

## Advancing Drug Development for Respiratory Syncytial Virus

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### Discussion Guide

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections (LRTIs) in infants and children around the world, resulting in three million hospitalizations and several hundred thousand deaths annually, the vast majority of which occur in developing nations. Treatment options for RSV are limited, and efforts to produce a vaccine have been unsuccessful thus far. Given the burden of disease and the morbidity linked to severe RSV-associated LRTIs, there is a need for new therapeutic agents to treat RSV infections. Improvements in scientific understanding of the disease as well as advances in key technologies have recently spurred a range of new development activities around RSV therapeutics. However, progress has been slowed by numerous challenges, including difficulties in clinical trial design and a lack of scientific consensus on robust and reliable clinical endpoints.

In light of these ongoing issues, and under a cooperative agreement with the U.S. Food and Drug Administration (FDA), the Duke-Margolis Center for Health Policy is convening this expert workshop to discuss solutions to clinical and regulatory barriers to the development of RSV therapeutics. Specifically, experts will be asked to share their input and recommendations on:

1. Exploring possible definitions for respiratory syncytial virus (RSV) disease severity;
2. Identifying and discussing populations suitable for clinical trials;
3. Identifying clinically meaningful efficacy endpoints;
4. Describing non-clinical and clinical development approaches for pediatric-focused products;
5. Exploring the types of proof-of-concept data needed to initiate clinical trials in infants and young children; and
6. Facilitating RSV drug development for other populations, such as elderly and immunocompromised patients.

### Respiratory Syncytial Virus

RSV affects children and adults worldwide, with outbreaks typically spiking in more temperate regions during the winter.<sup>1</sup> It is spread via direct or indirect contact with the oral or nasal secretions of an infected person, or through the air after an infected person coughs or sneezes.<sup>2</sup> Symptoms of RSV infection vary in severity. Healthy adults and older children typically exhibit symptoms similar to the common cold, including runny nose, sore throat, fever, and cough.<sup>3</sup> In the majority of cases, symptoms are mild and the disease clears up within one to two weeks.<sup>4</sup> However, in certain patient populations RSV can cause more serious LRTIs such as bronchiolitis and pneumonia. Symptoms of RSV-associated LRTIs include wheezing, crackles, cough, and abnormally rapid breathing. In infants, lethargy, irritability, and poor feeding can also occur. Some children develop post-bronchiolitic wheezing syndrome, which in most cases resolves on its own after several weeks.<sup>5</sup> In the most severe cases, RSV infections can cause apnea or respiratory failure and death.<sup>6</sup>

### Patient and Population Burden

RSV is common worldwide; nearly all children under the age of two will experience at least one RSV infection, and approximately 20-30% of those children will develop an LRTI.<sup>7</sup> The risk of RSV-related bronchiolitis or other LRTI is significantly higher in vulnerable populations such as preterm infants,

children with significant health complications such as congenital heart or lung conditions, adults over the age of 65, and the immunocompromised.<sup>8</sup>

RSV is responsible for roughly 30 million LRTIs, 3 million hospitalizations, and 200,000 deaths worldwide annually.<sup>9</sup> Despite the global ubiquity of RSV infections, the most serious burden falls disproportionately on low- and middle-income countries, where 99% of the estimated 253,000 annual global RSV-associated deaths occur.<sup>10</sup> By contrast, it is estimated that RSV causes fewer than 500 deaths among young children<sup>11,12</sup> and contributing to between 57,000 to 172,000 bronchiolitis-related hospitalizations in the US each year.<sup>13</sup> Domestically, RSV-associated mortality in the elderly population is higher, causing an estimated 10,000 deaths per year.<sup>14</sup> The economic burden of RSV is also significant, owing to both the direct costs of treatment and the indirect costs associated with income loss and other caregiver expenses. Recent estimates put the combined annual expenditures at nearly \$1.2 billion per year.<sup>15</sup>

### Current Treatment Options

There is no vaccine available to prevent RSV, and treatment options are limited. For the majority of patients, monitoring and supportive care are the primary treatment. Bronchodilators and anti-inflammatory medications are sometimes used to treat the symptoms of RSV bronchiolitis, though evidence of their effectiveness is lacking<sup>16</sup> and their use is discouraged in American Academy of Pediatrics (AAP) treatment guidelines. Aerosolized ribavirin was approved by FDA in 1980 to treat RSV in children.<sup>17</sup> However, the clinical benefit of aerosolized ribavirin in this population remains controversial and doubts regarding its efficacy have emerged.<sup>18</sup> Evidence from preclinical models has also raised concerns regarding the potential for aerosolized ribavirin to cause gene mutations, birth defects, and cancer, posing a safety risk to both patients who receive the drug and the healthcare workers who administer it.<sup>19</sup> The use of aerosolized ribavirin has subsequently been restricted only to high-risk populations, primarily stem cell or lung transplant recipients.<sup>20</sup>

Two prophylactic treatments— Polyclonal RSV immune globulin and human anti- RSV F protein monoclonal antibodies—have been shown to help reduce the risk of RSV bronchiolitis in certain populations of high-risk children.<sup>21</sup> RSV immune globulin (RespiGam) was approved in 1996 to prevent or reduce RSV complications but is no longer marketed. Palivizumab (Synagis), an RSV-specific monoclonal antibody, was approved in 1998 for the reduction of serious LRTI in children at high risk of severe disease and is currently the only available FDA-approved RSV immunoprophylaxis product used to prevent RSV bronchiolitis. In addition to helping reduce hospitalization rates due to RSV, evidence also suggests that RSV immunoprophylaxis may reduce the occurrence of recurrent wheezing in young children.<sup>22</sup> However, there is debate over how best to define the “high-risk” infants that should be given RSV immunoprophylaxis, as the treatment is expensive and its cost-effectiveness is unclear in some populations.<sup>23,24,25</sup> Neither of the approved immunoprophylaxis products has been shown to be clinically beneficial in treating established RSV infection.

### Advancing RSV Treatment Research and Development: Key Issues for Consideration

Owing in part to advances in scientific understanding of the virus and its pathogenesis, as well new technologies that can facilitate the discovery and development process (e.g., the emergence of point-of-care diagnostics), there is renewed interest and investment in RSV therapeutics. A number of development programs have been launched in the last decade, and several candidates are currently in clinical trials.<sup>26</sup>

The most significant barriers to the development of new RSV drugs relate to challenges in clinical trial design and the lack of robust and reliable clinical endpoints. Certain populations (e.g., the

immunosuppressed) are difficult to enroll in adequate numbers to power studies. Viral detection and diagnosis can also be difficult for some populations, such as the elderly. Conducting RSV studies in the infant population—which has the highest burden and would thus be the most obvious population to target—entails its own set of clinical and ethical challenges. For most infectious diseases, the natural history of illness in children is similar to that in adults, and the efficacy established in adult trials can be extrapolated to the pediatric population. Additional studies in children are then focused on establishing the correct dose and assessing safety. However, RSV bronchiolitis is a disease of young infants with no clear adult correlate, and thus requires a different development approach in order to establish proof-of-concept (i.e., that the drug candidate has demonstrated its intended effect on a given target, and can proceed to pivotal trials).

Furthermore, there is currently no clear consensus on the most relevant outcomes that should be selected for RSV treatment trials. Many Phase 2 trials have attempted to use viral load as a primary endpoint (i.e., the amount of virus present in a sample taken from patients), but there is conflicting evidence of how well this correlates to clinical benefit.<sup>27</sup> In the absence of a validated surrogate endpoint, a clinical endpoint is required for drug approval. While some studies have suggested higher viral load may correlate with more severe symptoms, in most patients, viral load declines spontaneously over a period of days and no specific viral load is predictive of symptoms in a given patient. Any endpoint for a pivotal trial will likely utilize a severity score to establish clinical improvement, but widely-accepted definitions of disease severity are lacking, and there are currently no validated or preferred instruments to measure either disease severity or clinical improvement for RSV disease.<sup>28</sup> There are also ongoing questions regarding how best to define the appropriate study population, both in terms of disease severity and in terms of underlying patient factors such as age and additional comorbidities.

RSV prophylaxis trials—which would assess a treatment’s effectiveness in preventing RSV-associated illness—face similar challenges regarding a lack of established clinical endpoints. Historically, the most common endpoint used for RSV drug trials in children has been a reduction in RSV-related hospitalizations.<sup>29</sup> However, the criteria for admitting a child with RSV may be subjective, and the threshold for hospitalization can vary widely throughout the world.<sup>30</sup> Additionally, there has been a shift toward outpatient management of RSV disease with a corresponding decline in RSV-related hospitalization rates in recent years, due in part to the increased use of RSV immunoprophylaxis as well as increased pressure from payers looking to reduce hospital admissions.<sup>31,32,33</sup> These changes in clinical practice have raised doubts about the utility and reliability of hospitalization as an endpoint. Alternative endpoints for prophylaxis trials have been proposed (e.g., reduction in RSV-associated, medically-attended LRTIs in outpatient settings), but there is no clear consensus.<sup>34</sup>

### **Facilitating RSV Drug Development for Children and Other Vulnerable Populations**

Given these development challenges and the substantial unmet medical need, there have been recent calls for greater regulatory clarity around the development of new therapeutics for RSV disease. In particular, there is a need to identify viable approaches to developing drugs primarily intended for the pediatric (i.e., infant) population, including the types of proof-of-concept data needed to initiate clinical trials in this population. There is also a need to identify effective strategies for studying small, vulnerable populations (e.g., transplant recipients), which present a different set of challenges for drug developers.

FDA has taken steps in recent years to expedite development for drugs that treat serious conditions with unmet need, such as RSV. The Food and Drug Administration Safety Improvement Act of 2012 (FDASIA) expanded the scope of products that qualify for expedited development and review by FDA, as well as the range of endpoints that may be used to gain such approval. FDASIA also made permanent

legislation aimed at facilitating and encouraging research in the pediatric population.<sup>35</sup> In addition, new collaborations such as the International Neonatal Consortium allow FDA to help facilitate the development of safe and effective therapies for neonates.

As noted previously, targeting the appropriate populations for study has been challenging in RSV due to the practical, financial, and ethical concerns of studying vulnerable populations, and additional clarity is needed to determine the evidentiary threshold for initiating pediatric trials. Today's workshop will bring representatives from across academia, industry, and health systems together to address some of these outstanding questions and identify potential solutions to the barriers that have hindered progress in this area.

## **Meeting Agenda and Discussion Questions**

### **Session 1: Issues Related to RSV Bronchiolitis Treatment Trials - Establishing Definitions and Identifying Endpoints**

Objective: This session will address: 1) How best to define the target population being studied, 2) The key characteristics of a robust instrument(s) that could be used to reliably measure the clinical severity of RSV in treatment trials, and 3) Primary and secondary outcome measures that can be used to establish treatment efficacy.

#### **Session 1a: Establishing definitions of at-risk populations and disease severity**

Questions for discussion:

- How do we define disease severity in the population to be studied (e.g., “moderate” disease, “severe” disease, or all symptomatic illness)?
- What other factors are important in defining the study population (e.g., chronological age, underlying risk factors for severe illness, upper versus lower respiratory tract illness)?

#### **Session 1b: Identifying Appropriate Endpoints for RSV Bronchiolitis Treatment Trials**

Questions for discussion:

- Which signs and symptoms should be included in an instrument used to capture clinical severity of RSV?
- What should the primary outcome measurement be to establish treatment efficacy? Time to reach a pre-determined score? Change in score on a pre-determined day of illness? Other possibilities?
- Can the same signs and symptoms (or the same instrument) be used for study inclusion criteria and for establishing treatment response?
- Are two symptom instruments needed to measure treatment response; one for clinicians and one for caregivers? How would they be combined in an endpoint?
- Is there support among the pediatric and infectious disease community for validating a clinical tool to measure disease severity for RSV illness among infants (e.g., < 12 months of age)?
- Are there potential secondary endpoints that might be considered clinically meaningful and supportive (e.g., RSV viral load, biomarkers)?

#### **Session II: Identifying Alternative Endpoints for Prevention of RSV Bronchiolitis**

Objective: This session will explore alternative endpoints that should be considered in RSV prevention trials not related to vaccine products.

Questions for discussion:

- Should a novel prophylaxis product prevent all symptomatic RSV-related illness or only the most severe manifestations? What degree of illness-reduction is clinically meaningful?
- Given the differences in natural history of the illness in different populations, are different endpoints needed for different populations (i.e. healthy infants, premature infants, or those with underlying conditions)?
- The pivotal studies supporting approval of RSV immune globulin and palivizumab employed hospitalization as the primary endpoint, which may no longer be the ideal endpoint, making a non-inferiority margin based on previous trials difficult to justify. What is the best way to assess novel prophylaxis products in the context of the approved product?
- To what extent can prophylaxis efficacy from one group of infants be extrapolated to another? For example, can efficacy in healthy full-term infants be extrapolated to infants at higher risk of severe illness (e.g. prematurity, chronic lung disease, congenital heart disease)?

### **Session III: Initiation of Pediatric Trials for RSV Bronchiolitis**

Objective: This session will seek to refine the regulatory path for RSV drug trials in the pediatric population and explore possible approaches to addressing challenges in drug development for that population.

Questions for discussion:

- What types of proof-of-concept studies are needed to support initiation of pediatric studies for treatment and prevention products?
  - Which adult populations/disease conditions are preferred?
  - To what extent can non-clinical data be used to support pediatric studies (i.e., animal models of disease)?
  - Are adult RSV challenge studies adequate to demonstrate proof-of-concept for infant bronchiolitis trials?

### **Session IV: Encouraging RSV Drug Development in Other Populations**

Objective: This session will explore optimal approaches for encouraging RSV drug development for other populations, including the elderly, older children, and the immunocompromised.

Questions for discussion:

- How do we encourage RSV drug development in other populations such as elderly or immunocompromised patients?
- What are the unique considerations for trials in older children and adults? Are different endpoints required?
- What is the optimal approach to studying small populations such as stem cell transplant populations, in which the sample size may be small and controlled trials are difficult to conduct?

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