ChAd3-EBO-Z
Update on Phase 1 Program

Second High-level meeting on Ebola vaccines access and financing
8 January 2015
Phase 1 trials of ChAd3-EBO-Z providing data for dose selection

<table>
<thead>
<tr>
<th>Trial</th>
<th>Site</th>
<th>PI</th>
<th>Product (dose)</th>
<th>N</th>
<th>Start Date</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>VRC 207</td>
<td>VRC, NIH, USA</td>
<td>Ledgerwood</td>
<td>Bivalent 2e10 &amp; 2e11 Dose escalation</td>
<td>20</td>
<td>2 Sept 2014</td>
<td>enrolled</td>
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<tr>
<td>EBL01</td>
<td>Oxford, UK</td>
<td>Hill</td>
<td>Monovalent 1e10 &amp; 2.5e10 &amp; 5e10 Dose escalation</td>
<td>60</td>
<td>17 Sept 2014</td>
<td>enrolled</td>
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<td>CVD-1000</td>
<td>Bamako, Mali</td>
<td>Sow/Levine</td>
<td>Monovalent 1e10 (n=10) ; 2.5e10 (n=35) ; 5e10 (n=35); 1e11 (n=11) Dose escalation</td>
<td>91</td>
<td>8 Oct 2014</td>
<td>enrolled</td>
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<tr>
<td>cAd3-EBOZ Lau</td>
<td>Lausanne, CH</td>
<td>Genton</td>
<td>Monovalent 2.5e10 &amp; 5e10, placebo Randomized (D=1:1; ND=2:2:1)</td>
<td>120</td>
<td>31 Oct 2014</td>
<td>enrolled</td>
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<td>VRC 207 Part 2</td>
<td>UMD, USA</td>
<td>Ledgerwood/Lyke</td>
<td>Monovalent 1e10 &amp; 1e11 Randomized 1:1</td>
<td>20</td>
<td>31 Oct 2014</td>
<td>enrolled</td>
</tr>
</tbody>
</table>

All Phase 1 studies used the same lot of monovalent bulk vaccine provided by NIH, (VRC bivalent study formulated from two monovalent bulks). Very similar methodologies used to follow and collect safety data at each site. Cleaned safety data provided to all investigators using a secure GSK on-line tool. Each site had right to perform and report its immunological readouts, but also agreed to provide sera and PBMC to VRC for analyses in common assays.
Preliminary Results from Phase 1 study VRC 207

Methods
• Open-label, dose-escalation from $2 \times 10^{10}$ particle units (n=10) to $2 \times 10^{11}$ particle units (n=10)
• Healthy adults 18-50 years of age. IM administration. Reactogenicity assessed for 7 days.
• Immuno at weeks 0, 2, and 4 against Zaire (Mayinga) and against Zaire (Guinea 2014), ChAd3, & Ad5 at weeks 0 and 4

Safety
• No SAE, SUSAR, or evidence of AEs suggestive of immunopathology
• Transient fever within 1 day in 2 participants at high dose ($T_{\text{max}}$ 38.1°C and 39.9°C)
• Mild or moderate neutropenia or leukopenia 3 to 4 days post-vaccination in 1 low-dose and 3 high-dose vaccine recipients
• AE profile very typical of what has been reported for other ChAd vectored vaccines
• Overall well tolerated at both doses

Preliminary Results from Phase 1 study VRC 207


All participants developed measurable immune responses against Ebola GP

- GP ELISA Zaire (Mayinga) = 90% seroconversion for low-dose (GMT 331 at week 4) and 100% for high-dose (GMT 2037)
- 90% ELISA response for both groups for Zaire using the capture antigen from recent Guinea strain
- CD4 response for 3 of 10 at low dose and 10 of 10 at high dose
- CD8 response for 2 of 10 at low dose and 7 of 10 at high dose
- Antibodies against ChAd3 vector increased by 1.9-fold at week 4 with moderate negative association between titer at baseline and EBO-Z CD8 response (-0.511; P=0.02)

Overall conclusions

- No dose limiting toxicities, more reactogenicity at high dose, but still acceptable
- Evidence for greater overall immunogenicity at 1e11 versus 1e10
- Data are promising for further development assuming similar results seen with monovalent vaccine

Status of other Phase 1 trials

• Safety data through post-vaccination day 28 is available for all vaccinees. Safety data from the majority of subjects have been reviewed by the GSK internal Safety Review Team (SRT) with review of all data expected this week

• Overall safety profile is consistent with what was reported in VRC 207 bivalent study

• No vaccine-related safety signals have been identified

• Most recent GSK SRT comprehensive review of data (18 Dec 2014) found:
  – No new safety signals detected
  – 2 episodes of fever >39 reported, one associated with documented streptococcal pharyngitis
  – 1 non vaccine related SAE (peritoneal TB in an HIV negative adult in Mali)
  – Transient drops in leukocytes, lymphocytes and platelets following vaccination that in almost all cases do not reach thresholds for Grade 1 adverse events
  – Because of arthritis signal reported from VSV trial in Lausanne, detailed analysis of arthralgia/arthritis data from the Phase 1 program was conducted
Status of other Phase 1 trials – Focus on arthralgia/arthritis

- A detailed review was performed of data available as of 18 December 2014 with ChAd3-EBO-Z at all doses across the Phase 1 Ebola trials.

- In trial VRC 207 (1e10 or 1e11 vp) arthralgia was not solicited. Six out of 20 subjects reported myalgia; 4 mild and 2 moderate. There were no reports of arthritis.

- In EBL01 (Oxford), nine (15%) subjects reported arthralgia; 7 cases were mild, 2 moderate. All had a time to onset between day of vaccination and Day 2 and all were self-limiting within 48 hours. No arthritis was reported.

- In EBL03 (Mali), six, (6.6%) subjects reported arthralgia, 4 cases were mild, 2 moderate. No arthritis was reported.

- The Phase 1 trial in Lausanne did not solicit arthralgia, however, 38/99 subjects (38%) reported musculoarticular pain (32 cases mild, and 6 moderate). The events were always reported together with other transient “flu-like” symptoms in the first 2 days post vaccination. No cases or suggestive of arthritis were reported.
• The SRT concluded that rates of solicited arthralgia with what has been observed in with another ChAd3 vectored vaccine candidate (HCV) in Phase 1-2. Of 230 subjects who had received ChAd3-HCV or placebo as of March 10, 2014, 30/230 (13%) reported arthralgia (7.8% mild, 5.2% moderate). No severe arthralgia or arthritis has been reported.

• The SRT also reviewed data from GSK vaccine trials in adults that use proprietary adjuvants AS01 and AS04 (Malaria, HPV) and where arthralgia was solicited. Similar rates of transient arthralgia have been reported (9-16%, transient and not associated with arthritis).

• SRT concluded that there is no safety signal for arthritis or signs or symptoms suggestive of arthritis in the Phase 1 ChAd3-EBOZ program. The pattern of arthralgia observed is benign (early onset after vaccination self-limiting within 2 days, reported in the frame of other flu-like symptoms). No cases of arthritis or severe arthralgia have been reported.
Next steps – Analysis of comprehensive immunological data and dose selection

• Data availability
  – GSK had hoped to have VRC ELISA data available from the Phase 1 program available by 9 Jan 2015 to permit a dose selection decision by 13 Jan 2015
  – Unfortunately, delays in shipping of samples over the Christmas holidays coupled with an NIH stock-out of a critical ELISA reagent (lectin used to bind plate antigen) is causing a delay in data availability
  – GSK believes that despite the encouraging data at 2e11 in VRC 207, and no evidence to date of dose-limiting toxicities at any of the tested doses, it is critical to see the full dose range results from Mali and to be able to compare them to the data obtained from the US and UK studies. Those data will not be available before Jan 15th at the earliest.
  – GSK’s position is that a solid dose selection justification is required
    • To support regulatory and ERC submissions
    • To potentially maximize the number of doses available for further use
    • It is medically sound to give no more vaccine than you need to achieve a desired effect
Upcoming data releases

- EBL01 results (Oxford) are nearly complete. Manuscript submitted to NEJM with possibility for adding final data from VRC at galley stage.

- Trend for a dose response seen between $1 \times 10^9$ and $5 \times 10^9$, but not all data available from VRC, CD4 responses appear to dominate over CD8, but those that are seen are polyfunctional (as in VRC207).

- EBL01 and EBL03 (Mali) have been amended to permit heterologous boosting with polyvalent MVA (Zaire, Sudan-Gulu, Marburg) from Bavarian Nordic and approximately 30 subjects from both trials have received an MVA booster dose.

- Preliminary data on MVA boosting in EBL01 shows that it works (as expected) with significant boosting of IgG and CD8 responses.