Vaccines and Related Biological Products Advisory Committee Meeting
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FDA Briefing Document

Considerations for Respiratory Syncytial Virus (RSV) Vaccine Safety in Pediatric Populations

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Glossary

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
bAb	binding antibody
BCAT	Blinded Clinical Assessment Team
BPD	bronchopulmonary dysplasia
CFR	Code of Federal Regulations
CHD	congenital heart disease
CI	confidence interval
CS	clinically significant
DSMB	Data Safety Monitoring Board
DMC	Data Monitoring Committee
ERD	enhanced respiratory disease
FDA	U.S. Food and Drug Administration
FI-RSV	formalin-inactivated respiratory syncytial virus
GA	gestational age
hMPV	human metapneuomovirus
H&E	hematoxylin and eosin
ICU	intensive care unit
IND	investigational new drug application
IRB	Institutional Review Board
IRPs	infectious respiratory particles
LLOQ	lower limit of quantification
LRTD	lower respiratory tract disease
LRTI	lower respiratory tract infection
mAb	monoclonal antibody
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
PCR	polymerase chain reaction
preF	prefusion F protein
postF	postfusion F protein
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RSV-LRTD	RSV-associated lower respiratory tract disease
RT-PCR	reverse transcriptase polymerase chain reaction
sLRTD	severe RSV-associated lower respiratory tract disease
sLRTI-RSV	severe RSV-associated lower respiratory tract illness
U.S.	United States
U.K.	United Kingdom
VAERD	vaccine-associated enhanced respiratory disease
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1. Executive Summary

Respiratory syncytial virus (RSV) is ubiquitous, causing infection and disease throughout the world, with significant morbidity and mortality in young children, especially infants. The global burden of RSV disease in children under 5 years of age is high, with estimates of approximately 3 million hospitalizations and ~50,000-100,000 deaths per year (Mazur, 2024). Nearly 100% of children have been infected with RSV by two years of age, and in the United States (U.S.) it is the leading cause of hospitalization in infants (Suh, 2022). RSV disease can manifest with a range of symptoms, including upper respiratory disease that can progress to lower respiratory tract disease (LRTD), leading to respiratory distress, respiratory failure, and death. Treatment options for RSV disease are limited and management of affected patients is largely supportive. Monoclonal antibodies (mAbs) with activity against RSV are a critical element of a preventive strategy in infants; however, availability and cost may limit global implementation. While recent advancements in vaccine technologies have facilitated development of RSV vaccines, including U.S. licensure of three vaccines in the past 2 years, the indicated populations are currently limited to individuals 18 years of age and older for the prevention of LRTD, and pregnant individuals at 32 through 36 weeks gestational age for the prevention of LRTD and severe LRTD (sLRTD) caused by RSV in infants from birth through 6 months of age. Therefore, there are no available RSV vaccines for active immunization in children.

Pediatric RSV vaccine development was stalled following the observation of vaccine-associated enhanced respiratory disease (VAERD), including two toddler deaths, following administration of formalin-inactivated respiratory syncytial virus (FI-RSV) vaccines to infants in the 1960s (Fulginiti, 1969; Kapikian, 1969; Kim, 1969). Over the ensuing years, nonclinical research elucidated putative immunopathologic mechanisms thought to drive VAERD. Animal studies suggested that inadequate neutralizing antibody (nAb) responses, low-avidity antibody responses, bias toward Th2-dominant immune responses, and pulmonary immune complex deposition with complement activation may all contribute to an exuberant inflammatory response to wild-type RSV infection. Additionally, a discovery that presentation of RSV fusion (F) glycoprotein antigen in a pre-fusion (preF) conformation elicited nAb titers similar to those elicited by natural RSV infection suggested that vaccine candidates with stabilized preF antigenic components may be less likely to result in nonfunctional antibody responses that may predispose recipients to VAERD.

As development of RSV vaccine technology progressed, the recognition that candidates would soon be ready for evaluation in infants and children prompted the U.S. Food and Drug Administration (FDA) to convene the Vaccines and Related Biological Products Advisory Committee (VRBPAC) in 2017 to discuss considerations for evaluation of RSV vaccine candidates in seronegative infants. VRBPAC discussed nonclinical and clinical data that contributed most directly to our understanding of the key features of RSV VAERD, with the notion that some or all these features could be used, prior to initiating clinical trials in RSV-naïve infants, in evaluating and characterizing RSV vaccine candidates compared with the FI-RSV vaccine to mitigate the risk of VAERD. In the context of the VRBPAC discussions, a more comprehensive understanding of the potential immunopathogenesis of VAERD, and advances in vaccine technology, a cautious approach was undertaken to reinstate evaluation of RSV vaccines in infants and toddlers. Risk mitigation strategies include rational design of vaccine candidates; nonclinical studies to ensure generation of adequate nAb responses, lack of Th2-biased immune responses, and lack of VAERD-like lung histopathology upon post-vaccination RSV challenge; and clinical study guardrails to ensure adequate safety monitoring and study stopping criteria, as well as age de-escalation study designs that assess immune responses in RSV-experienced older children prior to progressing to evaluation in infants and toddlers.

Using this cautious approach to pediatric studies of RSV vaccines, clinical development programs for two messenger ribonucleic acid (mRNA) vaccines, each containing an mRNA sequence which encodes the RSV F glycoprotein stabilized in the preF conformation, progressed to evaluations in young children and then infants only after: (1) data from nonclinical studies conducted in BALB/c mice and cotton rats, including cotton rat challenge models for RSV, were consistent with a general absence of immunological or pathological features associated with VAERD after RSV challenge; and (2) safety and immunogenicity data from ongoing studies in adults and RSV-seropositive children 12 months through 59 months of age supported progression to studies in younger cohorts. During the study, an imbalance in severe RSV cases was identified, based on a pre-specified study stopping criterion, among participants 5 months through <8 months of age who received the lower mRNA vaccine dose. In Cohorts 3 and 4, five (5) cases (12.5% of participants) of clinically significant (CS) severe/very severe RSV were identified in the vaccine groups (all of whom had received 1 or 2 doses of a 3-dose schedule), compared with one (1) case (5% of participants) in the placebo group. The percentage of participants with symptomatic RSV disease in Cohorts 3 and 4 who progressed to severe illness was 26.3% in the vaccine groups compared with 8.3% in the placebo group.

In a separate part of the study, the immune responses to vaccination in participants who had received the RSV mAb nirsevimab ≥ 6 months prior to vaccination appeared blunted when compared with participants who had not received nirsevimab.

We are convening VRBPAC to discuss considerations for RSV vaccine safety in pediatric populations (see Section 8) based on data from a pediatric RSV vaccine clinical development program evaluating mRNA vaccines (see Section 5 and Section 6), including the implications of the potential safety findings on ongoing and future development of other RSV vaccines in pediatric populations and of the potential RSV mAb – RSV vaccine interaction observed.

2. Unmet Need for RSV Vaccines in Infants and Toddlers

RSV is a highly contagious human pathogen that causes respiratory tract illness in individuals of all age groups worldwide. Transmitted as infectious respiratory particles (IRPs) by direct deposition, RSV replicates exclusively in the respiratory epithelium. The severity of RSV disease may range from mild upper respiratory illness to life-threatening bronchiolitis and pneumonia.

RSV is an enveloped, single-stranded, negative-sense ribonucleic acid (RNA) virus that is a *Orthopneumovirus hominis* species within the Pneumoviridae family. RSV strains are grouped within a single serotype but are separated into 2 major phylogenetic lineages (subtypes RSV-A and RSV-B) originally determined by cross neutralization studies and confirmed by antigenic differences in the RSV glycoprotein G (Cane, 2001; Johnson, et al., 1987; Sullender, 2000). Sequences within the N-terminal 270 nucleotides of the RSV glycoprotein G gene differentiate RSV-A and RSV-B subtypes. Both subtypes tend to co-circulate during seasonal outbreaks; however, the dominant RSV subtype varies during local annual outbreaks and is unpredictable.

2.1 Clinical Manifestations and Epidemiology of RSV in Infants and Toddlers

Symptomatic RSV infections and re-infections can manifest as acute upper and/or lower respiratory tract infections (LRTIs). RSV can cause symptoms similar to those caused by many other viral and bacterial respiratory pathogens. When clinically necessary, RSV infection can be confirmed by laboratory testing, such as reverse transcriptase polymerase chain reaction (RT-PCR) or antigen tests. Children may initially present with upper respiratory tract symptoms, including rhinorrhea, pharyngitis, cough, headache, fatigue, and fever. With the first infection,

approximately 20% to 30% of infants will progress to develop LRTD, including bronchiolitis and/or pneumonia, characterized by wheezing and/or crackles on auscultation and varying degrees of respiratory distress. In very young infants, apnea may be the only presenting symptom. Prematurity, heart disease, immunodeficiency, neuromuscular disease, and other chronic diseases increase the risk of RSV-associated hospitalization.

The risk of RSV infection is age-dependent, with virtually all children infected at least once by 3 years of age, although there may be epidemiologic and regional differences that affect pediatric seroprevalence (Nakajo, et al., 2023; Berbers, et al., 2021; Nyiro, et al., 2017). In a recent cohort study, 53% of U.S. children were infected with RSV by 1 year of age, as measured by active surveillance for infection and serologic testing (Cacho, et al, 2024).

RSV infection does not confer long lasting immunity and reinfections occur throughout an individual's lifespan. The durability of naturally acquired immunity after RSV infection is also not well understood. Studies of immune response after RSV infection indicate an initial rise in serum antibody levels, with a return to baseline by 16 months to 20 months post-infection (Falsey, et al, 2006). High rates of reinfection and short durability of protection after infection were observed in an RSV human challenge study in young adults (Hall, et al., 1991).

Significant morbidity and mortality are attributable to pediatric RSV disease, although the incidence and associated mortality can vary from year to year (Mazur, et al., 2024; Shi, et al., 2017). In an assessment of data from 2010, RSV was estimated to be second only to malaria as the leading cause of pediatric death due to a specific pathogen (Lozano, et al., 2013). Worldwide, it has been estimated that children under 5 years of age experience approximately 33 million episodes of RSV-associated LRTD (RSV-LRTD), including 3 million hospitalizations and ~50,000-100,000 deaths per year, with a high burden of disease severity observed in children younger than 6 months (Mazur, et al., 2024). In a recent meta-analysis, the authors estimated that over 45,000 RSV-attributable deaths are in children younger than 6 months of age, accounting for 3.6% of all deaths in children 28 days to 6 months of age (Li, et al., 2022). More than 90% of the observed mortality due to RSV is reported in low- and middle-income countries (Munro, et al., 2023; Li, et al., 2022). While in-hospital mortality in low- and middle-income countries has nearly halved over recent years (0.99% prior to 2012 and 0.54% since 2012), the decrease in high-income countries has been more modest (0.11 vs. 0.08%) (Munro, et al., 2023).

RSV disease is a substantial medical and economic burden in the U.S. Among children under 5 years of age, RSV is associated with an estimated 100-300 deaths, 58,000-80,000 hospitalizations, ~520,000 emergency department visits, and ~2,100,000 outpatient visits each year (CDC, 2023; CDC, 2024c; McLaughlin, et al., 2022; AAP, 2024). RSV is the most common cause of hospitalization in U.S. infants (~1-3% of children 12 months of age and younger), accounting for ~9% of all hospitalizations in this age group between 2009-2019 (Suh, 2022). In a recent systematic literature review of the cost of RSV infection in children under 5 years of age, hospitalization was found to represent two-thirds of RSV treatment costs. The annual cost of RSV treatment of infants in the U.S. is $709.6 million (adjusted to 2020 U.S. dollars)—an average cost of $187 per birth in the U.S. Adjusted to 2020 U.S. dollars, mean inpatient hospitalization costs per episode (all-payers) were ~$12,000. Outpatient care for RSV (outpatient clinics, emergency, and urgent care departments) also represents a significant economic burden, with a calculated weighted mean RSV-associated cost per year of $1446 (95% CI, $1354–$1538) (Bowser, et al., 2022). A recently published model projected the expected annual clinical and economic burden of medically attended RSV-LRTD in U.S. children less than 12 months of age to be an estimated $1.6 billion (Houde, et al., 2024).

2.2 Landscape of Available RSV Therapeutic and Prophylactic Interventions

2.2.1 Therapeutics

Aerosolized ribavirin is the only drug or biologic product approved for the treatment of RSV disease. Aerosolized ribavirin is indicated for the treatment of hospitalized infants with severe LRTIs (sLRTI) due to RSV; however, use of aerosolized ribavirin is limited due to administration challenges in conjunction with a ventilator and its teratogenic effects, including risk of environmental spread. In addition, the package insert for this formulation includes a boxed warning about possible accumulation of drug precipitate resulting in mechanical ventilator dysfunction, increased pulmonary pressures, and a risk for sudden respiratory decompensation.

2.2.2 Prophylaxis

2.2.2.1 Monoclonal Antibodies

Nirsevimab (Beyfortus) is approved by FDA for the prevention of RSV LRTD 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 in their second RSV season. (Sanofi/AstraZeneca 2023). Nirsevimab is a recombinant neutralizing human immunoglobulin G1 kappa monoclonal antibody directed against the prefusion conformation of the RSV fusion (F) protein.

Palivizumab (Synagis) is approved by FDA for the prevention of serious RSV lower respiratory disease in high-risk infants (Medimmune 1998). This indication was supported by trials in premature infants born at <35 weeks of gestation, infants with chronic lung disease of prematurity, and infants with hemodynamically significant congenital heart disease. Palivizumab, like nirsevimab, is a recombinant humanized monoclonal antibody directed against a conserved epitope on the RSV fusion (F) protein. Because palivizumab is not modified to extend its serum half-life, a monthly intramuscular injection is required. The first dose of palivizumab is administered prior to the start of the RSV season and remaining four doses are administered monthly during the RSV season.

2.2.2.2 Vaccines

Individuals 17 years of age and younger

No U.S.-licensed RSV vaccines are currently approved, including for infants and young children.

Individuals 18 years of age and older

Three vaccines are licensed in the U.S. for the prevention of LRTD caused by RSV: Arexvy (GlaxoSmithKline Biologicals), Abrysvo (Pfizer, Inc.), and mResvia (Moderna). These vaccines were originally approved by FDA on May 3, 2023, May 31, 2023, and June 14, 2024, respectively. The following indications are approved:

- Abrysvo for active immunization for the prevention of LRTD caused by RSV in:
  - individuals 60 years of age and older; and
  - individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV
- Arexvy for active immunization for the prevention of LRTD caused by RSV in:
  - individuals 60 years of age and older; and

  - individuals 50 through 59 years of age who are at increased risk for LRTD caused by RSV
- mResvia for active immunization for the prevention of LRTD caused by RSV in:
  - individuals 60 years of age and older

Pregnant individuals at 32 through 36 weeks gestational age

Although not licensed for use in children, Abrysvo was approved on August 21, 2023, for active immunization of pregnant individuals at 32 through 36 weeks gestational age (GA) for the prevention of LRTD and sLRTD caused by RSV in infants from birth through 6 months of age. On September 22, 2023, the ACIP recommended Abrysvo for pregnant persons at 32-36 weeks GA using seasonal administration (meaning September-January in most of the U.S.) to prevent RSV-LRTD in infants <6 months of age (CDC, 2024a).

2.3 Current Unmet Medical Need in Infants and Toddlers

Over the past several years, the landscape of available RSV preventive interventions in infants has expanded to include both long-acting RSV mAb (i.e., nirsevimab) and maternal immunization (i.e., Abrysvo). While uptake of nirsevimab and maternal vaccination with Abrysvo has started in high-income countries, lack of availability and cost has hindered widespread implementation where the burden of severe RSV disease is highest, i.e., low- and middle-income countries (Perez Casas, et al., 2024; Zar, et al., 2024). The value profile for RSV vaccines for active immunization in infants and children in low- and middle-income countries remains to be determined (Fleming, et al., 2023). Also, the available options are limited to passive immunization, which may not offer some of the potential benefits of active immunization. For example, active immunization could lead to immune priming that could significantly contribute to the prevention of sLRTD during future RSV seasons. Active immunization would allow for vaccination of children following their first RSV season. Active immunization would also provide an option for children born to individuals who were previously vaccinated during an earlier pregnancy, since maternal vaccination is currently not indicated during second or subsequent pregnancies. Additionally, it is important to note that the potential adverse impacts of passive immunization on the effectiveness of subsequent active immunization in infants and toddlers is yet to be determined.

These and other considerations may be important for RSV vaccine benefit-risk assessments and indications for use in populations where both passive and active immunization are recommended for use in infants and toddlers.

3. Vaccine-Associated Enhanced Respiratory Disease (VAERD)

As evidenced by the recent approval of three RSV vaccines for adults, there has been significant progress in the field of RSV vaccine development. However, due to observed events of VAERD following RSV vaccination in infants, the approach to pediatric development of RSV vaccines has proceeded with a high degree of caution, and was largely limited to live, attenuated vaccine candidates, which are thought unlikely to be associated with VAERD.

In the mid-1960s, multiple published reports described an association between FI-RSV vaccines and VAERD (Fulginiti, 1969; Kapikian, 1969; Kim, 1969). In one study of a FI-RSV vaccine in infants, 80% of vaccine recipients required hospitalization for severe RSV-LRTD upon natural RSV infection, including two children who died at the ages of 14 months and 16 months of age; in comparison, no deaths occurred and 5% of participants required hospitalization in the control group (Kim, et al., 1969).

3.1 Potential Mechanisms of VAERD

The mechanisms responsible for FI-RSV VAERD are still not fully understood; however, immune responses considered to contribute to the immunopathogenesis of VAERD (Chin, et al., 1969; Kapikian, et al., 1969; Fulginiti, et al., 1969; Polack, et al., 2002) include:

- low avidity or inadequate nAb responses;
- Th2-biased immune responses; and
- pulmonary immune complex depositions.

RSV neutralizing antibody (nAb) responses
Several factors related to antibody responses likely contribute to VAERD, including induction of low-avidity anti-RSV antibodies with poor neutralizing and fusion-inhibiting activity. Data from RSV-naïve infants given FI-RSV demonstrated that, although the total anti-RSV-F binding antibody (bAb) ratios were high, neutralizing and fusion-inhibiting activity was low when compared with antibodies elicited by natural RSV infection (Browne, et al., 2019; Murphy, et al., 1988). Additionally, studies in mice suggested that lack of affinity maturation due to deficient toll-like receptor activation in B cells may also contribute to the risk of VAERD (Delgado, et al., 2009).

RSV antigen conformation
The respiratory RSV fusion (F) glycoprotein is a membrane protein that is required for viral entry into host cells, is conserved across RSV-A and RSV-B strains, and is the antigenic focus of most neutralizing antibodies in human sera (Orenstein, et al, 2022). A discovery that there are both preF and post-fusion (postF) conformations of the F glycoprotein led to research that demonstrated that infectious RSV presents both the preF and postF conformations while the FI-RSV vaccines present only the postF conformation. Together with animal data that demonstrated that stabilized preF elicited nAb titers similar to those elicited by natural RSV infection, these findings suggested that vaccines with stabilized preF antigenic components may be less likely to elicit nonfunctional antibody responses that predispose recipients to VAERD (Killikelly, et al., 2016).

Th2-biased RSV immune responses
Multiple studies have demonstrated the role of Th2 immune responses in mediating VAERD. Immunization of mice with FI-RSV resulted in robust Th2 immune responses, with evidence of CD4+ T cells in the lungs following RSV challenge. In mouse models, Th2-associated cytokines and TNF-α production by Th1 cells were found to mediate VAERD (Knudson, et al., 2015). Experiments to assess the role of the Th2 immune response in VAERD demonstrated that depletion of both IL-4 and IL-10 prevented inflammatory cell infiltration around the bronchioles of FI-RSV-immunized mice (Connors, et al., 1994). Additional studies have implicated other Th2 cytokines in the development of VAERD, including IL-5 and IL-13 (Acosta, et al., 2016; De Swart, et al., 2022).

Pulmonary immune complex deposition
Pulmonary deposition of immune complexes with associated complement activation has been hypothesized to play an important role in VAERD, in which vaccine-induced antibodies with poor neutralizing activity lead to immune complex deposition and complement activation in airways due to large amounts of antigen during RSV infection (Polack et al., 2002). In a study by Polack, et al., 2002, lungs of mice immunized with FI-RSV and challenged with RSV were examined using hematoxylin and eosin (H&E) and showed “a patchy mononuclear cell infiltration of the alveolar walls and a peribronchiolar and

perivascular lymphomonocytic infiltration with a moderate number of interspersed neutrophils and eosinophils." Lungs of placebo recipients and mice immunized with live RSV contained fewer mononuclear cells after RSV challenge. To confirm the role of complement in the pathophysiology of VAERD, C3-deficient and wild-type mice were immunized with FI-RSV and then challenged with RSV infection. Both groups developed similar alveolar, peribronchiolar, and perivascular mononuclear cellular infiltration with neutrophils. While the histopathology findings for both groups were similar, differences were noted between the two groups on pulmonary function studies. FI-RSV-immunized, RSV-challenged wild-type mice had a significant increase in airway hyperresponsiveness as compared with C3-deficient mice, which demonstrated that complement is critical for bronchoconstriction in VAERD. Additionally, an antibody against C4d (which is a sensitive marker of complement activation mediated by immune complexes using the classical pathway) was used to stain lung sections obtained from the two children who died of VAERD, consistent with a role for immune complexes in VAERD in children immunized with FI-RSV.

3.2 Theoretical Risk of VAERD in Infants Following Waning Passive Immunity

Multiple studies have been conducted to confirm that passive immunity acquired through maternal antibodies or monoclonal antibodies are not associated with enhanced respiratory disease (ERD) upon subsequent exposure to RSV. In a randomized, double-blind, placebo-controlled study evaluating safety and immunogenicity of the RSV purified fusion protein-2 (PFP-2) vaccine in 35 healthy women in the third trimester of pregnancy and their infants, there was no increase in the frequency of morbidity associated with respiratory tract illnesses in infants of vaccine recipients, and there was no evidence of enhanced T-cell or cytokine activity in infants of vaccine recipients compared with infants of placebo recipients (Munoz, et al., 2003). Two immunization and challenge studies in animals (mice and rats) demonstrated that passive transfer of antibodies to naïve pups through maternal vaccination with FI-RSV prior to challenge did not result in ERD upon subsequent live RSV challenge (Blanco, et al., 2017; Kwon, et al., 2014).

Approximately 7,000 infants born to pregnant individuals in the Phase 3 study (NCT04424316) of Abrysvo were followed for severe RSV disease for a median of 9 months after birth. A protective effect against severe RSV disease and no evidence of ERD was observed among infants born to individuals who received RSV vaccine during pregnancy (Kampmann, et al., 2023). Postmarketing surveillance of Abrysvo has not revealed a signal for ERD among vaccine recipients or their infants, although these data are limited by passive reporting and the lack of a direct comparator group.

Palivizumab was approved over 20 years ago, and no evidence of a risk of ERD has been identified. To assess the risk of ERD with nirsevimab, children from the Phase 3 efficacy trial in infants born at ≥35 weeks GA were followed through their second RSV season. The incidence and severity of medically attended RSV-LRTD was comparable between the nirsevimab and placebo groups. There was no evidence of antibody-dependent enhancement of infection or disease severity (Dagan, et al., 2024).

Risk of VAERD in adults
In general, RSV-experienced children and adults have been considered at low risk for VAERD, due to immunological priming by prior naturally acquired RSV infection (Acosta, et al., 2016).

Extensive clinical experience to date with the currently licensed RSV vaccines (Abrysvo, Arexvy, and mResvia) have yielded no evidence of VAERD after vaccination in adult

populations, including in individuals with immunocompromising conditions and pregnant individuals. In the pre-licensure efficacy studies of these vaccines in individuals 60 years of age and older, based on study sizes of approximately 25,000-35,000 participants, the case split in severe RSV disease between the vaccine and placebo groups suggested vaccine effectiveness against severe RSV disease and did not suggest a signal for VAERD. Postmarketing surveillance of these vaccines also has not revealed a signal for VAERD among vaccine recipients, although these data are limited by passive reporting and the lack of a direct comparator group.

4. Guiding Principles for Recent Clinical Development of Pediatric RSV Vaccines

As RSV vaccine technology advanced and improved understanding of the immunopathogenesis of VAERD derived from animal models emerged, development of new candidate vaccines was stimulated, which engendered discussions among RSV experts about the safety data needed to advance these products into initial clinical development, and ultimately, into the target population of RSV-naïve infants. The recognition that multiple products would soon be ready for evaluation in infants and children prompted FDA to convene VRBPAC in 2017 to discuss considerations for evaluation of RSV vaccine candidates in seronegative infants.

4.1 VRBPAC 2017 Meeting: RSV Vaccine Clinical Development in RSV-Naïve Infants

On May 17, 2017, VRBPAC convened to discuss the data needed to support clinical trials of RSV vaccine candidates in RSV-naïve infants, with a particular focus on mitigating the risk of VAERD (Browne, 2020).

VRBPAC reviewed the following:

1. Clinical information immediately available from and subsequently identified following evaluation of FI-RSV vaccine recipients in trials conducted in the 1960s;
2. Factors proposed from decades of research in many laboratories that are thought to contribute to VAERD immunopathogenesis;
3. Utility and limitations of various animal models of RSV to further our understanding of disease pathogenesis and to assess the safety of RSV vaccine candidates; and
4. Overall need for nonclinical data to support evaluation of RSV vaccine candidates in RSV-naïve infants.

Overview

VRBPAC discussed nonclinical and clinical data that contributed most directly to our understanding of the key features of RSV VAERD, with the notion that some or all these features could be used, prior to initiating clinical trials in RSV-naïve infants, in evaluating and characterizing RSV vaccine candidates compared with the FI-RSV vaccine to mitigate the risk of VAERD.

Biological features of RSV vaccine candidates thought to mitigate the risk of VAERD included:

- eliciting high avidity neutralizing antibodies to RSV prefusion F protein;
- avoiding induction of exaggerated Th2 CD4+ T-cell responses;
- cytoplasmic antigen processing [i.e., avoid vaccine candidates that could result in poor or absent priming of CD8+ cytotoxic T cells (CTLs) needed to facilitate clearance of virus-infected cells; however, it remains unclear if CTLs mitigate the risk of VAERD; and

- avoiding induction of antibodies that result in immune complex deposition and complement activation in the lungs during an RSV infection.

VRBPAC members generally agreed that nonclinical data should be derived from at least two well-established animal models that adequately evaluate the parameters associated with VAERD and demonstrate consistent findings that an RSV vaccine candidate has an immune phenotype readily distinguishable from that of a FI-RSV vaccine.

RSV-experienced children and infants

VRBPAC members generally agreed that although other aspects of vaccine safety may be evaluable in RSV-experienced children including toddlers, the risk of VAERD is minimal, due to immunological priming by prior naturally acquired RSV infection(s) and to their more developed immune systems compared with infants. Longitudinal data showed substantial changes in individuals' immune responses over time, particularly during the first 6 months of life. Some data suggested that the immune system in early infancy (e.g., less than 6 months to 12 months of age) is prone to an imprinting phenomenon, wherein exposure to antigens can predispose to a Th2-predominant response even when re-exposure occurs months later after the immune system has matured. Thus, while RSV-experienced infants may not inform the risk of VAERD for RSV-naïve infants, clinical evaluation in RSV-experienced children could still provide important information about vaccine reactogenicity.

VRBPAC discussed the possibility that due to persistence of maternal antibody in the infant, some RSV-naïve infants enrolled in clinical trials would meet a seropositivity cutoff (i.e., the accepted practical strategy for identifying those who have had prior RSV infection) and be placed at unanticipated risk for VAERD due to misclassification as RSV-experienced. However, it was expected that by 6 months of age and thereafter, a positive RSV titer would most likely reflect prior natural infection and after 12 months of age it would be nearly indisputable, given the kinetics of maternal antibody in infants (Waaijenborg et al., 2013; Ochola et al., 2009).

Initial studies in seronegative infants

Given the history FI-RSV-vaccinated infants subsequently experiencing VAERD, the development of a vaccine for prevention of RSV disease in RSV-naïve infants must be undertaken with an abundance of caution. In addition to developing nonclinical data to support safety in the seronegative population, risk mitigation could include appropriate features in trial design. For example, the selected sample size should expose the fewest infants (recognizing that the whole study cohort might already be immunized by the time potential cases of VAERD are observed) while generating sufficient safety data to support a larger Phase 3 trial. Similarly, it could be important to explore how VAERD will be identified, as VAERD likely will not be clinically discernable from severe RSV disease, which also occurs intermittently in unvaccinated infants. To address the potential similarity in clinical presentation, VAERD could be evaluated by estimating a relative risk of severe RSV disease between vaccine recipients versus controls, assuming a background rate of hospitalization for severe RSV disease in the range of 3-5%. It would also be important to evaluate duration of protection since it may be necessary to follow young children through more than one RSV season (or until naturally acquired RSV infection has occurred) to evaluate the impact of waning immunity on the risk of VAERD. Ultimately, it was anticipated that answers to these questions would be product specific, and would also depend on the supporting nonclinical data, the mechanism of activity of the specific RSV vaccine candidate, and the magnitude of the antibody response seen. The consensus among VRBPAC members was that although studies in adults and RSV-experienced infants would not necessarily predict subsequent risk of VAERD for an RSV-

naïve infant population, immunogenicity (i.e., cellular and humoral responses) and safety data from these populations could be supportive of evaluation of RSV vaccine candidates in RSV-naïve infants. To ensure the safety of RSV-naïve infants in studies, VRBPAC also recommended that close and continuous monitoring be required and that eligibility criteria include healthy infants without underlying medical conditions with considerations for gestational age.

4.2 Safeguards to Support RSV Vaccine Development

Based on the history of FI-RSV VAERD (see Section 2.3) and following the May 17, 2017, VRBPAC meeting regarding the data needed to support evaluation of RSV vaccine candidates in RSV-naïve infants (see Section 3.1), a cautious approach across candidate pediatric RSV vaccine programs has been taken to mitigate the risk of VAERD in the at-risk population of RSV-naïve infants. The approach to pediatric RSV vaccine development incorporates (1) nonclinical assessments to assess for the potential risk of VAERD based on the nature of immune responses elicited by the vaccine and challenge studies of vaccinated animals and (2) clinical trial risk mitigation and management strategies that span the vaccine development lifecycle.

Globally, several manufacturers have pursued RSV vaccine candidates for use in pediatric populations (infants/children) with platforms that include live-attenuated RSV, live-attenuated chimeric respiratory viral, other viral vectored, mRNA, and recombinant particle/subunit vaccines (PATH, 2024). Under U.S. investigational new drug application (IND), there are approximately 42 RSV vaccine candidates at various stages of development, ranging from early preclinical studies to pivotal Phase 3 trials. Of these candidate vaccines, 26 (15 live-attenuated vaccine technologies and 11 other vaccine technologies) include a pediatric clinical development program. The 11 other vaccine technologies include RSV F glycoprotein antigen stabilized in the preF conformation state, expressed as recombinant protein or encoded by mRNA.

4.2.1 Nonclinical Data

Prior to testing RSV vaccine candidates in humans, results of nonclinical testing in relevant animal models are reviewed by FDA to support the safety and potential efficacy of the investigational vaccine. While no animal model exactly replicates RSV disease in humans, nonclinical studies provide essential preliminary data to support advancement of an investigational vaccine to clinical trials. Nevertheless, the mechanisms of VAERD in humans are not fully understood. As such, animal studies and other preclinical data have limitations in reliably predicting the risk of VAERD in RSV-naïve children.

Nonclinical testing of vaccines includes *in vitro* and *in vivo* studies used to characterize properties related to safety and immunogenicity. This testing can include toxicology studies to assess potential toxicities (due to active ingredients, excipients, or impurities) and pharmacology testing to assess safety and biological phenotype of vaccine candidates including studies to determine vaccine immunogenicity and ability to elicit protective immunity against a live challenge. General guidance on nonclinical testing of vaccines is provided by the World Health Organization (WHO) and is not discussed further here (WHO, 2005; EMA, 2010).

The following sections will focus on the approach to nonclinical testing of RSV vaccine candidates prior to clinical trials in RSV-naïve infants, i.e., those who are at greatest risk for developing VAERD.

4.2.1.1 Nonclinical Testing and In Vitro Studies

It was previously demonstrated that the process used to manufacture FI-RSV vaccine resulted in denaturation of critical epitopes on the RSV prefusion protein and loss of epitopes on the prefusion trimer that are crucial needed to inducing potent nAb responses (Killikelly, et al., 2016). Accordingly, RSV vaccine candidates based on RSV F antigens are required to show that prefusion epitopes critical to eliciting a strong nAb response are present on the antigen in the Final Container or the expressed antigen following in vitro and/or in vivo translation of the vaccine construct using binding of preF specific antibodies/monoclonal antibodies. While vaccines containing or expressing RSV-prefusion F antigen may be preferred over vaccine expressing RSV F in the postF conformation, these products still need to be evaluated using the parameters described below under in vivo testing since there are concerns that even preF protein may increase the risk of VAERD among RSV-naïve infants (Schneider-Ohrum, et al., 2017).

4.2.1.2 WHO 2020 Guideline on the Quality, Safety, and Efficacy of RSV Vaccines

WHO assembled RSV experts, vaccine manufacturers and regulatory authorities from around the world to discuss and formally outline the current thinking and approaches for use of nonclinical and clinical testing of RSV vaccine candidates during 2016 through 2019. The WHO Guideline on the quality, safety, and efficacy of RSV vaccines is attached to this briefing document for reference.

While the contents of the WHO document have many similarities with the information and advice provided during the 2017 VRBPAC meeting, the WHO Guideline also (1) describes the need for nonclinical testing by vaccine platform; (2) redefines the four basic immune properties of RSV vaccine candidates that need to be assessed in nonclinical testing prior to advancing clinical trials into RSV-naïve infants and reaffirms supplemental data that may prove helpful; and (3) considers the imperfections of all animals models for reproducing RSV human disease and VAERD while summarizing the rationale and benefits for a few selected animal models frequently used for comparative testing along with noting specific limitations of each.

4.2.1.2.1 Nonclinical Testing by Vaccine Technology

The WHO review committee noted live-attenuated RSV strains, including those strains attenuated by gene deletion and or codon deoptimization, need not be tested for VAERD prior to testing in RSV-naïve infants (Belshe, et al., 1982; Wright, et al., 2007). Nonclinical testing for attenuation phenotype along with Phase 1 testing in healthy adults and RSV-seropositive older children should provide sufficient evidence of safety of live-attenuated RSV vaccine candidates prior to testing in RSV-naïve infants. (A description of the nonclinical testing needed to confirm attenuation phenotype is beyond the scope of this document; please see the WHO Guideline, Section 8.2 for information pertaining to product characterization for live-attenuated RSV strains.) In contrast, the ability of all other RSV vaccine candidates, based on other vaccine technologies, to prime for VAERD is currently unknown. Accordingly, WHO recommends that all other vaccine technologies (including subunit and particle-based protein vaccines, viral-vectored vaccines, and mRNA vaccines), irrespective of route of administration, should be tested as outlined below to determine their immune phenotype relative to FI-RSV vaccine prior to evaluation in RSV-naïve infants.

4.2.1.2.2 Immune Properties Assessed During Nonclinical Testing

WHO guidance recommends that vaccine candidates will be evaluated using one or more animal models in well-controlled and designed studies to assess the following four properties:

1. ability to induce anti-RSV nAb responses;
2. avoid induction of non-nAbs and have a relatively low anti-RSV-F IgG binding to nAb ratio;
3. avoid induction of strong Th2-type CD4+ T-cell responses (e.g., IL-4, IL-5 and IL-3 and/or mucus production); and
4. should not provoke alveolitis after a valid, live RSV challenge.

A valid challenge test must include a group of animals immunized with the vaccine candidate with evidence of vaccine take (e.g., a positive serology test post-immunization in animals sero-naïve prior to challenge) with a high proportion of animals in the same group having evidence of virus replication in the lungs after challenge.

4.2.1.2.3 Animal Models

The WHO Guideline notes that all animal models have some limitations as they do not accurately mimic all aspects of human RSV disease or VAERD. The WHO Guideline does not state a preference for any one animal model over another. However, Part B of the document briefly notes the use of four common animal models (i.e., mice, cotton rats, non-human primates, and calves) that have significantly advanced our knowledge on RSV disease pathogenesis and VAERD. It is noted, however, that this knowledge is still incomplete and the exact mechanism(s) of action responsible for VAERD are not yet fully explained; each animal model may be deficient in some unknown way. The WHO Guideline carefully notes that the results of testing new vaccine candidates for VAERD in animals may not be predictive of outcomes in RSV-naïve infants and a cautious approach to clinical testing must follow even when negative results suggestive of VAERD are obtained during animal testing. Importantly, the WHO Guideline stresses that the exact predictive value of animal models will only be determined once vaccine candidates proceed into evaluation in RSV-naïve infants.

A review of animal models for RSV and VAERD is beyond the scope of this summary. Animal models proposed include those in mice, neonatal mice, genetically engineered mice, cotton rats, Syrian hamsters, chinchillas, guinea pigs, ferrets, calves, sheep, neonatal lambs. and non-human primates. Excellent reviews on the insights gained from nonclinical animal testing as well as the advantages and limitations of the various models for the study of RSV were published by Taylor, 2017; Altamirano-Lagos, et al., 2019; McGinley, et al., 2022; and Drysdale, et al., 2024.

Since the 2017 VRBPAC meeting and since the publication of the WHO Guideline on RSV vaccines in 2020 (WHO, 2020), no new animal models or technology have been introduced that significantly improve our ability to assess or predict the risk of VAERD.

4.2.2 Clinical Data

Provided that the nonclinical data support progression to Phase 1 clinical trials in humans (see Section 4.2.1), FDA reviews Sponsors' clinical protocols to evaluate study design, with a focus on safety measures and monitoring. For RSV vaccine candidates, Phase 1 first-in-human studies are conducted in RSV-experienced healthy younger adults prior to enrolling

pediatric and older adult RSV-experienced populations. While data from RSV-experienced populations will not necessarily predict subsequent risk of VAERD for RSV-naïve infants, the safety/reactogenicity and immunogenicity data can inform future vaccine candidate, dose, and schedule selection and provide information regarding cellular and humoral immune responses that may be important for protection and predictive of VAERD, prior to exposing RSV-naïve infants (Browne, et al., 2019).

If safety and immunogenicity data from RSV-experienced adults provide adequate reassurance of vaccine safety and evidence of potential vaccine effectiveness, age de-escalation to Phase 1 trials in RSV-naïve and/or infant and toddler populations may be considered. The requisite safety measures may vary across programs, depending on the specifics of the investigational vaccine (e.g., vaccine technology, nonclinical data, available clinical data). In general, the main goal of FDA review of proposed Phase 1 protocols in potentially RSV-naïve infant/toddler populations has been to ensure that the protocol will provide sufficient safety data (including RSV surveillance data) across a relatively small number of study participants, using a cautious approach with clearly delineated risk monitoring and risk mitigation measures, to support progression to larger, later phase studies and identify early evidence of potential VAERD risk. An additional goal has been to ensure that the protocol design includes collection of preliminary immunogenicity data that could identify markers for possible VAERD risk (e.g., Th2 > Th1 responses, low nAb titer in response to vaccination) and determine whether immune responses support further investigation of the RSV vaccine candidate.

FDA-recommended safety measures across pediatric RSV vaccine candidate clinical development programs for clinical protocols that enroll potentially RSV-naïve infants and toddlers have included the following:

- Initial enrollment criteria to include only healthy, full-term infants and toddlers.
- Collection of baseline blood samples for RSV serostatus, used for enrollment stratification (if feasible) and/or for later evaluation of potential safety signals.
- Enrollment strategies that include age de-escalation from toddlers to infants and, if possible, from baseline RSV-seropositive (RSV-experienced) individuals to RSV-seronegative (RSV-naïve) individuals.
- Study objectives to assess cellular immune responses, including Th1 and Th2 subtyping, in addition to humoral immune responses.
- Safety and immunogenicity monitoring through at least 2 RSV seasons.
- Adequate study pause rules, whereby study enrollment and dosing are paused in the event that pre-specified safety criteria are met, including a threshold of severe RSV cases.
- Inclusion of a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) responsible for:
    - Review of safety, clinical, and immunogenicity data in older/RSV-experienced participants, preferably through a complete RSV season post-vaccination, as a prerequisite to enrollment of younger/RSV-naïve participants.
    - Ad hoc review of data if a pause rule criterion is met.
    - Regular, ongoing review of study data throughout the duration of the study.
- Pre-specified RSV case definitions

5. Severe Respiratory Disease Safety Signal

In July 2024, FDA was notified of a study pause in Phase 1 study mRNA-1365-P101 due to a study pause criterion being met. A potential safety signal for RSV sLRTI was identified, and as additional information accrued, an imbalance in cases of RSV sLRTI was noted, with more cases identified in the vaccine groups compared with the control group. This raised a concern for possible VAERD.

mRNA-1365-P101 is a Phase 1 study evaluating the safety, tolerability, and immunogenicity of 2 dose levels (15 µg and 30 µg total antigen) of mRNA-1345 (RSV only vaccine) and mRNA-1365 (RSV/hMPV vaccine) in healthy participants 5 months to <24 months of age. The two mRNA vaccines each contain an mRNA sequence which encodes the RSV F glycoprotein stabilized in the preF conformation. Prior to initiation of this study, FDA reviewed nonclinical data from studies conducted in BALB/c mice and cotton rats, including cotton rat challenge models for both RSV and hMPV; neither test demonstrated immunological or pathological features associated with VAERD after challenge with the homologous virus in properly controlled studies. In addition, the available clinical data from ongoing studies in adults and RSV seropositive children 12 months through 59 months of age supported progression to studies in younger cohorts.

Recruitment for the Phase 1 study was initiated February 2023 in infants/children 8 months through <24 months of age, followed by DSMB review of safety and immunogenicity data after a full RSV season, which was required prior to age de-escalation to the 5-month to <8-month-old cohorts, considered more likely to be RSV-naïve. At the time of the DSMB review and recommendation to proceed to the younger cohorts, preliminary study data showed no indication of VAERD.

Following enrollment of the 5-month to <8-month-old cohorts, a potential safety signal for RSV sLRTI was identified. The protocol's study pause criterion of any sLRTI with positive polymerase chain reaction (PCR) for RSV in ≥2 participants was met. Once the pause rule was met, the study was immediately put on hold by the Sponsor, and no participants were subsequently enrolled or received additional doses. Additional respiratory surveillance data were accrued, and additional cases were observed as the RSV season continued. An imbalance was noted, with more RSV-confirmed infections in the vaccine groups progressing to sLRTI compared with the placebo group.

5.1 Study Design

All mRNA-1365-P101 study participants were intended to receive a 3-dose schedule (0, 2, and 4 months). The study has 3 parts (A, B, and C) and is being conducted in the U.S. (Parts A and C), Panama (Parts A and B), and the U.K. (Part B).

- Part A (Cohorts 1 and 2) is randomized, observer-blind, and placebo-controlled, and is designed to evaluate 30 µg mRNA-1345, 30 µg mRNA-1365, and placebo in approximately 90 participants 8 months to <24 months of age (randomized in a 1:1:1 ratio, respectively).
- Part B (Cohorts 3 through 6) is randomized, observer-blind, and placebo controlled, and is designed to evaluate 2 dose levels of mRNA-1345 and mRNA-1365 and placebo in approximately 120 participants 5 months to <8 months of age (randomized in a 1:1:1 ratio, respectively).

- Part C (Cohorts 7 and 8) is open-label and began enrollment following initiation of Part B Cohorts 3 and 4. It is designed to evaluate 3 doses of 30 µg mRNA-1345 administered to approximately 100 participants 8 months to <12 months of age who have (Cohort 7) or have not (Cohort 8) previously received nirsevimab.

Planned immunogenicity assessments include:

- RSV-A and RSV-B nAb as measured by microneutralization assay
- RSV preF- and postF-bAb
- Measures of cell-mediated immunity

All study participants in Part A (enrolled at 8 months to <24 months of age) had completed the 3-dose series (0, 2, 4 months). As mentioned above, a potential safety signal was observed in infants 5 months to <8 months enrolled in Part B, resulting in pause in additional dosing for all study participants for Parts B and C with continuing surveillance activities, safety follow-up, and immunogenicity assessments. At the time of study pause, Part B participants in Cohorts 3 and 4 had completed 2 doses (0, 2 months) and Cohorts 5 and 6 had completed 1 dose, while Part C participants had completed 1 dose. According to the protocol, blood was collected for immunogenicity assessments as follows:

- Part A: antibody-mediated immunogenicity to be collected from all participants at Days 1, 29 (28 days post-dose 1), 85 (28 days post-dose 2), and 141 (28 days post-dose 3). Blood for cell-mediated immunogenicity may be collected at Days 1 and 85 from a subset of participants ≥12 months of age at enrollment.

- Part B: antibody-mediated immunogenicity to be collected from all participants at Days 1, 85 (28 days post-dose 2), 141 (28 days post-dose 3), and 365 (252 days post-dose 3). Following the study pause, the protocol was updated to collect blood for cell-mediated immunogenicity at selected sites at an optional unscheduled visit and at Day 365.

- Part C: antibody-mediated immunogenicity to be collected from all participants at Days 1, 29 (28 days post-dose 1), 85 (28 days post-dose 2), and 141 (28 days post-dose 3). Blood for cell-mediated immunogenicity may be collected for participants at Days 1, 29, 85, and 141.

After review of the data from Part A, the DSMB recommended enrollment of Part B (Cohorts 3 and 4) participants to receive the first of 3 doses of 15 µg mRNA-1345, 15 µg mRNA-1365, or placebo. Administration of the second dose was based on DSMB recommendation, considering ongoing monthly review of cumulative, unblinded reactogenicity and safety data. Initiation of enrollment of Part B (Cohorts 5 and 6) participants 5 months to <8 months of age to receive 3 doses of 30 µg mRNA-1345, 30 µg mRNA-1365, or placebo commenced after DSMB review of safety data from Cohorts 3 and 4 through 7 days post-dose 1.

5.2 Study Findings

5.2.1 Identification and Management of Safety Signal

On July 17, 2024, the Sponsor was made aware that a study pause criterion (any severe LRTI with positive PCR for RSV in ≥2 participants) was met. The Sponsor paused further enrollment and dosing in the study as per the protocol-defined process and notified the DSMB Chair, investigators, regulatory authorities, and the Institutional Review Board (IRB).

On July 18, 2024, the first ad hoc meeting of the DSMB was convened to review clinical information regarding the cases that led to study pause, and on July 19, 2024, the DSMB recommended continued pause of study enrollment and dosing in all cohorts pending further review.

On July 19, 2024, the Sponsor notified FDA of the study-wide pause and their continuing safety investigation. In accordance with the Code of Federal Regulations (CFR), 21 CFR 312.42(d), FDA placed the IND on clinical hold the same day. The regulatory basis for the clinical hold was:

1. Human participants are or would be exposed to an unreasonable and significant risk of illness or injury, per 21 CFR 312.42(b)(1)(i).
2. The IND does not contain sufficient information, as required under 21 CFR 312.23, to assess the risks to participants of the proposed studies, per 21 CFR 312.42(b)(1)(iv).

The DSMB continued to hold ad hoc meetings on a frequent basis, including on July 18, July 19, July 25, and August 7, 2024, during the initial evaluation period to review accumulating study data, request additional information from the Sponsor, address Sponsor questions, and make further recommendations. The DSMB has continued to recommend that the study pause remain in place with enrollment and dosing suspended.

Based on the DSMB recommendation, the Sponsor established a Blinded Clinical Assessment Team (BCAT) to conduct regular reviews of available data for all RSV infections and to formalize a systemic approach to severity grading to facilitate safety oversight and communication. As additional severe RSV LRTI cases were reported, the Sponsor identified, on August 6, 2024, potential RSV VAERD in infants 5 months to <8 months of age in association with mRNA-1345 and mRNA-1365 as an emerging safety signal with significant impact on the benefit-risk profile of the investigational vaccines. On August 12, 2024, the Sponsor classified this safety signal as an important potential risk.

The Sponsor notified all study investigators of the potential RSV VAERD risk, updated participants by a communication letter, and initiated reconsent of all active participants with revised informed consent documents that included updated information about the potential risk of RSV VAERD. The study protocol was updated to discontinue enrollment and dosing while continuing surveillance activities, safety follow-up, and immunogenicity assessments. The revised protocol includes an additional optional blood collection for cell-mediated immunogenicity in a subset of Part B participants.

On September 12, 2024, the Sponsor publicly announced that the RSV program for seronegative children <2 years of age was listed under discontinued programs with the statement, “The company does not expect program to advance beyond the ongoing Phase 1 based on emerging clinical data.”

The BCAT continues to conduct regular reviews of available data. DSMB continues to receive real-time notifications for new sLRTI and BCAT aggregate assessments, and meets to review data frequently.

FDA continues to review safety, clinical, and immunogenicity data from Study mRNA-1365-P101 as it becomes available to FDA. In addition, FDA has reviewed Sponsor analyses from two other studies of mRNA-1345 that enrolled pediatric populations including baseline RSV-seropositive children 12 months through 59 months of age and children 2 through 4 years of

age. Those analyses did not identify any severe or serious RSV-related adverse events (AEs).

5.2.2 Study Enrollment and Dosing as of Study Pause

Study mRNA-1365-P101 was initiated with enrollment of Part A (Cohorts 1 and 2) participants from February 2023. Enrollment completed prior to the respective 2023 RSV seasons. Dosing was completed in Part A in October 2023, and participants have completed their first RSV season.

Cohorts 3 and 4 in Part B were fully enrolled in May 2024 and all participants had received two doses prior to the study pause. Cohorts 5 and 6 in Part B initiated enrollment in June 2024 and were not completely enrolled before the study pause. Participants had received a single dose at the time of the study pause.

Cohorts 7 and 8 in Part C initiated enrollment in June 2024 but were not fully enrolled before the study pause. Part C participants had received a single vaccine dose at the time of the study pause (see Appendix 1).

5.2.3 Reported RSV Severe Lower Respiratory Tract Infection Cases

Part A (8 months to <24 months of age participants)

One case of severe RSV LRTI was reported in a 24-month-old study participant with no significant past medical history enrolled in Cohort 2 (30 µg mRNA-1365). The event occurred 333 days after completion of the 3-dose series (0, 2, 4 months) during the participant's 2nd RSV season. The event was reported after age de-escalation and enrollment of the 5-month to <8-month-old cohorts had started. The participant was hospitalized for RSV pneumonia diagnosed on chest x-ray. They were treated with oxygen via face mask, unknown nebulized therapies, and amoxicillin (for concurrent pharyngotonsillitis). The participant was discharged to home on hospital Day 2. The event was considered resolved 15 days after onset. As of the date of data cut-off (November 18, 2024), there have been no other reported severe RSV LRTI cases in Part A study participants.

Part B (5 months to <8 months of age participants): Imbalance

As described in Section 5.2.1, the study pause rule criterion for any severe LRTI with positive PCR for RSV in ≥2 participants was met, with an imbalance in reported cases of vaccine recipients compared to placebo recipients in Part B. One participant in Cohort 3 (15 µg mRNA-1345) developed severe RSV LRTI and one participant in Cohort 4 (15 µg mRNA-1365) developed very severe RSV LRTI (see Appendix 2 for protocol case definitions). Following the study pause, participants have continued to be followed for the development of RSV disease.

Table 1 provides an overview of the reported cases of symptomatic RSV disease and those LRTI cases that were assessed as clinically significant severe/very severe (CS-severe/very severe) through the date of data cut-off (November 18, 2024). CS-severe/very severe LRTI was defined as RSV LRTI cases that met the protocol specified definition of severe or very severe and/or required hospitalization. There was an imbalance in the numbers of cases of CS-severe/very severe LRTI in the vaccine groups in Part B Cohorts 3 and 4 (mRNA-1345/1365 15 µg groups: 5 cases) as compared with the Part B Placebo group (1 case).

Table 1. Overview of Symptomatic RSV Cases and Clinically Significant-Severe/Very Severe RSV LRTIs, Study mRNA-1365-P101

Part/Cohort	Vaccination (Dose)	Symptomatic RSV n/N (%)	CS-Severe/ Very Severe RSV LRTI[a] n/N (%)	% of Symptomatic RSV Cases Classified as CS-Severe/Very Severe[a]
Part A Cohort 1	mRNA-1345 (30 µg)	11/29 (37.9%)	0	0%
Part A Cohort 2	mRNA-1365 (30 µg)	13/30 (43.3%)	**1/30 (3.3%)**	**7.7%**
Part A Cohorts 1 & 2	Placebo	14/31 (45.2%)	0	0%
Part B Cohort 3	mRNA1345 (15 µg)	9/20 (45.0%)	**2/20 (10%)**	**22.2%**
Part B Cohort 4	mRNA 1365 (15 µg)	10/20 (50.0%)	**3/20 (15%)**	**30.0%**
Part B Cohorts 3 & 4	Placebo	12/20 (60.0%)	**1/20 (5.0%)**	**8.3%**
Part B Cohort 5	mRNA-1345 (30 µg)	5/7 (71.4%)	0	0%
Part B Cohort 6	mRNA-1365 (30 µg)	1/7 (14.3%)	0	0%
Part B Cohorts 5 & 6	Placebo	4/7 (57.1%)	0	0%
Part C Cohorts 7 & 8	mRNA-1345 (30 µg)	0	0	0%

Abbreviations: CS=clinically significant, LRTI=lower respiratory tract infection, n=number of cases, N=total number of participants, RSV=respiratory syncytial virus
Date of data cut-off: November 18, 2024
Highlighted rows identify cohorts for which there was an imbalance in CS-Severe/Very Severe RSV LRTI cases between vaccine recipients and placebo recipients.
Part A: Participants 8 months to <24 months; Part B: Participants 5 months to <8 months; Part C: Participants 8 months to <12 months.
a. Any per protocol severe LRTI AND any per protocol very severe LRTI AND any RSV infection hospitalization, post hoc definition

Table 2 provides details for each of the CS-severe/very severe LRTI cases in Part B Cohorts 3 and 4. Five of the six cases required hospitalization with one infant requiring mechanical ventilation. All cases were considered resolved within a median of 19.5 days of symptom onset (range 8-31 days).

Table 2. Part B Cohorts 3 and 4 Cases of Clinically Significant-Severe/Very Severe RSV LRTI*, Study mRNA-1365-P101

RSV Case #	Vaccination	Age at Event (Months)	Doses Received Prior to Event	Days Between Event Onset and Most Recent Dose	Additional Clinical Details
#1	mRNA-1365 (15 µg)	8 m	1	23	• Hospitalized (non-ICU) • Max. support[a]: supplemental O_2 (unknown level)
#2	mRNA-1365 (15 µg)	8 m	2	26	• Hospitalized (non-ICU) • SARS-CoV-2 co-infection • Max. support: 2 L/min NC
#3	mRNA-1365 (15 µg)	8 m	2	10	• Hospitalized (ICU) • SARS-CoV-2 + Human rhinovirus/enterovirus co-infection • Bilateral pulmonary infiltrates • Max. support: Mechanical ventilation
#4	mRNA-1345 (15 µg)	9 m	2	3	• Not hospitalized (ED visit only) • Max. support: none
#5	mRNA-1345 (15 µg)	9 m	2	14	• Hospitalized (non-ICU) • Max. support: None
#6	Placebo	10 m	2	37	• Hospitalized (non-ICU) • Human metapneumovirus co-infection • Pneumonia • Max. support: 3 L/min NC

Abbreviations: CS=clinically significant, ED=emergency department, ICU=intensive care unit; L=liters, LRTI=lower respiratory tract infection, m=months, Max=maximum, NC=nasal cannula, RSV=respiratory syncytial virus

*Any per protocol severe LRTI AND any per protocol very severe LRTI AND any RSV infection hospitalization, post hoc definition

a. Max support=maximum level of respiratory support reported during LRTI event

5.2.4 Immunogenicity Results

5.2.4.1 Part A results

RSV nAb and bAb responses

RSV A and RSV B nAb responses for Part A participants are shown in Table 3. Day 85 RSV nAb responses were highest following mRNA-1345 (30 µg) as compared with mRNA-1365 (30 µg) and placebo. RSV infection occurred prior to the Day 85 antibody measurement for 2 vaccine recipients (mRNA-1365 30 days and 29 days before collection) and 1 placebo recipient (4 days before collection).

Table 3. RSV A and RSV B Neutralizing Antibody (nAb) Responses at Day 85, 8 Months – 24 Months of Age, Study mRNA-1365-P101, Part A Cohorts 1 and 2

Timepoint	RSV A nAb GMT (IU/mL) (Min, Max)	Fold Rise	RSV B nAb GMT (IU/mL) (Min, Max)	Fold Rise
mRNA-1345 (30 µg) Baseline N=29	81 (7, 1516)	--	42 (5, 738)	--
mRNA-1345 (30 µg) Day 85 N=29	12,848 (1745, 86251)	149	2412 (280, 19334)	53
mRNA-1365 (30 µg) Baseline N=26	119 (13, 1549)	--	108 (15, 10955)	--
mRNA-1365 (30 µg) Day 85 N=26	6300 (527, 49912)	53	1392 (168, 9940)	13
Placebo Baseline N=26	137 (7, 35641)	--	61 (5, 3921)	--
Placebo Day 85 N=26	250 (7, 13741)	2	103 (5, 8831)	2

Abbreviations: GMT=geometric mean titer, IU=international units, mL=milliliter, N=total participants with available data, nAb=neutralizing antibody, RSV=respiratory syncytial virus, µg=microgram
RSV events may have occurred prior to Day 85 antibody measurements

The bAb responses following mRNA-1345 (30 µg) as compared with mRNA-1365 (30 µg) and placebo are shown in Table 4.

Table 4. PreF and PostF bAb Responses, 8 Months – 24 Months of Age, Study mRNA-1365-P101, Part A Cohorts 1 and 2

Timepoint	RSV Pre-F bAb GMC (AU/mL) (Min, Max)	Fold Rise	RSV Post-F bAb GMC (AU/mL) (Min, Max)	Fold Rise	PreF/PostF Ratio
mRNA-1345 (30 µg) Baseline N=29	211 (18, 13711)	--	368 (29, 21253)	--	
mNA-1345 (30 µg) Day 85 N=29	89,306 (17705, 580533)	338	13,626 (455, 166675)	26	6.6
mRNA-1365 (30 µg) Baseline N=26	519 (18, 11277)	--	886 (29, 27517)	--	

Timepoint	RSV Pre-F bAb GMC (AU/mL) (Min, Max)	Fold Rise	RSV Post-F bAb GMC (AU/mL) (Min, Max)	Fold Rise	PreF/PostF Ratio
mNA-1365 (30 µg) Day 85 N=26	44,082 (6263, 239263)	85	12,104 (136, 161911)	14	3.6
Placebo Baseline N=26	552 (18, 112457)	--	979 (29, 27395)	--	
Placebo Day 85 N=26	1077 (18, 188320)	2	1119 (29, 137844)	1.1	1.0

Abbreviations: GMC=geometric mean concentration, AU=arbitrary units, max=maximum; min=minimum, mL=milliliter, bAb=binding antibody, RSV=respiratory syncytial virus, µg=microgram
RSV events may have occurred prior to Day 85 antibody measurements.

RSV Serostatus

Using the per protocol definition of seropositive (nAb ≥ lower limit of quantification [LLOQ]), 93.1% of mRNA-1345 recipients, 100% of mRNA 1365 recipients, and 96.2% of placebo recipients were seropositive at baseline. The Sponsor also performed post-hoc analyses of serostatus based on a seropositive definition of PostF bAb concentration ≥200AU/mL. Using this definition, 61.5% of mRNA-1345 recipients, 44.8% of mRNA 1365 recipients, and 65.4% of placebo recipients were seropositive at baseline.

RSV T-cell responses

Cytokines representative of Th1 (IL-2, TNF-α, and IFN-γ) and Th2 (IL-13, IL-5, and IL-4) responses were measured in a subset of Part A participants (mRNA-1345: N=5 at baseline, N=8 at day 85, N=5 at both timepoints; mRNA-1365: N=7 at baseline, N=8 at day 85, N=4 at both timepoints; Placebo: N=5 at baseline, N=6 at day 85, N=4 at both timepoints).

Preliminary analyses of data from this small subset of Part A participants suggested that, at baseline, participants defined as previously RSV-experienced had evidence of Th1 responses. Th2 responses were below the lower limit of quantitation (LLOQ). After mRNA RSV vaccination, a higher proportion of participants defined as RSV-naïve at baseline appeared to have an IL-5 response compared with participants previously RSV-experienced. Following vaccination, the levels of other Th2 cytokines, IL-13 and IL-4, appeared comparable between both RSV-naïve and previously RSV-experienced participants. Th1 responses at day 85 appeared to be generally similar between RSV-naïve and previously RSV-experienced participants. Th2 responses in all placebo recipients, including those previously RSV-experienced, remained below the lower limit of quantitation at day 85. These data suggest a potential trend towards increased frequency of IL-5 responses (a Th2 cytokine) in RSV naïve participants as compared with RSV experienced participants following vaccination. The small number of participants with available immunogenicity data and the absence of data from participants who developed RSV disease limit the interpretation of these results.

5.2.4.2 Part B results

RSV nAb and bAb responses

Participant RSV A and RSV B nAb responses by RSV case classification are shown in Table 5, and include Day 85 nAb responses, which per protocol, were not performed until Day 85 (1-month post-dose 2). However, for the mRNA1345 and mRNA1365 vaccine

recipients listed in Table 5, the events of Clinically Significant (CS)-Severe/ Very Severe RSV LRTI events had all occurred prior to the Day 85 sera collection, while the same events in the placebo group occurred after the Day 85 sera collection. For the participants with Other RSV infections, the values shown in Table 5 were measured either before (N=10) or after (N=15) RSV infection. The timing of these antibody measurements confounds the interpretation of these data.

Table 5. RSV A and RSV B Neutralizing Antibody (nAb) Responses Based on RSV Infection Classification, 5 Months – <8 Months of Age, Study mRNA-1365-P101, Part B Cohorts 3 and 4

Classification	RSV A nAb GMT (IU/mL) (Min, Max)	RSV A nAb Fold Rise	RSV B nAb GMT (IU/mL) (Min, Max)	RSV B nAb Fold Rise
CS-Severe/Very Severe RSV LRTI[a]	--	--	--	--
mRNA-1345 15 µg Baseline N=2	36 (34, 37)	--	55 (53, 57)	--
mRNA-1345 15 µg Study Day 85 N=2	60,721 (15990, 230585)	1712	52,511 (24515, 112476)	955.4
mRNA-1365 15 µg Baseline N=3	73 (33, 262)	--	76 (49, 111)	--
mRNA-1365 15 µg Study Day 85 N=2	33,622 (20812, 54317)	313.1	24,497 (7686, 78080)	393.7
Placebo Baseline N=1	26	--	21	--
Placebo Study Day 85 N=1	21	0.8	19	0.9
RSV RTI/LRTI[b]	--	--	--	--
mRNA-1345 15 µg Baseline N=7	140 (48, 653)	--	98 (45, 422)	--
mRNA-1345 15 µg Study Day 85 N=7	3299 (444, 13340)	23.6	1768 (240, 5184)	18.0
mRNA-1365 15 µg Baseline N=7	155 (41, 2994)	--	98 (30, 1620)	--
mRNA-1365 15 µg Study Day 85 N=6	1425 (86, 25418)	7.9	965 (122, 27706)	8.1
Placebo Baseline N=11	80 (31, 213)	--	91 (27, 281)	--
Placebo Study Day 85 N=9	833 (50, 5777)	10.4	285 (38, 1541)	3.2

Classification	RSV A nAb GMT (IU/mL) (Min, Max)	RSV A nAb Fold Rise	RSV B nAb GMT (IU/mL) (Min, Max)	RSV B nAb Fold Rise
No RSV Infection[c]	--	--	--	--
mRNA-1345 15 µg Baseline N=11	79 (24, 1478)	--	65 (22, 160)	--
mRNA-1345 15 µg Study Day 85 N=11	4093 (1116, 27195)	51.7	2215 (680, 5529)	33.9
mRNA-1365 15 µg Baseline N=10	61 (24, 2155)	--	47 (15, 139)	--
mRNA-1365 15 µg Study Day 85 N=9	2339 (72, 26846)	36.4	831 (35, 3306)	15.0
Placebo Baseline N=8	238 (69, 1248)	--	175 (64, 945)	--
Placebo Study Day 85 N=7	273 (30, 6494)	1.0	183 (22, 3969)	1.0

Abbreviations: CS=clinically significant, GMT=geometric mean titer, IU=international units, LRTI=lower respiratory tract infection, max=maximum, min=minimum, mL=milliliter, N=total number of participants with available data, nAb=neutralizing antibody, RSV=respiratory syncytial virus, RTI=respiratory tract infection, µg=microgram

a. CS-Severe/Very Severe: Any per protocol severe LRTI AND any per protocol very severe LRTI AND any RSV infection hospitalization, post hoc definition. For mRNA-1345 and mRNA-1365 recipients with CS-Severe/Very Severe RSV LRTI, the RSV event occurred prior to the Day 85 collection. For the placebo participant, the RSV event occurred after the Day 85 collection.

b. RSV RTI/LRTI: Any confirmed RSV infection not meeting the definition of CS-Severe/Very Severe RSV LRTI. For mRNA-1345 and mRNA-1365 recipients with RTI/LRTI not meeting the CS-severe/very severe definition, the RSV event occurred prior to the Day 85 collection for N=2 and N=5 respectively and after the Day 85 collection for N=5 and N=2. For the placebo recipients, the RSV event occurred prior to the Day 85 collection for N=8 and and after for N=3.

c. No confirmed RSV infection

The patterns of bAb responses were similar to those of the nAb responses (Table 6). The preF to postF ratios were highest in individuals vaccinated with mRNA-1345 and mRNA-1365.

Table 6. PreF and PostF bAb Responses Based on RSV Infection Classification, Part B Cohorts 3 and 4, 5 Months – <8 Months of Age, Study mRNA-1365-P101, Part B Cohorts 3 and 4

Classification	RSV PreF bAb GMC (AU/mL) (Min, Max)	RSV PostF bAb GMC (AU/mL) (Min, Max)	PreF/PostF Ratio
CS-Severe/Very Severe RSV LRTI[a]	--	--	--
mRNA-1345 15 µg Baseline N=2	193 (165, 225)	435 (384, 492)	--
mRNA-1345 15 µg Study Day 85 N=2	399,646 (275112, 580553)	61,218 (52835, 70930)	6.5
mRNA-1365 15 µg Baseline N=3	253 (203, 368)	319 (257, 401)	--
mRNA-1365 15 µg Study Day 85 N=2	392,259 (265036, 580553)	55,735 (38089, 81557)	7.0
Placebo Baseline N=1	184	273	--
Placebo Study Day 85* N=1	18	29	0.6
RSV RTI/LRTI [b]	--	--	--
mRNA-1345 15 µg Baseline N=7	676 (274, 6374)	552 (213, 2594)	--
mRNA-1345 15 µg Study Day 85 N=7	31,629 (4987, 85123)	1182 (193, 24216)	26.8
mRNA-1365 15 µg Baseline N=7	404 (83, 3488)	306 (28.5, 1942)	--
mRNA-1365 15 µg Study Day 85 N=6	15,074 (1322, 280540)	1227 (267, 16693)	12.3
Placebo Baseline N=11	289 (100, 972)	273 (82, 1020)	--
Placebo Study Day 85 N=9	3147 (122, 15309)	4129 (160, 25604)	0.8

Classification	RSV PreF bAb GMC (AU/mL) (Min, Max)	RSV PostF bAb GMC (AU/mL) (Min, Max)	PreF/PostF Ratio
No RSV Infection[c]	--	--	--
mRNA-1345 15 µg Baseline N=11	396 (51, 4484)	393 (100, 3589)	--
mRNA-1345 15 µg Study Day 85 N=11	32,780 (12817, 82388)	2165 (303, 46437)	15.1
mRNA-1365 15 µg Baseline N=10	92 (17.5, 2598)	115 (28.5, 8151)	--
mRNA-1365 15 µg Study Day 85 N=9	27,098 (2924, 578705)	1795 (68, 67572)	15.1
Placebo Baseline N=8	719 (492, 1749)	1140 (370, 7776)	--
Placebo Study Day 85 N=7	824 (56, 47609)	914 (28.5, 89397)	0.9

Abbreviations: AU=arbitrary units, bAb=binding antibody, GMC=geometric mean concentration, LRTI=lower respiratory tract infection, max=maximum, min=minimum, mL=milliliter, N=total number of participants with available data, nAb=neutralizing antibody, RSV=respiratory syncytial virus, RTI=respiratory tract infection, µg=microgram
a. CS-Severe/Very Severy: Any per protocol severe LRTI AND any per protocol very severe LRTI AND any RSV infection hospitalization, post hoc definition. For mRNA-1345 and mRNA-1365 recipients with CS-Severe/Very Severe RSV LRTI, the RSV event occurred prior to the Day 85 collection. For the placebo participant, the RSV event occurred after the Day 85 collection.
b. RSV RTI/LRTI: Any confirmed RSV infection not meeting the definition of CS-Severe/Very Severe RSV LRTI. For mRNA-1345 and mRNA-1365 recipients with RTI/LRTI not meeting the CS-severe/very severe definition, the RSV event occurred prior to the Day 85 collection for N=2 and N=5 respectively and after the Day 85 collection for N=5 and N=2. For the placebo recipients, the RSV event occurred prior to the Day 85 collection for N=8 and after for N=3.
c. No confirmed RSV infection

RSV Serostatus

The presence of maternally derived antibodies complicates determination of participant baseline serostatus. Consequently, all participants in Part B met the protocol definition of positive baseline serostatus (RSV A and/or B nAb concentrations ≥LLOQ).

The Sponsor performed exploratory post-hoc analyses to determine the most appropriate biomarker of participant RSV serostatus at baseline. Evaluated biomarkers included:

- nAb against RSV A and RSV B
- IgG bAb to RSV antigen PreF and PostF
- PreF/PostF ratios at D85 post-vaccination
- IgA bAb to RSV A antigen and RSV B PreF antigens using assays in development

Of these biomarkers, IgG bAb to RSV antigen PostF was identified by the Sponsor as the best performing measure of baseline serostatus for participants 5 months to <8 months of age.

RSV T-cell responses

Analyses of T-cell responses in Part B Cohort 3 and 4 participants are not available at the time of preparation of this briefing document.

5.2.5 Cases of hMPV Hospitalization

On November 22, 2024, the Sponsor provided updated information on cases of hMPV hospitalizations in Cohort 3 and 4. Two were vaccine recipients (Cohort 4, mRNA-1365), including one participant who required non-invasive positive pressure ventilation and one was a placebo recipient with a co-infection with RSV. Additional clinical and immunologic data are currently not available.

6. Vaccine Responses Following Nirsevimab

In Part C of Study mRNA-1365-P101, participants 8 months through <12 months of age either previously exposed to nirsevimab (N=9) or not previously exposed to nirsevimab (N=6) received 1 dose of 30 µg mRNA-1345. Antibody responses for these groups are shown in Table 7.

Table 7. RSV A and RSV B Neutralizing Antibody (nAb) Responses to mRNA-1345 in Nirsevimab-Exposed and Nirsevimab-Unexposed Participants 8 Months – 12 Months of Age, Study mRNA-1365-P101 Part C

Parameter	Nirsevimab-Exposed N=9	Nirsevimab-Unexposed N=6
Baseline GMT (min, max) (IU/mL)	--	--
RSV A	10712 (3665, 34824)	44 (7, 655)
RSV B	263 (121, 619)	49 (12, 379)
Day 29 Post-Dose 1 mRNA 1345 (30 µg) GMT (min, max) (IU/mL)	--	--
RSV A	7453 (3082, 19682)	4029 (79, 56688)
RSV B	249 (84, 1588)	1678 (36, 31309)
Fold-rise (95% CI)	--	--
RSV A	0.7 (0.5, 1.2)	60.3 (10.8, 334.9)
RSV B	1 (0.5, 2.1)	19.1 (2.1, 175.1)

Abbreviations: CI=confidence interval, GMT=geometric mean titer, IU=international units, max =maximum, min=minimum, mL=milliliters, N=total number of participants, RSV=respiratory syncytial virus, µg=microgram

These results suggest a potential lack of response to a single dose of mRNA-1345 (30 µg) when administered to individuals previously exposed to nirsevimab, most notably for post-dose 1 RSV B GMT (249 IU/mL) in nirsevimab-exposed compared with post-dose 1 RSV B GMT (1678 IU/mL) in nirsevimab-unexposed participants. Antibody responses following the 3-dose series are not available because participants did not receive additional doses due to the study pause.

7. Considerations for Ongoing Clinical Development of Pediatric RSV Vaccines

The observed imbalance in severe/very severe cases of RSV LRTI in the mRNA-1345 and mRNA-1365 vaccine development program among 5-month to <8-month-old recipients of mRNA-1345 (15 µg) and mRNA-1365 (15 µg) has uncertain implications for the ongoing and future pediatric development of other non-live attenuated RSV vaccines. The immunologic phenotype of cases of severe/very severe RSV disease in the vaccinated cohort have yet to be fully elucidated and histopathologic information is not available. Notably, differences in the mRNA vaccine candidates compared with FI-RSV vaccine and the available nonclinical data for the mRNA vaccine candidates were reassuring to mitigate risk of VAERD in infants and children in the clinical trial.

Preliminary analyses of humoral immunogentiy results from the clinical trial demonstrate nAb responses following vaccination of Part A (8-month to 24-month-olds) and Part B (5-month to <8-month-olds) participants that were many-fold higher than those in the placebo group.

Cell-mediated immunogenicity data were available for a small subset of Part A participants and were not available for any Part B participants; therefore, interpretability of these data may be limited. Preliminary analyses of cytokines representative of T-cell responses in the subset of Part A participants suggest a potential trend towards increased frequency of IL-5 responses (a Th2 cytokine) in RSV-naïve participants as compared with previously RSV-experienced participants following vaccination.

Currently, enrollment of children <2 years of age and RSV-naïve children 2 through 5 years of age is on hold for all clinical studies of RSV vaccine candidates under U.S. IND. In light of the available data from the mRNA-1345 and mRNA-1365 vaccine development program, the decision to re-initiate enrollment of at-risk populations for VAERD and allow future pediatric studies of other non-live attenuated RSV vaccines will need to consider:

1. Whether our current understanding of the pathophysiology of VAERD following administration of FI-RSV vaccine informs assessment of this potential risk across other vaccine technologies (e.g., live-attenuated chimeric respiratory viral, other viral vectored, mRNA, and recombinant particle/subunit vaccine candidates);
2. The need for additional clinical or other assessments to further characterize the nature of the potential VAERD safety signal;
3. Whether and what data may be helpful to stratify potential risk based on vaccine technology and/or antigenic composition;
4. The utility of nonclinical studies and data, additional nonclinical testing that may be necessary, and how and whether nonclinical studies can adequately predict or reassure against the risk of VAERD, and if this may vary across vaccine technologies and/or antigenic compositions;
5. Additional risk mitigation or risk management approaches that would be sufficient to address the potential for VAERD in a clinical trial;
6. A benefit-risk assessment approach that incorporates evidence of the benefit of a vaccine candidate in RSV-experienced children and uncertainties regarding the VAERD risk, all in the context of the available preventive landscape, including nirsevimab, other anti-RSV monoclonal antibodies in late phases of clinical development, and maternal immunization approaches; and
7. How potential RSV mAB – RSV vaccine interactions should be addressed in the design of clinical trials and the overall clinical development plan, including potential populations indicated for use.

8. VRBPAC Discussion Topics

8.1 Summary of Current State and Context for VRBPAC Discussion

Based on the current understanding of the immunopathogenesis of VAERD following FI-RSV vaccine administration (Section 2.3) and a requirement for nonclinical studies and data designed to mitigate the risk of VAERD (Section 4.1.1), pediatric development of RSV vaccines has proceeded cautiously, including assessment of immune responses in age de-escalation study designs prior to enrolling RSV-naïve participants, stringent eligibility criteria, study pausing rules, and other risk mitigation and management strategies. Factors that were thought to mitigate the risk of VAERD for mRNA-1345 and mRNA-1365 vaccine candidates included: (1) rational vaccine design, using a stabilized pre-F antigen; (2) nonclinical data that

demonstrated the absence of Th2-biased cytokine responses, adequate nAb responses, and lack of VAERD following post-vaccination RSV challenge; and (3) clinical safety and immunogenicity data from previously RSV-experienced adults and older children that demonstrated an acceptable safety profile and adequate nAb responses.

Despite these reassurances, an imbalance in severe RSV LRTI was noted following administration of mRNA-1345 and mRNA-1365 vaccine candidates to infants, which is concerning for VAERD. Additionally, vaccine immune responses in nirsevimab-exposed recipients were blunted, suggesting an adverse RSV mAb- RSV vaccine interaction. VRBPAC discussion topics will specifically address the interpretation of the safety data from the mRNA-1345 and mRNA-1365 vaccine pediatric clinical development program, the implications of these findings for ongoing and future pediatric development of other non-live attenuated RSV vaccines, and RSV mAb – RSV vaccine interactions. We envision the VRBPAC discussion to focus on: a) considerations of RSV Vaccine Safety in Pediatric Populations and b) Sequential Administration of RSV Monoclonal Antibodies (mAbs) followed by RSV Vaccines in Infants and Toddlers.

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10. Appendix 1

Enrolled participants at time of study pause

Part A: Participants 8 months to <24 months

Cohorts 1 and 2

- 29 participants received 3 doses of 30 µg mRNA-1345

- 30 participants received 3 doses of 30 µg mRNA-1365
- 31 participants received placebo

Part B: Participants 5 months to <8 months

Cohorts 3 and 4

- 20 participants received 2 doses of 15 µg mRNA-1345
- 20 participants received 2 doses of 15 µg mRNA-1365
- 20 participants received 2 doses of placebo

Part B: Participants 5 months to <8 months

Cohorts 5 and 6

- 7 participants received 1 dose of 30 µg mRNA-1345
- 7 participants received 1 dose of 30 µg mRNA-1365
- 7 participants received 1 dose of placebo

Part C: Participants 8 to <12 months who received 1 dose of 30 µg mRNA-1345

Cohorts 7 and 8

- 9 participants previously exposed to nirsevimab
- 6 participants not previously exposed to nirsevimab

11. Appendix 2

Table 8. 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]
Clinically Significant (CS)-Severe/Very Severe RSV LRTI[a]	Includes all Case Definitions included below
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]

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; SpO2=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 SpO2, 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.