BEYFORTUS™ (nirsevimab) for the Prevention of RSV Lower Respiratory Tract Disease in Infants and Children

Antimicrobial Drugs Advisory Committee

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Introduction

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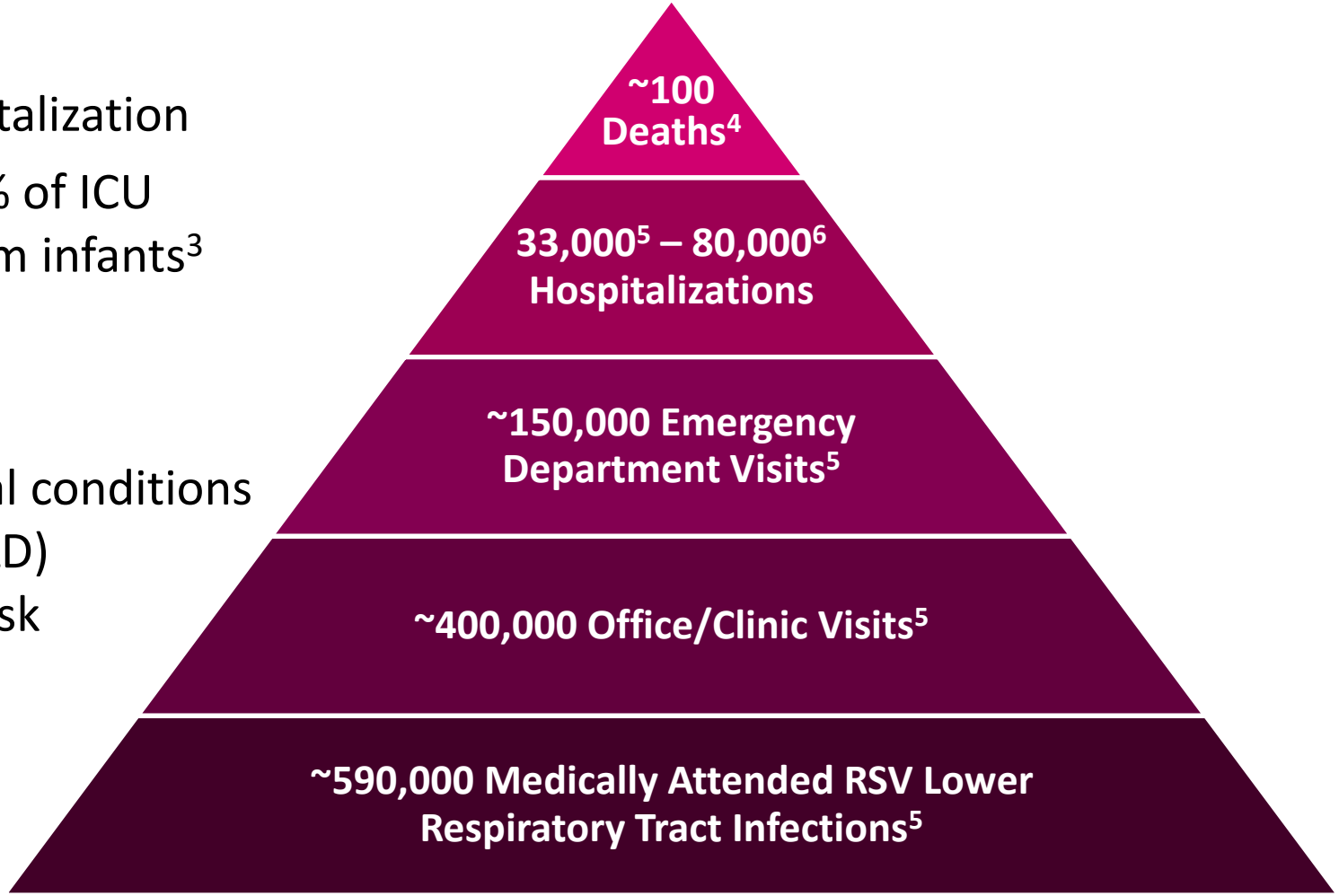
Preventing Respiratory Syncytial Virus (RSV) Disease in Infants: A Major Public Health Need

- Seasonal virus causing annual epidemics, typically Fall to Spring
- Most common cause of childhood acute LRTI[1]
- Major reason for hospitalization in infants and young children[2,3]
- Premature infants and those with underlying lung or heart disease at highest risk of severe illness
  - Palivizumab approved to prevent serious RSV disease[4]
- Most medically attended cases occur in otherwise healthy term infants[5]
  - No effective RSV prevention strategy

1. Murray et al, *PLoS ONE* 2014;9:e89186; 2. Lambert et al, *Front Immunol* 2014;5:466; 3. Li et al, *BMC Medicine* 2020;18:82;
4. Demont et al, *BMC Infectious Diseases* 2021;21:730; 5. Sommer et al, *Open Microbiol J* 2011;5:144-54.
Image credit Jill Lehmann Photography.

RSV Causes Significant Burden of Disease in US Infants

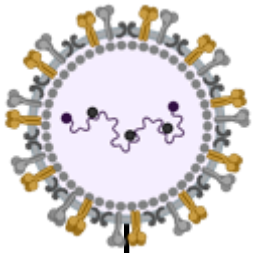
- First year of life[1,2]
  - Most common reason for hospitalization
  - 72% of hospitalizations and 66% of ICU admissions occur in healthy term infants[3]
- Second year of life[2]
  - Infants with pre-existing medical conditions (eg, immunodeficiency, CHD, CLD) are associated with increased risk



1. Glezen WP, et al. *Am J Dis Child*. 1986;140(6):543-6; 2. Centers for Disease Control and Prevention. RSV in Infants and Young Children. Updated December 18. Accessed June 29, 2021. https://www.cdc.gov/rsv/high-risk/infants-young-children.html; 3. Arriola CS, et al. *J Pediatric Infect Dis Soc*. 2020;9(5):587-595; 4. Hansen CL, et al. *JAMA Netw Open*. 2022;5(2):e220527; 5. Rainisch G, et al. *Vaccine*. 2020;38(2):251-257; 6. McLaughlin JM, et al. *J Infect Dis*. 2022;225(6):1100-1111.

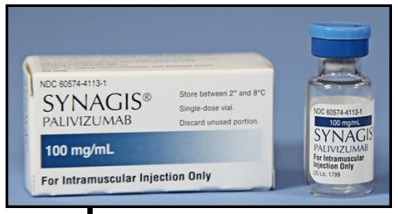
Long Road to Effective RSV Prevention Strategy for All Infants

1956: Discovery of RSV[1]



Mid-1980s: Proof-of-principle experiments in animal models for prophylactic antibody administration[1]

1998: Palivizumab licensed[1]

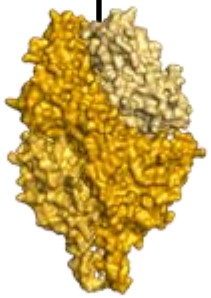


2014: Early studies of nirsevimab[1]

1950 | 1960 | 1970 | 1980 | 1990 | 2000 | 2010 | 2020

1965: First RSV vaccine trial begins using formalin-inactivated virus[1]

1996: RSV-IVIG approved[1]



2013: Pre-fusion F protein conformation mapped[2]

Images made with BioRender or licensed by AstraZeneca.

1. Villafana T, et al. *Expert Rev Vaccines*. 2017;16(7):1-13; 2. McLellan JS, et al. *Science.* 2013;342:592-598

Long-Acting Monoclonal Antibody Provides an Opportunity to Protect All Infants from RSV

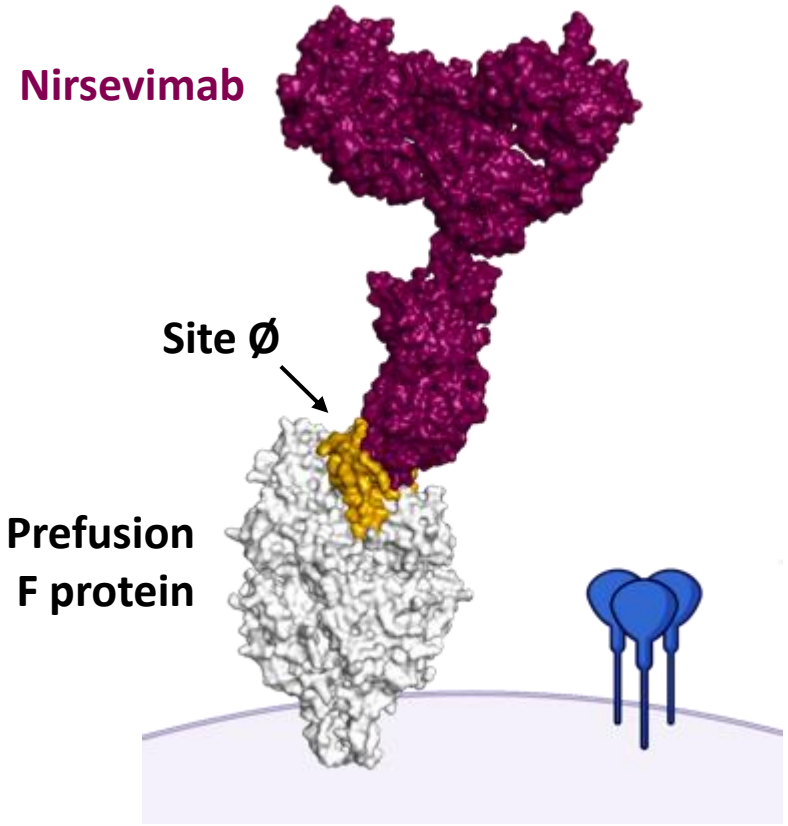
Technology

- Highly potent IgG1 from human donor
- Targets highly conserved epitope – site Ø on prefusion F protein
- Half-life extension

Product Advantages

- Passive immunization
- Rapid onset of protection
- Single IM dose provides coverage through a typical RSV season
- Well-defined levels of neutralizing Ab
- Ability to combine with routine pediatric immunizations

Nirsevimab Has Important Features That Enable Its Use for RSV Prevention in All Infants

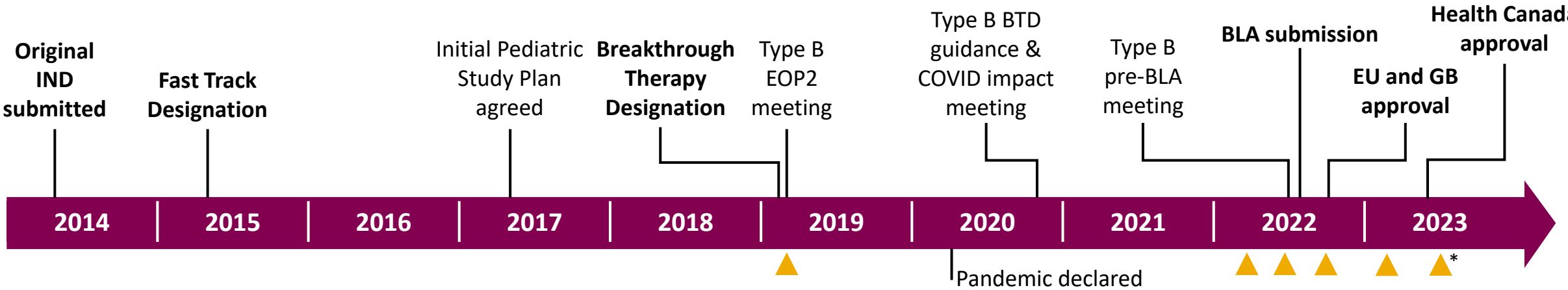


Nirsevimab inhibits conformational shift of pre-F protein, preventing viral membrane fusion

- Highly potent recombinant human IgG1 kappa mAb
- Targets highly conserved epitope on prefusion RSV F protein (site Ø)
- Prolonged serum half-life (YTE technology)

- Once per RSV season fixed IM dosing
- Flexible dosing: At birth or just prior to season
- Rapid protection

Key Milestones in Clinical Development of Nirsevimab



Early Studies

Trial 03 (Ph2b)
Preterm infants ≥29 to <35 wGA

Trial 04 (Ph3)
Term and late preterm infants born ≥35 wGA

Trial 05 (Ph2/3)
Infants at high risk of severe RSV disease

Trial 08 (Ph2)
Immunocompromised children ≤24 months of age

HARMONIE
Infants not eligible for palivizumab

▲ **Advisory Committee on Immunization Practices (ACIP) interactions**

EU = European Union; GB = Great Britain.
* Planned meeting in June.

Nirsevimab Proposed Indication

For the prevention of Respiratory Syncytial Virus (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 Implementation

		
Protect infants born…	**<u>Before</u> the RSV season (April – October)**	**<u>During</u> the RSV season (November – March)**
When?	**At beginning of season**	**At birth before discharge**
Where?	**In <u>office</u>, during existing well visit before start of season**	**In <u>hospital</u>**
How?	**Intramuscular injection with pre-filled syringe (stored at 2-8°C)**	

Simple, vaccine-like implementation provides protection to all infants throughout the RSV season

Agenda

Clinical Efficacy
Amanda Leach, MRCPCH
AstraZeneca

- **Clinically meaningful and statistically significant reduction in risk of MA RSV LRTI** across spectrum of disease in a broad range of infants
- **A single dose is efficacious for at least 5 months**

Safety
Manish Shroff, MBBS, MS, MBA
AstraZeneca

- **Safety profile of nirsevimab is favorable** and generally comparable with palivizumab in higher-risk infants and children

Clinical Perspective
William Muller, MD, PhD
Northwestern University Feinberg School of Medicine

- **No preventive strategies currently available for the majority of infants**
- **Data presented support use of nirsevimab for all infants entering their first RSV season and high-risk children in their second RSV season**

Benefit-Risk & Conclusions
Tonya Villafana, PhD, MPH
AstraZeneca

- **Clinical studies demonstrate that nirsevimab has a favorable benefit-risk profile for RSV prevention** in all infants and in children vulnerable to severe RSV disease through their second season

Additional Responders

Beth Kelly, PhD	Clinical Virology, AstraZeneca
Ulrika Hamrén, PhD	Clinical Pharmacology, AstraZeneca
Alexander Currie, MSc	Biometrics Team Leader, AstraZeneca
Vaishali Mankad, MD	Global Development Medical Director, AstraZeneca
Amy Grenham, MS	Global Regulatory Lead, AstraZeneca
Christian Felter, MD	RSV Global Medical Franchise Head, Sanofi

Efficacy

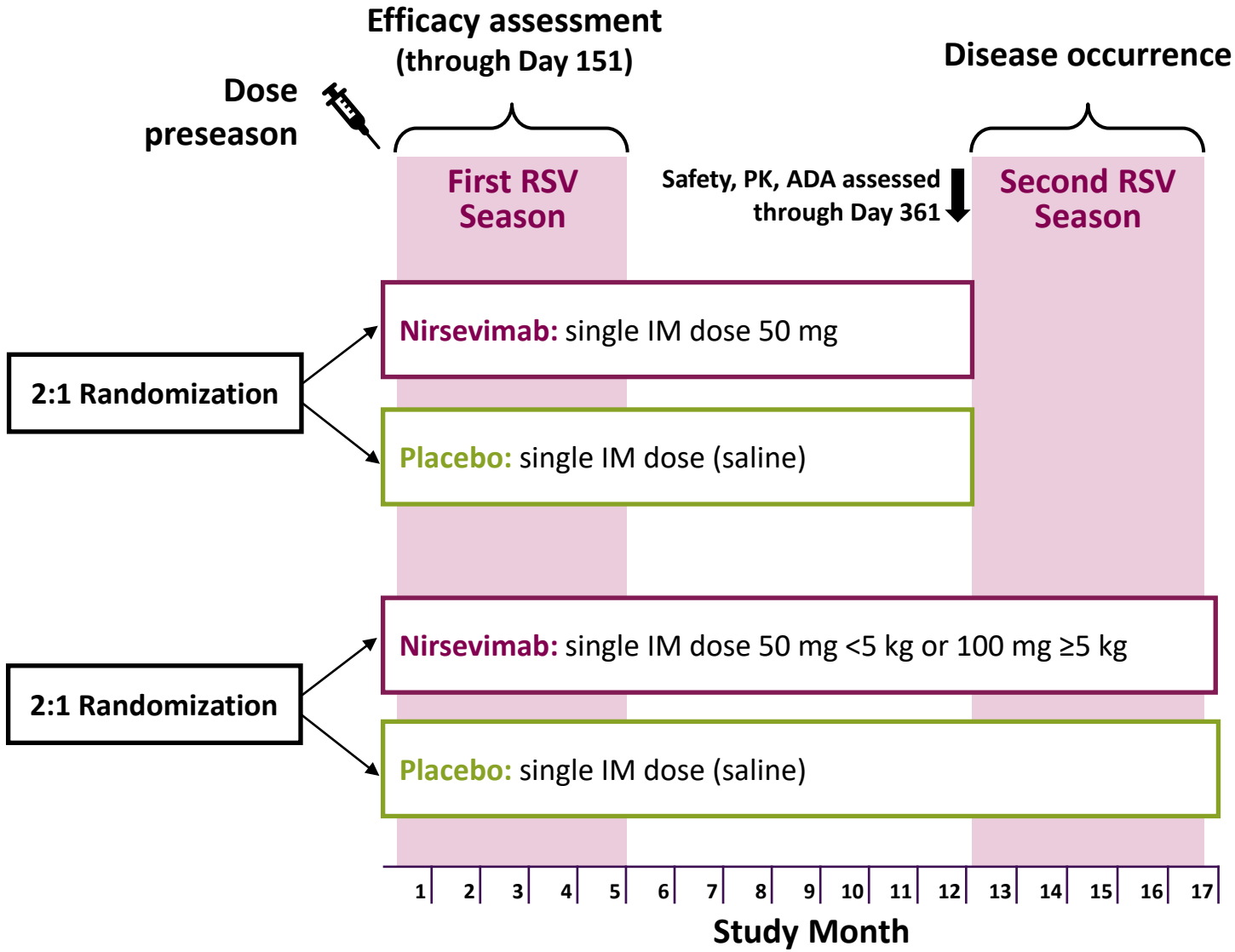
Amanda Leach, MRCPCH

Global Clinical Head
AstraZeneca

Clinical Development in Healthy Preterm and Term Infants

Trial 03: Phase 2b (infants GA ≥29 to <35 wGA)
~1500 infants

Trial 04: Phase 3 (infants ≥35 wGA)
~3000 infants



wGA = weeks gestational age.

Case Definition of Medically Attended RSV LRTI

Trial 03 and Trial 04

Primary efficacy endpoint event requires that the infant is presented for care
(Medical Attendance)

RSV positive	AND	**Lower respiratory tract involvement**	AND	**Sign of severity**
Positive by central laboratory RT-PCR assay		<u>At least one sign of:</u> • Rhonchi • Rales • Crackles • Wheeze		<u>At least one sign of:</u> • Increased respiratory rate[a] • Hypoxemia[b] • Acute hypoxic or ventilatory failure • New-onset apnea • Nasal flaring • Retractions • Grunting • Dehydration

RT-PCR = reverse transcriptase-polymerase chain reaction.

[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).

Case Definitions of More Severe Disease
Trial 03 and Trial 04

MA RSV LRTI With Hospitalization

- Attending physician hospitalized infants in line with local or national guidelines
  - Guidelines were evidence driven and broadly similar, requiring evidence of
    - Significant respiratory distress
    - Evidence of hypoxia, or
    - Reduced capacity to feed

MA RSV LRTI (very severe)

- Exploratory endpoint defined in response to EMA CHMP feedback
  - Includes cases meeting primary endpoint case definition with requirement for hospitalization plus supplemental oxygen or IV fluids

Statistical Methods: Primary Analysis
Trial 03 and Trial 04

- Analysis of MA RSV LRTI performed using Poisson regression model with robust variance[1]
  - Only first occurrence of MA RSV LRTI in an individual used in the primary analysis
- Efficacy calculated as RRR (95% CI) and 2-sided p-value
- Placebo multiple imputation used to impute the event outcome for participants not followed for at least 150 days post-dose and who did not have an RSV-associated LRTI
- Similar analysis methodology used for MA RSV LRTI with Hospitalization and MA RSV LRTI (very severe)
- Multiplicity-protected hierarchical testing prespecified for primary and secondary endpoints
  - P-values presented for pre-specified multiplicity-controlled analyses

1. Zou G. *Am J Epidemiol*. 2004;159(7):702-706.

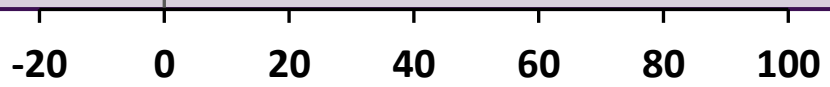
Baseline Demographics
Trial 03 (ITT Population)

Characteristic	Placebo N=484	Nirsevimab N=969
Gestational age group, n (%)		
≥29 to <32 weeks	101 (20.9)	193 (20.1)
≥32 to <35 weeks	383 (79.1)	769 (79.9)
Age, n (%)		
≤3 months	257 (53.1)	516 (53.3)
>3 to ≤6 months	153 (31.6)	320 (33.0)
>6 months	74 (15.3)	133 (13.7)
Female sex, n (%)	224 (46.3)	468 (48.3)
Race, n (%)		
White	355 (73.3)	693 (71.6)
Black or African American	67 (13.8)	189 (19.5)
Asian	10 (2.1)	5 (0.5)
Other	43 (8.9)	61 (6.3)
Hispanic or Latino ethnicity, n (%)	91 (18.8)	225 (23.2)
Weight group on Day 1, n (%)		
<5 kg	290 (59.9)	570 (58.8)
≥5 kg or missing	194 (40.1)	399 (41.2)

Griffin MP, et al. *N Engl J Med*. 2020;383(5):415-425.

Primary Endpoint Met
Trial 03 (ITT Population)

Endpoint (ITT analysis)	Observed Events (%) Placebo N=484	Observed Events (%) Nirsevimab N=969	Efficacy, % (95% CI)	P-value
MA RSV LRTI	46 (9.5)	25 (2.6)	**70.1** (52.3, 81.2)	<0.0001
MA RSV LRTI with Hospitalization	20 (4.1)	8 (0.8)	**78.4** (51.9, 90.3)	0.0002
MA RSV LRTI (very severe)	16 (3.3)	4 (0.4)	**87.5** (62.9, 95.8)	

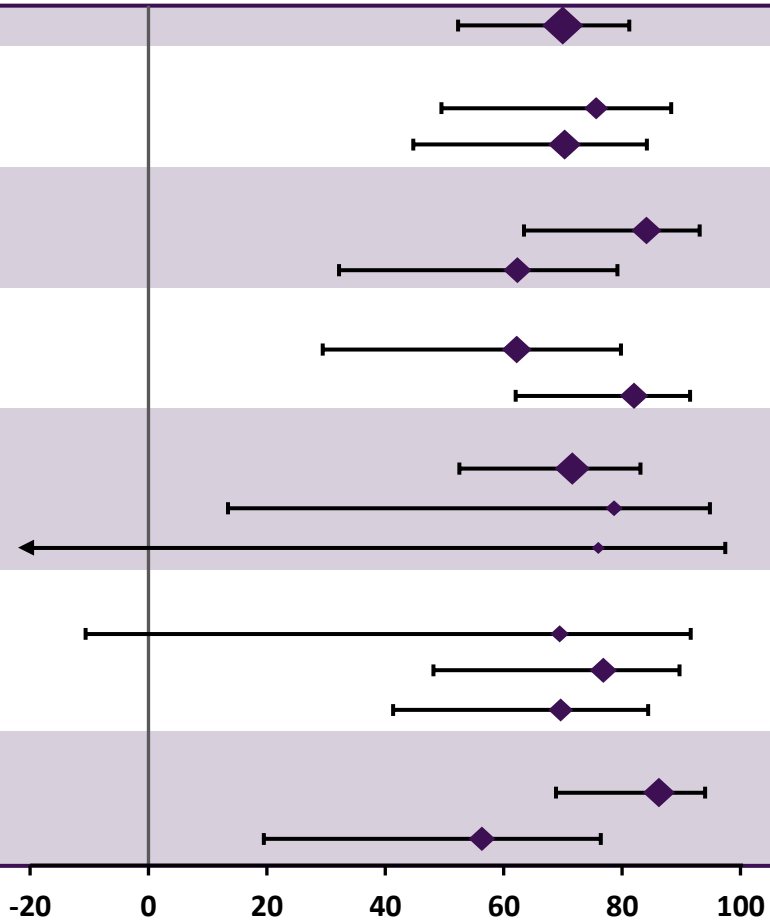


Griffin MP, et al. *N Engl J Med*. 2020;383(5):415-425.

Efficacy Against MA RSV LRTI by Subgroup

Trial 03 (ITT Population)

	Placebo (N=484)		Nirsevimab (N=969)		Efficacy, % (95% CI)
	Number of Infants	Observed Events (%)	Number of Infants	Observed Events (%)	
Overall	**484**	**46 (9.5)**	**969**	**25 (2.6)**	**70.1 (52.3, 81.2)**
Gestational age					
Age ≥29 to ≤32 weeks	185	21 (11.4)	363	10 (2.8)	**75.7** (49.5, 88.3)
Age >32 weeks	299	25 (8.4)	606	15 (2.5)	**70.4** (44.7, 84.2)
Age at randomization[a]					
≤3 months	257	22 (8.6)	516	7 (1.4)	**84.2** (63.4, 93.1)
>3 months	227	24 (10.6)	453	18 (4.0)	**62.4** (32.2, 79.2)
Sex					
Male	260	22 (8.5)	501	16 (3.2)	**62.3** (29.4, 79.8)
Female	224	24 (10.7)	468	9 (1.9)	**82.1** (62.0, 91.5)
Race					
White	355	38 (10.7)	693	21 (3.0)	**71.7** (52.5, 83.1)
Black/African American	67	5 (7.5)	189	3 (1.6)	**78.7** (13.4, 94.8)
Other	62	3 (4.8)	86	1 (1.2)	**76.0** (-125.6, 97.4)
Region					
North America	80	5 (6.3)	210	4 (1.9)	**69.5** (-10.6, 91.6)
Europe	226	19 (8.4)	412	8 (1.9)	**76.9** (48.1, 89.7)
Rest of the World	178	22 (12.4)	347	13 (3.7)	**69.7** (41.3, 84.4)
Weight on Day 1[a]					
Weight <5 kg	290	26 (9.0)	570	7 (1.2)	**86.3** (68.8, 94.0)
Weight ≥5 kg	191	20 (10.5)	394	18 (4.6)	**56.4** (19.5, 76.4)



[a] Interaction p-value <0.1 for age at randomization and weight on Day 1.

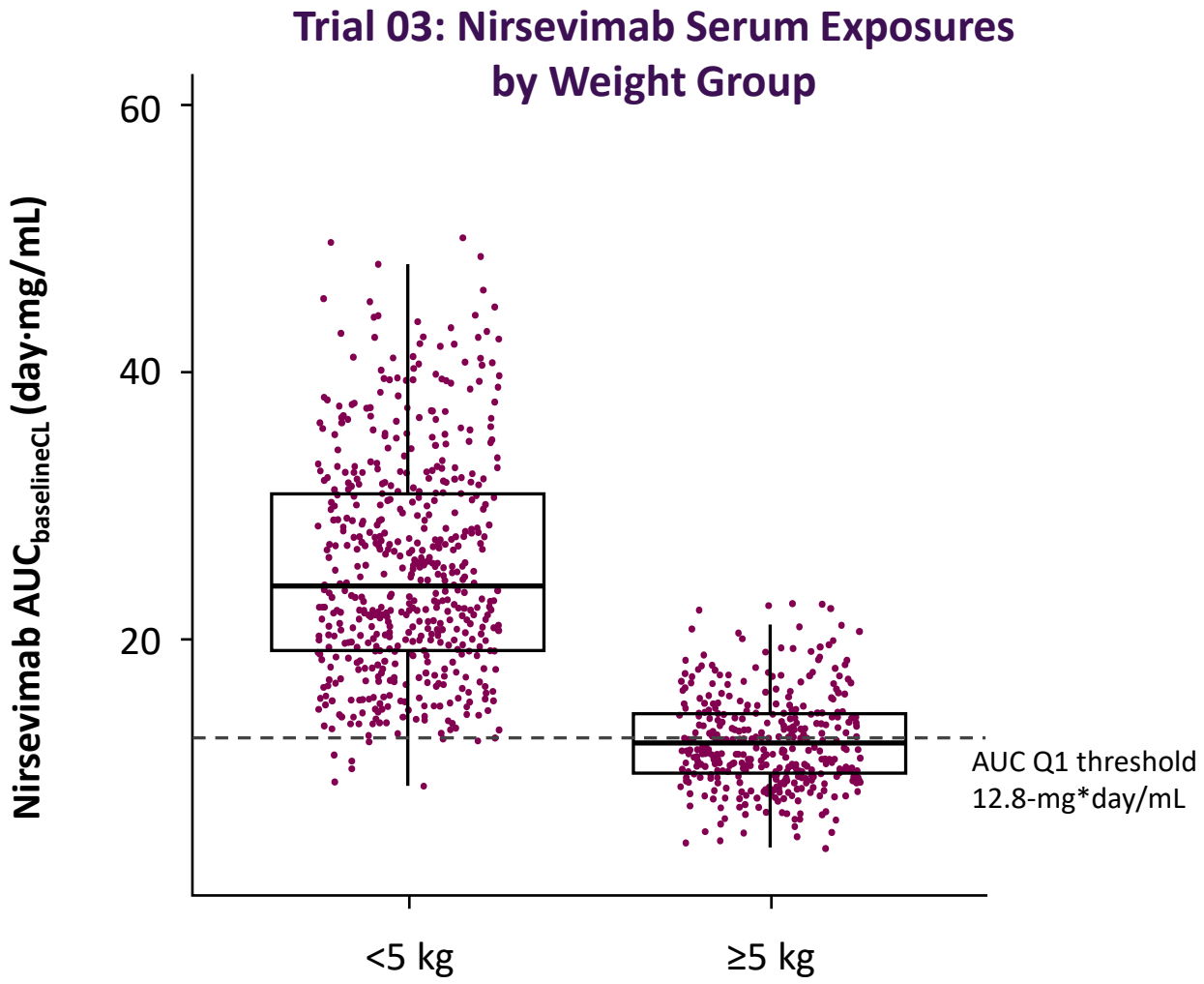
Size of point estimate symbols proportional to sample size in each subgroup relative to the overall analysis.

Griffin MP, et al. *N Engl J Med*. 2020;383(5):415-425.

Dose Optimization
Trial 03 (ITT Population)

- Post hoc exposure response analysis
- Trend to lower efficacy in infants with lowest nirsevimab serum exposure; the majority of these weighed ≥5 kg
- Decision to optimize the dose for infants ≥5 kg (100 mg)

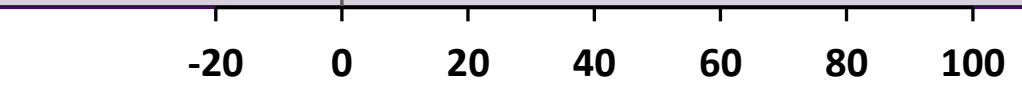
Weight band dosing:
- 50 mg if weight <5 kg
- 100 mg if weight ≥5 kg



Exploratory Efficacy in Infants <5 kg Who Received 50-mg Dose

Trial 03 (Proposed Dose Subpopulation)

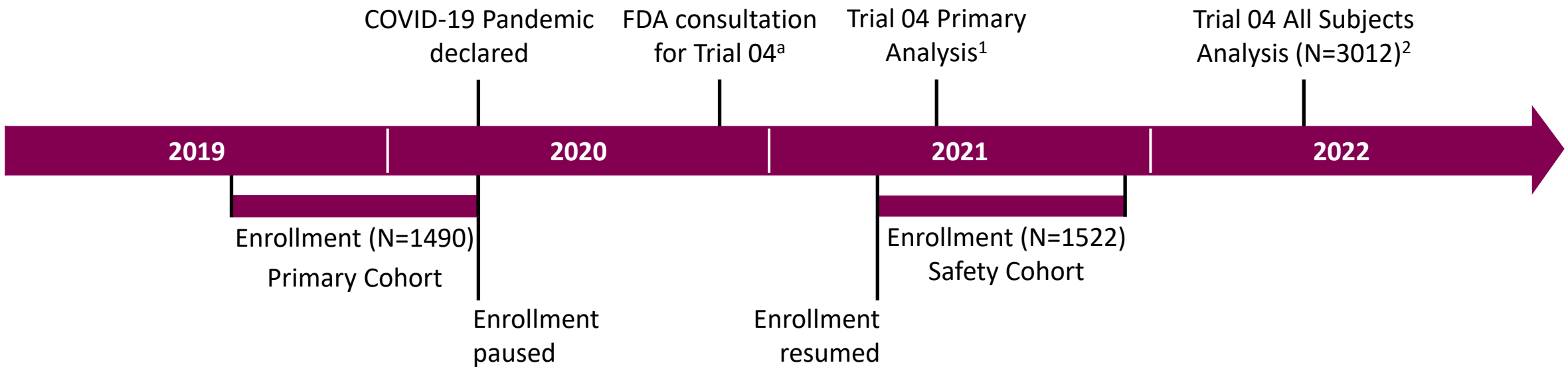
Endpoint	Observed Events (%) Placebo N=290	Observed Events (%) Nirsevimab N=570	Efficacy, % (95% CI)
MA RSV LRTI	26 (9.0)	7 (1.2)	**86.2** (68.0, 94.0)
MA RSV LRTI with Hospitalization	13 (4.5)	3 (0.5)	**86.5** (53.5, 96.1)
MA RSV LRTI (very severe)	11 (3.8)	0 (0)	**100** (79.7, NE)



Simões EAF, et al. *Lancet Child Adolesc Health*. 2023;7(3):180-189 (supplement).

Phase 3 Trial Overlapped With COVID-19 Pandemic

Trial 04



Situation and Mitigation

- Onset of COVID-19 pandemic (March 2020) led to several operational challenges leading to a pause in enrollment, and subsequently RSV cases fell globally
- After consultation with FDA and EMA, decision made to analyze primary endpoint after first 1490 enrolled (Primary Cohort)
- Study enrollment resumed in 2021 when operationally feasible and RSV cases were observed

[a] European Medicines Agency consulted in parallel.

1. Hammitt LL, et al. *N Engl J Med*. 2022;386(9):837-846; 2. Muller WJ, et al. *N Engl J Med*. 2023;388(16):1533-1534.

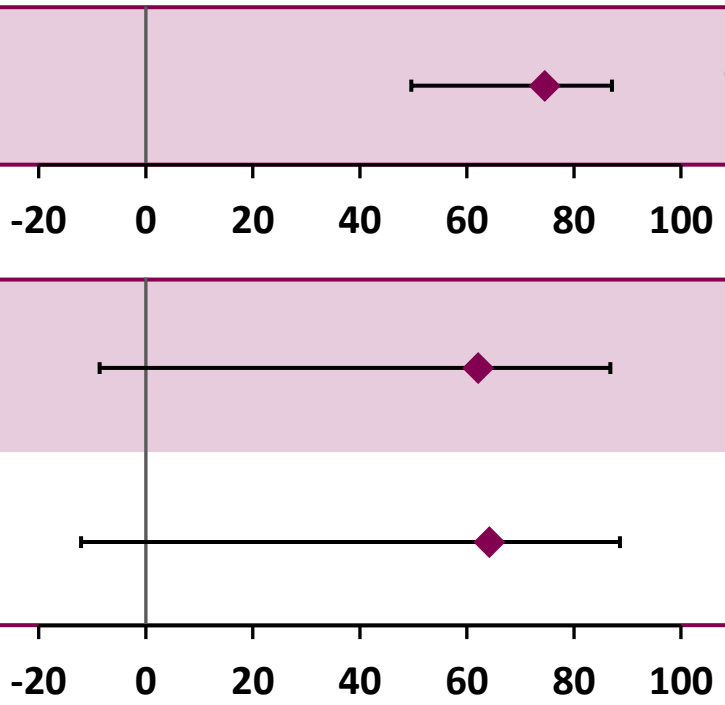
Baseline Demographics
Trial 04 (Primary Cohort)

Characteristic	Placebo N=496	Nirsevimab N=994
Gestational age group, n (%)		
≥35 to <37 weeks	76 (15.4)	132 (13.3)
≥37 weeks	419 (84.6)	861 (86.7)
Age, n (%)		
≤3 months	285 (57.5)	577 (58.0)
>3 to ≤6 months	162 (32.7)	317 (31.9)
>6 months	49 (9.9)	100 (10.1)
Female sex, n (%)	257 (51.8)	464 (46.7)
Race, n (%)		
White	272 (54.8)	524 (52.9)
Black or African American	136 (27.4)	286 (28.9)
American Indian or Alaskan Native	26 (5.2)	57 (5.8)
Asian	18 (3.6)	36 (3.6)
Other	38 (7.7)	70 (7.1)
Hispanic or Latino ethnicity, n (%)	51 (10.3)	100 (10.1)
Weight group on Day 1, n (%)		
<5 kg	192 (38.7)	403 (40.6)
≥5 kg	304 (61.3)	589 (59.4)

Hammitt LL, et al. *N Engl J Med*. 2022;386(9):837-846.

Primary Endpoint Met
Trial 04 (Primary Cohort)

Endpoint	Observed Events (%) Placebo N=496	Observed Events (%) Nirsevimab N=994	Efficacy, % (95% CI)	P-value
MA RSV LRTI	25 (5.0)	12 (1.2)	**74.5** (49.6, 87.1)	<0.0001
MA RSV LRTI with Hospitalization	8 (1.6)	6 (0.6)	**62.1** (-8.6, 86.8)	0.0708
MA RSV LRTI (very severe)	7 (1.4)	5 (0.5)	**64.2** (-12.1, 88.6)	

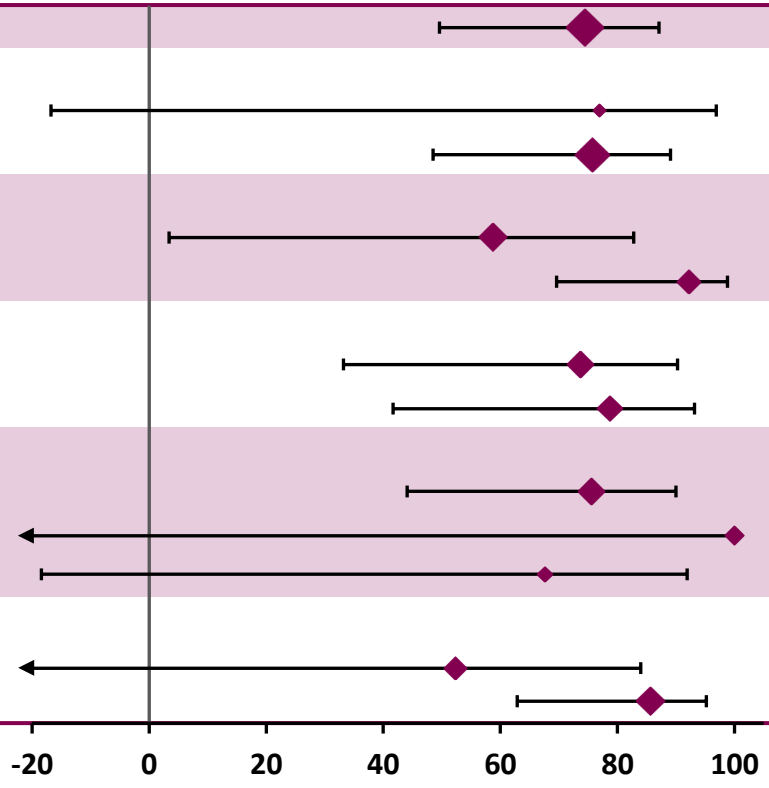


Hammitt LL, et al. *N Engl J Med*. 2022;386(9):837-846.

Efficacy Against MA RSV LRTI by Subgroup

Trial 04 (Primary Cohort)

	Placebo (N=496)		Nirsevimab (N=994)		Efficacy, % (95% CI)
	Number of Infants	Observed Events (%)	Number of Infants	Observed Events (%)	
Overall	**496**	**25 (5.0)**	**994**	**12 (1.2)**	**74.5 (49.6, 87.1)**
Gestational age					
Age ≥35 to <37 weeks	76	5 (6.6)	132	2 (1.5)	**77.0** (-16.8, 96.9)
Age ≥37 weeks	419	20 (4.8)	861	10 (1.2)	**75.7** (48.5, 89.1)
Age at randomization					
≤3 months	285	12 (4.2)	577	10 (1.7)	**58.8** (3.4, 82.8)
>3 months	211	13 (6.2)	417	2 (0.5)	**92.2** (69.6, 98.8)
Sex					
Male	239	12 (5.0)	530	7 (1.3)	**73.7** (33.2, 90.3)
Female	257	13 (5.1)	464	5 (1.1)	**78.7** (41.7, 93.2)
Race					
White	272	17 (6.3)	524	8 (1.5)	**75.6** (44.1, 90.0)
Black/African American	136	2 (1.5)	286	0 (0.0)	**100** (-65.1, NE)
Other	88	6 (6.8)	181	4 (2.2)	**67.6** (-18.4, 91.9)
Weight on Day 1					
Weight <5 kg	192	7 (3.6)	403	7 (1.7)	**52.4** (-41.9, 84.0)
Weight ≥5 kg	304	18 (5.9)	589	5 (0.8)	**85.7** (62.9, 95.2)



Interaction p-value <0.1 for age at randomization. No events were observed in the Southern Hemisphere, and thus region is excluded.

Baseline Demographics

Trial 04

Characteristic	Percent of Subjects					
	Primary Cohort		Safety Cohort		All Subjects	
	Placebo N=496	Nirsevimab N=994	Placebo N=507	Nirsevimab N=1015	Placebo N=1003	Nirsevimab N=2009
Gestational age group						
≥35 to <37 weeks	15.4	13.3	9.1	10.5	12.2	11.9
≥37 weeks	84.6	86.7	90.9	89.5	87.8	88.1
Age at randomization						
≤3 months	57.5	58.0	59.8	60.4	58.6	59.2
>3 to ≤6 months	32.7	31.9	31.8	31.4	32.2	31.7
>6 months	9.9	10.1	8.5	8.2	9.2	9.1
Female sex	51.8	46.7	47.9	46.7	49.9	46.7
Race						
White	54.8	52.9	53.1	52.0	53.9	52.4
Black or African American	27.4	28.9	0.4	1.3	13.8	14.9
American Indian or Alaskan Native	5.2	5.8	5.1	3.4	5.2	4.6
Asian	3.6	3.6	6.3	7.2	5.0	5.4
Other	7.7	7.1	33.1	34.5	20.5	20.9
Hispanic or Latino ethnicity	10.3	10.1	56.0	56.9	33.5	33.8
Weight group on Day 1						
<5 kg	38.7	40.6	39.4	39.2	39.1	39.9
≥5 kg	61.3	59.4	60.6	60.8	60.9	60.1

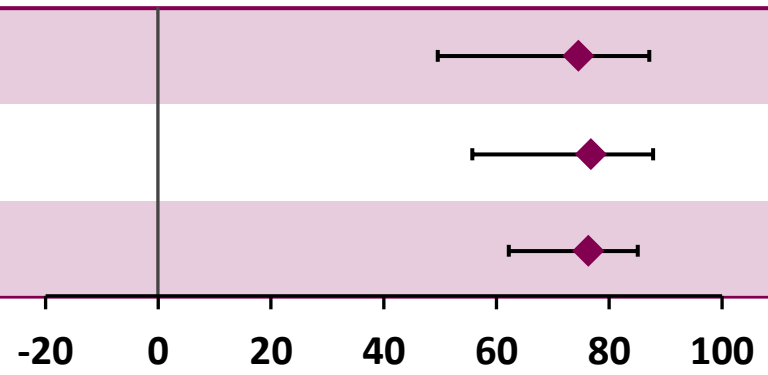
Muller WJ, et al. *N Engl J Med*. 2023;388(16):1533-1534.

Exploratory Analysis Improves Precision of Efficacy Against RSV LRTI With Hospitalization

Trial 04 (All Subjects)

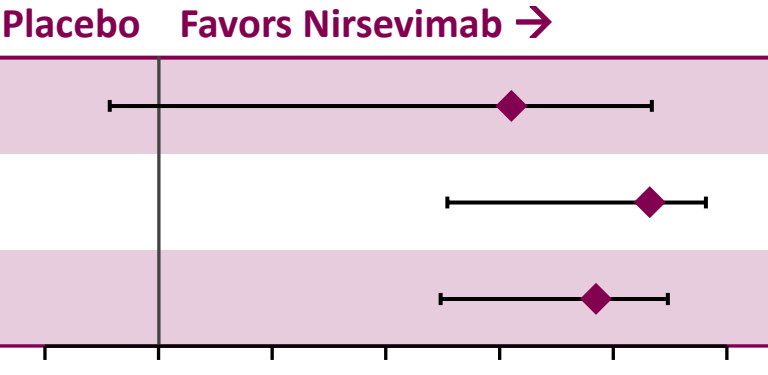
MA RSV LRTI

Cohort	Observed Events (%) Placebo	Nirsevimab	Efficacy, % (95% CI)
Primary	25/496 (5.0)	12/994 (1.2)	**74.5** (49.6, 87.1)
Safety	29/507 (5.7)	12/1015 (1.2)	**76.9** (55.8, 87.9)
All Subjects	54/1003 (5.4)	24/2009 (1.2)	**76.4** (62.3, 85.2)



RSV LRTI with Hospitalization

Cohort	Observed Events (%) Placebo	Nirsevimab	Efficacy, % (95% CI)
Primary	8/496 (1.6)	6/994 (0.6)	**62.1** (-8.6, 86.8)
Safety	12/507 (2.4)	3/1015 (0.3)	**86.2** (50.6, 96.1)
All Subjects	20/1003 (2.0)	9/2009 (0.4)	**76.8** (49.4, 89.4)



Hammitt LL, et al. *N Engl J Med*. 2022;386(9):837-846; Muller WJ, et al. *N Engl J Med*. 2023;388(16):1533-1534.

Exploratory Analysis Shows Clinically Meaningful Efficacy Against RSV LRTI With Hospitalization

Trial 04 (All Subjects)

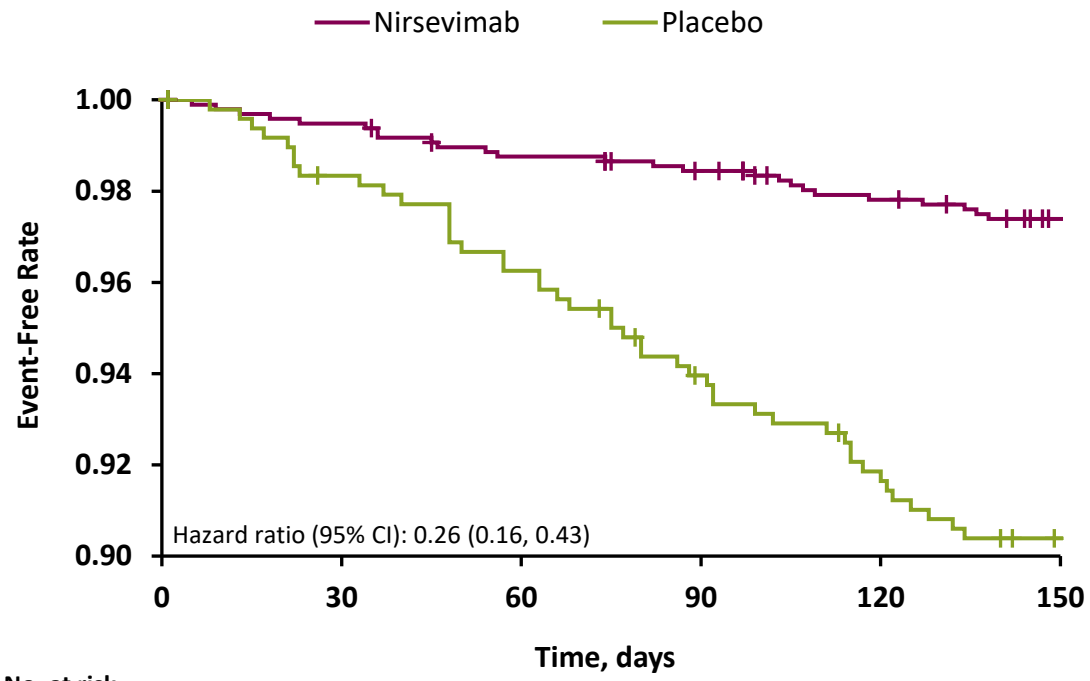
- The largest dataset allowing for analysis of less frequent events
  - Robust data collection in a double-blind manner
  - Consistent populations and admission practices
  - Consistent with the estimate of MA RSV LRTI with Hospitalization in preterm infants
    - » Trial 04 All Subjects 76.8% (49.4, 89.4)
    - » Trial 03 ITT 78.4% (51.9, 90.3)
    - » Trial 03 Proposed Dose 86.5% (53.5, 96.1)

Provides important information for health care providers and families

Efficacy Consistent Over 150 Days (5 Months)

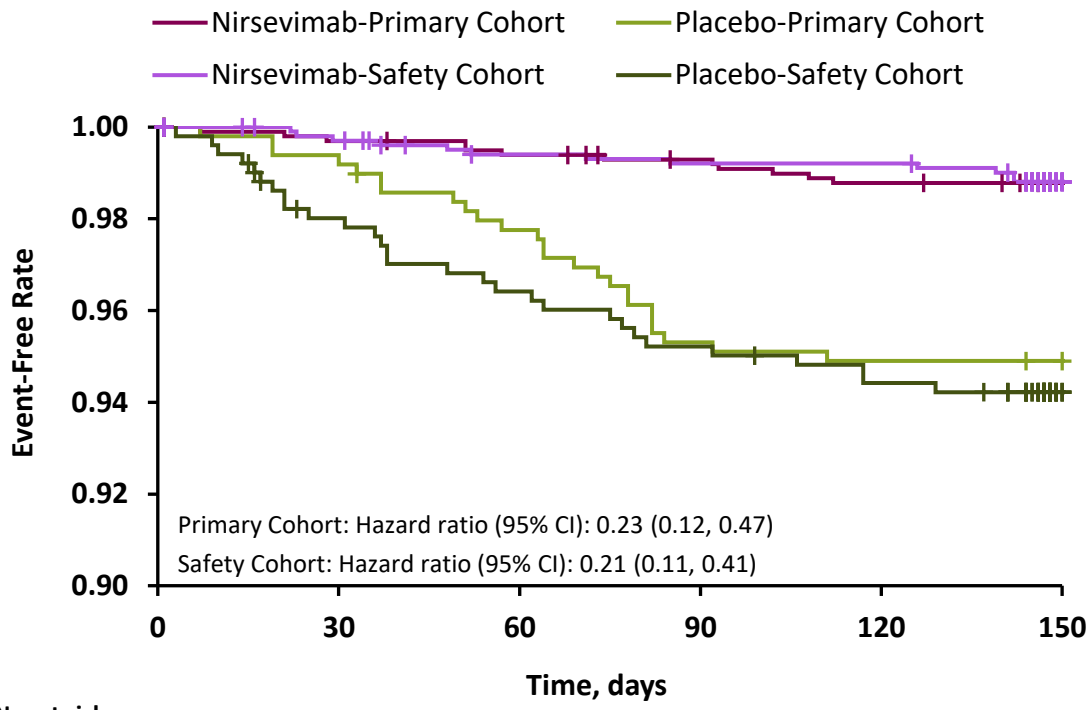
Trial 03 and Trial 04

Trial 03 (ITT Population)



No. at risk						
Nirsevimab	969	959	950	943	931	920
Placebo	484	472	462	448	437	427

Trial 04



No. at risk						
Nirsevimab-Primary Cohort	994	984	980	975	970	966
Nirsevimab-Safety Cohort	1015	1006	997	995	995	905
Placebo-Primary Cohort	496	488	479	467	465	464
Placebo-Safety Cohort	507	491	483	477	472	424

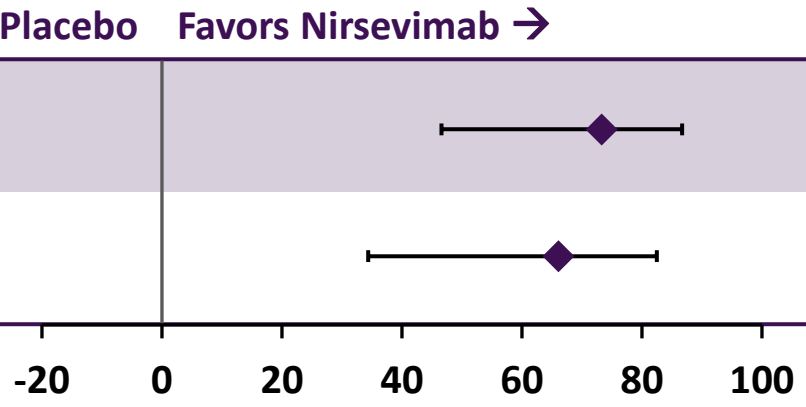
Griffin MP, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *N Engl J Med*. 2020;33(5):415-425.

Efficacy Against MA RSV LRTI Consistent by RSV Subtype

Trial 03 and Trial 04

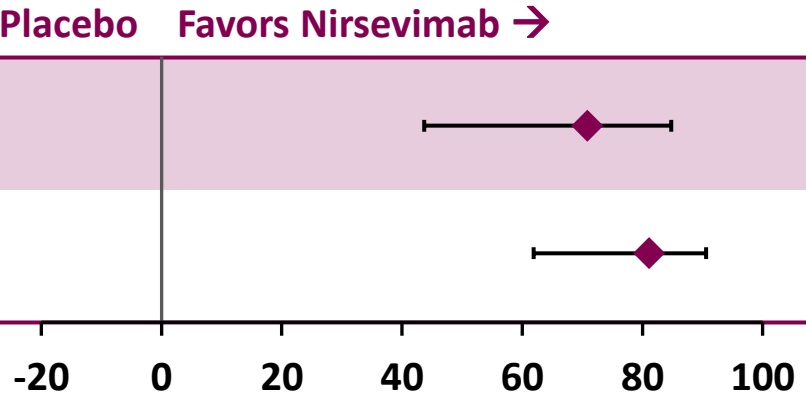
Trial 03 (ITT Population)

Subtype	Observed Events (%) Placebo N=484	Nirsevimab N=969	Efficacy, % (95% CI)
RSV A	24 (5.0)	11 (1.1)	**73.3** (46.6, 86.7)
RSV B	22 (4.5)	14 (1.4)	**66.1** (34.4, 82.5)



Trial 04 (All Subjects)

Subtype	Observed Events (%) Placebo N=1003	Nirsevimab N=2009	Efficacy, % (95% CI)
RSV A	25 (2.5)	14 (0.7)	**70.8** (43.7, 84.8)
RSV B	29 (2.9)	10 (0.5)	**81.1** (61.9, 90.6)

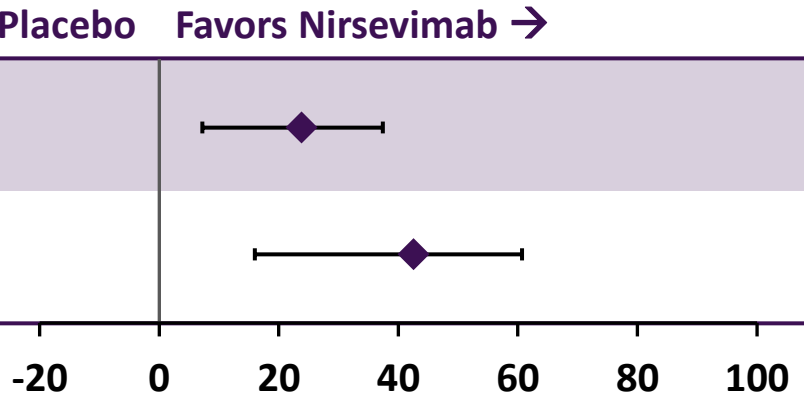


Other Exploratory Endpoints: All-Cause Disease

Trial 03 and Trial 04

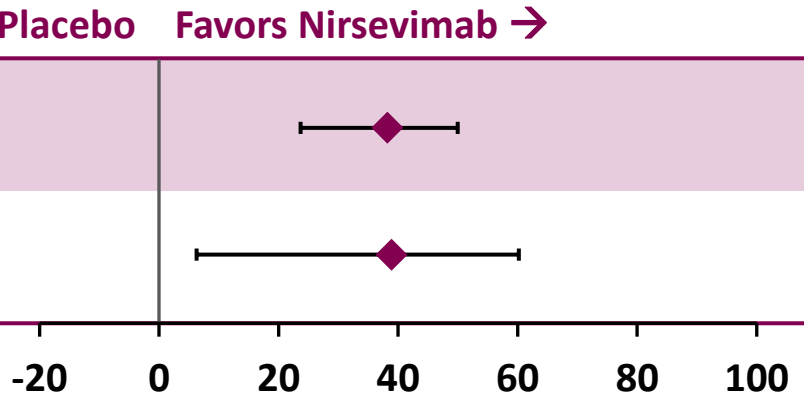
Trial 03 (ITT Population)

Endpoint	Observed Events (%) Placebo N=484	Nirsevimab N=969	Efficacy, % (95% CI)
All-cause MA LRTI	125 (25.8)	191 (19.7)	**23.8** (7.2, 37.4)
Hospitalization for respiratory illness	46 (9.5)	53 (5.5)	**42.5** (16.0, 60.7)



Trial 04 (All Subjects)

Endpoint	Observed Events (%) Placebo N=1003	Nirsevimab N=2009	Efficacy, % (95% CI)
All-cause MA LRTI	139 (13.9)	171 (8.5)	**38.2** (23.7, 50.0)
Hospitalization for respiratory illness	37 (3.7)	45 (2.2)	**38.9** (6.3, 60.2)



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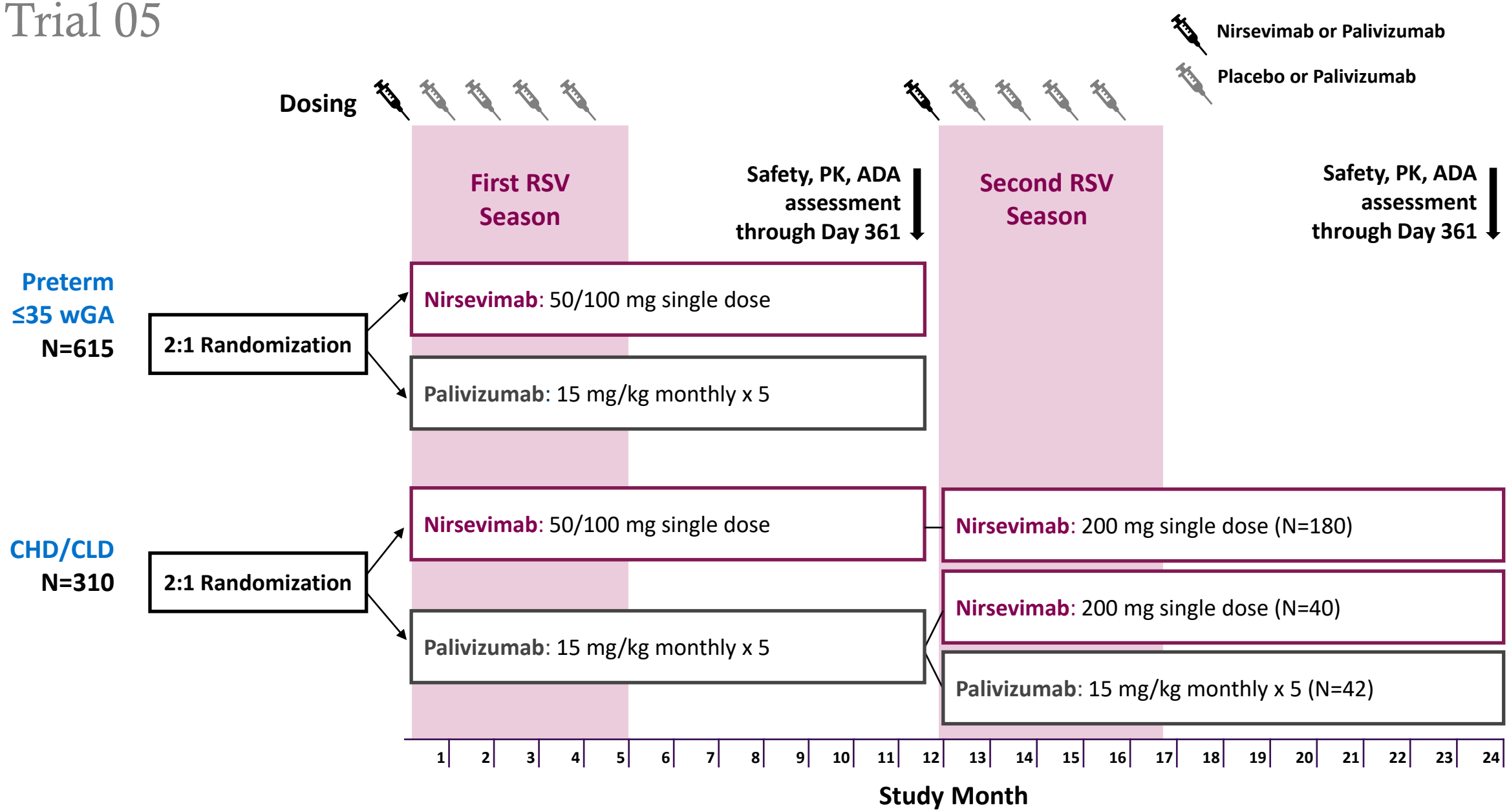
Vulnerable Populations: Efficacy Extrapolation Based on PK

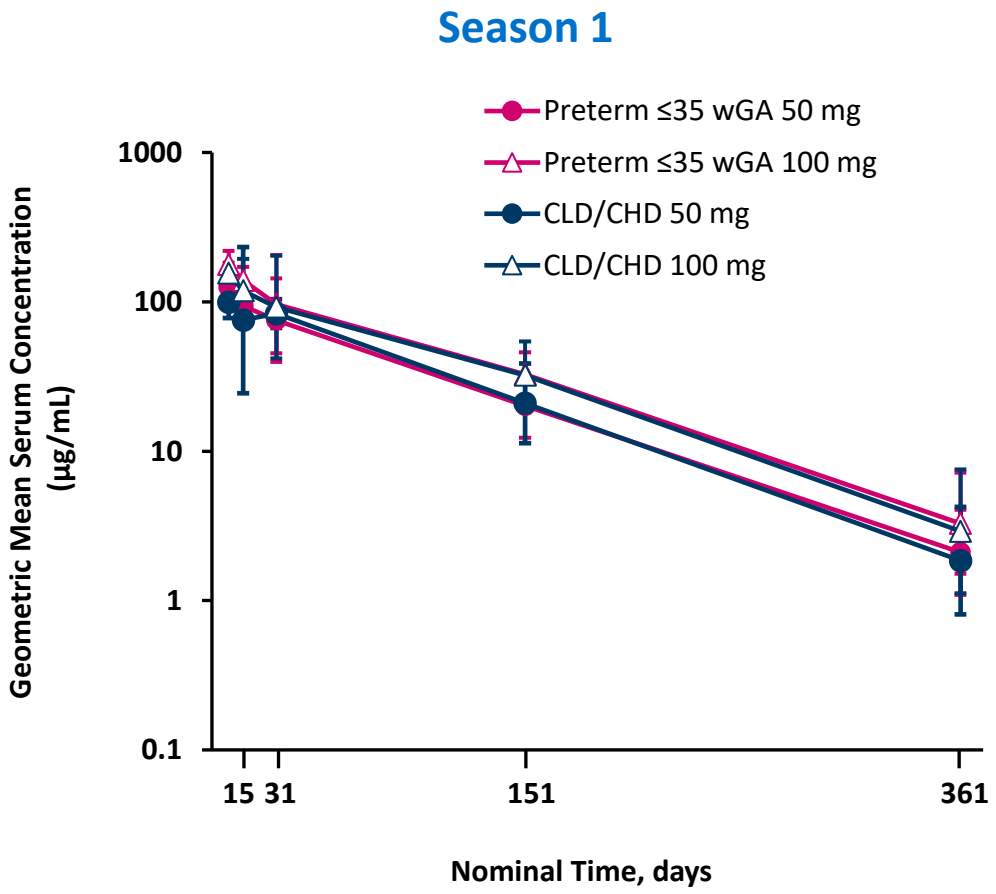
Clinical Study in the Palivizumab-Eligible Population

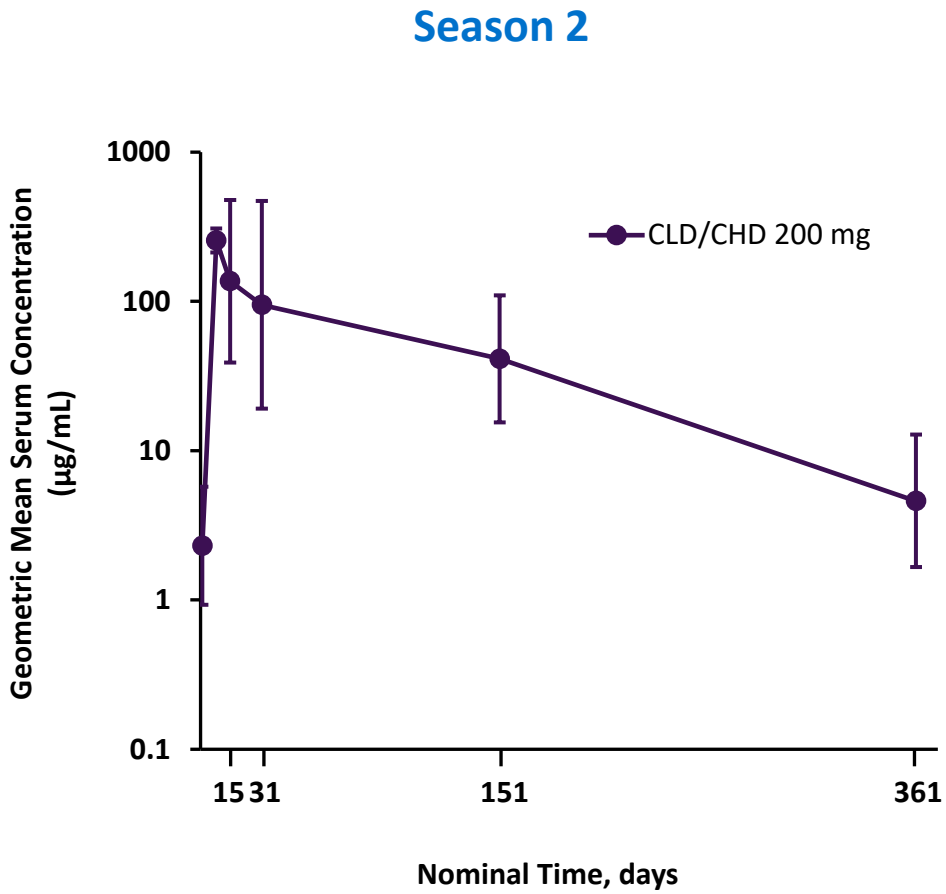
Trial 05



Nirsevimab Serum Concentrations Over Time

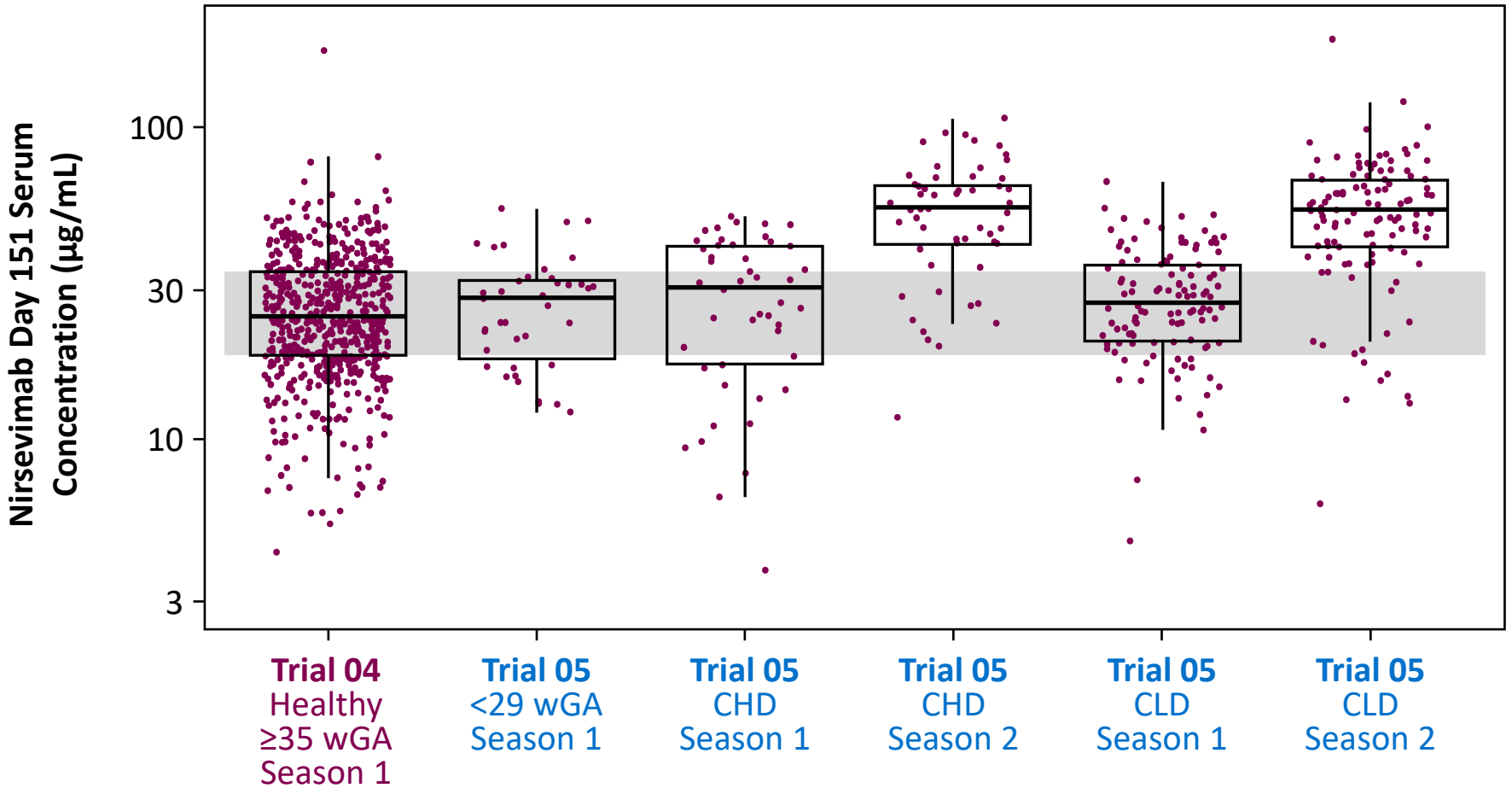
Trial 05





Efficacy Extrapolation Based on Pharmacokinetic Data

Trial 04 and Trial 05



Points represent individual infants; boxes represent IQRs; central lines correspond to the medians; whiskers extend to the largest and smallest values no further than 1.5 × IQR.

Incidence of MA RSV LRTI through Day 151
Trial 05

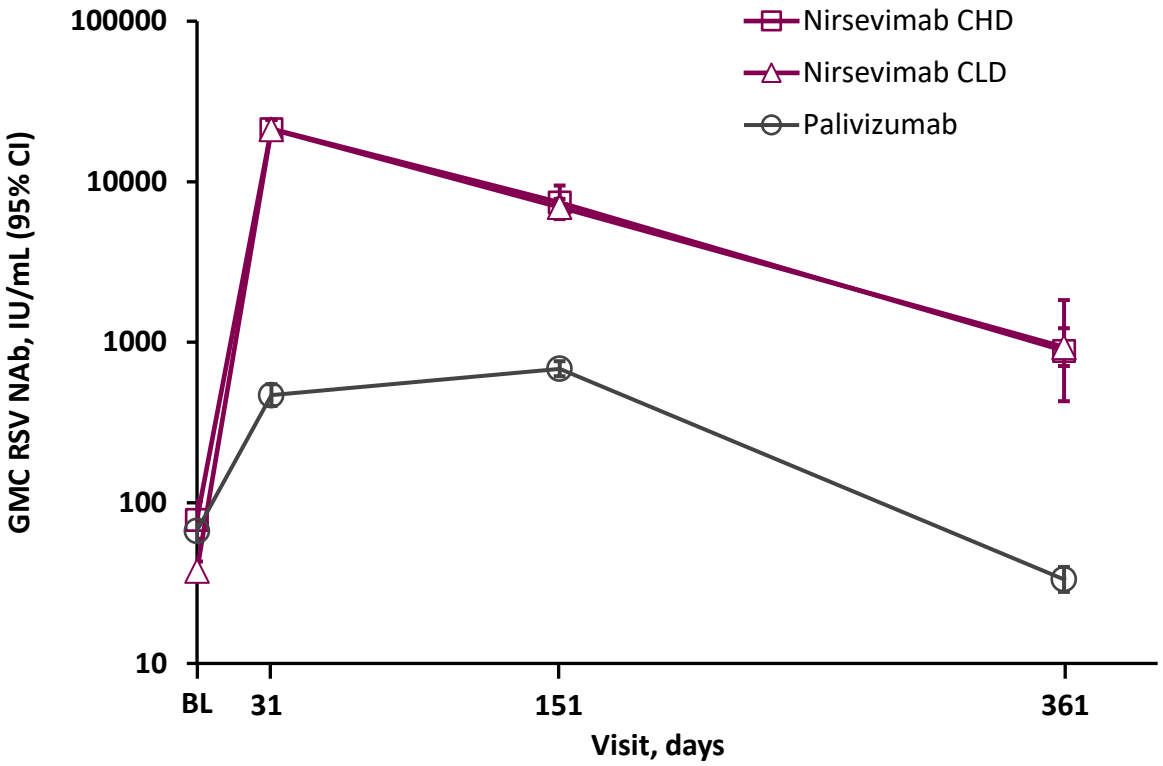
	Subjects With Observed Events, n (%)	
	Palivizumab	Nirsevimab
Trial 05 Season 1 Preterm & CHD/CLD	3/309 (1.0)	4/616 (0.6)

	Subjects With Observed Events, n (%)		
	Palivizumab/ Palivizumab	Palivizumab/ Nirsevimab	Nirsevimab/ Nirsevimab
Trial 05 Season 2 CHD/CLD	0/42	0/40	0/180

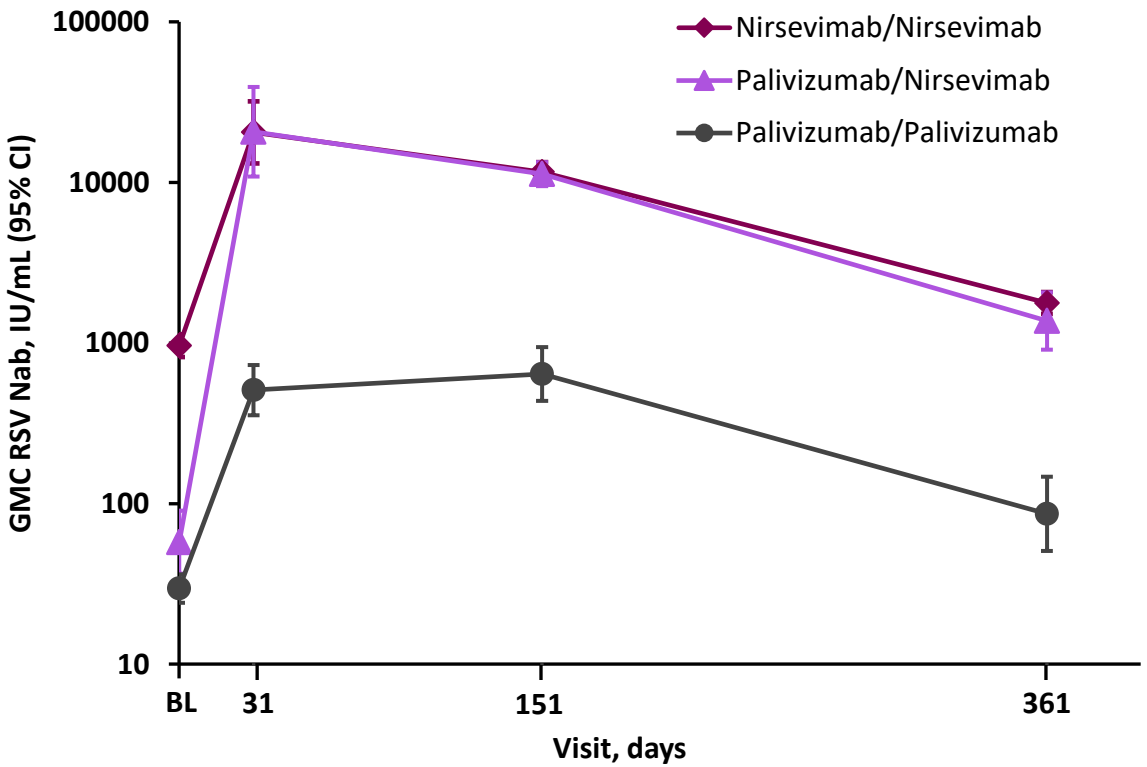
Nirsevimab RSV Neutralizing Antibody Levels Are Higher Than Palivizumab at All Times Post Dose

Trial 05 (CHD/CLD Cohort)

Season 1



Season 2



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ADA and Clinical Virology

Antidrug Antibodies (ADA) to Nirsevimab Detected at Low Frequency With No Discernible Clinical Effect

Trial 03, Trial 04, and Trial 05

	ADA Incidence, n/N (%)
Trial 03	50/929 (5.4)
Trial 04 (Primary Cohort)	57/951 (6.0)
Trial 05 Season 1	32/587 (5.5)

- Incidence of ADA to nirsevimab was generally low
- No discernible effect on overall estimate of clinical efficacy
- No apparent effect on safety of nirsevimab
- No anamnestic ADA response observed following second dose in second season in Trial 05

Nirsevimab Neutralized >99% of RSV Variants Isolated

Trial 03, Trial 04, and Trial 05

	Number of Sequences Analyzed (N = 267)
Trial 03 through Day 360	94
Trial 04 through Day 511	149
Trial 05 in Season 1 and 2	24

- No major variant binding site substitutions in RSV A; 2 prevalent binding site substitutions in RSV B (no change in nirsevimab susceptibility)
- Overall, >99% of RSV sequences were neutralized by nirsevimab
- Three variants from 2 infants in Trial 03 had mAb escape substitutions
  - Both infants had high serum concentrations of nirsevimab

Summary of Efficacy

- Two randomized, placebo-controlled trials in healthy infants demonstrated a single dose of nirsevimab is efficacious for a minimum of 5 months
- Consistent level of protection across
  - Subgroups
  - Spectrum of disease severity MA RSV LRTI to very severe RSV LRTI
- Efficacy established through extrapolation in vulnerable populations through first and second RSV seasons (comparable PK)
- Low incidence of ADA and no discernible clinical effect
- Nirsevimab escape variants are rare

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Safety

Manish Shroff, MBBS, MS, MBA

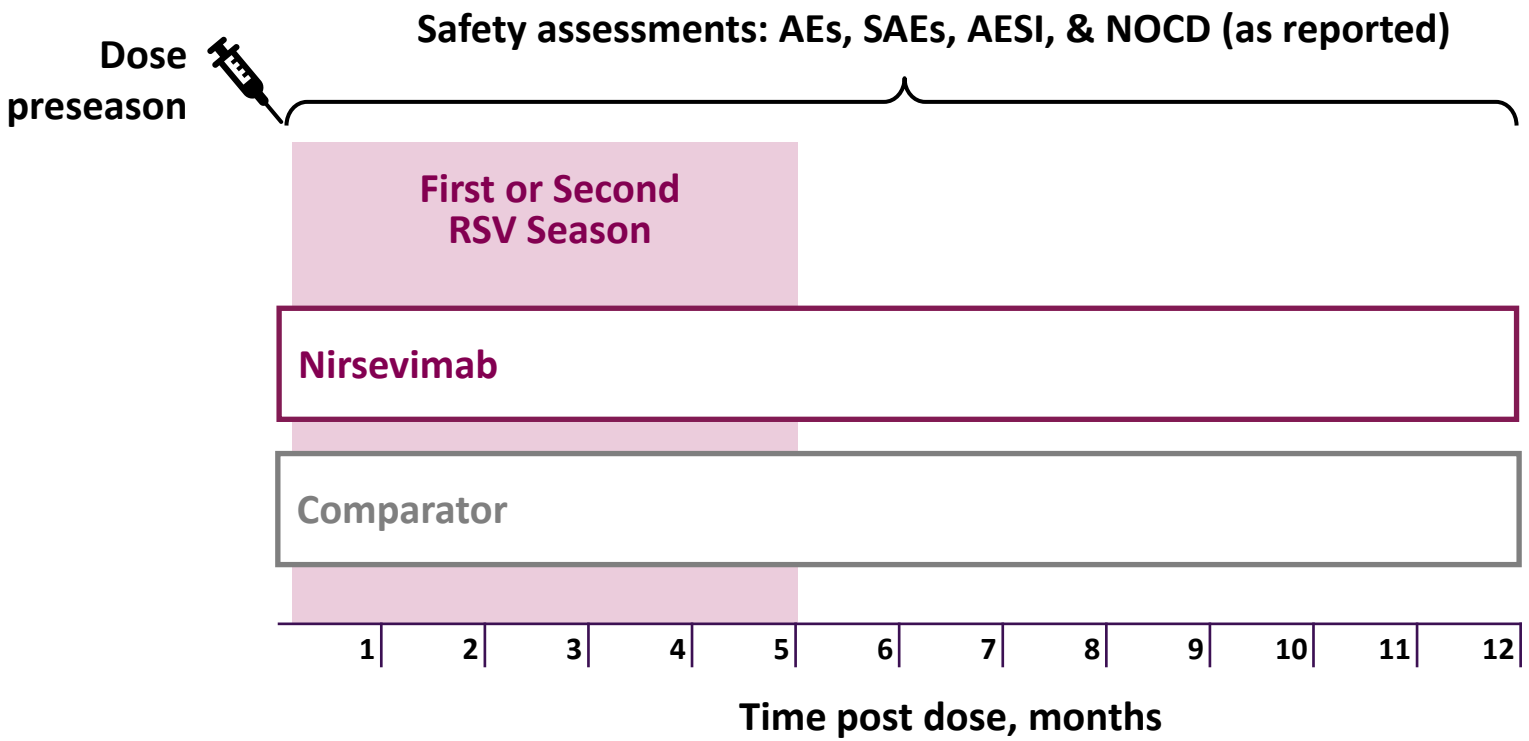
Senior Director, Global Patient Safety
AstraZeneca

Safety Database for Nirsevimab in First and Second RSV Seasons
Pivotal Trials

Safety Population That Received Nirsevimab	Number of Subjects
Total number of infants and children in the pivotal safety studies Trial 03, Trial 04 (All Subjects) and Trial 05 (Seasons 1 and 2)	**3620**
Infants who received the proposed dosing regimen	3224
Infants receiving nirsevimab in their first RSV season (at the proposed dose) Median safety follow-up (at the proposed dose): 361 days (mean: 318 days)	3580 (3184)
Children at higher risk receiving nirsevimab in their second RSV season Median safety follow-up: 198 days (mean: 250 days)	220

Conclusion: Safety database adequate to assess safety profile of nirsevimab in proposed indication.

Safety Assessments and Follow-up



AEs of special interest defined as

- Immediate hypersensitivity reactions, including anaphylaxis
- Immune complex disease
- Thrombocytopenia

Independent data monitoring committee identified no safety concerns

AESI = adverse events of special interest; NOCD = new onset of chronic disease.

Total Exposure by Dose and RSV Season

Trial 03, Trial 04, and Trial 05

		Dose Received	Subjects, n (%)
Nirsevimab received in first season[a]			**3580**
		50 mg	2114 (59.1)
	≥5 kg	100 mg	1456 (40.7)
Nirsevimab received in second season[b]			**220**
		200 mg	216 (98.2)

[a] 10 subjects received a non-standard dose either because of an incomplete dose (medication error) or re-dosing following cardiopulmonary bypass.
[b] 5 subjects received a non-standard dose either because of an incomplete dose (medication error) or re-dosing following cardiopulmonary bypass.

Overview of Safety in Healthy Term and Preterm Infants

Proposed-Dose Safety Pool: Trial 03 (<5 kg)/Trial 04 (All Subjects)

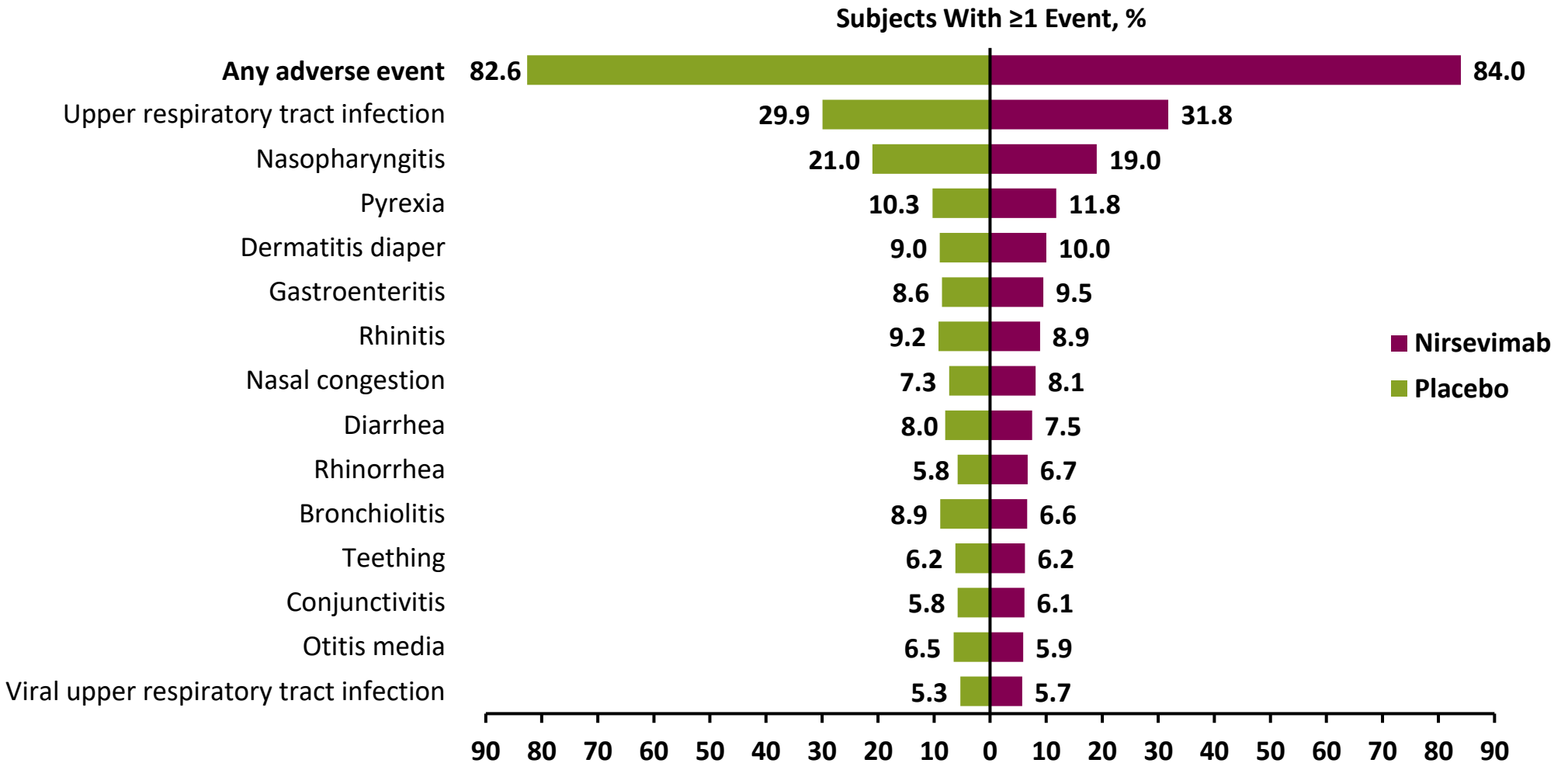
	Subjects With ≥1 Event, n (%)	
Events Through at Least Day 151	**Placebo** N=1284	**Nirsevimab** N=2570
Any adverse event	**1060 (82.6)**	**2158 (84.0)**
Any AE related to investigational product	18 (1.4)	33 (1.3)
AE grade ≥3	81 (6.3)	102 (4.0)
AE grade ≥3 related to investigational product	1 (<0.1)	1 (<0.1)
Serious AE	135 (10.5)	195 (7.6)
SAE related to investigational product	1 (<0.1)	0
Death (none considered related to investigational product)	3 (0.2)	6 (0.2)
AEs of special interest[a] by investigator assessment	0	6 (0.2)[b]
New onset of chronic disease	4 (0.3)	3 (0.1)

Conclusion: Overall safety profile of nirsevimab is favorable

[a] AESIs defined as Type I hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease.
[b] Observed events were all skin and subcutaneous tissue disorders, including rash (2 subjects), rash maculo-papular (2 subjects), petechiae (1 subject), and rash papular (1 subject).

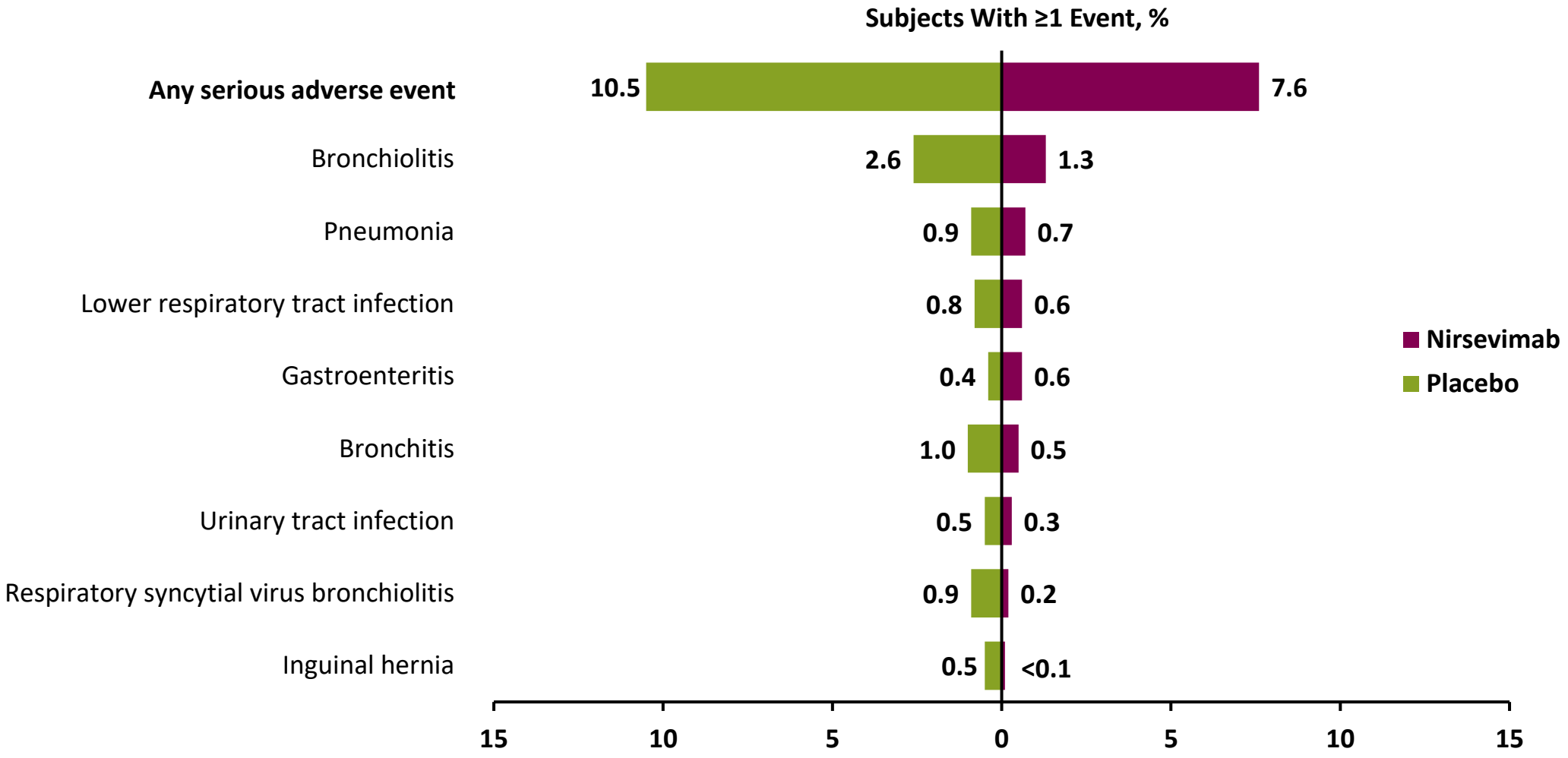
Most Frequently Reported Treatment-Emergent Adverse Events (≥5% Incidence) Through at Least Day 151

Proposed-Dose Safety Pool



Most Frequently Reported Treatment-Emergent Serious AEs (≥0.5% Incidence) Through at Least Day 151

Proposed-Dose Safety Pool



Treatment-Emergent AEs of Special Interest by Investigator
Proposed-Dose Safety Pool

Events Through at Least Day 151	Subjects With ≥1 Event, n (%)	
	Placebo N=1284	**Nirsevimab** N=2570
Any adverse event of special interest	**0**	**6 (0.2)**
Immediate hypersensitivity (including anaphylaxis)		
Rash	0	2 (<0.1)
Rash maculo-papular	0	2 (<0.1)
Petechiae	0	1 (<0.1)
Rash papular	0	1 (<0.1)
Immune complex disease	**0**	**0**
Thrombocytopenia	**0**	**0**

Conclusion: Overall incidence of AESIs was low and restricted to nonserious skin and subcutaneous reactions

Treatment-Emergent Skin and Skin Hypersensitivity Reactions
Proposed-Dose Safety Pool

Events Through at Least Day 151	Subjects With ≥1 Event, n (%)	
	Placebo N=1284	**Nirsevimab** N=2570
Any skin reaction	**332 (25.9)**	**650 (25.3)**
IP-related skin reaction	4 (0.3)	15 (0.6)
IP-related skin hypersensitivity reactions (AESI[a])	0	6 (0.2)

Conclusion: Skin reactions balanced between treatment groups with a low incidence of related events

[a] AESIs defined as Type I hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease.

Safety of Coadministration With Childhood Vaccinations

- Nirsevimab not expected to interfere with active immune response to coadministered vaccines[1]
- Available data on the safety of nirsevimab or placebo coadministration with 7 pre-specified vaccine groups[a]
- Safety and reactogenicity profile of the co-administered regimen similar to childhood vaccines given alone
- Over 20 years of experience with palivizumab in combination with childhood vaccines has not raised safety concerns[2]
  - Guidelines recommend coadministration of palivizumab with childhood vaccines[1]

[a] Vaccines include: Tuberculosis, Influenza, Measles/Mumps/Rubella/Varicella, Rotavirus, Polyvalent diphtheria-poliomyelitis-tetanus containing, Pneumococcal, and Hepatitis B.

1. Esposito S, et al. *Front Immunol*. 2021;12:708939; 2. Synagis US Prescribing Information.

No Evidence of Enhanced RSV Disease in the Second Season

Trial 04 (Primary Cohort) in First and Second RSV Season

Definition	Subjects With ≥1 Event, n (%)			
	Season 1 (through Day 151)		Season 2 (Days 362-511)	
	Placebo N=496	Nirsevimab N=994	Placebo N=482	Nirsevimab N=964
Medically attended RSV LRTI	25 (5.0)	12 (1.2)	2 (0.4)	7 (0.7)
Medically attended RSV LRTI with hospitalization	8 (1.6)	6 (0.6)	0	0
Medically attended RSV LRTI (very severe)	7 (1.4)	5 (0.5)	0	0
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]

Increasing Severity

Conclusion: No evidence to support theoretical risk of antibody-dependent enhancement of disease

[a] RSV confirmed by central or local test

[b] The 2 events were 483 days post initial dose in a set of twins, one a nirsevimab recipient and the other a placebo recipient, who had a similar clinical presentation and hospital course.

Higher-Risk Populations Studied in Trial 05 and Trial 08 Season 1 and/or Season 2

Trial 05 (Ph2/3)

Infants at high risk of severe RSV disease eligible for palivizumab (CHD, CLD, or preterm ≤35 wGA)

Trial 08 (Ph2 open-label)

Immunocompromised neonates, infants and children ≤24 months of age

Overview of Safety in Preterm Infants ≤35 wGA and Infants With CHD or CLD

Trial 05 Season 1 to Day 361

	Subjects With ≥1 Event, n (%)			
	Preterm Cohort		CHD/CLD Cohort	
	Palivizumab N=206	Nirsevimab N=406	Palivizumab N=98	Nirsevimab N=208
Any adverse event	**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
Serious AE	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)
Skin reactions related to IP[a]	1 (0.5)	1 (0.2)	1 (1.0)	1 (0.5)
AEs of special interest[b] by investigator assessment	0	1 (0.2)[c]	0	2 (1.0)[c]

Conclusion: Safety profile comparable with that of palivizumab in Season 1

[a] Observed events: rash macular (preterm cohort) and injection site induration (CHD/CLD cohort) in palivizumab group; rash maculopapular (AESI, preterm cohort) and rash (CHD/CLD cohort) in nirsevimab group.
[b] AESIs defined as Type I hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease.
[c] Observed events were a related skin hypersensitivity event of rash maculo-papular (preterm cohort) and unrelated thrombocytopenia (2 subjects with CHD).
1. Domachowske J, et al. *N Engl J Med*. 2022;386(9):892-894.

Overview of Safety in CHD/CLD Cohort

Trial 05 Season 2 to at Least Day 151

	Subjects With ≥1 Event, n (%) N=262		
Season 1	**Palivizumab**	**Palivizumab**	**Nirsevimab**
Season 2	**Palivizumab** N=42	**Nirsevimab** N=40	**Nirsevimab** N=180
Any adverse event	**29 (69.0)**	**29 (72.5)**	**126 (70.0)**
Through 30 days post first dose[a]	11 (26.2)	11 (27.5)	54 (30.0)
Any AE related to IP	0	0	0
AE grade ≥3	1 (2.4)	4 (10.0)	14 (7.8)
Through 30 days post first dose[a]	1 (2.4)	1 (2.5)	3 (1.7)
AE grade ≥3 related to IP	0	0	0
Serious AE	0	4 (10.0)	17 (9.4)
Through 30 days post first dose[a]	0	1 (2.5)	4 (2.2)
SAE related to IP	0	0	0
Death	0	0	0
Skin reaction related to IP	0	0	0
AEs of special interest[b] by investigator assessment	0	0	0

Conclusion: Favorable safety profile in children with CHD or CLD in second season

[a] Relative to the active nirsevimab dose for subjects in palivizumab/nirsevimab and nirsevimab/nirsevimab groups.
[b] AESIs defined as Type I hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease.

Overview of Safety in Immunocompromised Infants and Children

Trial 08 First or Second RSV Season

Events Through at Least Day 151	Subjects with ≥1 event, n (%) N=60
Any adverse event	**48 (80.0)**
Any AE related to IP	5 (8.3)
AE of grade ≥3 severity	19 (31.7)
AE of grade ≥3 severity related to IP	0
Serious AEs	18 (30.0)
SAE related to IP	0
Death	1 (1.7)
Skin reactions related to IP	2 (3.3)[b]
AEs of special interest[a] by investigator assessment	4 (6.7)[c]

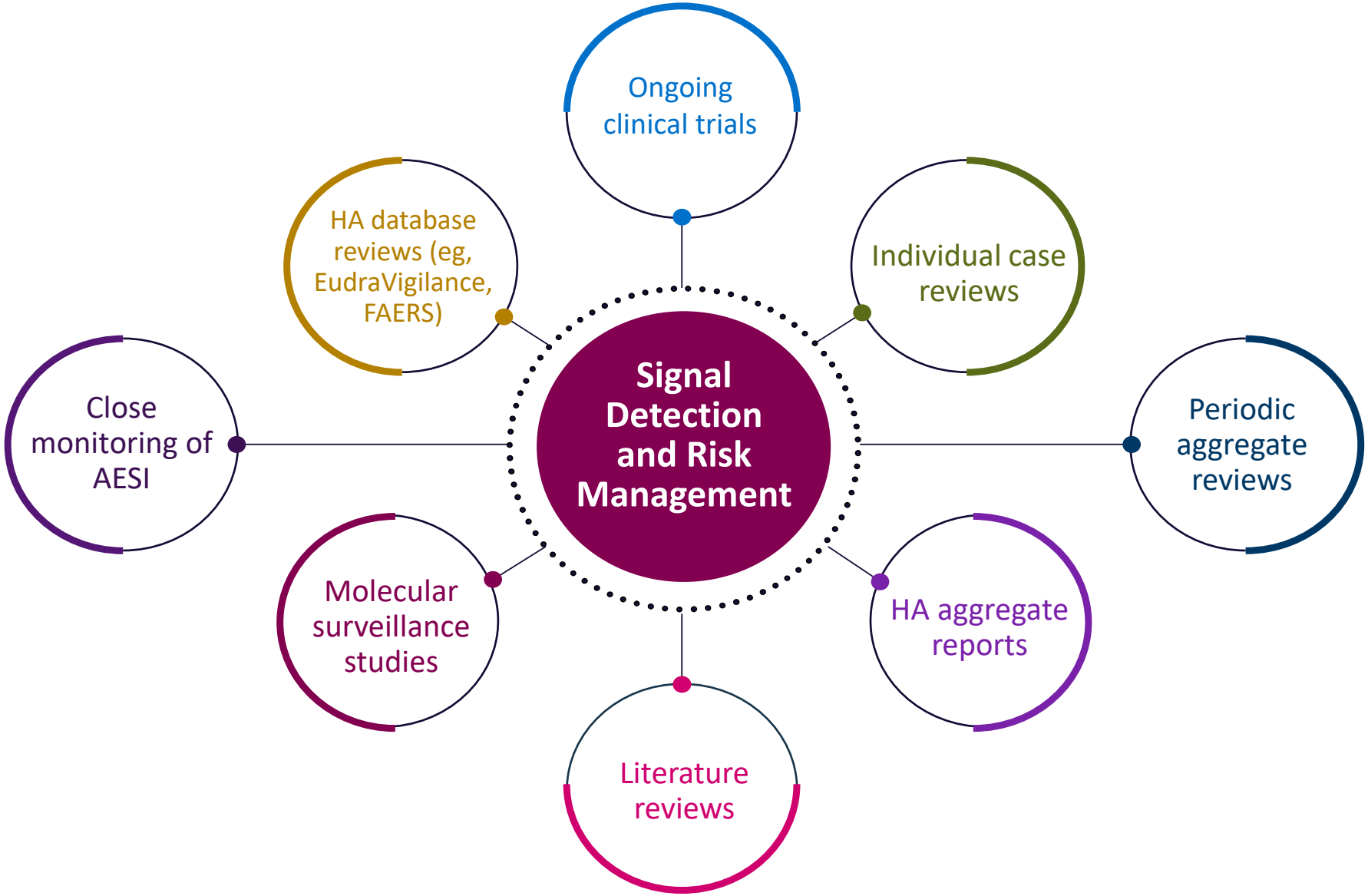
Conclusion: Safety profile consistent with that expected for the study population

[a] AESIs defined as Type I hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease.
[b] Observed events were erythema (AESI) and rash
[c] Observed events were erythema (related), food allergy, contrast media allergy, and urticaria (unrelated).

Summary of Safety

- Overall safety profile of nirsevimab is favorable in the first and second RSV seasons across studies and cohorts
- Safety profile in infants at higher risk of severe RSV generally comparable with that of palivizumab
- Safety profile in immunocompromised infants and children consistent with that expected for the study population
- Overall incidence of AESIs was low
  - No anaphylaxis, serious allergic reaction, or serious thrombocytopenia attributed to nirsevimab
  - No immune complex disease by investigator assessment

Global Pharmacovigilance Plan



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Clinical Perspective

William Muller, MD, PhD
Professor, Pediatrics, Northwestern University Feinberg School of Medicine

Scientific Director, Office of Clinical and Community Trials, Ann and Robert H. Lurie Children's Hospital of Chicago

Clinical Relevance of RSV in Pediatrics

Michigan children's hospital says it's 100% full due to RSV surge

The hospital says RSV cases are 46% higher than last year.

By Mary Kekatos
November 11, 2022, 2:07 PM

abc NEWS

https://abcnews.go.com/Health/michigan-childrens-hospital-100-full-due-rsv-surge/story?id=93116061

The New York Times

'This Is Our March 2020': Children's Hospitals Are Overwhelmed by R.S.V.

A drastic and unusually early spike in the respiratory infection is swamping pediatric units across the United States, causing long waits for treatment and worries about winter.

By Emily Baumgaertner Photographs by Jamie Kelter Davis
Published Nov. 1, 2022 Updated Nov. 3, 2022

https://www.nytimes.com/2022/11/01/science/rsv-children-hospitals.html

Winter surge in infections from RSV, flu, and COVID straining U.S. hospitals

Dec 15, 2022 6:45 PM EDT

PBS NEWS HOUR

https://www.pbs.org/newshour/show/winter-surge-in-infections-from-rsv-flu-and-covid-straining-u-s-hospitals

Clinical Relevance of RSV in Pediatrics

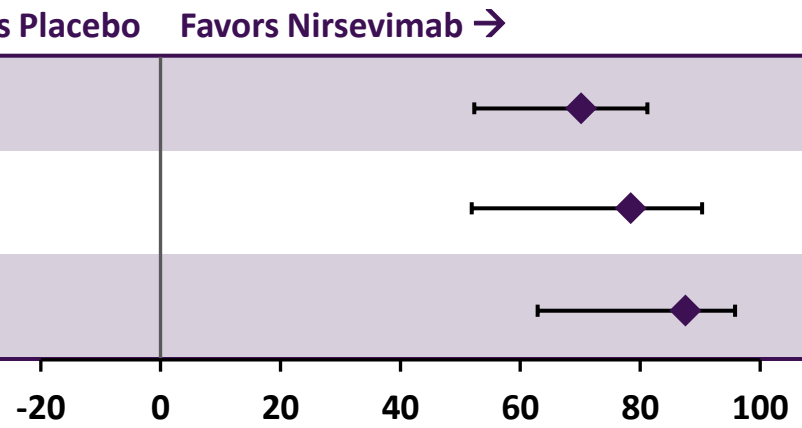
- Tens of thousands of hospitalizations annually[1]
- Annual cost to system of hospitalization in children under 2 years old exceeds $1 billion[2,3]

1. House SA, Ralston SL. Wheezing, bronchiolitis, and bronchitis. In: Kliegman RM, et al, eds. *Nelson Textbook of Pediatrics*. 21st ed. Philadelphia, PA: Elsevier; 2020: chap 418.
2. Hasegawa K, et al. *Pediatrics*. 2013;132(1):28-36.
3. Fujiogi M, et al. *Pediatrics*. 2019;144(6):e20192614.

Perspective on Benefit of Nirsevimab: Consistent Effect

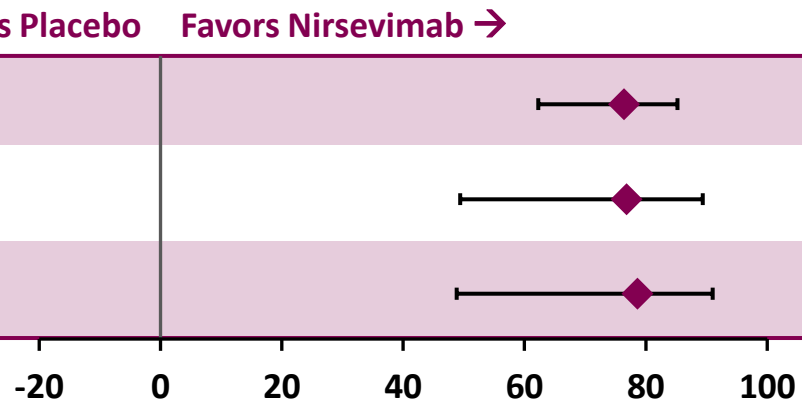
Trial 03 (ITT analysis)[1]

Endpoint	Observed Events (%) Placebo N=484	Nirsevimab N=969	Efficacy, % (95% CI)
MA RSV LRTI	46 (9.5)	25 (2.6)	**70.1** (52.3, 81.2)
MA RSV LRTI with Hospitalization	20 (4.1)	8 (0.8)	**78.4** (51.9, 90.3)
MA RSV LRTI (very severe)	16 (3.3)	4 (0.4)	**87.5** (62.9, 95.8)



Trial 04 (All Subjects)[2]

Endpoint	Observed Events (%) Placebo N=1003	Nirsevimab N=2009	Efficacy, % (95% CI)
MA RSV LRTI	54 (5.4)	24 (1.2)	**76.4** (62.3, 85.2)
MA RSV LRTI with Hospitalization	20 (2.0)	9 (0.4)	**76.8** (49.4, 89.4)
MA RSV LRTI (very severe)	17 (1.7)	7 (0.3)	**78.6** (48.8, 91.0)

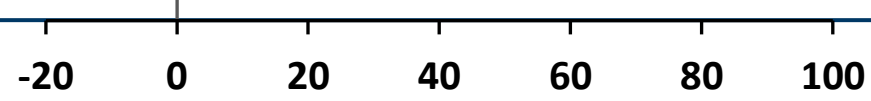


1. Griffin MP, et al. *N Engl J Med*. 2020;383(5):415-425.
2. Muller WJ, et al. Nirsevimab for Prevention of RSV in Term and Late-Preterm Infants. *N Engl J Med*. 2023;388(16):1533-1534.

Real-World Open-Label Phase 3b Effectiveness Study
HARMONIE

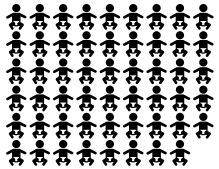
- N=8058
- Conducted in France, Germany, and United Kingdom
- Healthy infants ≥29 wGA entering or during first RSV season
- Randomized (1:1) vs no intervention

Endpoint	Observed Events (%) No Intervention N=4021	Observed Events (%) Nirsevimab N=4037	Efficacy, % (95% CI)
RSV LRTI Hospitalization	60 (1.5)	11 (0.3)	**83.2** (67.8, 92.0)
All-cause LRTI Hospitalization	98 (2.4)	45 (1.1)	**58.0** (39.7, 71.2)

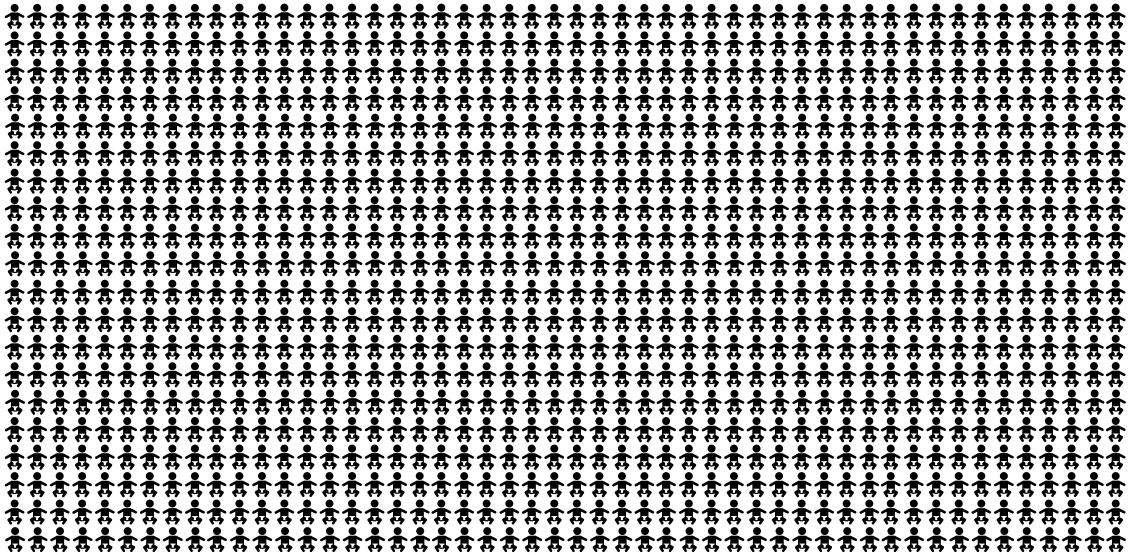


Drysdale SB, et al. Presented at European Society for Paediatric Infectious Diseases. 2023. Abstract O0082.

Perspective on Benefit of Nirsevimab: Number Needed to Immunize



Treating 53[a] infants with nirsevimab would prevent one all-cause LRTI hospitalization[1]



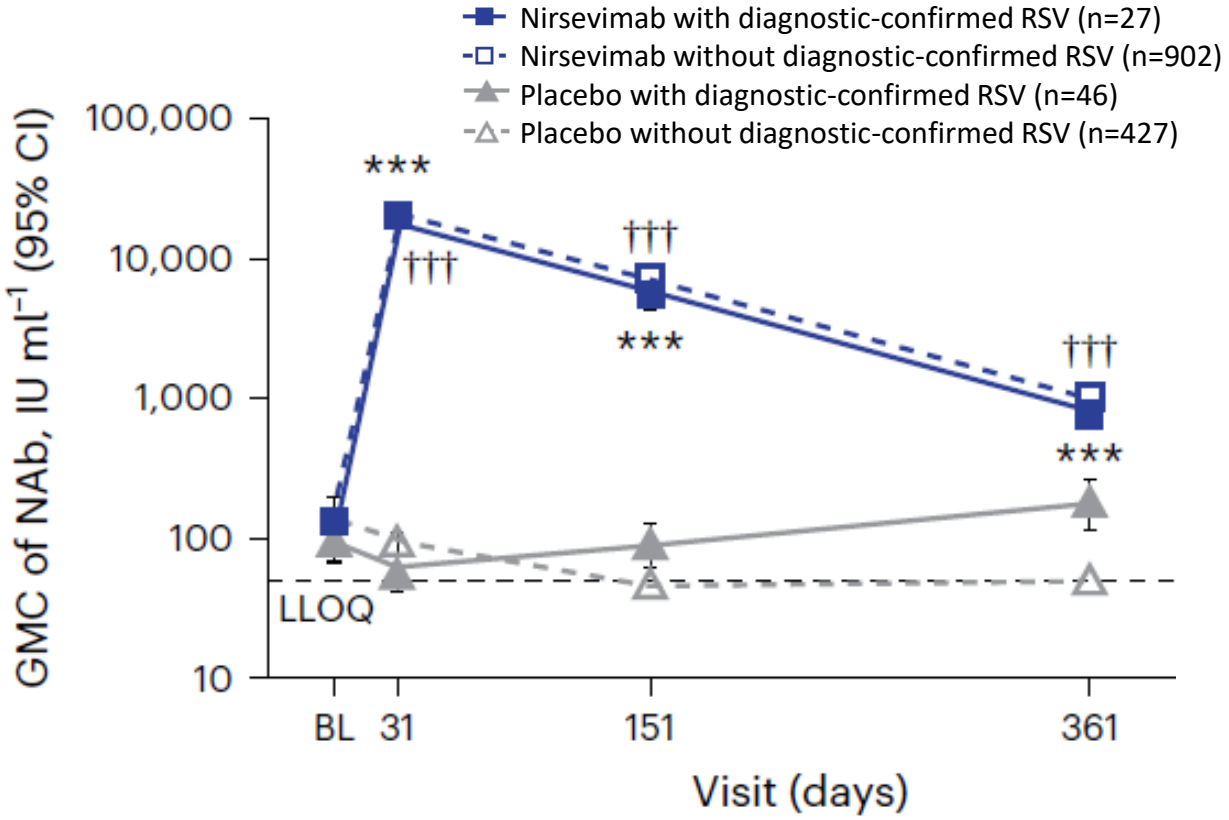
An influenza vaccine with 50% efficacy needs to be given to 1000-3000 6–23-month-old children to prevent one hospitalization[2]

[a] 95% confidence interval: 29, 250

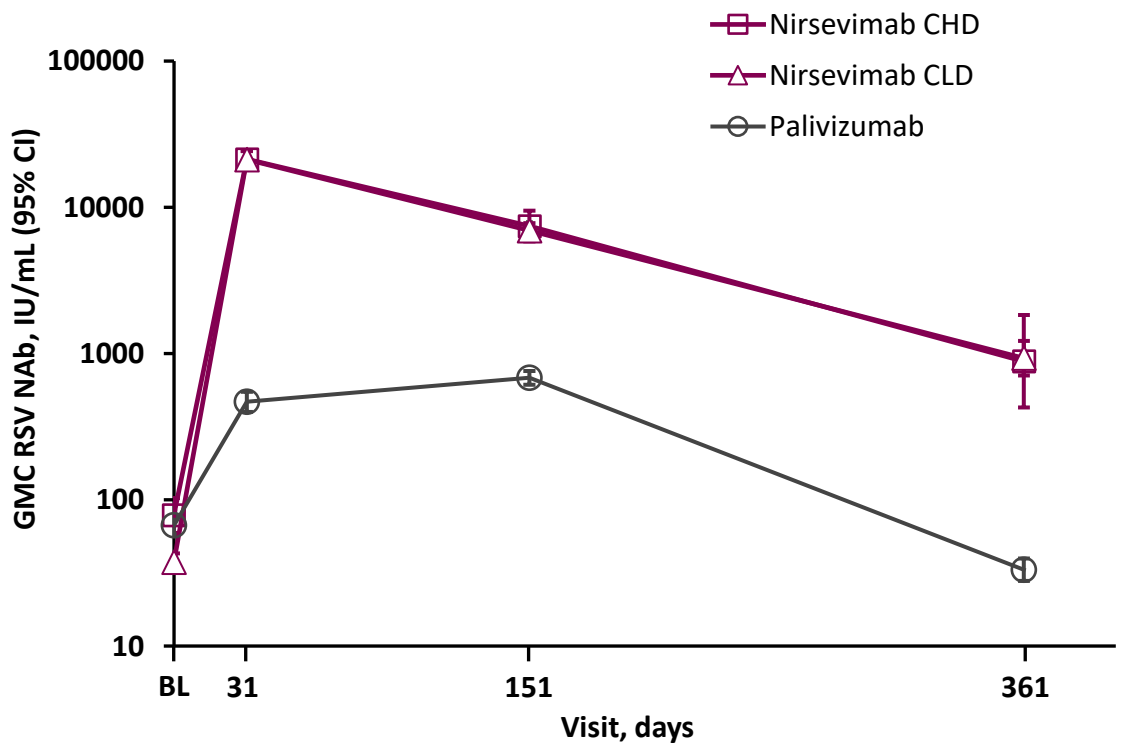
1. Muller WJ, et al. *N Engl J Med*. 2023;388(16):1533-1534 (Trial 04 All Subjects).
2. Lewis EN, et al. *Pediatrics*. 2007;120(3):467-472.

Perspective on Benefit: Neutralizing Antibody Levels

Trial 04 (Primary Cohort)
(healthy term and late preterm infants)



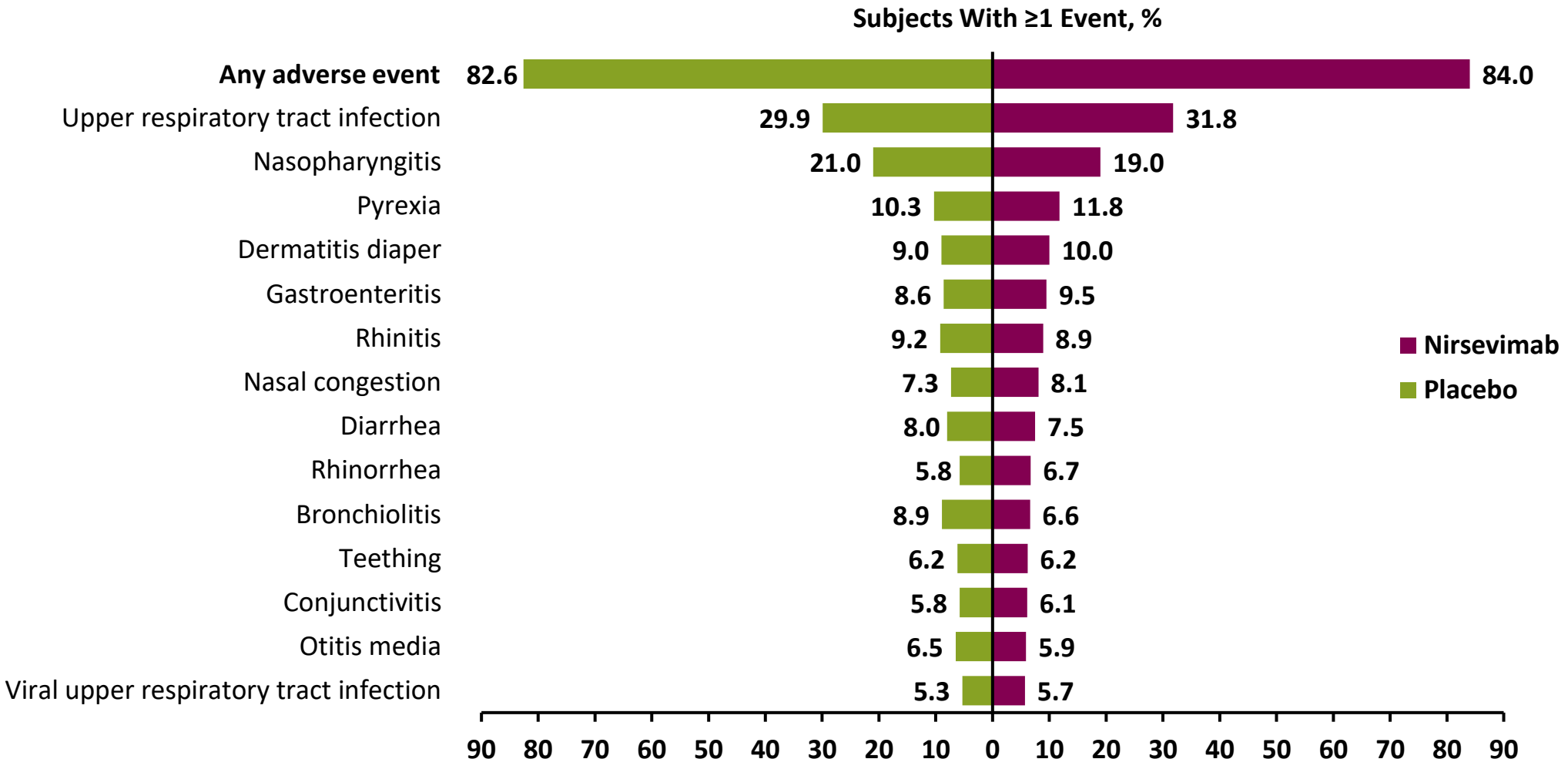
Trial 05
(palivizumab-eligible at high risk of severe RSV)



BL = baseline; LLOQ = lower limit of quantification.

***p<0.001, nirsevimab versus placebo with diagnostic-confirmed RSV; †††p<0.001, nirsevimab versus placebo without diagnostic-confirmed RSV. N denotes number of infants who had a serum sample available at baseline. Data are presented as GMCs ± 95% CIs, which were calculated assuming log normal distribution. Two-sided p values were calculated based on the F statistic from ANOVA, without adjustment.

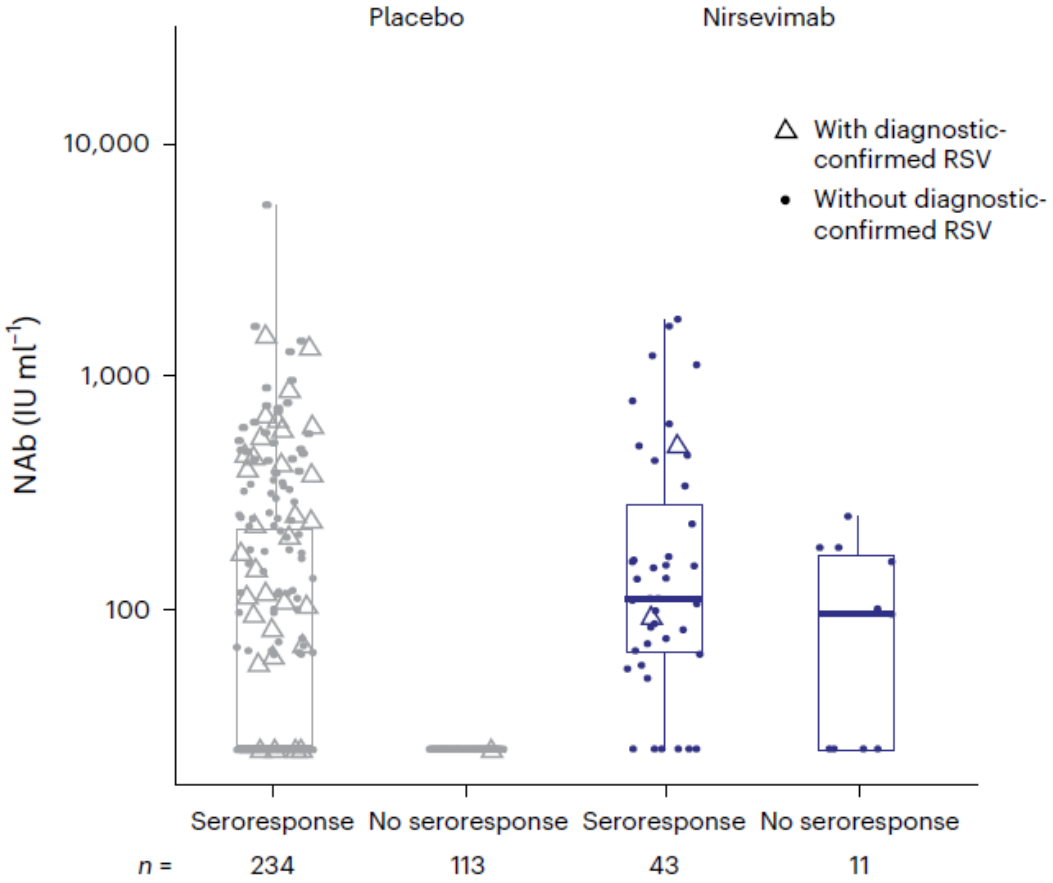
Perspective on Risk
Proposed-Dose Safety Pool



Perspective on Risk

- TEAE and SAE profiles reflect the study population and are comparable between treatment and placebo groups
- AESI profile is mild, does not raise concern
- Theoretical risk of ADE was addressed in the trial and no signal observed
- No reason to expect problems with coadministration with routinely recommended childhood vaccines
- No interference with generating an anti-RSV immune response after infection

Trial 04



How I Would Recommend Clinical Use of Nirsevimab

- Every infant entering their first RSV season and newborns during the season
  - Timing dependent on birth month and local RSV epidemiology
- Also use in second season for high-risk infants and children
- Anticipate role for protection of immunocompromised children

Nirsevimab After Maternal RSV Vaccination

- This question should ultimately be addressed by ACIP
  - Complexities: timing of birth relative to RSV season, EGA at delivery, etc.
  - Logistical considerations:
    - Ability of pediatrician to verify maternal dose
    - Single approach for infants entering or born during RSV season vs needing to implement multiple recommendations that depend on several variables
- Personal opinion: risk is low and there is a potential for benefit in most infants
- Provider and caregiver should always discuss risk and benefit in the context of ACIP recommendations

ACIP = Advisory Committee on Immunization Practices; EGA = estimated gestational age.

Public Health Implications of Nirsevimab

- Decreased hospital and outpatient demand for evaluation of RSV-related illness (bronchiolitis)
- Decreased secondary infections → decreased need for antibiotics
- Long half-life confers the potential for an impact on equity
  - Palivizumab compliance decreases through the RSV season, disproportionately in populations challenged to access health care[1]

Additional Considerations

- Fewer infant infections
  - → Fewer office and ED visits and less time away from work
  - → Fewer parents spending sleepless nights at a hospital, having to experience their infant children struggling to breathe

1. Krilov LR, et al. *BMC Pediatrics*. 2014;14:261.

Conclusions

- Effective interventions that prevent or treat RSV infection would be a major advance in pediatric medicine
- Nirsevimab shows a consistent benefit in all infants for clinically significant endpoints
- The safety of nirsevimab is supported by the data presented, showing little difference from placebo and adverse effects consistent with the study populations
- The data presented support a proposal to provide nirsevimab to all infants entering their first RSV season and high-risk children in their second RSV season

Benefit-Risk & Conclusions

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Vaccines and Immune Therapies
AstraZeneca

Nirsevimab Has a Favorable Benefit-Risk Profile for RSV Prevention in All Infants and High-Risk Children

Preventing RSV disease in infants is a major public health need

High Efficacy Across Disease Severities

- A single dose of nirsevimab is efficacious for a minimum of 5 months, typical RSV season

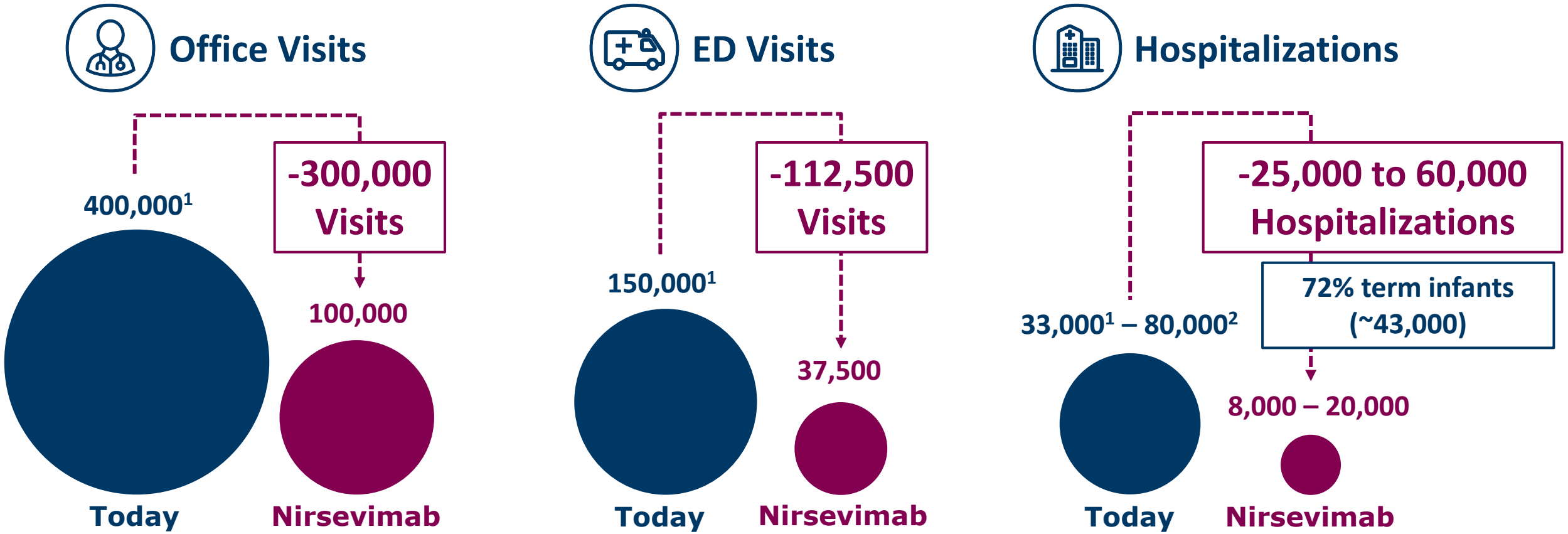
	MA RSV LRTI	RSV LRTI With Hospitalization
Term & late preterm ≥35 wGA	**74.5%**[a]	**76.8%**[b]
Preterm ≥29 to <35 wGA[c]	**86.2%**	**86.5%**
High-risk infants and children	Efficacy by extrapolation (PK)	

Favorable Safety Profile

- Nirsevimab was well tolerated with no safety concerns in term and preterm infants
- Nirsevimab demonstrated a safety profile comparable with palivizumab in high-risk infants and children

[a] Trial 04 (Primary Cohort).
[b] Trial 04 (All Subjects); exploratory analysis.
[c] Trial 03 (Proposed Dose Cohort); exploratory analysis.

Nirsevimab Could Prevent up to 500,000 Medical Interventions due to RSV in the US Annually



Assuming 100% uptake of nirsevimab and a conservative estimate of 75% relative risk reduction against key medically attended interventions

1. Rainisch G, et al. *Vaccine*. 2020;38(2):251-257; 2. McLaughlin JM, et al. *J Infect Dis*. 2022;225(6):1100-1111.

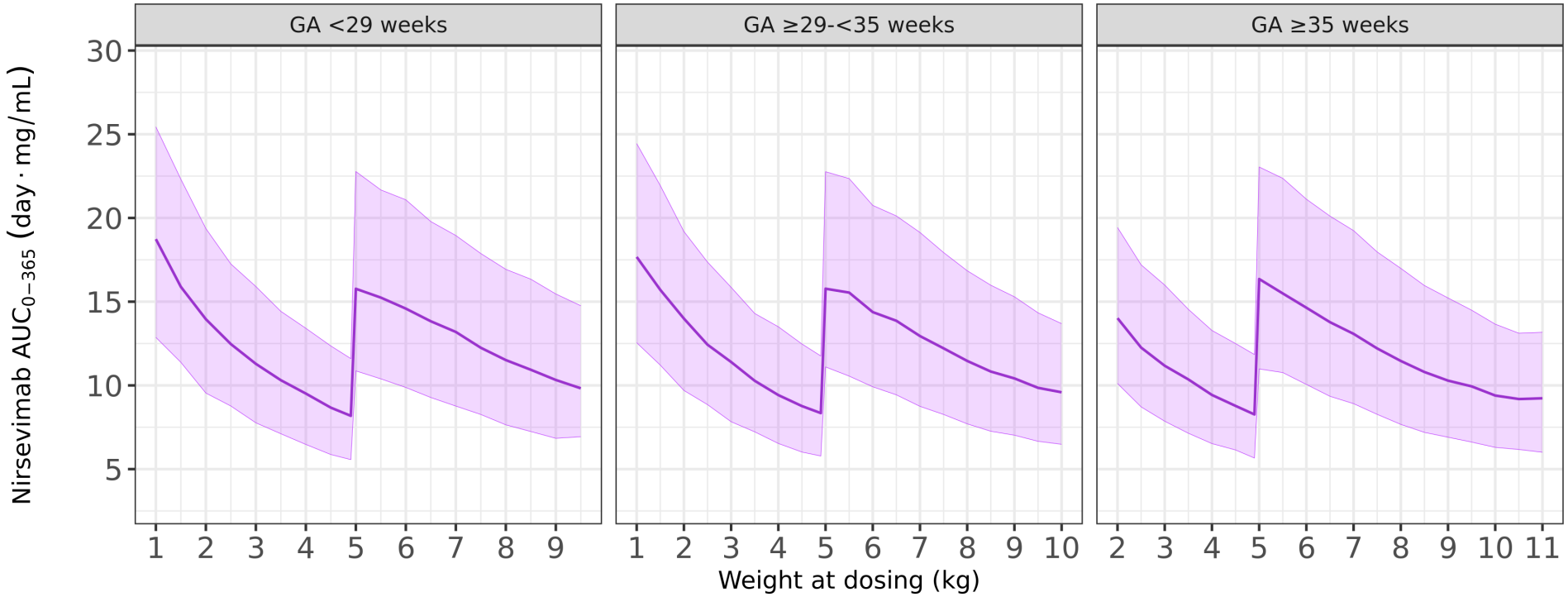
Clinical Studies Provided Substantial Evidence That Nirsevimab Has a Positive Benefit-Risk Profile for the Proposed Indication

For the prevention of Respiratory Syncytial Virus (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

Thank You

Nirsevimab Serum AUC Across Body Weight Range at Dosing, by GA at Birth



Weight-band dose:
- 50 mg if weight <5 kg
- 100 mg if weight ≥5kg

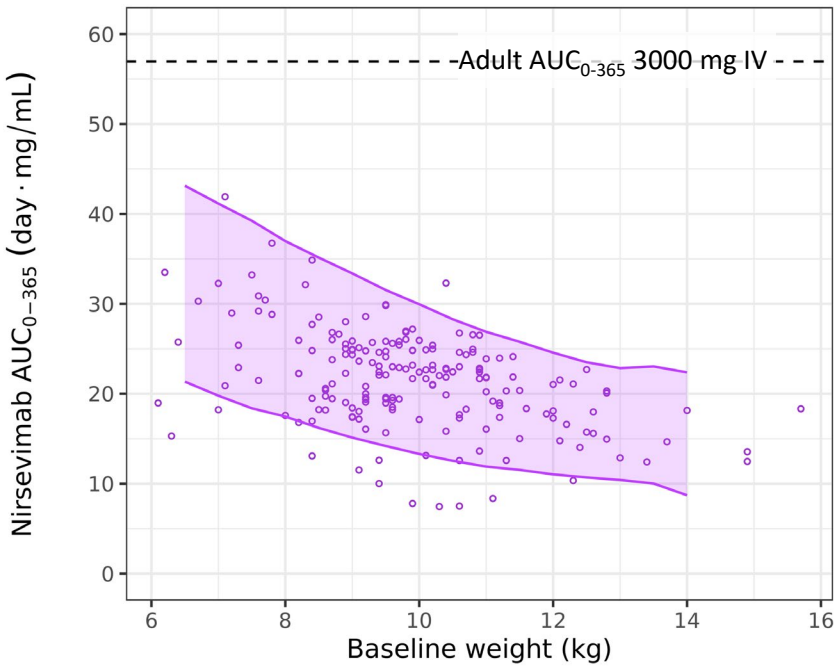
- Nirsevimab serum exposures vary with body weight
- Weight-band dosing results in exposures in similar range in <5 kg and ≥5 kg

Notes: Shaded bands show the 5th to 95th percentiles of the predictions for weight band dosing, solid line is the median.
$AUC_{0\text{-}365}$ = predicted area under the serum concentration-time curve from Days 0 to 365; GA = gestational age

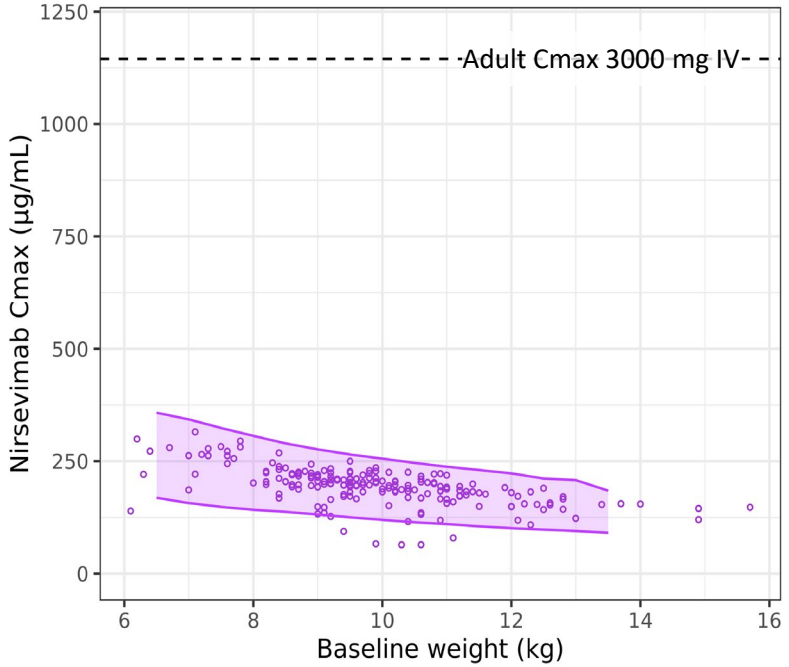
Nirsevimab Serum Exposure Across Body Weights at Dosing Compared With Adult Exposure

Trial 05 Season 2, 200 mg

AUC



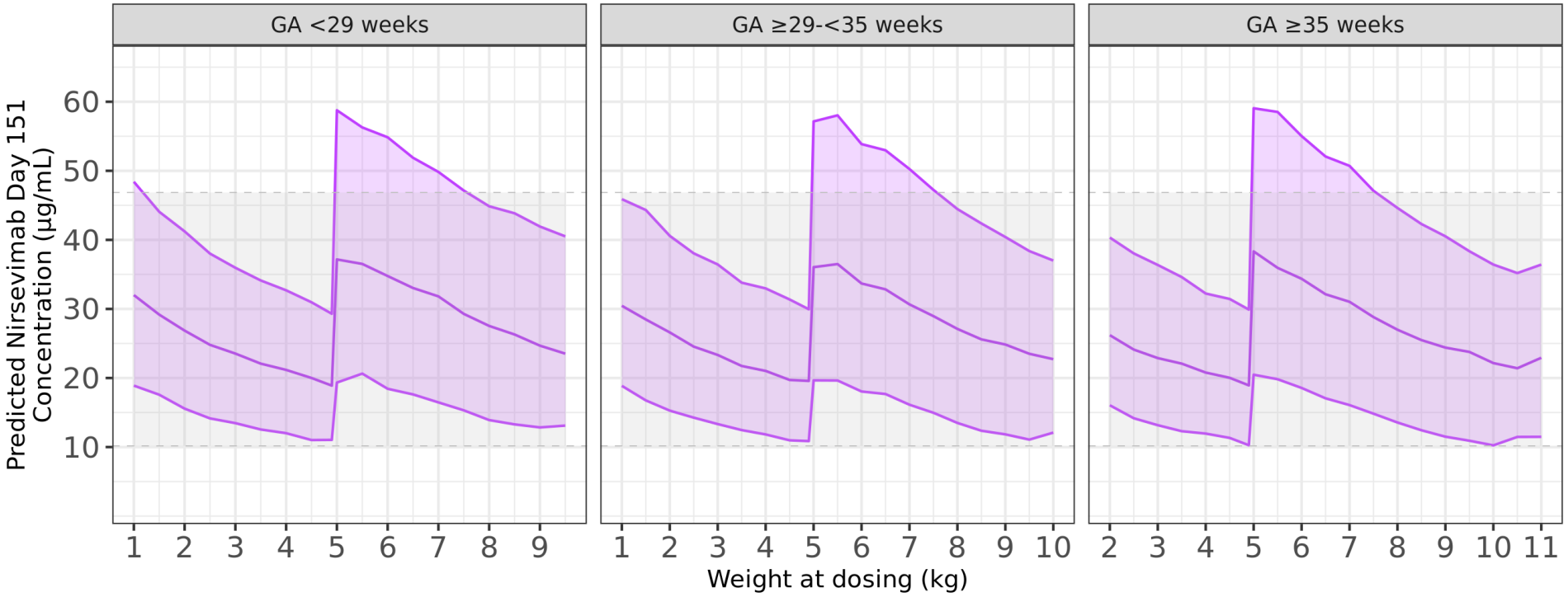
Cmax



Nirsevimab serum exposures below those following maximum dose studied in adults

Shaded area covers 5th to 95th predictions, points are individual data; broken line is median adult exposure from 3000-mg IV dose
AUC_{0-365} = predicted area under the serum concentration-time curve from Days 0 to 365.

Nirsevimab Day 151 Serum Concentration Versus Body Weight at Dosing, by GA at Birth – Compared With Trial 04



Weight-band dose:
- 50 mg if weight <5 kg
- 100 mg if weight ≥5kg

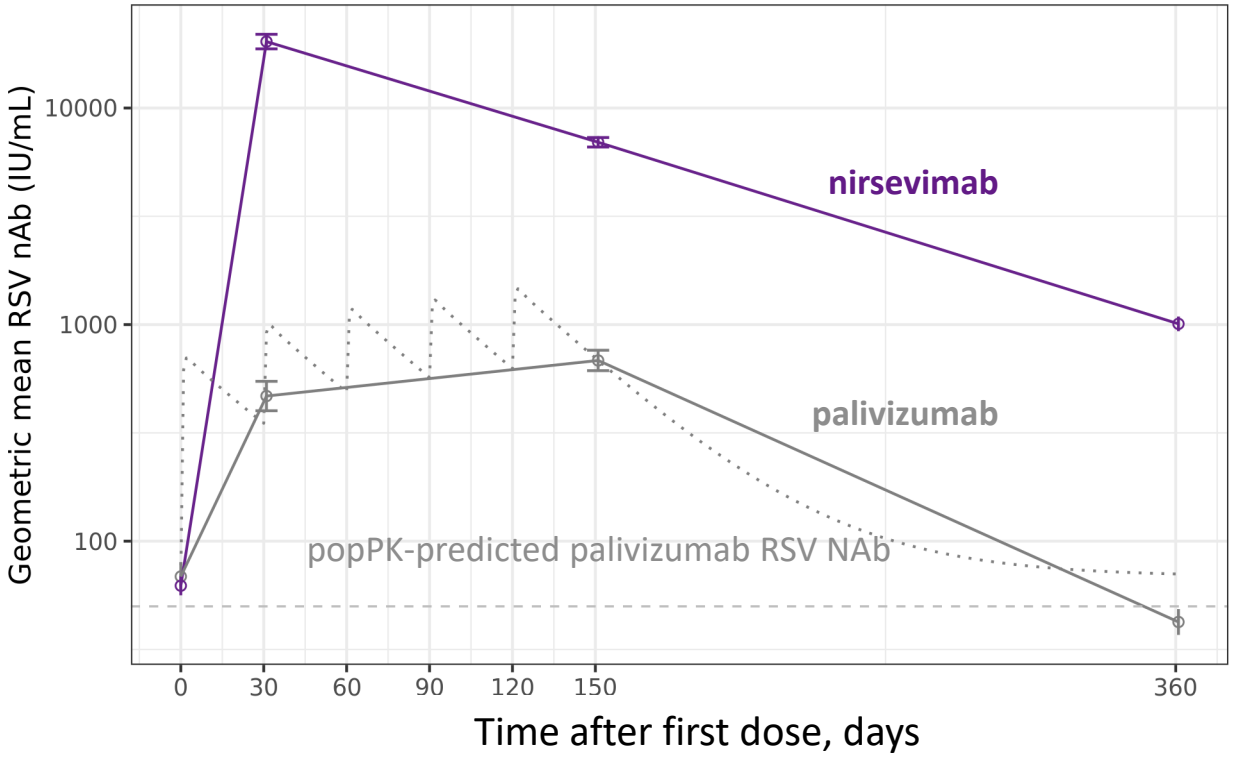
Weight-band dosing results in exposures in similar range in <5 kg and ≥5 kg

Shaded area shows the Trial 04 5th to 95th percentiles

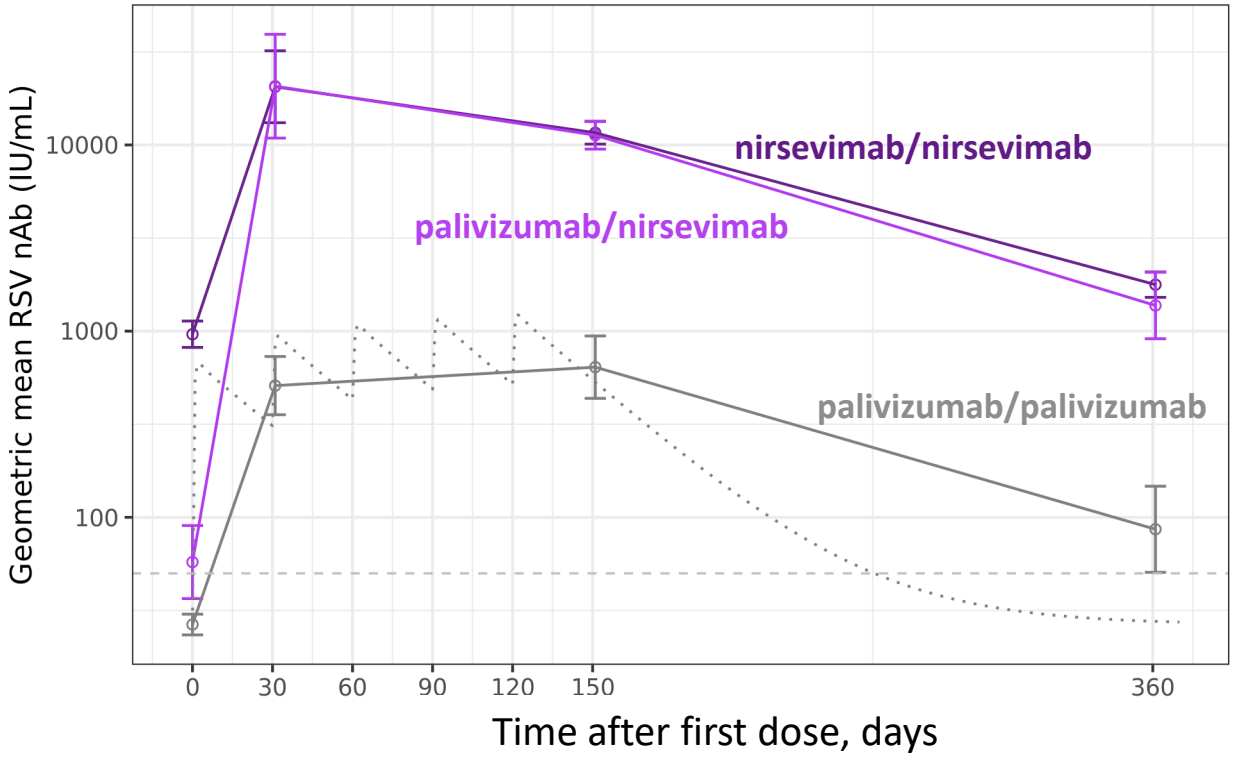
RSV Neutralizing Antibody Levels Are Higher for Nirsevimab Than for Palivizumab Throughout Season 1 and Season 2

Trial 05

Season 1



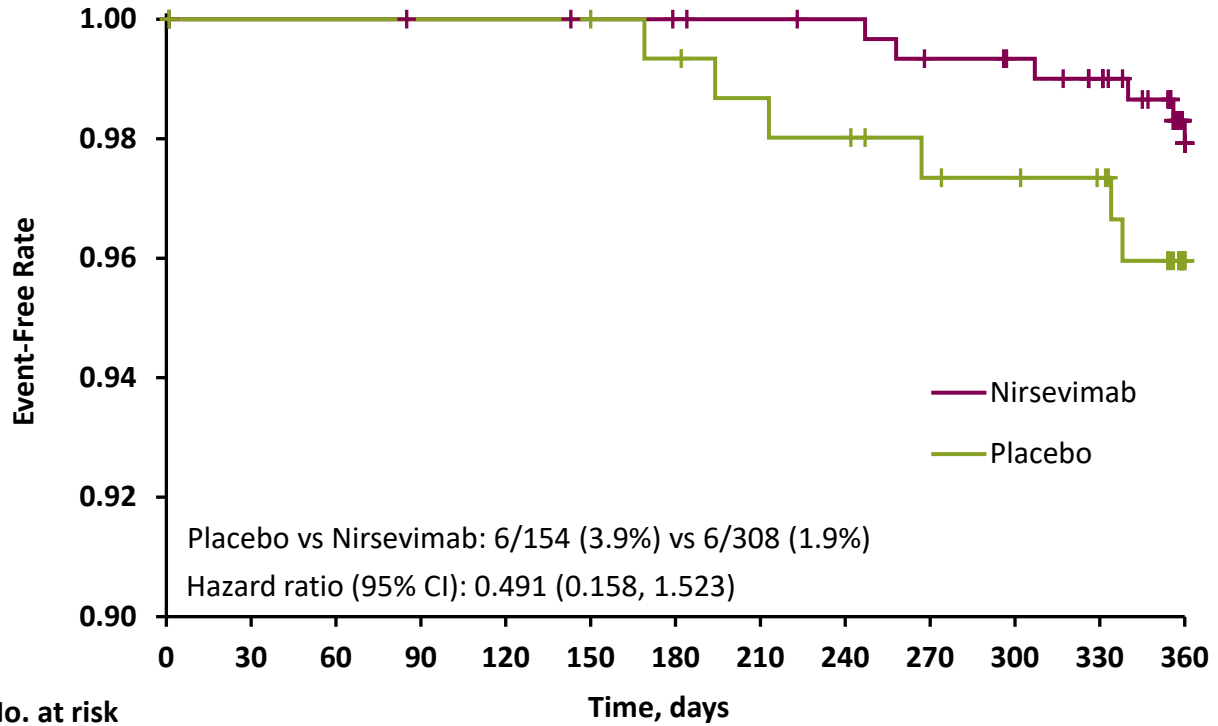
Season 2



Geometric mean (95% CI). Dashed blue line is population PK-predicted geometric mean RSV NAb for palivizumab.
Dashed gray line is lower limit of quantification. 7046 IU/mL RSV NAb = 1 mg/mL palivizumab

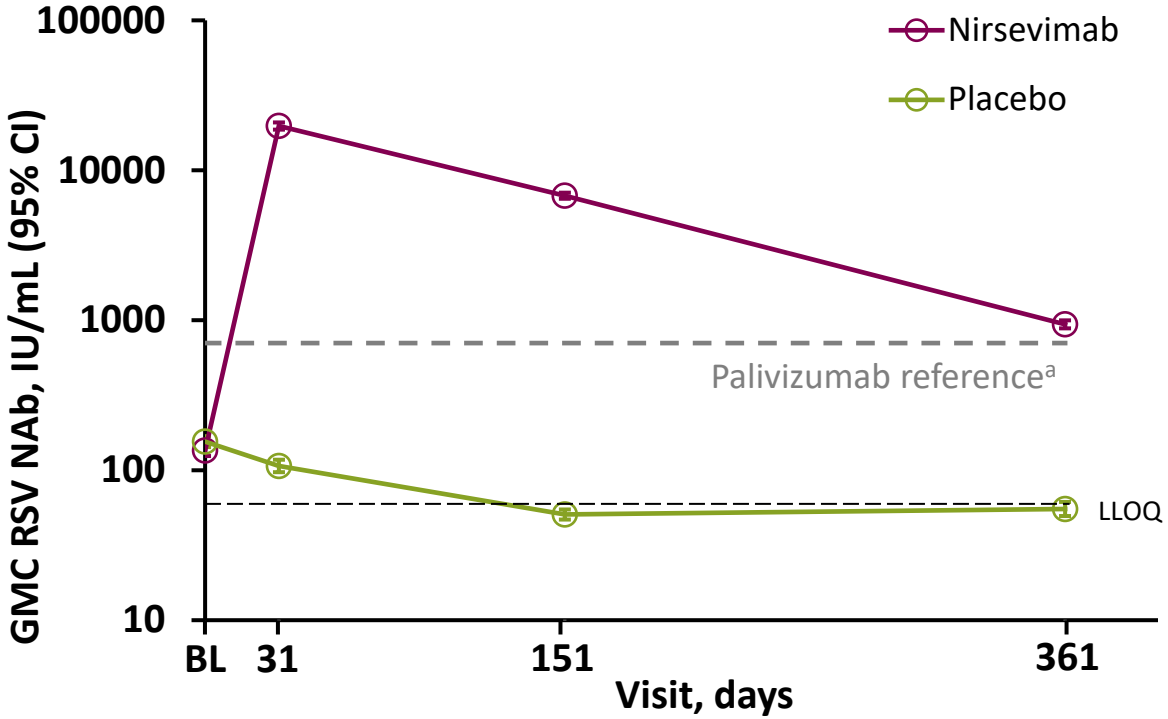
Evidence for Efficacy Beyond 5 Months

Time to First MA RSV LRTI
Trial 04 – South Africa



No. at risk													
Nirsevimab	308	307	307	306	306	305	304	303	302	299	297	292	257
Placebo	154	153	153	153	153	153	151	149	148	145	144	142	123

RSV Neutralizing Antibodies in
Trial 04 (Primary Cohort)

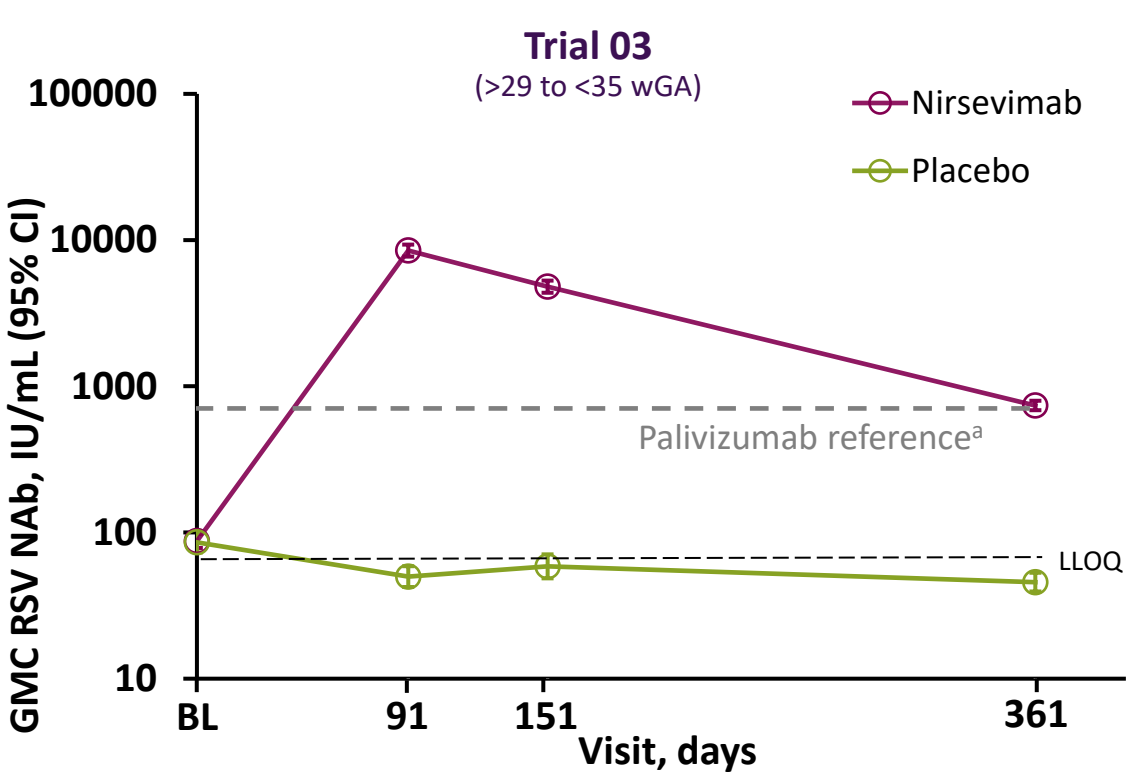


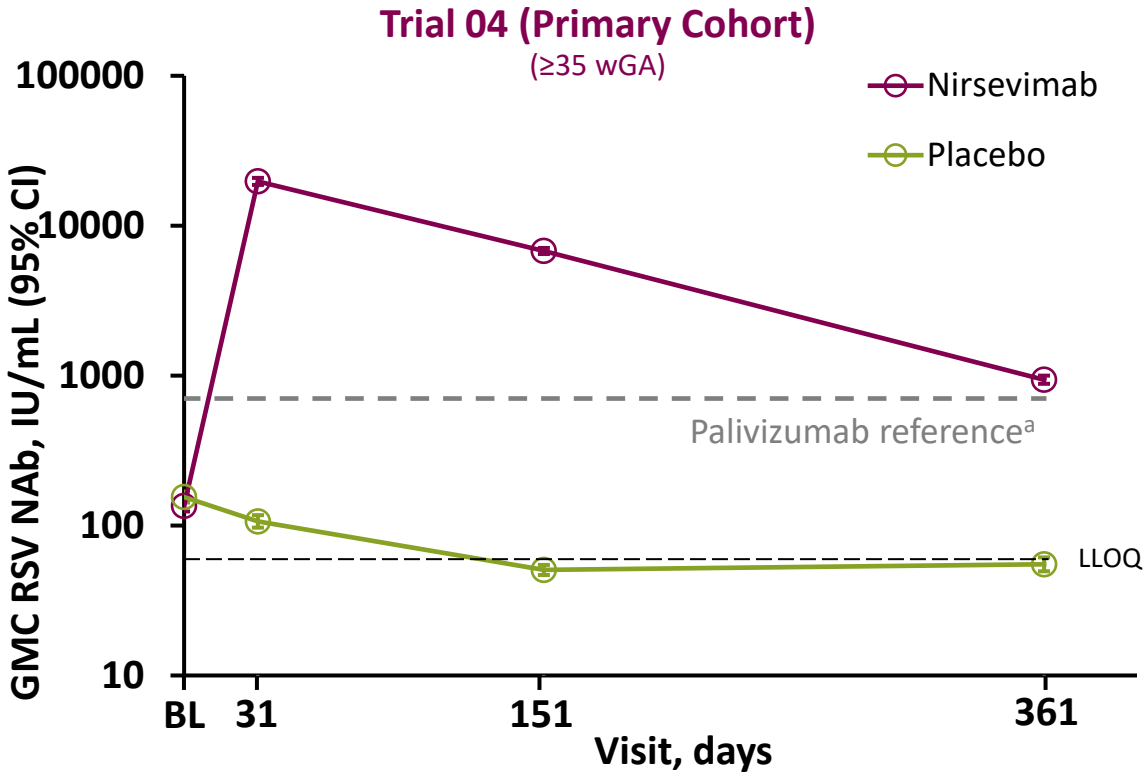
	940	594	836	853
	473	315	423	426

[a] Palivizumab reference line = 50% neutralizing titer of 100 µg/mL serum concentrations, the approximate peak levels observed after palivizumab first dose.

High and Sustained RSV Neutralizing Antibody Levels

Trial 03, Trial 04 (Primary Cohort)





Placebo	243	249	246	233	473	315	423	426
Nirsevimab	498	479	469	462	940	594	836	853

[a] Palivizumab reference line = 50% neutralizing titer of 100 µg/mL serum concentrations, the approximate peak levels observed after palivizumab 1st dose.

Robbie GJ, et al. *Antimicrob Agents Chemother*. 2012;56(9):4927-4936.

No Evidence of Enhanced RSV Disease in the Second Season

Trial 04 (All Subjects) in First and Second RSV Seasons

Definition	Subjects With ≥1 Event, n (%)			
	Season 1 (through Day 151)		Season 2 (Day 362-511)	
	Placebo N=1003	Nirsevimab N=2009	Placebo N=967	Nirsevimab N=1944
Medically attended RSV LRTI	54 (5.4)	24 (1.2)	10 (1.0)	19 (1.0)
Medically attended RSV LRTI with Hospitalization	20 (2.0)	9 (0.4)	3 (0.3)	3 (0.2)
Medically attended RSV LRTI (very severe)	17 (1.7)	7 (0.3)	3 (0.3)	3 (0.2)
All MA RSV (any test[a]) LRTI	75 (7.5)	34 (1.7)	20 (2.1)	35 (1.8)
All MA RSV (any test[a]) respiratory illness with Hospitalization	26 (2.6)	15 (0.7)	6 (0.6)	10 (0.5)

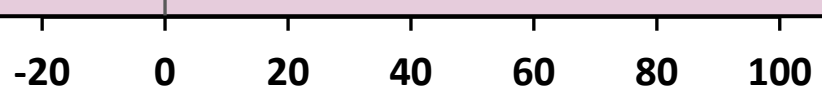
Increasing Severity

Conclusion: No evidence to support theoretical risk of antibody-dependent enhancement of disease

[a] RSV confirmed by central or local test.

Efficacy Consistent Over 0-90, 0-120, 0-150 Days

Study	Reporting Period	Events, n (%) Placebo	Events, n (%) Nirsevimab	Efficacy, % (95% CI)
Trial 03 (ITT)	0-90 days	30 (6.2)	15 (1.5)	**75.4** (54.3, 86.8)
	0-120 days	41 (8.5)	21 (2.2)	**75.2** (58.0, 85.3)
	0-150 days	46 (9.5)	25 (2.6)	**73.8** (57.4, 83.9)
Trial 04 (All Subjects)	0-90 days	47 (4.7)	15 (0.7)	**84.2** (71.7, 91.2)
	0-120 days	53 (5.3)	20 (1.0)	**81.5** (69.0, 88.9)
	0-150 days	54 (5.4)	24 (1.2)	**76.4** (62.3, 85.2)



Hazard Ratio (95% CI) by Interval for MA RSV LRTI

Trial 03 and Trial 04

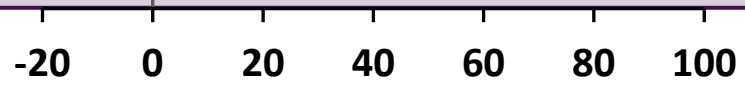
Study	Interval	Number of Events Placebo, n (%)	Number of Events Nirsevimab, n (%)	Hazard Ratio (95% CI)
Trial 03[a] (ITT)		**N=484**	**N=969**	
	0-30 days	8 (1.7)	5 (0.5)	0.32 (0.10, 0.97)
	>30-60 days	10 (2.1)	7 (0.7)	0.34 (0.13, 0.90)
	>60-90 days	12 (2.5)	3 (0.3)	0.12 (0.03, 0.43)
	>90-120 days	11 (2.3)	6 (0.6)	0.26 (0.09, 0.69)
	>120-150 days	5 (1.0)	4 (0.4)	0.37 (0.10, 1.37)
		N=1003	**N=2009**	
Trial 04[b] (All Subjects)	0-30 days	15 (1.5)	6 (0.3)	0.20 (0.08, 0.50)
	>30-60 days	14 (1.4)	6 (0.3)	0.22 (0.08, 0.57)
	>60-90 days	18 (1.8)	3 (0.2)	0.08 (0.02, 0.28)
	>90-120 days	6 (0.6)	5 (0.2)	0.39 (0.12, 1.29)
	>120-150 days	1 (0.1)	4 (0.2)	2.02 (0.23, 18.16)

[a] Hazard ratio and the corresponding 95% confidence interval were from a stratified Cox proportional hazard model with stratification factors (age at randomization and hemisphere) as the strata.
[b] Hazard ratio and the corresponding 95% confidence interval were from a stratified Cox proportional hazard model with stratification factors (age at randomization, hemisphere, and Cohort) as the strata.

Exposure-Response Analysis for Weight-Band Dosing ($Conc_{D151}$)

Trial 03 (Proposed Dose)/Trial 04 (Primary Cohort) Pool

	Placebo		Nirsevimab			Efficacy, % (95% CI)
	Subject	Events	N	Events	← Favors Placebo Favors Nirsevimab →	
Overall	**780**	**51**	**1502**	**18**		**82.3 (70.0, 90.0)**
Q1			376	8		70.0 (37.0, 86.0)
Q2			375	4		85.0 (59.0, 95.0)
Q3			375	2		92.0 (68.0, 98.0)
Q4			376	4		82.0 (48.0, 94.0)



Efficacy is consistent across the range of serum exposures achieved from weight-band dosing

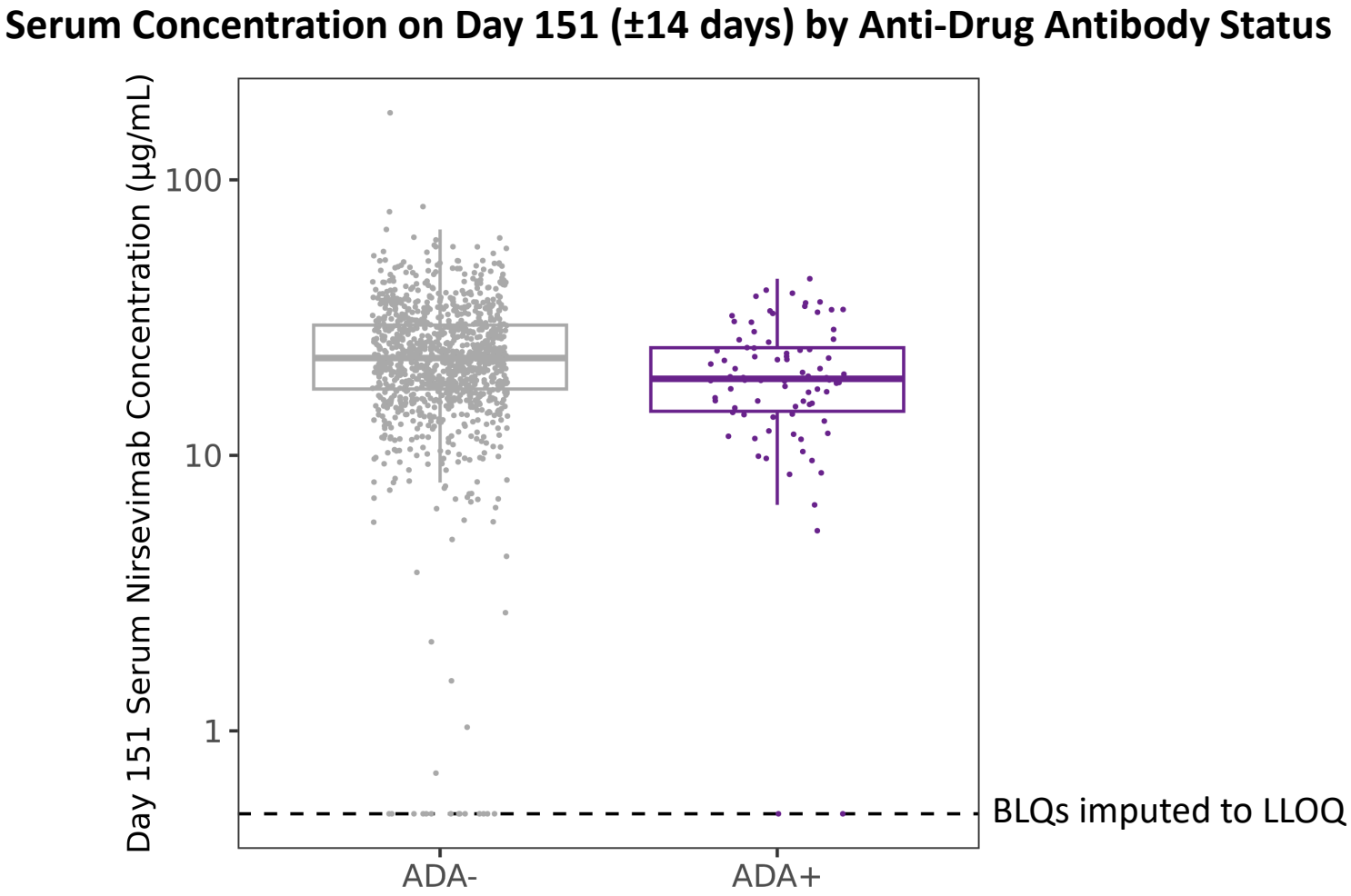
Q1:Q4 – nirsevimab serum exposure ($Conc_{D151}$) bins divided by quartiles

*(1- HR) × 100, based on Cox proportional hazard model stratified by study and age group

Estimate based on subset of subjects with available PK in nirsevimab group, using predicted concentration Day 151

No Apparent Effect of ADA on Day 151 Nirsevimab Serum Concentration

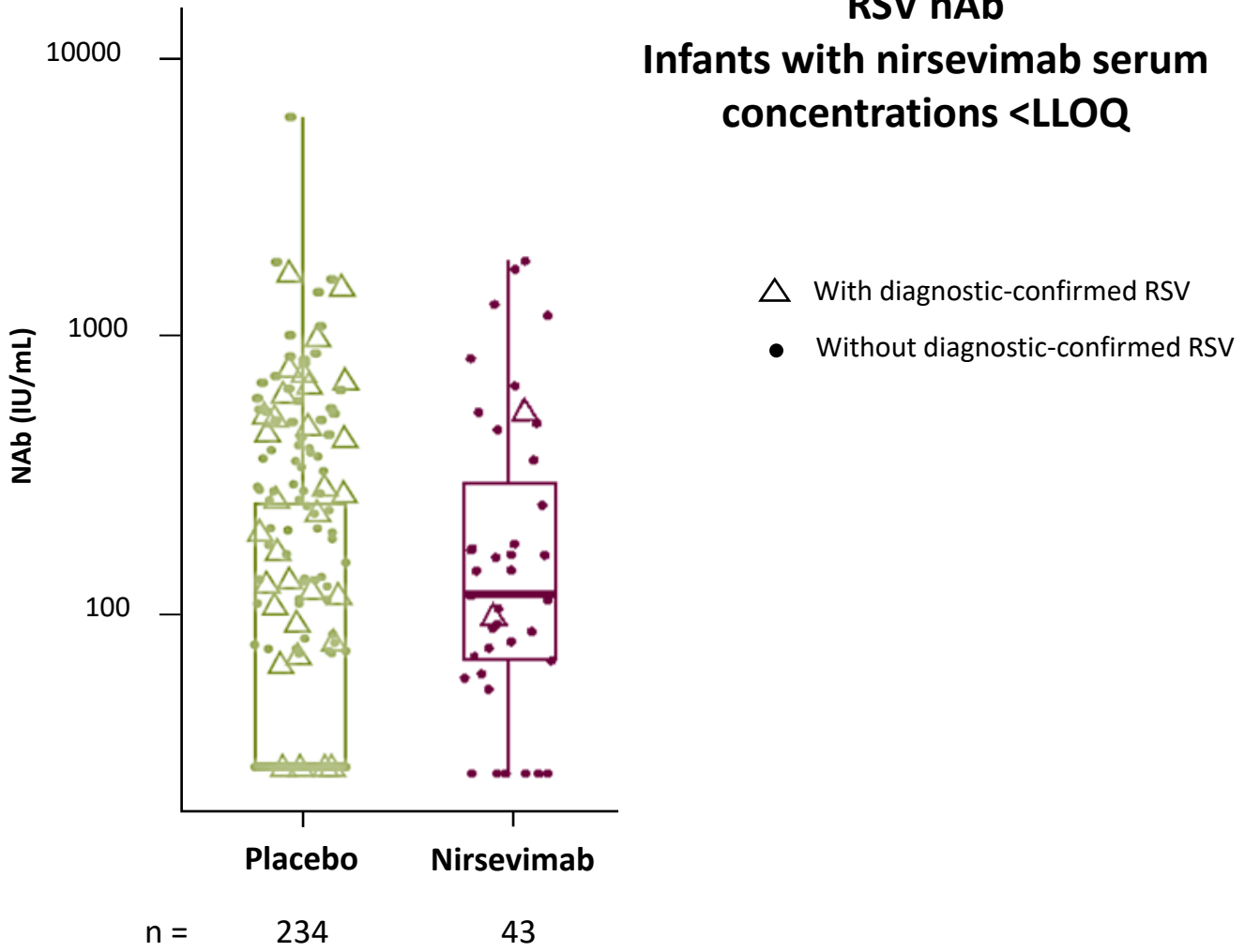
Trial 03 (Proposed Dose), Trial 04 (Primary Cohort)



ADA status is ADA+ at any time. BLQs imputed to LLOQ (dashed line).

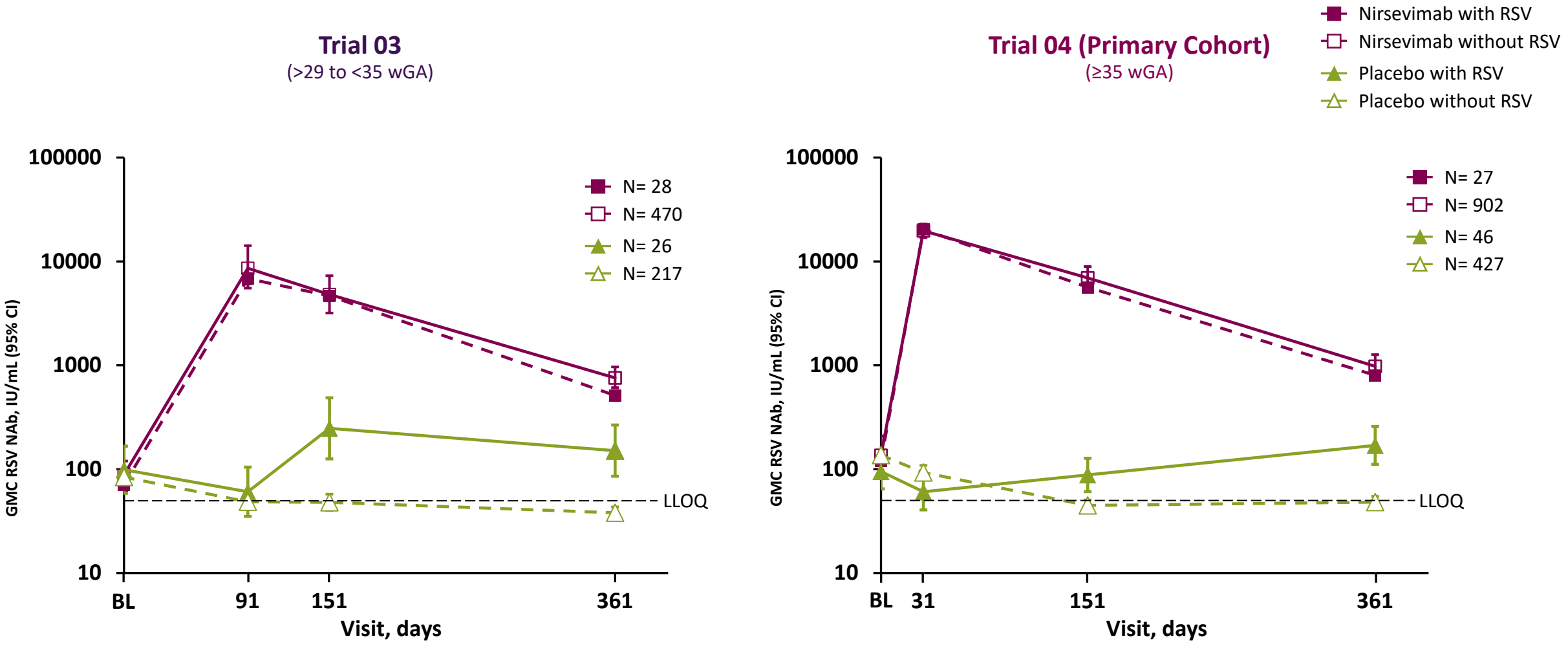
Nirsevimab Does Not Inhibit a Natural Immune Response to RSV in RSV Exposed Infants

Trial 04 (Primary Cohort), Day 361



RSV Neutralizing Antibody Levels are 50-fold Higher Than Baseline at Day 151

Trial 03, Trial 04 (Primary Cohort)

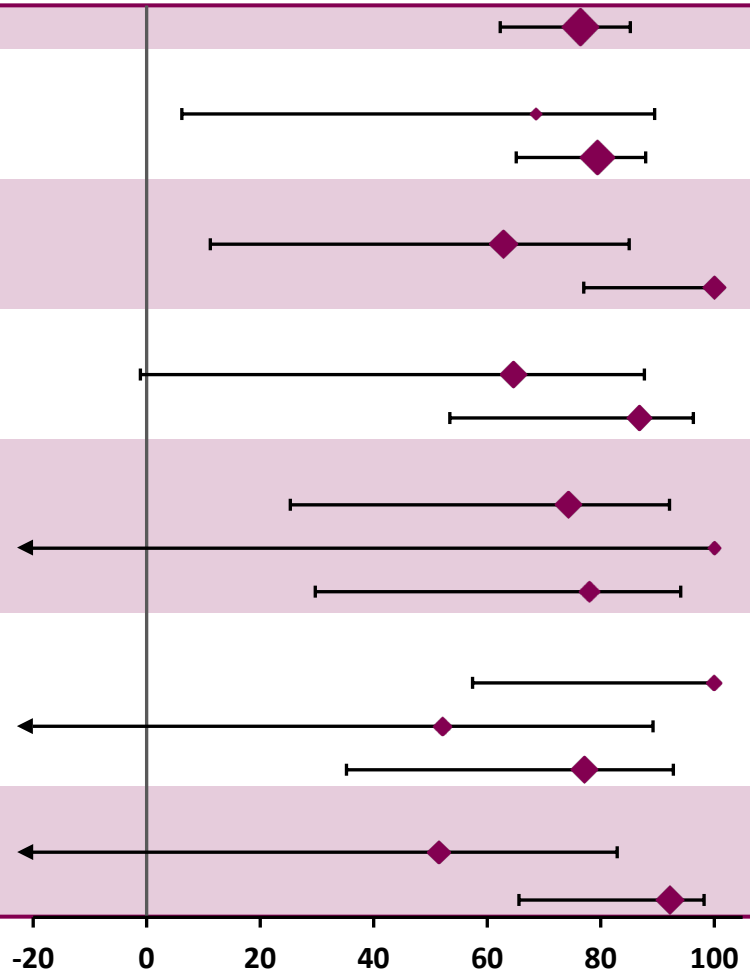


N represents number of infants with a baseline result.

Efficacy Against MA RSV LRTI With Hospitalization Through 150 Days Post Dose by Subgroup

Trial 04 (All Subjects)

	Placebo (N=1003)		Nirsevimab (N=2009)		Efficacy, % (95% CI)
	Number of Infants	Observed Events	Number of Infants	Observed Events	
Overall	**1003**	**54 (5.4)**	**2009**	**24 (1.2)**	**76.4 (62.3, 85.2)**
Gestational age					
≥35 to <37 weeks	122	8 (6.6)	239	5 (2.1)	**68.6** (6.2, 89.5)
≥37 weeks	880	46 (5.2)	1769	19 (1.1)	**79.4** (65.1, 87.9)
Age at randomization					
≤3.0 months	588	12 (2.0)	1190	9 (0.8)	**62.9** (11.2, 85.0)
>3.0 months	415	8 (1.9)	819	0 (0.0)	**100** (77.0, NE)
Sex					
Male	503	8 (1.6)	1071	6 (0.6)	**64.7** (-1.1, 87.7)
Female	500	12 (2.4)	938	3 (0.3)	**86.8** (53.4, 96.3)
Race					
White	541	10 (1.8)	1052	5 (0.5)	**74.3** (25.3, 92.1)
Black/African American	138	1 (0.7)	299	9 (0.0)	**100** (-776.9, NE)
Other	324	9 (2.8)	655	4 (0.6)	**78.0** (29.7, 94.1)
Region					
North America	195	5 (2.6)	376	0 (0.0)	**100** (57.4, NE)
Europe	263	4 (1.5)	549	4 (0.7)	**52.1** (-112.4, 89.2)
Rest of the World	545	11 (2.0)	1084	5 (0.5)	**77.1** (35.2, 92.8)
Weight on Day 1					
<5 kg	392	7 (1.8)	800	7 (0.9)	**51.5** (-37.2, 82.9)
≥5 kg	611	13 (2.1)	1206	2 (0.2)	**92.2** (65.6, 98.2)

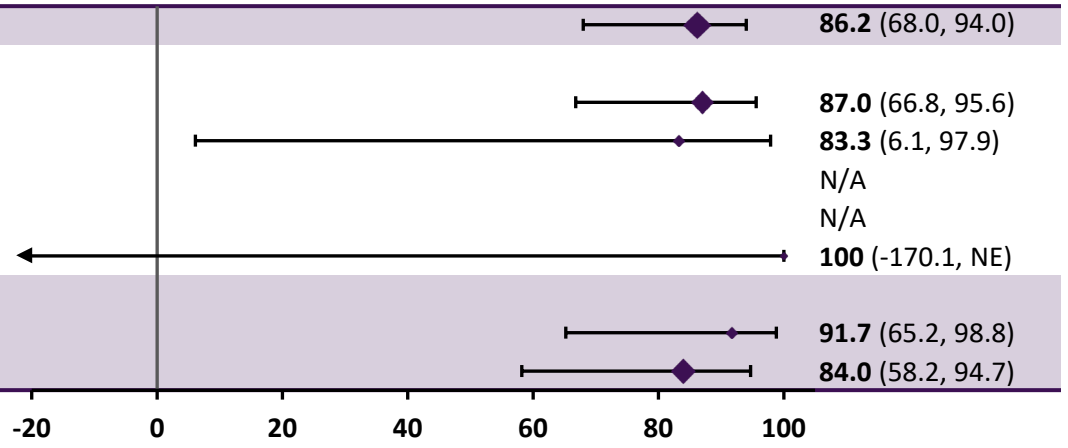


Unadjusted interaction p-value <0.1 for weight on Day 1.

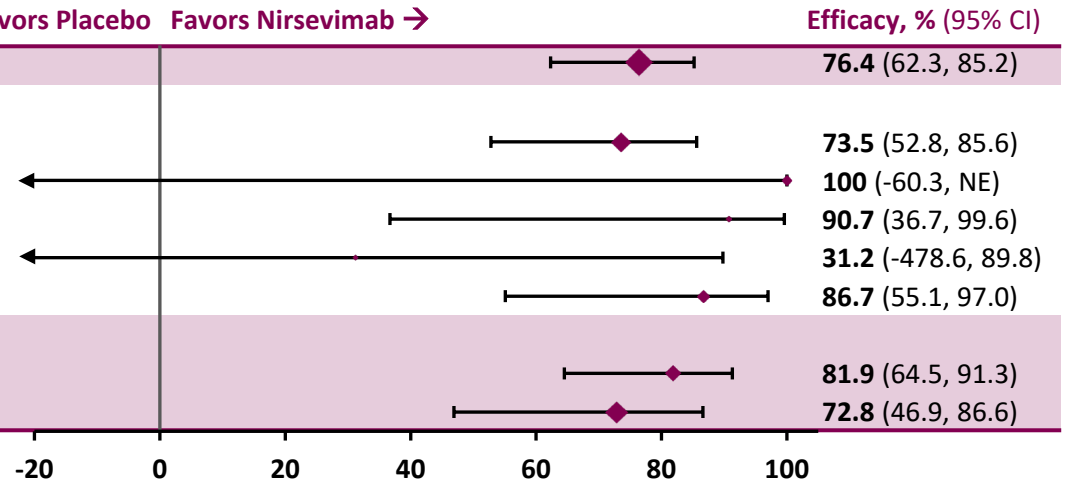
Efficacy Against MA RSV LRTI Through 150 Days Post Dose by Race and Ethnicity

Trial 03 and Trial 04

Trial 03 (Proposed Dose)	Placebo (N=290)		Nirsevimab (N=570)		Efficacy, % (95% CI)
	Number of Infants	Observed Events	Number of Infants	Observed Events	
Overall	**290**	**26 (9.0)**	**570**	**7 (1.2)**	**86.2** (68.0, 94.0)
Race					
White	206	20 (9.7)	395	5 (1.3)	**87.0** (66.8, 95.6)
Black/African American	40	4 (10.0)	120	2 (1.7)	**83.3** (6.1, 97.9)
Indigenous Populations	3	0 (0.0)	6	0 (0.0)	N/A
Asian	6	0 (0.0)	3	0 (0.0)	N/A
Other	35	2 (5.7)	45	0 (0.0)	**100** (-170.1, NE)
Ethnicity					
Hispanic or Latino	44	9 (20.5)	118	2 (1.7)	**91.7** (65.2, 98.8)
Not Hispanic or Latino	246	17 (6.9)	451	5 (1.1)	**84.0** (58.2, 94.7)

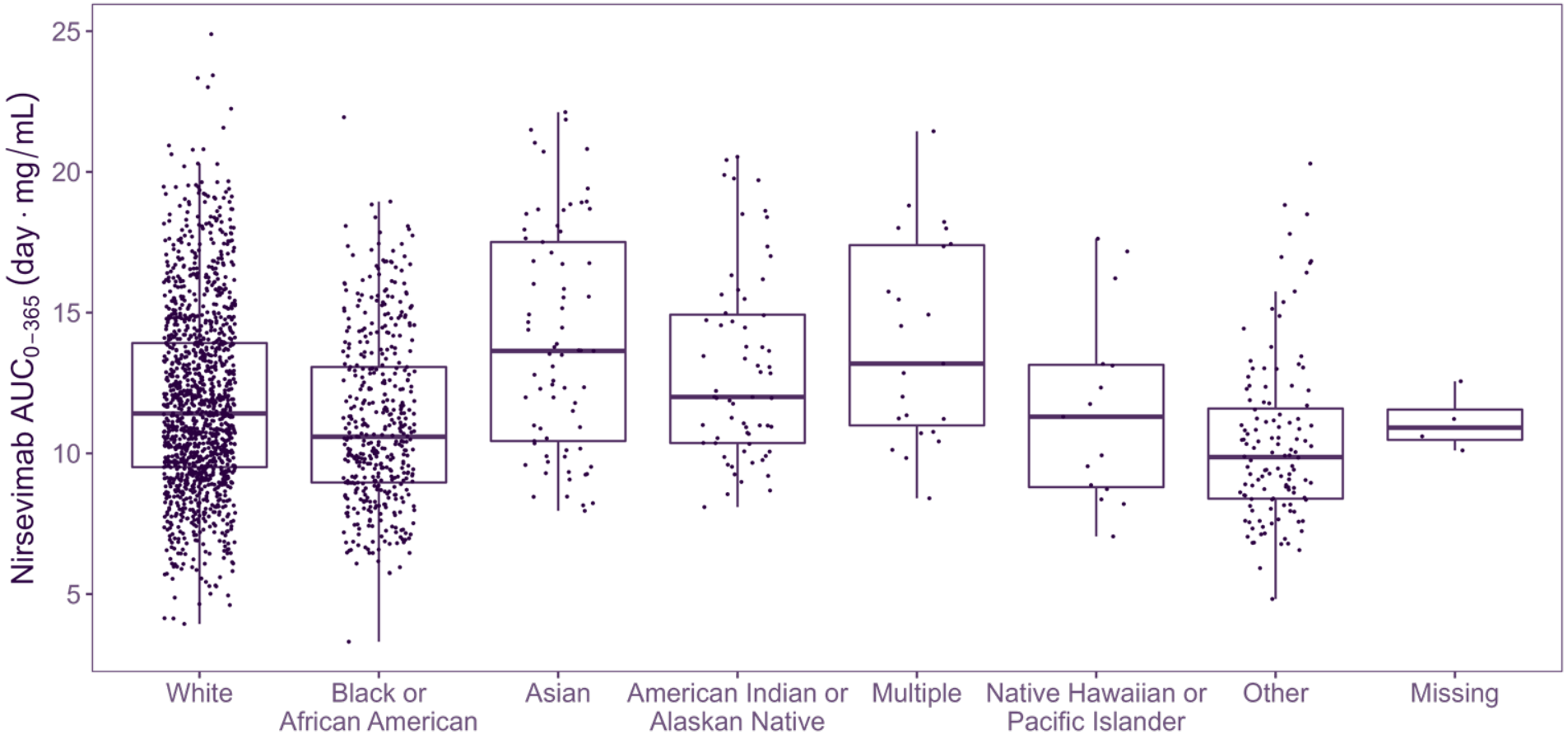


Trial 04 (All Subjects)	Placebo (N=1003)		Nirsevimab (N=2009)		Efficacy, % (95% CI)
	Number of Infants	Observed Events	Number of Infants	Observed Events	
Overall	**1003**	**54 (5.4)**	**2009**	**24 (1.2)**	**76.4** (62.3, 85.2)
Race					
White	541	33 (6.1)	1052	17 (1.6)	**73.5** (52.8, 85.6)
Black/African American	138	2 (1.4)	299	0 (0.0)	**100** (-60.3, NE)
Indigenous Populations	60	6 (10.0)	107	1 (0.9)	**90.7** (36.7, 99.6)
Asian	50	2 (4.0)	109	3 (2.8)	**31.2** (-478.6, 89.8)
Other	214	11 (5.1)	439	3 (0.7)	**86.7** (55.1, 97.0)
Ethnicity					
Hispanic or Latino	335	30 (9.0)	678	11 (1.6)	**81.9** (64.5, 91.3)
Not Hispanic or Latino	666	24 (3.6)	1327	13 (1.0)	**72.8** (46.9, 86.6)



Nirsevimab Serum Exposure Similar Across Race Groups

Trial 03 (<5 kg), Trial 04, Trial 05 (Season 1)



AUC_{0-365} = predicted area under the serum concentration-time curve from Days 0 to 365.

Demographics and Baseline Characteristics

Trial 08 Full Enrollment Cohort[a]

Inclusion Criterion	N=100
2(a) Diagnosed with combined immunodeficiency; antibody deficiency; or other immunodeficiency	33 (33.0)
2(b) Diagnosed with human immunodeficiency virus infection	8 (8.0)
2(c) History of organ or bone marrow transplantation	16 (16.0)
2(d) Was receiving immunosuppressive chemotherapy	20 (20.0)
2(e) Was receiving systemic high-dose corticosteroid therapy	29 (29.0)
2(f) Was receiving other immunosuppressive therapy	15 (15.0)

Characteristic	N=100
Age (months) at IP administration	
Median	12.25
Age group at IP administration (n [%])	
<12 months	46 (46.0)
≥12 months	54 (54.0)
Sex (n [%])	
Female	35 (35.0)
Race (n [%])	
Asian	28 (28.0)
American Indian or Alaskan Native	1 (1.0)
Black or African American	20 (20.0)
Native Hawaiian or Other Pacific Islander	0
White	45 (45.0)
Other	4 (4.0)
Multiple categories checked	2 (2.0)
Ethnicity (n [%])	
Hispanic or Latino	7 (7.0)

a Trial 08 second interim analysis conducted when all enrolled subjects were followed through Day 151. All safety data collected for these subjects at the time of the data cutoff are included in the interim analysis.