GSK’s Pediatric RSV vaccine program

FDA VRBPAC
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# Overview of GSK’s Pediatric RSV vaccine candidate

<table>
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<tr>
<th>Global intent</th>
<th>Active immunization of infants for the prevention of RSV LRTI</th>
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<td>Vaccination regimen</td>
<td>Two-dose regimen from 2 months onwards</td>
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<td>Adenovector coding for 3 antigens (F; N and M2.1)</td>
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<tr>
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<td>Phase I: completed</td>
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<td>Phase I/II: dose-escalation in seropositive infants ongoing</td>
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Key challenges linked to RSV pediatric vaccine development

- The early burden of disease requires vaccination early in life:
  - Immature immune system & presence of maternal antibodies
  - Crowded pediatric schedule:
    - Implementation hurdles
    - Possible interference with other pediatric vaccines

- History of enhanced disease after vaccination with FI-RSV impacts key elements of the program:
  1. Vaccine candidate selection
  2. Preclinical assessment
  3. Clinical development

FI-RSV: formalin inactivated RSV vaccine
Stages impacted by ERD:

1. Vaccine candidate selection
2. Preclinical assessment
3. Clinical development
GSK selected a Chimpanzee Adenovirus 155 (ChAd155-RSV) to mitigate the risk of ERD

- **ChAd155-RSV vaccine candidate:**
  - Codes for 3 RSV antigens: F, N, M2.1

- **Appropriate immune response induced by the adenovector:**
  - Intra-cellular expression of the RSV antigens, as with live RSV virus
  - Induction of a Th1 or balanced Th2/Th1 immune response

- **Control of viral replication by:**
  - Neutralizing antibodies (F antigen)
  - CD8 T cells to clear infected cells (F, N and M2.1 antigens)
Stages impacted by ERD:

1. Vaccine candidate selection
2. Preclinical assessment
3. Clinical development
GSK has generated a comprehensive data set in small and large animal species

- No single animal model can adequately predict the risk of vaccine-related ERD in humans
- Several models bring complementary information

### Mouse
- Induction of RSV-specific T cells
- Induction of functional antibodies
- Reduction of viral load in the lungs
- Th2/Th1 balance in lungs after challenge
- Lung histopathology/inflammation after challenge:
  - Goblet cells
  - Eosinophils

### Cotton Rat
- Induction of functional antibodies
- Reduction of viral load in the lungs
- Lung histopathology/inflammation after challenge:
  - Alveolitis

### Calf
- Induction of RSV-specific T cells
- Induction of functional antibodies
- Reduction of viral load in the lungs and nose
- Lung histopathology/inflammation after challenge:
  - Alveolitis
  - Lung consolidation

**Surrogate readouts of enhanced pathology**

**Clinical readouts**

Clinical manifestations of lower respiratory tract disease (LRTD)

GSK proprietary information
• Semi-permissive models requiring high challenge doses (10^5 - 10^6 pfu)
• No clinical signs of lower respiratory tract disease
• Commonly used for evaluation of ERD through surrogate markers

**Study design:**
• Vaccinated (2 doses) 3 - 4 weeks apart
• Homologous challenge with hRSV 14 – 21 days post last vaccine dose
• Groups evaluated:
  • GSK’s candidate vaccine (ChAd155-RSV)
  • FI-RSV
  • Live RSV
  • Placebo
In mice the ChAd155-RSV vaccine is immunogenic and fully protects from RSV challenge (Balb/c model)

**A.** ChAd155-RSV induces CD8 T-cells

M2.1 specific circulating CD8 T-cells

**B.** ChAd155-RSV induces neutralizing antibodies comparable to live RSV

**C.** ChAd155-RSV confers full protection post challenge

Lung viral load (4 days post challenge)

* LOD = 500 TCID50/g
In mice ChAd155-RSV does not induce signs of enhanced pathology post challenge in the lungs.

**A**
ChAd155-RSV induces CD4 Th1-bias*

**B**
ChAd155-RSV induces IFNγ⁺ CD8 T-cells

**C**
Levels of mucus producing cells and eosinophils are increased by FI-RSV but not by ChAd155-RSV

*Th2 marker: IL-13
*Th1 marker: IFNγ
In cotton rats the ChAd155-RSV vaccine protects from RSV challenge and does not cause alveolitis.

**A**

Dose-dependent reduction in viral load in cotton rat lungs after challenge (2 doses)

**B**

Alveolitis scores in animals vaccinated with ChAd155-RSV are significantly lower than in the FI-RSV group.
The calf model of RSV challenge

- Similarities in the epidemiology and pathogenesis of bovine RSV (bRSV) in calves and human RSV (hRSV) in infants
- High level of genetic and antigenic similarity between bRSV and hRSV
- Fully permissive to bRSV: only low challenge dose required
- A unique disease model to directly measure clinical signs of disease and does not depend on a surrogate marker for detection of enhanced disease

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Clinical manifestations of lower respiratory tract disease (LRTD)
Using the calf model to evaluate efficacy and enhanced disease

Study design:
- Vaccinated (2 doses) 4 weeks apart
- Heterologous challenge with bRSV 1 or 4 months post last vaccine dose
- Groups evaluated:
  - GSK’s candidate vaccine (ChAd155RSV)
  - Placebo

- Clinical signs
- Nasal swabs for viral load
- Broncho-alveolar lavage (BAL) for viral load, inflammation

Collect lungs for:
- Gross examination
- Histology (Inflammation)
In calves clinical signs of RSV disease are decreased in vaccinated animals.
In calves viral load is decreased in vaccinated animals.

**A. Broncho-alveolar lavage fluid**

Virus titration (infectious virus)

- Ctrl - 1 month
- ChAd155-RSV - 1 month
- Ctrl - 4 months
- ChAd155-RSV - 4 months

**B. Nasopharyngeal brush samples**

Virus titration (infectious virus)

- Ctrl - 1 month
- ChAd155-RSV - 1 month
- Ctrl - 4 months
- ChAd155-RSV - 4 months
In calves lung pathology is decreased in vaccinated animals

Consolidated lung area (macroscopic)

Other lung parameters (bronchitis, peribronchitis, interstitial pneumonia) show the same trend

Alveolitis (microscopic)

GSK proprietary information
In calves two doses of ChAd155-RSV induce RSV neutralizing antibodies.
GSK has generated a comprehensive data set in small and large animal species

- No single animal model can adequately predict the risk of vaccine-related ERD in humans
- Several models bring complementary information

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(eosinophils, goblet cells) (alveolitis)

NA: Not Applicable  ND: Not Determined
Stages impacted by ERD:

1. Vaccine candidate selection
2. Preclinical assessment
3. Clinical development
GSK’s clinical development plan

Sequential age de-escalation

- Increased confidence in the safety profile of the vaccine

**Extensive pre-clinical package**
- Phase I
  - 18-45 years Adults
- Phase I/II
  - >12 Mo S+ infants
  - 6Mo S- infants
  - 2Mo RSV naïve infants
- Phase III
  - 2Mo RSV naïve infants

All trials in infants are monitored by an IDMC

IDMC: Independent Data Monitoring Committee
Clinical development steps prior to RSV naïve infants

A comprehensive set of experiments in small and large animal species

Phase 1: adults → Phase 1/2: seropositive infants (>12Mo):
- Healthy adult population → infants screened for seropositivity
- Low risk of enhanced respiratory disease in the seropositive population
- Test the highest dose levels for safety and tolerability in adults and toddlers
- Immunogenicity not truly representative of the target population

IDMC/DSMB oversight as from the first trial in children
Further age de-escalation in RSV naïve infants

Age de-escalate in two stages in healthy full term RSV naïve infants:

• First in 6 months old infants, who are less vulnerable to severe RSV disease

• Then in 2 months old, the target population

Clinical studies will be conducted with maximum care:

• In settings with availability of advanced medical care

• Active surveillance for RSV infection and progression to disease in first study

• Document clinical parameters of RSV disease to detect pattern of increased severity

• 1:1 randomization ratio throughout the development

• 2 years follow up of all infants in Phase 2

• Use WHO case definition to compare disease incidence/group

• Measure the immune response

De-risking of ERD in RSV naïve infants prior to Ph III

GSK proprietary information
Conclusions and key messages

• GSK’s primary goal is to ensure the maximum safety of subjects at each step, and before moving into a Phase 3 study ➔ Patient safety first

• GSK development plan addresses the key challenges linked to prior history of ERD
  1. Vaccine candidate selection ➔ designed to elicit the appropriate immune response
  2. Preclinical assessment ➔ extensive data package in relevant animal models
  3. Clinical development ➔ careful age de-escalation; intensive disease monitoring

• The current preclinical data package shows no evidence of ERD following administration of the ChAd155-RSV vaccine

• The proposed stepwise age de-escalation will provide increasing confidence in the safety profile of the vaccine at each step

➔ Together, these data support the proposed approach to evaluate the ChAd155-RSV vaccine in RSV naïve children
Thank you