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Nirsevimab For The Prevention of RSV Disease In All Infants

June 22, 2022

AstraZeneca and Sanofi

About our Nirsevimab Program

- Nirsevimab is being developed and commercialized through a joint agreement between AstraZeneca and Sanofi.
- AstraZeneca is responsible for regulatory, clinical, manufacturing and development activities; Sanofi is responsible for commercialization activities.

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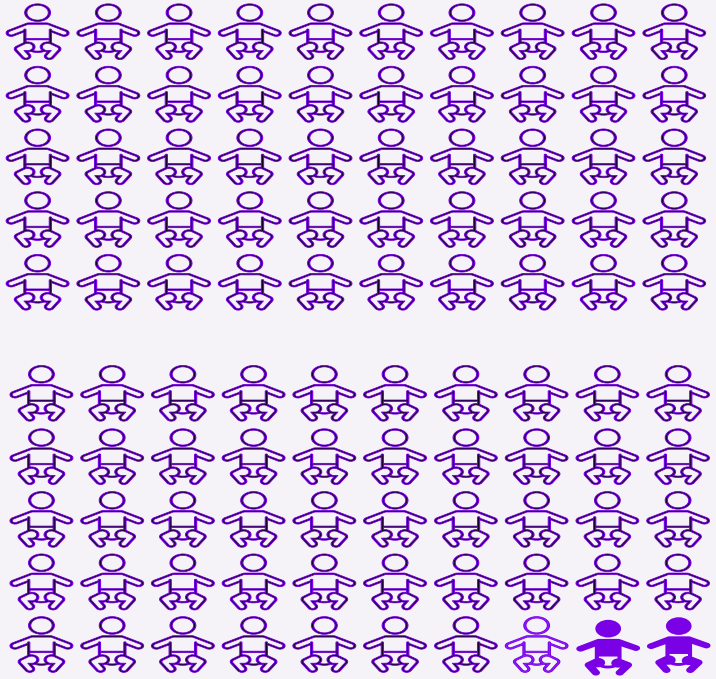
Nearly All Infants Are Unprotected from RSV Disease

Today's Infants Eligible



- Risk-based approach
- Monthly dosing throughout season
- Low population benefit

In the US, **only 2%** of infants are currently eligible for protection against RSV[1]

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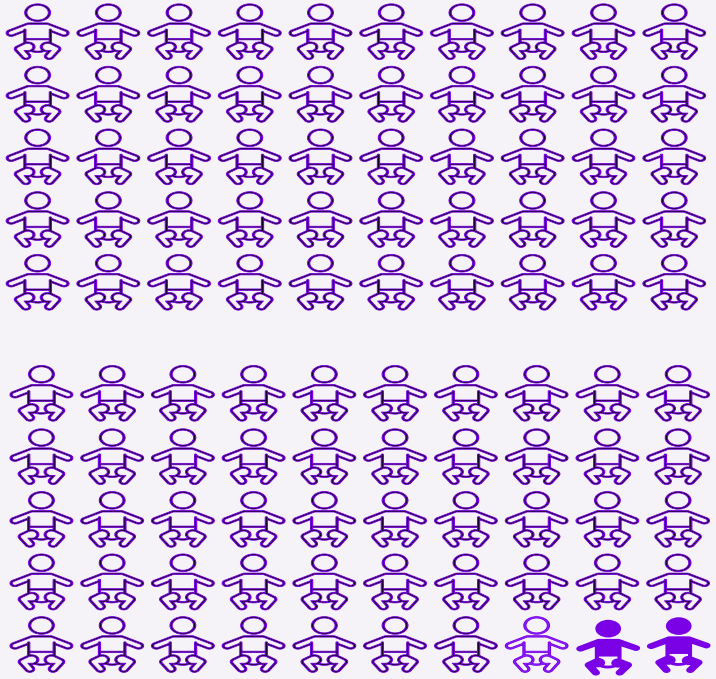
1. Births: Final data for 2020. National Vital Statistics Reports; vol 70 no 17. Hyattsville, MD: National Center for Health Statistics. 2022.

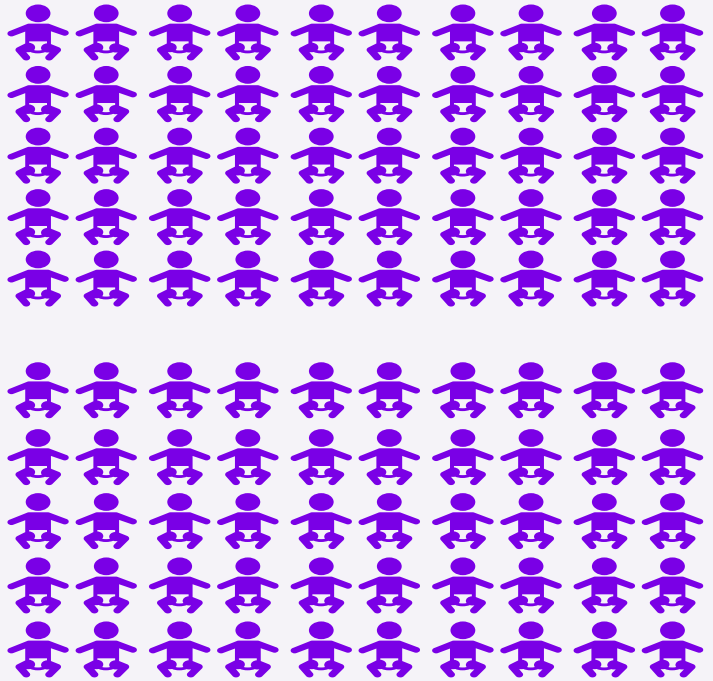
Nirsevimab is a Vaccine-like Strategy for All Infant Protection from RSV Disease

Today's Infants Eligible



- Risk-based approach
- Monthly dosing throughout season
- Low population benefit

Infants Eligible with Nirsevimab



- All infant approach
- Single dose for the season
- High population benefit

After 60 Years Of Study, We Are On The Verge
Of Making RSV Preventable For All Infants

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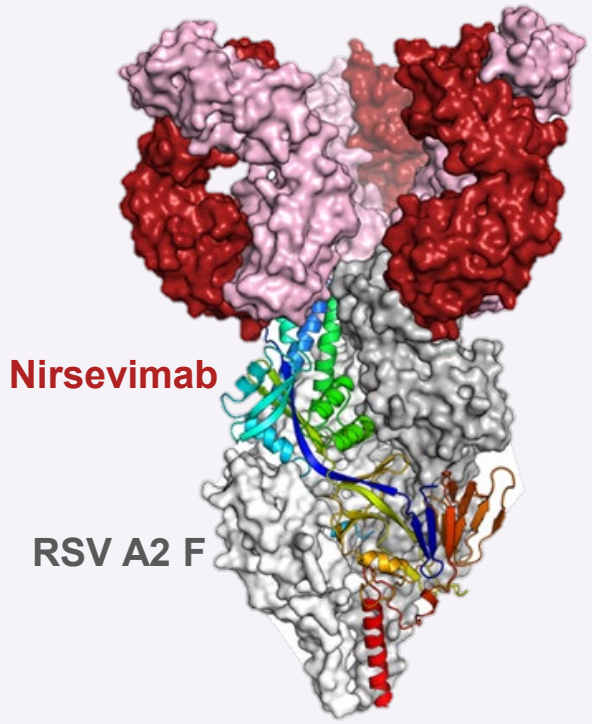
Nirsevimab for the Prevention of RSV LRTI

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]

- Most medically attended cases, including severe cases, occur in healthy infants born at term[3-8]
- Infants on Medicaid at increased risk of serious disease



- Highly potent recombinant[1,9] human IgG1 kappa MAb
- Conserved epitope on prefusion RSV F protein
- Prolonged serum half-life (YTE technology)

- Once per RSV season fixed IM dosing
- 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.

1. Rainisch G, et al. Vaccine. 2020;38(2):251-257 **2.** Zhu Q, et al. Sci Transl Med. 2017; 9(388) **3.**Sommer et al, Open Microbiol J 2011;5:144. **4.** Murray et al. PLoS ONE 2014;9:e89186, **5.** Bont et al, Infect Dis Ther 2016;5:217-298, **6.** Hall et al, Pediatrics 2013;132:e341-348, **7.** Rha et al, Pediatrics 2020;146:e20193611 **8.** Arriola CS et al, Pediatrics 2020;9(5):587-95 **9.** Domachowske JB et al, Pediatr Infect Dis J. 2018;37(9):886-892

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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] MELODY STUDY	PHASE 2b POC/Pivotal[2]	PHASE 2/3 Pivotal[3] 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
COMPARATOR	**2:1 Nirsevimab: Placebo**	**2:1 Nirsevimab: Placebo**	**2:1 Nirsevimab: Palivizumab**
	Efficacy, Safety and PK		**Safety and PK**

ADA, anti-drug antibodies; MA LRTI, medically attended lower respiratory tract infection; PK, pharmacokinetics.

1 Hammitt LL,et al N Engl J Med. 2022 Mar 3;386(9):837-846.. **2.** Griffin MP, et al. N Engl J Med. 2020 Jul 30;383(5):415-425. **3.** Domachowske Joseph et al. N Engl J Med 2022 Mar 386:9, 892-894.

Study Designs

Primary endpoint

- Incidence of MA LRTI (inpatient and outpatient) caused by RT-PCR confirmed RSV over 5 months

Secondary and exploratory endpoints

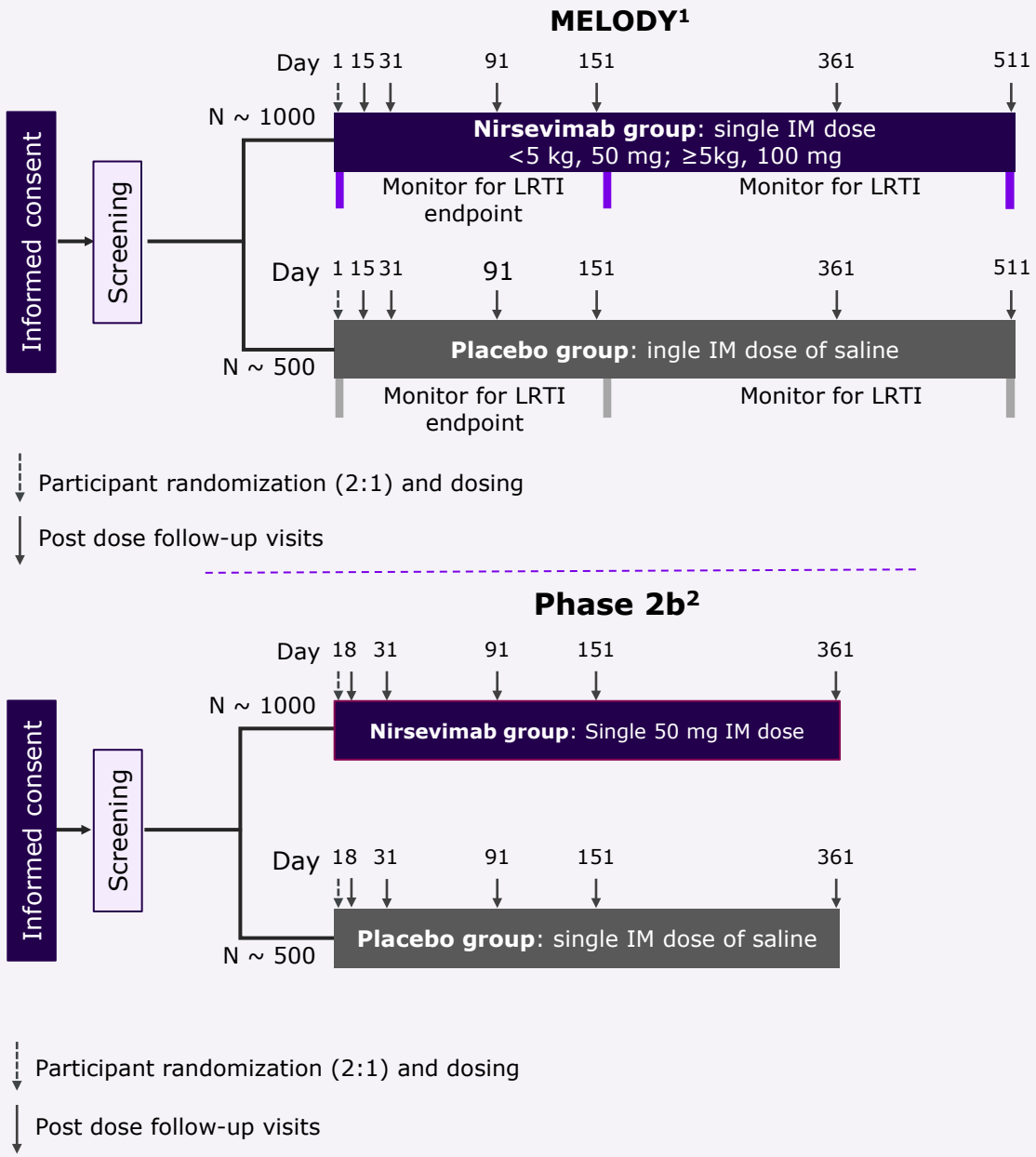
- Incidence of hospitalization due to RT-PCR-confirmed RSV over 5 months
- Safety (evaluated through one-year post-dose)
- Pharmacokinetics and anti-drug antibodies

Treatment

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

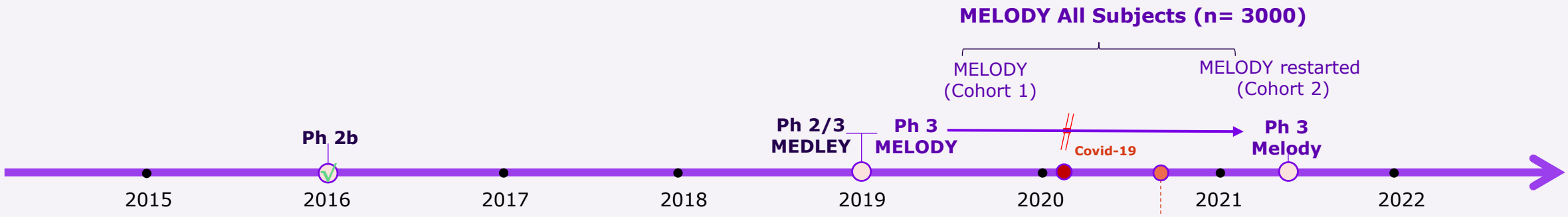
Pooled analysis of efficacy over 5 months (Day 151)

- Included:
  - All infants in MELODY
  - Phase 2b recipients of the proposed dose (all infants <5 kg who received 50 mg)



MA, medically attended; RT-PCR, reverse-transcriptase polymerase chain reaction. **1.** Hammitt et al, *N Engl J Med* 2022;386:837-46; **2.** Griffin et al, *N Engl J Med* 2020;383:415

Impact of RSV Circulation Changes due to COVID-19 on MELODY



FDA consultation for Melody

Due to Covid-19, no RSV cases were observed. Therefore, a joint decision with health authorities was taken to analyze the primary endpoint (cohort 1). Melody restarted to further characterize nirsevimab safety in this population (cohort 2).

Study enrollment and location

- Enrollment began 23 July 2019
- 150 sites (20 countries) in the Northern Hemisphere enrolled in 2019 1027 subjects
- 10 sites (in South Africa) in the Southern Hemisphere enrolled in 2020 462 subjects

Situation and mitigation

- Challenging environment to execute study during the pandemic led to pause of enrollment
- The typical Southern Hemisphere RSV season did not occur due to Covid 19 restrictions
- After consultation with regulatory authorities, decision taken to analyse the primary endpoint with ≈1500 enrolled (cohort 1).
- Study enrolment has been completed and the evaluation of safety and efficacy is ongoing (cohort 2).

1. Hammitt LL et al. N Engl J Med 2022;386:837-46. √ **Study completed**

Nirsevimab: A Development Program Across All Infants

	Term and Preterm Healthy Infants 29+ wGA		Infants Eligible to Receive Palivizumab
	PHASE 3 Pivotal[1] MELODY STUDY	**PHASE 2b POC/Pivotal[2]**	**PHASE 2/3 Pivotal[3]** MEDLEY STUDY
STUDY POPULATION	• Cohort 1 = 1490 Infants + Cohort 2 ≈ 1500 **≥35 wGA** • Not eligible to receive palivizumab (AAP or other national/local guidelines)	• 1453 Infants **29-<35 wGA** • Not eligible to receive palivizumab (AAP or other national/local guidelines)	• 615 preterm infants **<35 wGA** • 310 infants with CLD/CHD • (196 from both <29 wGA)
COMPARATOR	**2:1 Nirsevimab:Placebo**	**2:1 Nirsevimab:Placebo**	**2:1 Nirsevimab:Palivizumab**
ENDPOINT RESULTS	• **Primary Endpoint** (cohort 1): Efficacy: 74.5% (49.6, 87.1) • **Secondary Endpoint** (cohort 1): Efficacy: 62.1% (-8.6, 86.8)	• **Primary Endpoint**: Efficacy: 70.1% (52.3, 81.2) <5kg-50mg: 86.2% (68.1, 94.0) • **Secondary Endpoint**: Efficacy: 78.4% (51.9, 90.3) <5kg-50mg: 86.5% (53.5, 96.1)	• **Primary Endpoint**: Safety profile of nirsevimab was similar to palivizumab • Nirsevimab Efficacy Extrapolated via PK

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ADA, anti-drug antibodies; MA LRTI, medically attended lower respiratory tract infection; PK, pharmacokinetics.

1 Hammitt LL,et al N Engl J Med. 2022 Mar 3;386(9):837-846.. **2.** Griffin MP, et al. N Engl J Med. 2020 Jul 30;383(5):415-425. **3.** Domachowske Joseph et al. N Engl J Med 2022 Mar 386:9, 892-894.

Phase 2b and MELODY: Two Similar Randomized Placebo Controlled Trials in Complementary Populations[1,2]

Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

M. Pamela Griffin, M.D., Yuan Yuan, Ph.D., Therese Takas, B.S., Joseph B. Domachowske, M.D.,Shabir A. Madhi, M.B., B.Ch., Ph.D., Paolo Manzoni, M.D., Ph.D., Eric A.F. Simões, M.D., Mark T. Esser, Ph.D., Anis A. Khan, Ph.D., Filip Dubovsky, M.D., Tonya Villafana, Ph.D., and John P. DeVincenzo, M.D., for the Nirsevimab Study Group*

N Engl J Med 2020;383:415-25

Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

Laura L. Hammitt, M.D., Ron Dagan, M.D., Yuan Yuan, Ph.D., Manuel Baca Cots, M.D., Miroslava Bosheva, M.D., Shabir A. Madhi, Ph.D., William J. Muller, Ph.D., Heather J. Zar, Ph.D., Dennis Brooks, M.D., Amy Grenham, M.Sc., Ulrika Wählby Hamrén, Ph.D., Vaishali S. Mankad, M.D., Pin Ren, Ph.D., Therese Takas, B.Sc., Michael E. Abram, Ph.D., Amanda Leach, M.R.C.P.C.H., M. Pamela Griffin, M.D., and Tonya Villafana, Ph.D., for the MELODY Study Group*

N Engl J Med 2022;386:837-46

Rationale for pooling of data across the two studies:

- Infant populations were homogenous with respect to efficacy of nirsevimab.
- Similar study design, including but not limited to enrolment criteria, methods for surveillance, case assessment and case definitions
- Nirsevimab blocks entry of RSV at a cellular level
  - Same mechanism of action, regardless of gestational age at birth

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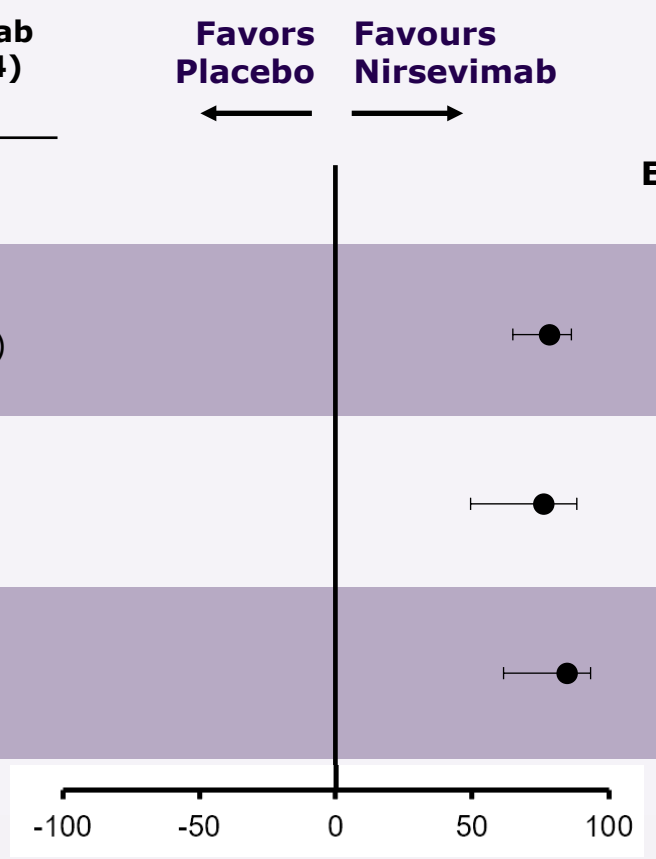
1. Griffin et al, *N Engl J Med* 2020;383:415; **2.** Hammitt et al, *N Engl J Med* 2022;386:837-46

Consistent efficacy across MA RSV LRTI of different severities

	Placebo (N=786) n (%)	Nirsevimab (N=1564) n (%)	Efficacy (%)	95% CI†	p-value†
Medically attended RSV LRTI‡	51 (6.5)	19 (1.2)	79.5	65.9, 87.7	<0.0001
Medically attended RSV LRTI with hospitalization‡	21 (2.7)	9 (0.6)	77.3	50.3, 89.7	0.0002
Medically attended RSV LRTI (very severe)#	18 (2.3)	5 (0.3)	86.0	62.5, 94.8	<0.0001

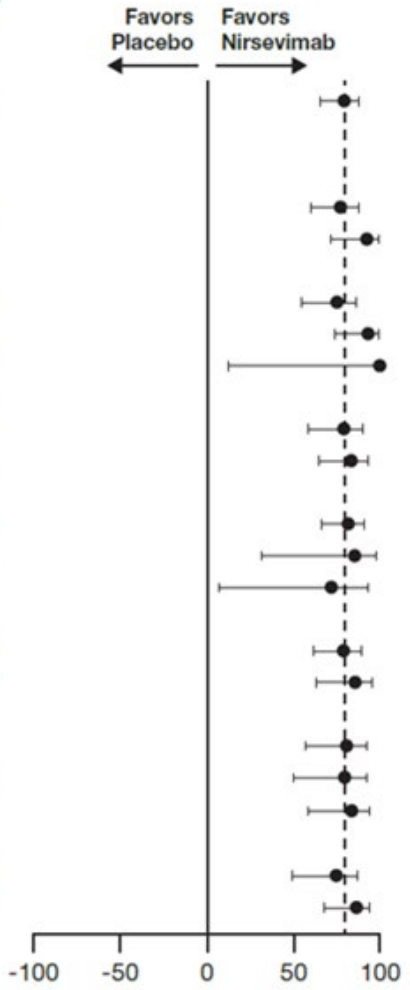


†Estimated based on Poisson regression with robust variance (including study as a covariate); not corrected for multiplicity. ‡Included imputation of missing data. #Defined as those cases requiring supplemental oxygen or intravenous fluids (exploratory endpoint). CI, confidence interval; ITT, intent-to-treat

1. Eric AF Simões1, et al (9-12th of May 2022) [Conference Presentation] ESPID 2022 Meeting, Athens, Greece & Online. https://espidmeeting.org/

Consistent Efficacy Against MA RSV LRTI Across Subgroups

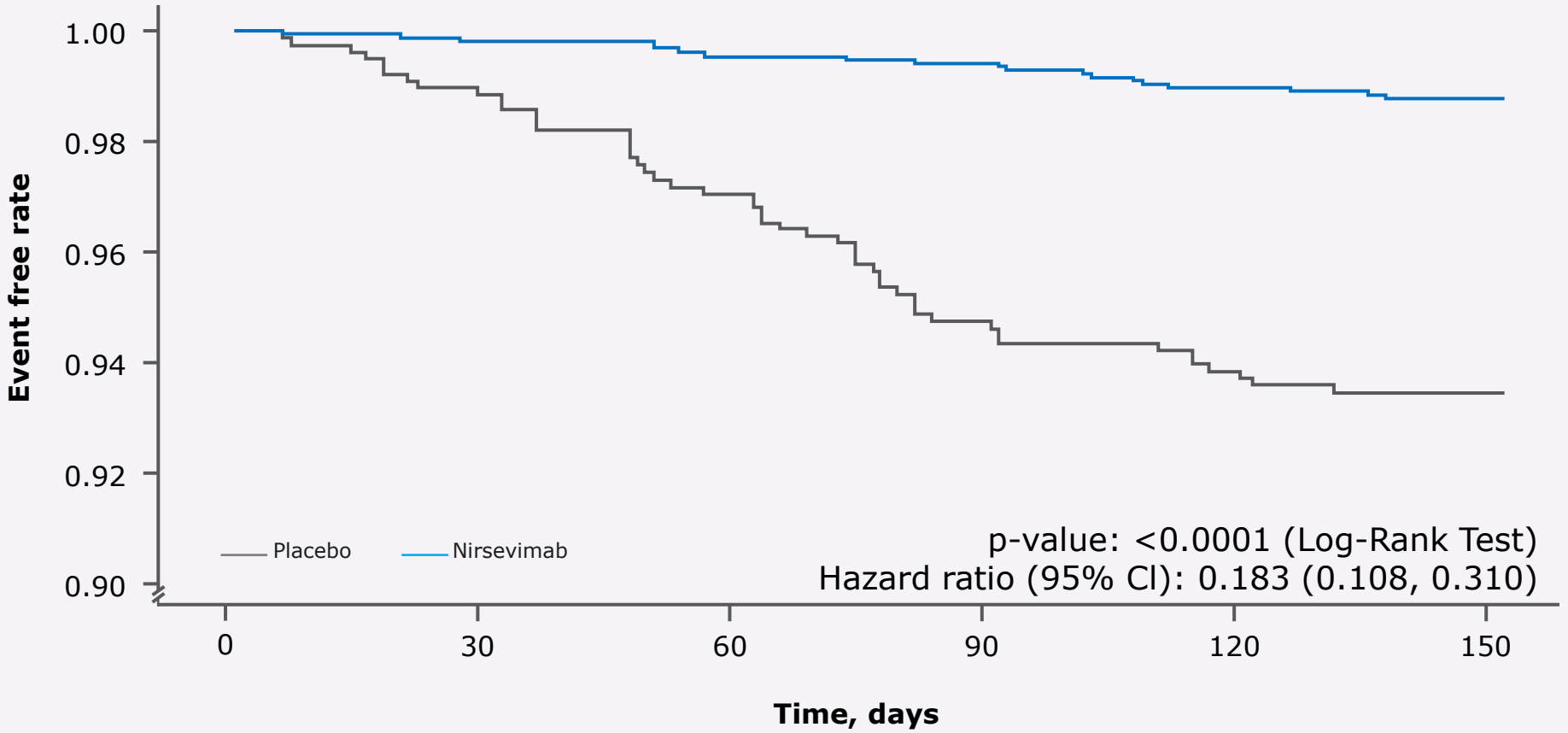
	Interaction p-value	Placebo (N = 786) Number of Infants	Placebo (N = 786) Observed Events	Nirsevimab (N = 1564) Number of Infants	Nirsevimab (N = 1564) Observed Events	RRR (95% CI)
Overall	N/A	786	51 (6.5)	1564	19 (1.2)	79.5 (65.9, 87.7)
Subgroup						
Hemisphere	0.0998					
Northern Hemisphere		536	37 (6.9)	1086	17 (1.6)	77.3 (60.1, 87.5)
Southern Hemisphere		250	14 (5.6)	478	2 (0.4)	92.5 (71.2, 98.9)
Age at randomization	N/A					
≤3.0 months		531	33 (6.2)	1066	17 (1.6)	74.3 (54.2, 86.0)
>3.0 months to ≤6.0 months		204	15 (7.4)	398	2 (0.5)	93.1 (73.9, 98.9)
>6.0 months		51	3 (5.9)	100	0 (0.0)	100.0 (12.6, NE)
Sex	0.6285					
Male		389	25 (6.4)	828	11 (1.3)	79.3 (58.5, 90.2)
Female		397	26 (6.5)	736	8 (1.1)	83.4 (64.3, 92.9)
Race	0.7475					
White		478	37 (7.7)	919	13 (1.4)	81.7 (66.2, 90.6)
Black or African American		176	6 (3.4)	406	2 (0.5)	85.6 (31.7, 98.0)
Other		132	8 (6.1)	235	4 (1.7)	71.9 (7.1, 92.6)
Weight on Day 1	0.4860					
<5 kg		482	33 (6.8)	973	14 (1.4)	79.0 (61.2, 89.1)
≥5 kg		304	18 (5.9)	589	5 (0.8)	85.7 (62.9, 95.2)
Region	0.9581					
North American		183	18 (9.8)	435	8 (1.8)	81.3 (57.6, 92.3)
Europe		290	16 (5.5)	548	6 (1.1)	80.2 (50.5, 92.9)
Rest of World		313	17 (5.4)	581	5 (0.9)	84.2 (58.7, 94.8)
Study Group	0.2851					
MELODY		496	25 (5.0)	994	12 (1.2)	74.5 (49.6, 87.1)
Phase 2b		290	26 (9.0)	570	7 (1.2)	86.2 (68.0, 94.0)



RRR, relative risk reduction, **1.** Eric AF Simões1, et al (9-12th of May 2022) [Conference Presentation] ESPID 2022 Meeting, Athens, Greece & Online. https://espidmeeting.org/

Efficacy Against MA LRTI Consistent Over 150 Days (5 Months)

Time to first RSV-confirmed MA LRTI



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Outpatient Visits and Antibiotic Use

Lower with Nirsevimab Compared with Placebo

	Placebo (N=786)	Nirsevimab (N=1564)	
	Events per 100 infants‡ (95% CI)	**Events per 100 infants‡ (95% CI)**	**RRR† (95% CI)**
Outpatient visits for all-cause MA LRTI	28.1 (23.5, 33.8)	16.3 (13.9, 19.3)	**41.9 (25.7, 54.6)**
Antibiotic course	34.6 (29.0, 41.2)	26.4 (22.8, 30.6)	**23.6 (3.8, 39.3)**

†Estimated based on Poisson regression with log follow-up time as offset. ‡Calculated as 100x total number of events/total follow-up time (5 months).

1. Eric AF Simões1, et al (9-12th of May 2022) [Conference Presentation] ESPID 2022 Meeting, Athens, Greece & Online. https://espidmeeting.org/

Nirsevimab: Favorable Safety Profile Across All Infants (2569 Received Nirsevimab)

Safety	Ph2b[1] 29-<35 w GA		MELODY[2] ≥ >35 w GA		MEDLEY[3] Preterm		MEDLEY[3] CHD/CLD	
	Placebo (N=479)	Nirsevimab (N=968)	Placebo (N=491)	Nirsevimab (N=987)	Palivizumab (N=206)	Nirsevimab (N=406)	Palivizumab (N=98)	Nirsevimab (N=208)
Serious adverse events	16.9%	11.2%	7.3%	6.8%	5.3%	6.9%	20.4%	19.2%
Adverse events of Grade 3 or higher	12.5%	8.0%	4.3%	3.6%	3.4	3.4%	13.3%	14.4%
Adverse events of special interest (AESI)	0.6%	0.5%	0%	0.1%	0.0%	0.2%	0.0%	0.5%
Deaths	3	2	0	3	0	2	1	3

- None of the serious adverse events or deaths were considered as related to nirsevimab
- Overall, incidence of nirsevimab antidrug antibody was low across studies with no safety concerns
  - MELODY: single AESI case of hypersensitivity limited to cutaneous signs and symptoms
  - MEDLEY: 2 AESIs (nirsevimab arm): Maculopapular rash (preterm cohort) 92 days post nirsevimab dose and heparin-induced thrombocytopenia (CHD/CLD cohort) unrelated to treatment

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1. Hammitt LL,et al N Engl J Med. 2022 Mar 3;386(9):837-846. 2. Domachowske Joseph et al. N Engl J Med 2022 Mar 386:9, 892-894. 3. Griffin MP, et al. N Engl J Med. 2020 Jul 30;383(5):415-425

Nirsevimab is Designed to Address the Large Unmet Need for RSV Protection in All Infants

More than 550,000 infants receive medical attention for RSV LRTI annually in US[1]

- Remains the leading cause of hospitalization in infants regardless of month of birth[1-2]
- Most medically attended cases, including severe cases, occur in healthy infants born at term[3-4]
- Large unmet need with more than 98% of infants left unprotected today against RSV LRTI[5]
- All infants can benefit from direct protection from LRTI:
  - regardless of gestational age
  - regardless of time of year they are born

Nirsevimab is designed to provide direct protection for all infants[6-8]

- Demonstrated efficacy in both full-term and pre-term infants for the RSV season
- Favorable safety profile compared to placebo and to palivizumab
- Implementation designed to be simple and with hospital dosing at birth during the season and office dosing before the season integrated with routine infant immunizations

1. Rainisch G, et al. Vaccine. 2020;38(2):251-257 **2.** Zhu Q, et al. Sci Transl Med. 2017; 9(388) **3.** Hall CB, et al. N Engl J Med. 2009;360(6):588-598. **4.** Arriola CS, et al. J Pediatric Infect Dis Soc. 2020;9(5):587-595. **5.** Births: Final data for 2020. National Vital Statistics Reports; vol 70 no 17. Hyattsville, MD: National Center for Health Statistics. 2022. 6.Griffin MP, et al. N Engl J Med. 2020 Jul 30;383(5):415-425. **7.** Hammitt LL,et al N Engl J Med. 2022 Mar 3;386(9):837-846. **8.** Domachowske Joseph et al. N Engl J Med 2022 Mar 386:9, 892-894.