Addressing a Worldwide Health Concern for Ebola

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Thank you Science!
• **Ebola Background**
  • 2014 Outbreak
  • Clinical Candidates During Outbreak
    • Merck’s Candidate
  • WHO Guinea Ring Efficacy Results
• **Merck’s Commitment to Ebola**
  • Merck’s Approach to Develop a Vaccine for Ebola
  • Typical Vaccine Development
  • Merck’s Ebola Vaccine Development Timeline
• **Process Development**
  • Scope of Work
  • Vaccine Path to PPQ
    • Upstream
    • Downstream
    • Drug Product
    • Site Readiness
• **Program Challenges**
• **Applicability to Other Vaccines and Biologics**
• **Conclusions**
• **Partners, Alliances, and Acknowledgements**
Ebola Virus

- Member of the filoviridae family of viruses, first discovered in 1976 in the Ebola river (Zaire, now, Democratic Republic of Congo)

- Hemorrhagic fever and deadly disease caused by infection with one of the Ebola virus strains (Human: Zaire, Sudan, Ivory Coast, Bundibugyo; non-human primates: Reston)

- Animal-borne virus, with fruit bats as most likely reservoir
  - Natural reservoir host not yet identified

- Transmission by direct contact (through broken skin or mucous membranes) with blood or body fluids of infected individual or contaminated objects, and infected fruit bats or primates
2014 – 2016 Ebola Virus Outbreak

• First case in Guinea March 2014 and peaked in Aug–Oct ’14
  – WHO declaration of Public Health Emergency of International Concern (PHEIC) on August 8th

• Zaire ebolavirus species

• Cumulatively 28,000+ cases and 11,000+ deaths by January 2016
  – > 10 times more cases during the current epidemic than in all previous outbreaks combined
  – Impacted: Guinea, Liberia, Sierra Leone
    • A few cases reported in Nigeria, Mali, Senegal, Spain, US, UK, and Italy

• WHO declares no longer a Public Health Emergency of International Concern on March 31, 2016
  – New cases have been detected in Sierra Leone since
### Ebola Clinical Candidates During 2014 – 2016 Western African Outbreak

<table>
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<tbody>
<tr>
<td><strong>Vaccines</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Phase 3</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>41</td>
</tr>
<tr>
<td><strong>Therapies</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td><strong>Phase 2</strong></td>
</tr>
<tr>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td><strong>Diagnostics</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td><strong>Phase 1</strong></td>
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<td>3</td>
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</table>

**% trials in Africa**
- **Vaccines**: 39%
- **Therapeutics**: 60%

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1. Considering different vaccine combinations/variants as distinct
2. Including therapies only given under compassionate use
3. Products that have received FDA or WHO emergency use listing; up to 80 are in some stage of development
4. Based on triangulation from public sources and stakeholder interviews. If a trial spans multiple phases or is unclassified, classification here is based on the highest phase or the trial's primary outcomes

SOURCE: Clinicaltrials.gov (September 2015), WHO ICTRP portal, Pan-African Trial Registry, Stakeholder interviews, WHO categorization of drugs for Ebola, WHO Diagnostics, FDA Emergency Use Authorizations

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Taken from WHO Report on Ebola R&D Landscape of Official Candidates and Trials (October 2015)
Application of the rVSV technology and initial development of the candidate Ebola vaccine was accomplished by Public Health Agency of Canada (PHAC)

PHAC licensed the filovirus vaccine technology to NewLink Genetics to further development and initiate clinical development

Initial PHAC clinical lot was manufactured in 2013 by a CMO
  • NewLink Genetics filed IND and started Phase I trials (3 sites) and oversaw the clinical development
  • Funding to support development and clinical lots completed by multiple partners
    • BARDA, DTRA, Wellcome Trust, NIH, NIAID and WHO
    • PHAC lot utilized to support Phase II/III in West Africa (Liberia, Guinea, Sierra Leone)
    • NewLink Genetics continued to work with CMO for additional clinical lots

Nov 2014, Merck and NewLink Genetics Corp. entered into an exclusive worldwide license agreement
  • Merck assumed responsibility to research, develop, manufacture, and distribute the investigational Ebola vaccine candidate (rVSV- ΔG-ZEBOV-GP) and other filovirus based vaccines based on rVSV technology

Merck, NewLink Genetics and a global network of partners are collaborating in unprecedented ways with the singular focus on speeding the research, development and deployment of a well-tolerated and effective Ebola vaccine
Composition of Merck’s Vaccine Candidate (rVSV ZEBOV-GP)

- **Vector = live attenuated recombinant vesicular stomatitis virus (rVSV)**
  - Antigen = Zaire Ebola virus (ZEBOV) glycoprotein (GP)
    - VSV G (envelope) GP replaced with Ebola-Zaire envelope GP
    - Eliminates VSV GP toxicity and changes host range
      - VSV is further attenuated by the GP substitution
**WHO Guinea Ring Vaccination Trial Efficacy Results**

**Lancet publication Dec 22, 2016**

- First evidence of efficacy in human subjects for any Ebola vaccine
- No EVD cases in either immediate or delayed arm from Day 6 post dose onward
- Study expanded into Sierra Leone with all additional subjects vaccinated upon enrollment (no delayed arm)
- Enrolled adolescents and children > 6 years old

### Table 3: Effect of vaccine on cases of Ebola virus disease in different study populations

<table>
<thead>
<tr>
<th></th>
<th>All clusters</th>
<th>Randomised clusters</th>
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<tbody>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of individuals (clusters)</td>
<td>3,775 (70)</td>
<td>3,775 (70)</td>
</tr>
<tr>
<td>Cases of Ebola virus disease (clusters affected)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Attack rate</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of individuals (clusters)</td>
<td>7,995 (116)</td>
<td>4,507 (104)</td>
</tr>
<tr>
<td>Cases of Ebola virus disease (clusters affected)</td>
<td>34 (05)</td>
<td>23 (11)</td>
</tr>
<tr>
<td>Attack rate</td>
<td>0.43%</td>
<td>0.51%</td>
</tr>
<tr>
<td>Vaccine efficacy/ effectiveness (95% CI)</td>
<td>100% (77.0-100.0)</td>
<td>100% (79.3-100.0)</td>
</tr>
<tr>
<td>p value</td>
<td>0.0012</td>
<td>0.0033</td>
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*Randomly assigned and non-randomly assigned individuals who were allocated to immediate vaccination were combined. Non-randomised immediate clusters are excluded from this analysis. 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 (columns 1, 2, 5, and 6), from a Cox proportional hazards model (column 3, 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)."
Merck’s Approach to Address Potential Vaccine Needs and Vaccine Availability

• **Move monovalent frozen product forward for licensure as efficiently as possible**
  – Complete clinical development to produce required safety database, demonstrate evidence of clinical benefit, and manufacturing consistency
  – Prepare commercial manufacturing facility and execute on manufacturing scale-up and PPQ activities

• **Collaborate with current dose owners and stakeholders to align on best use of existing doses of vaccine (~150 – 170K currently exist)**
  – Through expanded ring vaccination trials, new/expanded trials for at-risk US-based and ex-US populations, trials in special populations etc.

• **Ramp up Merck Clinical manufacturing capabilities to produce additional doses that could be deployed in the case of expanded or new outbreak**
  – Ethical obligation to ensure vaccine available in the event of another epidemic
  – Utilize the WHO Emergency Use Authorization process
Typical Timeline for Vaccine Development

• 10 to 20 Years
  • Standard timeline to develop a vaccine.

2014

2024+
Merck’s Vaccine Milestones and Accelerated Development Timeline

Over 18,000 volunteers vaccinated to date

- **May 15**: Initiate Manufacture of Bank/Seed and DS Process Development
- **31 July 15**: Phase III ring vaccination trial interim analysis results demonstrate vaccine efficacy
- **17 Aug 15**: Initiation of Merck Phase III Safety and Lot Consistency Study (P012) in US/EU/Canada
- **23 Aug 15**: Commercial Siting Decision and Range Finding Kicked-off Internally
- **Sep 15**: CAPEX Scoping Project Initiated at Manufacturing Site
- **Nov 15**: BARDA Lots F/F @ Merck
- **Dec 15**: Manufacture of BDS Lots for EMU at Anticipated Commercial Scale
- **Jan/Feb 16**: Manufacture of DP Lots for EMU within Merck Facility

**2014**
- **13 Oct 2014**: Start of Phase I trials rVSV-ZEBOV-GP
- **25 Jan 2015**: Dose selection decision for efficacy trials
- **2 Feb 2015**: Initiation of NIH-Liberia PREVAIL Phase II/III study
- **23 Mar 2015**: Initiation of WHO Phase III study in Guinea
- **09 April 2015**: Initiation of CDC STRIVE Phase III trial in Sierra Leone

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

**2016**
- **23 Jun 2016**: PRIME granted by EMA
- **29-Jun-2016**: Breakthrough Designation granted by FDA
Process Development

Develop commercial scale-up process

- Show comparability between clinical and expected commercial process
- Minimize changes to existing process to shorten timelines and accelerate program
- Generate Emergency Use supplies as fast as possible
CMO Vaccine Process Flow

- Cell Seeding
- Cell Passage
- Virus Infection
- Virus Harvest
- Enzyme Treatment
- Virus Purification and Concentration
- Freeze at ≤ -60°C

- Formulation (Thaw, Dilute, Blend)
- Fill Vials
- Stopper/Cap
- Inspect
- Label
- Package
- Freeze at ≤ -60°C
- Ship

- DS and DP is stored and kept at ≤ -60°C
- Data indicates DP stable at 2-8°C for up to 4 weeks
Process Development to Support Emergency Use Manufacture – Drug Substance

**Literature, CMO Data Review and Merck Expertise**

**Process Development Kicked Off [Jun2015]**

**Scale – Up experiments [Jun – Oct]**

### Upstream Development
- MOI
- Plant density
- Day of Infection
- Harvest Time

### Downstream Development
- Depth Filtration Vmax Studies
- Enzyme Rxn
  - Enzyme concentration
  - Time course studies
- TFF
  - Loading
  - No. of Cycles
  - Decrease Lumen Diameter
  - Decrease Recirc Rate
  - Concentration

### Scale – Up
- 3, 12, 90 and 400 Roller Bottle Scale – up studies were run
Scale-up at Merck is comparable to CMO and clinical experience.
- Improved overall purification recovery was achieved
- HCP and DNA levels met previous experience (data not shown)
Goal was to minimize process changes in DS scale-up

• Upstream changes
  – Increased cell expansion (2 PDLs)
  – Utilized Working Virus Seed

• Downstream
  – Clarification – increased surface area, maintain constant loading per m²
  – Ultrafiltration – increased surface area, 4X increase in loading per m², decreased lumen diameter to maintain shear, reduced recirculation rate
  – Final Container

Process was 100% Single Use Technology
DP Process Development

- Impact of shear and mixing on final formulated bulk (FFB)

- Short-term stability studies to investigate the impact of normal manufacturing times and temperatures on drug product potency
  - 2-8°C
  - Time Out of Refrigeration (TOR)

- Impact of DP freezing and thawing

- DS dilutability studies to target a final DP potency

- Long-term stability studies for DP stability studies
Impact of Freezing Rate on Potency

• Evaluated impact of freezing rate on DP
  • Quick freezing in LN2 blast freezer (15min)
  • Slow freezing in -70°C freezer (2 & 8hr)
  • 72hr control freeze in Lyophilization cabinet
    • Mimics expected large lot freezing time

• Method of freezing does not appear to impact potency
  • Allows flexibility for manufacturing and freeze process
Impact to Thawing Rate on Drug Product Potency

- Thaw rate impacts DP potency in 1D and 10D image

- Thawing protocol important for vaccine field use
  - Thaw at RT to minimize the thaw time
Impact of Shear on Drug Product

- DP not impacted by shear stress (tested up to 180 turnovers)
Drug Product Freeze / Thaw Stability

- Vaccine appears stable through 5 Freeze-thaw cycles
  - Flexibility in manufacturing for packaging and labelling
  - Vials frozen in -70°C freezer and thawed at room temperature
Dilutability of DS to DP Target Potency

- DS can be diluted to specified DP potency
- Increased confidence in achieving formulation and filling targets
Comparison of the Expected Merck Commercial Process with Clinical Process

Lab-scale and clinical processes comparable for potency and harvest times

Development fits well into operating space
End to End – 1 year!

• Produced Drug Substance sufficient to produce > 750,000 doses

• Produced >125,000 drug product doses (10D image)

• EUAL Vaccine for Ebola was filed May 30, 2016

• Available for Use – September 30, 2016
Commercialization

- **Obtain data to support BLA filing**
  - Generate necessary lab-scale data to support critical ranges
  - Generate comparison data of clinical and commercial processes

- **QbD Risk based approach to parameter studies**
  - Gained process knowledge and explore processing surface to ensure process parameters are in a stable zone
  - Team focused on key areas
    - Expedited final process definition and provides efficiency in delivering a commercial process
  - Utilizing clinical scale targets
    - Only adjusting unit operations necessary to ensure a robust manufacturing process is achieved
Vaccine Path to PPQ (Upstream and Downstream Drug Substance Range Finding)

Range Finding Kicked Off [Aug2015]

Reviewed and scored FMEA

Identified key experiments to support PPQ ranges

- **Upstream Development**
  - MOI
  - Plant density
  - Day of Infection
  - Harvest Time
  - PBS Rinse
  - Medium Age

- **Downstream Development**
  - Depth Filtration Vmax Studies
  - Enzyme Rxn
    - Time course studies
  - TFF
    - Impact of Loading

- **Other DS Studies**
  - Hold time studies
    - Stock seed
    - HVF
    - CH
    - RVH
  - Investigate various RB sizes
**Impact of MOI and Harvest Time: Finalized Response**

**Surface Design**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Levels</th>
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<tbody>
<tr>
<td>MOI</td>
<td>MOIs examined over 100-fold range</td>
</tr>
<tr>
<td>Harvest Timing (HPI)</td>
<td>Examined harvesting over multiple days post infection</td>
</tr>
</tbody>
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**JMP 11 design including replicates and 6 center points**

**30 conditions**

**Experiment 1**
- Conditions: 1-30

**Experiment 2**
- Conditions: 1-30

*Replicate experiment*

Same design used in both experiments, replicate to gain confidence around results
Relative Impact of MOI and Relative Harvest Time on Potency

- Proposed operating space highlighted
- Large operation window for Harvest time and MOI
MOI Sensitivity

Wide range of MOI can obtain comparable bulk potency. Allows for a wide operating range for commercial manufacture.
Tech Transfer Site Readiness Roadmap

Initiation, Planning, Capital Project, Quality System Assessment, Analytical TT

Process & Site Readiness

Engineering Lots

Process Simulations

Process Performance Qualification Lots (PPQ)

Filing Preparation, Comparability Report & Pre-launch Audit

Stage Gate 0

Stage Gate 1

Stage Gate 2

Stage Gate 3

Stage Gate 4

Stage Gate 5

File Submission, Routine Manufacturing and Stability
Program Challenges

- **Three parallel activities within Merck to drive program forward and inability to sequence**
  - Establish critical process ranges for Commercial Manufacturing
  - Manufacture Emergency Use Material to Support a Potential Future Zaire Ebola Outbreak
    - Ensure doses available prior to licensed product in an emergency / clinical setting
    - Site and Tech Transfer strategy and CapEx project to ready the facility as soon as possible

- **Different approaches to risk based decision making**
  - Team not investigating all areas of process, but rather focused on key areas
    - Expedites process development and increases team’s efficiency in delivering a commercial process

- **Rapidly evolving external environment**
  - Aug. 2015: Ebola Outbreak in progress; March 2016; WHO declares Ebola outbreak over
  - Numerous points to interact with during development for both development and funding
    - WHO, GAVI, BARDA, DTRA, DOD, Wellcome Trust, NewLink/BPS, NIH, NIAID
Applicability of Strategy Applied to Other Programs

• Examination of changes in scale and bulk process for later stage development
  • Managing scale changes as we progress from clinical to commercial
  • Different platforms for production
    • RB process to cell stacks or microcarriers for BDS production
    • Move from transient transfectants in early stage development to stable clones

• Formulation changes during development
  • Biologics utilizing “platform” formulations in early phase programs and later moving to commercial formulation
  • Moving from frozen liquid formulations to improved refrigerator stable and lyophilized formulations as move into Phase II and beyond

• Building strong analytical comparability to minimize clinical studies
• Merck committed to move the vaccine forward to licensure as quickly as possible and ensure vaccine availability for at-risk populations in advance of product licensure

• Strong preclinical data, including evidence of protection after single dose

• Merck has shown ability to scale process from clinical to commercial process rapidly

• Merck and NewLink working in collaboration with a large number of partners
  • Regulators, Academia, International Health Agencies, NGOs, US Military, and other US and ex-US government agencies have moved the vaccine forward at an unprecedented pace
Partnerships and Alliances

**Public Health Agency of Canada (PHAC)**

**NewLink Genetics (Bio-Protection Systems Corporation)**

**Phase I Studies**

- 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**
  - **BARDA**

**Phase II/III Studies**

- **Liberia**: Liberia – NIH Partnership (NIAID)
- **Sierra Leone**: CDC/Sierra Leone Medical School, BARDA
- **Guinea**: WHO/Norwegian Institute of Public Health/MSF/Health Canada
- **US Department of Defense (WRAIR, JVAP, USAMRIID, DTRA)**
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- Ed Bell
- Joe Califano
- Larry Dick
- Kim Hassis
- Jayanti Wolfe
- Lynne Isopi
- Richard Peluso
- Ray Ducoat
- Brad Thomas

- Emergency Use Manufacture Team
- Tom Monath (NewLink Genetics)
- Joan Fusco (New Link Genetics)
- Erica Strable
- Julie Waterbury
- Merck-NewLink Joint Steering Committee
- V920 IDST and PDT
- Merck Senior Leaders across the company
- Multiple external partners and collaborators
- Multiple external funding organizations

- Elements of this program has been funded in whole or in part with Federal Funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority under Contract Number: HHSO100201500002C
V920 Merck’s selection of the NewLink rVSVΔG-ZEBOV-GP LVV live attenuated candidate was validated with extremely positive efficacy results. The V920 internal Merck team is highly functioning, motivated and dedicated. They have accomplished an extraordinary amount of work with external partners in a relatively short time frame. “Best team I’ve ever worked with in my career.”