Considerations for clinical evaluation of Respiratory Syncytial Virus (RSV) vaccine candidates in RSV-naïve infants

Vaccines and Related Biological Products Advisory Committee
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Enhanced respiratory disease caused by formalin-inactivated RSV vaccine

- Vaccine preparation: FI-RSV
  - Wild-type RSV (“Bernett strain”) grown in cell culture, formalin-inactivated, and precipitated with alum.
- In one study*, infants 2 to 7 months of age were randomized to FI-RSV or parainfluenza virus (PIV) vaccine
  - Among those who subsequently contracted RSV, 16 of 20 (**80%**) FI-RSV vaccinated subjects compared with 1 of 21 (**5%**) control subjects required hospitalization.
- 50 years later, no licensed RSV vaccine

*Kim et al. Am J Epidemiol. 1969 Apr;89(4):422-34.

RSV burden of disease in children

- Global incidence per year in children <5 years
  - ~34 million episodes of lower respiratory tract infection (LRTI)*
  - ~3.4 million hospitalizations (in US, ~170,000)**
  - Approximately 66,000 to 199,000 deaths* (~500 in the US***)
  - Among infants age 28 – 365 days, RSV is second only to malaria as the leading cause of death worldwide****

*Nair et al. Lancet. 2010 May 1;375(9725):1545-55.
**Stockman et al. Pediatr Infect Dis J. 2012 Jan;31(1):5-9.
***Shay et al. J Infect Dis. 2001 Jan 1;183(1):16-22.
****Lozano et al. Lancet. 2012 Dec 15;380(9859):2095-128.

RSV burden of disease (2)

- Potential impact on airway hyper-responsiveness
  - In a study of otherwise healthy premature (33-35wk) infants, the proportion with recurrent wheeze in the first year of life was lower in those treated with palivizumab (11% vs. 21%).*
- Direct health care cost for children <5 years estimated at >$1 billion per year in the US.**

*Blanken et al. N Engl J Med. 2013 May 9;368(19):1791-9.
**Regnier. Vaccine. 2013 Sep 13;31(40):4347-54.

Progress in RSV vaccine development

- Passively administered antibody can prevent RSV
  - RespiGam approved in 1996; Synagis (palivizumab) approved in 1998
- Scientific and technical advances have facilitated new vaccine approaches
  - ~60 vaccine candidates in development
- WHO identified RSV as a top priority for vaccine development*

***Product Development for Vaccines Advisory Committee meeting Executive Summary, 2015.**
http://www.who.int/immunization/research/meetings_workshops/PDVAC_2015_executive_summary.pdf?ua=1

Clinical development strategies for RSV prevention

- **Older adults**
  - several candidate vaccines in advanced phase clinical development
- **Maternal immunization**
  - intended to prevent disease in early infancy via passive transfer of maternal antibody. Several candidate vaccines in development, including one in Phase 3.
- **RSV-naïve infants**
  - Passive immunization: one licensed monoclonal antibody (Synagis). Other antibody products in advanced clinical development
  - Active immunization: aside from live-attenuated RSV vaccines, no clinical studies conducted since the 1960s

Multiple vaccine technologies in development

- Protein-based
  - Whole, inactivated virus
  - Particle-based (e.g., virus-like particles, virosomes)
  - Subunit antigens (e.g., F, pre-F, and G proteins and peptides)
- Gene-based
  - Nucleic acids (e.g., naked DNA or RNA)
  - Replication-deficient vectors (e.g., adenovirus, MVA)
- Live virus
  - Recombinant live-attenuated (hRSV)
  - Chimeric (e.g., bPIV, SeV)

Today's Agenda

- **RSV Epidemiology**
  - Susan Gerber, M.D. Chief (Acting), Respiratory Viruses Branch, Centers for Disease Control and Prevention
- **History of Vaccine-Associated Enhanced Respiratory Syncytial Virus Disease and Characterization of Animal Models Designed to Mitigate Risk in Future Vaccine Studies**
  - Fernando Polack, M.D. Scientific Director Fundacion INFANT
- **FDA Presentation**
  - Sarah Browne, M.D. Medical Officer FDA/CBER/Office of Vaccines Research and Review (OVRR)
- **GlaxoSmithKline Presentation**
  - Ilse Dieussaert Director and Lead Vaccine Development, Maternal Immunization
- **Janssen Vaccines and Prevention B.V. Presentation**
  - Roland Zahn, Ph.D. Senior Scientific Director, Nonclinical
  - Melanie Saville, M.D. Head of Late Development, Clinical and Medical Affairs, Vaccines

Discussion topics for the committee

1. Please discuss the preclinical data essential to support studies of RSV vaccines in RSV-naïve infants, with regard to the potential risk of vaccine-associated ERD.
   - Please consider the impact of vaccine type, antigen, and/or other relevant factors.

2. Please discuss the role of clinical data from adults and RSV-experienced infants to support evaluation of RSV vaccines in RSV-naïve infants.

3. Please discuss how studies in RSV-naïve infants could be designed to mitigate concerns about ERD throughout clinical development.
   - Please consider aspects of initial study design such as eligibility criteria, age de-escalation, and duration of follow-up.
   - Please consider relevant aspects of Phase 3 study design.


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