CORRESPONDENCE

Safety of Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity

TO THE EDITOR: The efficacy and safety of nirsevimab in the treatment of medically attended respiratory syncytial virus (RSV) infections of the lower respiratory tract in otherwise healthy, late preterm and term infants were assessed in the phase 2B[1] and phase 3 MELODY[2] trials. An ongoing phase 2–3 trial (ClinicalTrials.gov number, NCT03959488) is evaluating the safety and pharmacokinetics of nirsevimab in infants at risk for severe RSV infection of the lower respiratory tract who are eligible to receive palivizumab. Here, we report the safety and pharmacokinetics of nirsevimab through the first RSV season in a study spanning two RSV seasons (see Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

We enrolled preterm infants who were eligible to receive palivizumab, who were born on or before 35 weeks of gestation, and who did not have congenital heart disease (CHD) or chronic lung disease (CLD) of prematurity (preterm cohort) and infants who had uncorrected, partially corrected, or medically treated CHD (Table S1) or CLD warranting therapeutic intervention within 6 months (CHD–CLD cohort) (see Section S2 and the protocol, available at NEJM.org, for the criteria for inclusion in the study). The study received approval from the institutional review boards at all study sites, and written informed consent was provided by a parent or guardian. Infants were randomly assigned to receive nirsevimab in a single, fixed intramuscular dose of 50 mg if they weighed less than 5 kg and a dose of 100 mg if they weighed 5 kg or more, to be followed by four once-monthly doses of placebo or five once-monthly intramuscular doses of palivizumab (15 mg per kilogram of body weight per dose). Data on adverse events that occurred during treatment and adverse events of special interest were collected through day 361. Pharmacokinetics and antidrug antibody levels were assessed (see Section S3).[3]

Overall, 925 infants were enrolled: 310 in the CHD–CLD cohort and 615 in the preterm cohort. At the time of the primary analysis, follow-up to day 151 had been completed for 886 of 925 infants (95.8%) and follow-up to day 361 had been completed for 365 of 925 infants (39.5%) (see Fig. S2). Baseline characteristics were generally balanced in the two cohorts (Table S2) and reflective of the countries where adequate care was available for neonates born prematurely or with CHD–CLD and where palivizumab is the standard of care (Table S3).

The incidence of adverse events was similar across treatment groups and cohorts (Tables 1 and S4). Two adverse events of special interest were reported, both of which occurred in the nirsevimab group: heparin-induced thrombocy-

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Table 1. Adverse Events Occurring during Treatment through 360 Days after Administration of the First Dose of Nirsevimab in the As-Treated Population.*

Event	Preterm Cohort		CHD–CLD Cohort	
	Palivizumab (N=206)	Nirsevimab (N=406)	Palivizumab (N=98)	Nirsevimab (N=208)
	number of infants (percent)			
≥1 Adverse event	134 (65.0)	268 (66.0)	72 (73.5)	148 (71.2)
≥1 Treatment-related adverse event	4 (1.9)	6 (1.5)	2 (2.0)	4 (1.9)
≥1 Adverse event of grade ≥3 severity†	7 (3.4)	14 (3.4)	13 (13.3)	30 (14.4)
≥1 Treatment-related adverse event of grade ≥3 severity†	0	0	0	0
Any adverse event with outcome of death (grade 5 severity)†	0	2 (0.5)	1 (1.0)	3 (1.4)
≥1 Serious adverse event‡	11 (5.3)	28 (6.9)	20 (20.4)	40 (19.2)
≥1 Serious adverse event, grade ≥3 adverse event, or both†	11 (5.3)	28 (6.9)	21 (21.4)	45 (21.6)
≥1 Treatment-related serious adverse event	0	0	0	0
≥1 Adverse event of special interest§	0	1 (0.2)	0	1 (0.5)
≥1 Covid-19–related adverse event¶	1 (0.5)	8 (2.0)	1 (1.0)	2 (1.0)

* The as-treated population included participants who received any study drug. In this population, participants were analyzed according to the actual treatment received (nirsevimab or palivizumab). Infants with multiple events in the same category were counted once in that category. Infants with events in more than one category were counted once in each of those categories. Adverse events were graded according to severity with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events and were coded with the use of the *Medical Dictionary for Regulatory Activities* (version 23.1). The data reported were those available as of May 3, 2021, which was the cutoff date for the primary analysis. CHD denotes congenital heart disease, CLD chronic lung disease, and Covid-19 coronavirus disease 2019.

† An adverse event of grade 3 denotes a severe event, an adverse event of grade 4 a life-threatening event, and an adverse event of grade 5 a fatal event.

‡ Serious adverse events were defined as death, events that were life-threatening or required inpatient hospitalization, events that prolonged hospitalization, events that were persistent or that were associated with clinically significant disability or incapacity, or events that were considered to be of medical significance.

§ Adverse events of special interest included hypersensitivity, immune complex disease, and thrombocytopenia and were determined on the basis of investigator assessment.

¶ Covid-19–related adverse events were symptomatic or asymptomatic Covid-19 cases with a confirmatory diagnostic test positive for severe acute respiratory syndrome coronavirus 2 or suspected cases for which signs and symptoms were judged by the investigator to be highly suspicious for Covid-19 but for which a confirmatory diagnostic test was unavailable or negative.

topenia in an infant with CHD and maculopapular rash following a placebo dose in a preterm infant. Five deaths occurred in the nirsevimab group: two in the preterm cohort and three in the CHD–CLD cohort (Table S5). One death occurred in the palivizumab group (CHD–CLD cohort). All deaths were thought to be unrelated to treatment by the investigator. Seven of the infants receiving nirsevimab had medically attended RSV infections of the lower respiratory tract (4 of 616 infants [0.6%] receiving nirsevimab and 3 of 309 infants [1.0%] receiving palivizumab [see Table S6 for case definitions]). At day 151, serum levels of nirsevimab were similar in the two cohorts and similar to those reported in the MELODY trial (Table S7).[2] The antidrug–antibody response at day 151 was low (occurring in 2 of 483 infants [0.4%] in the nirsevimab group and 9 of 251 infants in the palivizumab group [3.6%]). In infants with CHD or CLD and in those born preterm, the safety profile of nirsevimab was similar to that of palivizumab.

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The data sets generated or analyzed during the current study are available through Vivli (https://vivli.org/), in accordance with AstraZeneca's data-sharing policy (described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure).

Funded by MedImmune/AstraZeneca and Sanofi. Medical writing support was provided by CMC Connect under the direction of the authors and was funded by AstraZeneca and Sanofi. Nirsevimab and palivizumab were provided by MedImmune/AstraZeneca.

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

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DOI: 10.1056/NEJMc2112186

Effects of a Prolonged Booster Interval on Neutralization of Omicron Variant

TO THE EDITOR: The coronavirus disease 2019 (Covid-19) pandemic is still ongoing,[1] and the B.1.1.529 (or omicron) variant, first detected in November 2021, has already spread globally. The ability of the omicron variant to escape vaccine-elicited immunity is of great concern. Inactivat-

Figure 1 (facing page). Serum IgG Titers and Pseudovirus Neutralization against the Omicron Variant.
Serum samples were obtained from persons who had recovered from coronavirus disease 2019 (the convalescent group) or persons who had received three doses of an inactivated vaccine or the ZF2001 protein subunit vaccine. These samples were tested for binding and neutralizing antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) prototype and variants of concern (B.1.1.7 [or alpha], B.1.351 [or beta], B.1.617.2 [or delta], and B.1.1.529 [or omicron]). Panels A through D show the titers of serum IgG antibodies against the SARS-CoV-2 prototype strain or the omicron trimeric spike protein. The persons in the inactivated-vaccine group received the second priming dose 1 month after the first dose and then the third dose more than 6 months after the second dose. The persons in the short-interval ZF2001 group received the second priming dose 1 month after the first dose and then the third dose 1 month after the second dose. The persons in the prolonged-interval ZF2001 group received the second priming dose 1 month after the first dose and then the third dose 4 months after the second dose. A total of 8 samples from 8 persons were tested in each group. Panel E shows the percentage of samples that tested positive (as indicated by a titer of >1:20) for neutralizing antibodies against the omicron variant. "Prolonged-interval ZF2001 4–6 Mo" refers to the 13 serum samples from vaccinees who also had a prolonged interval between the second and third dose but were collected 4 to 6 months after the third dose. Panels F through I show the 50% pseudovirus neutralization titer ($pVNT_{50}$) in serum samples against the SARS-CoV-2 prototype and variants of concern; the $pVNT_{50}$ is the end-point titer of serum dilution that inhibits pseudovirus infection by 50%. A total of 16 samples from 16 persons were tested in each group. Panel J shows the $pVNT_{50}$ in the 13 samples from the prolonged-interval ZF2001 4–6 group. All neutralization assays were repeated twice. In all the panels except Panel E, geometric mean titers (GMTs) with 95% confidence intervals are shown, and the dashed lines indicate the lower limit of detection. In Panels A through D, the values above the bars are the GMT of the end-point titer in the enzyme-linked immunosorbent assay of SARS-CoV-2–binding IgG (see the Supplementary Analysis). In Panels F through J, the values above the bars are the GMT of the $pVNT_{50}$; $pVNT_{50}$ titers lower than 1:20 were considered to indicate that the sample was negative for neutralization antibodies.