The PREPARE trial: Lessons learned

Innovations in Maternal, Neonatal and Early Infant Vaccines
NYAS, 23 June 2020
Gregory M. Glenn M.D.
The first Phase 3 investigational vaccine trial in pregnancy

• Prepare trial: first ever Phase 3 investigational vaccine trial in pregnancy
  • Evidence of efficacy despite missing primary endpoint
    • Trial-related factors eroded efficacy, drove geographic variations in efficacy
  • Prevention of most severe, most-clinically relevant disease observed

Findings in P3 trial?
Prefusogenic F Is this a good construct?

Going forward
The Prepare™ Trial

Results & Lessons

• Evidence of efficacy despite missing primary endpoint
The first Phase 3 investigational vaccine trial in pregnancy

Findings in P3 trial?

Prefusogenic F
Is this a good construct?

Going forward

The Prepare™
Trial

Results & Lessons

• Why did the trial fail to meet the primary endpoints?

• Is the true efficacy 40-50%?

• Is the construct poorly immunogenic?

• Is there a better construct?
RSV fusion (F) protein is modified through the viral lifecycle

The RSV F protein is essential for viral cell entry and cell fusion, and undergoes a number of conformational changes

RSV Fusion Protein

Respiratory Syncytial Virus

Host Cell

Macropinocytosis

Prefusogenic F
Prefusion F
Postfusion F

How Novavax engineered a stable, prefusogenic F protein

- Stabilizes RSV F in prefusogenic form
- Prevents progression to prefusion F

Smith et al. PLOS ONE. 2012 7(11)e50852
Immune responses in recently infected infants recognize p27, indicating the prefusogenic form is present during infection.

Sandra Fuentes, Elizabeth M. Coyle, Judy Beeler, Hana Golding, Surender Khurana**
Division of Viral Products, Center for Biologics Evaluation and Research (CBER), FDA.
PLOS Pathogens 10.1371,2016
The full-length RSV F trimers are purified into a PS80 core forming nanoparticle vaccine
A full-length viral surface glycoprotein is likely to be an ideal immunogen
• Reflects the native configuration
• However, in nature many conserved epitopes are immunologically cryptic and do not induce immunity but ironically can be targeted by antibodies
  • Clear example of Site II, palivizumab and motavizumab

• A full-length surface glycoprotein is difficult to manufacture
  • Most recombinant approaches truncate and/or conjugate/fuse
  • The NVAX nanoparticle process creates a detergent/protein micelle
  • This creates a stable, natively configured highly flexible particle and presents generally cryptic, conserved, neutralizing epitopes

• Determination of the structure of a full-length viral surface glycoprotein required new imaging techniques
Krueger et al. Structural Characterization and Atomistic Modeling of a Respiratory Syncytial Virus Fusion Glycoprotein Nanoparticle Vaccine. (NIST)
SAXS/SANS—Small angle X-ray scattering and small angle neutron scattering can allow characterization of a full-length glycoprotein.

Small-angle neutron and X-ray scattering (SANS and SAXS) can determine the quaternary structure of large protein assemblies and complexes in solution.
TEM 2D imaging RSV Prefusogenic F and Hydrodynamic Properties (AUC) with PS80 non-ionic detergent

RSV F Prefusogenic Nanoparticles

RSV F Prefusogenic AUC

Polysorbate 80 (% w/v)

Z-Ave diameter (nm)

RSV F (mg mL^-1)
NIST: RSV Prefusogenic F
Small angle neutron scattering (SANS)

Ribbon model SasView curves calculated from the RSV F component of RSV F/PS80 nanoparticle compared with the interpolated SANS data (green points).
Projection of RSV F trimers with PS80 core nanoparticles
Patel et al. “Flexible RSV prefusogenic fusion glycoprotein exposes multiple neutralizing epitopes that may collectively contribute to protective immunity”

BioRxiv
RSV F constructs: Prefusogenic F; Prefusion DS, Cav1, and DS-Cav1; and Postfusion
RSV F prefusogenic and variant F immunogenicity and epitope-specific competing antibodies in cotton rats
RSV A and B neutralization and protection
RSV F prefusion and postfusion specific antibody responses in cotton rats
PREPARE (M301) clinical trial results

- First ever Phase 3 investigational vaccine trial in pregnancy
- Evidence of efficacy despite missing primary endpoint
  - Hypoxemia, hospital and pneumonia
- Why did the trial fail to meet the primary endpoints
  - Major contributions due to restricted collection of hypoxemia to sites only and not hospitals, stringency of Confidence Interval
- Trial-related factors eroded efficacy, drove geographic variations in efficacy
- Is the true efficacy 40-50%?
Primary and secondary PP and ITT trial results

FDA defined success: LBCI>30 at the 97.52% CI

Table 3: Per-protocol and expanded intent-to-treat analyses of maternal vaccination efficacy against lower respiratory tract infection (LRTI) in infants born to pregnant women vaccinated with RSV F vaccine or placebo.

<table>
<thead>
<tr>
<th>Per-Protocol Population Analyses*</th>
<th>Expanded data, Intent-to-Treat Population Analyses**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary and Secondary Endpoints</strong></td>
<td><strong>Exploratory Endpoints</strong></td>
</tr>
<tr>
<td>Efficacy Endpoint:</td>
<td>Placebo</td>
</tr>
<tr>
<td>Primary endpoint: Medically-significant RSV LRTI, Days 0 to 90</td>
<td></td>
</tr>
<tr>
<td>% (n/N)</td>
<td>2.4 (35/1430)</td>
</tr>
<tr>
<td>Secondary endpoint: RSV LRTI with hospitalization, Days 0 to 90</td>
<td></td>
</tr>
<tr>
<td>% (n/N)</td>
<td>3.7 (53/1430)</td>
</tr>
<tr>
<td>Secondary endpoint: RSV LRTI with severe hypoxemia, Days 0 to 90</td>
<td></td>
</tr>
<tr>
<td>% (n/N)</td>
<td>1.0 (14/1430)</td>
</tr>
</tbody>
</table>

Generally, the ITT, more real-world experience, is less than the PP LBCI. The primary difference is the use of pulse oximetry from the hospital and site.
Primary endpoint was a PCR+ LRTI with hypoxemia. Collection of hypoxemia from site only eliminated the most ill and ~50% of the cases.

Table 1: Hypoxemia Only as Primary Endpoint Criteria, PP Population

<table>
<thead>
<tr>
<th>Endpoint/Data Sources</th>
<th>Placebo</th>
<th>RSV F Vaccine</th>
<th>VE 97.52% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV LRTI with Hypoxemia &lt; 95%, Site Only (Days 0 - 90)</td>
<td>1.4% 20/1430</td>
<td>0.9% 26/2765</td>
<td>32.8 (-30.5, 65.4)</td>
</tr>
<tr>
<td>RSV LRTI with Hypoxemia &lt; 95%, Site and Hospital (Days 0 - 90)</td>
<td>3.3% 47/1430</td>
<td>1.7% 46/2765</td>
<td>48.1 (19.8-68.0)</td>
</tr>
</tbody>
</table>
Geographic heterogeneity observed in efficacy results

Analysis of two highest enrolling countries suggests a geographic difference

<table>
<thead>
<tr>
<th>Efficacy %: Per Protocol (Site Only Data)</th>
<th>USA</th>
<th>South Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 90 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS RSV LRTI</td>
<td>11.6%</td>
<td>42.5%</td>
</tr>
<tr>
<td>LRTI w/ severe hypoxemia</td>
<td>46.9%</td>
<td>49.4%</td>
</tr>
<tr>
<td>LRTI w/ hospitalization</td>
<td>-112.3%</td>
<td>58.5%</td>
</tr>
</tbody>
</table>

- Likely source of lower efficacy in US subjects: lower exposure to RSV and inherent heterogeneity of data collection
  - At 43 US sites/geographies, over 3 years, there were 16 total PP primary endpoint
    - One site had 2 cases, the majority had 0 cases
  - At 11 SA Sites, two main geographies and 47 PP primary endpoints over 3 years
    - The majority of sites had ≥3 cases
Driver of indeterminate US signal

US Attack Rate was very low, especially in the first 60 days

Figure 1: Time to First Placebo RSV Positive Illness Episode: US vs South Africa – Per Protocol Efficacy Population

Source: f_km_p.sas 12Feb2019
Table 4: Vaccine Efficacy (95% CI) in South Africa, Through Day 90

<table>
<thead>
<tr>
<th>Analysis Population</th>
<th>MS-LRTI</th>
<th>LRTI with Severe Hypoxemia</th>
<th>LRTI with Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP, Site Only</td>
<td>42.5 (-1.2, 67.4)</td>
<td>49.4 (-26.9, 79.8)</td>
<td>58.5 (34.3, 73.8)</td>
</tr>
<tr>
<td>ITT, Site Only</td>
<td>35.9 (-10.0, 62.7)</td>
<td>43.5 (-38.4, 77.0)</td>
<td>60.7 (39.1, 74.7)</td>
</tr>
<tr>
<td>PP, Site and Hospital</td>
<td>57.0 (32.7, 72.5)</td>
<td>75.7 (51.9, 87.7)</td>
<td>59.5 (36.1, 74.4)</td>
</tr>
<tr>
<td>ITT, Site and Hospital</td>
<td>56.1 (32.8, 71.3)</td>
<td>73.6 (50.0, 86.1)</td>
<td>61.6 (40.5, 75.2)</td>
</tr>
</tbody>
</table>

Again, the importance of using site and hospital derived hypoxemia is evident.
Prevention of pneumonia SAEs

Table 1: Pneumonia Serious Adverse Events

<table>
<thead>
<tr>
<th>Subject with At Least One Event, Period of Observation*</th>
<th>Safety Populations</th>
<th>Apparent Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n (%) N = 1561</td>
<td>Vaccine n (%) N = 3008</td>
</tr>
<tr>
<td>Pneumonia SAE, 0 to 180 Days</td>
<td>66 (4.2)</td>
<td>65 (2.2)</td>
</tr>
<tr>
<td>Pneumonia SAE with Chest X-ray +, 0 to 180 Days</td>
<td>42 (2.7)</td>
<td>34 (1.1)</td>
</tr>
<tr>
<td>Pneumonia SAE with RSV+, 0 to 180 Days</td>
<td>38 (2.4)</td>
<td>25 (0.8)</td>
</tr>
<tr>
<td>Pneumonia SAE with Chest X-ray + &amp; RSV+, 0 to 180 Days</td>
<td>23 (1.5)</td>
<td>12 (0.4)</td>
</tr>
<tr>
<td>Pneumonia SAE with RSV+ &amp; Tachypnea** or SpO2 &lt; 95%, 0 to 180 Days</td>
<td>25 (1.6)</td>
<td>10 (0.3)</td>
</tr>
<tr>
<td>Pneumonia SAE with RSV+ &amp; SpO2 &lt; 92%, 0 to 180 Days</td>
<td>19 (1.2)</td>
<td>6 (0.2)</td>
</tr>
<tr>
<td>Pneumonia SAE, 181 to 364 Days</td>
<td>18 (1.2)</td>
<td>17 (0.6)</td>
</tr>
<tr>
<td>Pneumonia SAE with Chest X-ray +, 181 to 364 Days</td>
<td>8 (0.5)</td>
<td>8 (0.3)</td>
</tr>
<tr>
<td>Pneumonia SAE, 0 to 364 Days</td>
<td>80 (5.1)</td>
<td>79 (2.6)</td>
</tr>
</tbody>
</table>

* Based on the SAE start date.
** ≥ 70 bpm 0 to 59 days of age, ≥ 60 bpm at ≥ 60 days of age

From the safety data

All-cause infant pneumonia
- VE 48.9% to day 180
- VE 48.8% to day 364

RSV+, hypoxic pneumonia
- VE 83.6% to day 180
Prevention of hospitalization

Time to RSV LRTI with hospitalization

- RSV LRTI with hospitalization is concentrated in subjects under 120 days of age
- Sustained difference in the temporal accumulation of endpoint events between vaccine and placebo subjects
PREPARE trial conclusions

- **ResVax™** is a prefusogenic RSV F nanoparticle vaccine
- The immunogenicity of the prefusogenic vaccine is similar to other well described stabilized F proteins
- **ResVax™** is efficacious but trial conduct and design factors led to less than optimal results
- This pioneering trial result advanced the field
  - The multiple learnings have been widely shared
- NVAX intends to develop the vaccine further
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