GSK Proposed Phase 2 Program for ChAd3 EBOV Vaccine Candidate
Vaccine availability for Phase 2 program

Dependent upon:

• Dose level selected in Phase 1
• Productivity of the current manufacturing process (at least two 200L lots)
• Expected range: 7500 to 15,000 doses, possibly more…
Outline of the Phase 2 program in West Africa

- Phase 2a randomized controlled trial (RCT) of ChAd3 EBOV vaccine in African countries outside the Ebola outbreak zone

  in parallel with

- Phase 2b emergency use of ChAd3 EBOV vaccine in HCW at high risk of Ebola infection due to participation in care of patients with EVD (options to be presented)
Phase 2a

A randomized controlled trial (RCT) of ChAd3-EBOV vaccine in West African countries outside of the Ebola outbreak zone
Countries considered for Phase 2a RCT
Phase 2a RCT assumptions

- Dose selected in Ph 1 based on safety and immunogenicity
- Multicountry, multisite RCT designed to collect comprehensive safety, immunogenicity, and outcomes data to help support licensure
- Pediatric component for children aged 4-17 with appropriate age de-escalation design, other at-risk groups TBD
- Oversight by WHO, Data Safety Monitoring Board, appropriate regulatory oversight
Phase 2a RCT study design

- Randomized, controlled (saline?), observer-blind study with cross-over at 3 months (TBD)
- N=3,000 including pediatric component
- Single common protocol approved at country level and implemented at all study sites with minor modifications allowed per ethical review board requirements
- Informed consent provided prior to study activities
- Healthy adults 18 years of age and older
Phase 2a RCT study design

- Pre- and post-vaccination blood taken for immunology and clinical safety labs
- Sub-cohort selected for cell mediated immunity (CMI), depending upon capacity to collect peripheral blood mononuclear cells
- Standard safety follow-up for 28 days post-vaccination.
- Serious adverse events (SAE) followed until study completion (12 months) with particular attention to medically attended AEs and deaths for suspected EVD
Phase 2a RCT in children aged 4-17 yrs

- Common protocol implemented in one or more study sites with minor modifications allowed per ERB requirements
- IC provided by parent or legal guardian, and child assent per local requirements
- Study start at least 30 days after start of adult study to permit review of safety data
- Appropriate age de-escalation design
- Randomised controlled Phase 2 study (N ≈ 500) with cross-over at 3 months
Phase 2a RCT in children aged 4-17 yrs

• Healthy children randomised to either ChAd3 EBOV vaccine (those aged 12-17 at adult dose and those aged 4-11 at half adult dose) or control vaccine (TBD)
• Pre-and post-vaccination blood taken from all subjects for safety labs
• Sub-cohort selected for CMI
• Safety follow up for 28 days post vaccination.
• SAE followed until study completion (12 months) with particular attention to medically-attended AE and deaths for suspected EVD
Emergency use of ChAd3 EBOV vaccine in HCW at high risk of Ebola infection due to participation in care of patients with EVD
Vaccination of HCW at high risk of EVD

Patients with EVD are being managed by HCW working in widely dispersed sites across three countries.

This presents very significant challenges for implementing and coordinating clinical trials of experimental Ebola vaccines.
Issues to consider

• Ethics (allocation, use of placebo, informed consent)
• Objectives (detect VE, uncommon safety signals)
• Design (prospective cohort/stepped-wedge vs RCT)
• Feasibility (logistics, transportation, security…)
• Implementation (who, how, where, when)
• Approvals and oversight (Regulators, WHO, DSMBs, others…)}
A prospective cohort, randomized stepped-wedge design with blinded assessment of vaccine efficacy
Prospective cohort study design

• Baseline survey to define EVD rates in at-risk population in the absence of vaccination

• Vaccination performed in ETF by mobile vaccination teams trained in what may be considered as an accelerated stepped-wedge design

• Randomization of ETF as to sequence of vaccination

• All HCW present during team visit (1-2 days) and willing to provide informed consent will be vaccinated (i.e., individuals are unblinded)
Prospective cohort study design

- Vaccinees will have baseline blood sample, e-diary card, and post-deployment blood sample
- All enrolled HCW as well as any HCW who are absent, ineligible, or decline vaccination entered into a study register and followed for outcome occurrence of Ebola infection/disease
- Assessment teams remain blinded as to individual vaccination status
- In-study procedures kept to an absolute minimum so as to minimize impact on ETF operations
Prospective cohort study design

• In the event of suspected EVD, blood for RT-PCR (positives sequenced to detect escape mutants), serum for NP ELISA at study end

• Analytic approach to be defined, but e.g., the relative risk could be calculated for occurrence of EVD by vaccination status over the total period of follow up for which data exist

• Study duration = end of deployment or 1 year

• Design contingent on logistical feasibility of staffing and supporting mobile vaccination teams
Phase 2b Option 2

Adaptive, randomized, observer blind, controlled trial design

(NIH and GSK preferred option)
Why consider a randomized controlled trial?

- Most powerful scientific design for detection of vaccine efficacy as it begins with truly randomized groups
- Less likely to give volunteers an unwarranted sense of protection, thus maximizing use of PPE
- No human data on Ebola vaccine efficacy (equipoise)
- Adaptive design to allow for discontinuation of control arm (or vaccination) based on predefined event-driven analyses of near-real time data collected during the trial
Randomized control trial design

- Vaccination performed in centers outside of ETF during in-processing/training of new staff or out-rotation of existing ETF staff, and/or by mobile vaccination team to maximize efficiency and minimize impact on ETF operations
- All HCW providing informed consent are randomized to vaccine or control (see modelization)
- Baseline blood sample, e-diary card, followed for outcome (occurrence of Ebola infection/disease), post-deployment blood sample for serology
Randomized control trial design

• In-study procedures kept to an absolute minimum, control vaccine could be PCV (or saline)
• In the event of suspected EVD, blood for RT-PCR and detect escape mutants), serum e.g., for gP and NP ELISA at study end
• Active case counting by blinded observers with success/failure boundaries monitored by DSMB
• Success dependent upon thorough and rapid case detection and confirmation, requires effective interfaces between all components
Sample size required to detect a range of VE

A sample size of 5000 will allow detection of VE of at least 50%, depending on randomization ratio and duration of F/U.

Calculations performed using PASS, with 2-sided alpha=0.05 and power=90%.
EVD cases required to detect a range of VE

Attack rate (control) = 5% over 6 months

For randomization ratios of 1:4 or less, 60 or fewer EVD cases are required to detect VE ≥ 60%

Calculations performed using PASS, with 2-sided alpha=0.05 and power=90%.