Janssen Ebola Vaccine
Emergency Track Program

Review of ebola vaccines in phase 1 clinical evaluation

WHO Meeting, January 8, 2015

Infectious Diseases and Vaccines

Johan Van Hoof, M.D.
Janssen R&D

Melinda, Goddess of Healing
Melinda’s artwork reflects her journey living with HIV.
Agenda

• Janssen Ebola Vaccine Regimen
  • Key attributes
  • Supply situation

• Clinical Development Plan

• Summary
Janssen/BN Filovirus vaccine

Proof of concept in highly stringent NHP model

- Multivalent vaccine developed with funding from DMID
- Heterologous prime boost schedule 0 - 2 months

<table>
<thead>
<tr>
<th>PRIME</th>
<th>BOOST</th>
<th>Original FIH Timelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26.ZEBOV</td>
<td>Ad35.ZEBOV</td>
<td>Q3 2016</td>
</tr>
<tr>
<td>Ad26.SUDV</td>
<td>Ad35.SUDV</td>
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<tr>
<td>Ad26.MARVA</td>
<td>Ad35.MARVA</td>
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</tr>
<tr>
<td>Ad26.ZEBOV</td>
<td>MVA-BN-Filo</td>
<td>Q1 2016</td>
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100% Protection After Vaccination In NHP Using Stringent Ebola Challenge Model

- Ad26/MVA-BN, MVA-BN/Ad26,
  Ad26/Ad35: 100% survival, no symptoms after challenge

MVA-BN-Filo: one single vector expressing 4 filovirus antigens (Ebola, Sudan and Marburg GP and Tai Forest NP)
A prophylactic Ebola Zaire vaccine leveraging on two existing platforms

AdVac® vector

Synthesized gene encoding Filo virus glycoproteins

Ad26.ZEBOV Vaccine

Production on complementing PER.C6® cells

Ad26.ZEBOV (prime)

Vaccine

Ad26.filo and MVA-BN-Filo deliver the Ebola GP transgenes inside human cells that then produce Ebola GP which elicits an Immune response

MVA-BN® vector

MVA-BN-Filo

Production on permissive primary Chicken Embryo Fibroblasts

MVA-BN-Filo (Boost)
Ad26.ZEBOV – technical characteristics

Manufacturability

• Established high yield process (PER.C6®-based)
• >400,000 doses (bulk) produced and released to date
• Final product available to date is 20,000 doses; remaining to be released March (250,000) through May (total of 400,000)
• Capacity for 2015 up to 5 million, if needs are confirmed

Stability Final Product

• Based on experience with Ad26 containing other inserts:
  • ≥ 3 years expected at -65°C
  • 2-8°C > 12 months
• Ad26.ZEBOV:
  • As of Q1 2015, minimally 3 months at 2-8°C
  • Later on in 2015: 6 months – 1 year at 2-8°C
  • Long-term perspective (>2016): Minimal 2 years stability at 2-8°C
Ad26.ZEBOV – clinical characteristics

- Ad26 & Ad35 based vaccines (with other inserts)
  - HIV (Ad26, N=230)
  - TB and malaria (Ad35; N≥700; incl. children age 4-9 months)
  - Optimal Ad26 immunogenicity profile found at 5x10^{10}
  - Tolerability profile is driven by vector dose; similar, independent of inserts
- Phase I, Ad26.ZEBOV/MVA-BN-Filo FIH study ongoing at Oxford:
  - Four sentinel subjects dosed; no AEs reported to date
Ad26.ENVA.01 prototype HIV vaccine candidate was safe and immunogenic at all doses tested.

- Ad26.ENVA.001 elicited HIV env-specific antibodies in 100% of volunteers within two weeks after priming.
- Cell-mediated immunity peaked between days 28-56 and was stable for at least 6 months.

MVA-BN-Filo - vaccine characteristics

Manufacturability
• Leverage established smallpox vaccine process (≈30M doses produced)
• Bulk available to date > 400 K, release pending
• Final product to be released March (250 K) through May (total of 400K)
• 700 doses available for use in phase I
• Capacity for 2015: up to 5 million, if needs are confirmed

Clinical Safety:
• Backbone licensed as smallpox vaccine in EU and Canada
  • In addition U.S. Strategic National Stockpile
• Acceptable safety profile in >7500 subjects immunized at clinical dose including HIV patients and children (age 0.5 – 6 years)

Stability Final Product
• ≥ 3 years expected at -65°C (current available MVA-BN-Filo GMP DP batch)
• ≥ 2 years expected at -20°C (based on MVA-BN with other inserts)
• > 3 months at 2-8°C after Q1 2015
• Mid-term up to 1 year
• Long-term perspective (>2016): Minimal 2 years stability at 2-8°C
High level clinical strategy (1/2)

• Partners for clinical development are:
  • Oxford University, UK (phase I and II)
  • National Institutes of Health (Phase I)
  • London School of Hygiene and Tropical Medicine, UK (phase I and III)
  • INSERM, France (phase II)
**High level clinical strategy (2/2)**

- **Phase I studies in UK and US**
  - Establish preliminary safety and immunogenicity
  - Identify optimal short schedule* (2 week to 2 month intervals)
  - One year follow up:
    - Investigate durability of immune responses
    - Late boost possibilities

- **Phase I studies in UG, KE, TZ**
  - Repeat of UK study
  - To be initiated based on preliminary EU/US safety data
  - Confirm preliminary safety and immunogenicity

- **Phase II studies (EU/Africa)**

  - **Collaborative Study** with GSK to assess possibility of using various combinations of Ebola vectors as prime and boost. (design under discussion)

  - **Efficacy study under discussion** (with a lead in safety/immuno study, RCT)
# Overall Phase I studies

- Establish safety and immunogenicity of various prime boost schedules

## Phase I studies, healthy adults

<table>
<thead>
<tr>
<th>Study</th>
<th>Total N</th>
<th>N of subjects with candidate vaccines</th>
<th>Safety</th>
<th>Immuno</th>
</tr>
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<tbody>
<tr>
<td>-1001</td>
<td>72</td>
<td>60</td>
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</tr>
<tr>
<td>-1002</td>
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<td>78</td>
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<td>-1004</td>
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<tr>
<td>Total</td>
<td>308</td>
<td>258</td>
<td>258</td>
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</tr>
</tbody>
</table>
**Phase II studies, N > 2000 (under discussion)**

- Enter Ph II based on Phase I post prime data
  - Focus on single regimen that is ‘outbreak responsive’
  - Africa: expanded safety + immuno of selected regimen; n=1200
  - EU: expanded safety + immuno of selected regimen; n=600
  - Timing: April 2015

- Special populations to be evaluated:
  - Children, aged 1 to 17 years
  - Elderly/older adults (50-70 years)
  - HIV+ adults
  - Western-based HCW, planning to work in the affected areas

- Countries under consideration:
  - FR, UK, US, Ghana, Côte d’Ivoire, Burkina Faso
- Study designs and populations to be agreed upon with Health Authorities
How to assess efficacy?

- We continue to look for opportunities to join any of the planned efficacy trials, especially if the ramp up of these is protracted
- London School of Hygiene and Tropical Medicine is our partner for efficacy testing of our vaccine candidate
- Potential for demonstrating efficacy is situation dependent:
  - Status of epidemic by time of study start
  - If not possible: consider potential for immune bridging, or application of animal rule?
# Janssen Ebola Vaccine – Preliminary Timeline

<table>
<thead>
<tr>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Q2</td>
</tr>
</tbody>
</table>

### Phase I (N=258)
- Adults 18-50
- UK, US, TZ, KE, UG

### Phase II EU
- **Prime**
  - N=600 Adults
- **Boost**

### Phase II Afr
- **Prime**
  - N=1200 (incl children)**
- **Boost**

### Sierra Leone
- (draft proposal, under discussion)
- **Phase IIIa – Lead in:**
  - Safety and immunogenicity in adults/children
  - Population TBD, N = 1000 adults, 200 children

### Phase IIIb – large scale:
- Methodology, TBD, options:
  - RCT
  - Wedge approach:
    - Stepwise by region/district

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Avail. of post prime data S/I

Full Regimen Safety and Immuno available

[Diagram of timeline and studies]
Janssen Ebola Vaccine - Executive Summary

- High yield manufacturing platforms (Ad26-PerC6 // MVA)
  - 450 K regimens to be released starting end March 2015
  - Production capacity 2015 up to 5 million doses (if needed).

- \( \geq 1 \) year thermostability for backbone vectors
  - Anticipated 3 months at 2 – 8 °C by start of use
  - At country level: central storage frozen (-20°C) - Distribution through normal ‘vaccine supply chain’ channels (2 - 8°C)

- Substantial human experience with both vectors
  - Ad26 post dose 1 (HIV) : robust humoral and CD8+ T cell responses

- Conduct a lead in safety (and immuno study) in Sierra Leone, prior to large scale (efficacy) trial, based on post dose 1 safety/immunogenicity in phase 1.
Thank you
Agenda

- Janssen Ebola Vaccine Regimen
  - key attributes
  - Supply situation
- Phase I clinical plan
- Phase II clinical plan
- Large scale efficacy trial
## EBL1001: FIH- UK

**Phase I study N=72, healthy adults**

<table>
<thead>
<tr>
<th>Group</th>
<th>Prime</th>
<th>Boost</th>
<th>Schedule</th>
<th>Number (active/placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MVA 1x10⁸ TCID50</td>
<td>Ad26 5x10¹⁰ vp</td>
<td>0, 28</td>
<td>15/3</td>
</tr>
<tr>
<td>2</td>
<td>MVA 1x10⁸ TCID50</td>
<td>Ad26 5x10¹⁰ vp</td>
<td>0, 56</td>
<td>15/3</td>
</tr>
<tr>
<td>3</td>
<td>Ad26 5x10¹⁰ vp</td>
<td>MVA 1x10⁸ TCID50</td>
<td>0, 28</td>
<td>15/3</td>
</tr>
<tr>
<td>4</td>
<td>Ad26 5x10¹⁰ vp</td>
<td>MVA 1x10⁸ TCID50</td>
<td>0, 56</td>
<td>15/3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Sentinel Cohort</th>
<th>Cohort 1 a)</th>
<th>Cohort 2 b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1/1 (active /placebo)</td>
<td>4/1 (active /placebo)</td>
<td>10/1 (active /placebo)</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>5/1 (active/placebo)</td>
<td>10/2 (active /placebo)</td>
</tr>
<tr>
<td>3</td>
<td>1/1 (active/placebo)</td>
<td>4/1 (active /placebo)</td>
<td>10/1 (active /placebo)</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>5/1 (active/placebo)</td>
<td>10/2 (active /placebo)</td>
</tr>
</tbody>
</table>

a) Cohort 1 will be enrolled after at least 24 hours after the prime vaccination in the Sentinel Cohorts.
b) Cohort 2 will be enrolled after at least 24 hours after the prime vaccination in the last subject in Cohort 1.
**EBL1002: Phase I study in US**

<table>
<thead>
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<th>Schedule</th>
<th>Number (active/placebo)</th>
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<tbody>
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<td>MVA $1 \times 10^8$ TCID50</td>
<td>Ad26 $5 \times 10^{10}$ vp</td>
<td>0, 14</td>
<td>15/3</td>
</tr>
<tr>
<td>2</td>
<td>MVA $1 \times 10^8$ TCID50</td>
<td>Ad26 $5 \times 10^{10}$ vp</td>
<td>0, 28</td>
<td>15/3</td>
</tr>
<tr>
<td>3</td>
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<td>0, 28</td>
<td>15/3</td>
</tr>
<tr>
<td>5</td>
<td>MVA $1 \times 10^8$ TCID50</td>
<td>MVA $1 \times 10^8$ TCID50</td>
<td>0, 14</td>
<td>3 (sentinel)</td>
</tr>
<tr>
<td></td>
<td>MVA $1 \times 10^8$ TCID50</td>
<td>MVA $1 \times 10^8$ TCID50</td>
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<tr>
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<td>Placebo</td>
<td>Placebo</td>
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</tr>
<tr>
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<td>Ad26 $5 \times 10^{10}$ vp</td>
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</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
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</tbody>
</table>
Study-1003: Kenya

Objectives:
- Primary: safety, tolerability
- Secondary: immunogenicity
  - ELISA
  - VNA
  - ELISpot
- Site: KAVI, Kilifi

Timing:
- Protocol finalized: Dec 18
- Submissions (EC/HA): Jan 6
- Approval: TBD (expedited)

Phase I study N=72, healthy adults

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Study-1004: Uganda/Tanzania

Objectives:
• Primary: safety, tolerability
• Secondary: immunogenicity
  • ELISA
  • VNA
  • ELISpot
• Sites: MRC/UVRI, MITU

Timing:
• Protocol finalized: Dec 18
• Submissions (EC/HA): Jan 6
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Phase I study N=72, healthy adults

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Emergency Track Program

Plans for extending safety database beyond phase 1

WHO Meeting, January 8, 2015

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Melinda, Goddess of Healing
Melinda’s artwork reflects her journey living with HIV.
Phase II studies (under discussion)

- Enter Ph II based on Phase I post prime data
  - Focus on single regimen that is ‘outbreak responsive’
  - Africa: expanded safety + immuno of selected regimen; n=1200
  - EU: expanded safety + immuno of selected regimen; n=600
  - Timing: April 2015

- Special populations to be evaluated:
  - Children, aged 1 to 17 years
  - Elderly/older adults (50-70 years)
  - HIV+ adults
  - Western-based HCW, planning to work in the affected areas

- Countries under consideration:
  - FR, UK, US, Ghana, Côte d’Ivoire, Burkina Faso
- Study designs and populations to be agreed upon with Health Authorities
Phase II preliminary design: Africa

- Multicenter, randomized, double blind placebo-controlled study
- Objectives: safety, immunogenicity, regimen finding
- Endpoints: adverse events, humoral (all) and cellular (subset) responses
- Population: healthy adults, HIV+ (200), elderly (200)

<table>
<thead>
<tr>
<th>Group</th>
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<th>Boost</th>
<th>Schedules</th>
<th>Number</th>
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<tbody>
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<td>MVA $1 \times 10^{8} \text{ TCID}50$</td>
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<td>2*</td>
<td>control</td>
<td>control</td>
<td>0, 28; 0,56</td>
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</tbody>
</table>

* Control will be licensed vaccine; 25 HIV+/25 elderly controls
Phase II preliminary design: children

- Multicenter, randomized, double blind, controlled study
- Objectives: safety, immunogenicity
- Single regimen (evaluated in adults in ph III)
- Endpoints: adverse events, humoral (all) and cellular (subset) responses
- Population: children: 13-17yrs, 6-12 yrs, 1-5yrs

### Phase II healthy children

<table>
<thead>
<tr>
<th>Group</th>
<th>Prime</th>
<th>Boost</th>
<th>Schedule*</th>
<th>Number Active/control*</th>
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<tbody>
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<td>1 (13-17)</td>
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<td>MVA $1 \times 10^8$ TCID50</td>
<td>0, 28; 0,56</td>
<td>56/14</td>
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<td>2 (6-12)</td>
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<td>56/14</td>
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<tr>
<td>Total</td>
<td></td>
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<td>210</td>
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</tbody>
</table>

* Control vaccine TBD
Phase II preliminary design: EU

- Multicenter, randomized, double blind placebo-controlled study
- Objectives: safety, immunogenicity
- Endpoints: adverse events, humoral (all) and cellular (subset) responses
- Population:
  - healthy adults and elderly [ ~50 HIV+]
- Health care workers, planning to travel to the affected areas will be eligible

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</thead>
<tbody>
<tr>
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<td>MVA 1x10^8 TCID50</td>
<td>0, 56; 0,28</td>
<td>500</td>
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<tr>
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<td>placebo</td>
<td>placebo</td>
<td>0, 56; 0,28</td>
<td>100</td>
</tr>
</tbody>
</table>
Phase II in western based HCW - preliminary design:

- **Population**: Health care workers, planning to travel to the affected areas (under discussion) N = > several hundreds

- **Methodology**: open / controlled – TBD

- **Objectives**: safety, immunogenicity, with long term follow up

- **Endpoints**: adverse events, humoral responses (all), cellular responses (subset)
Thank you