IMPAACT 2013
Protocol Overview

Phase I Placebo-Controlled Study of the Infectivity, Safety and Immunogenicity of a Single Dose of a Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine, D46/NS2/N/ΔM2-2-HindIII, Delivered as Nose Drops to RSV-Seronegative Infants 6 to 24 Months of Age

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Series of RSV vaccine studies

• Evaluate the vaccine candidates to determine which are most promising for further study based on:
  – Safety
  – Infectivity—vaccine virus shed in nose
  – Immunogenicity after vaccine—neutralizing Ab in blood
  – Immunogenicity and after RSV season—rise in neutralizing Ab in blood w/o reported RSV disease
2011/2012/2013 Vaccines

- **IMPAACT 2000**: LID ΔM2-2, might be under-attenuated
  - IMPAACT 2011/2012/2013, vaccines modified to add more attenuation:
- **IMPAACT 2013**: NS2/N/ΔM2-2-HindIII
  - Combines backbone of LID ΔM2-2 with additional mutations same as Medi ΔM2-2

**LID,cp,ΔM2-2**

- Further attenuated by the well-characterized set of 5 “cp” missense mutations in N, F, L genes

**LID/ΔM2-2/1030s**

- Slightly temperature sensitive; “1030s” missense mutation provides further restriction of replication

**NS2/N/ΔM2-2-HindIII**

- Amino acid sequence, M2-2 deletion, and SH noncoding region identical to MEDI ΔM2-2, which was more attenuated than LID ΔM2-2 in a previous clinical study
IMPAACT 2013 - hypothesis

• Study hypothesis
  – NS2/N/∆M2-2-HindIII will be safe and immunogenic in RSV-naive infants.
IMPAACT 2013—Primary Objectives

• Safety:
  – all AE through midnight of the 28\textsuperscript{th} day following inoculation
  – SAE through midnight on the 56\textsuperscript{th} day following inoculation

• Infectivity:
  – Peak titer of vaccine virus shed
  – Duration of virus shedding
  – Proportion of vaccinated infants participants infected with study vaccine

• Immunogenicity:
  – Antibody responses (Day 56) to the study vaccine
IMPAACT 2013—Secondary Objectives

• Outcomes with wild-type (wt) RSV during the subsequent RSV season
  – Clinical symptoms if medically attended
  – Antibody responses

• Detailed characterization of the B cell response to vaccine

• Characterize mucosal antibody response
IMPAACT 2013 Study Schema

- Double-blind, randomized, placebo-controlled study
- Randomized 2:1 vaccine: placebo
- Enroll 33 infants and children
  - Age ≥6 to <25 months of age
  - RSV seronegative (no neutralizing Ab, JHU lab test)

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Treatment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV seronegative infants and children ages ≥6 to &lt;25 months of age</td>
<td>22</td>
<td>Vaccine</td>
<td>$10^{5.0}$ PFU</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Placebo</td>
<td>0 PFU</td>
</tr>
</tbody>
</table>

PFU = plaque forming units
IMPAAACT 2013 study treatment

- One dose, intranasal
- Diluent and placebo are Leibovitz L-15 medium (a solution with amino acids, sugar and salt)
- First study of this vaccine in humans
- But, more attenuated in vitro and non-human primates NHP than LID RSV ΔM2-2 studied in 2000
IMPAACT 2013 Schema

ACUTE AND POST-ACUTE PHASE

- Screening/blood collection within 42 days of enrollment
- Nasal wash
- Clinical assessment: inoculation plus 8 visits
- Blood collection
- Phone or email contact
- RSV Season

RSV SEASON SCHEDULE

- Weekly phone contact or email
- Nasal wash if ill
- Blood collection
- Pre-season
- Nov
- Dec
- Jan
- Feb
- March
- April
IMPAACT 2013 Phases – important for determining what data is collected, what data is reported

• Acute Phase—Day 0- Day 28 (midnight)
  – Daily assessments in person or by phone
  – Weekend work
  – Clinician on call off hours

• Post-Acute Phase Day 29-Day 56 (midnight)

• “study hiatus”

• Pre-RSV Season Visit—October

• RSV Season Surveillance—Nov through March

• Post-RSV Season Visit—April
IMPAACT 2013—Why so many nasal washes?

You’re going to put what up my nose?!!

• Frequent nasal washes necessary to answer the primary objectives
  – Does the virus grow in the nares?
  – How much virus grows?
  – How long does the virus grow?
IMPAACT 2013—Why weekly calls

• Weekly calls for the whole winter?
• Needed to answer the secondary objective
  – Identify patients with RSV neutralizing Ab rises with wtRSV exposure with and without illness
  – Medically attended respiratory illness
IMPAACT 2013 Target population

• Super baby
• Study can be paused or stopped for specific events
• We don’t want to pause for something that is not actually related to the vaccine
IMPAACT 2013 inclusion criteria

• ≥6 months (>180 days) of age at the time of screening and <25 months (<750 days) at enrollment

• The infant/child is in good health based on review of
  – the medical record, history, and physical examination – get the PCP records
  – without evidence of chronic disease
  – any questions regarding interpretation of this criterion should be forwarded to the team
IMPAACT 2013 inclusion criteria

• Growing at a normal velocity for age
  – you need a growth chart with more than one time point

• Normal current height and weight
  – <1 year of age: above the 5th percentile
  – ≥1 year of age: above the 3rd percentile for age.
IMPAACT 2013 eligibility - routine vaccines

- Routine vaccines may not be given soon before or after the study inoculation
- Potential to interfere with assessment of safety and immune response
- At enrollment: must have received routine immunizations appropriate for age
  - Per Center for Disease Control Advisory Committee on Immunization Practices [ACIP]
  - Strategize this – you can immunize at screening and be in the window for enrollment
  - Do not delay immunizations to allow enrollment
  - Make plan for after enrollment

Inactivated vaccines/Rotavirus
- Window: 14 days
- Rotavirus is exception for a live vaccine

Live vaccines (other than rotavirus)
- Window: 28 days

https://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html
Eligibility for infants exposed to HIV

- If born to an HIV-infected woman
  - Never breastfed
  - Two negative HIV nucleic acid (RNA or DNA) tests
    OR
  - With both collected when ≥ 4 weeks of age
  - At least one collected when ≥ 16 weeks of age
  - No positive HIV nucleic acid (RNA or DNA) test or
  - Two negative HIV antibody tests, both collected at ≥24 weeks of age
Eligibility: never had RSV before

- Seronegative for RSV antibody- tested at JHU lab
  - serum RSV-neutralizing antibody titer <1:40
  - no more than 42 days prior to scheduled inoculation
- May use screening from one IMPAACT RSV study for other IMPAACT RSV studies
IMPAACT 2013 exclusion criteria
24 exclusions!

• Slides are summary/paraphrase
• Refer to protocol for precise language
Goal:
Participant is not at risk of severe RSV
Participant is not at risk of an adverse event that is hard to interpret

- Participant is
  - Not immunosuppressed
  - Not at risk of severe RSV
  - Healthy
  - No evidence of predisposition to have lower respiratory illness
  - Not ill at the time of inoculation
Goal:
Participant has not had prior exposure that will interfere with study assessment

Participant has not:
• Prior RSV vaccine
• Prior anti-RSV treatment
• Prior anaphylaxis
• Prior severe vaccine reaction
• Lived with a child that received an RSV live attenuated vaccine
Goal:
Participant contacts are not at risk of severe RSV

• Participant contacts
  – Not immunosuppressed
  – Not at risk of severe RSV
  – No young infants
    • Home
    • Daycare
Contacts with HIV

• Cut-offs set to avoid ambiguity about possible immunosuppression
• Cut-off set to avoid decline to immunosuppression during post vaccination phase
• CD4 parameter must have been measured within 6 months prior to enrollment
• Verbal report is sufficient but only if confident !!!
• Actually- lots of kids do meet these criteria!
IMPAACT 2013 Timeline

• Goal - complete enrollment by July 2017 (ok if sooner!)
• Cap 530 – hope to open in summer 2017
• Last day to enroll: October 14, prior to the start of RSV season
THANKS!!
Questions?