EBS-LASV, a dual-attenuated rVSV-vectored vaccine candidate for Lassa fever

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Lassa Fever

- Lassa fever (LF) is an acute viral illness, caused by infection with Lassa virus (LASV) that can manifest as a severe viral hemorrhagic fever in a subset of infected persons
- Endemic to several regions of sub-Saharan West Africa
- Estimated 300,000-500,000 cases per year; 80% asymptomatic
- ~5,000 deaths per year
- The case fatality rate of hospitalized cases is ~10-20%

- Reservoir for LASV is *Mastomys natalensis* (the multimammate rat)
- Infected rats shed virus in their urine and droppings
- Transmission to humans: direct contact with rats; inhalation or ingestion of rodents’ urine, saliva, or droppings
- Human-to-human transmission of LASV can occur through contact with blood, urine, or feces, or contact with contaminated objects
Clinical Features

Clinical Course

• Case definition is ill-defined
• Initial symptoms mirror other infectious diseases (e.g., malaria, influenza, Ebola)
  1. Fever, headache, malaise
  2. Cough, vomiting, myalgia, abdominal pain
  3. Hemorrhage, facial swelling, pulmonary edema

Pregnancy

• Pregnant women and their fetus are at high-risk for devastating outcomes if infected with LASV
• Mortality rates of 20-50% are reported for pregnant women infected with LASV
• Fetal mortality rates approach 100%

Neurological sequelae:
Hearing loss, ataxia, vertigo, vision distortion

Treatment

• Supportive care
• Ribavirin
• There are no other approved therapeutics or an approved vaccine for the treatment or prevention of LF
# Lassa Virus

- Enveloped virus with a single-stranded, bi-segmented RNA genome
- Each segment harbors two genes, in ambisense orientation
- Family *Arenaviridae*
- GPC gene codes for a polyprotein that is cleaved into a stable signal peptide (SSP), GP1 protein, and GP2 protein
- Mature GP spike is a trimer of GP1/GP2 heterodimers; with SSP also part of the complex
- Distinct clades circulate in different regions of West Africa

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**Lassa fever**
Vesicular Stomatitis Virus (VSV) and rVSV-vectored vaccine development

Wild type VSV

- Infects several species of insects, and livestock species (cattle, horses, pigs)
- Can be transmitted to livestock by insects, and by direct contact between infected animals
- Human infections can occur; mild illness
- Single-stranded negative sense RNA genome, 11 kb, coding for 5 proteins
- Common laboratory tool to study the family Rhabdoviridae; and also glycosylation

Advantages as a vaccine vector

- Simple genome, can be easily manipulated
- Can robustly and stably express a foreign transgene
- Produces a strong humoral and cellular immune response
- Pronounced 3’- 5’ transcriptional gradient
- Very little pre-existing immunity in human populations
- Easy to grow to high titer in continuous qualified cell lines
- Known effective attenuation strategies
rVSV Vector Development at Profectus Biosciences (now Auro Vaccines)

- Profectus Biosciences was spun out from Wyeth in 2008
- To improve the safety profile of first-generation rVSV vectors, Profectus systematically generated many rVSV constructs, and tested for attenuation
  - Position of the transgene insert
  - Gene shuffle of VSV genes
  - Truncation or deletion of the VSV G protein
- Generated multiple vaccine candidates based on the “N4CT1” backbone
- The EBS-LASV construct expresses Lassa GPC (Josiah strain; lineage IV)
- Ongoing formulation work and available data suggest that a more thermostable formulation may be available for Ph2/3 (long term storage at -20C and at least 6 months at 4C)

Gene shuffle (N4)
- VSV G protein truncation (CT1)

EBS-LASV vaccine candidate
- Gene shuffle (N4)
- VSV ΔG
Efficacy and Immunogenicity of EBS-LASV in Cynomolagus Macaques


- EBS-LASV was evaluated as part of a quadrivalent vaccine (containing EBS-LASV and components targeting EBOV, SUDV, and MARV)
- A single dose containing $1 \times 10^7$ PFU EBS-LASV elicited serum LASV neutralizing antibodies
- Two doses (days 0, 56) enhanced the neutralizing antibody response and elicited serum LASV-GP-specific IgG and antigen-specific cellular responses
- No adverse toxicity events were noted in vaccinated NHPs
- All vaccinated animals survived lethal heterologous LASV challenge (Nigeria strain; lineage II) (100% survival)
GLP Repeat Dose (N+1) Toxicity Study of EBS-LASV in New Zealand White Rabbits by IM Injection

<table>
<thead>
<tr>
<th>Group</th>
<th>Test Material</th>
<th>Dose Route</th>
<th>Dose Volume (mL)</th>
<th>Dosing Days</th>
<th>Number of Animals</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9% Sodium chloride</td>
<td>IM</td>
<td>0.5</td>
<td>1, 22, 43</td>
<td>M: 5, F: 5</td>
</tr>
<tr>
<td>2</td>
<td>EBS-LASV (5x10^7 PFU/animal)</td>
<td>IM</td>
<td>0.5</td>
<td>1, 22, 43</td>
<td>M: 5, F: 5</td>
</tr>
</tbody>
</table>

- Administration of EBS-LASV did not result in any changes in:
  - Early mortality or clinical observations, Local irritation assessment, Body temp, Body weights or food consumption
  - Ocular assessments, Hematology, Clinical chemistry, Urinalysis, Organ weights, Macroscopic and microscopic observations.

- No EBS-LASV shedding was detected in saliva or plasma

- Non-adverse transient increases in fibrinogen were noted in males on Day 3 and in CRP for males and females after each day of dosing, which are indicative of inflammation and/or an immune response. This is supported by the fact that all vaccinated animals seroconverted to EBS-LASV.

Administration of 5x10^7 PFU EBS-LASV (~ 5-fold higher than the highest proposed dose in humans) was well tolerated and demonstrated no product-specific safety concerns.
### Additional Completed Preclinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Notes and Results</th>
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| **Mouse Biodistribution** | • Determine the extent of EBS-LASV replication and spread to organs and tissues following IM inoculation  
• EBS-LASV undergoes limited propagation at the injection site and in the local draining lymph nodes and does not spread at quantifiable levels to other organs and tissues.  
• Plasma viremia was not detected |
| **Mouse Neurovirulence** | • Neurovirulence potential of EBS-LASV was evaluated in young mice after intracranial (IC) injection  
• Doses up to $1 \times 10^7$ PFU of EBS-LASV (highest dose) were safe; no animals died  
• $LD_{50}$ is > $1 \times 10^7$ PFU  
• Provides direct evidence that the neurovirulence potential of this vaccine vector has been reduced or eliminated through attenuation |
Emergent High-Level Clinical Development and Regulatory Plan for EBS-LASV

- Preclinical program is complete
- The FIH Phase 1 study has been initiated at two clinical sites in Ghana
- We are planning for an innovative, adaptive Phase 2/3 study, to be conducted in several countries in West Africa
- Regulatory Path
  - AVAREF Joint Review Process for the Phase 2/3 study
  - Early collaboration with NRAs is planned
- Country of initial licensure will be determined in part by country of manufacture, and NRA ability to support WHO prequalification and best regulatory strategy outcome
- Plan for EUL and WHO prequalification
- Seek licensure in multiple countries in West Africa affected by Lassa fever
Minimum needed for licensure:
- P1 dose finding
- P2 regimen finding
- P3 efficacy, ideally including 200 exposed adolescents

Phase 2
- Number of cohorts in P2 will be determined by d57 interim analysis of the P1 study
  - Determined by # of dose levels and need for a single dose cohort
- Provisional total study size: 600 subjects, regardless of the number of cohorts

Phase 3
- A seamless P2 / P3 study design could save on development costs and at least a year in the clinical development timeline
- Based on interim analysis, cohorts performing poorly are dropped
- Clinical outcomes (efficacy) in P2 collected after 1 and 2 years follow up
- If data are supportive, expand select cohorts into P3
# EBS-LASV FIH Phase 1 Clinical Study

## Navrongo Health Research Center

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Arm</th>
<th>Sample Size (N)</th>
<th>Treatment and Dose</th>
<th>Schedule</th>
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<tbody>
<tr>
<td>1</td>
<td>1.1</td>
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<td>EBS-LASV $1 \times 10^5$ TCID$_{50}$ (Low)</td>
<td>Day 1, 29</td>
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<td>1.2</td>
<td>3</td>
<td>Placebo</td>
<td>Day 1, 29</td>
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<td></td>
<td><strong>SMC safety review through Day 15</strong></td>
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<td>EBS-LASV $1 \times 10^6$ TCID$_{50}$ (Medium)</td>
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<td><strong>SMC safety review through Day 15</strong></td>
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<td>EBS-LASV $1 \times 10^7$ TCID$_{50}$ (High)</td>
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<tr>
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<td>Day 1, 29</td>
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<tr>
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<td></td>
<td><strong>SMC safety review through Day 15; Interim Analysis through Week 8 (Day 57±3)</strong></td>
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SMC, Safety monitoring committee; TCID$_{50}$, Fifty-percent tissue culture infective dose.

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Conclusions and Summary

• There is a large unmet need for an effective vaccine to prevent Lassa fever in West Africa
• Emergent is committed to the development of EBS-LASV with both internal and external funding support
• The completed preclinical program demonstrates that administration of EBS-LASV to animals is both safe and immunogenic
  • The neurovirulence study provides direct evidence of vector attenuation
  • These data supported vaccine advancement to Phase 1 FIH trial
• The current CMC process for drug substance is suitable for manufacturing scale-up to support stockpile and future Phase 3 clinical trials
• Thermostable formulation of EBS-LASV will be used in Ph2/3. Most likely long term storage at -20C and at least 6 months at 4C

Closing
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Closing