FDA Briefing Document

BLA# [761328]

Drug name: nirsevimab

Applicant: AstraZeneca AB

Antimicrobial Drugs Advisory Committee Meeting

June 8, 2023

Division of Antivirals (DAV)/Office of Infectious Diseases (OID)

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Glossary

AC	Advisory Committee
ADA	anti-drug antibody
AE	adverse event
AUC	area under the concentration-time curve
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CHD	congenital heart disease
CI	confidence interval
CL	clearance
CLD	chronic lung disease
EMA	European Medicines Agency
FDA	Food and Drug Administration
FMQ	FDA Medical Queries
GA	gestational age
IM	intramuscular
ITT	intent-to-treat
LRT	lower respiratory tract
LRTD	lower respiratory tract disease
LRTI	lower respiratory tract infection
MA RSV LRTI	medically attended respiratory syncytial virus lower respiratory tract infection
PK	pharmacokinetic
RRR	relative risk reduction
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SD	standard deviation

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The Food and Drug Administration (FDA) is convening this Advisory Committee meeting to discuss whether available data support a favorable benefit-risk assessment for the use of nirsevimab for the prevention of respiratory syncytial virus (RSV) lower respiratory tract (LRT) disease in neonates and infants born during or entering their first RSV season, and in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

1.2 Context for Issues to Be Discussed at the AC

RSV is the most common cause of lower respiratory tract infection (LRTI) in infants and young children both in the United States and worldwide. Approximately 20% to 30% of infants with RSV develop LRT disease with their first RSV infection (Committee on Infectious Diseases 2021-2024). RSV LRTI usually presents as bronchiolitis and/or pneumonia. According to a prospective study by Lively et al. (2019), RSV infection results in 59.6 emergency department visits per 1,000 children <24 months of age annually, as well as 205.7 pediatric practice visits per 1,000 children <24 months of age annually (Lively et al. 2019). Approximately 1% to 3% of children <12 months of age in the United States are hospitalized each year due to RSV (The Red Book). According to the Centers for Disease Control and Prevention (CDC), there are 100 to 300 deaths per year in children younger than 5 years of age in the United States. In one retrospective review of deaths from 1999 to 2018 in the United States, the mean mortality rate for RSV in infants <12 months of age was 96 per 100,000 (Hansen et al. 2022). Overall, RSV infection is a common respiratory infection in infants and children, and can be severe, serious or life-threatening.

Nirsevimab is a recombinant neutralizing human immunoglobulin G1 kappa monoclonal antibody directed against the prefusion conformation of the RSV fusion (F) protein. Nirsevimab has a three amino acid substitution (YTE) in C_{H2} to extend its half-life and reduce recruitment of Fc effector functions. Nirsevimab binds to the antigenic site, ø, on the prefusion conformation of the F protein, preventing the membrane fusion step in the viral entry process. Astra Zeneca (Applicant) has submitted a Biologics License Application (BLA) for nirsevimab to support an indication for the prevention of RSV LRT disease in neonates and infants born during and entering their first RSV season, and in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

Currently, only palivizumab (SYNAGIS^{R}) is approved for the prevention of serious RSV LRT disease in certain infants and children who are at high risk for RSV disease.[1] Palivizumab is also a recombinant neutralizing human immunoglobulin G1 kappa monoclonal antibody against the RSV fusion (F) protein and has a similar mechanism of action as nirsevimab, but targets antigenic site II on the RSV F protein which is exposed in both prefusion and postfusion conformations. Palivizumab has a shorter half-life than nirsevimab and is administered monthly during RSV season, while nirsevimab is to be administered once as a single dose prior to or during RSV season.

[1] Synagis is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia, infants with a history of premature birth (less than or equal to 35 weeks gestational age), and infants with hemodynamically significant congenital heart disease.

While no other drugs or biologics are approved for the prevention of RSV LRT disease, several infant and maternal vaccines are in development, including some in late stages of development.

1.3 Brief Description of Issues for Discussion at the AC

The proposed indication for nirsevimab is the prevention of RSV lower respiratory tract disease in:

- Neonates and infants born during or entering their first RSV season.
- Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

The proposed nirsevimab dose for the first RSV season is a single, 50-mg intramuscular (IM) injection for infants weighing <5 kg, and a single, 100-mg IM injection for infants weighing 5 kg and greater. For children less than 24 months of age who remain at increased risk for severe RSV in their second RSV season, the proposed dose is a single, 200-mg IM injection.

To support the proposed indication, the Applicant conducted 3 clinical trials (Trials 03, 04, and 05) which provide relevant efficacy and safety data (Table 1). In these 3 trials, efficacy was evaluated at Day 150 post-dose, and safety was evaluated through Day 360. Key findings from these trials are summarized below.

Trial 03, a double-blind, placebo-controlled trial, evaluated the safety and efficacy of nirsevimab for the prevention of medically attended respiratory syncytial virus lower respiratory tract infection (MA RSV LRTI) in infants born at ≥29 weeks to <35 weeks of gestation who were born during or entering their first RSV season. Nirsevimab was administered as a single 50-mg IM dose regardless of weight. The incidence of MA RSV LRTI through Day 150 post-dose was 25/969 (2.6%) in the nirsevimab arm and 46/484 (9.5%) in the placebo arm for a relative risk reduction of 70.1% (95% confidence interval (CI): 52.3% to 81.2%; p <0.0001).[2] The incidence of hospitalization due to RSV was a key secondary endpoint. Eight of 969 subjects (0.8%) in the nirsevimab arm were hospitalized with RSV compared to 20 of 484 subjects (4.1%) in the placebo arm for a relative risk reduction of 78.4% (95% CI: 51.9% to 90.3%; p=.0002).[3] The most common adverse reactions in the nirsevimab group reported during the 360-day safety follow-up period were rash (0.7%) and injection site reactions (0.4%).

Trial 04 (MELODY), a double-blind, placebo-controlled trial, also evaluated the safety and efficacy of a single-dose of nirsevimab for the prevention of MA RSV LRTI. Trial 04 enrolled infants born at ≥35 weeks of gestation who were born during or entering their first RSV season. A single IM dose of nirsevimab was administered according to body weight: infants weighing <5 kg received 50-mg and infants weighing ≥5 kg received 100-mg. Trial 04 included 2 cohorts which were enrolled sequentially. Efficacy was assessed in the "Primary" cohort, which included the first 1,478 subjects who were randomized and dosed with study product. After enrollment of subjects in the Primary cohort, the database was locked and efficacy was analyzed for subjects in the Primary cohort. The study subsequently enrolled additional subjects in both the nirsevimab and placebo arm (N=1516) to supplement the safety assessment. The cohort of subjects enrolled after completion of the Primary Cohort was called the "Safety" cohort. The primary objective of the Safety cohort was the assessment of safety; efficacy was assessed as an exploratory endpoint. The entire population for the trial (Primary cohort plus Safety cohort), referred to

[2] Results based on the Poisson regression adjusted for age and hemisphere and multiple imputations for missing data.

[3] Results based on the Poisson regression with multiple imputations for missing data.

as “All Subjects” cohort (N=2,994), is used for the safety analysis. In the Primary cohort, the incidence of MA RSV LRTI through Day 150 post-dose was 12/994 (1.2%) in the nirsevimab arm and 25/496 (5.0%) in the placebo arm for a relative risk reduction of 74.9% (95% CI: 50.6% to 87.3%; p <0.0001).[4] In the Primary cohort, the incidence of hospitalization due to RSV was a secondary endpoint; 6 of 994 subjects (0.6%) in the nirsevimab arm and 8 of 496 subjects (1.6%) in the placebo arm were hospitalized due to RSV for a relative risk reduction of 60.2% (95% CI: -14.6% to 86.2%; p=0.09).[5] The most common adverse reactions in the nirsevimab group reported during the 360-day safety follow-up period were rash (0.5%) and irritability (0.2%).

Trial 05 (MEDLEY), a double-blind, active-controlled trial, compared the safety of nirsevimab versus palivizumab in infants at high risk of severe RSV disease [premature infants born at <35 weeks of gestation, and infants with chronic lung disease (CLD) of prematurity or hemodynamically significant congenital heart disease (CHD)]. The study was not designed or powered to evaluate efficacy, but efficacy was assessed as a secondary endpoint. In the first RSV season, the incidence of MA RSV LRTI through 150-days post dose was (4/616) 0.6% in the nirsevimab group and (3/309) 1.0% in the palivizumab group. There were no cases of MA RSV LRTI in the second RSV season, which was conducted in 2020 during the COVID-19 pandemic. The most common adverse events judged as related to drug product in the nirsevimab group in RSV season 1 that were reported during the 360-day safety follow-up period were agitation or irritability (0.7%), increased temperature (0.5%), and rash (0.4%). In the 150-day post-dose follow-up period for RSV season 2, there were no adverse reactions (adverse events judged as drug-related); the most commonly reported adverse event was pyrexia, which was reported in 13.2% of subjects who received nirsevimab and 11.9% of subjects who received palivizumab.

This AC briefing document for nirsevimab summarizes key efficacy and safety considerations, as well as our pharmacovigilance strategy, to inform the AC’s consideration of these issues, as outlined below.

Efficacy Considerations:

- Efficacy of nirsevimab in preventing RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season
    - Efficacy in sub-populations (by GA and chronological age)

- Efficacy of nirsevimab in preventing RSV lower respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

Safety Considerations:

- Hypersensitivity reactions, including anaphylaxis and rash
- Imbalance in deaths

[4] Results based on the Poisson regression adjusted for age and hemisphere and multiple imputations for missing data.

[5] Results based on the Poisson regression with multiple imputations for missing data.

Pharmacovigilance Plan:

- Proposed pharmacovigilance strategy for nirsevimab, if approved

Other Considerations:

- Potential benefits and risks of nirsevimab in infants whose mothers may receive maternal RSV immunization (should such a maternal immunization be licensed)

1.4 Draft Points for Consideration

1. Is the overall benefit-risk assessment favorable for the use of nirsevimab for the prevention of RSV lower respiratory disease in neonates and infants born during or entering their first RSV season?
2. Please comment on the benefits and risks for nirsevimab when assessed by chronological and gestational age groups. Discuss the population or subpopulation for whom nirsevimab administration in the first RSV season would be most appropriate.
3. Is the overall benefit-risk assessment favorable for the use of nirsevimab for the prevention of RSV lower respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season?
4. In the context of potential, future availability of maternal RSV vaccine to protect infants from RSV disease during their first RSV season, what additional data may be helpful to inform future recommendations regarding the use of nirsevimab in infants born to mothers who received RSV vaccination?

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Human respiratory syncytial virus (RSV) is an orthopneumovirus in the Family Pneumoviridae, with a negative-sense, non-segmented RNA genome and lipid envelope. RSV consists of two antigenic subtypes, RSV-A and RSV-B, which vary in relative prevalence across seasons, and are further subdivided into different clades. The RSV fusion (F) surface glycoprotein mediates fusion between viral and host cell membranes, an essential step in the viral entry process. Niresvimab targets antigenic site Ø on the prefusion conformation of F protein which locks the F protein in the prefusion state, preventing the conformation change and virus-cell membrane fusion needed for cell entry.

RSV occurs in annual outbreaks each fall and winter in most of the United States. Most children and adults with symptomatic RSV infection have self-limited disease with signs and symptoms limited to the upper respiratory tract. However, RSV can present as a lower respiratory tract (LRT) disease, particularly in very young children and the elderly. Because of annual RSV outbreaks, almost all children have been infected with RSV by 2 years of age. (The Red Book 32nd Edition and www.cdc.gov/rsv/clinical/index.html).

RSV is the most common cause of LRT disease in infants and young children both in the United States and worldwide. Approximately 20% to 30% of infants with RSV develop LRT disease with their first RSV infection. RSV LRT disease (LRTD) usually presents as bronchiolitis and/or pneumonia. The CDC estimates that RSV infection results in 2.1 million outpatient visits yearly among children younger than 5 years of age. Investigators have estimated that RSV infections in pediatric patients results in 472,000 visits to Emergency Departments each year in children < 2 years of age. RSV LRTD is the most common of hospitalization for infants in the United States (Ektare et al. 2022). Approximately 1% to 3% of

children in the United States are hospitalized in the first 12 months of life due to severe RSV disease (Committee on Infectious Diseases 2021-2024). In children younger than 5 years of age, RSV LRTD results in 58,000 to 80,000 hospitalizations each year in the United States (Centers for Disease Control and Prevention 2022). The majority of children hospitalized with RSV LRTD improve with supportive care and are discharged in 2 to 3 days(Committee on Infectious Diseases 2021-2024). However, there are 100 to 300 deaths due to RSV LRTD in children younger than 5 years of age annually in the United States (Centers for Disease Control and Prevention 2022).

According to CDC, all infants (children ≤12 months of age), particularly those 6 months of age or younger are at increased risk of hospitalization (Centers for Disease Control and Prevention 2023). While some studies have shown that the highest risk for severe RSV LRTD in otherwise healthy infants is for infants in the second month of life, the risk of hospitalization continues to at least 12 months of age (Hall et al. 2013). In a study by Hall et al. (2009), 58% of children hospitalized with RSV LRTD were 0 to <6 months of age, and 17% were from 6 to <12 months of age. Hospitalizations due to RSV LRTD were not reported in children older than 5 years of age (Hall et al. 2009).

Severe RSV disease and hospitalization are more common in pediatric patients born prematurely and in those with certain underlying conditions. (www.cdc.gov/rsv/clinical/index.html) According to the CDC, the children at greatest risk for severe illness include premature infants in the first year of life, children younger than 2 years of age with chronic lung disease (CLD) of prematurity or hemodynamically significant congenital heart disease (CHD), immunocompromised children, and children with neuromuscular disorders that have difficulty swallowing or handling secretions. The risk of severe RSV LRTD in infants born prematurely increases with decreasing GA. Although the increased risk of severe RSV LRTD has been reported for all premature infants born at <35 weeks of gestation, the American Academy of Pediatrics (AAP) determined that most studies supported an increased risk of severe RSV LRTD in infants born before 29 weeks of gestation (American Academy of Pediatrics 2022).

The hospitalization rates for RSV decrease after the first year of life; approximately 75% of hospitalizations for RSV occur in the first year of life (Hall et al. 2009). However, some comorbidities, such as chronic lung disease of prematurity (CLD) with continued requirement for medical intervention and hemodynamically significant congenital heart disease (CHD), place children at risk of severe RSV disease in the second year of life (American Academy of Pediatrics 2022).

Palivizumab (Synagis®) is the only drug approved by FDA for the prevention of RSV lower respiratory disease.[1] Palivizumab is indicated for the prevention of serious RSV lower respiratory tract disease in high-risk infants. This indication was supported by trials in premature infants born at <35 weeks of gestation, infants with chronic lung disease of prematurity, and infants with hemodynamically significant congenital heart disease. The efficacy of palivizumab was assessed in 2 trials in which the primary efficacy endpoint was the incidence of RSV-associated hospitalization. In the first trial there was a 55% relative reduction in RSV-associated hospitalizations and in the second there was a 45% relative reduction in RSV- associated hospitalizations.

Palivizumab, like nirsevimab, is a recombinant humanized monoclonal antibody directed against a conserved epitope on the RSV fusion (F) protein. Because palivizumab is not modified to extend its serum half-life, a monthly intramuscular injection is required. The first dose of palivizumab is administered prior to the start of the RSV season and remaining four doses are administered monthly during the RSV season.

Aerosolized ribavirin is the only drug or biologic product approved for the treatment of RSV disease. (dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=adf16e64-345f-469a-b987-3fbdd17e0ac2). However, use of aerosolized ribavirin is limited due to its teratogenic effects and administration challenges, including risk of environmental spread. Aerosolized ribavirin must be administered in a hospital setting, and is generally administered using an oxygen tent.

While palivizumab is the only FDA approved drug for the prevention of RSV lower respiratory tract disease, multiple vaccines are under development to prevent RSV disease. These include maternal vaccines to prevent RSV disease in infants by passive transfer of maternal antibodies to the infant, as well as infant vaccines. There are also several drugs currently in development to treat RSV disease.

2.2 Pertinent Drug Development and Regulatory History

The applicant has conducted three pivotal trials in infants and children to support the proposed indications. Trials 03 and 04 were randomized, double-blind, placebo-controlled trials in infants born during or entering their first RSV season. Trial 05 was a randomized, double-blind, palivizumab-controlled trial over two RSV seasons in infants and children at high-risk of serious RSV LRT disease. Additionally, safety data are available from three supportive trials: Trial 01 and Trial 02 which were dose-escalating trials in adults and infants, and Trial 08, an ongoing single arm study in immunocompromised children (see Table 15, Appendix 1).

Key Regulatory Milestones

- The initial Pediatric Study Plan was agreed upon on April 28, 2017. This agreement described the three clinical trials needed to support the efficacy, safety and dosing of nirsevimab.
- An End-of-Phase 2 meeting between the Agency and the Applicant was held in February 2019 to discuss the designs of Trials 04 and 05 and nirsevimab dosing. FDA requested a safety database of at least 3,000 subjects at this meeting.
- The Agency and the Applicant met in December 2020 to discuss the effects of the COVID-19 pandemic on nirsevimab development. The Applicant had paused enrollment in Trials 04 and 05 at this point. It was agreed that the analysis of efficacy in Trial 04 could be based on the 1,478 subjects randomized and dosed prior to the pause in enrollment (Primary Cohort). The Agency again requested that the safety database for nirsevimab include at least 3,000 infants and children, of which at least 2,000 subjects should be term infants.
- After the December 2020 meeting, the Applicant proposed enrolling an additional cohort in Trial 04 to collect safety data only. In the revised Trial 04 protocol, the Applicant stated that there was "no intent to pool the efficacy data from the Safety Cohort with that from the Primary Cohort." Efficacy was considered an exploratory endpoint in the Safety Cohort of Trial 04.
- On January 28, 2022, an application for marketing authorization was submitted to the European Medicines Agency (EMA). The EMA application included the efficacy results of the Primary Cohort from Trial 04 (MELODY) with a data cutoff of March 11, 2021.
- A pre-BLA meeting was held between the Agency and the Applicant in July 2022. At this meeting, the Agency stated that the efficacy results from Trials 03 and 04 should *not* be pooled because of the difference in infant GA enrolled in the two trials, and different risks of severe RSV disease or hospitalization due to RSV. The Agency and the Applicant agreed on pooling safety data from subjects in Trial 03 who received the proposed nirsevimab dose and subjects in Trial 04.
- On September 15, 2022 the Committee for Medicinal Products for Human Use of the EMA adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product nirsevimab. The full indication is: nirsevimab is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season. Nirsevimab should be used in accordance with official recommendations.

public

3 Summary of Issues for the AC

3.1 Efficacy Considerations

- Efficacy of nirsevimab in preventing RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season
    - Efficacy in sub-populations (by GA and chronological age)

- Efficacy of nirsevimab in preventing RSV lower respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

3.1.1 Sources of Data for Efficacy

Efficacy data in support of this BLA come from one Phase 2b trial, Trial 03, and one Phase 3 trial, Trial 04. Table 1 provides an overview of these two trials.

Table 1. Clinical Trials Used to Support Efficacy Assessments

Study Identifier	Study Title	Study Design	Treatment	Primary Endpoint	Number of Subjects Randomized
D5290C00003 (Trial 03)	A Phase 2b randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of MEDI8897, a monoclonal antibody with an extended half-life against RSV, in healthy preterm infants born at≥29 to <35 weeks GA	Phase 2b, MC, R,PC, DB	Arm 1: Nirsevimab single 50-mg IM dose Arm 2: single placebo (saline) IM dose	Incidence of RSV-MA-LRTI	Arm 1: 969 Arm 2: 484
D5290C00004 Trial 04 (MELODY)	A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of nirsevimab, a monoclonal antibody with an extended half-life against RSV, in healthy late preterm and term infants born at >35 weeks GA	Phase 3, MC, R,PC, DB	Arm 1: Nirsevimab single 50-mg IM dose in infants <5 kg, single 100-mg dose in infants ≥5 kg Arm 2: single placebo (saline) IM dose	Primary Cohort: Incidence of RSV-MA-LRTI Safety Cohort: incidence and types of AEs, SAEs, and AESIs	Primary Cohort: Arm 1: 994 Arm 2: 496 Safety Cohort: Arm 1: 1,015 Arm 2: 507

Source: BLA 761328, Module 5.2, Tables 1 and 2 pages 3-6.

Abbreviations: AESI, adverse event of special interest; DB, double-blind; MC, multicenter; PC, placebo-controlled; R, randomized

Change in outcome status for subjects in Trial 04

3.1.2 During review of the application, the Agency identified a data discrepancy. There were two subjects in the Primary Cohort that were initially marked as non-events in the dataset and subsequently identified by the Applicant as lost to follow-up. These analysis results are based on the updated dataset that includes those subjects as lost to follow-up.

3.1.3 Efficacy Summary

Pharmacokinetic (PK) data are used to support the Applicant's proposed dosing regimen in healthy neonates and infants as well as efficacy extrapolation from healthy neonates and infants to high-risk infants and children. The proposed weight-based dosing regimen for RSV season 1 is a single, 50-mg IM dose for infants weighing <5 kg, and a single, 100-mg IM dose for infants weighing ≥5 kg. For children less than 24 months of age who remain at increased risk for severe RSV in their second RSV season, the proposed dose is a single, 200-mg IM dose.

PK analysis indicates that most subjects' nirsevimab serum concentrations remain above the EC_{90} value of 6.8 µg/mL at the end of the proposed protection period (i.e., Day 150 post-dose) following the proposed dosing regimen (See Trial 4 and Trial 5 below for details). EC_{90} (concentration for 90% effectiveness) value was determined based on RSV challenge studies in cotton rats, a model that was used for dose selection of palivizumab. In addition, most subjects' $AUC_{baselineCL}$ remains above the target exposure of 12.8-mg*day/mL identified by exposure-response analysis [See Trial 4 (below) and Trial 5 (below) for details]. $AUC_{baselineCL}$ is the AUC value calculated based on the individual clearance (CL) at baseline.

Trial 03

Trial 3 (also known as D5290C0003) was designed as a Phase 2b, randomized, placebo-controlled trial to assess efficacy of nirsevimab in very and moderately preterm infants born at ≥29 to <35 weeks of gestation, entering or during their first RSV season.

Subjects were randomized 2:1 to receive nirsevimab (N=969) or placebo (N=484). Randomization was stratified by the northern and southern hemispheres and by subject age at the time of randomization (i.e., ≤3 months, >3 to ≤6 months, and >6 months). All infants were to be followed for 360-days after dosing. Nirsevimab was administered as a single, 50-mg IM dose regardless of body weight.

A total of 1453 subjects were randomized. Baseline demographic characteristics were as follows: mean age of 3.3 months; mean weight of 4.6 kg; 52% male; 72% White, 18% Black or African American, 1% Asian; 22% Hispanic or Latino. The baseline demographic characteristics were balanced between the two arms.

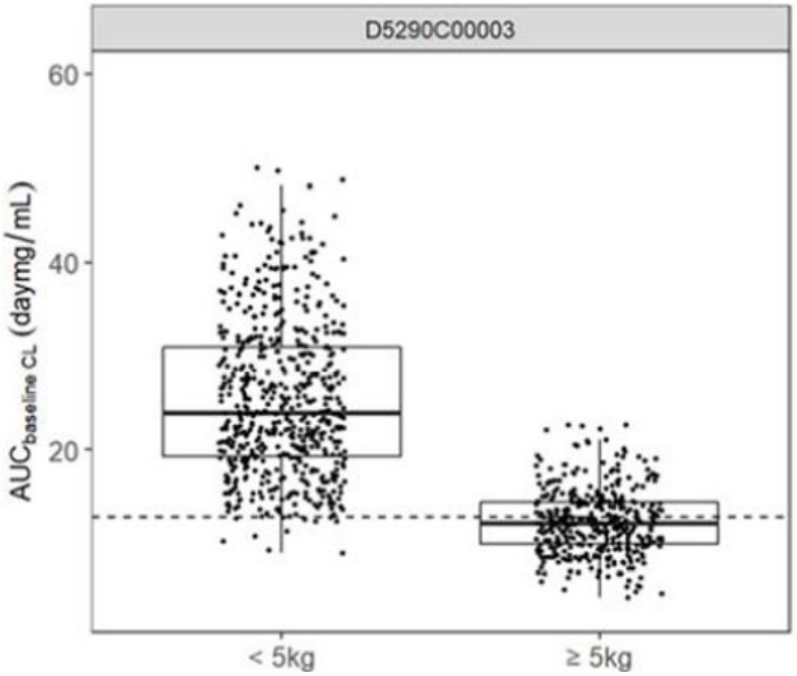
All efficacy analyses were conducted using all randomized subjects following the Intent- to-treat (ITT) principle. Subjects were included in their randomized treatment group, regardless of the treatment they received.

Dose Selection

In Trial 03, a single, 50-mg IM dose was administered to all infants regardless of weight, based on PK simulations in order to maintain nirsevimab serum concentrations above 6.8 µg/mL over the 5-month RSV season. Most subjects (97%) in Trial 03 achieved Day 150 post-dose nirsevimab serum concentrations above the target of 6.8 µg/mL. However, nirsevimab exposure (in terms of $AUC_{baselineCL}$) in

infants weighing <5 kg was higher than the exposure in infants weighing ≥5 kg (Figure 1). In addition, the incidence of MA RSV LRTI was higher in infants weighing ≥5 kg compared to infants weighing <5 kg (Figure 2). This led to a decision to modify the dosing regimen for Trial 04: a single, IM dose of 100-mg for infants weighing ≥5 kg; and a single, IM dose of 50-mg for infants weighing <5 kg. Please refer to Trial 04 below for additional discussion.

Figure 1. Box Plots of AUC Baseline CL Versus Weight Group in Trial 03 (D5290C0003)



Source: Applicant's Clinical Pharmacology Summary, Figure 10, modified
The dashed line is the AUC Q1 threshold of 12.8-mg*day/mL.

Incidence of MA RSV LRTI (Primary Endpoint)

The primary endpoint was the incidence of medically attended LRTI (regardless of hospitalization), due to reverse transcription polymerase chain reaction (RT-PCR)-confirmed RSV 150 days post dose in infants born during or entering their first RSV season. Day 150 post-dose represents 5 months of a typical RSV season, the proposed period of protection. In addition, the Day 150 post-dose time point was justified based on nirsevimab PK, which remains above the target EC_{90} through Day 150 post-dose.

Out of 1,453 subjects who were randomized, 35 (2.4%) discontinued and did not have their outcome status on Day 150 post-dose (primary endpoint). In addition, one subject on placebo who experienced an event of MA RSV LRTI, died before Day 150 post-dose. Most of the discontinuations were withdrawal by a parent or by a legal representative. The missing data rates for both primary endpoint (Day 150 post-dose) and the end of study (Day 361) were similar across treatment groups.

The number of subjects who experienced MA RSV LRTI by Day 150 post-dose in each of the treatment arms and the results of the analysis of the primary endpoint are presented in Table 2. The estimated relative risk reduction (RRR) was 70.1% (95%CI: 52.3% to 81.2%) with p-value <0.0001 in favor of nirsevimab.

Table 2. Incidence of MA RSV LRTI by Day 150 Post-Dose (Primary Endpoint) in Trial 03

	Trial 03	
Statistic	**Nirsevimab N=969**	**Placebo N=484**
Events (# of subjects, n (%))	25 (2.6)	46 (9.5)
Subjects requiring imputation* n (%)	24 (2.5)	11 (2.3)
RRR (95% CI)[§]	70.1% (52.3% to 81.2%) p <0.0001	

Source: FDA statistical reviewer

*Subjects with missing outcomes on Day 150 post-dose. The final status of those subjects was imputed based on the observed placebo rate conditional on stratification factors using multiple imputation approach.

[§]Based on Poisson regression model with robust variance with treatment group and age group at randomization (i.e., age ≤3 months, age >3 to ≤6 months, age >6 months) and dichotomous temperate (northern and southern) hemispheres as covariates

Abbreviations: CI, confidence interval; MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection; N, number of subjects; n, number of subjects with specific incident; RRR, relative risk reduction

Sensitivity Analysis (To Evaluate the Impact of Missing Data)

Following the primary analysis, where the final status for all subjects with missing outcome at Day 150 post-dose was imputed based on the observed placebo rate, a more conservative sensitivity analysis was performed. In this sensitivity analysis, all subjects on nirsevimab who had a missing outcome (i.e., subjects requiring imputation) had their outcomes imputed as events (MA RSV LRTI).

The outcome of this analysis yielded a relative risk reduction of 48.4% (95%CI: 24.2%, 64.9%) favoring nirsevimab. This result suggests that the outcome of the primary analysis was robust.

Incidence of hospitalization Due to MA RSV LRTI (Secondary Endpoint)

The results for the secondary endpoint analysis –number of subjects who experienced MA RSV LRTI and were hospitalized by Day 150 post-dose in each of the treatment arms –are presented in Table 3. The estimated RRR was 78.4% (95%CI: 51.9%, 90.3%) with p-value=0.0002 in favor of nirsevimab.

Table 3. Incidence of Hospitalization by Day 150 Post-Dose (Secondary Endpoint) in Trial 03

	Trial 03	
Statistic	**Nirsevimab N=969**	**Placebo N=484**
Events (# of subjects, n (%))	8 (0.8)	20[†] (4.1)
Subjects requiring imputation* n (%)	24 (2.5)	11 (2.3)
RRR (95% CI)[§]	78.4% (51.9%, 90.3%) p-value=0.0002	

Source: FDA statistical reviewer

[†]One subject who experienced MA RSV LRTI and died due to pneumonia with empyema one month after resolution of RSV.

*Subjects with missing outcomes on Day 150 post-dose. The final status of those subjects was imputed based on the observed placebo rate conditional on stratification factors using multiple imputation approach.

[§]Based on Poisson regression model with robust variance with treatment group as a covariate

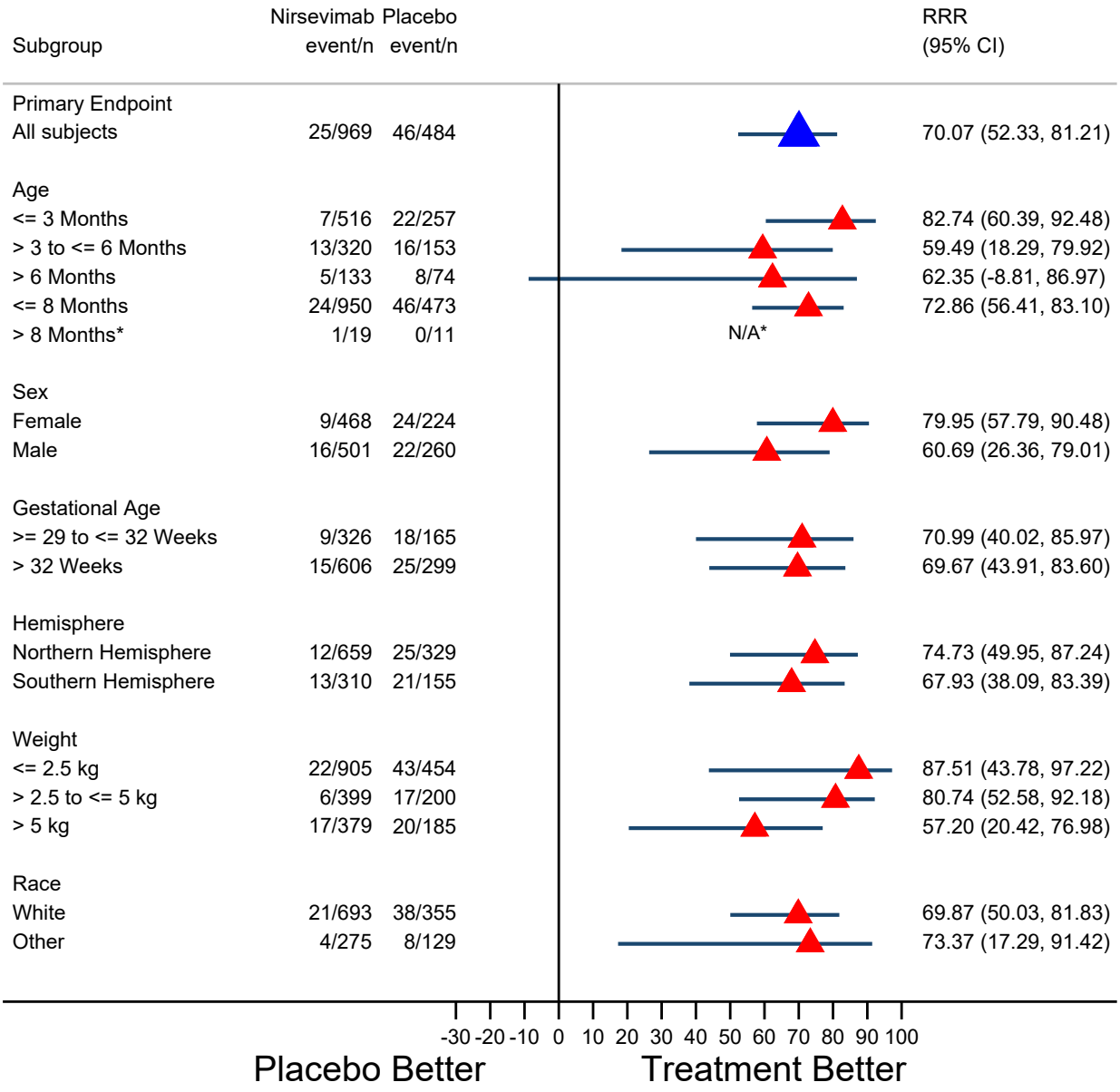
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with specific incident; RRR: relative risk reduction

Additional efficacy analyses are included in Appendix 2.

Subgroup Analysis of Primary Endpoint

The treatment effects based on the incidence of MA RSV LRTI (primary endpoint) were consistent across subgroups and were consistent with the overall treatment effect (Figure 2). Refer to Section 3.1.3 for additional discussion on subgroup analysis by chronological age and GA.

Figure 2. Subgroup Analyses of MA RSV LRTI in Trial 03



Source: FDA statistical reviewer

*The RRR cannot be calculated because the number of events was not sufficient

Abbreviations: CI, confidence interval; MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection; n, number of subjects; RRR, relative risk reduction

Trial 04

Trial 04 (also known as D5290C0004) was designed as a Phase 3, randomized, placebo-controlled trial to assess efficacy of nirsevimab in term and late preterm infants born at ≥35 weeks of gestation, during or entering their first RSV season.

Similar to Trial 03, in Trial 04, subjects were randomized 2:1 to receive nirsevimab or placebo. Randomization was stratified by hemisphere (northern and southern hemisphere) and subject age at randomization (i.e., ≤3.0 months, >3.0 to ≤6.0 months, >6.0 months).

Nirsevimab was administered as a single intramuscular dose based on body weight at baseline (50-mg for infants weighing <5 kg or 100-mg for infants weighing ≥5 kg). The primary and secondary endpoints were evaluated on Day 150 post-dose and subjects were followed for safety through Day 361.

Impact of COVID-19 Pandemic on Trial Conduct

Because of the COVID-19 pandemic's impact on operational aspects of study conduct and the reduced incidence of RSV during that time, enrollment in the trial was paused. The dataset collected before the pause is referred as the Primary Cohort in this document. After the discussion with the Agency, the study design was amended. Furthermore, the Statistical Analysis Plan (SAP) was revised and prespecified that the Primary Analysis would be based on the 1490 subjects randomized prior to the pause in enrollment (Primary Cohort). It was also agreed that the planned study sample size would be completed by enrollment of a complementary Safety Cohort.

New Sample Size and the Two Study Cohorts

The original planned sample size for this study was 3000 subjects. Because of the COVID-19 interruption, the recruitment approach changed. As a result, the Primary Cohort consisted of 1490 subjects (994 on Nirsevimab and 496 on placebo). The Safety Cohort consisted of 1522 subjects (1015 on nirsevimab and 507 on placebo). The overall trial design, randomization ratio, endpoints, and timing of those endpoints in both study cohorts were identical and followed the initial prespecified approach.

Database Lock and Unblinding

According to the Applicant, the database lock for the primary analysis occurred when all participants in the Primary Cohort were followed through Day 361. Database lock for the Primary Cohort occurred on 14 April 2021. All but 4 subjects from the Safety Cohort were randomized after April 14, 2021. The enrollment to the Safety Cohort was complete on 22 October 2021.

Change in outcome status for subjects in the Primary Cohort

During review the Agency identified a data discrepancy. There were two subjects in the primary Cohort that were initially marked as non-events in the dataset and subsequently identified by the Applicant as lost to follow-up. These analysis results are based on the updated dataset that includes those subjects as lost to follow-up. Pooling Studies for the Secondary Endpoint Analyses

The Applicant proposed to pool to across Trials 03 and 04 and across cohorts within Trial 04.[6] The Agency notes that any analyses that pool the Primary and Safety Cohorts from Trial 04 to evaluate

[6] The Applicant proposed to pool Trials 03 and 04 together to evaluate efficacy of nirsevimab in preventing RSV hospitalizations. The Agency disagreed with the proposal for several reasons, including:
Differences in the populations of Trial 03 and 04: Trial 03 included very and moderately preterm infants born at ≥29 to <35 weeks of gestation, and Trial 04 included term/late preterm infants born at ≥35 weeks 0 days of gestation)
Differences in risk: the risk of hospitalization in very and moderately preterm infants is higher than that in late preterm and full-term infants

efficacy endpoints, including the secondary endpoint of hospitalization, should be considered exploratory.

All prespecified efficacy analyses were conducted only in the Primary Cohort.

The prespecified analysis of the primary and secondary endpoints of the Trial 04 conducted in the Primary Cohort were submitted to EMA in support of the application for marketing authorization on January 28, 2022 (European Medicines Agency 2023).

Prespecified Analyses

The analyses of the primary and secondary endpoints were performed using only the data collected prior to the recruitment pause (Primary Cohort).

All efficacy analyses were conducted using all randomized subjects following the ITT principle. Subjects were included in their randomized treatment group, regardless of the treatment they received.

A total of 1490 subjects were randomized into the Primary Cohort. Baseline demographic characteristics were as follows: mean age of 2.9 months; mean weight of 5.5 kg; 52% male; 53% White, 28% Black or African American, 4% Asian; 10% Hispanic or Latino. The baseline demographic characteristics were balanced between the two arms.

Exposure-Response Analyses and Duration of Protection Based on Pharmacokinetic Evidence

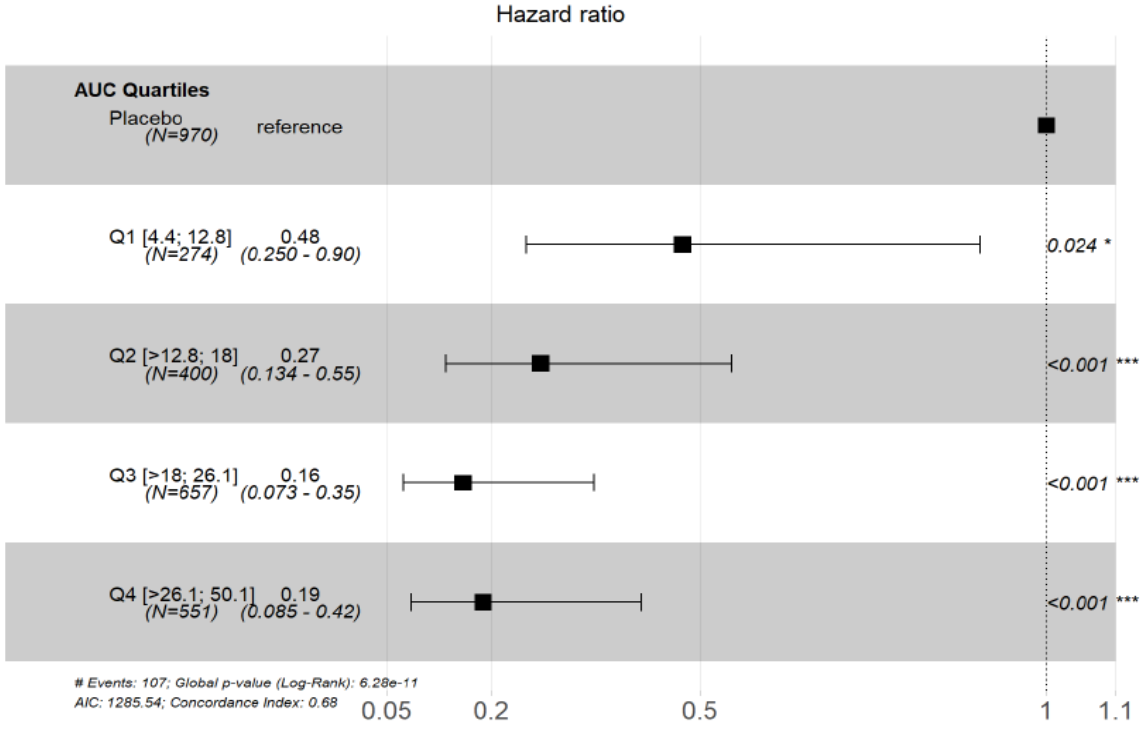
Trial 04 evaluated the efficacy, safety, and PK following a single weight-based IM dose of nirsevimab (50-mg if body weight <5 kg, 100-mg if body weight ≥5 kg) in late preterm and term infants (≥35 weeks GA) born during or entering their first RSV season.

Exposure-response Analyses to Identify the Target Exposure in Infants

Exposure-response analysis was conducted to explore the relationship between $AUC_{baselineCL}$ and MA RSV LRTI based on data from Trials 03 and 04. The analysis results indicated a positive correlation between $AUC_{baselineCL}$ above 12.8-mg*day/mL and a lower incidence of MA RSV LRTI (Figure 3). As shown in the figure, the exposure-response curve plateaus after achieving $AUC_{baselineCL}$ of 12.8-mg*day/mL. In Trial 04, >95% subjects achieved exposure over target $AUC_{baselineCL}$.

Differences in doses administered: nirsevimab dose was administered according to baseline body weight in Trial 04 (50-mg and 100-mg IM for infants weighing less than 5 kg and those weighing at least 5 kg, respectively); in Trial 03, all participants received 50-mg IM regardless of baseline body weight.
Because of these differences, the Agency disagrees with pooling of data from Trials 03 and 04 for efficacy analyses, therefore this analysis of pooled data was not performed by the Agency.

Figure 3. Forest Plot of Predictors in the Final Exposure-Response Model, Hazard Ratio (95% CI)

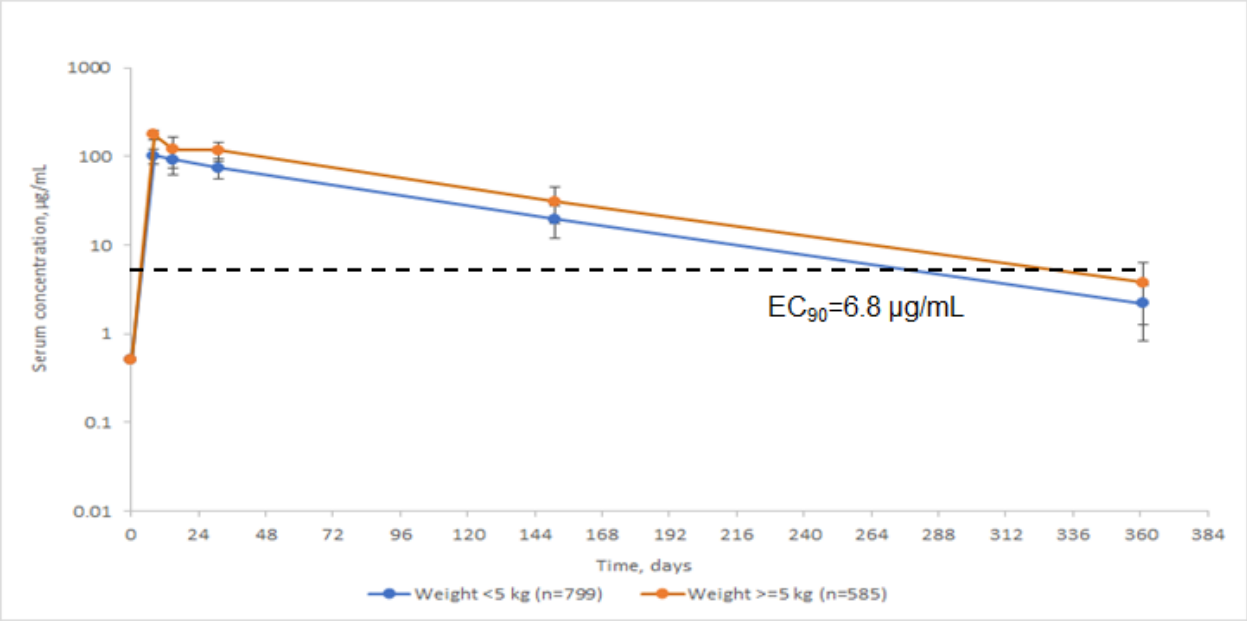


Source: Applicant's Population PK Report, Figure 34
Abbreviations: AUC, area under the serum concentration-time curve derived from post hoc clearance values at baseline; CI, confidence interval; CL, clearance; E-R, exposure response; N, number of subjects; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile

Duration of Protection

PK data from Trial 04 indicate that nirsevimab serum concentrations in infants up to 1 year of age are above EC_{90} (i.e., 6.8 µg/mL) at least through Day 150 post-dose (5 months) following the Applicant's proposed dosing regimen (i.e., a single IM dose of 50-mg in subjects weighing <5 kg; a single IM dose of 100-mg in subjects weighing ≥5 kg) (Figure 4). In Trial 04, nirsevimab serum concentrations decreased monoexponentially beyond the Day 31 sampling time point. Mean nirsevimab serum concentrations on Day 150 post-dose were 19.6 ±7.8 µg/mL in subjects <5 kg and 31.1±13.7 µg/mL in subjects ≥5 kg. On Day 361, mean nirsevimab serum concentrations were lower than the EC_{90} of 6.8 µg/mL. In addition, in Trial 04, >95% subjects achieved exposure greater than the target $AUC_{baselineCL}$, 12.8 mg*day/mL (see details in Exposure-response Analyses to Identify the Target Exposure in Infants above).

Figure 4. Mean (±SD) Serum Concentration of Nirsevimab Versus Time by Weight Group (Log-Linear Scale) in Trial 04



Source: Reviewer's analysis
The dashed line is the EC90 value of 6.8 µg/mL determined based on RSV challenge studies in cotton rat model.
Abbreviations: EC90, 90% effective concentration; SD, standard deviation; n, number of subjects

Primary Endpoint: Incidence of Medically Attended LRTI (Primary Cohort)

The primary endpoint was the incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV by Day 150 post-dose in infants born during or entering their first RSV season.

Out of 1,490 subjects who were randomized, 23 (1.5%) discontinued the study and did not have their status outcome on Day 150 post-dose (primary endpoint). Most of the discontinuations were withdrawal by a parent or by a legal representative. Of note, there were no deaths among subjects who experienced MA RSV LRTI. The missing rates (for both time of primary endpoint measurement and the end of study) were similar across treatment groups.

The number of subjects who experienced MA RSV LRTI by Day 150 post-dose in each of the treatment arms, and the results of the analysis of the primary endpoint are presented in Table 4. The estimated RRR was 74.9% (95%CI: 50.6% to 87.3%) with p-value <0.0001 in favor of nirsevimab.

Table 4. Primary Cohort: Incidence of MA RSV LRTI by Day 150 Post-Dose (Primary Endpoint) in Trial 04

	Trial 04 Primary Cohort	
Statistic	**Nirsevimab N=994**	**Placebo N=496**
Events (# of subjects, n (%))	12 (1.2)	25 (5.0)
Subjects requiring imputation* n (%)	16 (1.6)	7 (1.4)
RRR (95% CI)	74.9% (50.6% to 87.3%) p <0.0001	

Source: FDA statistical reviewer

* Subjects with missing outcomes on Day 150. The final status of those subjects was imputed based on the observed placebo rate conditional on stratification factors using multiple imputation approach.

Abbreviations: CI, confidence interval; MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection; N, number of subjects; n, number of subjects with specific incident; RRR: relative risk reduction

Sensitivity Analysis (to Examine the Impact of Missing Data)

Similar to the analysis of Trial 03, a sensitivity analysis was conducted following the primary analysis approach with an additional assumption that all subjects in the nirsevimab arm who had a missing outcome (i.e., subjects requiring imputation) had experienced MA RSV LRTI events. The analysis yielded a relative risk reduction of 44.8% (95% CI:6.7%, 67.3%) favoring nirsevimab. This result suggests that the outcome of the primary analysis was robust.

Incidence of hospitalization (Secondary Endpoint Based on the Primary Cohort Only)

A pre-specified secondary endpoint for the Primary Cohort was incidence of hospitalization due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season (by Day 150 post-dose).

The number of subjects who experienced MA RSV LRTI and were hospitalized by Day 150 post-dose in each of the treatment arms, and the results of the analysis of the secondary endpoint are presented in Table 5. The estimated RRR was 60.2% (95%CI: -14.6%, 86.2%) with p-value=0.09.

There were low numbers of subjects in both treatment and placebo groups who were hospitalized due to RSV (6 subjects on nirsevimab and 8 subjects on placebo). Lower hospitalization rates are typically seen in term or near-term infants.

Table 5. Primary Cohort: Incidence of RSV Hospitalizations by Day 150 Post-Dose (Secondary Endpoint) in Trial 04

	Trial 04 Primary Cohort	
Statistic	**Nirsevimab N=994**	**Placebo N=496**
Events (# of subjects, n (%))	6(0.6)	8(1.6)
Subjects requiring imputation* n (%)	16(1.6)	7(1.4)
RRR (95% CI)[§]	60.2% (-14.6% to 86.2%) p=0.09	

Source: FDA statistical reviewer

* Subjects with missing outcomes on Day 150. The final status of those subjects was imputed based on the observed placebo rate conditional on stratification factors using multiple imputation approach.

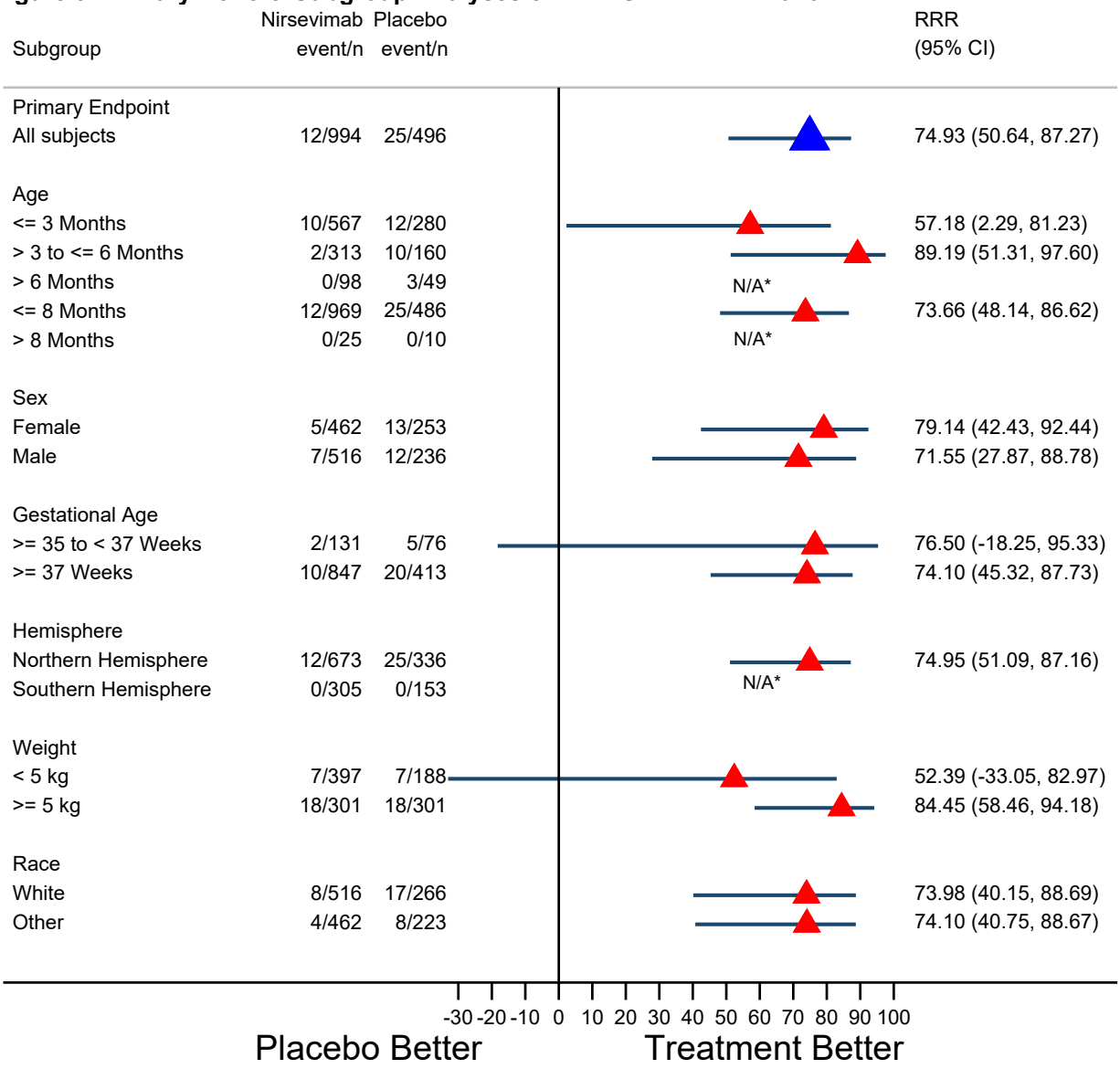
§ RRR based on initial Primary Cohort

Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with specific incident; RRR, relative risk reduction; RSV, respiratory syncytial virus

Subgroup Analyses (Primary Cohort)

The treatment effects based on the incidence of MA RSV LRTI (primary endpoint) were consistent across subgroups and were consistent with the overall treatment effect, as shown in Figure 5. There were no events in the subgroup of subjects older than 6 months of age among participants who received nirsevimab (compared to three events in the placebo treatment arm). In addition, there were no events in subjects older than 8 months of age in either arm. Similarly, there were no events in both groups among participants from the southern hemisphere. Because of the small number or lack of events, the outcomes in those subgroups could not be evaluated. For additional discussion on subgroup analysis based on chronological and gestational ages, refer to Section 3.1.3

Figure 5. Primary Cohort: Subgroup Analyses of MA RSV LRTI in Trial 04



Source: FDA statistical reviewer

*The RRR cannot be calculated because the number of events was not sufficient

Abbreviations: CI, confidence interval; MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection; n, number of subjects; RRR, relative risk reduction

3.1.4 Efficacy Considerations for Specific Populations

Benefit of Nirsevimab Based on Gestational Age at Birth and Chronological of Infants at the Time of Nirsevimab Administration

Background

The Applicant proposed an indication for the prevention of MA RSV LRTD in neonates and infants born during or entering their first RSV season.

Infants born during or entering their first RSV season were enrolled in Trial 03 and the Primary Cohort of Trial 04. Infants up to 12 months of age were enrolled in both trials. Infants born at ≥29 weeks to <35 weeks of gestation were enrolled in Trial 03; infants born at ≥35 weeks of gestation were enrolled in Trial 04. Infants born at <35 weeks of gestation (including <29 weeks of gestation) were enrolled in Trial 05, which is discussed in the following section.

Severe RSV is more common with younger infants, in premature infants, and in infants with underlying comorbidities, such as CLD of prematurity and hemodynamically significant CHD. In a prospective, surveillance study conducted at three New Vaccine Surveillance Network (NVSN) sites during the 2002 to 2004 RSV seasons, information on outpatient visits for RSV was collected (Lively et al. 2019). The highest rates of emergency department visits were in infants who were 4 months of age (116 per 1,000 children) and the highest rates for pediatric office visits were at 5 months of age (289.2 per 1,000 children). In a review of both the literature and a national claims database, Paramore et al. (2010) reported the range for rates of outpatient visits in term infants as 128.8 to 171.3 visits per 1,000 children.

The timing for nirsevimab administration will also be influenced by whether the infant lives in a tropical/subtropical or temperate area of the United States. In tropical/subtropical climates, RSV circulates throughout the year, and infants could receive nirsevimab shortly after birth. In temperate climates, RSV occurs as seasonal outbreaks that typically last for 5 months.

Infants in temperate climates who are born immediately before or during the RSV season (~November through March) would receive nirsevimab shortly after birth. Infants born outside of the RSV season (April through October) would have an age range of 1 to 7 months before they enter their RSV season. As a result, nearly all infants in both temperate and tropical/subtropical climates would have experienced their first RSV season (and potentially exposed to RSV) by 7 months of age. Infants 8 months of age and above would have received nirsevimab during their first RSV season, or would already have likely been exposed to RSV.

Assessment

Entry criteria for Trials 03 and 04 limited enrollment to infants born during or entering their first RSV season. Trial 03 enrolled infants born at a GA of ≥29 weeks to <35 weeks, while Trial 04 enrolled infants born at >35 weeks of gestation. The mean chronological age of infants enrolled in Trial 03 was 3.3 months (range of 0.1 to 11.9 months) and median of 2.8 months, and the mean chronological age of infants enrolled in Trial 04 was 2.9 months (range of 0.0 to 11.0 months) and median of 2.6 months.

Gestational age: The results of efficacy in infants born at ≥29 weeks <35 weeks GA are demonstrated in Trial 03; in this trial, the incidence of MA RSV LRTI was 0.8% in the nirsevimab arm and 4.1% in the placebo arm for a relative risk reduction of 78.4% (see Section 3.1.2). Efficacy results for infants ≥35

weeks GA were assessed in Trial 04. Because Trial 04 enrolled both infants born prematurely (≥35 weeks to <37 weeks GA) and term infants (≥37 weeks), the efficacy of these subgroups was assessed and is shown in Table 6. The incidence of MA RSV LRTI is lower in the nirsevimab arm than in the placebo arm for both GA subgroups. The 95% CI for the younger GA subgroup (≥35 weeks to <37 weeks) is wide and crosses 0 because of the smaller number of subjects in that subgroup. The incidence of MA RSV LRTI is similar in the two GA groups for subjects in the nirsevimab arm. Trial 05 included infants born at <29 weeks GA; but because the subgroup was too small with too few events, and efficacy was descriptive, no definitive conclusions can be drawn from Trial 05 (see Trial 05).

Table 6. Incidence of MA RSV LRTI by Gestational Age in the Primary Cohort of Trial 04

Gestational Age at Birth	Nirsevimab Arm	Placebo Arm	RRR (95%CI)
≥35 weeks to <37 weeks	2/132 (1.5%)	5/76 (6.6%)	76.97% (-16.79, 96.9)
≥37 weeks	10/861 (1.2%)	20/419 (4.8%)	75.67% (48.4, 89.1)

Source BLA 761328, CSR Trial 04, Figure 5, page 113.

Abbreviations: CI, confidence interval; MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection; RRR, relative risk reduction

Chronological age: The Applicant analyzed the efficacy of nirsevimab by age at randomization in both trials and used three chronological age cohorts for the analysis: 3 months of age and younger, older than 3 months of age to 6 months of age, and older than 6 months of age. The results of these analyses are shown in Table 7 for all subjects as well as by chronological age at randomization and GA at birth.

The incidence of MA RSV LRTI was numerically lower in the nirsevimab arm than in the placebo arm for each chronological age subgroup in each trial. The incidence of MA RSV LRTI was numerically higher in the nirsevimab arm in each age subgroup in Trial 03 compared to the nirsevimab arm in the corresponding age subgroup in Trial 04, which is likely to be related to GA. Efficacy was demonstrated in the overall population in both trials. The treatment effect was consistent across subgroups and was consistent with the overall treatment effect.

Table 7. Incidence of MA RSV LRTI in Trials 03 and 04 Through 150 Days Post Dose by Chronological Age at Randomization and by Gestational Age (ITT Population)

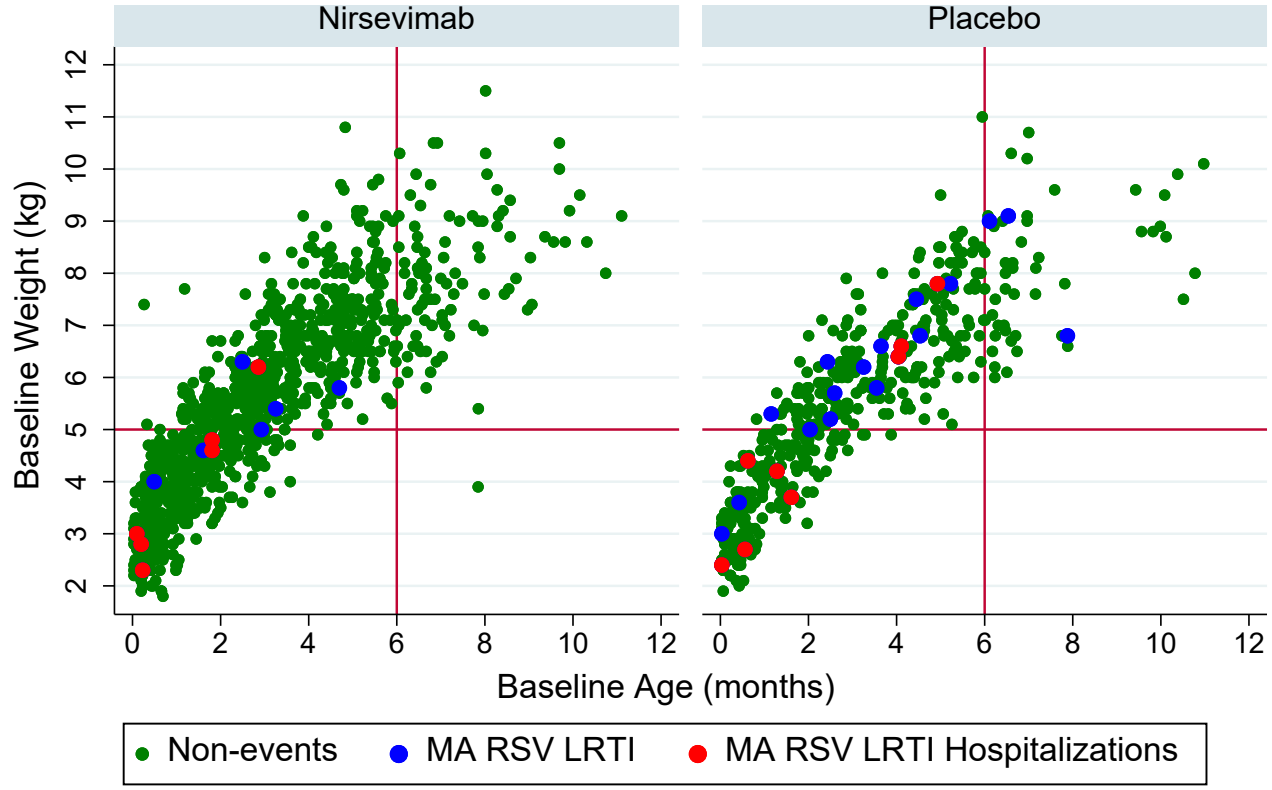
	Trial 03 (≥29 Weeks to <35 Weeks GA)		Trial 04 (Primary Cohort) (>35 Weeks GA)	
Age	Nirsevimab	Placebo	Nirsevimab	Placebo
All subjects	25/969 (2.6%)	46/484 (9.5%)	12/994 (1.2%)	25/496 (5.0%)
≤3 months	7/516 (1.4%)	22/257 (8.6%)	10/577 (1.7%)	12/285 (4.2%)
>3 to ≤6 months	13/320 (4.0%)	16/153 (10.4%)	2/317 (0.6%)	10/162 (6.2%)
>6 months	5/133 (3.7%)	8/74 (10.8%)	0/100 (0%)	3/49 (6.1%)

Source: BLA 761328, CSR Trial 3: Table 15, page 42, Table 16, page 43 and CSR Trial 4: Table 24, page 109; Figure 5, page 111.

Abbreviations: CI, confidence interval; GA, gestational age; ITT, intent-to-treat; MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection

As shown in Figure 6, the numbers of subjects who were older than 6 months of age at the time of enrollment are considerably fewer compared to the younger age groups. This difference is likely due to the age at which infants typically enter their first RSV season. Efficacy results by chronological age for infants in Trial 04 are shown in Figure 6. The majority of subjects in Trial 04 were younger than 6 months of age, and there were very few subjects older than 8 months of age. There were no cases of RSV LRTI hospitalizations (red dots) in nirsevimab or placebo arms in subjects >8 months of age.

Figure 6. Primary Cohort: Relationship Between Baseline Weight, Baseline Age, and Outcome Status (Day 150) in Trial 04



Source: FDA statistical reviewer
Legend: Relationship between baseline weight and baseline age for subjects who did not experience MA RSV LRTI (green circles), subjects who experienced MA RSV LRTI without hospitalization (blue circles), and those who experienced MA RSV LRTI and were hospitalized (red circles). Each circle represents age and weight at baseline so that each subject is represented only once.
Abbreviations: MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection

Conclusion

Efficacy was demonstrated in the overall population in both trials. The treatment effect was consistent across chronological age subgroups and was consistent with the overall treatment effect. However, few infants older than 8 months of age were enrolled. The prespecified analysis was for all infants enrolled; but in light of the limited enrollment of infants older than 8 months, and due to the small number of MA RSV LRTI events observed among these infants, the benefit and risks of nirsevimab for this age group may need additional consideration. However, there are times when it may be appropriate for infants over 8 months of age to receive nirsevimab, for example, infants who were lost to follow-up or who present late for health care, and when timing of RSV season is atypical.

b. Benefit of Nirsevimab in Infants at Highest Risk of RSV Disease, Including During Second RSV Season

Trial 05

Trial 05 (also known as D5290C00005 or MEDLEY) was a Phase 2/3, double-blind, palivizumab-controlled trial in infants and children at high-risk of severe RSV disease. The study enrolled infants in their first year of life who were born at <35 weeks of gestation, and who were eligible to receive palivizumab in accordance with national or local guidelines, as well as infants with CLD of prematurity, and infants with hemodynamically significant CHD. Infants who were born prematurely participated in the first year of

the study, while infants with CLD and CHD participated in RSV seasons 1 and 2. In the first RSV season, nirsevimab was administered as a single 50-mg IM dose in infants weighing <5 kg, and as a single 100-mg IM dose in infants weighing ≥5 kg. In the second RSV season, nirsevimab was administered as a 200-mg single IM dose to all children. A single 200-mg dose for the children entering the second RSV season is expected to provide serum AUC above target exposure of 12.8 day*mg/mL based on expected body weight range. Please refer to Trial 04 (above) for details of the target exposure. Trial 05 was designed to assess safety, as measured by the incidence and types of AEs, and SAEs, and pharmacokinetics of nirsevimab; the efficacy analyses are descriptive. Table 8 describes Trial 05 design.

Table 8. Clinical Design in Trial 05

Study Identifier	Study Title	Study Design	Treatment	Primary Endpoint	Number of Subjects Randomized
D5290C00005 (Trial 05 or MEDLEY)	A phase 2/3 randomized, double-blind, palivizumab-controlled study to evaluate the safety of MEDI8897, a monoclonal antibody with an extended half-life against Respiratory Syncytial Virus, in high-risk children (born at <35 weeks GA, with CLD, or with CHD)	Phase 2/3, MC, R, AC, DB RSV Season 1: Subjects randomized (2:1) to MEDI8897 or palivizumab RSV Season 2: Subjects with CLD or CHD who received nirsevimab in season 1 received nirsevimab in season 2. Subjects who received palivizumab in season 2 randomized (1:1) to nirsevimab or palivizumab	RSV Season 1: Nirsevimab: single 50-mg IM dose in infants <5 kg, single 100-mg IM dose in infants ≥5 kg Placebo (saline) monthly in months 2 -5 Palivizumab: Single 15-mg/kg dose monthly x 5 doses RSV Season 2: Nirsevimab: single 200-mg IM dose Placebo (saline) monthly in months 2 -5 Palivizumab: Single 15-mg/kg dose monthly x 5 doses	Safety: incidence and types of AEs, SAEs, and AESI	RSV Season 1: Nirsevimab: 614 Palivizumab: 304 RSV Season 2: Nirsevimab: 220 Palivizumab: 42

Source: BLA 761328, Module 5.2, Table 2, page4-6.

Abbreviations: AC, active controlled; AE, adverse event; AESI, adverse event of special interest; CHD, hemodynamically significant congenital heart disease; CLD, chronic lung disease of prematurity; DB, double blind; GA, gestational age; MC, multicenter; R, randomized; RSV, respiratory syncytial virus; SAE, severe adverse event

The Agency agreed with the Applicant that efficacy could be extrapolated from Trial 03 and Trial 04 to highest risk infants in Trial 05, and accepts that the efficacy of nirsevimab, as demonstrated in Trial 03 and the Primary Cohort of Trial 04, both adequate and well-controlled trials, can be leveraged to support the efficacy of nirsevimab in the high-risk population of Trial 05, provided that the observed nirsevimab exposures in Trial 05 were comparable to the exposures observed in Trial 04 (and 03). Therefore, the pharmacokinetic data were considered as bridging evidence to support the efficacy of nirsevimab for the population enrolled in Trial 05. Extrapolation of efficacy was considered appropriate because:

1. The pathophysiology of RSV infection is sufficiently similar between infants with and without certain medical comorbidities.
2. The mechanism of action, and the viral protein target of nirsevimab is the same regardless of the host conditions.
3. The response to prevention is expected to be similar between infants with and without additional medical comorbidities.

The design of Trial 05 was discussed with FDA and agreed upon in 2017. A placebo-controlled trial would not be acceptable in infants and children for whom palivizumab is indicated. In addition, while a non-inferiority trial comparing nirsevimab with palivizumab could be considered, the sample size needed to conduct such a trial was considered prohibitively large, and unlikely to be conducted within a reasonable time frame. Additionally, a non-inferiority margin cannot be determined because no randomized trials with the endpoint of MA RSV LRTI are available to estimate the treatment effect of palivizumab versus placebo.

Trial 05 Results

A total of 925 infants were enrolled and randomized in the trial, including 615 preterm infants and 310 infants with CLD or CHD. Demographics for season 1 included the following:

- In the preterm cohort, 13% of infants were born at ≥ 22 weeks to <29 weeks GA, 81% were born at ≥29 to <35 weeks GA, and 6% were born at ≥35 weeks GA.
- The CLD/CHD cohort included 24% subjects with CLD and 11% subjects with CHD. Of infants in the CLD/CHD cohort, 40% were <29 weeks GA, 28% of infants were ≥29 weeks to <35 weeks GA; and 15% were ≥35 weeks GA.
- In all infants (premature infants, CLD, and CHD), 54% were male; 79% were White; 10% were Black; 5% were Asian, 2% were American Indian/Alaskan Native; and 57% weighed less than 5 kg.
- The median age was 3.5 months (range: 0.07 to 12.3 months); 45% were less than or equal to 3 months; 34% were greater than 3 months to less than or equal to 6 months; and 21% were greater than 6 months of age.

Of the 310 subjects with CLD or CHD who participated in season 1, 262 (84.5%) subjects participated in season 2.

The efficacy endpoint was the incidence of MA RSV LRTI through Day 150 post-dose. In the first RSV season, the incidence of MA RSV LRTI through Day 150 post-dose was 0.6% in the nirsevimab arm and 1.0% in the palivizumab arm.

- In the preterm cohort, 2 subjects had MA RSV LRTI in the nirsevimab arm and 1 in the palivizumab arm.
- In the CHD/CLD cohort, 2 subjects had MA RSV LRTI in each arm.

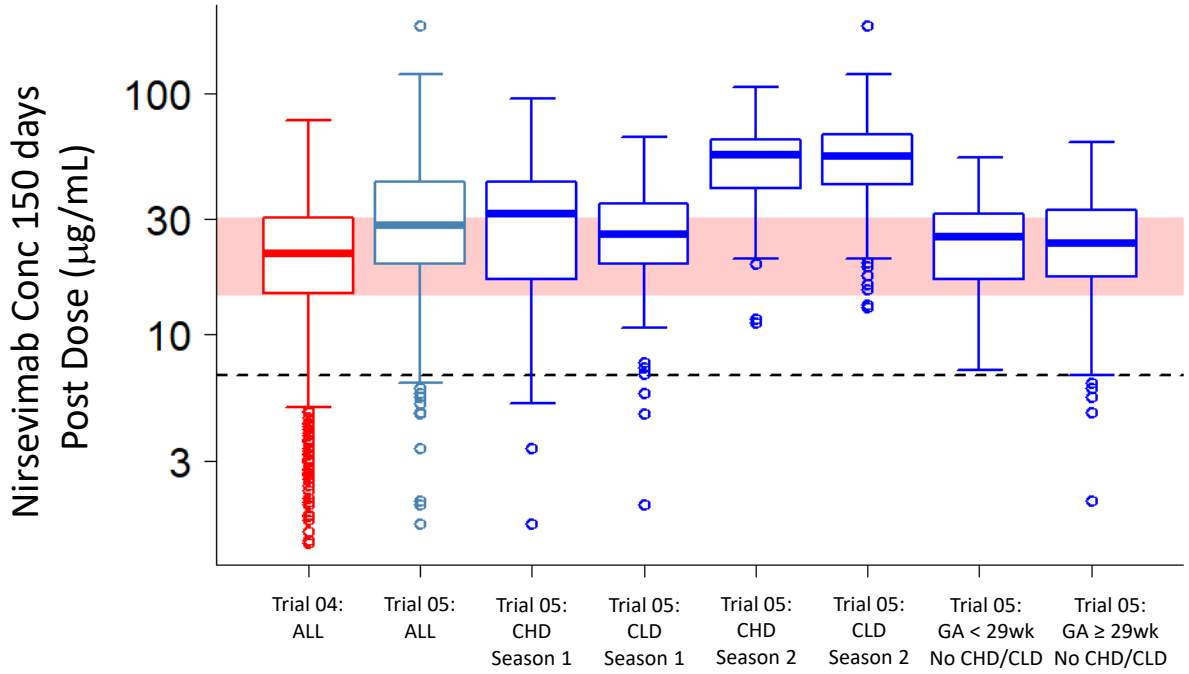
This trial enrolled subjects in 2019 and 2020, and the low numbers of RSV LRTI infections were likely related to the global COVID-19 pandemic. Despite a low incidence of RSV infections in season 1, a similar number and percentage of cases of MA RSV LRTI were observed in the nirsevimab and palivizumab arms [4 (0.6%) and 3 (1.0%), respectively]. There were no cases of MA RSV LRTI through Day 150 post-dose in season 2.

Pharmacokinetic Data to Support Efficacy Extrapolation

Day 150 post-dose nirsevimab serum concentration and $AUC_{baselineCL}$ were chosen as the two PK parameters for efficacy extrapolation from Trials 03 and 04 to Trial 05. Day 150 nirsevimab serum concentration was selected based on the expected period of protection (i.e., 5 months) and duration of RSV season. $AUC_{baselineCL}$ was selected based on the exposure-response analysis results with PK data from Trials 03 and 04. Please refer to Trial 04 above for details. The extrapolation of efficacy of nirsevimab from Trials 03 and 04 to Trial 05 was based on (1) the similar Day 150 post-dose serum nirsevimab concentrations in infants enrolled in Trials 03 and 04 and in infants enrolled in Trial 05 (Figure 7); and (2) percentage of Trial 05 subjects with nirsevimab exposure above the target $AUC_{baselineCL}$ of 12.8-mg*day/mL (Table 9). More than 95 percent of the subjects in Trial 04 had $AUC_{baselineCL}$ exceeding 12.8-mg*day/mL. The PK comparison was conducted in both season 1 and season 2 in Trial 05.

As shown in Figure 7, the Day 150 post-dose serum concentrations in subjects enrolled in Trial 05 during their first season were comparable to the Day 150 post-dose serum concentrations observed among subjects enrolled in Trial 04. The Day 150 post-dose serum concentrations in subjects enrolled in Trial 05 during their second RSV season were higher than the concentrations observed in subjects enrolled in Trial 04. In both cases, because the Day 150 post-dose serum concentrations observed in Trial 05 were comparable or higher than those observed in Trial 04, it can be reasonably concluded that nirsevimab would be expected to be as effective in very preterm infants or in infants with CHD/CLD.

Figure 7. Observed Nirsevimab Concentrations 150 Days Post-Dose in Trial 05 Subjects Compared to the Ones in Trial 04 Subjects



Source: Reviewer's Analysis
The dashed line is EC90 value of 6.8 µg/mL determined based on RSV challenge studies in cotton rat model.
Abbreviations: CHD, hemodynamically significant congenital heart disease; CLD, chronic lung disease of prematurity; EC90, 90% effective concentration; GA, gestational age

Table 9. Percent of Trial 05 Subjects With Nirsevimab Exposure Above Target $AUC_{baselineCL}$ of 12.8-mg*day/mL**

RSV Season	Extreme Preterm Infants <29 Weeks GA Without CLD or CHD	CLD	CHD
RSV Season 1	93.6% (44/47)	94.1% (128/136)	80.3% (53/66)
RSV Season 2	NA	93.9% (124/132)	91.4% (53/58)

Source: Applicant's Summary of Clinical Pharmacology, Table 7
**Target $AUC_{baselineCL}$ of 12.8-mg*day/mL is based on exposure-response analysis results from Trials 03 and 04.
Abbreviations: $AUC_{baselineCL}$, area under the concentration time curve from baseline to clearance; CHD, hemodynamically significant congenital heart disease; CLD, chronic lung disease of prematurity; GA, gestational age; RSV, respiratory syncytial virus

3.2 Safety Considerations

- Hypersensitivity reactions, including anaphylaxis and rash
- Imbalance in Deaths

3.2.1 Sources of Data for Safety

Safety data are derived from Phase 1, 2, and 3 trials, including Trials 01, 02, 03, 04, 05, and 08. However, the safety review focuses on the results from the 3,245 infants who received the proposed dose of nirsevimab, the overwhelming majority of whom were enrolled in Trials 03, 04, and 05. In each of these trials, subjects were to be followed for 360-days post-dose.

3.2.2 Safety Summary

Clinical Trials

Nirsevimab demonstrated an overall favorable safety profile in the clinical trials (Table 10). The incidence and types of adverse events (AEs) were generally similar between treatment groups in Trials 03, 04, and 05. The incidence of severe AEs and serious AEs (SAEs) were also similar between treatment groups. AEs leading to study or drug discontinuation are not included, because nirsevimab was administered as a single dose. There was an imbalance of deaths between nirsevimab arms and in control arms; this is discussed in depth in Section 3.2.2.

In Trial 03 and Trial 05, the percentage of subjects with serious or severe adverse events (regardless of causality) was higher than that reported in Trial 04. This was observed for both the nirsevimab arms and the control arms. This is consistent with the study populations in Trials 03 and 05. Trial 03 enrolled infants born at ≥29 weeks to <35 weeks of gestation; and Trial 05 enrolled subjects born at <35 weeks of gestation, infants with CLD of prematurity, and infants with hemodynamically significant CHD.

Table 10 shows an overview of adverse events reported in Trials 03, 04 and 05. Serious adverse events were defined in the protocol as any adverse event that:

- results in death,
- is immediately life-threatening,
- requires inpatient hospitalization or prolongs an existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes above.

Severity of adverse events was assessed by the investigator, with Grade 1 considered mild, Grade 2, moderate, Grade 3, severe, Grade 4, life-threatening, and Grade 5, death.

Table 10. Overview of Safety in Trials 03, 04 and 05

	Trial 03		Trial 04		Trial 05, Season 1	
Adverse Events (AEs)	**Nirsevimab N=968 n (%)**	**Placebo N=479 n (%)**	**Nirsevimab N=1998 n (%)**	**Placebo N=996 n (%)**	**Nirsevimab N=614 n (%)**	**Palivizumab N=304 n (%)**
Any AEs	834 (86.2)	416 (86.8)	1,673 (83.7)	815 (81.8)	444 (72.3)	215 (70.7)
Severe and worse	77 (8.0)	60 (12.5)	61 (3.1)	38 (3.8)	50 (8.1)	25 (8.2)
Moderate	265 (27.4)	145 (30.3)	375 (18.8)	208 (20.9)	113 (18.4)	65 (21.4)
Mild	492 (50.8)	211 (44.1)	1,237 (61.9)	569 (57.1)	281 (45.8)	125 (41.1)
Serious Adverse Events (SAEs)	108 (11.2)	81 (16.9)	125 (6.3)	74 (7.4)	80 (13.0)	38 (12.5)
Deaths	2 (0.2)	3 (0.6)	4 (0.2)	0 (0)	5 (0.8)	1 (0.3)

Source: BLA 761328: adae.xpt for Trials 03, 04, and 05

Abbreviations: AE, adverse event; N, number of subjects; n, number of subjects with specific adverse event; SAE, severe adverse event

The most common treatment-emergent AEs reported across arms in all three pivotal trials was upper respiratory tract infection, pyrexia, and nasopharyngitis –consistent with common childhood conditions. The most common treatment-emergent AEs reported more frequently in nirsevimab than in control arms in Trials 03, 04, and 05 (Season 1) are shown in Table 11. The differences in the incidences of AEs between the nirsevimab and control arms were small, and there were no AEs that were reported with a 5% or greater difference in frequency in the nirsevimab arm than in the control arm.

Table 11. Subjects With Adverse Events Occurring at a ≥2% Difference in Frequency and Reported in a Higher Percentage of Subjects in the Nirsevimab Arm than Control Arm, Safety Population in Trials 03, 04, and 05 (Season 1)

	Trial 03		Trial 04		Trial 05, Season 1	
Adverse Events	**Nirsevimab N=968 n (%)**	**Placebo N=479 n (%)**	**Nirsevimab N=1,998 n (%)**	**Placebo N=996 n (%)**	**Nirsevimab N=614 n (%)**	**Palivizumab N=304 n (%)**
Any AEs	834 (86.2)	416 (86.8)	1,673 (83.7)	815 (81.8)	444 (72.3)	215 (70.7)
Upper respiratory tract infection	236 (41.3)	107 (37.2)	590 (29.5)	287 (28.8)	148 (24.1)	48 (25.7)
Pyrexia	130 (13.4)	78 (16.3)	286 (14.3)	123 (12.3)	83 (13.5)	43 (14.1)
Gastroenteritis	71 (12.4)	25 (8.7)	173 (8.7)	85 (8.5)	25 (4.1)	16 (5.3)
Diaper dermatitis	47 (8.2)	23 (8.0)	206 (10.3)	92 (9.2)	28 (4.6)	6 (2.0)
Nasal congestion	45 (7.9)	10 (3.5)	162 (8.1)	84 (8.4)	41 (6.7)	13 (4.3)

Source: BLA 761328, CSR Trial 03, Table 33, pages 79-80; CSR Trial 04, Table 53, pages 160-162; CSR Trial 05, Table 40, pages 150-152.

Abbreviations: AE, adverse event; N, number of subjects; n, number of subjects with specific adverse event

Serious adverse events reported in at least 1% of subjects of any of the 3 trials were either respiratory tract infections (pneumonia, bronchitis and bronchiolitis) or gastroenteritis. The percentages of subjects in the nirsevimab and palivizumab arms with SAEs of pneumonia and bronchiolitis were low and similar in both arms. Gastroenteritis was reported as an SAE in 1% of subjects in Trial 05 and in less than 1% of subjects in Trials 03 and 04. However, the overall incidence of gastroenteritis SAEs in the trials of nirsevimab was very low. Overall, the incidence of SAEs was low, and types of SAEs reported are consistent with childhood illnesses.

In the three pivotal trials (Trials 03, 04, and 05), information on adverse events of special interest (AESIs) was collected during the 360-day safety follow-up. AESIs in these trials were immediate hypersensitivity reactions, including anaphylaxis, immune complex disease, and thrombocytopenia. There were no reports of anaphylaxis or of immune complex disease in the trials. There were two AESIs of thrombocytopenia reported, both were reported in Trial 05; and both subjects received nirsevimab. One AESI of thrombocytopenia was in a subject with CHD who experienced heparin-induced thrombocytopenia. The other AESI of thrombocytopenia was reported in a subject with CHD who was septic at the time. Neither AESI of thrombocytopenia was assessed as related to nirsevimab. Overall, only 2 AESIs were reported in the pivotal trials, and neither AESI appeared to be related to nirsevimab.

Information on new onset chronic diseases (NOCDs) was collected during the 360-day safety follow-up. NOCDs were defined as a newly diagnosed medical condition that is of a chronic, ongoing nature and that did not exist at enrollment. In the three pivotal trials [Trials 03, 04, and 05 (season 1)], there were 9 NOCDs diagnosed in subjects who received nirsevimab (0.3% of subjects) and 7 NOCDs diagnosed in subjects who received a control (0.4% of subjects). Among those who received nirsevimab, 6 subjects were diagnosed with asthma, 1 with wheezing, 1 with urinary calculi, and 1 with periodic fevers, aphthous stomatitis, pharyngitis, and adenitis syndrome. Three respiratory NOCDs (asthma in 2 subjects, chronic bronchitis in 1 subject, and infantile asthma in 1 subject) and hypothyroidism in 2 subjects were reported in the control arms of the 3 trials. The percentage of subjects with a respiratory NOCD was 0.2% in each arm. Overall, the incidence of subjects with a NOCD was similar in the nirsevimab arms and the control arms, and the incidence was very low.

Safety laboratory monitoring was assessed in subjects who were enrolled in Trials 04 and 05 at study sites in Japan. As a result, only a small number of subjects (132 who received nirsevimab and 56 who received control) had laboratory monitoring during these trials. Grade 3 or 4 abnormalities were reported for hemoglobin and for bilirubin but not for other laboratory parameters (white blood cells, platelets, creatinine, AST and ALT). Three subjects, all of whom received nirsevimab, had Grade 3 decreases in hemoglobin reported on Day 150 post-dose. All 3 subjects were diagnosed with iron deficiency anemia. In subjects who received nirsevimab, 17 (13%) had Grade 3 and 13 (9.8%) had Grade 4 increases in bilirubin. In subjects who received the control, 3 (5.3%) had Grade 3 and 12 (21%) had Grade 4 increases in bilirubin. None of the increases were associated with increases in ALT or AST. The majority of subjects were neonates, and all increases in bilirubin resolved. The increases in bilirubin were likely to be transient physiologic hyperbilirubinemia, which occurs in most neonates. Although the number of subjects with laboratory testing was small, no safety concerns were identified in these subjects.

Long Term Safety Follow-up

Incidence of MA RSV LRT in Season After Receiving Nirsevimab

The Primary Cohort in Trial 04 was followed until Day 511, without subjects receiving another dose of study product, to monitor for the incidence and severity of RSV disease in their second RSV season. Multiple endpoints were followed as shown in Table 12 below. Although the number of MA RSV LRTI events was low, the percentages of subjects with MA RSV LRTI in the second RSV season was similar in the nirsevimab and placebo arms. One subject in each arm was hospitalized with RSV, as diagnosed by any RSV test. There was no evidence of either an increase in the percentage of subjects with RSV the season after receiving nirsevimab, as might occur with a shift in the RSV burden to the second year of life, or of an increase in severity of RSV disease in the second season after receiving nirsevimab, which would raise concerns about antibody-dependent enhancement of RSV disease.

Table 12. Number and Percentage of Subjects in the Primary Cohort of Trial 04 With an RSV Respiratory Infection From Day 351 to Day 510

Respiratory Illnesses	Nirsevimab N=994	Placebo N=496
All MA RSV LRTI (by RT-PCR)	7 (0.7%)	2 (0.4%)
All MA RSV LRTI (any test for RSV)	8 (0.8%)	4 (0.8%)
All MA RSV respiratory illness with hospitalization (by RT-PCR)	0	0
All MA RSV respiratory illness with hospitalization (any test for RSV)	1 (0.1%)	1 (0.2%)

Source: BLA 761328, CSR Trial 04, Table 72, page 205

Abbreviations: MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection; N, number of subjects; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction

3.2.3 Safety Considerations in Detail

Hypersensitivity Reactions, including Anaphylaxis and Rash

Background

Immune-mediated adverse reactions, ranging from anaphylaxis to hypersensitivity skin reactions, are well-known adverse reactions associated with the use of monoclonal antibodies (Pintea et al. 2021). These adverse reactions have been reported during the postmarketing period with palivizumab, a monoclonal antibody against the RSV fusion protein with a similar mechanism of action as nirsevimab.

Anaphylaxis, a form of severe hypersensitivity reaction, can occur within minutes to hours after administration. Anaphylaxis typically involves a cluster of clinical signs and symptoms that may include changes in the skin and/or mucosa, respiratory changes, gastrointestinal symptoms, and/or a decrease in blood pressure. Please see the NIAID criteria for the diagnosis of anaphylaxis (Sampson et al. 2006).

Skin reactions and rashes have been reported with monoclonal antibody use. Hypersensitivity skin reactions can range from mild macular rash or urticaria, to more severe forms. Severe hypersensitivity skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis may be observed from 2 to 7 days after drug exposure. Other rashes typically occur within 2 to 3 weeks of starting a new medication, but the time of onset could be longer with a drug or product that has a long half-life, such as nirsevimab.

Allergic reactions to drugs can also occur days after drug product administration. Immune complex diseases may occur 1 to 3 weeks after drug exposure and may result in serum sickness, fever, rash, arthralgias, urticaria, glomerulonephritis, or vasculitis (Riedl and Casillas 2003; Isabwe et al. 2018).

Assessment

Hypersensitivity Reactions, Including Anaphylaxis

Nirsevimab was administered on Study Day 1 in the clinical trials. In order to search for hypersensitivity reactions, including anaphylaxis, adverse events with onset on Study Day 1 or 2 were examined by:

- Identification of adverse events consistent with hypersensitivity reactions such as MedDRA preferred terms of anaphylactic reaction, anaphylactoid reaction and drug hypersensitivity in all studies of nirsevimab;
- Analysis of adverse events in the pivotal nirsevimab trials, Trials 03, 04, and 05 using the narrow FDA Medical Queries (FMQs),[7] which is a group of related preferred terms for AEs for hypersensitivity;
- Analysis of adverse events in Trials 03, 04, and 05 using an algorithm developed by FDA Clinical Data Scientists. This algorithm was designed to identify adverse events clusters that fulfilled any of the three criteria for anaphylaxis, as defined by the NIAID and the Food Allergy and Anaphylaxis Network and used for diagnosing anaphylaxis.

No adverse events which were categorized as anaphylaxis, anaphylactic reaction, or hypersensitivity reaction were reported in any of the nirsevimab trials submitted with the BLA. No adverse events occurring within the two days of nirsevimab administration were identified by the FMQ search for hypersensitivity AEs. No cluster of adverse events consistent with the NIAID and Food Allergy Anaphylaxis Network definition for anaphylaxis were identified.

Safety data were also analyzed for hypersensitivity reactions or possible allergic reactions occurring more than 2 days after dosing with study product. This included a search for angioedema, which is a severe skin and/or mucosal tissue allergic reaction. One adverse event of angioedema was reported in Trial 04, in which a 1-month-old, white, female developed Grade 3 angioedema 142 days after receiving nirsevimab. Angioedema was attributed to a change in formula, and judged as unrelated to nirsevimab; the review team agrees with this assessment.

All adverse events of rashes identified in the analysis are discussed in the next section.

Rash (Hypersensitivity Skin Reaction)

Based on the FMQ hypersensitivity search criteria, the proportion of subjects for with rash events that were consistent with a hypersensitivity reaction or allergic reaction was low.

The incidence of all rashes occurring within 14 days of receipt of study product was assessed for Trials 03, 04, and 05. Rashes that were not considered allergic or part of a hypersensitivity reaction were excluded from the analysis (e.g., diaper dermatitis, insect bites, infantile acne, viral exanthem, and single

[7] FDA FMQs include acute generalized exanthematous pustules, administration site hypersensitivity, administration site recall reaction, administration site vasculitis, allergic cough, allergic cystitis, allergic gastroenteritis, allergic hepatitis, allergic otitis, allergic respiratory disease, allergic stomatitis, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, allergic arthritis, atopic cough, documented hypersensitivity to administered product, drug eruption, drug hypersensitivity, allergic encephalitis or encephalopathy, epidermal necrosis, epidermolysis, eye allergy, fixed eruption, hypersensitivity, hypersensitivity myocarditis, pneumonitis or vasculitis, injection site hypersensitivity, Kounis syndrome, allergic nephritis, Nikolsky's sign, oculo-respiratory syndrome, oral allergy syndrome, allergic pruritis, allergic scleritis, serum sickness, serum sickness-like reaction, Stevens-Johnson syndrome, toxic epidermal necrolysis, Type I, II, II, or IV hypersensitivity, cross sensitivity reaction.

skin lesions). The two-week time period captures the peak serum concentration of nirsevimab. The proportion of subjects with rash within the 2 weeks after dosing was <1% in both the nirsevimab and the control arm in all 3 trials. Finally, there was no consistent increase in any specific type of skin reactions, such as dermatitis, rash, erythema or exfoliation in the nirsevimab arm compared to the control arm across the 3 trials.

In the FMQ search for adverse events related to hypersensitivity during the 360-day follow-up period, 3 AEs of skin reactions possibly related to nirsevimab were identified. While there were other adverse events of rash identified in this search, all were thought to be due to other causative agents. The rash events, considered at least possibly related to nirsevimab included the following:

- A Grade 2 (moderate) drug eruption was reported on Day 6 post-dose in a 4-month-old female enrolled in Trial 04. The drug eruption was judged as related to nirsevimab and was treated with calamine lotion.
- Grade 1 urticaria was reported on Day 20 post-dose in a 6.9-month-old female enrolled in Trial 03. The urticaria required treatment with oral antihistamines and a topical steroid, and resolved in 5 days.
- Grade 1 urticaria was reported on Day 7 post-dose in a 6-month-old female enrolled in Trial 08. The urticaria resolved within 2 days without treatment.

In summary, after an analysis of possible hypersensitivity reactions in the pivotal trials by review of the datasets, the incidence of rash, judged as possible hypersensitivity skin reactions and considered possibly related to nirsevimab was less than 1%, and was only slightly higher in subjects who received nirsevimab compared to placebo.

Another analysis of skin adverse reactions was analysis of skin adverse reactions that were judged by the investigator as related to the study drug and as skin hypersensitivity reactions. In this analysis, skin adverse events consistent with these criteria were identified in no subjects who received placebo and in 6 subjects (0.2%) who received nirsevimab in Trials 03 and 04. Skin hypersensitivity reactions that were judged as drug related were identified in no subjects who received palivizumab and in 1 subject (0.2%) who received nirsevimab in Trial 05, season 1. There were no skin adverse events that were identified as drug-related and hypersensitivity reactions in Trial 05, season 2. All rashes were generalized in distribution. Four of the 7 skin hypersensitivity rashes occurred on Day 3 or earlier. All but one rash was Grade 1 in severity. One rash, that began on Day 7, was Grade 3; this rash was also temporally related to the infant starting a new probiotic. In this analysis, the percentage of subjects with a skin adverse event judged by the investigator as a drug-related skin hypersensitivity adverse event, the number of adverse events were higher in the nirsevimab arms compared to the control arms. However, the overall percentage of these rashes was low (<1%) and the majority of rashes were mild.

Conclusion

No adverse events of anaphylaxis were reported in any of the clinical trials. In addition, severe or serious skin reactions were uncommon in the trials of nirsevimab, as were rashes that were considered allergic reactions to nirsevimab. The incidence of rashes judged as possibly drug-related was <1% among subjects randomized to either the nirsevimab arm or the control arms over the 360-day safety follow-up period. In addition, the proportion of subjects with rashes was similar in the nirsevimab and control arms in Trials 03, 04, and 05 and there was no substantial increase in rash in the two weeks following

administration of nirsevimab. Overall, the incidence of rash in the trials of nirsevimab was low, regardless of the type of analysis performed.

Imbalance in Deaths

Background

Nirsevimab was studied in 5 pediatric clinical trials. In these trials, there were 12 deaths among subjects who received nirsevimab compared to 4 deaths in subjects who received the control (placebo or palivizumab). The number of deaths in the nirsevimab arms exceeds what one would expect with the 2:1 randomization in Trials 3, 4, and 5. For context, the global infant mortality rate in 2021 was 28 deaths per 1,000 live births (The World Bank 2021). Therefore, it is not surprising to have infant deaths occur during the global clinical development of nirsevimab. However, the imbalance in the number of deaths between the nirsevimab arms and the control arms necessitated a closer evaluation of causes and timing of deaths, as well as understanding underlying medical conditions or other confounding factors. Of note, the duration of safety follow-up in each study was at least 360-days for all subjects in these trials. In addition, the clinical trials were conducted in multiple countries, including in countries where access to or quality of healthcare may differ from that of the United States.

Assessment

There were 16 deaths during the clinical development of nirsevimab. As shown in Table 13, 12 deaths were reported in subjects who received nirsevimab and 4 were reported in subjects who received the control treatment (placebo or palivizumab). There were no deaths in Trial 2, a randomized, double-blind, placebo-controlled, dose escalation trial in infants < 12 months of age (Appendix 1). In Studies 03, 04, and 05, subjects were randomized in a 2:1 ratio to nirsevimab (N=3,580) or control (N=1,779); in these trials, there were 11 deaths (0.32%) in the nirsevimab arms and 4 (0.22%) in the control arms. Considering the unequal allocation ratio of the randomization scheme, the observed number of deaths in the nirsevimab was higher than expected. An additional death was reported in Trial 08, a single-arm, uncontrolled PK and safety study in immunocompromised children < 24 months of age (Appendix 1). A dose-response analysis for mortality did not identify an increased risk with higher dose across the clinical trials, the proportion of deaths in nirsevimab-treated subjects was 0.3% in both the 50-mg IM and 100-mg IM dose groups. While the number of subjects who received 200-mg nirsevimab in the clinical development program was small, no deaths occurred at this dose.

Table 13. Number (Percentage) of Deaths by Trial

Trial	Nirsevimab Arm	Control Arm
Trial 02	0/71	0/18
Trial 03	2/968 (0.2%)	3/479* (0.6%)
Trial 04	4/1,998 (0.2%)	0/996
Trial 05	5/613 (0.8%)	1/304 (0.3%)
Trial 08	1/60 (1.7%)	--
Total	12/3,710 (0.32%)	4/1,797 (0.22%)

Source: BLA 761328, Clinical Study Reports for all studies

*An additional death in the placebo arm of Trial 03 occurred 6 days after the study end.

The causes of death, timing of death relative to study drug administration, and relevant medical history for each subject who died, are provided in Table 14.

The causes of death were varied, and most were not related to the same general category or system organ class. The most common causes of death included cardiac, infection, malignancies and accidental

causes. In the nirsevimab group, for 8 subjects, the causes of death were clearly unrelated to study drug, including deaths in 3 subjects with congenital heart disease, two with untreated gastroenteritis, one with COVID-19, one with a tumor, and one with a skull fracture. Another two subjects died of lower respiratory tract infections. Of these two subjects, one had underlying severe protein calorie malnutrition and the other had multiple underlying conditions. One subject died at home and the other had been removed from the hospital against medical advice. Both deaths were likely related to underlying conditions rather than to nirsevimab. Finally, two subjects in the nirsevimab arm were reported as dying of “unknown” causes, having been found dead in their cribs. One of these subjects had multiple prior hospitalizations, and his health care provider hypothesized that this subject had an underlying congenital metabolic or chromosomal anomaly. The other subject was healthy without previous health issues. The circumstances of the death on Day 123 post-dose are consistent with sudden infant death syndrome; however, the cause is unknown, and the autopsy results are not available for review. The causes of death in the nirsevimab arms are consistent with the causes of death reported in the control arms.

Table 14. Causes of Death in Studies of Nirsevimab

Trial	Age at Enrollment	Demographics	Gestational Age (weeks)	Country	Cause of Death	Study Day of Death	Medical History and other Relevant Information
				Nirsevimab Arms			
03	14 weeks	Black female	31	South Africa	Unknown	123	Previously healthy, found dead in crib
03	1.9 months	White male	32	Estonia	Cardiac failure	97	Subject with undiagnosed pulmonary vein stenosis
04	5 months	Mixed Race female	38	Panama	Skull fracture	285	Hit by car
04	3 months	Black male	37	South Africa	Gastroenteritis	143	Previous episodes of gastroenteritis and history of poor weight gain Dead on arrival to emergency services
04	7 months	Black female	38	South Africa	Gastroenteritis	338	Found lifeless after 3 days of vomiting and diarrhea, Dead on arrival to emergency services
04	1 day	White male	40	Israel	Unknown	140	History of failure to thrive with recurrent hypoglycemia and anemia. Found dead in crib
05	5 weeks	White male	32	Bulgaria	Non-RSV bronchiolitis Cardiac failure	52	History of respiratory distress syndrome and congenital CMV infection. Severe protein calorie malnutrition at time of death
05	7.5 months	White male	29	Ukraine	COVID-19	162	Premature infant (born at 29 weeks GA). Diagnosed with COVID-19 and admitted to ICU, but died in hospital.
05	12 weeks	White female	39	Hungary	Bronchopneumonia	19	Subject with coarctation of aorta, congenital kidney disease, hypothyroidism and hypertonia

Trial	Age at Enrollment	Demographics	Gestational Age (weeks)	Country	Cause of Death	Study Day of Death	Medical History and other Relevant Information
05	2 months	Hispanic female	38	Mexico	Cardiogenic shock	66	Subject with ASD, VSD, Trisomy 21, hypothyroidism
05	6.5 months	White female	38	Russian Federation	Cardiac failure	19	Subject with pulmonary atresia, VSD, congenital artery anomalies
08	10.7 months	White female	39	United States	Tumor hemorrhage	125	Bled into malignant astrocytoma
				Control Arms			
03	14 weeks	Black male	32	South Africa	Pericardial effusion	343	Placebo arm: Found not breathing
03	1 month	Black male	30	South Africa	E. coli meningitis	26	Placebo arm: New onset of apnea, diagnosed with *E. coli* meningitis and sepsis and hospitalized. Died in hospital.
03	2 weeks	Black male	33	South Africa	Pneumonia	109	Placebo arm: Treated with traditional African medicine and was dead on arrival to hospital
05	20 days	White female	38	Lithuania	Respiratory insufficiency	155	Palivizumab arm: Subject with PDA, ASD, chromosomal anomaly. Hospitalized with bronchiolitis and progressively deteriorated.

Source: Clinical Study Report for Trials, 03, 04, 05, and 08, Section 14, narratives.

Abbreviations: ASD, atrial septal defect; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; GA, gestational age; ICU, intensive care unit; PDA, patent ductus arteriosus; VSD, ventricular septal defect

Conclusion

The number of deaths (N=12) in subjects who received nirsevimab was numerically higher than the number in the control arms (N=4), and the percentage of deaths was slightly higher in the nirsevimab arms (0.32%) compared to the placebo arms (0.22%). However, the percentage of deaths in the studies was much lower than global infant mortality rates reported in 2021. The global mortality rate was 28 deaths in infants per 1,000 live births. In the studies of nirsevimab, the mortality rate in the nirsevimab arms was calculated to be 3.1 per 1,000 infants. In addition, the causes of deaths varied and a single category or organ system class was not identified as the cause of death across the cases. The causes of death in the nirsevimab arms were consistent with those in the control arms. The majority of deaths were clearly related to causes other than the study drug product. Others were clearly complicated by underlying conditions. None of the deaths were judged as related to the study drug product. At this time, it is the assessment of the Agency that none of the deaths were likely related to the study drug.

3.3 Pharmacovigilance

If approved, nirsevimab may be widely used for the prevention of RSV lower respiratory tract disease in neonates and infants, and certain children with underlying medical conditions.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems (World Health Organization 2022). Clinical trials are critical to detect common adverse events, whereas postmarketing pharmacovigilance is critical to detect rare, serious adverse events, as well as to detect an increase in severity of known adverse events. Therefore, a pharmacovigilance plan is important for continued assessment and risk characterization after a drug or therapeutic biological product is approved/licensed for marketing.

The Agency plans to implement a broad pharmacovigilance strategy for nirsevimab. The key focus areas of the pharmacovigilance strategy are to: 1) identify new safety signal(s); 2) monitor for increased or unusual numbers of reports of a serious adverse event; and 3) monitor for increase in the severity of a serious adverse event. To help identify safety signals, the Agency will focus on unlabeled adverse events with the potential for serious outcomes, and labeled adverse events with unexpected characteristics such as an increase in severity.

The Agency plans to utilize several platforms to monitor postmarket safety adverse events across several postmarketing surveillance data streams, including:

- Reports submitted to the FDA's Adverse Event Reporting System (FAERS) database (Food and Drug Administration 2018b; Food and Drug Administration 2018a), which contains spontaneous adverse event reports for human drugs and therapeutic biologics,
- Published medical literature using Embase and PubMed for new safety signals
- Required, periodic safety reports (PSRs) submitted by the manufacturer
- Review of safety data from ongoing clinical trial(s) evaluating nirsevimab

Additionally, FDA is collaborating with CDC on safety data collection using near real-time active surveillance platform which encompasses claims-based data sources. Furthermore, FDA is considering other claims-based data sources for active surveillance approaches for nirsevimab.

Furthermore, the Agency is in discussion with the CDC to potentially develop educational materials for nirsevimab, similar to the Vaccine Information Statement(s) that are available for routine vaccinations.

One of the key purposes of such information sheet would be to familiarize parents and care givers on reporting of adverse events through MedWatch, the platform for adverse events reporting associated with use of drugs and therapeutic biologics.

3.4 Other Considerations

RSV Vaccine and Nirsevimab Interaction

As previously mentioned, there are several RSV vaccines under development, intended for adults or infants. Vaccines intended to protect infants are being studied for direct administration to infants, or for maternal vaccination to provide infant protection through placental transfer of antibodies. All of the nirsevimab trials excluded infants who had received an investigational RSV vaccine or whose mothers had received an investigational maternal RSV vaccine.

Should a maternal RSV vaccine be licensed, additional considerations include assessing the safety of nirsevimab in infants born to mothers vaccinated during pregnancy, and the benefit of nirsevimab in infants born to mothers vaccinated during pregnancy. We will be asking the AC to discuss additional data that may be helpful to inform future recommendations regarding the use of nirsevimab in infants born to mothers who received RSV vaccination.

See Appendices 3 and 4 for additional considerations regarding concomitant use of nirsevimab with childhood vaccines (Appendix 3) and anti-drug antibody (ADA) to nirsevimab (Appendix 4).

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5 Appendix

Appendix Table of Contents

Appendix 1: Table of Trials

Table 15. Clinical Trials of Nirsevimab

Study/Trial Identifier	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
D5290C00001 (Trial 01)D5290C00001 (Trial 01) NCT02114268	Phase 1, R, DB, PC, dose escalation study in healthy adults 18 years to <50 years of age	Phase 1, R, DB, PC, dose-escalating, safety, and PK trial of nirsevimab compared to placebo Control type: Placebo (nirsevimab vehicle) Randomization: 4:1 Blinding: Double-blind	Drug: Nirsevimab Dosage: 300-mg, 1,000-mg, or 3,000 IV and 100 or 300-mg IM Number treated: 102 Duration (quantity and units): Single dose on Day 1 Choose time unit.	Primary: AEs, SAEs, and AESIs Secondary: PK	136;136	1 country 1 site

Study/Trial Identifier	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
D5290C00002 (Trial 02) NCT02290340	Infants born during or entering first RSV season. Born at ≥29 to <35 weeks GA	Phase 1b/2a, R, DB, PC, dose-escalating, safety, and PK trial of nirsevimab compared to placebo Control: Saline placebo Randomization: 4:1 Blinding: Double-blind	Drug: Nirsevimab Dosage: Single 10-mg, 25-mg, or 50-mg IM dose Number treated:89 Duration: Single IM dose on Day 1	Primary: AEs, SAEs, AESIs Secondary: PK		3 countries 10 sites

Study/Trial Identifier	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
D5290C00003 (Trial 03) NCT02878330	Infants born during or entering first RSV season; Born at ≥29 to <35 weeks GA	Phase 2, R, DB, PC, safety, PK and efficacy trial of nirsevimab for the prevention of RSV MA-LRTI during their first RSV seasons Control: Saline placebo Randomization: 2:1 Blinding: Double-blind	Drug: Nirsevimab Dosage: Single 50-mg IM dose Number treated:966 Duration: Single IM dose on Day 1	Primary: Incidence of MA-LRTI due to RT-PCR-confirmed RSV over 5-month RSV season Secondary: Incidence of hospitalizations due to RT-PCR-confirmed RSV Nirsevimab PK Adverse events, SAEs, AESIs and incidence of ADA	1,500;1,453	23 countries 164 centers
D5290C00004 MELODY (Trial 04) NCT03979313	Infants born during or entering first RSV season; Born at ≥35 weeks GA	Phase 3, R, DB, PC, 2-cohort, safety, PK and efficacy trial of nirsevimab for the prevention of RSV MA-LRTI during their first RSV seasons Control: Saline placebo Randomization: 2:1 Blinding: Double-blind	Drug: Nirsevimab Dosage: 50-mg IM for subjects <5 kg and 100-mg for subjects ≥5 kg Number treated:1998 Duration: Single IM dose on Day 1	<u>Cohort 1 (Primary Cohort)</u> Primary: Incidence of MA-LRTI due to RT-PCR-confirmed RSV over 5 month RSV season Secondary: Incidence of hospitalizations due to RT-PCR-confirmed RSV <u>Cohort 2 (Safety Cohort)</u> Primary: AEs, SAEs, AESIs	3,000;3,012	31 countries 211 centers

Study/Trial Identifier	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
D5290C00005 MEDLEY (Trial 05) NCT03959488	Infants born during or entering first RSV season; Born at <35 weeks GA; Children ≤24 of age with CLD or CHD, entering first and second RSV seasons	Phase 2/3, R, DB, palivizumab-controlled, 2-cohort, safety, PK and effectiveness trial of nirsevimab for the prevention of RSV-MA-LRTI in pediatric subjects at high risk of severe RSV disease Control: palivizumab, administered monthly x 5 as recommended in the PI Randomization: 2:1 Blinding: Double-blind	Drug: Nirsevimab Dosage: In all study infants in first year of life:50-mg IM for subjects <5 kg and 100-mg for subjects ≥5 kg In subjects with CLD and CHD in second year of life: 200-mg IM Number treated:614 Duration: Single IM dose on Day 1	Primary: AEs, SAEs, AESIs Secondary: PK Incidence of MA-LRTI due to RT-PCR-confirmed RSV over 5 month RSV season	900;925	25 countries 126 centers

Study/Trial Identifier	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
D5290C00008 MUSIC (Trial 08) NCT 04484935	Immuno-compromised infants and children ≤24 months of age	Phase 2, OL, single arm, safety, PK and effectiveness study of nirsevimab in immunocompromised children	Drug: Nirsevimab Dosage: In infants in first year of life:50-mg IM for subjects <5 kg and 100-mg for subjects ≥5 kg In subjects in second year of life: 200-mg IM Number treated:60 Duration: Single IM dose on Day 1	Primary: AEs, SAEs, AESIs Secondary: PK Incidence of MA-LRTI due to RT-PCR-confirmed RSV over 5 month RSV season	100;60	6 countries 22 centers

Source: Clinical Reviewer.

[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

[2] If no randomization, then replace with "Actual Enrolled."

Abbreviations: ADA, antidrug antibody; AEs, adverse events; AESIs, adverse events of special interest; BID, twice daily; DB, double-blind; GA, gestational age; IM, intramuscular; IV, intravenous; LTE, long-term extension; MC, multicenter; N, number of subjects; NCT, national clinical trial; OL, open-label; PC, placebo-controlled; PG, parallel group; PK, pharmacokinetics; R, randomized; SAEs, serious adverse events

Appendix 2. Additional Efficacy Analyses

Trial 03

Relationship Between Baseline Age, Weight, and Occurrence of MA RSV LRTI Events (Trial 03)

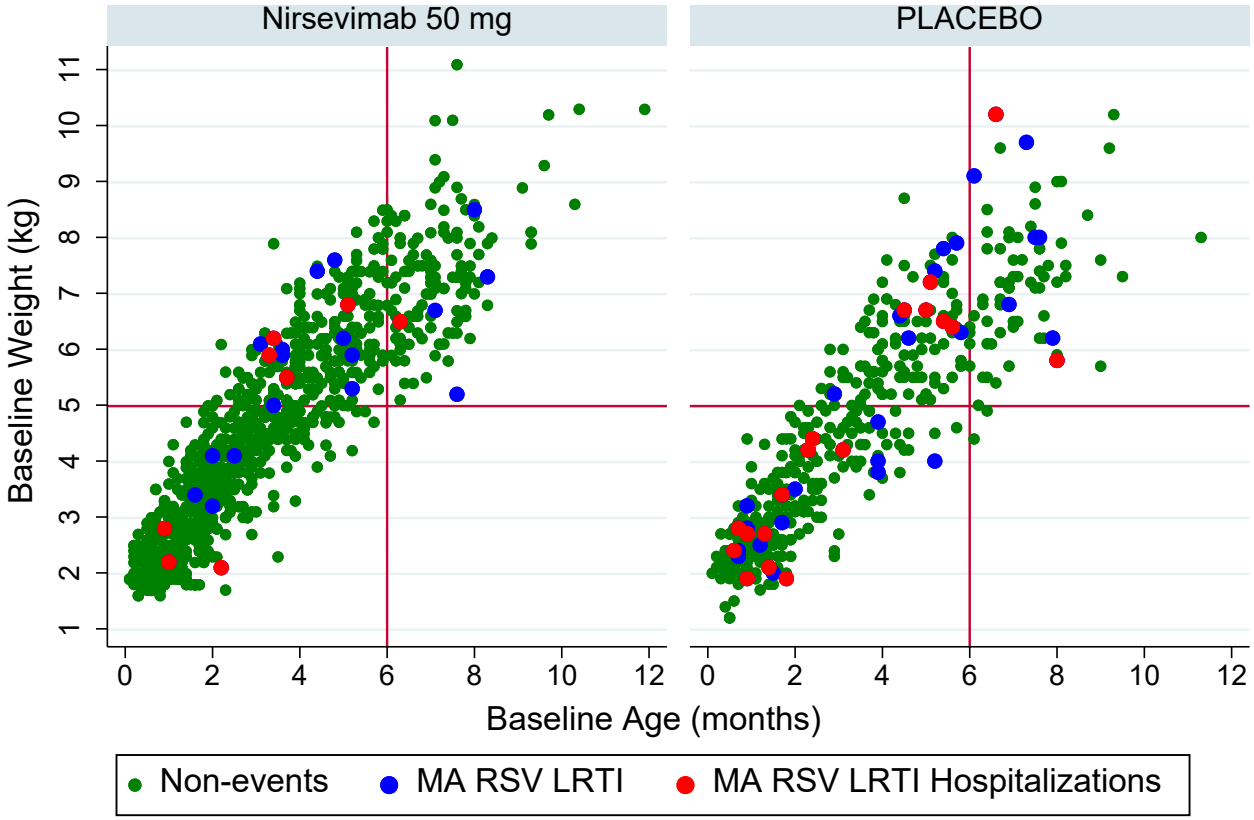
Because infants younger than 6 months of age are at highest risk for MA RSV LRTI, and because of dependence of the nirsevimab dose on body weight, it is crucial to examine the relationship between baseline age, weight, and occurrence of MA RSV LRTI events. Overall there were fewer MA RSV LRTI events (with and without hospitalization) in the group that received nirsevimab compared to the group that received placebo (Figure 8).

As previously mentioned, in Trial 03, all subjects randomized to the nirsevimab treatment group received 50-mg IM regardless of baseline body weight. Within the nirsevimab arm, the were fewer events of MA RSV LRTI in subjects weighing <5 kg compared to ≥5 kg. Because of this difference in event incidence, the Applicant reconsidered the adequacy of the dose for infants weighing ≥5 kg after the trial was completed. Subsequently, nirsevimab dose was increased from 50-mg to 100-mg for subjects weighing greater than 5 kg who enrolled in Trial 04.

As expected, only a few infants who were older than 6 months of age and weighing less than 5 kg (n=3) were enrolled in Trial 03. All of those subjects were in the placebo arm (Figure 8). Therefore, in this trial, the proposed weight-based dosing for nirsevimab was only examined in subjects younger than 6 months of age. Most MA RSV LRTI events in this trial, including hospitalization, were reported in infants less than 6 months of age.

The following figure (below) shows the relationship between baseline weight, age and outcome at Day 150 post-dose.

Figure 8. Relationship Between Baseline Weight, Baseline Age, and Outcome Status (Day 150 Post-Dose)



Source: FDA statistical reviewer

Legend: Relationship between baseline weight and baseline age for subjects who did not experience MA RSV LRTI (green circles), subjects who experienced MA RSV LRTI without hospitalization (blue circles), and those who experienced MA RSV LRTI and were hospitalized (red circles). Each circle represents age and weight at baseline so that each subject is represented only once.

Abbreviations: MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection

Trial 04

Relationship Between Baseline Age, Weight, and Occurrence of MA RSV LRTI Events (Trial 04, Primary Cohort)

Because infants younger than 6 months of age are at the highest risk for MA RSV LRTI, and because of dependence of the nirsevimab dose on body weight, it is crucial to examine the relationship between baseline age and weight, and occurrence of MA RSV LRTI events. See the scatter plot (Figure 9).

Baseline body weight (<5 kg versus ≥5 kg) essentially followed chronological age because, as generally expected, most infants weighing less than 5 kg are younger than 4 months of age. Only 1 subject older than 6 months weighed less than 5 kg at baseline. Thus, all other subjects older than 6 months who were randomized to nirsevimab received a 100-mg dose.

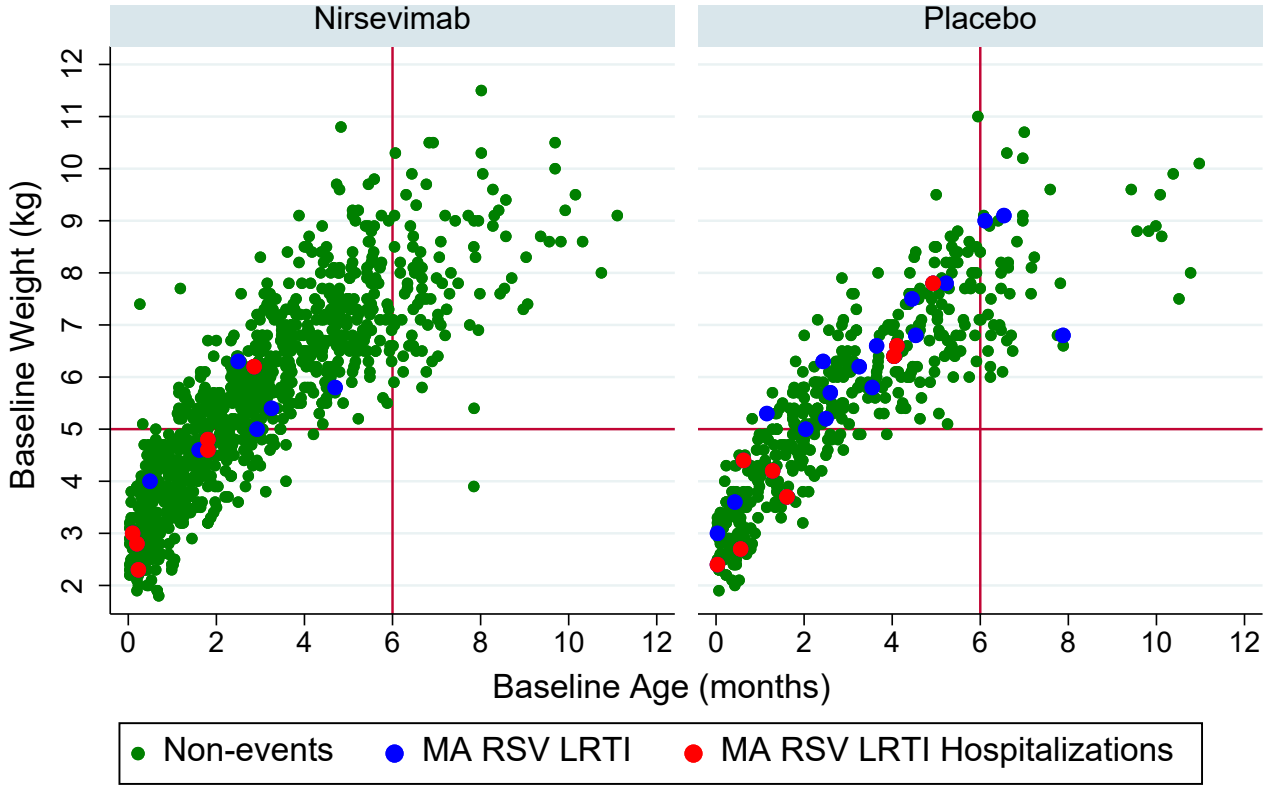
Overall, more subjects in the placebo group experienced MA RSV LRTI events (with or without hospitalization) than nirsevimab-treated subjects. The events mostly occurred in infants who were 6 months of age or younger at the time of enrollment. Events of MA RSV LRTI were less common in subjects older than 6 months of age in both treatment groups. With respect to hospitalizations, there were no hospitalizations in either treatment group among infants who were older than 6 months of age at the time of randomization. Because of low number of MA RSV LRTI events in subjects who were 6

months of age or older, there is limited data from which to draw definitive conclusions about efficacy in this age subgroup.

As shown in Figure 9, there were only a few subjects who were older than 8 months of age at the time of enrollment (25 on nirsevimab and 10 on placebo). None of those subjects experienced MA RSV LRTI during the first 150 days post-dose in the trial.

In addition, no nirsevimab-treated subjects weighing 7 kg or more at baseline experienced MA RSV LRTI, while subjects weighing 9 kg or less on placebo experienced events in all weight categories. Baseline body weight (<5 kg versus ≥5 kg) essentially followed chronological age because, as generally expected, most infants weighing less than 5 kg are younger than 4 months of age. Only 1 subject older than 6 months weighed less than 5 kg at baseline. Thus, all other subjects older than 6 months who were randomized to nirsevimab received a 100-mg dose. None of the nirsevimab-treated subjects older than 6 months experienced an MA RSV LRTI event. There were 3 MA RSV LRTI events among subjects on placebo who were older than 6 months at baseline.

Figure 9. Primary Cohort: Relationship Between Baseline Weight, Baseline Age, and Outcome Status (Day 150 Post-Dose) in Trial 04



Source: FDA statistical reviewer

Legend: Relationship between baseline weight and baseline age for subjects who did not experience MA RSV LRTI (green circles), subjects who experienced MA RSV LRTI without hospitalization (blue circles), and those who experienced MA RSV LRTI and were hospitalized (red circles). Each circle represents age and weight at baseline so that each subject is represented only once.

Abbreviations: MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection

Appendix 3: Nirsevimab and Routine Childhood Vaccines

The Applicant provided information regarding nirsevimab or placebo administration and exposure to routine childhood vaccines for subjects in Trial 04. Trial 04 enrolled subjects who were born at late preterm or term gestation; therefore, the vaccine schedule administered to subjects in Trial 04 was most consistent with local or regional recommendations. Only 8% of subjects in the nirsevimab arm and 10% in the placebo arm received a childhood vaccine within 7 days of administration of study drug; 31% of subjects in the nirsevimab arm and 34% in the placebo arm received a childhood vaccine within 14 days of administration of study drug. The most commonly received childhood vaccine was the diphtheria, tetanus, and pertussis vaccine, which was administered to 21% of subjects in the nirsevimab arm and 20% of subjects in the placebo arm within 14 days of study drug administration. The percentage of subjects in the nirsevimab arm who experience any AE in the subgroup who had received a childhood vaccine within 14 days was 27% and was 25% in subjects who had not received a childhood vaccine with the previous 14 days. There was a slight increase in the percentage of subjects in the nirsevimab arm who had been vaccinated in the previous 14 days and reported fever (1.5%) compared to subjects in the nirsevimab arm who had not received a childhood vaccine (0.7%). The percentage of subjects in the placebo arm who had received a childhood vaccine within the previous 14 days and had fever was 0.6%, which suggests that fever may be more common when routine childhood vaccines are administered within 14 days of nirsevimab. In conclusion, there may have been a slight increase in fever among subjects who received nirsevimab and routine childhood vaccines within 14 days of each other, but the overall percentage of subjects with fever was small.

Appendix 4: Nirsevimab and Anti-Drug Antibodies

In all trials of nirsevimab, the incidence of anti-drug antibodies (ADAs) to nirsevimab was measured pre-dose and post-dose with nirsevimab or control. However, differences in assay methods used in the different trials prevent meaningful comparisons of the incidence of ADA across the trials. The incidence of anti-nirsevimab antibodies at Day 361 was 3.3% (16/492) in Trial 03, 6.5%, (54/830) in Trial 04, and 5.8% (30/514) in Trial 05. AEs in subjects who developed ADAs in Trial 04 were compared to AEs in subjects who did not develop ADAs. There was a slight increase in the percentage of subjects with any AE (96%) in subjects who received nirsevimab and were ADA positive at Day 361 compared to subjects who received nirsevimab and were ADA-negative at Day 361 (89%). However, the types of AEs that were most commonly reported were the same in the 2 subgroups: upper respiratory tract infection, pyrexia, nasal congestion, and teething. Overall, the percentage of subjects who developed ADAs was low and there did not appear to be any substantial differences in safety between subjects who were ADA-positive and those who were ADA-negative at Day 361.