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

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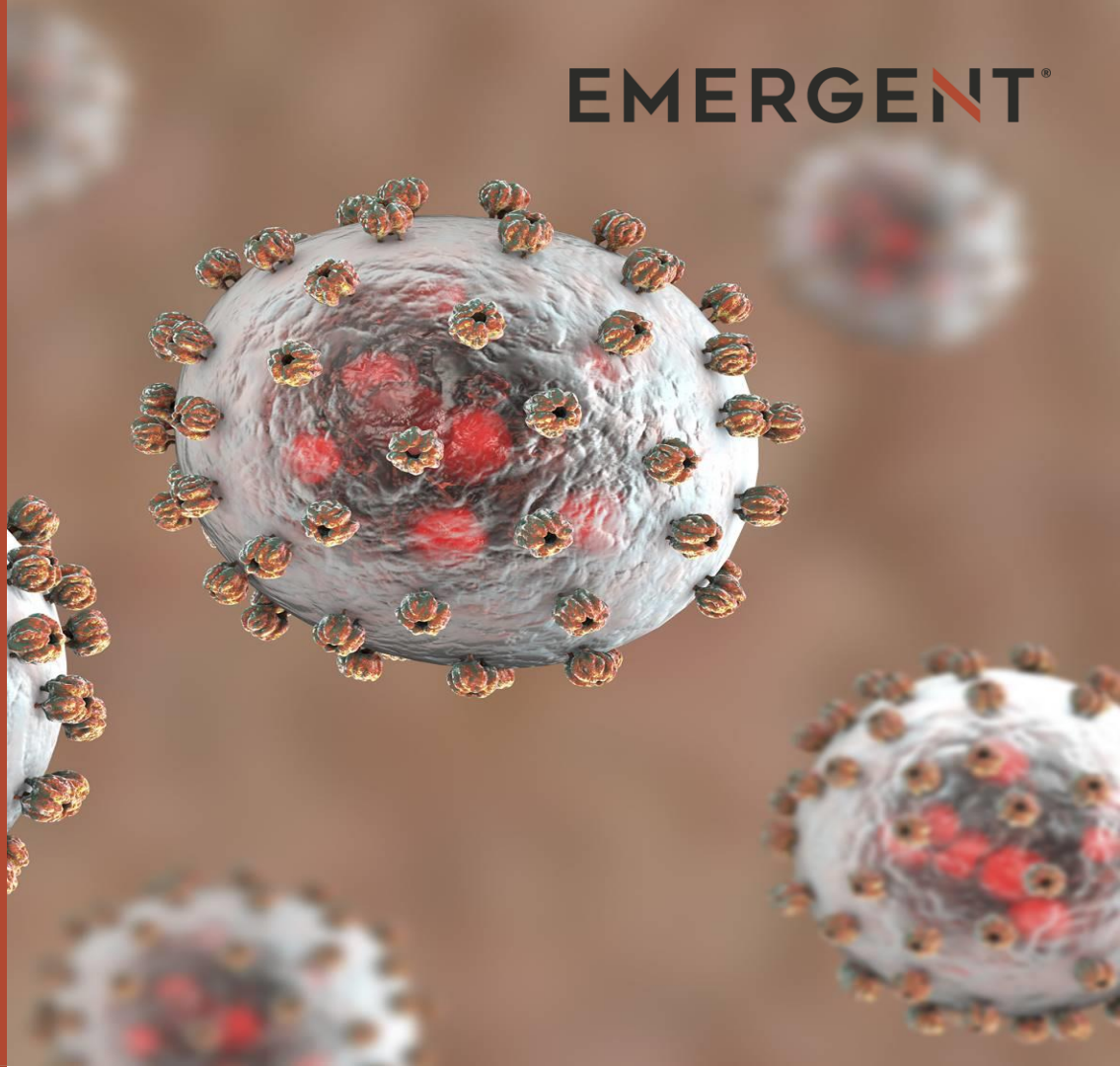
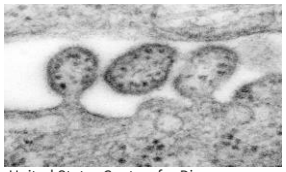


Lassa Fever

- 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%

United States Centers for Disease Control & Prevention. Public Health Image Library (PHIL). Image #14282.



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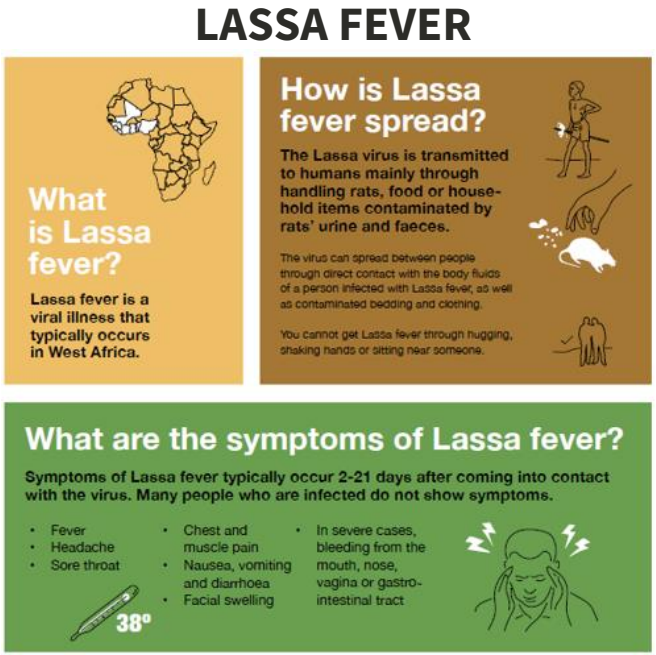
- Reservoir for LASV is *Mastomys natalensis* (the multimammate rat)
- Infected rats shed virus in their urine and droppings
- Transmission to humans: direct contact with rats; inhalation or ingestion of rodents' urine, saliva, or droppings
- Human-to-human transmission of LASV can occur through contact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

Neurological sequalae:

Hearing loss, ataxia, vertigo, vision distortion

Treatment

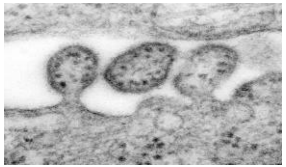
- Supportive care
- Ribavirin
- There are no other approved therapeutics or an approved vaccine for the treatment or prevention of LF

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%

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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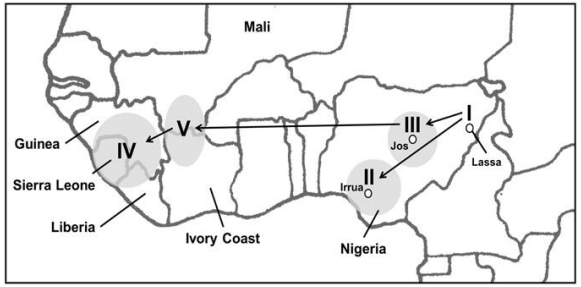
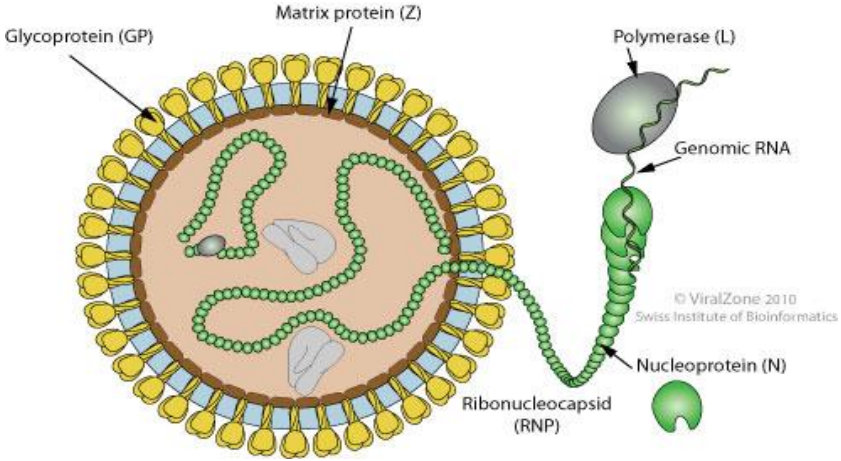


Image obtained from Manning JT, Forrester N, and Paessler S. *Front Microbiol.* 2015;6:1037. doi: 10.3389/fmicb.2015.01037.



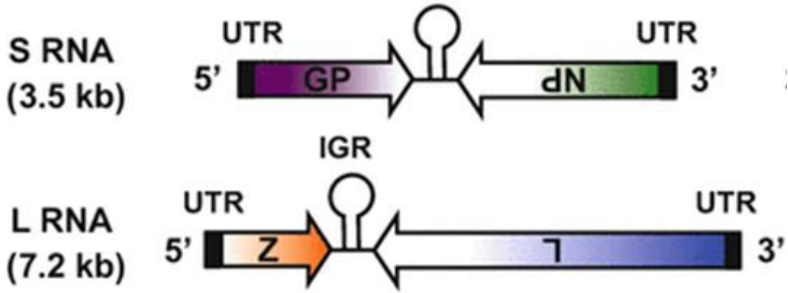
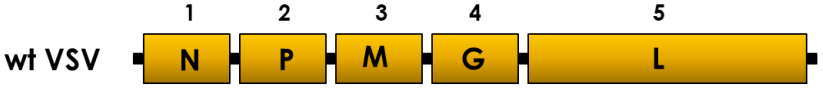


Image obtained from Martinz-Sobrido L & De la Torre JC. *Viruses*. 2016;8(7):197. doi: 10.3390/v8070197.

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

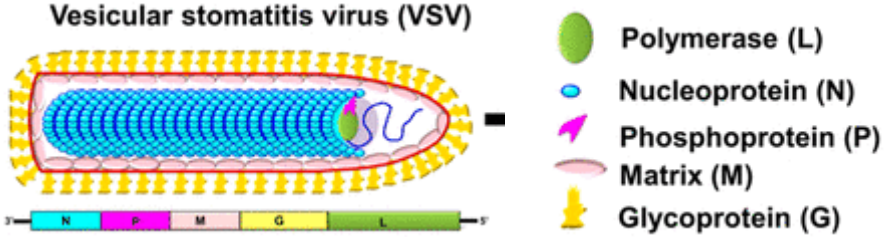


Image obtained from: Sheeba R, et al. *ACS Omega*. 2022 Sep 6;7(37):32840-32848. https://doi.org/10.1021/acsomega.2c03517.

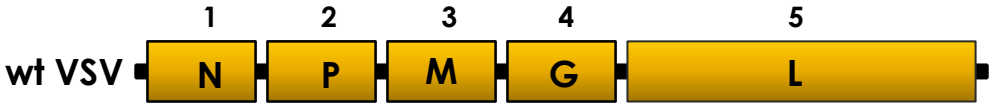
Advantages as a vaccine vector

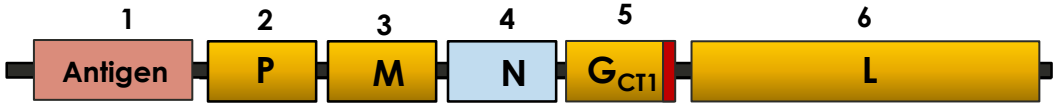
- Simple genome, can be easily manipulated
- Can robustly and stably express a foreign transgene
- Produces a strong humoral and cellular immune response
- Pronounced 3'- 5' transcriptional gradient
- Very little pre-existing immunity in human populations
- Easy to grow to high titer in continuous qualified 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)**

"VesiculoVax N4CT1 Vector"

- **EBS-LASV vaccine candidate**
- **Gene shuffle (N4)**
- **VSV ΔG**

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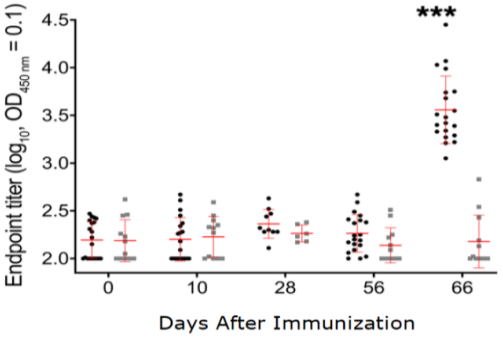
Efficacy and Immunogenicity of EBS-LASV in Cynomolgus Macaques

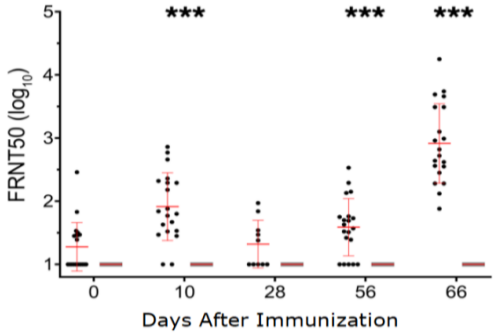
Cross RW et al. *J Clin Invest*. 2020 Jan 2;130(1):539-551.

- EBS-LASV was evaluated as part of a quadrivalent vaccine (containing EBS-LASV and components targeting EBOV, SUDV, and MARV)
- A single dose containing $1x10^7$ 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)**

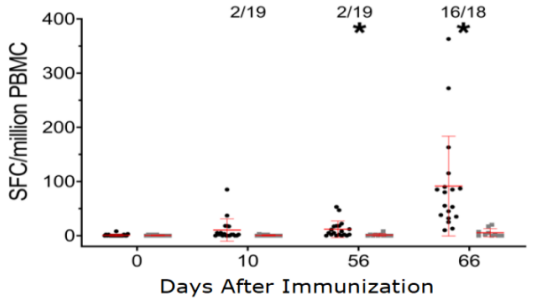
LASV GP – IgG ELISA Titers



LASV GP Neutralization Antibody Response



LASV GP – INFγ ELISpot Response



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GLP Repeat Dose (N+1) Toxicity Study of EBS-LASV in New Zealand White Rabbits by IM Injection

Group	Test Material	Dose Route	Dose Volume (mL)	Dosing Days	Number of Animals			
					Main Study		Recovery Study	
					M	F	M	F
1	0.9% Sodium chloride	IM	0.5	1, 22, 43	5	5	5	5
2	EBS-LASV ($5x10^7$ PFU/animal)	IM	0.5	1, 22, 43	5	5	5	5

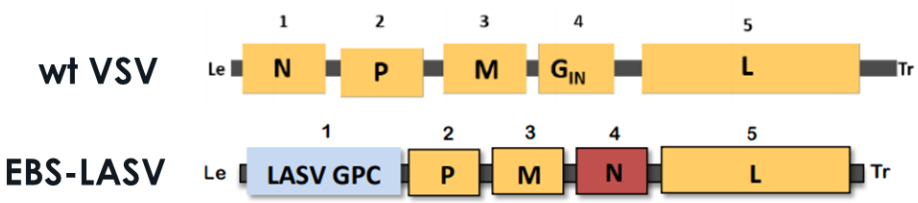
- Administration of EBS-LASV did not result in any changes in:
  - Early mortality or clinical observations, Local irritation assessment, Body temp, Body weights or food consumption
  - Ocular assessments, Hematology, Clinical chemistry, Urinalysis, Organ weights, Macroscopic and microscopic observations.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

Study	Notes and Results
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 $1x10^7$ PFU of EBS-LASV (highest dose) were safe; no animals died • **LD_{50} is > $1x10^7$ 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

Clinical Development Plan

Minimum needed for licensure:

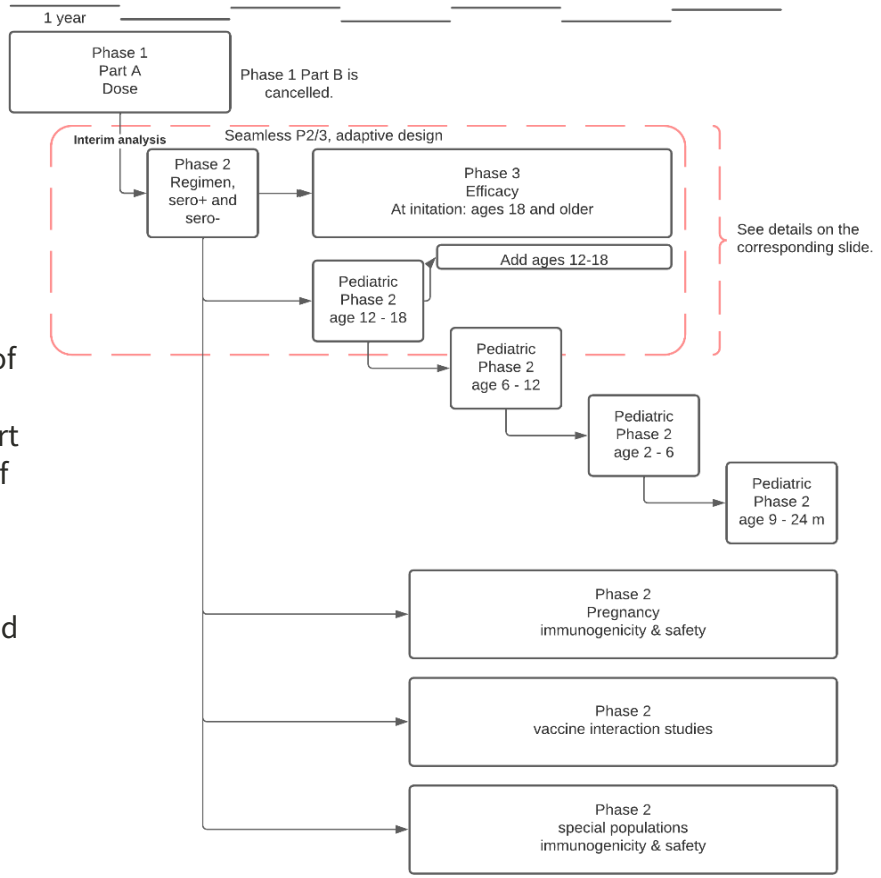
- P1 dose finding
- P2 regimen finding
- P3 efficacy, ideally including 200 exposed adolescents

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

Patrick Ansah,MD, MGCP

Kintampo Health Research Center

Director
DR. KWAKU POKU ASANTE

Cohort	Arm	Sample Size (N)	Treatment and Dose	Schedule
1	1.1	9	EBS-LASV 1×10^5 $TCID_{50}$ (Low)	Day 1, 29
	1.2	3	Placebo	Day 1, 29
SMC safety review through Day 15				
2	2.1	9	EBS-LASV 1×10^6 $TCID_{50}$ (Medium)	Day 1, 29
	2.2	3	Placebo	Day 1, 29
SMC safety review through Day 15				
3	3.1	9	EBS-LASV 1×10^7 $TCID_{50}$ (High)	Day 1, 29
	3.2	3	Placebo	Day 1, 29
SMC safety review through Day 15; Interim Analysis through Week 8 (Day 57±3)				

SMC, Safety monitoring committee; $TCID_{50}$ Fifty-percent tissue culture infective dose

Image modified from The World Factbook 2021. Washington, DC: Central Intelligence Agency, 2021. https://www.cia.gov/the-world-factbook/countries/ghana/map.

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

Acknowledgements

Phase 1 Sites

Navrongo Health Research Center

Kintampo Health Research Center

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