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A Phase 1b/2a Trial of a Half-life Extended Respiratory Syncytial Virus Neutralizing Antibody, Clesrovimab, in Healthy Preterm and Full-term Infants

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Background. Clesrovimab is an investigational monoclonal antibody with an extended half-life targeting site IV of the respiratory syncytial virus (RSV) fusion protein for the prevention of RSV disease in infants.

Methods. In this phase 1b/2a, double-blind study, 183 healthy preterm and full-term infants 2 weeks to 8 months of age were randomized 4:1 within 5 panels (preterm 20, 50, 75, or 100 mg; full-term 100 mg) to receive 1 dose of clesrovimab or placebo. The objectives were to evaluate safety, pharmacokinetics, serum neutralizing antibodies (SNA), and antidrug antibodies (ADA). The incidence of RSV-associated end points (medically attended lower respiratory tract infection, hospitalization, and acute respiratory infection) were also evaluated through 150 days postdose.

Results. The most common adverse event through day 14 was irritability; no treatment-related serious AEs were reported. Clesrovimab serum concentrations displayed a geometric mean apparent half-life of 44.9 days. Of participants receiving clesrovimab, 51 (36.7%) developed ADA with no apparent impact in pharmacokinetics. SNA titers increased in a dose-dependent manner at day 150. The incidences of RSV-associated end points were lower in infants treated with clesrovimab compared with placebo.

Conclusions. Clesrovimab was generally well tolerated and exhibited an extended half-life compared to typical IgG1 antibodies, supporting its ongoing development in late-stage trials.

Clinical Trial Registration. NCT03524118.

Keywords. RSV; clesrovimab; monoclonal antibody.

LAY SUMMARY

Respiratory syncytial virus (RSV) is a major cause of hospitalizations and death among infants. This is the first study of clesrovimab, an anti-RSV antibody, in infants. It was given as a single injection, in 4 different dose groups and compared to placebo. Clesrovimab was designed to have an extended half-life, meaning it stays in the body for longer than most antibodies. This prolonged presence could potentially provide an extended period of protection against RSV. The side effects reported after a single injection were similar across the placebo and clesrovimab dose groups. The half-life of clesrovimab was approximately 45 days, which is around 2 times longer than typical antibodies. These findings demonstrate that clesrovimab was generally well tolerated and may have potential as a single-dose preventive measure against RSV in infants. It is currently being studied in late-stage clinical trials.

Respiratory syncytial virus (RSV) is a common cause of respiratory infections resulting in substantial morbidity and mortality in infants and young children worldwide [1]. Two subtypes, RSV-A and RSV-B, circulate globally [2]. Infections typically exhibit a seasonal pattern where case counts rise following a decrease in temperature in temperate climates or during rainy seasons in tropical regions [3]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-based societal restrictions and their subsequent removal contributed to recent disruptions in patterns of RSV circulation [4].

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Many RSV infections present as mild or moderate upper respiratory illness. Those that progress to the lower respiratory tract may lead to more severe outcomes such as bronchiolitis, pneumonia, hospitalization, and sometimes death. Almost all children are infected with RSV within the first 2 years of life [5]. The highest risk factors for severe RSV disease include age under 6 months, premature birth, chronic lung disease, congenital heart disease, and immunocompromising conditions [6–8]. Severe RSV illness early in life is also associated with longer-term pulmonary sequalae, including asthma [9].

To address this disease burden in infants, significant advances have recently been made for 2 RSV prophylactic approaches. One is maternal immunization, in which an active vaccine against RSV is administered during late pregnancy resulting in transplacental RSV antibody transfer to the fetus [10]. In 2023, an RSV prefusion (F) bivalent vaccine (Abrysvo, Pfizer, New York, NY), was licensed for use in the United States and the European Union (EU) in pregnant individuals for the prevention of RSV disease in infants from birth through 6 months of age. Additionally, 2 prophylactic RSV-neutralizing antibodies are currently approved for pediatric use. Palivizumab (Synagis, MedImmune, Gaithersburg, MD) is a humanized antibody that binds to site II of the RSV F protein; it is administered as monthly injections and use is generally limited to the highest-risk children. In 2022 in the EU and 2023 in the United States, nirsevimab (Beyfortus, AstraZeneca, Cambridge, UK and Sanofi Pasteur, Paris, France), a half-life extended monoclonal antibody (mAb) targeting site Ø of RSV F, was approved for use in infants and children with once per RSV season dosing. While substantial progress has been made in pediatric RSV prevention, it would be beneficial to have an additional licensed RSV mAb with a different binding epitope given the potential for emergent viral variants. An RSV F site V antibody, suptavumab [11], was discontinued due to a circulating RSV B resistant variant. Furthermore, a few resistant viruses that have not widely circulated have been identified for nirsevimab [12].

Clesrovimab, derived from the fully human parental antibody RB1, is an RSV neutralizing antibody that targets site IV of the RSV F protein [13]. The antibody contains the 3 amino acid substitutions (YTE) in the Fc region, which extend the antibody half-life [14, 15]. The clesrovimab binding epitope is highly conserved with 99.8% identity among over 11 000 reported RSV A and RSV B sequences from GenBank. The antibody demonstrated in vitro equipotent neutralization against RSV A and B, with high potency against a wide breadth of clinical isolates [13]. Clesrovimab was generally well tolerated in 2 clinical studies in adults with an adverse event profile generally comparable to placebo and a demonstrated extended half-life of approximately 73–91 days [16, 17]. Here, we report the results of a single ascending dose study of clesrovimab in preterm and full-term infants.

METHODS

Study Design

This was a phase 1b/2a, double-blind, randomized, placebo-controlled single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics of clesrovimab in preterm and full-term infants (protocol 1654-002). The study was conducted at 26 sites in 6 countries (Chile, 2 sites; Colombia, 6 sites; Republic of Korea, 1 site; Spain, 2 sites; South Africa, 2 sites; and the United States, 13 sites) between September 2018 and September 2022.

The trial was designed to enroll approximately 180 participants randomized in a 4:1 ratio within 1 of 5 panels to receive an intramuscular injection of clesrovimab or placebo (0.9% sodium chloride, USP sterile saline) on day 1 (Supplementary Figure 1). The doses in panels A, B, C, and D were 20, 50, 75, and 100 mg of clesrovimab, respectively, administered to preterm infants. The dose for panel E was 100 mg administered to full-term infants. Randomization was performed centrally using an interactive response technology system. Randomization was stratified by weight (2 to 5 kg, and >5 kg) in panels B, C, and D. After participants had been randomized to a treatment group within a panel, they were further randomized to 1 of 4 blood sampling schedules (see details in Supplementary Material). Clesrovimab or placebo was prepared, dispensed, and administered by unblinded study personnel who were not involved in any subsequent participant assessments.

Clesrovimab drug concentration was 100 mg/mL. The 20-mg dose was administered as a single 0.2-mL injection, 50-mg dose was administered as a single 0.5-mL injection, 75-mg dose was administered as 0.5 mL in the right thigh and 0.25 mL in the left thigh, and the 100-mg dose was administered as 0.5 mL in each thigh. Placebo was administered as matched volume and regimen to the active drug within the panel.

To evaluate safety in the context of ascending doses there was at least a 14-day period after the last dosed participant in panel A, B, and C prior to administering the first dose in the next panel. The trial was designed with planned pause for a standing internal data monitoring committee meeting to evaluate available safety, tolerability, and pharmacokinetic (PK) data from panels A, B, and C prior to dosing of panels D and E. Participants in all panels were followed for at least 365 days after dosing for safety, PK, serum neutralizing antibody (SNA), and levels of antidrug antibodies (ADA). Additionally, participants enrolled in panels D and E prior to a protocol amendment (number 4) who chose to, and all participants enrolled in panels D and E after the protocol amendment, participated in a modified schedule in which they were followed through day 545 for safety, SNA, and ADA (termed panels D2 and E2, respectively).

The trial was conducted in conformance with Good Clinical Practices, approved by the appropriate institutional review boards and regulatory agencies. Written informed consent

was obtained from each participant's legally acceptable representative prior to any study procedure.

Participants

Healthy preterm (born at 29 weeks to 35 weeks gestational age) and full-term boys and girls (born at over 35 weeks gestational age) with an age of 2 weeks to 8 months and a minimum weight of 2 kg at the time of screening were eligible for enrollment. Good general health was based on screening of safety laboratory values, medical history, and physical examination. Key exclusion criteria included infants who were recommended to receive palivizumab per local standard of care, out-of-range safety laboratory results at screening, known hypersensitivity to any component of clesrovimab, immunodeficiencies, coagulation disorders, documented previous RSV infection, recent febrile illness, receipt of inactivated, subunit, or conjugate vaccines within the previous 14 days, or receipt of a live, attenuated vaccine (except for oral rotavirus and oral polio) within the previous 30 days. Additionally, infants who had prior administration of any vaccine or mAb for the prevention of RSV and those whose mother participated in RSV vaccine clinical study while pregnant (and participant was under 3 months of age) were ineligible.

Assessments

Adverse events (AEs) following receipt of study drug were recorded using an electronic diary and subsequently assessed and reported by the investigator. Any elevated body temperature, injection-site reactions (injection-site erythema, injection-site swelling, and injection-site pain), and systemic AEs (irritability, drowsiness, fever, and appetite loss) were solicited from days 1–5 after immunization and allergic reactions (hives or welts, lip swelling, wheezing, and difficulty breathing) were solicited from days 1–30 after immunization. Participants were followed for other unsolicited nonserious AEs on days 1–14 postdose and serious adverse events (SAEs) were collected from the time of signed consent through the end of study. All injection-site events were considered as treatment related; for systemic AEs, the investigator assessed relatedness to treatment.

Clesrovimab serum concentrations were measured using a validated liquid chromatography tandem mass spectrometry as described previously [16] with a lower limit of detection of 0.5 μg/mL. ADAs were measured using a validated electrochemiluminescence immunoassay [16] (refer to Supplementary Material for additional details on the ADA assay). PK and ADA were measured only in serum from participants who received clesrovimab. SNA against RSV A were measured using a cell-based qualified virus reduction neutralization test [18] in participants who received either clesrovimab or placebo.

Starting from day 14 until the end of the first RSV season, study sites conducted weekly RSV surveillance calls in which the participant's representative were asked about the presence of protocol-defined acute respiratory infection (ARI) symptoms (runny or stuffy nose, cough, fever, trouble feeding, respiratory tract congestion, difficult or labored breathing, wheezing, or chest wall indrawing). Participants with 2 or more symptoms for at least 2 days were evaluated for RSV assessment. In addition to the weekly phone calls, participant's representative was asked to contact the study site if 2 or more of the above symptoms were present for at least 2 days. Participants with suspected ARI were to be evaluated at the study site as soon as feasible and within 10 days of symptom onset. If respiratory symptoms were suggestive of RSV infection (as described above), a nasal swab was collected for reverse transcription-polymerase chain reaction (RT-PCR) for RSV A and B and other respiratory viruses. RSV-associated ARI was defined as the presence of any ARI symptoms (as described above) and a positive RSV detection by RT-PCR. RSV-associated medically attended lower respiratory infection (MALRI) was defined as the presence of cough or difficulty breathing, *and* 1 or more of the following: wheezing, chest wall indrawing/retractions, rales/crackles, hypoxemia (<95% on room air at sea level or <92% at altitude ≥1800 meters), tachypnea (breaths per minute, ≥60 for under 2 months of age, ≥50 for 2–12 months of age, and ≥40 for ≥12–24 months of age), *and* an RSV-positive RT-PCR nasopharyngeal sample.

Statistical Analyses

This was a phase 1b/2a trial and no formal hypothesis testing was planned. Safety data were summarized descriptively using the all participants as treated population, defined as all randomized participants who received study intervention, using the group corresponding to the clinical material they actually received. PK, ADA, and SNA were analyzed using the per-protocol population, defined as all randomized participants with exclusion for important protocol deviations that could substantially affect results. Results from samples obtained outside of the protocol-defined windows were excluded from the analyses. Estimation of efficacy was a prespecified exploratory end point performed using the full analysis set, defined as all randomized participants who received 1 dose of study treatment, where the study treatment corresponds to study treatment they were randomized to.

Sparse PK collection was protocol stipulated to minimize the blood draw burden in the infant population. Therefore, population PK modeling was used to characterize the PK of clesrovimab. A 2-compartment model with first-order absorption and elimination best described the serum concentrations. Clearance and volume parameters were allometrically scaled based on time-varying body weight. Simulation was used to derive PK profiles for each participant in the study and noncompartmental analysis was conducted to estimate individual PK parameters (eg, area under the curve from time zero to infinity [$AUC_{0\text{-inf}}$], maximum serum concentration [C_{max}], time of

maximum serum concentration [T_{max}], and elimination half-life [$t_{½}$]). Population PK analysis was conducted in NONMEM (version 7.4.3, ICON Development Solutions). Noncompartmental analysis was conducted using R (version 4.1.2 or higher, https://www.R-project.org/) and the PKNCA package (version 0.9.5).

For each PK parameter, the following summary statistics were calculated by dose group: the geometric mean and geometric percent coefficient of variation. PK concentrations were displayed by group mean over time; group means for a time point were not reported if ≥50% of the participant data were below the assay limit of detection.

The association between ADA status and PK parameters was evaluated for each dose and at the time points where both results were available. SNA data were summarized as the group geometric mean and 95% confidence interval (CI) by time point. Efficacy for the combined dose groups of clesrovimab versus placebo and for the clesrovimab 100-mg dose versus placebo for the exploratory end points of RSV-associated MALRI, RSV-associated hospitalization, and RSV-associated ARI was estimated using the exact binomial method by Chan and Bohidar [19]. Data were analyzed using SAS software, version 9.4 or higher (SAS Institute, Inc).

RESULTS

A total of 183 infants were randomized of whom 181 were dosed and 93.4% completed the study (Figure 1). Demographics and baseline characteristics were generally comparable across the study groups. A diverse population was enrolled; 39.2% identified as White, 33.1% as Black or African American, and 18.8% as multiple races (Table 1).

The proportion of participants with solicited injection-site AEs, solicited systemic AEs, and SAEs were generally comparable across all clesrovimab dose groups and placebo (Table 2). The proportion of participants with solicited AEs did not appear to increase with increasing doses of clesrovimab. The most commonly reported solicited injection site AEs were injection-site erythema and injection-site pain; the most common solicited systemic AE was irritability (Table 2). No acute hypersensitivity/allergic reactions related to any study intervention were reported in the 2 hours postdose. There were no allergic reactions of hives or lips swelling days 1 to 30. Solicited allergic reactions of difficulty breathing (1 participant in the 75-mg group) and wheezing (1 participant each in placebo, 50, and 75-mg dose group) were reported through day 30; these were each of mild intensity and not considered as treatment related by the investigator. There were no treatment-related SAEs, clinical events of interest, or deaths in the study. The most frequently reported AEs in this study up to day 14 postdose were irritability, nasal congestion, somnolence, upper respiratory tract infection, and diarrhea (Supplementary Table 1).

A summary of clesrovimab serum PK parameters is shown in Table 3. The geometric mean of the apparent half-life of clesrovimab was generally comparable across the 5 panels (ranging from 43.0 to 48.8 days; Table 3), and was 44.9 days overall.

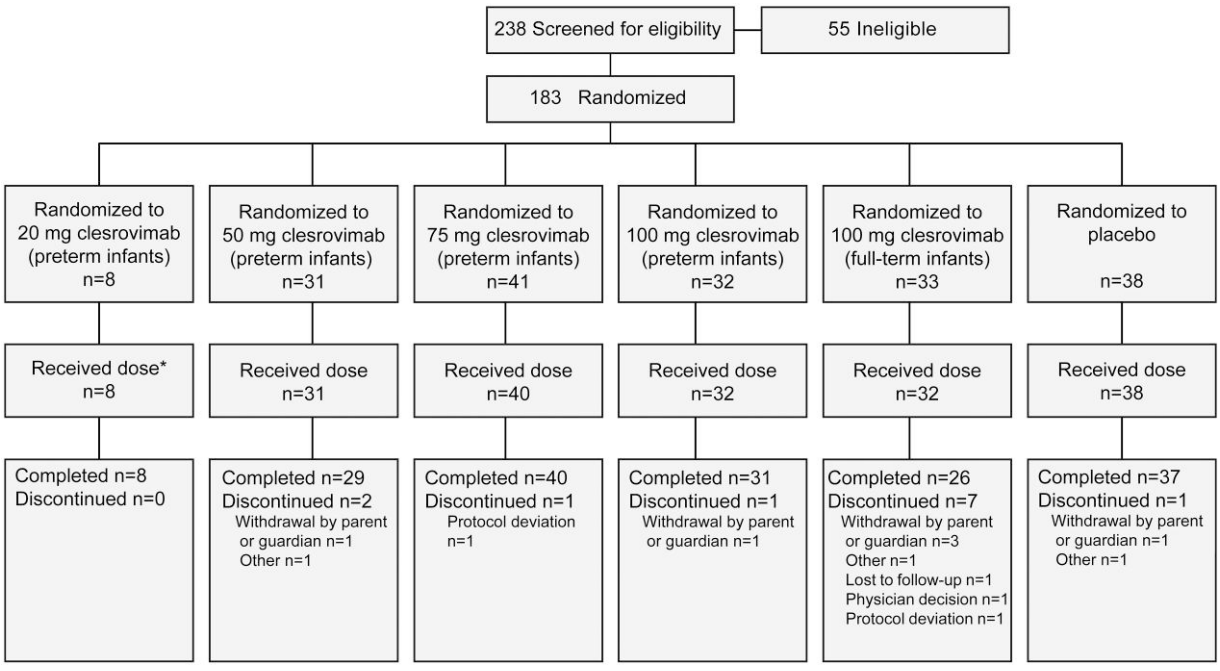

Figure 1. Participant disposition. *Two participants who were randomized to the clesrovimab 20-mg group actually received a 50-mg dose of clesrovimab and were included in the 50-mg clesrovimab group for safety, pharmacokinetic, serum neutralizing antibody, and antidrug antibodies analyses.

Table 1. Baseline Characteristics

Characteristic	Clesrovimab					Placebo	Total
	20 mg	50 mg	75 mg	100 mg Preterm	100 mg Full-Term		
Participants, n	8	31	40	32	32	38	181
Sex, n (%)							
Male	2 (25.0)	16 (51.6)	20 (50.0)	15 (46.9)	19 (59.4)	19 (50.0)	91 (50.3)
Female	6 (75.0)	15 (48.4)	20 (50.0)	17 (53.1)	13 (40.6)	19 (50.0)	90 (49.7)
Age, d, mean (SD)	118.0 (96.1)	122.4 (75.4)	103.4 (67.4)	141.3 (71.4)	168.8 (62.8)	134.8 (74.9)	132.1 (73.9)
Race, n (%)							
White	4 (50.0)	20 (64.5)	14 (35.0)	8 (25.0)	11 (34.4)	14 (36.8)	71 (39.2)
Black or African American	4 (50.0)	8 (25.8)	9 (22.5)	14 (43.8)	14 (43.8)	11 (28.9)	60 (33.1)
Multiple	0 (0.0)	1 (3.2)	16 (40.0)	2 (6.3)	6 (18.8)	9 (23.7)	34 (18.8)
Asian	0 (0.0)	1 (3.2)	0 (0.0)	5 (15.6)	0 (0.0)	0 (0.0)	6 (3.3)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (2.5)	1 (3.1)	1 (3.1)	2 (5.3)	5 (2.8)
Missing[a]	0 (0.0)	1 (3.2)	0 (0.0)	2 (6.3)	0 (0.0)	2 (5.3)	5 (2.8)
Ethnicity, n (%)							
Hispanic or Latino	1 (12.5)	12 (38.7)	24 (60.0)	9 (28.1)	13 (40.6)	18 (47.4)	77 (42.5)
Not Hispanic or Latino	7 (87.5)	19 (61.3)	16 (40.0)	23 (71.9)	19 (59.4)	20 (52.6)	104 (57.5)
Weight, kg, mean (SD)	5.2 (2.0)	5.2 (2.0)	5.1 (2.0)	5.9 (2.3)	7.6 (1.7)	5.8 (1.9)	5.9 (2.1)

All dosed participants shown.

[a]Includes 5 participants who reported a race that was not a standard category on the form.

Table 2. Safety Summary

	Clesrovimab					
	20 mg, n (%)	50 mg, n (%)	75 mg, n (%)	100 mg Preterm, n (%)	100 mg Full-Term, n (%)	Placebo
Participants	6	33	40	32	32	38
≥1 AE	6 (100.0)	27 (81.8)	33 (82.5)	26 (81.3)	27 (84.4)	33 (86.8)
Solicited injection-site AEs[a,b]	3 (50.0)	3 (9.1)	3 (7.5)	2 (6.3)	2 (6.3)	2 (5.3)
Injection-site erythema[a,b]	1 (16.7)	2 (6.1)	1 (2.5)	1 (3.1)	1 (3.1)	1 (2.6)
Injection-site pain[a,b]	2 (33.3)	0 (0.0)	2 (5.0)	2 (6.3)	0 (0.0)	1 (2.6)
Injection-site swelling[a,b]	2 (33.3)	1 (3.0)	0 (0.0)	0 (0.0)	1 (3.1)	1 (2.6)
Solicited systemic AEs[a,b]	2 (33.3)	8 (24.4)	9 (22.5)	2 (6.3)	3 (9.4)	9 (23.7)
Appetite loss[a,b]	1 (16.7)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Drowsiness[a,b]	1 (16.7)	2 (6.1)	5 (12.5)	1 (3.1)	1 (3.1)	3 (7.9)
Fever[a,b]	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)
Irritability[a,b]	2 (33.3)	5 (15.2)	5 (12.5)	2 (6.3)	2 (6.3)	9 (23.7)
Treatment-related AEs[c]	3 (50.0)	9 (27.3)	11 (27.5)	4 (12.5)	8 (25.0)	7 (18.4)
SAEs	1 (16.7)	4 (12.1)	1 (2.5)	3 (9.4)	6 (18.8)	6 (15.8)
Treatment-related SAEs[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Solicited allergic reactions	0 (0.0)	1 (3.0)	2 (5.0)	0 (0.0)	0 (0.0)	1 (2.6)
Treatment-related solicited allergic reactions[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

All participants as treated population. Nonserious AEs were collected from day 1 to day 14 postdose, solicited AEs of allergic reactions were collected from day 1 to day 30 postdose, respiratory adverse events were collected from day 1 to day 365 postdose, and SAEs were collected from day 1 throughout the study duration.

Abbreviations: AE, adverse event; SAE, serious adverse event.

[a]Solicited injection-site and solicited systemic adverse events were collected days 1–5 postdose.

[b]Every participant is counted a single time for each applicable row and column.

[c]Determined by investigator to be related to treatment.

The C_{max} and $AUC_{0\text{-}inf}$ of clesrovimab appeared to increase in a manner that was approximately dose-proportional in preterm infants. Full-term infants had approximately 20% lower exposures at the 100-mg dose, which is likely attributed to body weight differences. The median T_{max} observed across all clesrovimab doses was approximately 4 days. Similar rates of elimination were observed for all dose levels (Figure 2). In line with the half-life of clesrovimab, the majority of the participant samples were below the limit of detection for PK at day 365 and thus group means are not

Table 3. Summary of Clesrovimab Serum Pharmacokinetic in Infants

Dose Group	n	Geometric Mean (%GCV)[a]							
		Cmax, µg/mL	Tmax[b], d	AUC0-inf, d·µg/mL	AUC0–150, d·µg/mL	t1/2, d	C150, µg/mL	Vz/F, L	CL/F, L/d
20 mg	5	26.3 (19.3)	4.00 (3.80–4.60)	1560 (43.5)	1370 (32.9)	48.8 (34.6)	2.24 (80.6)	0.901 (14.8)	0.0128 (43.6)
50 mg	33	61.7 (21.8)	4.20 (3.70–5.30)	3530 (22.8)	3200 (21.5)	44.6 (10.9)	4.98 (34.2)	0.910 (16.7)	0.0142 (22.9)
75 mg	40	94.5 (20.5)	4.20 (3.00–5.80)	5510 (22.4)	4950 (20.5)	46.1 (15.1)	8.05 (37.7)	0.905 (16.0)	0.0136 (22.5)
100 mg preterm	32	117 (23.5)	4.10 (3.70–6.00)	6790 (25.4)	6120 (23.6)	45.2 (13.7)	9.70 (40.2)	0.960 (16.3)	0.0147 (25.4)
100 mg full-term	31	99.9 (13.7)	4.10 (3.70–4.90)	5690 (15.9)	5180 (14.6)	43.0 (9.72)	7.96 (26.7)	1.09 (12.3)	0.0176 (15.9)

n = Number of participants eligible for inclusion in the per-protocol population. GCV was calculated in the natural log scale with the equation 100 × sqrt(exp(σ2) – 1), where σ2 is the observed variance on the natural log scale.

Abbreviations: AUC0–150, area under the curve from time zero to day 150; AUC0-inf, area under the curve from time zero to infinity; C150, serum concentration on day 150; C365, serum concentration on day 365; CL/F, apparent clearance; Cmax, maximum serum concentration; GCV, geometric coefficient of variation; PK, pharmacokinetics; t1/2, elimination half-life; Tmax, time of maximum serum concentration; Vz/F, apparent volume of distribution.

[a]The population PK model was used to predict full PK profiles based on sparse observed PK data. Noncompartmental analysis was conducted on these simulated profiles to estimate PK parameters.

[b]Median (min–max).

shown at this time point (Figure 2 and Supplementary Figures 2).

Of the 143 clesrovimab participants in the per-protocol population a total of 51 had positive ADA responses during the study (2 [33.3%], 9 [28.1%], 4 [10.3%], 16 [50.0%], and 20 [66.7%] in the 20, 50, 75, 100-mg preterm, and 100-mg full-term groups, respectively). All of these were treatment emergent (negative at baseline and positive postdose) except for 1 participant in the 20-mg group that was treatment boosted (positive at baseline and postdose titer of ≥2-fold higher than baseline). Analysis by time point shows that the proportion of clesrovimab-treated infants with positive ADA response was 13.1% through day 150, 22.8% through day 365%, and 36.7% through day 545. ADA status was not associated with differences in PK (Supplementary Figure 3). No safety concerns were identified related to ADA positivity.

SNA titers increase in a dose dependent manner in the preterm infant groups at day 150 (Figure 3) and were generally comparable between the 100-mg preterm and full-term dose groups. Overall, a 16- to 23-fold increase in SNA titers, compared to baseline, was observed at day 150 in the 100-mg full-term and preterm dose groups, respectively.

Prespecified exploratory efficacy end points are displayed in Table 4. The observed incidences of RSV-associated MALRI, ARI, and hospitalization were lower in the infants in the combined clesrovimab dose groups versus placebo and in the 100-mg dose group versus placebo. None of the participants who received clesrovimab, and 3 who received placebo were hospitalized for RSV-associated infection through day 150. RSV A and RSV B infections were each reported during this study; the estimated efficacy by subtype is shown in Supplementary Tables 2 and 3.

DISCUSSION

Clesrovimab is currently under development for the prevention of RSV lower respiratory tract disease in neonates and infants who are born or entering their first RSV season or infants and children up to 2 years of age who remain vulnerable to severe RSV disease in their second RSV season. In this context, we present the findings from the first clinical study of clesrovimab in infants.

Clesrovimab was generally well tolerated at all dose levels evaluated. The proportions of clesrovimab-treated participants with solicited AEs were generally comparable to the placebo group, and the most commonly reported AEs in the 2 weeks after immunization were symptoms typically observed in children of this age group. This safety profile is generally consistent with studies of half-life extended RSV mAb administration in preterm and full-term infants [20–22].

Clesrovimab displayed an extended half-life in infants of approximately 45 days compared to the licensed antibody

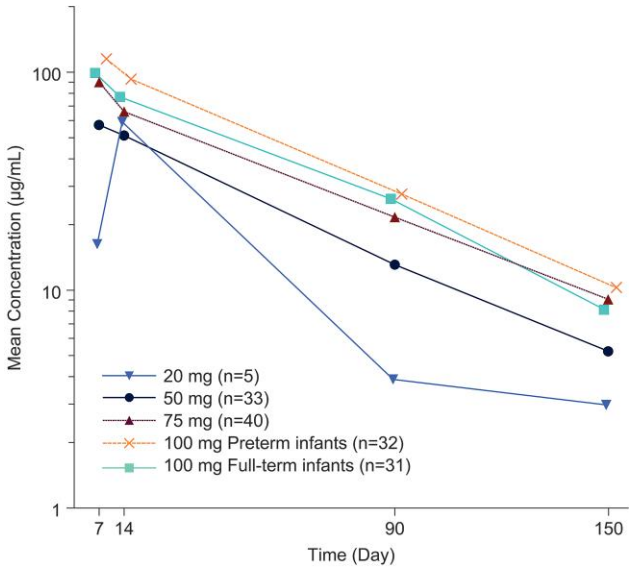

Figure 2. Observed mean clesrovimab serum concentration after a single dose in infants. Arithmetic mean serum concentrations are displayed for each group versus time in days after clesrovimab administration. Data are graphed at days 7, 14, 90, and 150; some points were staggered on x-axis to enable viewing. The majority of concentrations at day 365 were below the lower limit of quantification (0.5 µg/mL); group mean was not displayed at this time point. Data for the 20-mg time point at day 14 were calculated from 2 participants.

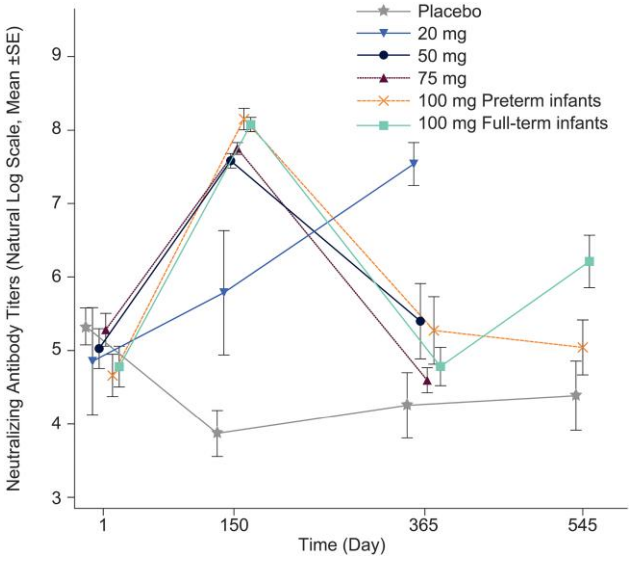

Figure 3. Serum-neutralizing antibody titers after a single dose of clesrovimab in infants. Respiratory syncytial virus serum concentration (50% inhibitory concentration) titers in natural log scale versus nominal time in days. Points represent the group arithmetic mean and error bars display the standard error. Data are graphed at days 1, 150, 365, and 545; points were staggered on x-axis to enable viewing. Number of participants included (n) for each group mean for days 1, 150, 365, and 545 (if applicable), respectively, are the following: 20-mg group = 5, 5, 2; 50-mg group = 32, 29, 12; 75-mg group = 39, 30, 17; 100-mg preterm group = 28, 22, 19, 20; 100-mg full-term group = 26, 27, 20, 21; and placebo group = 32, 29, 20, 11.

Table 4. Efficacy Through Day 150 Postdose

RSV-Associated Clinical End Point	Comparison	Clesrovimab				Placebo				Estimated Efficacy, % (95% CI)
		Participants	Cases	Total Follow-up Time, mo	Incidence Rate over 5 mo	Participants	Cases	Total Follow-up Time, mo	Incidence Rate over 5 mo	
MALRI	100 mg clesrovimab vs placebo	64	1	312.5	0.016	38	3	181.6	0.083	80.6 (−141.2 to 99.6)
	Combined[a] clesrovimab dose group vs placebo	143	3	703.0	0.021	38	3	181.6	0.083	74.2 (−92.9 to 96.5)
ARI	100 mg clesrovimab vs placebo	64	2	312.0	0.032	38	4	176.9	0.113	71.6 (−97.8 to 97.4)
	Combined[a] clesrovimab dose group vs placebo	143	8	689.7	0.058	38	4	176.9	0.113	48.7 (−132.8 to 86.3)
Hospitalization	100 mg clesrovimab vs placebo	64	0	315.2	0.00	38	3	182.0	0.082	100 (−39.7 to 100)
	Combined[a] clesrovimab dose group vs placebo	143	0	708.1	0.00	38	3	182.0	0.082	100 (37.8 to 100)

Full analysis set population.

Abbreviations: ARI, acute respiratory infection (this encompasses lower and upper respiratory infections); MALRI, medically attended lower respiratory infection; RSV, respiratory syncytial virus.

[a]Combined 20, 50, 75, and 100-mg dose groups.

palivizumab, which is approximately 20 days [23], supporting the potential for once-per RSV season dosing. The extended half-life is attributed to the 3 amino acid substitutions (YTE) in the Fc region, which increase binding to the neonatal Fc receptor, leading to reduced antibody degradation in the lysosome [14, 15]. The half-life of nirsevimab, which also contains the YTE point substitutions, is approximately 69 days in infants [22]. This difference in serum half-life between clesrovimab and nirsevimab may be a result of a difference in tissue partitioning. Clesrovimab has an isoelectric point (pI) of 8.52, compared to ≤7.0 for nirsevimab, giving clesrovimab a net higher charge, which may lead to higher tissue retention. Positively charged antibodies are retained to a higher degree in human tissue, which is negatively charged [24–27]. This is further supported by pharmacokinetic analysis, where the volume of distribution reported here represents the sum distribution to intravascular and extravascular spaces. The intravascular volume of distribution is dictated by plasma volume and is generally similar across antibodies. The higher volume of distribution of clesrovimab reported here (0.910 for 50-mg dose group) compared to that reported in a previous study for nirsevimab (0.633 in the 50-mg group [21]) is consistent with increased partitioning to the tissue. The high tissue penetration of clesrovimab was also demonstrated in a study in the nasal epithelium lining fluid of healthy adults [28]. Because RSV infects mucosal sites such as nose and lung, the high availability of clesrovimab in the tissue could be beneficial for protection from RSV.

ADA were detected in 22.8% of clesrovimab-treated participants at 1 year postdose, which is similar to the reported ADA incidence for the same time point in the phase 1b/2a study of nirsevimab (26.5%) [21]. However, a comparison of ADA incidence between studies should be interpreted with caution as different assays were used, which may have different sensitivities. The proportion of clesrovimab-treated participants with positive ADA was higher in the later time points (day 365 and 545) compared to day 150; a similar trend was observed with nirsevimab where ADA frequency was higher at 1 year compared to day 150 [21, 22]. This trend was fully explored in a separate article, along with an analysis of the binding specificity of the ADA, which was shown to be against YTE in all infants with high (≥1000 titers) ADA titers [29]. ADA status was not associated with any safety concerns, including any allergic/hypersensitivity reactions, and had no apparent impact on clesrovimab PK in this study.

A single dose of clesrovimab resulted in substantial increases in RSV serum neutralization titers in preterm and full-term infants. As expected, based on the pharmacokinetic profile, SNA titers returned to near baseline levels 1 year postimmunization. An exception was in the 20-mg dose group, which is likely attributed to an RSV infection in 1 or more participants in this small cohort (n = 8). A previously published model based meta-analysis established a quantitative relationship between RSV neutralization titers and protection against RSV disease [30]. Simulations from that model predicted that a single 100-mg dose clesrovimab would provide ≥76% efficacy for the prevention of RSV MALRI through 150 days postadministration [30]. This aligns with the estimated efficacy of 100-mg dose versus placebo (80.6%; 95% CI, −141.2 to 99.6) in this study and adds confidence to the potential effectiveness of clesrovimab for the prevention of RSV disease.

In conclusion, these data show that doses of 20 to 100-mg in preterm infants and 100-mg of clesrovimab in full-term infants were generally well tolerated. Additionally, the antibody demonstrated an extended half-life, supporting the potential for once-per-season dosing. The estimated efficacy from this trial, though promising, is subject to the limitations of small sample size. Overall, the entirety of the data shown here supports the ongoing development of clesrovimab, which is currently being evaluated in phase 3 clinical studies in healthy preterm and full-term infants (NCT04767373) and in infants and children at increased risk for severe RSV disease (NCT04938830).

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. R. A. R, A. O. A., and A. W. L. were involved in the conceptualization or design of the study. S. A. M., E. A. F. S., A. A., J. M. N. P., and J. S. S. participated in the collection or generation of study data. R. A. R, X. C., B. M. M., X. Z., A. K., B. R., K. V., and A. S. were involved in data analysis or interpretation. All authors reviewed the manuscript and approved the final version for submission.

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Data availability. The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ (MSD), is available at https://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to Data Access mailbox (dataaccess@msd.com).

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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