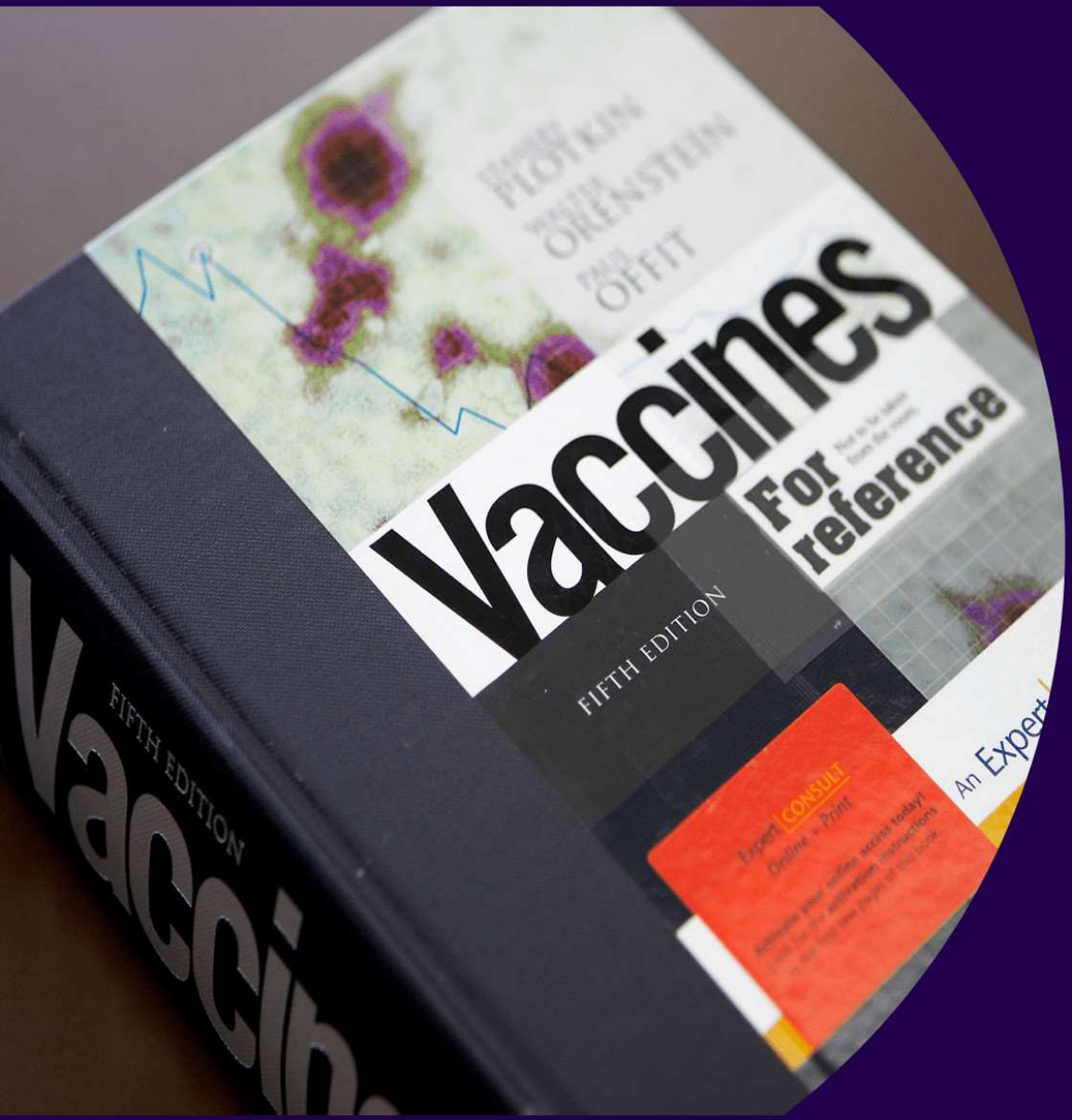

MSL-TITLE-004 - P - DISTRIB - EXP

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Sagar Shah, PharmD

Medical Science Liaison

Sanofi Vaccines

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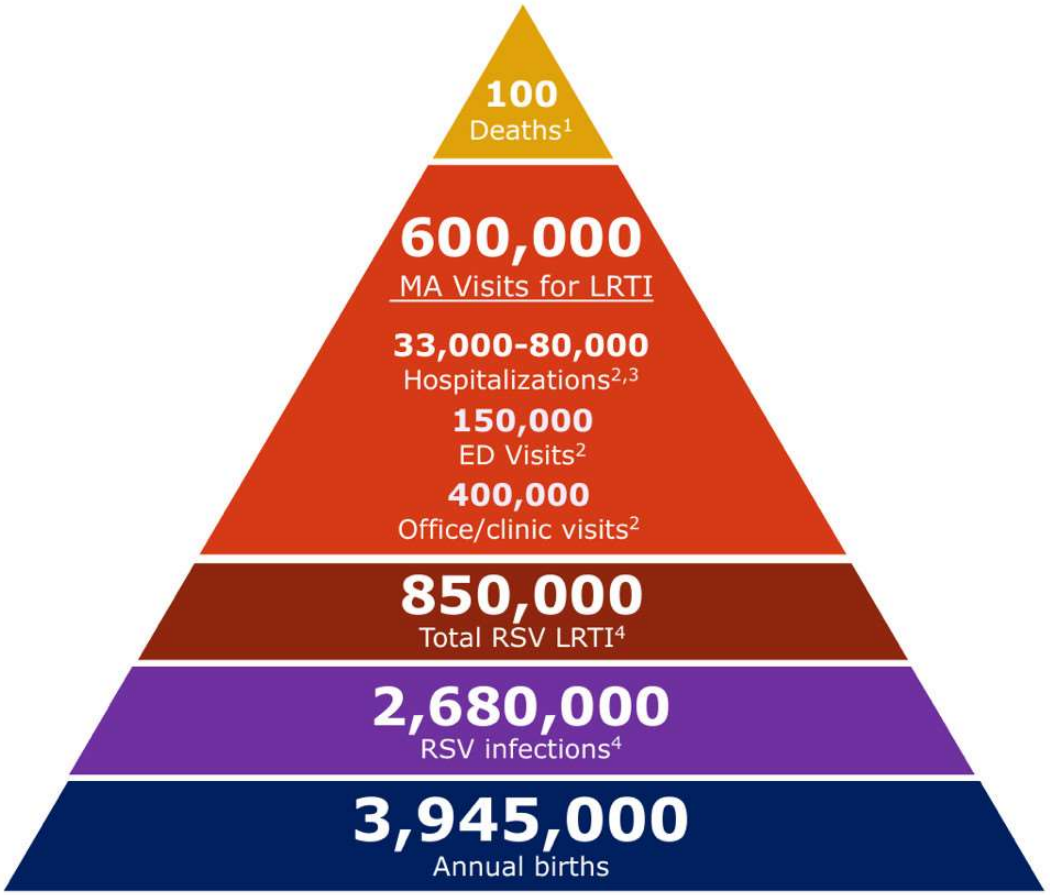
Nirsevimab is Designed to Protect All Infants from RSV Lower Respiratory Tract Infection

Annual RSV Burden in US Infants <12 Months of Age[a]



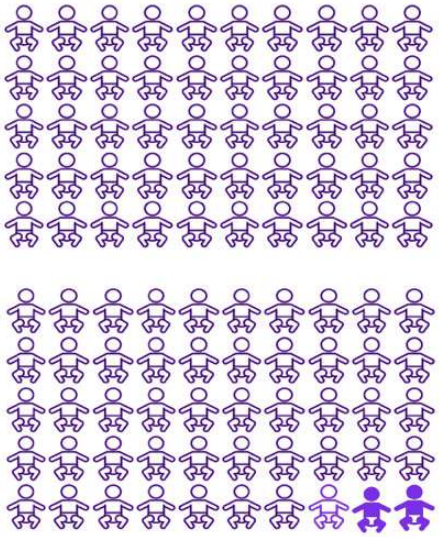
1 in 7
Infants develop LRTI requiring medical attention annually[2]

[a]Estimated typical RSV season based on references.[1-4]
ED, emergency department; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus.

Reference: 1. Hansen CL, et al. *JAMA Netw Open*. 2022;5(2):e220527. **2.** Rainisch G, et al. *Vaccine*. 2020;38(2):251-257. **3**. McLaughlin JM, et al. *J Infect Dis*. 2020;jiaa752. **4.** Glezen WP, et al. *Am J Dis Child*. 1986;140(6):543-546.

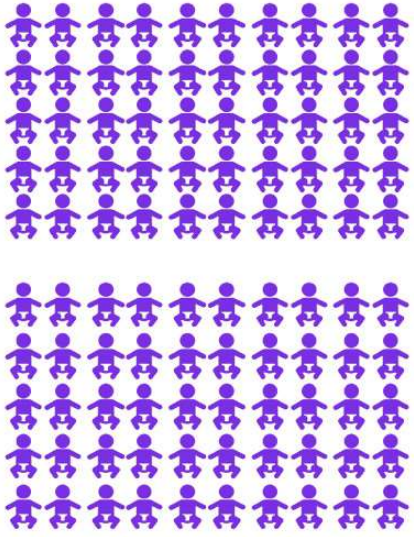
What is Needed: A Vaccine-like Strategy Designed to Protect All Infants from RSV Disease

Infants Previously Eligible



- High unit cost
- Challenging administration process
- Risk-based approach
- Low population benefit

Vaccine-like Strategy



- Lower unit cost
- Flexible administration timing and setting
- All infant approach
- High population benefit

After nearly 60 years of study, RSV disease is potentially preventable in all infants

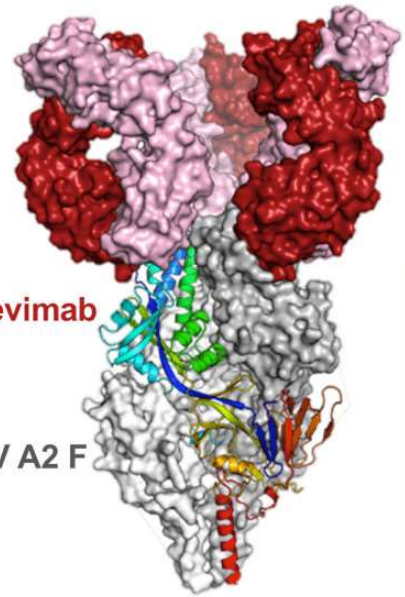
Reference: 1. Births: Final data for 2020. National Vital Statistics Reports; vol 70 no 17. Hyattsville, MD: National Center for Health Statistics. 2022.

MAT-US-2209673 – R – DISTRIB – EXP 12/9/2024

Nirsevimab for the Prevention of RSV LRTI

An Unmet Public Health Need

- >550,000 infants receive medical attention for RSV LRTI annually in US[1]
- Leading cause of infant hospitalization regardless of birth month[1,2]



- Highly potent recombinant[7,8] human IgG1 kappa MAb
- Conserved epitope on pre-fusion RSV F protein
- Prolonged serum half-life (YTE technology)

- Most medically attended cases, including severe cases, occur in healthy infants born at term[3-6]
- Infants on Medicaid at increased risk of serious disease

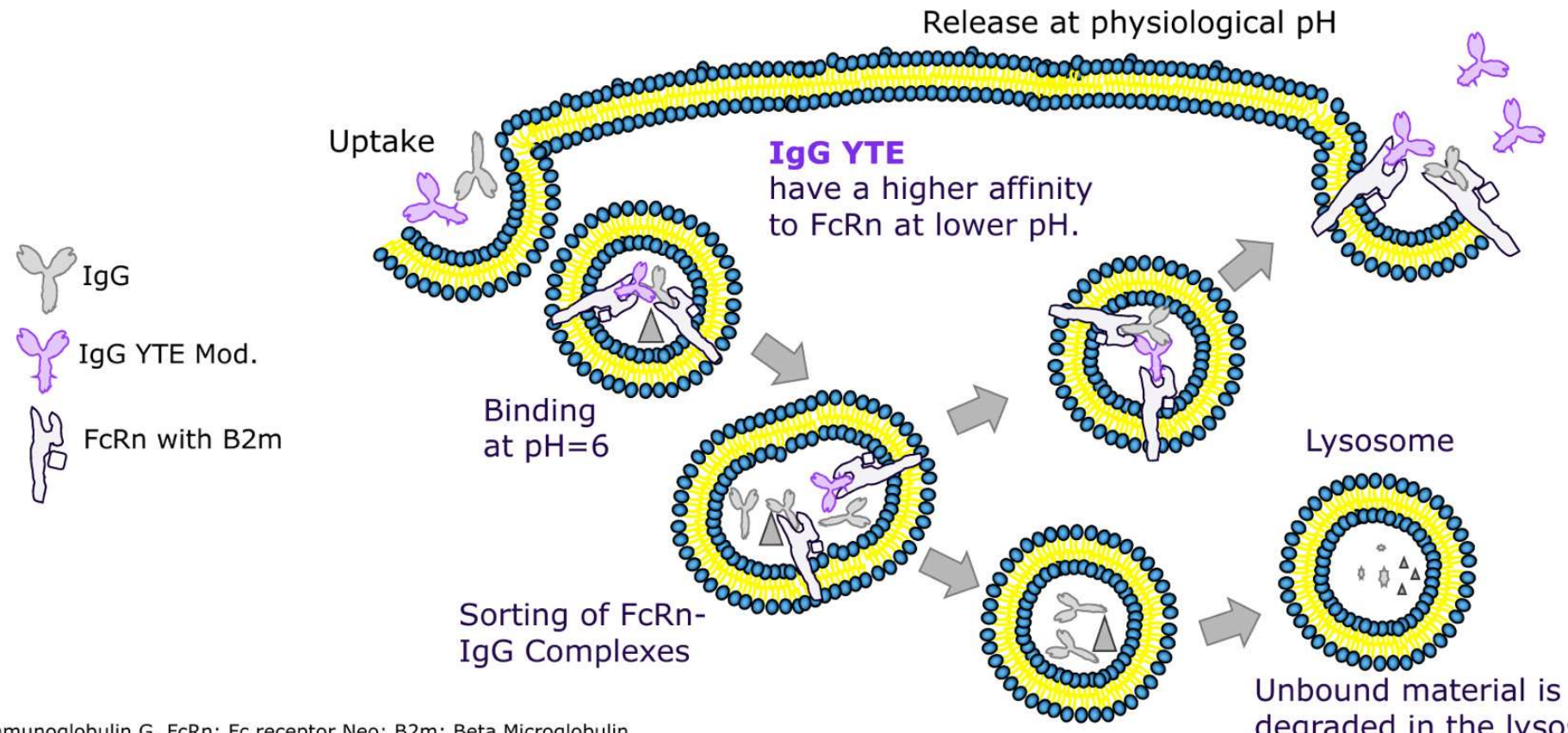
- Once per RSV season fixed IM dosing (due to increased affinity for pre-F *and* extended T½)
- Rapid protection
- Flexible administration relative to seasonality

IgG, immunoglobulin G; IM, intramuscular; LRT, lower respiratory tract; LRTI, lower respiratory tract infection; MAb, monoclonal antibody; RSV, respiratory syncytial virus.

References: **1.** Leader S, et al. *J Pediatr* 2003;143:S127-32. **2.** Suh M, et al. *J Infect Dis* 2022;226:S154-63. **3.** Murray, et al. *PLoS ONE* 2014;9:e89186. **4.** Hall, et al. *Pediatrics* 2013;132:e341-348. **5.** Rha, et al. *Pediatrics* 2020;146:e20193611. **6.** Arriola CS, et al. *Pediatrics* 2020;9(5):587-95. **7.** Domachowske JB, et al. *Pediatr Infect Dis J.* 2018;37(9):886-892. **8.** Zhu Q, et al. *Sci Transl Med.* 2017; 9(388).

MAT-US-2209673 – R – DISTRIB – EXP 12/9/2024

The FcRn Receptor Binding Allows Recycling of IgG Antibodies



IgG: Immunoglobulin G. FcRn: Fc receptor Neo; B2m: Beta Microglobulin

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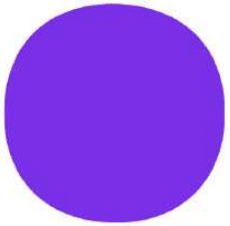
References: **1**. Zhu Q, et al. *Sci Transl Med* 2017;9:eaaj1928. **2.** Roopenian DC, et al. *Nat Rev Immunol* 2007;7:715–725.

Clinical trials



Nirsevimab: A Development Program Conducted Across All Infants

	Term and Preterm Healthy Infants 29+ wGA		Infants Eligible to Receive Palivizumab
	Similar Study Design Across Complementary Populations		
	PHASE 3 Pivotal[1] (N ~ 3000) MELODY STUDY	PHASE 2b POC/Pivotal[2] (N ~ 1500)	PHASE 2/3 Pivotal[3] (N = 925) MEDLEY STUDY
STUDY POPULATION	• **Infants ≥35 wGA** • Not eligible to receive palivizumab (AAP or other national/local guidelines)	• **Infants 29-<35 wGA** • Not eligible to receive palivizumab (AAP or other national/local guidelines)	• **Preterm Infants <35 wGA Infants with CLD/CHD** • Eligible to receive palivizumab (AAP or other national/local guidelines)
COMPARATOR	**2:1 Nirsevimab: Placebo**	**2:1 Nirsevimab: Placebo**	**2:1 Nirsevimab: Palivizumab**
	Efficacy, Safety and PK		**Safety and PK (Efficacy via PK)**

PK, pharmacokinetics.

References: **1**. Muller WJ, et al. N Engl J Med. 2023;10.1056/NEJMc2214773. **2**. Griffin MP, et al. N Engl J Med. 2020;383(5):415-425. **3.** Domachowske J, et al. N Engl J Med. 2022;386(9):892-894

Complementary and Similar Study Designs

Primary endpoint

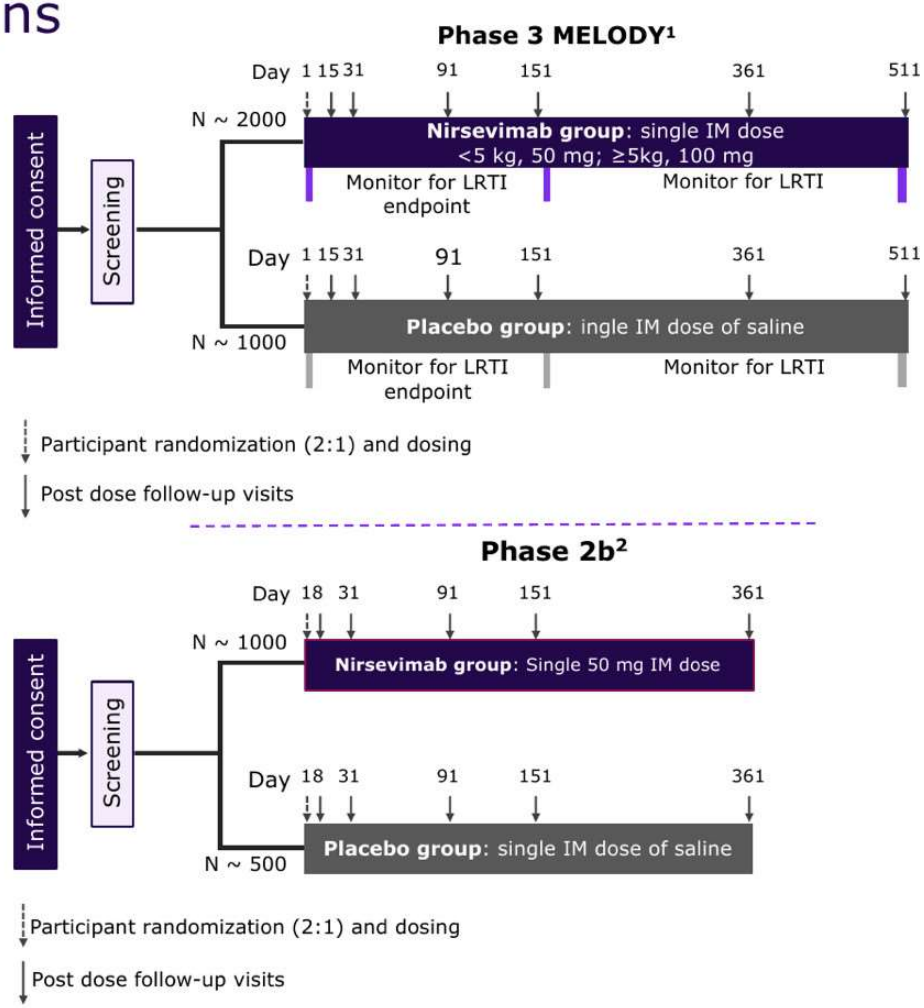
- Incidence of MA LRTI (inpatient and outpatient) caused by RT-PCR confirmed RSV through 150 days

Secondary and exploratory endpoints

- Incidence of hospitalization due to RT-PCR-confirmed RSV through 150 days
- Safety (evaluated through at least one year post-dose)
- Pharmacokinetics and anti-drug antibodies
- In MELODY, infants were followed for LRTI through 511 days

Treatment

- Infants were randomized 2:1 to receive a single IM dose of nirsevimab or placebo
  - MELODY: if <5 kg, 50 mg; if ≥5 kg, 100 mg
  - Phase 2b: all infants received 50 mg, regardless of weight



MA, medically attended; RT-PCR, reverse-transcriptase polymerase chain reaction.

References: **1**. Hammitt et al, N Engl J Med 2022;386:837-46 **2**. Griffin MP, et al. N Engl J Med. 2020;383(5):415-425.

Summary of Study Results (MELODY Full Study, Phase 2b, and MEDLEY)

	Term and Preterm Healthy Infants 29+ wGA		Infants Eligible to Receive Palivizumab
	PHASE 3[1] (N = 3012) MELODY STUDY	**PHASE 2b POC/Pivotal[2] (N = 1453)**	**PHASE 2/3 Pivotal[3] (N = 925)** MEDLEY STUDY
STUDY POPULATION	• **Infants ≥35 wGA** • Not eligible to receive palivizumab (AAP or other national/local guidelines)	• **Infants 29-<35 wGA** • Not eligible to receive palivizumab (AAP or other national/local guidelines)	• **615 Preterm <35 wGA** • **310 Infants CLD/CHD** • (Among both groups, 196 were <29 wGA)
COMPARATOR	**2:1 Nirsevimab: Placebo**	**2:1 Nirsevimab: Placebo**	**2:1 Nirsevimab:Palivizumab**
ENDPOINT RESULTS	• **All Medically-Attended LRTI**: Efficacy: 76.4% (62.3, 85.2) • **Hospitalization**: Efficacy: 76.8% (49.4, 89.4)	• **All Medically-Attended LRTI**: Efficacy: 70.1% (52.3, 81.2) <5kg-50mg: 86.2% (68.1, 94.0)[1] • **Hospitalization**: Efficacy: 78.4% (51.9, 90.3) <5kg-50mg: 86.5% (53.5, 96.1)[1]	• **Primary Endpoint**: Safety profile of nirsevimab was similar to palivizumab • Nirsevimab Efficacy Extrapolated via PK

PK, pharmacokinetics. ACIP, Advisory Committee on Immunization Practices.

References: **1.** Muller WJ, et al. N Engl J Med. 2023;10.1056/NEJMc2214773. **2.** Griffin MP, et al. *N Engl J Med.* 2020;383(5):415-425. **3.** Domachowske J, et al. *N Engl J Med* 2022;386(9):892-894.

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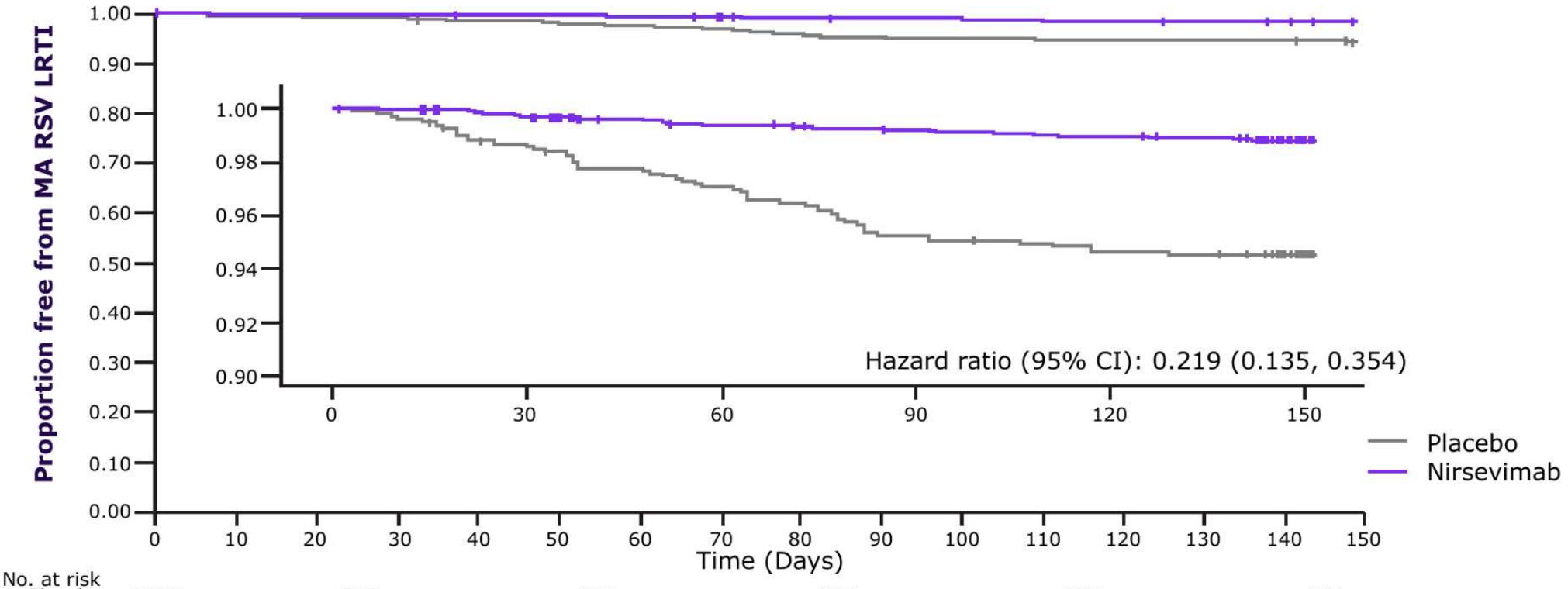
MELODY

Time to First MA RSV LRTI Through 150 Days (ITT Population*)



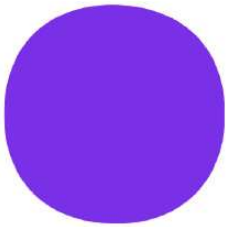
No. at risk						
Placebo	1003	979	962	944	937	888
Nirsevimab	2009	1990	1977	1970	1965	1871

*All infants who underwent randomization.

The p-value is from a stratified log-rank test with stratification factors (age at randomization, hemisphere, and cohort) as the strata. The hazard ratio is from a stratified Cox proportional hazard model with stratification factors (age at randomization, hemisphere, and cohort) as the strata. Tick marks indicate censored data.

References: **1.** Muller WJ, et al. N Engl J Med. 2023;10.1056/NEJMc2214773 (Figure S3).

Safety



Safety of Nirsevimab

Adverse Reactions With Incidence Higher than Placebo (Safety Population*)

Adverse Reaction	Nirsevimab N=2,570 %	Placebo N=1,284 %
Rash[ł] (occurring within 14 days post-dose)	0.9	0.6
Injection site reaction[¥] (occurring within 7 days post-dose)	0.3	0

* The Safety Population includes all subjects who received the recommended dose of nirsevimab in Phase 2b and Phase 3 MELODY All Subjects studies.
ł Rash was defined by the following grouped preferred terms: rash, rash macular, rash maculo-papular, rash papular.
¥ Injection site reaction was defined by the following grouped preferred terms: injection site reaction, injection site pain, injection site induration, injection site edema, injection site swelling.

Reference: 1. Beyfortus (nirsevimab). US prescribing information. Sanofi Pasteur Inc., AstraZeneca Pharmaceuticals LP; July 2023.

No Safety Signals Were Identified Through 360 Days Post-dose

Variable, n (%)	Placebo (N=996)	Nirsevimab (N=1998)
≥1 AE	815 (81.8)	1673 (83.7)
≥1 treatment-related AE	15 (1.5)	25 (1.3)
≤1 day post-dose	11 (1.1)	38 (1.9)
≤3 days post-dose	52 (5.2)	118 (5.9)
≤7 days post-dose	130 (13.1)	252 (12.6)
≥1 AE of Grade ≥3 severity	38 (3.8)	61 (3.1)
≥1 SAE	74 (7.4)	125 (6.3)
≥1 treatment-related SAE	1 (0.1)	0 (0.0)
Deaths	0 (0.0)	4 (0.2)
≥1 COVID-19-related AE	44 (4.4)	72 (3.6)
≥1 confirmed[a]	41 (4.1)	62 (3.1)
≥1 suspected[b]	3 (0.3)	10 (0.5)

- Safety events were balanced between treatment groups
  - AEs related to treatment were reported in 1.3% nirsevimab and 1.5% placebo recipients
- Deaths were considered unrelated to treatment:
  - 1 suspected undiagnosed metabolic disease
  - 2 acute gastroenteritis
  - 1 skull fracture due to automobile accident

Safety analysis includes all participants who were randomized and received any treatment. [a]Included positive asymptomatic or symptomatic cases; [b]Included those for which signs and symptoms were judged by the investigator to be highly suggestive of COVID-19 but for which results from a confirmatory diagnostic test were unavailable or were negative. **AE,** adverse event; **SAE,** serious adverse event.

References: **1.** Muller WJ, et al. N Engl J Med. 2023;10.1056/NEJMc2214773 (Table S6).

Treatment-Emergent Adverse Events

Through D360, post first dose, (As-Treated-Population)

Variable, n (%)[1]	Preterm (N=612)		CHD/CLD (N=306)	
	Palivizumab (N=206)	Nirsevimab (N=406)	Palivizumab (N=98)	Nirsevimab (N=208)
≥1 AE	134 (65.0)	268 (66.0)	72 (73.5)	148 (71.2)
≥1 AE of Grade ≥3 severity†	7 (3.4)	14 (3.4)	13 (13.3)	30 (14.4)
≥1 treatment-related AE	4 (1.9)	6 (1.5)	2 (2.0)	4 (1.9)
≥1 treatment-related AE Grade ≥3 severity†	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥1 SAE	11 (5.3)	28 (6.9)	20 (20.4)	40 (19.2)
≥1 SAE and/or Grade ≥3 severity AE†	11 (5.3)	28 (6.9)	21 (21.4)	45 (21.6)
≥1 treatment-related SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any AE with outcome death (Grade 5 severity)†	0 (0.0)	2 (0.5)	1 (1.0)	3 (1.4)
≥1 AE of special interest‡	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.5)
≥1 COVID-19-related AE	1 (0.5)	8 (2.0)	1 (1.0)	2 (1.0)

- Safety events were balanced between treatment groups
- Of the 5 deaths in the nirsevimab arm:
  - 2 in the preterm cohort
    - Bronchiolitis
    - COVID-19 pneumonia
  - 3 in the CHD/CLD cohort
    - cardiac failure congestive
    - cardiogenic shock
    - Pneumonia
- 2 AEs of special interest (nirsevimab arm) were reported:
  - maculopapular rash following a placebo dose in a preterm infant
  - Heparin-induced thrombocytopenia (CHD/CLD cohort), unrelated to treatment

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SAE criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event. †Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal. ‡hypersensitivity, immune complex disease, and thrombocytopenia. §Patient mistakenly received a second dose of nirsevimab on Day 31 (Season 1). SAE, serious adverse event

1.Domachowske JB, et al. N Engl J Med 2022; 386:892-894

Nirsevimab Indications and Important Safety Information

INDICATION

Nirsevimab is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease

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

IMPORTANT SAFETY INFORMATION

Contraindication

Nirsevimab is contraindicated in infants and children with a history of serious hypersensitivity reactions, including anaphylaxis, to nirsevimab or its excipients.

Warnings and Precautions

- **Hypersensitivity Including Anaphylaxis:** Serious hypersensitivity reactions, including anaphylaxis, have been observed with other human IgG1 monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, initiate appropriate medications and/or supportive therapy.
- **Use in Individuals with Clinically Significant Bleeding Disorders:** As with other IM injections, nirsevimab should be given with caution to infants and children with thrombocytopenia, any coagulation disorder, or to individuals on anticoagulation therapy.

The most common adverse reactions with nirsevimab were rash (0.9%) and injection site reactions (0.3%).

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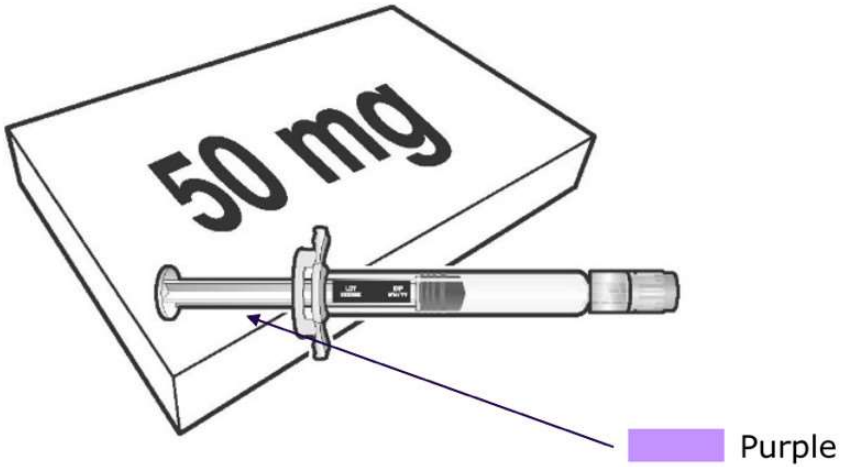
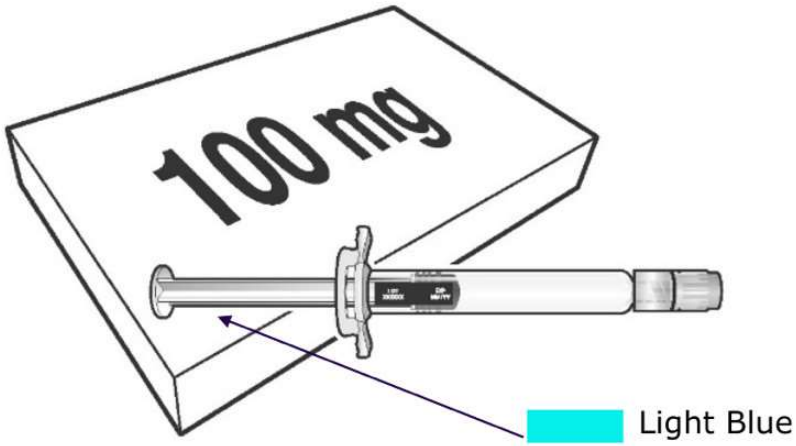
Reference: 1. Beyfortus (nirsevimab). US prescribing information. Sanofi Pasteur Inc., AstraZeneca Pharmaceuticals LP; July 2023.

How Supplied, Storage, Handling, and Coadministration

Nirsevimab 50 mg (50 mg/0.5 mL) pre-filled syringe with a purple plunger rod and box.	Nirsevimab 100 mg (100 mg/mL) pre-filled syringe with a light blue plunger rod and box.
	

- Stored in the refrigerator at 2°-8° C
- Must be used within 8 hours of removal from refrigerator or discarded
- May be administered concomitantly with childhood vaccines

Reference: 1. Beyfortus (nirsevimab). US prescribing information. Sanofi Pasteur Inc., AstraZeneca Pharmaceuticals LP; July 2023.

ACIP Recommendations Published in MMWR

First RSV season[1]

One dose of nirsevimab for all infants aged <8 months born during or entering their first RSV season

- 50 mg for infants weighing <5 kg [<11 lb]
- 100 mg for infants weighing ≥5 kg [≥11 lb]

Second RSV season[1]

One dose of nirsevimab for infants and children aged 8–19 months who are at increased risk for severe RSV disease and entering their second RSV season

- 200 mg, administered as two 100 mg injections given at the same visit

American Indian or Alaska Native children are considered at increased risk in their second season.

The recommendations for nirsevimab apply to infants and children recommended to receive palivizumab by AAP.

Nirsevimab added to the Vaccines for Children program (VFC)[2]

ACIP, Advisory Committee on Immunization Practices

References: 1. Jones JM, Fleming-Dutra KE, Prill MM, et al. Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72(34):920–925. DOI: http://dx.doi.org/10.15585/mmwr.mm7234a4. **2.** CDC press release. CDC Recommends a Powerful New Tool to Protect Infants from the Leading Cause of Hospitalization. Available at https://www.cdc.gov/media/releases/2023/p-0803-new-tool-prevent-infant-hospitalization-.html. Accessed August 31, 2023.

AAP Recommendations Align with those of ACIP

First RSV Season

Nirsevimab is recommended for all infants younger than 8 months born during or entering their first RSV season, including those recommended by AAP to receive palivizumab

Second RSV Season

Nirsevimab is recommended for infants and children aged 8 through 19 months who are at increased risk of severe RSV disease and entering their second RSV season, including those recommended by the AAP to receive palivizumab

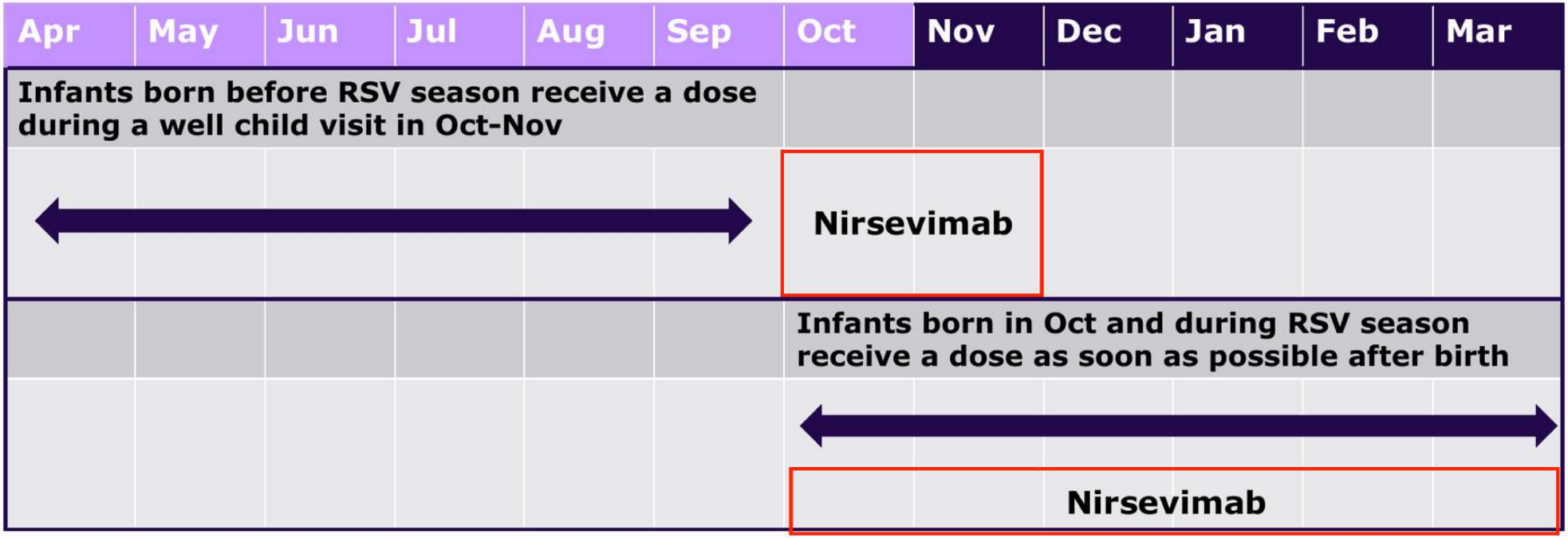
The AAP agrees to add American Indian and Alaska Native children in their second season recommendations for nirsevimab.

AAP, American Academy of Pediatrics

Reference: 1. AAP Publications: Red Book Online. "ACIP and AAP Recommendations for Nirsevimab" published August 15, 2023. Available at https://publications.aap.org/redbook/resources/25379/ACIP-and-AAP-Recommendations-for-Nirsevimab?searchresult=1?autologincheck=redirected. Accessed August 31, 2023.

Implementation of Nirsevimab for Infants Entering or Born During First RSV Season

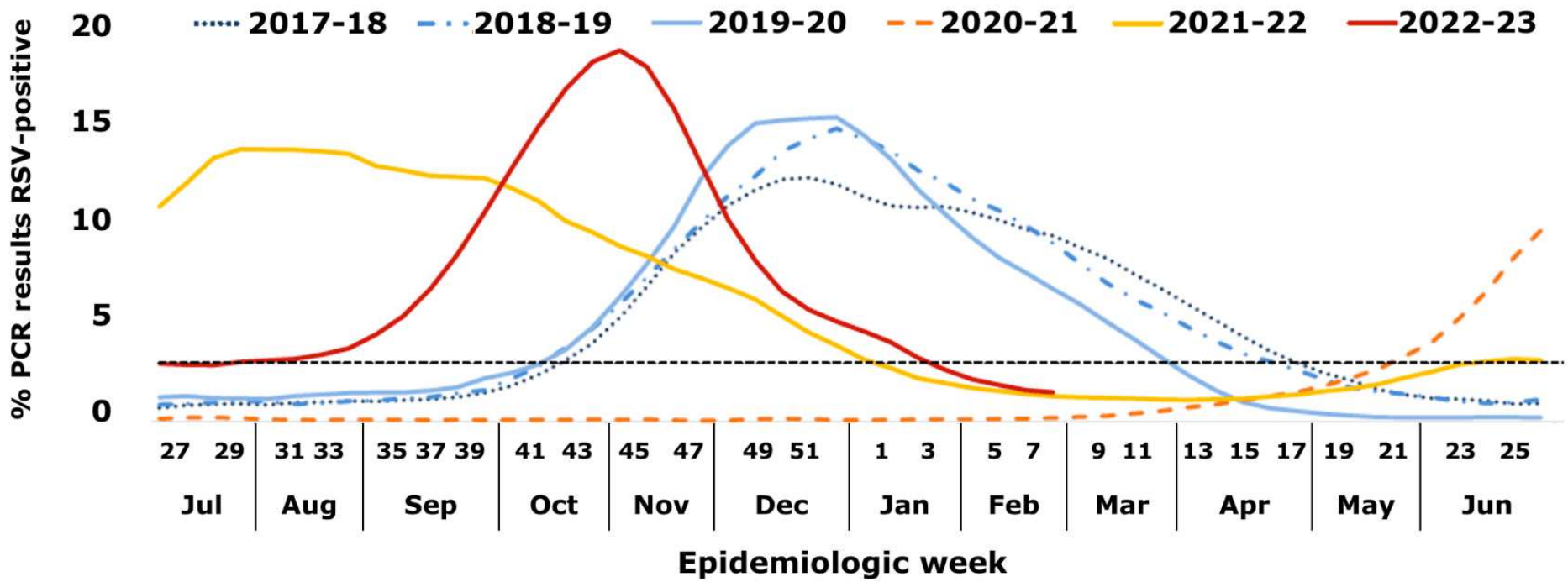
Typical RSV Season*



*Providers in tropical climates (S. Florida, Hawaii, etc.) and Alaska, which may have more unpredictable or longer RSV seasons, should consult local guidance on the timing of nirsevimab administration.

Reference: 1. Jones JM, Fleming-Dutra KE, Prill MM, et al. Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72(34):920–925. DOI: http://dx.doi.org/10.15585/mmwr.mm7234a4.

Changes in Seasonality of RSV Transmission Following SARS-CoV2 Introduction– NREVSS, 2017-2023



*3-week centered moving averages of percentage of RSV-positive PCR results nationwide. The black dotted link represents the threshold for a seasonal epidemic (3% RSV-positive laboratory PCR results.)

PCR, polymerase chain; RSV, respiratory syncytial virus

Reference: 1. Hamid S, Winn A, Parikh R, et al. Seasonality of Respiratory Syncytial Virus — United States, 2017–2023. MMWR Morb Mortal Wkly Rep 2023;72:355–361. DOI: http://dx.doi.org/10.15585/mmwr.mm7214a1

Scan QR code to access nirsevimab US prescribing information

Reference: 1. Beyfortus (nirsevimab). US prescribing information. Sanofi Pasteur Inc., AstraZeneca Pharmaceuticals LP; July 2023.

Thank you!

For more information on this topic or other vaccine-preventable illnesses, please contact

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