Advisory Committee Briefing Document	
Drug Substance	Nirsevimab
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BEYFORTUS™ (Nirsevimab) for the Prevention of RSV Lower Respiratory Tract Disease in Infants and Children

BLA 761328

Briefing Document for

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Antimicrobial Drugs Advisory Committee Meeting

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this document:

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ADA	anti-drug antibody(ies)
ADE	antibody-dependent enhancement
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AUC	area under the concentration-time curve
BLA	Biologics License Application
CHD	congenital heart disease
CI	confidence interval
CL	Clearance
CLD	chronic lung disease
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CSP	clinical study protocol
CRF	case report form
EC_{50}	half-maximal effective concentration
EMA	European Medicines Agency
EU	European Union
F	fusion protein
Fc	fragment crystallizable
FDA	Food and Drug Administration
HFNC	high flow nasal cannula
HRU	health resource utilization
ICU	intensive care unit
IV	Intravenous
HIV	human immunodeficiency virus
IgG1κ	immunoglobulin gamma type 1, kappa
IM	Intramuscular
IP	investigational product
iPSP	interim pediatric study plan
IRR	Incident rate ratio
K_D	dissociation constant
LRTI	lower respiratory tract infection
MA	medically attended
mAb	monoclonal antibody

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MEDI8897	Nirsevimab
OR	Odds ratio
nAb	neutralizing antibody
NH	Northern Hemisphere
nirsevimab	MEDI8897
NOCD	new onset chronic disease
palivizumab	SYNAGIS®
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
Proposed-Dose Safety Pool	Pooled data of all recipients of the proposed dose of nirsevimab (50 mg in subjects < 5kg and 100 mg in subjects ≥ 5kg) in the placebo-controlled pivotal trials, including Trial 04 (All Subjects) and Trial 03 subjects weighing < 5 kg.
PT	preferred term
RR	relative risk
RRR	relative risk ratio
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SH	Southern Hemisphere
SOC	System Organ Class
TEAE	treatment-emergent AE
Trial 03	Study D5290C00003 (Study 3)
Trial 03 (Proposed Dose)	Randomized subjects from Trial 03 weighing < 5 kg at dosing
Trial 04	Study D5290C00004 (MELODY)
Trial 04 (All Subjects)	Includes all subjects enrolled in Trial 04
Trial 04 (Primary Cohort)	Includes subjects in the primary analysis cohort from Trial 04
Trial 05	Study D5290C00005 (MEDLEY)
URTI	upper respiratory tract infection
USA	United States of America
wGA	weeks gestational age
YTE	M252Y/S254T/T256E triple amino acid substitution

1 EXECUTIVE SUMMARY

AstraZeneca (the Sponsor) in partnership with Sanofi are seeking marketing approval of nirsevimab for prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants born during or entering their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. The clinical data summarized in this briefing document show that nirsevimab is safe and efficacious, supporting the favorable benefit-risk of nirsevimab for the proposed indication.

1.1 Summary of Disease Background and Unmet Medical Need

Respiratory syncytial virus is the principal pathogen responsible for lower respiratory tract infections (LRTI) in infants and young children. Prevention of RSV illnesses in all infants is a major public health priority (Giersing et al 2019). Respiratory syncytial virus LRTI is the most common reason for admission to hospital in infants < 1 year of age. All children, including healthy term infants, are at risk for severe RSV LRTI with primary RSV infection during infancy. Overall, 72% of infants admitted to hospital with RSV LRTI are born at term and have no underlying serious comorbidity (Hall et al 2013 and Arriola et al 2020). Beyond their first RSV season, some children with serious underlying comorbidities remain vulnerable for severe RSV LRTI, including infants with prematurity, chronic lung disease (CLD), congenital heart disease (CHD), cystic fibrosis, neuromuscular conditions, Down syndrome, or immunocompromised states (Chaw et al 2020a, Chaw et al 2020b, Resch et al 2009, Manzoni et al 2017; AAP 2014).

Currently, there is no licensed RSV vaccine for children. Palivizumab (SYNAGIS®; USA approval 1998, EU approval 1999) is the only licensed product for RSV prophylaxis in infants who are at the highest risk for severe RSV disease (ie, preterm infants born at ≤ 35 weeks gestational age (wGA) and < 6 months of age at the start of the season, and children < 2 years of age with CLD of prematurity or hemodynamically significant CHD) (Synagis PI 2020, Synagis SmPC 2021). With a half-life of approximately one month, palivizumab must be administered monthly (intramuscular [IM] injection) throughout the RSV season, and the burden of repeated clinic visits can be a barrier to compliance (Wong et al 2018).

Further details are provided in Section 2.1

1.2 Nirsevimab Description and Mechanism of Action

Nirsevimab (MEDI8897) was designed to provide direct protection from RSV disease with a single dose timed to the RSV season. Nirsevimab is a recombinant, neutralizing, fully human IgG1κ long-acting monoclonal antibody (mAb) that provides passive immunization by binding to a highly conserved epitope on site Ø on the prefusion RSV F protein (that is distinct from the binding site of palivizumab), thereby inhibiting the essential membrane

fusion step in the viral entry process (Figure 5). Nirsevimab directly neutralizes RSV and blocks cell-to-cell fusion, with similar neutralization potency for RSV subtypes A and B. Nirsevimab has been modified with a triple amino acid substitution (YTE) in the fragment crystallizable (Fc) region to extend serum half-life. Further details are provided in Section 2.2.

The planned commercial nirsevimab drug product is a sterile liquid presented in pre-filled syringes containing either a 50 mg (0.5 mL) or 100 mg (1.0 mL) dose, intended for IM administration.

1.3 Proposed Indication and Dose

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

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

Nirsevimab should be administered from birth for infants born during the RSV season. For others born outside the season, nirsevimab should be administered ideally prior to the first RSV season.

A fixed dose by weight-band strategy is proposed for nirsevimab, to facilitate ease of use and implementation in the broad population. For infants entering their first RSV season, the recommended dose is a single fixed IM dose of 50 mg for infants with body weight < 5 kg or a single fixed dose of 100 mg for infants with body weight ≥ 5 kg. For children who remain vulnerable to severe RSV disease entering their second RSV season, the recommended dose is a single 200 mg dose given as two IM injections (2 x 100 mg).

Further details are provided in Section 2.3.

1.4 Nonclinical Summary

Nonclinical pharmacology and toxicology studies showed that nirsevimab potently neutralizes RSV and did not reveal any nirsevimab-related safety concerns. No evidence of enhancement of RSV disease was observed. Further details are provided in Section 2.4.2.

1.5 Nirsevimab Clinical Development Program

Two complementary placebo-controlled pivotal efficacy and safety studies were conducted in healthy infants: Trial 03 in preterm (≥ 29 to < 35 wGA) and Trial 04 in term and late preterm infants (≥ 35 wGA) (Section 4.1; Figure 12). Trial 05 compared nirsevimab to palivizumab (standard of care) in infants who were palivizumab-eligible being born preterm, and infants and children with CLD of prematurity or hemodynamically significant CHD (Figure 19).

Table 1 Pivotal Clinical Studies Supporting the Proposed Indication

Healthy and preterm infants		Infants and children at higher risk of severe RSV disease
Trial 03 (Study 3) Phase IIb pivotal [a]	Trial 04 (MELODY) Phase III pivotal [b, c]	Trial 05 (MEDLEY) Phase II/III pivotal [d]
Infants > 29 to < 35 wGA Not eligible for palivizumab under local guidelines	Infants ≥ 35 wGA	Preterm infants < 35 wGA Children < 24 months with CLD/CHD
2:1 nirsevimab: placebo	2:1 nirsevimab: placebo	2:1 nirsevimab: palivizumab
Efficacy, safety, PK		Safety, PK

[a] Griffin et al 2020. N Engl J Med. 383(5):415-425.
[b] Hammitt et al 2022 N Engl J Med. 386(9):837-846.
[c] Muller et al 2023 N Engl J Med. 388(16):1533-1534.
[d] Domachowske et al 2022 N Engl J Med. 386(9):892-894.
CHD = (hemodynamically significant) congenital heart disease; CLD = chronic lung disease (of prematurity); PK = pharmacokinetics; RSV = respiratory syncytial virus; GA = weeks gestational age.

1.6 Summary of Clinical Pharmacology

The proposed fixed dose by weight-band in RSV Season 1 (50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg), and 200 mg in Season 2, is supported by clinical pharmacology evaluations (Section 3).

- The pharmacokinetics (PK) of nirsevimab is dose proportional.
- The median time to maximum concentration of nirsevimab following IM administration was 6 days, based on adult data.
- The nirsevimab mean elimination half-life in infants is approximately 71 days, the elimination and distribution of nirsevimab increase with increasing body weight.
- Serum anti-RSV neutralizing antibody (nAb) concentrations correlate with nirsevimab serum concentrations, confirming the anti-RSV nAb activity of nirsevimab (Section 3.2).
- Clinical RSV nAb data provide support for the observed protective effect of nirsevimab for at least 5 months.
- Nirsevimab did not inhibit a natural immune response to RSV exposure.
- Exposure-response analyses support the proposed nirsevimab fixed dose by weight band (50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg) in the first RSV season, with a 200 mg dose proposed in children who remain vulnerable in RSV season 2 (based on expected body weight range) (Section 3.3).

1.7 Summary of Clinical Efficacy

The data from Trial 04 and Trial 03 in healthy infants, with supportive data from Trial 05 in higher risk infants, confirm the efficacy of a single dose of nirsevimab across a broad population of term and preterm infants entering their first RSV season (Section 4). The data from Trial 05 also support nirsevimab efficacy in children (aged ≤ 24 months) who remain vulnerable to severe RSV disease in their second RSV season.

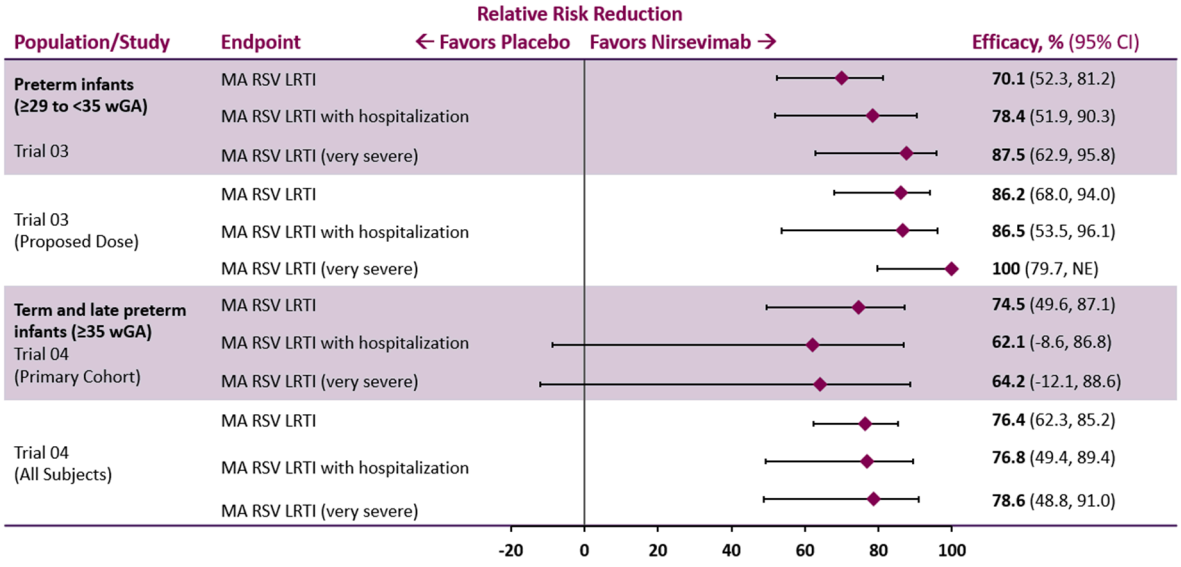
Trial 04 was conducted as a 2-part study, due to a requirement to pause enrollment in July 2020 due to the COVID-19 pandemic (Section 2.4.3.1). The study design was amended, and it was prespecified to conduct the primary analysis in data from subjects enrolled prior to the study pause, ie, in the Trial 04 (Primary Cohort). Once enrollment restarted in April 2021, subjects were recruited into a second cohort to complete the original planned sample size for Trial 04. Data from the 2 cohorts were collected in a double-blind manner and under the same protocol, with identical inclusion/exclusion criteria. An exploratory combined analysis of data was conducted from all-randomized subjects: Trial 04 (All Subjects) is the largest dataset available to evaluate the efficacy of nirsevimab against more severe forms of medically attended (MA) RSV LRTI in term and late preterm infants born ≥ 35 wGA (Section 4.1).

The following findings support the use of nirsevimab for all infants in their first RSV season:

- The primary endpoint was met in both Trial 03 (very and moderately preterm infants born ≥ 29 and < 35 wGA) and Trial 04 (term and late preterm infants born ≥ 35 wGA) (Section 4.2.2):
  - Nirsevimab demonstrated statistically significant efficacy against the primary endpoint, MA RSV LRTI, in Trial 03 and Trial 04 (Primary Cohort) (Figure 1)
  - This endpoint comprised the incidence of MA LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season (ie, through 150 days post dose)
  - Subgroup analyses support consistent efficacy of nirsevimab versus placebo across the study populations.
- The secondary endpoint, protection against MA RSV LRTI with hospitalization, was met in Trial 03 (Figure 1; Section 4.2.3).
- MA RSV LRTI with hospitalization (secondary endpoint) in Trial 04 (Primary Cohort) alone did not meet the criteria for statistical significance (p-value < 0.05).
  - Efficacy against MA RSV LRTI with hospitalization was supported by the analysis conducted in the larger analysis set incorporating all-randomized subjects, Trial 04 (All Subjects) (Figure 1).

- Nirsevimab efficacy was consistent against disease of increasing levels of severity, including MA RSV LRTI, MA RSV LRTI with hospitalization, and MA RSV LRTI (very severe) (Figure 1; Section 4.2.4).
- Nirsevimab efficacy was also consistent in the Trial 03, Trial 04 (Primary Cohort), and Trial 04 (All Subjects) (Figure 1).
- Time to event analyses showed clear divergence between nirsevimab and placebo curves in accumulation of events over the entire 150-day efficacy period indicating consistency of efficacy for nirsevimab throughout the course of a typical 5-month RSV season (Section 4.2.5).
- Efficacy findings are also supported by health resource utilization (HRU) data, with lower percentages of subjects being admitted to hospital or intensive care unit (ICU), reduced requirement for respiratory support or supplementary oxygen, and fewer outpatient visits with nirsevimab versus placebo (Section 4.2.6).
- Protection was also observed against all-cause MA LRTI and all-cause respiratory illness with hospitalization (Section 4.2.6).

Figure 1 **Nirsevimab Efficacy in Term and Preterm Infants Born ≥ 29 WGA Entering Their First RSV Season – Trial 03 and Trial 04**



Efficacy estimates are based on follow-up through 150 Days post dose.
Please see Table 6: Summary of Case Definitions for Assessment of Efficacy.
CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; NE = not evaluated; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus; wGA = weeks gestational age.

For infants at higher risk of severe RSV disease in their first season and children remaining vulnerable to severe RSV disease in their second season, efficacy was extrapolated from healthy infants based on comparable PK, an approach agreed to with the FDA. Based on

comparable PK, a similar level of protection is anticipated in children at higher risk for severe RSV disease. These include infants born extremely preterm (< 29 wGA) and children with CLD and/or hemodynamically significant CHD aged ≤ 24 months of age (Section 4.3).

1.8 Summary of Clinical Virology

Clinical virology assessments in the nirsevimab clinical development program demonstrated that:

- Nirsevimab has clinical efficacy against RSV A and B subtypes (Section 5.1).
- Nirsevimab neutralized > 99% of RSV sequences across all clinical studies (Section 5.1).
- Monoclonal antibody escape is rare in circulating strains, as determined in global molecular surveillance studies (Section 5.2).

1.9 Summary of Clinical Safety

A total of 3620 infants and children were dosed with nirsevimab across the pivotal studies (Trial 03, Trial 04, Trial 05). Of these, 3224 subjects received the proposed dose regimen. Safety was monitored through 360 days post dose (in each season for Trial 05), corresponding to 5 half-lives for nirsevimab elimination. Adverse events of special interest (AESI) for the development program included immediate hypersensitivity (including anaphylaxis), immune complex disease, and thrombocytopenia.

The overall safety package supports a favorable safety profile for nirsevimab and includes:

- All infants in their first RSV season (50 mg or 100 mg dose) based on exposure in 3580 infants (3184 receiving the proposed dose) from Trial 03, Trial 04, Trial 05. The data presented for infants dosed in their first RSV season from these pivotal trials included a median duration of safety follow-up of 361 days (in both the overall population and the proposed-dose population), as of the data cut off for the BLA submission.
- Children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season (200 mg dose), based on 220 children with CHD/CLD dosed with nirsevimab in their second RSV season in Trial 05 (including 180 children who received a second dose of nirsevimab and 40 children who received a first dose of nirsevimab in Season 2). The data presented for children dosed in their second RSV season (all of whom received the proposed Season 2 dose) included a median duration of safety follow-up of 250 days following the Season 2 dose, as of the data cut off for the BLA submission.

Safety in Healthy Term and Preterm Infants

Overview of Adverse Events

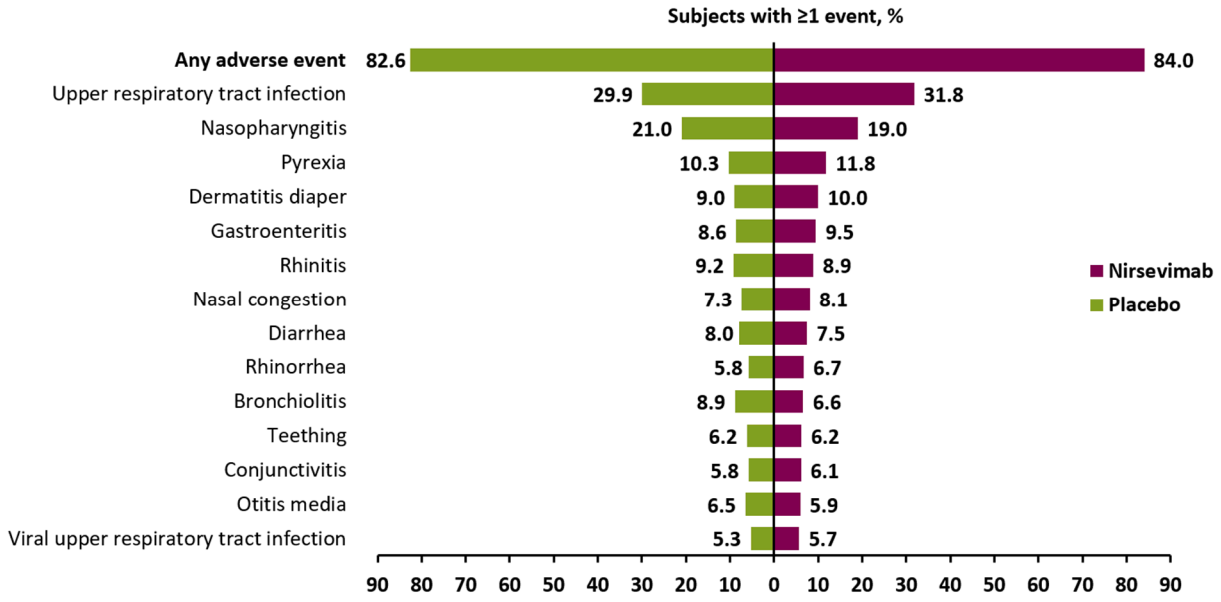
In healthy term and preterm infants born ≥ 29 wGA, the safety of nirsevimab was evaluated in comparison to placebo, based on pooled analyses of data from dosed subjects in Trial 03 and Trial 04. In the Proposed-Dose Safety Pool (recipients of the proposed dose of nirsevimab including Trial 04 [All Subjects] and Trial 03 subjects < 5 kg at dosing/Day 1), the percentage of subjects with adverse events (AEs) in the nirsevimab group was generally comparable to those in the placebo group across the event categories (Table 2). The most common AEs by Preferred Term are listed in Figure 2.

Table 2 Overview of Safety in Healthy Term and Preterm Infants Through at Least Day 150 Post Dose: Proposed-Dose Safety Pool

	Subjects with ≥ 1 event, n (%)	
	Placebo (N = 1284)	**Nirsevimab (N = 2570)**
Any AE	1060 (82.6)	2158 (84.0)
Any AE related to IP	18 (1.4)	33 (1.3)
AE ≥ Grade 3	81 (6.3)	102 (4.0)
AE ≥ Grade 3 related to IP	1 (< 0.1)	1 (< 0.1)
Serious AE	135 (10.5)	195 (7.6)
Serious AE related to IP	1 (< 0.1)	0
Death (none considered IP related)	3 (0.2)	6 (0.2)
AEs of special interest [a] (Investigator assessment)	0	6 (0.2) [b]
New Onset of Chronic Disease (none considered IP related)	4 (0.3) [c]	3 (0.1) [d]

[a] AESIs defined as Type I hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease.
[b] Observed events were all skin and subcutaneous tissue disorders and considered IP related: rash (2 subjects), rash maculopapular (2 subjects), petechiae (1 subject), and rash papular (1 subject).
[c] Observed events were hypothyroidism (2 subjects), bronchitis chronic (1 subject), childhood asthma (1 subject).
[d] Observed events were PFAPA syndrome (1 subject), asthma (2 subjects).
AEs were graded according to Common Terminology Criteria for Adverse Events (CTCAE).
AE = adverse event; IP = investigational product; N = number of subjects; n = number of subjects with event.
PFAPA = Periodic Fever, aphthous stomatitis, pharyngitis, adenitis.

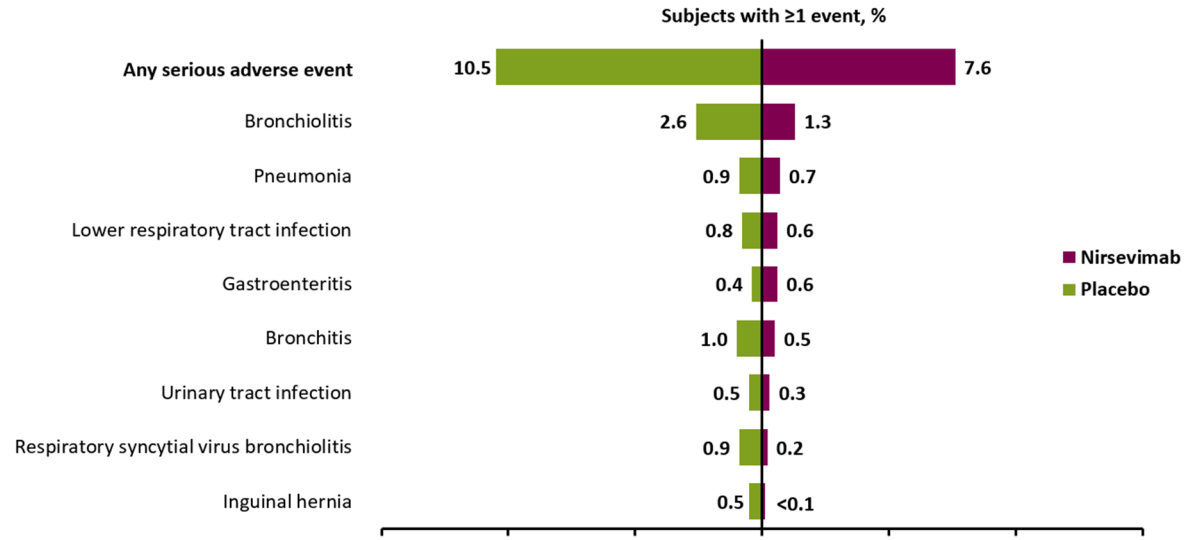
Figure 2 **Most Frequent Treatment-Emergent Adverse Events (≥ 5% of Subjects) Through at Least Day 150 Post Dose (Proposed-Dose Safety Pool)**



A similar percentage of subjects in the nirsevimab and placebo groups had AEs of ≥ Grade 3 severity (4.0% and 6.3%, respectively) and SAEs (7.6% and 10.5%, respectively).

The most common SAEs by Preferred Term are listed in Figure 3.

Figure 3 **Most Frequent Treatment-Emergent Serious Adverse Events (≥ 0.5% of Subjects) Through at Least Day 150 Post Dose (Proposed-Dose Safety Pool)**



Deaths occurred with the same incidence (0.2%) in the nirsevimab (6 subjects) and placebo group (3 subjects) and none were considered related to investigational product (IP). Based on investigator assessment, AESIs occurred with a low incidence (0.2%) in 6 subjects in the nirsevimab group, all of which were assessed as non-serious hypersensitivity events limited to cutaneous findings and considered related to IP (ie, IP-related skin hypersensitivity reactions); events were mild to moderate severity with the exception of a single Grade 3 severity rash with onset 6 days post dosing which resolved after 3 weeks without treatment.

Further details of safety in healthy term and preterm infants born ≥ 29 wGA are provided in Section 6.3.1.

Safety in Infants at Higher Risk and Children Who Remain Vulnerable in Their Second RSV Season

At data cut off, AEs were analyzed through 360 days post first dose (ie, first IP dose in the respective season/active nirsevimab dose for nirsevimab recipients) for Trial 05 Season 1 and through at least 150 days post first IP dose for Season 2.

Trial 05 Season 1 and Season 2

In the Trial 05 population in Season 1, the frequency of AEs through 360 days post first dose was similar between the nirsevimab and palivizumab groups in the preterm and CLD/CHD cohorts (Table 3). In the overall population, the majority of AEs were mild or moderate in severity. The AESIs occurred with a low incidence in 3 subjects in the nirsevimab group; an event of nonserious IP-related skin hypersensitivity reaction of Grade 1 severity in a subject in the preterm cohort temporally associated with a placebo dose (92 days post active nirsevimab dose) after which the subject was discontinued from IP, and 2 events of nonserious thrombocytopenia (Grade 1-2 severity) occurred in 2 subjects with CHD considered unrelated to IP. Six deaths were reported in the Preterm and CLD/CHD cohorts none of which were considered related to IP; all these subjects had serious underlying comorbidities at baseline.

Table 3 Safety in Trial 05 (Season 1): Preterm Infants ≤ 35 wGA and Infants with CHD or CLD Through At Least Day 360 Post First Dose

Subjects with ≥ 1 event, n (%)	Preterm Cohort		CHD/CLD Cohort	
	Palivizumab N = 206	Nirsevimab N = 406	Palivizumab N = 98	Nirsevimab N = 208
Any AE	141 (68.4)	287 (70.7)	74 (75.5)	157 (75.5)
Any AE related to IP	4 (1.9)	6 (1.5)	2 (2.0)	4 (1.9)
AE Grade ≥ 3	8 (3.9)	18 (4.4)	17 (17.3)	32 (15.4)
AE Grade ≥ 3 related to IP	0	0	0	0
SAE	13 (6.3)	35 (8.6)	25 (25.5)	45 (21.6)
SAE related to IP	0	0	0	0
AE leading to discontinuation of IP	0	1 (0.2)	0	0
Death	0	2 (0.5)	1 (1.0)	3 (1.4)
AEs of special interest [b] by investigator assessment	0	1 (0.2) [c]	0	2 (1.0) [c]

[a] Relative to the active nirsevimab dose for subjects in palivizumab group.
[b] AESIs defined as Type I hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease.
[c] Observed events were an IP-related skin hypersensitivity event of rash maculopapular (preterm cohort) and unrelated thrombocytopenia (2 subjects with CHD).
AE = adverse event; AESI = AE of special interest; CHD = congenital heart disease (hemodynamically significant); CLD = chronic lung disease (of prematurity); IP = investigational product; SAE = serious adverse event; wGA = weeks gestational age.

In Trial 05, 262 subjects in the CLD/CHD cohort continued to the Season 2 phase of the study. In Season 2, through at least 150 days post first IP dose, the frequency of AEs was 70.0%, 72.5%, and 69.0%, in the nirsevimab/nirsevimab, palivizumab/nirsevimab, and palivizumab/palivizumab groups (so named to indicate the Season 1 and Season 2 treatment groups), respectively. There were no deaths, IP-related AEs, or AESIs in any subjects. Notably no hypersensitivity was reported in 180 subjects who received a repeat dose of nirsevimab in Season 2 (nirsevimab/nirsevimab group) or any other treatment group.

Further details of safety in Trial 05 are provided in Section 6.3.2.

Overall Safety Conclusions

The safety of nirsevimab for all infants in their first RSV season and for children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season is supported by:

- The size of the safety database and the duration of follow-up as per FDA guidance to allow adequate assessment of the safety profile of nirsevimab as prophylaxis against RSV LRTI in the first and second RSV seasons.

- A favorable safety profile was observed for nirsevimab (50 mg or 100 mg) across the diverse populations of infants entering their first RSV season and for nirsevimab (200 mg) in children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season (Section 6.3 through Section 6.10).
- Adverse events of special interest were reported in a few subjects in the nirsevimab groups (Section 6.7) and nearly all events were mild to moderate in severity. None were SAEs and none of the subjects with AESIs had any post baseline ADA detected with samples available for analysis.
  - Hypersensitivity events were limited to cutaneous findings. All but one of the events were mild to moderate in severity; a single nonserious Grade 3 event of rash occurred 6 days post dose and resolved after 3 weeks without treatment. Notably, no hypersensitivity was observed with a repeat dose of nirsevimab in a second season. Per investigator assessment, there were no anaphylaxis or other serious allergic reaction attributed to IP.
  - No thrombocytopenia was attributed to nirsevimab. Two unrelated nonserious thrombocytopenia events of mild to moderate severity were reported in Trial 05 subjects with CHD in Season 1.
  - No AESIs of immune complex disease were reported in any participant.
- No SAEs were considered related to nirsevimab (Section 6.4).
- None of the deaths reported in the nirsevimab or comparator groups were considered by the Investigator to be associated with IP administered and none were known or reported to be due to RSV. Deaths were attributed to underlying conditions or common causes of infant mortality in the respective country or region where the subject was enrolled (see Section 6.5).
- There was no evidence to support the theoretical risk of antibody-dependent enhancement of disease based on evidence of efficacy across the spectrum of disease severity and follow-up through a second RSV season without additional RSV prophylaxis (Trial 04): no increase in the disease incidence of MA RSV LRTI was observed in the second season and no increased severity of disease for infants who reported MA RSV LRTI and had received nirsevimab compared with placebo recipients (Section 6.9).
- Since nirsevimab is a mAb mediating a passive immunization specific for RSV, it is not expected to interfere with the active immune response to co-administered routine childhood vaccines (Esposito et al 2021). In the small number of infants during the clinical trials who were given nirsevimab with routine childhood vaccines, the safety and reactogenicity profile of the co-administered regimen was similar to the childhood vaccines given without nirsevimab (Section 6.10).

1.10 Summary of Immunogenicity

- Across the nirsevimab clinical program, the incidence of anti-drug antibodies (ADA) to nirsevimab was low (approximately 6%).
- ADA had no discernible effect on PK through Day 151, efficacy, or safety (Section 7).

1.11 Benefit-Risk Assessment

- All children, including healthy term infants, are at risk for severe RSV LRTI with primary RSV infection during infancy. It is estimated that RSV causes up to 90% of childhood bronchiolitis and up to 40% of pediatric pneumonias (Hall, 2001).
- There is no licensed vaccine for RSV in infants, and the only prophylaxis available (palivizumab, licensed over 20 years ago) is limited to preterm infants or infants with CLD or CHD, leaving the broader population of infants unprotected.
- Therefore, there is a clear unmet medical need for interventions to provide protection from RSV lower respiratory tract disease in all infants in their first RSV season.
- The pivotal studies established that a single IM dose of nirsevimab provides effective protection from RSV LRTI for all infants in their first RSV season, with consistent levels of efficacy demonstrated across populations (ie, term or late preterm infants born ≥ 35 wGA and very and moderately preterm infants born ≥ 29 to < 35 wGA) and disease severities.
- Based on comparable PK, a similar level of protection is expected in infants born < 29 wGA in their first RSV season, and in children up to 24 months of age at higher risk of severe RSV disease in their first and second RSV season, including those with CHD and/or CLD of prematurity.
- A single IM dose of nirsevimab (50/100 mg weight-band dose for infants entering RSV Season 1 or 200 mg fixed dose for children up to 24 months of age entering RSV Season 2) was well tolerated with no apparent safety concerns.
- Across all infant subpopulations, there were no reported AESIs of anaphylaxis, thrombocytopenia, or immune complex disease attributed to nirsevimab.
- Adverse drug reactions assessed as having a reasonable possibility of a causal association with nirsevimab and noted in the proposed prescribing information include rash within 14 days post dose, and injection site reaction and pyrexia within 7 days post dose.
- There are no anticipated risks associated with concomitant administration of nirsevimab and routine pediatric vaccines, including the influenza vaccine.
- Based on the favorable efficacy and safety profile across the broad population of infants entering their first RSV season and in children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season, combined with the advantage of a single dose, nirsevimab offers the ability to provide protection against

RSV lower respiratory tract disease and significantly reduce the disease burden for all infants.

2 BACKGROUND INFORMATION

2.1 RSV Disease and Unmet Medical Need

2.1.1 RSV Disease in Infants and Children

Respiratory syncytial virus is the most common cause of LRTI among infants and young children globally and is the major cause of hospital admission, with an estimated 33 million clinical cases and 3.6 million hospitalizations in children < 5 years of age in 2019 (Li et al 2022; Figure 4). While the mortality rate due to RSV infection is low in high-income countries, inpatient disease burden is high, with the greatest burden occurring in young infants. It has been estimated that, in the absence of immunization, there are ~590000 cases of MA RSV LRTI annually among US infants (Rainisch et al 2020). Epidemiological and molecular studies have classified RSV into 2 highly divergent phylogenetic subgroups (RSV A and RSV B), which co-circulate with alternating predominance (Baek et al 2012, Komoyo et al 2021, Reiche and Schweiger 2009, Venter et al 2001).

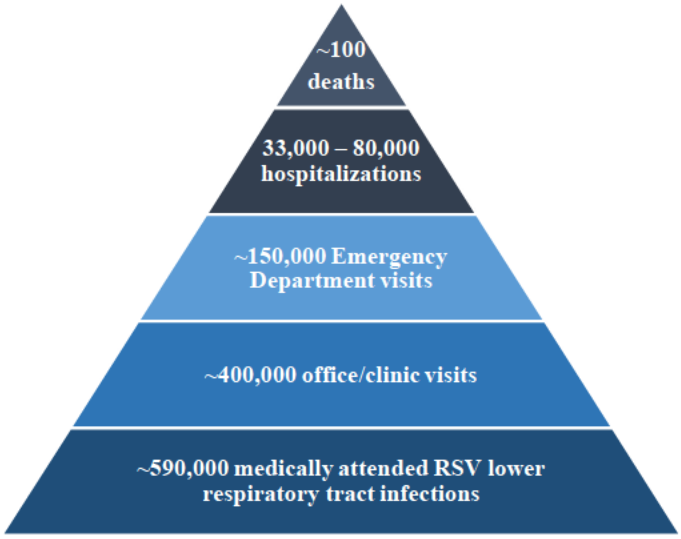
In the USA, RSV is estimated to cause up to 90% of cases of childhood bronchiolitis and up to 40% of pediatric pneumonias (Hall, 2001). In infants < 1 year of age, mean hospitalization rates for RSV infection in the US were 16 times higher than rates for influenza viral infections (Zhou et al 2012). Among children 0 to 3 years of age, RSV hospitalization rates were found to be 4 and 9 times greater than the hospitalization rates associated with parainfluenza and influenza viral infections, respectively (Forster et al 2004). Furthermore, the excess respiratory mortality rate among infants in the US was 5-fold higher for RSV versus influenza (Hansen et al 2022).

Respiratory syncytial virus LRTI is a serious and potentially life-threatening disease characterized by infection and inflammation of the alveoli and bronchioles. It is associated with necrosis and sloughing of the epithelium of the small airways, with edema and increased secretion of mucus. This can lead to airway obstruction and a typical clinical picture of hyperinflation, atelectasis, and wheezing (Hall, 2001). It is most severe when the disease occurs in the first year of life associated with smaller airway diameter in infants. Known factors increasing the risk of hospitalization with RSV include male sex, age under 6 months, crowding, siblings, and day-care exposure (Bont et al 2016).

All infants are at risk of RSV disease requiring medical intervention. Respiratory syncytial virus LRTI is the most common reason for admission to hospital in infants < 1 year of age (Hall, 2001, Hall, 2012, Murray et al 2014, Rha et al 2020). The majority of infants admitted to hospital with RSV LRTI are born at term and have no underlying serious comorbidity, as illustrated by data from Europe and North America (Hall, 2012, Murray et al 2014, Bont et al 2016, Rha et al 2020; Hall et al 2013; Arriola et al 2020).

Approximately 1 in 7 infants develop an RSV LRTI and receive medical attention annually in the USA (Rainisch et al 2020). The burden of disease resides among otherwise healthy infants born at term in whom RSV severity is unpredictable.

Figure 4 RSV Burden of Disease in the United States in the First Year of Life



Source: Reeves et al 2020, Bont et al 2016

In addition to the considerable hospitalization burden among infants, there is also a substantial outpatient burden, extending throughout the first year of life (Lively et al 2019, Forster et al 2004). Disease managed in the outpatient setting is almost as severe as that in the hospital setting, with labored respiration in 73% and 85% of children with office or emergency room visits, respectively (Hall et al 2009). In a study in the USA, RSV accounted for 18% of emergency room visits and 15% of outpatient visits for acute respiratory infections in children < 5 years of age during the RSV season (Hall et al 2009). In England, among children < 5 years of age, 16% of all general practitioner consultations for acute respiratory illness throughout the year were attributed to RSV (Cromer et al 2017). Additionally, absenteeism and work impairment in working parents of infants < 1 year of age hospitalized for RSV leads to higher socioeconomic cost (Heikkinen et al 2017, Mitchell et al 2017, Pokrzywinski et al 2019).

Controlling RSV disease in infants may have additional benefits that become apparent in the long-term. Infant RSV LRTI is associated with long-term respiratory morbidity (eg, wheezing, asthma, and impaired lung function in adult life). Long-term studies prospectively following cohorts from infancy until childhood suggest an association between a history of RSV bronchiolitis in infancy with an increased incidence of subsequent wheezing episodes and/or development of asthma (Escobar et al 2013, Pérez-Yarza et al 2007, Romero et al 2010, Ruotsalainen et al 2010, Sigurs et al 2005; Billard and Bont 2023).

2.1.2 Infants at Higher Risk and Children Who Remain Vulnerable to Severe RSV Disease in Their Second Season

Lung immaturity, impaired vascular or pulmonary function, inability to clear secretions, or immunocompromised states can all exacerbate the pathophysiology of RSV LRTI and increase the severity of the disease (Chaw et al 2020a, Chaw et al 2020b). Multiple pre-existing medical conditions, including chromosomal abnormalities, cardiac lesions, neuromuscular disease, CLD, airway abnormality, and immunodeficiency, are associated with a significantly higher risk of severe disease and death from severe RSV infection (Manzoni et al 2017, Chaw et al 2020a, Chaw et al 2020b, Resch et al 2009, Thorburn 2009).

Children with CHD experiencing RSV LRTI have increased rates of RSV-associated hospitalization (IRR 2.8) and case fatality (RR 16.5) compared to children without CHD (Chaw et al 2020a). They also frequently require more aggressive treatment, including ICU admission (RR 3.9), supplemental oxygen therapy (RR 3.4), and mechanical ventilation (RR 4.1) (Chaw et al 2020a).

Similarly, children with CLD of prematurity experiencing RSV LRTI have increased rates of hospitalization (OR 2.6) and case fatality (OR 12.8), with more frequent requirement for ICU admission (RR 2.9), supplemental oxygen therapy (OR 4.2), and mechanical ventilation (OR 8.2) compared to children without these conditions (Chaw et al 2020b).

Immunocompromised children may experience particularly severe disease, with prolonged hospitalization and high ICU admission rates (Asner et al 2013, Moyes et al 2013, Manzoni et al 2017). Furthermore, RSV-associated mortality rates can reach 60% in untreated children with immunodeficiencies, compared to < 0.5% in healthy infants with RSV (Asner et al 2013, Moyes et al 2013).

Other children at increased risk of severe RSV disease include those with Down syndrome, cystic fibrosis, or neurological/neuromuscular disorders (Table 4).

These vulnerable populations need protection against RSV.

Table 4 Other Medical Conditions Associated with Increased Risk of Severe RSV Disease in Children

Condition	Impact of RSV disease
Immunocompromised children (Asner et al 2013, Moyes et al 2013, Manzoni et al 2017)	RSV-associated mortality rates (Asner et al 2013, Moyes et al 2013): • Up to 60% in untreated children with immunodeficiencies vs < 0.5% in healthy infants with RSV RSV-associated hospitalization rates (immunocompromised children/young adults) (Manzoni et al 2017): • 11–187 per 1000 • Average of 6–10 days hospitalization with • Up to 29% admitted to ICU • Up to 21% requiring intubation and/or mechanical intervention HIV-infected vs non-infected children (Moyes et al 2013): • 3–5-fold increased risk of hospitalization for acute RSV LRTI • Higher odds of death (adjusted OR 31.1; 95% CI 5.4–179.8) • Higher odds of hospitalization for > 5 days (adjusted OR 4.0; 95% CI 1.5-10.6)
Down syndrome (Manzoni et al 2017)	Risk factor for RSV hospitalization, even when concomitant risk factors (CHD and prematurity) are excluded: • Rate ratio: 3.5–10.5 in children < 3 years vs otherwise healthy children • RSV hospitalization rate: 70–195 per 1000 children • Increased severity of disease, longer duration of hospital stays, and greater risk of respiratory support (intubation and/or mechanical ventilation) versus otherwise healthy children
Cystic fibrosis (Manzoni et al 2017)	Risk factor for RSV hospitalization: • Rate ratio: 2.5–4.3 in children < 2 years versus otherwise healthy children • RSV hospitalization rate: 64–181 per 1000 children • RSV morbidity (length of hospital stay, ICU, mechanical ventilation) in children with various forms of underlying lung disease (including cystic fibrosis) similar to those with CLD
Neurological and neuromuscular disorders, congenital malformations; other chronic conditions (Manzoni et al 2017)	Neurological and neuromuscular conditions (including spina bifida, cerebral palsy, and muscular dystrophy) associated with: • Significantly increased risk of RSV hospitalization ($p < 0.05$) and increased morbidity ($p < 0.05$) Other congenital malformations and chronic conditions: • Significantly increased risk of RSV hospitalization ($p < 0.05$)

CHD = congenital heart disease; CI = confidence interval; CLD = chronic lung disease; HIV = human immunodeficiency virus; ICU, intensive care unit; LRTI = lower respiratory tract infection; OR = Odds ratio; RSV = respiratory syncytial virus.

2.1.3 RSV LRTI Seasonality

Respiratory syncytial virus occurs in largely predictable annual epidemics. Globally, RSV activity shows a latitudinal gradient in the timing of epidemics in each hemisphere (Li et

al 2019). Generally, RSV transmission in the USA is predominant from October to March, peaking in January (Li et al 2019). The median duration of RSV activity in the USA ranges 11 to 17 weeks, varying by geographical region.

Unusually, RSV activity dramatically declined globally during the 2020/2021 season, as COVID-19 mitigation measures impacted RSV circulation. As exposure decreased, there was a consequent increase in the susceptible population of infants and children who did not have the typical level of exposure during the COVID-19 restrictions. Epidemiological models predicted that this increase in RSV susceptibility would affect the timing and increase the severity of future RSV incidence (Baker et al 2020). Such off-season outbreaks occurred widely (CDC 2021a, CDC 2021b, Ujiie et al 2021, van Summeren et al 2021, Williams et al 2021). Potential drivers of RSV rebound and out-of-season epidemics included re-opening of schools and increased population susceptibility (Li et al 2022). RSV circulation data for the 2022/2023 RSV season in the USA indicates a return to pre-COVID-19 pandemic seasonality (CDC 2023).

Seasonal surges in RSV infection place intense pressure on primary care, emergency department, and pediatric critical care services (ACPRC 2021). In data from Europe and North America for infants < 2 years of age hospitalized with RSV, the median length of hospital stay ranged from 2 to 12 days, with ~ 2% to 12% of infants admitted to the intensive care unit (Bont et al 2016). Data shows annual demand for pediatric intensive care peaks in November and December, driven largely by unplanned admissions due to respiratory infections such as bronchiolitis and pneumonia primarily in infants < 1 year of age (NHS 2017). This can be impactful, leading to the delay of elective surgery in children in the winter months.

2.1.4 Current RSV Therapies and Unmet Medical Need

Management of RSV infection as an outpatient is essentially supportive with the maintenance of hydration. Inpatient treatment of RSV infection in an infant who has been hospitalized may include oxygen supplementation, or respiratory support by CPAP, HFNC, or mechanical ventilation, depending on the severity of the respiratory compromise (Baraldi et al 2014, Turnham et al 2017).

The only approved treatment for severe RSV disease is ribavirin for inhalation, licensed in several EU countries, the United Kingdom, and the USA (EMA 2018, UKHSA 2021, Virazole PI, 2019, Martindale, 2021). It is a synthetic guanosine nucleoside analogue that inhibits RSV replication and needs to be initiated early in the course of the disease. Ribavirin has a number of limitations, including the need for prolonged aerosol administration, potential toxic effects among exposed healthcare personnel, and cost. More importantly, efficacy has not been established due to limited clinical study data (Hoover et al. 2018) and its use is not recommended.

Prevention of RSV illnesses in all infants is a major public health priority (Giersing et al 2019). While non-pharmaceutical interventions may temporarily reduce RSV incidence, as observed in response to the COVID-19 pandemic, they are not a sustainable long-term preventive approach. Despite more than 60 years of attempted vaccine development (Ruckwardt et al 2019), there is no licensed vaccine for prevention of RSV disease in infants.

The only currently approved prophylaxis for RSV in pediatric populations is palivizumab (SYNAGIS®; US approval 1998, EU approval 1999), licensed only for infants who are at the highest risk for severe RSV disease (ie, preterm infants born at ≤ 35 wGA and < 6 months of age at the start of the season, and children < 2 years of age with CLD of prematurity or hemodynamically significant CHD) (Synagis PI 2020, Synagis SmPC 2021). Palivizumab is a humanized RSV mAb directed against the F protein of RSV (Johnson et al 1997). The site of the F protein targeted by palivizumab is distinct from the site targeted by nirsevimab (Section 2.2). With a half-life of approximately one month, palivizumab must be administered monthly (IM injection) throughout the RSV season. The burden of monthly healthcare visits during the season can be a barrier to compliance, diminishing the benefits of palivizumab (Wong et al 2018). The American Academy of Pediatrics guidance for use of palivizumab is more restrictive than the US Prescribing Information, with palivizumab recommended only for use in a limited population of infants at high risk (AAP 2014); its effect on the total disease burden of RSV infection is therefore limited.

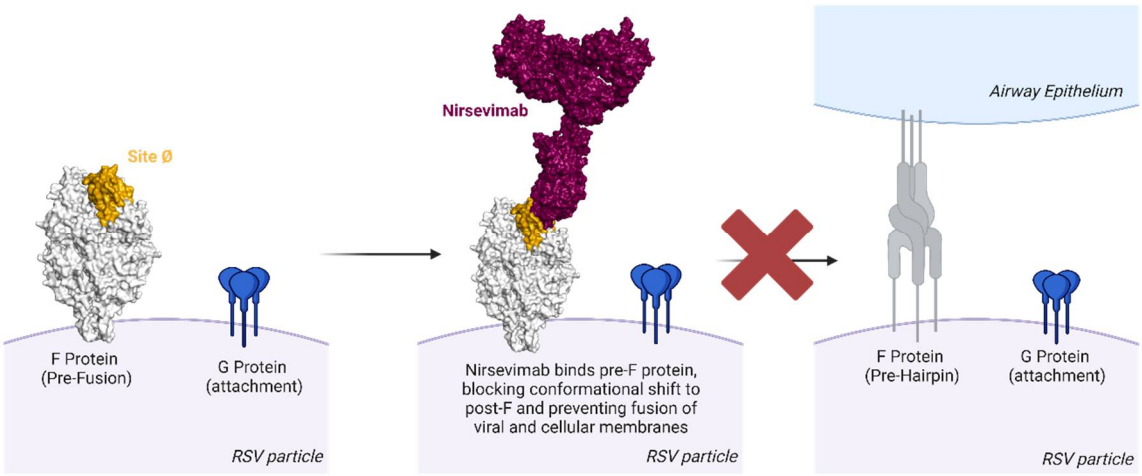
In summary, there is no approved prophylaxis or recommended treatment for RSV for the general infant population and most infants have no specific protection against RSV.

2.2 Nirsevimab Description and Mechanism of Action

Nirsevimab (MEDI8897) was designed to provide direct protection from RSV disease with a single dose timed to the RSV season. Nirsevimab is a recombinant, neutralizing, fully human IgG1κ long-acting monoclonal antibody (mAb) that provides passive immunization by binding to a highly conserved epitope on site Ø on the prefusion RSV F protein (that is distinct from the binding site of palivizumab), thereby inhibiting the essential membrane fusion step in the viral entry process (Figure 5). Nirsevimab directly neutralizes RSV and blocks cell-to-cell fusion. Nirsevimab has been modified with a triple amino acid substitution (YTE) in the fragment crystallizable (Fc) region to extend serum half-life. Nirsevimab has similar neutralization EC_{50} values for RSV subtypes A and B strains (3.2 and 2.9 ng/mL, respectively).

Nirsevimab is engineered with a triple amino acid (M252Y/S254T/T256E[YTE]) substitution within its Fc region. The YTE substitution enhances the binding of nirsevimab to the neonatal Fc receptor (FcRn) under the acidic conditions (pH 6.0) of the lysosome. This prevents degradation and increases recirculation to the surface of the cell, thereby prolonging the serum half-life of the antibody (Dall'Acqua et al 2006).

Figure 5 Nirsevimab Mechanism of Action Involves Inhibition of Conformational Shift of Pre-F Protein, Preventing Viral Membrane Fusion



2.3 Proposed Indication and Dose

AstraZeneca (the Sponsor) seeks marketing approval of nirsevimab for the following indication and posology.

2.3.1 Proposed Indication

Nirsevimab is indicated for the prevention of RSV lower respiratory tract disease in:

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

2.3.2 Dosage and Administration

Nirsevimab is intended for administration by a healthcare provider. Nirsevimab should be administered from birth for infants born during the RSV season. For others born outside of the season, nirsevimab should be administered ideally prior to the RSV season. For infants entering their first RSV season, the recommended dose is a single fixed IM dose of 50 mg for infants with body weight < 5 kg and a single fixed dose of 100 mg for infants with body weight ≥ 5 kg. Children who remain vulnerable to severe RSV disease entering their second RSV season, the recommended dose is a single 200 mg dose given as two IM injections (2 x 100 mg).

The planned commercial nirsevimab drug product is a sterile liquid presented in a pre-filled syringe containing either 50 mg (0.5 mL) or 100 mg (1.0 mL), for IM injection intended for administration by a healthcare provider.

2.4 Nirsevimab Development Program

2.4.1 Regulatory Actions and Marketing History

Nirsevimab was granted Fast Track and Breakthrough Therapy designations by the US FDA. Nirsevimab was approved for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season in the European Union on 31 October 2022 and in Great Britain on 07 November 2022. Health Canada approved nirsevimab on 19 April 2023 for the prevention of RSV lower respiratory tract disease in neonates and infants 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. Nirsevimab is not currently marketed in any country or region; therefore, no post-marketing data are available.

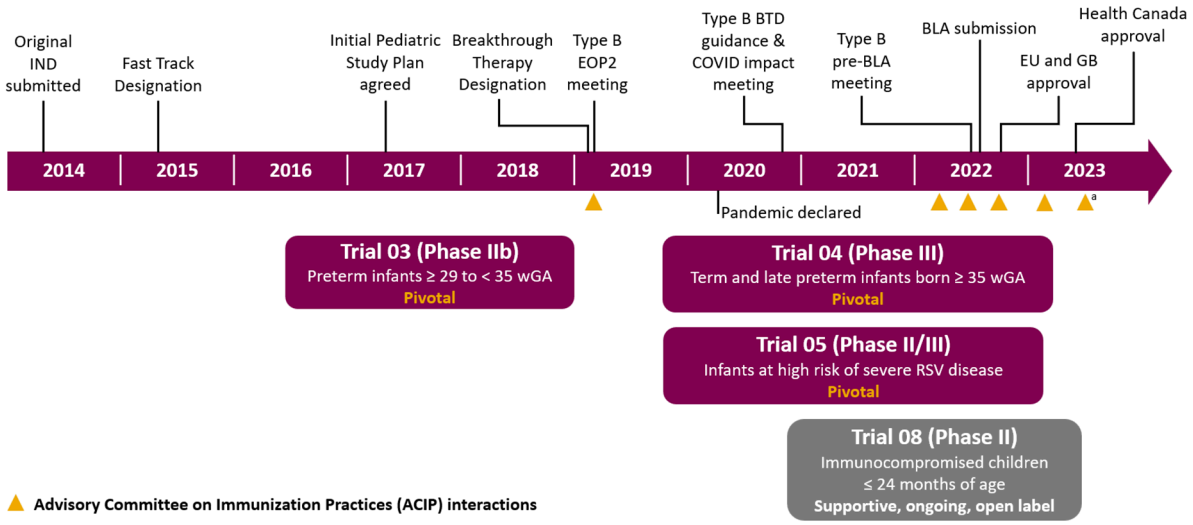
Summary of Interactions with Food and Drug Administration

During the clinical development of nirsevimab, multiple regulatory consultations took place with the US FDA (Figure 6) and other regulatory authorities (European Medicines Agency, Japan Pharmaceuticals and Medical Devices Agency, UK Medicines and Healthcare products Regulatory Agency, China Center for Drug Evaluation of NMPA). The following key topics were discussed and agreed with the FDA:

- The proposed dosing regimen for the pivotal studies
- The final pivotal study designs, including study population, efficacy endpoints, the MA RSV LRTI case definition, and statistical analysis plans
- The extrapolation of efficacy via PK to the high-risk Trial 05 pediatric study population
- The viral resistance monitoring plan
- The safety analyses and data package expected to support licensure

An initial Pediatric Study Plan (iPSP) was agreed with the FDA for immunization of all infants entering their first RSV season and children with CLD or CHD entering their first and second RSV season for prevention of LRTI caused by RSV. The agreed iPSP includes a partial waiver for preterm and term infants > 12 months of age and for infants with CLD and CHD > 24 months of age (dated 28 April 2017, Reference ID: 4090237).

Figure 6 Key Regulatory and Policy Milestones in Nirsevimab Clinical Development



[a] Planned meeting in June

BLA = Biologics License Application; BTD = Breakthrough Therapy Designation; COVID = coronavirus disease; EU = European Union; GB = Great Britain; IND = Investigational New Drug application.

Nirsevimab data have also been presented and discussed with the Advisory Committee on Immunization Practices (ACIP) to facilitate recommendations and use in the USA.

2.4.2 Nonclinical Overview

Nonclinical pharmacology studies showed that nirsevimab potently neutralized RSV A and B subtypes in vitro, with more than 150-fold greater potency than palivizumab. Nirsevimab also provided rapid and complete protection from viral replication in a nonclinical model of RSV infection, demonstrating 11-fold higher potency than palivizumab for RSV A2 infection and 9-fold higher potency for RSV B9320 infection.

Nirsevimab was evaluated in a comprehensive toxicology program that included a 1-month repeat IV and IM dose toxicity study at doses up to and including 300 mg/kg IV or 300 mg IM, and two Good Laboratory Practice human tissue cross-reactivity studies. Results from the repeat-dose toxicity study demonstrated no adverse local or systemic effects of nirsevimab; and the no observed adverse effect level was 300 mg/kg IV and 300 mg IM. Results from tissue cross-reactivity studies showed that nirsevimab did not cross-react with any human tissues.

The potential for antibody-dependent enhancement (ADE) of RSV infection was evaluated in a nonclinical model of RSV infection. No evidence of enhancement of RSV infection was observed at any dose evaluated, including sub-efficacious doses.

Overall, data from these nonclinical studies showed nirsevimab potently neutralized RSV and did not reveal any nirsevimab-related safety concerns. These results supported further clinical development of nirsevimab.

2.4.3 Clinical Development Overview

The clinical data with nirsevimab included in the BLA for licensure was generated across a program of 6 studies (Table 5). The pivotal clinical program includes 2 complementary, pivotal, double-blind, placebo-controlled, randomized studies that evaluated the efficacy, safety, PK and immunogenicity of nirsevimab in infants in their first RSV season (Trial 03; Trial 04), and a third pivotal, randomized trial compared nirsevimab with palivizumab in children at higher risk for severe RSV disease through their second season (Trial 05). These 3 pivotal studies are the basis of the clinical data package for licensure.

A phase II single-arm, open-label Trial 08 is ongoing to evaluate nirsevimab in immunocompromised infants and children aged ≤ 24 months (Figure 6).

The clinical program also includes 2 completed dose-escalation, safety, PK, and ADA studies (Trial 01 in adults, and Trial 02 in infants).

At the time of the BLA, a total of 3620 infants and children received nirsevimab including 3224 at the proposed dose, across the 3 complementary (Trial 03, Trial 04, Trial 05) pivotal studies in infants and children, which was considered to be a sufficient prelicensure safety database of at least 3000 exposed subjects by the FDA. The extent of exposure is summarized in Section 6.1.

Table 5 Studies Contributing to the Nirsevimab Clinical Package for BLA

Study number (abbreviation) Status	Study design (primary/secondary objectives)	Study population	Dosing regimen	Number randomized (dosed)
Completed				
Trial 01 **D5290C00001** **(Study 1)**	Phase I, dose escalation, randomized, double-blind, placebo-controlled (safety, PK, and ADA)	Healthy adults, aged ≥ 18 to < 50 years.	**Nirsevimab:** 300, 1000, or 3000 mg single IV dose 100 or 300 mg single IM dose **Placebo:** single IM/IV dose	**Nirsevimab:** 102 (102) **Placebo:** 34 (34)
Trial 02 **D5290C00002** **(Study 2)**	Phase Ib/IIa, dose escalation, randomized, double-blind, placebo-controlled (safety, PK, and ADA)	Preterm infants born 32 to < 35 wGA entering their first RSV season	**Nirsevimab:** 10, 25, or 50 mg single IM dose **Placebo:** single IM dose	**Nirsevimab:** 71 (71) **Placebo:** 18 (18)
Trial 03 **D5290C00003** **(Study 3)** **Pivotal**	Phase IIb, randomized, double-blind, placebo-controlled, (efficacy, safety, PK, and ADA). Primary efficacy endpoint = MA RSV LRTI secondary endpoint = MA RSV LRTI with hospitalization.	Very and moderately preterm infants born ≥ 29 to < 35 wGA, entering their first RSV season 23 countries, including US.	**Nirsevimab:** 50 mg single IM dose **Placebo:** single IM dose	**Nirsevimab:** 969 (968) (including 570 [572] infants weighing < 5 kg randomized to the proposed dose) **Placebo:** 484 (479) (including 290 [288] infants weighing < 5 kg randomized to the proposed dose)
Ongoing				
Trial 04 **D5290C00004** **(MELODY)** **Pivotal** • **Primary Cohort** (complete; all subjects followed up to Day 511). • **Safety Cohort** (all subjects followed up to at least Day 151;	Phase III, randomized, double-blind, placebo-controlled (efficacy, safety, PK, and ADA). Primary efficacy endpoint = MA RSV LRTI Secondary endpoint = MA RSV LRTI with hospitalization.	Term and late preterm infants born ≥ 35 wGA, entering their first RSV season. 21 countries, including US and Japan.	**Nirsevimab:** 50 mg (infants < 5 kg) or 100 mg (infants ≥ 5 kg) single IM dose. **Placebo:** single IM dose.	**Primary Cohort:** • **Nirsevimab:** 994 (987) • **Placebo:** 496 (491) **All subjects:** • **Nirsevimab:** 2009 (1998) • **Placebo:** 1003 (996)

Table 5 Studies Contributing to the Nirsevimab Clinical Package for BLA

Study number (abbreviation) Status	Study design (primary/secondary objectives)	Study population	Dosing regimen	Number randomized (dosed)
follow-up ongoing to Day 511).				
Trial 05 **D5290C00005** **(MEDLEY)** **Pivotal** • **RSV Season 1** (complete; all subjects followed up to Day 361). • **RSV Season 2** (all subjects followed up to at least Day 151; follow-up ongoing to Day 361).	Phase II/III, randomized, double-blind, palivizumab-controlled (safety, descriptive efficacy, PK, and ADA).	Infants and children entering their first or second RSV season, eligible to receive palivizumab. **RSV Season 1:** Preterm infants born < 35 wGA (without CLD or CHD) (referred as preterm cohort) and term and preterm infants with CLD or CHD (referred as CLD/CHD cohort). **RSV Season 2:** Children ≥ 12 and ≤ 24 months with CLD or CHD (in CLD/CHD cohort) who received nirsevimab or palivizumab in RSV Season 1 25 countries, including US and Japan.	**RSV Season 1** **Nirsevimab:** 50 mg (infants < 5 kg) or 100 mg (infants ≥ 5 kg) single IM dose followed by 4 once-monthly doses of IM placebo. **Palivizumab**: 15 mg/kg IM (5 once-monthly doses). **RSV Season 2** Subjects in CLD/CHD cohort who received nirsevimab in Season 1, received 200 mg nirsevimab single IM dose followed by 4 once-monthly doses of IM placebo. Subjects in CLD/CHD cohort who received palivizumab in Season 1, received either 200 mg nirsevimab single IM dose followed by 4 once-monthly doses of IM placebo or palivizumab 15 mg/kg IM (5 once-monthly doses) in 1:1 re-randomized manner.	**Primary Analysis (Season 1)** **Overall population** (comprised of preterm and CLD/CHD cohorts): • **Nirsevimab:** 616 (614), including 407 (406) in the preterm cohort + 209 (208) in the CLD/CHD cohort • **Palivizumab:** 309 (304), including 208 (206) in the preterm cohort + 101 (98) in the CLD/CHD cohort. **Season 2 Analysis** **CLD/CHD cohort:** • Nirsevimab/nirsevimab: 180 (180) • Palivizumab/nirsevimab: 40 (40) • Palivizumab/palivizumab: 42 (42)
Trial 08 **D5290C00008** **(MUSIC)** **RSV Season 1 and RSV Season 2** (all subjects followed up to at least Day 151; follow-up ongoing to Day 361)	Phase II, Open-label, uncontrolled, single-dose study (safety, descriptive efficacy, PK, and ADA)	Immunocompromised infants in their first year of life and entering their first RSV season at the time of dose administration, and children ≤ 24 months of age in their second year of life and entering their second RSV season at the time of dose administration. 6 countries, including US and Japan.	**First year of life cohort:** **Nirsevimab:** 50 mg (infants < 5 kg) or 100 mg (infants ≥ 5 kg) single IM dose **Second year of life cohort:** **Nirsevimab:** 200mg single IM dose	**Interim analysis (data not presented in this document):** A total of 60 non-randomized, immunocompromised subjects who received the proposed dose of nirsevimab (35 subjects in the first year of life and 25 subjects in the second year of life)

ADA = anti-drug antibodies; BLA = Biologics License Application; CHD = (hemodynamically significant) congenital heart disease; CLD = chronic lung disease (of prematurity); IM = intramuscular; IV = intravenous; LRTI = lower respiratory tract infection; MA = medically attended; PK = pharmacokinetic(s); RSV = respiratory syncytial virus; US = United States; wGA = weeks gestational age.

2.4.3.1 Impact of the COVID-19 Pandemic on Clinical Development

After the initiation of the Trial 04 and Trial 05 studies, the COVID-19 pandemic was declared by the World Health Organization on 11 March 2020 (Cucinotta and Vanelli 2020) and was ongoing during the conduct of these studies. Trial 03 was complete prior to the start of the pandemic.

Following the onset COVID-19 pandemic, it was deemed necessary to pause enrollment in Trial 04 (efficacy study) in March 2020. This was due to reduced RSV disease incidence rates (ie, there would be fewer efficacy events) resulting from reduced incidence and circulation of RSV (van Summeren et al 2021) and the impact of COVID-19-related restrictive measures on operational aspects of study conduct (eg, difficulties in attending study visits). Enrollment into Trial 04 resumed in April 2021 (and completed in October 2021).

Enrollment into Trial 05 (safety study) was paused in March 2020 and resumed in July 2020 (and the planned enrollment target was completed in December 2020).

In both Trial 04 and Trial 05, steps were taken to minimize the impact on efficacy and safety data collection, in alignment with regulatory guidance. Scientific advice was sought from the FDA and agreement was reached on plans to mitigate potential delays to the development plan. Guidance from the FDA and other national regulatory authorities for clinical studies during COVID-19 was followed.

Consequently, the CSPs for Trial 04 and Trial 05 were amended to align with the agreed data package to support the BLA:

- In Trial 04, the primary analysis of efficacy was planned to be based on data from ~ 3000 subjects (ie, in Trial 04 [All Subjects]). However, in response to the pandemic, study enrollment was paused and the CSP was amended to allow analysis of the primary endpoint on data from the 1490 subjects already ongoing in the study at the time of the pause. This subpopulation is referred to as the 'Primary Cohort'.
- After recommencement of Trial 04 enrollment (ie, after restrictions related to the pandemic had been relaxed), an additional 1522 subjects were recruited to Trial 04 to achieve the original planned sample size. This provided an overall population of 3012 subjects (referred to as the 'All Subjects' population).
- The Trial 05 CSP was amended to cease enrollment with the accrued sample size of approximately 600 subjects in the Preterm Cohort and approximately 300 subjects in the CLD/CHD Cohort.

The overall study conduct, integrity of data generated, and validity of conclusions drawn, have been assessed in the context of the potential impact of the COVID-19 pandemic and the effectiveness of mitigation actions employed to minimize such impact:

- 48.1% of subjects in Trial 04 (Primary Cohort) experienced a disruption due to COVID-19, but the majority of these disruptions were limited to only one scheduled visit
- Study drop-out rates were low
- Important protocol deviations due to COVID-19 were assessed and judged not to have meaningfully impacted the overall study quality, including study conduct, data integrity, and interpretation of results
- Measures such as telemedicine were implemented to avoid under-reporting of safety data. Remote monitoring at sites was implemented to ensure adequate source data verification during COVID. All sites were open for full monitoring prior to database lock.
- Additional sensitivity analyses, considering the impact of disruptions due to COVID-19 on efficacy, showed a consistent and similar relative risk reduction for the primary endpoint MA RSV LRTI with nirsevimab versus placebo to the primary efficacy analysis.

It is therefore concluded that the impact of COVID-19 on study data integrity was effectively minimized. It is, however, acknowledged that the powering of the Trial 04 (Primary Cohort) to assess the secondary endpoint MA RSV LRTI with hospitalization was reduced as a result of the greatly reduced sample size. To mitigate this, efficacy was analyzed in all subjects enrolled into Trial 04. Trial 04 (All Subjects) is the originally intended population for the assessment of efficacy and provides the largest dataset available to evaluate the efficacy of nirsevimab against more severe forms of MA RSV LRTI in term and late preterm infants born ≥ 35 wGA.

3 CLINICAL PHARMACOLOGY

Pharmacokinetics, pharmacodynamics, and immunogenicity of nirsevimab were assessed in Trial 01, Trial 02, Trial 03, Trial 04, and Trial 05. Population PK analyses were performed to evaluate the PK in infants, and to support extrapolation of efficacy to infants at higher risk of RSV disease based on PK comparability (Section 4.3). Exposure-response analyses of efficacy were conducted in support of dose selection for phase 3 studies (Section 3.3). Evaluation of anti-drug antibody effect on PK is described in Section 7.1.

3.1 Pharmacokinetics

Evaluation of nirsevimab PK was based on frequent sampling in adults following single dose IV or IM administration and sparse sampling in infants following single dose IM administration (using population PK analysis), with the following conclusions:

- The PK of nirsevimab is dose proportional in the relevant dose range.
- The median time to maximum concentration following IM administration is 6 days based on adult data.

- The estimated clearance for nirsevimab is 3.42 mL/day for a typical infant weighing 5 kg and a postmenstrual age of 11.1 months.
- The model-predicted mean terminal elimination half-life of nirsevimab was 71.4 days (standard deviation 11.4) for infants.

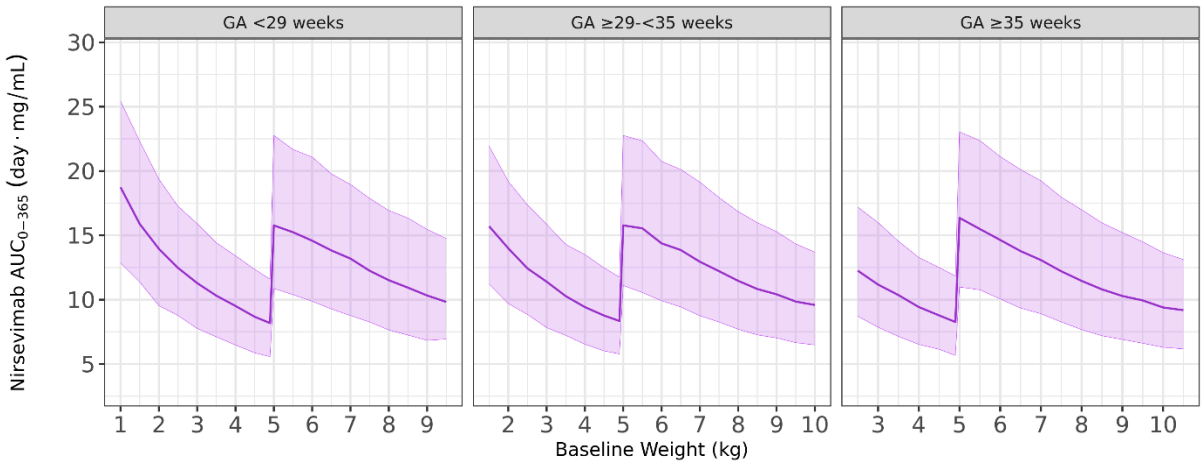
Like other mAbs, nirsevimab is degraded by proteolytic enzymes widely distributed in the body, and not primarily cleared via renal or hepatic pathways. No clinical studies were conducted to investigate the effect of renal or hepatic impairment on nirsevimab, as change in these functions are not expected to influence nirsevimab clearance.

3.1.1 Population Pharmacokinetics

Population PK analysis was used throughout the development of nirsevimab, with the model updated as data became available from clinical studies. The final model included data from adults (Trial 01) plus preterm and term infants (Trial 02, Trial 03, Trial 04, and Trial 05).

The final model was a linear two-compartment model with first-order absorption following IM administration. Body weight is the most important covariate affecting nirsevimab PK, effects of body weight on clearance and volume of distribution were described by allometric functions with estimated exponents. In addition to body weight, an effect of postmenstrual age was estimated on nirsevimab clearance. There is a high correlation between body weight and postmenstrual age, and the combined effects of body weight and postmenstrual age on clearance indicated a near linear increase in clearance with increasing body weight in infants. The model-predicted nirsevimab AUC versus body weight, for the proposed dose, is shown in Figure 7. The significance of other potential covariates (race, CHD or CLD, ADA) of nirsevimab PK were examined in the model. Race and ADA were found to be statistically significant covariates; however, the estimated effects were small (< 20%) in relation to the overall variability. There were no statistically significant effects of CHD or CLD on nirsevimab clearance. Sex was not evaluated for influence on nirsevimab PK, as differences in children ≤ 2 years of age are not expected.

Figure 7 Predicted Nirsevimab AUC for the Proposed Dose in Season 1 Versus Body Weight, by Gestational Age group



AUC_{0-365} is the area under the serum concentration-time curve (mg·days/mL) derived from time 0 to 365 days derived from the population PK model.
Shaded bands cover the 5th to 95th percentiles of the predictions, solid lines are the predicted medians, based on the final population PK model, for weight-band dosing (50 mg if < 5kg, 100 mg if ≥ 5kg).
GA = gestational age; PK = pharmacokinetic.

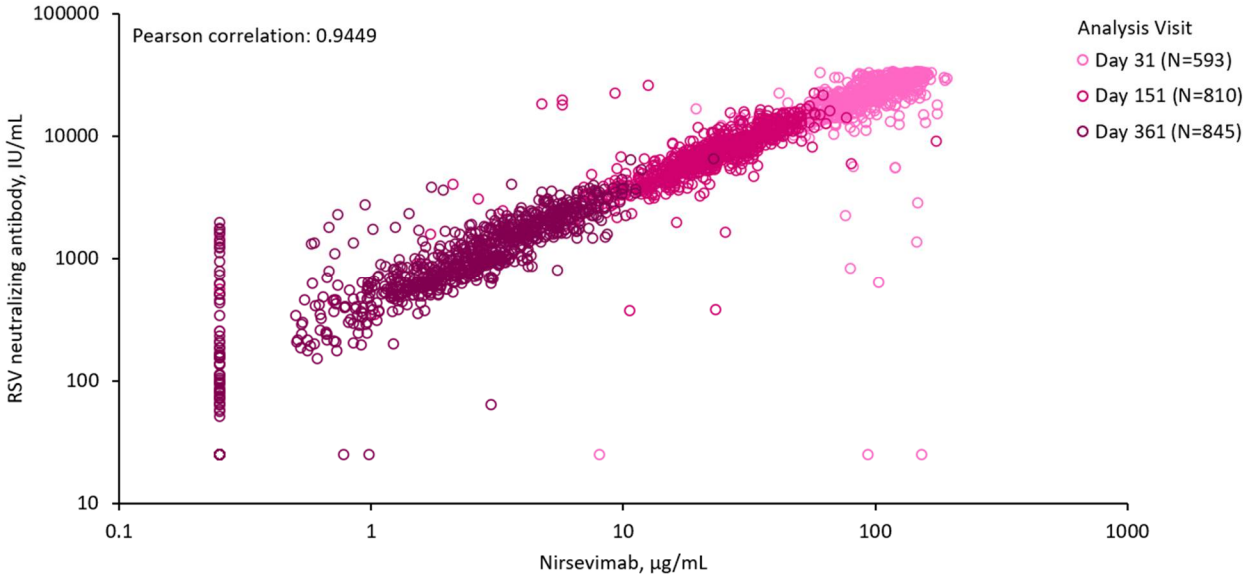
3.1.2 Drug-Drug Interaction

No drug-drug interaction studies have been conducted with nirsevimab. Monoclonal antibodies do not typically have significant interaction potential. Nirsevimab is not expected to interfere with the active immune response to co-administered vaccines (Section 6.10).

3.2 Pharmacodynamics

The primary pharmacodynamic effect of nirsevimab was assessed by evaluating serum anti-RSV nAb concentrations following dosing. As expected, the concentration of RSV nAb correlated with nirsevimab serum concentrations over time (Figure 8).

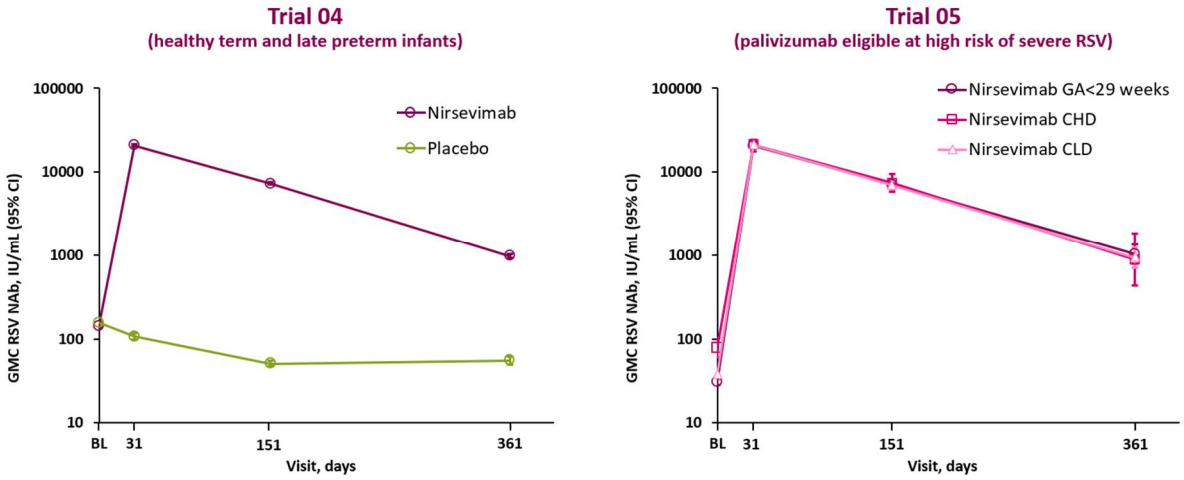
Figure 8 Correlation of RSV Neutralizing Antibody with Nirsevimab Serum Concentration – Trial 04 (Primary Cohort, Nirsevimab Group)



Note: in this graph, data below the lower limit of quantification (LLOQ) were plotted as LLOQ/2. Nirsevimab serum concentration LLOQ = 0.5 µg/mL; RSV neutralizing antibody concentrations LLOQ = 50 IU/mL.

Following nirsevimab dosing in Trial 04, RSV nAbs levels were increased more than 140-fold over baseline on Day 31 (Figure 9), and ~99% of the infants with samples measured for RSV nAbs experienced a ≥ 4-fold increase over baseline. The geometric mean concentration of RSV nAbs levels were approximately 50 times higher than baseline at Day 151, and more than 7 times higher than baseline at Day 361. The RSV nAb concentrations in infants with CLD, CHD and extreme prematurity (< 29 wGA) was examined in Trial 05, with no differences in serum neutralization observed across these subgroups compared to healthy infants in Trial 04 (Figure 9).

Figure 9 High and Sustained RSV Neutralizing Antibody Levels in Trial 04 (Primary Cohort) and Trial 05 Season 1



BL = baseline; CHD = congenital heart disease; CI = confidence interval; CLD = chronic lung disease; GA = gestational age (weeks); GMC = geometric mean concentration; IU = International Units; nAb = neutralizing antibody; RSV = respiratory syncytial virus.

The potential impact of nirsevimab on the development of a natural response to RSV was interrogated in Trial 03 and Trial 04 (Wilkins et al 2023a). The RSV post-F antibody measurements in infants who had a diagnostic-confirmed RSV infection were used to determine a statistical cut-point method to define seroresponse to RSV. Overall, the seroresponse rates to RSV among infants who did not have a medically attended, diagnostic-confirmed RSV infection were 70% and 63% of placebo recipients in Trial 03 and Trial 04 studies and 69% and 68% of the nirsevimab recipients, respectively. Geometric mean concentrations of post-F antibodies were similarly balanced between the two study arms in both studies. Neutralizing antibody responses were also evaluated, through assessment of RSV nAb levels in nirsevimab recipients with undetectable nirsevimab serum concentrations. RSV nAb levels were similar or slightly higher in nirsevimab recipients, suggesting that nirsevimab recipients mounted a nAb response following RSV exposure.

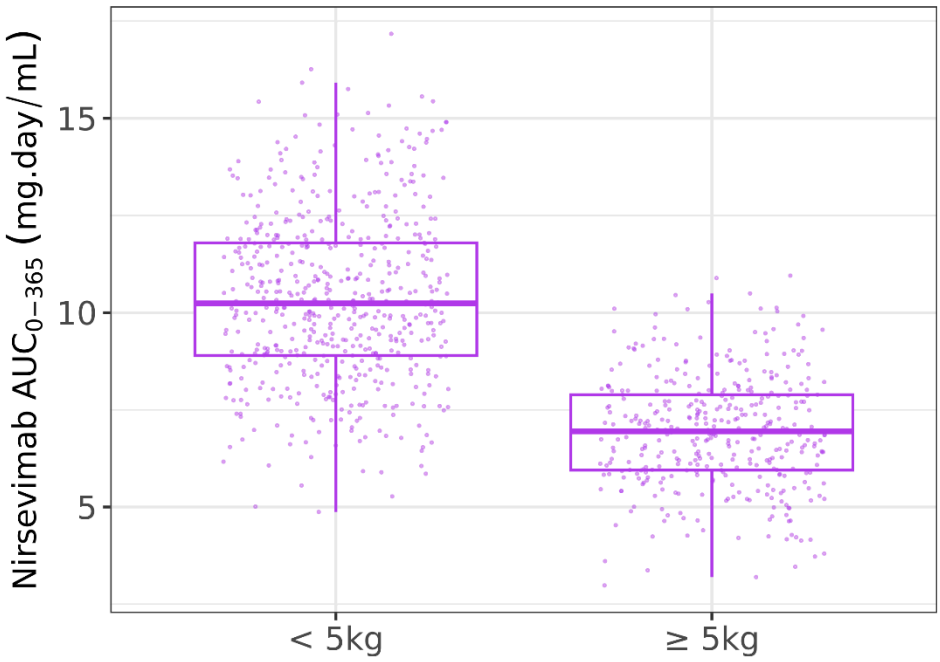
3.3 Dose Selection

A fixed dose by weight-band strategy was implemented in the nirsevimab program and is proposed for the indication (Section 2.3.2), aiming to deliver nirsevimab via pre-filled syringe to facilitate ease of use and implementation in the broad population. The dose selection was guided by population PK and exposure-response analyses.

A single dose of nirsevimab 50 mg IM was selected for use Trial 03, aiming to achieve serum concentrations on Day 150 post dosing above the nonclinical EC_{90} (6.8 µg/mL) target (Zhu et al 2017). This nirsevimab dose showed in efficacy in Trial 03 (Section 4.2), however,

subgroup analyses suggested lower efficacy in heavier infants. Post-hoc exposure-response analysis for MA RSV LRTI through Day 150 post dosing, using AUC binned by quartiles as the exposure metric, indicated lower efficacy in infants with exposures in the lowest AUC quartile bin (Q1). Nirsevimab serum exposure (AUC) depends on body weight (Figure 10), and the majority of infants with AUCs in the Q1 bin weighed ≥ 5 kg. Therefore, to optimize exposure, a nirsevimab 100 mg dose was selected for infants weighing ≥ 5 kg.

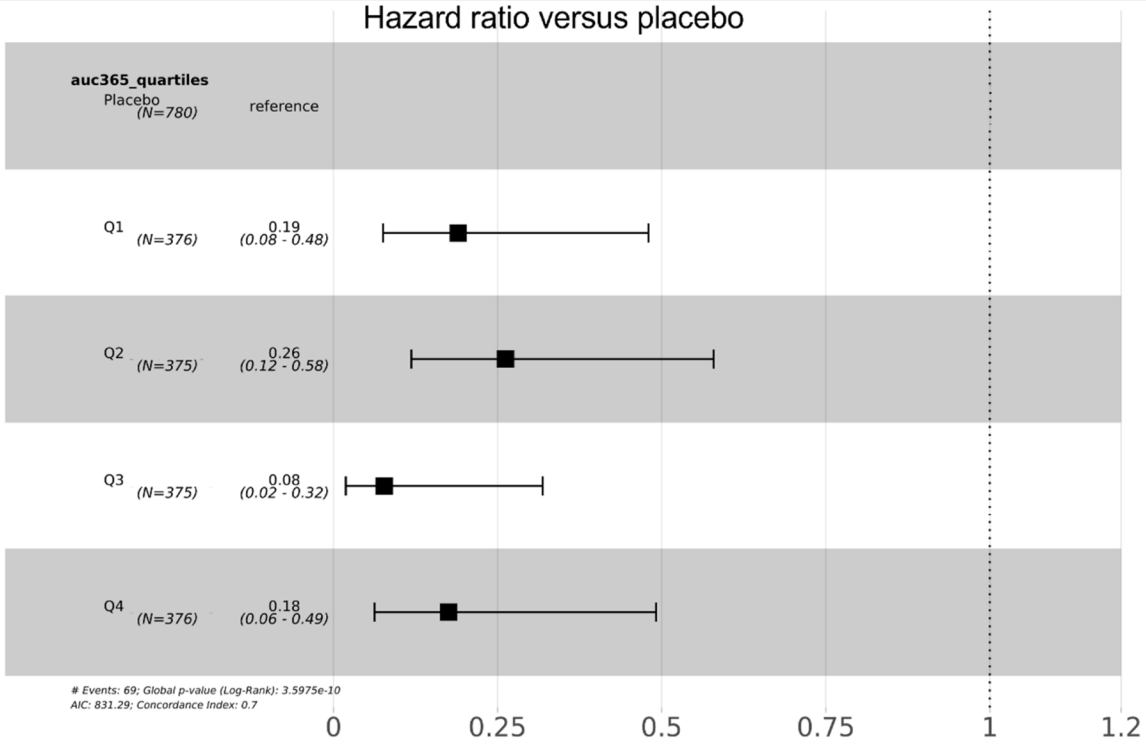
Figure 10 Nirsevimab AUC by Body Weight Group - Trial 03



$AUC_{0\text{-}365}$ = area under the serum concentration-time curve (mg·days/mL) derived from time 0 to 365 days derived from the population pharmacokinetic (PK) model.

The regimen with a fixed dose by weight band (single IM dose of nirsevimab 50 mg for subjects weighing < 5 kg or 100 mg for subjects weighing ≥ 5 kg at the time of dosing) was introduced in Trial 04 and Trial 05 as the 'proposed dose' in the first RSV season. The dosing regimen demonstrated efficacy in Trial 04 (Section 4.2). Furthermore, exposure-response analysis was performed based on pooled data from subjects who received the proposed weight-band dosing regimen in RSV Season 1 (Trial 04 [Primary Cohort] and infants < 5 kg in Trial 03). For this analysis, serum exposures (AUC) in subjects dosed with nirsevimab were divided into four bins, by quartiles. In all exposure bins, hazard ratios were below 0.3, with no apparent ordering, thus supporting consistent efficacy over the exposure range (Figure 11).

Figure 11 Exposure-Response for MA RSV LRTI Through Day 151 in RSV Season 1 in Pooled Data for Subjects Receiving the Proposed Dose - Hazard Ratio (95% CI) versus Placebo



Based on Cox proportional hazard model stratified by study and age group. Estimate based on the subset of subjects with available PK in nirsevimab group, and placebo, pooled data from the proposed dose (ie, Trial 03 (< 5 kg) and Trial 04 (Primary Cohort). Nirsevimab $AUC_{0\text{-}365}$ were divided in four bins (Q1-Q4), based on quartiles, and compared to placebo.
$AUC_{0\text{-}365}$ = area under the serum concentration-time curve (mg·days/mL) from time 0 to 365 days;
CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; N = number of subjects; PK = pharmacokinetic; Q1 = first quartile bin; Q2 = second quartile bin; Q3 = third quartile bin; Q4 = fourth quartile bin; RSV = respiratory syncytial virus.

Overall, results support the proposed nirsevimab fixed dose by weight band (50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg) in the first RSV season. A 200 mg dose was proposed in RSV Season 2, based on the expected body weight range.

3.4 Clinical Pharmacology Conclusions

The proposed nirsevimab fixed dose by weight-band in RSV Season 1 (50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg), and 200 mg in Season 2, is supported by clinical pharmacology evaluations.

- The PK of nirsevimab is dose proportional.
- The median time to maximum concentration of nirsevimab following IM administration is approximately 6 days based on adult data.

- The nirsevimab mean elimination half-life in infants is approximately 71 days; the elimination and distribution of nirsevimab increase with increasing body weight.
- There was no difference in PK in infants with CHD or CLD compared to healthy infants. Similar nirsevimab serum concentrations were also achieved in preterm infants < 29 wGA.
- Serum anti-RSV nAb concentrations correlated with nirsevimab serum concentrations, confirming the anti-RSV nAb activity of nirsevimab.
- RSV nAbs concentrations increased to more than 140-fold increase from baseline at Day 31 in Trial 04 and remained approximately 50-fold higher than baseline at Day 150 post dose following nirsevimab administration; ~99% of the infants experienced ≥ 4-fold rise in RSV nAbs in Trial 04; similar results were observed for Trial 05. Clinical RSV nAb data provide support for the observed protective effect of nirsevimab for at least 5 months.
- Nirsevimab did not inhibit a natural immune response to RSV exposure.
- Exposure-response analyses support the proposed nirsevimab fixed dose by weight band (50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg) in the first RSV season, with a 200 mg dose proposed in RSV season 2 (based on expected body weight range).

4 CLINICAL EFFICACY

This section presents data from the clinical studies (Trial 04, Trial 03, and Trial 05) supporting the efficacy of the proposed dose of nirsevimab in all neonates and infants born during or entering their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV through their second RSV season. If approved, nirsevimab will fill the current unmet need for RSV prophylaxis for a broader population of infants who currently have no protection against RSV.

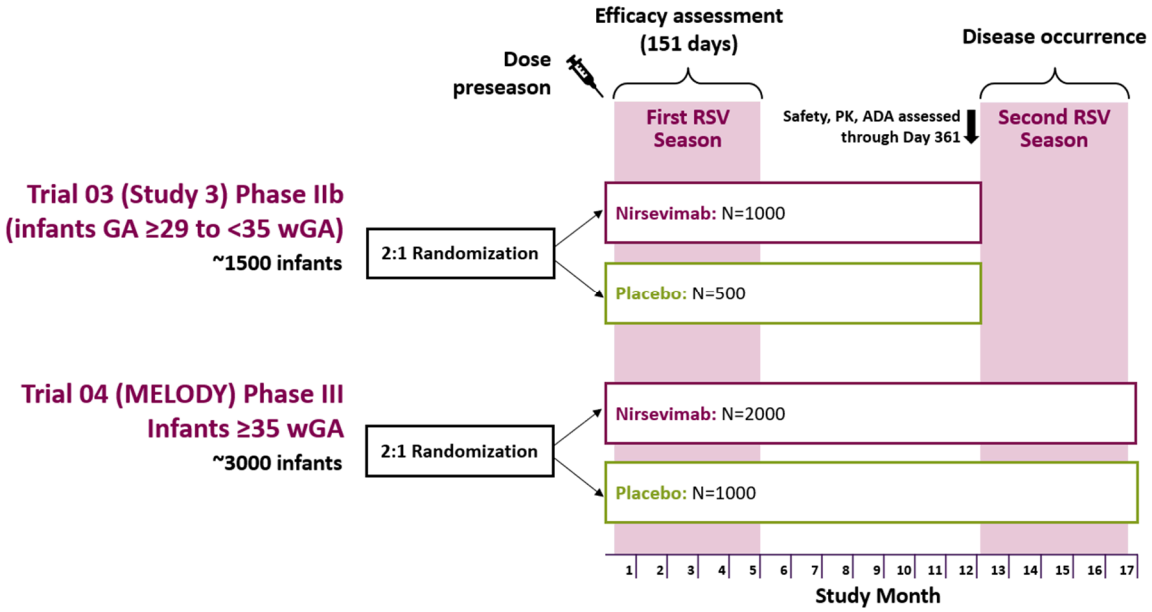
4.1 Methods to Assess Clinical Efficacy Against MA RSV LRTI

The efficacy of nirsevimab against MA RSV LRTI was demonstrated in two double-blind, randomized, placebo-controlled trials with similar study designs. Trial 03 and Trial 04 evaluated the efficacy of nirsevimab in premature infants born 29 to < 35 wGA and in term and late preterm infants born ≥ 35 wGA, respectively (Figure 12). As described in Section 2.4.3.1, due to the COVID-19 pandemic, enrollment into Trial 04 was split into 2 cohorts.

Both Trial 03 and Trial 04 enrolled healthy infants in their first year of life, who were not eligible to receive palivizumab and were entering their first RSV season. No history of renal or hepatic disfunction, chronic seizure or evolving or unstable neurologic disorder, fever

(≥ 100.4°F [≥ 38.0°C]) or acute illness within 7 days prior to randomization, any history of LRTI or active LRTI prior to or at the time of randomization were allowed.

Figure 12 Study Designs – Trial 03 and Trial 04 in Healthy Preterm and Term Infants



PK sampling was performed pre-dose, and Day 8 (Japan only); Days 15 (EU only) or 31 (non-EU), 151 and 361 post-dose.
ADA = anti-drug antibodies; N = number of subjects; PK pharmacokinetics; RSV = respiratory syncytial virus; wGA = weeks gestational age.

The primary endpoint of each study was to assess the efficacy of nirsevimab when administered as a single fixed IM dose to infants entering their first RSV season in reducing MA RSV LRTI, compared to placebo, through Day 150 post dosing. The key secondary endpoint was to assess the efficacy of nirsevimab in reducing MA RSV LRTI with hospitalization.

All subjects who sought medical attention for a respiratory illness in an inpatient or outpatient setting were evaluated for the occurrence of LRTI by the Investigator, based on examination of all available evidence. Medical records were requested from all healthcare provider visits outside of study sites. Respiratory samples were to be obtained for all subjects found to have an LRTI and all subjects who required hospitalization for a respiratory infection (even without diagnosis of LRTI). Testing for RSV was performed centrally using the US FDA-approved in vitro diagnostic real-time RT-PCR assay. Guidance was provided to obtain the sample within 2 days of the initial healthcare provider assessment and diagnosis. If this was not possible, sampling was to take place as soon as possible, up to a limit of 14 days.

The case definitions for RSV LRTI for analysis are presented in Table 6.

Table 6 Summary of Case Definitions for Assessment of Efficacy

Outcome	Criteria
MA RSV LRTI	Lower respiratory tract involvement on chest auscultation, indicated by at least one of the following: rhonchi/rales/crackles/wheeze **AND** at least one of the following signs of severity: • Increased respiratory rate [a] • Hypoxemia [b] • Acute hypoxic or ventilatory failure • New onset apnea • Nasal flaring • Retractions • Grunting • Dehydration due to respiratory distress **AND** RSV positive by central laboratory RT-PCR assay
MA RSV LRTI with hospitalization	MA RSV LRTI **AND** Hospitalized
MA RSV LRTI (very severe)	MA RSV LRTI **AND** Hospitalized **AND** requiring oxygen or IV fluids
All MA LRTI (any cause)	LRTI in the judgment of the investigator of any cause [c]
ALL respiratory illness with hospitalization	Respiratory illness leading to hospitalization of any cause [d]

[a] Increased respiratory rate at rest (age < 2 months, ≥ 60 breaths/min; age 2 to 6 months, ≥ 50 breaths/min; age > 6 months to 2 years, ≥ 40 breaths/min).
[b] Hypoxemia (in room air - oxygen saturation < 95% at altitudes ≤ 1800 meters or < 92% at altitudes > 1800 meters).
[c] Does not necessarily meet the criteria for LRTI as in MA RSV LRTI.
[d] Does not exclude URTI requiring admission.
IV = intravenous; LRTI = lower respiratory tract infection; MA = medically attended; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase polymerase chain reaction; URTI = upper respiratory tract infection.

4.1.1 Statistical Methods

Efficacy analyses were conducted according to the ITT population principle (all participants who were randomly allocated). The primary analyses of Trial 03 and Trial 04 were conducted when subjects had completed follow-up through 150 days post dosing. The primary analysis of Trial 04 was conducted on the Primary Cohort (subjects enrolled prior to the enrollment pause due to the COVID-19 pandemic).

The primary endpoint analysis of efficacy against MA RSV LRTI was performed using a Poisson regression model with robust variance (Zou 2004), including treatment and

randomization stratification factors as covariates in the model. Only the first occurrence of MA RSV LRTI in an individual was used in the primary analysis. Efficacy, presented as relative risk reduction (RRR), was calculated as one minus the relative risk estimated from the Poisson model and expressed as a percentage reduction versus placebo (with 95% CIs). In addition, the 2-sided p-value, testing the null hypothesis that the incidence of MA RSV LRTI between nirsevimab and placebo groups are the same, was obtained from the model. Statistical significance was achieved if the 2-sided p-value was ≤ 0.05.

Multiple imputation techniques were used to impute the event outcome for infants who were not followed up for at least 150 days post-dose and who did not have an MA RSV LRTI, assuming the observed event rate in the placebo group and with randomization stratification factors included as a predictor.

Supplementary Analyses of the primary efficacy endpoint were prespecified and performed including:

- Cochran-Mantel Haenszel test
- Poisson Regression with robust variance adjusting for follow-up time
- Kaplan-Meier curves were generated for time to first MA RSV LRTI until 150 days post-dose along with hazard ratios and their 95% CIs estimated from Cox Proportional Hazards models
- Sensitivity analyses for RSV LRTI through 150 days post dose addressing subjects who did not have an event or who were not followed through 150 days post dose.

For the prespecified subgroup analysis, the treatment-by-subgroup interaction were tested (at the 10% significance level) using the Poisson regression with robust variance model with the terms of treatment, randomization stratification factors, subgroup, and treatment-by-subgroup interaction. A reduced model was used if the full model did not converge. In the event the Poisson regression model did not converge for any stratum of a subgroup, the RRRs and corresponding 95% CIs (mid-p adjusted) were estimated on basis of the exact conditional method (Breslow-Day) for all subgroup strata.

The same analysis methodology was used to estimate the efficacy of the secondary efficacy endpoint of MA RSV LRTI with hospitalization. The analysis of exploratory efficacy endpoints of MA RSV LRTI (very severe), any cause MA LRTI, and respiratory illness with hospitalization were conducted using a reduced model and without multiple imputation for missing data.

In Trial 03, the primary and secondary efficacy hypotheses were assessed in the primary analysis by a hierarchical order. That is, the secondary hypothesis was tested at a significance level of $p \leq 0.05$ only if the treatment effect on the primary efficacy endpoint was

demonstrated at the significance level of the 2-sided $p \leq 0.05$. With that, the overall Type I error is controlled at 0.05.

Additional Cohorts of Analysis

Analyses in three additional cohorts are also presented to support understanding of the efficacy profile of nirsevimab: Trial 03 (Proposed Dose) and Trial 04 (All Subjects).

Analyses were performed in these cohorts to support understanding of the efficacy profile of nirsevimab. These cohorts are described below:

- Trial 03 (Proposed Dose): based on the results of Trial 03, the nirsevimab dose was optimized: 50 mg was retained as the dose for infants weighing < 5 kg and a new dose of 100 mg was introduced for infants weighing ≥ 5kg. The analysis cohort restricted to randomized subjects weighing < 5 kg at the time of dosing in Trial 03 is referred to as "Trial 03 (Proposed Dose)" cohort.
- Trial 04 (All Subjects): in Trial 04, the primary efficacy assessment was originally planned to be based on data from ~ 3000 subjects. However, in response to the COVID-19 pandemic, study enrollment was paused, and the primary analysis was performed on 'Trial 04 [Primary Cohort]' (Section 2.4.3.1). Enrollment resumed in a double-blind manner to complete the total planned recruitment and this population is referred to as 'Trial 04 (All Subjects)'. This population reflects how Trial 04 was initially designed.

For analyses based on the Trial 04 (All Subjects), cohort was also included in the Poisson models, respectively.

Analysis of MA RSV LRTI with Hospitalization in Trial 04 (All Subjects)

An exploratory analysis of more severe forms of MA RSV LRTI with hospitalization was conducted in all-randomized subjects in Trial 04, ie, in the Trial 04 (All Subjects) analysis set. The combined analysis of data from the Primary (N = 1490) and Safety cohorts (N = 1522) enrolled in Trial 04 provides the most precise estimates of efficacy against the hospitalization endpoints for the following reasons.

In Trial 04, the two cohorts were originally designed as one cohort, therefore endpoints, case definitions, and analysis methods are the same. This exploratory analysis was prespecified after the results of the primary analysis were known.

Trial 04 recruited late preterm and term infants into the two cohorts under the same protocol and according to the same inclusion and exclusion criteria. Trial 04 (Primary Cohort) includes subjects from the NH 2019/2020 and SH 2020 enrollment seasons (South Africa was the only SH country). The Safety Cohort includes subjects enrolled in the SH 2021 and NH 2021/2022 season. The Safety Cohort was conducted in a double-blind manner. All site personnel, study

participants, and the study team members involved in advice or decisions involving study participants or day-to-day interactions remained blinded until the end of the study (ie, after all subjects completed the Day 511 visit). At the time of the database lock for the Primary Cohort, a team of independent progammers ensured that no data from the Safety Cohort were provided to the study programming team conducting the primary analysis.

Combined analysis is also supported by the general similarity of the populations recruited to both cohorts, in terms of disposition and baseline demographic characteristics. Supplementary data Table 38 and Table 39 show the similar disposition and baseline characteristic in Trial 04 (Primary Cohort) and Trial 04 (All Subjects), respectively. Furthermore, the majority of infants were enrolled in countries that follow published clinical guidelines which define criteria for RSV hospitalization, thus minimizing the potential for region-specific differences in healthcare practices affecting hospitalization endpoints.

Prespecification and multiplicity protection

To aid the understanding of degree of robustness of the primary, secondary, and exploratory statistical analyses, the degree of prespecification (eg, in the study protocol, SAP, or post hoc) and multiplicity protection are summarized in Table 7. Except for interaction p-values that were unadjusted, p-values and statements of statistical significance presented in this document are provided only for protocol specified, multiplicity-controlled analyses. No multiplicity adjustment was made to CIs for exploratory efficacy analyses.

Table 7 Summary of Prespecification and Multiplicity Protection by Endpoint and Cohort Analyzed – Trial 03 and Trial 04

Prespecification and multiplicity protection	Primary MA RSV LRTI	Secondary MA RSV LRTI with hospitalization	Exploratory MA RSV LRTI (very severe)	Exploratory case definitions of any cause LRTI [a]
Multiplicity-protected analyses prespecified in study protocol	• Trial 03 • Trial 04 (Primary Cohort)	• Trial 03 • Trial 04 (Primary Cohort)	NA	NA
Analyses prespecified in the SAP or a SAP Addendum (not multiplicity protected)	• Trial 04 (All Subjects)	• Trial 04 (All Subjects)	• Trial 04 (All Subjects)	NA
Post-hoc analyses	• Trial 03 (Proposed Dose)	• Trial 03 (Proposed Dose)	• Trial 03 • Trial 03 (Proposed Dose) • Trial 04 (Primary Cohort)	• Trial 04 (Primary Cohort) • Trial 03 • Trial 03 (Proposed Dose)

[a] Any cause LRTI: All MA LRTI, All MA respiratory illness with hospitalization (any cause).
LRTI = lower respiratory tract infection; MA = medically attended; NA = not applicable; RSV = respiratory syncytial virus; SAP = Statistical Analysis Plan.

4.2 Results: Efficacy Against MA RSV LRTI

4.2.1 Subject Disposition, Demographic and Baseline Characteristics

The analysis populations in Trial 04 and Trial 03 are shown in Table 8. Supplementary Table 38 shows the disposition of subjects in Trial 04 and Trial 03. Overall, the disposition was similar between treatment arms within each study and across the studies.

Supplementary Table 39 presents demographic and baseline characteristics in Trial 04 and Trial 03, which were comparable between the nirsevimab and placebo groups and allowed for robust efficacy assessment. Subject demographics, baseline characteristics, and medical history indicate that the subjects randomized across the two studies are representative of the intended population of healthy and preterm infants in their first RSV season.

Table 8 Analysis Populations – Trial 04 and Study Trial 03

Analysis Population	Term and late preterm infants born ≥ 35 wGA				Very and moderately preterm infants born≥ 29 to < 35 wGA			
	Trial 04 (Primary Cohort)		Trial 04 (All Subjects)		Trial 03		Trial 03 (Proposed Dose)	
	Placebo	Nirsevimab	Placebo	Nirsevimab	Placebo	Nirsevimab	Placebo	Nirsevimab
ITT	496	994	1003	2009	484	969	290	570
AT [a]	491	987	996	1998	479	968	288	572
PP [b]	488	979	NA	NA	479	965	288	570

[a] The AT Populations included subjects who were randomized and received any amount of IP, with subjects analyzed by the IP received.
[b] The PP Populations included subjects in the ITT Population who received the correct dose of randomized treatment and had no serious protocol deviation.
Data presented = number of subjects.
AT = as-treated; IP = investigational product; ITT = intent-to-treat; NA = not applicable; PP = per-protocol; NA = not applicable; wGA = weeks gestational age.

4.2.2 Efficacy Against MA RSV LRTI

The primary endpoint in both Trial 03 and Trial 04 was met: nirsevimab demonstrated clinically relevant and highly significant protection against MA RSV LRTI through 150 days post dose in preterm and term infants (Table 9). Furthermore, supporting analyses models and supplementary analyses were consistent with the primary efficacy analyses in both studies. Sensitivity analyses assessing the impact of COVID-19 on efficacy in Trial 04 were consistent with the primary efficacy analysis in Trial 04 (Primary Cohort). Trial 03 was completed prior to the start of the COVID-19 pandemic.

Table 9 Efficacy Against MA RSV LRTI Through 150 Days Post Dose in Term and Preterm Infants Born ≥ 29 wGA

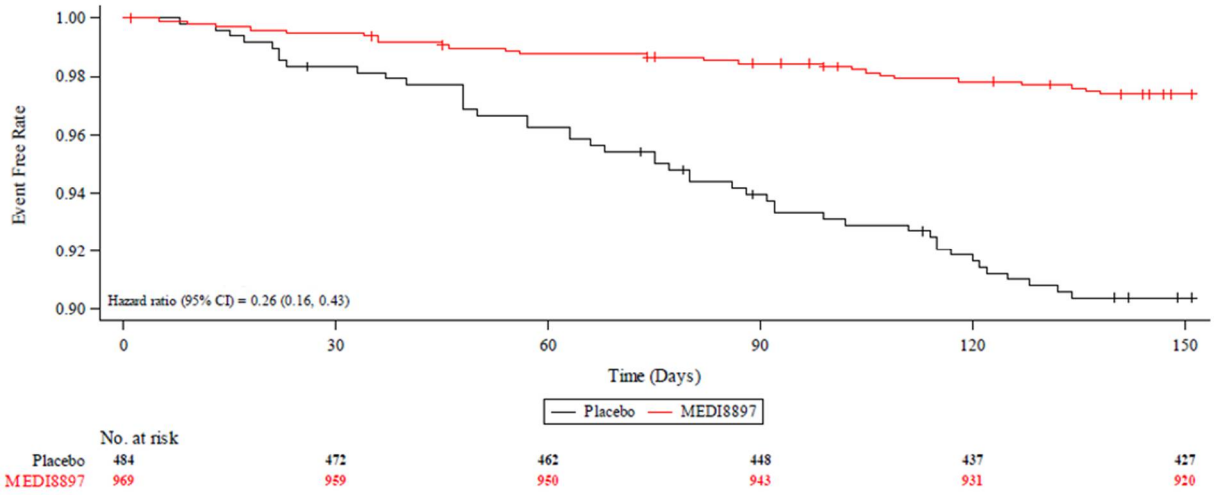
Statistic	Term and late preterm infants born ≥ 35 wGA		Very and moderately preterm infants born ≥ 29 to < 35 wGA	
	Trial 04 (Primary Cohort)		Trial 03	
	Placebo	Nirsevimab	Placebo	Nirsevimab
	N = 496	N = 994	N = 484	N = 969
Subjects with events n (%)	25 (5.0)	12 (1.2)	46 (9.5)	25 (2.6)
Subjects requiring imputation n (%)	6 (1.2)	15 (1.5)	11 (2.3)	24 (2.5)
RRR (95% CI)	74.50% (49.6% to 87.1%)		70.10% (52.3% to 81.2%)	
p-value	p < 0.0001		p < 0.0001	

Data presented for the Number (%) of subjects with events; for subjects with multiple events, only the first event is included in the analysis.
CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; n = number of observed events; N = number of subjects; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus; wGA = weeks gestational age.

At time of the final database lock for Trial 04 (Primary Cohort), two subjects originally categorized as ongoing through 150 days post dose were changed to "lost to follow-up". Based on the updated data, the primary analysis was re-run and is provided as supplementary data in Section 10.2.1. The overall interpretation of the result for the Trial 04 primary endpoint is unchanged.

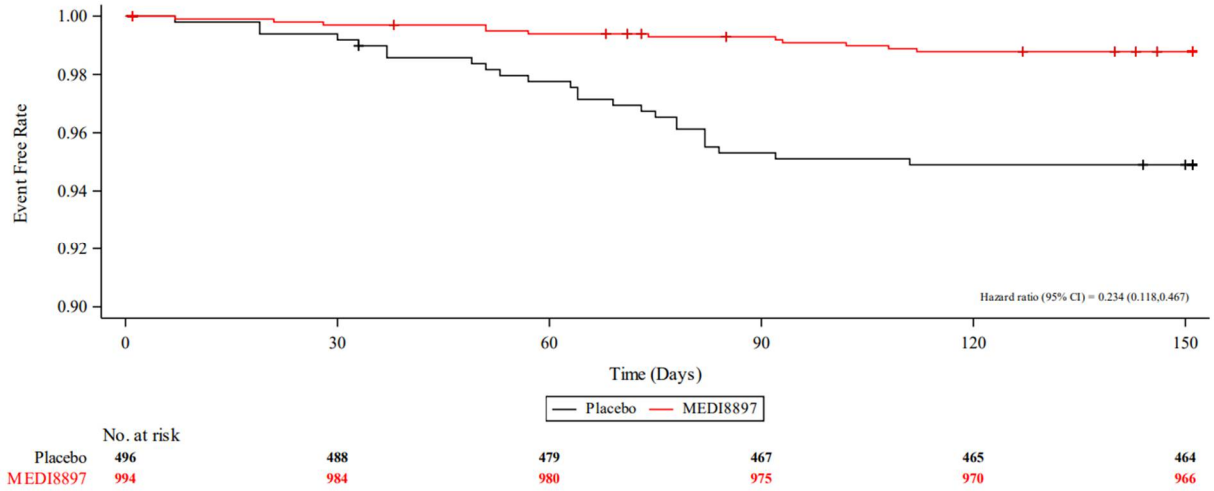
The consistency of the benefit of nirsevimab throughout the typical 5-month RSV season was supported by the Kaplan-Meier curves for time to first MA RSV LRTI in Trial 03 (Figure 13) and Trial 04 (Primary Cohort) (Figure 14).

Figure 13 Time to First MA RSV LRTI Through 150 Days Post Dose in Very and Moderately Preterm Infants Born ≥ 29 to < 35 wGA – Trial 03



Hazard ratio and the corresponding 95% confidence interval were from a stratified Cox proportional hazard model with stratification factors (age at randomization and hemisphere). Tick marks indicate censored data.
CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; MEDI8897 = nirsevimab; RSV = respiratory syncytial virus; wGA = weeks gestational age.

Figure 14 Time to First MA RSV LRTI Through 150 Days Post Dose in Term and Late Preterm Infants Born ≥ 35 wGA – Trial 04 (Primary Cohort)



Hazard ratio and the corresponding 95% confidence interval were from a stratified Cox proportional hazard model with stratification factor (age at randomization). Tick marks indicate censored data.
CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; MEDI8897 = nirsevimab; RSV = respiratory syncytial virus; wGA = weeks gestational age.

The summary of efficacy against MA RSV LRTI in Table 10 shows that nirsevimab demonstrated consistent, clinically relevant protection through 150 days post dose in the individual studies and across the cohorts analyzed. Nirsevimab efficacy in term and preterm infants born ≥ 29 wGA was supported by the analysis of more severe forms of MA RSV

LRTI, associated with hospitalization (Section 4.2.3) or very severe cases that required hospitalization plus additional supplementation with oxygen therapy or IV fluids (Section 4.2.4).

Table 10 Summary of Nirsevimab Efficacy Against MA RSV LRTI Through 150 Days Post Dose

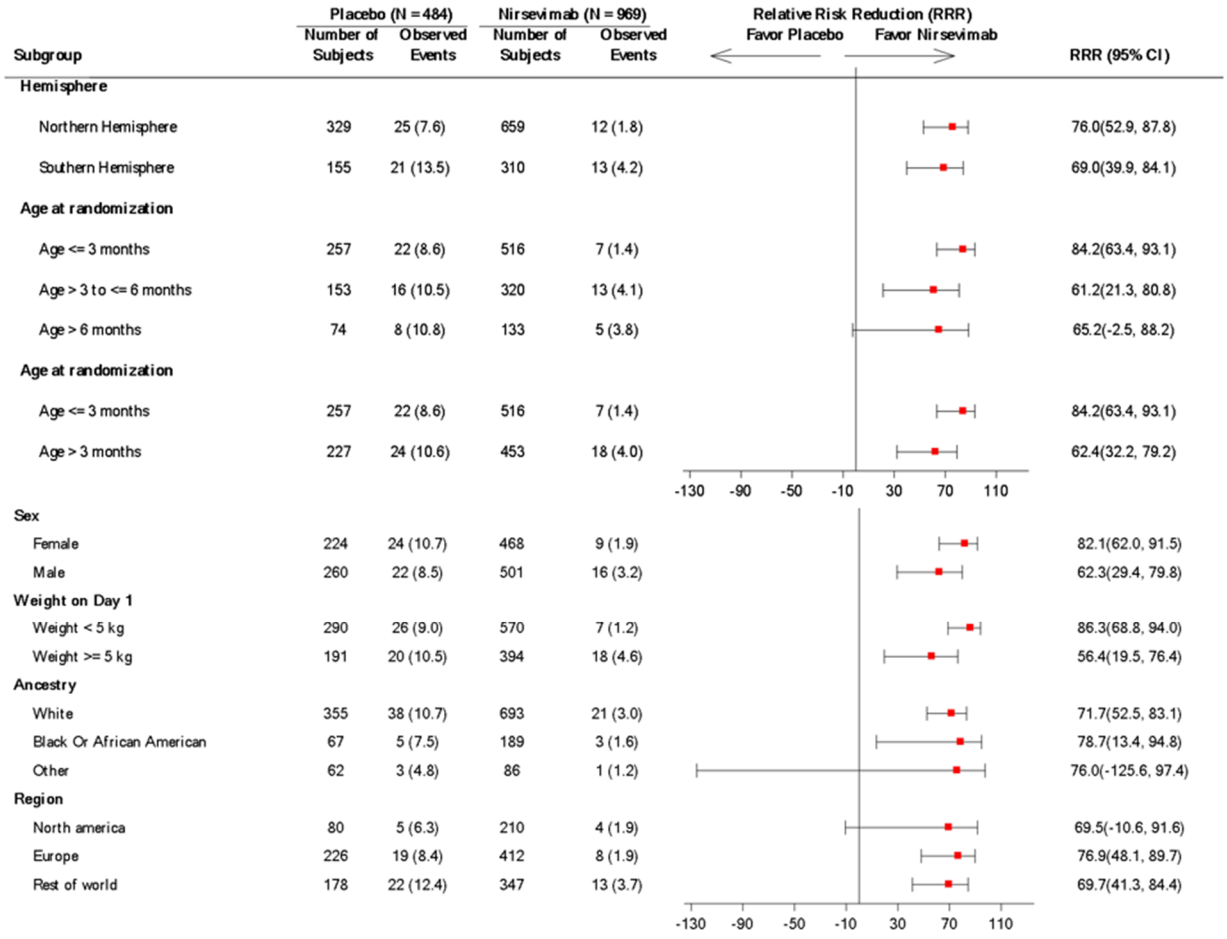
	Term and late preterm infants born ≥ 35 wGA				Very and moderately preterm infants born ≥ 29 to < 35 wGA			
	Trial 04 (Primary Cohort)		Trial 04 (All Subjects)		Trial 03		Trial 03 (Proposed Dose)	
Statistic	Placebo N = 496	Nirsevimab N = 994	Placebo N = 1003	Nirsevimab N = 2009	Placebo N = 484	Nirsevimab N = 969	Placebo N = 290	Nirsevimab N = 570
Subjects with events n (%)	25 (5.0)	12 (1.2)	54 (5.4)	24 (1.2)	46 (9.5)	25 (2.6)	26 (9.0)	7 (1.2)
RRR (95% CI) p-value	74.5% (49.6% to 87.1%) p < 0.0001		76.4% (62.3% to 85.2%)		70.1% (52.3% to 81.2%) p < 0.0001		86.20% (68.0% to 94.0%)	

CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; n = number of events observed; N = number of subjects; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus; wGA = weeks gestational age.

4.2.2.1 Subgroup Analyses of Efficacy Against MA RSV LRTI

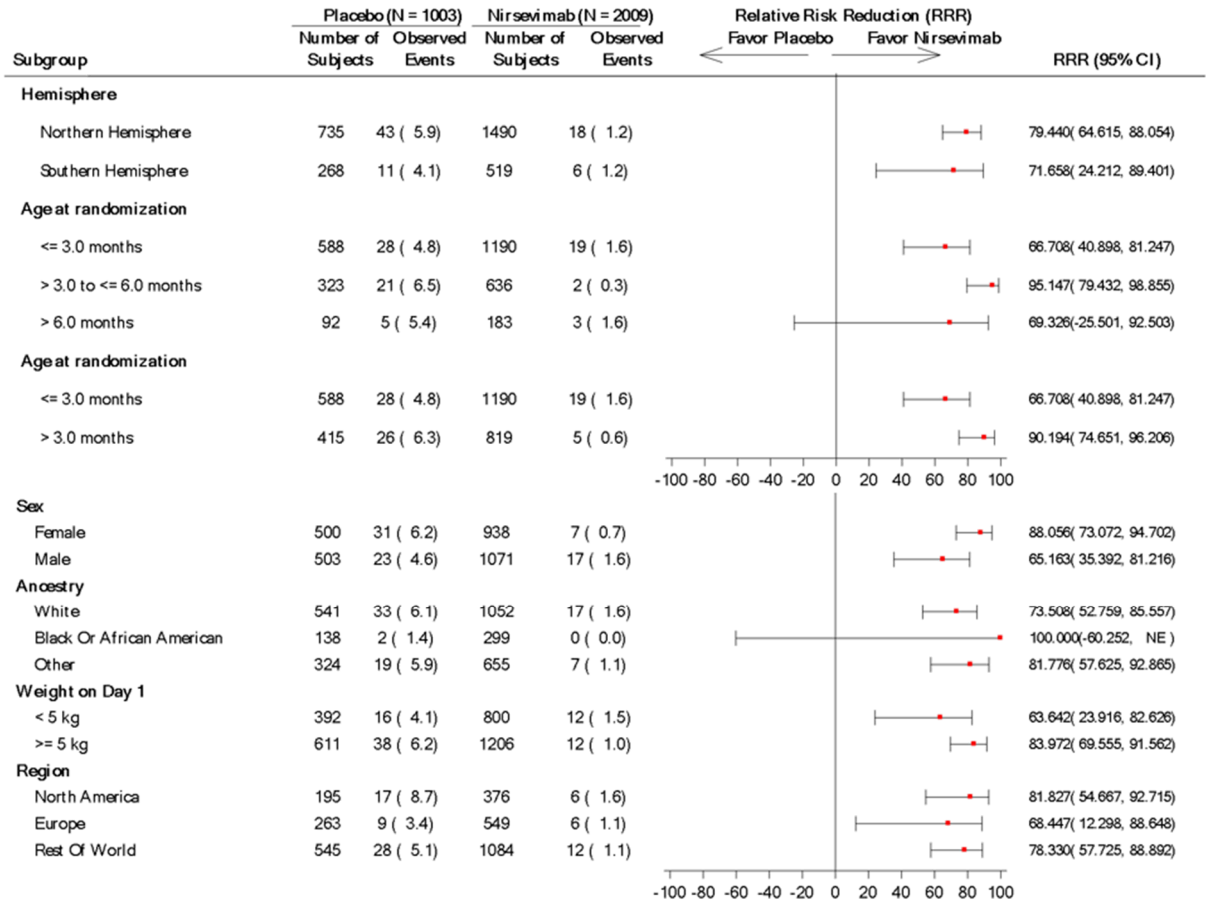
Subgroup analyses are presented for efficacy against MA RSV LRTI in very and moderately preterm infants born ≥ 29 to < 35 wGA (Trial 03; Figure 15). As discuss in Section 3.3, exposure-response analysis in Trial 03, in which all subjects received nirsevimab 50 mg, showed differential efficacy in the subjects weighing < 5 kg versus ≥ 5 kg. Subgroup analyses are presented for term and late preterm infants born ≥ 35 wGA in Trial 04 (All Subjects) in Figure 16 and Trial 04 (Primary Cohort) in Supplementary Figure 30.

Figure 15 Subgroup Analysis of MA RSV LRTI Through 150 Days Post Dose in Very and Moderately Preterm Infants Born ≥ 29 to < 35 wGA - Trial 03 (All Subjects)



The relative risk reduction and its corresponding 95% CI were estimated using a Poisson regression with robust variance with the term of treatment.
If RRR - 100% or - Inf, one-sided 97.5% CI was reported.
For Age at randomization (2-level) and Weight on Day 1, unadjusted interaction p-value < 0.1.
CI = confidence interval; Inf = infinity; LRTI = lower respiratory tract infection; MA = medically attended; N = number of subjects; RRR = relative risk reduction; RSV = respiratory syncytial virus; wGA = weeks gestational age.

Figure 16 Subgroup Analysis of MA RSV LRTI through 150 Days Post Dose in Term and Late Preterm Infants Born ≥ 35 wGA - Trial 04 (All Subjects)



The relative risk reduction and its corresponding 95% CI were estimated using a Poisson regression with robust variance with the term of treatment (without stratum). For Ancestry, Relative risk reduction and its corresponding 95% CI (mid-p adjusted) were estimated based on exact conditional method using PROC GENMOD with no strata.
If RRR was 100% or -Inf, one-sided 97.5% CI was reported.
For Age at randomization and Sex, unadjusted interaction p-value < 0.1.
CI = confidence interval; Inf = infinity; LRTI = lower respiratory tract infection; N = number of subjects; N/A = not applicable; NE = not evaluated; RRR = relative risk reduction; RSV = respiratory syncytial virus; wGa = weeks gestational age.

4.2.3 Efficacy Against MA RSV LRTI With Hospitalization

In Trial 03, nirsevimab demonstrated clinically and statistically significant efficacy against the secondary endpoint, MA RSV LRTI with hospitalization, in preterm infants 29 to < 35 wGA (Table 11).

Table 11 Efficacy Against the Secondary Endpoint, MA RSV LRTI with Hospitalization Through 150 Days, in Preterm Infants Born ≥ 29 wGA to < 35 wGA – Trial 03

	Placebo N = 484	Nirsevimab N = 969
Subjects with events, n (%)	20 (4.1)	8 (0.8)
Subjects requiring imputation, n (%)	11 (2.3)	24 (2.5)
RRR (95% CI)	78.40% (51.9% to 90.3%)	
p-value	p = 0.0002	

CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; n = number of events observed; N = number of subjects; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus; wGA = weeks gestational age.

In Trial 04, analysis of the secondary endpoint MA RSV LRTI with hospitalization did not reach statistical significance, due to the low number of events (Table 12).

Table 12 Efficacy Against the Secondary Endpoint, MA RSV LRTI with Hospitalization Through 150 Days, in Term and Late Preterm infants born ≥ 35 wGA – Trial 04 (Primary Cohort)

	Placebo N = 496	Nirsevimab N = 994
Subjects with events, n (%)	8 (1.6%)	6 (0.6%)
Subjects requiring imputation, n (%)	6 (1.2%)	15 (1.5%)
RRR (95% CI	62.1% (-8.6, 86.8)	
P value	0.0708	

CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; n = number of events observed N = number of subjects; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus.

Supplementary data in Section 10.2.1 presents the results of the analysis of MA RSV LRTI with hospitalization, which was re-run to account for the reclassification of two subjects originally categorized as ongoing through 150 days post dose in the Primary Analysis and were changed to "lost to follow-up" at the time of the database lock for the second interim analysis. The overall interpretation of the result for the Trial 04 key secondary endpoint is unchanged.

The accumulated data from the full Trial 04 (All Subjects) population provides a more precise estimate of the efficacy of nirsevimab against MA RSV LRTI with hospitalization of 76.8% (95% CI 49.4% to 89.4%); Table 13) than was seen with the smaller Trial 04 (Primary Cohort).

Supplementary data in Table 42 show that the overall frequency of symptoms associated with MA RSV LRTI with hospitalization was similar across the two cohorts enrolled in Trial 04, and in Trial 04 (All Subjects). Supplementary Table 43 shows the treatment modalities associated with the case definitions of RSV hospitalization. Overall, the cases occurring in the two different Trial 04 cohorts were similar with respect to the frequency and duration of oxygen use, respiratory support, and intensive care unit stays.

The consistency of benefit seen across populations supports the conclusion that nirsevimab provides a compelling and clinically meaningful efficacy for MA RSV LRTI with hospitalization for all infants entering their first RSV season.

Table 13 Summary of Efficacy Against MA RSV LRTI with Hospitalization Through 150 Days Post Dose

	Term and late preterm infants born ≥ 35 wGA				**Very and moderately preterm infants born ≥ 29 to < 35 wGA**			
	Trial 04 (Primary Cohort)		**Trial 04 (All Subjects)**		**Trial 03**		**Trial 03 (Proposed Dose)**	
Statistic	**Placebo (N = 496)**	**Nirsevimab (N = 994)**	**Placebo (N = 1003)**	**Nirsevimab (N = 2009)**	**Placebo (N = 484)**	**Nirsevimab (N = 969)**	**Placebo (N = 290)**	**Nirsevimab (N = 570)**
Subjects with events, n (%)	8 (1.6)	6 (0.6)	20 (2.0)	9 (0.4)	20 (4.1)	8 (0.8)	13 (4.5)	3 (0.5)
RRR (95% CI) p-value	62.1% (-8.6% to 86.8%) p = 0.0708		76.8% (49.4% to 89.4%)		78.4% (51.9% to 90.3%) p = 0.0002		86.5% (53.5% to 96.1%)	

CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; n = number of events observed N = number of subjects; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus; wGA = weeks gestational age.

Further support is given to the analysis in Trial 04 (All Subjects) by the comparable RSV disease risks observed between the 2 study cohorts; the consistency of the effect observed against MA RSV LRTI in Trial 04 (Primary Cohort) and Trial 04 (All Subjects) further supports combining data from the two cohorts enrolled into the study. The incidence of RSV was similar in both cohorts: in the placebo arms of the Primary and Safety Cohorts respectively, the percentages of subjects who experienced an event were 5.0% and 5.7% for MA RSV LRTI and 1.6% and 2.4% for MA RSV LRTI with hospitalization. In addition, analysis of disease symptoms (supplementary Table 42) and treatment modalities (supplementary Table 43) supports the similarity of cases requiring hospitalization in both cohorts. The cases occurring in the two different Trial 04 cohorts were similar with respect to the frequency and duration of oxygen use, respiratory support, and intensive care unit stays.

To further examine whether the treatment effect is consistent across the cohorts, the Cochran–Mantel–Haenszel test (CMH) was used to test the association between treatment and RSV LRTI hospitalization while accounting for potential confounding through any cohort differences. The equality of the treatment effect across strata was examined using the Breslow-Day test. The results fail to reject the null hypothesis of homogeneity of the odds ratios from each stratum ($p = 0.1818$) thus supporting that it is appropriate to combine the two cohorts. The Trial 04 (All Subjects) estimate is similar to the findings of the Trial 04 (Primary Cohort) and provides a precise and representative estimate of efficacy across the population.

The consistency of benefit seen across populations supports the conclusion that nirsevimab provides a compelling and clinically meaningful efficacy for MA RSV LRTI with hospitalization for all infants entering their first RSV season.

4.2.4 Efficacy against MA RSV LRTI (Very Severe)

Table 14 shows a summary of the efficacy of nirsevimab against MA RSV LRTI (very severe) in term and preterm infants born ≥ 29 wGA. MA RSV LRTI (very severe) was defined as the subset of cases of MA RSV LRTI with hospitalization that require oxygen or IV fluids.

Supplementary data in Table 42 show that the overall frequency of symptoms associated with MA RSV LRTI (very severe) was similar across the two cohorts enrolled into Trial 04 and in Trial 04 (All Subjects), providing further support for the similarity of disease across these cohorts.

Table 14 Summary of Efficacy Against MA RSV LRTI (Very Severe) Through 150 Days Post Dose

	Term and late preterm infants born ≥ 35 wGA				**Very and moderately preterm infants born ≥ 29 to < 35 wGA**			
	Trial 04 (Primary Cohort)		**Trial 04 (All Subjects)**		**Trial 03**		**Trial 03 (Proposed Dose)**	
Statistic	**Placebo N = 496**	**Nirsevimab N = 994**	**Placebo N = 1003**	**Nirsevimab N = 2009**	**Placebo N = 484**	**Nirsevimab N = 969**	**Placebo N = 290**	**Nirsevimab N = 570**
Subjects with events, n (%)	7 (1.4)	5 (0.5)	17 (1.7)	7 (0.3)	16 (3.3)	4 (0.4)	11 (3.8)	0 (0)
RRR (95% CI)	64.2% (-12.1% to 88.6%)		78.6% (48.8% to 91.0%)		87.5% (62.9% to 95.8%)		100.0% (79.7% to NE)	

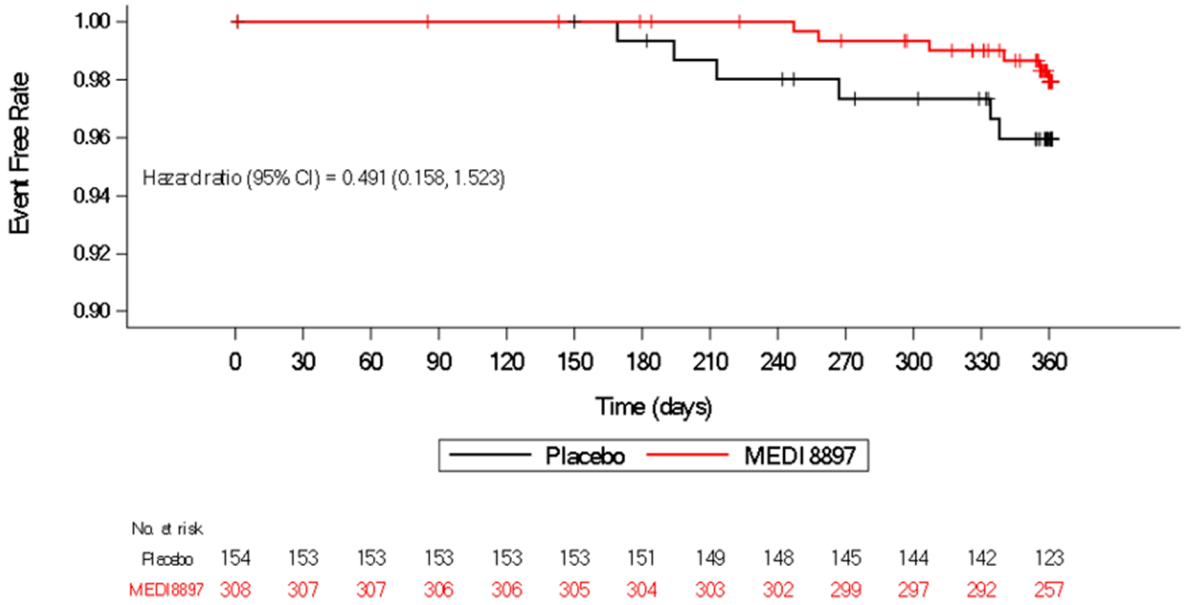
CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; n = number of events observed N = number of subjects; NE= not estimable; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus; wGA = weeks gestational age.

4.2.5 Persistence of Efficacy

The nirsevimab studies supporting this BLA were designed to evaluate the efficacy of nirsevimab over a 5-month RSV season; infants were dosed prior to the RSV season and followed through 5 months. As expected, there was minimal RSV transmission outside the usual RSV season and consequently data to evaluate the efficacy of nirsevimab beyond this 5-month period are limited.

However, due to the COVID-19 pandemic, the usual RSV season did not occur in South Africa where subjects remained unexposed and naïve to RSV in the 5-month period following dosing with nirsevimab. When restrictions were lifted, there was a 'rebound' of RSV and subjects were exposed to RSV transmission. In Trial 04 (Primary Cohort), 6/154 (3.9%) subjects in the placebo group experienced an event of MA RSV LRTI compared to 6/308 (1.9%) in nirsevimab group through 360 days post dose. In a post-hoc exploratory analysis of the primary endpoint (time to first MA RSV LRTI through 360 days post dose) in Trial 04 (Primary Cohort), there was a trend towards benefit (HR 0.491; 95% CI 0.158 to 1.523), suggesting potential protection beyond Day 150 post dose (Figure 17).

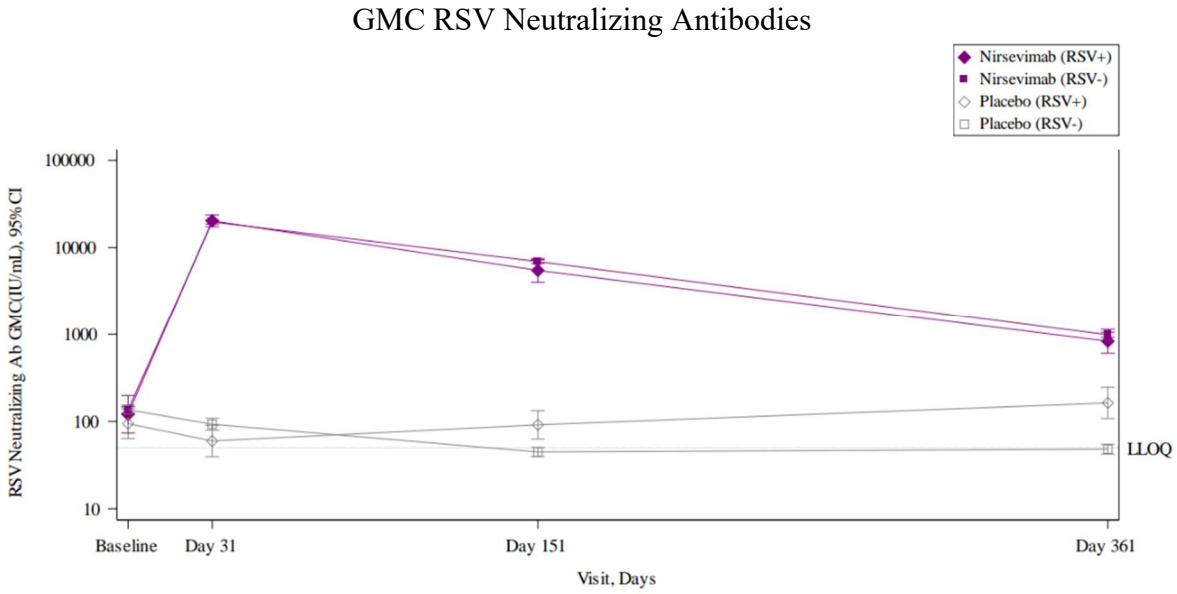
Figure 17 Kaplan-Meier Plot for Time to First MA RSV LRTI (Protocol Defined) through 360 Days Post Dose in Subjects from South Africa – Trial 04 (Primary Cohort)



Tick marks indicate censored data.
CI = confidence intervals; LRTI = lower respiratory tract infection; MA = medically attended; MEDI8897 = nirsevimab; RSV = respiratory syncytial virus.

Nirsevimab efficacy persisting beyond Day 150 post dosing is also suggested by the observation that anti-RSV neutralizing antibodies remained persistently higher in subjects who received nirsevimab versus placebo up to Day 360 post dose (Figure 18).

Figure 18 Serum RSV Neutralizing Antibody Levels by RSV Status Through 360 Days Post Dose – Trial 04 (Primary Cohort)



Ab = antibody; CI = confidence interval; GMC = geometric mean concentration; IU = international units; LLOQ = lower limit of quantification; MEDI8897 = nirsevimab; Min = minimum; n = number of subjects in treatment group; RSV = respiratory syncytial virus; RSV+ = diagnostic-confirmed positive RSV infection based on Central RT-PCR or local testing and RSV- = no diagnostic-confirmed RSV infection based on Central RT-PCR or local testing; RT-PCR = reverse transcriptase polymerase chain reaction.

4.2.6 Public Health Value

Efficacy Against Any Cause Respiratory Illness

Exploratory analyses assessed the impact of nirsevimab on 'any cause' respiratory illness, ie, illness not limited to RSV, in Trial 03 and Trial 04 (Table 15).

The potential for replacement of one pathogen by another must be considered when evaluating a prophylactic intervention such as nirsevimab. Reducing the incidence of RSV could be associated with an increase in another respiratory disease, such that the overall rate of disease is not reduced. While the 'any cause' analyses do not preclude such 'replacement disease' with another pathogen, efficacy against the 'any cause' endpoint does indicate an overall benefit for nirsevimab versus placebo (Table 15) and, therefore, provides reassurance that any potential for 'replacement' is outweighed by the overall treatment benefit.

Table 15 Overview of Efficacy Against Case Definitions of Any Cause Respiratory Illness Endpoints Through Day 150 Post Dose

Statistic	Term and late preterm infants born ≥ 35 wGA				Very and moderately preterm infants born ≥ 29 to < 35 wGA			
	Trial 04 (Primary Cohort)		Trial 04 (All Subjects)		Trial 03		Trial 03 (Proposed Dose)	
	Placebo (N = 496)	Nirsevimab (N = 994)	Placebo (N = 1003)	Nirsevimab (N = 2009)	Placebo (N = 484)	Nirsevimab (N = 969)	Placebo (N = 290)	Nirsevimab (N = 570)
All MA LRTI (any cause) – exploratory endpoint based on alternative case definition								
Subjects with events n (%)	77 (15.5)	92 (9.3)	139 (13.9)	171 (8.5)	125 (25.8)	191 (19.7)	72 (24.8)	99 (17.4)
RRR (95% CI)	40.3% (20.7% to 55.0%)		38.2 (23.7, 50.0)		23.8% (7.2% to 37.4%)		29.9% (8.3% to 46.4%)	
All MA respiratory illness with hospitalization (any cause) – exploratory endpoint based on alternative case definition								
Subjects with events n (%)	16 (3.2)	24 (2.4)	37 (3.7)	45 (2.2)	46 (9.5)	53 (5.5)	35 (12.1)	33 (5.8)
RRR (95% CI)	24.9% (-40.0% to 59.7%)		38.9% (6.3% to 60.2%)		42.5% (16.0% to 60.7%)		52.1% (24.6% to 69.6%)	

Data presented for the Number (%) of subjects with events; for subjects with multiple events, only the first event is included in the analysis.
CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; n = number of events observed N = number of subjects; RRR = relative risk reduction; wGA = weeks gestational age.

Healthcare Resource Utilization

There is trend towards reduction in HRU associated with cases of MA RSV LRTI through 150 days post dose for Trial 04 (All Subjects) and Trial 03 (Proposed dose) summarized in Table 16.

Table 16 Healthcare Resource Utilization for MA RSV LRTI Through 150 Days Post Dose

	Term and late preterm infants born ≥ 35 wGA		Very and moderately preterm infants born ≥ 29 to < 35 wGA	
	Trial 04 (All Subjects)		Trial 03 (Proposed Dose)	
HRU parameter, n (%)	Placebo (N = 1003)	Nirsevimab (N = 2009)	Placebo (N = 290)	Nirsevimab (N = 570)
Admission to hospital	20 (2.0)	9 (0.4)	13 (4.5)	3 (0.5)
Admission to ICU	1 (0.1)	1 (0.0)	5 (1.7)	0 (0.0)
Respiratory support use	2 (0.2)	1 (0.0)	4 (1.4)	0 (0.0)
CPAP or HFNC	2 (0.2)	1 (0.0)	4 (1.4)	0 (0.0)
Mechanical ventilation	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Supplemental oxygen use	16 (1.6)	6 (0.3)	11 (3.8)	0 (0.0)
Outpatient visit	50 (5.0)	21 (1.0)	7 (2.4)	0 (0.0)
Outpatient ED	14 (1.4)	3 (0.1)	2 (0.7)	0 (0.0)
Urgent care	4 (0.4)	4 (0.2)	2 (0.7)	0 (0.0)
Outpatient clinic	42 (4.2)	19 (0.9)	4 (1.4)	0 (0.0)

Subjects were counted once for each category regardless of the number of events. Incidence rate was calculated using the number of ITT subjects followed through 150 days post dose as the denominator.
CPAP = continuous positive airway pressure HFNC high flow nasal cannula); ED = emergency department; HRU = healthcare resource utilization; ICU = intensive care unit; ITT = intent-to-treat; LRTI = lower respiratory tract infection; MA = medically attended; n = number of subjects; RSV = respiratory syncytial virus; wGA = weeks gestational age.

Impact Assessment

Impact assessment was undertaken to estimate the number of cases averted over a typical 5-month RSV season (based on the seasonal difference in the estimated number of cases between nirsevimab and placebo and expressed per 1000 infants immunized) and the number of subjects that would need to be immunized to prevent one case (Table 17). This was conducted in Trial 03 (Proposed Dose) and subjects in Trial 04 (Primary Cohort) from Northern Hemisphere countries, where there was a normal RSV season prior to the impact of the COVID-19 pandemic.

In the term and late preterm infants, the number of prevented cases of any cause LRTI is beyond the number of prevented cases of RSV LRTI using the expansive case definition including those identified by local RSV testing (Table 17). Similarly, in preterm infants

≥ 29 wGA, the number of prevented cases of any cause respiratory illness hospitalization is greater than All MA RSV (any test) respiratory illness with hospitalization. The potential difference between these endpoints may be explained by under-detection of RSV cases due to missing samples for confirmation of RSV, or possibly the contribution of an effect due to secondary bacterial pathogens (Madhi et al 2004, Weinberger et al 2015).

In the 2 populations of preterm (born ≥ 29 to < 35 wGA) and term and late preterm (born ≥ 35 wGA) infants, the number needed to immunize to prevent a case of All MA LRTI (any cause) was similar (being 13 and 11, respectively, Table 17). However, as expected, given the higher hospital admission rates in premature infants, a lower number needed to immunize is required to prevent a case of All MA respiratory illness with hospitalization (any cause; 16 versus 57, respectively). These results are consistent with projected estimates for RSV monoclonal antibodies with extended half-lives (Finelli et al 2020) and compare very favorably with routinely recommended pediatric vaccines (Lewis et al 2007; Milne and Grimwood, 2009; Palmu et al 2018).

Table 17 Impact Analysis for Case Definitions of MA LRTI RSV Over the Typical 5-Month RSV Season – Trial 04 (Primary Cohort), and Trial 03 (Proposed Dose)

	Term and late preterm infants born ≥ 35 wGA		Very and moderately preterm infants born ≥ 29 to < 35 wGA	
	Trial 04 (Primary Cohort) [a]		Trial 03 (Proposed Dose)	
Endpoint	Cases averted per 1000 immunized (95% CI)	Number needed to immunize to prevent 1 case (95% CI)	Cases averted per 1000 immunized (95% CI)	Number needed to immunize to prevent 1 case (95% CI)
All MA RSV (any test) LRTI	83.4 (62.0 to 105.0)	12 (10 to 16)	73.0 (53.0 to 95.0)	14 (11 to 19)
All MA RSV (any test) respiratory illness with hospitalization	19.0 (5.5 to 32.0)	53 (31 to 182)	37.8 (22.0 to 53.0)	27 (19 to 46)
All MA LRTI (any cause)	93.6 (63.0 to 124.0)	11 (8 to 16)	74.8 (39.5 to 109.0)	13 (9 to 25)
All MA respiratory illness with hospitalization (any cause)	17.7 (2.0 to 33.0)	57 (30 to 500)	63.4 (39.0 to 88.0)	16 (11 to 26)

[a] For Trial 04 (Primary Cohort), analysis includes subjects in Northern Hemisphere countries only (ie, where the RSV transmission season occurred).

CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; RSV = respiratory syncytial virus; wGA = weeks gestational age.

The number of cases averted over the typical 5-month RSV season was calculated from the seasonal difference in the estimated number of cases between nirsevimab and placebo and expressed per 1000 infants immunized. The 95% CI was estimated by bootstrapping, using the 2.5 and 97.5 percentiles of 1000 replicates obtained by sampling subjects.

Number needed to immunize to prevent 1 case was calculated through dividing 1000 by the number of cases averted per 1000 immunized. The 95% CI was calculated through dividing 1000 by the 97.5% and 2.5% confidence limits of the number of cases averted per 1000 immunized.

4.3 Efficacy Extrapolation to Infants and Children at Higher Risk of RSV Disease

Trial 05 (Section 4.3.1) evaluated safety and PK of nirsevimab in infants with a higher risk of severe RSV disease, including those who remain vulnerable to RSV disease through their second season. Nirsevimab efficacy was extrapolated to these higher risk infants from the established efficacy in healthy infants based on comparable PK, as agreed with the FDA (End-of-Phase II meeting, February 2019). In randomized Trial 05, comparing nirsevimab and palivizumab, formal hypothesis testing for efficacy (non-inferiority versus palivizumab) was precluded, as a non-inferiority margin could not be established due to lack of historical efficacy data for the MA RSV LRTI endpoint for palivizumab.

The assumptions for extrapolation of efficacy based on comparable PK are:

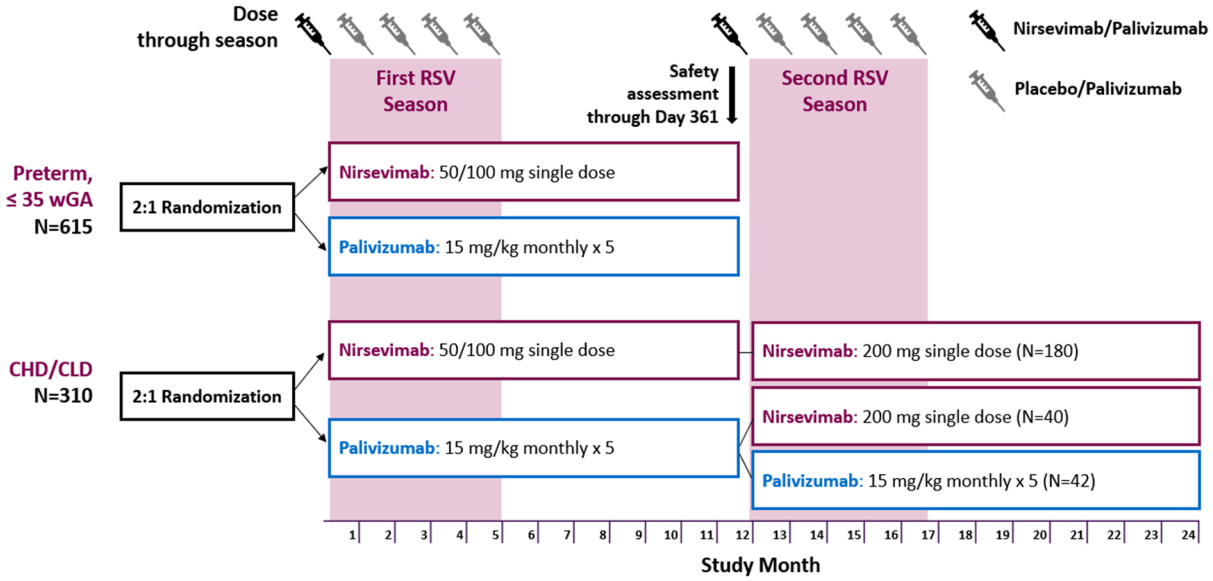
- Comparable viral etiology between healthy infants and infants/children at higher risk.
- No expected difference in mechanism of action based on subgroup (age or medical condition) since nirsevimab acts by binding to a protein on the causative pathogen (RSV) and does not bind any endogenous targets in human. Similar exposure-response between nirsevimab serum levels and neutralizing ability is therefore expected.

Extrapolation of efficacy was performed by comparison of nirsevimab serum exposures (observed concentrations on Day 150 post dose, and $AUC_{0\text{-}365}$ derived based on individual parameters from the final population PK model) in Trial 05 to those in Trial 04.

4.3.1 Trial 05 Study Design

Trial 05 enrolled a population of palivizumab-eligible infants and provided a direct comparison between palivizumab and nirsevimab. Two cohorts were enrolled, preterm infants ≤ 35 wGA and infants with CLD of prematurity or hemodynamically significant CHD. The study design is shown in Figure 19. Subjects in the nirsevimab group received a single IM dose of nirsevimab followed by 4 once-monthly IM doses of placebo and subjects in the palivizumab group received 5 once-monthly IM doses of palivizumab 15 mg/kg. The CLD/CHD cohort continued to a second year of follow-up, subjects randomized to nirsevimab in RSV Season 1 received a second dose of nirsevimab in Season 2 and, those who were randomized to palivizumab in Season 1 were re-randomized 1:1 to palivizumab or nirsevimab. Subjects in the RSV Season 2 nirsevimab groups received a single dose of 200 mg IM nirsevimab followed by 4 once-monthly IM doses of placebo. Subjects in the palivizumab group received 5 once-monthly IM doses of 15 mg/kg palivizumab.

Figure 19 Overview of the Trial 05 Study Design



Within each cohort, randomization was stratified by hemisphere (Northern or Southern) and subject age at the time of RSV Season 1 randomization (≤ 3.0 months, > 3.0 to ≤ 6.0 months, > 6.0 months).
PK sampling was performed pre-dose, and Day 8 (Japan only), Day 15 (EU only) or 31 (non-EU), 151 and 361 post-dose.
CHD = congenital heart diseases; CLD = chronic lung disease; EU = European Union; RSV = respiratory syncytial virus; wGA = weeks gestational age.

The primary objective was the safety and tolerability of nirsevimab versus palivizumab and the key secondary objective was PK. Descriptive data on ADA and the occurrence of MA RSV LRTI were collected.

Specific subgroups of interest in Trial 05 (ie, subgroups not studied in Trial 03 or Trial 04) included extremely preterm infants < 29 wGA in Season 1, and children with CLD of prematurity or hemodynamically significant CHD in Season 1 and Season 2.

As described in Section 2.4.3.1, enrollment into Trial 05 was paused in March 2020 due to the COVID-19 pandemic and resumed in October 2020 (with the planned enrollment target completed).

4.3.2 Trial 05 Disposition, Demographics and Baseline Characteristics

Overall, 925 subjects were randomized in Season 1, included 310 subjects in the CLD/CHD cohort and 615 subjects in the preterm cohort (Table 18). After completing follow-up in Season 1, 262 subjects with CHD/CLD continued into Season 2 (Table 19).

Table 18 Trial 05 Subject Disposition (Season 1)

Overall population	Number (%) of Subjects	
	Palivizumab	Nirsevimab
Subjects randomized	309	616
Preterm cohort	208 (67.3)	407 (66.1)
CHD/CLD cohort	101 (32.7)	209 (33.9)
Subjects randomized and dosed	304 (98.4)	614 (99.7)
Subjects who completed treatment	273 (88.3)	554 (89.9)
Subjects who discontinued treatment	31 (10.0)	60 (9.7)
Adverse event	0 (0.0)	1 (0.2)
Death	1 (0.3)	5 (0.8)
Lost to follow-up	2 (0.6)	8 (1.3)
Withdrawal by parent/guardian	17 (5.5)	31 (5.0)
Due to COVID-19 pandemic	6 (1.9)	12 (1.9)
Other	5 (1.6)	3 (0.5)
Study phase status		
Completed Season 1, Day 150 post dose follow-up	293 (94.8)	593 (96.3)
Completed Season 1	263 (85.1)	543 (88.1)
Early study discontinuation	46 (14.9)	73 (11.9)
Death	1 (0.3)	5 (0.8)
Lost to follow up	7 (2.3)	17 (2.8)
Withdrawal by parent/guardian	28 (9.1)	43 (7.0)
Due to COVID-19 pandemic	3 (1.0)	2 (0.3)
Other	7 (2.3)	6 (1.0)

CHD = congenital heart disease; CLD = chronic lung disease.

Table 19 Trial 05 Subject Disposition (Season 2)

Subjects with CHD/CLD continuing into Season 2	Number (%) of Subjects		
	Palivizumab/ Palivizumab	Palivizumab/ Nirsevimab	Nirsevimab/ Nirsevimab [a]
Subjects re-randomized	42	40	180
Subjects re-randomized and dosed	42 (100.0)	40 (100.0)	180 (100.0)
Subjects who completed treatment	39 (92.9)	38 (95.0)	173 (96.1)
Subjects who discontinued treatment	3 (7.1)	2 (5.0)	7 (3.9)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (0.6)

Table 19 Trial 05 Subject Disposition (Season 2)

Subjects with CHD/CLD continuing into Season 2	Number (%) of Subjects		
	Palivizumab/ Palivizumab	Palivizumab/ Nirsevimab	Nirsevimab/ Nirsevimab [a]
Withdrawal by parent/guardian	1 (2.4)	1 (2.5)	3 (1.7)
Due to COVID-19 pandemic	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (4.8)	1 (2.5)	3 (1.7)
Study phase status			
Completed Season 2, Day 150 post-dose follow-up	40 (95.2)	38 (95.0)	174 (96.7)
Completed the study	17 (40.5)	18 (45.0)	69 (38.3)

[a] The subjects randomized to nirsevimab in Season 1 were not re-randomized in Season 2.
CHD = congenital heart disease; CLD = chronic lung disease.

In Trial 05, subjects' baseline characteristics were balanced between the 2 treatment arms in both cohorts (Table 20). Trial 05 included 104 subjects with CHD and 217 with CLD; 13 subjects had both CHD and CLD (including 5 subjects born < 29 wGA); and 117 subjects with CLD and one subject with CHD were born < 29 wGA.

Table 20 Demographic and Baseline Characteristics for Overall Population, Preterm and CLD/CHD Cohorts (Season 1) – ITT Population

Characteristic	Overall			Preterm			CLD/CHD		
	Palivizumab (N = 309)	Nirsevimab (N = 616)	Total (N = 925)	Palivizumab (N = 208)	Nirsevimab (N = 407)	Total (N = 615)	Palivizumab (N = 101)	Nirsevimab (N = 209)	Total (N = 310)
Age group, n (%)									
≤ 3.0 months	144 (46.6)	274 (44.5)	418 (45.2)	113 (54.3)	214 (52.6)	327 (53.2)	31 (30.7)	60 (28.7)	91 (29.4)
> 3.0 to ≤ 6.0 months	101 (32.7)	210 (34.1)	311 (33.6)	59 (28.4)	126 (31.0)	185 (30.1)	42 (41.6)	84 (40.2)	126 (40.6)
> 6.0 months	64 (20.7)	132 (21.4)	196 (21.2)	36 (17.3)	67 (16.5)	103 (16.7)	28 (27.7)	65 (31.1)	93 (30.0)
Neonates, n (%)									
Age < 28 days at randomization	29 (9.4)	46 (7.4)	75 (8.1)	22 (10.6)	40 (9.8)	62 (10.1)	7 (6.9)	6 (2.9)	13 (4.2)
Sex, n (%)									
Female	133 (43.0)	297 (48.2)	430 (46.5)	93 (44.7)	201 (49.4)	294 (47.8)	40 (39.6)	96 (45.9)	136 (43.9)
Male	176 (57.0)	319 (51.8)	495 (53.5)	115 (55.3)	206 (50.6)	321 (52.2)	61 (60.4)	113 (54.1)	174 (56.1)
Race, n (%) [a]									
American Indian or Alaska Native	5 (1.6)	11 (1.8)	16 (1.7)	5 (2.4)	11 (2.7)	16 (2.6)	0	0	0
Asian	14 (4.5)	36 (5.8)	50 (5.4)	9 (4.3)	26 (6.4)	35 (5.7)	5 (5.0)	10 (4.8)	15 (4.8)
Black or African American	29 (9.4)	59 (9.6)	88 (9.5)	24 (11.6)	49 (12.0)	73 (11.9)	5 (5.0)	10 (4.8)	15 (4.8)
Native Hawaiian/other Pacific Islander	1 (0.3)	4 (0.6)	5 (0.5)	1 (0.5)	3 (0.7)	4 (0.7)	0	1 (0.5)	1 (0.3)
White	249 (80.8)	483 (78.4)	732 (79.2)	160 (77.3)	305 (74.9)	465 (75.7)	89 (88.1)	178 (85.2)	267 (86.1)
Other	6 (1.9)	17 (2.8)	23 (2.5)	6 (2.9)	10 (2.5)	16 (2.6)	0	7 (3.3)	7 (2.3)
Multiple categories checked	4 (1.3)	6 (1.0)	10 (1.1)	2 (1.0)	3 (0.7)	5 (0.8)	2 (2.0)	3 (1.4)	5 (1.6)
Ethnicity, n (%)									
Hispanic or Latino	41 (13.3)	99 (16.1)	140 (15.2)	35 (16.9)	77 (18.9)	112 (18.2)	6 (5.9)	22 (10.5)	28 (9.0)
Not Hispanic or Latino	267 (86.7)	517 (83.9)	784 (84.8)	172 (83.1)	330 (81.1)	502 (81.8)	95 (94.1)	187 (89.5)	282 (91.0)

Table 20 Demographic and Baseline Characteristics for Overall Population, Preterm and CLD/CHD Cohorts (Season 1) – ITT Population

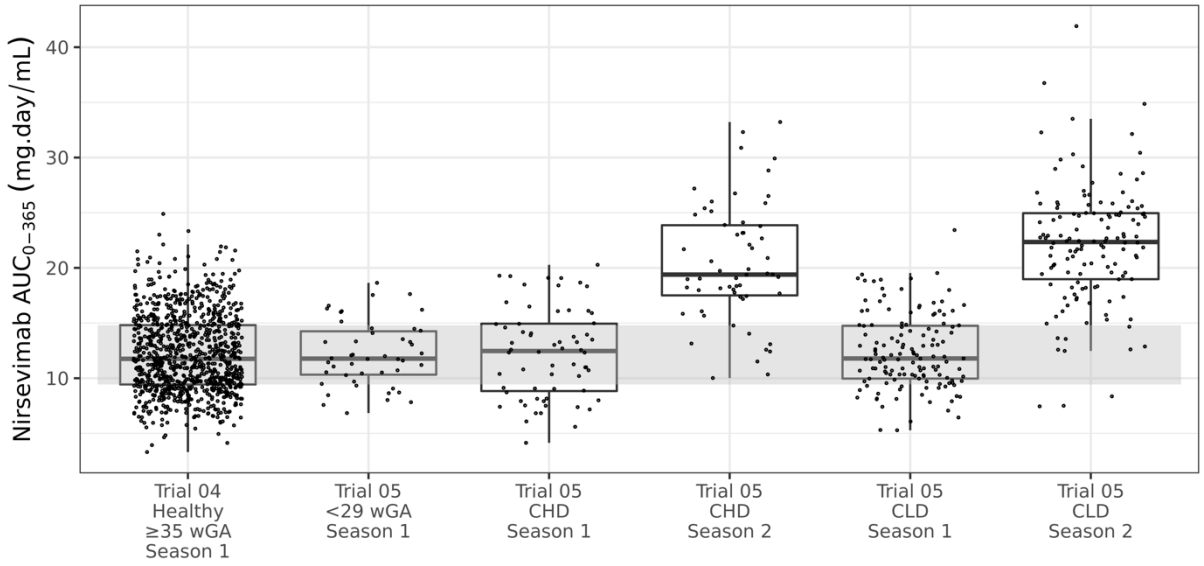
Characteristic	Overall			Preterm			CLD/CHD		
	Palivizumab (N = 309)	Nirsevimab (N = 616)	Total (N = 925)	Palivizumab (N = 208)	Nirsevimab (N = 407)	Total (N = 615)	Palivizumab (N = 101)	Nirsevimab (N = 209)	Total (N = 310)
Weight group on Day 1, n (%)									
< 5 kg	174 (57.2)	344 (56.1)	518 (56.5)	123 (59.7)	243 (60.0)	366 (59.9)	51 (52.0)	101 (48.6)	152 (49.7)
≥ 5 kg	130 (42.8)	269 (43.9)	399 (43.5)	83 (40.3)	162 (40.0)	245 (40.1)	47 (48.0)	107 (51.4)	154 (50.3)
Gestational age group, n (%)									
< 29 weeks	70 (22.7)	130 (21.1)	200 (21.6)	28 (13.5)	49 (12.0)	77 (12.5)	42 (41.6)	81 (38.8)	123 (39.7)
≥ 29 to < 32 weeks	71 (23.0)	128 (20.8)	199 (21.5)	59 (28.4)	91 (22.4)	150 (24.4)	12 (11.9)	37 (17.7)	49 (15.8)
≥ 32 to < 35 weeks	126 (40.8)	262 (42.5)	388 (41.9)	114 (54.8)	235 (57.7)	349 (56.7)	12 (11.9)	27 (12.9)	39 (12.6)
≥ 35 weeks	42 (13.6)	96 (15.6)	138 (14.9)	7 (3.4)	32 (7.9)	39 (6.3)	35 (34.7)	64 (30.6)	99 (31.9)
Birth weight group, n (%)									
≤ 2.5 kg	274 (88.7)	534 (86.7)	808 (87.4)	203 (97.6)	375 (92.1)	578 (94.0)	71 (70.3)	159 (76.1)	230 (74.2)
> 2.5 kg	35 (11.3)	82 (13.3)	117 (12.6)	5 (2.4)	32 (7.9)	37 (6.0)	30 (29.7)	50 (23.9)	80 (25.8)
Multiple birth, n (%)									
Yes	107 (34.6)	189 (30.7)	296 (32.0)	90 (43.3)	149 (36.6)	239 (38.9)	17 (16.8)	40 (19.1)	57 (18.4)
No	202 (65.4)	427 (69.3)	629 (68.0)	118 (56.7)	258 (63.4)	376 (61.1)	84 (83.2)	169 (80.9)	253 (81.6)
CHD, n (%)	34 (11.0)	70 (11.4)	104 (11.2)	0	0	0	34 (33.7)	70 (33.5)	104 (33.5)
CLD, n (%)	70 (22.7)	147 (23.9)	217 (23.5)	0	0	0	70 (69.3)	147 (70.3)	217 (70.0)
Down syndrome, n (%)	3 (1.0)	9 (1.5)	12 (1.3)	0	2 (0.5)	2 (0.3)	3 (3.0)	7 (3.3)	10 (3.2)
Cystic fibrosis, n (%)	0	2 (0.3)	2 (0.2)	0	2 (0.5)	2 (0.3)	0	0	0

[a] Each race category counts subjects who selected only that category; "Multiple categories checked" counts subjects who selected more than one race category.
CHD = congenital heart disease; CLD = chronic lung disease; ITT = intent-to-treat; n = number of patients in category; N = number of patients.

4.3.3 Trial 05 Pharmacokinetic Results

Efficacy was successfully extrapolated from the healthy infants in Trial 04 (Primary Cohort) to the Trial 05 subgroups of interest. Nirsevimab serum exposures (AUC) in infants in Trial 05 Season 1 (CHD, CLD, or extremely premature) were comparable to those in infants in Trial 04 (Primary Cohort) (Figure 20; see also supplementary Table 44). Slightly higher AUCs were achieved in children in RSV Season 2 than in infants in Trial 04 (Primary Cohort). Based on these data, a similar level of protection is expected across populations.

Figure 20 Efficacy Extrapolation to Infants at Higher Risk and Children Who Remain Vulnerable in Their Second RSV Season Based on PK Data - Trial 05



Box hinges show the interquartile range, middle line is the median, whiskers extend to the largest/smallest value no further than 1.5 x interquartile range, dots are individual predictions of $AUC_{0\text{-}365}$, the shaded area is the Trial 04 (Primary Cohort) interquartile range.
$AUC_{0\text{-}365}$ = area under the concentration-time curve from 0 to 365 days; CHD = congenital heart disease; CLD = chronic lung disease; wGA = weeks gestational age.

In Trial 05 (Season 1), MA RSV LRTI occurred in a similar proportion of subjects in each treatment group during follow-up through 150 days post first dose (4/616 subjects [0.6%] in the nirsevimab group; 3/309 subjects [1.0%] in the palivizumab group). In Season 2, there were no cases of MA RSV LRTI through 150 days post first dose in either group.

4.4 Clinical Efficacy Conclusions

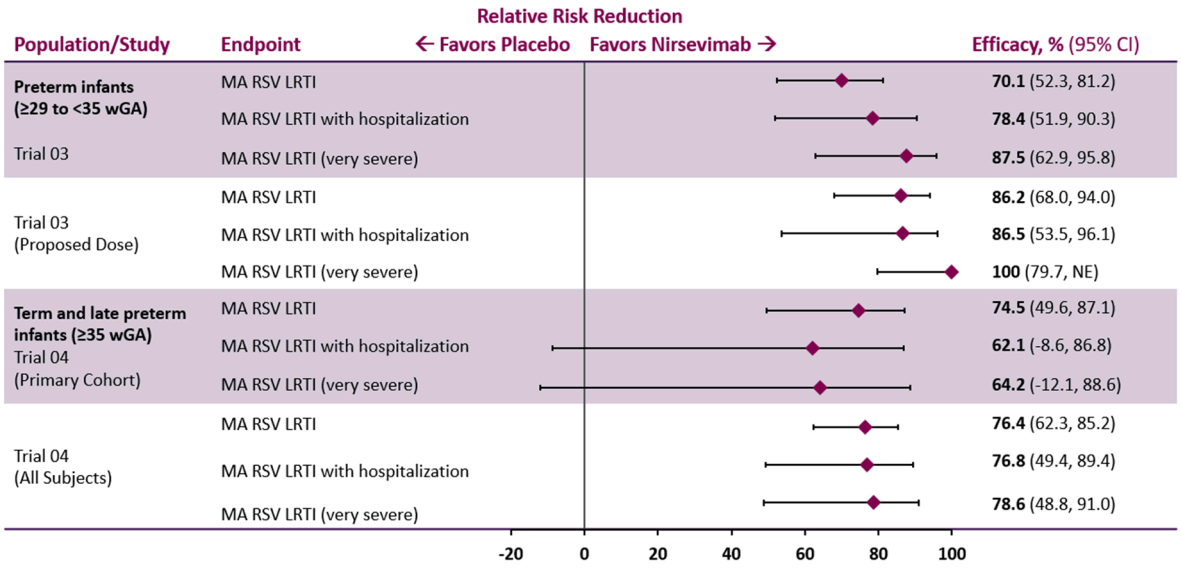
The data from Trial 04 and Trial 03 in healthy infants, with supportive data from Trial 05 in higher risk infants, confirm the efficacy of nirsevimab across a broad population of term and preterm infants entering their first RSV season. The data from Trial 05 also support

nirsevimab efficacy in children who remain vulnerable to severe RSV disease in their second RSV season.

The following findings support the use of nirsevimab for all infants in their first RSV season:

- The primary endpoint was met in both Trial 03 (very and moderately preterm infants born ≥ 29 wGA) and Trial 04 (term and late preterm infants born ≥ 35 wGA):
  - Nirsevimab demonstrated statistically significant efficacy against the primary endpoint, MA RSV LRTI, in both studies (Figure 21)
  - This endpoint comprised the incidence of MA LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season (ie, through 150 days post dose)
  - Subgroup analyses support consistent efficacy of nirsevimab versus placebo across the study populations.
- The secondary endpoint, protection against MA RSV LRTI with hospitalization, was met in Trial 03.
- MA RSV LRTI with hospitalization (secondary endpoint) in Trial 04 (Primary Cohort) alone did not meet the criteria for statistical significance (p-value < 0.05).
  - Efficacy against MA RSV LRTI with hospitalization was supported by the analysis conducted in the larger analysis set incorporating all-randomized subjects, Trial 04 (All Subjects) (Figure 21).
- Nirsevimab efficacy was consistent against disease of increasing levels of severity, including MA RSV LRTI, MA RSV LRTI with hospitalization, and MA RSV LRTI (very severe) (Figure 21).
- Time to event analyses showed clear divergence between nirsevimab and placebo curves in accumulation of events over the entire 150-day efficacy period indicating consistency of efficacy for nirsevimab throughout the course of a typical 5-month RSV season.
- Efficacy findings are also supported by HRU data, with lower percentages of subjects being admitted to hospital or ICU, reduced requirement for respiratory support or supplementary oxygen, and fewer outpatient visits with nirsevimab versus placebo.
- Protection was also observed against all-cause and all-cause respiratory illness with hospitalization.

Figure 21 Nirsevimab Efficacy in Term and Preterm Infants Born ≥ 29 WGA Entering Their First RSV Season – Trial 03 and Trial 04



Efficacy estimates are based on follow-up through 150 Days post dose.
CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus; wGA = weeks gestational age

For infants at higher risk of severe RSV disease in their first season and children remaining vulnerable to severe RSV disease in their second season, efficacy was extrapolated from healthy infants based on comparable PK. Based on comparable PK, a similar level of protection is anticipated in infants at higher risk for severe RSV disease, including children at higher risk for severe RSV disease. These include high-risk subpopulations of infants born extremely preterm (< 29 wGA) in their first RSV season, and children with CLD and/or hemodynamically significant CHD dosed in their first or second RSV season achieved comparable serum exposures to the healthy infant population in which efficacy was established.

5 CLINICAL VIROLOGY

5.1 Experience in Clinical Trials

Nirsevimab exhibited activity against both RSV subtype A and subtype B through 150 days post dose for the Trial 03 and Trial 04 primary endpoint, MA RSV LRTI, as shown in Table 21.

Table 21 MA RSV LRTI Through 150 Days Post Dose According to RSV Subtype – Trial 04 (All Subjects) and Trial 03 (Proposed Dose)

Statistic	MELODY (All Subjects) Term and late preterm infants born ≥ 35 wGA				Study 3 (Proposed Dose) Very and moderately preterm infants born ≥ 29 to < 35 wGA			
	RSV A		RSV B		RSV A		RSV B	
	Placebo (N = 1003)	Nirs (N = 2009)	Placebo (N = 1003)	Nirs (N = 2009)	Placebo (N = 290)	Nirs (N = 570)	Placebo (N = 290)	Nirs (N = 570)
Subjects with events, n (%)	25 (2.5)	14 (0.7)	28 (2.9)	10 (0.5)	14 (4.8)	2 (0.4)	12 (4.1)	5 (0.9)
Subjects requiring imputation n (%)	18 (1.8)	31 (1.5)	17 (1.7)	32 (1.6)	4 (1.4)	10 (1.8)	5 (1.7)	10 (1.8)
RRR (95% CI)	70.8% (43.7% to 84.8%)		81.1% (61.9% to 90.6%)		91.1% (60.7% to 97.9%)		76.9% (35.5% to 91.7%)	

Analyses conducted using the same methodology as for the primary endpoint (Poisson regression with robust variance).
CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; n = number of events observed; N = number of subjects; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus; wGA = weeks gestational age.

In the nirsevimab clinical development program, the potential for monoclonal antibody escape was evaluated by next generation sequencing of the RSV F protein. The prevalence of all RSV F protein sequence variations relative to consensus sequences of recent circulating RSV A and RSV B strains was assessed. RSV F sequence polymorphisms differing from reference sequences were reverse genetically engineered and evaluated for nirsevimab susceptibility in an in-vitro microneutralization assay. In Trial 03, Trial 04, and Trial 05, no major variant substitutions (defined as a consensus allele fraction of ≥ 25%) in the RSV A binding site were observed in subjects who met the definition of a MA RSV LRTI case (primary case definition) or required hospitalization for RSV LRTI (secondary case definition). Two infants who met an exploratory RSV endpoint case definition had RSV A with a binding site substitution (K209R) that did not affect nirsevimab susceptibility.

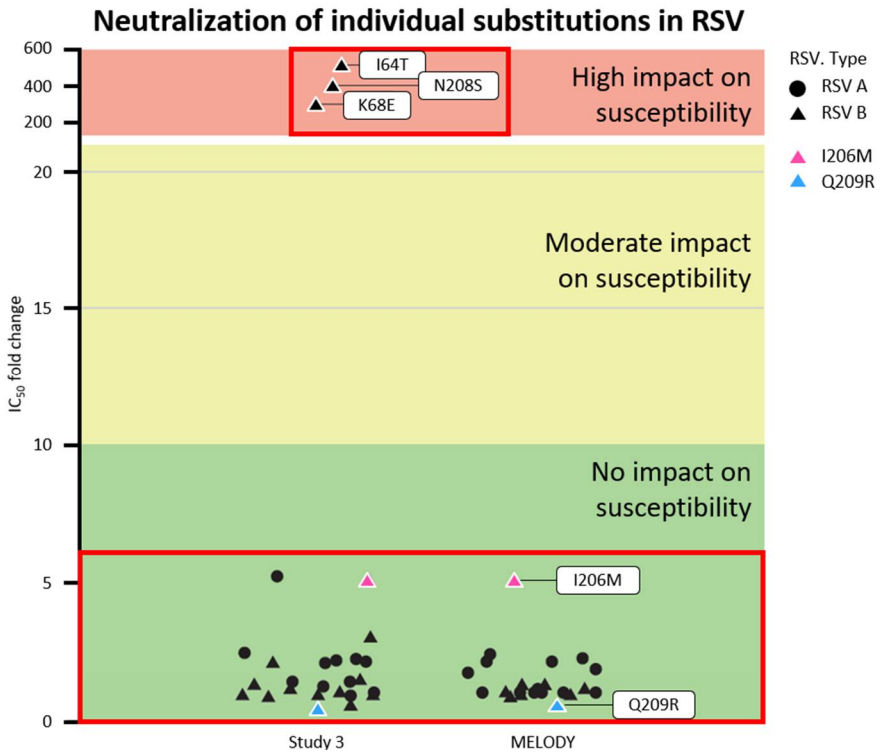
In the RSV B binding site, I206M, Q209R, and S211N substitutions became increasingly prevalent over the course of clinical development (as seen in molecular surveillance studies), but viruses with all three substitutions maintained susceptibility to nirsevimab (including when these substitutions co-occurred). The now globally dominant Q209R substitution was associated with trends towards increased susceptibility to nirsevimab.

Only three major variant substitutions (I64T, N208S, K68E) from two nirsevimab recipients infected with RSV B (both in Trial 03) were associated with nirsevimab escape, with increases of > 200-fold in the half-maximal inhibitory concentration (IC_{50}) (Figure 22). Both study

participants had nirsevimab serum concentrations within the range of those in the weight-banded dosing regimen and also had similar viral titers to those of other nirsevimab recipients infected with RSV. These substitutions have not been observed in further clinical trials or surveillance studies. Viruses containing N208S and substitutions at amino acid 68 in RSV B have been previously described as having similar growth kinetics as reference viruses (Zhu et al 2018).

No monoclonal antibody escape substitutions were identified beyond 150 days post-dose (the typical length of an RSV season), suggesting that waning concentrations of nirsevimab do not lead to an increase in the frequency of such substitutions.

Figure 22 Nirsevimab Neutralized > 99% of RSV Variants Isolated



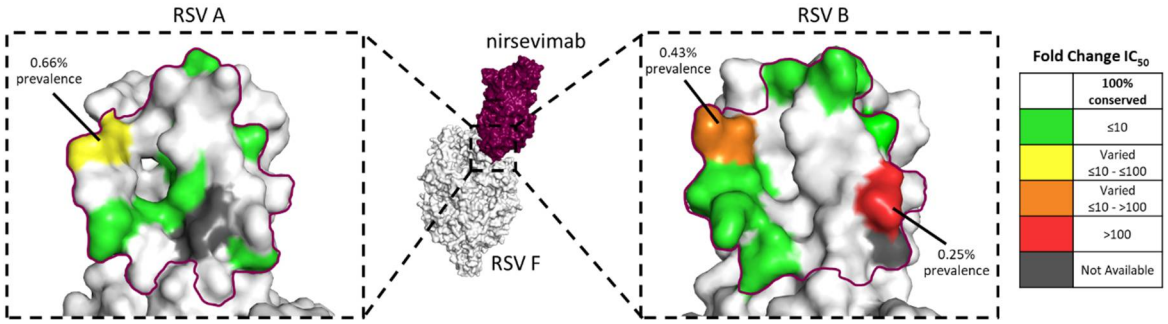
IC_{50} = half-maximal inhibitory concentration; RSV = respiratory syncytial virus.

5.2 Molecular Surveillance of RSV

To evaluate the conservation of residues in the nirsevimab binding site and establish a molecular baseline of RSV F protein sequence variability among recent RSV strains before widespread use of nirsevimab, multiple prospective, multicenter, observational RSV molecular surveillance studies (OUTSMART-RSV, INFORM-RSV, pilot South Africa study) were conducted and RSV sequences analyzed between 2015 and 2021 (Wilkins et al 2023b). Overall, 5675 RSV F sequences (N = 2875 RSV A; N = 2800 RSV B) were analyzed from 17 countries across 5 continents, with low genetic diversity within the nirsevimab binding site

being observed (Figure 23). Two polymorphisms (I206M, Q209R) in the nirsevimab binding site of RSV B emerged in 2015 and became globally dominant by 2021. Nirsevimab effectively neutralized a diverse panel of the recombinant RSV variants identified in these prospective surveillance studies, including the highly prevalent site Ø I206M:Q209R polymorphisms. The frequency of monoclonal antibody escape variants in naturally circulating viruses was rare (< 1%) (and has not persisted or increased in frequency with successive RSV seasons.

Figure 23 Nirsevimab Escape Substitutions in RSV A and B are Rare in Molecular Surveillance Studies



IC_{50} = half-maximal inhibitory concentration; F = F protein; RSV = respiratory syncytial virus.

Evaluation of mAb escape variants globally will continue through prospective, observational molecular surveillance studies and will include data on use of nirsevimab and/or RSV vaccines in participants from whom RSV is isolated.

5.3 Clinical Virology Conclusions

Clinical virology assessment demonstrated that:

- Nirsevimab has clinical efficacy against RSV A and B subtypes.
- Nirsevimab neutralized > 99% of RSV sequences across all clinical studies.
- Monoclonal antibody escape is rare in circulating strains, as determined in global molecular surveillance studies.

6 CLINICAL SAFETY

A total of 3620 infants and children were dosed with nirsevimab across the pivotal studies (Trial 03, Trial 04, Trial 05). Of these, 3224 received the proposed dose regimen (the remaining 396 were subjects from Trial 03 [evaluating a 50 mg dose of nirsevimab) who weighed ≥ 5 kg at dosing (or did not have weight recorded] and received nirsevimab 50 mg).

The safety package supports a favorable safety profile for the nirsevimab 50 mg or 100 mg dose used as prophylaxis against RSV LRTI for all infants in their first RSV season, based on 3580 infants dosed with nirsevimab in their first RSV season (3184 receiving the proposed dose) from Trial 03, Trial 04, and Trial 05, including extremely preterm infants (born < 29 wGA), infants with CLD and CHD.

The safety package also supports a favorable safety profile for the nirsevimab 200 mg dose used as prophylaxis against RSV LRTI in children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season, based on 220 children with CHD/CLD dosed with nirsevimab in their second RSV season in Trial 05 (all of whom received the proposed Season 2 dose). These included 180 children who received a second dose of nirsevimab in Season 2 and 40 children who received a first dose of nirsevimab in Season 2 after receiving palivizumab in Season 1.

Safety findings from early phase dose-escalation studies (Trial 01 in adults and Trial 02 in preterm infants) were consistent with findings in the later phase studies.

For an overview of the studies contributing to the safety database, including a detailed list of each study design, population, dosing regimen, and number randomized and dosed, see Table 5.

6.1 Extent of Exposure

The size of the safety database (3620 infants dosed in the pivotal clinical trials; including 3224 receiving the proposed dose) is adequate to support review of the BLA based on both the recommendations in the Draft Guidance for Industry "Respiratory Syncytial Virus Infection: Developing Antiviral Drugs for Prophylaxis and Treatment" (FDA 2017) and discussions with the Agency regarding a prelicensure safety database of 3000 exposed subjects (see Section 2.4.3).

The exposure and duration of follow-up for subjects that received nirsevimab in their first and second RSV season across the 3 pivotal studies is provided in Table 22. For the 3580 infants dosed in their first RSV season and 220 children dosed in their second RSV season (Trial 05), the median duration of safety follow-up at the time of the data cut offs for the BLA submission was 361 days (in both the overall population and the proposed-dose population) and 250 days, respectively.

The demographic and baseline characteristics of the Proposed-Dose Safety Pool and the Trial 05 safety populations were representative of the diverse target population of all infants entering their first RSV season and children who remain vulnerable to severe RSV disease in their second RSV season. Although the majority of subjects were late preterm or term infants, the study population also included extremely preterm infants who received nirsevimab during the first months of life.

Table 22 Safety Database is Adequate to Assess Safety Profile of Nirsevimab in the Intended Population

Safety population that received nirsevimab	Number of subjects (%)
Infants and children in the safety studies: Trial 03, Trial 04 (Primary and Safety Cohorts), and Trial 05 (Season 1 and 2)	3620
Infants who received the proposed dosing regimen in the safety studies	3224
Infants dosed with nirsevimab in their first RSV season	**3580**
Infants who received the proposed dose in their first RSV season	3184[a]
Safety follow up: median 361 days; mean 318 days [a]	
Completed follow up through Day 150 post dose [a]	3041 (95.5)
Completed follow up through Day 360 post dose [a]	2051 (64.4)
Children dosed with nirsevimab in the second RSV season[b]	**220**
Safety follow up: median 198 days; mean 250 days	
Completed follow up through Day 150 post dose	212 (96.4)
Completed follow up through Day 360 post dose	87 (39.5)

[a] Data for subjects receiving the proposed dose.
[b] Subjects with CHD/CLD from Trial 05; all received the proposed Season 2 dosing regimen.
RSV = respiratory syncytial virus

6.2 Safety Data Collection and Analysis

Nirsevimab is a fully human mAb that specifically binds to the prefusion conformation of the RSV F protein and does not have any endogenous target in humans. Nonclinical toxicology data did not indicate any nirsevimab-related safety concerns and there was no cross-reactivity with human tissue (Section 2.4.2). As a result, the important potential risks for nirsevimab during clinical development were based on generic safety risks associated with any immunoglobulin (including mAbs), which include immediate hypersensitivity (including anaphylaxis) and immune complex disease. Additionally, the risk of thrombocytopenia was considered an important potential risk for nirsevimab during clinical development based on reported cases in post-approval use of SYNAGIS® (palivizumab), a mAb with a similar mechanism of action as nirsevimab (thrombocytopenia is included in the Synagis product label) (Synagis PI 2020, Synagis SmPC 2021). These important potential risks of immediate hypersensitivity (including anaphylaxis), immune complex disease, and thrombocytopenia were adverse events of special interest (AESIs) for the nirsevimab clinical program. Adverse events of special interest were evaluated comprehensively, based both on reporting by the investigator and by queries of the AEs occurring in the database based on sponsor-defined MedDRA search criteria for PTs compatible with each of the AESI categories (Section 10.5).

In prior clinical studies of motavizumab, a different anti-RSV F mAb (that binds RSV F at a site distinct from the binding site of nirsevimab and was dosed monthly during the RSV season), events suggestive of immediate hypersensitivity with cutaneous manifestations were

observed in studies of infants at higher risk of severe RSV disease (Carbonell-Estrany et al 2010; Feltes et al 2011). Therefore, additional data were collected on post-dose skin related adverse events in the nirsevimab studies to ensure thorough evaluation of the important potential risk of hypersensitivity, specifically cutaneous manifestations thereof. Adverse events that involved the skin and subcutaneous tissues were collected as 'skin reactions', with a few exceptions for skin related AEs that could be definitively diagnosed (eg, impetigo, scabies, or varicella) or isolated skin lesions. A dedicated skin reaction CRF was developed to collect detailed information on skin reactions, including the investigator's own assessment of etiology and hypersensitivity. For the 3 complementary pivotal studies, CRF guidelines specified reporting of skin reactions as skin hypersensitivity only if the investigator considered the event IP-related. While the principal methodology to determine a signal of hypersensitivity and determine etiology was by investigator report, information collected on the dedicated skin reaction CRF helped ensure that hypersensitivity cases did not go unrecognized.

Safety evaluation was standardized across trials including safety assessments and statistical methods. Assessments included treatment-emergent AEs (as reported by the Investigator; no events were solicited), SAEs, NOCDs, and AESIs, and skin reactions through 360 days post dose (ie, Study Day 361). An NOCD was defined as a newly diagnosed medical condition that was of a chronic, ongoing nature observed after receipt of the IP and assessed by the Investigator as medically significant.

In Trial 04, subjects were followed through a second RSV season without additional RSV prophylaxis to evaluate the theoretical risk of ADE in the setting of low serum concentrations of nirsevimab, and accordingly, events limited to respiratory illnesses that required a medical visit were collected to assess disease occurrence in the second season (Day 362 to 511; Figure 12).

The severity of all AEs was to be graded according to the current version of the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE), where applicable for pediatric assessments.

As subjects in Trial 03 and Trial 04 received a single dose of IP, adverse events resulting in discontinuation of IP were not applicable and thus not evaluated. Since subjects in Trial 05 received multiple doses of IP, AEs leading to discontinuation of IP were evaluated. Across the 3 pivotal studies, AEs leading to discontinuation from the study were evaluated and there were no discontinuations from the study due to an AE in dosed subjects, apart from those resulting in a fatal outcome.

The safety of a single IM dose of nirsevimab (50 mg or 100 mg) was evaluated in comparison to placebo in term and preterm infants born ≥ 29 wGA, based on pooled analyses of data from

all dosed subjects in Trial 03 and Trial 04. Safety analysis was conducted in 2 pools (both prespecified in the SAP for the Integrated Safety Analysis):

- The Trial 04 (All Subjects)/Trial 03 Safety Pool included all dosed subjects from the Trial 04 Primary and Safety Cohort and Trial 03. For this document, the 'All-subject Safety Pool' reference is associated with the Trial 04 (All Subjects)/Trial 03 (All Subjects) Safety Pool.
- The Proposed-Dose Safety Pool included all dosed subjects in the Trial 04 Primary and Safety cohorts and dosed subjects in Trial 03 who weighed < 5 kg at the time of dosing (ie, those who received the proposed dose). For this document, the 'Proposed-Dose Safety Pool' reference is associated with the Trial 04 (All Subjects)/Trial 03 (Proposed Dose) Safety Pool.

The All-Subjects Safety Pool provides the largest pool of placebo-controlled data for nirsevimab and was used to evaluate the ADRs and potential risks for the prescribing information.

The Proposed-Dose Safety Pool showed consistent safety findings to the All-Subjects pool, for subjects with the level of exposure expected in clinical practice.

The focus of the safety presentation in this briefing document is on the Proposed-Dose Safety Pool, which includes all dosed subjects in the Trial 04 Primary and Safety cohorts and Trial 03 subjects who received the proposed dose of nirsevimab (ie, those who weighed < 5 kg at the time of dosing/on Day 1). The Proposed-Dose Safety Pool is considered to provide the most relevant summaries of safety data to evaluate the AE profile based on feedback from the Agency at the pre-BLA meeting (26 July 2022) and represents the intended use of nirsevimab in the healthy infant population born during or entering their first RSV season. Results of the second Integrated Safety Analysis (data cutoff 31 March 2022) are presented including all safety and ADA data based on follow-up through 360 days post dose in Trial 03 and the Trial 04 (Primary Cohort) and through at least 150 days post dose in the Trial 04 (Safety Cohort). Safety follow-up for subjects in Trial 04 (Safety Cohort) was ongoing to Day 361 at the time of interim analysis (Trial 05 Season 2 analysis).

The safety of nirsevimab was also evaluated in infants eligible to receive palivizumab (preterm infants ≤ 35 wGA and infants with CLD or CHD, including extremely preterm infants born < 29 wGA), based on data from the palivizumab-controlled Trial 05. In addition, children up to 24 months of age from the Trial 05 CLD/CHD cohort remained in the study and received nirsevimab or palivizumab in RSV Season 2. Trial 05 therefore allowed comparison of the safety of nirsevimab with another anti-RSV monoclonal antibody both in RSV Season 1 and RSV Season 2 and an assessment of the safety of a repeat dose of nirsevimab in a second RSV season. Results of the Trial 05 Season 2 analysis (data cutoff 30 April 2022) are

presented including safety and ADA data based on follow-up through at least 360 days post first dose in Season 1, and through at least 150 days post first or second dose in Season 2 for the children up to 24 months of age from the CLD/CHD cohort who remained in the study and received nirsevimab or palivizumab in RSV Season 2. Safety follow-up for subjects dosed in Season 2 for Trial 05 was ongoing to Day 361 at the time of the interim analysis (Trial 05 Season 2 analysis). In each Season, AEs analyzed through 30 days post first IP dose of the respective Season permitted an assessment of AEs relative to the active nirsevimab dose compared with one active dose of palivizumab.

Subjects from Trial 05 were evaluated separately from the pooled analyses of Trial 03 and Trial 04 due to differences in study design and the expectation that the nature/rate of AEs would differ across populations given underlying comorbidities.

The same external Independent Data Monitoring Committee consisting of 2 clinicians, both with a Pediatric Infectious Disease background, and a biostatistician oversaw the accumulating safety data from Trial 03, Trial 04, and Trial 05; no study modifications were requested.

6.2.1 Safety Analysis Methods

Safety and ADA data were summarized based on the pooled Safety Population or individual study Safety Population using descriptive statistics unless otherwise specified. All continuous variables were summarized using descriptive statistics reporting N, mean, standard deviation, median, maximum, and minimum. All categorical variables were summarized using frequency counts and percentages. For demographic and baseline variables, subjects were excluded from the summary (eg, means and percentages) of an individual parameter if data were missing. No statistical testing was performed for safety parameters. For risk assessment in Figure 29, the 2-sided 95% CI of the difference in proportions between nirsevimab versus placebo stratified by study were computed from the Miettinen-Nurminen confidence limits (Miettinen and Nurminen, 1985) for the stratum proportion differences as described previously (Agresti 2013). Adverse events were coded using MedDRA version 23.1 for the pooled analyses and Trial 05. The number and percentage of subjects with at least one event were summarized by treatment group and by SOC and PT. If the same AE occurred multiple times within a particular subject, the highest severity and level of relationship observed was reported.

6.3 Overall Summary of Adverse Events

Adverse events in the Proposed-Dose Safety Pool of healthy term and preterm infants born ≥ 29 wGA entering their first RSV season in Trial 03 and Trial 04 are discussed in Section 6.3.1. Safety in vulnerable populations of palivizumab-eligible preterm infants and infants with CLD/CHD in Trial 05 RSV Season 1 and Season 2 are discussed in Section 6.3.2.

6.3.1 Overview of Adverse Events in the Proposed-Dose Safety Pool

Table 23 summarizes treatment-emergent AEs for the Proposed-Dose Safety Pool through at least 150 days post dose (based on follow-up through 360 days post dose in Trial 03 and Trial 04 [Primary Cohort], and at least 150 days post dose for the second cohort enrolled into Trial 04 (ie, the Trial 04 [Safety Cohort]).

The percentages of subjects with at least one AE were comparable between the nirsevimab and placebo groups, when assessed for all AEs through at least 150 days post dose, and for AEs that occurred within 1, 3, 7, 14, and 30 days post dose. The majority (78.8%) of AEs were Grade 1 or 2 in severity. The percentage of subjects with IP-related AEs, IP-related skin reactions, and NOCDs was low and comparable between treatments. None of the NOCDs were considered by the investigator to be IP-related. The percentage of subjects with at least one SAE through at least 150 days post dose was 7.6% vs 10.5% for nirsevimab vs placebo, respectively. None of the SAEs or deaths in the nirsevimab group were considered by the Investigator to be related to IP and none were known or reported to be due to RSV. Deaths were attributed to underlying conditions or common causes of infant mortality in the respective country or region where the subject was enrolled (Table 27).

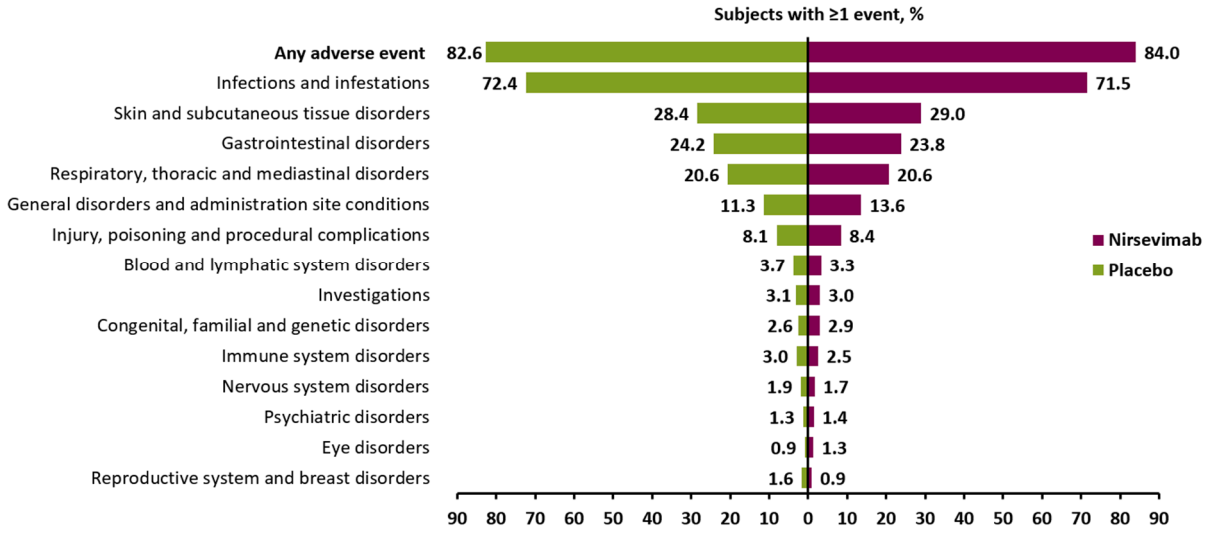
Table 23 Overall Summary of Treatment-Emergent Adverse Events Through at Least 150 Days Post Dose – Proposed-Dose Safety Pool

Subjects [a] with	Number (%) of Subjects		
	Placebo N = 1284	Nirsevimab N = 2570	Total N = 3854
At least 1 event	1060 (82.6)	2158 (84.0)	3218 (83.5)
Occurring ≤ 1 day post dose	14 (1.1)	50 (1.9)	64 (1.7)
Occurring ≤ 3 days post dose	68 (5.3)	151 (5.9)	219 (5.7)
Occurring ≤ 7 days post dose	170 (13.2)	316 (12.3)	486 (12.6)
Occurring ≤ 14 days post dose	309 (24.1)	632 (24.6)	941 (24.4)
Occurring ≤ 30 days post dose	505 (39.3)	1044 (40.6)	1549 (40.2)
At least 1 IP-related event	18 (1.4)	33 (1.3)	51 (1.3)
At least 1 event of ≥ Grade 3 [b]	81 (6.3)	102 (4.0)	183 (4.7)
Occurring ≤ 1 day post dose	0	0	0
Occurring ≤ 3 days post dose	2 (0.2)	4 (0.2)	6 (0.2)
Occurring ≤ 7 days post dose	5 (0.4)	9 (0.4)	14 (0.4)
Occurring ≤ 14 days post dose	8 (0.6)	14 (0.5)	22 (0.6)
Occurring ≤ 30 days post dose	17 (1.3)	23 (0.9)	40 (1.0)
At least 1 IP-related event of ≥ Grade 3 [b]	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Any AE with outcome death	3 (0.2)	6 (0.2)	9 (0.2)
At least 1 serious [c] event	135 (10.5)	195 (7.6)	330 (8.6)
At least 1 serious [c] and/or ≥ Grade 3 severity [b] event	143 (11.1)	208 (8.1)	351 (9.1)
At least 1 IP-related serious [c] event	1 (< 0.1)	0	1 (< 0.1)
At least 1 AESI based on investigator assessment	0	6 (0.2) [d]	6 (0.2) [d]
At least 1 NOCD	4 (0.3)[e]	3 (0.1)[f]	7 (0.2)
At least 1 IP-related NOCD	0	0	0

[a] Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.
[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal.
[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).
[d] All were IP-related skin hypersensitivity events.
[e] Observed events were hypothyroidism (2 subjects), bronchitis chronic (1 subject), childhood asthma (1 subject).
[f] Observed events were PFAPA syndrome (1 subject), asthma (2 subjects).
MedDRA version 23.1.
AE = adverse event; AESI = adverse event of special interest; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; NOCD = new onset chronic disease; PFAPA = periodic fever, aphthous stomatitis, pharyngitis, adenitis.

The most common treatment-emergent AEs by SOC (≥ 1% of subjects) were balanced in frequency between nirsevimab and placebo groups in the Proposed-Dose Safety Pool (Figure 24).

Figure 24 Treatment-Emergent Adverse Events by SOC (≥ 1% of Subjects) Through at Least Day 151 (Proposed-Dose Safety Pool)

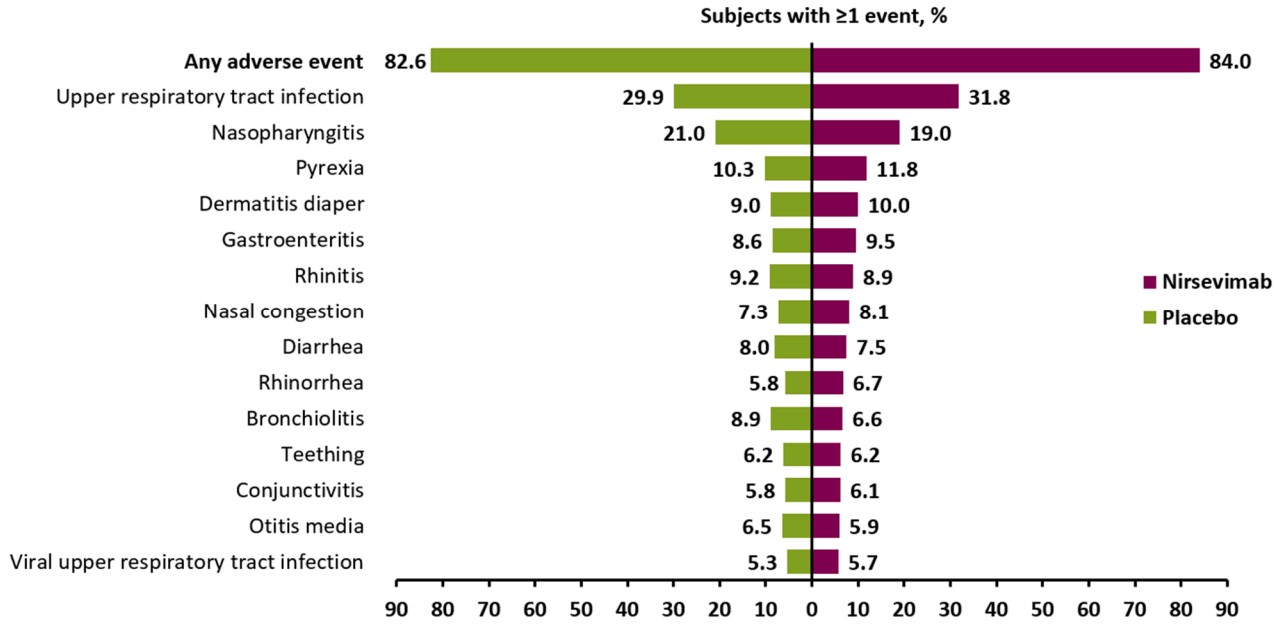


Subjects with multiple events in the same SOC are counted only once in each of those SOC.
Subjects with events in more than one SOC are counted once in each of those SOC.
SOC = system organ class.

The most common AEs (≥ 5% of subjects in either treatment group) by PT were similarly balanced in frequency between nirsevimab and placebo groups (Figure 25). The most common AEs (>10% of subjects) by PT for nirsevimab and placebo, respectively, were upper respiratory tract infection (31.8% vs 29.9%), nasopharyngitis (19.0% vs 21.0%), and pyrexia (11.8% vs 10.3%)

In the first 7 days following administration of IP, a low percentage of subjects had PTs associated with manifestations of reactogenicity, including pyrexia (0.5% vs 0.6%) and injection site reactions (0.3% vs 0.0%), for nirsevimab vs placebo, respectively.

Figure 25 Most Frequent Treatment-Emergent Adverse Events by PT (≥ 5% of Subjects) Through at Least Day 151 (Proposed-Dose Safety Pool)



Subjects with multiple events in the same preferred term are counted only once in each of those preferred term.
Subjects with events in more than one preferred term are counted once in each of those preferred terms.
PT = preferred term.

Safety in Subgroups

Subgroups of interest included neonates (< 28 days of age at randomization), and infants with a weight < 2.5 kg at the time of dosing (Day 1) who had higher exposures normalized for weight (approximately 20 to 30 mg/Kg). The largest safety database in these subgroups includes 564 and 216 subjects dosed with nirsevimab, respectively, in the placebo-controlled studies. All infants in both subgroups received the proposed dose of nirsevimab.

Treatment-emergent AEs for neonates and infants < 2.5 kg at dosing are summarized in Table 24. Among neonates in the Proposed-Dose Safety Pool, the types and frequency of AEs were generally comparable between the nirsevimab and placebo treatment groups. No clinically meaningful imbalance by MedDRA SOC or PT between treatment groups for AEs and SAEs. The percentage of subjects with IP-related AEs was low and generally comparable between the nirsevimab and placebo groups, with IP-related AEs ≥ Grade 3 severity reported in one subject each in the nirsevimab and placebo groups. Investigator-assessed AESIs were reported in 2 (0.4%) of nirsevimab recipients (see Section 6.7). Adverse events with outcome of death occurred in one subject each in the nirsevimab (due to unknown cause in a subject from Israel in Trial 04; the Investigator suspected an undiagnosed chronic illness) and placebo (due to pneumonia complicated by left sided empyema in a Trial 03 subject) groups (Table 27). No NOCDs were reported among neonates.

The AE profile for subjects < 2.5 kg on Day 1 was generally comparable between nirsevimab and placebo treatment groups, with no clinically meaningful imbalance between the treatment groups. Investigational product-related AEs were reported for 2 subjects (0.9%) in the nirsevimab group. There were no IP-related AEs ≥ Grade 3 severity, IP-related SAEs, or NOCDs in any subjects. Adverse events of special interest based on investigator assessment and IP-related skin reaction were reported in one subject in the nirsevimab group (0.5%) for the same event (petechiae) which was assessed as a skin hypersensitivity reaction (Section 6.7.1). No deaths occurred in the nirsevimab group and 2 deaths (both due to pneumonia in subjects from Trial 03) occurred in the placebo group in subjects < 2.5 kg on Day 1 (Table 24).

Table 24 Safety Profile in Neonates and Infants < 2.5 kg (Proposed-Dose Safety Pool)

Number (%) of subjects	Neonates		Infants < 2.5 kg	
Subjects [a] with	Placebo N = 291	Nirsevimab N = 564	Placebo N = 102	Nirsevimab N = 216
At least 1 event	224 (77.0)	447 (79.3)	78 (76.5)	175 (81.0)
At least 1 IP-related event	2 (0.7)	3 (0.5)	0	2 (0.9)
At least 1 event of ≥ Grade 3 [b]	25 (8.6)	33 (5.9)	13 (12.7)	22 (10.2)
At least 1 IP-related event of ≥ Grade 3 [b]	1 (0.3)	1 (0.2)	0	0
Any AE with outcome death	1 (0.3)	1 (0.2)	2 (2.0)	0
At least 1 serious event [c]	31 (10.7)	73 (12.9)	20 (19.6)	46 (21.3)
At least 1 IP-related serious event [c]	1 (0.3)	0	0	0
At least 1 AESI based on investigator assessment	0	2 (0.4) [d]	0	1 (0.5) [e]

[a] Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.
[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal.
[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).
[d] Observed events were petechiae and rash.
[e] Observed event was petechiae (the subject was also a neonate).
AE = adverse event; AESI = adverse event of special interest; N = number of subjects; IP = investigational product.

6.3.2 Overview of Adverse Events in Trial 05 in RSV Season 1 and Season 2

Trial 05 RSV Season 1

Treatment-emergent AEs reported through 360 days post first dose in RSV Season 1 in Trial 05 are summarized for the overall population and its constitutive cohorts in Table 25. In the overall population, the percentage of subjects with an AE, IP-related AE, ≥ Grade 3 event, SAE and/or ≥ Grade 3 event, AESI, and IP-related skin reaction was generally balanced

between the nirsevimab and palivizumab groups when assessed through 360 days post first dose, and within 1, 3, 7, or 14 days of first (or any) IP dose in RSV Season 1. The types and frequency of AEs within 30 days post first dose were generally balanced between the nirsevimab and palivizumab groups for the overall population and preterm and CLD/CHD cohorts. The majority (> 90%) of AEs were of Grade 1 or 2 severity. The most common AEs (> 10% of subjects) were upper respiratory tract infection (24.1% vs 25.7%), pyrexia (10.3% vs 7.7%), rhinitis (12.2% vs 13.2%), and nasopharyngitis (9.3% vs 12.8%), for nirsevimab vs palivizumab, respectively. No IP-related ≥ Grade 3 events, IP-related SAEs, or IP-related NOCDs were reported in the study. Six events with fatal outcome were reported in Trial 05 Season 1 (5 in nirsevimab treatment group and 1 in palivizumab treatment arm); all these subjects had serious underlying conditions at baseline (Table 27). None of the deaths were considered related to IP by the Investigator.

Table 25 Overall Summary of Treatment-emergent Adverse Events Through 360 Days Post First Dose in RSV Season 1 – Trial 05

	Number (%) of subjects					
	Overall		Preterm		CLD/CHD	
Subjects [a] with	Palivizumab N = 304	Nirsevimab N = 614	Palivizumab N = 206	Nirsevimab N = 406	Palivizumab N = 98	Nirsevimab N = 208
At least 1 event	215 (70.7)	444 (72.3)	141 (68.4)	287 (70.7)	74 (75.5)	157 (75.5)
Occurring ≤ 1 day post first dose	5 (1.6)	14 (2.3)	4 (1.9)	8 (2.0)	1 (1.0)	6 (2.9)
Occurring ≤ 3 days post first dose	16 (5.3)	28 (4.6)	13 (6.3)	17 (4.2)	3 (3.1)	11 (5.3)
Occurring ≤ 7 days post first dose	32 (10.5)	50 (8.1)	21 (10.2)	31 (7.6)	11 (11.2)	19 (9.1)
Occurring ≤ 14 days post first dose	63 (20.7)	100 (16.3)	43 (20.9)	66 (16.3)	20 (20.4)	34 (16.3)
Occurring ≤ 30 days post first dose	100 (32.9)	184 (30.0)	65 (31.6)	121 (29.8)	35 (35.7)	63 (30.3)
At least 1 IP-related event	6 (2.0)	10 (1.6)	4 (1.9)	6 (1.5)	2 (2.0)	4 (1.9)
At least 1 event of ≥ Grade 3 [b]	25 (8.2)	50 (8.1)	8 (3.9)	18 (4.4)	17 (17.3)	32 (15.4)
Occurring ≤ 1 day post first dose	1 (0.3)	1 (0.2)	1 (0.5)	0	0	1 (0.5)
Occurring ≤ 3 days post first dose	2 (0.7)	1 (0.2)	2 (1.0)	0	0	1 (0.5)
Occurring ≤ 7 days post first dose	3 (1.0)	2 (0.3)	3 (1.5)	0	0	2 (1.0)
Occurring ≤ 14 days post first dose	5 (1.6)	4 (0.7)	3 (1.5)	0	2 (2.0)	4 (1.9)
Occurring ≤ 30 days post first dose	7 (2.3)	8 (1.3)	3 (1.5)	1 (0.2)	4 (4.1)	7 (3.4)
At least 1 IP-related event of ≥ Grade 3 [b]	0	0	0	0	0	0
Any AE with outcome death	1 (0.3)	5 (0.8)	0	2 (0.5)	1 (1.0)	3 (1.4)
At least 1 serious event [c]	38 (12.5)	80 (13.0)	13 (6.3)	35 (8.6)	25 (25.5)	45 (21.6)

Table 25 Overall Summary of Treatment-emergent Adverse Events Through 360 Days Post First Dose in RSV Season 1 – Trial 05

Subjects [a] with	Number (%) of subjects					
	Overall		Preterm		CLD/CHD	
	Palivizumab N = 304	Nirsevimab N = 614	Palivizumab N = 206	Nirsevimab N = 406	Palivizumab N = 98	Nirsevimab N = 208
Occurring ≤ 30 days post first dose	10 (3.3)	18 (2.9)	4 (1.9)	4 (1.0)	6 (6.1)	14 (6.7)
At least 1 serious [c] and/or ≥ Grade 3 [b] event	39 (12.8)	84 (13.7)	13 (6.3)	35 (8.6)	26 (26.5)	49 (23.6)
At least 1 IP-related serious [c] event	0	0	0	0	0	0
At least 1 AESI based on Investigator assessments	0	3 (0.5)	0	1 (0.2) [d]	0	2 (1.0) [e]
At least 1 NOCD	0	2 (0.3) [f]	0	1 (0.2)	0	1 (0.5)
At least 1 IP-related NOCD	0	0	0	0	0	0

[a] Subjects with multiple events in the same category were counted once in that category. Subjects with events in > 1 category were counted once in each of those categories.
[b] Grade 3: severe; Grade 4: life-threatening; Grade 5: fatal.
[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).
[d] IP-related skin hypersensitivity event temporally correlated with a placebo IP dose, 92 days after the active nirsevimab dose.
[e] Unrelated events of thrombocytopenia in participants with CHD.
[f] Observed events were asthma (Preterm cohort subject) and calculus urinary (CLD/CHD cohort subject).
Data from the 'Season 2 Analysis' of data for subjects in RSV Season 1.
Treatment-emergent adverse events reporting period for Season 1 is from Season 1, Day 1 to Season 1, Day 361 or the last day prior to first dose of Season 2, whichever comes earlier.
MedDRA version 23.1.
AESI = adverse event of special interest; CHD = congenital heart disease; CLD = chronic lung disease; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; NOCD = new onset chronic disease; RSV = respiratory syncytial virus.

Trial 05 RSV Season 2

Adverse events were assessed in RSV Season 2 in Trial 05 in 262 of the subjects from the CLD/CHD cohort who continued in the study and received a second course of IP (200 mg nirsevimab single IM dose followed by 4 once-monthly doses of IM placebo, or 5 once-monthly doses of palivizumab 15 mg) in RSV Season 2. Subjects were analyzed in 3 treatment groups in RSV Season 2, so named to indicate treatments received in Season 1 and Season 2: nirsevimab (Season 1)/nirsevimab (Season 2) (NIRS/NIRS; n = 180), palivizumab (Season 1)/nirsevimab (Season 2) (PALI/NIRS; n = 40), and palivizumab (Season 1)/palivizumab (Season 2) (PALI/PALI; n = 42). Treatment-emergent AEs reported through at least 150 days post first dose in RSV Season 2 in are summarized for the 3 treatment groups in Table 26.

Through at least 150 days post first dose in Season 2, the incidence of any AEs was generally balanced across treatment groups. The incidence of ≥ Grade 3 events and SAEs was numerically higher in the NIRS/NIRS and PALI/NIRS groups vs the PALI/PALI group through at least 150 days post first Season 2 dose, but this was not observed through 30 days post first Season 2 dose. The most common AEs ≥ Grade 3 and/or SAEs (see Section 6.4.2) were reported in the SOC of Infections and Infestations and were not suggestive of any clinically relevant trends or concerns; or were related to clinical manifestations or complications associated with underlying medical conditions. Events of ≥ Grade 3 severity included a single Grade 4 AE of cardiac surgery for Tetralogy of Fallot in the NIRS/NIRS group. There were no Grade 5 AEs (with an outcome of death), IP-related AEs, NOCDs, or AESIs based on investigator assessments in any treatment group.

In RSV Season 2 in Trial 05, the safety profile of nirsevimab was consistent with that expected for the study population and generally comparable to that observed across clinical studies in RSV Season 1. There was no indication that receiving nirsevimab in 2 consecutive seasons or receiving nirsevimab in RSV Season 2 after having received palivizumab in RSV Season 1, had a deleterious effect on safety, and no evidence of increased hypersensitivity.

No safety concerns were identified for nirsevimab.

Table 26 Overall Summary of Treatment-emergent Adverse Events Through at Least 150 Days Post First Dose in Season 2 – Trial 05

	Number (%) of subjects		
Subjects [a] with	**PALI/PALI (N = 42)**	**PALI/NIRS (N = 40)**	**NIRS/NIRS (N = 180)**
≥ 1 event	29 (69.0)	29 (72.5)	126 (70.0)
Occurring ≤ 1 day post first dose	0 (0.0)	0 (0.0)	2 (1.1)
Occurring ≤ 3 days post first dose	0 (0.0)	1 (2.5)	4 (2.2)
Occurring ≤ 7 days post first dose	2 (4.8)	4 (10.0)	7 (3.9)
Occurring ≤ 14 days post first dose	9 (21.4)	4 (10.0)	28 (15.6)
Occurring ≤ 30 day post first dose	11 (26.2)	11 (27.5)	54 (30.0)
≥ 1 IP-related event	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 event of ≥ Grade 3 [b]	1 (2.4)	4 (10.0)	14 (7.8)
Occurring ≤ 1 day post first dose	0 (0.0)	0 (0.0)	0 (0.0)
Occurring ≤ 3 days post first dose	0 (0.0)	0 (0.0)	0 (0.0)
Occurring ≤ 7 days post first dose	0 (0.0)	0 (0.0)	0 (0.0)
Occurring ≤ 14 days post first dose	0 (0.0)	0 (0.0)	0 (0.0)
Occurring ≤ 30 days post first dose	1 (2.4)	1 (2.5)	3 (1.7)
≥ 1 IP-related event of ≥Grade 3 [b]	0 (0.0)	0 (0.0)	0 (0.0)
Any AE with outcome death	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 serious [c] event	0 (0.0)	4 (10.0)	17 (9.4)

Table 26 Overall Summary of Treatment-emergent Adverse Events Through at Least 150 Days Post First Dose in Season 2 – Trial 05

Subjects [a] with	Number (%) of subjects		
	PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
Occurring ≤ 30 days post first dose	0	1 (2.5)	4 (2.2)
≥ 1 serious [c] and/or ≥ Grade 3 [b] event	1 (2.4)	4 (10.0)	20 (11.1)
≥ 1 IP-related serious [c] event	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 AESI based on investigator assessments	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 IP-related skin reaction	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 NOCD	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 IP-related NOCD	0 (0.0)	0 (0.0)	0 (0.0)

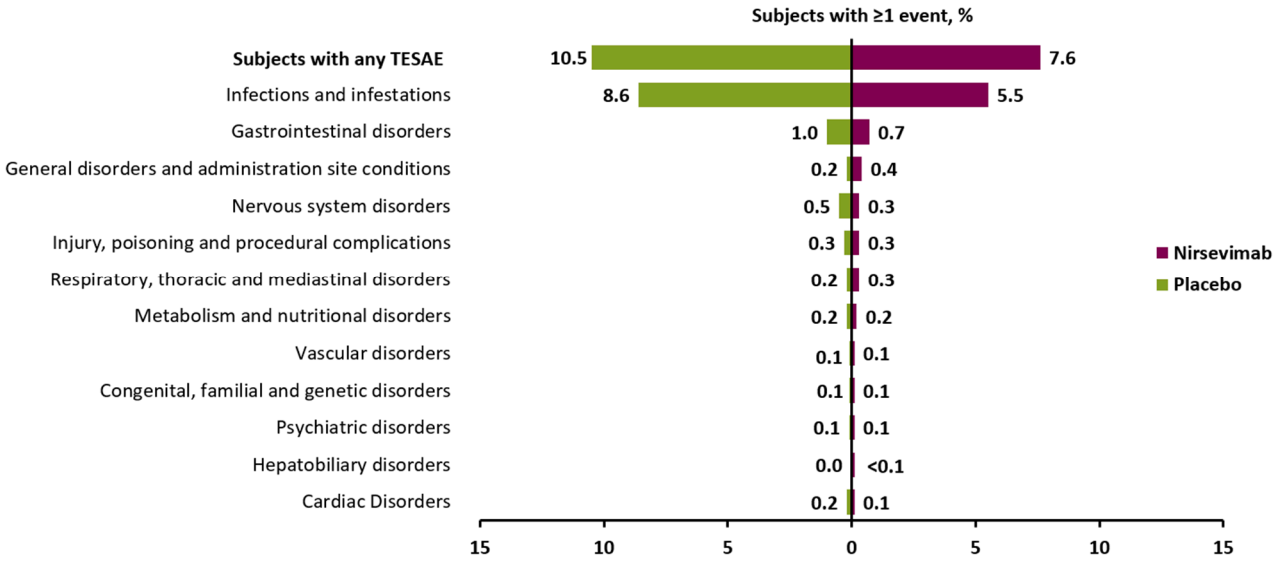
[a] Subjects with multiple events in the same category were counted once in that category. Subjects with events in > 1 category were counted once in each of those categories.
[b] Grade 3: severe; Grade 4: life-threatening; Grade 5: fatal.
[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).
Data from the 'Season 2 Analysis' of data for subjects in RSV Season 2.
Treatment-emergent adverse events reporting period for Season 2 is from Season 1, Day 1 to Season 1, Day 361.
MedDRA version 23.1.
AESI = adverse event of special interest; CHD = congenital heart disease; CLD = chronic lung disease; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; NOCD = new onset chronic disease; RSV = respiratory syncytial virus.

6.4 Serious Adverse Events

6.4.1 Serious Adverse Events: Proposed-Dose Safety Pool

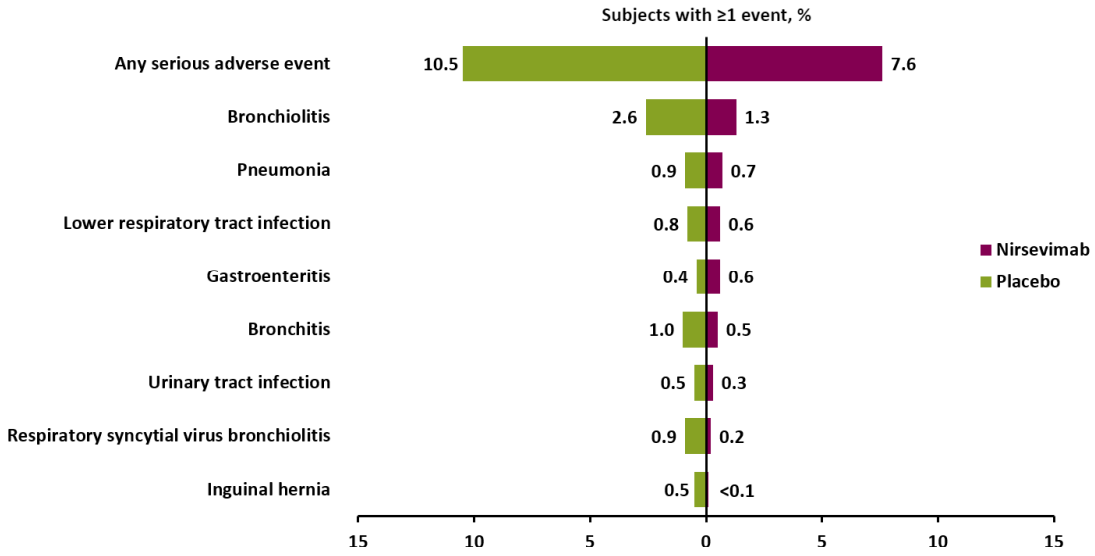
The frequency of SAEs was comparable between the nirsevimab and placebo groups (7.6% and 10.5%, respectively) (Figure 26). The most frequently reported events in both treatment groups occurred in the MedDRA SOC of Infections and infestations (5.5% nirsevimab group and 8.6% placebo group). The percentage of subjects with individual PTs was generally balanced between the treatment groups. The most common SAEs (≥ 0.5% of subjects in either treatment group) included respiratory infections and gastroenteritis (Figure 27). There were no clinically relevant trends or safety concerns identified based on review of SAEs in the Proposed-Dose Safety Pool.

Figure 26 Treatment-Emergent Serious AEs by SOC (≥ 0.1% of Subjects) Through at Least Day 150 Post Dose (Proposed-Dose Safety Pool)



Subjects with multiple events in the same SOC are counted only once in each of those SOC.
Subjects with events in more than one SOC are counted once in each of those SOC.
AE = adverse event; SOC = system organ class; TESAE = treatment-emergent serious adverse events.

Figure 27 Most Frequent Treatment-Emergent Serious AEs (≥ 0.5% of Subjects) Through at Least Day 150 Post Dose (Proposed-Dose Safety Pool)



Subjects with multiple events in the same preferred term are counted only once in each of those preferred term.
Subjects with events in more than one preferred term are counted once in each of those preferred terms.
AE = adverse event.

No IP-related SAEs were reported in the nirsevimab group. One subject in the placebo group had an IP-related SAE of fever neonatal. No subjects had an SAE within 1 day post dose.

Within 7-, 14-, and 30-days post dose, a similar percentage of subjects in both treatment groups had an SAE.

6.4.2 Serious Adverse Events: Trial 05

Overall Population, Preterm and CLD/CHD Cohorts in RSV Season 1

In the overall population, the frequency of SAEs was similar between the nirsevimab and palivizumab groups (13.0% vs 12.5%, respectively). Serious AEs were most frequently reported (≥ 2% of subjects in either the nirsevimab or palivizumab group) in the MedDRA SOCs of infections and infestations (8.3% vs 6.6%, respectively). The most common SAEs (in > 2 subjects in either treatment group) reported for nirsevimab (vs palivizumab) were bronchiolitis (2.0% vs 1.3% subjects), gastroenteritis (1.0% vs 0.3% subjects), bronchitis (0.8% vs 0.7% subjects, respectively), pneumonia (0.8% vs 0.3% subjects, respectively), respiratory syncytial virus bronchiolitis (0.7% vs 0.7% subjects, respectively), COVID-19, and viral URTI (0.5% vs 0.3% subjects each, respectively). Within 1, 3-, 7-, 14-, and 30-days post first dose, a similar percentage of subjects in the nirsevimab and palivizumab groups had an SAE.

The incidence of SAEs was also balanced between the nirsevimab and palivizumab groups in the preterm (8.6% vs 6.3%, respectively) and CLD/CHD (21.6% vs 25.5%, respectively) cohorts. The frequency of SAEs (and ≥ Grade 3 events) was higher in the CLD/CHD cohort than the preterm cohort for both the nirsevimab and palivizumab groups. The nature and rate of AEs were expected to differ across these cohorts given the underlying comorbidities of subjects with CHD/CLD.

None of the SAEs was considered by the Investigator to be IP-related.

Overall (CLD/CHD Cohort) in RSV Season 2

The incidence of SAEs was low overall and numerically higher in the NIRS/NIRS and PALI/NIRS groups than in the PALI/PALI group (9.4% vs 10.0% vs 0% for NIRS/NIRS, PALI/NIRS, and PALI/PALI, respectively); the numerical difference was driven by events in the SOC of Infections and Infestations and was not observed through 30 days post first dose (Table 26). Through at least 150 days post first dose, serious AEs were most frequently reported (≥ 2% of subjects in any treatment group) in the MedDRA SOCs of infections and infestations (7.2% vs 10.0% vs 0%, respectively) and nervous system disorders (0% vs 2.5% vs 0%, respectively). The most common SAEs (≥ 2 subjects in any treatment group) reported through at least Day 151 for NIRS/NIRS, PALI/NIRS, and PALI/PALI groups were bronchitis viral (1.7% vs 0% vs 0% subjects, respectively), COVID-19 (1.1% vs 0% vs 0% subjects, respectively), gastroenteritis (1.1% vs 0% vs 0% subjects, respectively), lower respiratory tract infection (1.1% vs 2.5% vs 0% subjects, respectively), and upper respiratory tract infection (1.1% vs 0% vs 0% subjects, respectively). There were no trends in SAEs by PT.

No subjects in any treatment group had an SAE within 7 days post first dose in Season 2. Within 30 days post first dose, 2.2%, 2.5%, and 0% of subjects in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively, had an SAE. None of the SAEs was considered by the Investigator to be IP-related.

6.5 Adverse Events Leading to Death

Across pivotal studies, no deaths were considered to be IP-related or known to be due to RSV (Table 27). Treatment-emergent deaths through 360 days post dose were included in the safety analyses.

All deaths in Trial 04 and Trial 03 were in subjects who received the proposed dose. A total of 9 treatment-emergent deaths were reported in the Proposed-Dose Safety Pool through 360 days post dose, 6 (0.2%; 6/2570) deaths occurring in subjects who received nirsevimab and 3 (0.2%; 3/1284) deaths occurring in subjects who received placebo. For Trial 03, cause of death was unknown (Day 123 post dose) for a preterm infant who was reported to be well when put to bed, whereas the twin who also received nirsevimab completed the study; and another moderately preterm infant reported pulmonary vein stenosis (Day 97 post dose) as the primary cause of death. In Trial 04, 2 infants from South Africa reported gastrointestinal events suggestive of infection (Day 143 and Day 338 post dose). In South Africa, the background infant morbidity and mortality in children is relatively high and gastroenteritis or diarrhea is a frequent cause of mortality in children, accounting for approximately 20% of deaths in children under 5 years of age (Chola et al 2015; Statistics South Africa 2012). One infant from Panama reported a trauma event (Day 286 post dose) leading to death. While the cause of death was unknown for an infant from Israel (Day 140 post dose), the Investigator reported undiagnosed chronic illness as a possible cause of death. There were no trends associated with reported events and the cause of death can be attributed to underlying medical condition or common cause of infant mortality reported in the region where the infant was enrolled.

Overall in Trial 05, 6 treatment-emergent deaths were reported in the Preterm (nirsevimab: 2 subjects [0.5%]; palivizumab 0 subjects) and CLD/CHD cohorts (nirsevimab: 3 subjects [1.4%]; palivizumab 1 subject [1.0%]) during the first RSV season through 360 days post dose in RSV Season 1. Note that all subjects in Trial 05 had serious underlying conditions and none of the deaths were considered related to the IP. No deaths were reported in Season 2.

Across the pivotal studies, deaths occurring before or after protocol specified safety data collection period were reported in 3 subjects and were considered unrelated to IP. In Trial 03, one additional death (due to acute bronchopneumonia) occurred in the placebo group 6 days after the end of study on Day 367. In Trial 04 one death due to a road traffic accident occurred in the nirsevimab group on Day 440. In addition, one subject was enrolled and died due to Streptococcal meningitis without receiving IP.

In summary, deaths were attributed to underlying conditions or common causes of infant mortality in the respective country or region where the subject was enrolled. None of the deaths was considered related to IP by the Investigator.

Table 27 Listing of Deaths Reported in Pivotal Nirsevimab Studies Through 360 Days Post-dose

Treatment group/Study	Underlying comorbidity [a]	Country	Study Day (Age) at death	Cause of death [b]
Proposed-Dose Safety Pool				
Placebo				
Trial 03	Moderately preterm	South Africa	343 (~15 months)	Pericardial effusion that led to death
Trial 03	Very preterm; respiratory distress syndrome; Klebsiella sepsis (resolved prior to enrollment)	South Africa	26 (~2 months)	Nosocomial pneumonia, E coli meningitis
Trial 03	Moderately preterm	South Africa	109 (~4 months)	Pneumonia complicated by left-sided empyema
Nirsevimab [c]				
Trial 03	Very preterm	South Africa	123 (~8 months)	Unknown; infant well when put to bed; twin (nirsevimab group) completed study
Trial 03	Moderately preterm; respiratory distress syndrome	Estonia	97 (~5 months)	Pulmonary vein stenosis
Trial 04	Term	South Africa	143 (~8 months)	Diarrhea
Trial 04	Term	South Africa	338 (~18 months)	Acute gastroenteritis
Trial 04	Term	Israel	140 (~5 months)	Unknown; suspected undiagnosed chronic illness; AEs of recurrent vomiting, hypoglycemia, anemia
Trial 04	Term	Panama	286 (~14.5 months)	Skull base fracture from automobile accident
Trial 05 RSV Season 1				
Nirsevimab [c]				
Trial 05 Season 1	Very preterm; neonatal encephalopathy	Ukraine	162 (~13 months)	Severe COVID-19 pneumonia
Trial 05 Season 1	Moderately preterm; congenital Cytomegalovirus infection	Bulgaria	52 (~3 months)	Atrophy-caused acute bronchiolitis, leading to acute cardiovascular and respiratory failure leading to death
Trial 05 Season 1	Term with CHD (partially corrected VSD [d], ASD, coarctation of the aorta, PDA); dysgenesis of the corpus callosum; congenital cystic kidney disease	Hungary	19 (~3 months)	Sudden death due to bronchopneumonia

Table 27 Listing of Deaths Reported in Pivotal Nirsevimab Studies Through 360 Days Post-dose

Treatment group/Study	Underlying comorbidity [a]	Country	Study Day (Age) at death	Cause of death [b]
Trial 05 Season 1	Term with CHD (VSD [d], ASD); Trisomy 21; Hypothyroidism	Mexico	66 (~4.5 months)	Cardiogenic shock
Trial 05 Season 1	Term with CHD (congenital pulmonary valve atresia with VSD [d], MAPCA with unifocalization and creation of systemic pulmonary anastomosis); cerebral ischemia	Russian Federation	19 (~3 months)	Congestive heart failure, pulmonary atresia
Palivizumab				
Trial 05 Season 1	Term with CHD (ASD [d], PDA); agenesis of the corpus callosum; cytogenic abnormality – feminine chromosomal mutation 46XX[11;22][q13.2;11.2])	Lithuania	155 (~6 months)	Respiratory insufficiency due to bronchiolitis
Trial 05 RSV Season 2 – No deaths through at least 150 days post first-dose				

[a] Extremely preterm 22-28 wGA; Very preterm 29-31 wGA; Moderately preterm 32-34 wGA; Late preterm 35-36 wGA; Term ≥ 37 wGA.
[b] Cause of death as reported by the Investigator.
[c] All deaths in subjects who received the proposed dose.
[d] Primary cardiac lesion.
AE = adverse event; ASD = atrial septal defect; CHD = congenital heart disease; CLD = chronic lung disease; MAPCA = Major aortopulmonary collateral arteries; PDA = patent ductus arteriosus; VSD = ventricular septal defect; wGA = weeks gestational age

6.6 Adverse Events Leading to Discontinuation

Trial 03 and Trial 04 evaluated the safety and efficacy of a single dose of nirsevimab. Therefore, adverse events resulting in discontinuation of IP were not applicable. In Trial 05 where subjects received 5 doses of IP per season, one subject (0.2%) in the nirsevimab group in RSV Season 1 discontinued IP due to a nonserious Grade 1 AESI of skin hypersensitivity (rash maculopapular) temporally associated with a placebo IP dose, 92 days after the active nirsevimab dose; the subject had no detectable post baseline ADA to nirsevimab. This subject remained in the study and was included in the safety analysis.

Across the 3 pivotal studies, there were no discontinuations from the study due to an adverse event in dosed subjects (apart from those with a fatal outcome; Section 6.5).

6.7 Adverse Events of Special Interest

Immediate hypersensitivity (including anaphylaxis), immune complex disease, and thrombocytopenia were scrutinized as AESIs for the clinical development program. Accordingly, enhanced pharmacovigilance activities were performed with periodic review of AESI during the clinical development.

Across the pivotal studies, AESIs based on investigator assessment were reported in very few subjects (Section 6.3). None were reported as an SAE and none of the subjects with AESIs had any post-baseline ADA detected with samples available for analysis. Nearly all events were mild to moderate in severity. No AESIs were reported in Trial 05 RSV Season 2. No events of anaphylaxis or other serious allergic reaction, no thrombocytopenia attributed to nirsevimab, and no immune complex disease were reported in any subject.

Overall, across the studies, there were no safety concerns based on the assessment of AESIs based on investigator assessment or when AESIs were assessed using sponsor-defined MedDRA Search Criteria (described in Supplementary Section 10.5).

6.7.1 Immediate Hypersensitivity (Including Anaphylaxis)

AESIs of hypersensitivity based on Investigator assessment were all assessed as non-serious skin hypersensitivity events and comprised (Table 28):

- All 6 events in the Proposed-Dose Safety Pool were reported in 6 subjects (0.2%) in the nirsevimab group and considered IP-related.
- One event in Trial 05 RSV Season 1 in a nirsevimab recipient in the Preterm Cohort, which was temporally associated with a placebo dose, 92 days post active nirsevimab dose, and considered IP-related; the subject was discontinued from IP but remained in the study and included in the safety analysis.

Nearly all AESIs of hypersensitivity based on Investigator assessment were of mild to moderate (Grade 1 to 2) severity; a single Grade 3 severity rash was reported in a subject in Trial 04 with onset 6 days post dosing which resolved after 3 weeks without treatment (Table 28). Across the pivotal studies, none of the events was characterized as urticarial or involving angioedema. Notably no hypersensitivity was observed through 30 days post first dose in Trial 05 Season 1 and through at least 150 days post first dose in Trial 05 Season 2.

AESIs of hypersensitivity based on sponsor-defined MedDRA search criteria were comparable between nirsevimab and comparator groups through the relevant time points close to IP dosing (within 1, 3, 7, 14, or 30 days post dose [first IP dose for Trial 05]), inclusive of expected timeframe for immediate hypersensitivity (Section 10.5).

Table 28 Case Descriptions of AESI of Hypersensitivity Based on Investigator Assessment – Nirsevimab Group

Study	Relationship to IP	Toxicity grade/ seriousness	Study day of AE onset	Preferred Term	Description	Resolved after
Proposed-Dose Safety Pool						
Trial 03	Related	Grade 1/ nonserious	Day 3	Rash	Maculopapular rash with generalized symmetrical distribution on neck and trunk	13 days
Trial 03	Related	Grade 1/ nonserious	Day 120	Petechiae	Based on parental description of skin lesions with a generalized distribution on face, trunk, and arms; no laboratory assessments	2 days
Trial 04	Related	Grade 1/ nonserious	Day 1	Rash papular	Erythematous maculopapular rash with generalized distribution on face, trunk, hands, and legs	6 days
Trial 04	Related	Grade 1/ nonserious	Day 1	Rash maculopapular	Erythematous maculopapular rash with symmetrical distribution on legs	11 days
Trial 04	Related	Grade 1/ nonserious	Day 1	Rash maculopapular	Erythematous maculopapular rash with generalized distribution on head, face, neck, trunk, arms, and legs; treated with oral antihistamine	3 days
Trial 04	Related	Grade 3/ nonserious	Day 7	Rash	Macular rash with generalized distribution on head, face, neck, trunk, arms, hands, legs, feet, buttocks/groin	20 days
Trial 05 RSV Season 1						
Trial 05 Season 1	Related	Grade 1/ nonserious	Day 93 following placebo IP dose	Rash maculopapular	Maculopapular rash with generalized distribution on face and trunk following a placebo IP dose; IP withdrawn	1 day (same day)

IP = investigational product

Skin Reactions and Skin Hypersensitivity Reactions

The incidences of skin and skin hypersensitivity reactions in the Proposed-Dose Safety Pool, Trial 05 RSV Season 1 and 2 are presented in Table 29, Table 30, and Table 31, respectively.

Table 29 Skin Reactions Through at Least 150 Days Post Dose – Proposed-Dose Safety Pool

Subjects [a] with	Number (%) of Subjects		
	Placebo N = 1284	Nirsevimab N = 2570	Total N = 3854
At least 1 skin reaction	332 (25.9)	650 (25.3)	982 (25.5)
At least 1 IP-related skin reaction	4 (0.3)	15 (0.6)	19 (0.5)
At least one IP-related skin hypersensitivity reaction (AESI)	0	6 (0.2)	6 (0.2)

[a] Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.

Table 30 Skin Reactions Through 360 Days Post First Dose in RSV Season 1 – Trial 05

Subjects [a] with	Number (%) of subjects					
	Overall		Preterm		CLD/CHD	
	Palivizumab N = 304	Nirsevimab N = 614	Palivizumab N = 206	Nirsevimab N = 406	Palivizumab N = 98	Nirsevimab N = 208
At least 1 skin reaction	57 (18.8)	137 (22.3)	38 (18.4)	84 (20.7)	19 (19.4)	53 (25.5)
At least 1 IP-related skin reaction	2 (0.7)	2 (0.3)	1 (0.5)	1 (0.2)	1 (1.0)	1 (0.5)
At least 1 IP-related skin hypersensitivity reaction (AESI)	0	1 (0.2)	0	1 (0.2)	0	0

[a] Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.

Table 31 Skin Reactions Through at Least 150 Days Post First Dose in Trial 05 Season 2 – As-Treated Population (Season 2)

Subjects [a] with	Number (%) of subjects		
	PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
At least 1 skin reaction	5 (11.9)	4 (10.0)	24 (13.3)
At least 1 IP-related skin reaction	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 IP-related skin hypersensitivity reaction (AESI)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.

Skin reactions were generally balanced between nirsevimab and comparator groups without any particular trend by PT across the pivotal studies.

Skin reactions considered related to IP comprised injection site reactions and rashes, including those that were or were not assessed as hypersensitivity events by the Investigator. There was a low incidence of IP-related skin reactions and the percentage of subjects with IP-related skin reactions was balanced between nirsevimab and comparator groups across the pivotal studies for infants entering their first RSV season based on results in the Proposed-Dose Safety Pool (Table 29) and Trial 05 RSV Season 1 (Table 30). In addition, there were no IP-related skin reactions in Trial 05 RSV Season 2 (Table 31).

Similarly, there was a very low incidence of investigator-assessed IP-related skin hypersensitivity reactions across studies, all of which were also recorded as AESIs by the investigator (Table 29, Table 30, and Table 31). In Trial 05, it is of note that no skin hypersensitivity reactions were reported within 30 days post first IP dose in RSV Season 1 or through at least 150 days post first IP dose in RSV Season 2. Furthermore, no such events were reported in the NIRS/NIRS group, who received a second dose of nirsevimab in Season 2.

Immediate hypersensitivity, including typical cutaneous manifestations like urticaria and angioedema, typically presents minutes to hours after exposure. By PT, no AEs of urticaria, angioedema, or hypersensitivity were reported within 7 days of IP dosing (first IP dosing in Trial 05) and no IP-related skin reaction (including related skin hypersensitivity reaction) was characterized as urticarial or involving angioedema on the skin reaction CRF, irrespective of time related to dosing across the complementary pivotal studies.

6.7.2 Thrombocytopenia

Based on Investigator assessment, AESIs of thrombocytopenia comprised 2 events in nirsevimab recipients with CHD in Trial 05 RSV Season 1, both considered unrelated to IP (Table 32).

There was a low incidence AESIs of thrombocytopenia based on sponsor-defined MedDRA search criteria across pivotal studies and all events were Grade 1 to 2 severity (Section 10.5).

Table 32 Case Descriptions of AESI of Thrombocytopenia Based on Investigator Assessment – Nirsevimab Group

Study Cohort	Relationship to IP	Toxicity grade/ seriousness	Study day of AE onset	Preferred Term	Description	Resolved after
Trial 05 Season 1 CHD (hypoplastic left heart syndrome [a])	Not related	Grade 2/ nonserious	Day 52	Heparin-induced thrombocytopenia	Thrombocytopenia following heparin administration for cardiac catheterization for stent angioplasty of aortic coarctation in an infant with CHD who also received a dose of palivizumab outside the study (Day 22) prior to the event. Platelet nadir 23000/µL 4 days after heparin administration; recovery to 202000/µL following platelet transfusion	5 days
Trial 05 Season 1 CHD (VSD [a], ASD) Down Syndrome	Not related	Grade 1/ nonserious	Day 40	Thrombocytopenia	Reported as thrombocytopenia due to nosocomial sepsis (on same day as event of sepsis) during hospitalization for cardiac failure complicated by nosocomial pneumonia (non-RSV), sepsis, and ultimately death (Day 66) from cardiogenic shock following urgent surgery for repair of ASD. No treatment	12 days

[a] Primary cardiac lesion

AESI = adverse event of special interest; ASD = atrial septal defect; CHD = congenital heart disease; IP = investigational product; VSD = ventricular septal defect.

6.7.3 Immune Complex Disease

There were no AESIs of immune complex disease reported based on investigator's assessment or based on sponsor defined MedDRA search criteria in the nirsevimab or comparator groups across pivotal studies.

6.8 New Onset of Chronic Disease

New Onset of Chronic Disease occurred with a very low incidence in the Proposed-Dose Safety Pool and in Trial 05 (Season 1) and none were considered IP-related (Table 33). No NOCDs were reported in Trial 05 (Season 2).

Table 33 New Onset of a Chronic Disease – Proposed-Dose Safety Pool and Trial 05 (Season 1)

Category	Subjects (%) with ≥ 1 event	
Proposed-Dose Safety Pool to at Least Day 151	**Placebo N = 1284**	**Nirsevimab N = 2570**
Any NOCD (none related)	**4 (0.3)**	**3 (0.1)**
Hypothyroidism	2 (0.2)	0
PFAPA syndrome	0	1 (< 0.1)
Asthma	0	2 (< 0.1)
Bronchitis chronic	1 (< 0.1)	0
Childhood asthma	1 (< 0.1)	0
Trial 05 (Season 1) to Day 361	**Palivizumab N = 304**	**Nirsevimab N = 614**
Any NOCD (none related)	**0**	**2 (0.3)**
Calculus urinary	0	1 (0.2) [a]
Asthma	0	1 (0.2) [b]

[a] CLD/CHD cohort.
[b] Preterm cohort.
CHD = congenital heart disease; CLD = chronic lung disease; N = number of subjects; NOCD = new onset of chronic disease; PFAPA = periodic fever, aphthous stomatitis, pharyngitis, adenitis.

6.9 Theoretical Risk of Antibody-Dependent Enhanced (ADE) Disease

To date, there is no evidence of ADE of RSV disease following administration of nirsevimab. Since a severe clinical presentation can occur with the natural infection and there are no biomarkers to distinguish this from enhanced disease, clinical study assessment entails comparison of frequency of severe cases in intervention and control groups (Arvin et al 2020). In clinical studies the most serious concern of enhanced disease upon first natural infection with RSV was excluded: high protection against hospitalization with MA RSV LRTI and against MA RSV LRTI (very severe) through Day 150 post dosing was observed for Trial 04 (All Subjects) and Trial 03 (Proposed dose) (see Section 4.2.3 and Section 4.2.4).

Furthermore, there was a trend for hospitalized cases of RSV LRTI in Trial 03 to be less severe in nirsevimab recipients than placebo recipients (Table 42).

Subjects in Trial 04 were followed through a second RSV season (without additional dosing prior to the second season) to allow evaluation of the potential for enhanced RSV disease, hypothesized to occur in the setting of sub-neutralizing or non-neutralizing concentrations of anti-RSV antibodies. Available data from the second RSV Season (Day 362 to 511) for Trial 04 (Primary Cohort) did not show an increase in cases of medically attended RSV LRTI or increased severity of disease for infants administered nirsevimab compared to infants administered placebo (Table 34). Results were similar for any cases of MA LRTI due to RSV, confirmed by central or local test.

Table 34 No Evidence of Enhanced RSV Disease in the Second Season: Trial 04 (Primary Cohort) in RSV Season 1 and 2

	Subjects with ≥ 1 event, n (%)			
	Season 1		Season 2	
	Placebo (N = 496)	Nirsevimab (N = 994)	Placebo (N = 482)	Nirsevimab (N = 964)
MA RSV LRTI: increasing severity				
MA RSV LRTI	25 (5.0)	12 (1.2)	2 (0.4)	7 (0.7)
MA RSV LRTI with hospitalization	8 (1.6)	6 (0.6)	0	0
MA RSV LRTI (Very Severe)	7 (1.4)	5 (0.5)	0	0
All MA RSV (any test [a]): increasing severity				
All MA RSV (any test [a]) LRTI	37 (7.7)	17 (1.7)	4 (0.8)	8 (0.8)
All MA RSV (any test [a]) respiratory illness with hospitalization	11 (2.2)	9 (0.9)	1 (0.2) [b]	1 (0.1) [b]

[a] RSV confirmed by central or local test.
[b] The 2 events were 483 post initial dose in a set of twins, one a nirsevimab recipient and the other a placebo recipient, who had similar clinical presentation and hospital course.
LRTI = lower respiratory tract infection; MA = medically attended; n = number of events observed; N = number of subjects; RSV = respiratory syncytial virus.

6.10 Co-administration of Routine Childhood Vaccines

As nirsevimab is a recombinant fully human monoclonal antibody for passive immunization and is specific for RSV, it is not expected to interfere with the active immune response to co-administered vaccines (Esposito et al 2021).

The safety of nirsevimab co-administration with 7 prespecified vaccine groups (polyvalent diphtheria-pertusis-tetanus containing vaccine, measles/mumps/rubella/varicella vaccine,

rotavirus vaccine, pneumococcal vaccine, tuberculosis vaccine, hepatitis B vaccine, or influenza vaccine) was evaluated in the pooled placebo-controlled studies when vaccine was administered on the same day (0.9% [35/3854] of subjects in the Proposed-Dose Safety Pool) and within 7 (7.8% [300/3854] of subjects in the Proposed-Dose Safety Pool) or 14 days (27.6% [1065/3854] of subjects in the Proposed-Dose Safety Pool) of nirsevimab or placebo administration. The safety and reactogenicity profile of the co-administered regimen was similar to the childhood vaccines given alone.

Palivizumab, a monoclonal antibody for prophylaxis against RSV with a similar mechanism of action to nirsevimab, has been used for more than 2 decades in infants who also receive routine vaccinations. To date, concerns related to vaccine efficacy or safety have not been reported (Synagis PI 2020). Various guidelines (Advisory Committee on Immunization Practices [ACIP], Joint Committee on Vaccination and Immunization [JCVI], National Advisory Committee on Immunization [NACI], Centers for Disease Control and Prevention [CDC], American Academy of Pediatrics [AAP], The Association of the Scientific Medical Societies in Germany [AWMF]) support co-administration of palivizumab with routine pediatric vaccines, as it is highly unlikely that palivizumab interferes with the immune response to other vaccines (Esposito et al 2021).

6.11 Adverse Drug Reactions

Based on detailed assessment of data from the nirsevimab clinical program by an internal peer review panel, pertinent information from other elements of the development program (eg, completed studies and nonclinical information); and from outside the nirsevimab development program (eg, literature review), few adverse events are considered to have a reasonable possibility of having a causal association with nirsevimab. The events that the Sponsor considers as ADRs for nirsevimab occurred with a frequency of < 1% in the Proposed-Dose Safety Pool (Table 35).

Table 35 Adverse Drug Reactions

Preferred Term	Proposed-Dose Safety Pool (% of subjects)		Frequency [a]
	Placebo N = 1284	Nirsevimab N = 2570	
Rash [b]	0.3	0.7	Uncommon
Injection site reaction [c]	0	0.3	Uncommon
Pyrexia [d]	0.6	0.5	Uncommon

[a] Frequencies: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from available data).
[b] Rash was defined by the following grouped Preferred Terms: rash, rash maculopapular, rash macular, occurring within 14 days post dose.
[c] Injection site reaction was defined by the following grouped preferred terms: injection site reaction, injection site pain, injection site induration, injection site oedema, injection site swelling, occurring within 7 days post dose.

[d] Preferred term of pyrexia occurring within 7 days post dose.

6.12 Pharmacovigilance Plan

AstraZeneca has not identified any safety concerns from the clinical trial safety data and the safety profile is considered to be acceptable. Therefore, no post marketing commitment studies are required at this time. The product has been approved in the European Union, Great Britain, and Canada without any requirement for post-authorisation safety studies. Safety profile monitoring will continue through routine surveillance of all data sources for detection and evaluation of potential safety signals in a timely manner as per applicable regulations. Additionally, close monitoring of AESI will continue once the product is placed on the market.

6.13 Clinical Safety Conclusions

The safety of nirsevimab for all infants in their first RSV season and for children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season is supported by:

- The size of the safety database and the duration of follow-up was as per FDA guidance to allow adequate assessment of the safety profile of nirsevimab as prophylaxis against RSV LRTI in the first and second RSV seasons.
- A favorable safety profile was observed for nirsevimab (50 mg or 100 mg) across the diverse populations of infants entering their first RSV season and for nirsevimab (200 mg) in children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season.
- AESIs were reported in a few subjects in the nirsevimab groups and nearly all events were mild to moderate in severity. None were SAEs and none of the subjects with AESIs had any post baseline ADA detected with samples available for analysis.
  - Hypersensitivity events were limited to cutaneous findings. All but one of the events were mild to moderate in severity; there was a single nonserious Grade 3 AESI of skin hypersensitivity (a rash; onset 6 days post dosing; resolved after 3 weeks without treatment). Notably, no hypersensitivity was observed with a repeat dose of nirsevimab in a second season. Per investigator assessment, there were no anaphylaxis or other serious allergic reaction was attributed to IP.
  - No thrombocytopenia was attributed to nirsevimab. Two unrelated nonserious thrombocytopenia events of mild to moderate severity were reported in Trial 05 subjects with CHD in Season 1.
  - No AESIs of immune complex disease were reported in any participant.
- No SAEs were considered related to nirsevimab.

- None of the deaths reported in the nirsevimab or comparator groups were considered by the Investigator to be associated with drug administered and none were known or reported to be due to RSV. Deaths were attributed to underlying conditions or common causes of infant mortality in the respective country or region where the subject was enrolled (see Section 6.5).
- There was no evidence to support the theoretical risk of antibody-dependent enhancement of disease based on evidence of efficacy across the spectrum of disease severity and follow-up through a second RSV season without additional RSV prophylaxis (Trial 04): no increase in the disease incidence of MA RSV LRTI was observed in the second season and no increased severity of disease for infants who reported MA RSV LRTI and had received nirsevimab compared with placebo recipients.
- Since nirsevimab is a mAb mediating a passive immunization specific for RSV, it is not expected to interfere with the active immune response to co-administered routine childhood vaccines. In the small number of infants during the clinical trials who were given nirsevimab with routine childhood vaccines, the safety and reactogenicity profile of the co-administered regimen was similar to the childhood vaccines given without nirsevimab.

7 IMMUNOGENICITY

Across the nirsevimab clinical program, the incidence of anti-drug antibodies (ADA) to nirsevimab was low (Table 36). Among infants who received a single dose of nirsevimab in Trial 04 (Primary Cohort) and Trial 03, ADA to nirsevimab were detected in 6.0% and 5.4% of subjects, respectively, during follow-up through Day 360 post dosing. The incidence of ADA targeting the nirsevimab YTE substitution was similar to the overall ADA incidence (5.7% and 3.2% of subjects in Trial 04 and Trial 03, respectively). Neutralizing ADA constituted a relatively minor proportion of overall ADA, with an incidence of 1.6% and 0.3% in Trial 04 and Trial 03, respectively. ADA were generally detected at Day 361, and with median titers ranging from 150 to 400. In Trial 05 (Season 1), the ADA incidence was similar, with ADA detected in 5.5% of infants through Day 360 post dosing.

In subjects receiving nirsevimab in 2 consecutive RSV seasons in Trial 05, there was no evidence that the first dose of nirsevimab primed subjects for anamnestic ADA response in Season 2 or boosted ADA responses in subjects who had ADA to nirsevimab in Season 1. Of 180 subjects who received a second dose of nirsevimab, 8 subjects (4.4%) were ADA-positive through Day 360 post dose of the first RSV season, ADA were not detected in these subjects following their dose in Season 2. ADAs were detected in 10 subjects who received their second nirsevimab dose, none of which had ADA detected following their first dose. For subjects who received nirsevimab in Season 2 after receiving palivizumab in Season 1 (PALI/NIRS; N = 40), post-baseline ADA against nirsevimab in Season 2 was detectable in one subject (2.5%).

Overall, ADA to nirsevimab were detected in only a small percentage of subjects and did not appear to have a clinically relevant effect on nirsevimab PK (Section 7.1) or a discernable impact on clinical effect (Section 7.2) or safety (Section 7.3).

Table 36 Overview of Immunogenicity Results in Pivotal Studies

ADA result	Very and moderately preterm infants born ≥ 29 to < 35 wGA		Term and late preterm infants born ≥ 35 wGA		Higher risk infants	
	Trial 03		Trial 04 (Primary Cohort)		Trial 05 (Season 1)	
	Placebo N = 479	Nirsevimab N = 968	Placebo N = 491	Nirsevimab N = 987	Palivizumab N = 304	Nirsevimab N = 614
Incidence, % (n/N) [a]	3.6% (17/469)	5.4% (50/929)	0.8% (4/473)	6.0% (57/951)	6.9% (20/289)	5.5% (32/587)
Neutralizing ADA incidence, % (n/N) [a]	0.2% (1/451)	0.3% (3/887)	0.4% (2/450)	1.6% (14/896)	Not Assessed	0.4% (2/564)
Anti-YTE ADA incidence, % (n/N) [a]	0.9% (4/451)	3.2% (28/887)	0.7% (3/450)	5.7% (51/896)	Not Applicable	5.5% (31/564)
Median titer:	50	150	75	400	60	200
25th, 75th percentile	50, 50	50, 400	50, 250	100, 800	30, 240	100, 400
Range (min, max)	50, 400	50, 6400	50, 400	50, 204800	30, 960	50, 12800

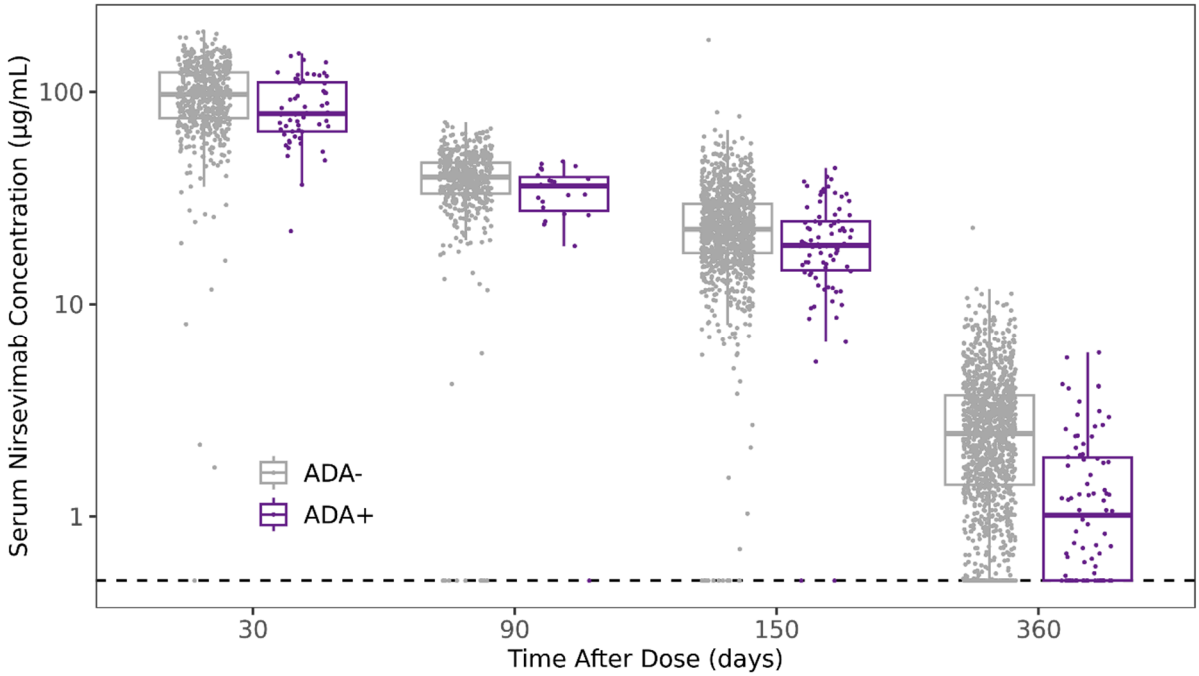
[a] n represents the number of subjects who were either ADA negative at baseline and ADA positive post baseline or ADA positive at baseline and had a ≥ 4-fold increase in titer from baseline; N represents the number of subjects with ADA results at baseline and at least one post baseline result.
Different analytical methods were used for detection of ADA against nirsevimab and palivizumab; immunogenicity results between the two antibodies cannot be compared.
ADA = anti-drug antibody; wGA = weeks gestational age; YTE = M257Y/S259T/T261E triple amino acid substitution. A sample is considered ADA-positive with a titer ≥ 50 for nirsevimab or ≥ 30 for palivizumab.

7.1 Impact of Immunogenicity on PK

The impact of ADA on the PK of nirsevimab was assessed via summaries of nirsevimab serum concentrations by ADA status based on pooled data from Trial 03 (proposed dose) and Trial 04 (Primary Cohort).

There was no clear impact of ADA on nirsevimab serum concentrations through Day 151; serum concentrations in ADA-positive subjects were within the range of those in ADA-negative subjects (Figure 28). On Day 361, nirsevimab serum concentrations were lower, and there was a larger proportion of subjects with samples below the lower limit of quantification in ADA-positive subjects relative to in ADA-negative subjects, indicating a minor effect of ADA on PK beyond Day 151.

Figure 28 **Nirsevimab Serum Concentrations by Schedule Timepoint by ADA-Positive (At Any Timepoint) or ADA negative – Trial 04 (Primary Cohort)/Trial 03 (Proposed Dose) Pool**



Boxplots: hinges show interquartile range, horizontal lines show medians, whiskers extend to 1.5 × interquartile range. Data limited to Visit day ± 14 days.
ADA = anti-drug antibody.

7.2 Impact of Immunogenicity on Efficacy

ADA to nirsevimab were detected in only a small percentage of subjects and therefore did not have a discernible effect on the overall estimate of clinical efficacy.

In Trial 04 (All Subjects) and Trial 03, there were a total of 5 ADA-positive subjects in the nirsevimab treatment group having primary endpoint events (MA RSV LRTI through Day 150 post dosing) (Table 37). In the ADA-positive subjects with MA RSV LRTI, the maximum ADA titer was 400 in Trial 04 and 100 in Trial 03. In Trial 04 (All Subjects), there was a numerically higher proportion of ADA-positive subjects who had a primary efficacy endpoint event (11.1% [4/36]) compared to ADA-negative subjects (1.0% [20/1973]). However, this is considered to be the result of chance, due to the small number of subjects with events and ADA-positive status. There was no apparent difference in Trial 03 (3.8% [1/26] ADA-positive subjects versus 2.5% (24/943] ADA-negative subjects).

Table 37 Incidence of MA RSV LRTI through Day 150 (Primary Endpoint) and MA RSV LRTI With Hospitalization (Secondary Endpoint) by ADA status – Trial 04 (All Subjects) and Trial 03

	Nirsevimab		
	N	**MA RSV LRTI**	**MA RSV LRTI with hosp.**
Trial 04 (All Subjects): any post-baseline positive ADA through 150 days post dose			
Yes	36	4 (11.1)	2 (5.6)
No	1973	20 (1.0)	7 (0.4)
Trial 03: any post-baseline positive ADA through 150 days post dose			
Yes	26	1 (3.8)	0 (0.0)
No	943	24 (2.5)	8 (0.8)

Data presented for number (%) of subjects with events.
ADA= anti-drug antibody; LRTI = lower respiratory tract infection; MA = medically attended; N = number of subjects; RSV = respiratory syncytial virus.

7.3 Impact of Immunogenicity on Safety

ADA to nirsevimab were detected in a small percentage of subjects in Trial 03, Trial 04, and Trial 05 (Section 7). No AESIs of hypersensitivity or immune complex disease were reported in subjects with detectable post-baseline ADA. Subjects in the nirsevimab group who were positive for ADA post-baseline had a similar safety profile compared to those who were negative for ADA post-baseline or the comparator groups. Notably, no hypersensitivity reactions were observed in 180 subjects receiving a repeat dose of nirsevimab in a second RSV season in Trial 05.

7.4 Immunogenicity Conclusions

- Across the nirsevimab clinical program, the incidence of ADA to nirsevimab was low (approximately 6%).
- ADA had no discernible effect on PK through Day 151, efficacy, or safety.

8 BENEFIT-RISK SUMMARY

AstraZeneca is seeking marketing approval for nirsevimab to provide protection for all infants from birth entering their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season, for the prevention of RSV lower respiratory tract disease.

Respiratory syncytial virus is the primary cause of LRTI among infants. In the first year of life, RSV LRTI is the most common reason for hospital admission. Most infants admitted to hospital with RSV LRTI are healthy, born at term, and have no known predisposing risk

factors. In addition, some infants with serious underlying comorbidities remain vulnerable in their second RSV season and need protection beyond the first year of life.

There is no licensed vaccine for RSV in infants, and the only prophylaxis (palivizumab, licensed over 20 years ago) is limited to preterm infants or infants with CLD or CHD, leaving the broader population of infants unprotected. In addition, palivizumab requires monthly injections throughout the RSV season (ie, 5 once-monthly injections in a typical RSV season), which places a burden on healthcare systems, caregivers, and recipients.

Therefore, there is a clear unmet medical need for interventions to provide protection from RSV lower respiratory tract disease in all infants in their first RSV season. In addition, for infants who remain vulnerable to severe RSV disease in their second RSV season, caregivers, healthcare providers, and recipients will benefit from the convenience of a single, fixed dose administered IM via pre-filled syringe, which offers administration flexibility to address local geographic disease timing.

8.1 Benefits of Nirsevimab

Efficacy in Term and Preterm Infants in RSV Season 1

Efficacy analysis was based primarily on data from 2 global placebo-controlled pivotal efficacy studies in complementary populations of very and moderately preterm infants born ≥ 29 to < 35 wGA (Trial 03) and term or late preterm infants born ≥ 35 wGA (Trial 04) in RSV Season 1. Overall, 2579 subjects were randomized to receive the proposed dose of nirsevimab (50 mg for infants < 5 kg or 100 mg for infants ≥ 5 kg at time of dosing) and 1293 to receive placebo. Nirsevimab was administered prior to the RSV season for infants born outside the season, or from birth for infants born during the season.

The robustness of the efficacy assessment is supported by the study integrity (eg, maintenance of blind through the database locks and high subject retention rates), rigorous assessment of disease incidence (despite the impact of COVID-19), and Independent Data Monitoring Committee review in these large multinational studies.

The primary endpoint of both trials was efficacy against MA RSV LRTI over 150 Days post dose. Nirsevimab demonstrated clinically relevant and highly significant protection against MA RSV LRTI in Trial 03 and Trial 04 achieving the primary endpoint for both studies (Table 9).

A similar level of efficacy (to that seen against MA RSV LRTI) was demonstrated against MA RSV LRTI with hospitalization in very and moderately preterm infants for Trial 03, and in term and late preterm infants for Trial 04 (Primary Cohort) and Trial 04 (All Subjects).

In addition, efficacy was demonstrated against the more stringent exploratory endpoint MA RSV LRTI (very severe), which selected for the subset of hospitalized infants requiring supplemental oxygen or intravenous fluids in Trial 04 (All Subjects).

Efficacy is further supported by HRU data, which showed lower incidence of hospital admission, supplemental oxygen use, and outpatient visits associated with MA RSV LRTI for nirsevimab vs placebo. Also, examination of treatment modalities for hospitalized cases indicated that breakthrough events were less severe with nirsevimab vs placebo (ie, lower percentages of subjects with supplemental oxygen use, respiratory support with CPAP/HFNC, or ICU admission, and shorter mean duration of oxygen use and hospital stay).

From impact analyses, the number needed to immunize to prevent one case of All MA LRTI (any cause) in late preterm and term infants was 11, and to prevent one case of All MA respiratory illness with hospitalization (any cause) was 57 in Trial 04 (Primary Cohort). In very and moderately preterm infants, the corresponding figures were 13 and 16 (Trial 03 [Proposed Dose]).

Protection in Higher Risk Infants in RSV Season 1 and Children up to 24 Months of Age in RSV Season 2

Nirsevimab serum exposures were comparable across the populations of healthy preterm and term infants (for whom efficacy was established) and higher risk infants in RSV Season 1 and children in RSV Season 2 who remain vulnerable to severe RSV disease. No statistically significant effect of CHD or CLD on nirsevimab PK was found based on population PK analysis. These findings support the conclusion that administration of the proposed nirsevimab dose will provide protection from RSV LRTI in these higher risk populations of infants and children in their first and second RSV seasons.

Virology

Surveillance virology analyses based on prospective, observational, molecular surveillance studies demonstrated that the nirsevimab binding site is well conserved among recent RSV A and RSV B strains and that variants containing mAb escape substitutions are rare (< 1%) and have not persisted or increased in frequency from one season to the next. Furthermore, nirsevimab neutralizes a diverse set of recombinant RSV viruses containing F sequence variations derived from isolates obtained from the NH and SH.

Clinical virology analyses based on the pivotal clinical studies demonstrated efficacy against both RSV subtypes through 150 days post dose and neutralization activity of nirsevimab against RSV A and B strains throughout the clinical studies. Across all treatment groups and reporting periods, RSV isolates containing nirsevimab resistance-associated substitutions were rare in subjects who had an RSV LRTI or non-LRTI event.

Based on these findings, a single IM dose of nirsevimab is expected to neutralize > 99% of current circulating RSV strains, resulting in enduring protection from RSV disease through a typical RSV season. Potential emergence of neutralization escape variants that may impact drug effectiveness will be monitored and characterized through genotypic and phenotypic assessment of RSV isolates collected in ongoing RSV molecular surveillance studies.

Conclusion on the Benefits of Nirsevimab

The pivotal studies demonstrated that a single IM dose of nirsevimab provides effective protection from RSV LRTI for all infants in their first RSV season, with consistent levels of efficacy demonstrated across populations (ie, term or late preterm infants born ≥ 35 wGA and very and moderately preterm infants born ≥ 29 to < 35 wGA) and disease severities.

Based on comparable PK, a similar level of protection is expected in children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season, including those with CHD and/or CLD of prematurity.

The effectiveness of a single dose of nirsevimab, administered IM via pre-filled syringe, provides a significant advantage over the multiple monthly injections required for palivizumab in each season, with improved treatment administration convenience, reduced burden on patients, caregivers, and healthcare providers, and reduced the potential for dosing errors.

8.2 Risks of Nirsevimab

A single IM dose of nirsevimab (50/100 mg weight-band dose for infants entering RSV Season 1 or 200 mg fixed dose for children up to 24 months of age entering RSV Season 2) was well tolerated with no safety concerns identified.

Nirsevimab was compared with placebo in 4441 term and preterm infants born ≥ 29 wGA (2966 nirsevimab and 1475 placebo); including 3854 infants in the Proposed-Dose Safety Pool (2570 nirsevimab 1284 placebo). The types and frequencies of AEs were generally balanced between the nirsevimab and placebo groups through 360 days post dose and within post-dose timepoints (1, 3, 7, 14, and 30 days). The majority of events were nonserious or mild/moderate in intensity and recovered without any medical treatment. During the 7-day post dosing period, the percentage of subjects with AEs associated with reactogenicity measures of injection site reaction or pyrexia was low (< 1%) for nirsevimab and placebo in the Proposed-Dose Safety Pool. Similarly, the percentage of subjects with IP-related skin reactions and investigator-assessed skin hypersensitivity reactions was low and balanced between the treatments. There were no events of anaphylaxis or other serious hypersensitivity reactions related to nirsevimab.

In Trial 05, the safety profile of nirsevimab (assessed through at least 360 days post first dose in RSV Season 1 in 918 preterm infants without CLD/CHD and infants with CLD/CHD,

including extremely preterm infants born < 29 wGA from both cohorts) was comparable to palivizumab, the standard of care for infants and children at higher risk for RSV. In addition, safety findings through 150 days post dose in RSV Season 2 were generally comparable between treatment groups in the 262 subjects from the Season 1 CLD/CHD cohort who continued into a second season. This included 180 subjects who received nirsevimab in both seasons (NIRS/NIRS), 40 who received palivizumab in Season 1 and nirsevimab in Season 2 (PALI/NIRS), and 42 who received palivizumab in both seasons (PALI/PALI), through at least 150 days post in RSV Season 2. Overall, the safety profile in RSV Season 1 and 2 in Trial 05 was consistent with the safety profile in term and preterm infants born ≥ 29 wGA in RSV Season 1 in Trial 03 and Trial 04. Of note, there was no indication of increased hypersensitivity, or any safety signal, in children who received a second dose of nirsevimab. None of the subjects with ADA in Season 1 had ADA in Season 2 (and vice versa), again supporting the conclusion that receipt of a second dose of nirsevimab does not pose any safety risks.

Across all infant subpopulations, there were no reported AESIs of anaphylaxis or other serious hypersensitivity reactions, thrombocytopenia, or immune complex disease attributed to nirsevimab. Hypersensitivity AESIs attributed to nirsevimab were limited to non-serious skin hypersensitivity reactions (nearly all of mild to moderate intensity) and occurred in a small percentage of subjects who all recovered, most without medical treatment. Severe thrombocytopenia, a risk reported based on post market experience for palivizumab, was not observed following nirsevimab dosing, and non-serious thrombocytopenia (based on investigator assessment and sponsor-defined MedDRA search criteria) was observed rarely and all cases included confounding factors and alternate plausible explanations. Recommendations and precautionary language for hypersensitivity (including anaphylaxis) and thrombocytopenia are included in the proposed prescribing information.

Adverse drug reactions assessed as having a reasonable possibility of a casual association with nirsevimab and noted in the proposed prescribing information include rash within 14 days post dose, and injection site reaction and pyrexia within 7 days post dose. These events are considered manageable in routine clinical practice and do not impact the benefit-risk of nirsevimab.

There are no anticipated risks associated with concomitant administration of nirsevimab and routine pediatric vaccines or influenza vaccine. Nirsevimab targets RSV and therefore should not interfere with the immune response to co-administered pediatric vaccines. Additionally, there were no clinically meaningful differences in the AE profile of infants who concomitantly received nirsevimab or placebo and a vaccine.

8.3 Benefit-Risk Assessment

Respiratory syncytial virus is estimated to cause up to 90% of childhood bronchiolitis and up to 40% of pediatric pneumonias (Hall, 2001) and is the primary cause of hospitalization for infants < 1 year of age. As most hospitalized infants were previously healthy term infants with no known predisposing risk factors, an effective prophylaxis for RSV LRTI for all infants would reduce the burden of disease. However, the only approved prevention, palivizumab, is for infants at highest risk for RSV disease, including preterm infants ≤ 35 wGA and infants with CLD or CHD, and requires monthly injections during the RSV season. Nirsevimab can address this serious unmet medical need and provide safe and efficacious protection against RSV LRTI for all infants in their first RSV season with a single IM dose, as demonstrated by the clinical data in this submission.

Figure 29 presents a Forest plot of the summary of benefit-risk for a single IM dose of nirsevimab in the broad population of term and preterm infants born ≥ 29 wGA, based on the Trial 04 (All Subjects) and Trial 03 (Proposed Dose) for measures of benefit and the Proposed-Dose Safety Pool for measures of risk. The plot is divided into two sections, with the top (in green) presenting evidence supporting the efficacy of nirsevimab and the bottom (in red) presenting evidence evaluating safety. The risk assessment of nirsevimab is presented for the 3 AESIs based on Sponsor-defined MedDRA search criteria (see Section 10.5), which were important potential risks for the clinical development program, in the Proposed-Dose Safety Pool. For the AESI of immediate hypersensitivity (including anaphylaxis), the risk assessment is presented for events occurring within 3 days post IP dose, which is consistent with the time course for such reactions. While neither serious nor severe, the 3 ADRs are presented in the benefit-risk plot for completeness. The plot is configured so that all point estimates to the right of the middle line for both efficacy and safety favor nirsevimab.

Figure 29 Benefit-Risk of Nirsevimab in Infants in Their First RSV Season

For impact analysis, number of cases averted over the typical 5-month RSV season was calculated from the seasonal difference in the estimated number of cases between nirsevimab and placebo and expressed per 1000 infants immunized. The 95% CI was estimated by bootstrapping, using the 2.5 and 97.5 percentiles of 1000 replicates obtained by sampling subjects. Absolute risk reduction was obtained by dividing number of cases averted per 1000 immunized by 1000.
For Safety Analysis, 95% CIs of the common difference in proportions of placebo and nirsevimab groups (placebo – nirsevimab) stratified by study are computed from the Miettinen-Nurminen confidence limits for the stratum proportion differences.
Safety endpoints for HSR, injection site reaction, fever, and rash were assessed relative to the day of dosing with nirsevimab or placebo. HSR (including anaphylaxis), thrombocytopenia, and immune complex disease were based on sponsor-defined MedDRA search criteria.
Study (ie, analysis population): Trial 03 < 5 kg = Trial 03 (Proposed Dose); Trial 04 NH Prim = subjects in Trial 04 (Primary Cohort) enrolled in the NH (where the RSV season occurred); Prop dose pool = Trial 04 (All Subjects) + Trial 03 (Proposed Dose) Safety Pool.
n/N = number of subjects with at least one event over the total number of subjects; NE = not evaluable; HSR = hypersensitivity reaction; incl. = including; LRTI = lower respiratory tract infection; MA = medically attended; NH = Northern Hemisphere; prop = proposed; RSV = respiratory syncytial virus.

A clinically important benefit for the proposed dose of nirsevimab through 150 days post dose vs placebo was demonstrated for the primary and secondary efficacy endpoints of MA RSV LRTI and MA RSV LRTI with hospitalization, respectively, in Trial 03 and Trial 04 (All Subjects), as well as for each of the impact endpoints in the studies. Overall, a single IM dose of nirsevimab was well tolerated, and an assessment of the potential risks indicated no increased risk with nirsevimab versus placebo.

Nirsevimab also demonstrated a safety profile comparable to palivizumab, in the Trial 05 population of infants at higher risk for severe RSV disease, including extremely preterm infants born < 29 wGA and infants with CLD or CHD. Palivizumab has been the standard of care for prophylaxis among this infant population for more than 20 years with an established safety profile. Protection from RSV LRTI in this population of palivizumab-eligible infants was supported for nirsevimab based on comparable PK. Furthermore, the safety profile of nirsevimab in RSV Season 2 in Trial 05 was comparable with palivizumab and there was no indication of increased hypersensitivity in children who received nirsevimab in 2 subsequent RSV seasons as compared to first nirsevimab administration in Season 2.

8.4 Benefit-Risk Conclusions

- All children, including healthy term infants, are at risk for severe RSV LRTI with primary RSV infection during infancy. It is estimated that RSV causes up to 90% of childhood bronchiolitis and up to 40% of pediatric pneumonias (Hall, 2001).
- There is no licensed vaccine for RSV in infants, and the only prophylaxis treatment available (palivizumab, licensed over 20 years ago) is limited to preterm infants or infants with CLD or CHD, leaving the broader population of infants unprotected.
- Therefore, there is a clear unmet medical need for interventions to provide protection from RSV lower respiratory tract disease in all infants in their first RSV season.
- The pivotal studies established that a single IM dose of nirsevimab provides effective protection from RSV LRTI for all infants in their first RSV season, with consistent levels of efficacy demonstrated across populations (ie, term or late preterm infants born ≥ 35 wGA and very and moderately preterm infants born ≥ 29 to < 35 wGA) and disease severities.
- Based on comparable PK, a similar level of protection is expected in infants born < 29 wGA in their first RSV season, and in children up to 24 months of age at higher risk of severe RSV disease in their first and second RSV season, including those with CHD and/or CLD of prematurity.
- A single IM dose of nirsevimab (50/100 mg weight-band dose in RSV Season 1, or 200 mg fixed dose in RSV Season 2) was well tolerated with no apparent safety concerns.
- Across all infant subpopulations, there were no reported AESIs of anaphylaxis, thrombocytopenia, or immune complex disease attributed to nirsevimab.

- Adverse drug reactions assessed as having a reasonable possibility of a causal association with nirsevimab and noted in the proposed prescribing information include rash within 14 days post dose, and injection site reaction and pyrexia within 7 days post dose.
- There are no anticipated increased risks associated with concomitant administration of nirsevimab and routine pediatric vaccines, including the influenza vaccine.
- Based on the favorable efficacy and safety profile across the broad population of infants entering their first RSV season and in children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season, combined with the advantage of a single dose, nirsevimab offers the ability to provide protection against RSV lower respiratory tract disease and significantly reduce the disease burden for all infants.

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10 SUPPLEMENTARY DATA

10.1 Subject Disposition and Baseline Characteristics in Trial 03 and Trial 04

Table 38 Subject Disposition – Trial 04 and Trial 03

Statistic	Number (%) of Subjects							
	Term and late preterm infants born ≥ 35 wGA				Very and moderately preterm infants born ≥ 29 to < 35 wGA			
	Trial 04 (Primary Cohort)		Trial 04 (All Subjects)		Trial 03		Trial 03 (Proposed Dose)	
	Placebo	Nirsevimab	Placebo	Nirsevimab	Placebo	Nirsevimab	Placebo	Nirsevimab
Subjects screened (total)	1626		3319		1540		860	
Screen failures	136/1626 (8.4)		307/3319 (9.2)		87/1540 (5.6)		0/860 (0.0)	
Did not meet inclusion/ exclusion criteria	98/136 (72.1)		190/307 (61.9)		66/87 (75.9)		0 (0.0)	
Lost to follow-up	6 (4.4)		11 (3.6)		1 (1.1)		0 (0.0)	
Withdrawal of consent	25 (18.4)		92 (30.0)		13 (14.9)		0 (0.0)	
Other	7 (5.1)		14 (4.6)		7 (8.0)		0 (0.0)	
Subjects randomized	496	994	1003	2009	484	969	290	570
Subjects randomized, not dosed	5 (1.0)	7 (0.7)	7 (0.7)	11 (0.5)	3 (0.6)	3 (0.3)	0 (0.0)	0 (0.0)
Subjects randomized and dosed	491 (99.0)	987 (99.3)	996 (99.3)	1998 (99.5)	481 (99.4)	966 (99.7)	290 (100.0)	570 (100.0)
Study phase status								
Completed Day 151 follow-up	488 (98.4)	977 (98.3)	938 (93.5)	1886 (93.9)	472 (97.5)	945 (97.5)	285 (98.3)	560 (98.2)
Completed Day 361 follow-up [a]	453 (91.3)	914 (92.0)	482 (48.1)	964 (48.0)	NA	NA	NA	NA
Completed the study	43 (8.7)	89 (9.0)	450 (44.9)	907 (45.1)	454 (93.8)	913 (94.2)	273 (94.1)	542 (95.1)
Early study discontinuation	21 (4.2)	40 (4.0)	61 (6.1)	114 (5.7)	30 (6.2)	56 (5.8)	17 (5.9)	28 (4.9)
Death	0 (0.0)	4 (0.4)	0 (0.0)	5 (0.2)	4 (0.8)	2 (0.2)	4 (1.4)	2 (0.4)
Lost to follow-up	3 (0.6)	9 (0.9)	21 (2.1)	47 (2.3)	11 (2.3)	26 (2.7)	5 (1.7)	12 (2.1)
Withdrawal by parent/legal/representative	14 (2.8)	20 (2.0)	27 (2.7)	38 (1.9)	11 (2.3)	21 (2.2)	5 (1.7)	9 (1.6)
COVID-19 pandemic	1 (0.2)	3 (0.3)	1 (0.1)	3 (0.1)	NA	NA	NA	NA

Table 38 Subject Disposition – Trial 04 and Trial 03

Statistic	Number (%) of Subjects							
	Term and late preterm infants born ≥ 35 wGA				Very and moderately preterm infants born ≥ 29 to < 35 wGA			
	Trial 04 (Primary Cohort)		Trial 04 (All Subjects)		Trial 03		Trial 03 (Proposed Dose)	
	Placebo	Nirsevimab	Placebo	Nirsevimab	Placebo	Nirsevimab	Placebo	Nirsevimab
Other	3 (0.6)	4 (0.4)	12 (1.2)	21 (1.0)	4 (0.8)	7 (0.7)	3 (1.0)	5 (0.9)

[a] The analysis in the Safety Cohort reported here occurred when all subjects were followed up through Day 150 post dose.
AE = adverse event; COVID-19 = coronavirus disease 2019; NA = not applicable; wGA = weeks gestational age.

Table 39 Selected Demographic and Baseline Characteristics – Trial 04 and Trial 03

Statistic	Term and late preterm infants born ≥ 35 wGA						Very and moderately preterm infants born ≥ 29 to < 35 wGA					
	Trial 04 (Primary Cohort)			Trial 04 (All Subjects)			Trial 03			Trial 03 (Proposed Dose)		
	Placebo	Nirsev	Total	Placebo	Nirsev	Total	Placebo	Nirsev	Total	Placebo	Nirsev	Total
	N = 496	N = 994	N = 1490	N = 1003	N = 2009	N = 3012	N = 484	N = 969	N = 1453	N = 290	N = 570	N = 860
Age at randomization, months												
Mean	3.01	2.91	2.95	2.92	2.91	2.91	3.28	3.29	3.29	1.79	1.84	1.83
SD	2.25	2.21	2.22	2.27	2.22	2.24	2.31	2.22	2.25	1.17	1.1	1.12
Median	2.60	2.60	2.60	2.5	2.53	2.53	2.80	2.90	2.80	1.55	1.70	1.60
(min, max)	(0.03, 10.97)	(0.03, 11.10)	(0.03, 11.10)	(0.03, 14.00)	(0.00, 11.86)	(0.00, 14.00)	(0.1, 11.3)	(0.1, 11.9)	(0.1, 11.9)	(0.1, 6.4)	(0.1, 5.7)	(0.1, 6.4)
Age at randomization stratum, n (%)												
≤ 3.0 months	285 (57.5)	577 (58.0)	862 (57.9)	588 (58.6)	1190 (59.2)	1778 (59.0)	257 (53.1)	516 (53.3)	773 (53.2)	246 (84.8)	489 (85.8)	735 (85.5)
> 3.0 to ≤ 6.0 months	162 (32.7)	317 (31.9)	479 (32.1)	323 (32.2)	636 (31.7)	959 (31.8)	153 (31.6)	320 (33.0)	473 (32.6)	42 (14.5)	81 (14.2)	123 (14.3)
> 6.0 months	49 (9.9)	100 (10.1)	149 (10.0)	92 (9.2)	183 (9.1)	275 (9.1)	74 (15.3)	133 (13.7)	207 (14.2)	2 (0.7)	0	2 (0.2)

Table 39 Selected Demographic and Baseline Characteristics – Trial 04 and Trial 03

	Term and late preterm infants born ≥ 35 wGA						Very and moderately preterm infants born ≥ 29 to < 35 wGA					
	Trial 04 (Primary Cohort)			Trial 04 (All Subjects)			Trial 03			Trial 03 (Proposed Dose)		
	Placebo	Nirsev	Total	Placebo	Nirsev	Total	Placebo	Nirsev	Total	Placebo	Nirsev	Total
Statistic	N = 496	N = 994	N = 1490	N = 1003	N = 2009	N = 3012	N = 484	N = 969	N = 1453	N = 290	N = 570	N = 860
Age at randomization group, n (%)												
< 28 days	109 (22.0)	239 (24.0)	348 (23.4)	221 (22.0)	434 (21.6)	655 (21.7)	79 (16.3)	136 (14.0)	215 (14.8)	78 (26.9)	136 (23.9)	214 (24.9)
Sex, n (%)												
Female	257 (51.8)	464 (46.7)	721 (48.4)	500 (49.9)	938 (46.7)	1438 (47.7)	224 (46.3)	468 (48.3)	692 (47.6)	140 (48.3)	272 (47.7)	412 (47.9)
Male	239 (48.2)	530 (53.3)	769 (51.6)	503 (50.1)	1071 (53.3)	1574 (52.3)	260 (53.7)	501 (51.7)	761 (52.4)	150 (51.7)	298 (52.3)	448 (52.1)
Race, n (%) [a]												
American Indian or Alaska Native	26 (5.2)	57 (5.8)	83 (5.6)	52 (5.2)	92 (4.6)	144 (4.8)	1 (0.2)	0	1 (0.1)	0	0	0
Asian	18 (3.6)	36 (3.6)	54 (3.6)	50 (5.0)	109 (5.4)	159 (5.3)	10 (2.1)	5 (0.5)	15 (1.0)	6 (2.1)	3 (0.5)	9 (1.0)
Black or African American	136 (27.4)	286 (28.9)	422 (28.4)	138 (13.8)	299 (14.9)	437 (14.5)	67 (13.8)	189 (19.5)	256 (17.6)	40 (13.8)	120 (21.1)	160 (18.6)
Native Hawaiian or other Pacific Islander	5 (1.0)	6 (0.6)	11 (0.7)	8 (0.8)	15 (0.7)	23 (0.8)	3 (0.6)	8 (0.8)	11 (0.8)	3 (1.0)	6 (1.1)	9 (1.0)
White	272 (54.8)	524 (52.9)	796 (53.5)	541 (53.9)	1052 (52.4)	1593 (52.9)	355 (73.3)	693 (71.6)	1048 (72.2)	206 (71.0)	395 (69.4)	601 (70.0)
Other	38 (7.7)	70 (7.1)	108 (7.3)	206 (20.5)	420 (20.9)	626 (20.8)	43 (8.9)	61 (6.3)	104 (7.2)	32 (11.0)	39 (6.9)	71 (8.3)

Table 39 Selected Demographic and Baseline Characteristics – Trial 04 and Trial 03

	Term and late preterm infants born ≥ 35 wGA						Very and moderately preterm infants born ≥ 29 to < 35 wGA					
	Trial 04 (Primary Cohort)			Trial 04 (All Subjects)			Trial 03			Trial 03 (Proposed Dose)		
	Placebo	Nirsev	Total	Placebo	Nirsev	Total	Placebo	Nirsev	Total	Placebo	Nirsev	Total
Statistic	**N = 496**	**N = 994**	**N = 1490**	**N = 1003**	**N = 2009**	**N = 3012**	**N = 484**	**N = 969**	**N = 1453**	**N = 290**	**N = 570**	**N = 860**
Multiple categories	1 (0.2)	12 (1.2)	13 (0.9)	8 (0.8)	19 (0.9)	27 (0.9)	5 (1.0)	12 (1.2)	17 (1.2)	3 (1.0)	6 (1.1)	9 (1.0)
Ethnicity, n (%)												
Hispanic or Latino	51 (10.3)	100 (10.1)	151 (10.2)	335 (33.5)	678 (33.8)	1013 (33.7)	91 (18.8)	225 (23.2)	316 (21.8)	44 (15.2)	118 (20.7)	162 (18.9)
Not Hispanic or Latino	443 (89.7)	890 (89.9)	1333 (89.8)	666 (66.5)	1327 (66.2)	1993 (66.3)	393 (81.2)	743 (76.8)	1136 (78.2)	246 (84.8)	451 (79.3)	697 (81.1)
Weight group on Day 1, n (%)												
< 2.5 kg	12 (2.4)	25 (2.5)	37 (2.5)	25 (2.5)	48 (2.4)	73 (2.4)	78 (16.2)	168 (17.4)	246 (17.0)	78 (26.9)	168 (29.5)	246 (28.6)
< 5 kg	192 (38.7)	403 (40.6)	595 (40.0)	392 (39.1)	800 (39.9)	1192 (39.6)	290 (60.3)	570 (59.1)	860 (59.5)	290 (100.0)	570 (100.0)	860 (100.0)
≥ 5 kg	304 (61.3)	589 (59.4)	893 (60.0)	611 (60.9)	1206 (60.1)	1817 (60.4)	191 (39.7)	394 (40.9)	585 (40.5)	0	0	0
Birth weight group n (%)												
≤ 2.5 kg	88 (17.7)	145 (14.6)	233 (15.6)	140 (14.0)	272 (13.5)	412 (13.7)	454 (93.8)	905 (93.4)	1359 (93.5)	276 (95.2)	541 (94.9)	817 (95.0)
> 2.5 kg	408 (82.3)	848 (85.4)	1256 (84.4)	863 (86.0)	1736 (86.5)	2599 (86.3)	30 (6.2)	64 (6.6)	94 (6.5)	14 (4.8)	29 (5.1)	43 (5.0)
Gestational age group, n (%)												
< 29 weeks	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
≥ 29 to < 32 weeks	NA	NA	NA	NA	NA	NA	101 (20.9)	193 (20.1)	294 (20.3)	64 (22.1)	125 (22.2)	189 (22.2)
≥ 32 to < 35 weeks	NA	NA	NA	NA	NA	NA	383 (79.1)	769 (79.9)	1152 (79.7)	226 (77.9)	438 (77.8)	664 (77.8)

Table 39 Selected Demographic and Baseline Characteristics – Trial 04 and Trial 03

	Term and late preterm infants born ≥ 35 wGA						Very and moderately preterm infants born ≥ 29 to < 35 wGA					
	Trial 04 (Primary Cohort)			Trial 04 (All Subjects)			Trial 03			Trial 03 (Proposed Dose)		
	Placebo	Nirsev	Total	Placebo	Nirsev	Total	Placebo	Nirsev	Total	Placebo	Nirsev	Total
Statistic	**N = 496**	**N = 994**	**N = 1490**	**N = 1003**	**N = 2009**	**N = 3012**	**N = 484**	**N = 969**	**N = 1453**	**N = 290**	**N = 570**	**N = 860**
≥ 35 weeks to < 37 weeks	76 (15.4)	132 (13.3)	208 (14.0)	122 (12.2)	239 (11.9)	361 (12.0)	NA	NA	NA	NA	NA	NA
≥ 37 weeks	419 (84.6)	861 (86.7)	1280 (86.0)	880 (87.8)	1769 (88.1)	2649 (88.0)	NA	NA	NA	NA	NA	NA
Multiple birth, n (%)												
Yes	45 (9.1)	96 (9.7)	141 (9.5)	71 (7.1)	163 (8.1)	234 (7.8)	185 (38.2)	366 (37.8)	551 (37.9)	119 (41.0)	213 (37.4)	332 (38.6)
Down Syndrome, n (%)												
Yes	0 (0)	3 (0.3)	3 (0.2)	0 (0)	4 (0.2)	4 (0.1)	NE	NE	NE	NE	NE	NE
Cystic fibrosis, n (%)												
Yes	1 (0.2)	0 (0)	1 (0.1)	1 (0.1)	3 (0.1)	4 (0.1)	NE	NE	NE	NE	NE	NE

[a] Each race category counts subjects who selected only that category; "Multiple categories checked" counts subjects who selected more than one race category.
max = maximum; min = minimum; NA = not applicable; NE = not evaluated; Nirsev = nirsevimab; SD = standard deviation; wGA = weeks gestational age.

10.2 Additional Data Presentations - Trial 04 (Primary Analysis)

10.2.1 Re-Analysis of MA RSV LRTI in Trial 04 (Primary Cohort) Accounting for Subjects Reclassified as Lost to Follow-Up

The analyses of MA RSV LRTI and MA RSV LRTI with hospitalization in Trial 04 (Primary Cohort) were re-run to account for 2 subjects who were classified as ongoing through 150 days post dose at the time of the Primary Analysis (data cut-off date 11 March 2021), but were later reclassified as lost to follow-up prior to 150 days post dose at time of the database lock for the second interim analysis (data cut-off date 31 March 2022) (Table 40 and Table 41). Subgroup analyses of MA RSV LRTI through 150 days post dose were also re-run to account for the reclassifications; no change to the efficacy estimates presented in Figure 30 was observed.

Table 40 Re-Analysis of MA RSV LRTI Through 150 Days Post Dose - Trial 04 (Primary Cohort)

Statistic	Trial 04 (Primary Cohort)	
	Placebo N = 496	Nirsevimab N = 994
Subjects with observed events, n (%)	25 (5.0)	12 (1.2)
Subjects requiring imputation [a], n (%)	7 (1.4)	16 (1.6)
RRR (95% CI)	74.9% (50.6% to 87.2%)	
p-value	p < 0.0001	

[a] Subjects who had no events and were not followed through 150 days post dose.
Data presented for the number (%) of subjects with events; for subjects with multiple events, only the first event is included in the analysis.
CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; n = number of events observed N = number of subjects; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus.

Table 41 Re-Analysis of MA RSV LRTI with Hospitalization Through 150 Days Post Dose - Trial 04 (Primary Cohort)

Statistic	Trial 04 (Primary Cohort)	
	Placebo N = 496	Nirsevimab N = 994
Subjects with observed events, n (%)	8 (1.6)	6 (0.6)
Subjects requiring imputation [a], n (%)	7 (1.4)	16 (1.6)
RRR (95% CI)	60.2% (-14.6% to 86.2%)	
p-value	p < 0.0878	

[a] Subjects who had no events and were not followed through 150 days post dose.

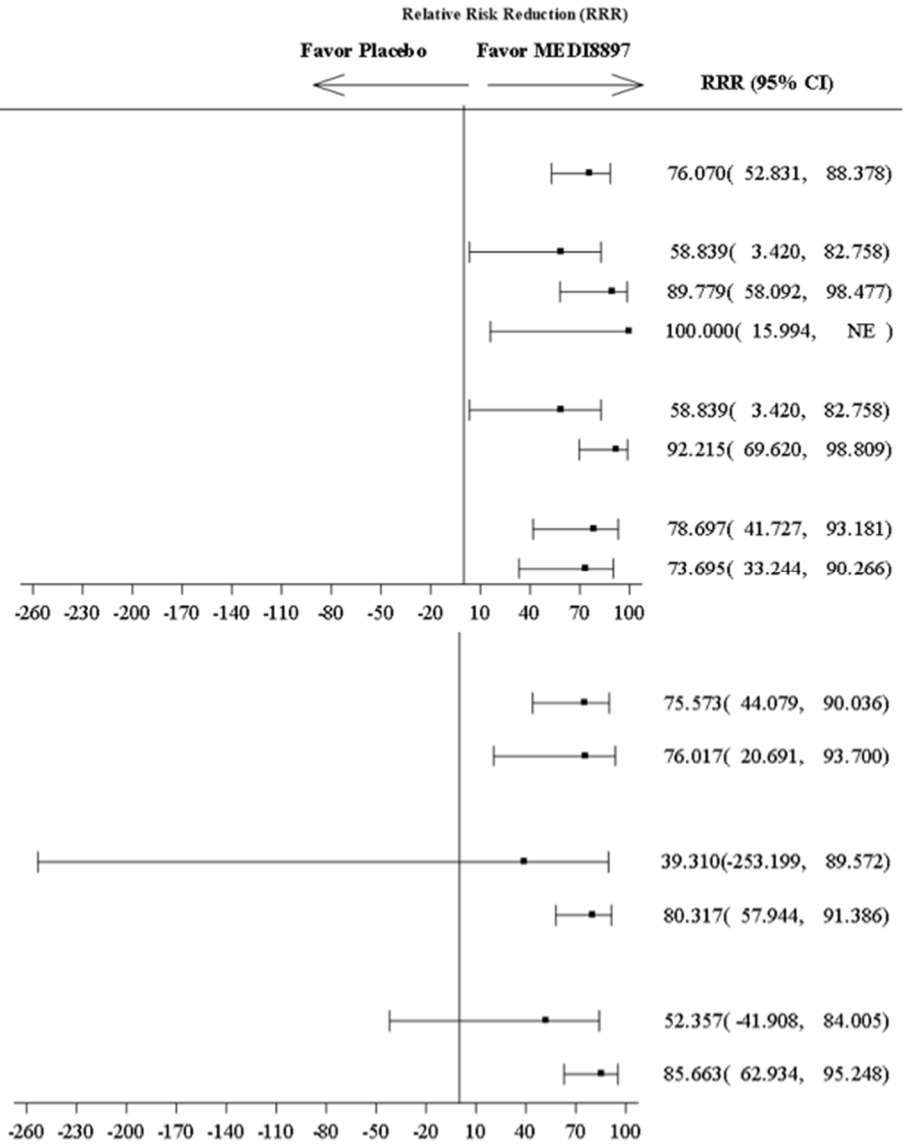
Data presented for the number (%) of subjects with events; for subjects with multiple events, only the first event is included in the analysis.
CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; n = number of events observed N = number of subjects; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus.

10.2.2 Subgroup Analysis of MA RSV LRTI in Trial 04 (Primary Cohort)

Figure 30 presents subgroup analyses of MA RSV LRTI conducted in Trial 04 (Primary Cohort).

Figure 30 Subgroup Analysis: Medically Attended RSV LRTI Through 150 Days Post Dose - Trial 04 (Primary Cohort)

Subgroup	Placebo (N = 496) Number of Subjects	Placebo (N = 496) Observed Events(%)	MEDI8897 (N = 994) Number of Subjects	MEDI8897 (N = 994) Observed Events(%)	RRR (95% CI)
Hemisphere					
Northern Hemisphere	342	25 (7.3)	686	12 (1.7)	76.070(52.831, 88.378)
Age at randomization					
<= 3.0 months	285	12 (4.2)	577	10 (1.7)	58.839(3.420, 82.758)
> 3.0 to <= 6.0 months	162	10 (6.2)	317	2 (0.6)	89.779(58.092, 98.477)
> 6.0 months	49	3 (6.1)	100	0 (0.0)	100.000(15.994, NE)
Age at randomization					
<= 3.0 months	285	12 (4.2)	577	10 (1.7)	58.839(3.420, 82.758)
> 3.0 months	211	13 (6.2)	417	2 (0.5)	92.215(69.620, 98.809)
Sex					
Female	257	13 (5.1)	464	5 (1.1)	78.697(41.727, 93.181)
Male	239	12 (5.0)	530	7 (1.3)	73.695(33.244, 90.266)
Race					
Caucasian	272	17 (6.3)	524	8 (1.5)	75.573(44.079, 90.036)
Non-Caucasian	224	8 (3.6)	467	4 (0.9)	76.017(20.691, 93.700)
Weight at birth					
<= 2.5 kg	88	3 (3.4)	145	3 (2.1)	39.310(-253.199, 89.572)
> 2.5 kg	408	22 (5.4)	848	9 (1.1)	80.317(57.944, 91.386)
Weight on Day 1					
< 5 kg	192	7 (3.6)	403	7 (1.7)	52.357(-41.908, 84.005)
>= 5 kg	304	18 (5.9)	589	5 (0.8)	85.663(62.934, 95.248)



RRR and its corresponding 95% CI (mid-p adjusted) were estimated based on exact conditional method using PROC GENMOD with no strata.
If RRR was -100% or -Inf, one-sided 97.5% CI was reported.
For Age at randomization (2-level), unadjusted interaction p-value <0.1.
CI = confidence interval; Inf = infinity; LRTI = lower respiratory tract infection; MA = medically attended; MEDI8897 = nirsevimab; N = number of subjects; N/A = not applicable; NE = not evaluated; RRR = relative risk reduction; RSV = respiratory syncytial virus; wGA = weeks gestational age.

10.3 Indicators of Disease Severity and Treatment Modalities According to MA RSV LRTI Severity – Trial 04 (All Subjects)

The frequency of symptoms associated with MA RSV LRTI case definitions is shown in Table 42. The overall frequency of symptoms was similar across Trial 04 (Primary Cohort), Trial 04 (Safety Cohort), and Trial 04 (All Subjects).

The treatment modalities associated with the case definitions of RSV hospitalization are shown in Table 43. Overall, the cases occurring in the different Trial 04 cohorts were similar with respect to the frequency and duration of oxygen use, respiratory support, and intensive care unit stays.

Table 42 Incidence of Objective Indicators of Clinical Severity Through 150 Days Post Dose by Trial 04 Cohort

Subjects, n (%) [b]	Primary Cohort			Safety Cohort [a]			All Subjects		
	MA RSV LRTI N = 37	MA RSV LRTI with hosp N = 14	MA RSV LRTI (very severe) N = 12	MA RSV LRTI N = 41	MA RSV LRTI with hosp N = 15	MA RSV LRTI (very severe) N = 12	MA RSV LRTI N = 78	MA RSV LRTI with hosp N = 29	MA RSV LRTI (very severe) N = 24
Increased respiration rate	23 (62.2)	9 (64.3)	7 (58.3)	21 (51.2)	11 (73.3)	10 (83.3)	44 (56.4)	20 (69.0)	17 (70.8)
Hypoxaemia	12 (32.4)	7 (50.0)	7 (58.3)	11 (26.8)	9 (60.0)	9 (75.0)	23 (29.5)	16 (55.2)	16 (66.7)
O_2 saturation < 92%	8 (21.6)	7 (50.0)	7 (58.3)	6 (14.6)	6 (40.0)	6 (50.0)	14 (17.9)	13 (44.8)	13 (54.2)
O_2 saturation < 90%	6 (16.2)	6 (42.9)	6 (50.0)	4 (9.8)	4 (26.7)	4 (33.3)	10 (12.8)	10 (34.5)	10 (41.7)
Acute hypoxic or ventilatory failure	2 (5.4)	2 (14.3)	2 (16.7)	5 (12.2)	5 (33.3)	5 (41.7)	7 (9.0)	7 (24.1)	7 (29.2)
New onset apnoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal flaring	8 (21.6)	5 (35.7)	5 (41.7)	4 (9.8)	2 (13.3)	2 (16.7)	12 (15.4)	7 (24.1)	7 (29.2)
Retractions [c]	24 (64.9)	13 (92.9)	11 (91.7)	30 (73.2)	14 (93.3)	11 (91.7)	54 (69.2)	27 (93.1)	22 (91.7)
Grunting	6 (16.2)	4 (28.6)	4 (33.3)	4 (9.8)	2 (13.3)	2 (16.7)	10 (12.8)	6 (20.7)	6 (25.0)
Dehydration	2 (5.4)	2 (14.3)	2 (16.7)	2 (4.9)	2 (13.3)	2 (16.7)	4 (5.1)	4 (13.8)	4 (16.7)

[a] The Trial 04 (Safety Cohort) includes subjects randomized into the second Trial 04 cohort, ie, after the enrollment pause due to COVID-19 pandemic.
[b] If a subject has multiple events during the reporting period, only the first event is contributed to the summary.
[c] Intercostal, subcostal, or supraclavicular retractions.

Hosp = hospitalization; LRTI = lower respiratory tract infection; MA = medically attended; n = number of subjects with symptom; N = number of subjects with event; RSV = respiratory syncytial virus.

Table 43 Treatment Modalities for MA RSV LRTI with Hospitalization by Trial 04 Cohort and All Subjects

Treatment group	Primary Cohort		Safety Cohort		All Subjects	
	Nirsevimab	Placebo	Nirsevimab	Placebo	Nirsevimab	Placebo
Admission to hospital: number subjects	6	8	3	12	9	20
Treatment modality, n (%)						
Oxygen	4 (66.7)	6 (75.0)	2 (66.7)	10 (83.3)	6 (66.7)	16 (80.0)
CPAP or HFNC	1 (16.7)	1 (12.5)	0 (0.0)	1 (8.3)	1 (11.1)	2 (10.0)
Mechanical ventilation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Admission to ICU	0 (0.0)	1 (12.5)	1 (33.3)	0 (0.0)	1 (11.1)	1 (5.0)
Duration, mean days (SD)						
Duration of hospital stay	7.2 (4.6)	4.0 (2.2)	6.0 (2.0)	5.6 (2.0)	6.8 (3.8)	5.0 (2.2)
Duration of oxygen	3.5 (1.9)	4.3 (2.3)	5.0 (2.8)	4.3 (1.7)	4.0 (2.1)	4.3 (1.9)
Duration of ICU stay	N/A	5.0 (N/A)	6.0 (N/A)	N/A	6.0 (N/A)	5.0 (N/A)

CPAP = Continuous positive airway pressure; HFNC = high flow nasal canulae; ICU = intensive care unit; LRTI = lower respiratory tract infection; MA = medically attended; N/A = not applicable; RSV = respiratory syncytial virus; SD = standard deviation.

10.4 Efficacy Extrapolation in Trial 05: Supplementary Tables

Table 44 Mean (90%CI) AUC_{0-365} in Trial 05 and Trial 04

	n	AUC_{0-365}	
		Mean	90% CI
Trial 04 Healthy < 35 wGA Season 1	954	12.2	(12, 12.4)
Trial 05			
< 29 wGA Season 1	46	12.2	(11.5, 12.9)
CHD Season 1	64	12.3	(11.4, 13.2)
CLD Season 1	137	12.4	(11.9, 12.9)
CHD Season 2	58	20.4	(19.2, 21.6)
CLD Season 2	132	22.1	(21.3, 22.9)
≥ 29 wGA	344	12.2	(11.9, 12.5)

AUC = area under the time-concentration curve; CHD = congenital heart disease; CI = confidence interval; CLD = chronic lung disease; wGA = weeks gestational age.

10.5 Adverse Events of Special Interest Based on Sponsor-Defined MedDRA Search Criteria

A supplementary analysis was conducted for adverse events occurring in the database for AESIs based on sponsor-defined MedDRA search criteria (Table 45).

Table 45 Sponsor-Defined MedDRA Search Criteria for Adverse Events of Special Interest

Hypersensitivity	Thrombocytopenia	Immune Complex Disease

• Narrow SMQ Hypersensitivity reaction
• Narrow and broad SMQ Anaphylactic reactions
	• All preferred terms under MedDRA HLT "Thrombocytopenia"
	• Additional preferred terms of:
	  ◦ Petechiae
	  ◦ Epistaxis
	  ◦ Contusion
	  ◦ Ecchymosis
	  ◦ Hemorrhage
	  ◦ Hematoma
	• Any reported AE term containing 'bleed' or 'bleeding'
		• Preferred terms of:
		  ◦ Glomerulonephritis
		  ◦ Endocarditis
		  ◦ Neuritis
		  ◦ Polyarthritis
		  ◦ Joint swelling
		  ◦ Arthralgia
		  ◦ Type III Immune Complex Mediated Reaction
		  ◦ Serum sickness
		  ◦ Serum sickness-like reaction
		  ◦ Vasculitis
		  ◦ Purpura
		• Any reported AE term containing 'arthritis' or 'arthus'

AE = adverse event; HLT = high level terms; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA queries.

AESIs based on sponsor-defined MedDRA search criteria were predominantly comprised of events in the hypersensitivity category across the pivotal randomized studies (Table 46, Table 47, Table 48).

In the Proposed-Dose Safety Pool (Table 46), there was little difference in AESI based on sponsor-defined MedDRA search criteria between the nirsevimab and placebo groups.

In Trial 05 CHD/CLD cohort in RSV Season 1 (Table 47), a numerically higher percentage of subjects in the nirsevimab group compared to the palivizumab group had an AESI based on sponsor-defined MedDRA search criteria, driven by events in the hypersensitivity category.

Notably, the rates were comparable between nirsevimab and comparator groups through any of the relevant time points close to IP dosing (within 1, 3, 7, 14, or 30 days post dose [first IP dose for Trial 05]), inclusive of expected timeframe for immediate hypersensitivity in both Trial 05 RSV Season 1 and the Proposed-Dose Safety Pool. In Trial 05 RSV Season 2 (Table 48), the percentage of subjects with an AESI based on sponsor-defined MedDRA search criteria was comparable across all 3 treatment groups.

Table 46 Adverse Events of Special Interest Based on Sponsor-Defined MedDRA Search Criteria Through at Least 150 Days Post Dose – Proposed-Dose Safety Pool

Subjects[a] with	Number (%) of Subjects		
	Placebo N = 1284	Nirsevimab N = 2570	Total N = 3854
At least 1 AESI based on sponsor-defined MedDRA search criteria	290 (22.6)	590 (23.0)	880 (22.8)
Hypersensitivity[b]	287 (22.4)	578 (22.5)	865 (22.4)
Within 3 days post dose	6 (0.5)	23 (0.9)	29 (0.8)
Within 14 days post dose	35 (2.7)	79 (3.1)	114 (3.0)
Thrombocytopenia	5 (0.4)	18 (0.7)	23 (0.6)
Immune complex disease	0	0	0
At least 1 IP-related AESI based on sponsor-defined MedDRA search criteria	3 (0.2)	13 (0.5)	16 (0.4)

[a] Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.
[b] All were all skin hypersensitivity events.
AESI = adverse events of special interest; IP = investigational product; N = total number of subjects.

Table 47 Adverse Events of Special Interest Based on Sponsor-Defined MedDRA Search Criteria Through 360 Days Post First Dose in Trial 05 (RSV Season 1)

Subjects [a] with	Number (%) of subjects					
	Overall		Preterm		CLD/CHD	
	Palivizumab N = 304	Nirsevimab N = 614	Palivizumab N = 206	Nirsevimab N = 406	Palivizumab N = 98	Nirsevimab N = 208
At least 1 AESI based on sponsor-defined MedDRA search criteria	47 (15.5)	117 (19.1)	32 (15.5)	68 (16.7)	15 (15.3)	49 (23.6)
Hypersensitivity	46 (15.1)	112 (18.2)	32 (15.5)	67 (16.5)	14 (14.3)	45 (21.6)
Within 3 days post first dose	2 (0.7)	3 (0.5)	2 (1.0)	1 (0.2)	0	2 (1.0)
Within 14 days post first dose	7 (2.3)	13 (2.1)	4 (1.9)	10 (2.5)	3 (3.1)	3 (1.4)
Thrombocytopenia	1 (0.3)	6 (1.0)	0	1 (0.2)	1 (1.0)	5 (2.4)
Immune complex disease	0	0	0	0	0	0
At least 1 IP-related AESI based on sponsor-defined MedDRA search criteria	1 (0.3)	2 (0.3)	1 (0.5)	1 (0.2)	0	1 (0.5)

[a] Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.
AESI = adverse events of special interest; IP = investigational product; N = total number of subjects.

Table 48 Adverse Events of Special Interest Based on Sponsor-Defined MedDRA Search Criteria Through at Least 150 Days Post First Dose in Trial 05 (RSV Season 2)

Subjects [a] with	Number (%) of subjects		
	PALI/PALI N = 42	PALI/NIRS N = 40	NIRS/NIRS N = 180
At least 1 AESI based on sponsor-defined MedDRA search criteria	4 (9.5)	4 (10.0)	24 (13.3)
Hypersensitivity	4 (9.5)	3 (7.5)	22 (12.2)
Within 3 days	0	0	0
Within 14 days post first dose	1 (2.4)	1 (2.5)	1 (0.6)
Thrombocytopenia	0	1 (2.5)	4 (2.2)
Immune complex disease	0	0	0
At least 1 IP-related AESI based on sponsor-defined MedDRA search criteria	0	0	0

[a] Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.
AESI = adverse events of special interest; IP = investigational product; N = total number of subjects.

AESIs of hypersensitivity based on sponsor-defined MedDRA search criteria were comparable between nirsevimab and comparator groups through the relevant time points close to IP dosing (within 1, 3, 7, 14, or 30 days post dose [first IP dose for Trial 05]), inclusive of expected timeframe for immediate hypersensitivity. Immediate Type I hypersensitivity reactions typically start within minutes to hours (Khan et al 2022; Brockow et al 2015), whereas a typical sensitization latency could occur within 5 to 10 days (Brockow et al 2015). To conduct a meaningful assessment of hypersensitivity events that may be causally related in this population, specifically rash conditions that are extremely common in infant population (O'Connor et al 2008); assessment was limited to 14 days post administration.

There was a low incidence AESIs of thrombocytopenia based on sponsor-defined MedDRA search criteria across studies (Table 46, Table 47, Table 48). All events were Grade 1 to 2 severity. A single event of petechiae in a Trial 03 subject was reported as an AESI of skin hypersensitivity based on parental reporting but not clinically confirmed; however, was reported as IP-related by the Investigator (Table 46).