IAVI VSV Lassa Fever Vaccine Candidate Development Overview

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Dr. Swati Gupta, Vice President
Emerging Infectious Diseases and Epidemiology
IAVI
WHO-CEPI Lassa Workshop, Abuja, Nigeria
IAVI gratefully acknowledges the generous support provided by the following major funders:

[Logos of various funders]

Biomedical Advanced Research and Development Authority (BARDA) | Foundation for the National Institutes of Health | National Institute of Allergy and Infectious Diseases | amfAR, The Foundation for AIDS Research | Broadway Cares/Equity Fights AIDS | Cancer Research UK | The City of New York, Economic Development Corporation | Congressionally Directed Medical Research Program (DoD) | GSK | The Hearst Foundations | Keith Haring Foundation | Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the USA and Canada)

And many other generous individuals and partners around the world

As of April 2022
IAVI and an extensive network of partners are advancing multiple VSV-Vectored vaccines

- **VSVΔG-SUDV***
  - Funded by Biomedical Advanced Research and Development Authority (BARDA)
  - Pre-clinical studies underway

- **VSVΔG-MARV***
  - Funded by US Defense Threat Reduction Agency (DTRA)
  - Pre-clinical studies complete

- **VSVΔG-LASV***
  - Funded by Coalition for Epidemic Preparedness Innovation (CEPI) and European & Developing Countries Clinical Trials Partnership (EDCTP)
  - Ph1 in U.S. and W. Africa

- **VSVΔG-SARS-CoV-2***
  - Funded by DTRA, Japan MOF/World Bank
  - Pre-clinical studies underway

- **VSVΔG-SARS-CoV-2***
  - Funded by Merck, BARDA, DTRA, Japan MOF
  - Ph1 Trial Complete –

*Licensed through the Public Health Agency of Canada*
Key attributes of our rVSVΔG-LASV-GPC (lineage IV) vaccine

- A single IM injection is **100% efficacious** in cynomolgus macaques – protection is **durable out to 1-year** post vaccination
  - The original research vaccine (2x10e7 PFUs) protected when LASV challenge (IM challenge; Lineage IV) was conducted 1 month after vaccination (Geisbert et al, 2005, PMID: 15971954)
  - Vaccine prepared from the IAVI-CEPI preMVS (2x10e7 or 2x10e5 PFU doses) protected at 1 month and 12 months after vaccination

- Murine biodistribution study **supports an acceptable tolerability and safety profile**
  - No viable virus distribution to the brain after mice were injected (IM) with a human dose
  - From the large number of samples evaluated only a single injection site sample from Day 3 had a viable viral titer above the LLOQ

- Vaccination of macaques induces **detectable serum nAbs** active against Lineage IV GPC
  - Detectable cross-neutralization against geographically diverse Lineages I-III, V and VII

- Capable of inducing **fast-acting immunity** that will be important in outbreak situations
  - High dose (2x10e7 PFUs) of IAVI-CEPI vaccine induced detectable binding antibodies by d10 in macaques
  - Protection against a Lineage II challenge virus as soon as 3 or 7 days following vaccination (Cross et al, 2022, PMID: 35858566)

- Builds on the **VSV technology used for licensed ERVEBO® vaccine**
  - High probability of success moving through product development
  - VSVΔG-LASV-GPC US Phase 1 trial safety data is encouraging (currently blinded¹)

- **Promising immunogenicity** in Phase 1 clinical study

¹ All safety data are blinded; data current as of July 28, 2022
**Clinical**

**Phase 1 trial design and update**

- FIH at US sites achieved 15 July 2021
- All volunteers in the U.S. have been enrolled and day 28 immunogenicity data are complete
- Regulatory and ethics approval received in Liberia and participants are being enrolled
- Protocol amended to include a booster dose for half the participants in all 3 dose groups in Liberia

<table>
<thead>
<tr>
<th>Dose Escalation</th>
<th>Study Design</th>
<th>Vaccine Dosage (pfu)</th>
<th>N (Active / Placebo)</th>
<th>Month 0</th>
<th>Week 6</th>
</tr>
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<tbody>
<tr>
<td>US Sites</td>
<td>1</td>
<td>(2 \times 10^4)</td>
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<td>(2 \times 10^5)</td>
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<td>3</td>
<td>(2 \times 10^6)</td>
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<td>4B</td>
<td>(2 \times 10^7)</td>
<td>8/2</td>
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<table>
<thead>
<tr>
<th>SMC Review</th>
<th>Dose Group Expansion</th>
<th>Liberia (and US sites if needed)</th>
<th>Vaccine Dosage (pfu)</th>
<th>N (Active / Placebo)</th>
<th>Month 0</th>
<th>Week 6</th>
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<td>5A</td>
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**Total = 110 (88/22)**
Safety Summary – General Information

Study Status¹

52 participants enrolled in a US population between July 2021 - June 2022

- Group 1: $2 \times 10^4$ pfu (n=10)
- Group 2: $2 \times 10^5$ pfu (n=10)
- Group 3: $2 \times 10^6$ pfu (n=10)
- Groups 4A: $2 \times 10^7$ pfu, single dose (n=11)
- Group 4B: $2 \times 10^7$ pfu, prime/boost (n=11)
- All groups were randomized 4:1 active: placebo

Enrollment is complete in the US and participants are being followed

Enrollment in Liberia is open, and participants are being screened

¹ All safety data are blinded; data current as of July 28, 2022
## Phase 1A Reactogenicity Summary

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (N=10)</th>
<th>Group 2 (N=10)</th>
<th>Group 3 (N=10)</th>
<th>Group 4A/4B Dose 1 (N=22)</th>
<th>Group 4B Dose 2 (N=11)</th>
</tr>
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<tbody>
<tr>
<td>Participants ever experiencing an event</td>
<td>8 (80.0%)</td>
<td>8 (80.0%)</td>
<td>9 (90.0%)</td>
<td>22 (100%)</td>
<td>10 (90.9%)</td>
</tr>
<tr>
<td>Participants with local site reactions</td>
<td>3 (30.0%)</td>
<td>4 (40.0%)</td>
<td>6 (60.0%)</td>
<td>18 (81.8%)</td>
<td>8 (72.7%)</td>
</tr>
<tr>
<td>Participants with systemic reactions</td>
<td>8 (80.0%)</td>
<td>7 (70.0%)</td>
<td>8 (80.0%)</td>
<td>22 (100%)</td>
<td>7 (63.6%)</td>
</tr>
<tr>
<td><strong>Maximum Reported Severity</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Grade 1</td>
<td>4 (40.0%)</td>
<td>5 (50.0%)</td>
<td>4 (40.0%)</td>
<td>4 (18.2%)</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4 (40.0%)</td>
<td>3 (30.0%)</td>
<td>4 (40.0%)</td>
<td>8 (36.4%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td>Grade 3 *</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (10.0%)</td>
<td>10 (45.5%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Average onset of events (days post vaccination)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.1</td>
<td>3.1</td>
<td>2.1</td>
<td>2.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Grade 3+ events</td>
<td>10</td>
<td>2.2</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average duration of events (days)</td>
<td>1.3</td>
<td>1.6</td>
<td>2.2</td>
<td>2.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Grade 3+ events</td>
<td>2.0 **</td>
<td>1.2</td>
<td>2.0</td>
<td></td>
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</tbody>
</table>

* All systemic events
** Event lasted 12-hours but spanned two days and is therefore counted on each day in the patient diary
Safety Conclusions

• No related SAEs
• No unsolicited adverse event pattern of concern reported
• No hearing loss
• Average duration of reactogenicity is between 1.3-2.2 days and resolved without sequelae
• Grade 3 reactogenicity are mainly systemic events and the vast majority are in Groups 4A and 4B
• Reactogenicities did not result in any participant discontinuing from study participation and there has been no safety signal warranting a study pause per the Independent Safety Monitoring Committee review

NOTE: In the Phase 2a trial we will evaluate two doses, 2x10^6 pfu and 1x10^7 pfu (half the highest dose in Phase 1) to determine which dose provides the optimal safety and immune response profile
Clinical

Phase 1 Immunogenicity – Serum Antibody response against Lineage IV LASV GP at Day 28

6/10 participants seroconverted
2 placebos

7/10 participants seroconverted
2 placebos

8/10 participants seroconverted
2 placebos

15/19 participants seroconverted
4 placebos

Study Group | Dose (pfu) | Active/Placebo
---|---|---
1 | $2 \times 10^4$ | 8/2
2 | $2 \times 10^5$ | 8/2
3 | $2 \times 10^6$ | 8/2
4A/B | $2 \times 10^7$ | 16/4

Key

Lower Limit of quantification
IgG binds GPC from multiple Lassa virus lineages
Research assay (ELISA, day 28)

Figure 1. Titration curves of a pool of high responding vaccinee samples (from G1, G3 & G4) to LASV GP from Lineages II, III, IV and VII.

Figure 2. A pool of high responding vaccinee samples was tested at 1:500 dilution for binding to LASV GP from Lineages II, III, IV and VII.
Clinical Phase 2a Trial Design

WRP-N (Walter Reed Program - Nigeria)
   Abuja, Nigeria

KGH (Kenema Government Hospital)
   Kenema, Sierra Leone

PREVAIL, Redemption Hospital
   Monrovia, Liberia

Adults 18 – 70 yo (N=192)

Adolescents 12-17 yo (N=120)

Children 6-11 yo (N=120)

Children 18mo - 5yo (N=120)

HIV-infected adults 18-50 yo (N=60)
Phase 2a Study Endpoints, Evaluations & Goal

**Goal:** Select one dose that is safe and immunogenic for the general population (healthy adults and adolescents) and in children and HIV+ and prepare sites for a larger efficacy trial. Phase 2a trial to include $1 \times 10^7$ pfu as higher dose and $2 \times 10^6$ pfu as lower dose based on tolerability data and immunogenicity in Phase 1 dose escalation trial.

**Primary:** Safety & Tolerability at 2 dose levels (chosen from Phase 1 data)

**Secondary:**
- Immunogenicity [percent of volunteers responding and magnitude of neutralizing and binding antibody response to LASV-GPC]
- Vaccine Viremia
- Vaccine Viral Shedding

**Exploratory:** Additional immunogenicity assessments may include Anti-GPC IgG effector functions; Anti-GPC epitope specificity; Anti-GPC T-cell frequencies; Cytokine profiles; Immune responses to VSV; Gene expression profiles (transcriptomics); B cells, plasma and/or serum may also be analysed for epitope specificity and human monoclonal antibodies may be produced.
Late-Stage Development Thoughts

• The objective of the late-stage clinical development plan is to demonstrate efficacy through conduct of a field study with a clinical disease endpoint

• Site selection will depend on country-specific surveillance data from ongoing epidemiological studies to identify regions expected to have the highest incidence of Lassa virus infection

• A 2nd Phase 2 study is being considered in high-risk areas to evaluate site readiness, prior to pivotal efficacy trial

• Phase 2B/3 safety/efficacy registration study in adults and children (aged ≥18 months) is planned for Sierra Leone, Liberia and Nigeria

• Safety and immunogenicity trials to support a path toward larger trials designed to support an indication for pregnant and lactating women and children from 6 months of age for prophylaxis and possibly younger for acutely exposed infants.

• Important to determine timing for a lot-to-lot consistency trial
Lassa Epidemiology studies

ENABLE, funded by CEPI
- Benin, Guinea, Liberia, Nigeria and Sierra Leone
- N=24,000
- Enrollment complete, follow up underway (12 and 18 month study visits)
- Incidence of symptomatic LF; sero-prevalence and sero-incidence

IAVI X100 LF Epi study, funded by Wellcome Trust
- Sierra Leone (Kenema and Port Loco)
- N=8,010
- Enrollment complete, follow up to start soon (Q4 2022)
- Sero-prevalence and sero-incidence

Walter Reed EID 032
- Nigeria (Owo and Abakaliki)
- N=450
- Enrollment and follow up underway
- Prevalence and incidence
ENABLE and LEAP4WA Consortiums

**Nigeria**

- **WRF-N (Walter Reed Program – Nigeria)**
  - Abuja, Federal Capital Territory
  - PI: Dr. Michael Iroezindu

- **Federal Medical Center**
  - Owo, Ondo State
  - PI: Dr. Oluwemi Ayodeji

- **Irua Specialist Teaching Hospital (ISTH)**
  - Irua, Edo State
  - PI: Prof Danny Asogun

**Alex Ekwueme Federal University Teaching Hospital**

- Abakaliki, Ebonyi State
  - PI: Dr. Benedict Azuogu

- **Liberia**

  - Phoebe Hospital
    - Suakoko
    - PI: Drs. Bernice Dahn, Stephen Kennedy, James Duworoko
    - PI: Dr. Jefferson Sibley (UNC: David Wohl and Billy Fischer)

  - PREVAIL - Redemption Hospital
    - Monrovia
    - PI: Dr. Mark Kien

**Sierra Leone**

- **Kenema Government Hospital**
  - Kenema District
  - PI: Drs. Donald Grant & Robert Garry

**Key**

- CEPI Enable epidemiology study
- Phase I clinical trial
- ENABLE Consortium
- LEAP4WA Consortium
- Wellcome IAVI X100 epidemiology study
- Phase II clinical trial (planned)
- WRAIR EID 032 epidemiology study
IAVI gratefully acknowledges the generous support provided by the following major funders:

- PEPFAR
- USAID
- Bill & Melinda Gates Foundation
- The World Bank
- Ministry of Foreign Affairs of the Netherlands
- UK aid
- From the People of Japan
- Department of Defence, United States of America
- Department of Defence, India
- E D C T P
- CEPI
- New vaccines for a safer world
- Ministry of Foreign Affairs of Denmark
- Danida
- International Development Cooperation
- Wellcome
- Serum Institute of India
- The Research Council of Norway

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