Progress Toward a Vaccine for Maternal Immunization to Prevent Respiratory Syncytial Virus Lower Respiratory Tract Illness in Infants

October 29, 2018
Safe harbor statement

Certain information, particularly information relating to future performance and other business matters, including expectations regarding clinical development, our planned use of the proceeds from the offering, market opportunities and anticipated milestones constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act.

Forward-looking statements may generally contain words such as “believe,” “may,” “could,” “will,” “possible,” “can,” “estimate,” “continue,” “ongoing,” “consider,” “intend,” “indicate,” “plan,” “project,” “expect,” “should,” “would,” or “assume” or variations of such words or other words with similar meanings. Novavax cautions that these forward-looking statements are subject to numerous assumptions, risks and uncertainties that change over time and may cause actual results to differ materially from the results discussed in the forward-looking statements.

Uncertainties include but are not limited to clinical trial results, dependence on third party contractors, competition for clinical resources and patient enrollment and risks that we may lack the financial resources to fund ongoing operations.

Additional information on Risk Factors are contained in Novavax’ filings with the U.S. Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2017, our Quarterly Reports on Form 10-Q, and our Current Reports on Form 8-K, which are all available at http://www.sec.gov.

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Current results may not be predictive of future results.

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Agenda

- RSV: Pathophysiology and burden of disease
- ResVax: Characterization and comparative immunity
- Prepare trial update
RSV-A disease found in largely term infants

~70% of all babies will be infected with RSV before 1 year of age

Signs of RSV:
- Symptoms may be cough, runny or stuffy nose, trouble breathing or sometimes, fever.
- Frequently confused with the common cold
- Serious in young babies, significantly affecting breathing and sometimes requiring hospitalization

Facts of RSV:
- The highest rates of RSV infection in babies occur in 6 weeks to 6 months of age
- Babies less than 3 months are most likely to be hospitalized due to RSV
- Hospitalization of babies for RSV in the US typically lasts 4-9 days

3. Hall CB. Pediatrics 2013;132:e341
While RSV can impact all infants, babies 6 weeks-6 months have the highest rates of hospitalization\(^1\)

\[\text{\ldots disguised as a familiar illness but, in reality, a harmful virus that can result in hospitalization or even death\ldots I had no idea what respiratory syncytial virus, or RSV, was, but it was about to rock our world.}\]


Over 75% of hospitalizations occur within the first 6 months of life\textsuperscript{1}

![Graph showing average age-specific rate and number of RSV hospitalizations among children in first year of life, 2000-2005](graph.png)

RSV season is now recognized by CDC as extending to 7-8 months\(^1\)

This change in methodology [PCR testing and new statistical analysis] has resulted in a relative lengthening of the RSV seasons.

- MMWR / January 19, 2018 / Vol. 67 / No. 2; pg 71-76

1. Rose, EB., et al., MMWR, January 19, 2018, Vol. 67; No. 2 pg 71; annually, US including HI and FL
Among U.S. infants, RSV is the #1 cause of hospitalization\(^1\)

A significant burden to families and the healthcare system, especially in infants <6 months

- \(~33,400 – 76,155\)^4,5 Hospital Admissions
- \(~109,000\)^4 ER Visits
- \(~260,000\)^4 Outpatient Visits
- \(~15-34\)^6,7 Deaths

- 69% of infants <1 year contract RSV
- 77% of these RSV infections occur before 6 months
- 400,000 medical interventions
- 2-4% of infants ≤ 6 months are admitted to the hospital
RSV infection may lead to long term consequences

Currently there is no vaccine for preventing RSV disease.

~100% of U.S. children are infected with RSV by 2 years of age.\(^1\)

RSV bronchiolitis is the #1 cause of all infant hospitalizations in US.\(^2\)

In full term infants, RSV led to:
- 3.1 fold increase in asthma,
- 3.2 fold increase in wheeze and
- 6.8% decrease in FEV\(_1\)%\(^3\)

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Maternal vaccination becoming a priority for healthcare providers

Maternal immunization offers the best method of protection from RSV disease in infants through the first months of life

Transplacental transfer of immunity

Well established as a maternal immunization approach to infant protection:

- Neonatal Tetanus
- Whooping cough (Pertussis)$^2$
- Influenza$^2$

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RSV burden during infancy far exceeds pertussis

<table>
<thead>
<tr>
<th>RSV</th>
<th>Pertussis Pre Maternal Immunization w Tdap</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence Rate</strong></td>
<td><strong>Incidence Rate</strong></td>
</tr>
<tr>
<td>~ 33,400 – 76,155 hospitalizations / year (&lt;6 mos old)</td>
<td>~ 1,450 hospitalizations / year (&lt;6 mos old)</td>
</tr>
<tr>
<td><strong>52%</strong></td>
<td><strong>0.17%</strong></td>
</tr>
<tr>
<td>15 to 34 US infant deaths</td>
<td>~ 16 US infant deaths</td>
</tr>
<tr>
<td>6.7% of global infant deaths</td>
<td>3.2% of global infant deaths</td>
</tr>
<tr>
<td>~ $405M to $932M cost of hospitalization</td>
<td>~ $44M cost of hospitalization</td>
</tr>
</tbody>
</table>

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2. CDC Pertussis Surveillance Reports 2013-2017
https://www.cdc.gov/pertussis/surv-reporting.html
3. Hall CB. Pediatrics 2013;132:e541

* CDC notes that up to 37% of infants may have completed primary DTap series (3+ doses).2
ResVax: the RSV F nanoparticle vaccine
After attachment to a respiratory epithelial cell, the virus is taken in via micropinocytosis. There the fusion protein undergoes profound structural changes and creates a pore, allowing ingress of RSV RNA into the host cell leading to production of virus progeny.
Rationale for selection of fusion protein as vaccine

Proven target

- The RSV Fusion Protein is critical to virus infectivity
- As a labile RNA virus, it evolves over the seasons, however, the F protein is highly conserved, with some important exceptions
- mAbs targeting the highly conserved site II on the F protein have been demonstrated in multiple randomized clinical trials to protect infants against RSV disease
  - 78% to 87% VE against RSV hospitalizations in healthy preterm (Connor 1998) and term infants (O’Brien 2015)
- Polyclonal and monoclonal used in RCTs shown to be efficacious:
Fusion (F) protein key to infectivity, structure evolves during infection

<table>
<thead>
<tr>
<th>Site A</th>
<th>Site B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefusogenic F</td>
<td>Prefusogenic F</td>
</tr>
<tr>
<td>Prefusion F</td>
<td>Prefusion F</td>
</tr>
<tr>
<td>Postfusion F</td>
<td>Postfusion F</td>
</tr>
</tbody>
</table>

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

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

Whole genome fragment phage display libraries
Pre-fusion and Post-fusion structures

Neutralizing antibody epitopes

Pre-fusion specific mAbs binding sites

Common to Pre-F and Post-F

From, Mas et al, Vaccine, 2018
Rationale for selection of fusion protein as vaccine

Conservation

- 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

**Frequency of Amino Acid Changes**

<table>
<thead>
<tr>
<th>Site</th>
<th>F Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site I</td>
<td>0.422</td>
</tr>
<tr>
<td>Site II</td>
<td>0.141</td>
</tr>
<tr>
<td>Site III</td>
<td>0.205</td>
</tr>
<tr>
<td>Site IV</td>
<td>0.002</td>
</tr>
<tr>
<td>Site V</td>
<td>0.403</td>
</tr>
<tr>
<td>Site φ</td>
<td>0.252</td>
</tr>
<tr>
<td>All Sites</td>
<td>0.234</td>
</tr>
</tbody>
</table>

V. Mas et al. /Vaccine xxx (2018) xxx–xxx

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

Fusion (F) protein key to infectivity, structure evolves during infection

- **Site A**: Prefusogenic F
- **Site B**: Prefusogenic F

**F-Protein Form**
- FO Precursor
- Prefusogenic F
- Prefusion F
- Postfusion F
- Post-fusion F

**Furin Cleavage**
- Site A: F2=F1
- Site B: F2=F1

**RSV**
- Fusion Protein
- Macropinocytosis
- Macropinosomes
- RSV cleavage
- RSV F virus – cell membrane fusion
- RSV RNA

RSV F constructs: RESVax is based on a prefusogenic F protein

Highly characterized F protein constructs

A Pre-fusogenic F BV 1184

B Pre-fusion F BV 2145

C* Post-fusion F BV 2128

TMCT: transmembrane C-terminus
FP: fusion peptide; fp: truncated fusion peptide
SP: signal peptide

ResVax is a near full length nanoparticle with mutation of the second Furin cleavage site and retention of p27
Construct characterization

Binding to F by mAbs

<table>
<thead>
<tr>
<th>Antigenic Site</th>
<th>Monoclonal Antibody</th>
<th>Pre-fusogenic F</th>
<th>Pre-F</th>
<th>Post-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\textsuperscript{1}</td>
<td>95%</td>
<td>89%</td>
<td>77%</td>
</tr>
<tr>
<td>Site II/IV</td>
<td>R.4.C6</td>
<td>94%</td>
<td>85%</td>
<td>78%</td>
</tr>
<tr>
<td>P27</td>
<td>RSV.7.10</td>
<td>91%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- No binding
- Intermediate binding
- Strong binding
Particle nature of ResVax GMP drug substance
Comparative immunogenicity and protective efficacy

RSV Lung Virus and RSVA Neutralization Titers

Lung Virus Titers

RSVA Neutralization

NOVAVAX
Induction and transfer of antibodies competing with mAbs specific for known epitopes or domains in Humans

Competitive antibody equivalents (CAE) detected by biolayer interferometry using characterized mAbs to RSV F protein. Day 14 fold-rise in mothers (left panel) and comparative cord blood CAE (right panel).
Conclusions

• ResVax is produced from a prefusogenic RSV F construct that forms discrete nanoparticles.
• The prefusogenic form appears to be favored in natural infection.
• Site II and Site IV are highly conserved.
• Site II mAbs have been shown to be efficacious in 5 RCTs demonstrating efficacy.
• The vaccine induces a broad array of antibodies, including site II antibodies, that compete with both pre-fusion and post-fusion specific mAbs.
  • These are transferred efficiently to infants of ResVax immunized mothers.
• The head to head immunogenicity of extensively characterized pre-F and post-F constructs favors the pre-fusogenic vaccine.
Update on the Prepare trial
To be practical and effective, we reasoned our vaccine had to:

a) Have a strong impact on mothers with the lowest baseline RSV MN titers— the highest risk group
b) Provide a rapid response to one dose for compliance
c) Induce a robust and sustained antibody response

AUC for single dose equal or superior to 56 days

RSV F IgG antibodies and protection against severe RSV Disease

Decreased RSV Disease Severity correlates with anti-RSV F IgG titer. Each 2 fold increase associated with 0.56 unit decrease in Global Respiratory Severity Scale. Walsh et al, JID, 2018.

ResVax induced 10-12 fold rises in anti-F IgG in women of childbearing age and placentally transferred antibodies have a t1/2 in infants of 30-40 days.

Table 3. Results of Bivariante and Multiivariate Analysis of Association of Severity with Antibody Titers in Acute Illness Serum

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Estimate (β)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bivariante</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at infection</td>
<td>−0.70</td>
<td>0.001</td>
</tr>
<tr>
<td>Anti-RSV F titer</td>
<td>−0.56</td>
<td>0.009</td>
</tr>
<tr>
<td>Analysis 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at infection</td>
<td>−0.35</td>
<td>0.07</td>
</tr>
<tr>
<td>Anti-RSV Gb titer</td>
<td>−0.08</td>
<td>0.81</td>
</tr>
<tr>
<td>Analysis 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at infection</td>
<td>−0.41</td>
<td>0.007</td>
</tr>
<tr>
<td>Anti-RSV Gb titer</td>
<td>−0.15</td>
<td>0.40</td>
</tr>
<tr>
<td>Analysis 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at infection</td>
<td>−0.44</td>
<td>0.019</td>
</tr>
<tr>
<td>Anti-RSV Gb titer for group A infection</td>
<td>−0.11</td>
<td>0.59</td>
</tr>
<tr>
<td>Analysis 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at infection</td>
<td>−0.21</td>
<td>0.35</td>
</tr>
<tr>
<td>Anti-RSV Gb titer for group B infection</td>
<td>0.05</td>
<td>0.87</td>
</tr>
<tr>
<td>Analysis 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at infection</td>
<td>−0.56</td>
<td>0.005</td>
</tr>
<tr>
<td>Neutralizing antibody titer for group A infection</td>
<td>−0.31</td>
<td>0.22</td>
</tr>
<tr>
<td>Analysis 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at infection</td>
<td>−0.28</td>
<td>0.16</td>
</tr>
<tr>
<td>Neutralizing antibody titer for group B infection</td>
<td>−0.23</td>
<td>0.63</td>
</tr>
</tbody>
</table>
### Phase 3 trial goals and design

<table>
<thead>
<tr>
<th><strong>Primary objective</strong></th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Randomized, observer-blind, placebo-controlled</td>
</tr>
<tr>
<td><strong>Number of participants</strong></td>
<td>• Minimum of 4,600 third trimester pregnant women and their infants</td>
</tr>
<tr>
<td><strong>Global study</strong></td>
<td>• 87 sites in 11 countries</td>
</tr>
</tbody>
</table>
| **Length of study participation** | • Maternal participants: up to 9 months  
• Infant participants: 1 year after delivery                                                                                                                                                    |
| **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                                                                                                                     |
Primary and secondary endpoints

Primary Endpoint: Medically-significant RSV 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

Secondary Endpoints

- RSV LRTI with hospitalization

- RSV LRTI with severe hypoxemia
Global enrollment in the Prepare trial since 2015

- Single protocol approved by 13 Regulatory Authorities
- Enrollment at 87 sites in 11 countries
- Seasonal enrollment (Northern & Southern Hemisphere) completed over 31 months
- Total of 4,636 maternal subjects enrolled
Accrual of medically-significant RSV LRTI by age

- ~90% of MS RSV LRTI cases (with hypoxemia or tachypnea), and
- ~95% of RSV-related hospitalization occur within the first 120 days of life, or about 3 antibody half-lives.
- ~44% of all cases with RSV, LRTI findings, and hypoxemia or tachypnea are hospitalized.
ResVax safety

• Oversight of safety via DSMB:
  • Multiple pre-planned serial futility analyses.
  • Iterative completely unblinded review of safety outcomes by an international DSMB of obstetricians and pediatricians, supported by an independent statistician.

• 15 consecutive DSMB reviews: no advice to slow, pause, or alter protocol

• 2015 Brighton Collaboration list of pregnancy and peri-partum safety endpoints adopted as adverse events of special interest (AESI) and treated as serious adverse events (SAE).
  • Overall blinded AESI rates are below global backgrounds, and
  • AESI rates are similar to, or less than, published country-specific rates in the U.S. and South Africa, which together are responsible for ~76% of the data.
  • South African rates also compare favorably w/influenza vaccine trials.
Novavax performed an informational analysis in 4Q 2017

- Novavax wanted to ensure that the ongoing investment in this multi-year Phase 3 clinical trial was justified based on a high probability of a commercially-viable determination of efficacy.

- After discussion with the FDA, the analysis included a threshold set with a posterior probability of ≥90% that vaccine efficacy was ≥0%.

- Novavax commissioned an independent, unblinded statistician to perform this analysis.

- At that point in time, the analysis indicated that the vaccine met or exceeded this threshold.
Phase 3 outcome de-risked by successful informational analysis

Above result based on 1,307 infants, assumption of perfect randomization, and simple ratios of event rates

Data from the informational analysis allowed Novavax to calculate an observed vaccine efficacy point estimate in the range of 45-100% at that time.

Vaccine Efficacy (VE) Against Primary Endpoint

- 100%
- 60%
- 40%
- 0%
ResVax: pathway to licensure

- **4,636 mothers enrolled**
  - Completed **2Q 2018**

- **3,000+ infants born to mothers receiving ResVax**
  - Completed **July 2018**

- **Final efficacy analysis**
  - By **1Q 2019**

- **BLA/MAA filing**
  - By **1Q 2020**

Enrollment at 87 sites across 11 countries
Thanks to the many dedicated investigators
Thanks to:

- Our conscientious advisors and investigators and clinical site staff around the world
- The Novavax regulatory, clinical operations, biostatistics, pharmacovigilance and clinical immunology teams
- The DSMB members
- Jen Meece and the Marshfield Clinical Research Foundation
- The Bill and Melinda Gates Foundation and PATH

$89 Million in grants

$7 Million in grants
Thank you