Maternal Immunization with the RSV F Nanoparticle Vaccine On Behalf of Young Infants

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RSV Vaccines for the World
Porto, Portugal
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Pediatric Respiratory Syncytial Virus (RSV)

Who is the addressable population? What are the clinical plans/TPP for these populations? What is the most rational approach?

<table>
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<th>Treatment Site and Year</th>
<th>0–5</th>
<th>6–11</th>
<th>12–23</th>
<th>24–59</th>
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<td>(0.2–0.7)</td>
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<td>(2.3–2.7)</td>
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<td>(15–50)</td>
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<td>157</td>
<td>160</td>
<td>80</td>
<td>77</td>
<td>99</td>
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<td>2002–2004</td>
<td>132</td>
<td>177</td>
<td>66</td>
<td>57</td>
<td>80</td>
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</table>

* The presence of RSV infection was confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR) and culture for inpatients and by
US RSV Hospitalization Rates in Children <2 years of age

Figure 1. Numbers of hospitalizations by years (left) and by months (right). Data from the National Hospital Discharge Survey, 2005-9.
Maternal Transfer of Antibodies

- Active transport of mother’s antibodies into baby’s circulation
  - Mother’s antibodies from past infections or immunization are actively concentrated
  - Begins at 20th week of gestation.
  - At full term baby has >100% of mother’s antibody levels.

- Concentration effect can be quite large
  - Tetanus abs >160% of mothers level

- Known to provide limited protection to infants against RSV

Placental Fc Receptors and the Transfer of Maternal IgG
**Figure 5:** Total IgG concentrations in cord serum samples from newborns in different gestational weeks [46, 60]. *Number of samples in each period.*
Correlation of Maternal Antibodies with Cord Blood Antibodies

Figure 2: Correlation indexes and placental transfer ratios of maternal and term cord blood IgG levels reactive with tetanus toxoid, O111 LPS from enteropathogenic *E. coli* and Hib polysaccharide. Correlation indexes and placental transfer is higher to thymus-dependent antigens, as tetanus toxoid than to thymus-independent antigens type I and II, as LPS and polysaccharides, respectively.
RSV is a Constantly Changing Virus

Attachment (G) Protein
Fusion (F) Protein

Budding RSV Virus

Changes mostly occur in one of the key surface glycoproteins: the G protein

The Fusion protein is highly conserved

Site II on the Fusion protein is the target of palivizumab
The F protein Site II is targeted by palivizumab (Synagis) and motavizumab (Numax)

These monoclonal antibodies have been shown clinically to prevent RSV disease in multiple randomized clinical trials

These data can de-risk program as they provide a level of and type of immunity to be targeted

Antigenic site II: Amino acids 254-278
NSELLSLINDMPITNDQKKLMSNNV

Serum Palivizumab Levels After Injection

<table>
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<th>Time of Serum Samples</th>
<th>Intravenous (^{12,13})</th>
<th>Intramuscular</th>
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<tr>
<td>2 days after Dose 1</td>
<td>N = 19</td>
<td>N = 44</td>
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<tr>
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<td>165.7 ± 20.1*</td>
<td>91.1 ± 3.8</td>
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<tr>
<td>14/15 days after Dose 1</td>
<td>N = 20</td>
<td>N = 43</td>
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<td>92.6 ± 9.9</td>
<td>65.0 ± 3.3</td>
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<td>30 days after Dose 1</td>
<td>N = 21</td>
<td>N = 39</td>
</tr>
<tr>
<td></td>
<td>60.6 ± 7.1</td>
<td>49.2 ± 3.6</td>
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<tr>
<td>2 days after Dose 2</td>
<td>N = 19</td>
<td>N = 38</td>
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<tr>
<td></td>
<td>206.4 ± 23.6</td>
<td>150.3 ± 8.6</td>
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<tr>
<td>14/15 days after Dose 2</td>
<td>N = 20</td>
<td>N = 31</td>
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<td></td>
<td>116.6 ± 9.3</td>
<td>106.6 ± 5.7</td>
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<tr>
<td>30 days after Dose 2</td>
<td>N = 21</td>
<td>N = 37</td>
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<td></td>
<td>70.7 ± 6.0</td>
<td>69.4 ± 4.3</td>
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<tr>
<td>30 days after Dose 3</td>
<td>N = 18</td>
<td>N = 23</td>
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<tr>
<td></td>
<td>88.5 ± 7.2</td>
<td>69.5 ± 4.7</td>
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<tr>
<td>30 days after Dose 4</td>
<td>N = 10</td>
<td>N = 22</td>
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<tr>
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<td>96.9 ± 8.7</td>
<td>70.3 ± 5.3</td>
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<tr>
<td>30 days after Dose 5</td>
<td>N = 19</td>
<td>N = 19</td>
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<tr>
<td></td>
<td></td>
<td>73.4 ± 6.2</td>
</tr>
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</table>

* Mean ± se.  

**TABLE 1.** Mean serum MEDI-493 concentrations (μg/ml) after 15-mg/kg im and iv doses

Safety and pharmacokinetics of an intramuscular humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia

SÁEZ-LLORENS, XAVIER; CASTAÑO, ELIZABETH; NULL, DONALD; STEICHEN, JEAN; SÁNCHEZ, PABLO J.; RAMILO, OCTAVIO; TOP, FRANKLIN H. JR.; CONNOR, EDWARD; THE MEDI-493 STUDY GROUP
6.4.2.1 Incidence of RSV Hospitalization

The incidence of RSV hospitalization in the MI-CP117 ITT population is presented in Table 6.4.2.1-1. The efficacy of motavizumab was confirmed, with motavizumab demonstrating a statistically significant 83% relative reduction in the incidence of RSV hospitalization (RR: 0.168, 95% CI: [0.086, 0.308]; p < 0.001) as compared to placebo.

<table>
<thead>
<tr>
<th>Population</th>
<th>Placebo</th>
<th>Motavizumab</th>
<th>Fisher’s Exact Test p-value</th>
<th>Relative Risk</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>ITT population</td>
<td>39/472 (8.3%)</td>
<td>13/938 (1.4%)</td>
<td>&lt; 0.001</td>
<td>0.168</td>
<td>(0.086, 0.308)</td>
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</tbody>
</table>

*a Prespecified interim analysis alpha spending level was 0.032
RSV Vaccine: Target Populations

Plan Needed for each population

Young infants via Maternal Immunization
Infants and Children
Elderly
RSV Vaccine: Target Populations

Data in the target population

- Young infants via Maternal Immunization
- Infants and Children
- Elderly
RSV Vaccine
- Summary of Completed Clinical Studies

- Study 101: Safety and Immunogenicity in healthy adults complete
  - Observed robust immune response, palivizumab/neutralizing antibodies (n=120)

- Study M201: Safety and Immunogenicity, women of childbearing age
  - Confirmation of safety and immunogenicity in target population (n=330)

- Study E101: Safety and Immunogenicity in elderly adults-complete
  - Confirmation of safety and immunogenicity in target population (n=220)
Principal Immunologic Findings

- Populations with decades of repeat RSV infections develop neutralizing antibodies, but low to no palivizumab binding antibodies
  - Explains limited effectiveness of immunity from natural infection?

- The Novavax recombinant F nanoparticle vaccine induces robust immunity and particularly induces palivizumab-like antibody in:
  - Healthy adults
  - Women of childbearing age
  - Elderly adults

- Antibodies induced by the recombinant F vaccine are remarkably protective in relevant preclinical studies
  - Active and passive immunity
  - Measured level of palivizumab-like antibodies and their potency in cotton rats are appear greater than palivizumab
  - Raises questions of the best measures of immunity
Young infants via Maternal Immunization
A Phase II Randomized, Observer-Blinded, Placebo-Controlled, Dose-Ranging Study to Evaluate the Immunogenicity and Safety of an RSV F Protein Nanoparticle Vaccine, with or without Aluminum, in Healthy Women of Child-Bearing Age: M201

- Randomized, observer-blind, placebo controlled, multi-centered
- Healthy WOCBA 18 to 35 y.o., sera at 0, 28 and 56d
- Safety reported through day 56, will be followed to day 180
- Alum vs no alum, 1 vs 2 immunizations and 60 vs 90 µg

<table>
<thead>
<tr>
<th>Group</th>
<th>RSV F dose</th>
<th>AlPO₄</th>
<th>Day 0</th>
<th>Day 28</th>
<th>N</th>
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<tr>
<td>A</td>
<td>60µg</td>
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<td>Active</td>
<td>Active</td>
<td>30</td>
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<td>B</td>
<td>60µg</td>
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<td>Active</td>
<td>Placebo</td>
<td>30</td>
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<td>C</td>
<td>60µg</td>
<td>No</td>
<td>Active</td>
<td>Active</td>
<td>30</td>
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<td>D</td>
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<td>Active</td>
<td>Placebo</td>
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<td>E</td>
<td>90µg</td>
<td>Yes/Yes</td>
<td>Active</td>
<td>Active</td>
<td>30</td>
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<td>F</td>
<td>90µg</td>
<td>Yes/No</td>
<td>Active</td>
<td>Placebo</td>
<td>30</td>
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<td>G</td>
<td>90µg</td>
<td>No</td>
<td>Active</td>
<td>Active</td>
<td>30</td>
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<td>H</td>
<td>90µg</td>
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<td>Active</td>
<td>Placebo</td>
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<tr>
<td>J (P1)</td>
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<td>Active</td>
<td>Active</td>
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<td>K</td>
<td>0</td>
<td>No</td>
<td>Placebo</td>
<td>Placebo</td>
<td>60</td>
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</table>
Demography, Safety Summary

- All female, mean age ~26 y/o, ~50% >26 years old, 38-54% with school-age children
- Safety results of Phase II are generally confirmatory of phase I.
  - Principal finding is mild-moderate injection site pain in 60-80% of aluminum-adjuvanted vaccinees, 35-65% of unadjuvanted vaccinees, and 25% of placebo recipients
  - No related SAEs, 1 severe (1 fever, 17 days after vaccination)
- **No safety issues limiting to continued development.**
Primary Immunogenicity Endpoint: Anti F IgG to Day 56

- Fold Rise to day 56
Primary Immunogenicity Endpoint used Anti-F Data to Day 56

- **Q: Is there a positive effect of AlPO₄?**
  - **A: Yes**
  - Al vs. no Al within pooled 1-dose regimens
  - Al vs. no Al within pooled 2-dose regimens
    - Day 28 GMR (95% CI) 1.4 (1.1-1.7) 1.4 (1.1-1.7)
    - p value 0.01 0.011
    - Day 56 GMR (95% CI) 1.4 (1.1-1.7) 1.7 (1.3-2.2)
    - p value 0.006 <0.001

- **Q: Are two doses better than one?**
  - **A: With aluminum, yes.**
  - 1 vs. 2 doses within pooled adjuvanted regimens
  - 1 vs. 2 doses within pooled unadjuvanted regimens
    - Day 56 GMR (95% CI) 1.4 (1.2-1.8) 1.2 (0.9-1.5)
    - P value 0.001 0.137

- **Q: Is 90µg better than 60µg?**
  - **A: Not much**
  - 60 vs. 90 within pooled 1-dose regimens
  - 60 vs. 90 within pooled 2-dose regimens
    - Day 56 GMR (95% CI) 1.1 (0.9-1.4) 1.3 (1.0-1.6)
    - p value 0.326 0.054
Vaccine-induced antibodies compete with palivizumab for binding to Site II on the F Protein

Measure validated by the cotton rat model
Concordance of Anti-F IgG vs. Palivizumab-Competitive Antibodies - Study M201

Anti-F IgG responses closely tied to palivizumab-like antibodies

Concordance slope w/o placebo = 1.08 (0.95–1.22)
Adjuvant Groups only: Day 28

Concordance Slope = 1.04
Palivizumab Competing Antibodies by Groups

- 25-30µg/ml decreases the lung viral load in a cotton rat by 2 log₂
- LLoQ 33µg/ml in this assay
Modeling the Effect of Palivizumab-like Antibodies via Maternal Immunization: Protection of infants to 5-6 months
GMT: RSV/A Responses

- Baylor College of Medicine Assay
- Risk reduction for Hospitalization of ~25% at log$_2$ 6
GMR: RSV/A Responses

- Fold Rise

Summary of RSV/A MN Responses

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Placebo (N=53)</th>
<th>Phase 1 Model (N=19)</th>
<th>1x (N=23)</th>
<th>2x (N=20)</th>
<th>1x+AL (N=26)</th>
<th>2x+AL (N=25)</th>
<th>1x (N=28)</th>
<th>2x (N=26)</th>
<th>1X+AL (N=30)</th>
<th>2x+AL (N=25)</th>
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<td>60 µg</td>
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</table>

Day 7

Day 28

Day 56
GMT: RSV/B Responses

- BCM assay
GMR: RSV/B Responses

- Fold rise
MNA: Day 28 Comparison of Un-adjuvented and Adjuvented by Reverse Cumulative Distributions

- 1- and 2-dose groups are pooled (identical at Day 28).
- 60 and 90µg groups are pooled to show overall impact of alum adjuvant at Day 28.
- Peak GMT log$_2$ 10.0-10.5
- Rise in MN proportional to rise in pali-like antibodies (Glenn et al, Vaccine)
Women with Lowest Baseline MN Titers Benefit the Most, and Show a Strong Adjuvant Effect

**RSV/A Microneutralization Titer Response After One Dose:**
Effect of Baseline Titer and Presence of Adjuvant

Numbers = N for the group analyzed
Impact of Exogenous Palivizumab on Human Adult Serum MN Titers

Baseline MN titers: 64, 136, 292, 342, 456

Adult sera with high baseline titers consistent with baselines in this study show only modest fold-increases in MN activity despite adding high and clinically-relevant concentrations of palivizumab; a pattern similar to clinical samples from vaccinees.
Highlights of the Clinical Data to Date

- The RSV F nanoparticle is immunogenic
  - RSV F IgG that is in concordance with high affinity antibodies
  - Palivizumab-like antibodies in excess of levels historically associated with protection in randomized clinical trials
  - Neutralizing antibodies, rising consistent with increase of palivizumab-like antibodies

- The greatest responses are seen in subjects with the lowest antibodies

- The general population appears to have little to no functional site II antibody after years of infection

- The levels observed post-vaccination are consistent with clinical protection, both for PCA and neutralizing antibodies
• M202 dose confirmation in women of childbearing age
  – FSI Q4 2013-study underway
  – Expanded safety data to support first pregnancy study
  – Formulation-alum dose finding and confirmation
  – Detailed antibody kinetics

• M203 dose confirmation in 3\textsuperscript{rd} trimester women (2014)
  – POC for transfer of maternal antibodies to infants
    • Transplacental transfer of Palivizumab-like antibodies levels in infants
  – Safety in mothers/infants

• M204 in Pregnant women, 3\textsuperscript{rd} trimester
  – Point efficacy
    • Prevention of medically attended RSV+ respiratory disease
  – Safety in mothers/infants
  – Power for pivotal efficacy study

• M301 in Pregnant women
  – Pivotal efficacy study
    • Prevention of medically attended RSV+ respiratory disease