Partnership for Research on Ebola Vaccines in Liberia

Presentation to the Vaccines and Related Biological Products Advisory Committee to the Center for Biologics Evaluation and Research of the Food and Drug Administration

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Background

- March – December 2014
  - Ebola outbreak escalates in West Africa
- August – October 2014
  - Communiques between Liberian and US government re: research partnership
- September 2014
  - Phase I studies of Ebola vaccine candidates initiated
- October 2014
  - NIAID visit to Liberia to discuss overall goals of a clinical research program
- October 2014
  - WHO consultation endorsed concept of a Phase 3 clinical trial in Liberia

Research Partnership Principles

- Must fit within priorities / needs of Liberia
- Envisioned to include studies of pathogenesis, vaccines and therapeutics
- Requires substantial investment and commitment on the part of both countries
- Will benefit from being able to leverage existing capabilities / structures

Liberian – US Joint Clinical Research Partnership

Partnership for Research on Ebola Virus in Liberia (PREVAIL)

- PREVAIL I- Ebola Vaccine Study
- PREVAIL II- Ebola Treatment Study
- PREVAIL III- Ebola Natural History Study

Research Partnership Structure

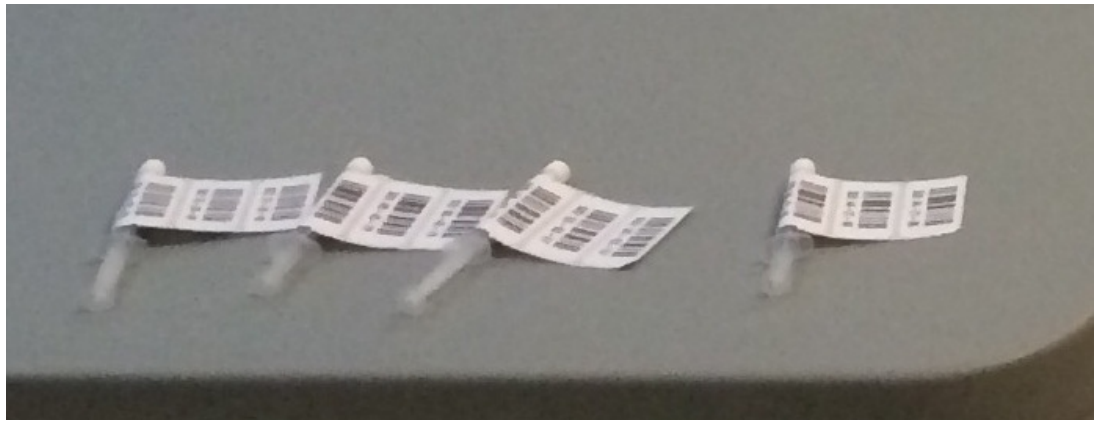
- Governance –
  - Liberian Minister of Health & Social Welfare
  - US Ambassador
- Executive committee
  - Liberian and US senior scientists
- Operations team
  - social mobilization, psychosocial, monitoring & evaluation, data & information technology, principal investigators, pharmacy, site development, laboratory, training, regulatory & ethics

Rationale for Study Design

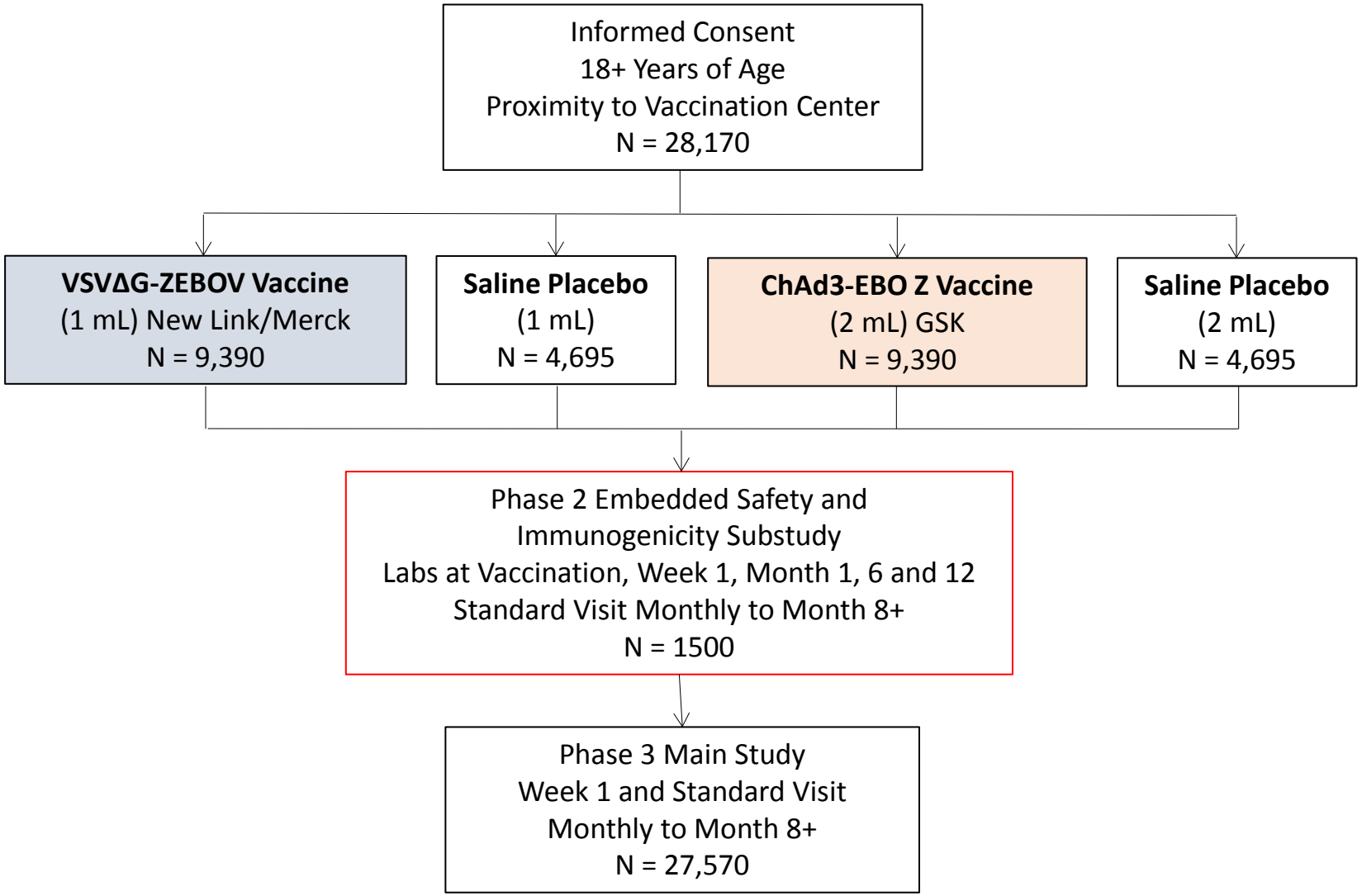
- Randomized, placebo-controlled trial provides most rapid route to identification of a safe and effective vaccine
- Investigational products – thus, placebo-controlled trial allows rigorous assessment of safety and efficacy
- Designs that will allow rigorous assessment of safety and efficacy will provide confidence for future use if products are later used in wide-scale vaccination programs

Vaccines / Design

- ChAd3-EBO Z vaccine
  - dose of 2 x 10^{11} particle units
- VSVΔG-ZEBOV vaccine
  - dose of 2 x 10^{7} plaque forming units
- Normal Saline placebo
- 2/1/2/1 allocation
  - ChAd3-EBO Z (2ml) / placebo (2ml) / VSVΔG-ZEBOV (1ml) / placebo (1ml)
  - Permuted block randomization
  - Study staff and research participants blinded



PREVAIL Vaccine Trial



PREVAIL Vaccine Trial

Primary Objective:

- To determine the efficacy and safety of the ChAd3-EBO Z vaccine and the VSVΔG-ZEBOV vaccine as compared to placebo (pooled placebo groups)

Primary Safety Endpoint:

- Serious adverse events within 30 days of vaccination

Primary Efficacy Endpoint:

- Ebola virus disease (EVD) occurring 21 days or more following randomization and confirmed by a positive blood sample (while alive) or a positive blood or buccal swab sample if deceased

Event-Driven Trial:

- For efficacy, need 112 primary events for each vaccine vs. placebo comparison

Eligibility Criteria

- Inclusion Criteria
  - Informed consent
  - Age ≥ 18 years
  - Likely to be in the surrounding area of the vaccination center for at least one year

- Exclusion Criteria
  - Fever > 38° Celsius
  - History of EVD (self-report)
  - Current pregnancy (negative urine pregnancy test is required for women of child-bearing potential)

Study Schedule

Baseline (Day 0)	Phase 2 substudy	All randomized volunteers (phases 2 and 3)
Informed consent / Demographics / Contact Information / Indicators of increased risk		x
Clinical information / Blood sample / HIV pre-counseling	x	
Week 1 and Month 1		
Clinical information / Blood sample / AEs / HIV & Syphilis results counseling at week 1	x	
Day 3, 10 and 14		
VSV viral RNA measurement for subset of 24 participants	x	
Week 2		
Interview on targeted signs and symptoms (subset of phase 2 substudy)		
Month 6 and 12		
Blood samples for immunogenicity testing	x	
Week 1, Month 1, Month 2 and every 2 months to end of study		
EVD events / SAEs / Deaths		x

Brussels to Redemption Hospital

Redemption Hospital

Visit Compliance in Sub-study
(as of 30 April 2015)

Visit	Number expected	Number (%) attended
Week 1	984	977 (99.3)
Month 1	566	547 (98.4)
Month 2	294	294 (100.0)

DSMB structure / function / recommendations

- Representatives from West Africa, Europe, North America
- Frequent monitoring of AE/laboratory/immunology data during phase 2 portion of study
- Review of 1-month post-vaccination immunology data and lack of AE concerns resulted in recommendation to proceed to phase 3 portion of study in a region where incidence provides rationale to continue
- Limit distribution of pooled outcome data

Baseline Characteristics by Gender

(As of 1 May 2015, n = 1500)

DEMOGRAPHICS / MEASUREMENTS	Overall
Age	32.9 ± 11.3
Female (%)	549 (36.6)
Body temperature °C	36.7 ± 0.3
Weight (lbs)	139.9 ± 25.6
Height (in)	65.8 ± 3.3
BMI (kg/m^2)	22.8 ± 4.4
RISK FACTORS	
Contact in past month with Ebola patient (%)	11 (0.7)
Work involving an Ebola patient (%)	69 (4.6)

Baseline Characteristics by Gender

(as of 1 May 2015, n = 1500)

MEDICAL HISTORY	
High blood pressure (%)	31 (2.1)
Diabetes (%)	5 (0.3)
Cancer (%)	1 (0.1)
Arthritis (%)	10 (0.7)
HIV (%)	9 (0.6)
SPECIMEN DOCUMENTATION	
Blood specimens collected (%)	1498 (99.9)

Baseline blood markers, percentage of participants outside of normal range

(DSMB Report of 21 April 2015, n = 1194)

Chemistries	Normal Range	Mean ± SD	Low Levels	High Levels	Low or High
ALT (U/L)	5-30	10.5 ± 24.5	301 (36.0)	40 (4.8)	341 (40.8)
AST (U/L)	7-31	16.4 ± 20.1	65 (7.8)	49 (5.9)	114 (13.7)
Creatinine (mg/dL)	0.6 – 1.3	1.1 ± 0.5	5 (0.6)	68 (8.1)	73 (8.7)
Chloride (mmol/L	98 – 106	104.6 ± 2.5	3 (0.4)	215 (25.7)	218 (26.1)
Potassium (mmol/L)	3.7 – 4.2	4.2 ± 0.4	68 (8.1)	410 (49.1)	478 (57.2)
Sodium (mmol/L)	135 – 145	140.9 ± 2.4	6 (0.7)	42 (5.0)	48 (5.7)

Baseline blood markers, percentage of participants outside of normal range

(DSMB Report of 21 April 2015)

Hematology	Normal Range	Mean ± SD	Low Levels	High Levels	Low or High
WBC (10e3/ul)	3.7-10.1	5.5 ± 1.5	92 (7.7)	15 (1.3)	107 (9.0)
Neutrophils (10e3/uL)	1.63-6.96	2.6 ± 1.1	212 (17.8)	9 (0.8)	221 (18.6)
Lymphocytes (10e3/uL)	1.09-2.99	2.1 ± 0.6	22 (1.8)	104 (8.7)	126 (10.6)
Monocytes (10e3/uL)	0.24-0.79	0.5 ± 0.2	56 (4.7)	36 (3.0)	92 (7.7)
Eosinophils (10e3/uL)	0.03-0.44	0.3 ± 0.3	34 (2.9)	238 (20.0)	272 (22.8)
Basophils (10e3/uL)	0.00-0.08	0.1 ± 0.0	0 (0.0)	230 (19.3)	230 (19.3)
Neutrophils (%)	39.3-73.7	46.0 ± 10.8	346 (29.1)	7 (0.6)	353 (29.6)
Lymphocytes (%)	18.0-48.3	38.9 ± 9.2	14 (1.2)	179 (15.0)	193 (16.2)
Monocytes (%)	4.4-12.7	8.5 ± 2.5	34 (2.9)	62 (5.2)	96 (8.1)
Eosinophils (%)	0.60-7.30	5.4 ± 4.6	32 (2.7)	289 (24.3)	321 (27.0)

Baseline blood markers, percentage of participants outside of normal range

(DSMB Report of 21 April 2015)

Hematology	Normal Range	Mean ± SD	Low Levels	High Levels	Low or High
Basophils (%)	0.0-1.7	1.3 ± 0.5	0 (0.0)	224 (18.8)	224 (18.8)
RBC (10e6/uL)	4.7-6.1	5.1 ± 0.6	339 (28.5)	92 (7.7)	431 (36.2)
HGB (g/dL)	13.0-18.0	13.7 ± 1.7	367 (30.8)	7 (0.6)	374 (31.4)
MCV (fl)	81.1-96.0	81.2 ± 7.0	507 (42.6)	10 (0.8)	517 (43.4)
MCH (pg)	27.0-31.2	27.0 ± 3.1	515 (43.2)	67 (5.6)	582 (48.9)
MCHC (g/dL)	31.8-35.4	33.2 ± 1.4	186 (15.6)	48 (4.0)	234 (19.6)
HCT (%)	37.7-53.7	41.2 ± 4.5	239 (20.1)	4 (0.3)	243 (20.4)
RDW (%)	11.5-14.5	13.2 ± 1.5	73 (6.1)	167 (14.0)	240 (20.2)
PLT (10e3/uL)	155-366	219.6 ± 60.3	145 (12.2)	23 (1.9)	168 (14.1)
MPV (fl)	6.9-10.6	7.8 ± 1.5	367 (30.8)	57 (4.8)	424 (35.6)

Baseline blood markers, percentage of participants outside of normal range

(DSMB Report of 21 April 2015)

Other Markers	Normal Range	Mean ± SD	Low Levels	High Levels	Low or High
APTT (sec)	26-40	38.9 ± 6.3	2 (0.2)	408 (34.2)	410 (34.3)
D-dimer (µg/mL)	0.0-0.5	0.6 ± 0.8	0 (0.0)	349 (29.3)	349 (29.3)

Baseline lab grade toxicity

(DSMB Report of 21 April 2015)

Blood Measure	No Toxicity (%)	Grade 1	Grade 2	Grade 3	Grade 4
ALT (U/L) High	803 (96.2)	21 (2.5)	9 (1.1)	1 (0.1)	1 (0.1)
		1.25-2.5 ULN	2.6-5.0 ULN	5.1-10.0 ULN	> 10.0 ULN
AST (U/L) High	800 (95.8)	28 (3.4)	4 (0.5)	2 (0.2)	1 (0.1)
		1.25-2.5 ULN	2.6-5.0 ULN	5.1-10.0 ULN	> 10.0 ULN
Creatinine (mg/dL) High	796 (95.3)	23 (2.8)	13 (1.6)	2 (0.2)	1 (0.1)
		1.1-1.3 ULN	1.4-1.8 ULN	1.9-3.4 ULN	>=3.5 ULN
Potassium (mmol/L) High	835 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		5.6-6.0	6.1-6.5	6.6-7.0	> 7.0
Potassium (mmol/L) Low	819 (98.1)	14 (1.7)	2 (0.2)	0 (0.0)	0 (0.0)
		3.0-3.4	2.5-2.9	2.0-2.4	< 2.0
Lymphocytes (10e3/uL) Low	1190 (99.9)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
		0.60-0.65	0.50-0.59	0.35-0.49	<0.35
Neutrophils (10e3/uL) Low	1124 (94.4)	50 (4.2)	14 (1.2)	3 (0.3)	0 (0.0)
		1.00-1.30	0.75-0.99	0.50-0.75	<0.50
HGB (g/dL) Low	1136 (95.4)	38 (3.2)	9 (0.8)	6 (0.5)	2 (0.2)
		10.0-10.9	9.0-9.9	7.0-8.9	< 7.0
PLT (10e3/uL) Low	1153 (96.8)	29 (2.4)	7 (0.6)	2 (0.2)	0 (0.0)
		100-125	50-99	25-49	< 25
WBC (10e3/uL) Low	1189 (99.8)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
		2.0-2.5	1.5-2.0	1.0-1.5	< 1.0

Status and Next Steps

- Phase II sub-study vaccinations complete
  - Continue collection of AE data
  - Continue collection of samples
- Phase III expansion
  - Discussions continue regarding expansion to Guinea
  - Event driven study
  - Given current situation of decreasing incidence, sample size anticipated to increase 9 to 10-fold

Acknowledgements

- Liberian partners and collaborators
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  - US Public Health Service
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  - US Department of Defense
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