Clinical, Clinical Pharmacology, Cross-Discipline Team Leader, and Director Review

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Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	761328/S-05
Applicant	AstraZeneca
Date of Submission	10/31/2023
PDUFA Goal Date	8/31/2024
Proprietary Name	Beyfortus
Established or Proper Name	Nirsevimab
Dosage Form(s)	Solution for intramuscular (IM) injection
Indication(s)/Population(s)	Prevention of RSV lower respiratory tract disease in: - Neonates and infants entering or during their first RSV season - Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season
Dosing Regimen(s)	Neonates and infants entering first RSV season: single IM dose 50 mg if weighing <5 kg, single IM dose of 100 mg if weighing ≥ 5 kg Children entering their second RSV season: single IM dose of 200 mg
Recommendation on Regulatory Action	Approval

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1. Executive Summary

This combined Clinical, Clinical Pharmacology, Cross Discipline Team Leader (CDTL), and Director Review provides an overview of the submitted clinical data, summarizes the findings of the FDA multi-disciplinary team of reviewers, describes the conclusions and recommendations presented by all relevant disciplines, and provides an overall risk-benefit assessment for the use of nirsevimab-alip in immunocompromised children as well as a safety update for term neonates and infants and for infants and children at high risk of severe RSV disease.

Nirsevimab-alip, referred to as nirsevimab in this review, is currently indicated for the prevention of RSV lower respiratory tract disease (LRT) in:

- Neonates and infants entering or during 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.

The data reviewed for this supplemental BLA were the final Clinical Study Reports (CSRs) for Trials 04, 05, and 08, which were conducted in term neonates and infants (≥35 weeks gestational age (GA)), in infants and neonates at highest risk for severe RSV LRT disease, and in immunocompromised infants and children, respectively. The complete CSRs and datasets for these three trials were submitted to satisfy Postmarketing Commitments 4470-6, 4470-7, and 4470-8, which were issued in the BLA approval letter dated July 23, 2023.

Interim CSRs for Trial 04 and 05 were included in the original nirsevimab BLA submission. The efficacy results and much of the safety data from these two trials were reviewed as part of the original nirsevimab BLA review. The final CSRs for these two trials, which were included in this supplemental BLA, only include long term safety data for Trials 04 and 05. No new safety signals were identified in Trial 04 or Trial 05.

Trial 08 was a Phase 2, single arm, uncontrolled, safety, pharmacokinetic, and efficacy study of nirsevimab in immunocompromised infants and children 24 months of age and younger. The final CSR for this trial was submitted in this BLA supplement and included safety, PK, and efficacy data for this trial. Trial 08 was not designed to demonstrate efficacy. Efficacy in immunocompromised patients was assessed by extrapolation of efficacy based on PK, e.g., comparison of nirsevimab exposures in subjects in Trial 08 to exposures in subjects in Trials 03[1], 04, and 05. The mean nirsevimab exposures were lower in Trial 08 compared to the other trials; however, the nirsevimab exposures in Trial 08 were within the range shown to be effective in subjects who received the recommended dose of nirsevimab in Trials 03, 04, and 05. Therefore, the review team determined that the efficacy of nirsevimab in immunocompromised infants and children was demonstrated by extrapolation. The safety of Trial 08 was consistent with the study population and with common conditions and illnesses observed in childhood. The incidence of nirsevimab-related adverse events in Trial 08 was similar to the incidence in Trials 04 and 05. No new safety signals were identified in Trial 08.

[1] Trial 03 was a randomized, double-blind, placebo-controlled trial of nirsevimab in infants born at a gestational age of ≥29 weeks to <35 weeks. Trial 03 was reviewed with the original BLA submission.

The nirsevimab indication was not revised to specifically include use of nirsevimab in immunocompromised patients, because the indication currently allows for the use of nirsevimab in infants and children who are vulnerable to severe RSV, such as immunocompromised patients. The additional safety data from all three trials included in this supplement are consistent with the safety data currently included in the nirsevimab package insert. Therefore, only minor changes reflecting the number of subjects exposed to nirsevimab were made to Section 6, ADVERSE REACTIONS of the package insert. The nirsevimab package insert was revised to include information from Trial 08 in USE IN SPECIFIC POPULATIONS and to include pharmacokinetic and antidrug antibody data from Trial 08 in the CLINICAL PHARMACOLOGY section.

2. **Background**

Nirsevimab is a respiratory syncytial virus (RSV) F protein-directed fusion inhibitor human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. On July 17, 2023, nirsevimab was approved for the prevention of RSV LRT disease in neonates and infants entering or during 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. The safety and efficacy of nirsevimab was established by the results of three pivotal clinical trials: two safety and efficacy trials in preterm and term neonates and infants (≥29 weeks GA) (Trials 03 and 04) and a trial in infants and neonates at highest risk for severe RSV LRT disease; i.e., those <29 weeks GA, those with chronic lung disease (CLD) of prematurity, and those with hemodynamically significant congenital heart disease (CHD) (Trial 05). The original BLA also included the interim results for a supportive trial, Trial 08, which was an uncontrolled study in immunocompromised children ≤ 24 months of age.

The final Clinical Study Report (CSR) for Trial 03 was included in the original BLA. Trial 03 was a randomized, double-blind, placebo-controlled trial of nirsevimab in infants who were born during RSV season or were entering their first RSV season and who were born at a gestational age (GA) of ≥29 weeks to <35 weeks. See the Integrated Review of the original BLA for a discussion of Trial 03.

Interim CSRs for Trials 04, 05, and 08 were included in the original BLA. The datasets and final CSRs for Trials 04, 05, and 08 were submitted in this supplemental BLA to fulfill Post-Marketing Commitments 4470-6, 4470-7, and 4470-8 issued in the approval letter for the original BLA, which was issued on July 19, 2023. While Trials 04, 05, and 08 are also referred to as MELODY, MEDLY and MUSIC, respectively; the three trials will be referred to by trial number in this review. The three trials for which final CSRs were included in this supplement are described in Table 1.

Table 1. Nirsevimab Trials in BLA 761328, Supplement 05

Trial	Design	Population	Nirsevimab Dosage	Number of Subjects Who Received Nirsevimab
04	Phase 3, randomized, double-blind, placebo-controlled, safety, PK and efficacy trial	Infants entering first RSV season; Born at ≥ 35 weeks GA	50 mg IM for subjects <5 kg and 100 mg for subjects ≥5 kg	1,997
05	Phase 2/3, randomized, double-blind, palivizumab-controlled, safety, PK and effectiveness trial of nirsevimab	Infants born at <35 weeks GA entering first RSV season Children ≤24 months of age with CLD or CHD, entering first and second RSV seasons	In all trial 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	220*
08	Phase 2, open-label, single arm, safety, PK and effectiveness trial	Immuno-compromised pediatric patients ≤24 months of age	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	100

Source: Table generated by clinical reviewer
*Although 614 subjects received nirsevimab in the first year of Trial 05, this submission contains safety information from the second year of Trial 05, in which 220 subjects received nirsevimab.

Subjects in Trial 04 received a single intramuscular dose of nirsevimab prior to or during the RSV season. Subject in Trials 05 received a single intramuscular dose of nirsevimab prior to or during RSV Season 1 and a second intramuscular dose prior to RSV Season 2. Subjects in Trial 08 were enrolled in their first or second year of life and participated in the trial for one year. Therefore, subjects in Trial 08 received one intramuscular dose of nirsevimab administered as appropriate for subjects age (first year or second year of life).

The current supplemental BLA includes the final CSRs for Trials 04, 05 and 08. The study reports for Trials 04 and 05 contain long-term safety data that was not included in the original BLA. The trial design and overall results of Trials 04 and 05 are described in detail in the integrated review of the original BLA, which is available in CDER's Document Archiving Reporting and Regulatory Tracking System (DARRTS). The designs of Trials 04 and 05 will be summarized in this review. There are no new efficacy results for Trials 04 and 05 and efficacy for both trials was discussed in the original review; therefore, the efficacy results for

these trials will not be discussed in this review. This review will focus on the safety results for these trials. At the time of the original BLA, 60 of 100 planned subjects had been enrolled in Trial 08. This review will include describe the design, safety, and effectiveness data for the entire study population of Trial 08.

3. Benefit-Risk Assessment

3.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	**Respiratory Syncytial Virus (RSV)** • RSV is an enveloped RNA virus that causes respiratory tract infection. • RSV occurs in annual outbreaks each fall and winter in the majority 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. • RSV is the most common cause of LRT infection (LRTI) in infants and young children both in the U.S. and worldwide. Approximately 20% to 30% of infants with RSV develop LRT disease with their first RSV infection. RSV LRTI usually presents as bronchiolitis and/or pneumonia. The Centers for Disease Control and Prevention (CDC) estimates that RSV infection results in 2.1 million outpatient visits yearly among children younger than 5 years of age. Based on CDC's New Vaccine Surveillance Network (NVSN) analysis, it is estimated that RSV infections in pediatric patients < 24 months of age results in 472,000 visits to	RSV virus is one of the most common causes of viral respiratory tract infection. While most experience mild upper respiratory tract infection, certain populations are at risk of lower respiratory tract disease, including pneumonia and bronchiolitis. RSV can lead to severe or serious disease in infants, including healthy term and preterm infants. Nirsevimab is currently indicated for use in all neonates and infants born during or entering their first year of life. Some infants remain at risk of severe or serious RSV disease, therefore, nirsevimab is also indicated for children up to 24 months of age who remain vulnerable to severe RSV through their second RSV season. Children who are at the greatest risk for severe or serious disease include extreme preterm infants (e.g., <29 weeks of GA), infants/children with chronic lung disease of prematurity, infants/children with hemodynamically significant congenital heart disease, immunocompromised infants/children, and infants/children receiving immunosuppressive drugs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Emergency Departments each year (Lively et al. 2019). • RSV LRTI is the most common cause of hospitalization for infants in the United States. Approximately 1% to 3% all children in the U.S. will be hospitalized due to severe RSV disease. In children younger than 5 years of age, RSV infection results in 58,000 to 80,000 hospitalizations each year in the U.S. The majority of children hospitalized with RSV infection improve with supportive care and are discharged in 2 to 3 days. • Severe RSV disease and hospitalization are more common in certain pediatric populations. 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 year of years of age with chronic lung disease (CLD) of prematurity or hemodynamically unstable congenital heart disease (CHD), immunocompromised children, and children with neuromuscular disorders that have difficulty swallowing or handling secretions. The risk of severe RSV LRTI in infants born prematurely increases with decreasing gestational age (GA). Although the increased risk of severe RSV LRTI has been reported for all premature infants born at <35 weeks GA, the American Academy of Pediatrics (AAP) determined that the majority of studies show that the greatest risk for severe RSV LRTI is in infants born before 29 weeks GA. • According to the CDC, RSV infection leads to 100 to 300 deaths in children younger than 5 years of age in the U.S. each year. The Global Burden	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of Diseases, Injuries, and Risk Factors reported that there were more than 41,000 deaths due to RSV worldwide in 2016 in children <5 years of age. A recent meta-analysis reported 101,400 RSV-associated deaths globaly in children <5 years of age in 2019.	
Current treatment options	**Treatment** Ribavirin is the only currently approved drug for the treatment of RSV infection and is indicated for the treatment of severe RSV LRTI in hospitalized infants and young children. Ribavirin is only available as an inhalation solution, which is administered as an aerosol using a face mask, oxygen hood, or oxygen tent. Ribavirin is administered continuously over 12 to 18 hours per day for 3 to 7 days. **Prevention** RSVpreF and nirsevimab are both approved for the prevention of RSV.	**Treatment** Although ribavirin is approved for the treatment of RSV, the use of ribavirin for RSV treatment is not recommend by the CDC or the AAP. The administration of ribavirin is difficult; it is administered continuously over long periods. Ribavirin precipitates in the ventilatory circuit in patients receiving mechanical ventilation and may result in ventilator dysfunction. In addition, ribavirin is lethal to embryos and teratogenic in animal studies. As a result, aerosolized ribavirin may place pregnant care takers or family members at risk. There is a need for safe, effective oral and intravenous drugs for the treatment of RSV in infants and children. **Prevention** The RSVpreF vaccine is approved for pregnant individuals at 32 through 36 weeks gestational age for the prevention of RSV in infants from birth through 6 months of age. In the phase 3 clinical trial supporting the safety and efficacy of the vaccine, RSVpreF vaccine reduced the risk of the neonate/infant being hospitalized for RSV by 57% and of having a healthcare visit for RSV by 51% within 6 months after birth. Nirsevimab is indicated for the prevention of RSV LRT disease in: • Neonates and infants entering or during their first RSV season and • Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		In Phase 3 trials, both the RSVpreF vaccine and nirsevimab demonstrated a statistically significant decrease in RSV-associated LRTI in infants entering their first RSV season. There have been no trials comparing the two products. The CDC recommends that health care providers discuss the two options with their patients and consider patient preferences when determining whether to vaccine the mother or administer nirsevimab to the neonate /infant.
Benefit	The primary efficacy endpoint used for the pivotal trials supporting efficacy in the original BLA was the incidence of MA RSV LRTI caused by RT-PCR-confirmed RSV, characterized predominantly as bronchiolitis or pneumonia through 150 days after dosing. MA visits include all healthcare provider visits such as physician office, urgent care, emergency room visits and hospitalizations. The three pivotal trials supporting the original BLA were Trials 03, 04, and 05. The results of these trials are breifly described below. Please see the original BLA review for additional details. • Trial 03 was a randomized, placebo-controlled trial that evaluated nirsevimab for prevention of MA RSV LRTI in preterm neonates and infants born at ≥29 weeks to <35 weeks GA. In Trial 03, the incidence of MA RSV LRTI was 2.6% in those who received nirsevimab and 9.5% in those who received placebo, for an estimated relative risk reduction of 70.1% (95% confidence interval (CI):52.3% to 81.2%) with a p-value of <0.0001 in favor of nirsevimab.	Based on the results of Trials 03, 04 and 05, in 2023 nirsevimab was approved for the prevention of RSV LRT infection in neonates and all infants and children in the first year of life and in neonates, infants, and children who are vulnerable to severe RSV disease in through their second RSV season. In Trial 08 in immunocompromised patients, no events of MA RSV LRTI were reported through Day 151. Trial 08 was conducted during the COVID-19 pandemic, which resulted in the decreased circulation of RSV. Therefore, the lack of MA RSV LRTI events may have been related to the COVID-19 pandemic. Further, Trial 08 was not designed to statistically assess efficacy. PK parameters from Trial 08 were compared to those in Trials 03, 04, and 05. Although the mean nirsevimab exposures were lower in Trial 08 than in the other trials, nirsevimab exposures were within the range found to be effective in Trials 03 and 04. Therefore, the review team concluded that efficacy in immunocompromised patients could be extrapolated from Trials 03, 04, and 05 by demonstration of similar nirsevimab PK parameters. As nirsevimab is currently indicated for subjects who are vulnerable to severe RSV disease, the indication already encompasses immunocompromised neonates, infants, and children, and no changes to the indication are needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Trial 04 was a Phase 3 trial which enrolled neonates and infatns born at born at ≥35 weeks. In Trial 04, the incidence of MA RSV LRTI was 1.2% in those who received nirsevimab and 5.0% in those who received placebo, for an estimated risk reduction of 74.9% (95% CI: 50.6% to 87.3%) with a p-value of <0.0001. • Trial 05 was a study of infants at risk of severe or serious RSV disease. Efficacy in this population was extrapolated from efficacy in otherwise healthy infants based on similar nirsevimab exposures in Trial 04 and 05. The results of this study supported the approval of nirsevimab in infants and children who are vulnerable to severe RSV disease through their second RSV season. Trial 08 was ongoing at the time of the original BLA review and the final CSR was included in this supplemental BLA. Trial 08 was a phase 2, open-label, uncontrolled, safety, pharmacokinetics, and efficacy study for nirsevimab in immunocompromised children ≤24 months of age. All study subjects were followed for the occurrence of MA RSV LRTI through Day 151. However the trial was not designed to directly evaluate efficacy. Efficacy was established by extrapolation, based on a comparison of nirsevimab exposures in subjects in Trial 08 to exposures in subjects in Trials 03, 04, and 05.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• The original safety database included 3,751 pediatric patients who received any dose of nirsevimab. The safety results in Section 6, ADVERSE REACTIONS of the Beyfortus package insert include rash and injection site reactions as the adverse events reported at a higher incidence after nirsevimab compared to placebo. • The final CSRs for Trials 04 and 05 included long term safety data. In Trial 04, all subjects were followed through a second RSV season (Day 362 to Day 511) for MA RSV LRTI and RSV-associatied hospitalizations. Nirsevimab was not administered prior to the second RSV season. These data regarding MA RSV LRTI and hospitalizations in the second season are of interest as a means of characterizing the risk of antibody dependent enhancement of RSV disease in infants who receive nirsevimab in the first year of life and are exposed to RSV in their second year of life, and/or shifting of severe RSV LRT disease to the child's second RSV season. • The final CSR for Trial 08, a single arm, uncontroled trial in immunocompromised subjects ≤ 24 months of age, was also included in the current submission and included study results for the entire study population. The safety results for Trial 08 reflected both the serious underlying conditions of the study population and common childhood conditions.	No new safety issues related specifically to the use of nirsevimab were identified by our review of this supplemental BLA. The safety data in the final CSRs for Trials 04 and 05 were consistent with the safety in the current Beyfortus package insert. Further the safety results from Trial 08 were consistent with the study population (i.e., the adverse events reflected common childhood illnesses/conditions as well as complications of the underlying immunocompromising conditions/therapies). The percentage of subjects with nirsevimab-related adverse events or nirsevimab-related serious adverse events in Trial 08 was low and was similar to the percentages observed in Trial 04. There were three deaths; none of the three deaths were related to nirsevimab and all appeared to be related to the subjects' underlying disease. Although the long-term safety data from children enrolled in Trial 04 who were followed through their second season were affected by the low ciruclation of RSV during the COVID-19 pandemic, there was no apparent increase in MA RSV LRTIs or RSV associated hospitalizations in the second RSV season. As part of a prior postmarket committment, long-term safety data from infants enrolled in other ongoing trials (e.g. HARMONIE trial) will be submitted to further characterize the risk of antibody dependent enhancement of RSV disease and/or shifting of severe RSV LRT disease to the child's second RSV season. The package insert was revised to include a description of Trial 08 in Section 8, USE IN SPECIAL POPULATIONS, of the package insert. The design of Trial 08 and safety results for the trial are included in this section.

3.2. Conclusions Regarding Benefit-Risk

RSV is the most common cause of lower respiratory tract infection (LRTI) in infants and young children both in the United States and worldwide. RSV LRTI is a serious and potentially life-threatening illness in infants and children. 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. Approximately 1% to 3% of children <12 months of age in the United States are hospitalized each year due to RSV (Committee on Infectious Diseases 2021-2024). According to the CDC, there are 100 to 300 deaths from RSV 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).

Nirsevimab, a monoclonal antibody against RSV F protein, has clearly demonstrated clinical benefit in preventing MA RSV LRTI in otherwise healthy preterm and term infants in their first RSV season and was approved by FDA in July 2023. The efficacy of nirsevimab in preventing MA RSV LRTI in neonates, infants, and children with extreme prematurity, CLD of prematurity, hemodynamically significant CHD, or other underlying conditions which place children at high risk for severe RSV disease in their second RSV season was extrapolated from moderate preterm and term infants, based on similarity of disease pathophysiology and demonstration of similar nirsevimab exposures in moderate preterm and term infants and in those with CLD or CHD. Since the time of approval, the efficacy of nirsevimab has been further supported by multiple scientific reports. The New Vaccine Surveillance Network (NVSN) conducts prospective surveillance of acute respiratory illness in pediatric patients <18 years of age at seven U.S. pediatric academic medical centers (efaidnbmnnnibpcajpcglclefindmkaj/https://www.cdc.gov/mmwr/volumes/73/wr/pdfs/mm7309a4-H.pdf). In this controlled prospective study of nirsevimab, only six (1%) of hospitalized infants had received nirsevimab compared to 18% of the control patients resulting in 90% effectiveness of nirsevimab against RSV-associated hospitalization.

In Trial 08, nirsevimab was studied in immunocompromised infants and children ≤ 24 months of age. Trial 08 was a single arm study and was not designed to statistically evaluate efficacy. Efficacy in immunocompromised infants and children was determined by exposure-matching between subjects in Trial 08 and subjects in Trial 03, 04, and 05. The mean nirsevimab exposure levels were lower in immunocompromised infants and children in Trial 08 than in the study populations of Trials 03, 04, 05. However, nirsevimab exposures in Trial 08 were within the range shown to be effective in subjects who received the recommended dose of nirsevimab in Trials 03, 04, and 05. Therefore, efficacy of nirsevimab in immunocompromised infants and children was demonstrated by extrapolation of efficacy from subjects in Trials 03, 04, and 05 to immunocompromised patients.

On review of the original BLA, nirsevimab was found to have a favorable safety profile. Rash and injection site reactions are included in the Beyfortus package insert as adverse reactions reported at a higher incidence in subjects who received nirsevimab compared to those who received placebo. Since the original approval, the package insert has been updated to include reports of signs and symptoms consistent with hypersensitivity reactions. Long term safety from

two trials, Trial 04 and 05 and safety from Trial 08 were reviewed in this BLA supplement. There were no new safety concerns identified in these studies. There were no reports of hypersensitivity reactions or anaphylaxis. In general, the types of adverse events reflected common childhood conditions; and in Trial 08, safety also reflected the serious underlying conditions of the study population.

The overall benefit-risk profile of nirsevimab as observed on review of this supplemental BLA continues to support the nirsevimab indication for prevention of RSV LRT disease, including in immunocompromised patients.

4. Product Quality

Not applicable (approved product).

5. Nonclinical Pharmacology/Toxicology

Not applicable.

6. Clinical Pharmacology

6.1. Overview of Clinical Pharmacology

This submission includes final data sets for Trials 04 (PK, ADA, safety in term and late preterm infants), 05 (PK, ADA, safety in preterm infants and in pediatric subjects with CLD of prematurity or CHD) and 08 (PK, ADA, safety and descriptive efficacy in immunocompromised (IC) pediatric subjects). In addition, the Applicant submitted a population PK modeling report amendment describing the prediction of nirsevimab pharmacokinetic (PK) data, and efficacy extrapolation based on nirsevimab drug exposure, in IC infants and children in Trial 08. The clinical pharmacology reviewers reviewed the complete pharmacokinetic data for Trials 04, 05, and 08.

Selected key PK metrics for efficacy extrapolation in Trial 08

Trial 08 was not designed to demonstrate efficacy through inferential statistics in this IC population. Efficacy in this population was extrapolated from Trials 03 (in infants who received label recommended dose), 04, and 05 based on similar serum nirsevimab exposures. Nirsevimab serum concentrations 150 days postdose (Day 151) and $AUC_{baselineCL}$ were chosen as the two PK parameters for efficacy extrapolation from Trials 03 and 04 to Trials 08 and 05 (refer to BLA-762318 integrated review in DARRTS dated 7/14/2023 for details). These two PK parameters were continued as key PK metrics for this submission. Day 151 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 (E-R) analysis results from Trials 03 and 04. Please refer to BLA-762318 integrated review in DARRTS dated 7/14/2023 for details. Additionally, $AUC_{0\text{-}365}$ from Trials 04, 05, and 08 was summarized in Applicant response dated 05/13/2024 upon an FDA Information Request. The PK comparison was conducted for both the first and second RSV seasons in Trial 08 versus the corresponding seasons in Trials 03, 04, and 05.

Nirsevimab exposure in Trials 04, 05, and 08

In Trial 08, 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. The doses used in Trial 8 are the same as the label recommended dose[2].

The overall nirsevimab serum exposures in subjects enrolled in Trials 04, 05, and 08 were summarized in Table 3 through Table 6 as shown below, Day 151 serum concentrations (Table 3), $AUC_{baselineCL}$ (Table 4), $AUC_{0\text{-}365}$ (Table 5), and the percentage of subjects with Day 151 serum concentrations above the nonclinical EC90 threshold of 6.8 µg/mL or $AUC_{baselineCL}$ above 12.8 mg*day/mL defined based on exposure-response analysis (Table 6). The EC90 value of 6.8 µg/mL (concentration for 90% effectiveness) was determined based on RSV challenge studies in cotton rats, a model that was used for dose selection of palivizumab (refer to BLA-762318 integrated review in DARRTS dated 7/14/2023). ER analysis demonstrated that a serum nirsevimab AUC above Q1 (12.8 day*mg/mL) was the target exposure to provide protection against MA RSV LRTI throughout the 5-month RSV season (refer to BLA-762318 integrated review in DARRTS dated 7/14/2023). The results indicate that the nirsevimab exposures in Trial 08 were lower than those in subjects enrolled in Trials 04 and 05 season 1 or those in Trial 05 season 2.

Table 3. Day 151 Serum Nirsevimab Concentrations (Unit: µg/mL) in Pediatrics in Trials 04, 05, 08

Day 151 serum conc, µg/mL	Trial 04 primary cohort	Trial 05 Season 1	Trial 05 Season 2	Trial 08 Season 1	Trial 08 Season 2
Sample size	636	457	163	37	42
Arithmetic mean (SD)	26.6 (11.1)	27.8 (11.1)	55.6 (22.8)	25.6 (13.4)	33.2 (19.3)
Median	24.5	26	55.3	24.9	38.2
Min to max range	2.1, 76.6	2.1, 66.2	11.2, 189.3	5.1, 67.4	0.9, 68.5

Source: Reviewer compilation based on IR response dated 05/13/2024 based on the complete data sets of Trials 04, 05, 08

Table 4. Serum Nirsevimab $AUC_{baselineCL}$ (Unit: mg*day/mL) in Pediatrics in Trials 04, 05, 08

$AUC_{baselineCL}$, mg*day/mL	Trial 04 primary cohort	Trial 05 Season 1	Trial 05 Season 2	Trial 08 Season 1	Trial 08 Season 2
Sample size	954	591	189	46	50
Arithmetic mean (SD)	21.3 (6.5)	22.6 (6.2)	23.6 (7.8)	16.7 (7.3)	21 (8.4)
Median	20.4	22.3	23.4	15.5	21.1

[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761328s007lbl.pdf accessed on June 10, 2024

$AUC_{baselineCL}$, mg*day/mL	Trial 04 primary cohort	Trial 05 Season 1	Trial 05 Season 2	Trial 08 Season 1	Trial 08 Season 2
Min to max range	5.2, 48.7	7, 43.8	8.2, 56.4	3.1, 43.4	5.6, 35.5

Source: Reviewer compilation based on IR response dated 05/13/2024 based on the complete data sets of Trials 04, 05, 08

Table 5. Serum Nirsevimab AUC_{0-365} (Unit: mg*day/mL) in Pediatrics in Trials 04, 05, 08

AUC_{0-365}, mg*day/mL	Trial 04 primary cohort	Trial 05 Season 1	Trial 05 Season 2	Trial 08 Season 1	Trial 08 Season 2
Sample size	954	591	189	46	50
Arithmetic mean (SD)	12.2 (3.5)	12.3 (3.3)	21.5 (5.5)	11.2 (4.3)	16 (6.3)
Median	11.8	11.8	21.8	10.8	16.6
Min to max range	3.3, 24.9	4.1, 23.4	7.5, 41.9	1.2, 24.6	2.2, 25.5

Source: Reviewer compilation based on IR response dated 05/13/2024 based on the complete data sets of Trials 04, 05, 08

Table 6. Summary Statistics for Observed Nirsevimab Concentration on Day 151 and Estimated $AUC_{baselineCL}$ in Trials 04, 05, 08

Day 151 serum conc	Trial 04 primary cohort	Trial 05 Season 1	Trial 05 Season 2	Trial 08 Season 1	Trial 08 Season 2
Sample size	638	458	164	37	42
C_{day} 151 ≥ 6.8 µg/mL	99% (629/638)	99% (454/458)	100% (164/164)	95% (35/37)	86% (36/42)
C_{day} 151 < 6.8 µg/mL	1% (9/638)	1% (4/458)	0%	5% (2/37)	14% (6/42)
$AUC_{baselineCL}$					
Sample size	954	590	189	46	50
$AUC_{baselineCL}$≥ 12.8 mg*day/mL	93% (887/954)	97% (574/590)	98% (186/189)	72% (33/46)	78% (39/50)
$AUC_{baselineCL}$< 12.8 mg*day/mL	7% (67/954)	3% (16/590)	2% (3/189)	28% (13/46)	22% (11/50)

Source: Reviewer compilation based on IR response dated 02/22/2024 and 05/13/2024 based on the complete data sets of Trials 04, 05, 08

Pediatric subjects with low nirsevimab exposure in Trial 08

In Trial 08, 24 subjects achieved $AUC_{baselineCL}$ lower than the target of 12.8 day*mg/mL; of these 24 subjects, 13 were identified by the Applicant with increased clearance of nirsevimab (listed in

Table 7), and the remaining 11 subjects demonstrated lower initial nirsevimab concentrations (listed in Table 8). The causes of the low initial nirsevimab concentrations were unknown.

The potential causes of the increased clearance of nirsevimab were evaluated by the review team. The Applicant attributed the increased clearance to protein losing condition in these pediatric patients. However, based on subject narratives, the clinical reviewer, Dr. Baylor, could not conclude that any of the clinical conditions, reported to be associated with protein-losing, were actual causes of protein loss in the subjects with increased clearance. Although the conditions in Table 7 may be associated with protein loss, the Applicant did not collect any physiological or laboratory parameters to document protein loss in these subjects. Therefore, based solely on subject narratives, the clinical reviewer, Dr. Baylor, could not conclude that the listed clinical conditions among subjects with increased clearance (Table 7) indeed led to protein losing conditions. Additionally, the Applicant reported that they did not identify any cases of protein-losing conditions in Trials 03, 04, 05. Further exploratory analyses conducted by the Pharmacometrics review team did not identify any potential causes for the high nirsevimab clearance in these pediatric patients based on the available data (see Pharmacometrics review section (Section 6.2) for details).

Table 7. Subjects With Increased Clearance of Nirsevimab in Trial 08 (A Total of 14 Subjects Were Identified With Increased Clearance of Nirsevimab, 13 of These 14 Subjects Had $AUC_{baselineCL}$ Lower Than 12.8 mg*day/mL)

Subject ID	RSV Season	Dose received, mg	Baseline BW, kg	GA, wks	PNS, months	Clinical condition
(b) (6)	2	200	7.7	37	13	Chronic liver disease
	2	200	9.4	40	15	Chronic liver disease
	2	200	8.7	39	12	Chronic liver disease
	2	200	8.9	39	18	Chronic liver disease
	1	100	6.2	40	7.8	Malignancy: Juvenile myelomonocytic leukemia
	2	200	9.5	39	13.8	Nephrotic syndrome
	1	100	8.9	40	11.7	Chronic liver disease
	2	200	7.8	31	19.3	HIV
	1	100	7.6	38	6.5	Malignancy: Congenital retinoblastoma
	1	100	6.7	38	8.8	HIV
	1	50	3.5	38	0.7	Omenn syndrome

Subject ID	RSV Season	Dose received, mg	Baseline BW, kg	GA, wks	PNS, months	Clinical condition
(b) (6)	2	200	9.4	39	19.8	Malignancy: carcinoma
	2	200	9.5	36	13.9	GVH disease and Omenn Syndrome
	2	200	11.8	38	18.6	GVH disease

Source: Reviewer compilation based on Clinical Overview submitted on 10/31/2023
Note: The subject (b) (6) with AUCbaselineCL at 17.03 mg*day/mL (> 12.8 mg*day/mL), added for a complete list of subjects identified with high nirsevimab clearance by the applicant
Abbreviations: BW: body weight; GA: gestational age; PNS: Postnatal age

Table 8. Eleven Subjects With Low Initial Nirsevimab Concentrations in Trial 08

Subject ID	RSV Season	Dose received, mg	Baseline BW, kg	GA, wks	PNS, months	Clinical condition
(b) (6)	1	100	8	34	11.1	Bilateral retinoblastoma
	1	100	7.9	38	10.5	Bilateral retinoblastoma
	1	50	4.9	40	2.8	Epilepsy
	1	100	9.3	40	10.5	Epilepsy
	1	100	8.6	40	10.9	Epilepsy
	1	100	7.9	40	6.7	Thymomegaly
	1	50	4.9	40	2.6	Epilepsy
	2	200	13.4	39	22.6	Epilepsy
	2	200	12.3	40	16.7	Epilepsy
	2	200	10.1	40	12.1	Epilepsy
	1	100	8.6	39	7.4	Thymomegaly

Source: Reviewer compilation based on IR response dated 2/22/2024
Abbreviations: BW: body weight; GA: gestational age; PNS: Postnatal age

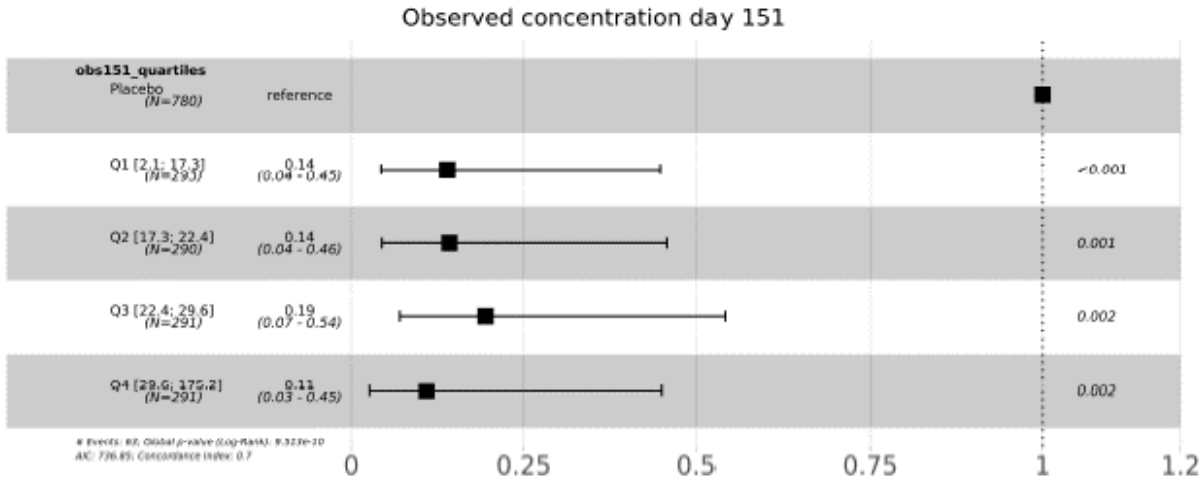
Reviewer comments

The mean and median serum nirsevimab-alip concentrations in Trial 08 were lower than the concentrations in Trials 04 and 05. The review team evaluated whether the lower nirsevimab exposures in Trial 08 may affect the expected effectiveness of nirsevimab based on the E-R relationships from different PK metrics, including C151 (concentration on Day 151 post dose), $AUC_{baselineCL}$, and AUC_{365}, vs. the risk of a MA RSV LRTI event.

*The Applicant conducted E-R analyses of nirsevimab for the primary endpoint MA RSV LRTI through 150 days post dose, based on pooled data from the proposed dose (i.e., Trial 04 and label recommended dose from Trial 03), which indicated no apparent relationship between nirsevimab exposure (C151, $AUC_{baselineCL}$, AUC_{365}) and the risk of a MA RSV LRTI event (*Figure 1*). The ranges for C151, $AUC_{baselineCL}$, and AUC_{365} in pediatric subjects who received label recommended doses in Trials 03 and 04 are 2.1—170 μg/mL, 3.5—59.6 mg*day/mL, and 2.7—25.6 mg*day/mL,*

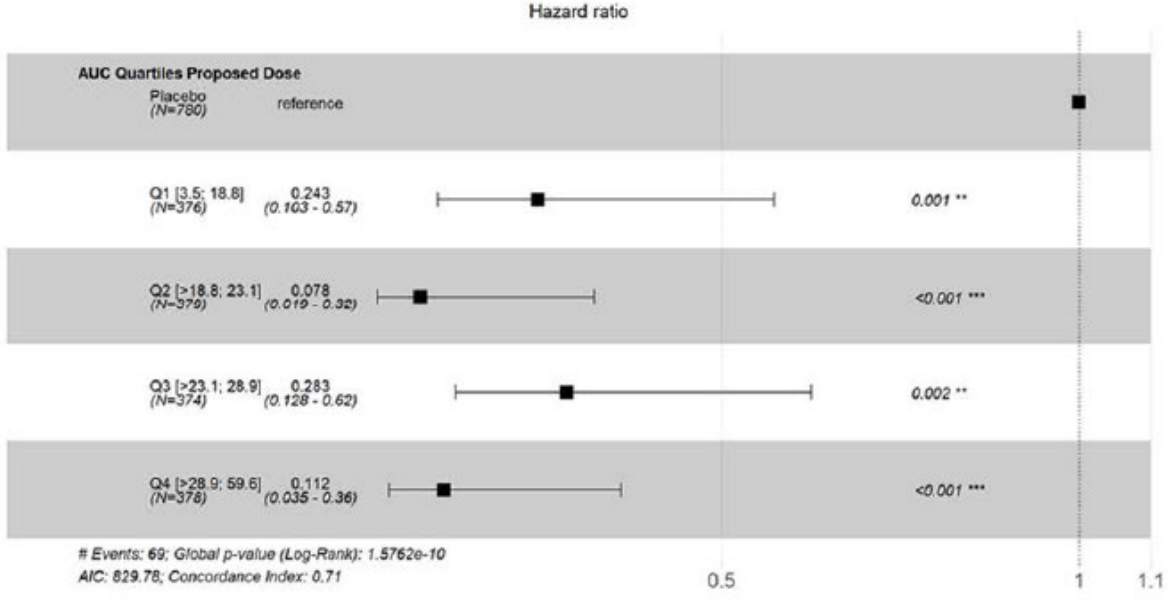
*respectively. The ranges for C151, $AUC_{baselineCL}$, and AUC_{365} in Trial 05 both seasons are 2.1—189 µg/mL, 7—56.4 mg*day/mL, and 4.1—41.9 mg*day/mL, respectively. The range of C151, $AUC_{baselineCL}$, and AUC_{365} in Trial 08 in both seasons are 0.9—69 µg/mL, 3.1—43.4 mg*day/mL, and 1.2—25.5 mg*day/mL, in Trial 08, respectively. Therefore, Trial 08 exposures were generally within the range shown to be effective in those who received the recommended dosage in Trials 03, 04, and 05.*

Figure 1. Exposure (C151)-Response for MA RSV LRTI Through Day 151 Season 1, Hazard Ratio (95% CI) Based on Pooled Data From Trials 04 and 03 at the Recommended Doses



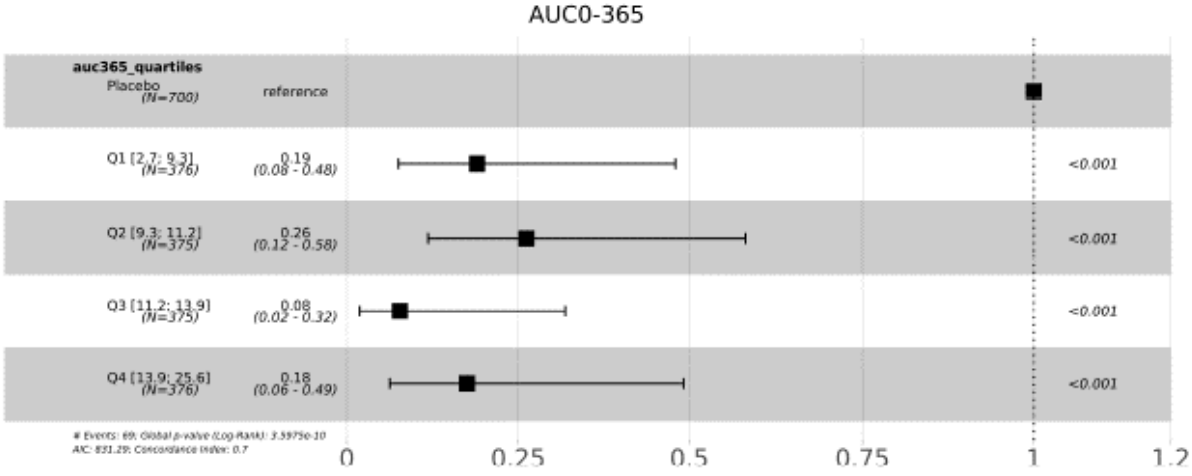
Source: Original BLA-761328 IR response dated 04/17/2023

Figure 2. Exposure ($AUC_{baselineCL}$)-Response for MA RSV LRTI Through Day 151 Season 1, Hazard Ratio (95% CI) Based on Pooled Data From Trials 04 and 03 at the Recommended Doses



Source: Original BLA-761328 Figure 12 in Summary of Clinical Pharmacology Studies

Figure 3. Exposure (AUC_{365})-Response for MA RSV LRTI Through Day 151 Season 1, Hazard Ratio (95% CI) Based on Pooled Data From Trials 04 and 03 at the Recommended Doses



Source: Original BLA-761328 IR response dated 04/17/2023

6.2. **Pharmacometrics Review**

6.2.1. Review Summary

In general, the Applicant's population PK analysis is considered acceptable for the purpose of description of nirsevimab exposure in plasma in immunocompromised children ≤ 24 months of age. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table .

Table . Specific Comments on Applicant's Final Population PK Model

Utility of the final model	Reviewer's Comments
(b) (4)	

Utility of the final model		Reviewer's Comments
Derive exposure metrics for Exposure-response analyses	C_{min}, C_{max}, C_{avg}, AUC	The Applicant's final model is generally acceptable for generating exposure metrics for Trial 08.

Introduction

The primary objectives of Applicant's analysis were to:

- To predict of the PK parameters for individuals in Trial 08 using the final model that was developed based on Trials 01 – 05 and reviewed previously by the Agency (see the review in DARRTs for BLA761328, SDN 1).
- Generate individual PK estimates for subjects in Trial 08.

Model development

Data

The analyses utilized PK data from Trial 08 and the Applicant's final population PK model from Trials 01 - 05. Brief descriptions of the study included are presented in Table .

The NONMEM data file from the sponsor's proposed final model for analysis contained 273 PK observations from 96 subjects. Table provides summary statistics of the baseline demographic covariates in the analysis dataset**.**

Table . Summary of Study With PK Sampling Included in Population PK Analysis

Protocol # & Study Design	**Dosage Regimen & Study Description**	**Number of new Subjects in PopPK Evaluation, Subject Type and Food Status**	**Dose(s) [mg]**
TRIAL 08	A Phase 2, Open-label, Uncontrolled, Single-dose Study to Evaluate the Safety and Tolerability, Pharmacokinetics, and Occurrence of Antidrug Antibody for Nirsevimab in Immunocompromised Children ≤ 24 Months of Age. **PK sampling:** Dosing, Day 31, Day 151, Day 361 and any day with lower respiratory tract infection.	N = 96 Subject: Healthy subject	Single dose of 50 mg, 100 mg, or 200 mg nirsevimab

* Source: Applicant's Population PK report, Table 4

Table . Summary of Baseline Demographic Covariates by Dose Levels for Analysis

Covariate	Covariate	MUSIC Season 1 (N = 46)	MUSIC Season 2 (N = 50)	Total (N = 96)
Baseline weight (kg)	Mean (SD%)	7.23 (1.69)	10.1 (1.82)	8.70 (2.26)
	Median (Q1, Q3)	7.60 (6.13,8.10)	9.65 (9.00,11.1)	8.75 (7.53,10.1)
	Min, max	2.90, 11.2	6.20, 14.7	2.90, 14.7
Postmenstrual age at dosing (months)	Mean (SD%)	16.6 (3.36)	26.6 (3.67)	21.8 (6.14)
	Median (Q1, Q3)	17.3 (14.5,19.3)	26.6 (23.3,29.4)	21.2 (17.5,26.7)
	Min, max	9.40, 21.4	21.0, 33.0	9.40, 33.0
ADA	Negative	43 (93.5%)	42 (84.0%)	85 (88.5%)
	Positive	3 (6.5%)	8 (16.0%)	11 (11.5%)
Race	White	18 (39.1%)	23 (46.0%)	41 (42.7%)
	Black or African American	9 (19.6%)	11 (22.0%)	20 (20.8%)
	Asian	16 (34.8%)	12 (24.0%)	28 (29.2%)
	American Indian or Alaskan Native	1 (2.2%)	0 (0%)	1 (1.0%)
	Native Hawaiian or Pacific Islander	0 (0%)	0 (0%)	0 (0%)
	Multiple	0 (0%)	2 (4.0%)	2 (2.1%)
	Other	2 (4.3%)	2 (4.0%)	4 (4.2%)
	Missing	0 (0%)	0 (0%)	0 (0%)
Japanese	Japanese	15 (32.6%)	11 (22.0%)	26 (27.1%)
	Non-Japanese	31 (67.4%)	39 (78.0%)	70 (72.9%)
IC Condition	Combined immunodeficiency	14 (30.4%)	11 (22.0%)	25 (26.0%)
	HIV	5 (10.9%)	3 (6.0%)	8 (8.3%)
	Organ or bone marrow transplant	1 (2.2%)	0 (0%)	1 (1.0%)
	Immunosuppressive chemotherapy	8 (17.4%)	10 (20.0%)	18 (18.8%)
	Systemic high-dose corticosteroid therapy	11 (23.9%)	11 (22.0%)	22 (22.9%)
	Other immunosuppressive therapy	1 (2.2%)	2 (4.0%)	3 (3.1%)
	Multiple	6 (13.0%)	13 (26.0%)	19 (19.8%)

Source: Study 08 (TRIAL 08) Pop-analysis-report addendum, Table 1, Page 5.
Notes: Subjects (b) (6) (TRIAL 08) were dosed 100mg at age 12.2 months (flagged as Season 2) but were included in Season 1 for extrapolation; both subjects had serum exposures above 12.8 day·mg/mL.
IC condition definitions: combined immunodeficiency=diagnosed with combined immunodeficiency (severe combined immunodeficiency, X-linked hyper- IgM syndrome, etc.), antibody deficiency (X-linked agammaglobulinemia, common variable immunodeficiency, non-X-linked hyper-IgM syndromes, etc.), or other immunodeficiency (Wiskott-Aldrich syndrome, DiGeorge syndrome, etc.); HIV=diagnosed with human immunodeficiency virus infection; immunosuppressive chemotherapy=subject is receiving immunosuppressive chemotherapy; organ or bone marrow transplant=history of organ or bone marrow transplantation; other immunosuppressive therapy=subject is receiving other immunosuppressive therapy (e.g., azathioprine, methotrexate, mizoribine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, cytokine inhibitors, etc.); systemic high-dose corticosteroid therapy=subject is receiving systemic high-dose corticosteroid therapy (prednisone equivalents $\geqslant$ 0.5 mg/kg every other day, other than inhaler or topical use)
Abbreviations: ADA, antidrug antibody; HIV, human immunodeficiency virus; IC, immunocompromised; IgM, immunoglobulin M; max, maximum; min, minimum; N, number of subjects with available information; PK, pharmacokinetic; Q1, first quartile; Q3, third quartile; SD, standard deviation

Applicant's population PK model

A population PK model was previously developed and reviewed in the BLA cycle (refer to the pharmacometrics review by Drs. Justin Earp and Hao Zhu, 07/14/2023).

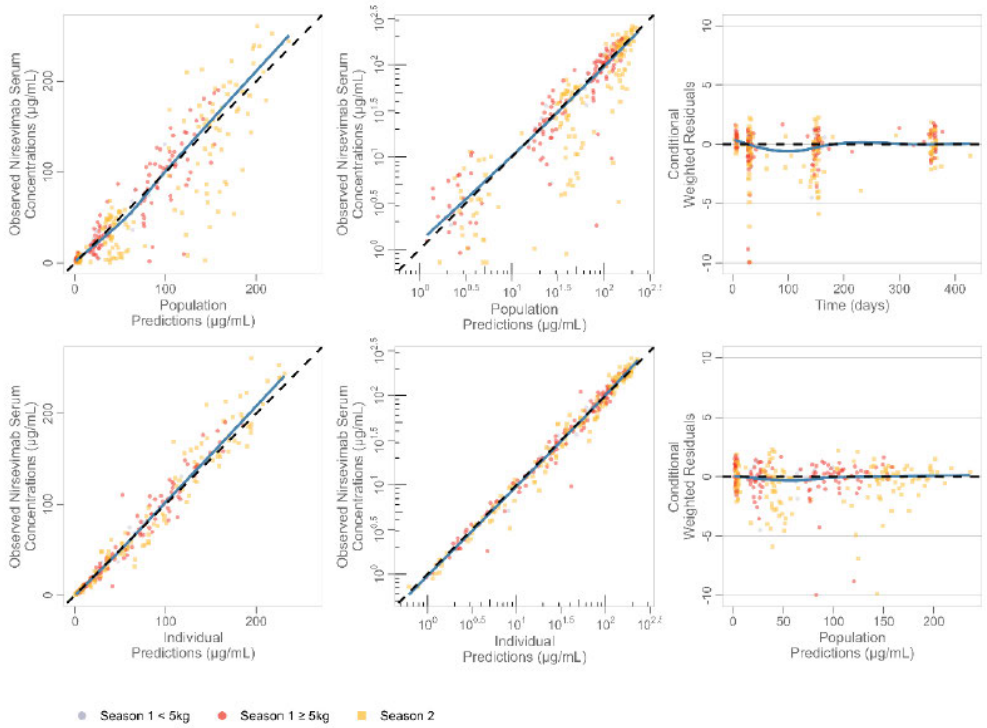
The final base model was a linear two-compartment PK model, first-order absorption, and first order elimination from the central compartment. The effect of weight was included as a fixed allometric exponent on CL/F, Vc/F, Vp/F, and Q/F and the effect of maturation on CL was modeled using an asymptotic exponential function:

$$CL_i = CL_{pop} * \left(\frac{WT_i}{70}\right)^{\theta 1} * \left(1 - (1 - \beta_{CL}) * e^{\left(-\left(PAGE_i - \left(\frac{40}{4.35}\right)\right) * \frac{LN(2)}{T50_{CL}}\right)}\right) * e^{\eta_{CL}}$$

where CL_i is the individual CL and CL_{pop} is the typical clearance. βCL denotes the fractional change in the clearance of a premature infant with respect to a term infant, T50CL denotes the corresponding maturation half-life of the parameter with respect to that of an adult, PAGEi represents the sum of gestational age and postnatal age in months for each infant, ηCL is the individual clearance between-subject variability, θ1 is the estimated clearance allometric scaling exponent, and gestational age for adults was imputed to 40 weeks.

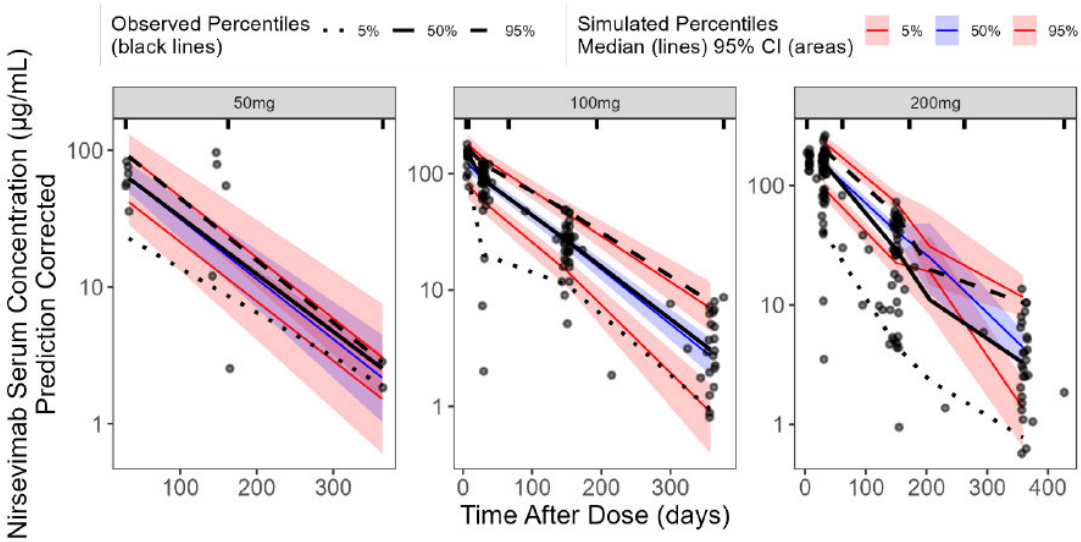
Refer to Table 82 in the integrated review (07/14/2023) in the pharmacometrics review section for the final parameter estimates for the final population PK model. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 4. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in Figure 5.

Figure 4. Goodness-of-Fit Plots for Immunocompromised Children (TRIAL 08) for Predicted Observations (MAXEVAL=0) by Weight and Season



Source: Study 08 (TRIAL 08) Pop-analysis-report addendum, Figure 2, Page 7.
Notes: Dots are individual data points for TRIAL 08 subjects (red= Season 1 ⩾5 kg, gray= Season 1 <5 kg, yellow: Season 2), and solid blue lines are smoothed LOESS lines. The dashed lines in columns 1 and 2 are lines of identity. In the 2 plots on the right, horizontal lines are reference lines.
Abbreviations: GOF, goodness-of-fit; IC, immunocompromised; LOESS, locally weighted smoothing

Figure 5. Prediction-Corrected VPC; Prediction of Trial 08 Based on Final PopPK Model by Dose



Source: Study 08 (TRIAL 08) Pop-analysis-report addendum, Figure 2, Page 7.
Notes: Black dots are observed data points for pediatric subjects who are <5kg receiving 50mg, ⩾5kg receiving 100mg, or receiving 200mg. Black solid line is the observed median. Black dotted and dashed lines are observed 5th and 95th percentiles. The blue shaded area is the 95% PI of the simulated median (blue line), and pink shaded areas are the 95% PI of the simulated 5th and 95th percentiles (red lines).
Abbreviations: CI, confidence interval; IC, immunocompromised; PI, prediction interval; VPC, visual predictive check.

Reviewer comments

Goodness-of -fit plots and pcVPCs for nirsevimab indicated that the present model adequately described the data from Trial 08. Therefore, the final population PK model was deemed to be acceptable for PK estimation purposes.

6.2.2. Nirsevimab Exposure in Trial 08

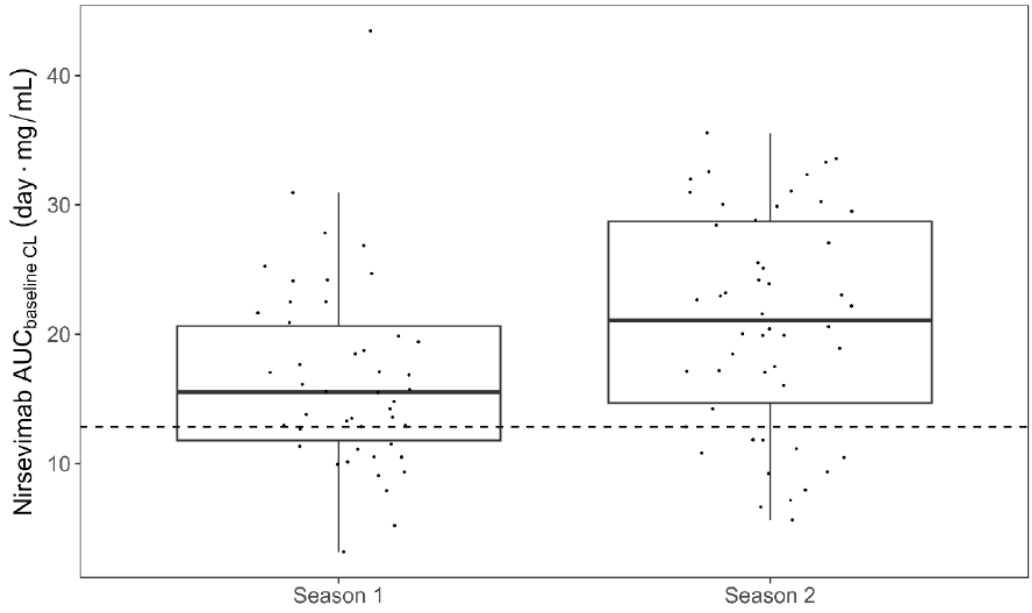
Overall, 75% of children were predicted to achieve $AUC_{baseline\ CL}$ above target (12.8 day·mg/mL); 71.7% in Season 1, and 78.0% in Season 2 (Table 9 and Figure 6).

Table 9. Percentage of Pediatric Subjects Above and Below the Target Exposure in TRIAL 08 Stratified by Season

	Season 1 (N = 46)	Season 2 (N = 50)	Total (N = 96)
$AUC_{baseline\ CL} \geq$ Target	33 (71.7%)	39 (78.0%)	72 (75.0%)
$AUC_{baseline\ CL} <$ Target	13 (28.3%)	11 (22.0%)	24 (25.0%)

Source: Study 08 (TRIAL 08) Pop-analysis-report addendum, Table 2, Page 9.
Notes: The target exposure of $AUC_{baseline\ CL}$ is 12.8 day·mg/mL. Subjects (b) (6) (TRIAL 08) were dosed 100mg at age 12.2 months (flagged as Season 2) but were included in Season 1 for extrapolation; both subjects had serum exposures above 12.8 day·mg/mL.
Abbreviations: AUCbaseline CL, area under the serum concentration-time curve derived from post hoc clearance values at dosing from the final population pharmacokinetics model; N, number of subjects with available information

Figure 6. Boxplots of $AUC_{baselineCL}$ for TRIAL 08 Subjects Grouped by Season



Source: Study 08 (TRIAL 08) Pop-analysis-report addendum, Figure 4, Page 10.
Notes: The horizontal dashed black line is the target exposure (12.8 day·mg/mL). Subjects (b) (6) (TRIAL 08) were dosed 100mg at age 12.2 months (flagged as Season 2) but were included in Season 1 for extrapolation; both subjects had serum exposures above 12.8 day·mg/mL.
Abbreviations: AUCbaseline CL, area under the serum concentration-time curve derived from post hoc clearance values at dosing from the final population pharmacokinetics model.

Reviewer comments

The percent of Trial 08 subjects with $AUC_{baseline,\ CL} <$ Target of 12.8 day·mg/mL is higher than that observed in Study 04 and Study 05. Therefore, the reviewer conducted cross-study comparison. The results are summarized in Table . *The results indicate that the nirsevimab clearance from Trial 08 appears higher than those observed in Studies 04 and 05 across all dose levels. The higher drug clearance was mainly due to a subset of pediatric patients*

*identified by the Applicant as outliers (14 subjects were identified with increased clearance of nirsevimab–refer to Table 7, 13 of these 14 subjects had AUCbaselineCL lower than 12.8 mg*day/mL, see the discussion of "Subjects with Increased Clearance of Nirsevimab" below for details). The etiology of this higher clearance is unclear. Mechanistically there is no known reason to think that being immunocompromised would itself lead to the increased clearance and that we are not aware of other examples of this.*

Table 13. Cross-Study Comparison for Clearance and Body Weight Normalized Clearance at Baseline in Studies 04, 05 and 08

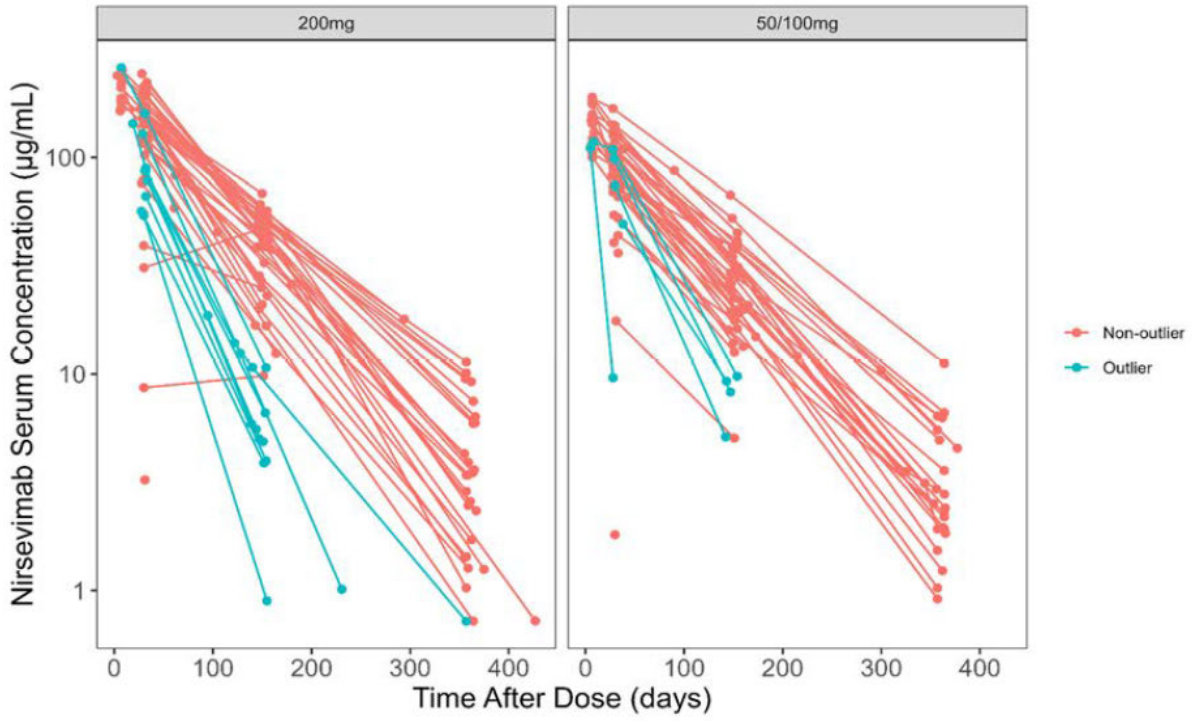
	Study 04 MELODY				Study 05 MEDLEY				Study 08 MUSIC			
CL (mL/day)												
DOSE (mg)	N	Mean	Median	SD	N	Mean	Median	SD	N	Mean	Median	SD
50	393	2.8	2.7	0.88	334	2.5	2.4	0.76	6	3.7	3.9	1.3
100	570	4.8	4.5	1.8	258	4.6	4.2	1.7	39	7.5	6.4	5
200					168	7.4	6.7	2.4	50	12	9.5	6.9
CL/kg (mL/day/kg)												
DOSE (mg)	N	Mean	Median	SD	N	Mean	Median	SD	N	Mean	Median	SD
50	393	0.77	0.74	0.2	334	0.77	0.71	0.22	6	0.89	0.81	0.34
100	570	0.72	0.68	0.21	258	0.71	0.66	0.22	39	0.98	0.8	0.6
200					168	0.75	0.67	0.23	50	1.2	0.93	0.73
WT (kg)												
DOSE (mg)	N	Mean	Median	SD	N	Mean	Median	SD	N	Mean	Median	SD
50	393	3.7	3.8	0.87	334	3.4	3.3	0.88	6	4.2	4.6	0.84
100	570	6.7	6.5	1.2	258	6.5	6.3	1.2	39	7.7	7.7	1.3
200					168	9.9	9.6	1.7	50	10	9.6	1.8

6.2.3. Subjects With Increased Clearance of Nirsevimab

In the final analysis of data from immunocompromised subjects in Trial 08, 24 subjects were identified with lower than target AUC, and 13 out of these 24 subjects were identified as outliers with increased clearance of nirsevimab (Figure 7) (note: a total of 14 subjects were identified with increased clearance of nirsevimab, 13 of these 14 subjects had $AUC_{baselineCL}$ lower than 12.8 mg*day/mL, refer to Table 7 for details).

The Applicant suggests that the increased clearance of nirsevimab could be associated with underlying protein losing conditions in these patients.

Figure 7. Individual Concentration Versus Time Profiles for Immunocompromised Subjects (TRIAL 08) With Outliers Highlighted



Source: clinical overview addendum, Figure 3, Page 9
Dots are individual data points for subjects from TRIAL 08. Blue indicates subjects identified as outliers with increased clearance. Red indicates subjects not identified as outliers.

Reviewer comments

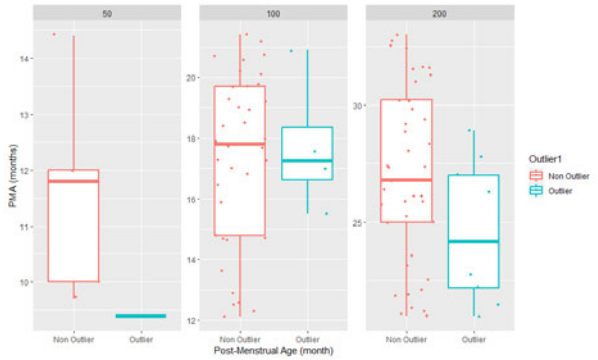
An information request was sent to the Applicant on 02/05/2024, seeking clarification for the protein losing condition for these outliers.

*The responses from the Applicant were received on 2/22/2024. However, the Applicant stated that the outliers were identified by visual inspection of the serum concentration time profile (*Figure 8*), and they did not have any other specific criteria for determining the outliers. The Applicant also attributed the high nirsevimab clearance to the protein losing conditions. However, no data/evidence were collected to support the protein loss in these children.*

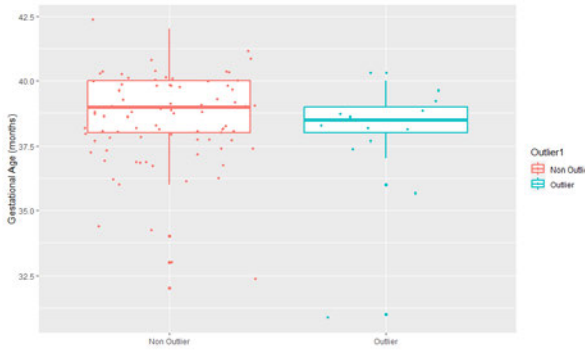
*The reviewer conducted additional analyses and concluded that no covariates, including postmenstrual age (PMA), gestational age (GA), baseline body weight, anti-drug antibody (ADA) status, sex, race, and immunosuppressed subgroups, were associated with the high nirsevimab clearance of these outliners as the distribution of these covariates are not significantly different between outliers and non-outliers (*Figure 8*).*

Figure 8. Representative Plots for the Impact of Different Covariates in Outliers Versus Non-Outlier Groups

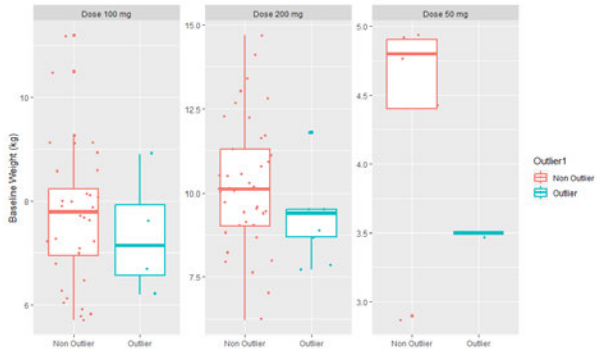
Postmenstrual Age



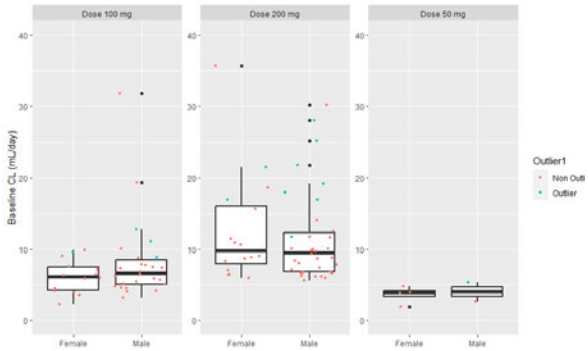
Gestational Age



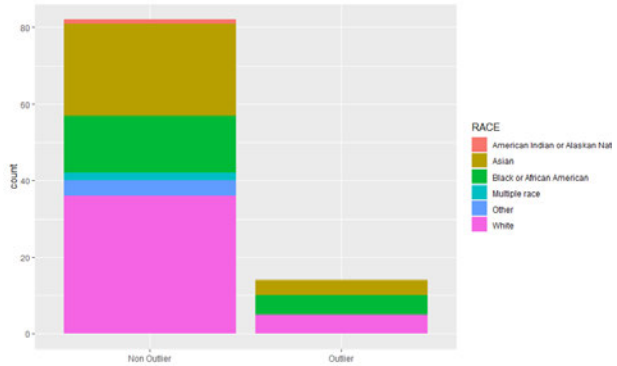
Baseline body weight



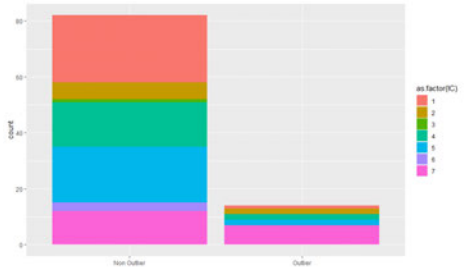
Sex



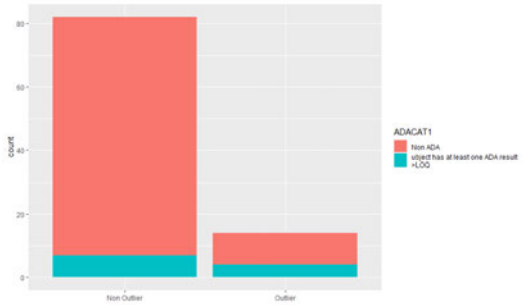
Race



Immunosuppressed subgroups



ADA status



Source: reviewer's analyses.

6.3. Immunogenicity

This supplement provides updated immunogenicity data for Trials 04, 05, and 08. Table 10 contains (1) the information for the three clinical trials assessing immunogenicity, and (2) a high-level summary of study results for PK (concentration on Day 361).

Summary of clinical studies

Table 10. Summary of Clinical Trials Information and Immunogenicity Incidence

	Trial 04	Trial 05		Trial 08	
Dose regimen, mg as a single IM dose	50 or 100	50 or 100	200	50 or 100	200
Season	NA	1	2	1	2
Sampling time	Predose, Day 31, 151, 361				
Number of subjects who received recommended dose of nirsevimab	987 [a]	614 [b]	180 [c]	48	52
Applicant reported ADA incidence at Day 361	5% (95/1778)	6% (32/538)	9% (13/144)	13% (9/67)	13% (9/67)
Applicant reported NAb incidence at Day 361	21% (20/95)	6% (2/32)	8% (1/13)	11% (1/9)	11% (1/9)
Applicant reported anti-YTE incidence at Day 361	77% (73/95)	91% (29/32)	62% (8/13)	100 (9/9)	100 (9/9)
.					
All subjects	NA	NA	7.4 (4.1) N=63	NA	4.2 (3.1) N=26
<5 kg received 50 mg	2.4 (1.3) N=215)	2.7 (1.3) N=259	NA	2.3 (0.7) N=2	NA
≥5 kg received 100 mg	3.9 (2.4) N=457	4.3 (3.2) N=215	NA	3.6 (2.6) N=20	NA

Source: IR response dated 05/13/2024
a The efficacy cohort
b Preterm and CHD/CLD cohorts combined
c CLD/CHD cohort only
Abbreviations: N, number of subjects; RSV, respiratory syncytial virus; SD, standard deviation

Highlight of key characteristics of immunogenicity assays relevant to this review

The two versions of validated ADA assays are deemed to display adequate sensitivity. However, the nirsevimab concentrations of most samples collected before or on Day 151 postdose exceeded the drug tolerance limit of the ADA assays. Thus, the ADA status of these samples is not reliable. Therefore, only data from Day 361 are reliable to evaluate the impact of ADA on PK. Table 11 and Table 12 show several ADA and NAb assay characteristics that are relevant for the analysis.

Table 11. Summary of Key Assay Characteristics Related to Immunogenicity Assessment

Characteristic	Trial 04, 05 and 08
Assay validation report number (ADA and NAb)	RMUD2
ADA assay sensitivity (ng/mL)	5.43
ADA assay drug tolerance	12.5 µg/mL in the presence of 100 ng/mL of PC

Source: Integrated Summary of Immunogenicity
Abbreviations: ADA, anti-drug antibody; PC, positive control

Table 12. Summary of Key Assay Characteristics Related to NAb Assessment

Characteristic	Trial 04, 05 and 08
Assay validation report number	RMUE2
NAb assay sensitivity (ng/mL)	23.4
NAb assay drug tolerance	50 µg/mL in the presence of 70 ng/mL of PC

Source: Integrated Summary of Immunogenicity
Abbreviations: NAb, neutralizing antibody; PC, positive control

Methods for evaluating the effect of immunogenicity on PK of nirsevimab

To evaluate the impact of immunogenicity on PK, we compared the observed concentrations in two groups (ADA+ and ADA-) in subjects with time-matched PK and ADA data using Immunogenicity Specimen (IS) tool developed in-house. At each timepoint, nirsevimab concentrations were summarized by ADA+ and ADA- groups. Graphically, ADA- group was presented in boxplot and ADA+ group was presented as a line graph. The average nirsevimab concentrations (ADA+ and ADA- groups) were calculated at each timepoint and graphically presented. Summary of nirsevimab concentrations by ADA status (ADA+ or ADA-) were tabulated along with the average concentration by timepoint as well as the number of subjects. For the statistical comparisons of concentration data between ADA+ and ADA- groups, the geometric mean ratio (GMR) of ADA+/ADA- and the corresponding 90% confidence interval (CI) were also presented graphically. The effect of NAb on PK was not evaluated in this analysis.

Effect of immunogenicity on PK of nirsevimab

The analysis results for Trials 04, 05, and 08 were summarized by trial below. The results indicate that the development of ADA against nirsevimab is associated with a reduced systemic concentration of nirsevimab, and the effect of ADA was observed starting on Day 151 even with the assay uncertainty caused by drug tolerance in reliably detecting ADA.

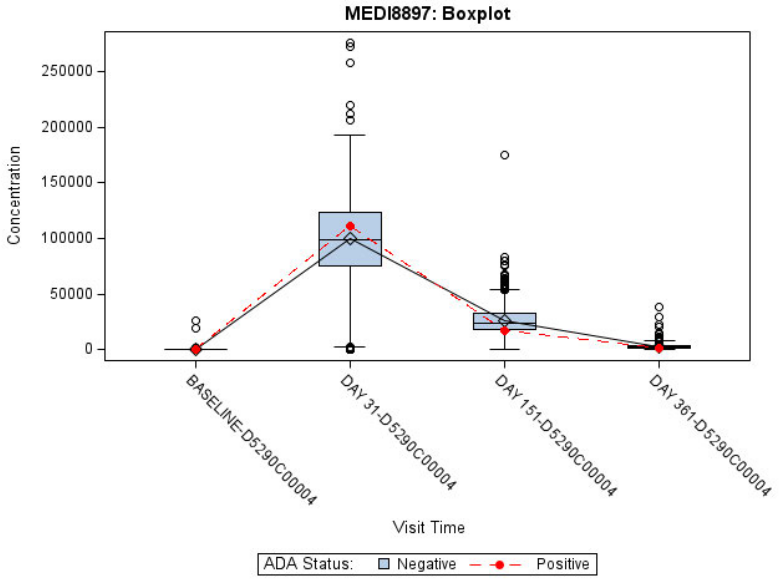
Trial 04

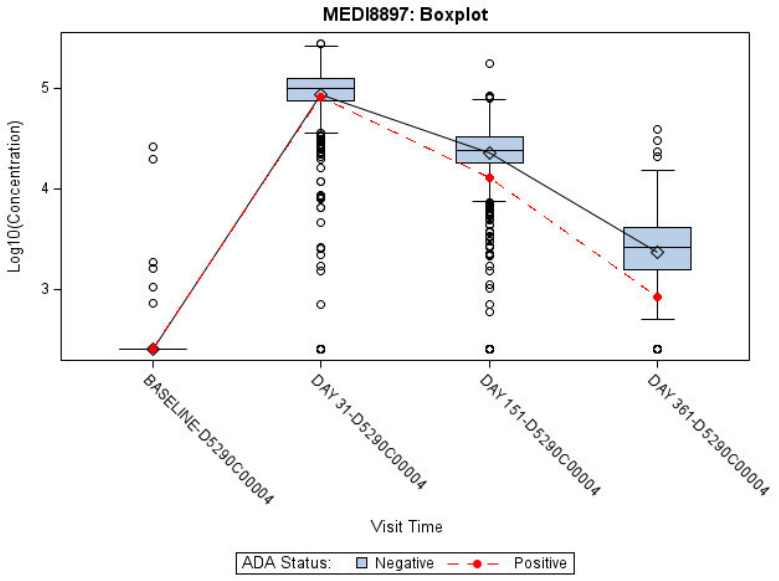
Figure 9 and Table 13 show that ADA+ group had a lower nirsevimab concentration than ADA- group at Day 151 and 361 indicating that ADA had a negative effect on PK of nirsevimab.

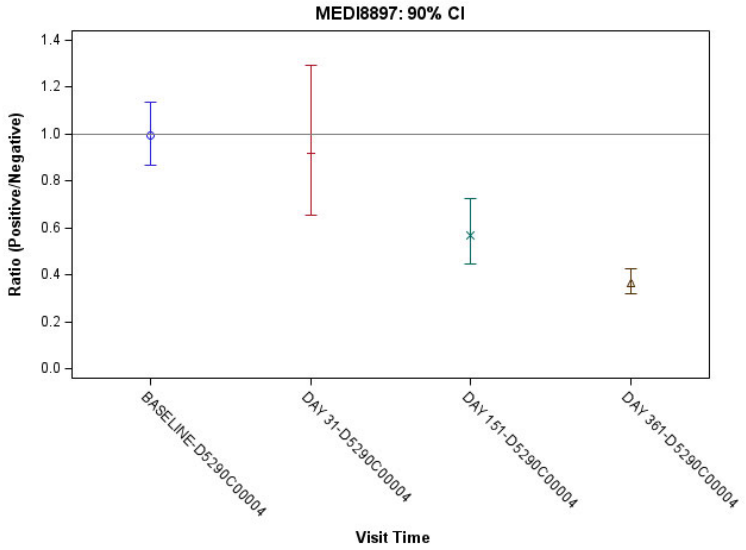
Based on the data over the trial duration of 361 days, the upper limit of the 90% CI of GMR values were <1 for the last two timepoints (Day 151 and 361).

In Trial 04 (n=1913) the impact of ADA on PK, i.e., lower concentrations in ADA+ group, was observed starting from day 151 visit (Figure 9). The top and middle panels in Figure 9 show the drug concentration up to day 361 for the ADA+ and ADA- population in linear and semi-log scales. The bottom panel shows the 90% CI of GMR of drug concentration at each visit. See Table 13 for a tabular summary.

Figure 9. Top and Middle Panels: Box Plot Analysis of Drug Concentration From ADA-Negative Samples and Line Graph of ADA-Positive Samples During the Treatment Period (361 Days) in Linear and Semi-Log Scale, Respectively. Bottom Panel: 90% Confidence Interval







Source: Reviewer analysis
Abbreviations: ADA, anti-drug antibody; CI, confidence interval; GMR, geometric mean ratio

Table 13. Summary of Geometric Mean Nirsevimab Concentration by ADA Status, GMR and 90%CI at Each Trial Visit, Trial 04

Visit #	Treatment Day	Total N	Nirsevimab Concentration (µg/mL); Geometric Mean				GMR (90%CI)
			ADA+ Group	N	ADA- Group	N	ADA+/ADA-
1	Baseline	1913	0.250	4	0.252	1909	0.99 (0.9, 1.1)
2	31	1367	79.91	14	86.96	1353	0.92 (0.7, 1.3)
3	151	1764	12.72	21	22.34	1743	0.60 (0.5, 0.7)
4	361	1788	0.85	95	2.30	1693	0.40 (0.3, 0.4)

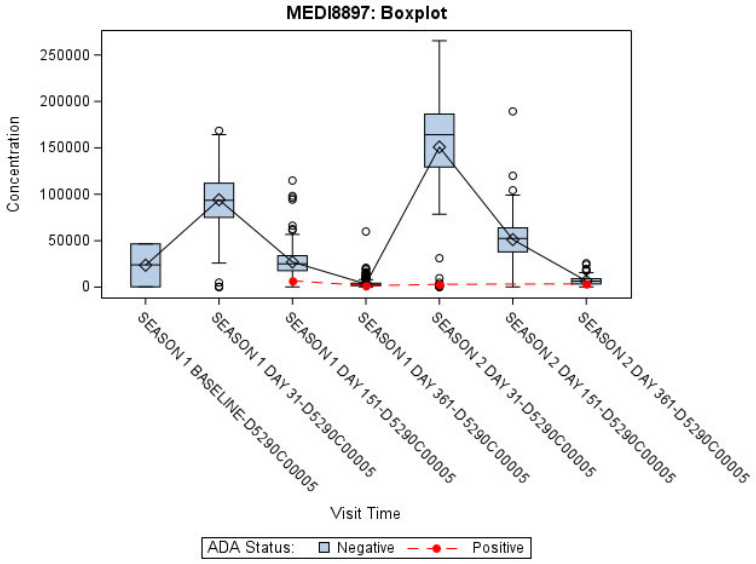
Source: Reviewer analysis
Abbreviations: ADA, anti-drug antibody; CI, confidence interval; GMR, geometric mean ratio; N, number of subjects

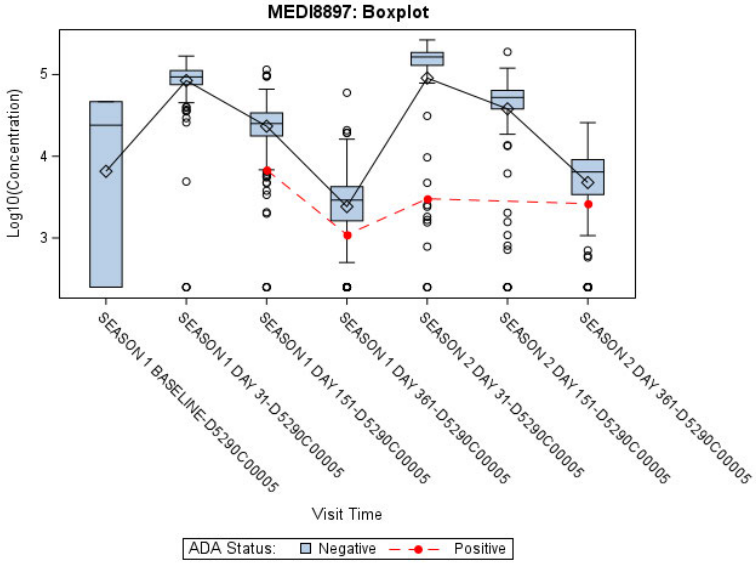
Trial 05

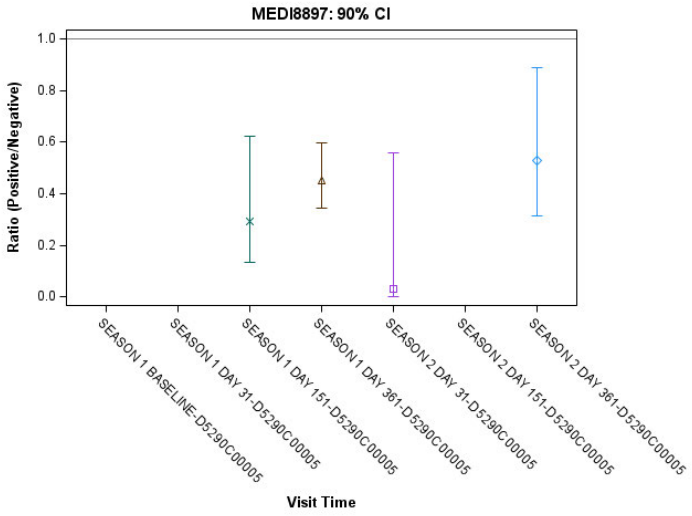
Figure 10 and Table 14 showed that ADA+ group had a lower nirsevimab concentration than ADA- group at Day 151 and 361 indicating that ADA had a negative effect on PK of nirsevimab. Based on the data over the trial duration of 361 days, the upper limit of 90% CI of GMR values were <1 at all timepoints.

In Trial 05 first and second RSV Season the impact of ADA on PK, i.e., lower concentrations in ADA+ group, was observed starting from Day 151 visit. The top and middle panels in Figure 10 showed the drug concentration up to Day 361 for the ADA+ and ADA- population in linear and semi-log scale. The bottom panel showed the 90% CI of GMR of drug concentration at each visit. See Table 14 for a tabular summary.

Figure 10. Top and Middle Panels: Box Plot Analysis of Drug Concentration From ADA-Negative Samples and Line Graph of ADA-Positive Samples During the Treatment Period (361 Days) in Linear and Semi-Log Scale, Respectively. Bottom Panel: 90% Confidence Interval







Source: Reviewer analysis
Abbreviations: ADA, anti-drug antibody; CI, confidence interval; GMR, geometric mean ratio

Table 14. Trial 05 - Summary of Geometric Mean Nirsevimab Concentration by ADA Status, GMR and 90%CI at Each Trial Visit for Season 1 and 2

Visit #	Treatment Day	Total N	Nirsevimab Concentration (µg/mL); Geometric Mean				GMR (90%CI)
			ADA+ Group	N	ADA- Group	N	ADA+/ADA-
2	Season 1, Day 151	548	6.80	2	23.33	546	0.29 (0.1,0.6)
3	Season 1, Day 361	535	1.10	32	2.42	503	0.45 (0.3.0.6)
4	Season 2, Day 31	90	3.02	1	90.54	89	0.03 (0.0,0.6)*
5	Season 2, Day 361	144	2.25	13	4.26	131	0.53 (0.3,0.9)

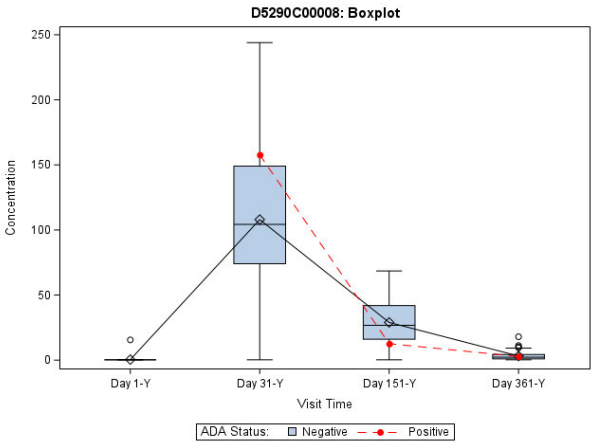
Source: Reviewer analysis
* The 90%CI of GMR was calculated by pooling the individual variance of ADA+ and ADA- groups. Since the variance is not available for the group with n=1, the 90%CI of GMR is derived from the variance of the other group that has n>1 exclusively.
Abbreviations: ADA, anti-drug antibody; CI, confidence interval; GMR, geometric mean ratio; N, number of subjects

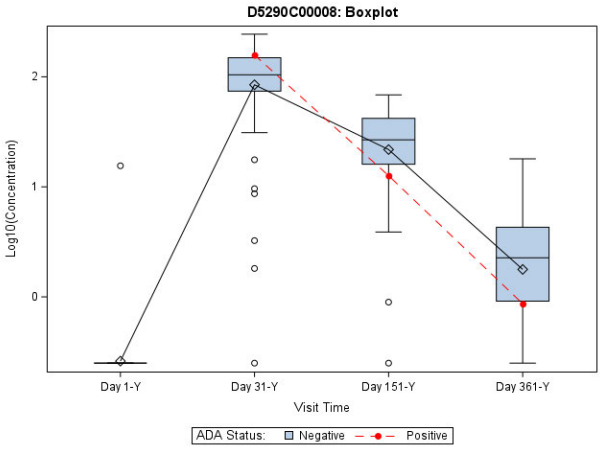
Trial 08

Figure 11 and Table 15 showed that ADA+ group had a lower nirsevimab concentration than ADA- group at Day 151 and 361 indicating that ADA appears to have a negative effect on PK of nirsevimab. Based on the data over the trial duration of 361 days, the lower limit of 90% CI of GMR values were <1 at the last two timepoints (Day 151 and 361), but the upper limit of 90% CI of GMR values were not <1 suggesting the variability of ADA impact on PK in this trial.

In Trial 08 the impact of ADA on PK, i.e., lower concentrations in ADA+ group, was observed starting from Day 151 visit (Figure 11). The top and middle panels in Figure 11 showed the drug concentration up to Day 361 for the ADA+ and ADA- population in linear and semi log scale. The bottom panel showed the 90% CI of GMR of drug concentration at each visit. See Table 15 for a tabular summary.

Figure 11. Top and middle Panels: Box Plot Analysis of Drug Concentration From ADA-Negative Samples and Line Graph of ADA-Positive Samples During the Treatment Period (361 Days) in Linear and Semi-Log Scale, Respectively. Bottom Panel: 90% Confidence Interval





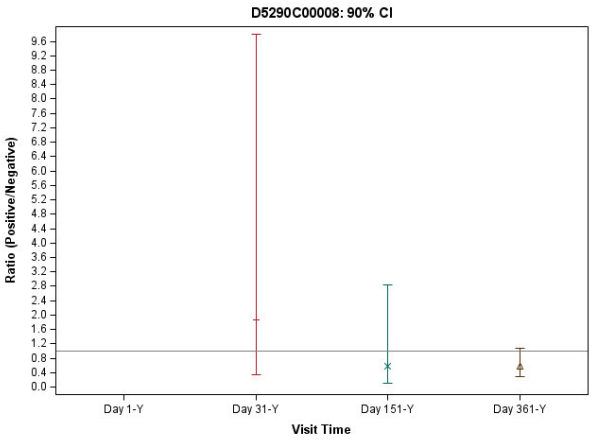


Table 15. Summary of Geometric Mean Nirsevimab Concentration by ADA Status, GMR and 90%CI at Each Trial Visit for Trial 08

			Nirsevimab Concentration (µg/mL); Geometric Mean				GMR (90%CI)
Visit #	Treatment Day	Total N	ADA+ Group	N	ADA- Group	N	ADA+/ADA-
3	31	97	157.79	1	83.63	96	1.85 (0.4,9.8)*
4	151	82	12.63	1	21.81	81	0.58 (0.1,2.8)*
5	361	68	0.98	9	1.71	59	0.57 (0.3,1.1)

Source: Reviewer analysis
* The 90%CI of GMR was calculated by pooling the individual variance of ADA+ and ADA- groups. Since the variance is not available for the group with n=1, the 90%CI of GMR is derived from the variance of the other group that has n>1 exclusively.
Abbreviations: ADA, anti-drug antibody; CI, confidence interval; GMR, geometric mean ratio; N, number of subjects

Immunogenicity conclusions

This submission provided updated immunogenicity data for the Trials 04, 05, and 08. As previously noted, nirsevimab concentrations of most samples collected before or on Day 151 postdose exceeded the drug tolerance limit of the ADA assays and therefore the ADA status of these samples is not reliable. Most importantly, we did not observe major difference in the ADA impact on PK at Day 361 compared to the original submission. Please refer to the original submission, section 14.4.1.5., Effect of Immunogenicity on PK of Nirsevimab on the potential impact of immunogenicity on clinical outcomes.

7. Clinical Microbiology

Please see Dr. Michael Thomson's Clinical Virology review.

The Applicant submitted the final clinical virology study reports for Trials 04, 05, and 08. The Applicant also submitted an interim report for ongoing RSV surveillance activities being conducted in China (SEARCH-RSV). The surveillance data were consistent with previously reviewed virology data, other than the absence of S211N substitution, which has been reported in other surveillance activities. The N208I substitution was observed at <25% frequency in one subject in Trial 04 and causes >417-fold loss of susceptibility to nirsevimab. This substitution was added to Section 12.4, Microbiology of the nirsevimab package insert.

8. Clinical/Statistical- Efficacy

All efficacy results for Trials 04 and 05 were included in the initial BLA submission for nirsevimab and are described in the integrated review of the initial BLA. No new efficacy data from Trials 04 and 05 were included in this supplemental BLA. Detailed descriptions of both trial protocols are also included in the integrated review. Please see Sections 9.2 and 9.3 for a description of the safety results from Trials 04 and 05.

This section will focus on Trial 08. Only interim results from this study were reviewed with the Original BLA and a final CSR has now been submitted.

8.1. Trial 08

Study protocol

Title

A phase 2, open-label, uncontrolled, single-dose study to evaluate the safety and tolerability, pharmacokinetics, and occurrence of antidrug antibody for nirsevimab in immunocompromised children ≤24 months of age

Objectives

The primary endpoint of Trial 08 was to evaluate the safety and tolerability of nirsevimab when administered to immunocompromised children ≤ 24 months of age.

The secondary endpoints of Trial 08 were:

- To evaluate the PK of nirsevimab,
- To evaluate the antidrug antibody (ADA) responses to nirsevimab in serum, and
- To assess the efficacy of nirsevimab when administered as a single intramuscular dose to infants ≤ 24 months of age.

Please see Section 6, Clinical Pharmacology, for the review of the results for the secondary objectives: evaluation of nirsevimab pharmacokinetics and evaluation of antidrug antibody responses to nirsevimab.

Study design

Trial 08 was an open-label, uncontrolled, single-arm safety, PK, and effectiveness trial in immunocompromised children who were ⩽24 months of age at the time of dose administration. Subjects who were immunocompromised due to an underlying condition or receipt of an immunosuppressive medication were enrolled in either their first year of life or second year of life; subjects participated in the trial for one year only.

Study subjects received a single intramuscular dose of nirsevimab prior to or during the RSV season. The nirsevimab dose was based on weight and year of life. Subjects in their first year of life who weighed < 5 kg received a single 50 mg dose, while subjects in their first year of life who weighed ⩾ 5 kg received a single 100 mg dose. Subjects in their second year of life received a single 200 mg dose, regardless of body weight. The 200 mg dose was administered as two separate intramuscular injections of 100 mg each.

Nirsevimab was administered in the study clinic on Day 1. Visits to the study site were on Days 8, 31, 91, 151, and 361. Subjects were followed until Day 151 for LRTI endpoint and safety was monitored for 360 days post-nirsevimab dose. The trial was conducted during the COVID-19 pandemic; the first subject was enrolled on August 19, 2020, and the last subject visit was on February 17, 2023. For this reason, if a subject was unable to attend an on-site visit, the visit could be conducted by telephone.

Study subjects were followed for presence of a respiratory illness throughout the entire study period. Study personnel telephoned parents or guardians every two weeks from Day 1 to Day 151 to ask whether the study subject has had a MA LRTI or currently had a respiratory illness. Parents/guardians were called monthly from Day 152 to Day 361. All subjects who sought medical attention for a respiratory illness (inpatient or outpatient setting) were evaluated for the occurrence of LRTI.

The use of palivizumab was discouraged; however, if RSV circulation in the community continued after Day 151, the administration of palivizumab was allowed if deemed necessary by the Investigator.

Entry criteria

Trial 08 enrolled neonates, infants, and children ≤ 24 months of age who were either in their first year of life and entering their first RSV season or in their second year of life and entering their second RSV season.

Study subjects must have one of the following conditions at the time of informed consent:

- Diagnosed with a condition associated with immunodeficiency such as combined immunodeficiency (severe combined immunodeficiency or cross-linked hyper IgM syndrome); antibody deficiency (crosslinked agammaglobulinemia, common variable immunodeficiency, or non-crosslinked hyper IgM syndromes); or other immunodeficiency (Wiskott-Aldrich syndrome or DiGeorge syndrome).
- Diagnosed with HIV infection.
- History of organ or bone marrow transplantation.

- Receiving immunosuppressive medication:
– Immunosuppressive chemotherapy,
– High-dose corticosteroid therapy (prednisolone equivalents ⩾ 0.5 mg/kg every other day, other than inhaler or topical use, or
– Other immunosuppressive therapy such as azathioprine, methotrexate, mizoribine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, or cytokine inhibitors.

Individual with any of the following were excluded from study participation:
- Individual was ⩽ 12 months of age and was born at ⩽ 28 weeks gestation or individual was ⩽ 6 months of age and was born at 29 to 35 weeks gestation;
- Received palivizumab;
- History of bronchopulmonary dysplasia that required medical management within the 6 months prior to enrollment.
- Current hemodynamically significant congenital heart disease.
- Down syndrome.
- Required oxygen supplementation, mechanical ventilation, extracorporeal membrane oxygenation, continuous positive airway pressure, or other mechanical respiratory or cardiac support at screening;
- Current, active infection at the time of screening;
- Temperature ⩾ 38.0C or acute illness within 7 days prior to study drug administration;
- Any serious, concurrent medical condition (renal failure, hepatic dysfunction, suspected active or chronic hepatitis infection, seizure disorder, unstable neurologic disorder, etc.), except those resulting in immune deficiency condition; or
- Clinically significant congenital anomaly of the respiratory tract.

Endpoints

The primary endpoint was the evaluation of safety. Primary endpoints were treatment-emergent adverse events (TEAEs), TE serious adverse events (SAEs), AEs of special interest (AESIs), skin reactions, and new onset of chronic diseases (NOCDs). AESIs for this study were hypersensitivity, including anaphylaxis, judged as related to nirsevimab; thrombocytopenia, and immune complex disease (vasculitis, endocarditis, neuritis, glomerulonephritis). NOCDs are defined in the protocol as newly diagnosed medical conditions that are of a chronic, ongoing nature.

The secondary endpoints for effectiveness were medically attended RSV LRT infection (MA RSV LRTI) and RSV-associated hospitalizations through 150 days post-nirsevimab. Medically attended LRT infection was defined as:
- At least one physical examination finding of rhonchi, rales, crackles, or wheeze;
- PLUS at least 1 of the following clinical signs:
– Increased respiratory rate at rest (age < 2 months, ≥ 60 breaths/min; age 2 to 6 months, ≥ 50 breaths/min; age > 6 months, ≥ 40 breaths/min), OR
– Hypoxemia (on room air: oxygen saturation < 95% at altitudes ≤ 1,800 meters or < 92% at altitudes > 1,800 meters), OR

– Clinical signs of severe respiratory disease (e.g., acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for IV fluid).

Subjects with MA RSV LRTI met the definition for MA LRTI and had nasopharyngeal (NP) swab for RSV that was tested by the central study laboratory. Nasopharyngeal swabs for RSV RT-PCR were obtained within two days after diagnosis or hospital admission for:

- All inpatient and outpatient subjects with a LRTI
- All subjects hospitalized for a respiratory infection, even if the hospitalized respiratory infection did not meet the protocol definition for LRTI, and
- All subjects with a respiratory deterioration during hospitalization.

An RSV hospitalization was defined in the protocol as either (1) a respiratory hospitalization with a positive RSV test within approximately 2 days of hospital admission or (2) a new onset of respiratory symptoms in an already hospitalized subject, with an objective measure of worsening respiratory status and positive RSV test (nosocomial).

Please see Section 6, Clinical Pharmacology, for the review of the other secondary endpoints, summary of nirsevimab serum concentrations and incidence of antidrug antibodies to nirsevimab.

Statistical methods

Safety and effectiveness were analyzed using descriptive statistics. All AEs were coded using MedDRA version 25.0.

Study results

Subject demographics and baseline characteristics

A total of 100 subjects were enrolled in Trial 08 and received nirsevimab: 46 subjects were younger than 12 months of age and 54 were 12 months to < 24 months of age. Study demographics and baseline characteristics are shown in the following table.

Table 16. Subject Demographics and Baseline Characteristics in Trial 08

Characteristic	**Total Population N = 100***
Mean age at study entry	12.97 months
Age range at study entry	0.7 – 23.9 months
Sex	
Female	35 (35%)
Male	65 (65%)
Race	
White	45 (45%)
Asian	28 (28%)
Black or African American	20 (20%)
American Indian or Alaskan Native	1 (1%)
Mixed Race or Other	6 (6%)

Characteristic	Total Population N = 100*
Ethnicity	
Hispanic or Latino	7 (7%)
Weight on Day 1	
< 5 kg	7 (5%)
≥ 5 kg and < 10 kg	65 (65%)
≥ 10 kg	28 (28%)
Smoking in the house	
Yes	21 (21%)
Currently in day care	
Yes	11 (11%)

Source: BLA 761328, S-05, CSR for Trial 08, Table 11, pages 59-60
*Reported as n (%) unless otherwise specified.

The mean age of study subjects was 12.97 months with an age range of 0.7 months to 23.9 months. Most subjects weighed between 5 kg and 10 kg on Day 1 of the study, which is consistent with the majority of subjects being in their second year of life and with a mean age of slightly over one year. The majority of subjects were White (45%), followed by Asian (20%) and Black/African American (14%); only 7% of subjects were Hispanic or Latino. Although the data are not shown, 26% of subjects were enrolled in Japan, 21% in Ukraine, 19% in the U.S., 14% in South Africa, and 10% in Spain. Smoking in the house and day care attendance are risk factors for severe RSV disease; for 21% of the subjects, someone in the subject's household smoked, and 11% of the subjects attended day care.

The reasons for immunocompromise are shown in the following table. Subjects are grouped according to the inclusion criteria in the study protocol. Subjects could have more than one condition; therefore, the percentage of subjects with each condition totals more than 100%.

Table 17. Reason for Immunocompromise for Subjects in Trial 08

Condition	Number (%) N = 100
Primary immunodeficiency	33 (33%)
Receiving high-dose corticosteroids	29 (29%)
Receiving immunosuppressive chemotherapy	20 (20%)
History of organ or bone marrow transplantation	16 (16%)
Receiving other immunosuppressive therapy	15 (15%)
HIV infection	8 (8%)

Source: BLA 761328, S-05, CSR for Trial 08, Table 11, pages 59-60

One third of subjects had a primary immunodeficiency, 16% had a history of organ or bone marrow transplantation, and 8% were HIV-infected. Sixty-four percent of subjects were immunocompromised because of a medication: high-dose steroids (29%), chemotherapy (20%), or other immunosuppressive therapy (15%).

Subject disposition

Only six subjects (6%) discontinued the study early, and the majority (94%) completed the one-year follow-up. The early discontinuations include three subjects who died (the causes of death are described below in a subsection of Section 9). One parent/guardian withdrew consent, one subject was lost to follow-up, and one subject was discontinued from the study by the Investigator because the subject was participating in another investigational trial.

Protocol deviations

According to the Applicant, 10 subjects had protocol deviations; however, the Applicant did not include study visit disruptions due to the COVID-19 pandemic or due to the war in Ukraine as a protocol deviation. The 10 subjects with protocol deviations per the Applicant were two subjects with entry criteria violations: one had blood drawn before signing the informed consent form and one had a recent history of fever. Importantly, six subjects had LRTIs but did not have a NP swab obtained for RSV RT-PCR. While this could have affected the efficacy results, this was a single arm study and efficacy was determined by extrapolation of nirsevimab PK values in Trials 03, 04, and 05 to nirsevimab PK values in Trial 08. Two subjects who were in their second year of life received 100 mg of nirsevimab instead of the 200 mg dose recommended in the study protocol and in the package insert.

Fourteen subjects (14%) missed at least one visit due to the COVID-19 pandemic. According to the Applicant, the majority of visits were conducted remotely by telephone calls. Another 21 subjects (21%) enrolled in Ukraine missed at least one study visit due to the war in that country. This included 13 Day 151 visits and 10 Day 361 visits; all of these visits were conducted by telephone. No blood for PK or for ADAs was drawn from subjects in Ukraine at Day 361. It is difficult to determine if these missed study visits and the use of remote visits by telephone interfered with efficacy or safety results.

Efficacy

Trial 08 was a single armed, uncontrolled trial in which efficacy was a secondary endpoint. Trial 08 was not designed to demonstrate efficacy through inferential statistics in this immunocompromised study population. Efficacy in this population was to be demonstrated by extrapolation of efficacy from Trials 03, 04, and 05 to the trial population of Trial 08, provided that the exposures are comparable between the populations enrolled in Trials 03, 04, and 05 and Trial 08. Please see Section 6 for a discussion of extrapolation of efficacy.

The secondary efficacy endpoint was the percentage of subjects with medically attended RSV LRT infection (MA RSV LRTI) and RSV-associated hospitalizations through 150 days post-nirsevimab. There were no events of MA RSV LRTI or RSV-associated hospitalizations through 150 days in this trial. Three subjects did have RSV MA LRTI during the study period from Day 151 to Day 361. Two of the subjects had outpatient RSV MA LRTIs on Days 215 and 346 with positive RT-PCR testing from the study's central laboratory; these events did not meet the protocol definition for MA RSV LRTI, because they occurred after Day 151. The efficacy of nirsevimab has only been studied through Day 151; serum nirsevimab concentration beyond Day 151 is not anticipated to be protective against LRTI RSV. The third subject had an RSV-associated hospitalization on Day 326 with a positive test for RSV

performed locally instead of by the central trial laboratory. This event does not count as an RSV-associated hospitalization because it did not occur during the time period for assessing efficacy (through Day 151) and because the RSV testing was not done by the central laboratory.

The efficacy results of the trial were likely affected by the COVID-19 pandemic. The trial enrolled subjects from 2020 to 2023; 60% of subjects were enrolled by June 2022. By March 2020, cases of COVID-19 had been reported in 114 countries, and the World Health Organization declared COVID-19 a pandemic on March 11, 2020. The COVID-19 pandemic affected the circulation of RSV, likely because of the nonpharmaceutical measures for COVID prevention, such as school closures and masking. As a result, the 2019-2020 RSV season ended early, and the typical RSV winter epidemic was absent during 2020-2021. The 2021-2022 RSV season occurred much earlier than in pre-pandemic years. As a result, it is likely that RSV was not circulating or was not circulating during the same months as before the COVID-19 for much of the time that Trial 08 was being conducted.

Although the incidence of MA RSV LRTI Trial 08 was likely to have been affected by the COVID-19 pandemic, Trial 08 was a single arm study was not designed to statistically determine efficacy. Efficacy in immunocompromised patients was extrapolated from Trials 03, 04, and 05 by demonstration of similar nirsevimab PK parameters. In addition, nirsevimab is indicated for patients who are vulnerable to severe RSV disease; therefore, the current indication includes immunocompromised neonates, infants, and children.

9. Safety

9.1. Trial 08

Safety monitoring

Subjects in Trial 08 were seen at the trial site on Days 1, 8, 31, 91, 151, and 361. Parents/guardians were contacted by telephone every two weeks from Day 1 to Day 151 and monthly from Day 152 to Day 361 and were asked about adverse events and serious adverse events during these telephone calls. The primary endpoint was treatment-emergent adverse events, serious adverse events, AEs of special interest, skin reactions, and new onset of chronic diseases (NOCDs) through Day 361.

Nirsevimab was administered on Day 1 at the clinical trial site. Vital signs (temperature, blood pressure, heart rate, and respiratory rate) were obtained within 60 minutes prior to dosing, and at 30 minutes and 60 minutes after administration of nirsevimab. Parents/guardians were given a hypersensitivity card and instructed to call the study site immediately for signs of hypersensitivity or allergic reaction. Parents/guardians were told to bring the study subject into the study site for any rash within the first 7 days after receipt of nirsevimab.

Clinical safety laboratory evaluation was only performed at the Japanese study sites. Blood for safety laboratory testing was obtained on Day 1, predose, and on Days 8, 31, and 151. Safety laboratory tests were a complete blood count with differential and platelets, AST, ALT, total bilirubin, BUN, and creatinine.

Safety results

All safety results presented in this section include events through Day 361.

Overview of adverse events

Adverse events were followed for 360 days after administration of nirsevimab. An overview of adverse events is shown in the following table. The individual types of adverse events will be discussed in the following sections of this review.

Table 18. Overall Summary of Treatment Emergent Adverse Events in Trial 08

Subjects with	Total N = 100 N (%)
≥ 1 adverse event	81 (81%)
≥ 1 nirsevimab-related adverse event	6 (6%)
Adverse event with outcome of death	3 (3%)
≥ 1 serious adverse event	32 (32%)
≥ 1 nirsevimab-related serious adverse event	0
≥ 1 adverse event of special interest	29 (29%)

Subjects with	Total N = 100 N (%)
≥ 1 nirsevimab-related adverse event of special interest	2 (2%)

Source: BLA 761328, S-05, CSR for Trial 08, Table 20, pages 82-83

There is no control arm for comparison of safety. The overall percentage of subjects who experienced at least one adverse event or at least one nirsevimab-related adverse event is consistent with the results of Trial 04, which was conducted in healthy newborns. However, the percentage of subjects in Trial 08 with serious adverse events is higher than reported in Trial 04. The higher percentage of subjects in Trial 08 with serious adverse events is consistent with enrollment of subjects with very serious underlying diseases.

Deaths

There were three deaths in the study; each death was related to the subject's underlying disease. All were judged by the investigators as not being related to nirsevimab. This reviewer agrees that none of the deaths were related to nirsevimab. The deaths are described as follows.

- Subject (b) (6). A 10.7-month-old White female in the United States with malignant astrocytoma was found dead in her sleep on Day 124 and is believed to have had acute hemorrhage. She had no new symptoms prior to her death. No autopsy was done.
- Subject (b) (6) A 15.8-month-old Black female in South Africa with AML and neutropenia developed pneumonia on chest radiograph and was admitted to the hospital on Day 58. Gram-positive cocci in clusters were seen on blood culture, and her laboratory values included a white blood cell count of 0.04 x 109/L. She was treated with subcutaneous filgrastim as well as intravenous amikacin and piperacillin/tazobactam, acyclovir, and fluconazole. Her condition continued to deteriorate, and she died on Day 68. Her death was attributed to lower respiratory tract infection.
- Subject (b) (6) A 0.7-month-old White male in Spain with combined immunodeficiency had a complicated course with febrile neutropenia diagnosed on Day 75, venoocclusive liver disease diagnosed on Day 80, and sepsis on Day 102. He was hospitalized again on Day 331 with acute hemolytic anemia and shock. Blood cultures were positive for Klebsiella pneumoniae. He was treated with multiple medications including antibiotics, steroids, immunoglobulins, and catecholamines; but continued to deteriorate and died 9 days later on Day 340.

There were three deaths in Trial 08; all three deaths appear to be related to the subject's underlying disease.

Serious treatment emergent adverse events

Serious adverse events were reported in 32 subjects (32%) in Trial 08. SAEs that were reported in at least 2 subjects are shown in Table 19.

Table 19. Treatment Emergent Serious Adverse Events Reported in at Least 2 Subjects in Trial 08

Serious Adverse Event	Number (%) N = 100
Pneumonia	5 (5%)
Lower respiratory tract infection	4 (4%)
COVID-19	4 (4%)
Pyrexia	3 (3%)
Bacteremia	2 (2%)
Candida sepsis	2 (2%)
Klebsiella sepsis	2 (2%)
Rhinovirus infection	2 (2%)
Gastroenteritis	2 (2%)
Viral diarrhea	2 (2%)
Febrile neutropenia	2 (2%)
Thrombocytopenia	2 (2%)
Nephrotic syndrome	2 (2%)

Source: BLA 761328, S-05, CSR for Trial 08, Table 37, pages 122-124

The majority of serious adverse events were due to infections. While some of the serious infections, such as pneumonia and LRTI may be seen in healthy children, it is likely that many of these infections were a result of the subjects' underlying conditions/treatment for their underlying conditions. Other SAEs such as nephrotic syndrome, which was reported in two subjects, gastrostomy failure (n=1), graft vs host disease (n=1), adrenal insufficiency (n=1), and hemolytic anemia (n=1) are also consistent with the study population which included subjects2 with significant underlying diseases. None of the serious adverse events were assessed by the investigator to be related to nirsevimab. Overall, the types and number of serious adverse events are consistent with the study population, the one-year safety follow-up (which resulted in a larger number of AEs), and common childhood illnesses.

Adverse events leading to treatment discontinuation

Nirsevimab was administered as a single intramuscular dose. As a result, premature discontinuation did not change either the number of subjects dosed, or the amount of trial drug administered. Three subjects discontinued from the trial prematurely due to an adverse event. All three subjects died and were described earlier in this review.

Treatment emergent adverse events

Information on adverse events was collected through Day 361. The majority of subjects (81%) had at least one adverse event, which is not surprising given the one-year follow-up, common childhood conditions, and the underlying diseases. Adverse events reported in at least 10% of subjects are shown in Table 20.

Table 20. Treatment Emergent Adverse Events Reported in ≥ 10% of Subjects Trial 08

Adverse Reaction	Number (%) N = 100
Subjects with ≥ 1 AE	81 (81%)
Upper respiratory tract infection	36 (36%)
Pyrexia	26 (26%)
Vomiting	21 (21%)
COVID-19	20 (20%)
Diarrhea	18 (18%)
Rhinorrhea	13 (13%)
Diaper dermatitis	12 (12%)
Nasopharyngitis	11 (11%)
Cough	10 (10%)

Source: BLA 761328, S-05, CSR for Trial 08, Table 14.3.1.1.1, pages 468-483

URTI was the most commonly reported AE and is consistent with a common childhood condition. Pyrexia was reported in 26% of subjects. Although this is a higher percentage of subjects than in the nirsevimab study in healthy newborns (Trial 04), it is consistent with the study population in which the infants and children were likely to have both common childhood infections and infections related to the underlying immunodeficiencies and immunosuppressive drugs. Vomiting and diarrhea were more common than in Trial 04, but the increased frequency in Trial 08 may be related to chemotherapy and other immunosuppressive medications. Of note, none of the events of vomiting and diarrhea in Trial 08 were judged as related to nirsevimab. Finally, this study was conducted during the COVID-19 pandemic, and COVID-19 infections were commonly reported (20%).

It is surprising that there were no injection site reactions reported in Trial 08. The reason for this is unclear. It is possible that injection site reactions were underappreciated because they were expected or that they were not observed because of visits conducted virtually due to COVID. Additionally, immunocompromised patients may be less likely to mount a robust local inflammatory reaction following injections.

Treatment emergent adverse reactions

Treatment emergent nirsevimab related adverse events, or adverse reactions, were reported in 6 subjects. All adverse reactions occurred within seven days of receiving nirsevimab. All were Grade 1 or Grade 2 in severity. Adverse reactions reported in Trial 08 are shown in the following table.

Table 21. Treatment Emergent Nirsevimab-Related Adverse Events Reported in Trial 08

Adverse Reaction	Number (%) N = 100
Subjects with ≥ 1 nirsevimab-related AE	6 (6%)
Pyrexia	4 (4%)
Erythema	1 (1%)
Rash	1 (1%)

Adverse Reaction	Number (%) N = 100
Maculopapular rash	1 (1%)
Abdominal pain	1 (1%)

Source: BLA 761328, S-05, CSR for Trial 08, Table 23, page 94

Most of the adverse reactions reported in Trial 08 were pyrexia and skin reactions. Treatment-related pyrexia was reported in a higher percentage of subjects in Trial 08 compared to Trial 04, in which nirsevimab-related pyrexia was reported in < 1% of subjects. In addition, all adverse reactions of pyrexia were temporally related to nirsevimab administration, occurring within 7 days of receipt of nirsevimab. While it is possible that pyrexia after nirsevimab administration is more common in immunocompromised patients, the higher rate of pyrexia in Trial 08 compared to Trial 04 may have been related to the small study size of Trial 08. In addition, the reason for an increase in pyrexia in immunocompromised subjects is unclear, and there is no control arm for comparison. However, pyrexia was only Grade 1 in severity (3 subjects) or Grade 2 in severity (one subject). In addition, pyrexia lasted for only one day in 3 subjects and 3 days in one subject. Rashes and skin adverse events have been reported with other monoclonal antibodies; rash, maculopapular rash, and erythema were reported in Trial 08. Rash and maculopapular rash are included in the ADVERSE EVENTS section of the nirsevimab (Beyfortus) package insert. Overall, there were only 6 subjects with adverse reactions and all adverse reactions were Grade 1 or Grade 2 in severity. There were no new concerning adverse reactions or increase in adverse reactions in Trial 08.

Adverse events of special interest and skin-related adverse events

The protocol-defined method for assessment of AESIs used a the standardized MedDRA queries for hypersensitivity and anaphylaxis plus the preferred terms for thrombocytopenia and immune complex disease (vasculitis, endocarditis, neuritis, glomerulonephritis). Because of the long half-life of nirsevimab, AESIs were followed for the entire safety follow-up. AESIs are shown in Table 22.

Table 22. Adverse Events of Special Interest Reported in Trial 08

Adverse Reaction	Number (%) N = 100
Subjects with ≥ 1 Adverse event of special interest	29 (29%)
Skin adverse events	22 (22%)
Thrombocytopenia	3 (3%)
Contusion	2 (2%)
Eyelid edema	1 (1%)
Juvenile idiopathic arthritis	1 (1%)

Source: BLA 761328, S-05, CSR for Trial 08, Table 26, pages 98-99

There were no AESIs of hypersensitivity, anaphylaxis, or drug reaction. In the study protocol, hypersensitivity reactions were defined as immediate (Type I) hypersensitivity reactions with an acute onset of illness and involvement of several organ systems that may include the skin, mucosal tissue, or both. Isolated skin reactions, such as rash or pruritis, were classified as "simple" allergic reactions in the study protocol.

The most commonly reported AESIs were skin reactions. These AESIs included (by MedDRA preferred term) rash (n=5), infantile eczema (n=4), eczema (n=3), urticaria (n=3), and atopic dermatitis (n=2); and skin reactions reported in one subject each were macular rash, maculopapular rash, vesicular rash, dermatitis, petechiae, and skin reaction. Of these skin AESIs, four were reported within seven days of receipt of nirsevimab: one subject each with atopic dermatitis, rash, maculopapular rash, and urticaria. Only the rash and maculopapular rash events were judged as related to nirsevimab. Two AESIs of urticaria were reported on Days 212 and 337, the AESI of eyelid edema was reported on Day 51. None of the skin reactions were serious adverse events. Although thrombocytopenia was reported in three subjects, thrombocytopenia can be associated with diseases that cause immunocompromise and can be a result of immunosuppressive medications. Thrombocytopenia was judged as not related to nirsevimab in all three subjects. Although the event of juvenile idiopathic arthritis was reported as an immune complex disease, juvenile idiopathic arthritis was diagnosed prior to study entry. Finally, it is unclear why contusion was included as an AESI. Overall, it appears that rash may be reported in immunocompromised subjects who receive nirsevimab; the association of rash with nirsevimab administration is described in the current nirsevimab labeling.

Because of the association of rash and monoclonal antibodies, the number of subjects with rashes and the types of rashes were assessed for the entire study period and for the 14-day period after nirsevimab administration. Although there is little evidence that nirsevimab-related rashes are limited to the 14 days after nirsevimab administration, this time period was assessed because this short time period after may result in rashes that are more likely to be related to nirsevimab. Adverse events in the MedDRA Skin and Subcutaneous Tissue Disorder System Organ Class are shown in the following table.

Table 23. Adverse Events in the MedDRA Skin and Subcutaneous Tissue Disorder System Organ Class in Trial 08

Skin or SC Tissue Reaction	**Number (%)**	
	Through Study Day 361	**Through Study Day 14**
Subjects with ≥ 1 adverse event in Skin or SC Tissue SOC	20 (20%)	6 (6%)
Eczema infantile	4 (4%)	1 (1%)
Eczema	3 (3%)	0
Rash	3 (3%)	1 (1%)
Urticaria	3 (3%)	1 (1%)
Erythema	3 (3%)	2 (2%)
Macular rash	1 (1%)	0
Maculopapular rash	1 (1%)	1 (1%)
Papular rash	1 (1%)	0
Vesicular rash	1 (1%)	0
Dermatitis	1 (1%)	0
Atopic dermatitis	1 (1%)	0
Dermatitis – hand	1 (1%)	0
Skin reaction	1 (1%)	0

Source: BLA 761328, S-05, CSR for Trial 08, Tables 28-29, pages 103-105

Twenty percent of subjects had a skin or subcutaneous tissue AE through Day 361 of the study, while six subjects had a skin or SC tissue AE within 14 days of receiving nirsevimab. As stated previously, rash is already included in the package insert for nirsevimab. No new information regarding rash was obtained in this single arm trial.

New onset chronic diseases

No subjects experienced a new onset chronic disease.

Safety laboratory test results

Safety laboratory values were obtained at Japanese sites only. One subject had Grade 3 thrombocytopenia, one subject had a Grade 3 leukopenia, and two subjects had a Grade 4 leukopenia. Adverse events of Grade 3 and Grade 4 neutropenia were also reported in subjects at non-Japanese sites who had febrile neutropenia. One subject had a Grade 4 increase in ALT, and one subject had Grade 3 increase in AST. No subject had ALT $\geqslant 3 \times$ ULN or AST $\geqslant 3 \times$ ULN and TBL $\geqslant 2 \times$ ULN (i.e., no subjects met Hy's Law criteria). None of the abnormal laboratory values were judged as nirsevimab related. It is difficult to reach any conclusions about laboratory abnormalities because laboratory tests were only obtained in 26% of subjects and because of the underlying conditions and medications administered in this trial which could also impact laboratory results.

Subjects with possible protein losing conditions

Please see Dr. Zhao's discussion of protein losing conditions and increased nirsevimab clearance in Section 6 of this review.

In the analysis of nirsevimab pharmacokinetic data in Trial 08, 24 subjects were identified with lower than target AUC, and 13 out of these 24 subjects were identified as outliers with increased clearance of nirsevimab (of note, a total of 14 subjects were identified with increased clearance of nirsevimab, but only 13 of these 14 subjects had AUCbaselineCL lower than 12.8 mg*day/mL). The Applicant hypothesized that the increased clearance in these subjects was due to protein-losing conditions. Although the Applicant identified conditions that may be associated with protein loss in each of these subjects, there was no formal definition of a protein losing condition included in the study protocol or Statistical Analysis Plan. More importantly, the Applicant stated that no specific laboratory parameters, such as serum albumin or immunoglobulin, were collected during the study that could confirm that any of these subjects identified were actually experiencing protein loss.

In response to an Information Request, the Applicant submitted the narratives for the subjects they had identified as having protein losing conditions. Five of the subjects had chronic liver disease and had undergone liver transplantation, three had a malignancy, two had graft-versus-host disease, two were HIV-infected, one had nephrotic syndrome (notably, although this participant had increased clearance of nirsevimab, the participant had an increased rather than decreased nirsevimab exposure), and two had Omenn syndrome. Although protein loss *may* have occurred in some of the subjects identified, laboratory tests to identify protein loss were not obtained. In addition, none of the investigators considered the possibility of protein loss

during study participation. As a result, subjects in Trial 08 with protein loss cannot be identified, and the potential effect of protein loss on clearance cannot be determined.

Conclusion

Trial 08 was a single arm, uncontrolled trial conducted in immunocompromised children ≤ 24 months of age. Analysis of safety was complicated by the lack of a control arm and the complicated underlying diseases in the study population. In addition, many of the adverse events, such as URTIs and diaper dermatitis, were consistent with common childhood conditions. It is notable that pyrexia was reported more commonly in immunocompromised subjects in Trial 08 than in the trial of healthy newborns (Trial 04), but the reason for this is unclear. Although the increase in pyrexia could be related to the underlying conditions or medications, it is difficult to determine nirsevimab relatedness without a control arm. However, in general, the safety results were consistent with both the underlying diseases and common childhood conditions. No new safety signals were identified and no updates to Section 6, ADVERSE REACTIONS, are needed. Information regarding the design and safety results of Trial 08 will be added to Section 8, USE IN SPECIFIC POPULATIONS, of the package insert.

9.2. Trial 04

Trial 04 was a Phase 3, randomized, double-blind, placebo-controlled, safety and efficacy trial comparing nirsevimab to placebo in the prevention of MA RSV LRTI in healthy late preterm and term infants (≥ 35 weeks GA). The interim CSR for Trial 04 was reviewed as part of the original nirsevimab BLA; Trial 04 was one of the pivotal trials supporting the safety and efficacy in the original approval of nirsevimab. The design and conduct of Trial 04 were affected by the COVID-19 pandemic. The trial was ongoing when the pandemic was declared, and enrollment in the trial was temporarily stopped on March 11, 2020. Enrollment was restarted in March of 2021. Subjects who were enrolled prior to the pandemic were referred to as the Primary Cohort, and this was the cohort used for analysis of efficacy. The Safety Cohort was the entire study population, regardless of when enrolled. The primary objective for the Safety Cohort was assessment of safety; assessment of efficacy was an exploratory endpoint for the Safety Cohort. The number of subjects and length of follow-up from the Primary and Safety Cohorts are shown in the following table. The number of subjects who reached Day 151 were those who completed the time necessary for assessment of efficacy (incidence of MA RSV LRTI through Day 151) and the number of subjects who reached Day 361 were those who completed the safety follow-up.

Table 24. Number of Subjects Dosed With Study Drug and Length of Follow-Up for Subjects in Trial 04 at Time of Original BLA

Study Population	Number of Subjects Received Study Drug		Reached Day 151		Reached Day 361	
	Nirs.	Placebo	Nirs	Placebo	Nirs	Placebo
Primary Cohort	987	491	977	488	914	453

Study Population	Number of Subjects Received Study Drug		Reached Day 151		Reached Day 361	
	Nirs.	Placebo	Nirs	Placebo	Nirs	Placebo
Safety Cohort (All Subjects)	1998	996	1886	938	964	482

Source: BLA 761328, initial BLA submission, CSR for Trial 04, Figure 2, page 83

As shown in Table 24, the majority of subjects (97%) in the Primary Cohort reached Day 151 at time of data lock for the original BLA; therefore, the review of efficacy as reviewed in the original BLA and described in the Beyfortus package insert is complete and will not be included in this review. For the efficacy results of Trial 04, please see the integrated review for the original BLA nirsevimab review. Of the total Safety Cohort, 94% had reached Day 151 and 48% of subjects had reached Day 361 at the time of data lock for the original BLA. Because safety information through Day 151 was provided in the original BLA submission for the majority of subjects in Trial 04, safety events that occur soon after drug administration, such as hypersensitivity events and skin reactions, will not be described in this review. This review will provide updated safety information with a focus on how the safety differs from the safety review as described in the integrated review of the original BLA as well as how the safety differs from what is in the current package insert. In the Beyfortus package insert, the safety results from subjects who received the to be marketed dose of nirsevimab in Trial 03 and the safety results from subjects in Trial 04 were pooled. The table of adverse reactions from the Beyfortus package insert is shown as follows.

Table 25. Adverse Reactions Reported at an Incidence Higher Than Placebo in the Safety Population* (Trials 03 and 04)

Adverse Reaction	Beyfortus N=2,570	PLACEBO N=1,284
Rash† (occurring within 14 days post-dose)	0.9	0.6
Injection site reaction‡ (occurring within 7 days pos-dose)	0.3	0

Source: Beyfortus package insert.
* The Safety Population includes all subjects who received the recommended dose of BEYFORTUS in Trials 03 and 04: Primary and Safety cohorts from Trial 04; infants who weighed less than 5 kg and who received the recommended dose of BEYFORTUS (single 50 mg IM dose) in Trial 03.
† Rash was defined by the following grouped preferred terms: rash, rash macular, rash maculo-papular, rash papular.
‡ Injection site reaction was defined by the following grouped preferred terms: injection site reaction, injection site pain, injection site induration, injection site edema, injection site swelling.

Adverse events, including serious AEs and AESIs, were followed through Day 361 of Trial 04. All study subjects in Trial 04 were also followed in the second year of life from Day 362 to Day 511 but only for the incidence of MA RSV LRTI and RSV hospitalizations. Subjects did **not** receive a second dose of nirsevimab prior to their second RSV season. This long-term follow-up for subjects was considered safety follow-up to rule out a shift of MA RSV LRTI from the first year of life to the second and to assess for evidence of antibody dependent enhancement of RSV disease. The data for the follow-up to Day 511 for the Primary Cohort was interrupted by the COVID-19 pandemic, and the final results for this analysis are described in this review. As noted, this trial was interrupted by the COVID-19 pandemic. Overall, 48% of subjects were enrolled prior to March 2020, when the study was temporarily

halted due to COVID-19. The trial was restarted on April 9, 2021. As described previously, RSV circulation was absent during the 2020 -2021 winter season, and RSV circulation was much earlier than usual in the 2021-2022 RSV season. Therefore, COVID-19 may have affected the incidence of RSV infections during Days 362 to Day 511.

Safety results

Subject disposition

The "As Treated" population as described in the current package insert changed by one subject, because one subject who was originally included as having had received nirsevimab, actually received placebo. The number of subjects in the safety population in Section 6, ADVERSE REACTIONS, of the Beyfortus package insert was revised to reflect this subject's actual treatment.

Deaths

No new deaths were reported in the final CSR.

Serious treatment emergent adverse events

Treatment-emergent serious adverse events through Day 361 are shown in the following table. The table includes SAEs that were reported in at least 0.2% of subjects in the nirsevimab arm.

Table 26. Number and Percentage of Subjects With Serious Adverse Events in Trial 04 (SAEs Reported in ≥ 0.2% of Subjects in Nirsevimab Arm)

Serious Adverse Event	Number (%) of Subjects	
	Nirsevimab Arm N=1997	Placebo Arm N=997
Subjects with ≥ 1 SAE	149 (8%)	83 (8%)
Bronchiolitis	27 (1.4%)	17 (1.7%)
Gastroenteritis	14 (0.7%)	5 (0.5%)
Pneumonia	13 (0.7%)	5 (0.5%)
Urinary tract infection	7 (0.4%)	5 (0.5%)
Pyrexia	6 (0.3%)	1 (0.1%)
Lower respiratory tract infection	6 (0.3%)	0
RSV bronchiolitis	5 (0.3%)	10 (1.0%)
Febrile seizure	4 (0.2%)	0
Diarrhea	3 (0.2%)	0
Bronchitis	3 (0.2%)	4 (0.4%)
Laryngitis	3 (0.2%)	3 (0.3%)

Source: BLA 761328, S-05, CSR for Trial 04, Table 79, pages 225-226

The percentage of subjects with at least one SAE was 8% in each study arm. As shown in Table 26, the percentage of subjects with individual SAEs was low, and no individual SAE was reported in ≥ 2% of subjects. The differences between the two arms were small; there was no individual SAE reported in 1% more subjects in the nirsevimab arm compared to the placebo arm. Only one SAE was judged as nirsevimab-related. A one-month-old White male from the U.S. developed a fever, judged as related to nirsevimab, on Day 2 after receipt of

nirsevimab. The subject had a sepsis work-up and was hospitalized for intravenous antibiotics. All cultures were negative, and the subject was discharged on Study Day 4. Overall, the SAE results are consistent with the results reported in the original BLA.

Treatment emergent adverse events

Treatment emergent AEs were reported in 865 of all subjects, 86% in the nirsevimab arm and 85% in the placebo arm. Twenty-five percent of the AEs occurred within 14 days of receipt of study drug. Treatment emergent adverse events reported in at least 5% of subjects through day 361 are shown in the following table.

Table 27. Number and Percentage of Subjects With Adverse Events in Trial 04 (AEs Reported in ≥ 5.0% of Subjects in Nirsevimab Arm)

Serious Adverse Event	Number (%) of Subjects	
	Nirsevimab Arm N=1997	Placebo Arm N=997
Subjects with ≥ 1 SAE	1,722 (86%)	843 (85%)
Upper respiratory tract infection	641 (32%)	317 (32%)
Nasopharyngitis	441 (22%)	237 (24%)
Pyrexia	293 (15%)	123 (12%)
Diaper dermatitis	224 (11%)	103 (10%)
Gastroenteritis	213 (11%)	103 (10%)
Rhinitis	201 (10%)	102 (10%
Diarrhea	172 (9%)	89 (9%)
Nasal congestion	164 (8%)	86 (9%)
Otitis media	154 (8%)	78 (8%)
Rhinorrhea	152 (8%)	65 (7%)
Bronchiolitis	138 (7%)	86 (9%)
Teething	138 (7%)	70 (7%)
Conjunctivitis	137 (7%)	56 (6%)
Viral upper respiratory infection	136 (7%)	60 (6%)
Cough	115 (6%)	58 (6%)
COVID-19 infection	100 (5%)	61 (6%)

Source: BLA 761328, S-05, CSR for Trial 04, Table 58, pages 176-178

The most commonly reported adverse event was upper respiratory tract infection. The types of individual TEAEs are consistent with conditions commonly observed during childhood, such as teething, diaper dermatitis, and rhinorrhea. However, there were a number of infants who were infected with COVID-19 reflecting the time in which this trial was conducted. The percentage of subjects with each individual AE was similar between the two study arms; there were no AEs that were reported with a 5% or greater difference between the two study arms. The results shown in Table 27 are consistent with the percentage of subjects with and the types of TEAEs reported in the interim CSR for Trial 04, which was reviewed as part of the original BLA.

Treatment emergent adverse reactions

The number and percentage of subjects with treatment-related adverse events are shown in Table 28. The table includes treatment-related AEs reported in at least 2 subjects in the nirsevimab arm.

Table 28. Number and Percentage of Subjects in Trial 04 With Treatment-Related Adverse Events in Trial 04 (Reported in ≥ 1 Subjects in Nirsevimab Arm)

Serious Adverse Event	Number (%) of Subjects	
	Nirsevimab Arm N=1997	Placebo Arm N=997
Subjects with ≥ 1 Treatment-Related AE	25 (1.3%)	15 (1.5%)
Maculopapular rash	6 (0.3%)	0
Irritability	4 (0.2%)	3 (0.3%)
Rash	2 (0.1%)	0
Pyrexia	2 (0.1%)	2 (0.2%)
Diarrhea	2 (0.1%)	0

Source: BLA 761328, S-05, CSR for Trial 04, Table 60, pages 183-184

The percentage of subjects with a treatment-emergent AE was similar in both treatment arms and was low in both arms. The only treatment-related AEs reported more commonly in subjects who received nirsevimab was maculopapular rash and rash, which together were reported in 8 subjects (0.4%) in the nirsevimab arm but were not reported in the placebo arm. The majority of nirsevimab-related rashes were reported within 17 days of administration of nirsevimab. The incidence of rash within 14 days is included in the current package insert.

Adverse events of special interest

The results for the number and percentage of AESIs in the final CSR were similar to those included in the original BLA. There were four treatment-related AESIs; all were reported in subjects who received nirsevimab and all four were rashes [maculopapular rash (N=2), rash (N=1), and papular rash (N=1)]. As previously stated, the incidence of rash in Trials 03 and 04 is included in the package insert.

New onset chronic diseases

The number and percentage of subjects in Trial 04 with a new onset chronic disease (NOCD) in shown in the following table.

Table 29. Number and Percentage of Subjects in Trial 04 With New Onset Chronic Disease

New Onset Chronic Disease	Number (%) of Subjects	
	Nirsevimab Arm N=1997	Placebo Arm N=997
Subjects with ≥ 1 NOCD	7 (0.4%)	3 (0.3%)
Asthma	4 (0.2%)	1 (0.1%)
Bronchial obstruction	2 (0.1%)	0
PFAPA syndrome*	1 (0.1%)	0
Hypothyroidism	0	2 (0.2%)

Source: BLA 761328, S-05, CSR for Trial 04, Table 60, pages 183-184
*PFAPA = Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis

NOCDs were uncommon and were reported in < 1% of subjects in each treatment arm. There were too few subjects to identify any differences between the two treatment arms. These results are consistent with those reported in the interim CSR for Trial 04.

MA RSV LRTI and RSV-associated hospitalization from Day 362 through Day 511

All subjects in both treatment arms were followed from Day 362 though Day 511 to assess the incidence of MA RSV LRTI and of RSV associated hospitalizations in the second RSV season. Subjects did not receive study drug prior to the second RSV season. The number of subjects in this analysis is slightly lower than in other safety analyses, because when the trial was temporarily halted for the COVID-19 pandemic, some of the subjects in the Primary Cohort who had reached Day 361 did not have any additional follow-up.

Table 30. Number and Percentage of Subjects in Trial 04 With Medically-Attended RSV Lower Respiratory Tract Infections or RSV-Associated Hospitalizations From Day 362 Through Day 511

RSV Event	Number (%) of Subjects	
	Nirsevimab Arm N=1944	Placebo Arm N=967
MA RSV LRTI	19 (1.0%)	10 (1.0%)
RSV associated hospitalization	3 (0.2%)	3 (0.3%)

Source: BLA 761328, S-05, CSR for Trial 04, Table 77, page 222

The number and percentage of subjects with MA RSV LRTI or RSV associated hospitalization was similar in both treatment arms. However, only a small number of subjects in both arms reported MA RSV LRTI or RSV associated hospitalization in RSV season 2. This could be due to the changes in RSV circulation associated with the COVID-19 pandemic. Because of the concerns that RSV circulation was low during Days 362 to 511 in Trial 04, post marketing commitment 4470-4 was issued and the Applicant agree to:

- Conduct an observational, U.S.-based long-term follow-up study of infants eligible to receive nirsevimab in their first year of life to assess the impact of RSV disease through Day 511 post dosing. This study should include assessment of MA-RSV-LRTI and RSV hospitalization. The study may be conducted using existing databases for the 2023 and 2024 RSV seasons.

In addition, a second post marketing commitment, 4470-3, was issued to obtain data from an ongoing, non-IND study, the HARMONIE study.

- Conduct a long-term follow-up study (Study D5290N00001: HARMONIE study extension for the UK cohort) to evaluate antibody dependent enhancement of RSV disease after nirsevimab administration to neonates and infants prior to or during their first RSV season. The assessment for antibody dependent enhancement of RSV disease should include RSV lower respiratory tract infection (LRTI) hospitalization events. The follow-up period should continue through Day 511 post-dosing.

The HARMONIE study is a randomized, open-label study comparing a single intramuscular dose of nirsevimab to no intervention in the prevention of RSV LRTI. HARMONIE was designed to mimic the real-world use of nirsevimab in the United Kingdom, France, and

Germany. The study will enroll 28,860 healthy infants who were born at ⩾ 29 weeks GA and who are entering or born during their first RSV season; all subjects will be followed through their first RSV season for collection of information on LRTI hospitalizations. Subjects in the United Kingdom may participate in follow up (study extension) for an additional 12 months from Day 366 to Day 731 post-dosing to collect information on LRTI hospitalizations in the second RSV season.

Although the results of Trial 04 do not show a difference in MA RSV LRTIs and RSV associated hospitalizations in RSV season 2, the Applicant will conduct a study to assess the incidence of RSV disease through Day 511.

Conclusions

Overall, the updated safety results in the final Clinical Study Report for Trial 04 were similar to those described in the interim CSR included in the original BLA. These safety results are described in Section 6, ADVERSE REACTIONS of the Beyfortus package insert. There were no new safety signals or concerns noted on review of the final CSR, and no revisions to the safety findings in Trial 04 were made as a result of this review.

9.3. Trial 05, Season 2

Trial 05 was a Phase 2/3, randomized, double-blind, controlled, safety, PK and efficacy trial of nirsevimab compared to palivizumab in subjects at increased risk of severe RSV disease. Trial 05 was conducted over two years including two RSV seasons with study treatment administered prior to or during the first RSV season and prior to RSV season in the second year of the trial. Infants born prematurely (< 35 weeks GA) and infants with congenital heart disease (CHD) and/or chronic lung disease (CLD) were enrolled in the first year of the study; infants with CHD and/or CLD were also enrolled in both years. The percentage of subjects with MA LRTI was followed through Day 151; however, efficacy in neonates, infants, and children at increased risk of severe RSV disease was determined by extrapolation with comparable nirsevimab PK variables in Trials 03 and 04 and in Trial 05. Safety was followed through Day 361 in both years of the study.

The interim CSR for Trial 05 that was included in the original BLA included safety and efficacy results for all subjects in Year 1 as well as safety and efficacy results through Day 151 of Year 2 for all subjects. Because efficacy endpoints were followed through Day 151 in both years, the interim CSR included efficacy for both years of the trial. As a result, efficacy from both RSV seasons was reviewed with the original BLA and is included in the current Beyfortus package insert. The safety results for the entire first year of the trial and through Day 151 in the second year are also included in labeling. In the current Beyfortus package insert, the safety in Trial 05, Season 2 is described as consistent with the safety observed in Season 1.

> "The safety profile of Beyfortus in these children during their second RSV season was consistent with the safety profile of Beyfortus observed during their first RSV season."

The final CSR provided with this supplement includes the complete safety findings from the second year of Trial 05. This review focuses on safety from Day 152 to Day 361 in Year 2.

At the end of the first year of the trial, infants with CHD and/or CLD were reconsented for participation in the second year of Trial 05. Prior to the start of RSV Season in the second year of Trial 05, subjects participating in the second year were rerandomized. Infants who received nirsevimab in RSV Season 1 also received nirsevimab in RSV Season 2; infants who received palivizumab in RSV Season 1 were randomized in a 1:1 ratio to receive nirsevimab or palivizumab in RSV Season 2. After receipt of study drug prior to the predicted RSV season, subjects were followed for safety through Day 361 of the second year. As a result of the rerandomization in year 2, there were 180 subjects who received nirsevimab in the first and second years of the study, 42 subjects who received palivizumab in both years of the study, and 40 subjects who received palivizumab in year 1 and nirsevimab in year 2. Because of the small number of subjects receiving palivizumab in the second year of Trial 05, it is difficult to reach conclusions about differences in safety findings between Year 1 and Year 2.

Of note, Trial 05 was not halted during the COVID-19 pandemic, and all subjects in the second year of Trial 05 were randomized and received study drug during the COVID-19 pandemic. Thirty-one subjects (11%) had confirmed COVID-19; three additional subjects (1%) had suspected COVID-19. Study disruptions for the total study population that were due to the COVID-19 pandemic are shown in the following table.

Table 31. Number and Percentage of Subjects With Study Disruptions Due to the COVID-19 Pandemic in Trial 05

Type of Disruption	**N=262**
Subjects with ≥ 1 missed visit	2 (0.8%)
Subjects with ≥ 1 delayed visit	11 (4.2%)
Subjects with ≥ 1 missed study sample obtained	2 (0.8%)
Subjects with ≥ 1 missed dose of study drug	0
Subjects with ≥ 1 delayed dose of active drug (not placebo)	2 (0.8%)
Subjects who discontinued due to COVID-19	0

Source: BLA 761328, S-05, CSR for Trial 05, Table 23, page 110

As shown in Table 31, the Applicant was able to continue the study during the COVID-19 pandemic with very few missed study visits or missed doses of study drugs. In the opinion of this reviewer, the safety data were collected appropriately despite the pandemic.

Safety results

Deaths

There were no deaths in Season 2

Serious treatment emergent adverse events

Serious adverse events were followed through Day 361 in Year 2 of Trial 05. The number and percentage of subjects with a SAE are shown in Table 32.

Table 32. Number and Percentage of Subjects With Serious Adverse Events in Trial 05, Year 2 (SAEs Reported in ≥ 2 Subjects Who Received Nirsevimab in Year 2)

Serious Adverse Event	Number (%) of Subjects	
	All Nirsevimab N=220	Palivizumab Arm N=42
Subjects with ≥ 1 SAE	27 (12%)	2 (5%)
Gastroenteritis	4 (1.8%)	1 (2.4%)
Pneumonia	4 (1.8%)	0
Viral bronchitis	3 (1.4%)	0
Lower respiratory tract infection	3 (1.4%)	0
COVID-19	2 (0.9%)	0
Pleural effusion	2 (0.9%)	0

Source: BLA 761328, S-05, CSR for Trial 05, Table 79, pages 254-255

Serious adverse events were reported in 12% of subjects who received nirsevimab and in 5% of subjects who received palivizumab in the second year of Trial 05. None of the SAEs were judged as treatment related. Although there was an overall increase in SAEs in the nirsevimab arm, the individual types of SAEs varied and there was not an increase in any individual type of SAE.

Treatment emergent adverse events

Treatment emergent adverse events are shown in the following table.

Table 33. Number and Percentage of Subjects With Treatment Emergent Adverse Events in Trial 05, Year 2 (TEAEs Reported in ≥ 2 Subjects Who Received Nirsevimab in Year 2)

Adverse Event	Number (%) of Subjects	
	All Nirsevimab N=220	Palivizumab Arm N=42
Subjects with ≥ 1 AE	161 (73%)	29 (69%)
Upper respiratory tract infection	56 (25%)	9 (21%)
Rhinitis	35 (16%)	6 (14%)
Nasopharyngitis	33 (15%)	9 (21%)
Pyrexia	32 (15%)	6 (14%)
Rhinorrhea	28 (13%)	2 (4%)
Viral upper respiratory tract infection	23 (10%)	2 (5%)
COVID-19 infection	19 (9%)	2 (5%)
Gastroenteritis	16 (7%)	3 (7%)
Acute otitis media	16 (7%)	2 (5%)
Otitis media	16 (7%)	2 (5%)
Conjunctivitis	12 (5%)	3 (7%)
Diarrhea	12 (5%)	7 (17%)
Bronchitis	11 (5%)	1 (2%)

Source: BLA 761328, S-05, CSR for Trial 05, Table 74, pages 236-237

The most commonly reported TEAE in the nirsevimab and palivizumab arms was upper respiratory tract infection. All other frequently reported TEAEs were also common childhood

illness except for COVID-19. Year 2 was conducted during the COVID-19 pandemic and COVID was reported in 9% of subjects in the nirsevimab arm and in 5% of subjects in the palivizumab arm. For some TEAEs, there was a larger difference between treatment arms in Year 2 than in Year 1, this is likely due to the smaller number of subjects who participated in Year 2, particularly in the palivizumab arm, which only included 42 subjects. Although URTI, viral URTI, and rhinorrhea were reported more frequently in the nirsevimab arm, nasopharyngitis and rhinitis were reported more often in the palivizumab arm. This inconsistency in upper respiratory symptoms suggests that the differences are not likely related to the trial drugs. Overall, there was no substantial increase incidence of any individual TEAE in Year 2 of Trial 05

Treatment emergent adverse reactions

There were no adverse events in the second year of Trial 05 that were judged as treatment related.

Adverse events of special interest

AESIs were assessed by MedDRA group terms for hypersensitivity. In the second year of Trial 05, AESIs were reported in 33 (15%) of subjects in the nirsevimab arm and 5 (12%) of subjects in the palivizumab. There were no events of anaphylaxis, hypersensitivity reaction, or immune complex disease. The percentage of subjects with skin adverse events was similar in the nirsevimab (9%) and palivizumab arms (10%). None of the AESIs were judged as treatment related.

Conclusion

The adverse events and SAEs reported in the second year of Trial 05 were consistent with common childhood conditions, and the most commonly reported AEs were infections, such as URTI and nasopharyngitis. Although there were some differences in the percentages of AEs between the two arms, the differences were not consistent, for example, some upper respiratory conditions were reported at a higher percentage in the nirsevimab arm, and some were reported at a higher percentage in the palivizumab arm. These inconsistent differences in the incidences of individual AEs in Year 2 may have been related to the small study size. Of note, there were no nirsevimab-related AEs during Year 2. Overall, there is no new safety signal, and the safety results from Year 2 of Trial 05 in the Beyfortus package insert were not revised.

10. Advisory Committee Meeting

Not Applicable

11. Pediatrics

This application contains pediatric data for subjects from birth to ≤ 24 months of age. The trial results in this submission were submitted to satisfy the following postmarketing commitments, which were issued in the approval letter dated 17Jul2023.

- 4470-6: Submit the final study report and datasets for Trial D5290C00004 (MELODY), a phase 3 randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of nirsevimab for the prevention of medically attended RSV respiratory tract infection (MA RSV LRTI) in preterm and term infants.
- 4470-7: Submit the final study report and datasets for Trial D5290C00005 (MEDLEY), a double-blind, active-controlled trial to evaluate the safety, efficacy, and pharmacokinetic of nirsevimab for the prevention of medically attended RSV respiratory tract infection (MA RSV LRTI) in high-risk infants and children.
- 4470-8: Submit the final study report and datasets for Trial D5290C00008 (TRIAL 08), "A Phase 2, Open-label, Uncontrolled, Single-dose Study to Evaluate the Safety and Tolerability, Pharmacokinetics, and Occurrence of Antidrug Antibody for Nirsevimab in Immunocompromised Children ≤ 24 Months of Age. "

These postmarketing commitments were fulfilled by the submission of this supplemental BLA.

This supplemental BLA did not trigger PREA because it was not submitted for a new dosing regimen, a new dosage form, a new active ingredient, or a new route of administration. In addition, the indication is the same, i.e., prevention of RSV LRT disease.

12. Other Relevant Regulatory Issues

Financial Disclosure

The financial disclosures were reviewed as part of the review of the original BLA submission. This review was submitted to DARRTS on July 14, 2023. The review concluded that the likelihood that trial results were biased based on financial interests was minimal.

Conduct of Trials

According to the Applicant, the three trials were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonization and Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Study sites for Trials 04 and 05 were inspected by the Office of Scientific Investigations in support of the original BLA. Based on the results of these inspections, the trials appeared to have been conducted adequately, and the data generated by the clinical investigator sites appeared acceptable in support of the indication. See the review of the original BLA submission, which is available in DARRTS.

13. Labeling

The nirsevimab labeling has been updated to reflect minor changes in safety and PK data from Trials 04 and 05 and to include safety and PK data from Trial 08. The changes with the supplemental BLA primarily affected the following sections.

2.0 DOSAGE AND ADMINISTRATION
Minor edits were made to Section 2, Recommended Dosage, to add clarity regarding dosing in the first RSV season compared to the second in order to prevent potential medication errors.

5.0 WARNINGS AND PRECAUTION
The Applicant added a subsection, Use in Individuals with (b) (4)

6.0 ADVERSE REACTIONS
Minor edits to the number of subjects exposed to nirsevimab were made. (b) (4)

8.0 USE IN SPECIFIC POPULATIONS
The subsection, 8.4, Pediatric Use was revised to add information from Trial 08.
The proposed subsections, (b) (4) were deleted. (b) (4)

12 CLINICAL PHARMACOLOGY
Section 12.3 Pharmacokinetics was revised to include information regarding the pharmacokinetics of nirsevimab in immunocompromised subjects enrolled in Trial 08.
Section 12.4 Microbiology was revised to include additional RSV variants with reduced susceptibility to nirsevimab.
Section 12.6 Immunogenicity was revised to add information on antidrug antibodies from Trials 04, 05, and 08.

14 CLINICAL STUDIES
The Sponsor proposed that information on Trial 08 be included in Section 14. However, per 21 CFR 201.57(c)(14), trials described in Section 14 of the package insert must be adequate and well-controlled. Trial 08 was a single arm study with no control. The information regarding Trial 08 did not add to the efficacy data already included in the package insert. Therefore, the information regarding Trial 08 was removed from Section 14.

14. **Postmarketing Recommendations**

No new postmarketing commitments were issued with this supplemental BLA.

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