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Imbalance in Severe Respiratory Syncytial Virus (RSV) Cases in a Clinical Trial of an RSV Vaccine in Infants and Young Children

Implications for Pediatric RSV Vaccine Development

Vaccines and Related Biological Products Advisory Committee Meeting (VRBPAC)

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Presentation Outline

- Overview of pediatric RSV vaccine development
- Imbalance observed in severe/hospitalized RSV cases in infant clinical trial
- Severe/hospitalized human metapneumovirus (hMPV) cases
- Summary & considerations for pediatric RSV vaccine development
- Discussion topics

Overview of Pediatric RSV Vaccine Development

Unmet Need for RSV Vaccines in Children

- Large global burden of pediatric RSV disease, especially low- and middle-income countries
- Age dependent risk of RSV infection risk, reinfection is common
- No active immunization options for use in individuals < 18 years old
  - Passive immunization options include monoclonal antibodies and maternal immunization
  - These have greater availability in high-income countries
- Active RSV immunization may offer additional benefits:
  - More RSV preventative options
  - Immune priming
  - Vaccination of children in subsequent RSV seasons
  - Vaccination of children whose mothers had been vaccinated in a prior pregnancy

RSV Vaccine-Associated Enhanced Respiratory Disease (RSV VAERD)

- Defined as a higher frequency of severe lower respiratory tract disease due to wild type RSV infection following RSV vaccination as compared to control
- Observed in the 1960s among RSV-naïve formalin-inactivated RSV vaccine (FI-RSV) recipients
  - Absent pre-fusion (pre-F) antigen in FI-RSV vaccine
  - Low neutralizing antibody (nAb) responses to FI-RSV vaccination
  - Unbalanced T-cell priming (Th2-biased $CD4^+$ T-cell responses)
  - Cytokine-mediated pulmonary injury
- Subsequent pediatric RSV vaccine development informed by research evaluating FI-RSV vaccine immune responses & VAERD pathogenesis

2017 VRBPAC Meeting

- Renewed interest in filling the unmet need for pediatric RSV vaccines
- May 17, 2017: VRBPAC met to discuss pediatric RSV vaccine development
- VRBPAC Recommendations:
  - Nonclinical data should distinguish candidate vaccine responses from FI-RSV
  - Clinical studies to include specific criteria to detect potential enhanced respiratory disease (ERD)
  - Nonclinical and clinical data may support study in RSV-naïve participants but close & continuous monitoring for VAERD is essential during clinical studies

Current Nonclinical Safeguards

- All vaccine technologies, except live-attenuated RSV vaccines, should be assessed for VAERD potential prior to evaluation in RSV-naïve infants
- Nonclinical data should demonstrate that the candidate vaccine:
  - Expresses or presents RSV F antigen pre-fusion epitopes (if applicable)
  - Induces anti-RSV nAb responses while avoiding induction of non-nAb responses
  - Avoids induction of strong Th2-type $CD4^+$ T-cell responses
  - RSV-challenge model does not demonstrate pulmonary injury following vaccination
- Nonclinical data reviewed by FDA prior to initiation of clinical studies

Current Clinical Safeguards

- Age de-escalating pediatric clinical development
- Restricted study population: healthy children without known risk factors
- Safety and immunogenicity data in presumed RSV-experienced infants/children to support studies in presumed RSV-naïve infants/children
- Study pause rules and pre-specified RSV case definitions
  - DSMB or DMC for ongoing review of study data
- Additional recommended measures: data to evaluate T-cell responses to vaccination and determine participant baseline serostatus

Current Status of Pediatric RSV Vaccine Development

- RSV vaccine candidate platforms include live-attenuated RSV, live-attenuated chimeric respiratory viral, other viral vectored, mRNA, and recombinant particle/subunit vaccines (PATH, 2024)

- U.S. INDs: 26 candidate RSV vaccines in pediatric clinical development
  - 15 live-attenuated RSV vaccines
  - 11 other vaccine technologies include RSV F glycoprotein antigen stabilized in the preF conformation state (recombinant protein or mRNA)

- An imbalance in severe/hospitalized RSV cases in young RSV-naïve children has been identified in one clinical study of a candidate mRNA vaccine

Imbalance in Severe/Hospitalized RSV Cases:

Part B only (5 to <8 months old)

Phase 1 Study Design Highlights

DSMB review
Part B enrollment after no VAERD signal through 2023/2024 RSV season

Part A (Cohorts 1 and 2): Children 8 to <24 months

- N=81
  - RSV-only vaccine (30µg RSV)
  - RSV+hMPV vaccine (15µg RSV+15µg hMPV)
  - Placebo

Part B (Cohorts 3 and 4):

Children 5 to <8 months

- N=60
  - RSV-only vaccine (15µg RSV)
  - RSV+hMPV vaccine (7.5µg RSV + 7.5µg hMPV)
  - Placebo

Part B (Cohorts 5 and 6): Children 5 to <8 months

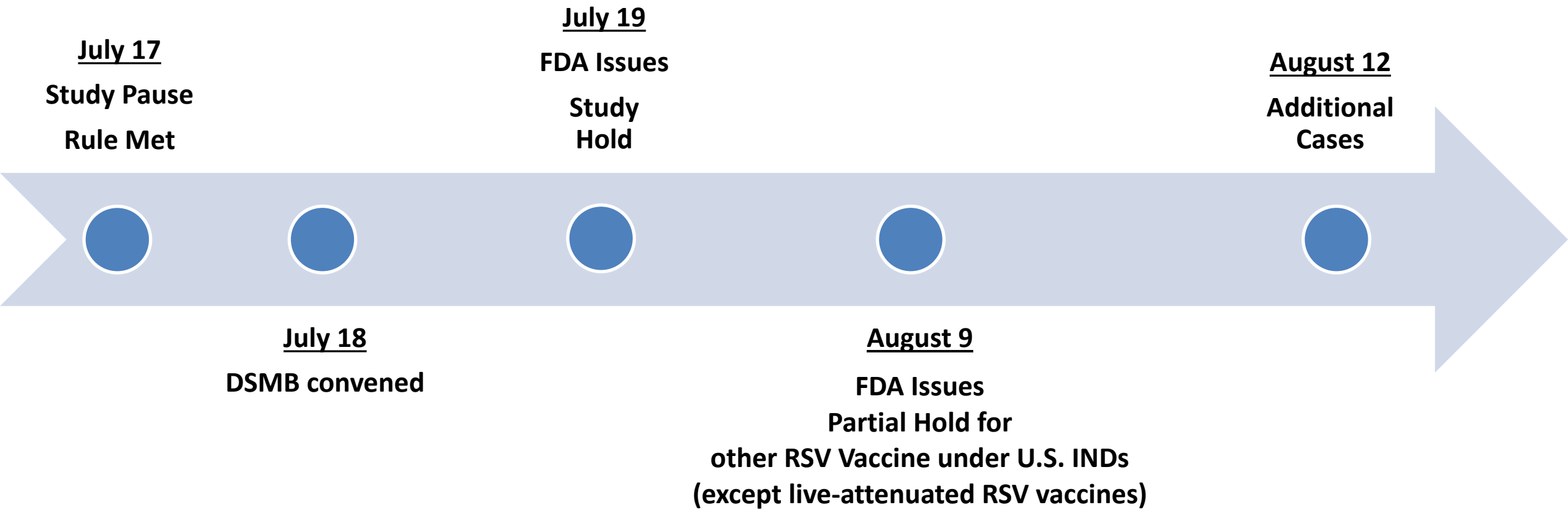
- N= 21
- RSV-only vaccine (30µg RSV)
- RSV+hMPV vaccine (15µg RSV+15µg hMPV)
- placebo

Part C (Cohorts 7 and 8): Children 8 to <12 months

- Open label
- RSV-only vaccine (30µg RSV)
- Nirsevimab-exposed (N=9)
- Nirsevimab-unexposed (N=6)

Schedule: 0, 2, 4 months
Placebo: saline

Timeline of Safety Signal Identification & Regulatory Actions



RSV Disease Severity: All Cohorts

Part Cohort	Vaccination (Dose)	*Symptomatic Cases* x (%, x/N)	*Severe/Hospitalized Cases* y (%, y/N)	Symptomatic Cases *Progressing* to Severe/Hospitalized Cases % (y / x)
Part A Cohort 1 (N=29)	RSV-only vaccine (30 µg RSV)	11 (38%)	0	0%
Part A Cohort 2 (N=30)	RSV + hMPV vaccine (15 µg RSV + 15 µg hMPV)	13 (43%)	1 (3%)	8%
Part A Cohorts 1 & 2 (N=31)	Placebo	14 (45%)	0	0%
Part B Cohort 3 (N=20)	RSV-only vaccine (15 µg RSV)	9 (45%)	**2 (10%)**	**22%**
Part B Cohort 4 (N=20)	RSV + hMPV vaccine (7.5 µg RSV + 7.5 µg hMPV)	10 (50%)	**3 (15%)**	**30%**
Part B Cohorts 3 & 4 (N=20)	Placebo	12 (60%)	**1 (5%)**	**8%**
Part B Cohort 5 (N=7)	RSV-only vaccine (30 µg RSV)	4 (57%)	0	0%
Part B Cohort 6 (N=7)	RSV + hMPV vaccine (15 µg RSV + 15 µg hMPV)	1 (14%)	0	0%
Part B Cohorts 5 & 6 (N=7)	Placebo	4 (57%)	0	0%
Part C Cohorts 7 & 8 (N=15)	RSV-only vaccine (30 µg RSV)	0	0	0%

Imbalance highlighted and bold

RSV Disease Imbalance: Cohorts 3 & 4

Cohort	Symptomatic Cases (x)	Severe/Hospitalized Cases (y)	Symptomatic Cases *Progressing* to Severe/Hospitalized Cases % (y/x)
Cohorts 3 & 4 Vaccine Recipients N=40	19	5	**26%**
Cohorts 3 & 4 Placebo Recipients N=20	12	1	**8%**

Clinical Overview of Severe/Hospitalized RSV Cases Cohorts 3 & 4

Group	Onset Relative to Last Dose	Hospitalized (n)	Respiratory Support (n)	Participants with Co-Infection (n)
Vaccine Recipients N=5	4 cases: 3 to 26 days PD 2 1 case: 23 days after dose 1	4	3 (1 required mechanical ventilation)	1 (SARS-CoV-2)
Placebo Recipients N=1	1 case: 37 days PD2	1	1	1 (hMPV)

PD= post-dose

Part A: Preliminary Immunogenicity Results

(No imbalance in RSV cases)

Preliminary Immunogenicity Data
Part A (8 to <24 months)

- Percentages of seropositive participants at baseline (PostF IgG bAb ≥200 AU/mL)

RSV-only vaccine (30 µg)	62%
RSV+hMPV vaccine (30 µg)	45%
Placebo	65%

- Day 85 RSV nAb and bAb responses
  - RSV-only vaccine (30 µg RSV) > RSV+hMPV vaccine (15 µg RSV + 15 µg hMPV) > placebo
- Preliminary T-cell data (representative cytokines from a small subset) suggest
  - Baseline: RSV-experienced had quantifiable Th1 responses with Th2 responses < LLOQ
  - Day 85 (vaccine recipients):
    - Generally similar Th1 responses for RSV-naïve and RSV-experienced
    - RSV-naïve: greater % with detectable IL-5 responses vs. RSV-experienced but responses were low and significance is unclear, other Th2 cytokine responses were comparable
  - Day 85 (placebo recipients):
    - Th2 responses were <LLOQ, including participants who were previously RSV-experienced

Part B: Preliminary Immunogenicity Results

(Observed imbalance in RSV cases)

Preliminary Immunogenicity Data: Part B Cohorts 3 & 4 (5 to <8 months)

- Sample collection: Baseline (Day 1) and Day 85 (28 days post-dose 2)
  - RSV infections in these cohorts may have occurred prior to Day 85
- Severe/hospitalized RSV case occurrence relative to collection:
    - 4 vaccine recipients*: Cases occurred before Day 85
    - 1 placebo recipient: Case occurred after Day 85
- Day 85 RSV nAb and bAb responses
  - Vaccine recipients with severe/hospitalized RSV cases: highest responses
  - Placebo recipients: lowest responses
- Maternal antibodies complicated RSV serostatus determination
- Sponsor conducted *post hoc* exploratory analyses that suggest that the severe/hospitalized RSV cases were seronegative prior to vaccination

*1 vaccine recipient did not have Day 85 collection

Part C: Preliminary Immunogenicity Results:

(No imbalance in RSV cases)

Preliminary Immunogenicity Data: Part C (8 to <12 months)

- Potential blunted immune response to a single dose of the RSV-only vaccine (30 µg) administered to nirsevimab-exposed participants (especially RSV B)

Parameter	Nirsevimab-Exposed N=9	Nirsevimab-Unexposed N=6
Baseline GMT (IU/mL) (min, max)	--	--
RSV A	10712 (3665, 34824)	44 (7, 655)
RSV B	**263 (121, 619)**	49 (12, 379)
Day 29 post-dose 1 GMT (IU/mL) (min, max)	--	--
RSV A	7453 (3082, 19682)	4029 (79, 56688)
RSV B	**249 (84, 1588)**	1678 (36, 31309)

- Measurements following 3-dose series are not available

Severe/Hospitalized hMPV Cases

Severe/Hospitalized hMPV Cases
Part B

- Preliminary data: 3 hMPV cases in combined RSV+hMPV vaccine recipients required hospitalization
  - 2 cases in RSV+hMPV (7.5 µg RSV + 7.5 µg hMPV) vaccine recipients (Cohort 4)
    - One participant required noninvasive positive pressure ventilation
  - 1 case in an RSV+hMPV (15 µg RSV + 15 µg hMPV) vaccine recipient (Cohort 6)

Summary and Considerations for Pediatric RSV Vaccine Development

Summary of Imbalance and Current Status of Pediatric RSV Vaccine Development

- Imbalance in severe/hospitalized RSV cases was observed in 1 study
  - Safeguards were in place based on pathogenesis of VAERD following FI-RSV
  - mRNA vaccine construct and nonclinical studies designed and assessed to mitigate VAERD risk
- Preliminary immunogenicity data suggest differences in Part B cases from VAERD after FI-RSV
  - Characterization of cases is incomplete
- Implications of observed imbalance in cases are uncertain
- Clinical development of RSV vaccine candidates* under U.S. IND remains on hold for < 2-year-olds and seronegative individuals 2 - 5 years of age

* Except live-attenuated RSV vaccines

Considerations for Pediatric RSV Vaccine Development under U.S. IND

Considerations for enrollment of presumed RSV-naïve infants and children for RSV vaccine candidates under U.S. IND include:

1. If and how our current understanding of FI-RSV VAERD pathophysiology may inform benefit-risk assessments of other vaccine technologies
2. What critical additional assessments may further characterize the observed safety signal
3. What additional data may help stratify potential VAERD risk across vaccine technologies and antigenic compositions
4. How nonclinical studies may further inform potential VAERD risk in clinical studies
5. What additional risk mitigation/management strategies may address potential VAERD risk in clinical studies
6. How benefit-risk assessments may incorporate vaccine candidate benefits in RSV-experienced children, uncertainties regarding potential VAERD risk, and available preventative interventions (e.g., RSV mAb and maternal immunization)
7. How to address potential RSV mAb – RSV vaccine interactions in clinical development plans and pediatric clinical study designs

Discussion Topics

Discussion Topics

1. RSV Vaccine Safety in Pediatric Populations

1.1 Please discuss whether the currently available evidence indicates a potential safety concern more broadly applicable to the evaluation of RSV vaccine candidates in infants and toddlers. Please discuss the applicability to:

a. different vaccine technologies (e.g., live-attenuated RSV, viral-vectored, mRNA, and subunit protein vaccines); and

b. different antigenic conformations (e.g., stabilized preF or other RSV protein prototypes).

1.2 Based on the currently available evidence, please discuss current nonclinical and clinical safeguards, and recommend whether any additional nonclinical and clinical information should be considered and/or precautions taken when evaluating RSV vaccine candidates in infants and toddlers.

Discussion Topics

2. Sequential Administration of RSV Monoclonal Antibodies (mAbs) followed by RSV Vaccines in Infants and Toddlers

2.1 Please discuss whether currently available evidence suggests potential RSV mAb (e.g., nirsevimab) - RSV vaccine interactions that may affect active immunization in infants and toddlers.

2.2 Based on currently available evidence, please discuss and recommend whether any additional factors and data should be considered when evaluating RSV mAb - RSV vaccine interactions, including potential impact of administration of RSV mAbs on safety and/or effectiveness of subsequent parenteral or mucosal administration of RSV vaccines.

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Questions/Comments

Back-up Slides

RSV Case Definitions

Terminology	Definition
RSV-RTI or hMPV-RTI	Runny nose OR blocked nose OR cough AND Confirmed RSV or hMPV infection[a]
RSV-LRTI or hMPV-LRTI	Cough OR difficulty breathing[b] AND SpO_2 <95%[c] OR RR increase[d] AND Confirmed RSV or hMPV infection[a]
RSV severe LRTI or hMPV severe LRTI	Meeting the case definition or RSV-LRTI or hMPV-LRTI AND SpO_2 <93%[c] OR lower chest wall in-drawing[e]
RSV very severe LRTI or hMPV very severe LRTI	Meeting the case definition or RSV-LRTI or hMPV-LRTI AND SpO_2 <90%[c] OR inability to feed[e] OR failure to respond/unconscious[e]
RSV hospitalization or hMPV hospitalization	Confirmed RSV or hMPV infection[f] AND Hospitalized for acute medical condition[g]
Clinically significant (CS) Severe/Very Severe LRTI	RSV severe LRTI + RSV very severe LRTI + RSV hospitalization (*post hoc)*

Abbreviations: hMPV=human metapneumovirus; LAR=legally authorized representative; LRTI=lower respiratory tract illness; RR=respiration rate; RSV=respiratory syncytial virus; RTI-respiratory tract infection; RT-PCR=reverse transcription-polymerase chain reaction; SpO_2=blood oxygen saturation

a. RSV or hMPV infection confirmed on nasal swab positive by RT-PCR. However, in the event that RT-PCR testing is not available (i.e., hospitalization), positive restult in a locally available diagnostic test of RSV or hMPV infection will be accepted

b. based on history reported by parents/LARs and includes difficulty breathing (e.g., showing signs of wheezing or stridor, tachypnea, flaring [of nostrils], chest in-drawing, apnea) associated with nasal obstruciton

c. for SpO_2, the lowest stable value monitored will be used

d. RR increase defined as ≥50 braths/minute (5 to <12 months of age), >40 breaths/minute (12 to 24 months of age), >34 breaths/minute (over 24 months of age)

e. lower chest wall in-drawing, inability to feed, and failure to respond/unconcous based on physician assessment

f. RSV and hMPV sampling and testing is based on medical judgement of medical practitioner or driven by algorithm

g. hospitalization is defined as a medical decision in which the participant requires overnight admission for observation or treatment

Note: definitions based on (Modjarrad, 2016). If a coinfection of RSV and hMPV is present as determined by PCR, these case definitions will be counted for both incidences of infection.