UPDATE ON NOVAVAX INVESTIGATIONAL NanoFlu VACCINE AND COVID-19-INFLUENZA COMBINATION VACCINE DEVELOPMENT

VIVEK SHINDE, MD

APRIL 20, 2022 | NOVAVAX
SAFE HARBOR STATEMENT

Certain information, particularly information relating to the future of Novavax, its operating plans and prospects, its partnerships, the ongoing development of NVX-CoV2373, including Novavax’ plans to initiate a pediatric study in Q2 2022, NanoFlu, its COVID-seasonal influenza investigational vaccine candidate, COVID-NanoFlu combination vaccine, including Novavax’ plans to initiate a Phase 2 clinical trial for COVID-NanoFlu combination vaccine, Omicron-specific vaccine, and other Novavax vaccine product candidates, the timing of results from clinical trials, the potential impact of Novavax and NVX-CoV2373 in addressing vaccine access, controlling the pandemic and protecting populations, including the potential for a booster dose of NVX-CoV2373 to provide protection against COVID-19 (including variants), and the efficacy, safety, and intended utilization of NVX-CoV2373; the scope, timing, and outcome of future regulatory filings and actions, including Novavax’ plans to supplement global regulatory filings with the pediatric data and pediatric investigations plans agreed to by regulatory authorities, the global market opportunities for NVX-CoV2373, the readiness of our global supply chain and future availability of NVX-CoV2373 at a global scale and the commercialization and expected delivery of NVX-CoV2373, and key upcoming milestones constitute forward-looking statements.

Forward-looking statements may generally contain words such as "believe," "may," "could," "will," "possible," "can," "estimate," "continue," "ongoing," "consider," "anticipate," "intend," "seek," "indicate," "plan," "project," "expect," "should," "would," "aim," 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.

These risks and uncertainties include, without limitation, challenges satisfying, alone or together with partners, various safety, efficacy, and product characterization requirements, including those related to process qualification and assay validation, necessary to satisfy applicable regulatory authorities; difficulty obtaining scarce raw materials and supplies; resource constraints, including manufacturing capacity, including human capital and manufacturing capacity, on the ability of Novavax to pursue planned regulatory pathways; challenges meeting contractual requirements under agreements with multiple commercial, governmental, and other entities; and those other risk factors identified in the "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of Novavax' Annual Report on Form 10-K for the year ended December 31, 2021, as filed with the Securities and Exchange Commission, which are available at www.sec.gov and www.novavax.com.

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 considerable reliance on forward-looking statements which speak only as of the date hereof.

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OVERVIEW

NanoFlu (qNIV) Vaccine Program Development

COVID-Influenza Combination (CIC) Vaccine Development
*NanoFlu identifies a recombinant hemagglutinin (HA) protein nanoparticle influenza vaccine candidate produced by Novavax. This investigational candidate was evaluated during a controlled phase 3 trial conducted during the 2019-2020 influenza season.
## Characteristics Addressed

<table>
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<tr>
<th>VACCINE TYPE</th>
<th>EGG-ADAPTIVE CHANGES</th>
<th>ANTIGENIC DRIFT</th>
<th>IMMUNOSENESCENCE</th>
<th>ANTI-BODIES</th>
<th>T-CELLS</th>
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<tbody>
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<td>✗</td>
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<td>✓</td>
<td>✓</td>
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<td>Cell-derived inactivated(^5,8)</td>
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<td>✗</td>
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<tr>
<td>Recombinant(^2,3,4)</td>
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<td>✓</td>
<td>✗</td>
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<tr>
<td><strong>NanoFlu (qNIV)(^9,10)</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>[recombinant + adjuvanted]</td>
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</tbody>
</table>

**NanoFlu (qNIV)** has been shown to induce **BOTH** broadly cross-reactive antibodies **AND** potent polynofunctional CD4+ T-cell responses **AND** avoids egg-adaptive antigenic changes.

These are product characteristics only and no head-to-head studies have been done and are not meant to imply clinical efficacy.

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NanoFlu (qNIV) Investigational Vaccine Design

1. Genes inserted into insect virus
   Four Influenza Hemagglutinin (HA1, HA3, HAB1, HAB2) genes are engineered into baculovirus for independent expression.

2. Sf9 cells infected
   Recombinant baculovirus infects moth cells in the S. frugiperda (Sf9) expression system.

3. DNA enters Sf9 cell nucleus
   HA DNA is transcribed.

4. Sf9 cells produce proteins
   HA proteins are each expressed in their native conformation.

5. Nanoparticle formation
   Proteins are harvested. Vaccine nanoparticles assemble as proteins arranged around a Polysorbate 80 (PS80) core.

6. Final vaccine
   HA vaccine nanoparticles are mixed with Matrix-M™ adjuvant to create the ready-to-use investigational vaccine.
PHASE 3: A NON-INFERIORITY IMMUNOGENICITY TRIAL

AIMS
• Demonstrate immunologic non-inferiority to licensed influenza vaccine (Fluzone Quadrivalent) on 4 homologous strains
• Establish pivotal clinical trial dataset to support filing of BLA via accelerated approval path

DESIGN
• 2650 adults ≥65 years of age, across 19 US sites
• Randomized to 1:1 to either NanoFlu or Fluzone Quadrivalent
• Stratified by receipt of prior year seasonal influenza vaccine
• Single dose of test vaccine on Day 0

Primary objectives:
• Demonstrate non-inferior immunogenicity of NanoFlu vs. Fluzone Quadrivalent:
  • Day 0 and 28 egg-propagated virus HAI titers against the 4 homologous strains
  • Describe the safety profile of both vaccines

Day 0 Trial Treatment Injection

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Vaccine</th>
<th>HA Dose per Strain, µg (H1N1/H3N2/Bv/Bv)</th>
<th>Matrix-M1 Adjuvant Dose, µg</th>
<th>Formulation</th>
<th>Subjects Per Group</th>
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<tbody>
<tr>
<td>A</td>
<td>NanoFlu (qNIV)</td>
<td>60, 60, 60, 60</td>
<td>75</td>
<td>Co-form</td>
<td>1325</td>
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<td>B</td>
<td>Fluzone Quad [standard dose]</td>
<td>15, 15, 15, 15</td>
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<td>N/A</td>
<td>1325</td>
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</table>

Total Trial Subjects: 2650
PHASE 3 SUMMARY: PRIMARY ENDPOINT MET

- Primary **immunogenicity** endpoint met on all homologous strains assessed with egg-adapted HAI antibody responses
  - GMT ratio and seroconversion difference success criteria met for non-inferiority

- NanoFlu: **24—66%** higher **wild-type** HAI antibody responses vs Fluzone quadrivalent against 4 homologous strains

- NanoFlu: **34—46%** higher **wild-type** HAI antibody responses vs Fluzone quadrivalent against 6 A/H3N2 drift strains

- Wild-type microneutralization antibody responses confirmed wild-type HAI antibody responses
PHASE 3 CMI: POTENT INDUCTION OF POLYFUNCTIONAL CD4+ T CELL RESPONSES

RCD plot of Day 0 and 7 counts of double cytokine+ effector CD4+ T cells against A/Kansas (H3N2)

- qNIV **right shifted** distribution
- Virtually all qNIV participants became “**CMI responders**,” including those with low baseline
- Similar pattern of CMI responses seen for triple and quadruple cytokine+ responses, and against B/Maryland (B-Vic)

Shinde et al. Lancet ID. 2021. DOI: 10.1016/S1473-3099(21)00192-4
Day 7, 28, 364 geometric mean fold rise (GMFRs) relative to Day 0, of double cytokine+ effector CD4+ T cells against A/Kansas (H3N2), B/Maryland (B-Vic), A/Cambodia (drifted H3N2), or A/Wisconsin (drifted H1N1)

qNIV induced higher fold-rises of CD4+ T cells as compared to Fluzone against homologous and drifted strains and these responses remained elevated at 1 year
PHASE 3: SUMMARY AND CONCLUSIONS

Primary endpoint met:

- Demonstrated immunologic non-inferiority to Fluzone Quad (egg-adapted HAI antibody responses)

Statistically significant higher wild-type HAI antibody responses compared to Fluzone Quadrivalent:

- 24—66% improved Day 28 GMTs against homologous strains
- 34—46% improved Day 28 GMTs against multiple drifted A/H3N2 strains

Wild-type neutralizing antibody responses corroborated wild-type HAI antibody responses, including against drift strains

Potent induction of polyfunctional CD4+ T-cell responses, with persistence one year later

- Virtually all NanoFlu subjects became “CMI responders”, including, notably, those with low baseline CMI
COVID-INFLUENZA COMBINATION (CIC) VACCINE DEVELOPMENT
RATIONALE FOR A COVID-INFLUENZA COMBINATION VACCINE

RECURRENT BOOSTERS OF A SARS-COV-2 VACCINE MAY BE NEEDED IN FUTURE

- Ongoing potential for emergence of variants escaping natural/vaccine immunity
- Continued SARS-CoV-2 circulation, potentially in a seasonally recurrent pattern
- Waning of neutralizing antibody responses in the 4 to 12 months following vaccination or infection

THERE IS AN ONGOING NEED FOR ANNUAL SEASONAL INFLUENZA VACCINATION

- Despite little influenza transmission during the COVID-19 pandemic in 2020 and 2021, influenza transmission likely to rebound in 2022 and beyond with reopening of society
- Continued urgent public health need to develop more effective seasonal influenza vaccines

ADDRESS TWO MAJOR PUBLIC HEALTH PROBLEMS WITH ONE POTENTIAL VACCINE SOLUTION

Development of combination vaccine anticipates future need to annually immunize against both SARS-CoV-2 and influenza virus in advance of the winter transmission season
The study will evaluate dose ranges for both Spike and Hemagglutinin antigens, using a Design of experiments (DoE) approach with 14 treatments groups.

Key antibody and cell-mediated immunity responses will be used to select one or more doses to advance into further development.

Participants are administered the reference formulation of a single vaccine, at the dose level evaluated in previous Phase III trials.
OBJECTIVES

- Assess **safety and reactogenicity** of various COVID-19 Influenza combination (CIC) vaccine formulations
- Assess **immunogenicity** of various CIC formulations
- Optimize HA and rS **dose selection** for combo vaccine

DESIGN

- **640 adults aged 50 – 70 years, seropositive** by infection or vaccination ≥ 8 week prior
- **2 doses** of various CIC formulations, **56 days apart**
  - rS dose range **2.5-22.5 µg/dose**
  - HA dose range **5-60 µg/strain/dose**
  - Matrix-M adjuvant dose: **50 µg/dose**
- Safety and reactogenicity: through Day 70 and 182
- Immunogenicity (Anti-S IgG and HAI): Day 0, 28, 56, 70
- Cell mediated immune (CMI) responses: Day 0, 7, 63

<table>
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<tr>
<th>Vaccine Group</th>
<th>N</th>
<th>Day 0 HA Dose per Strain, µg</th>
<th>rS, µg</th>
<th>Matrix-M, µg</th>
<th>Day 56 (± 4 days) HA Dose per Strain, µg</th>
<th>rS, µg</th>
<th>Matrix-M, µg</th>
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<td>qNIV with Matrix-M adjuvant reference formulation</td>
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PRELIMINARY RESULTS OF PHASE 1/2 CIC VACCINE TRIAL
BASELINE CHARACTERISTICS, REACTOGENICITY AND SAFETY RESULTS

Treatment groups were comparable at baseline

- Median age 59 years
- 62% male / 38% female
- 100% had received prior primary series EUA COVID-19 vaccine; median 10.7 weeks prior to Day 0
- ~0.2% had been previously infected with SARS-CoV-2

CIC formulations were well tolerated with:

- Comparable reactogenicity to standalone reference rS (NVX-CoV2373) and HA (qNIV) formulations
- Most common solicited local AEs were pain and tenderness
- Most common solicited systemic AEs were fatigue, headache, malaise, muscle pain; fever was rare
- Generally Grade 0, 1 or 2. Grade 3 rare. No Grade 4.
- Solicited local and systemic AEs did not vary substantially by rS dose level
- Slightly higher solicited local AEs by increasing HA dose level
- Comparable reactogenicity between dose 1 and dose 2

Safety through Day 70:

- CIC formulations demonstrated comparable rates of unsolicited AEs to standalone reference rS and HA formulations
- Severe unsolicited AEs were rare; and none assessed as related to vaccine
- Serious AEs (SAEs) were rare; and none assessed as related to vaccine
- No reports of adverse event of special interest (AESIs)
ANTI-S IgG DOSE RESPONSE WITH INCREASING rS DOSE ACROSS ALL LEVELS OF HA DOSE

Anti-Spike IgG antibody geometric mean ELISA units (GMEU) by dose and visit

Anti-Spike IgG antibody geometric mean ELISA units (GMEU) by dose and visit

Matrix-M 50µg

Day 0 28

1,000

10,000

100,000

10,000

1,000

HA 5µg

HA 10µg

HA 35µg

HA 60µg

HA 0µg (Ref)

rS 22.5µg

rS 7.5µg

rS 2.5µg

rS 5.0µg

Matrix-M 50µg

Matrix-M 50µg

Matrix-M 50µg

Matrix-M 50µg

Matrix-M 50µg

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PEAK INFLUENZA HAI ANTIBODY DOSE RESPONSE WITH INTERMEDIATE LEVELS OF HA DOSE

Hemagglutination inhibition (HAI) antibody geometric mean titers (GMT) by dose and visit – A/Brisbane H1N1

- **HA 5µg**
  - Matrix-M 50µg

- **HA 10µg**
  - Matrix-M 50µg

- **HA 35µg**
  - Matrix-M 50µg

- **HA 60µg**
  - Matrix-M 50µg

- **HA 60µg (Ref)**
  - Matrix-M 75µg

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<th>Day 0</th>
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<td>Day 0</td>
<td>28</td>
</tr>
<tr>
<td>Day 0</td>
<td>28</td>
</tr>
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</table>

HAI GMT (log\(10\))
PEAK INFLUENZA HAI ANTIBODY DOSE RESPONSE WITH INTERMEDIATE LEVELS OF HA DOSE

Hemagglutination inhibition (HAI) antibody geometric mean titers (GMT) by dose and visit – A/Kansas H3N2

- **HA 5µg**
  - Matrix-M 50µg

- **HA 10µg**
  - Matrix-M 50µg

- **HA 35µg**
  - Matrix-M 50µg

- **HA 60µg**
  - Matrix-M 50µg

- **HA 60µg (Ref)**
  - Matrix-M 75µg

### GMT (log10)

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<tr>
<th>Time</th>
<th>Level 1 (2.5µg)</th>
<th>Level 2 (7.5µg)</th>
<th>Level 3 (22.5µg)</th>
<th>Level 4 (rS 0µg)</th>
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PEAK INFLUENZA HAI ANTIBODY DOSE RESPONSE WITH INCREASING LEVELS OF HA DOSE
Hemagglutination inhibition (HAI) antibody geometric mean titers (GMT) by dose and visit – B/Maryland (Vic)

<table>
<thead>
<tr>
<th>HA Dose (µg)</th>
<th>Matrix-M (µg)</th>
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<tbody>
<tr>
<td>HA 5µg</td>
<td>Matrix-M 50µg</td>
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<tr>
<td>HA 10µg</td>
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<td>HA 35µg</td>
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<td>Matrix-M 50µg</td>
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<tr>
<td>HA 60µg (Ref)</td>
<td>Matrix-M 75µg</td>
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Day 0  28

HAI GMT (log₁₀)

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PEAK INFLUENZA HAI ANTIBODY DOSE RESPONSE WITH INTERMEDIATE LEVELS OF HA DOSE

Hemagglutination inhibition (HAI) antibody geometric mean titers (GMT) by dose and visit – B/Phuket (Yam)

HA 5µg
Matrix-M 50µg

HA 10µg
Matrix-M 50µg

HA 35µg
Matrix-M 50µg

HA 60µg
Matrix-M 50µg

HA 60µg (Ref)
Matrix-M 75µg

HAI GMT (log₁₀)
MODELING CAN PREDICT AN OPTIMAL DOSE OF rS AND HA
Design of experiments (DoE) response surface modeling methods

3 separate multiple regression modeling approaches were employed. Each approach:

• Constructed 5 separate second order models (i.e., main rS and HA dose effects, quadratic of rS and HA dose, and interaction terms)
  • One model each for the Day 28 (post-first dose) antibody response to each strain: SARS-CoV-2 IgG and each of the 4 homologous flu strain HAI responses

• Considered different covariates: age, sex, BMI, baseline IgG or HAI, time since EUA COVID-19 vaccine, and EUA vaccine brand

• Produced an antibody response “surface” for each antibody measure; imagine a 3-D shape, could be a hill, a valley, a saddle, etc.

• Used different methods for dose optimization, which involved simultaneously varying the rS and HA dose values and observing where that puts us on each of the 5 antibody response surfaces, to find an optimal dose level of rS and HA that maximize antibody responses to each antigen and matches reference standalone vaccine responses (red region)

Multiple combinations of HA and rS dose levels that represents an optimal or desirable formulation can be considered for further development
MODELING CAN PREDICT AN OPTIMAL DOSE OF rS AND HA

Design of experiments (DoE) response surface modeling for dose optimization

- We used these models to predict the impact of every permutation of combinations of HA dose and rS dose on the IgG and HAI response, and then compared the predicted responses versus reference standalone HA and rS responses.
- As an example, selected output is shown below for permutations of combinations of rS 25µg with HA dose level ranging from 24-34µg that produce optimal HAI and IgG responses comparable to the reference standalone.
- Across a range of sample dose levels shown, responses closely match or exceed reference values for H1N1, H3N2, B-Vic, IgG.

<table>
<thead>
<tr>
<th>HA dose (µg)</th>
<th>rS dose (µg)</th>
<th>Predicted A/Bris H1N1</th>
<th>Reference A/Bris H1N1</th>
<th>Predicted A/Kans H3N2</th>
<th>Reference A/Kans H3N2</th>
<th>Predicted B/MD B-Vic</th>
<th>Reference B/MD B-Vic</th>
<th>Predicted B/Phu B-Yam</th>
<th>Reference B/Phu B-Yam</th>
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<th>Reference IgG</th>
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<tr>
<td>27</td>
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<td>133.9</td>
<td>140.8</td>
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<td>65.8</td>
<td>64.3</td>
<td>100.8</td>
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<td>16,818</td>
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<tr>
<td>28</td>
<td>25</td>
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<td>133.9</td>
<td>142.7</td>
<td>145.1</td>
<td>64.0</td>
<td>65.8</td>
<td>64.9</td>
<td>100.8</td>
<td>15,428</td>
<td>16,818</td>
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<tr>
<td>29</td>
<td>25</td>
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<td>133.9</td>
<td>144.6</td>
<td>145.1</td>
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<td>64.4</td>
<td>100.8</td>
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<td>149.3</td>
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<td>65.9</td>
<td>100.8</td>
<td>15,055</td>
<td>16,818</td>
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<tr>
<td>33</td>
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<td>65.8</td>
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<td>66.1</td>
<td>65.8</td>
<td>66.8</td>
<td>100.8</td>
<td>14,859</td>
<td>16,818</td>
</tr>
</tbody>
</table>
The 3 different modeling approaches broadly converged on a similar set of results with regards to optimal dose combinations, increasing the robustness of the overall interpretation and conclusions:

- Both rS and HA antigens as a combined formulation modestly interfere with each other, however, interference can be overcome with dose adjustment.
- Higher rS dose levels (>20µg) can overcome the interference of HA dose, and can match (standalone) reference rS vaccine responses.
- Intermediate dose levels of HA (24-40µg per strain) can overcome the interference of rS dose, and can match (standalone) reference HA responses for H3N2, H1N1, B-Vic strains; but modestly lower for B-Yam strain.
• The first study to demonstrate that a COVID-Influenza combination vaccine is feasible, well-tolerated, and immunogenic, and these data warrant continued development

• A novel DoE modeling-based approach to dose finding/optimization is a powerful tool that may allow:
  • Granular resolution of immune responses across a response surface, and
  • Fine-tuned dose selection

• Various CIC formulations may induce antibody responses comparable to the standalone qNIV and COVID-19 vaccine formulations (for H1N1, H3N2, B-Vic, and rS)
  • Higher rS dose needed in CIC than standalone rS
  • Lower dose of HA needed in CIC than standalone HA
  • Implies up to 50% reduction in total antigen content in the CIC formulation compared to the sum of standalone rS and HA components – potentially dose sparing
• This study evaluated **CIC formulations with 50µg of Matrix-M adjuvant**, which was **lower than the 75µg Matrix-M previously used in the standalone qNIV**
  • A higher Matrix-M adjuvant dose of 75µg in CIC might further enhance antibody responses, and lead to further dose sparing. To be evaluated in future trial.

• **Additional immunogenicity data are expected** on microneutralization antibody and CMI responses, as well as 2\textsuperscript{nd} dose and durability of antibody responses

• Data from this study will inform a **planned Phase 2** dose confirmation study which will:
  • Confirm the combination vaccine dose/formulation
  • Assess lower doses of standalone qNIV
THANK YOU

CONTRIBUTORS

VIVEK SHINDE, WAYNE WOO, SHARON LIU, SUSAN NEAL, JOYCE PLESTED, TIM VINCENT, MINGZHU ZHU, SHANE CLONEY-CLARK, IKSUNG CHO, LOU FRIES, FILIP DUBOVSKY, GREG GLENN
BACKUPS
The NanoFlu vaccine

Hemagglutinin nanoparticle antigen and Matrix-M adjuvant

- Recombinant hemagglutinin (HA) nanoparticles
  - Produced in a Baculovirus/Sf9 insect cell system
  - Expressed as recombinant, full-length, wild-type, uncleaved HA0 that assembles into homotrimers
  - Purified homotrimers form higher order nanoparticle structures of 20-40 nm with PS-80

- Manufactured in a rapid, high-yield, high purity process

Potent saponin-based Matrix-M adjuvant

- Purified fractions extracted as saponins from the bark of Quillaja saponaria Molina
  - Formulated with cholesterol and phospholipid, forming cage-like particles

- Characterized by mechanisms of action that include:
  - Enhancement of antigen delivery to draining lymph nodes
  - Enhancement of activated T cell, B cell, and APC populations in draining lymph nodes
  - Induction of functional, and broadly cross-reactive antibodies (e.g. influenza)
  - Enhancement in peak and durability of antibody responses (e.g. RSV, influenza, SARS-CoV-2)
  - Induction of polyfunctional T cells, including CD4+ (e.g. Ebola, influenza, SARS-CoV-2), and CD8+ (e.g. Ebola, SARS-CoV-2)

- Antigen sparing in the context of novel antigens: pandemic influenza, Ebola, and SARS-CoV-2 antigens

---

Matrix-M™ Adjuvant Production Process

Saponins, from the Quillaja saponaria tree, help generate a robust immune response

1. Trees are pruned and bark is harvested
   - Saponins are found in the tree’s bark. Bark is harvested sustainably, without felling the whole tree.

2. Bark is processed
   - Bark extract is processed into Fraction-A and Fraction-C, then freeze-dried (lyophilized). These powders contain “raw” saponin molecules.

3. Liquid formulation prepared
   - Fraction-A and Fraction-C, as liquids, are formulated with phospholipids and cholesterol, producing distinctive nanostructures.

4. Matrix-M adjuvant formation
   - Matrix-A and Matrix-C components are mixed to form Matrix-M adjuvant.

5. Final vaccine
   - Matrix-M adjuvant is mixed with the vaccine antigen to form the final vaccine product.
PHASE 1: NanoFlu (tNIV) INDUCED HIGHER WILD-TYPE HAI ANTIBODY RESPONSES (GMFRs) VS. FLUZONE-HIGH DOSE (IIV3-HD) AGAINST 5 GENERATIONS OF ANTIGENICALLY DRIFTED A(H3N2) STRAINS

Phase 1 design:
330 US adults aged ≥60 years
Randomized 1:1:1
- tNIV: 15µg each HA (45µg total) + 50µg Matrix-M, or
- tNIV: 60µg each HA (180µg total) + 50µg Matrix-M, or
- Fluzone High Dose: 60µg each HA (180µg total)

Objectives/endpoints:
- Day 21 wild-type HAI antibody responses against homologous and drift strains
- Safety profile through 1 year
• Demonstration of an "adjuvant effect"
  • Matrix-M adjuvant resulted in significant enhancement of immune responses when compared to unadjuvanted formulation

• Higher wild-type HAI antibody responses against homologous A/H3N2 and drifted A/H3N2 strains as compared to Fluzone HD

• Similar wild-type HAI antibody responses against homologous and drifted strains as compared to Flublok

• Potent induction of polyfunctional CD4+ T cell responses, which were higher than both Fluzone HD and Flublok

• Well-tolerated, with acceptable safety profile
COVID-Influenza Combination (CIC) Investigational Vaccine Design

1. Genes inserted into insect virus
   - SARS-CoV-2 spike and four Influenza Hemagglutinin (HA1, HA3, HAB1, HAB2) genes are engineered into baculovirus for independent expression.

2. Sf9 cells infected
   - Recombinant baculovirus infects moth cells in the S. frugiperda (Sf9) expression system.

3. DNA enters Sf9 cell nucleus
   - Spike and HA DNA is transcribed.

4. Sf9 cells produce proteins
   - Proteins are each expressed in their native conformation.

5. Nanoparticle formation
   - Proteins are harvested. Vaccine nanoparticles assemble as proteins arranged around a Polysorbate 80 (PS80) core.

6. Final vaccine
   - Spike and HA vaccine nanoparticles are mixed with Matrix-M™ adjuvant to create the ready-to-use vaccine.
The NanoFlu vaccine

Hemagglutinin nanoparticle antigen and Matrix-M adjuvant

Recombinant hemagglutinin (HA) nanoparticles
• Produced in a Baculovirus/Sf9 insect cell system
• Expressed as recombinant, full-length, wild-type, uncleaved HA0 that assembles into homotrimers
• Purified homotrimers form higher order nanoparticle structures of 20-40 nm with PS-80
• Manufactured in a rapid, high-yield, high purity process

Potent saponin-based Matrix-M adjuvant
• Purified fractions extracted as saponins from the bark of Quillaja saponaria Molina
• Formulated with cholesterol and phospholipid, forming cage-like particles
• Characterized by mechanisms of action that include:
  • Enhancement of antigen delivery to draining lymph nodes
  • Enhancement of activated T cell, B cell, and APC populations in draining lymph nodes
  • Induction of functional, and broadly cross-reactive antibodies (e.g. influenza)
  • Enhancement in peak and durability of antibody responses (e.g. RSV, influenza, SARS-CoV-2)
  • Induction of polyfunctional T cells, including CD4+ (e.g. Ebola, influenza, SARS-CoV-2), and CD8+ (e.g. Ebola, SARS-CoV-2)
• Antigen sparing in the context of novel antigens: pandemic influenza, Ebola, and SARS-CoV-2 antigens

Matrix-M™ Adjuvant Mechanism of Action

1. Matrix-M-adjuvanted vaccine is injected into the muscle
2. Recruitment and activation of innate immune cells
3. Rapid delivery and activation in lymph node
4. Effective antigen presentation
5. Long-lasting memory response

- Plasma cells
- Memory B-cells
- High affinity antibodies
- CD4+ Th1 T-cell
- CD4+ Th2 T-cell
- Antigen-specific effector and memory T-cells

Cytokines
- MHCII
- TCR
- Cytokines are released

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# Phase 3 Immunogenicity: Enhanced Responses Against Homologous and Drifted A/H3N2 and B-Victoria Strains

Day 28 wild-type HAI vs wildtype Neutralizing antibody (NanoFlu / Fluzone)

<table>
<thead>
<tr>
<th>Strain</th>
<th>HAI: Wild-type</th>
<th>Microneutralization: Wild-type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NanoFlu</td>
<td>Fluzone Quad</td>
</tr>
<tr>
<td>A/Brisbane/02/2018 (H1N1) pdm09 (Homologous)</td>
<td>76.6</td>
<td>62.7</td>
</tr>
<tr>
<td>A/Kansas/14/2017 (H3N2) (Homologous)</td>
<td>153.6</td>
<td>90.7</td>
</tr>
<tr>
<td>B/Maryland/15/2016 (Homologous)</td>
<td>62.8</td>
<td>47.2</td>
</tr>
<tr>
<td>B/Phuket/3073/2013 (Homologous)</td>
<td>118.3</td>
<td>78.4</td>
</tr>
<tr>
<td>A/California (&quot;Drifted&quot; H3N2; Clade 3C2a1b-131K)</td>
<td>115.0</td>
<td>80.6</td>
</tr>
<tr>
<td>A/Cardiff (&quot;Drifted&quot; H3N2; Clade 3C2a1b-135N)</td>
<td>63.9</td>
<td>45.4</td>
</tr>
<tr>
<td>A/Netherlands (&quot;Drifted&quot; H3N2; Clade 3C3a)</td>
<td>102.3</td>
<td>74.7</td>
</tr>
<tr>
<td>A/So. Aus. (&quot;Drifted&quot; H3N2; Clade 3C2a1b-131K)</td>
<td>98.1</td>
<td>70.4</td>
</tr>
<tr>
<td>A/Idaho (&quot;Drifted&quot; H3N2– Clade 3C3a)</td>
<td>202.5</td>
<td>136.8</td>
</tr>
<tr>
<td>A/Tokyo (&quot;Drifted&quot; H3N2– Clade 3C2a2)</td>
<td>78.0</td>
<td>54.5</td>
</tr>
<tr>
<td>A/Hong Kong (&quot;Drifted&quot; H3N2-2019)</td>
<td>192.6</td>
<td>107.2</td>
</tr>
<tr>
<td>A/Wisconsin (&quot;Drifted&quot; H1N1-2019)</td>
<td>78.3</td>
<td>70.3</td>
</tr>
<tr>
<td>B/Washington (&quot;Drifted B-Victoria)</td>
<td>88.2</td>
<td>71.4</td>
</tr>
<tr>
<td>B/Colorado (B/Maryland-like homologous strain)</td>
<td>185.7</td>
<td>142.9</td>
</tr>
</tbody>
</table>

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COVID-INFLUENZA COMBINATION VACCINE DEVELOPMENT

**KEY MILESTONES**

**MAY 2021**
Announced positive preclinical data*

**JUNE 2021**
Announced data from co-administration sub-study**

**SEPTEMBER 2021**
Initiated phase I/II clinical trial of COVID-NanoFlu Combination Vaccine

---

**Clinical Proof of Concept**
- UK Phase III co-administration sub-study completed
- Demonstrated viability of simultaneous COVID-19 and influenza vaccination

**Preclinical Development**
- Hemagglutination inhibition (HAI) and ACE2 titers were comparable between individual and combination vaccines (hamster and ferrets)
- Maintained clinical and virologic protection against experimental challenge with SARS-CoV-2 (hamster model)
- Induced antibodies against SARS-CoV-2 neutralizing epitopes common between USA-WA1 (original strain) and Beta (B.1.351) variant

**Clinical Development**
- Phase I/II trial in Australia initiated and fully enrolled
  - Safety, immunogenicity, and dose finding

---

Source: *Massare et al. 2021; DOI: 10.1101/2021.05.05.442782, **Toback et al. 2021; DOI: 10.1101/2021.06.09.21258556
**PHASE 3 IMMUNOGENICITY: PRIMARY ENDPOINT MET ON ALL HOMOLOGOUS STRAINS**

Day 28 egg-based or wild-type HAI GMTs and GMT ratios (NanoFlu / Fluzone)

<table>
<thead>
<tr>
<th>Assay</th>
<th>Strain</th>
<th>NanoFlu</th>
<th>Fluzone Quad</th>
<th>D28 GMT Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HAI: EGG</strong></td>
<td>A/Brisbane/02/2018 (H1N1) pdm09 (Homologous)</td>
<td>49.3</td>
<td>45.0</td>
<td>1.09</td>
<td>(1.03, 1.15)</td>
</tr>
<tr>
<td></td>
<td>A/Kansas/14/2017 (H3N2) (Homologous)</td>
<td>151.5</td>
<td>126.8</td>
<td>1.19</td>
<td>(1.11, 1.27)</td>
</tr>
<tr>
<td></td>
<td>B/Maryland/15/2016 (Vic) (Homologous)</td>
<td>110.7</td>
<td>106.3</td>
<td>1.03</td>
<td>(0.99, 1.07)</td>
</tr>
<tr>
<td></td>
<td>B/Phuket/3073/2013 (Yam) (Homologous)</td>
<td>168.5</td>
<td>133.9</td>
<td>1.23</td>
<td>(1.16, 1.29)</td>
</tr>
<tr>
<td><strong>HAI: WT</strong></td>
<td>A/Brisbane/02/2018 (H1N1) pdm09 (Homologous)</td>
<td>76.6</td>
<td>62.7</td>
<td>1.24</td>
<td>(1.17, 1.32)</td>
</tr>
<tr>
<td></td>
<td>A/Kansas/14/2017 (H3N2) (Homologous)</td>
<td>153.6</td>
<td>90.7</td>
<td>1.66</td>
<td>(1.53, 1.79)</td>
</tr>
<tr>
<td></td>
<td>B/Maryland/15/2016 (Vic) (Homologous)</td>
<td>62.8</td>
<td>47.2</td>
<td>1.32</td>
<td>(1.26, 1.39)</td>
</tr>
<tr>
<td></td>
<td>B/Phuket/3073/2013 (Yam) (Homologous)</td>
<td>118.3</td>
<td>78.4</td>
<td>1.47</td>
<td>(1.40, 1.55)</td>
</tr>
</tbody>
</table>

- GMT ratio success criteria met for non-inferiority
- NanoFlu: 3—23% increased using egg-based HAI
- NanoFlu: 24—66% increased using wild-type HAI, a more biologically and clinically relevant measure

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PHASE 3 CMI: COMPARISON TO ENHANCED INFLUENZA VACCINES IN UNIV OF HK STUDY

Day 7 / 0 geometric mean fold rise (GMFRs) of IFN-γ cytokine+ total CD4+ T cells against A/H3N2 or B-Victoria strain

NanoFlu induced substantially higher fold-rises of IFN-γ+ CD4+ T cells as compared to Fluzone HD, Flublok, or FLUAD based on comparable literature estimates.
PHASE 1: EGG-ADAPTED REAGENTS MAY GIVE A MISLEADING RESULT

Microneutralization antibody responses (GMFRs) against egg-adapted vs. wild-type A/Singapore A/H3N2 virus

NanoFlu induced improved neutralization responses against wild-type vs. egg-adapted A/Singapore H3N2 viruses underscoring the problem of egg-adaptive mutations

Neutralization antibody responses against wild-type circulating viruses are more clinically relevant
### PHASE 3 SAFETY DATA THROUGH DAY 365

Nanoflu well tolerated

<table>
<thead>
<tr>
<th>Through Day 365</th>
<th>NanoFlu</th>
<th>Fluzone Quad (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1333</td>
<td>1319</td>
</tr>
<tr>
<td>Counts (%) of Subjects with Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any treatment emergent adverse event (TEAE)</td>
<td>783 (58.7)</td>
<td>697 (52.8)</td>
</tr>
<tr>
<td>Any Solicited TEAE</td>
<td>551 (41.3)</td>
<td>420 (31.8)</td>
</tr>
<tr>
<td>Local solicited</td>
<td>372 (27.9)</td>
<td>243 (18.4)</td>
</tr>
<tr>
<td>Severe local solicited</td>
<td>8 (0.6)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Systemic Solicited</td>
<td>369 (27.7)</td>
<td>292 (22.1)</td>
</tr>
<tr>
<td>Severe systemic solicited</td>
<td>15 (1.1)</td>
<td>11 (0.8)</td>
</tr>
<tr>
<td>Unsolicited TEAE</td>
<td>469 (35.2)</td>
<td>466 (35.3)</td>
</tr>
<tr>
<td>Severe unsolicited</td>
<td>75 (5.6)</td>
<td>59 (4.5)</td>
</tr>
<tr>
<td>Severe &amp; related unsolicited</td>
<td>10 (0.8)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Medically-attended unsolicited</td>
<td>353 (26.5)</td>
<td>354 (26.8)</td>
</tr>
<tr>
<td>Serious adverse events (SAEs)*</td>
<td>81 (6.1)</td>
<td>78 (5.9)</td>
</tr>
</tbody>
</table>

*No SAEs in either treatment group were assessed by study investigators as related to vaccine at either timepoint.*

Shinde et al. Lancet ID. 2021; DOI: 10.1016/S1473-3099(21)00192-4