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RSV immunization approaches

sanofi

RSV Is Seasonal, With Peak Incidence Varying by Region[1,2]

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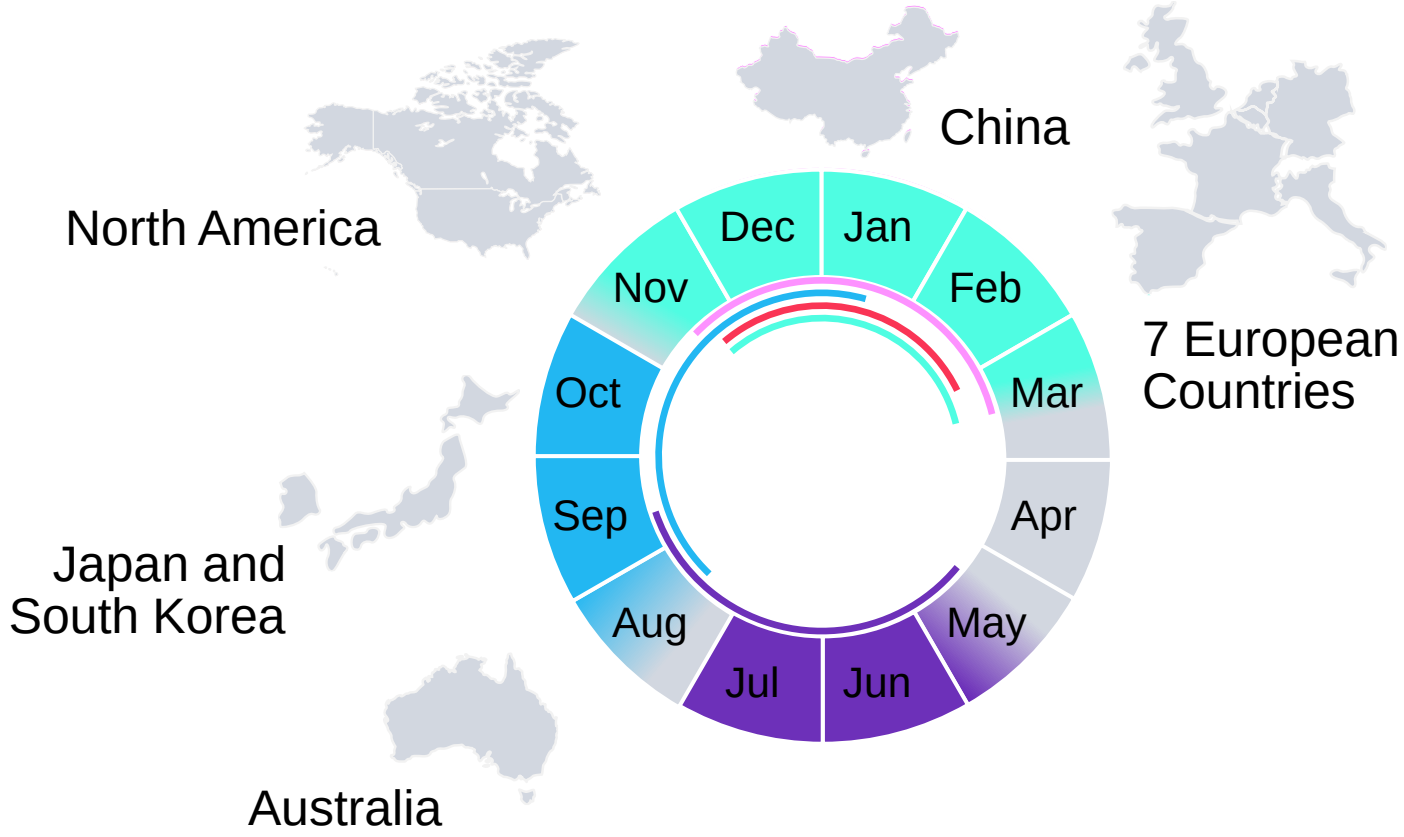

Duration of Season

Northern Hemisphere:

generally, from **October/November** to **February/March**.

Southern Hemisphere:

generally, from **May to September** (aligned with cold season temperatures)

Tropical and Subtropical Climates:

less consistent—peak closely aligned with **rainy season** and/or higher temperatures

1. Staadegaard L, et al. *Infl Oth Respir Vir.* 2021;10.1111/irv.12885. **2.** Obando-Pacheco P, et al. *J Infect Dis.* 2018;217(9):1356-1364.

Important Considerations for an Effective Strategy to Offer Protection to Infants Against RSV in Their First Season

From World Health Organization

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Indication/Efficacy

Does the strategy prevent severe RSV disease in early infancy as this is a period of highest risk of high morbidity and mortality?

Co-administration

Is there a possibility of interference with active immunization?

Timing of immunization

Is the prevention strategy easy to administer in accordance with timing of RSV season?

Acceptance of different strategies

Will acceptance and uptake of the prevention strategy in the community be sufficiently high?

Target population

Does the approach aim to offer protection to all infants during their first RSV season?

Duration of protection

Does the strategy offer protection for the entire duration of RSV season?

RSV variability

Does the strategy protect against both RSV A and B subtypes and evolving strains?

Access and affordability

Is the strategy accessible and affordable to allow broad administration?

1. WHO preferred product characteristics of monoclonal antibodies for passive immunization against respiratory syncytial virus (RSV) disease. Available from: https://www.who.int/publications/i/item/9789240021853 [Accessed Aug 8, 2022]. 2. World Health Organization. WHO Preferred Product Characteristics for Respiratory Syncytial Virus Vaccines. 2017. https://apps.who.int/iris/bitstream/handle/10665/258705/WHO-IVB-17.11-eng.pdf [Accessed Aug 8, 2022]. 3. Esposito S et al. *Front Immunol.* 2022;13:880368.

Potential Strategies for protection of RSV in infants

Indirect protection

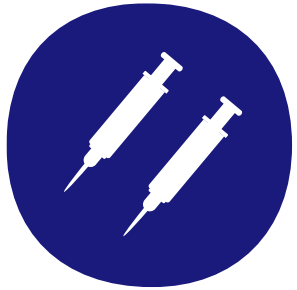
Herd immunity

Cocooning strategies

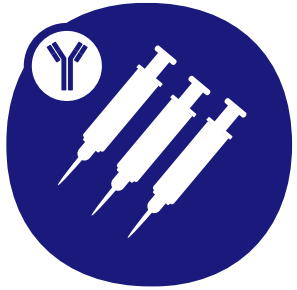
Vaccination during pregnancy

Direct protection

Infant Vaccination



Traditional monoclonal antibodies



Extended-life monoclonal antibodies

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RSV, respiratory syncivial virus.

1. Esposito S et al. Front Immunol. 2022;13:880368.2. Alexia Kieffer et alThe Journal of Infectious Diseases, 2022, 226,(2)Pages S282–S292, 3. Ashby B et al Curr Biol. 2021 Feb 22;31(4):R174-R177. doi: 10.1016/j.cub.2021.01.006. Epub 2021 Jan 12. PMID: 33621500.4. Samuel PC et al eLife 9:e47003.

Barriers to Development of Safe and Effective RSV Pediatric Vaccine

1 Reduced responsiveness of immature infant immune system to vaccination[1-3]

- Potential inhibition from maternally derived RSV antibodies[1,3]
- Inability to generate an efficient immune response until ~4 months[2,7]
- Tendency of neonatal immune system towards tolerogenic immune responses[1]

2 First RSV exposure usually occurs very shortly after birth which provides a very short time frame for vaccination[1]

- RSV hospitalization are most common in younger infants[4-6]

3 Concerns for potential of development of vaccine enhanced respiratory disease (ERD)[1]

- FI-RSV vaccine trial in the 1960's resulted in increased rates of hospitalization and two deaths in vaccinated infants[1]
- The vaccine enhanced RSV disease upon natural infection with higher risk to develop severe form[1]
- Antigen structure critical for effective vaccine response was not well understood until 2013[7]

1. Eichinger KM et al. *Ther Adv Vaccines Immunother*. 2021;9:10.1177/2515135520981516 2. Sande CJ et al. *Vaccine*. 2014;32(37):4726-4729. 3. Ruckwardt TJ, et al. *Immunity.* 2019 Sep 17;51(3):429-442. 4. Hall CB, et al. *Pediatrics*. 2013;132(2):e341-e348. 5. Lively JY, et al. *J Pediatr Infect Dis Soc*. 2019;8(3):284-286. 6. Rha B, et al. *Pediatrics*. 2020;146(1):e20193611 7. McClellen, JS, et al. *Science*. 2013;340(6136):1113-1117. 7. Jounai N et al EBioMedicine. 2017 Feb;16:124-135.

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Licensed approaches to help protect infants against RSV disease

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	Traditional mAbs[1]	Vaccines[1,4-6]	Long-acting mAbs[1,7-9]
Availability	Palivizumab licensed for >20 years **Restricted to <5% of infants**[2,3,10]	First vaccine licensed for use in pregnancy (RSVpreF)	Long-acting mAbs, licensed (nirsevimab)

mAb, monoclonal antibody; RSV, respiratory syncytial virus.

1. Esposito S, et al. *Front Immunol* 2022;13:880368. 2. Azzari C, et al. *Ital J Pediatr* 2021;47:198; 3. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. *Pediatrics* 2014;134:415–20; 4. FDA, 21 Aug 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-pregnant-individuals-prevent-rsv-infants (Accessed 23 Sept 2023); 5. FDA, 14 Sept 2023 https://www.fda.gov/vaccines-blood-biologics/abrysvo (Accessed 16 Dec 2023); 6. EMA, 15 Sept 2023 https://www.ema.europa.eu/en/medicines/human/EPAR/abrysvo (Accessed 16 Dec 2023); 7. FDA, 17 July 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-prevent-rsv-babies-and-toddlers (Accessed August 2023); 8. FDA, 17 July 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761328s000lbl.pdf (Accessed 16 Dec 2023). 9. EMA, 6 Dec 2023 https://www.ema.europa.eu/en/medicines/human/EPAR/beyfortus (Accessed 16 Dec 2023) 10. Jones JM. et al. MMWR Morb Mortal Wkly Rep 2023;72:920–925.

Nirsevimab Clinical Development Program

	Phase 2b Study[1] (POC/Pivotal trial)	Phase 3 – MELODY Study[2,3] (Pivotal trial)	Phase 2/3 – MEDLEY First and Second Season Study[4*] (Pivotal trial)
Study Population	• 1453 healthy infants 29 to <35 wGA • Not eligible to receive palivizumab (AAP or other local guidelines)	• 3010 healthy infants ≥35 wGA ○ Primary cohort: 1490 infants ○ Full cohort: 3012 infants • Not eligible to receive palivizumab	• 615 preterm infants born <35 wGA ○ 200 preterm infants born <29 wGA • 310 infants with CLD of prematurity or CHD • CLD/CHD infants were given a **second dose in the second season**: (N/N); palivizumab infants were re-randomized 1:1 to either 200 mg nirsevimab followed by four once-monthly doses of placebo (P/N) or five once-monthly intramuscular doses of palivizumab (15 mg/kg weight per dose) (P/P).
Interventions	• 2:1 Randomization • Single Dose of Nirsevimab 50 mg : Placebo	• 2:1 Randomization • Single dose of Nirsevimab : Placebo • Dosing: 50 mg if <5 kg or 100 mg if ≥5 kg	• 2:1 Randomization • Single dose of Nirsevimab: Palivizumab ○ Nirsevimab Dosing single dose: 50 mg if <5 kg or 100 mg if ≥5 kg (first season), 200mg if second season. Followed by 4 once-monthly placebo doses ○ Palivizumab Dosing: 5 monthly doses of 15 mg/kg
Primary Endpoint	• Incidence of **RSV confirmed MA-LRTI** through 150 days after dosing **Efficacy, % (95% CI):** 70.1% (52.3, 81.2) *Post hoc* (<5kg): 86.2% (68.1, 94.0)	**Efficacy, % (95% CI):** Primary cohort: 74.5% (49.6, 87.1) Full cohort: 76.4% (62.3, 85.2)	• **Safety & tolerability** of nirsevimab Safety profile of nirsevimab was similar to palivizumab
Secondary Efficacy Endpoints	• Incidence **of RSV-LRTI hospitalization** through 150 days after dosing **Efficacy, % (95% CI):** 78.4% (51.9, 90.3) *Post hoc* (<5kg): 86.5% (53.5, 96.1) n=403 Nirsevimab; n=192 placebo	**Efficacy, % (95% CI):** Primary cohort: 62.1% (-8.6, 86.8) Full cohort: 76.8% (49.4, 89.4)	• Descriptive efficacy of nirsevimab in reducing RSV confirmed MA-LRTI and RSV-LRTI hospitalization‡ • Pharmacokinetics for extrapolation of efficacy observed in healthy infants

*Infants eligible to receive palivizumab according to local guidelines. Preterm cohort: Infants in their first year of life and born ≤35 weeks 0 days gestational age without CHD/CLD and eligible to receive palivizumab as per applicable guidelines. CHD/CLD cohort: Infants in their first year of life with documented, hemodynamically significant CHD requiring a daily medication for its management; or those with a diagnosis of CLD of prematurity requiring medical intervention/management within the 6 months prior to randomization.

AAP: American Academy of Pediatrics; ADA: Anti-Drug Antibody; CHD: Congenital heart defects; CLD: Chronic liver disease; MA-LRTI: Medically attended lower respiratory tract infection; PK: Pharmacokinetics; POC: Proof of concept; RSV: Respiratory syncytial virus; wGA: weeks gestational age.

1. Griffin MP, et al. *N Engl J Med*. 2020;383(5):415-425. **2.** Hammitt LL, et al. *N Engl J Med*. 2022;386(9):837-846. **3.** Muller WJ, et al. *N Engl J Med.* 2023; 388:1533-1534.
4. Domachowske J, et al. *N Engl J Med.* 2022;386(9):892-894.

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Nirsevimab: Safety Profile Across a Broad Infant Population

	Phase 2b[1] 29 to <35 wGA		MELODY[2] All Subjects ≥35 wGA		MEDLEY[3] Season 1 Preterm		MEDLEY[3] Season 1 CHD/CLD		MEDLEY[4]* Season 2 CHD/CLD		
	Placebo (n=479)	Nirsevimab (n=968)	Placebo (n=996)	Nirsevimab (n=1998)	Palivizumab (n=206)	Nirsevimab (n=406)	Palivizumab (n=98)	Nirsevimab (n=208)	Pali/Pali (n=42)	Pali/Nirs (n=40)	Nirs/Nirs (n=180)
Serious adverse events	16.9%	11.2%	7.4%	6.3%	5.3%	6.9%	20.4%	19.2%	0.0%	10.0%	9.4%
Adverse events of Grade 3 or higher	12.5%	8.0%	3.8%	3.1%	3.4	3.4%	13.3%	14.4%	2.4%	10.0%	7.8%
Adverse events of special interest	0.6%	0.5%	0%	0.2%	0.0%	0.2%	0.0%	0.5%	0.0%	0.0%	0.0%
Deaths	3	2	0	4	0	2	1	3	0	0	0

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None of the serious adverse events or deaths were considered related to nirsevimab

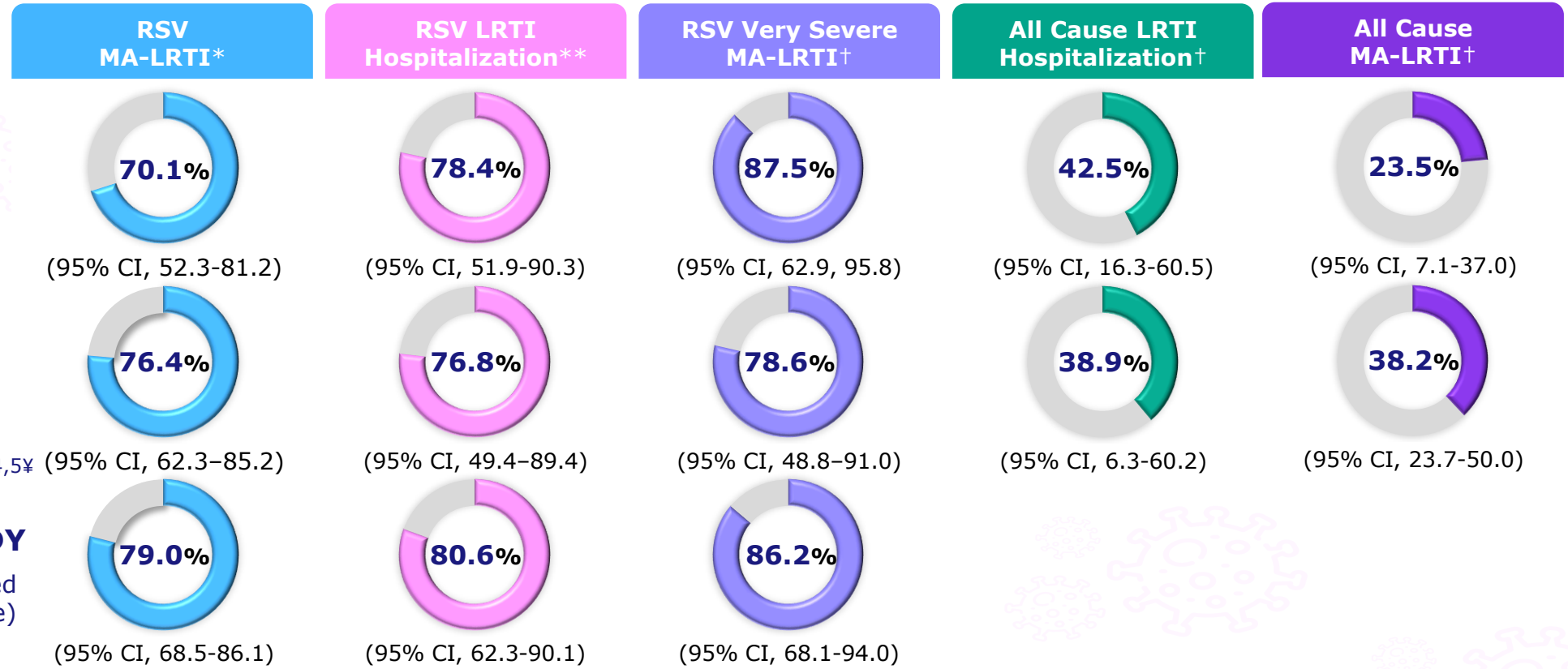
Overall, incidence of nirsevimab anti-drug antibody was low across studies with no safety concerns

Nirsevimab had a favorable safety profile with similar types and frequencies of adverse events compared with the placebo or palivizumab arms

*Groups labels indicate which product the participants received in both seasons (Season 1 / Season 2)
CHD, congenital heart disease; CLD; chronic lung disease; Nirs, nirsevimab; Pali, palivizumab; wGA, weeks gestational age.

1. Griffin MP, et al. *N Engl J Med*. 2020;383(5):415-425. **2.** Muller WJ, et al. *N Engl J Med*. 2023;388:1533-1534. **3.** Domachowske J, et al. *N Engl J Med.* 2022;386(9):892-894.
4. Domachowske JB, et al. *J Pediatric Infect Dis Soc*. 2023;12(8):477-480.

Consistent efficacy has been seen against medically-attended RSV LRTI in clinical trials.



*Primary Endpoint; **Secondary Endpoint; †Exploratory Endpoint

‡ A Phase 2b Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897 against Respiratory Syncytial Virus, in Healthy Preterm Infants†A Phase 3 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897 Against Respiratory Syncytial Virus, in Healthy Late Preterm and Term. ¥ Included infants from both studies that received the approved doses according to the label. A limitation of this analysis is that, although the efficacy of nirsevimab and the difference by treatment group in modalities of health resource use have been described, it is not possible to generalise the findings to assess the effect on either disease burden or health resource use in the general population, because the proportion of infants born preterm included in this dataset is higher than that in the general population.

1. Griffin MP, et al. N Engl J Med. 2020;383(5):415-425; 2. Beyfortus Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/beyfortus-epar-product-information_en.pdf (Accessed September 2023); 3. Muller WJ, et al. N Engl J Med. 2023;388(16):1533-1534; 4. ACIP – October 19-20,2022 – Nirsevimab updated safety and efficacy https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-10-19-20/02-RSV-Mat-Ped-Felter-508.pdf (Accessed 20 Dec 2023) 5. Simões EAF,Lancet Child Adolesc Health. 2023 6. ACIP – October 19-20,2022 – Nirsevimab updated safety and efficacy

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Nirsevimab clinical experience continued with HARMONIE:

A pragmatic, open-label, randomized trial in a near real-world setting

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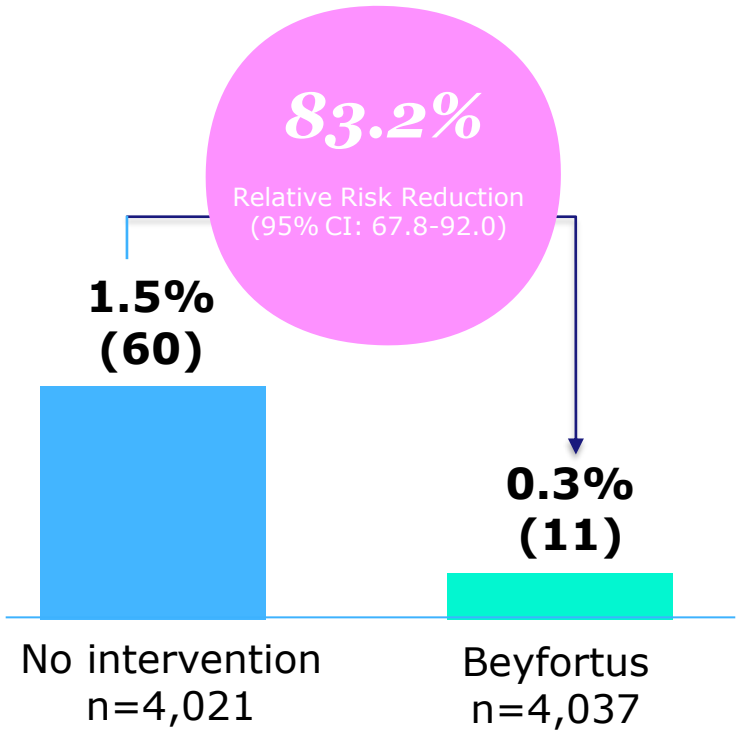
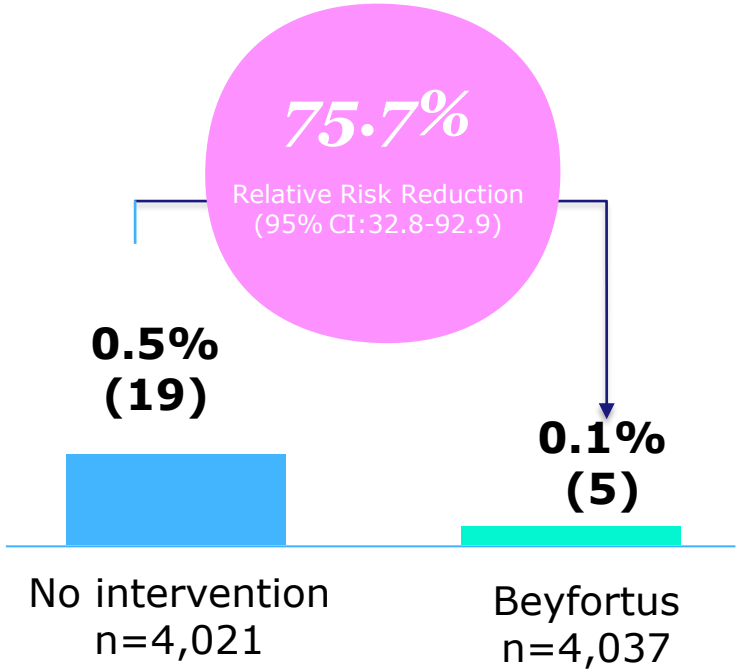
Primary Endpoint

Incidence of RSV-LRTI hospitalization

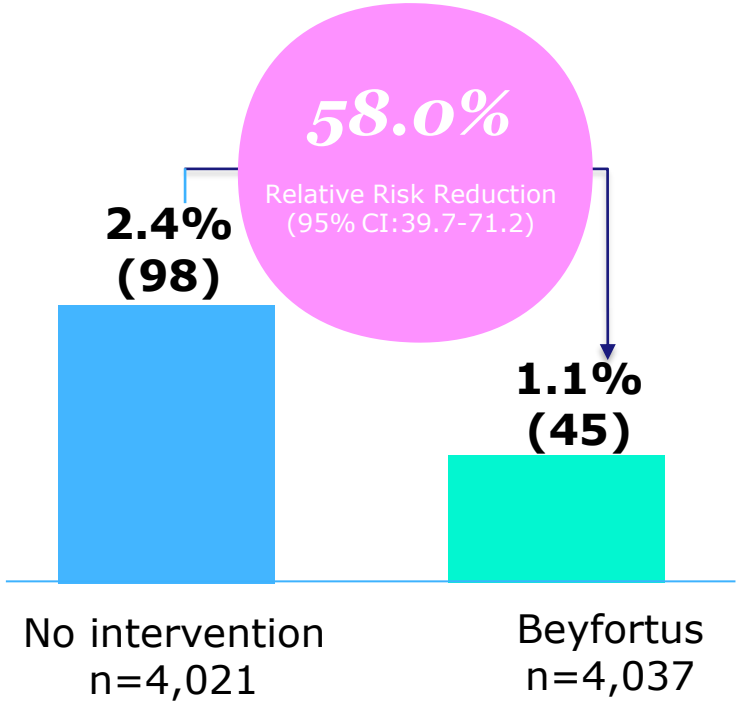


Secondary Endpoints

Incidence of very severe RSV-LRTI hospitalization*



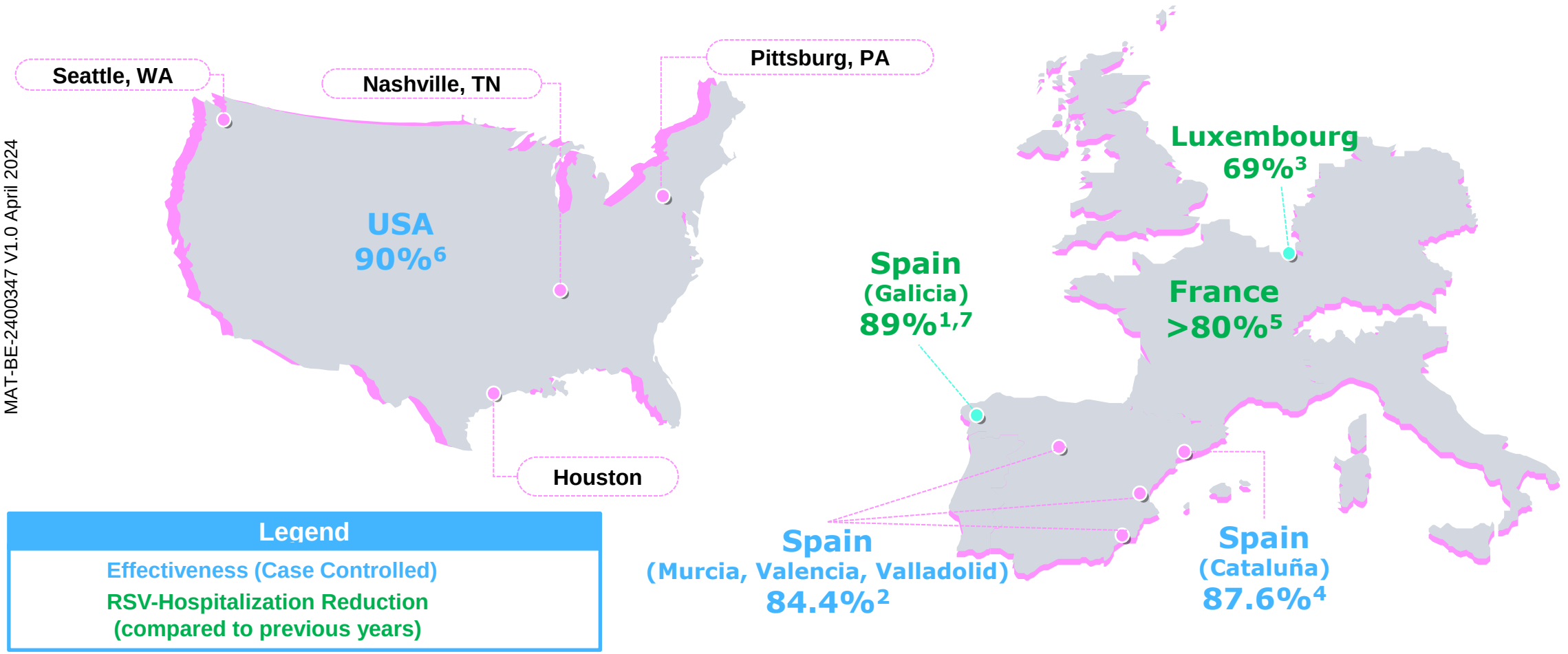
Incidence of all-cause LRTI hospitalization‡



*Severe RSV LRTI are defined as confirmed RSV hospitalization for LRTI with an oxygen saturation (SaO2) < 90% (at any time) and oxygen supplementation. ‡ Number of RSV LRTI hospitalization in all 3 countries combined through the RSV season. 12 months post-dosing/randomization for France, Germany and UK non-reconsented participants, 24 months post-dosing/randomization for UK reconsented participants. D01 will be the day of randomization (both study groups) and immunization (nirsevimab group).

SB Drysdale et al. N Engl J Med. 2023 Dec 28; 389:2425-2435 DOI: 10.1056/NEJMoa2309189.

Summary of Effectiveness & Reduction of RSV-Hospitalization Real World Estimates



Legend

Effectiveness (Case Controlled)

RSV-Hospitalization Reduction (compared to previous years)

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1.https://www.nirsegal.es/en 2. López-Lacort M. et al Euro Surveill. 2024;29(6):pii=2400046. 3. Ernst C et al. Euro Surveill. 2024;29(4):pii=2400033. 4. Coma E. et al, Preprints with the Lancet,: https://ssrn.com/abstract=4749763 5. https://www.infovac.fr/actualites/bulletin-n-1-janvier-2024 6. Moline HL et al., MMWR Morb Mortal Wkly Rep 2024;73:209–214. 7. ESWI Respiratory Virus Summit 2024 | ESWI

Strategies aimed to help protect against RSV MA-LRTI in infants

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Immunization strategies against RSV entering the first RSV season

Immunization of infants with vaccines(not available)[1]

- Not yet shown to be effective in young infants
- Potential strategy for toddlers entering their second or third RSV season

Immunization of infants with traditional mAb[1]

- Palivizumab is approved for use in specific population of infants (preterm infants or in infants with specific comorbidities)
- Requires monthly injections throughout the RSV season and compliance can be poor

Immunization of pregnant individuals with vaccines[1]

- The concept of immunization of pregnant individuals is used for protection of mothers and infants against other pathogens e.g.(e.g., influenza, pertussis).
- RSV maternal vaccine RSVPreF approved for protection of RSV LRTI in infants up to 6 months after birth[2,3]
- No reported efficacy on mother
- Dependent on maternal antibody transfer in third trimester
- Short window of administration in some countries (UK 28-36w gestation[6], US 32-36w gestation)[4,5]

Immunization of infants with long-acting mAbs[1]

- Strategy to offer protection for infants against RSV LRTD during the season with administration timed to coincide with the RSV season
  - Approved in e.g. EU, US, UK, Canada*: nirsevimab[6-9]
  - In late-stage development: clesrovimab[10]

* Examples only and is approved in other countries outside this list.mAb, monclonal antibody; RSV, respiratory syncivial virus. 1. Adapted from Esposito S, et al. Front Immunol 2022;13:880368; 2. EMA, 15 Sept 2023 https://www.ema.europa.eu/en/medicines/human/EPAR/abrysvo (Accessed 16 Dec 2023); 3. FDA. ABRYSVO label, August 2023. https://www.fda.gov/vaccines-blood-biologics/abrysvo (Accessed 16 Dec 2023); 4. Fleming-Dutra KE, et al. *Morb Mort Weekly Rep*, 72(41);1115–1122; 5. UK-MHRA. ABRYSVO label. https://mhraproducts4853.blob.core.windows.net/docs/80a3ef928288c4d31cea1f8e2c1bdbcdd7245c6a (Accessed 19 Dec 2023); 6. Beyfortus Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/beyfortus-epar-product-information_en.pdf (Accessed September 2023); 7. FDA. BEYFORTUS label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761328s000lbl.pdf (Accessed 13 Dec 2023); 8. Beyfortus Summary of Product Characteristics. https://mhraproducts4853.blob.core.windows.net/docs/82221c5f76fb54c6036f8564b67a283fc3ae81fe (Accessed December 2023); 8. Beyfortus. Product Monograph. https://pdf.hres.ca/dpd_pm/00070439.PDF (Accessed 19 Dec 2023); 10. Clinical trials.gov. Clesrovimab. https://clinicaltrials.gov/study/NCT04767373 (Accessed 19 Dec 2023);

Summary

Two approaches are now available for prevention of RSV LRTD in infants:

1. Extended half-life mAb prophylaxis
   - Duration of protection afforded following single dose is at least 5 months
   - Timed to RSV season
2. Vaccination in pregnancy
   - Depends on maternal antibody transfer
   - Protection starting at birth

F, F protein; mAb, monoclonal antibody; LRTI, lower respiratory tract infection; RSV, respiratory syncivial virus.

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