GSK’s RSV vaccine product development overview
Introduction

- GSK maternal and paediatric RSV programs are in early stage of development (Phase I/II)
- For both programs, GSK is targeting a global development
- Early input and continuous dialogue is needed to ensure that products under development will meet the expectations of regulators and vaccine recommending bodies
- In particular, guidance is needed on:
  - Endpoints to be used in Phase III studies
  - Case definition
    - Ready for use worldwide in different medical/socio-economical settings (HRC vs LRC)
    - Acceptable for regulators as licensure criteria
    - Acceptable for vaccine recommending bodies
    - Pre-defined and agreed upon before Phase III
  - Required duration of protection
Overview of Maternal RSV vaccine candidate

• **Global intent:**
  – Active immunization of pregnant women during the 3rd trimester of pregnancy to prevent RSV (subtypes A and B)-associated LRTI in infants

• **Development principles:**
  – Immunization in the third trimester, when the risk of major malformations has substantially decreased and placental transfer of maternal Ab is getting optimal
  – Administration of a single dose of vaccine to boost pre-existing immune response

• **Vaccine Composition:**
  – Recombinant subunit PreF antigen (Dosage TBD)
  – With or without Alum

• **Stage of development:**
  – Initiation Phase II in Q1 2015
Overview of maternal clinical development plans to licensure

- **Phase I**
  - 18-45 years
  - Adults
  - Safety
  - Immuno

- **Phase IIa**
  - Non-pregnant women
  - Formulation selection

- **Phase IIb**
  - Pregnant women
  - POC

- **Phase III**
  - Pregnant women
  - Efficacy

Draft outline subject to change post regulatory consultations
Overview of paediatric RSV vaccine pipeline

• **Global intent:**
  – Active immunization of infants for the prevention of RSV (subtypes A and B)-associated LRTI

• **Development principles:**
  – Immunization from 6 wks onwards
  – Two-dose regimen => to offer protection during a minimum of 1 year (first RSV season)
  – Flexible vaccination schedule to match existing diversity of paediatric immunization schedules
  – Co-administration with routine paediatric vaccines

• **Vaccine Composition:**
  – Adenovector encoding for 3 antigens (F, N and M2.1)

• **Stage of development:**
  – Initiation Phase I in Q2-Q3 2015
Overview of Paediatric clinical development plans to licensure

Phase I
18-45 years
Adults
Safety

Phase I/II
12-24 Mo
S+/S-Toddlers
Safety

Phase I/II
6-12 Mo
Infants
Formulation
pre-selection

Phase IIb
2-3 Mo
Infants
Formulation
Selection
POC

Phase III
2-3Mo
Infants
Efficacy

Draft outline subject to change post regulatory consultations
Summary of clinical studies to date to support each indication

- **Maternal: RSVF-001: Phase I study:**
  - All vaccine candidates were safe and well tolerated
  - All vaccine candidates were able to boost the pre-existing immune response as demonstrated by increased levels of neutralising antibodies, IgG and PCA

- **Pediatric: RSV-PED-001: Phase I study:**
  - Study start planned Q3 2015
Possible Primary Efficacy Endpoints

• Double-blind placebo controlled efficacy trial needed because no formal immunological correlate of protection is available

• Possible efficacy endpoints for Phase III:
  – Death: low incidence
  – URTI: does not address the major medical need
  – Hospitalization: high regional/socio-economical variability in hospitalization criteria
  – Severe LRTI including hospitalization
  – Medically attended LRTI (MA LRTI)

→ BUT since the burden of disease is different in very young infants vs infants beyond 6Mo of age the same vaccine efficacy endpoints might not fit both programs

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<thead>
<tr>
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<th>Severe LRTI</th>
<th>Severe LRTI</th>
<th>MA LRTI</th>
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<tbody>
<tr>
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<tr>
<td>VE</td>
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<tr>
<td>Sample size</td>
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<td>33340</td>
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<td>Incidence</td>
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<tr>
<td>VE</td>
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<tr>
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<tr>
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<tr>
<td>Incidence</td>
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<tr>
<td>VE</td>
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<td>Sample size</td>
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Alpha: 2.5% (95%CI); Power: 90%; LL: >20%
GSK’s effort towards a case definition and severity scale

- **Objective**: to validate and standardize case definitions for LRTI and severe LRTI that can be used worldwide and are acceptable by both regulators and recommending bodies.

- **GSK proposed case definitions are currently tested in a large epidemiological study (planned N = 2400) conducted in 9 different countries worldwide (HRC & LRC).**

<table>
<thead>
<tr>
<th>RTI</th>
<th>LRTI</th>
<th>Severe LRTI</th>
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<tbody>
<tr>
<td>Runny nose, OR Blocked nose, OR Cough</td>
<td>Child with RTI AND SaO2 &lt; 95%, OR RR increase:</td>
<td>Child with LRTI AND SaO2 &lt; 92%, OR Difficulty breathing leading to:</td>
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* Measured by oximeter.

RR = Respiratory Rate; SaO2 = Blood Oxygen Saturation; m = months; RTI = Respiratory Tract Infections; LRTI = Lower Respiratory Tract Infections.
To end...

Additional points for which guidance would be needed:

- Safety in pregnant women and access to background rates on pregnancy outcomes
- Definition of target population (e.g. age, complicated vs non complicated pregnancies)
- Immunological & RSV lab confirmation read-outs and standardization
- Preclinical model for ERD
- Duration of protection
- Routine pediatric immunizations: schedules, co-ad , ...

Key messages:

- GSK acknowledges that the development of a safe and efficacious vaccine against RSV is a public health priority worldwide
- The development of such vaccines is challenging
- No specific guidance exists on the development of RSV vaccines
- There is a need for early and regular interactions with WHO and regulators