Progress Towards an Improved Seasonal Influenza Vaccine:
NanoFlu - Nanoparticle Influenza Vaccine (NIV)

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.

Forward-looking statements are based on current expectations and assumptions and currently available data and are neither predictions nor guarantees of future events or performance.

Current results may not be predictive of future results.

You should not place undue reliance on forward-looking statements which speak only as of the date hereof.

The Company does not undertake to update or revise any forward-looking statements after they are made, whether as a result of new information, future events, or otherwise, except as required by applicable law.

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Agenda

The current need for an improved influenza vaccine

NanoFlu: Novavax’ nanoparticle vaccine and Matrix-M adjuvant

Broadly cross-reactive A(H3N2) immune responses in ferrets

Phase 1/2 clinical data

Phase 2 clinical trial design

Pathway to licensure
H3N2 in the 2017/18 flu season highlights need for better vaccine

Two issues contributing to **MISMATCH** and poor flu vaccine effectiveness

**Antigenic evolution and drift**

Vaccines are derived from recommended strains, but when viruses “drift” – natural genetic evolution – vaccines may not protect as well.

**Egg adaptation**

Viruses are modified to grow better in chicken eggs. Over multiple egg-growth passages, these changes can result in mismatch between vaccine and circulating viruses.

Image Source: https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm336267.htm
Rapid evolution and diversity of H3N2

Egg adaptation of influenza viruses

Egg-based flu vaccines are predominant
• ~87% of commercial flu vaccines in U.S. manufactured in eggs
• Same manufacturing technology used for over 50 years

Egg propagation can result in mismatch that impacts vaccine effectiveness
• Flu viruses that infect humans are difficult to grow in eggs
• Egg-based viruses must be passaged numerous times to grow better
• Virus changes across these passages result in mutations and potential mismatch that can lead to poor vaccine effectiveness

1. Paules, C. Chasing Seasonal Influenza – The Need for a Universal Influenza Vaccine. NEJM November 29 2017
Not all influenza vaccines are the same

~87% of flu vaccine doses are egg-based\(^1\)

Novavax is advancing an improved flu vaccine

NanoFlu is different

✓ Recombinant nanoparticle
✓ Non-egg based
✓ Adjuvanted with Matrix-M

- Exact genetic match to recommended vaccine strains
- Broader immune response addresses antigenic drift

NanoFlu:
Nanoparticle influenza vaccine (NIV) with Matrix-M adjuvant

- **Recombinant hemagglutinin (HA) nanoparticle vaccine**
  - Baculovirus/Sf9 insect cell system
  - Express recombinant, full-length, wild-type HA that assembles into HA homotrimers
  - Purified HA homotrimers form higher order nanoparticle structures of 20-40 nm
  - 2 to 9 HA homotrimers per nanoparticle held together by hydrophobic interactions
  - Rapid, high-yield, high purity, production process

- **Potent saponin-based Matrix-M adjuvant**
  - Saponins extracted from bark of *Quillaja saponaria* Molina
  - Formulated with cholesterol and phospholipid, forming particles
  - Enhanced APC entry into injection sites; expansion of activated T cell, B cell, and APC populations in draining nodes
  - Induction of functional, and broadly cross-reactive antibodies
  - Induction of polyfunctional T cell responses, both CD4+ and CD8+
  - Antigen sparing in the context of pandemic influenza
In ferrets, trivalent nanoparticle influenza vaccine (tNIV) induced broadly cross-neutralizing immune responses to drifted A(H3N2) viruses.

Novel hemagglutinin nanoparticle influenza vaccine with Matrix-M™ adjuvant induces hemagglutination inhibition, neutralizing, and protective responses in ferrets against homologous and drifted A (H3N2) subtypes.

### Microneutralizing Titers (TCID<sub>50</sub> ng/mL)

<table>
<thead>
<tr>
<th>Virus Strains A(H3N2)</th>
<th>A2.91.3 mAb (HAI +)</th>
<th>A2.4.1 mAb (HAI –)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Hong Kong/4801/2014</td>
<td>3.1</td>
<td>57</td>
</tr>
<tr>
<td>A/S. Australia/55/2014</td>
<td>2.1</td>
<td>975</td>
</tr>
<tr>
<td>A/Switzerland/9715293/2013</td>
<td>7.1</td>
<td>149</td>
</tr>
<tr>
<td>A/Texas/50/2012</td>
<td>14.1</td>
<td>118</td>
</tr>
<tr>
<td>A/Victoria/361/2011</td>
<td>0.6</td>
<td>134</td>
</tr>
<tr>
<td>A/Perth/16/2009</td>
<td>1.8</td>
<td>288</td>
</tr>
<tr>
<td>A/Brisbane/10/2007</td>
<td>6.3</td>
<td>176</td>
</tr>
</tbody>
</table>

### Hemagglutination Inhibition Endpoint Titers (ng/mL)

<table>
<thead>
<tr>
<th>Virus Strains A(H3N2)</th>
<th>Microneutralizing Titer (TCID&lt;sub&gt;50&lt;/sub&gt; ng/mL)</th>
<th>Hemagglutination Inhibition Endpoint Titer (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Hong Kong/4801/2014</td>
<td>195</td>
<td>Neg.</td>
</tr>
<tr>
<td>A/Switzerland/9715293/2013</td>
<td>195</td>
<td>Neg.</td>
</tr>
</tbody>
</table>

### Hemagglutinin Binding Affinity (K<sub>d</sub>, nM)

<table>
<thead>
<tr>
<th>Virus Strains A(H3N2)</th>
<th>Microneutralizing Titer (TCID&lt;sub&gt;50&lt;/sub&gt; ng/mL)</th>
<th>Hemagglutination Inhibition Endpoint Titer (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Hong Kong/4801/2014</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>A/Switzerland/9715293/2013</td>
<td>1.9</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Monoclonal antibodies derived from mice immunized with NIV containing A/Hong Kong (H3N2) demonstrated potent, broadly neutralizing, HA head-directed responses against a broad range of drifted A(H3N2) viruses.

These broadly neutralizing mAbs demonstrated either positive (A2.91.3 mAb) or negative (A2.4.1 mAb) HAI antibody responses, respectively.
NIV derived mouse mAbs demonstrated potent, HA head directed broadly neutralizing, responses against a range of drifted A(H3N2) viruses.

mAb A2.91.3 Fab
HA head binding interferes with hemagglutination (HAI+)

mAb A2.4.1 Fab
HA head binding does NOT interfere with hemagglutination (HAI-)

Monoclonal antibodies derived from mice immunized with NIV containing A/Hong Kong (H3N2) demonstrated potent, broadly neutralizing, HA head-directed responses against a broad range of drifted A(H3N2) viruses.

These broadly neutralizing mAbs demonstrated either positive (A2.91.3 mAb) or negative (A2.4.1 mAb) HAI antibody responses, respectively.
Phase 1/2 clinical trial of NanoFlu in adults ≥60 years of age

TO THE EDITOR: Paulus et al. recently advocated for the development of influenza vaccines “that will protect against seasonal influenza drift variants” and “not be subject to the limitations of egg-based vaccine technology.” Improving vac-

NCT03293498). The trial was approved by an institutional review board, and all the participants provided written informed consent. Participants received a single intramuscular injection of tNIV, at a dose of 15 μg or 60 μg of HA per
Phase 1/2 clinical trial design

- Conducted at 3 U.S. clinical trial sites
- 330 clinically-stable adults ages ≥60 years
- Randomized 1:1:1, stratified by age (60-74, and 75+)

Single IM dose on day 0 of:
- tNIV: 15µg each HA (45µg total) + 50µg Matrix-M, or
- tNIV: 60µg each HA (180µg total) + 50µg Matrix-M, or
- Licensed egg-based high-dose (180µg total), trivalent, inactivated influenza vaccine (IIV3-HD)(Fluzone-HD)

Day 21 rescue dose of IIV3-HD or placebo

All 3 vaccines included 2017-18 WHO recommended NH strains:
- A/Michigan (H1N1); A/Hong Kong (H3N2); B/Brisbane

Objectives
- Safety: assessed through Day 21
- Immunogenicity: HAI and MN against vaccine-homologous and drifted H3N2 strains through Day 21
HAI antibody responses (GMTs) against *wild-type* vaccine-homologous strains (2017-18)

Geometric Mean Titer (GMT)
HAI antibody response (GMFRs) against wild-type vaccine-homologous strains (2017-18)

Ratio of Day 21 GMTs
47% ↑ p=0.0056
HAI antibody responses (GMFRs) against 5 generations of drifted *wild-type* A(H3N2) strains

- **Ratio of Day 21 GMTs**
  - 38% ↑ *p*=0.0058
  - 28% ↑ *p*=0.036
  - 54% ↑ *p*=0.0065
  - 47% ↑ *p*=0.0056
  - 64% ↑ *p*=0.0009

<table>
<thead>
<tr>
<th>Geometric Mean Fold Titer Rise (95% CI)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>45µg NanoFlu</td>
<td>180µg NanoFlu</td>
<td>IIV3-HD</td>
<td>45µg NanoFlu</td>
<td>180µg NanoFlu</td>
</tr>
<tr>
<td><strong>A/Victoria H3N2</strong></td>
<td><strong>A/Texas H3N2</strong></td>
<td><strong>A/Switzerland H3N2</strong></td>
<td><strong>A/Hong Kong H3N2</strong></td>
<td><strong>A/Singapore H3N2</strong></td>
</tr>
</tbody>
</table>
HAI antibody responses (GMFRs) against 5 generations of drifted *wild-type* A(H3N2) strains

<table>
<thead>
<tr>
<th>Strain</th>
<th>45µg NanoFlu</th>
<th>180µg NanoFlu</th>
<th>IIV3-HD</th>
<th>Ratio of Day 21 GMTs</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Victoria H3N2</td>
<td>2.3</td>
<td>2.3</td>
<td>3.4</td>
<td>38% ↑</td>
<td>p=0.0058</td>
<td></td>
</tr>
<tr>
<td>A/Texas H3N2</td>
<td>2.2</td>
<td>2.2</td>
<td>3</td>
<td>28% ↑</td>
<td>p=0.036</td>
<td></td>
</tr>
<tr>
<td>A/Switzerland H3N2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.5</td>
<td>54% ↑</td>
<td>p=0.0065</td>
<td></td>
</tr>
<tr>
<td>A/Hong Kong H3N2</td>
<td>2.5</td>
<td>2.5</td>
<td>2.7</td>
<td>47% ↑</td>
<td>p=0.0056</td>
<td></td>
</tr>
<tr>
<td>A/Singapore H3N2</td>
<td>2.1</td>
<td>1.9</td>
<td>2.2</td>
<td>64% ↑</td>
<td>p=0.0009</td>
<td></td>
</tr>
</tbody>
</table>

**A(H3N2) clades/subclades currently circulating in North America**
Comparison of HAI responses against H3N2 strains

Significantly higher hemagglutination inhibition ("HAI") immune responses against the homologous and four generations of drifted wild-type H3N2 strains:

• 64% higher NanoFlu response against forward-drifted strain (A/Singapore)

• 47% higher NanoFlu response against homologous strain (A/Hong Kong)

• 54% higher NanoFlu response against historic strain (A/Switzerland)

• 28-38% higher NanoFlu response against distant historic drifted strain (A/Texas) and (A/Victoria)

In a separate trial, IIV3-HD vs. IIV3-SD demonstrated 80% better ratio of GMTs

• Which translated into 23% better relative efficacy

1. Fluzone-HD [package insert]. Sanofi Pasteur, Swiftwater, PA; 2017
Playing catch-up and does “one strain fit all”? 
Rapid evolution and diversity of A(H3N2) viruses

Playing catch-up and does “one strain fit all”?  

NanoFlu has the potential to provide broader protection against antigenic drift

NanoFlu vaccine has potential to provide broader protection against antigenic drift

Need for a better influenza vaccine

Preliminary adjusted vaccine effectiveness against medically attended influenza by age group, 2017–18

<table>
<thead>
<tr>
<th>Any influenza A or B virus</th>
<th>Influenza positive</th>
<th>Influenza negative</th>
<th>Vaccine Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N vaccinated /Total</td>
<td>(%)</td>
<td>N vaccinated /Total</td>
</tr>
<tr>
<td>Overall</td>
<td>1296/3097</td>
<td>(42)</td>
<td>2969/5538</td>
</tr>
<tr>
<td>Age group (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mos–8</td>
<td>201/616</td>
<td>(33)</td>
<td>760/1380</td>
</tr>
<tr>
<td>9–17</td>
<td>166/529</td>
<td>(31)</td>
<td>221/584</td>
</tr>
<tr>
<td>18–49</td>
<td>315/966</td>
<td>(33)</td>
<td>813/1893</td>
</tr>
<tr>
<td>50–64</td>
<td>301/571</td>
<td>(53)</td>
<td>583/938</td>
</tr>
<tr>
<td>≥65</td>
<td>313/415</td>
<td>(75)</td>
<td>592/743</td>
</tr>
</tbody>
</table>

* Multivariable logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time. ** P-value <0.001 for age group-VE interaction term compared to all other ages combined.
Several factors conspired to make a bad flu season; it is undeniable that VE needs to improve.
### NanoFlu Phase 2 clinical trial goals and design

<table>
<thead>
<tr>
<th><strong>Primary and secondary objectives</strong></th>
<th>Determine the dose and formulation, demonstrate Matrix-M adjuvant effect, and evaluate the safety and tolerability of a single intramuscular injection of NanoFlu in quadrivalent formulations with or without Matrix-M1 adjuvant in older adults ≥65 years of age, as compared to two licensed influenza vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Randomized, observer-blinded, active-comparator controlled trial</td>
</tr>
<tr>
<td>Vaccine strains</td>
<td>• All vaccines contain the WHO recommended 2018-19 Northern Hemisphere influenza vaccine strains</td>
</tr>
<tr>
<td>Stratification</td>
<td>• History of receipt of 2017-18 influenza vaccine</td>
</tr>
<tr>
<td>Number of participants</td>
<td>• 1,375 clinically-stable adults ≥65 years of age</td>
</tr>
<tr>
<td>U.S. study</td>
<td>• Multiple sites</td>
</tr>
<tr>
<td>Length of study participation</td>
<td>• 1 year</td>
</tr>
<tr>
<td>Safety assessment</td>
<td>• Through 1 year</td>
</tr>
<tr>
<td>Immunogenicity assessment</td>
<td>• Hemagglutinin inhibition (HAI) antibody assessment through Day 28</td>
</tr>
</tbody>
</table>
FDA agreed that the accelerated approval pathway could be available for NanoFlu

- Granted for certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses

- For seasonal influenza vaccines, the HAI antibody response may be an acceptable surrogate marker of activity that is reasonably likely to predict clinical benefit

We plan to discuss the Phase 2 clinical trial data and the proposed Phase 3 study design, and reach agreement on the use of accelerated approval, with the FDA during an End-of-Phase 2 meeting in the first half of 2019.

If Nanoflu is granted accelerated approval, our NanoFlu BLA would include results from a well-controlled Phase 3 trial designed to meet immunogenicity endpoints, with a commitment to conduct confirmatory post-marketing trials to demonstrate clinical effectiveness.
NanoFlu completed and next steps

- **PUBLISH / PRESENT**
  - Phase 1/2 trivalent clinical trial results
  - Completed

- **DISCUSS**
  - Data and Phase 2 quadrivalent clinical trial design with FDA
  - Completed

- **ONGOING**
  - Phase 2 quadrivalent clinical trial
  - Completed enrollment

- **REPORT**
  - Data from Phase 2 clinical trial
  - Projected for 1Q 2019

- **INITIATE**
  - Phase 3 clinical trial
  - Projected for 2H 2019
Thank you