Biologics License Application (BLA) 761328
Nirsevimab

Antimicrobial Drugs Advisory Committee Meeting

June 8, 2023

Division of Antivirals, Office of Infectious Diseases
Center for Drug Evaluation and Research

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FDA Opening Remarks

John Farley, MD, MPH
Director, Office of Infectious Diseases

Advisory Committee Meeting Introduction

The FDA is convening this Advisory Committee to discuss whether the available data support an overall favorable benefit-risk assessment for the use of nirsevimab for 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.

Nirsevimab

- Nirsevimab
  - Nirsevimab is a monoclonal antibody directed against the prefusion conformation of the RSV fusion (F) protein, which is required for cell entry.
  - Nirsevimab is not a vaccine and is being regulated as a drug.
- Proposed indication: prevention of 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
- Proprietary name: Beyfortus (conditionally granted)

Nirsevimab

- Proposed Dosing
  - First RSV season: a single 50-mg intramuscular (IM) injection for infants weighing <5 kg, and a single 100-mg IM injection for infants weighing 5 kg and greater
  - Children less than 24 months of age who remain at increased risk for severe RSV in their second RSV season: a single, 200-mg IM injection

- For today's discussion, we define an infant as a child not more than 12 months of age.

Other Drugs or Biologics for Prevention of RSV Disease in the U.S.

- Palivizumab: FDA-approved monoclonal antibody for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease
  - Indicated for use in infants with a history of premature birth (≤35 weeks gestational age), children with chronic lung disease (CLD) of prematurity, and children with hemodynamically significant congenital heart disease (CHD)
  - Administered monthly during RSV season
- RSV vaccines – multiple vaccines currently in clinical development for maternal immunization and for immunization of infants and children

Clinical Trials

- **Trial 03**, a double-blind, placebo-controlled trial, evaluated the safety and efficacy of nirsevimab for the prevention of medically attended respiratory syncytial virus lower respiratory tract infection (MA RSV LRTI) in infants born at ≥29 weeks to <35 weeks of gestation who were born during or entering their first RSV season.
- **Trial 04** (MELODY), a double-blind, placebo-controlled trial, also evaluated the safety and efficacy of a single-dose of nirsevimab for the prevention of MA RSV LRTI. Trial 04 enrolled infants born at ≥35 weeks of gestation who were born during or entering their first RSV season.

Clinical Trials

- **Trial 05** (MEDLEY), a double-blind, active-controlled trial, compared the safety of nirsevimab versus palivizumab in infants at high risk of severe RSV disease (premature infants born at <35 weeks of gestation, and infants with CLD of prematurity or hemodynamically significant CHD)

Regulatory Considerations – Data Pooling

- Trial 04, which enrolled infants born at ≥35 weeks of gestation, had an enrollment pause related to COVID-19 after enrolling approximately 1500, and the Agency had requested a safety data base of approximately 3000 (considering all trials).
- Patients enrolled prior to the pause are referred to as the Primary Cohort. Patients enrolled after the pause are referred to as the Safety Cohort.
- The Statistical Analysis Plan for Trial 04 prespecified that the primary analysis for efficacy would be conducted in the Primary Cohort.
- While analyses pooling the Primary Cohort and Safety Cohort may be helpful for subgroup analyses, the Agency regards such analyses as exploratory.

Regulatory Considerations – Pediatric Extrapolation of Efficacy

- Based on adult studies: "A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted" (21 CFR §201.57)
- From one pediatric age group to another: "A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group." (Pediatric Research Equity Act of 2003)

Questions for the Committee

1. **VOTE:** Is the overall benefit-risk assessment favorable for the use of nirsevimab for the prevention of RSV lower respiratory disease in neonates and infants born during or entering their first RSV season?

2. **DISCUSSION:** Please comment on the benefits and risks for nirsevimab when assessed by chronological and gestational age groups. Discuss the population or subpopulation for whom nirsevimab administration in the first RSV season would be most appropriate.

Questions for the Committee (Continued)

3. **VOTE:** Is the overall benefit-risk assessment favorable for the use of nirsevimab for the prevention of RSV lower respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season?

4. **DISCUSSION:** In the context of potential, future availability of maternal RSV vaccine to protect infants from RSV disease during their first RSV season, what additional data may be helpful to inform future recommendations regarding the use of nirsevimab in infants born to mothers who received RSV vaccination?

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Overview

Melisse Baylor, MD, Clinical Reviewer

Yang Zhao, PhD, Clinical Pharmacology Reviewer

Outline for FDA Presentation

- Overview of Nirsevimab Clinical Trials
- Nirsevimab Dosing
- Efficacy Results
- Key Efficacy Considerations:
  - Efficacy by chronological age and gestational age
  - Efficacy in infants who remain vulnerable to severe RSV disease through their second season
- Safety Considerations:
  - Anaphylaxis, rash, other hypersensitivity reactions
  - Imbalance in deaths
- Other Considerations
- Pharmacovigilance Strategy

Nirsevimab Clinical Trials

Trial	Comparator	Population	No. Subjects Who Received Nirsevimab	Primary Endpoint
03	Placebo	≥29 to <35 weeks GA	968	MA RSV LRTI at Day 150 postdose
04	Placebo	≥35 weeks GA	1998*	MA RSV LRTI at Day 150 postdose
05	Palivizumab	<35 weeks GA; CLD and CHD	654#	Safety

GA= gestational age

* The number of subjects in Primary Cohort plus Safety Cohort

In Trial 05, 614 subjects received nirsevimab in RSV Season 1 and 40 subjects received their first dose of nirsevimab in RSV Season 2.

Medically Attended RSV LRT Infection

FDA considers MA RSV LRTI to be a clinically meaningful endpoint based on the following considerations:

- Epidemiology data
- Prospective surveillance study over 3 RSV seasons (2002-2004); (Hall et.al. NEJM. 2009. 360; 588-598)
  - Rate of emergency department visits in infants < 12 months of age ranged from 39 to 69/1,000 patients
  - Rate of pediatric office visits in infants < 12 months of age ranged from 108 to 194/1,000 patients
- FDA and public discussion on RSV clinical endpoints:
  - FDA and Duke University/Duke-Margolis Center for Health Policy held a workshop on May 2, 2016 to discuss drug development for the treatment and prevention of RSV infection
  - FDA published Draft Guidance: "Respiratory Syncytial Virus Infection: Developing Antiviral Drugs for Prophylaxis and Treatment Guidance for Industry" in October 2017 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/respiratory-syncytial-virus-infection-developing-antiviral-drugs-prophylaxis-and-treatment-guidance)

High-Risk Populations

- According to the Centers for Disease Control, groups at greatest risk for severe illness from RSV include:
  - All infants, especially those ≤6 months of age
  - Premature infants
  - Children <2 years of age with certain underlying medical condition (e.g., CLD or CHD)
- Risk assessment is based on an increased RSV hospitalization rate in the population.

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Nirsevimab Dosing

Nirsevimab Proposed Dosage Regimen

- First RSV season: a single 50-mg IM injection for infants weighing <5 kg, and a single 100-mg IM injection for infants weighing 5 kg and greater

- Children less than 24 months of age who remain vulnerable to severe RSV disease during their second RSV season: a single, 200-mg IM injection

Nirsevimab Dose Determination

- The proposed dosage regimen in term and preterm (≥29 weeks GA) neonates and infants born during or entering RSV Season 1:
  - Primarily supported by the clinical efficacy results of Trials 03 and 04
  - Supported by observed higher MA RSV LRTI incidence in infants receiving less than the proposed dose in Trial 03
  - Supported by flat exposure-response relationship between the area under the concentration-time curve (AUC) and MA RSV LRTI incidence with the proposed dose
- The dosage regimen selection for preterm (including <29 weeks GA) neonates and infants (Season 1), and for infants/children with certain underlying medical conditions (Season 1 & 2) is:
  - Supported by similar nirsevimab serum exposures observed in Trial 05 vs. in Trial 04
  - Supported by descriptive efficacy results in Trial 05

Exposure Measures Used to Support Nirsevimab Dosage

Serum nirsevimab concentration on Day 150 vs. EC90 of 6.8 µg/mL

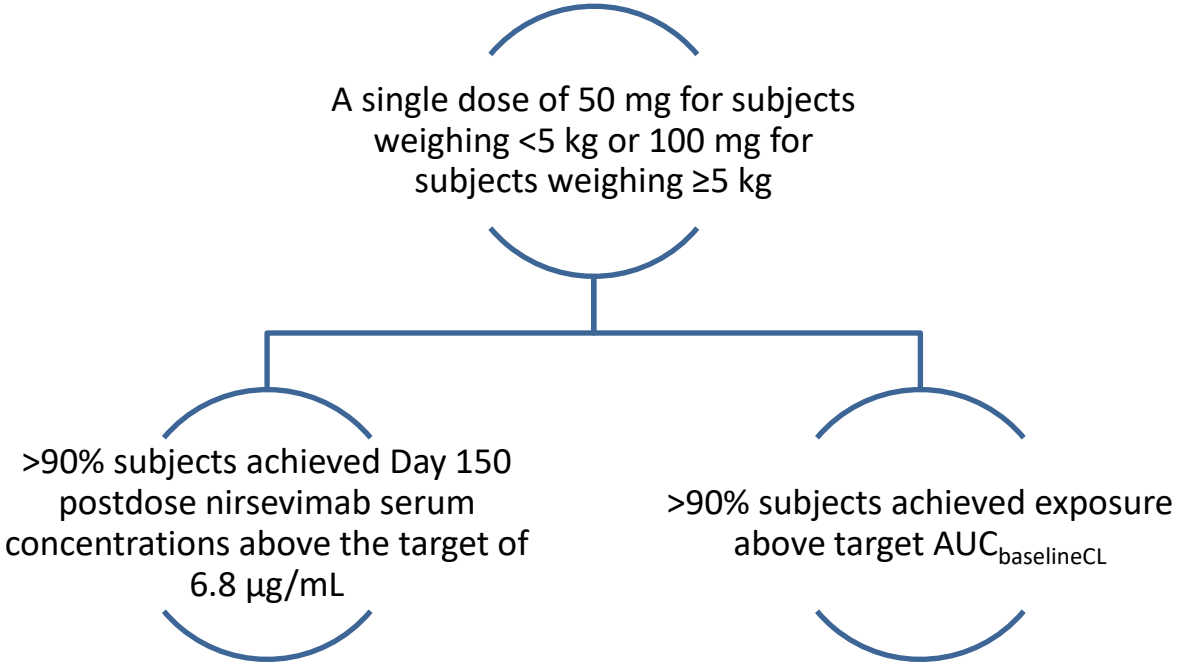
- Determined based on data from a cotton rat RSV challenge model

AUC (determined based on individual baseline clearance) of 12.8 mg*day/mL

- Identified by nirsevimab exposure ($AUC_{baselineCL}$)-response (primary efficacy endpoint) analysis based on data from Trials 03 and 04

EC_{90}: concentration for 90% effectiveness;
$AUC_{baselineCL}$: Area under the concentration-time curve (AUC) calculated based on the individual clearance (CL) at baseline

Pharmacokinetic Evidence Supporting Nirsevimab Dosage for Neonates and Infants in RSV Season 1



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Efficacy and Safety Issues

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Melisse Baylor, MD, Clinical Reviewer
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DeAngelo McKinley, PhD, Clinical Data Scientist

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Clinical Efficacy

Design of Placebo-Controlled Trials

- The clinical program included 2 placebo-controlled trials
  - one Phase 2b trial, and one Phase 3 trial
- Both trials were randomized, double-blind, with identical primary and secondary endpoints
- Both endpoints were evaluated from baseline through Day 150 postdose
- Key differences between the trials:
  - Study populations
  - Selected dose
  - Duration of safety follow-up

Statistical Assessment of Efficacy

Trials 03 and 04

- Design and baseline demographics
- Primary and secondary endpoints: efficacy results
- Subgroup analyses

Trial 04

- COVID-related interruption and prespecified analyses

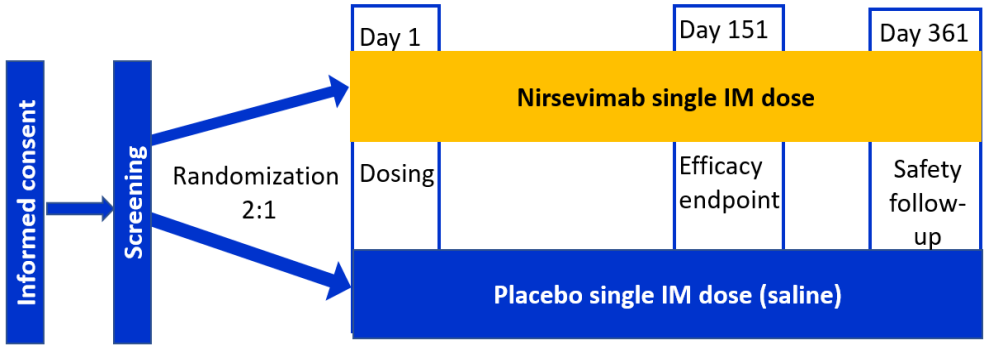
Conclusions

Efficacy Analyses: Trials 03 and 04

- **Primary endpoint**
  - The incidence of medically attended lower respiratory tract infection (LRTI), including hospitalization, due to RT-PCR-confirmed RSV through Day 150 postdose in infants born during or entering their first RSV season
- **Secondary endpoint**
  - The incidence of RSV hospitalization by Day 150 postdose
- **Analysis approach (primary endpoint)**
  - Poisson regression model with robust variance with treatment group and age group at randomization (i.e., age ≤3 months, age >3 to ≤6 months, age >6 months) and dichotomous temperate (northern and southern) hemispheres as covariates
  - Missing outcomes were imputed based on the observed placebo RSV LRTI rate conditional on stratification factors using multiple imputation approach
- **Evaluation of impact of missing data (sensitivity analysis)**
  - Primary analysis for all randomized participants with an additional assumption that all subjects on nirsevimab who had a missing outcome had their outcomes imputed as events

Trial 03: Trial Design

- Phase 2b, double-blind, 2:1
- Randomization stratification factors:
  - Chronological Age (≤3 months, >3 to ≤6 months, and >6 months)
  - Hemisphere (northern and southern)



- Study Participants: ≥29 to <35 weeks of gestation
- All subjects on nirsevimab received 50 mg dose

Trial 03: Select Baseline Characteristics

Randomized subjects (N=1453)

- ≥29 to <35 weeks of gestation*
- 52% Male
- 72% White, 18% Black or African American
- 20% of subjects from US
- 68% from Northern Hemisphere
- Mean Age 3.3 months
- Mean Weight 4.6kg
- 98% subjects were younger than 8 month of age

* Seven subjects on nirsevimab were 35 wGA

Trial 03: Incidence of MA-RSV-LRTI Through Day 150 Postdose

Primary Analysis Results Trial 03

	Nirsevimab N=969	Placebo N=484
Events (# of subjects, n (%))	25 (2.6)	46 (9.5)
Subjects requiring imputation* n (%)	24 (2.5)	11 (2.3)
RRR‡ (95% CI) §	70.1% (52.3% to 81.2%) p < 0.0001	

*Subjects with missing outcomes through Day 150 postdose. The final status of those subjects was imputed based on the observed placebo rate conditional on stratification factors using multiple imputation approach.
‡RRR: relative risk reduction
§ Poisson regression model with robust variance with of treatment group and age group at randomization and dichotomous temperate hemispheres as covariates; CI: confidence interval

Trial 03: Incidence of MA-RSV-LRTI Through Day 150 Postdose

Sensitivity Analysis: Trial 03

(impact of missing data)

Primary analysis with assumption that all subjects on nirsevimab with missing outcomes had experienced MA RSV LRTI

RRR 48.4%
95% CI (24.2% to 64.9%)
in favor of nirsevimab

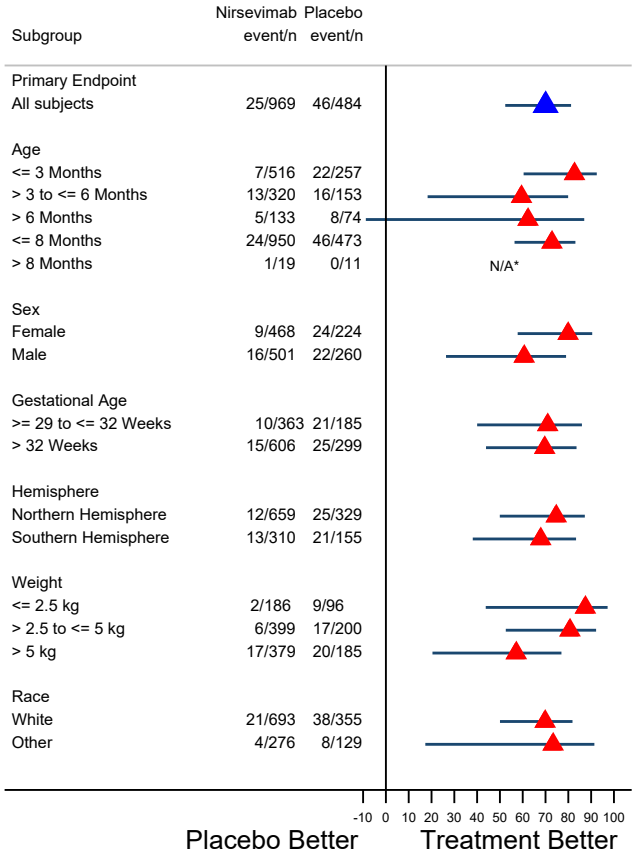
Trial 03: Incidence of RSV Hospitalizations Through Day 150 Postdose

Secondary Endpoint Analysis Results Trial 03

	Nirsevimab N=969	Placebo N=484
Events (# of subjects, n (%))	8 (0.8)	20 (4.1)
Subjects requiring imputation* n (%)	24 (2.5)	11 (2.3)
RRR‡ (95% CI) §	78.4% (51.9%, 90.3%) p-value=0.0002	

*Subjects with missing outcomes through Day 150 postdose. The final status of those subjects was imputed based on the observed placebo rate conditional on stratification factors using multiple imputation approach.
‡RRR: relative risk reduction
§Poisson regression model with robust variance with treatment group as a covariate; CI: confidence interval

Trial 03 Subgroup Analyses: Incidence of MA RSV LRTI

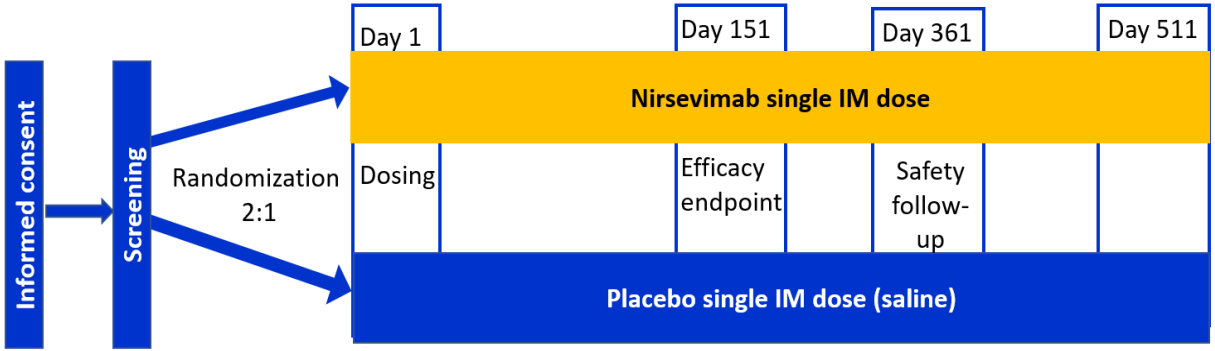


Relative Risk Reduction (%)

*The RRR cannot be calculated because the number of events was not sufficient

Trial 04: Trial Design

- Phase 3, double-blind, 2:1
- Randomization stratification factors:
  - Chronological Age (≤3 months, >3 to ≤6 months, and >6 months)
  - Hemisphere (northern and southern)



- Study Participants: ≥35 weeks of gestation
- Nirsevimab dose: <5 kg received 50 mg, ≥5 kg received 100 mg

Trial 04 and COVID-19 Related Interruption

- Enrollment in Trial 04 Primary cohort was paused because of COVID-19 pandemic's impact on operational aspects of study conduct
  - The prespecified primary analysis was based on the data collected before the interruption (Primary Cohort)
  - After interruption, additional participants were subsequently randomized to collect more safety data (Safety Cohort)
  - The randomization, safety monitoring, and efficacy assessments were conducted similarly in both cohorts
  - Combining Primary and Safety cohorts for analysis of efficacy was a prespecified exploratory analysis in the Applicant's Statistical Analysis Plan

Trial 04: Select Baseline Characteristics

Randomized subjects (N= 1490)

- ≥35 weeks of gestation*
- 52% Male
- 53% White, 29% Black or African American
- 29% of subjects from US
- 69% from Northern Hemisphere
- Mean Age 2.9 months
- Mean Weight 5.5 kg
- 97% of subjects younger than 8 months of age

* One subject on placebo was 32 weeks of gestation

Trial 04: Incidence of MA-RSV-LRTI Through Day 150 Postdose

Primary Analysis Results Trial 04 (Primary Cohort)

	Nirsevimab N=994	Placebo N=496
Events (# of subjects, n (%))	12(1.2)	25(5.0)
Subjects requiring imputation* n (%)	16(1.6)	7(1.4)
RRR‡ (95% CI)	74.9% (50.6% to 87.3%) p < 0.0001	

*Subjects with missing outcomes on Day 150 postdose. The final status of those subjects was imputed based on the observed placebo rate conditional on stratification factors using multiple imputation approach.
‡RRR: relative risk reduction
§ Poisson regression model with robust variance with of treatment group and age group at randomization as covariates; CI: confidence interval

Trial 04: Incidence of MA-RSV-LRTI Through Day 150 Postdose

Sensitivity Analysis: Trial 04

(impact of missing data)

Primary analysis with assumption that all subjects on nirsevimab with missing outcomes had experienced MA RSV LRTI

RRR 44.8%
95% CI (6.7% to 67.3%)
in favor of nirsevimab

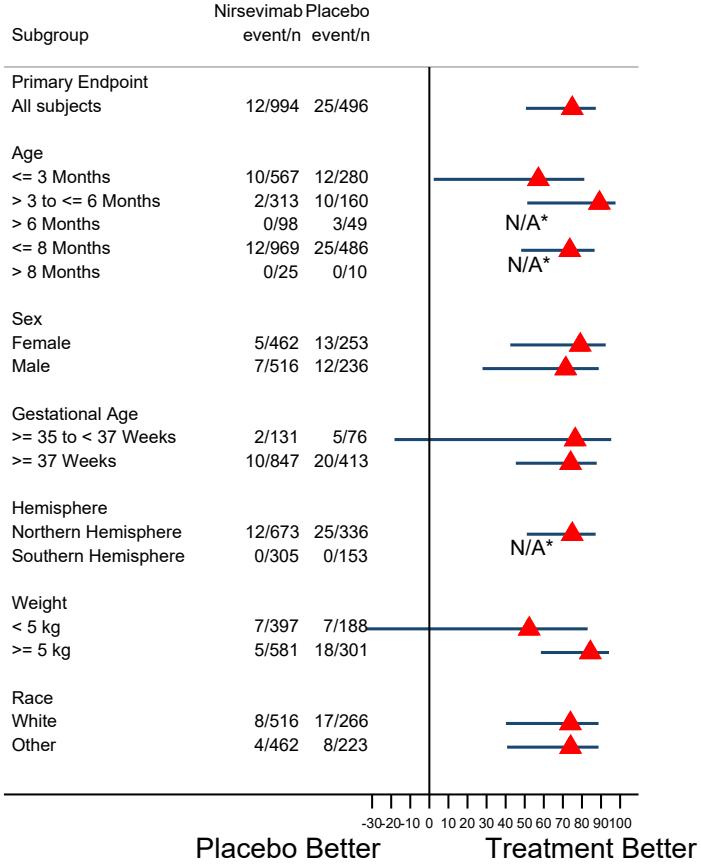
Trial 04: Incidence of RSV Hospitalization Through Day 150 Postdose

Secondary Endpoint Analysis Results: Trial 04 (Primary Cohort)

	Nirsevimab N=994	Placebo N=496
Events (# of subjects, n (%))	6(0.6)	8(1.6)
Subjects requiring imputation* n (%)	16(1.6)	7(1.4)
RRR‡ (95% CI)§	60.2% (-14.6% to 86.2%) p=0.09	

*Subjects with missing outcomes on Day 150 postdose. The final status of those subjects was imputed based on the observed placebo rate conditional on stratification factors using multiple imputation approach.
‡RRR: relative risk reduction
§Poisson regression model with robust variance with treatment group as a covariate; CI: confidence interval

Trial 04 Subgroup Analyses: Incidence of MA RSV LRTI



*The RRR cannot be calculated because the number of events was not sufficient

Conclusions

- Primary endpoint was met in both trials (prevention of MA RSV LRTI)
  - Trial 03 RRR 70.1%, 95% CI (52.3%, 81.2%)
  - Trial 04 Primary Cohort RRR 74.9%, 95% CI (50.6%, 87.3%)
- Missing data did not impact conclusion of superiority of nirsevimab to placebo in prevention of MA RSV LRTI
- Subgroup analyses for the primary endpoint were consistent across all groups
- The prespecified secondary endpoint, incidence of RSV hospitalization, was met in Trial 03 and there was a trend towards efficacy in Trial 04 in infants born at ≥35 weeks gestational age (GA).

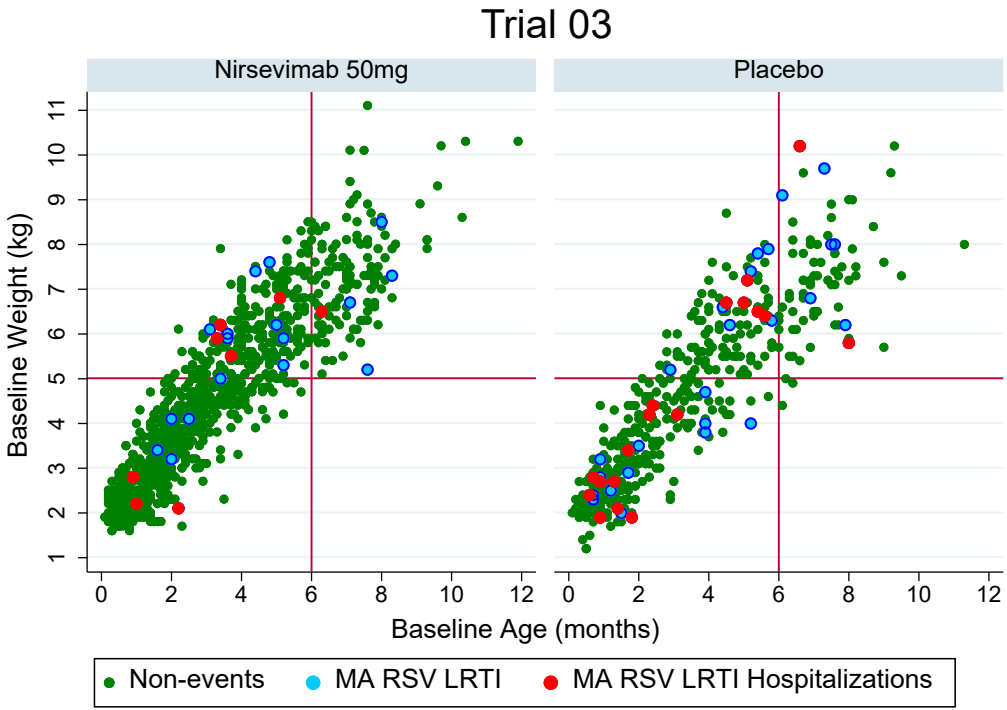
Key Efficacy Considerations

Key Efficacy Considerations

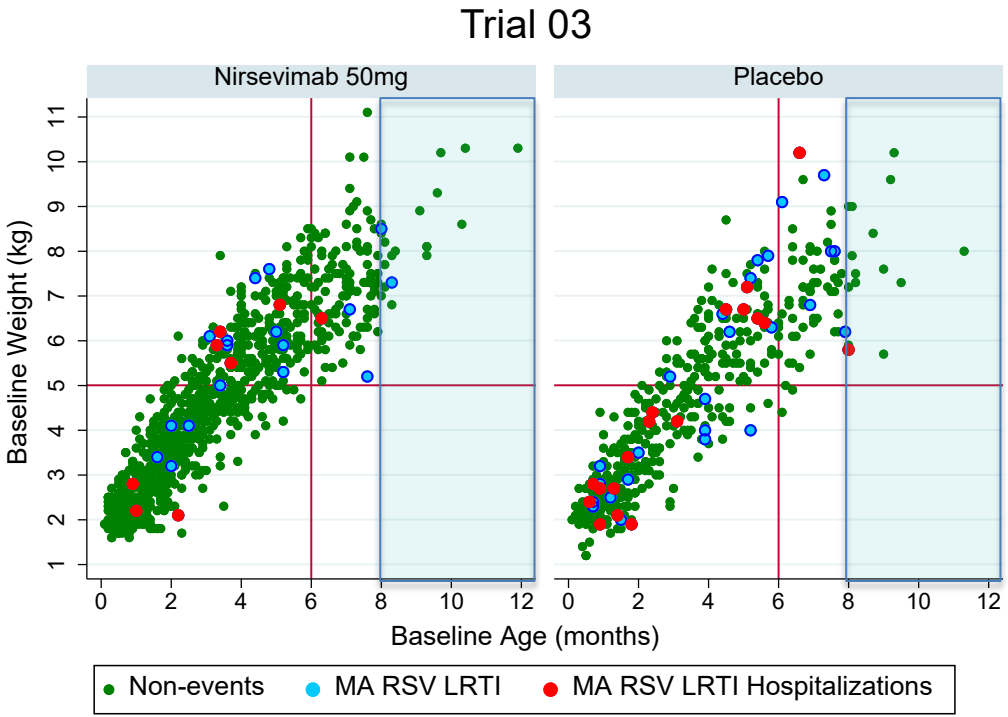
- The evidence for the efficacy of nirsevimab to prevent RSV lower respiratory tract disease during the first RSV season across the chronological and gestational age subgroups.
- Support for the use of nirsevimab in the prevention of RSV lower respiratory tract disease in children who remain vulnerable to severe RSV disease through their second RSV seasons

Efficacy by Chronological Age and Gestational Age

Trial 03: Relationship Between Baseline Age and Efficacy Outcome (Day 150 Postdose)



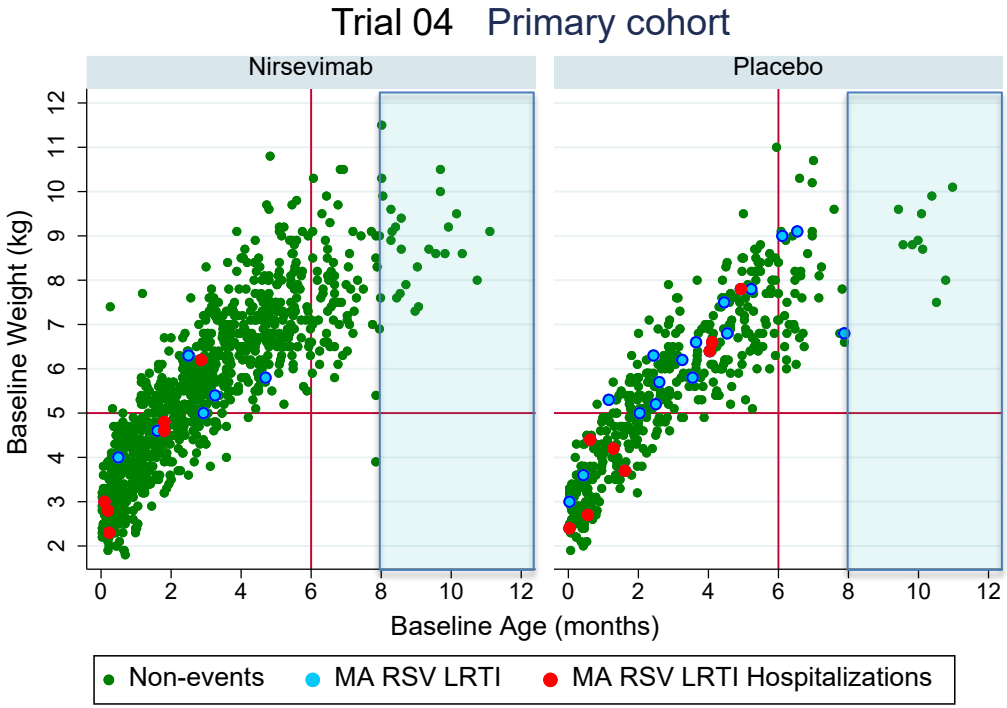
Trial 03: Relationship Between Baseline Age and Efficacy Outcome (Day 150 Postdose)



Subjects age >8 months

- Nirsevimab: 19
- Placebo: 11

Trial 04: Relationship Between Baseline Age and Efficacy Outcome (Day 150 Postdose)



Subjects age >8 months

- Nirsevimab: 25
- Placebo: 10

Age of Infants at First Exposure to RSV

- RSV circulation varies by climate
  - Tropical climates: RSV circulates year round
  - Temperate climates: RSV circulates yearly in seasons that start in fall, peak in winter and end in spring
    - Typically starts in mid-September to mid-November and ends in mid-April to mid May
- Infants born in tropical climates are exposed shortly after birth
- Infants born in temperate climates are usually exposed to RSV by approximately 7 months of life

Gestational Ages of Neonates and Infants Enrolled in Trials of Nirsevimab

Trial	Gestational Age	No. of Subjects Who Received Nirsevimab
Trial 03	≥29 weeks to <35 weeks	968
Trial 04 (Primary Cohort)	≥35 weeks to <38 weeks	253
	≥38 weeks (term)	732
Trial 05 (Season 1)	<29 weeks	128
	≥29 weeks to <35 weeks	390
	≥35 weeks to <38 weeks	51
	≥38 weeks (term)	45

Incidence of MA RSV LRTI by Gestational Age

Trial	Gestational Age	Nirsevimab	Placebo	RRR (95% CI)
Trial 03	**No. of Subjects**	968	479	70.1%
	≥29 to <35* weeks	25 (2.6%)	46 (9.5%)	(52.3, 81.2)
Trial 04 (Primary Cohort)	**No. of Total Subjects**	994	496	74.9%
	MA RSV LRTI, n (%)	12 (1.2%)	25 (5.0%)	(50.6, 87.3)
	No. of Subjects ≥35 to <38 weeks	257	134	69.0%
	MA RSV LRTI, n (%)	5 (2%)	9 (6.7%)	(12.2%, 89.1%)
	No. of Subjects ≥38 weeks	737	362	77.1%
	MA RSV LRTI, n (%)	7 (1%)	16 (4.4%)	(44.5%, 90.5%)

*Includes 38 subjects born at 35 weeks GA and one born at 40 weeks GA

Efficacy in Trial 05 for Infants Born at <29 Weeks Gestational Age

- In Trial 05, 196 of 918 infants (21%) enrolled were born at <29 weeks of gestational age
- Incidence of MA-RSV-LRTI through Day 150 postdose was a secondary endpoint
- 2 MA RSV LRTI events in this subgroup, nirsevimab (1) and palivizumab (1)

Conclusion

- Chronological Age
  - Few infants >8 months of age were enrolled in Trials 03 and 04
  - In the U.S., most infants would be exposed to RSV by approximately 7 months of age
  - There may be times when use of nirsevimab in infants >8 months to <12 months of age is appropriate
    - ✓ Some infants may present to health care late or be lost to follow-up
    - ✓ Unusual timing of the RSV season
- Gestational Age
  - Trial 03 and the Primary Cohort of Trial 04 were powered to demonstrate efficacy in infants ≥29 weeks GA
    - ✓ Efficacy in subgroups, including term infants, was consistent with results for the primary endpoint
  - Efficacy in infants born at <29 weeks of GA established by extrapolation

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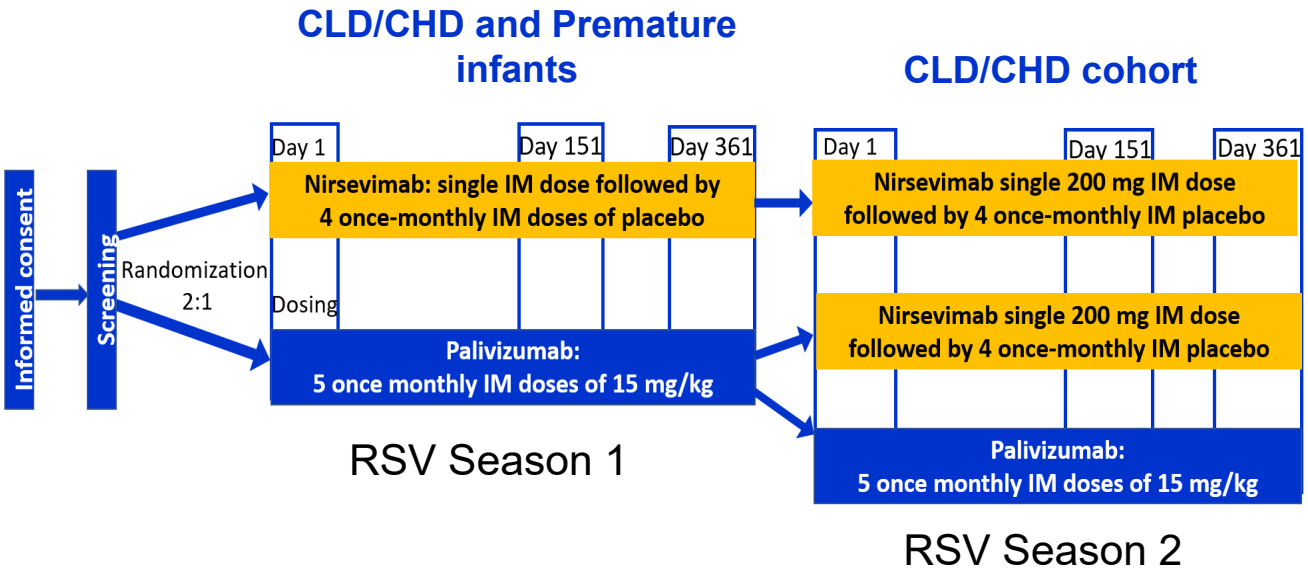
Efficacy of Nirsevimab in Preterm (including <29 weeks GA) Neonates and Infants, and Infants and Children with Certain Underlying Medical Conditions

Trial 05

- Trial 05 was a randomized, double-blind, palivizumab-controlled trial in infants and children at high-risk of severe RSV disease:
  - Infants at <35 weeks GA, including infants at <29 weeks, born during or entering first RSV Season
  - Infants and children with CLD of prematurity and hemodynamically significant CHD born during or entering their first RSV season and entering their second RSV season
- Efficacy (incidence of MA RSV LRTI) was a secondary endpoint
- Efficacy in both RSV season 1 and RSV season 2 was supported by extrapolation

Trial 05: Trial Design



Trial 05 Population

RSV Season 1	Palivizumab	Nirsevimab	Total
Total number of subjects*	304	614	918
Preterm Cohort	206 (68%)	406 (66%)	612
CLD/CHD Cohort	98 (32%)	208 (34%)	306
CLD	64	138	202
CHD	29	61	90
CLD and CHD	4	9	13
Down Syndrome	1	0	1

*Number of subjects who received at least one dose of study drug.

RSV Season 2

262 **CLD/CHD** subjects (85.6%) participated in RSV season 2:

- Nirsevimab = 220
- Palivizumab = 42

Of these 262 subjects:
CLD – 180
CHD – 72
CLD/CHD – 9
Down Syndrome - 1

Incidence of MA RSV LRTI Through Day 150 Postdose in Trial 05

	RSV Season 1		RSV Season 2	
	Palivizumab Arm* N=309	**Nirsevimab Arm* N=616**	**Palivizumab Arm N=42**	**Nirsevimab Arm N=220**
Number (%) Subjects with MA RSV LRTI	3 (1.0%)	4 (0.6%)	0	0
95% CI	0.20, 2.81	0.18, 1.65	--	--

*Numbers of subjects randomized.

Efficacy Extrapolation

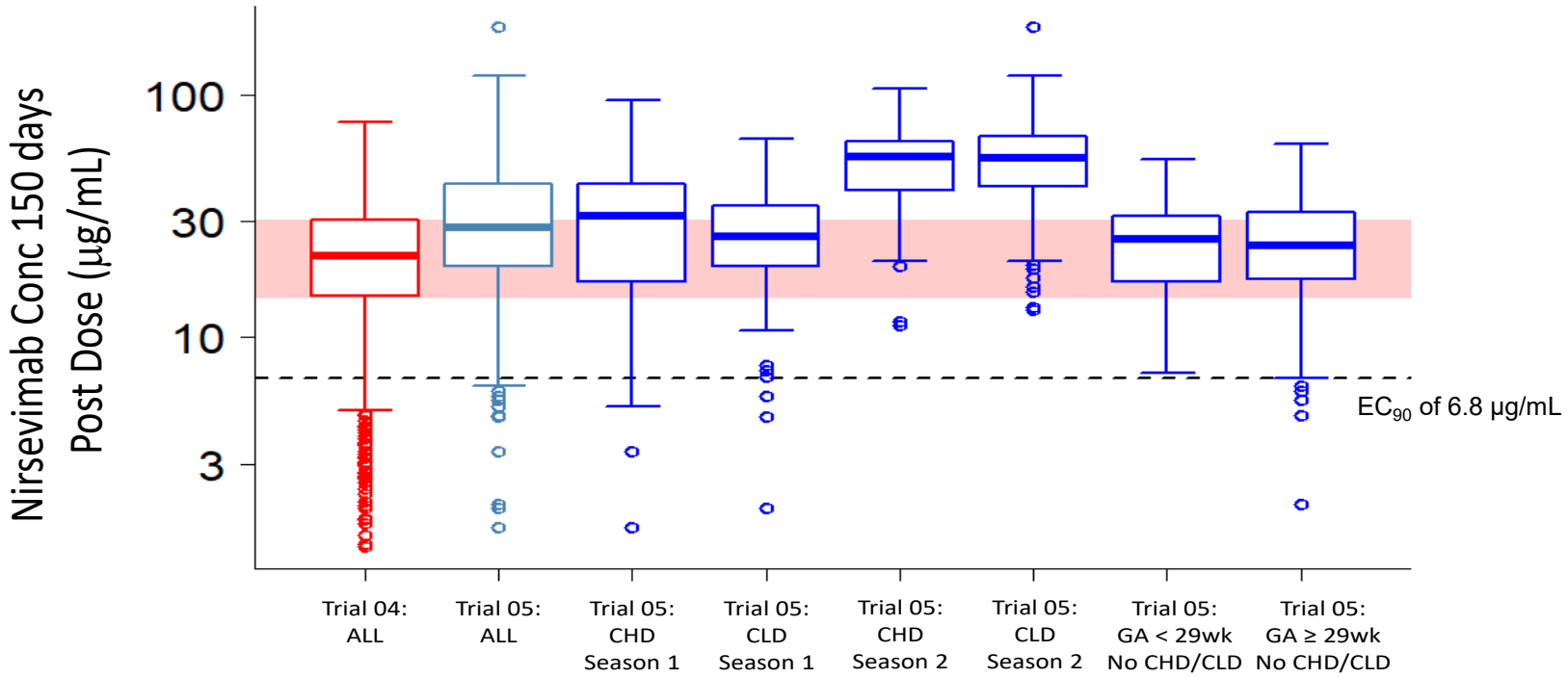
Neonates & Infants (Trial 03, 04 population) → **Neonates, Infants & Children (Trial 05 population)**

- Key Principles
  - Disease is similar in the two populations
  - Same drug mechanism of action in both populations; target is the same
  - Expected similar exposure-response relationship of the drug in the two populations
- Extrapolation based on Similar Therapeutic Concentrations

Matching Nirsevimab Exposure

- Concentration @ 150 days postdose
- $AUC_{baselineCL}$

Nirsevimab Concentrations at Day 150 Are Similar Between Trials 04 & 05



dashed line is preclinical EC90 value of 6.8 µg/mL

Percentage of Subjects With $AUC_{baselineCL}$ Above Target Level in Trial 05

	RSV Season 1	RSV Season 2
Preterm infants <29 weeks GA without CLD or CHD	93.6% (44/47)	NA
CLD	94.1% (128/136)	97.7% (129/132)
CHD	80.3% (53/66)	100% (58/58)

- 92.5% (891/963) of patients in Trial 04 had exposures >Target of 12.8 mg·day/mL

Target $AUC_{baselineCL}$ of 12.8 mg · day/mL is based on exposure-response analysis results from Trials 03 and 04.

Conclusions: Trial 05

- Nirsevimab exposures are comparable between infants in Trial 04 (Primary Cohort) and infants and children in both season 1 and season 2 of Trial 05.
  - Supports extrapolation of efficacy to Trial 05
  - Overlapping preterm neonatal populations in Trials 03 and 05
- Incidence of MA RSV LRTI in RSV season 1 was similar in nirsevimab and palivizumab arms
  - No cases of MA RSV LRTI reported in season 2

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Safety Considerations

Nirsevimab Clinical Safety Database

Population of Study Subjects	No. of Subjects Who Received Nirsevimab
Infants and children who received the proposed dose	**3,285**
Infants and children who received the proposed dose in the 3 main trials	3,224
Trial 03	572
Trial 04	1998
Trial 05	654

Length of Safety Follow-up in Main Clinical Trials

Trial	Trial Group /Subgroup	Days of Safety Follow-Up	Days of Safety Follow-Up Submitted in BLA
03	Entire study population	360	360
04	Primary Cohort	510	510
	Safety Cohort	510	360
05	Year 1	360	360
	Year 2	360	150

Key Safety Considerations

- Anaphylaxis, rash and other hypersensitivity reactions
- Imbalance in Deaths

FDA Rash Analyses

- Analysis used a group query for rash that included rashes that could possibly be related to drug use
  - Omitted rashes with another clear etiology, such as diaper dermatitis
  - Omitted single lesion rash diagnoses
  - Omitted chronic skin conditions, such as eczema
  - Omitted all mild rashes reported after Day 75
- Rashes identified within 14 days of study drug administration
  - Temporal relationship to study drug administration
  - Time period of highest nirsevimab serum concentration

Anaphylaxis, Rash and Other Hypersensitivity Reactions

- Anaphylaxis: no reports in clinical trials
- Serious skin reactions (for example, Stevens-Johnson Syndrome): no reports in clinical trials
- Angioedema: 1 serious adverse event (SAE) on Day 142 in Trial 05, may have been related to change in formula
- Urticaria: 2 adverse events (AEs), both mild (Days 7 and 20 postdose)
- Drug eruption: 1 AE, moderate, Day 6 postdose
- Rash within 14 days postdose: AE reported in <2% subjects in both nirsevimab and control arms (most mild or moderate)

Conclusions: Hypersensitivity Reactions

- No adverse events of anaphylaxis
- Skin and mucous membrane adverse events consistent with hypersensitivity reactions were observed at a low incidence in subjects who received either nirsevimab or control.
- Anaphylaxis, hypersensitivity reactions, and rash have been reported with palivizumab and other monoclonal antibodies. Therefore, postmarketing reports of these events are likely for nirsevimab, if approved.

Imbalance in Deaths

Deaths in Nirsevimab Clinical Trials

Trial	Nirsevimab Arm		Control Arm	
	Subjects N	Deaths n (%)	Subjects N	Deaths n (%)
02	71	0	18	0
03	968	2 (0.2%)	479	3* (0.6%)
04	1,998	4 (0.2%)	996	0
05	613	5 (0.8%)	304	1 (0.3%)
08	60	1 (1.7%)	---	--
Total	3,710	12 (0.32%)	1,797	4 (0.22%)

*An additional death in the placebo arm of Trial 03 occurred 6 days after the study end.

Causes of Death in Subjects Who Received Nirsevimab

Types of Death	Examples	Number of Deaths
Underlying disease	Cardiac disease (4), tumor (1)	5
Other infectious etiology	Gastroenteritis (2), COVID-19 (1)	3
Contributing illness	Protein calorie malnutrition	1
Accident	Hit by car	1
Unknown	Possible sudden infant death syndrome (2), one with undiagnosed chronic illness	2

Conclusions: Imbalance in Deaths

- In the trials of nirsevimab, the absolute number of deaths was higher in the nirsevimab arms than in the control arms, but the percentage of deaths was low and similar between the nirsevimab and control arms.
- The causes of death varied – there was no pattern in cause of death or deaths related to a single organ system.
- None of the deaths appeared to be related to nirsevimab.

Other Considerations

Maternal RSV Vaccine

- Several Maternal RSV Vaccines under development
  - Advisory Committee held for maternal RSV vaccine on May 18, 2023
- Infants whose mothers had received an investigational maternal RSV vaccine were excluded from nirsevimab trials
- Knowledge Gaps:
  - Does use of nirsevimab in infant whose mother received a maternal RSV vaccine provide added benefit?
  - Is there a concern for safety related to use of nirsevimab in this setting?

Long Term Follow-Up

Trial 04: Primary Cohort (Day 362 to Day 511 Through Second RSV Season)*

	Nirsevimab N=994	Placebo N=496
All MA RSV LRTI (by RT-PCR)	7 (0.7%)	2 (0.4%)
All MA RSV LRTI (any test for RSV)	8 (0.8%)	4 (0.8%)
All MA RSV respiratory illness with hospitalization (by RT-PCR)	0	0
All MA RSV respiratory illness with hospitalization (any test for RSV)	1 (0.1%)	1 (0.2%)

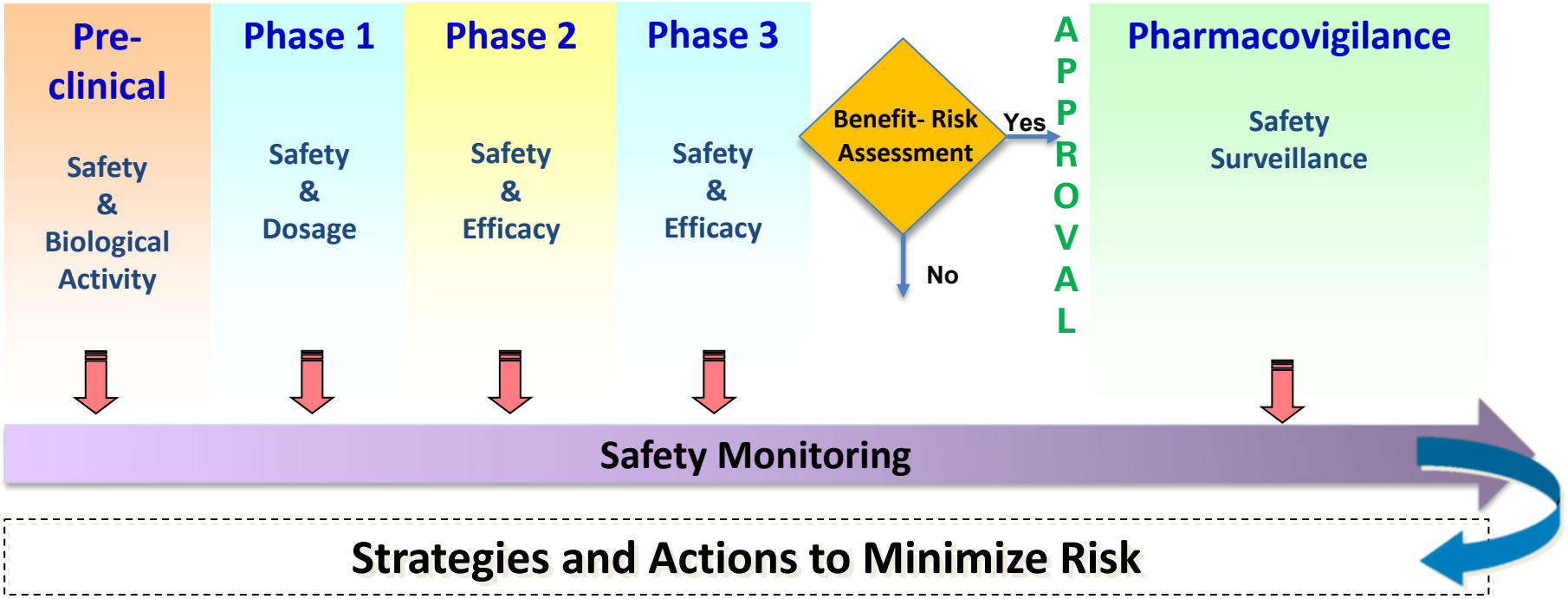
*Subjects in Trial 04 were followed for medically attended (MA) respiratory illnesses from Day 361 to 511, e.g., through second RSV season, without receiving nirsevimab prior to second RSV season.

Proposed Pharmacovigilance Strategy

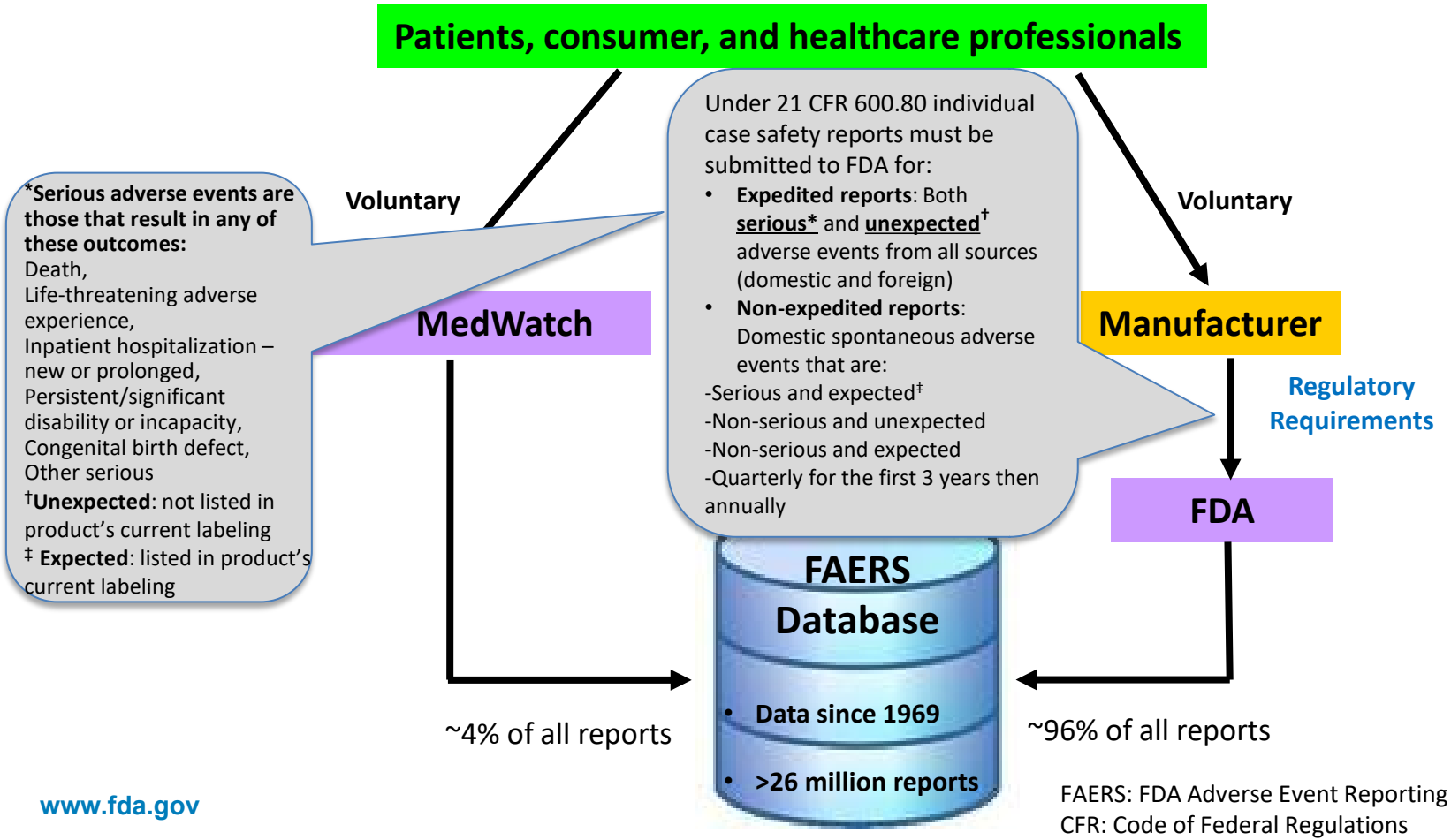
Neha Gada, PharmD, BCPS, Cross Discipline Safety Advisor

Office of Surveillance and Epidemiology

Lifecycle Approach to Safety Assessment



Postmarketing Adverse Events & FAERS Submission



FAERS: FDA Adverse Event Reporting System
CFR: Code of Federal Regulations

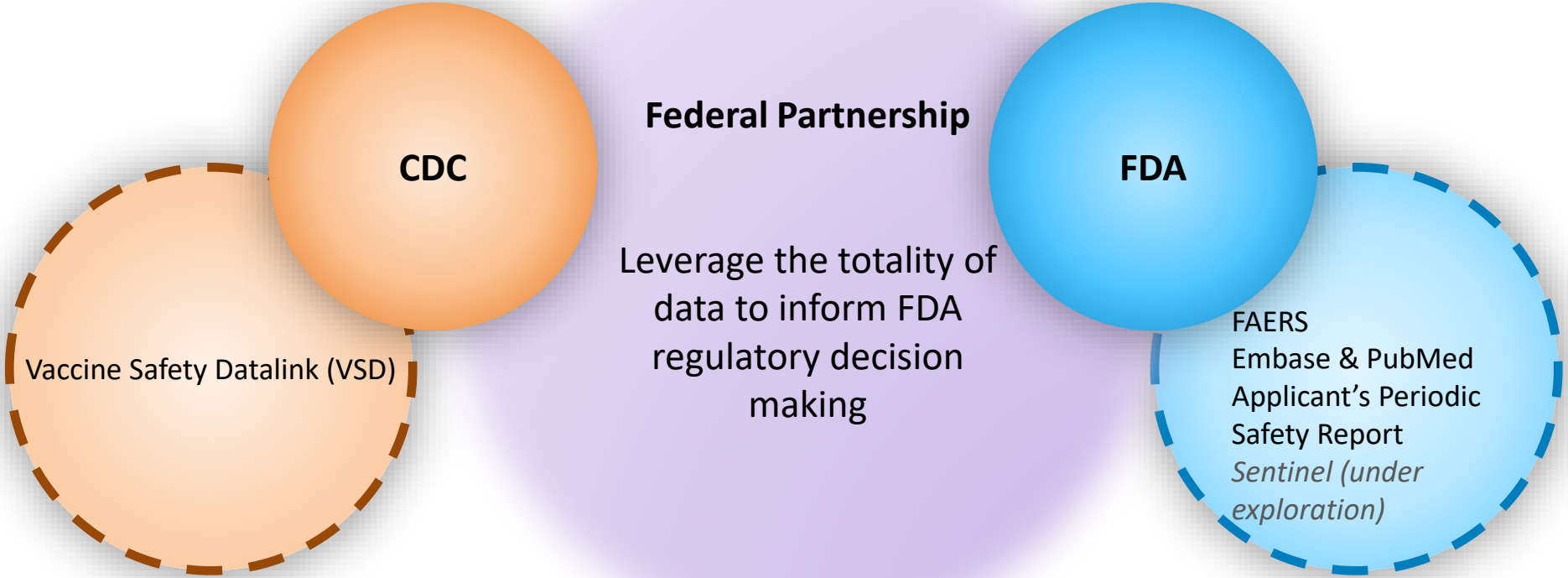
How to Report Adverse Events to FDA

Food and Drug Administration
MedWatch

- How to Report:
  - Online (www.fda.gov/medwatch)
  - Download the form
    - Mail
    - Fax 1–800–332–0178
- For questions about the form:
  - 1–800–332–1088

U.S. Food and Drug Administration. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Available at: https://www.fda.gov/Safety/MedWatch/default.htm

Proposed Pharmacovigilance Strategy- Active and Passive Surveillance



CDC: Centers for Disease Control and Prevention

FAERS: FDA Adverse Event Reporting System

FDA: Drug Safety Information to the Public

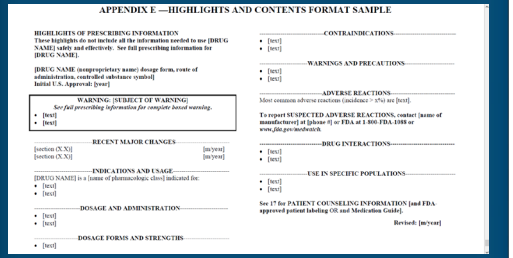
FAERS Public Dashboard [1]

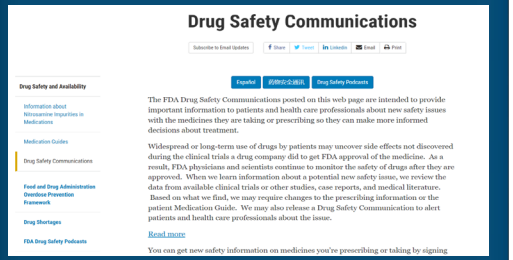
An interactive web-based tool that allows for the querying of FAERS data

Potential Signals [2]

FDA shares early safety signals or potential signals identified through FAERS

Communications [3, 4]





U.S. Prescribing information, Drug Safety Communications, and other communication tools

Resources

[1] https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard
[2] https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system
[3] https://www.fda.gov/drugs/drug-safety-and-availability/drug-safety-communications
[4] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

All accessed May 4, 2023

FDA U.S. FOOD & DRUG ADMINISTRATION

Overall Summary

Melisse Baylor, MD, Clinical Reviewer

Overall Summary

- Nirsevimab efficacy for the prevention of MA RSV LRTI was demonstrated in 2 adequate and well controlled trials.
- Nirsevimab efficacy for the prevention of RSV hospitalization was demonstrated in infants born at ≥29 to <35 weeks of GA and there was a trend toward efficacy in infants born at ≥35 weeks GA.
- Efficacy of nirsevimab in infants <24 months of age who remain vulnerable to severe RSV disease in their second RSV season was established by extrapolation.
- No major safety concerns were identified.
- FDA plans to conduct postmarketing surveillance to further assess nirsevimab safety, if approved, using several data sources.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Charge to the Committee

Yodit Belew, MD
Associate Director for Therapeutic Review
Division of Antivirals

Proposed Nirsevimab Indication and Dosing

- **Proposed indication**: prevention of 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
- **Proposed dosing**
  - **First RSV season**:
  - a single, 50-mg IM injection for infants weighing <5 kg, and a single, 100-mg IM injection for infants weighing at least 5 kg
  - **Second RSV season:**
  - a single, 200-mg IM injection for children less than 24 months of age who remain vulnerable to severe RSV disease through their second RSV season

Background

- RSV infection can be severe or life-threatening in neonates and infants, and in children with certain underlying medical conditions

- Palivizumab is FDA-approved for prevention of RSV disease in certain pediatric patients

- Palivizumab indication: the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients
  - with a history of premature birth (≤35 weeks gestational age) and who are ≤6 months of age at the beginning of RSV season,
  - with bronchopulmonary dysplasia (BPD) requiring medical treatment within the previous 6 months, and who are ≤24 months of age at the beginning of RSV season,
  - with hemodynamically significant CHD and who are ≤24 months of age at the beginning of RSV season

BLA 761328

- Clinical trials conducted to support safety and efficacy of nirsevimab
  - **Trial 03** in neonates and infants born at ≥29 to <35 weeks of gestation and entering their first RSV season
  - **Trial 04** in neonates and infants born at ≥ 35 weeks of gestation and entering their first RSV season
  - **Trial 05**
    - Season 1: neonates and infants born at <35 weeks of gestation (including <29 weeks of gestation); infants with CLD of prematurity or hemodynamically significant CHD
    - Season 2: children <24 months of age who remain vulnerable to severe RSV disease

Key Considerations

- Efficacy of nirsevimab in neonates and infants born during or entering their first RSV season, as assessed by chronological or gestational age
- Efficacy of nirsevimab in children less than 24 months of age who remain vulnerable to severe RSV disease during their second RSV season
- Hypersensitivity reactions, including anaphylaxis, and other serious adverse events, including death

Charge to the Committee

Vote

1. Is the overall benefit-risk assessment favorable for the use of nirsevimab for the prevention of RSV lower respiratory disease in neonates and infants born during or entering their first RSV season?

Discuss

2. Please comment on the benefits and risks for nirsevimab when assessed by chronological and gestational age groups. Discuss the population or subpopulation for whom nirsevimab administration in the first RSV season would be most appropriate.

Charge to the Committee (cont.)

Vote

3. Is the overall benefit-risk assessment favorable for the use of nirsevimab for the prevention of RSV lower respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season?

Charge to the Committee (cont.)

Discuss

4. In the context of potential, future availability of maternal RSV vaccine to protect infants from RSV disease during their first RSV season, what additional data may be helpful to inform future recommendations regarding the use of nirsevimab in infants born to mothers who received RSV vaccination?


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Backup Slides

MA RSV LRTI Definition in Trials 03, 04 and 05

Requires all 3 criteria:

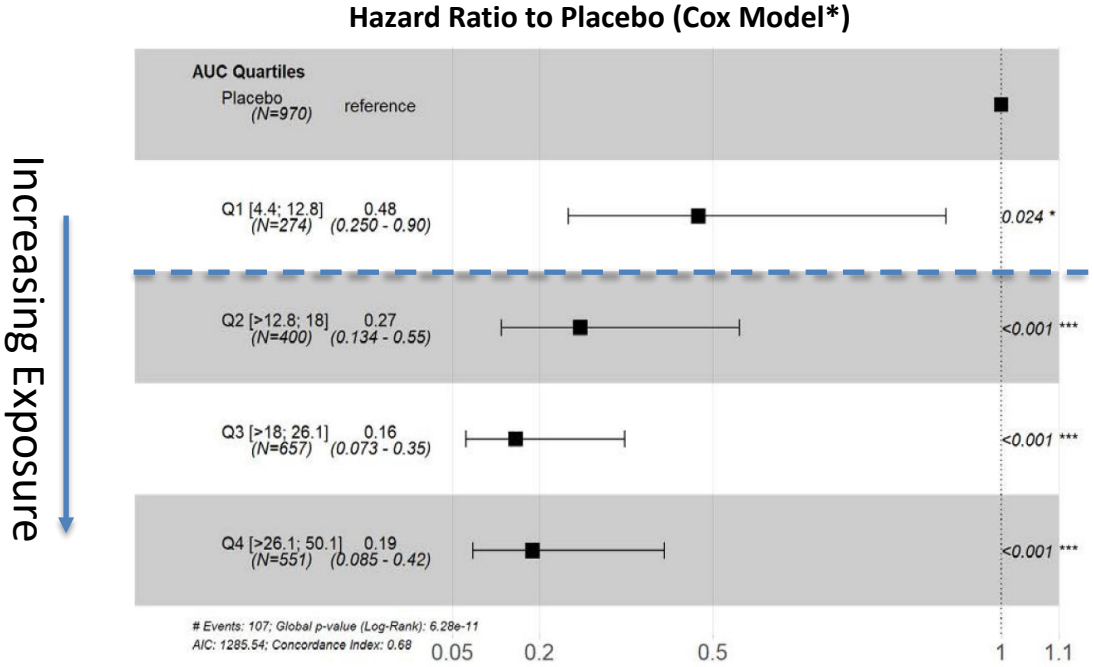
- RSV positive by central lab RT-PCR;
- At least one physical exam findings related to LRTI: rhonchi, rales, crackles or wheeze; AND
- At least one measure of clinical severity:
  - Increased respiratory rate for age (<2months ≥60/min, 2 to 6 months ≥50/min, >6 months ≥40 min); or
  - Hypoxemia on room air (02 sat <95%)
  - Clinical signs of severe respiratory disease – acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal/subcostal/supraclavicular retractions, grunting, or need for IV fluids for dehydration

Trial 05: Trial Design Rationale

Placebo-controlled trial not acceptable:

- Enrolled infants at high-risk of severe RSV disease and who were eligible for palivizumab in the country or at the site where enrolled; therefore, use of placebo control was not acceptable.
- Non-inferiority trial design was not considered feasible:
  - Would require a large sample size,
  - Unlikely that such a large trial could be conducted within a reasonable time frame, and
  - Non-inferiority margin could not be determined because no randomized, placebo-controlled trials with the endpoint of MA RSV LRTI are available to estimate the treatment effect of palivizumab versus placebo.

ER Based on Trials 03 and 04 Data



Target AUC:
12.8 mg·day/mL

Data from all subjects in Trials 03 and 04.
Figure Source: submitted CP summary