RSV F Nanoparticle Vaccine: Infants via Maternal Immunization

World Vaccine Congress
April 4, 2018
The Novavax RSV F vaccine is in Phase 3
- Vaccine is for infants, and is administered via maternal immunization
- Global trial, in season 4
- On track to conduct an efficacy analysis in <12 months

Utilizes a physiologic mechanism, placental antibody transfer, for infant protection

Supervised by a highly qualified Safety Monitoring Board

De-risked by a recent positive informational analysis

Enabled through international collaborations across 12 countries

In collaboration with the Bill & Melinda Gates Foundation
• F Protein Structure

• RSV F Nanoparticle vaccine

• Immunogenicity of Pre-Fusion verses RSV F Nanoparticle vaccine

• RSV F Vaccine Phase 3 Program Update

• Conclusions
Rationale for selection of fusion protein as vaccine

**F Protein**
- Surface glycoprotein key to infectivity
- Generally conserved
- Several broadly neutralizing sites, some highly conserved
- Site II and Site IV highly conserved and associated with clinical efficacy

33 novel RSV subgroup A genomes from strains sampled over the last decade, mapping amino acid substitutions.2

Fusion (F) protein structure evolves during infection

RSV entry into host cells and fusion (F) protein processing leads to an activated F protein, membrane fusion and delivery of RSV RNA into cytoplasm

Fusion (F) protein structure evolves during infection

Immune responses in recently-infected infants recognize p27, indicating prefusogenic F forms are present during infection.

Whole genome fragment phage display libraries

Fuentes, et al. Antigenic fingerprinting following primary RSV infection in young children identifies novel antigenic sites and reveals unlinked evolution of human antibody repertoires to fusion and attachment glycoproteins. CBER, FDA, Silver Spring, MD. PLOS Pathogens 10.1371, 2016
Novavax RSV F nanoparticle vaccine

- Two mutations to F0
  - Fusion peptide (FP) is truncated by 10 amino acids
  - Site B furin site at aa136 is modified and uncleaved
  - No longer fusogenic in SF9 cells

- Peptide 27 (p27) is at the N-terminus of F1 and is retained in the vaccine
- F2 and F1 are covalently linked
- Purified prefusogenic F forms multiple-trimer/PS80, discrete detergent nanoparticles (20 – 40nm)
FACS: RSV F p27 confirmed to be present on the Novavax RSV F vaccine

Red: RSV 7.10 mAb
Grey: Control mAb

RSV F Vaccine: Sf9 cells

RSV Prefusion F: Sf9 cells
Immunogenicity Evaluation of RSV F Vaccine Constructs

Wild Type RSV F

Novavax Vaccine Drug Substance

Novavax PreFusion BV2145

PreFusion* BV2069

Highly characterized F protein vaccine constructs

+ Transmembrane domain
* Krarup et al. 2015. Nature Comm. DOI:10.1038/ncomms9142
RSV/A MN (ELISA) and Reduction in Lung RSV Titers in Cotton Rats: Novavax RSV F Vaccine Responses Comparable to Pre-F

Microneutralization

Lung Titer

* Krarup et al. 2015. Nature Comm. DOI:10.1038/ncomms9142
RSV F Vaccine Induces Competitive Antibodies against “Pre-F” and “Post-F” Neutralizing Antibodies (mAbs)

* Kuarup et al. 2015. Nature Comm. DOI:10.1038/ncomms9142
The NVAX RSV F Induces a variety of mAb competing antibodies that transfers to the infant
Novavax RSV F nanoparticle vaccine

- The RSV F vaccine is a prefusogenic ‘like’ construct, not postfusion
- Prefusogenic F is found on infectious viruses as evidenced by p27 responses in infants
- The NVAX vaccine is similar in immunogenicity to a pre-fusion vaccine
- The NVAX vaccine stimulates antibodies that bind to multiple, known neutralizing sites
- The competing antibody responses sum to a high-titer, neutralizing, protective responses

Observations from 5 clinical trials using the RSV F vaccine:
- Reduction of serologically detected infections in women of childbearing age in two, serial immunogenicity trials\(^1,2\)
- Reduction in lower respiratory infection in the elderly in two prospective efficacy trials\(^3\)
- Reduction of COPD exacerbations (post-hoc) in Phase 3 setting\(^4\)

2. August et al., Vaccine. 2017 Jun 27;35(30):3749-3759
3,4 RSV Conference, 2017
Respiratory Syncytial Virus (RSV) Burden of Disease (BoD)

All infants ≤ 6 Months old

- **Deaths**
  - 15 to 34
  - 6,715 to 34,155

- **Hospitalization**
  - ≈ 33,343 to 76,155
  - Rate = 16.9/1000 to 38.6/1000

- **Emergency Department**
  - ≈ 108,511 ER Visits
  - Rate = 55/1000

- **Outpatient Pediatric Practice**
  - ≈ 260,428 Office Visits
  - Rate = 132/1000

- **RSV Infection Cases in ≤ 6 mos old**
  - ≈ 2,090,367 (Year 2016)

- **US Census 2016 All Births**
  - ≈ 3,945,875

* @ 22% incidence, Symptomatic RSV-LRTI = 459,881
* includes all pre-term infants (≤37 wks = 9.85% of All Births)

2. Glezen (AJDC, 1986)
3. Hall 2013
4. Hall 2009
5. CDC-Stockman 2012
7. Byington 2015
Maternal immunization: normative practice, utilizes natural mechanism of infant protection

**Maternal antibodies** are derived from decades of mothers’ immune responses to common infections, are transferred from mother to infants via neonatal FC receptor mediated placental transport in the placenta.

**Maternal immunity** is conferred to the infant before birth and will protect the infant in the first months of life.

**Maternal immunization** can be highly effective for diseases where naturally derived maternal antibodies are not sufficient to confer protection. Examples include:

- Neonatal Tetanus
- Whooping cough (Pertussis)
- Influenza

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Naturally derived immunity to RSV is robust and present in infants, yet infants have the highest rates of RSV hospitalization.

RSV Antibodies in Mothers are High Transferred to their Infants

| RSV type | Serum source | GMT (log)_2 | P value
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Mothers</td>
<td>8.8 ± 1.3 (75)</td>
<td>8.8 ± 1.5 (106)</td>
</tr>
<tr>
<td></td>
<td>Newborns</td>
<td>8.3 ± 1.4 (90)</td>
<td>8.8 ± 1.5 (106)</td>
</tr>
<tr>
<td>B</td>
<td>Mothers</td>
<td>8.7 ± 1.4 (75)</td>
<td>7.9 ± 1.3 (106)</td>
</tr>
<tr>
<td></td>
<td>Newborns</td>
<td>8.7 ± 1.3 (83)</td>
<td>8.0 ± 1.6 (108)</td>
</tr>
</tbody>
</table>

* Determined by the microneutralization test. Values are means ± standard deviations. Values in parentheses are n values.
* Differences between GMTs of mothers and newborns from The Gambia and those of mothers and newborns from Houston were determined with the two-tailed Student t test. NS, no significance.

Can a vaccine change this outcome by enhancing the quality and quantity of immunity conferred to infants?
Phase 3 evaluation of the RSV F nanoparticle vaccine
## Phase 3 RSV F Vaccine for Infants via Maternal (IVM) Trial Goals and Design

<table>
<thead>
<tr>
<th>Primary Objective</th>
<th>Determine the efficacy of maternal immunization with the RSV F vaccine against symptomatic RSV lower respiratory tract infection (LRTI) with objective measures of medical significance of LRTI from 90-180 days of life in infants</th>
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<tbody>
<tr>
<td>Design</td>
<td>Randomized, Observer-Blind, Placebo-Controlled,</td>
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<tr>
<td>Number of Participants</td>
<td>• Minimum 4,600 women</td>
</tr>
<tr>
<td>Global Study</td>
<td>• ~80 sites in 11 countries</td>
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</tbody>
</table>
| Length of Study Participation | • Maternal Participants: up to 9 months  
• Infant Participants: 1 year                                                                                                                                                                           |
| 1 IM Injection (RSV F Vaccine or Placebo), 28-36 weeks EGA |                                                                                                                                                                                                      |
| Safety Assessment: | Through 6 months post-partum in mothers, 1 yr in infants                                                                                                                                               |
| Immunogenicity Assessment: | Days 0, 14, delivery, delivery + 35, and 180 in mothers  
Cord blood and 6 timepoints through day 180 in infants                                                                                                                                                           |
| Efficacy Assessment: | Active/passive surveillance in mothers and infants                                                                                                                                                      |
Case definitions derived from global consultations

“The case definitions included clinical features considered to be objective, easily standardized, generalizable across settings, and generally accepted markers of severe or very severe RSV disease.”
RSV IVM program: primary and secondary endpoints

- **Primary Endpoint:** medically-significant RSV lower respiratory tract infection (LRTI)
  - Presence of RSV detected by RT-PCR during a continuous illness episode, **AND**
  - At least one manifestation of LRTI (cough, nasal flaring, lower chest wall indrawing, subcostal retractions, stridor, rales, rhonchi, wheezing, crackles or observed apnea), **AND**
  - At least one of the following:
    - $\text{SpO}_2 < 95\%$ at sea level or $< 92\%$ at $> 1800\text{m}$
    - Respiratory rate $\geq 70$ bpm in infants 0 to 59 days of age or $\geq 60$ bpm in infants $\geq 60$ days of age

- **Additional Endpoints**
  - RSV LRTI with hospitalization
  - RSV LRTI with severe hypoxemia
  - Maternal RSV infection
RSV IVM program: Ongoing worldwide

- Currently completing enrollment in Global Year 3 and beginning enrollment in Global Year 4
- ~80 sites in 11 countries

>4,300 enrolled to date

Project ~4,600 by 2Q 2018
Milestones for Prepare™ trial

• DSMB
  • No safety concerns raised in 14 sequential meetings
  • Passed first two futility analyses

• Informational Analysis
  • Successful informational analysis in November 2017

• Interim Analysis
  • Enabled by recruitment of 4,600 subjects (including 3,000 active vaccinees)
  • Analysis will be:
    • Conducted by DSMB and independent statistician (company blinded)
    • On Per-Protocol endpoints for infants <90 days of age
  • Success = primary endpoint has LBCI >30%
Novavax performed an informational analysis in 4Q 2017

- In a 4-year Phase 3 trial, we wanted to ensure that the ongoing investment in the Phase 3 program was justified based on a high probability of a commercially-viable determination of efficacy.

- Targeted a minimum efficacy threshold against the primary endpoint at day 90 of ~ 40%
  - Likelihood that other medically significant secondary endpoints would exceed the VE for primary endpoint (e.g., hospitalizations and more severe disease)
  - Large unmet need, no alternative vaccine on the horizon

- The DSMB statistician performed the analysis/The company remains blinded
  - The DSMB communicated that the analysis was positive
Phase 3 outcome de-risked by successful informational analysis

Data from the informational analysis indicate an observed vaccine efficacy in the range of 45-100%.
RSV IVM program: Interim analysis plan

- ~4,600 mothers treated by 2Q 2018
- 3,000+ active infants born by 1Q 2019 (conducted by DSMB)
- Interim analysis completed by 1Q 2019
- BLA filing by 4Q 2019/1Q 2020
Preparing the groundwork for vaccine implementation requires policy and physician support

• **Building on a Proven Strategy**
  - Growing acceptance of maternal vaccination for flu and pertussis among HCPs and mothers
    - Vaccine administration by obstetricians increasingly common
  - American College of Obstetrics and Gynecology now conducts CME-accredited webinar entitled: “Respiratory Syncytial Virus: The Need for a Maternal Immunization Strategy

• **Vaccine Injury Compensation Program (VICP)**
  - Amendment in 21st Century Cures Act: As of December 13, 2016, program covers “both a woman who received a covered vaccine while pregnant and any child who was in utero” under government no-fault insurance program

• **ACIP RSV Working Group**
  - CDC Advisory Committee on Immunization Practices (ACIP) established RSV Working Group, May 2016
  - First step towards ACIP consideration for recommendation
Concluding remarks

- RSV is a universal pediatric infection
- RSV is the most common cause of infant hospitalization in the US; second only to malaria as a global cause of infant mortality
- 60 years of vaccine research may shortly result in an effective vaccine
- The Prepare trial evaluating the RSV F vaccine may conclude in <12 months
- A development program such as the Prepare trial can only be implemented via a broad, global collaboration between academic, public health, regulatory, private sector and the enablement by charitable trust and investors
The power of collaboration through our partners

THANK YOU!

$89 Million in grants
Added Role – Site selection, KOL contribution, clinical strategy, WHO engagement

$7 Million in grants
Added Role – Site selection, KOL contribution
RSV-M-301 Global Collaborators

Novavax
- Dhruv Agneshwar
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- Marshall Benbow
- Oleg Bess
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- James Cain
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- Gary Soucie
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Thank you