DEVELOPMENT OF AN EBOLA VACCINE IN THE MIDST OF AN UNPRECEDENTED EPIDEMIC

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Merck, Sharp & Dohme
Presentation Outline

• Vaccine Development for Emerging Infectious Diseases
• Rapid Response to the Ebola Crisis:
  – Background on Ebola Virus Disease
  – MSD’s Ebola Vaccine
• Summary
• Q&A
Emerging Infectious Diseases

Infections that have recently appeared within a population or those whose incidence or geographic range is rapidly increasing or threatens to increase in the near future.
Emerging Infectious Diseases: Contributing Factors

- Exotic pets
- Climate change influencing arthropods
- Translocation of infected animals or persons
- Exotic foods (bush meat)
- Infection of humans or animals
- Companion animals
- Tourism
- Alteration in livestock management practices
- Changes in land use
- Acquisition of new virulence traits
- Pathogen adaptation to new host species
Vaccine development takes many years and requires significant investment in clinical development and manufacturing capabilities.

**Challenge:** How can this process be accelerated to develop **safe** and **effective** vaccines to combat emerging infectious diseases?

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†Figure adapted from Waye A, Jacobs P, Schryvers AB. Vaccine development costs: a review. *Expert Rev Vaccines.* 2013;12(12):1495-1501.
Requirements for Vaccine Licensure

Typical requirements include:
- Demonstration of preclinical and clinical safety
- Evaluation of product quality and manufacturing consistency
- Demonstration of \textit{clinical benefit}

\textbf{Challenge:} Difficult to demonstrate vaccine efficacy during rapid disease outbreaks
Regulatory Pathways in US and Europe

Food and Drug Administration (FDA)

- *Traditional approval pathway*: Direct demonstration of efficacy/effectiveness
- *Accelerated approval pathway*: Bridging human immune responses to immune responses demonstrated to be protective in animals, with effectiveness demonstrated postlicensure
- *Animal rule*: When it is not feasible to establish an immunologic bridge between animals and humans or practically or ethically possible to directly demonstrate clinical benefit in human subjects

European Medicines Agency (EMA)

- *Full Marketing Authorisation (MA)*: Full data package available to support licensure
- *Conditional MA*: Products without comprehensive data for life-threatening diseases, where benefit outweighs risks and full data package can eventually be provided
- *Exceptional MA*: When it is not feasible to obtain full data package (eg, indications encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence)
Regulatory Designations to Expedite Development

- Enhanced support for the development of medicines that target an unmet medical need for life-threatening diseases with major public health interest
- Enable formal and consistent dialog/interactions with regulators on product development and aligning on processes/timelines prior to filing
- Granted based on evidence that the candidate demonstrates potential to address unmet medical need
  - Breakthrough Therapy designation requires preliminary clinical evidence
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Background on Ebola Virus

- First discovered in 1976; named after the Ebola River in the Democratic Republic of the Congo (DRC)
- 27 outbreaks before 2014, initiating in 4 African countries
  - DRC, South Sudan, Uganda, and Gabon
- Animal-borne, with bats being the most likely reservoir
  - 5 species of Ebola virus (Zaire ebolavirus, Sudan ebolavirus, Taï Forest ebolavirus, Bundibugyo ebolavirus, Reston ebolavirus)
- 4 species cause disease in humans
Transmission of Ebola Virus

- Zoonotic virus – bats the most likely reservoir, although species unknown
- Spillover event from infected wild animals (e.g., fruit bats, monkey, duiker) to humans, followed by human-human transmission

Ebola Virus Disease: Clinical Features

- Acute onset is typically 8–10 days after exposure (range 2–21 days)
- Nonspecific early clinical signs and symptoms
  - Initial: Fever, chills, myalgia, malaise, anorexia
  - After 5 days, GI symptoms: Nausea, vomiting, watery diarrhea, abdominal pain
  - Hemorrhagic symptoms in 18% of cases
  - Other possible infectious conditions: Malaria, typhoid fever, Lassa fever, cholera, and other bacterial infections, all of which are common in Ebola-affected countries
- Symptoms progress to:
  - Hemorrhagic disease
  - Hypovolemic shock, multi-organ failure
  - Death (case fatality rate 40-90%)

www.cdc.gov/
Evolving Epidemiological Data

- Patients who survive often have signs of clinical improvement by the second week of illness
- Associated with the development of virus-specific antibodies
- Antibody with neutralizing activity against Ebola persists greater than 12 years after infection
- Prolonged convalescence
  - Includes arthralgia, myalgia, abdominal pain, extreme fatigue, and anorexia; many symptoms resolve by 21 months
- Significant arthralgia and myalgia may persist for >21 months
- Skin sloughing and hair loss has also been reported
- Ebola virus persistence
  - Ebola virus remains in certain body fluids even after recovery, including semen, ocular fluid in the eye, breast milk, and cerebrospinal fluid

Filovirus Outbreaks

- Ebola and Marburg outbreaks have historically been small and infrequent.
- Prior to the 2014-16 Zaire outbreak, there are only a handful of countries where these filoviruses have emerged with little overlap in countries.

### Filovirus Outbreaks

<table>
<thead>
<tr>
<th>Ebola Type</th>
<th>Year Identified</th>
<th># of Epidemics</th>
<th># of Isolated Cases (1-4)**</th>
<th>Total Cases</th>
<th>Total Deaths</th>
<th># Countries Affected*</th>
<th>Countries Listed*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marburg</td>
<td>1967</td>
<td>4</td>
<td>8</td>
<td>466</td>
<td>373</td>
<td>3</td>
<td>DRC, Angola, Uganda, Germany</td>
</tr>
<tr>
<td>Sudan Ebola</td>
<td>1976</td>
<td>6</td>
<td>2</td>
<td>779</td>
<td>412</td>
<td>2</td>
<td>South Sudan, Uganda</td>
</tr>
<tr>
<td>Zaire Ebola</td>
<td>1976</td>
<td>13</td>
<td>4</td>
<td>1,456</td>
<td>1,148</td>
<td>3</td>
<td>Rep of Congo, DRC, Gabon</td>
</tr>
</tbody>
</table>

Adapted from [http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.htm](http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.htm)

* Countries with infected laboratory workers or isolated travelers with less than 1 death were not included (noted instead as isolated cases)
δ Epidemic is defined above as >4 cases and/or >1 death.
** Incidents that resulted in 1 or no deaths
Ebola Virus Outbreak 2014-2016

The 2014-16 Zaire Ebola outbreak was vastly unique in its size and geographic reach. Zaire Ebola virus was new to the Mano River region and Nigeria in 2014 when the outbreak started.

- First case identified in Guinea March 2014
- WHO Declared a Public Health Emergency of International Concern (PHEIC) in Aug 2014 which was declared ended on March 29th 2016

<table>
<thead>
<tr>
<th>Year Identified</th>
<th># of Epidemicsδ,*</th>
<th># of Isolated Cases (1-4)**</th>
<th>Total Cases</th>
<th>Total Deaths</th>
<th># Countries Affected*</th>
<th>Countries Listed *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaire Ebola</td>
<td>1976</td>
<td>13</td>
<td>4</td>
<td>1,456</td>
<td>3</td>
<td>Rep of Congo, DRC, Gabon</td>
</tr>
<tr>
<td>2014-16 Zaire Outbreak</td>
<td></td>
<td></td>
<td>&gt;28,600</td>
<td>&gt;11,300</td>
<td>5</td>
<td>Guinea, Liberia, Sierra Leone, Mali, Nigeria</td>
</tr>
</tbody>
</table>

Adapted from http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.htm

* Countries with infected laboratory workers or isolated travelers with less than 1 death were not included (noted instead as isolated cases)
δ Epidemic is defined above as >4 cases and/or >1 death.
** Incidents that resulted in 1 or no deaths
Outbreak 2014-2016: Impact in Guinea, Sierra Leone and Liberia

From a single case identified in Guinea in March 2014, all prefectures within Sierra Leone and Liberia and 70% of prefectures in Guinea were touched by Ebola.

WHO Ebola situation report
http://apps.who.int/ebola/current-situation/ebola-situation-report-6-january-2016
Outbreak 2014-2016: Spread to 10 countries

- Extensive spread of Ebola Zaire was efficiently and successfully managed in 7 of the 10 affected countries.
- Following flare-ups in 2016, Guinea and Liberia declared Ebola free on June 1st and 9th respectively.

* WHO Ebola situation report; data up to 30December 2015
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MSD’s Engagement in Zaire Ebola Vaccine R&D

- In November 2014, MSD and NewLink Genetics Corp. entered into an exclusive worldwide license agreement wherein MSD assumed responsibility to research, develop, manufacture, and distribute the investigational Ebola vaccine candidate (rVSVΔG-ZEBOV-GP, referred to as V920)
- MSD, NewLink Genetics, and a global network of partners are collaborating in unprecedented ways with the singular focus of speeding the research, development, and deployment of a well tolerated and effective Ebola vaccine
- The efforts of all of our partners in the midst of the largest Ebola epidemic in history highlight what we, as a public health community, can accomplish if we work together
Extensive Partnerships and Alliances Enabled V920 development

Phase I Studies
N=8

- WHO Clinical Consortium/Wellcome Trust
- Switzerland: University Hospitals of Geneva
- Germany: University Medical Center Hamburg/Clinical Trial Center North
- Gabon: Centre de Recherches Medicales de Lambarene/University of Tuebingen
- Kenya: Kenya Medical Research Institute Marburg Laboratory
  - CCV – Halifax, Canada
  - US Department of Defense (WRAIR, JVAP, USAMRIID, DTRA)
  - NIAID/NIH
  - NewLink Genetics

Funding & support from BARDA

Phase II/III Studies
N=5

- Liberia (PREVAIL): Liberia – NIH Partnership (NIAID)
- Sierra Leone (STRIVE): CDC/Sierra Leone Medical School/BARDA
- Guinea (Ebola ça suffit and Front-Line Workers): WHO/Norwegian Institute of Public Health/MSF/HealthCanada
- US/Canada/Spain (V920-012): MSD/BARDA

Additional Funding & Support:
- US Department of Health and Human Services (BARDA)
- US Department of Defense (DTRA, JVAP)
V920: rVSVΔG-ZEBOV-GP Vaccine

V920 is a recombinant, replication-competent, vesicular stomatitis virus (VSV)-vectored-vaccine containing the glycoprotein of Zaire Ebola virus.

The Zaire Ebola virus (ZEBOV) glycoprotein (GP) antigen is displayed in native conformation on the surface of VSV.
Strong Preclinical Data Positioned V920 as a Candidate for Development

- Studies of rVSVΔG-ZEBOV-GP demonstrated 100% protection against ZEBOV challenge (intramuscular, high-dose/high-virulence strain) in cynomolgus macaques following a single immunization\(^1\)
- Complete and partial protection was achieved in nonhuman primates (NHPs) with a single dose given as late as 7 and 3 days before challenge, respectively\(^2\)
- rVSVΔG-ZEBOV-GP protects immunodeficient (SHIV-infected) NHPs\(^3\)
- rVSVΔG-ZEBOV-GP lacks neurovirulent properties in NHPs\(^4\)
- rVSV vaccines are well tolerated in NHPs\(^5\)

References:
Vaccine-Induced Protection by rVSVΔG-ZEBOV-GP Appears to be Primarily Antibody Mediated

• IgG antibody levels correspond to survival in mouse and guinea pig challenges\(^1\)
• Cell-mediated immunity does not appear to be critical for protection\(^2\)
  • CD8+ T cell depletion of non-human primates at vaccination has no impact on survival
  • CD4+ T cell depletion at time of vaccination reduces survival, while depletion at time of challenge does not
• Additional studies in NHPs are ongoing/planned to try and identify an immunological correlate of protection

References:
V920 Preclinical Efficacy Study Design

Immunogenicity and efficacy study in cynomolgus macaques

<table>
<thead>
<tr>
<th>Group</th>
<th># of Animals</th>
<th>Vaccine Dose (plaque-forming units, pfu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>3x10^6</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>2x10^7</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>1x10^8</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

- Single dose of vaccine administered at Day 0
- IM challenge day 42 with Ebola virus Zaire Kikwit 7U, target dose of 1,000 pfu
- Blood collections for immunogenicity assessment on study days 0, 7, 28, and 35
- Immunogenicity assessments include GP-ELISA and PsVNA50

Study conducted by United States Army Medical Research Institute for Infectious Diseases (USAMRIID), Fort Detrick, Maryland, USA.
V920 Protects Cynomolgus Macaques

Day 28 postdose IgG GP-ELISA titers (units/mL)

Blue symbols represent animals that survived
Pink symbols represent animals that succumbed to challenge

All animals that received V920 dose of 2x10^7 pfu or higher survived, while 7/8 animals that received 3x10^6 pfu survived
Nonclinical Evaluation in Public Health Emergencies†

- The nonclinical package to support initiation of early-phase clinical trials can use supportive information derived from vaccine platform
- Omission of toxicity studies may be possible if there is adequate platform toxicology data and clinical safety experience
- For the viral vectored vaccines evaluated during the 2014-2016 Ebola epidemic, toxicity studies were not required prior to starting clinical evaluation
- Use of a minimum nonclinical package is supported by additional nonclinical data collected during clinical development

†Taken from WHO’s Draft Guidelines on the Quality, Safety and Efficacy of Ebola Vaccines (2016)
The International Partnership Facilitating V920 Clinical Trial Evaluation

NewLink
8 Cities in USA

WRAIR
Silver Springs, MD, USA

NIH
Bethesda, MD, USA

CCV
Halifax, Nova Scotia, Canada

University Medical Center Hamburg + Clinical Trial Center North
Hamburg, Germany

HUG
Geneva, Switzerland

KEMRI
Kilifi, Kenya

CERMEL + University of Tuebingen
Lambarene, Gabon

MSD
Multiple sites in the USA, Canada, Spain

WHO + Norwegian Institute of Public Health + Health Canada
Guinea

CDC + Sierra Leone Medical School
Sierra Leone

Liberia-NIH Partnership
Liberia
### Phase I Clinical Trials With V920

- Eight Phase I trials conducted in Canada, Germany, Gabon, Kenya, Switzerland, and US (N=835)
- Evaluated safety and immunogenicity of a variety of vaccine dose levels, ranging from $3 \times 10^3$ to $1 \times 10^8$ plaque forming units (pfu)

<table>
<thead>
<tr>
<th>Sponsor, Location</th>
<th>N</th>
<th>Description</th>
<th>Dose levels (pfu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRAIR, US</td>
<td>39</td>
<td>Randomized, single-center, double-blind, placebo-controlled, dose-escalation study of 3 sequential cohorts</td>
<td>$3 \times 10^6$, $2 \times 10^7$, $1 \times 10^8$ (each, n=10), or Placebo (n=9)</td>
</tr>
<tr>
<td>NIAID, US</td>
<td>39</td>
<td>Randomized, double-blind, placebo-controlled, dose-escalation study of a 2-dose prime (day 0)-boost (day 28) regimen</td>
<td>$3 \times 10^6$, $2 \times 10^7$, $1 \times 10^8$ (each, n=10), or Placebo (n=9)</td>
</tr>
<tr>
<td>Halifax, Canada</td>
<td>40</td>
<td>Randomized, single-center, double-blind controlled, dose-ranging study</td>
<td>$1 \times 10^5$, $5 \times 10^5$, $3 \times 10^6$ (each, n=10), Placebo (n=10)</td>
</tr>
<tr>
<td>NewLink-Ib, US</td>
<td>512</td>
<td>Randomized, multi-center, double-blind, placebo-controlled, dose-response study</td>
<td>$3 \times 10^3$, $3 \times 10^4$, $3 \times 10^5$ (each, n=64), $3 \times 10^6$ (n=84), $9 \times 10^6$, $2 \times 10^7$ (each, n=47), $1 \times 10^8$ (n=48), Placebo (n=94)</td>
</tr>
<tr>
<td>WHO*, Geneva</td>
<td>115</td>
<td>Dose-finding, randomized, single-center, double-blind†, placebo-controlled study</td>
<td>$3 \times 10^5$ (n=50), $1 \times 10^7$ (n=35), $5 \times 10^7$ (n=15), Placebo (n=15)</td>
</tr>
<tr>
<td>WHO*, Hamburg</td>
<td>30</td>
<td>Open-label, single-center, dose-escalation study</td>
<td>$3 \times 10^6$, $3 \times 10^7$, $2 \times 10^7$ (each, n=10)</td>
</tr>
<tr>
<td>WHO*, Gabon</td>
<td>155</td>
<td>Randomized, open-label, dose-escalation study</td>
<td>$3 \times 10^6$ (n=20), $3 \times 10^7$ (n=20), $3 \times 10^8$ (n=20), $3 \times 10^9$ (n=39), $2 \times 10^7$ (n=16)</td>
</tr>
<tr>
<td>WHO*, Kenya</td>
<td>40</td>
<td>Open-label, dose-escalation study</td>
<td>$3 \times 10^6$, $1 \times 10^7$ (each, n=20)</td>
</tr>
</tbody>
</table>

†Excluding 19 run-in subjects and those in the deployable group (entire group received V920)
‡Additional 40 pediatric subjects
*Coordinated by WHO’s African and European VSV-Ebola consortium (VEBCON)
Immunoassays Used in Animal and Human Studies

- **IgG ELISA**
  - Method used in Phase I trials
  - Analogous method used for non-human primates
  - Standardized ELISA has been developed and validated by the Filovirus Animal Non-clinical Group (FANG) under the oversight of U.S. Army Medical Materiel Development Activity (USAMMDA) at Battelle and Focus Diagnostics

- **Neutralizing antibody assays**
  - Species neutral methods
  - Pseudovirion assay (PsVNA) used for most Phase I trials (USAMRIID)
  - Plaque-reduction (PRNT) assay used for both human and NHP studies, validated by MSD/NewLink Genetics at Focus Diagnostics

- Validated IgG ELISA and PRNT assays will be used to assay samples from Phase II/III studies
IgG ELISA antibody titers were sustained through 180 days.

# Phase II/III Clinical Trials With V920

- Five Phase II/III trials conducted in Guinea, Liberia, Sierra Leone, Canada, Spain, and US
  - Tested a vaccine dose of $\geq 2 \times 10^7$ pfu in more than 16,000 subjects

<table>
<thead>
<tr>
<th>Sponsor, Location, Type of Study</th>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;PREVAIL&quot;, NIH, Liberia</td>
<td>~500</td>
<td>Safety and efficacy compared to placebo; immunogenicity sub-study</td>
</tr>
<tr>
<td>Placebo Controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Ebola, ça Suffit&quot;, WHO, Guinea</td>
<td>~5,000</td>
<td>Safety and efficacy of immediate vs delayed (21 days) ring vaccination</td>
</tr>
<tr>
<td>Cluster-randomized, immediate vs. delayed ring vaccination clusters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO/MSF, Guinea</td>
<td>~1,800</td>
<td>Safety and immunogenicity study of front-line workers</td>
</tr>
<tr>
<td>No randomization, all vaccinated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;STRIVE&quot;, CDC, Sierra Leone</td>
<td>~8,000</td>
<td>Safety and efficacy of immediate vs delayed (18-24 weeks) vaccination</td>
</tr>
<tr>
<td>Randomized, immediate vs. delayed vaccination groups</td>
<td></td>
<td>Safety and immunogenicity sub-studies</td>
</tr>
<tr>
<td>Lot Consistency Study, MSD USA, Canada, Spain</td>
<td>~1,200</td>
<td>Safety through D42, including detailed workups of joint and skin symptoms Immunogenicity assessments at D28 and D180, including lot consistency assessment at D28 Subset of subjects extended follow-up out to 2 years</td>
</tr>
<tr>
<td>Randomized, Placebo Controlled</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Confirmed weekly Ebola virus disease cases reported from Guinea, Liberia and Sierra Leone*

Guinea (Patient database), Liberia (Situation report, as of 6 May 2015), Sierra Leone (Patient database up to 1 May 2015, Situation report from 8 March 2015)
WHO’s “Ebola ça Suffit” Ring Vaccination Trial in Guinea

- A cluster-randomized trial design
  - Defined a cluster or “ring” around a confirmed Ebola case
  - Clusters were the units for randomization
WHO’s “Ebola ça Suffit” Ring Vaccination Trial in Guinea

- **Primary Objective:** To assess vaccine efficacy against confirmed EVD by comparing immediate vs delayed ring vaccination.

- Following confirmed EVD case, epidemiologically defined sociogeographical ring was identified based on contact tracing and place of residence of the case.

- Clusters were the units for randomization to immediate or delayed vaccination.

- Following randomization, adults were offered vaccination.

Reference: Adapted from BMJ 2015;351:h3740 doi
WHO’s “Ebola ça Suffit” Ring Vaccination Trial: Interim Analysis Efficacy Results July 2015

- First evidence of efficacy in human subjects for any Ebola vaccine
- **100% efficacy in interim analysis**
- No EVD cases in either immediate or delayed arm from Day 10 post dose onward
- Study was expanded into adolescents and children > 6 y.o. and into Sierra Leone following demonstration of efficacy with all additional subjects vaccinated upon enrollment (no delayed arm)

<table>
<thead>
<tr>
<th>Number of individuals (clusters)</th>
<th>All vaccinated in immediate versus all eligible in delayed (primary analysis)</th>
<th>All eligible and consented</th>
<th>All eligible (eligible adults, contacts and contacts of contacts)</th>
<th>All (all contacts and contacts of contacts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>2014 (48)</td>
<td>2048 (48)</td>
<td>3035 (48)</td>
<td>4123 (48)</td>
</tr>
<tr>
<td>Delayed</td>
<td>2380 (42)</td>
<td>1930 (42)</td>
<td>2380 (42)</td>
<td>3528 (42)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of cases at &lt;10 days (affected clusters)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Delayed</td>
<td>16 (12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of cases at ≤10 days (affected clusters)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Delayed</td>
<td>16† (7)</td>
</tr>
</tbody>
</table>

Vaccine efficacy/ effectiveness: 100% / 100% (74.7 to 100) / (70.8 to 100)

| p values | 0.0036 | 0.0194 | 0.1791 | 0.3351 |

*All cases occurred in unvaccinated individuals. †Four cases were vaccinated and developed symptoms on day 0, 2, 6, or 6 after vaccination. ‡From fitting a β-binomial distribution to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy (first two columns), from Cox proportional hazards model to estimate vaccine effectiveness (last two columns). §From Fisher’s exact test (two-sided).

Table 2: Calculations of vaccine efficacy and vaccine effectiveness based on different study populations
WHO’s “Ebola ça Suffit” Ring Vaccination Trial: Final Results December 2016 Confirm 100% efficacy

### Final analysis

<table>
<thead>
<tr>
<th></th>
<th>All vaccinated in immediate (group A) vs all contacts and contacts of contacts in delayed plus all never-vaccinated in immediate or non-randomised (group B)</th>
<th>All vaccinated in immediate (group A) vs all eligible never-vaccinated in immediate (group B)</th>
<th>All contacts and contacts of contacts in immediate or non-randomised (group B) vs delayed (group B)</th>
<th>All vaccinated in immediate (group A) vs all eligible never-vaccinated in immediate (group B)</th>
<th>All vaccinated in immediate (group A) vs all eligible delayed in immediate (group B) vs delayed (group B)</th>
<th>All eligible in immediate (group A) vs all eligible delayed in immediate (group B) vs delayed (group B)</th>
<th>All contacts and contacts of contacts in delayed (group B) vs all contacts and contacts of contacts in immediate (group B) vs delayed (group B)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of individuals (clusters)</td>
<td>3775 (70)</td>
<td>3775 (70)</td>
<td>7142 (70)</td>
<td>3775 (70)</td>
<td>2108 (51)</td>
<td>2108 (51)</td>
<td>3212 (51)</td>
</tr>
<tr>
<td>Cases of Ebola virus disease (clusters affected)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>12 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Attack rate</td>
<td>0%</td>
<td>0%</td>
<td>0.17%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0.22%</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of individuals (clusters)</td>
<td>7995 (116)</td>
<td>4507 (104)</td>
<td>4529 (47)</td>
<td>1432 (57)</td>
<td>1429 (46)</td>
<td>3075 (42)</td>
<td>3075 (47)</td>
</tr>
<tr>
<td>Cases of Ebola virus disease (clusters affected)</td>
<td>34 (15)</td>
<td>23 (12)</td>
<td>22 (8)</td>
<td>7 (4)</td>
<td>10 (4)</td>
<td>16 (7)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Attack rate</td>
<td>0.43%</td>
<td>0.51%</td>
<td>0.49%</td>
<td>0.49%</td>
<td>0.7%</td>
<td>0.52%</td>
<td>0.52%</td>
</tr>
<tr>
<td>Vaccine effect</td>
<td>100% (77.0% to 100.0%)</td>
<td>100% (79.2% to 100.0%)</td>
<td>70.1% (-4.9% to 91.5)</td>
<td>100% (56.5% to 100.0%)</td>
<td>100% (62.5% to 100.0%)</td>
<td>100% (68.9% to 100.0%)</td>
<td>64.6% (-46.5% to 91.4%)</td>
</tr>
<tr>
<td>p-value(s)</td>
<td>0.0012</td>
<td>0.0033</td>
<td>0.2759</td>
<td>0.125</td>
<td>0.0471</td>
<td>0.0045</td>
<td>0.344</td>
</tr>
</tbody>
</table>

*Randomly assigned and non-randomly assigned individuals who were allocated to immediate vaccination were combined. tNon randomised immediate clusters are excluded from this analysis. From fitting a binomial distribution to the cluster level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy (columns 1, 2, 5, and 6), from a Cox proportional hazards model (column 7 and 8); from signed test (two-sided): probability of observing endpoints in control groups among treatment-control mismatched pairs and under the null hypothesis that the vaccine has no efficacy (column 4). From Fisher’s exact test (two-sided), which is approximate for columns 1 and 2. From signed test (two-sided), probability of observing endpoints in control groups among treatment-control mismatched pairs and under the null hypothesis that the vaccine has no efficacy (column 4).

V920 Overall Safety Conclusions to Date

Preliminary data in healthy, non-pregnant adults suggest an acceptable safety profile that in the context of demonstrated efficacy supports a positive benefit-risk ratio:

- Few vaccine-related SAEs reported to date
- V920 is generally well tolerated. Common AEs include headache, pyrexia, fatigue, myalgia; majority mild to moderate, short duration
- Injection-site reactions very common; majority mild to moderate
- Joint pain (arthralgia) has been seen in 5%-50% of participants, but joint swelling (arthritis) has been less common (<5%) in most studies
- Majority of joint events were mild to moderate and resolved within several days (arthralgia) to weeks (arthritis); several subjects have reported recurrent or persistent joint symptoms for at least 6 months after vaccination
- Rash has been seen in up to 11% of subjects; also generally mild to moderate in intensity, short duration
- First reports of V920 administration in adolescents/children indicate similar safety profile to adults
- Vaccine virus shedding is not frequent in adults; secondary transmission has not been demonstrated to date
Ongoing Efforts in Advance of Product Licensure

• **Expanded Access Protocol**
  – Working with partners to put expanded access clinical protocols in place in countries at highest risk of a new outbreak

• **Emergency Use Assessment and Listing (EUAL)**
  – New mechanism of WHO to allow vaccine deployment outside of clinical trials prior to licensure in an emergency
  – MSD filed an EUAL application for V920 with WHO in December 2015

• **Studies in pediatric population and HIV+ subjects**
  – A small number of pediatric subjects were included in Phase I/II clinical trials
  – Additional safety/immunogenicity data will be obtained in pediatric studies
  – A study in HIV+ subjects (adults and adolescents) is planned
Regulatory Designations to Expedite Development of V920

- **EMA’s Priority Medicines status (PRIME)**
  - Eligibility confirmed 23-Jun-2016

- **FDA’s Breakthrough Therapy Designation**
  - Granted 29-Jun-2016

- Enhanced support for the development of medicines that target an unmet medical need for life-threatening diseases with major public health interest
- Enables formal and consistent dialog/interactions with regulators on product development and aligning on processes/timelines **prior to filing**
- Granted based on preliminary evidence that the candidate may demonstrate substantial improvement over existing therapies
Manufacturing Overview

• **V920 clinical trial supplies were made at IDT Biologika in Germany**
  – All clinical Drug Substance (DS) material and pivotal Drug Product (DP) supplies were generated at IDT Biologika GmbH, Dessau-Rosslau, Germany
  – Clinical consistency DP materials formulated and filled at MSD’s facility in West Point, Pennsylvania, USA

• **MSD successfully scaled the IDT Biologika clinical process to the commercial scale process at West Point facility in Pennsylvania, USA**
  – Utilized commercial scale process to successfully manufacture additional clinical supplies and potential emergency use materials
  – Available analytical data from supplies made at IDT and MSD have been submitted to EMA and FDA

• **Commercial manufacturing will be implemented throughout 2017 at MSD’s Burgwedel facility located in Germany**
  – Technology transfer and site readiness activities including facility modifications at the MSD’s Burgwedel site are in progress; process performance qualification (PPQ) is planned to start in 2017
  – Manufacturing process will be similar to the process developed at the MSD West Point facility
  – Single dose DP image is the planned commercial product
V920 Vaccine Milestones: 2014–present

Accelerated timeline to develop the Ebola vaccine

25 Jan 2015
Dose selection decision for efficacy trials

31 July 2015
Phase III ring vaccination trial in Guinea; interim results demonstrate vaccine efficacy

Jan-Mar 2016
Manufacturing of additional clinical supplies

Ongoing 2017
Technology transfer to commercial manufacturing site

2014
13 Oct 2014
Start of Phase I trials

Feb–Aug 2015
Start of Phase II/III studies:
02 Feb: NIH PREVAIL in Liberia
23 Mar: WHO study in Guinea
09 Apr: CDC STRIVE in Sierra Leone
17 Aug: MSD lot consistency in US, EU, and Canada

2015
22 Dec 2015
WHO agrees to review an Emergency Use Assessment and Listing submission

2016
Jun 2016
23 Jun: Granted PRIME eligibility by EMA
29 Jun: Granted Breakthrough Therapy Designation by FDA

2017
112 Jan 2015
Dose selection decision for efficacy trials

31 July 2015
Phase III ring vaccination trial in Guinea; interim results demonstrate vaccine efficacy

Jan-Mar 2016
Manufacturing of additional clinical supplies

Ongoing 2017
Technology transfer to commercial manufacturing site
Summary

- Strong preclinical data, including evidence of protection after a single dose, positioned the rVSVΔG-ZEBOV-GP (V920) vaccine to be an important candidate for development in response to the most recent Ebola outbreak.
- MSD and NewLink Genetics working in collaboration with a large number of partners have moved this vaccine forward at an unprecedented pace.
- Clinical trials results are expected to provide a solid body of data supporting the safety and efficacy of the vaccine.
- V920 was demonstrated to be highly efficacious in a Ring Vaccination Trial conducted by the WHO in Guinea during the last outbreak.
- PRIME and Breakthrough Therapy Designation will help to move this vaccine forward to filing as quickly as possible.
- MSD is committed to ensure vaccine availability for at-risk populations in advance of product licensure.
ACKNOWLEDGEMENTS AND SINCERE THANKS

- Study volunteers and study investigators
- MSD-NewLink Joint Steering Committee; V920 product development team and all sub-teams
- Our many external partners, collaborators, and funding organizations
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