VRBPAC – 17 May 2017

Development of a vaccine for prevention of Respiratory Syncytial Virus (RSV) disease in RSV - naïve infants

Janssen Vaccines & Prevention B.V.

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Janssen RSV junior Vaccine: Ad26.RSV.preF

**Vector**
- Replication-incompetent human type 26 adenovirus
- Produced on human PER.C6® cell line
- Elicits Th1 response
- Expected to be similar to natural infection and live attenuated vaccines which do not predispose to ERD in humans

**Antigen**
- RSV fusion protein from the RSV A2 strain
- Native F protein used in the prototype vaccine Ad26.RSV.FA2
- Optimised prefusion stabilised F protein used in the vaccine lead candidate Ad26.RSV.preF
- FA2 and preF protein sequences only differ by 5 amino acids

**Administration**
- Begin immunization at 2 month of age
- IM, 2 to 3-doses
- Co-administered with other childhood vaccines
Ad26 expressing PreF provides higher efficacy than Ad26 expressing wild-type RSV F in cotton rats challenged with RSV A2

- The majority of potent neutralizing antibodies are directed against preF-specific sites ¹, ²
- FI-RSV predominately displays post-F ³

Ad26.RSV.preF junior RSV vaccine
Non-clinical data package

Roland Zahn
Non-clinical plan to demonstrate that Ad26.RSV.preF is an effective vaccine that does not predispose to ERD

- **High Virus Neutralization titers and preF/postF binding Ab ratio**
- **Th1 biased cellular responses**

- **Cotton rats**
  - High Virus Neutralization and VNA/ELISA titer ratio
  - High level of lung protection and no ERD predisposition

- **Adult and neonatal mice**
  - High potency and Th1 biased cellular response in neonatal mice
  - Effective priming even in presence of passively transferred RSV F specific antibodies to mimic maternal antibody

- **Adult mice**

- Provides rationale to proceed into

  - RSV naive infants & toddlers
  - <6 month old infants
Ad26.RSV.preF vaccination elicits a Th1 biased response compared to Th2 biased FI-RSV response in neonatal mice

Similar Th1 bias observed in adult mice
Multiple factors contribute to FI-RSV vaccine induced ERD in cotton rats following RSV challenge

- High ratio of binding antibody to neutralizing RSV antibody titers
- Limited protection in the lung after RSV challenge
- Change of multiple histopathological parameters in the lung of infected animals:
  - Peribronchiolitis
  - Perivasculitis
  - Interstitial pneumonia
  - Alveolitis
Three control groups should be included in cotton rat studies to assess ERD predisposition after RSV challenge

- FI-RSV at a known dose to induce ERD after RSV challenge:
  Vaccine that predisposed to ERD in humans

- Intranasal pre-exposure with live RSV:
  Previous natural infection does not predispose to ERD in humans

- Buffer control:
  should mimic histopathology of natural RSV infection
Outcome of control groups lung histopathology scores in the cotton rats after RSV challenge

- Both buffer and live RSV pre-exposure controls have lower scores than FI-RSV positive control but can differ from each other
- Comparison of test vaccines to RSV pre-exposure, which is known to not predispose to ERD, is most appropriate

Note: Cumulative scoring is an unweighted composite of Alveolitis, Peribronchiolitis, Perivasculitis and Interstitial Pneumonia which are scored on a nonlinear 1-4 scale
Experimental conditions to assess vaccine-induced predisposition to ERD in Cotton Rats

- Key experiments should include:
  - Vaccine dose range to mimic waning immunity
  - RSV A and B challenge

- Detectable RSV lung replication in the presence of vaccine take may identify animals especially at risk to develop ERD

- Published data* suggests that detectable RSV lung replication is not absolutely required to induce histopathology indicative of ERD

*Murphy et al. Vaccine 1990, Schneider-Ohrum, JVI 2017
Ad26.RSV.preF vaccine evaluation in the RSV A2 challenge model in cotton rats

General study design:

Ad26.RSV.preF ➔ dose range $1 \times 10^5$ vp to $2 \times 10^{10}$ vp

10^5 pfu RSV A2 Challenge

Immunology

Pooling of 3 independent valid cotton rat studies

Provide an overview of Ad26.RSV.preF evaluation in RSV A2 challenge model
Ad26.RSV.preF induces high virus neutralization titers in conjunction with binding titers in contrast to FI-RSV

- Ad26.RSV.preF induces higher ratio of VNA/ELISA titer in contrast to FI-RSV
- The Ad26.RSV.preF induced VNA/ELISA titer ratio is not dose dependent
Ad26.RSV.preF vaccination provides protection of the lower respiratory tract against RSV A2 in contrast to FI-RSV.

**Nasal viral load**

**Lung viral load**

Pooled data from Study reports #DS-TEC-70156, DS-TEC-81837, DS-TEC-77115
Ad26.RSV.preF vaccination does not induce ERD in the RSV A2 cotton rat challenge model

**Peribronchiolitis**

**Perivasculitis**

**Interstitial pneumonia**

**Alveolitis**

Pooled data from Study reports #DS-TEC-70156, DS-TEC-81837, DS-TEC-77115
Ad26.RSV.preF vaccination does not induce ERD in a RSV A2 cotton rat challenge model

Note: Cumulative scoring is an unweighted composite of Alveolitis, Peribronchiolitis, Perivasculitis and Interstitial Pneumonia which are scored on a nonlinear 1-4 scale.
Nonclinical evaluation to demonstrate that Ad26.RSV.preF is an effective vaccine and does not predispose to ERD

**Adult mice**
- High Virus Neutralization titers and preF/postF binding Ab ratio
- Th1 biased cellular responses

**Cotton rats**
- High Virus Neutralization and VNA/ELISA titer ratio
- High level of lung protection and no ERD predisposition

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- High potency and Th1 biased cellular response in neonatal mice
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Clinical Development

Melanie Saville

Infectious Diseases and Vaccines
Clinical approach to develop a RSV vaccine for infants

Supportive preclinical data
- Favorable immunogenicity
- Lack of ERD predisposition
- Neonatal mouse model

Supportive platform data
- Safety
- Immunogenicity

Clinical development
- Safely progress into vulnerable target populations while ruling out ERD risk

High unmet need in 0-6M

Target Product Profile:
- Begin immunization at 2 month of age
- 2-3 doses co-administered with childhood vaccines
- Routine immunization (not seasonal)
Supportive safety data of Janssen AdVac platform based vaccines

- **Safety database with Ad26 vectors**
  - **10 completed studies** (Ebola, HIV, Malaria and RSV)
    - 584 adults immunized
    - 712 doses administered
    - $1 \times 10^9$ to $1 \times 10^{11}$ vp per dose
  - **14 ongoing studies (07APR17)** (Ebola, HIV and RSV)
    - > 3000 adults immunized
    - Healthy adults, HIV+ and older adults
    - $5 \times 10^{10}$ and $1 \times 10^{11}$ vp per dose

- **Safety database with related serotype (Ad35) in infants**
  - 349 infants received Ad35 vaccine (Tuberculosis program)
    - 192 as young as 4 months of age
    - 216 infants received a dose of $1 \times 10^{11}$ vp

- Both Ad26 and Ad35 vectors have a satisfactory safety profile
- Mostly mild to moderate AEs of early onset and short duration
Available human safety data with Ad26 based RSV vaccines

- Two phase 1 studies completed with prototype Ad26.RSV.FA2 vaccine in adults ¹, ²
  - 58 healthy adults (18-50 years)
  - 70 vaccine doses at $5 \times 10^{10}$ vp

- One phase 1 study ongoing with Ad26.RSV.preF in older adults ³
  - 48 older adult subjects (> 60 years)
  - 24 subjects immunized with $5 \times 10^{10}$ and 24 with $1 \times 10^{11}$ vp

- Ad26.RSV.FA2 and Ad26.RSV.preF vaccines were well-tolerated
- Mostly mild to moderate AEs of early onset and short duration
- No related SAE or AE leading to withdrawals

¹:NCT02561871, 2:NCT02440035, 3: NCT02916430
Immunogenicity of a single dose of Ad26.RSV.FA2 in healthy adults

- Single immunization in RSV pre-exposed adults boosts humoral and cellular immune responses and maintains the Th1 predominance
- Durable humoral and cellular immune responses
- Preliminary data (D29) with Ad26.RSV.preF in older adults show comparable or higher immune responses
Clinical Development Plan Key Objectives

Safely progress into vulnerable RSV-seronegative populations while ruling out ERD risk measured by frequency of severe RSV-LRTI

- Assessment of reactogenicity in adults and RSV-seropositive children
- Studies in RSV-seropositive children have limited value for ERD assessment
  - RSV-seropositive subjects are considered at minimal risk for ERD \(^1\)
  - Vaccine immunogenicity assessment biased by RSV pre-exposure
- Age de-escalation in seronegative populations from less to most vulnerable
  - 12-24M → 6-12M → 2-6M

1: Roberts et al. Vaccine 2016
Evaluation of ERD risk in pediatric studies of RSV seronegative infants and toddlers

- **Case definition**
  - ERD = Increased frequency of severe RSV-LRTI
    - Severe LRTI as per WHO definition
    - Cannot be distinguished clinically from severe RSV-LRTI
    - Laboratory confirmed by RT-PCR
    - Confirmed by an independent Clinical Endpoint Committee

- **Monitoring RSV infection**
  - Swabbing of RTIs with pre-defined symptoms during RSV season
  - Serological evaluation of infection rate

- **Assessment of vaccine immune profile**
  - VNA and ELISA titer ratio
  - Th1 and Th2 balance

- **Duration of follow-up**
  - All subjects will be followed over two RSV seasons
  - Age de-escalation after one RSV season follow-up
ERD monitoring in pediatric studies

- **Active and passive surveillance**
  - Regular phone calls to remind parents or guardians to report RTI during the RSV seasons
  - Sites to follow all RTIs until resolution
  - Routine surveillance of hospital and pediatric records

- **Confirmation of RSV severe-LRTI**
  - All severe LRTI swabbed for virological confirmation
  - Evaluation of any suspected case on an ongoing basis by a blinded Clinical Endpoint Committee (CEC)

- **ERD risk monitored per and across studies by the IDMC using a statistical algorithm to advise the Sponsor on further study conduct**

- **Actions in case of ERD signal**
  - Immediate communication to sites, RA and EC
  - Pause vaccination
  - Increased surveillance
Approach to age de-escalation into RSV seronegative infants

Phase 1/2a in 12-24M
Adults ➞ RSV seropositive ➞ RSV seronegative
Safety, reactogenicity and immunogenicity (including Th1/Th2)

Phase 1/2a in 6-12M
Safety, reactogenicity and immunogenicity (including Th1/Th2)

Phase 1/2b in 2-6M
Co-administration with childhood vaccines
Safety, reactogenicity, immunogenicity (including Th1/Th2) and PoC

Phase 3 efficacy, 2M+
Phase 1/2a in 12-24M toddlers
72 toddlers in total, 40 receiving vaccines (24 seronegatives)

**Immunogenicity and safety data of Ad26.RSV.preF in older adults**

**Adults 18-50 years (n=12)**

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<tr>
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<tr>
<td>Group 1</td>
<td>8</td>
<td>Ad26 (1 \times 10^{11}) vp</td>
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<td>Group 2</td>
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7-day post-dose 1 safety (PI/SRP assessment)

12 to 24M RSV seropositive (n=24)

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<tr>
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3 sentinels

**IDMC review: 7-day post-dose 1 safety in subset**

12 to 24M RSV seronegative (n=48)

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4 sentinels

**IDMC review: 7-day post-dose 1 safety in subset**
Phase 1/2a in 12-24M toddlers

- **Primary objectives:**
  - General safety and tolerability

- **Secondary objectives:**
  - Immunogenicity (including Th1/Th2 balance, ELISA titer and VNT)
  - Monitoring of severe RSV-LRTI

- **Sample size:**
  - Descriptive study
  - Preliminary ERD risk assessment in small number of RSV seronegative 12-24 month old through two RSV seasons
  - With 24 subjects per arm, ability to detect a risk of ERD similar to the one observed with the FI RSV vaccine assuming an RSV infection rate ≥ 30%
Phase 1/2a in 6-12M RSV seronegative infant
108 subjects in total, 72 receiving vaccines

Data available from RSV2001 in 12-24M:
- General safety and reactogenicity
- Immunogenicity
- Follow-up for RSV infection for 1 season

6 to 12M RSV seronegative (n=36)
Dose: $5 \times 10^{10}$ vp

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3 sentinels
IDMC review: 7-day safety post-dose 1 in all subjects

6 to 12M RSV seronegative (n=72)
Dose: $1 \times 10^{11}$ vp

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<th>Day 29</th>
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<td>Group 3</td>
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3 sentinels
IDMC review: 7-day safety post-dose 1 in subset
Phase 1/2a in 6-12M RSV seronegatives infants

- **Primary objectives:**
  - General safety and tolerability
  - Monitoring of severe RSV-LRTI

- **Secondary objectives:**
  - Immunogenicity (including Th1/Th2 balance, ELISA titer and VNT)

- **Sample size:**
  - To show the severe RSV-LRTI rate is not increased in vaccine groups compared to placebo groups
  - Assumptions:
    - expected background incidence of RSV-severe disease of 1%
    - 15% drop-out
    - Non-inferiority test with one sided alpha = 5%
    - Expected RSV incidence in placebo groups between 20-40%
  - A sample size of 108 subjects (pooling both cohorts) gives >90% power to demonstrate non-inferiority in the difference in proportions with a non-inferiority margin of 10%
Initiating studies in 2 month old infants

- Data requirements prior to initiation:
  - Safety data in 12-24M and 6-12M
  - Immunogenicity assessment in 12-24M and 6-12M
  - Follow-up for RSV infection for 2 seasons in 12-24M
  - Follow-up for RSV infection for 1 season in 6-12M
  - Additional preclinical data assessing impact of passively transferred RSV specific Ab

- Following thorough review of all available data, a dose finding, regimen selection and proof of concept study will be initiated in 2 month old infants
Conclusions

- Preclinical assessment of ERD in the cotton rat model should be sufficient to initiate clinical studies:
  - Enough animals can be tested over a wide range of vaccine induced immune responses.
  - Comparisons to immunization regimens that do not predispose to ERD such as live RSV pre-exposure and that do predispose to ERD such as FI-RSV
  - Use of cumulative histopathology scores can compare vaccines to controls.

- Histopathological scoring in cotton rats immunized with Ad26.RSV.preF was similar to live RSV pre-exposure and lower than FI-RSV following RSV challenge

- Preclinical data are supportive, but cannot provide evidence of complete absence of ERD predisposition

- Vaccine associated ERD risk needs eventually to be ruled out via a cautious clinical development