appetite	106 (4.4)	61 (5.1)	−0.7 (−2.3 to 0.7)
Irritability	450 (18.7)	237 (19.7)	−1.0 (−3.8 to 1.7)
Somnolence	303 (12.6)	171 (14.2)	−1.6 (−4.1 to 0.7)
With fever	13 (0.5)	14 (1.2)	−0.6 (−1.4 to −0.0)
Adverse event of special interest on days 1–42 after injection			
Anaphylaxis or hypersensitivity	1 (<0.1)	0	0.0 (−0.3 to 0.2)
Rash	11 (0.5)	4 (0.3)	0.1 (−0.4 to 0.5)

* Safety analyses were performed in the as-treated population, which included all the participants who had undergone randomization and received an injection of clesrovimab or placebo, assessed according to the injection they actually received. Three participants underwent randomization and received an injection at two different trial sites and were excluded from the safety analyses. The relatedness of the adverse event to clesrovimab or placebo was determined by the investigator.

† Estimated differences and 95% confidence intervals were calculated with the Miettinen and Nurminen method.

‡ Reported adverse events include nonserious adverse events that occurred between day 1 and day 42 and serious adverse events that occurred between day 1 and day 365.

§ One death in the clesrovimab group that is included in this table occurred on day 487, outside the trial, in a participant who discontinued the trial on day 85.

mab or placebo or attributed to RSV. Details regarding deaths are provided in Section S10.

DISCUSSION

In this phase 2b–3 trial, a single 105-mg dose of clesrovimab protected healthy preterm and full-term infants against mild, moderate, or severe RSV disease. In addition, the estimated efficacy against hospitalization for lower respiratory infection of any cause was 49%. This finding provides a potential additional public health benefit because lower respiratory infection remains a predominant cause of infant hospitalization and death worldwide.[26] In addition, we observed no increased incidence or severity of RSV infection in the second RSV season in the clesrovimab group as compared with the placebo group. This finding aligns with previous findings that infants who are protected against RSV infection in their first RSV season do not have more severe disease when exposed to RSV thereafter.[27]

We evaluated a breadth of RSV-associated disease severity to describe the efficacy profile of clesrovimab. Efficacy increased with increasing severity of RSV-associated disease and was similar through 6 months as compared with through 5 months across end points. Protection through 6 months could allow for dosing flexibility relative to the onset of the RSV season. In addition, the non–weight-based dosing of clesrovimab offers simplicity of administration for health care providers and may reduce dosing errors.[28]

We observed efficacy against hospitalization for lower respiratory infection of any cause. The importance of RSV as a copathogen in childhood pneumonia has been shown with data obtained during the SARS-CoV-2 pandemic that indicated a significant reduction in hospitalization for all-cause pneumonia and pneumococcal bacteremia associated with pneumonia when RSV circulation was reduced.[29] RSV and pneumococcus may interact through several mechanisms,[30] which suggests that prevention of RSV infection may further reduce the incidence of lower respiratory infection beyond the direct effect on RSV infection.

The diagnostic criteria for medically attended lower respiratory infection that we used in the calculation of the primary end point were based on published literature and information from clinical studies, opinions of expert panels on RSV, and guidelines of the World Health Organization and Centers for Disease Control and Prevention.[19-21] Given the lack of standard diagnostic criteria for medically attended lower respiratory infection, it is challenging to directly compare the efficacy reported here against that of other prophylactic therapies. In the MELODY trial of nirsevimab involving healthy infants,[5] the primary end point required two or more indicators of lower respiratory infection and disease severity, which yielded approximately 74% efficacy. Using similar criteria in a post hoc analysis, we determined an efficacy of approximately 88% for clesrovimab. Caveats remain against comparing trial outcomes, including different populations, trial dates, surveillance procedures, and respiratory-symptom collection.

Among clesrovimab recipients, we observed seven RSV infections with a sequence variation in the clesrovimab binding site at position 446. Previously, sequence G446E was identified during in vitro testing[8] as having reduced neutralization by the parental antibody to clesrovimab, RB1, as compared with a laboratory reference strain. However, viral growth curves suggested reduced viral fitness. This cost to fitness suggests that these viruses are unlikely to have an increased growth-kinetics advantage over naturally occurring strains in vivo or become dominant with widespread use of clesrovimab. Additional work to evaluate G446R and G446W in vitro is ongoing.

We observed a low level of antidrug antibodies during the primary efficacy period with no apparent effect on pharmacokinetics, serum neutralizing antibodies, or safety. Most of the antidrug antibodies to clesrovimab have been shown to be toward the YTE half-life extending substitutions in the Fc portion of the antibody,[31] which are outside the active binding site. This factor may explain why the serum neutralization activity of clesrovimab was not affected by antidrug antibodies. The percentage of infants who were positive status for antidrug antibodies was higher at later time points than at day 150, as was also observed in our phase 1b–2a study.[31] A similar observation was reported in the MELODY trial of nirsevimab.[5] An analysis of data regarding antidrug antibodies from the phase 1b–2a study of clesrovimab showed that the development of antidrug antibodies at later time points was associated with RSV exposure, which resulted in both anti-RSV neutralizing titers and antidrug-antibody responses.[31] Adverse events that have been associated with antidrug antibodies, such as serious hypersensitivity reactions including anaphylaxis and serious skin hypersensitivity reactions, were not observed.

Overall, the adverse-event profile of clesrovimab was similar to that of placebo, with the most common adverse events being conditions commonly observed in infants in the trial age group. However, rare serious adverse events may not be detected in a trial of this size.

These findings show that clesrovimab, administered as one 105-mg dose before or during the first RSV season, provided protection against mild, moderate, and severe RSV disease in healthy preterm and full-term infants.

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AUTHOR INFORMATION

[1] Department of Pediatrics and Child Health and Medical Research Council Unit on Child and Adolescent Health, University of Cape Town, Cape Town, South Africa; [2] Children's Hospital Colorado and the University of Colorado School of Medicine, Aurora; [3] South African Medical Research Council: Vaccines and Infectious Diseases Analytics Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg; [4] St. Jude Children's Research Hospital, Memphis, TN; [5] Senders Pediatrics, Cleveland; [6] Ohio Pediatric Research Association, Dayton; [7] Prince of Songkla University, Songkhla, Thailand; [8] Clínica de la Costa, Barranquilla, Colombia; [9] Hospital Padre Alberto Hurtado, Santiago, Chile; [10] Biomedical Sciences Institute, University of Chile School of Medicine, Santiago; [11] Centre Hospitalier Universitaire de Québec–Université Laval, Québec City, Canada; [12] Center of Postgraduate Medical Education and Bielanski Hospital, Warsaw, Poland; [13] Children's Hospital of Chongqing Medical University, Chongqing, China; [14] Fukui Aiiku Hospital, Fukui, Japan; [15] Saitama City Hospital, Saitama, Japan; [16] Merck, Rahway, NJ; [17] MSD, London.

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