Phase 3 and beyond: The RSV F nanoparticle vaccine for infants via maternal immunization

Presentation at World Vaccine Congress
April 16, 2019
• RSV disease burden in infants
• ResVax - the RSV prefusogenic F nanoparticle vaccine
  • Structure
  • Antigenicity
  • Immunogenicity
• Prepare trial - A randomized blinded placebo controlled trial in the context of maternal immunization
  • Trial design and conduct
  • Efficacy
  • Safety
  • Immunogenicity
• Potential public health benefit of ResVax
Maternal immunization for the prevention of RSV disease in infants: The thesis

Immunization during pregnancy has emerged as an important and successful public health intervention in both industrialized and developing countries.

—FDA

To provide transplacentally transferred, high affinity, polyclonal neutralizing antibodies targeting multiple epitopes to infants via maternal immunization

To exceed the quality and quality of antibodies generated in mothers already present from natural infection to enhance and extend protection of infants against RSV disease early in infancy

Respiratory syncytial virus

Largest unmet need for a vaccine-preventable disease

1. Leading cause of hospitalizations in infants in the U.S., especially in the first 6 months of life
2. Leading cause of death in children under one year of age worldwide

Timing of RSV hospitalizations in infants

69% of infants <1 year contract RSV

77% of these RSV infections occur before 6 months of age

400,000 medical interventions

2-4% of infants < 6 months are admitted to the hospital

1. Shi T/Nair H. Lancet. 2017/Sep2;390:946
ResVax – the RSV prefusogenic F nanoparticle vaccine

Prefusogenic F in a structured nanoparticle
Structure and antigenicity of the fusion (F) protein, evolves during infections

Novavax RSV F vaccine genetic modifications:

Stable Prefusogenic F

1. Mutation furin site B
   - Stabilize RSV F as prefusogenic
   - Prevent formation of metastable prefusion F

2. Deletion 10aa fusion peptide
   - Increase yields
   - Minimize aggregation

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Smith et al. PLOS ONE. 2012 7(11)e50852
ResVax is a defined nanoparticle

• RSV F trimers are arranged around a core of PS80

• The nanoparticle forms in a stable colloidal system

• On average there are 5 RSV prefusogenic F trimers per nanoparticle
RSV prefusogenic F nanoparticle thermostability (DSC)

Differential scanning colorimeter (DSC)
1. RSV prefusogenic F  $T_m = 92 – 100^\circ C$
2. RSV prefusogenic sF  $T_m = 93 – 100^\circ C$
3. RSV prefusion F  $T_m = 50 – 60^\circ C$

Note: two DSC peaks may reflect thermo-transition of protomers then monomers.
Binding of mAbs to RSV F prefusogenic, prefusion and postfusion epitopes

- **Antigenic sites**
  - Prefusion F only
  - Prefusion & Postfusion F
  - Prefusogenic F

**RSV prefusion F**

<table>
<thead>
<tr>
<th>Antigenic Site</th>
<th>Monoclonal Antibody</th>
<th>Prefusogenic F Vaccine</th>
<th>Prefusion F SCTM</th>
<th>Postfusion F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site Ø</td>
<td>D25</td>
<td>40%</td>
<td>126%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>hRSV106</td>
<td>15%</td>
<td>104%</td>
<td>0%</td>
</tr>
<tr>
<td>Site VIII</td>
<td>hRSV90</td>
<td>39%</td>
<td>149%</td>
<td>0%</td>
</tr>
<tr>
<td>Site II</td>
<td>Palivizumab</td>
<td>113%</td>
<td>126%</td>
<td>108%</td>
</tr>
<tr>
<td>Site IV</td>
<td>RSHZ19</td>
<td>104%</td>
<td>112%</td>
<td>107%</td>
</tr>
<tr>
<td></td>
<td>R1.42</td>
<td>95%</td>
<td>89%</td>
<td>77%</td>
</tr>
<tr>
<td>P27</td>
<td>RSV.7.10</td>
<td>91%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Graham BS, et al adapted from Current Opinion Virology 2017

Patel N, et al submitted
M203: RSV F nanoparticle vaccine antibodies induced in women are efficiently adsorbed by RSV prefusion F
The poly-epitopic nature of the vaccine is evident in immune responses to the RSV F vaccine: Competitive (CAE) antibodies transferred mother to infant.
The Prepare trial - A randomized blinded placebo controlled trial in the context of maternal immunization
Prevention of RSV disease in infants via maternal immunization

The investigators are grateful to the 4,636 pregnant women across the globe who volunteered for this study.
Determine the efficacy of maternal immunization with the RSV F vaccine against medically significant symptomatic RSV lower respiratory tract infection (LRTI) through 90, 120, 150 and 180 days of life in infants.

### Design

<table>
<thead>
<tr>
<th>Number of Participants</th>
<th>4,636 third trimester pregnant women randomized 2:1 (vaccine:placebo)</th>
</tr>
</thead>
</table>
| Length of Study Participation | Maternal Participants: up to 9 months  
| | Infant Participants: 1 year after delivery |
| Dosing | 1 intramuscular (IM) Injection of RSV F vaccine or placebo at 28-36 weeks Estimated Gestational Age (EGA) |
| Safety Assessment | Through 6 months post-partum in mothers  
| | Through 1 year in infants |
| Efficacy Assessment | Active/passive surveillance in mothers and infants  
| | Confirmation of RSV infection by RT-PCR  
| | Medically significant tachypnea or pulse oximetry (infants only)  
| | Confirmation of LRTI (infants only) |
Multi-year global trial

Enrollment occurred at 87 sites in 11 countries

4,636 women volunteers in their third trimester of pregnancy enrolled
Endpoints

- **Primary endpoint** (site only data)
  - Medically-significant RSV LRTI
    - RSV detected by RT-PCR and
    - At least one manifestation of LRTI, and
    - At least one of the following:
      - SpO2 <95 or,
      - Tachypnea respiratory rate ≥70 bpm in infants 0 to 59 d or ≥60 bpm in infants ≥60 d

- **Secondary endpoints** (site only data)
  - RSV LRTI with **hospitalization**
  - RSV LRTI with **severe hypoxemia, SpO2 <92**

- **Exploratory efficacy** endpoints (data from **sites plus hospitalizations**)
  - Same as primary and secondary criteria
  - (also referred to as expanded data)
We observed the expected hierarchy of attack rates by severity

RSV attack rates^1

- **15.5%** Infections
- **13.6%** LRTI
- **6.1%** LRTI w/ hypoxemia or tachypnea
- **3.9%** Primary endpoint
- **3.8%** LRTI Hospitalization
- **2.2%** Severe hypoxemia

1. Expanded data from sites and hospitalizations, through 90 days, * LB 95%CI >0
What was our expectation for relative efficacy against the RSV infections/endpoints?

- **RSV attack rates**
  - 15.5%
  - 13.6%
  - 6.1%
  - 3.9%
  - 3.8%
  - 2.2%

- **Expected vaccine efficacy rates**
  - **HIGH**
  - **LOW**

- **Infections**
  - LRTI
  - LRTI w/ hypoxemia or tachypnea

- **Endpoints**
  - Primary endpoint
  - LRTI Hospitalization
  - Severe hypoxemia

---

1. Expanded data from sites and hospitalizations, through 90 days, * LB 95%CI >0
A hierarchy of efficacy by severity of disease

RSV attack rates

15.5%

13.6%

6.1%

3.9%

3.8%

2.2%

Infections

LRTI

LRTI w/ hypoxemia or tachypnea

Primary endpoint

LRTI

Hospitalization

Severe hypoxemia

Observed vaccine efficacy rates

11%

15%

19%

40.9%*

41.7%*

59.6%*

1. Expanded data from sites and hospitalizations, through 90 days, * LB 95%CI >0
Consistent patterns of RSV disease and efficacy in M301

RSV attack rates

- 15.5%
- 13.6%
- 6.1%
- 3.9%
- 3.8%
- 2.2%

Infections

- LRTI
- LRTI w/ hypoxemia or tachypnea
- Primary endpoint
- LRTI Hospitalization
- Severe hypoxemia

Observed vaccine efficacy rates

- 11%
- 15%
- 19%
- 40.9%*
- 41.7%*
- 59.6%*
- 27.8%*
- 46.0%*

1. Expanded data from sites and hospitalizations, through 90 days, * LB 95%CI >0
Summary of key efficacy findings:

Per protocol population

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<th>Efficacy (%)</th>
<th>MS LRTI</th>
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<td>Primary and secondary RSV+ w/ Site data through 90 days</td>
<td>39.4 (-1, 63.7)¹ (5.3, 61.2)²</td>
<td>44.4 (19.6, 61.5)</td>
<td>48.3 (-8.2, 75.3)</td>
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<td>35/1430, 41/2765</td>
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<td>59.6 (95% CI)</td>
</tr>
<tr>
<td></td>
<td>(15.9, 58.5)</td>
<td>(16.7, 59.2)</td>
<td>(32.1, 76.0)</td>
</tr>
<tr>
<td></td>
<td>56/1430, 64/2765</td>
<td>55/1430, 62/2765</td>
<td>32/1430, 25/2765</td>
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## Summary of key efficacy findings:

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</tr>
<tr>
<td><strong>All-cause LRTI data through 180 days Expanded data (RSV+ not required)</strong></td>
<td>20.2 (3.5, 34.0)</td>
<td>25.3 (5.3, 41.0)</td>
<td>39.1 (14.6, 56.6)</td>
</tr>
<tr>
<td></td>
<td>175/1430, 270/2765</td>
<td>117/1430, 169/2765</td>
<td>62/1430, 73/2765</td>
</tr>
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1. (97.5% CI); 2. (95.0% CI)
All-cause exploratory endpoints:

Durable effect

Endpoints using the same definitions, LRTI with severe hypoxemia, and LRTI hospitalization, but without a requirement for RSV

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=1547)</th>
<th>Active (n=2980)</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LRTI w/ severe hypoxemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 90 d</td>
<td>45</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>0 to 180 d</td>
<td>62</td>
<td>73</td>
<td>39.1</td>
</tr>
<tr>
<td><strong>LRTI w/ hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 90 d</td>
<td>86</td>
<td>120</td>
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<td>0 to 180 d</td>
<td>117</td>
<td>169</td>
<td>25.3</td>
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- Benefit of the vaccine on high impact outcomes present at day 90, through 6 months after vaccination.
- Additional incremental benefit against all cause disease.
Framing the “all-cause” findings

- The effect of the pneumococcal vaccine against all-cause LRTI hospitalization was 7-9\%\(^1\), or against all-cause ‘clinical pneumonia’ was 4-7\%\(^2,3\).

- By contrast, ResVax showed a 25\%\(^5\) reduction in all hospitalizations with LRTI signs or symptoms constitutes a major benefit of a vaccine.

- Similarly, ResVax showed a 40\% reduction of severe hypoxemia and could lower the risk of death and therefore has significant public health ramifications.
  - Hypoxemia: 4-5x increased risk of death with severe hypoxemia\(^4,5,6\).

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Top-line safety
Safety summary

Maternal subjects

• Solicited reactogenicity reported in 57% of vaccinees vs. 41.3% in placebo group
  • Primary driver are injection site pain and swelling, but <1% severe and <1% persists beyond 7 days
  • Minimal difference in systemic reactogenicity, no increase in fever in the 7 days post-treatment

• No notable differences in:
  • All unsolicited AEs, or severe, related, or severe and related AEs
  • Medical attendance for AEs
  • SAEs

• Adverse events related to pregnancy and delivery complications and adverse delivery outcomes were collected as SAEs
  • No significant differences in incidence between vaccinees and placebo recipients
  • Observed rates well within global and/or national expectations
Safety Summary

Infants

• 98.7% placebo recipients and 98.8% vaccinees delivered live infants:
  • 6.1% of placebo infants and 5.8% of vaccine group infants delivered at < 37 weeks
  • 1 and 5 minute APGARS are essentially identical between treatment groups
  • No significant difference in rates of any peri-partum AESIs

• No negative impact of maternal immunization on:
  • All AEs, or severe or severe and related AEs over 180 days
  • Medical attendance over 180 days
  • Overall SAE profile
Immune responses
Palivizumab-competitive antibodies (PCA) through Day 180:
Mothers and infants

Seroresponse rates in vaccinees = 99.4%
4-fold rise in vaccines = 88.1%

Cord serum/maternal serum 1.04 (1.06, 1.02)
$T_{1/2} = 49.1$ days in active vaccine infants
Anti-F IgG antibodies through Day 180:

Mothers and infants

Seroresponse rates in vaccinees = 98.3%
4-fold rise in vaccinees = 91.8%

Cord serum/maternal serum 1.17 (1.19, 1.14)
$T_{1/2} = 38.3$ days in active vaccine infants
RSVA and RSV/B microneutralization* (Seasons 1 and 2 only):

Mothers and infants

*MN data are normalized to international RSV/A standard. Day 14 values and resultant fold-rise are based on a subset, baseline and delivery are a full population.
Potential public health benefit of ResVax
Vaccine preventable disease incidence (VPDI) per 100,000 child months

Based on Prepare Trial ITT population through 180 days of follow-up

Adapted from Gessner B, Felkin D. Vaccine. 2014 May; 32(26): 3133-3138
Conclusions / next steps

- The RSV F prefusogenic vaccine is a discrete, stable, well-characterized nanoparticle
  - Induces poly-epitopic responses characterized by high affinity, neutralizing antibodies
  - Although based on an RSV A virus sequence, the vaccine protects against RSV A and B infections, likely driven by responses to conserved F protein epitopes

- In a Phase 3 global randomized, placebo controlled trial using maternal immunization to protect infants against RSV disease the vaccine was
  - Shown to be safe in 4,636 women and their infants
  - Efficacious against the most serious outcomes of an RSV infection in young infants
  - Shown to significantly decrease the ‘all cause’ LRTI related hospitalizations and severe hypoxemia, which suggests the vaccine effects were more profound than could be detected by surveillance
Conclusions / next steps

- The consistency of effect and totality of the data indicate that the vaccine has potential to protect infants against the most severe manifestations of RSV infection with major effects on infant health.

- Geographic inhomogeneity in efficacy was noted in the trial due to small subject numbers/events in some regions:
  - Driven by inherent difficulty in conducting trials in this population
  - US VE similar to ROW in the PP/site data for primary and severe hypoxemia

- Vaccine preventable disease incidence (VPDI) per 100,000 child months looks similar to highly effective licensed pediatric vaccines.

- Data to be presented to regulatory authorities to seek advice on pathway to licensure.
Thanks to:

- Our conscientious advisors and investigators and clinical site staff around the world; and of course the subjects themselves
- The Novavax manufacturing, QA, regulatory, clinical operations, biostatistics, pharmacovigilance and clinical immunology teams
- The DSMB members
- Baylor College of Medicine Molecular Virology and Microbiology lab
- The Marshfield Clinical Research Foundation
- The Bill and Melinda Gates Foundation and PATH

$89 Million in grants

$7 Million in grants
Thank you