Motavizumab for Prophylaxis of Respiratory Syncytial Virus in High-Risk Children: A Noninferiority Trial

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KEY WORDS

clinical trial, motavizumab, palivizumab, pediatric, respiratory infection, respiratory syncytial virus

ABBREVIATIONS

RSV—respiratory syncytial virus
CLD—chronic lung disease of prematurity
MALRI—medically attended lower respiratory tract infection
OM—otitis media
AE—adverse event
SAE—serious adverse event
ADA—anti-drug antibody
ITT—intention to treat
ATP—according-to-protocol
CI—confidence interval
RR—relative risk

This trial has been registered at www.clinicaltrials.gov (identifier NCT00129766).

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WHAT'S KNOWN ON THIS SUBJECT: Monthly prophylaxis with palivizumab has been shown to reduce RSV hospitalizations by ~50% overall compared with placebo in children at high risk for severe RSV disease. Motavizumab, a monoclonal antibody developed from palivizumab, has enhanced preclinical activity against RSV.

WHAT THIS STUDY ADDS: Motavizumab may offer an improved alternative in prophylaxis for serious RSV disease in children at high risk. Motavizumab was noninferior to palivizumab for prevention of RSV hospitalization (primary end point) and superior to palivizumab for reduction of RSV-specific outpatient MALRI (a secondary end point).

abstract

OBJECTIVE: Palivizumab reduces respiratory syncytial virus (RSV) hospitalization in children at high risk by ~50% compared with placebo. We compared the efficacy and safety of motavizumab, an investigational monoclonal antibody with enhanced anti-RSV activity in preclinical studies, with palivizumab.

METHODS: This randomized, double-blind, multinational, phase 3, noninferiority trial assessed safety and RSV hospitalization in 6635 preterm infants aged ≤6 months at enrollment or children aged ≤24 months with chronic lung disease of prematurity who received 15 mg/kg palivizumab or motavizumab monthly. Secondary end points included outpatient medically attended lower respiratory tract infections (MALRIs), RSV-specific LRIs, otitis media, antibiotic use, development of antimotavizumab antibodies, and motavizumab serum concentrations.

RESULTS: Motavizumab recipients had a 26% relative reduction in RSV hospitalization compared with palivizumab recipients, achieving noninferiority. Motavizumab was superior to palivizumab for reduction of RSV-specific outpatient MALRIs (50% relative reduction). Overall, adverse events (AEs) were not significantly different between groups. Cutaneous events were reported in 2 percentage points more motavizumab recipients (7.2% vs 5.1%); most were mild, but 0.3% resulted in dosing discontinuation. Antidrug antibodies (ADA) were detected in 1.8% of motavizumab recipients. Patients with anti-drug antibody reported 6 RSV events and 17 cutaneous events.

CONCLUSIONS: Children receiving prophylaxis with motavizumab or palivizumab had low rates of RSV hospitalization; motavizumab recipients experienced 50% fewer RSV MALRIs than palivizumab recipients. AEs were similar in both groups, although cutaneous AEs were higher for motavizumab recipients. Motavizumab may offer an improved alternative in prophylaxis for serious RSV disease in infants and children at high risk. *Pediatrics* 2010;125:e35–e51

Palivizumab (Synagis [MedImmune, Gaithersburg, MD]), a humanized monoclonal antibody that recognizes a highly conserved neutralizing epitope on the fusion protein of respiratory syncytial virus (RSV),[1] is recommended for RSV prophylaxis of children at high risk.[2,3] Monthly palivizumab reduced RSV hospitalizations by ~50% compared with placebo in children at high risk.[4–6]

Motavizumab (Medi-524 [MedImmune]), an investigational monoclonal antibody developed by affinity maturation of palivizumab, has significantly higher affinity for RSV fusion protein than palivizumab.[7,8] Compared with palivizumab, motavizumab was ~20-fold more potent in microneutralization studies and, in the cotton rat model, reduced nasal and lung RSV titers 25- and 100-fold, respectively.[8,9]

In early pediatric trials of motavizumab, no dose-limiting toxicities were found, and serum pharmacokinetics were consistent with published data with palivizumab.[10,11] In a phase 1 study, a single dose of intravenous motavizumab significantly reduced cultivatable RSV in nasal aspirates of children who were hospitalized with RSV.[11] Significant antiviral effects were not seen in the upper respiratory tract in a similar study conducted with palivizumab.[12] This noninferiority study was designed to test the hypothesis that motavizumab was at least as good as palivizumab for reduction of serious RSV disease.

METHODS

Study Design

This phase 3, randomized, double-blind, palivizumab-controlled study was conducted between November 2004 and May 2006 during 2 RSV seasons in the northern hemisphere and 1 season in the southern hemisphere.[5,6] The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice and was approved by the institutional review board or independent ethics committee of each participating center and safety was monitored by an independent data safety monitoring board. Parents or legal guardians provided written informed consent for each child.

Recognizing the difficulty in showing superiority compared with an effective agent, this study was designed to evaluate whether motavizumab was noninferior and possibly superior to palivizumab in the reduction of RSV hospitalization and other RSV-associated end points. Preterm children were randomly assigned 1:1 (by using an interactive voice-response system) to receive intramuscular injections of 15 mg/kg motavizumab or palivizumab at ~30-day intervals. All personnel at all sites were blind to study treatment. Five doses were chosen to maximize overlap of the RSV season at all study sites and to provide uniform drug exposure and end point surveillance for all patients. Motavizumab and palivizumab were provided in identical vials in coded kits. Randomization was stratified by site and diagnosis of protocol-defined chronic lung disease of prematurity (CLD). Patients were involved during only 1 season and were followed up for 150 days after randomization.

Study End Points

The primary efficacy end point was met when a child had a positive RSV test and was hospitalized (on the basis of the assessment of the admitting physician) for respiratory symptoms or had a new onset of RSV-positive lower respiratory illness with worsening respiratory status while already in the hospital or when a death caused by RSV occurred. Secondary efficacy end points included the incidence of any (all sites) and RSV-specific (all patients at a subset of sites) outpatient medically attended lower respiratory tract infection (MALRI), frequency and incidence of medically attended otitis media (OM), and the frequency of prescribed antibiotics for LRI and OM. Outpatient MALRI required medical management (physician's office, clinic, or emergency department) with a diagnosis of bronchiolitis or pneumonia or an LRI as determined by the site investigator after review of medical documentation, on the basis of the presence of cough, retractions, rhonchi, wheezing, crackles, or rales associated with coryza, fever, or apnea. Safety end points included adverse events (AEs) and serious AEs (SAEs) graded for severity and causality by the site investigators. An AE was any change from the patient's baseline status. An SAE was any event that resulted in a significant disability (a substantial impairment of baseline function) or death, required or prolonged hospitalization, or otherwise was considered an important medical event.

Participants

Eligible preterm children (gestational age $\leq$ 35 weeks) either were $\leq$24 months of age with CLD that required medical management within 6 months before randomization or were $\leq$6 months of age. Exclusion criteria were hospitalization at randomization (unless discharge was anticipated within 10 days); mechanical ventilation or other mechanical support; life expectancy $<$6 months; active RSV infection; known renal, hepatic, chronic seizure, unstable neurologic, or hemodynamically significant congenital heart disorders; immunodeficiency; use of palivizumab or RSV intravenous immunoglobulin $<$3 months before randomization or anticipated use during the study; receipt of RSV vaccine; and participation in any other investigational study.

Laboratory Assessments

Respiratory secretions for RSV testing were collected within 2 days of or as soon as possible after a respiratory hospitalization or nosocomial event or an outpatient MALRI. Nasal secretions (aspirates or posterior nasopharyngeal swabs) were preferred; however, when intubated, tracheal secretions were permitted. Respiratory specimens were tested by reverse transcriptase–polymerase chain reaction specific for the N gene of RSV A and RSV B at a central laboratory by personnel who were blind to treatment assignment.[13] Before the analysis of study samples, the real-time reverse transcriptase–polymerase chain reaction assays were validated for specificity, sensitivity, and accuracy. These assays were not subject to potential interference by either study drug.

Serum samples for anti-drug antibodies (ADA) and motavizumab concentration were obtained from all study subjects before the first and last dose with an additional randomly assigned sample taken before 1 of the other 3 doses. ADA was assessed using a new assay that was developed after unblinding. Tiered homogeneous, double bridging immunoassays were developed to screen, confirm, and titer ADAs using electrochemiluminescent technology (Meso Scale Discovery, Gaithersburg, MD). Cut point factors (screening assay) and cut points (confirmatory assays) were established through statistical evaluations.[14] The tolerance for the presence of motavizumab in the assay was determined using a purified polyclonal anti-idiotypic reagent to motavizumab as surrogate for ADA. The sensitivity in the absence of motavizumab was 4.69 ng/mL; ≤250 ng/mL ADA was detectable in the presence of 100 μg/mL motavizumab. Samples positive for ADA were confirmed in the presence of excess drug; an individual's pre-dose (day 0) sample was assessed simultaneous with the post-dose sample. Samples confirmed to contain ADA were tested and titered for IgE ADA. IgE ADA assays were homogenous assays consisting of biotinylated drug, test sample, and ruthenylated anti-human IgE. The sensitivity of the IgE screening assay was 1.46 ng/mL and drug tolerance was ≤15.6 ng/ml in the presence of 300 μg/mL drug assessed using a chimeric mouse/human IgE anti-idiotypic monoclonal antibody to motavizumab. A positive antimotavizumab titer was ≥1:30.

Study Populations

The intention-to-treat (ITT) population included all randomly assigned patients or, for the RSV outpatient MALRI end point, all randomly assigned patients in the subset. The according-to-protocol (ATP) population included all randomly assigned patients who received the same treatment for all 5 doses without a major protocol violation. The safety population included all patients who received any study medication and had any safety follow-up. Patients who were randomly assigned to motavizumab and received commercial palivizumab within 3 months before receiving study drug were excluded from the safety, immunogenicity, and pharmacokinetic analyses.

Statistical Analyses

The analyses for RSV hospitalization first examined noninferiority, then superiority, because the efficacy of palivizumab was previously demonstrated for this end point.[5] Noninferiority of motavizumab compared with palivizumab required the upper bound of the 2-sided 95% confidence interval (CI) for the relative risk (RR) to be <1.265 (chosen to preserve at least 50% of the benefit observed for palivizumab over placebo). The study protocol specified that, if noninferiority were achieved, then superiority was to be assessed. Superiority required the upper bound of the 95% CI of the RR to be <1. Sample size calculations assumed an RSV hospitalization rate of 3% in palivizumab recipients[5,6,15] with a 45% reduction of RSV hospitalization by motavizumab compared with palivizumab.[4–6] Assuming a 5% dropout rate, 2875 patients provided ~99% and ≥90% power to demonstrate noninferiority or superiority, respectively, of motavizumab to palivizumab. For the primary analysis, a 95% CI for the RR was constructed by using the exact conditional binomial method conditioning on the total number of cases with midprobability adjustment.[16] The primary analysis included a 2-level categorical covariate to control for CLD.

Secondary end points were evaluated by using a Cochran-Mantel-Haenszel approach that was stratified by CLD and based on an assumption of superiority. Sample size calculations for RSV MALRI assumed a rate of 4% among palivizumab recipients and that motavizumab was superior to palivizumab by 50%, providing at least 90% power. Subgroups were analyzed by demographics and region. Exploratory logistic regression models investigated the effects of covariates with treatment, without adjustment for multiple comparisons. Fisher's exact test was used for comparison of the number of patients who reported at least 1 AE, related AEs, SAEs, and deaths.

RESULTS

A total of 6635 children were randomly assigned to motavizumab ($n = 3329$) or palivizumab ($n = 3306$) at 347 sites in 24 countries. A mean of 19 patients were enrolled at each site (median: 18 [range: 1–101; interquartile range: 11–25]); no site contributed >1.5% of the study population. The ATP population comprised 6367 children (motavizumab, $n = 3183$; palivizumab, $n =$

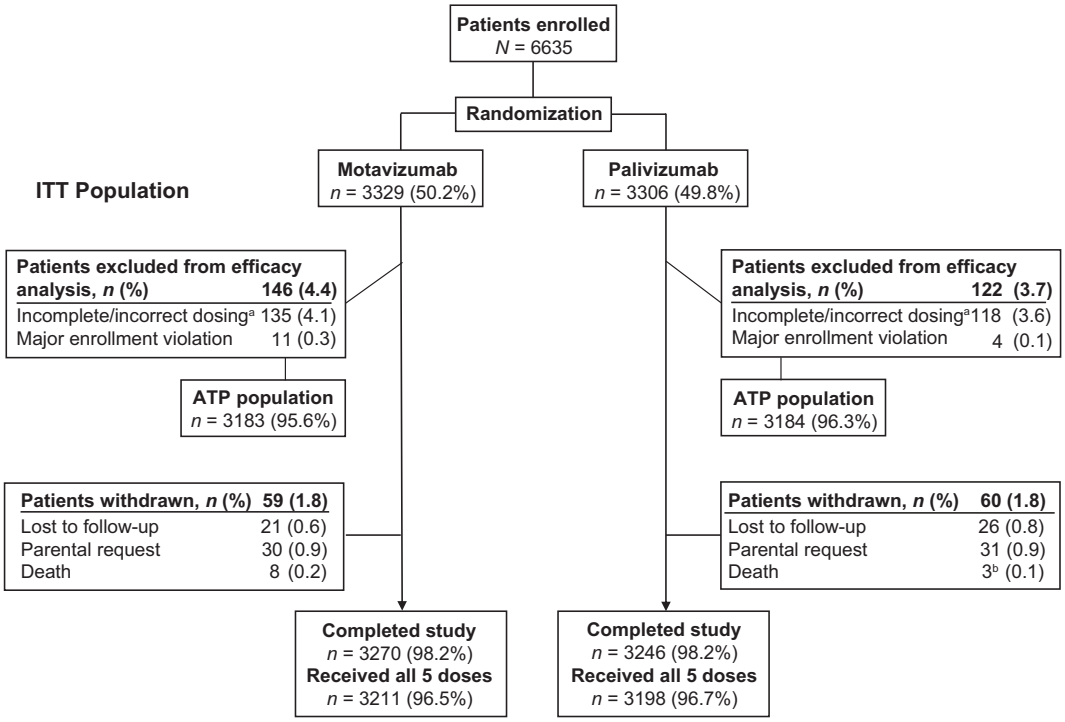

FIGURE 1

Patient disposition. [a] The most frequent reason for a patient classified as having "incomplete/incorrect dosing" was for not having received all 5 doses; however, this category also includes patients who received an incorrect dose of study drug, who received commercial palivizumab during the trial, or who received commercial palivizumab within 3 months of randomization. [b] One additional patient died after meeting the primary end point and thus completed the study.

3184; Fig 1). Entry violations and drug-dispensing errors were infrequent (<1%) and balanced between the 2 groups.

Groups were well matched, with no statistically significant differences for demographics, baseline characteristics, or RSV risk factors (Table 1). The mean ± SD gestational age was 31.1 ± 3.1 weeks, and 1445 (21.8%) children had CLD. Baseline characteristics of participants at sites that tested for RSV MALRI were also balanced (Table 2). Overall, 6516 (98.2%) children completed the study (Fig 1) and 6409 (97%) children received all 5 doses of study drug.

RSV Hospitalization

Low rates of RSV hospitalizations were observed in both groups (ITT population: motavizumab, 1.4%; palivizumab, 1.9%; Fig 2, Table 3). Motavizumab recipients had a 26% relative reduction in RSV hospitalization compared with palivizumab recipients (RR: 0.74 [95% CI: 0.503–1.083), meeting the noninferiority criteria but not the superiority criteria for the primary end point (Figs 2 and 3, Table 3). RSV hospitalization outcomes were similar in the ATP population and in analyses that accounted for premature discontinuation and missed samples for RSV testing.

Subgroup analyses of RSV hospitalization by gestational age, CLD status, and other characteristics (Fig 2B) were consistent with the overall noninferiority outcome. The observed rate of RSV hospitalization for North America and all children who were >32 weeks' gestation was similar between groups; the rates for preterm infants who did not have CLD and were ≤32 weeks' gestation or >32 weeks' gestation and for other regions were lower in motavizumab recipients compared with palivizumab recipients. In logistic regression analyses, no treatment interactions were found by age, gender, weight, gestational age, race, and region, indicating consistent treatment effects across baseline covariates.

RSV-Specific Outpatient MALRI

The incidence of RSV MALRI was assessed in all randomly assigned children at 133 sites (motavizumab, $n = 1227$; palivizumab, $n = 1183$). Motavizumab was superior to palivizumab, reducing RSV-specific outpatient MALRI by 50% compared with palivizumab (2.0% vs 3.9%; $P = .005$; Fig 4, Table 4). These results were consistent by geographic region, gestational age, CLD status, and other demographic characteristics and were supported by a sensitivity analysis that accounted for children with follow-up of <150 days and patients with missing RSV testing. This outcome was not

TABLE 1 Demographic Characteristics of the ITT Population

Characteristic	Motavizumab ($N = 3329$)	Palivizumab ($N = 3306$)
Age, mean ± SD, mo	3.99 ± 3.75	3.98 ± 3.78
Gestational age at birth		
Mean ± SD, wk	31.1 ± 3.1	31.1 ± 3.1
≤32, *n* (%)	1958 (58.8)	1924 (58.2)
>32, *n* (%)	1371 (41.2)	1382 (41.8)
Boys, *n* (%)	1816 (54.6)	1811 (54.8)
Race/ethnicity, *n* (%)		
White/non-Hispanic	2612 (78.5)	2601 (78.7)
Hispanic	289 (8.7)	280 (8.5)
Black	250 (7.5)	271 (8.2)
Asian	41 (1.2)	44 (1.3)
Other	136 (4.1)	109 (3.3)
Missing	1 (<0.1)	1 (<0.1)
Geographic region		
North America[a]	1229 (39.0)	1264 (38.2)
European Union[b]	1224 (36.8)	1237 (37.4)
Rest of world[c]	806 (24.2)	805 (24.3)
Multiple birth, *n* (%)	1411 (42.4)	1328 (40.2)
Weight, mean ± SD, kg[d]	4.453 ± 1.964	4.438 ± 2.011
CLD, *n* (%)	722 (21.7)	723 (21.9)
Preterm, no CLD, *n* (%)	2607 (78.3)	2583 (78.1)
≤32 wk gestational age	1306 (39.2)	1265 (38.3)
>32 wk gestational age	1301 (39.1)	1318 (39.9)
Previous RSV hospitalization, *n* (%)[e]	17 (0.6)	28 (1.0)
Child in child care, *n* (%)[f]	105 (3.6)	106 (3.7)
Family history of atopy, *n* (%)		
Any	1490 (44.8)	1469 (44.4)
Asthma	931 (28.0)	926 (28.0)
Hay fever	667 (20.0)	685 (20.7)
Eczema	566 (17.0)	526 (15.9)
≥1 smoker in household, *n* (%)	1081 (32.5)	1108 (33.5)
Children <6 y in household, *n* (%)	1972 (59.2)	1907 (57.7)

None of the differences between groups were statistically significant.

[a] United States and Canada.

[b] Austria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Poland, Spain, Sweden, and the United Kingdom.

[c] Argentina, Australia, Brazil, Bulgaria, Chile, Iceland, Israel, New Zealand, Russia, and Turkey.

[d] $n = 3320$ (motavizumab); $n = 3299$ (palivizumab).

[e] Excludes children who had not yet been discharged from their birth hospitalization at the time of randomization. A total of 434 (13.0%) were missing/excluded for motavizumab; 479 (14.5%) for palivizumab.

[f] Excludes children who had not yet been discharged from their birth hospitalization at the time of randomization. A total of 423 (12.7%) were missing/excluded for motavizumab; 469 (14.2%) for palivizumab.

confounded by RSV hospitalization; only 1 palivizumab recipient had both an RSV-specific outpatient MALRI and an RSV hospitalization, indicating an independent effect.

Other End Points

The rate of all-cause outpatient MALRI did not differ significantly between groups (motavizumab, 19.5%; palivizumab, 21.1%; $P = .110$). Significant differences were not found in the incidence of medically attended OM or the frequency of prescribed antibiotics for LRI or OM.

At RSV hospitalization, patients in both groups were similar in CLD status and gestational age. In a posthoc analysis (Table 5), a smaller proportion of patients who received motavizumab than palivizumab required mechanical ventilation (2 of 3329 [0.1%] vs 11 of 3306 [0.3%], respectively; $P = .012$) for shorter periods (days per 100 patients: motavizumab, 0.5; palivizumab, 3.8; $P = .012$).

Safety

Overall AEs and SAEs were consistent with the underlying medical conditions that are common in this high-risk population and were similar in incidence and severity for both treatment groups (Tables 6 and 7). Significant differences were found only in 2 body systems: psychiatric AEs (including agitation and insomnia) were more common in palivizumab recipients (2.9% vs 1.9%; $P = .010$), and skin AEs were more common in motavizumab recipients (7.2% vs 5.1%, $P < .001$; Table 6).

Skin events are summarized in Fig 5. Skin AEs were transient, and most resolved within 7 days of onset; 80% were nonspecific rash events that did not result in dosing discontinuation. No association was found between the occurrence of skin events and the number of doses received. More motavizumab recipients experienced events consistent with possible cutaneous hypersensitivity (including urticaria, allergic dermatitis, eyelid edema, and drug hypersensitivity) within 2 days of dosing (motavizumab, 22 of 3329 [0.7%]; palivizumab, 8 of 3306 [0.2%]; $P = .016$). No clear distinctions were seen in the frequency of cutaneous reactions by gender, gestational age (<32 weeks or >32 weeks), CLD status, race, or region. Skin events that were of level 3 or 4 severity or classified as SAEs occurred in 14 (0.4%) motavizumab and 2 (0.1%) palivizumab recipients ($P = .004$). There were no cases of anaphylaxis or evidence of respiratory hypersensitivity in either treatment group. One motavizumab recipient was hospitalized for observation within 2 days of dose 5 for drug hypersensitivity. Three other AEs (angioneurotic edema [4 days after dose 2], urticaria [7 days after dose 2], and rash [12 days after dose 5]) were judged to be unrelated to motavizumab and occurred in hospitalized children with staphylococcal infection, viral illness with fever and diarrhea, and suspected ampicillin rash, respectively.

TABLE 2 Demographic Characteristics of the ITT RSV-Specific MALRI Population

Characteristic	Motavizumab ($N = 1227$)	Palivizumab ($N = 1183$)
Mean (SD) age, mo	4.10 (4.10)	4.20 (4.31)
Gestational age at birth		
Mean (SD), wk	31.4 (3.0)	31.3 (3.0)
≤32 wk, *n* (%)	699 (57.0)	671 (56.7)
>32 wk, *n* (%)	528 (43.0)	512 (43.3)
Boys, *n* (%)	655 (53.4)	636 (53.8)
Race/ethnicity, *n* (%)		
White/non-Hispanic	940 (76.6)	897 (75.8)
Hispanic	80 (6.5)	72 (6.1)
Black	117 (9.5)	135 (11.4)
Asian	25 (2.0)	25 (2.1)
Other	65 (5.3)	54 (4.6)
Geographic region		
North America[a]	588 (47.9)	555 (46.9)
European Union[b]	181 (14.8)	179 (15.1)
Rest of world[c]	458 (37.3)	449 (38.0)
Multiple birth, *n* (%)	535 (43.6)	472 (39.9)
Weight, mean (SD), kg[d]	4.533 (2.083)	4.568 (2.195)
CLD of prematurity, *n* (%)	259 (21.1)	263 (22.2)
Preterm, no CLD, *n* (%)	968 (78.9)	920 (77.8)
≤32 wk gestational age	491 (40.0)	446 (37.7)
>32 wk gestational age	477 (38.9)	474 (40.1)
Previous RSV hospitalization, *n* (%)[e]	6 (0.6)	15 (1.4)
Child in day care, *n* (%)[f]	43 (4.0)	48 (4.6)
Family history of atopy, *n* (%)		
Any	519 (42.3)	499 (42.2)
Asthma	357 (29.1)	343 (29.0)
Hay fever	225 (18.3)	218 (18.4)
Eczema	189 (15.4)	181 (15.3)
≥1 smoker in household, *n* (%)	400 (32.6)	392 (33.2)
Children <6 y in household, *n* (%)	747 (60.9)	691 (58.4)

None of the differences between groups were statistically significant.

[a] United States and Canada.

[b] Austria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Poland, Spain, Sweden, and the United Kingdom.

[c] Argentina, Australia, Brazil, Bulgaria, Chile, Iceland, Israel, New Zealand, Russia, and Turkey.

[d] $n = 1224$ (motavizumab); $n = 1181$ (palivizumab).

[e] Excludes children who had not yet been discharged from their birth hospitalization at the time of randomization. One hundred forty-eight (11.5%) were missing/excluded for motavizumab; 136 (14.5%) for palivizumab.

[f] Excludes children who had not yet been discharged from their birth hospitalization at the time of randomization. One hundred forty (11.4%) were missing/excluded for motavizumab; 132 (11.1%) for palivizumab.

Overall, drug discontinuations as a result of any AE were not significantly different between groups: 13 (0.4%) motavizumab and 10 (0.3%) palivizumab recipients. Discontinuation as a result of skin AEs was infrequent (motavizumab, 9 [0.3%] of 3315; palivizumab, 0 of 3298; $P = .004$). Motavizumab was not discontinued because of any initial skin AE with onset >2 days after a dose. Approximately half of motavizumab recipients (9 of 22; 0.7% of all motavizumab recipients) with events consistent with possible hypersensitivity within 2 days after a dose had drug discontinued; 2 of 10 children had recurrences of the same or lower severity after subsequent doses.

The incidence of injection-site reactions was similar between groups (motavizumab, 106 of 3315 [3.2%]; palivizumab, 88 of 3298 [2.7%]; $P = .216$). The incidence of alanine and/or aspartate aminotransferase increases reported as AEs was also similar (motavizumab, 59 of 3315 [1.8%]; palivizumab, 63 of 3298 [1.9%]; $P = .715$; Table 8).

Mortality rates were not significantly different between the 2 groups (motavizumab, 8 [0.2%]; palivizumab, 4 [0.1%]; $P = .387$); none was considered related to study medication or RSV. The rates of sudden infant death syndrome/sudden unexplained death were also similar (motavizumab, 4 of 3315 [0.1%]; palivizumab, 2 of 3298 [0.1%]).

Antimotavizumab Antibodies and Motavizumab Serum Concentrations

Fifty-eight (1.8%) motavizumab recipients had detectable ADA with titers from 1:30 to 1:122 880. No specific IgE was detected. More subjects with ADA compared with those without ADA had reports of skin AEs (17 of 58 [29.3%] vs 217 of 3173 [6.8%]; $P < .001$) or Level 3 or serious skin AEs (6 of 58 [10.3%] vs 8 of 3173 [0.3%]; $P < .001$). Among the 17 subjects with ADA with skin events, 5 had potential alternative etiologies and 14 were given subsequent doses (including 3 subjects with more severe or serious events): 9 had no recurrences (including 1 subject with an initial level 3 urticaria), 3 had level 1 or 2 recurrences (including 2 subjects with initial serious or level 3 events), and 2 had dissimilar skin events after subsequent doses (1 patient with a seborrhea rash after dose 2 reported erythema multiforme minor concurrent with DPT vaccination after dose 4 and 1 patient with a rash thought to be due to amoxicillin [level 1 urticaria 7 days after dose 2] experienced level 1 hives at the motavizumab injection site within 1 day of dose 3).

Mean trough serum concentrations of motavizumab were 64.59, 80.24, and 88.52 μg/mL at 30 days after doses 2, 3, and 4, respectively. Children with ADA had lower observed mean trough serum motavizumab concentrations, although individual trough motavizumab concentrations were within the ranges of trough serum concentrations reported in children without detectable ADA.

While few patients had ADA, an increase was observed in the incidence

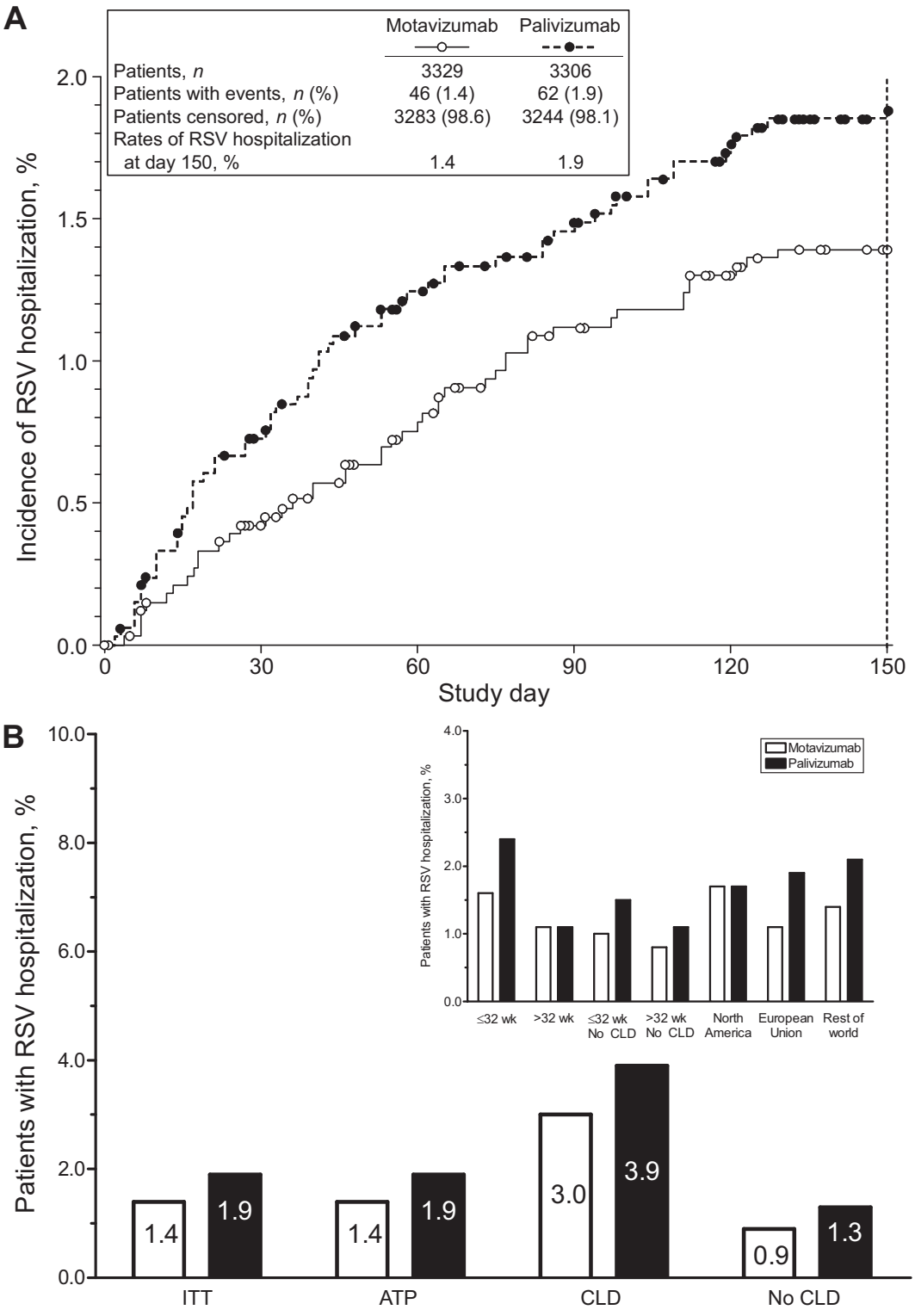

FIGURE 2

A, Kaplan-Meier curves for time to RSV hospitalization. B, Incidence of RSV hospitalization. The subgroup analyses (inset) are consistent with the noninferiority outcome of RSV hospitalization in motavizumab recipients compared with palivizumab recipients. North America includes United States and Canada; European Union, Austria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Poland, Spain, Sweden, and the United Kingdom; Rest of world, Argentina, Australia, Brazil, Bulgaria, Chile, Iceland, Israel, New Zealand, Russia, and Turkey.

TABLE 3 Incidence of RSV Hospitalization

Population	Motavizumab			Palivizumab			RR[b]	95% CI[b]
	N[a]	*n*	%	*N*[a]	*n*	%		
Overall								
ITT population	3329	46	1.4	3306	62	1.9	0.740	(0.503–1.083)
ATP population	3183	43	1.4	3184	59	1.9	0.730	(0.490–1.081)
By geographic region (ITT population)								
North America[c]	1299	22	1.7	1264	21	1.7	1.017	(0.555–1.866)
European Union[d]	1224	13	1.1	1237	24	1.9	0.553	(0.273–1.078)
Rest of world[e]	806	11	1.4	805	17	2.1	0.649	(0.294–1.387)
By baseline characteristics (ITT population)								
Gender								
Boys	1816	30	1.7	1811	40	2.2	0.748	(0.462–1.200)
Girls	1513	16	1.1	1495	22	1.5	0.737	(0.380–1.406)
Gestational age								
≤32 wk	1958	31	1.6	1924	47	2.4	0.656	(0.413–1.031)
>32 wk	1371	15	1.1	1382	15	1.1	1.002	(0.483–2.077)
Race								
White/non-Hispanic	2612	29	1.1	2601	41	1.6	0.713	(0.439–1.146)
Other	716	17	2.4	704	21	3.0	0.781	(0.406–1.487)
Weight at entry								
≤5 kg	2187	33	1.5	2156	41	1.9	0.791	(0.497–1.251)
>5 kg	1133	13	1.1	1143	21	1.8	0.630	(0.307–1.256)
By CLD status (ITT population)								
CLD of prematurity	722	22	3.0	723	28	3.9	0.789	(0.447–1.382)
Premature, no CLD	2607	24	0.9	2583	34	1.3	0.700	(0.410–1.180)
≤32 wk	1306	13	1.0	1265	19	1.5	0.664	(0.320–1.347)
>32 wk	1301	11	0.8	1318	15	1.1	0.742	(0.331–1.625)
Sensitivity analysis								
RSV hospitalization rate[f] adjusted for patients with follow-up of <150 d	3329	47	1.4	3306	63	1.9	0.740	(0.503–1.083)
RSV hospitalization rate[g] adjusted for patients with missed RSV sample for hospitalization[h]	3329	46.3	1.4	3306	62.3	1.9	0.740	(0.503–1.083)

[a] *N* indicates the total number of patients in each subpopulation for each treatment group; *n* indicates the number affected by RSV hospitalization.
[b] 95% CI and RR were adjusted for stratification according to the presence or absence of CLD of prematurity.
[c] United States and Canada.
[d] Austria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Poland, Spain, Sweden, and the United Kingdom.
[e] Argentina, Australia, Brazil, Bulgaria, Chile, Iceland, Israel, New Zealand, Russia, and Turkey.
[f] Motavizumab RSV hospitalization rate was equivalent to palivizumab RSV hospitalization rate (ie, 1.9%).
[g] Adjusted for the number of children who did not reach a primary end point and had no end-point assessment (at 150 days from randomization) and would have been hospitalized for RSV if the proportion of children hospitalized was equal to that of the other treatment group.
[h] A patient was counted as having a missed sample if the patient did not have a sample within the specified window and the patient did not otherwise meet the end point.

of RSV hospitalization and RSV MALRI in patients with motavizumab ADA (4 of 58 [6.9%] and 2 of 23 [9.7%], respectively) compared with patients without ADA (40 of 3173 [1.3%] and 22 of 1169 [1.9%], respectively). Some of these RSV events occurred before ADA detection or had appropriate serum drug levels before or after the event, making it difficult to determine causality.

DISCUSSION

Palivizumab has been used since 1998 in the United States and 61 other countries for passive prevention of serious RSV in children at high risk.[5,15,17–19] Although motavizumab has greater neutralization activity against RSV in preclinical studies, it was unclear whether this would translate into improved clinical efficacy.[7–9]

This pivotal study assessed the efficacy and safety of motavizumab in high-risk infants. A placebo-controlled design was not possible because the efficacy of palivizumab has been well established.[5,6] A low rate of hospitalization among palivizumab recipients was anticipated to make the hypothesized superior efficacy of motavizumab difficult to demonstrate with a reasonable population size; therefore, an active-controlled trial to assess noninferiority to the standard of care (ie, motavizumab is not worse than palivizumab), as well as superiority, was used.

Treatment with motavizumab met the noninferiority criteria for RSV hospitalization, with a 26% relative reduction in RSV hospitalization. The rate of RSV hospitalization among palivizumab recipients was low (1.9%), which represented a challenge for the superiority test. The study, however, included an RSV-specific second-

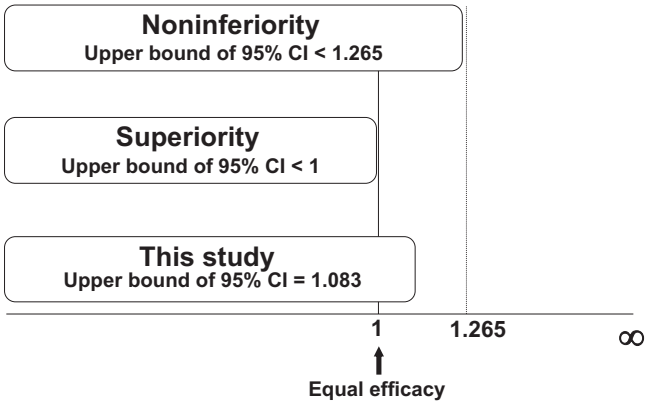

FIGURE 3
RR of motavizumab versus palivizumab for RSV hospitalization. Criteria used to define noninferiority and superiority are shown in relation to the results of RSV hospitalization, the primary end point. The 26% relative reduction in RSV hospitalization in recipients who received motavizumab compared with those who received palivizumab (RR: 0.74 [95% CI: 0.503–1.083]) met the noninferiority criteria but not the superiority criteria for the primary end point.

ary end point (RSV outpatient MALRI) that was expected to occur more frequently than RSV hospitalization.[8,11] If motavizumab had a clinical advantage over palivizumab, then differences in outpatient RSV MALRI should be apparent. Here, motavizumab was shown to be superior to palivizumab for RSV MALRI, with a 50% relative reduction in motavizumab recipients ($P = .005$). No statistical differences were observed in non–RSV-specific secondary end points.

Relevant subgroups were assessed to evaluate the consistency of the efficacy results. Because the rates of RSV hospitalization and RSV outpatient MALRI were lower than expected in both treatment groups, the differences between treatments must be interpreted with caution. The rates for RSV hospitalization and RSV outpatient MALRI were lower in children with CLD and in preterm infants who did not have protocol-defined CLD (≤32 weeks' or >32 weeks' gestation) and received motavizumab than in comparable children who received palivizumab. Although the RR for RSV hospitalization in children in North America and in children of >32 weeks' gestation (regardless of CLD) was ~1 (consistent with the overall noninferiority outcome), the RR for RSV outpatient MALRI in these subgroups was substantively <1 (0.577 and 0.424, respectively); this result was consistent with the superiority outcome seen overall. Logistic regression analyses of RSV hospitalizations and outpatient MALRI indicated consistent treatment effects across baseline characteristics.

Because palivizumab has an excellent record of safety in clinical trials and in postmarketing experience,[4,5,20] the safety profile of motavizumab is an important consideration in assessing the risk/benefit ratio of the drug. Overall, the rates of AEs and SAEs in motavizumab recipients were similar to those in palivizumab recipients. For both treatment groups, the overall death rate was well below the postneonatal rate of 0.9% recently reported in the United States for preterm infants, as was the 0.1% rate of sudden infant death syndrome/sudden unexplained death.[21,22] Events that coded to the skin and subcutaneous category were significantly higher in motavizumab recipients. These included nonspecific reports of rash as well as events that were consistent with cutaneous hypersensitivity (eg, urticaria, edema) and were generally mild or moderate and transient and did not result in discontinuation of study drug. Although nearly half of the patients who experienced events that were consistent with cutaneous hypersensitivity and were temporally associated with receipt of motavizumab discontinued treatment, these events were not observed in 80% of the children who received subsequent doses, suggesting that they were not consistent with immediate hypersensitivity reactions. Skin reactions (and severe reactions) were also significantly increased in motavizumab recipients with ADA compared with those without ADA. However, because few patients developed ADA (1.8%), the overall effect was small. The inability to detect IgE and the lack of recurrences or increase in the severity of skin reactions after subsequent doses in the majority of patients with ADA with skin reactions (9 of 14 patients) is reassuring and similar to the overall experience for all patients without ADA who had skin reactions in this study.

Motavizumab recipients with ADA accounted for a minority (<10%) of subjects with RSV events in this study and, overall, improved efficacy was observed among motavizumab recipients compared with palivizumab recipients. Even among patients with ADA, a causal link between ADA and those events was not certain.

The serum trough concentrations of motavizumab that were seen in this study are consistent with previous observations.[10] The similarities in the serum trough concentrations of motavizumab compared with those reported for palivizumab suggest that the realization of the efficacy benefits of motavizumab require maintaining the dose and frequency currently recommended for palivizumab.

CONCLUSIONS

In this large, multinational, well-controlled trial, motavizumab was shown to be noninferior to palivizumab

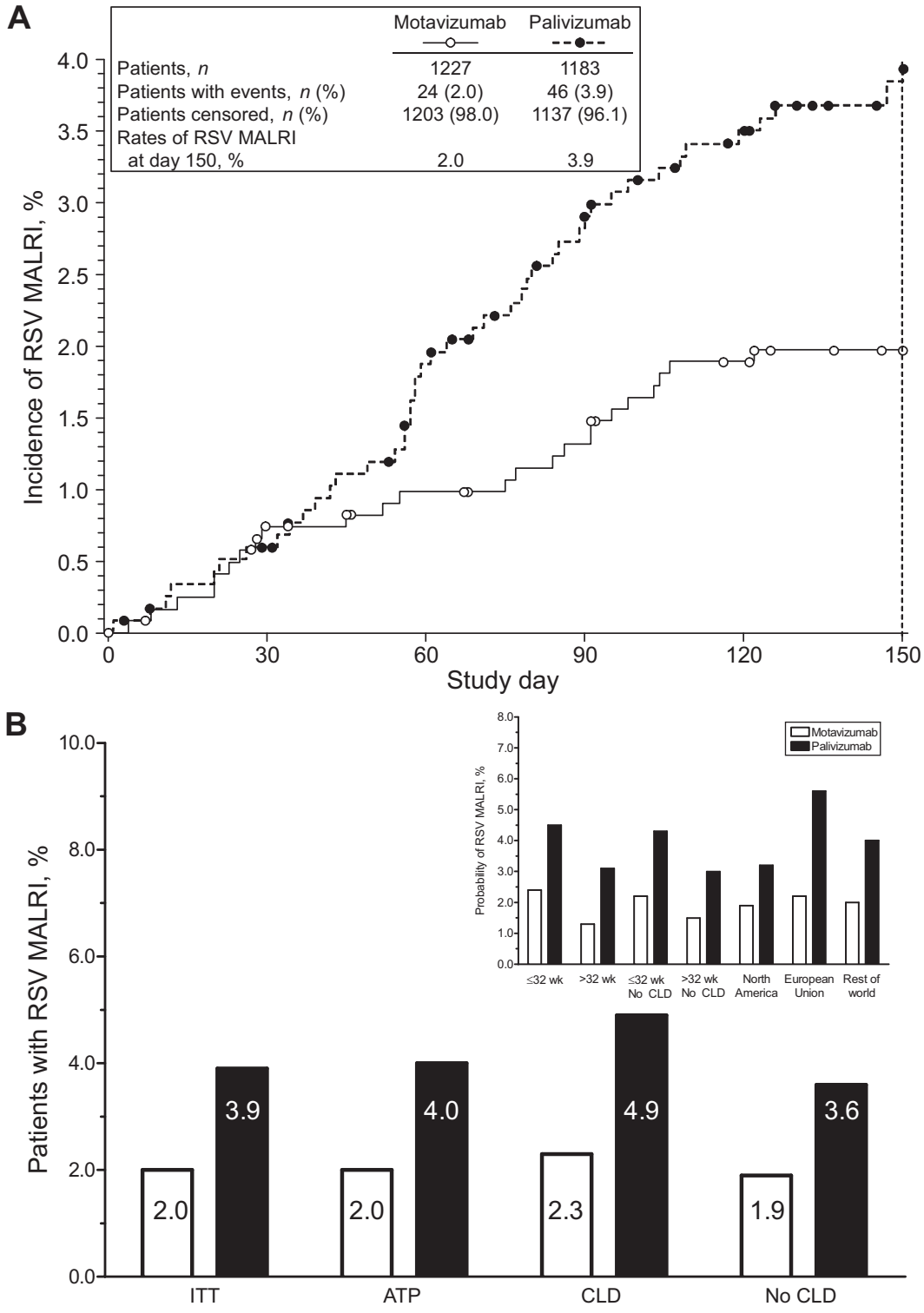

FIGURE 4

A, Kaplan-Meier curves for time to RSV-specific outpatient MALRI. B, Incidence of RSV-specific outpatient MALRI. The subgroup analyses (inset) are consistent with the superiority outcome of RSV outpatient MALRI in those who received motavizumab compared with those who received palivizumab. North America includes United States and Canada; European Union, Austria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Poland, Spain, Sweden, and the United Kingdom; Rest of world, Argentina, Australia, Brazil, Bulgaria, Chile, Iceland, Israel, New Zealand, Russia, and Turkey.

TABLE 4 Incidence of RSV-Specific Outpatient MALRI

Population	Motavizumab			Palivizumab			RR[b]	*P*[c]
	N[a]	*n*	%	*N*[a]	*n*	%		
Overall								
ITT population	1227	24	2.0	1183	46	3.9	0.503	.005
ATP population	1160	23	2.0	1123	45	4.0	0.497	.005
By geographic region (ITT population)								
North America[d]	588	11	1.9	555	18	3.2	0.575	.142
European Union[e]	181	4	2.2	179	10	5.6	0.405	.112
Rest of world[f]	458	9	2.0	449	18	4.0	0.489	.069
By baseline characteristics (ITT population)								
Gender								
Boys	655	13	2.0	636	28	4.4	0.452	.013
Girls	572	11	1.9	547	18	3.3	0.590	.167
Gestational age								
≤32 wk	699	17	2.4	671	30	4.5	0.545	.041
>32 wk	528	7	1.3	512	16	3.1	0.422	.048
Race								
White/non-Hispanic	940	19	2.0	897	36	4.0	0.505	.013
Other	287	5	1.7	286	10	3.5	0.493	.189
Weight at entry								
≤5 kg	782	12	1.5	755	21	2.8	0.545	.088
>5 kg	442	12	2.7	426	25	5.9	0.452	.018
By CLD status (ITT population)								
CLD of prematurity	259	6	2.3	263	13	4.9	0.469	.109
Premature, no CLD	968	18	1.9	920	33	3.6	0.516	.021
≤32 wk	491	11	2.2	446	19	4.3	0.526	.080
>32 wk	477	7	1.5	474	14	3.0	0.497	.119
Sensitivity analysis								
MALRI rate adjusted for patients with follow-up of <150 d[g]	1227	24.8	2.0	1183	47.1	4.0	0.503	.005
MALRI rate[h] adjusted for patients with missed RSV sample[i]	1227	26.3	2.1	1183	47.2	4.0	0.503	.009

[a] *N* indicates the total number of patients in each subpopulation for each treatment group; *n* indicates the number affected by RSV-specific outpatient MALRI.

[b] Prespecified analysis was Cochran-Mantel-Haenszel; however, RR (adjusted for the stratification factor of presence or absence of CLD of prematurity) is presented for comparison with the primary end point.

[c] The Cochran-Mantel-Haenszel test was stratified according to the presence or absence of CLD of prematurity.

[d] United States and Canada.

[e] Austria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Poland, Spain, Sweden, and the United Kingdom.

[f] Argentina, Australia, Brazil, Bulgaria, Chile, Iceland, Israel, New Zealand, Russia, and Turkey.

[g] Motavizumab RSV-specific outpatient MALRI rate was equivalent to the palivizumab rate.

[h] Adjusted for the number of children who did not reach a primary end point and had no end-point assessment (at 150 days from randomization) and would have been characterized as having RSV-specific MALRI if the proportion of children with MALRI was equal to that of the other treatment group.

[i] A patient was counted as having a missed sample if the patient did not have a sample within the specified window and the patient did not otherwise meet the end point.

for prevention of RSV hospitalization (primary end point) and was superior to palivizumab for reduction of RSV-specific outpatient MALRI (a secondary end point). Overall, the safety profile (rates and severity of AEs) of motavizumab seemed similar to palivizumab. However, cutaneous reactions were higher in motavizumab recipients. Although not better than palivizumab in reducing RSV-associated hospitalizations, motavizumab did demonstrate a significant reduction in outpatient MALRI compared with palivizumab. As such, motavizumab may offer an improved alternative for preventing serious RSV disease in high-risk infants and children.

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TABLE 5 Severity of RSV Hospitalization

Parameter	Motavizumab ($N = 3329$)	Palivizumab ($N = 3306$)	P[a]
Duration of RSV hospitalization, d[b]			
Total d per 100 patients	9.1	18.1	.112
During RSV hospitalization			
Patients with ≥1 instance of supplemental oxygen, *n* (%)	26 (0.8)	40 (1.2)	.080
Duration of supplemental oxygen, total d per 100 patients	4.1	9.5	.077
Patients admitted to the ICU,[c] *n* (%)	10 (0.3)	19 (0.6)	.092
Duration of ICU stay, total d per 100 patients	2.0	6.3	.091
Patients on mechanical ventilation, *n* (%)	2 (0.1)	11 (0.3)	.012
Duration of mechanical ventilation, total d per 100 patients	0.5	3.8	.012

[a] The Cochran-Mantel-Haenszel test was stratified according to the presence or absence of CLD.
[b] Duration within the time period from study day 0 through study completion or discontinuation; if a patient had multiple events, the durations for each event were summed for this analysis.
[c] ICU admissions for a respiratory reason.

TABLE 6 Overview of AEs

Parameter	Motavizumab ($N = 3315$), *n* (%)	Palivizumab ($N = 3298$), *n* (%)
AEs[a]	12 467	12 640
Patients reporting		
≥1 AE	2839 (85.6)	2837 (86.0)
Psychiatric disorders[b]	64 (1.9)	96 (2.9)[c]
Skin and subcutaneous tissue disorders	687 (20.7)[d]	609 (18.5)
≥1 level 3 AE as the highest severity	271 (8.2)	292 (8.9)
≥1 level 4 AE	54 (1.6)	61 (1.8)
≥1 SAE	485 (14.6)	506 (15.3)
≥1 AE resulting in discontinuation of study drug	13 (0.4)	10 (0.3)

[a] The differences between groups were not statistically significant except as indicated.
[b] Terms mapping to "psychiatric disorders" include restlessness, sleepiness, unsettled, and irritability.
[c] $P = .010$.
[d] $P < .001$.

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TABLE 7 Incidence of AEs Reported in ≥1% of Patients

AE	Motavizumab ($N = 3315$), *n* (%)	Palivizumab ($N = 3298$), *n* (%)
Upper respiratory tract infection	964 (29.1)	993 (30.1)
Pyrexia	544 (16.4)	559 (16.9)
Rhinitis	441 (13.3)	446 (13.5)
OM	435 (13.1)	421 (12.8)
Teething	299 (9.0)	282 (8.6)
Respiratory disorder	296 (8.9)	276 (8.4)
Bronchiolitis[a]	275 (8.3)	327 (9.9)
Nasal congestion	269 (8.1)	265 (8.0)
Diarrhea	256 (7.7)	279 (8.5)
Conjunctivitis	246 (7.4)	251 (7.6)
Nasopharyngitis	241 (7.3)	264 (8.0)
Constipation	236 (7.1)	227 (6.9)
Gastroenteritis	223 (6.7)	234 (7.1)
Cough	221 (6.7)	216 (6.5)
Gastroesophageal reflux disease	205 (6.2)	209 (6.3)
Bronchitis	202 (6.1)	227 (6.9)
Irritability	193 (5.8)	164 (5.0)
Diaper dermatitis	174 (5.2)	192 (5.8)
Vomiting	164 (4.9)	170 (5.2)
LRI	136 (4.1)	139 (4.2)
Eczema[a, b]	132 (4.0)	96 (2.9)
Rash	131 (4.0)	103 (3.1)
Flatulence	126 (3.8)	121 (3.7)
Oral candidiasis	102 (3.1)	106 (3.2)
Immunization reaction	102 (3.1)	99 (3.0)
Rhinorrhea	99 (3.0)	92 (2.8)
Viral infection	90 (2.7)	105 (3.2)
Inguinal hernia	80 (2.4)	76 (2.3)
Umbilical hernia	78 (2.4)	64 (1.9)
Anemia	71 (2.1)	76 (2.3)
Pharyngitis	70 (2.1)	92 (2.8)
Acute OM	65 (2.0)	54 (1.6)
Viral upper respiratory tract infection	61 (1.8)	62 (1.9)
Seborrheic dermatitis	57 (1.7)	54 (1.6)
Abdominal pain	56 (1.7)	73 (2.2)
Wheezing	55 (1.7)	72 (2.2)
Candidiasis	53 (1.6)	72 (2.2)
Bronchitis acute	50 (1.5)	60 (1.8)
Bronchial hyperactivity	49 (1.5)	60 (1.8)
Injection site pain	45 (1.4)	49 (1.5)
Dermatitis atopic	44 (1.3)	53 (1.6)
Pneumonia[a]	42 (1.3)	65 (2.0)
Gastroenteritis viral	42 (1.3)	38 (1.2)
Injection site erythema	41 (1.2)	28 (0.8)
Asthma	39 (1.2)	40 (1.2)
Agitation	35 (1.1)	46 (1.4)
Dacryostenosis acquired	35 (1.1)	34 (1.0)
Blood urea increased	35 (1.1)	25 (0.8)
Dry skin	35 (1.1)	25 (0.8)
Plagiocephaly	34 (1.0)	29 (0.9)
Urinary tract infection	33 (1.0)	36 (1.1)
Hemangioma	31 (0.9)	41 (1.2)
Bronchopulmonary dysplasia	31 (0.9)	32 (1.0)
Croup infectious	28 (0.8)	33 (1.0)
Gastroenteritis rotavirus[a]	18 (0.5)	33 (1.0)

[a] $P < .05$; other comparisons were not statistically significant.

[b] In addition to eczema, other preferred terms considered to be synonyms for eczema were combined for analysis: dermatitis atopic, dermatitis contact, diaper dermatitis, eczema infantile, prurigo, seborrhea, and seborrheic dermatitis. Overall, the incidence of these AEs was comparable between treatment groups (motavizumab: 403 [12.2%]; palivizumab: 384 [11.6%]); the difference was not statistically significant.

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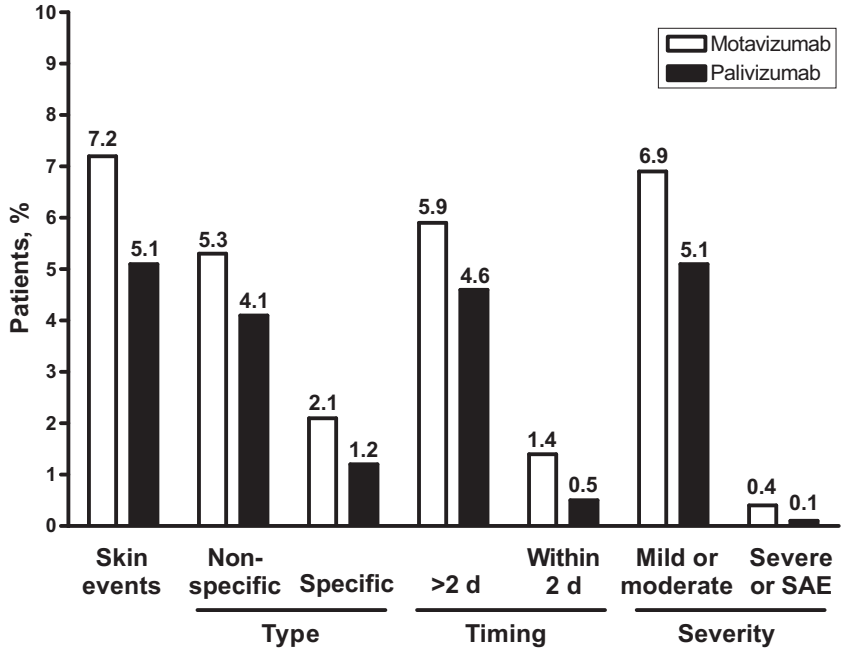

FIGURE 5

Incidence of hypersensitivity events. Nonspecific skin events consistent with rash were erythema, exanthema, flushing, pruritus, rash, erythematous rash, macular rash, maculopapular rash, and pruritic rash. Skin events consistent with possible cutaneous hypersensitivity were anaphylactoid reaction, angioedema, angioneurotic edema, allergic dermatitis, drug eruption, drug hypersensitivity, erythema annulare, erythema marginatum, erythema multiforme, eye swelling, eyelid edema, face edema, hypersensitivity, injection-site erythema (an event with localized urticaria), laryngeal edema, lip swelling, edema, periorbital edema, generalized rash, swelling, facial swelling, tracheal edema, urticaria, generalized urticaria, and papular urticaria.

TABLE 8 Changes in Serum Chemistry Results Recorded as AEs

Event	Motavizumab ($N = 3315$), *n* (%)	Palivizumab ($N = 3298$), *n* (%)
≥1 event	59 (1.8)	63 (1.9)
Alanine aminotransferase increased	26 (0.8)	26 (0.8)
Aspartate aminotransferase increased	23 (0.7)	31 (0.9)
Hepatic enzyme increased	11 (0.3)	14 (0.4)
Liver function tests abnormal	4 (0.1)	4 (0.1)
Transaminase increased	2 (0.1)	3 (0.1)
Aspartate aminotransferase abnormal	1 (<0.1)	0 (0.0)
Alanine aminotransferase abnormal	0	1 (<0.1)

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