Nirsevimab for the prevention of RSV in all infants

October 20, 2022

AstraZeneca and Sanofi

Topics

- Additional data from clinical trials
- Duration of protection
- Implementation

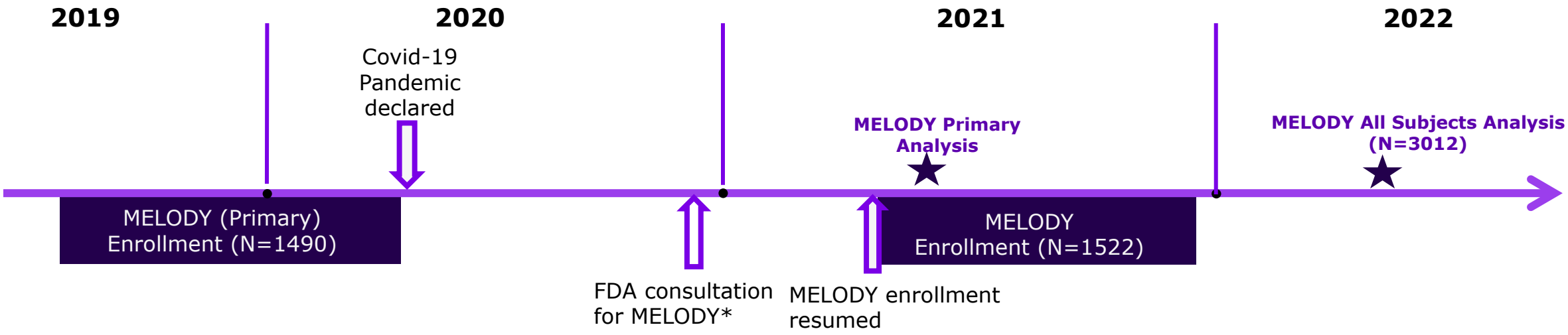
Nirsevimab: A Development Program Conducted Across All Infants

	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 ~ 1500) 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)**

sanofi AstraZeneca

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.

Impact of COVID-19 Pandemic on the Phase 3 MELODY Trial



Study enrollment and location

- Enrollment began 23 July 2019
- 150 sites (20 countries) in the Northern Hemisphere enrolled 1028 subjects in 2019 and experienced a typical RSV season
- 10 sites (in South Africa) in the Southern Hemisphere enrolled 462 subjects in early 2020

Situation and mitigation

- Onset of the COVID-19 pandemic in March 2020 led to several operational challenges leading to a pause in enrollment for MELODY
- No RSV cases occurred during the typical 2020 Southern Hemisphere
- After consultation with FDA, decision was made to analyze the primary endpoint after first 1490 enrolled (Primary).
- Study enrollment resumed in 2021.

sanofi AstraZeneca

1. Hammitt LL et al. N Engl J Med 2022;386:837-46.
* EMA consultation in parallel

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	• 1490 Infants **≥35 wGA** (Primary cohort only) • 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** (N=1490): Incidence of RSV confirmed MA-LRTI through 150 days after dosing • **Efficacy:** 74.5% (49.6, 87.1) • **Secondary Endpoint** (N=1490): • Incidence of RSV-LRTI hospitalization through 150 days after dosing • Safety, PK, and ADA • **Efficacy:** 62.1% (-8.6, 86.8)	• **Primary Endpoint**: Incidence of RSV confirmed MA-LRTI through 150 days after dosing • **Efficacy:** 70.1% (52.3, 81.2) <5kg-50mg: 86.2% (68.1, 94.0) • **Secondary Endpoint**: Incidence of RSV-LRTI hospitalization through 150 days after dosing • Safety†, PK, and ADA • **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 • **Secondary Endpoint:** Incidence of RSV-LRTI hospitalization through 150 days after dosing • Safety†, PK, and ADA

sanofi AstraZeneca

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.

Additional Data

- MELODY All Subjects through D151 efficacy and safety
- Pooled MELODY All Subjects AND Phase 2b recommended dose
  - Efficacy through D151
  - Efficacy by subgroup
  - Efficacy by subtype RSV A and RSV B
  - MELODY (primary cohort) 2nd season RSV incidence D361 - D511

MELODY All Subjects

MELODY All Subjects – Efficacy through D151

Definition	Placebo (N=1003)		Nirsevimab (N=2009)		Efficacy	
	n	%	n	%	**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

LRTI, lower respiratory tract infection; MA, medically attended; RSV, respiratory syncytial virus.
Very severe = hospitalization + requirement for supplemental oxygen and/or intravenous fluids

MELODY All Subjects – Safety Summary

Safety through D151

MedDRA SOC	MedDRA Preferred Term	Frequency
Skin and subcutaneous tissue disorders	Rash[1]	Uncommon
General disorders and administration site conditions	Injection site reaction[2]	Uncommon
	Pyrexia[3]	Uncommon

[1] Rash was defined by the following grouped preferred terms: rash, rash maculo-papular, rash macular, occurring within 14 days post dose.

[2] Injection site reaction was defined by the following grouped preferred terms: injection site reaction, injection site pain, injection site induration, injection site oedema, injection site swelling, occurring within 7 days post dose.

[3] Pyrexia occurring within 7 days post dose.

- No SAEs or deaths were considered related to nirsevimab by the investigator
- No anaphylaxis or serious allergic reactions attributable to nirsevimab

Uncommon = frequency ≥ 1/1000 to <1/100

Pooled MELODY All Subjects AND Phase 2b recommended dose

Complementary and Similar Study Designs

Primary endpoint

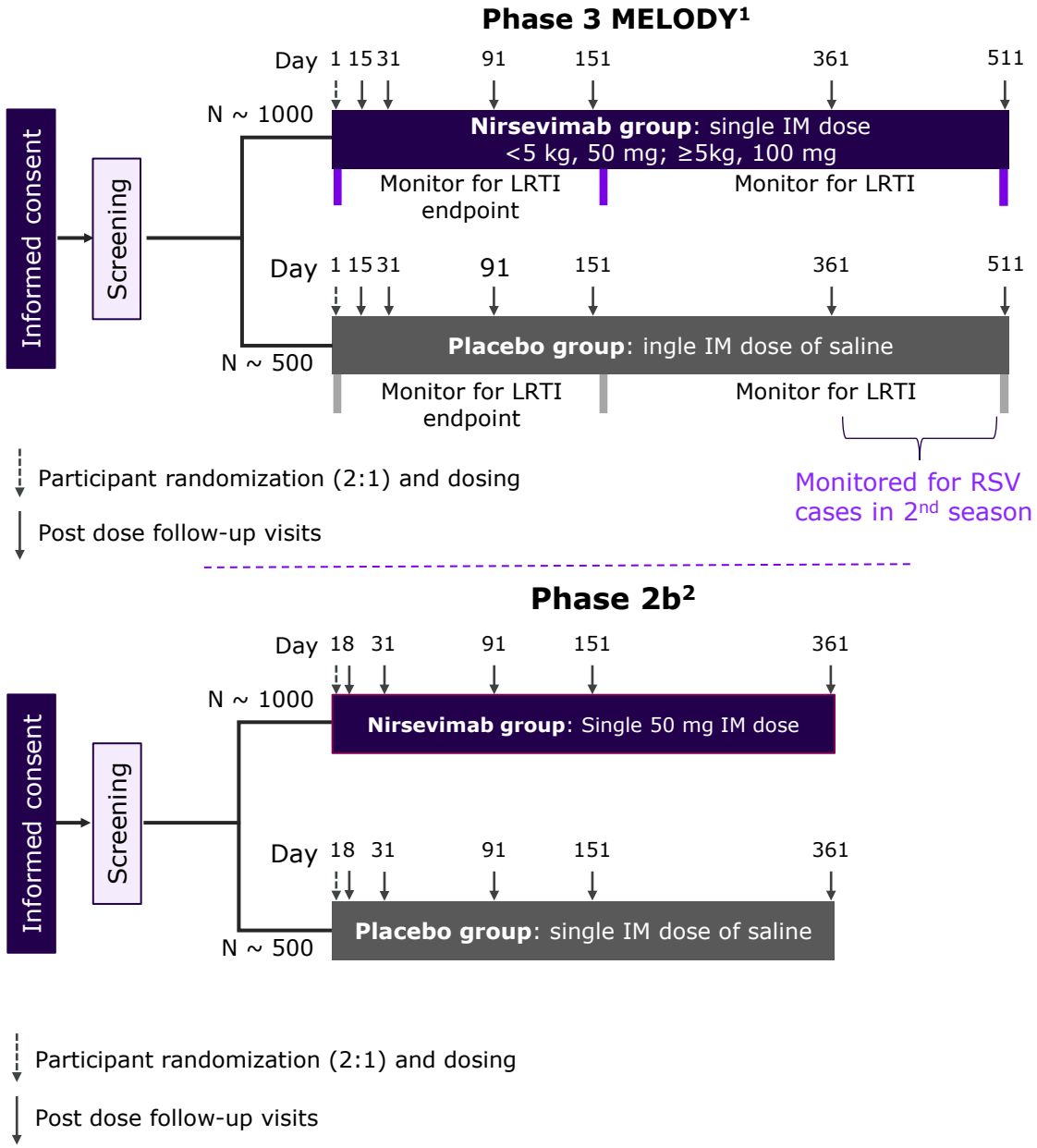
- Incidence of MA LRTI (inpatient and outpatient) caused by RT-PCR confirmed RSV through 150 days

Secondary and exploratory endpoints

- Incidence of hospitalization due to RT-PCR-confirmed RSV through 150 days
- Safety (evaluated through 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. **1.** Hammitt et al, *N Engl J Med* 2022;386:837-46; **2.** Griffin et al, *N Engl J Med* 2020;383:415

Pooled MELODY All Subjects AND Phase 2b Recommended Dose

Efficacy through D151

MELODY subjects N=3012
Ph 2b recommended dose subjects N=860

Definition	Placebo (N=1293)		Nirsevimab (N=2579)		Efficacy	
	n	%	n	%	**Efficacy**	**95% CI**
MA RSV LRTI	80	6.2	31	1.2	**79.0**	68.5-86.1
MA RSV LRTI with hospitalization	33	2.6	12	0.5	**80.6**	62.3-90.1
MA RSV LRTI (very severe)	28	2.2	7	0.3	**86.2**	68.1-94.0

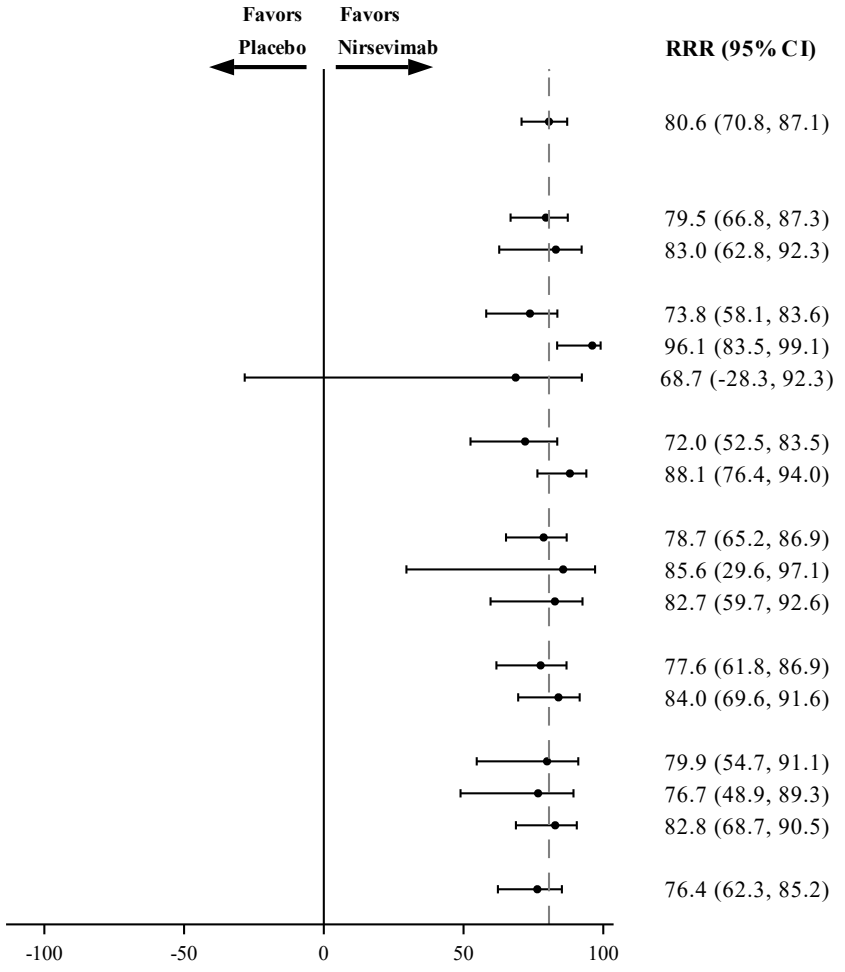
sanofi AstraZeneca

LRTI, lower respiratory tract infection; MA, medically attended; RSV, respiratory syncytial virus.
Very severe = hospitalization + requirement for supplemental oxygen and/or intravenous fluids

Pooled MELODY All Subjects AND Phase 2b Recommended Dose

Efficacy through D151 for MA RSV LRTI by subgroup

	Interaction p-value	Placebo (N = 1293) Number of Infants	Placebo (N = 1293) Observed Events	Nirsevimab (N = 2579) Number of Infants	Nirsevimab (N = 2579) Observed Events
Overall	N/A	1293	80 (6.2)	2579	31 (1.2)
Subgroup					
Hemisphere	0.6720				
Northern Hemisphere		929	55 (5.9)	1890	23 (1.2)
Southern Hemisphere		364	25 (6.9)	689	8 (1.2)
Age at randomization	0.0031				
<= 3.0 months		834	49 (5.9)	1679	26 (1.5)
> 3.0 months to <= 6.0 months		365	26 (7.1)	717	2 (0.3)
> 6.0 months		94	5 (5.3)	183	3 (1.6)
Sex	0.0458				
Male		653	36 (5.5)	1369	21 (1.5)
Female		640	44 (6.9)	1210	10 (0.8)
Ancestry	0.8561				
White		747	53 (7.1)	1447	22 (1.5)
Black or African American		178	6 (3.4)	419	2 (0.5)
Other		368	21 (5.7)	709	7 (1.0)
Weight on Day 1	0.4288				
< 5 kg		682	42 (6.2)	1370	19 (1.4)
>= 5 kg		611	38 (6.2)	1206	12 (1.0)
Region	0.8335				
North American		241	19 (7.9)	505	8 (1.6)
Europe		396	19 (4.8)	799	9 (1.1)
Rest of World		656	42 (6.4)	1275	14 (1.1)
Study Group	0.3010				
MELODY		1003	54 (5.4)	2009	24 (1.2)



sanofi AstraZeneca

Efficacy against MA LRTI for RSV A and RSV B through D151

Pooled MELODY All Subjects and Phase 2b Recommended Dose

	Placebo N=1293		Nirsevimab N=2579		Efficacy	
	n	%	n	%	**Efficacy**	**95% CI**
RSV A	39	3.0	16	0.6	**78.1**	61.1-87.7
RSV B	41	3.2	15	0.6	**80.0**	63.7-89.0

2nd season RSV incidence D361 - D511 after single dose prior to 1st season

MELODY (PRIMARY COHORT)

A low incidence of RSV LRTI was observed during season two with no hospitalized cases

Increasing severity

Definition, n (%)	RSV Season 1 (2019-2020): To Day 151		RSV Season 2 (2020-2021): Days 361 – 511	
	Placebo (n=496)	Nirsevimab (n=994)	Placebo (n=482)	Nirsevimab (n=964)
MA RSV LRTI (protocol-defined)	25 (5.0)	12 (1.2)	2 (0.4)	7 (0.7)
MA RSV LRTI with hospitalization (protocol-defined)	8 (1.6)	6 (0.6)	0 (0.0)	0 (0.0)
MA RSV LRTI (very severe)	7 (1.4)	5 (0.5)	0 (0.0)	0 (0.0)

LRTI, lower respiratory tract infection; MA, medically attended; RSV, respiratory syncytial virus.
Very severe = hospitalization + requirement for supplemental oxygen and/or intravenous fluids

Cases of any cause MA RSV LRTI were balanced by group

Definition, n (%)	RSV Season 1 (2019-2020): To Day 151		RSV Season 2 (2020-2021): Days 361 – 511	
	Placebo (n=496)	Nirsevimab (n=994)	Placebo (n=482)	Nirsevimab (n=964)
All MA LRTI (any cause)*	77 (15.5)	92 (9.3)	22 (4.6)	37 (3.8)
All MA respiratory illness with hospitalization (any cause)*	16 (3.2)	24 (2.4)	3 (0.6)	4 (0.4)

*Any medically attended LRTI; includes cases of MA RSV LRTI.
LRTI, lower respiratory tract infection; MA, medically attended; RSV, respiratory syncytial virus.

Duration of Protection

Duration of Protection

- Primary and secondary endpoints for MELODY evaluated the efficacy of nirsevimab through 150 days
- Efficacy did not decline over the time period of this evaluation
- There is some evidence that suggests that this protection extends beyond 150 days although the degree of this protection is yet to be determined
  - An analysis of the data from the South African cohort, that experienced a delayed RSV season, showed a hazard ratio of 0.491 (95% CI 0.158, 1.523)
  - Neutralizing antibody titers where 7x higher than baseline at day 361 in nirsevimab treated subjects and were significantly higher than those with natural infection

Implementation

Nirsevimab Vaccine-Like Implementation Can Provide Direct Protection of Infants for their first RSV Season

Regardless of the time of year they are born

Protect infants born…	 Before the RSV season April - October	 During the RSV season November to March
When	Prior to start of the season	At birth before hospital discharge
Where	In office, during an existing well visit before the start of the season	In hospital
How	Intramuscular Injection with a Pre-Filled Syringe	
Similarity to Current Vaccine Implementation	Recommended Pediatric Immunizations administered during well visits*	Birth Dose of Hepatitis B Vaccine*

*Birth-18 Years Immunization Schedule | CDC

Nirsevimab – Consistent Efficacy and Safety Across Studies/ Populations

- **New data confirms safety and efficacy against medically attended RSV LRTI and hospitalization**
  - MELODY all subjects safety and efficacy against MA-LRTI is consistent with the primary cohort analysis
  - MELODY all subjects analysis has demonstrated efficacy against hospitalization endpoints with an efficacy of 76.8% (49.4-89.4)
  - Efficacy without waning over 150 days and suggestion of extended efficacy
- **Safety profile favorable**
  - Low levels of reactogenicity
- **Implementation of an all infant program for nirsevimab would be a combination of office administration for those born before the season and in-hospital administration for those born during the season**

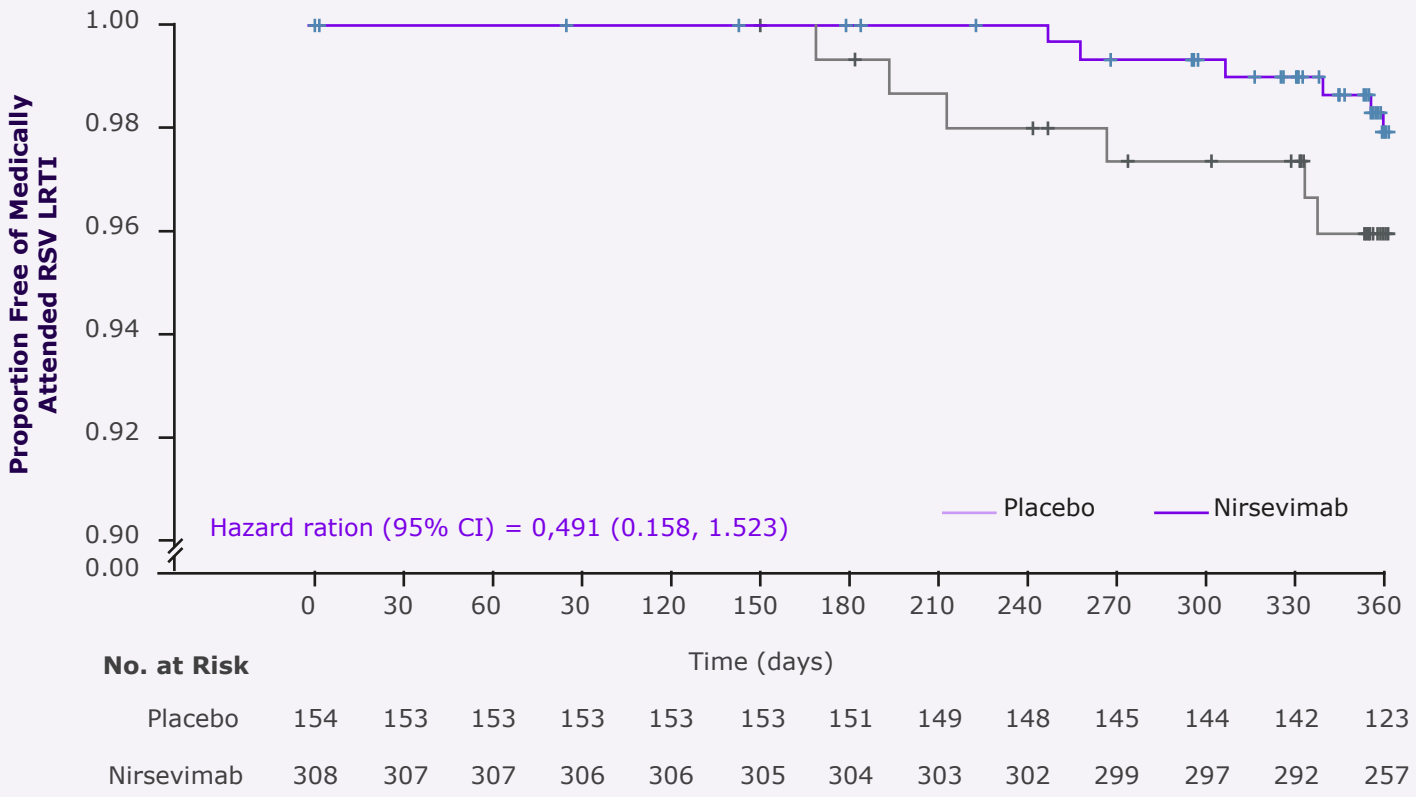
.

Thank You

sanofi AstraZeneca

South Africa: Delayed Onset of RSV Season

Time to first RSV-confirmed MA LRTI in South Africa (ITT)

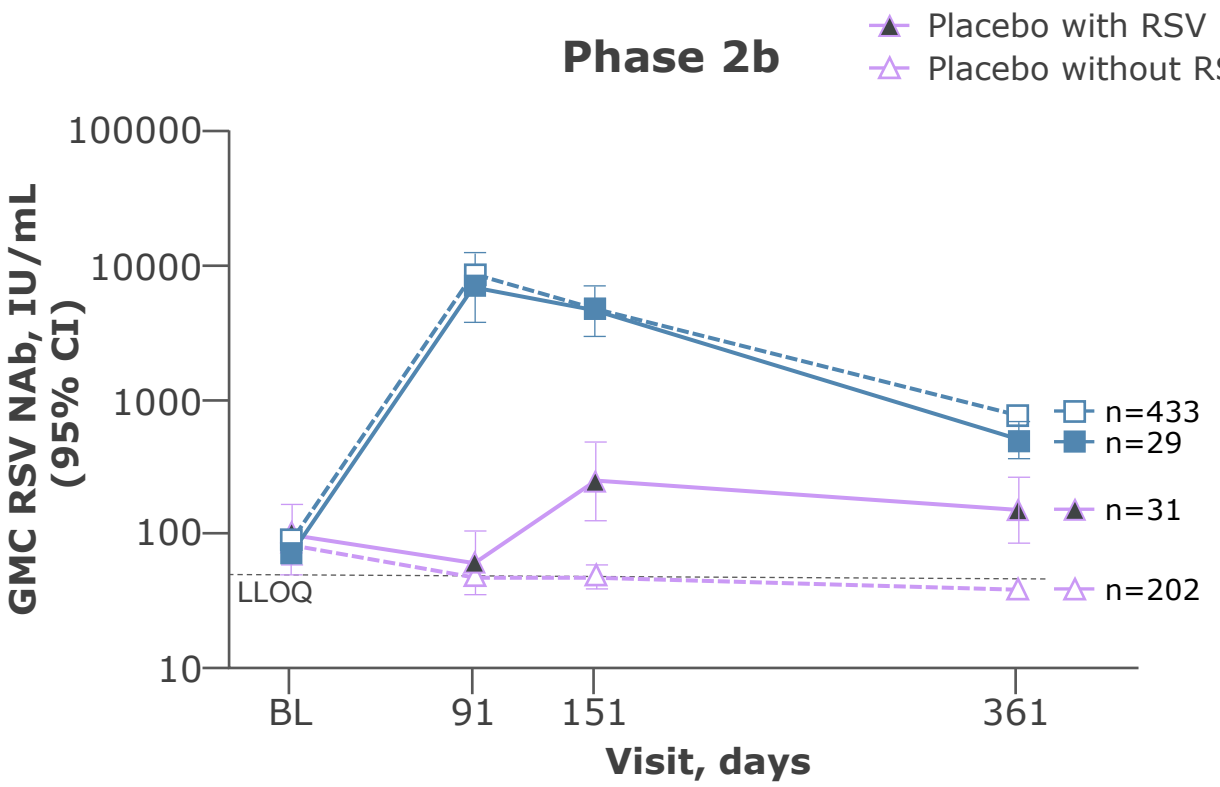


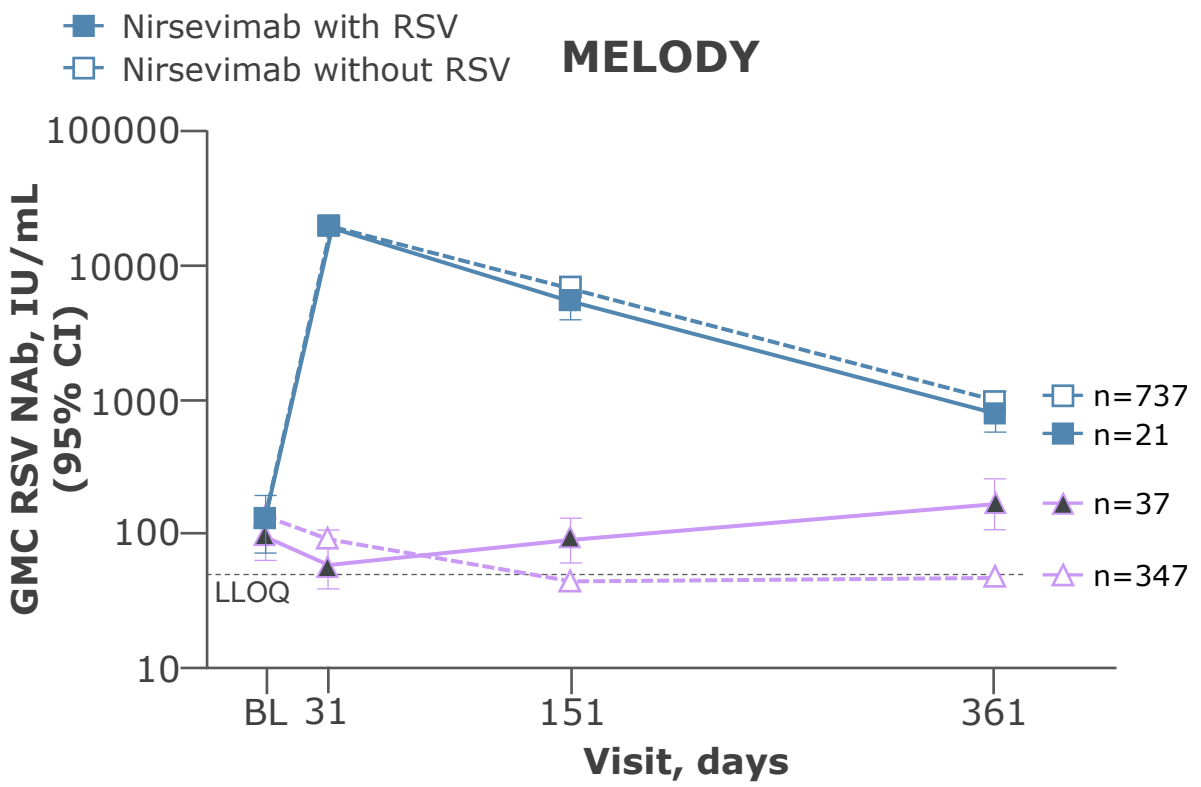
- **Unseasonal RSV transmission**
- South African participants remained unexposed to RSV until D151 due to COVID-19 pandemic[1-2].
- Case differentials in RSV LRTI after D151 is supportive of efficacy extended beyond 5 months[1].
- 12 cases occurred up to Day 361[1]:
  - Nirsevimab: 6/308 (1.9%)
  - Placebo: 6/154 (3.9%)

ITT population–participants from South Africa. Kaplan–Meier curve from a time-to-event analysis shows an estimate of the proportion of participants who were free from a medically attended RSV-associated LRTI. The hazard ratio and corresponding 95% CIs were obtained from a proportional-hazard model. Tick marks indicate censored data. ITT, intent-to-treat.

1. Hammitt LL, et al. *N Engl J Med.* 2022;386:837-46. 2. Tempia S, et al. *Euro Surveill.* 2021;26(29):2001600.

RSV NAb levels higher in nirsevimab recipients versus placebo, regardless of presence or absence RSV infection



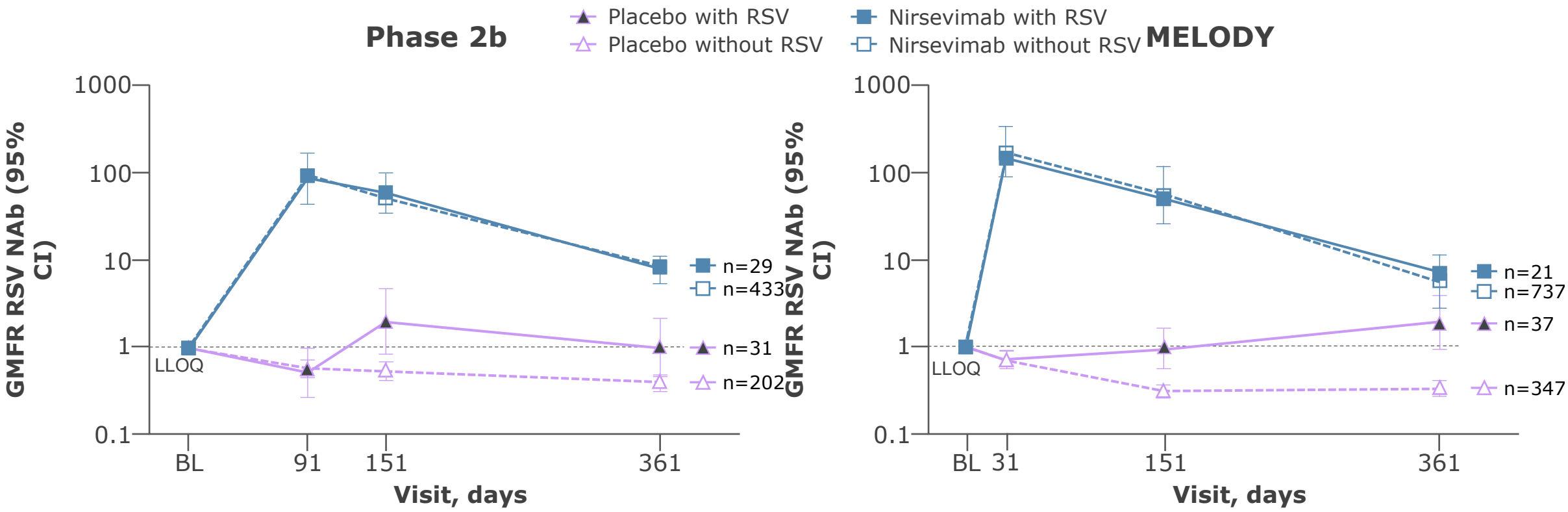


- **In nirsevimab recipients, RSV NAb levels vs baseline were >50 fold higher at Day 151 and ~7-fold higher at Day 361**
- **This suggests a level of protection extending beyond 5 months**

sanofi AstraZeneca

BL, baseline; GMC, geometric mean concentration; LLOQ, lower limit of quantification; with RSV, with confirmed RSV infection; without RSV, without confirmed RSV infection

RSV NAb levels in infants with and without RSV infections

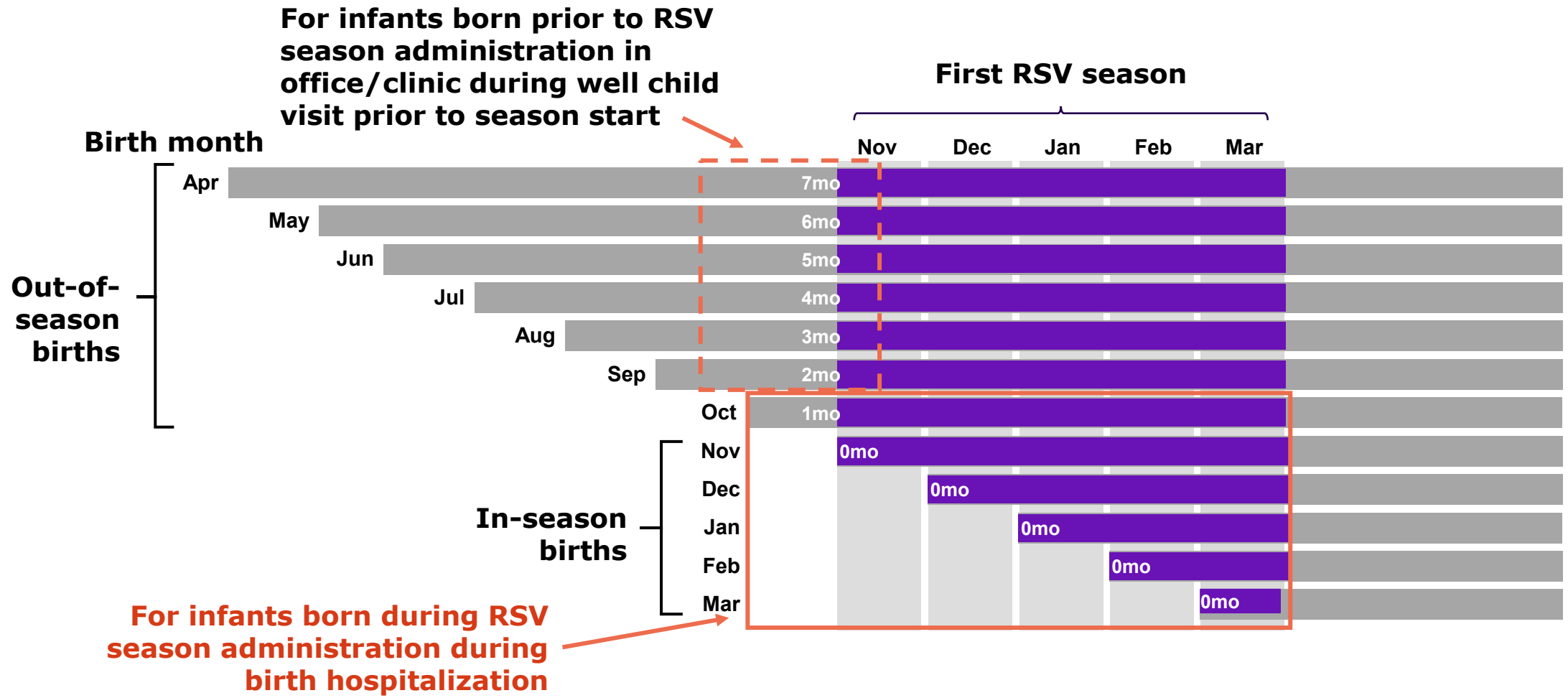


- **In nirsevimab recipients, RSV NAb levels vs baseline were >50 fold higher at Day 151 and ~7-fold higher at Day 361**

BL, baseline; GMFR, geometric mean fold rise; LLOQ, lower limit of quantification; with RSV, with confirmed RSV infection; without RSV, without confirmed RSV infection

Potential Implementation of Nirsevimab for Routine Use

Birth month and age relative to RSV season and timing of administration



mAb, monoclonal antibody; mo, month; RSV, respiratory syncytial virus.

References: 1. American Academy of Pediatrics Periodicity schedule (updated March 2021) https://www.aap.org/periodicityschedule [Accessed December 8, 2021]. **2.** Janet S, et al. *Hum Vaccin Immunother.* 2018;14(1):234-244.