



**MRC**

MRC/UVRI Uganda  
Research Unit on AIDS

## CLINICAL TRIAL PROTOCOL

**Trial title:** Open label, dose escalation and age de-escalation for ChAdOx1 85A in Ugandan adults and adolescents, followed by a Phase IIa randomised, open-label trial among adolescents comparing ChAdOx1 85A prime followed by MVA85A boost versus BCG re-vaccination

**Short title:** EMaBS<sup>1</sup> TB Vaccine Study

**Trial Reference:** TB042

**UVRI/REC Ref:**

**UNCST Ref:**

**National Drug Authority Ref:**

**LSHTM Ref:**

**OXTREC Ref:** 2-18

**Date and Version No:** 25.08.2017, version 1.1

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**Other Investigators:** Anne Wajja, Pontiano Kaleebu  
**Trial Site:** Entebbe Hospital and MRC/UVRI Uganda Research Unit on AIDS  
**Sponsor:** University of Oxford  
**Funder:** Medical Research Council, UK

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<sup>1</sup> EMABS: Entebbe Mother and Baby Study

## Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committees and other regulatory bodies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Professors Helen McShane and Alison Elliott.

## Statement of Compliance

The trial will be conducted in compliance with the protocol, the International Conference on Harmonisation Good Clinical Practice Guideline E6 (R2) (ICH-GCP), Medicines for Human Use (Clinical Trial) Regulations 2004 (as amended) and all other applicable regulatory requirements.

## Chief Investigator approval and agreement

I hereby approve this version of the protocol and declare no conflict of interest:

Conflict of interest details: None

Chief Investigator:   
**Helen McShane, Chief Investigator, University of Oxford**


**Date:** 25<sup>th</sup> August 2017

## Principal Investigator Agreement

I have read the trial protocol and agree to conduct the trial in compliance with the protocol, the International Conference on Harmonisation Good Clinical Practice Guideline E6 (R1) (ICH-GCP) and all applicable regulatory requirements.

I declare no conflict of interest:

Conflict of interest details: None

Principal Investigator:   
**Alison Elliott, Principal Investigator, MRC/UVRI Uganda Research Unit on AIDS**

**Date:** 25<sup>th</sup> August 2017

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# 1. AMENDMENT HISTORY

## Protocol v1.1 Substantial/Non-substantial Amendment

| Section | From   | Changed To   |
|---------|--|--|
| 4       | LSC (Local Safety Committee) deleted   | DSMB (Data and Safety Monitoring Board) added  |
| 7.2     | [Addition]   | A consultative group of selected parents will be set up; this group will advise us on issues such as the timing of activities in relation to the school year.  |
| 7.9     | The Local Safety Committee will be consulted if there are any issues of concern.   | The data and safety monitoring board (DSMB) will be consulted if there are any issues of concern.  |
| 7.9     | The follow up period will be six months after first vaccination in accordance with findings from previous studies in which adequate safety data and reliable markers of immunogenicity have been obtained in this time interval. All follow up visits will last approximately 15 to 30 minutes.  | The follow up period will be 24 weeks for groups 1-4, one year for groups 5 and 6, after first vaccination in accordance with findings from previous studies in which adequate safety data and reliable markers of immunogenicity have been obtained in this time interval. All follow up visits will last approximately 15 to 30 minutes.                                     |
| 7.12    | The Local Safety Monitor (LSM) may recommend withdrawal of volunteers.   | Deleted, this role has been replaced by the DSMB   |
| 10.1    | In addition, the Phase IIa randomised trial will be held, and the LSM will be consulted, if any of the following holding criteria occurs.  | In addition, the Phase IIa randomised trial will be held, and the DSMB will be consulted, if any of the following holding criteria occurs.   |
| 10.1    | In addition to these pre-defined criteria, the study can be put on hold upon advice of the Local Safety Monitor, Chief Investigator, Principal Investigator, Study Sponsor, Regulatory Authority, Ethical Committee(s) or Local Safety Committee, for any single event or combination of multiple events which, in their professional opinion, jeopardise the safety of the volunteers or the reliability of the data. | In addition to these pre-defined criteria, the study can be put on hold upon advice of the Chief Investigator, Principal Investigator, Study Sponsor, Regulatory Authority, Ethical Committee(s) or DSMB, for any single event or combination of multiple events which, in their professional opinion, jeopardise the safety of the volunteers or the reliability of the data. |
| 10.5.1  | The local safety monitor (LSM) will be notified of SAEs that are deemed possibly, probably or definitely related to study interventions; the LSM will be notified immediately (within 24 hours) of the Investigators' being aware of their occurrence.   | The data and safety monitoring board (DSMB) will be notified of SAEs that are deemed possibly, probably or definitely related to study interventions; the DSMB will be notified immediately (within 24 hours) of the Investigators' being aware of their occurrence.   |
| 10.5.1  | SAEs will not normally be reported immediately to the Oxford or LSHTM ethical committee(s) unless there is a clinically important increase in occurrence rate, an unexpected outcome, or a new event that is likely to affect safety of trial volunteers, at the discretion of the Chief Investigator and/or   | SAEs will not normally be reported immediately to the Oxford or LSHTM ethical committee(s) unless there is a clinically important increase in occurrence rate, an unexpected outcome, or a new event that is likely to affect safety of trial volunteers, at the discretion of the Chief Investigator and/or DSMB.   |

|      |  |  |
|------|--|--|
|      | LSM.   |  |
| 10.8 | <p><b>Local Safety Committee</b></p> <p>A Local Safety Committee (LSC) will be appointed to provide real-time safety oversight. The LSC will be notified within 24 hours of the Investigators' being aware of the occurrence of SAEs. The LSC has the power to place the trial on hold if deemed necessary following a trial intervention-related SAE. The LSC will be chaired by clinician experienced in early-phase clinical trials. There will be a minimum of two other appropriately qualified committee members. All correspondence between Investigator and LSC will be conveyed by the Chief Investigator to the trial Sponsor. The Chair of the LSC will be contacted for advice and independent review by the Investigator or trial Sponsor in the following situations:</p> <ul style="list-style-type: none"> <li>• Following any SAE deemed to be possibly, probably, or definitely related to the trial challenge agent.</li> <li>• Any other situation where the Investigator or trial Sponsor feels independent advice or review is important.</li> </ul> <p>A Data Safety Monitoring Board is not proposed because the trial is small and not blinded.</p> | <p><b>Data and Safety Monitoring Board (DSMB)</b></p> <p>A data and safety monitoring board (DSMB) will be appointed to provide real-time safety oversight. The DSMB will be notified within 24 hours of the Investigators' being aware of the occurrence of SAEs. The DSMB has the power to place the trial on hold if deemed necessary following a trial intervention-related SAE. The DSMB will be chaired by clinician experienced in early-phase clinical trials. There will be a minimum of two other appropriately qualified committee members. Membership will include a statistician, and at least one Ugandan member. All correspondence between Investigator and DSMB will be conveyed by the Chief Investigator to the trial Sponsor. The Chair of the DSMB will be contacted for advice and independent review by the Investigator or trial Sponsor in the following situations:</p> <ul style="list-style-type: none"> <li>• Following any SAE deemed to be possibly, probably, or definitely related to the trial challenge agent.</li> <li>• Any other situation where the Investigator or trial Sponsor feels independent advice or review is important.</li> </ul> <p>Reports will be provided to the DSMB on completion of recruitment to groups 1 and 2 (adult dose escalation) before proceeding to group 3; and on completion of recruitment to groups 3 and 4 (adolescent dose escalation), before proceeding to the randomised trial (groups 5 and 6).</p> |
| 15.3 | [Addition]   | The Ethics Committees and Regulatory Authorities for this trial comprise the Research Ethics Committee of the UVRI, the Oxford Tropical Research Ethics Committee, the Ethics Committee of the London School of Hygiene & Tropical Medicine, the Uganda National Council for Science and Technology and the Uganda National Drug Authority.  |
| 15.6 | Volunteers will be compensated <i>pro rata</i> for their time, travel and for trial procedures while participating in the trial, amounting to a total of approximately £50, depending on the exact number of visits, site of recruitment and whether any repeat or additional visits are necessary.  | Volunteers will be compensated <i>pro rata</i> for their time, travel and for trial procedures while participating in the trial, amounting to a total of approximately £70, depending on the exact number of visits, site of recruitment and whether any repeat or additional visits are necessary. A small gift will be given to participants on completion.  |



## 2. KEY TRIAL CONTACTS AND ROLES

|                                |   |
|--------------------------------|---|
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### 3. SYNOPSIS

#### 3.1. Trial Synopsis

|                      |   |  |
|----------------------|---|--|
| Trial Title          | Open label, dose escalation and age de-escalation for ChAdOx1 85A, followed by a Phase IIa randomised, open-label trial among adolescents comparing ChAdOx1 85A prime followed by MVA85A boost versus BCG re-vaccination  |  |
| Trial Identifier     | TB042   |  |
| Trial Centres        | MRC/UVRI Uganda Research Unit on AIDS [MRC/UVRI]<br>P.O. Box 49<br>Entebbe<br>Uganda<br>Tel: +256 (0)417 704000<br>Fax: +256 (0) 414 321137   |  |
| Clinical Phase       | Phase IIa   |  |
| Design               | Open label, dose escalation and age de-escalation for ChAdOx1 85A followed by a randomised, open-label trial among adolescents, comparing ChAdOx1 85A prime followed by MVA85A boost versus BCG re-vaccination  |  |
| Trial participants   | Adolescents participating in the Entebbe Mother and Baby Study (EMaBS) birth cohort and their parents   |  |
| Planned Sample Size  | <p>Total: 72 healthy, previously BCG-vaccinated volunteers receiving either ChAdOx1 85A intramuscularly at different doses, or a prime-boost regimen of ChAdOx1 85A intramuscularly followed by MVA85A intramuscularly, or BCG re-vaccination intradermally.</p> <p><i>Dose escalation in adults</i><br/>Group 1: 3 adults who are parents of EMaBS participants, to receive ChAdOx1 85A at <math>5 \times 10^9</math> vp<br/>Group 2: 3 adults who are parents of EMaBS participants, to receive ChAdOx1 85A at <math>2.5 \times 10^{10}</math> vp</p> <p><i>Age de-escalation and dose escalation in adolescents</i><br/>Group 3: 3 adolescents who are EMaBS participants, to receive ChAdOx1 85A at <math>5 \times 10^9</math> vp<br/>Group 4: 3 adolescents who are EMaBS participants, to receive ChAdOx1 85A at <math>2.5 \times 10^{10}</math> vp</p> <p><i>Randomised comparison of ChAdOx1 85A-MVA85A versus BCG revaccination</i><br/>Group 5: 30 adolescents who are EMaBS participants, to receive ChAdOx1 85A at <math>2.5 \times 10^{10}</math> vp followed by MVA85A boost<br/>Group 6: 30 adolescents who are EMaBS participants, to receive BCG revaccination</p> |  |
| Vaccination Schedule | ChAdOx1 85A or BCG revaccination on day zero; where applicable MVA85A on day 56   |  |
| Follow-up Duration   | 24 weeks after vaccination for groups 1-4; one year after first vaccination for groups 5 and 6  |  |
| Trial Interventions  | Intramuscular or intradermal vaccination<br>Venepuncture  |  |
| Trial Duration       | Estimated 30 months   |  |
| Planned Trial Period | Prospective start date for enrolment 01.02.2018   |  |
|                      | Objectives  | Outcome Measures   |
| Primary              | To evaluate the safety and immunogenicity of ChAdOx1 85A – MVA85A prime-boost vaccination in Ugandan adolescents  | Actively and passively collected data on adverse events<br>T-cell Interferon- $\gamma$ ELISpot response to antigen 85A and PPD |
| Secondary            | To further characterise immunogenicity  | Antibody response to antigen 85A and   |

|                          |  |  |
|--------------------------|--|--|
|                          | of ChAdOx1 85A – MVA85A prime-boost vaccination in Ugandan adolescents   | PPD; exploratory immunology including flow cytometry, gene expression, and mycobacterial growth inhibition assays  |
| Tertiary                 | <ol style="list-style-type: none"> <li>To compare the response to ChAdOx1 85A – MVA85A prime-boost vaccination with the response to BCG revaccination in Ugandan adolescents</li> <li>To compare the response to ChAdOx1 85A – MVA85A prime-boost vaccination in Ugandan adolescents with the response in Oxford adults</li> <li>To investigate pre-immunisation epidemiological and immunological characteristics associated with the immune response induced by ChAdOx1 85A – MVA85A prime-boost vaccination in Ugandan adolescents</li> </ol>   | <p>T-cell Interferon-<math>\gamma</math> ELISpot response to antigen 85A and PPD</p> <p>Antibody response to antigen 85A and PPD; exploratory immunology including flow cytometry, gene expression, and mycobacterial growth inhibition assays</p> |
| Investigational products | Investigational products: ChAdOx1 85A, MVA85A<br>Comparator: Bacille Calmette Guerin (BCG); strain in use in Uganda at the time of the trial   |  |
| Dose(s)                  | ChAdOx1 85A: $5 \times 10^9$ vp and $2.5 \times 10^{10}$ vp<br>MVA85A: $1 \times 10^8$ pfu<br>BCG: 0.1 ml  |  |
| Route of administration  | ChAdOx1 85A: intramuscular needle injection in the deltoid region of the arm<br>MVA85A: intramuscular needle injection in the deltoid region of the arm<br>BCG: intradermal needle injection in the deltoid region of the arm  |  |
| Allocation Method        | <p>Group 1: the first three adults will receive ChAdOx1 85A at <math>5 \times 10^9</math> vp<br/>Group 2: the next three adults will receive ChAdOx1 85A at <math>2.5 \times 10^{10}</math> vp</p> <p>Group 3: the first three adolescents will receive ChAdOx1 85A at <math>5 \times 10^9</math> vp<br/>Group 4: the next three adolescents will receive ChAdOx1 85A at <math>2.5 \times 10^{10}</math> vp</p> <p>Thereafter, 60 adolescents will be randomised, 30 (group 5) to receive ChAdOx1 85A at <math>2.5 \times 10^{10}</math> vp followed by MVA85A boost and 30 (group 6) to receive BCG revaccination</p> |  |

### 3.2. Schedule of visits and procedures for groups 1-4

| Visit number  | 1         | 2    | 3       | 4       | 5       | 6       | 7        |
|---|-----------|------|---------|---------|---------|---------|----------|
| Timeline (days)*  | Screening | 0    | 2       | 14      | 28      | 56      | 168      |
| Timeline (weeks)*   |           | 0    |         | 2       | 4       | 8       | 24       |
| Time windows (days)   | -90 to -7 |      | $\pm 1$ | $\pm 3$ | $\pm 5$ | $\pm 5$ | $\pm 14$ |
| Vaccination, ChAdOx1 85A  |           | x    |         |         |         |         |          |
| Inclusion/exclusion criteria  | x         | x    |         |         |         |         |          |
| Review contra-indications   | x         | x    |         |         |         |         |          |
| Informed consent  | x         |      |         |         |         |         |          |
| Medical history   | x         | (x)  | (x)     | (x)     | (x)     | (x)     | (x)      |
| Physical examination  | x         | (x)  | (x)     | (x)     | (x)     | (x)     | (x)      |
| Vital signs   | x         | x    | x       | x       | x       | x       | x        |
| Urinalysis  | x         |      |         |         |         |         |          |
| $\beta$ -HCG urine test (female only)   | x         | x    |         |         |         |         |          |
| Stool parasitology  | x         | x    | x       |         |         |         | x        |
| Anthelmintic treatment  |           |      |         |         |         | x       |          |
| Local & systemic events/reactions   |           | x    | x       | x       | x       | x       | x        |
| Diary cards provided  |           | x    |         |         |         |         |          |
| Diary cards collected   |           |      |         | x       |         |         |          |
| Biochemistry (4mL)**/**   | x         |      |         | x       |         |         |          |
| HBV, HCV, HIV (6mL)   | x         |      |         |         |         |         |          |
| Haematology: full blood count and storage (2mL)                                     | x         |      | x       | x       |         |         |          |
| Mansonella perstans (1mL)***  | x         |      |         |         |         |         | x        |
| Malaria RDT/slide; PCR (1mL)  | x         | x*** |         | x       | x       |         | x        |
| Assessments of immunogenicity and exploratory immunology incl ELISpot (10-20mL)**** | x         | x    | x       | x       | x       | x       | x        |
| Gene expression (2mL)   | x         |      | x       |         |         |         |          |
| Blood vol (mL)  | 36        | 0    | 6       | 28      | 9       | 5       | 24       |
| Cumulative blood vol (mL)   | 36        | 36   | 42      | 70      | 79      | 84      | 108      |

X Event scheduled to occur

(X) If considered necessary, emphasising any complaint or change in medications

\* Timeline is approximate only, as exact timings ( $\pm$  windows periods) of visits relate to the actual (not intended) date of the previous visit

\*\* Urea & electrolytes, liver function tests

\*\*\* Repeated on vaccination day if delay from screening is more than 28 days

\*\*\*\* Exploratory immunology blood volume will be guided by guidelines from Harvard Mass General, where a maximum of 3ml/kg body weight is taken at any one time point and not more than 3ml/kg is taken over any 8 week period (ref [http://www.drgreene.com/21\\_1616.html](http://www.drgreene.com/21_1616.html).) These guidelines have been followed in previous studies vaccinating adolescents and children with MVA85A (in South Africa [1]). The total blood volume planned is 84 ml over the initial intensive sampling period of 8 weeks. Revision of sample volumes based on weight will only be required for children who weigh less than 28 kg; the average weight of children aged 11 is expected to be greater than 35kg, with greater weights for older children.

Table 1.1. Schedule of trial procedures groups 1-4

### 3.3. Schedule of visits and procedures for groups 5 and 6

| Visit number  | 1         | 2     | 3   | 4   | 5   | 6              | 7   | 8   | 9   | 10    |
|---|-----------|-------|-----|-----|-----|----------------|-----|-----|-----|-------|
| Timeline (days)*  | Screening | 0     | 2   | 14  | 28  | 56             | 63  | 84  | 168 | 365   |
| Timeline (weeks)*   |           | 0     |     | 2   | 4   | 8              | 9   | 12  | 24  |       |
| Time windows (days)   | -90 to -7 |       | ±1  | ±3  | ±5  | ±5             | ±1  | ±5  | ±14 | ±/-28 |
| Vaccination, ChAdOx1 85A or BCG   |           | x     |     |     |     |                |     |     |     |       |
| Vaccination, MVA85A <sup>§</sup>  |           |       |     |     |     | x <sup>§</sup> |     |     |     |       |
| Inclusion/exclusion criteria  | x         | x     |     |     |     |                |     |     |     |       |
| Review contra-indications   | x         | x     |     |     |     | x              |     |     |     |       |
| Informed consent  | x         |       |     |     |     |                |     |     |     |       |
| Medical history   | x         | (x)   | (x) | (x) | (x) | (x)            | (x) | (x) | (x) | (x)   |
| Physical examination  | x         | (x)   | (x) | (x) | (x) | (x)            | (x) | (x) | (x) | (x)   |
| Vital signs   | x         | x     | x   | x   | x   | x              | x   | x   | x   | x     |
| Urinalysis  | x         |       |     |     |     |                |     |     |     |       |
| β-HCG urine test (female only)  | x         | x     |     |     |     | x              |     |     |     |       |
| Stool parasitology  | x         | x     | x   |     |     |                |     |     |     | x     |
| Anthelmintic treatment  |           |       |     |     |     |                |     | x   |     |       |
| Local & systemic events/reactions   |           | x     | x   | x   | x   | x              | x   | x   | x   | x     |
| Diary cards provided  |           | x     |     |     |     | x              |     |     |     |       |
| Diary cards collected   |           |       |     | x   |     |                | x   |     |     |       |
| Biochemistry (4mL)**/**   | x         |       |     | x   |     | x              | x   |     |     |       |
| HBV, HCV, HIV (6mL)   | x         |       |     |     |     |                |     |     |     |       |
| Haematology: full blood count and storage (2mL)                                     | x         |       | x   | x   |     | x              | x   |     |     | x     |
| Mansonella perstans (1mL)***  | x         |       |     |     |     |                |     |     |     | x     |
| Malaria RDT/slide; PCR (1mL)  | x         | x**** |     | x   | x   | x              |     | x   |     | x     |
| Assessments of immunogenicity and exploratory immunology incl ELISpot (10-20mL)**** | x         | x     | x   | x   | x   | x              | x   | x   | x   | x     |
| Gene expression (2mL)   | x         |       | x   |     |     |                |     |     |     |       |
| Blood vol (mL)  | 36        |       | 16  | 28  | 5   | 13             | 28  | 5   | 5   | 24    |
| Cumulative blood vol (mL)   | 36        | 36    | 52  | 80  | 85  | 98             | 126 | 131 | 136 | 160   |

X Event scheduled to occur

(X) If considered necessary, emphasising any complaint or change in medications

\* Timeline is approximate only, as exact timings (± windows periods) of visits relate to the actual (not intended) date of the previous visit

§ Group 5 only

\*\* Urea & electrolytes, liver function tests

\*\*\* Repeated on vaccination day if delay from screening is more than 28 days

\*\*\*\* Exploratory immunology blood volume will be guided by guidelines from Harvard Mass General, where a maximum of 3ml/kg body weight is taken at any one time point and not more than 3ml/kg is taken over any 8 week period (ref [http://www.drgreene.com/21\\_1616.html](http://www.drgreene.com/21_1616.html).) These guidelines have been followed in previous studies vaccinating adolescents and children with MVA85A (in South Africa [1]).The total blood volume planned is 98 ml over the initial intensive sampling period of 8 weeks. Revision of sample volumes based on weight will only

be required for children who weigh less than 33 kg; the average weight of children aged 11 is expected to be greater than 35kg, with greater weights for older children.

*Table 1.2. Schedule of trial procedures groups 5-6*

## 4. ABBREVIATIONS

|                    |  |
|--------------------|--|
| <b>AE</b>          | Adverse Event  |
| <b>AR</b>          | Adverse Reaction   |
| <b>BCG</b>         | Bacille Calmette-Guérin                                  |
| <b>β-HCG</b>       | Beta - Human Chorionic Gonadotropin                      |
| <b>CBF</b>         | Clinical Biomanufacturing Facility, University of Oxford |
| <b>CCVTM</b>       | Centre for Clinical Vaccinology and Tropical Medicine    |
| <b>CFU</b>         | Colony-forming unit                                      |
| <b>ChAdOx1</b>     | Chimpanzee Adenovirus vector                             |
| <b>CI</b>          | Chief Investigator                                       |
| <b>CRF</b>         | Case Report Form   |
| <b>DNA</b>         | Deoxyribonucleic Acid                                    |
| <b>DSMB</b>        | <b>Data and Safety Monitoring Board</b>                  |
| <b>ELISpot</b>     | Enzyme-linked Immunospot                                 |
| <b>EMaBS</b>       | Entebbe Mother and Baby Study                            |
| <b>FBC</b>         | Full Blood Count   |
| <b>GCP</b>         | Good Clinical Practice                                   |
| <b>HBsAg</b>       | Hepatitis B Surface Antigen                              |
| <b>HBV</b>         | Hepatitis B Virus  |
| <b>HCV</b>         | Hepatitis C Virus  |
| <b>HIV</b>         | Human Immunodeficiency Virus                             |
| <b>HLA</b>         | Human Leukocyte Antigen                                  |
| <b>ICH</b>         | International Committee on Harmonisation                 |
| <b>ID</b>          | Intradermal  |
| <b>IDT</b>         | IDT Biologika GmbH                                       |
| <b>IFN-γ</b>       | Interferon Gamma   |
| <b>IGRA</b>        | Interferon-Gamma Release Assay                           |
| <b>IM</b>          | Intramuscular  |
| <b>LFT</b>         | Liver Function Test                                      |
| <b>MHRA</b>        | Medicines & Healthcare Regulatory Authority              |
| <b><i>M.tb</i></b> | <i>Mycobacterium tuberculosis</i>                        |
| <b>MVA</b>         | Modified vaccinia Virus Ankara                           |
| <b>REC</b>         | Research Ethics Committee                                |
| <b>SAE</b>         | Serious Adverse Event                                    |
| <b>SAR</b>         | Serious Adverse Reaction                                 |
| <b>SmPC</b>        | Summary of Product Characteristics                       |
| <b>SOP</b>         | Standard Operating Procedure                             |
| <b>SUSAR</b>       | Suspected Unexpected Serious Adverse Reaction            |
| <b>TB</b>          | Tuberculosis   |
| <b>TMF</b>         | Trial Master File  |
| <b>TST</b>         | Tuberculin skin test                                     |
| <b>U&amp;Es</b>    | Urea & Electrolytes                                      |



## 5. BACKGROUND AND RATIONALE

### 5.1. Context

*Mycobacterium tuberculosis* (*M.tb*) is a pathogen with worldwide preponderance which infects humans causing tuberculosis (TB), a transmissible disease resulting in very high mortality and morbidity. A third of the world's population is latently infected with *M.tb*, and these people carry a 10% lifetime risk of developing active life-threatening disease [2]. In 2015, there were 10.4 million new cases worldwide and 1.4 million people died of TB [3]. Co-infection with human immunodeficiency virus (HIV) greatly increases risk of TB reactivation and death [4, 5]. Diagnosis is challenging and drug treatment can be prolonged, harmful, costly and complex. For these reasons an effective vaccine is a global public health priority. An effective vaccine could revolutionise TB control [6].

The Bacille Calmette-Guérin (BCG) vaccine is the only licensed *M.tb* vaccine and it has been administered globally to several billion people over a 90 year period [7]. BCG is effective in preventing disseminated TB disease including tuberculous meningitis in childhood [5, 8, 9] but, against pulmonary tuberculosis, its efficacy varies. Infectious, sputum smear positive, pulmonary disease classically emerges in adolescents and young adults and this is what drives the continuing epidemic [10]. Thus booster immunisation against TB in adolescence is an important strategy [11].

The variability in efficacy of BCG is associated with latitude. It ranges from 94% in Danish school children to 0% in some studies in the tropics [12]. Studies on BCG immunisation in young adults from the UK and Malawi showed reduced immunogenicity in Malawi [13]. However, variability has also been observed within the tropics. In Brazil, BCG immunisation in adolescents (whether first dose or booster dose) conferred benefit against tuberculosis in Salvador (a tropical, coastal city), but not in Manaus (an inland city, close to the equator, in the Amazon basin) [14]. At first, differential exposure to non-tuberculous mycobacteria (NTM) was considered the most probable explanation for these regional differences [15]. Later, recognition of the complexity of the geographical distribution of NTM, and variable cross-reactivity of NTM species with BCG, led to the suggestion that other forms of "environmental sensitisation" might also impact BCG immunogenicity in adolescence [14].

Recently, heterologous "prime-boost" vaccination strategies, in which different candidate vaccines expressing antigens in common are given weeks or months apart, have generated strong and sustained cellular immune responses correlating with an *M.tb* protective effect in preclinical animal models. In such a "prime-boost" strategy, BCG can act as the priming vaccine. Indeed, continued use of BCG in infants in endemic settings is desirable because of the protection it affords against severe disease in infancy and early childhood. Candidate TB vaccine MVA85A (recombinant modified Vaccinia Ankara virus expressing the immunodominant *M.tb* protein, antigen 85A) has been considered as a booster, to be given after BCG either in infancy, or in adolescence, but this vaccine has not shown efficacy when used as a booster in South African infants [16] or in HIV-positive adults [17] and also shows lower immunogenicity in Africa than in Europe [18, 19].

Lack of efficacy of MVA85A alone as a boost to BCG immunisation suggests that more immunogenic vaccination regimens are required. Compared to single-dose vaccines, a prime-boost combining adenoviral and MVA vectors shows dramatically enhanced immunogenicity and efficacy for infections including malaria, and has been found safe in adults and children, including African populations [20]. For TB, a human adenovirus construct (Aeras-402) followed by MVA85A showed enhanced immunogenicity and durability of response [21]. A chimpanzee adenovirus vector encoding the *M.tb* antigen 85A, named ChAdOx1 85A, combined with MVA85A, shows enhanced immunogenicity and efficacy against tuberculosis in animals [22], and has just completed a phase I human trial in Oxford [23]. We now propose to investigate this regimen in a Phase IIa trial among adolescents in Uganda.

Although experience on safety and immunogenicity with vaccines based on adenoviral vectors is accumulating for a number of infections [20, 24-27], the specific construct to be used here, ChAdOx1 85A, has so far only been evaluated in one trial in human subjects: this was among adults in the UK. Therefore this protocol comprises an initial investigation to provide safety data among Ugandan adults and adolescents (dose escalation and age de-escalation) before conducting the proposed randomised trial in adolescents.

### **5.1.1. BCG revaccination of adolescents in Uganda**

As noted above, vaccination against tuberculosis in adolescents is a key strategy for TB control because, epidemiologically, this is the age at which infectious, pulmonary disease emerges after a relatively protected period in early childhood. BCG vaccination or re-vaccination in adolescence has variable efficacy by setting, and tends to be least effective in the tropics: while the underlying mechanism of this variability is not known, exposure to environmental, non-tuberculous mycobacteria may contribute, as well as a range of other infectious or environmental factors [14]. To our knowledge, the efficacy of BCG revaccination for adolescents in Uganda has not been tested. BCG remains the only available standard against which to compare the response to new vaccines: a current trial in South Africa is comparing the efficacy of BCG versus a new vaccine regimen being developed by Aeras and Sanofi Pasteur (H4/IC31) for protection against TB infection [28]. A recent analysis suggests that, despite variable efficacy, BCG revaccination of adolescents is cost-effective, particularly among those who are not tuberculin skin test (TST) positive [29]. Because there is some potential benefit of BCG revaccination, but also the need for a more effective vaccine, we propose BCG revaccination for the comparison group in this study.

### **5.1.2. Description and pre-clinical experience of MVA and MVA85A**

Modified vaccinia virus Ankara (MVA) is a highly-attenuated strain of vaccinia virus which cannot replicate in human cells. It is known to be highly immunogenic in UK adults but has been less immunogenic in African children and infants. It is suitable for use as a viral vector in a prime-boost regime in new vaccine development. It has an excellent safety record as it was administered intradermally to approximately 120,000 people during the smallpox eradication campaign [30-33], and has since been used in numerous clinical trials of candidate vaccines against viral, mycobacterial and protozoal infections [34, 35]. Meanwhile recombinant MVA vaccines administered by respiratory mucosal and gut mucosal routes have demonstrated protective efficacy and elicited strong immune responses in both rodents and non-human primates [36].

Antigen 85A is a highly conserved antigen expressed by *M.tb*, BCG, and all other mycobacterial species sequenced to date. It is a 32-kDa protein, and is an enzyme, mycolyl transferase, which is involved in cell wall biosynthesis [37]. Antigen 85A is highly immunodominant in both animal and human studies [38-40], and protects against *M.tb* challenge in mice, guinea pigs and non-human primates [41, 42]. The recombinant MVA85A vaccine incorporates the 1176 base pair gene for antigen 85A into the viral DNA allowing expression of this secreted antigen.

Experiments in mice, guinea pigs, cattle, and non-human primates have shown that a prime-boost schedule of vaccination with BCG followed by MVA85A, either intradermally, intramuscularly or mucosally, can improve protective efficacy against subsequent *M.tb* challenge, compared to BCG alone [42-45]. Animal toxicity studies using the intradermal route of administration revealed no differences from PBS-injected controls apart from irritation at the site of administration.

### **5.1.3. Clinical studies with MVA85A**

Over 2500 volunteers have now received MVA85A, of which (in completed trials) 72 were by the intramuscular route, 24 by the aerosol route and the remainder intradermally. 22 phase I/II clinical studies of MVA85A have been completed, a further one is ongoing. These are summarised in table 2.

MVA85A has been shown to be immunogenic as a booster vaccine in BCG-primed subjects [18]; however, as discussed above, a phase IIb efficacy trial in 2797 BCG-vaccinated infants in South Africa reported no enhancement of BCG-induced protection [16]. In this trial, the immunogenicity was significantly lower than that seen in adults, and more potent routes of administration are of interest in the field. A phase IIb trial in HIV infected adults in South Africa and Senegal also demonstrated no efficacy [17]. Immunogenicity in this trial was also lower than that seen in UK adults and innovative ways of enhancing immunogenicity are urgently needed [17].

To that end we are currently evaluating the safety and immunogenicity of a prime-boost regime using a simian adenovirus, ChAdOx1 85A prime - MVA85A boost regime.

| Protocol | Phase                              | Population   | Treatment groups <sup>a</sup>   | N <sup>b</sup>   | Study Status   |
|----------|------------------------------------|--|---|--|--|
| TB002    | Phase I open label non-randomised  | Healthy BCG-naïve adults, UK                                       | 5 x 10 <sup>7</sup> pfu MVA85A (Days 0 & 21)  | 14   | Completed  |
| GM920    | Phase I open label non-randomised  | Healthy BCG-naïve or vaccinated adults, Gambia                     | 5 x 10 <sup>7</sup> pfu MVA85A (Days 0 & 21) BCG naïve<br>5 x 10 <sup>7</sup> pfu MVA85A (Day 0) BCG-vaccinated   | 11<br>10   | Completed  |
| TB004    | Phase I open label non-randomised  | Healthy BCG-naïve adults, UK                                       | 1 x 10 <sup>6</sup> pfu BCG prime (Day 0)<br>5 x 10 <sup>7</sup> pfu MVA85A boost (after 1 month)   | 10   | Completed  |
| TB005    | Phase I open label non-randomised  | Healthy BCG-vaccinated adults, UK                                  | 5 x 10 <sup>7</sup> pfu MVA85A (Day 0)  | 21   | Completed  |
| TB007    | Phase I open label non-randomised  | Healthy adults latently infected with <i>M.tb</i> , UK             | 5 x 10 <sup>7</sup> pfu MVA85A (Day 0)  | 12   | Completed  |
| TB008    | Phase I open label non-randomised  | Healthy BCG-naïve or vaccinated adults & adolescents, South Africa | 5 x 10 <sup>7</sup> pfu MVA85A (Day 0) adults<br>5 x 10 <sup>7</sup> pfu MVA85A (Day 0) adolescents   | 24<br>12   | Completed  |
| TB009    | Phase I open label non-randomised  | Healthy BCG-vaccinated adults, UK                                  | 1 x 10 <sup>7</sup> pfu MVA85A (Day 0)<br>1 x 10 <sup>8</sup> pfu MVA85A (Day 0)  | 12<br>12   | Completed  |
| TB010    | Phase I open label non-randomised  | HIV-positive adults, UK  | 5 x 10 <sup>7</sup> pfu MVA85A (Day 0)<br>1 x 10 <sup>8</sup> pfu MVA85A (Day 0)  | 10<br>10   | Completed  |
| TB011    | Phase I open label non-randomised  | Adults infected with <i>M.tb</i> , HIV, or both, South Africa      | 5 x 10 <sup>7</sup> pfu MVA85A (Day 0) TB<br>5 x 10 <sup>7</sup> pfu MVA85A (Day 0) HIV<br>5 x 10 <sup>7</sup> pfu MVA85A (Day 0) TB & HIV<br>5 x 10 <sup>7</sup> pfu MVA85A (Day 0) HIV on ART   | 12<br>12<br>12<br>12   | Completed  |
| TB012    | Phase II open label non-randomised | Healthy BCG-vaccinated infants, South Africa                       | <u>Stage 1</u><br>EPI alone (Day 0)<br>2.5 x 10 <sup>7</sup> pfu MVA85A with EPI (Day 0)<br>2.5 x 10 <sup>7</sup> pfu MVA85A alone (Day 0) <sup>c</sup><br>EPI alone (Day 0)<br>5 x 10 <sup>7</sup> pfu MVA85A with EPI (Day 0)<br>5 x 10 <sup>7</sup> pfu MVA85A alone (Day 0) <sup>c</sup><br><u>Stage 2</u><br>EPI alone<br>5 x 10 <sup>7</sup> pfu MVA85A with EPI (Day 0)<br>5 x 10 <sup>7</sup> pfu MVA85A alone (Day 0) <sup>c</sup> | 12<br>12<br>12<br>12<br>12<br>12<br>47<br>47 <sup>f</sup><br>48 <sup>f</sup> | <u>Stage 1</u><br>Completed<br><br><br><br><br><br><br><u>Stage 2</u><br>Completed |

|       |                                      |   |  |                                      |                        |
|-------|--------------------------------------|---|--|--------------------------------------|------------------------|
| TB014 | Phase II open label non-randomised   | Healthy BCG-vaccinated children & infants, South Africa   | 5 x 10 <sup>7</sup> pfu MVA85A (Day 0) children<br>2.5 x 10 <sup>7</sup> pfu MVA85A (Day 0) infants<br>5 x 10 <sup>7</sup> pfu MVA85A (Day 0) infants<br>1 x 10 <sup>8</sup> pfu MVA85A (Day 0) infants<br>Prevenar (variable dose) (Day 0) infants      | 24<br>36<br>36<br>36<br>36           | Completed              |
| TB017 | Phase I open label non-randomised    | Healthy BCG-vaccinated adults, UK                         | 5 x 10 <sup>7</sup> pfu FP85A (Day 0)<br>5 x 10 <sup>7</sup> pfu MVA85A (Day 0) then 5 x 10 <sup>7</sup> pfu FP85A (Day 28)<br>5 x 10 <sup>7</sup> pfu FP85A (Day 0) then 5 x 10 <sup>7</sup> pfu MVA85A (Day 28)  | 12<br>12<br>7                        | Completed <sup>d</sup> |
| TB018 | Phase I open label non-randomised    | Healthy BCG-vaccinated adults, UK                         | 1 x 10 <sup>8</sup> pfu MVA85A (Day 0)<br>1 x 10 <sup>8</sup> pfu MVA85A (Day 0), 1g/kg deuterium-labelled glucose (Day 4)<br>1 x 10 <sup>8</sup> pfu MVA85A (Day 0), 1g/kg deuterium-labelled glucose (Day 10)  | 4<br>4<br>4                          | Completed              |
| TB019 | Phase I open label non-randomised    | HIV-infected adults, Senegal                              | 1 x 10 <sup>8</sup> pfu MVA85A (Day 0 & 168)<br>1 x 10 <sup>8</sup> pfu MVA85A (Day 0 & 168) on ART  | 12<br>12                             | Completed              |
| TB020 | Phase II double blinded randomised   | Healthy BCG-vaccinated HIV-negative infants, South Africa | 1 x 10 <sup>8</sup> pfu MVA85A (Day 0)<br>Candin <sup>®</sup> (Day 0)  | 1399<br>1398 <sup>g</sup>            | Completed              |
| TB021 | Phase II double blinded randomised   | Healthy HIV-infected adults, South Africa & Senegal       | 1 x 10 <sup>8</sup> pfu MVA85A (Days 0, 168-252)<br>Candin <sup>®</sup> (Days 0, 168-252)  | 324 <sup>i</sup><br>326 <sup>i</sup> | Completed              |
| TB022 | Phase I open-label randomised        | Healthy BCG-vaccinated adults, UK                         | 1 x 10 <sup>8</sup> pfu MVA85A (IM) (Day 0)<br>1 x 10 <sup>8</sup> pfu MVA85A (ID) (Day 0)   | 12<br>12                             | Completed              |
| TB023 | Phase I open-label non-randomised    | Healthy BCG-naïve or vaccinated adults, UK                | 1x10 <sup>8</sup> pfu MVA85A (Day 0), BCG challenge (Day 28)<br>BCG; 100µl ~ 2-8 x10 <sup>5</sup> cfu  | 24<br>24                             | Completed              |
| TB026 | Phase I randomised blinded           | Healthy BCG-vaccinated adults, UK                         | 1x10 <sup>8</sup> pfu MVA85A (aerosol inhaled), saline placebo (ID) <sup>e</sup><br>1x10 <sup>7</sup> pfu MVA85A (aerosol inhaled), saline placebo (ID) <sup>e</sup><br>1x10 <sup>7</sup> pfu MVA85A (ID), saline placebo (aerosol inhaled) <sup>e</sup> | 2<br>10<br>12                        | Completed              |
| TB028 | Phase I randomised blinded           | Health BCG-vaccinated adults, UK                          | 1x10 <sup>7</sup> pfu MVA85A-IMX313 (ID) (Day 0)<br>5x10 <sup>7</sup> pfu MVA85A-IMX313 (ID) (Day 0)<br>5x10 <sup>7</sup> pfu MVA85A (ID) (Day 0)  | 6<br>12<br>12                        | Completed              |
| TB029 | Phase II randomised controlled trial | Infants of HIV infected mothers, South Africa             | 1x10 <sup>8</sup> pfu MVA85A or Candin <sup>®</sup> control at birth<br>BCG: 0.05ml 1-4 x 10 <sup>5</sup> cfu at 8 weeks of age (HIV uninfected)   | 124<br>124                           | Completed              |

|       |  |  |   |                             |           |
|-------|--|--|---|-----------------------------|-----------|
| TB032 | Phase I open-label non-randomised                  | Healthy BCG-vaccinated adults, UK                    | 1 x 10 <sup>11</sup> vp AERAS-402 (Day 0 & 28) followed by 1 x 10 <sup>8</sup> pfu MVA85A (Day 119)<br>1 x 10 <sup>11</sup> vp AERAS-402 (Day 0) followed by 1 x 10 <sup>8</sup> pfu MVA85A (Day 56)<br>1 x 10 <sup>11</sup> vp AERAS-402 (Day 0, 28 and 119)   | 12<br>16 <sup>h</sup><br>12 | Completed |
| TB034 | Phase I open-label randomised trial                | Healthy BCG-vaccinated adults, UK                    | 5 x 10 <sup>9</sup> vp ChAdOx1 85A (Day 0)<br>2.5 x 10 <sup>10</sup> vp ChAdOx1 85A (Day 0)<br>2.5 x 10 <sup>10</sup> vp ChAdOx1 85, (Day 0), 1 x 10 <sup>8</sup> pfu MVA85A (Day 56)<br>2.5 x 10 <sup>10</sup> vp ChAdOx1 85A (Day 0 and 28), 1 x 10 <sup>8</sup> pfu MVA85A (Day 119)   | 6<br>12<br>12<br>12         | Completed |
| TB035 | Phase I open-label randomised trial                | Healthy BCG-vaccinated adults, UK                    | 5 x 10 <sup>7</sup> pfu MVA85A (aerosol inhaled); placebo (ID) (Day 0), 5 x 10 <sup>7</sup> pfu MVA85A (ID); placebo (aerosol inhaled) (Day 28) <sup>e</sup><br>5 x 10 <sup>7</sup> pfu MVA85A (ID), placebo (aerosol inhaled) (Day 0), 5 x 10 <sup>7</sup> pfu MVA85A (aerosol inhaled), placebo (ID), (Day 28) <sup>e</sup><br>5 x 10 <sup>7</sup> pfu MVA85A (ID), placebo (aerosol inhaled) (Day 0), 5 x 10 <sup>7</sup> pfu MVA85A (ID), placebo (aerosol inhaled) (Day 28) <sup>e</sup> | 12<br>13 <sup>k</sup><br>12 | Completed |
| TB036 | Phase II open label trial                          | Healthy BCG-vaccinated adolescents, Uganda           | 1 x 10 <sup>8</sup> pfu MVA85A (IM); D0<br>1 x 10 <sup>8</sup> pfu MVA85A (IM); D0  | 18<br>18                    | Completed |
| TB040 | Phase I randomised, partially blinded <sup>l</sup> | Healthy adults with latent <i>M.tb</i> infection, UK | 1 x 10 <sup>7</sup> pfu aerosol inhaled MVA85A; D0<br>5 x 10 <sup>7</sup> pfu aerosol inhaled MVA85A and IM saline placebo; D0 <sup>j</sup><br>5 x 10 <sup>7</sup> pfu IM injection of MVA85A and aerosol inhaled saline placebo; D0 <sup>j</sup>   | 3<br>6<br>6                 | Enrolling |

Table 2. Summary of clinical trials of MVA85A

- a. Intradermal route of administration unless otherwise stated
- b. Number of subjects is actual number enrolled for studies that have completed enrolment, and planned number of subjects for studies in which enrolment is ongoing or which are still blinded
- c. EPI deferred for 1 week
- d. Enrolment in TB017 was terminated early, due to issues with the supply of the FP85A vaccine
- e. Subjects blinded as to whether they received MVA85A via the ID or aerosol inhaled route
- f. 47 subjects were randomised to receive MVA85A with EPI and 48 were randomised to receive MVA85A alone. As a result of an error, 1 subject switched groups, resulting in 48 subjects receiving MVA85A with EIP and 47 receiving MVA85A alone
- g. Two of the 1398 subjects randomised to the Candin<sup>®</sup> group were not vaccinated
- h. Two of these 16 subjects were vaccinated with AERAS-402 but discontinued from the study before receiving MVA85A
- i. One of the 324 subjects randomised to MVA85A/AERAS-485 was not vaccinated; one subject randomised to Candin<sup>®</sup> received MVA85A/AERAS-485
- j. The subjects, the bronchoscopist and immunologists were blinded to treatment assignment; the investigator administering the vaccinations was not blinded
- k. One subject withdrew post first vaccination but prior to boost vaccination, and was replaced
- l. Starter group not blinded. For groups A and B the subjects, the bronchoscopist, and immunologists are blinded to treatment assignment; the investigator administering the vaccinations is not blinded.

### *Safety profile*

No signs of any Koch reaction (i.e. exacerbation of tissue damage at a focus of TB infection) have been seen in volunteers infected with *M.tb* with this or any other candidate TB vaccine to date. One possible vaccine related SAE – early unmasking of pre-existing tuberculous meningitis - occurred in a patient with HIV in South Africa.

Typical local and systemic reactions to IM injection, and the preliminary analysis of local and systemic reactions induced by the aerosol route that were reported in the completed Phase I safety trial are summarised in section 5.3 “Risks and Benefits”.

### *Dosing*

Dose studies of MVA85A have been performed in a step-wise fashion to minimise the risk of a Koch reaction and the incidence of adverse events. The main systemic (as opposed to aerosol) dose-finding trial compared boosting doses of  $1 \times 10^7$  pfu and  $1 \times 10^8$  pfu to previous trials using boosting doses of  $5 \times 10^7$  pfu. An intradermal dose of  $1 \times 10^8$  pfu was found to be significantly more immunogenic than the lower doses without concomitant worsening of adverse event profile, and has been adopted as the standard dose in all subsequent trials [46, 47].

### *Immunogenicity*

When evaluated by various assays of cellular immunology including interferon gamma (IFN- $\gamma$ ) ELISpot and intracellular cytokine staining assays, MVA85A has induced a strong and sustained cell-mediated immune response which is known to be important for protective immunity [48]. As the phase IIb efficacy trial of MVA85A in BCG-vaccinated infants in South Africa did not show protection against TB disease or *M.tb* infection above that of BCG alone, work to identify correlates of protection from this trial’s samples is now underway. So far there is evidence that T cell activation prior to MVA85A was associated with increased risk for subsequent TB disease, whereas BCG-specific T cells (as assessed by IFN- $\gamma$  ELISpot) and antigen 85A specific antibodies are associated with protection [49].

### *Route*

No significant difference in adverse events or immunogenicity has been seen when comparing IM and ID delivery of MVA85A [50].

#### **5.1.4. Description and pre-clinical experience of ChAdOx1 and ChAdOx1 85A**

ChAdOx1 85A is an adenoviral vaccine based on a vector that is a chimpanzee adenovirus isolate Y25 expressing the *M.tb* antigen 85A [51]. Adenoviruses are attractive candidates for use as viral vectors and have been used as vaccine vectors for a number of conditions; however, the use has been limited by the high level of anti-vector immunity present in humans in whom adenovirus is a ubiquitous infection. This has led to the consideration of simian adenoviruses, which are not known to cause pathology or illness in humans and to which the prevalence of anti-vector antibodies is low. The ChAdOx1 vector has been developed by the University of Oxford and been used with different inserts for vaccination, for example the vaccine ChAdOx1 NP+M1 has demonstrated an excellent safety profile in the Influenza trial FLU004. A BCG – ChAdOx1 85A – MVA85A prime boost regime is more protective than BCG alone in mice [22].

#### **5.1.5. Clinical studies with ChAdOx1 85A**

ChAdOx1 85A has been used in one human clinical trial. TB034 was a phase 1 randomised trial to evaluate the safety and immunogenicity of ChAdOx1 85A with and without heterologous boosting by MVA85A in BCG-vaccinated UK adults, 42 healthy volunteers aged 18 to 55 years. 42 volunteers received ChAdOx1 85A. The study was completed on 20/04/2016 with no safety concerns.

| Protocol | Phase  | Population                              | Treatment groups <sup>a</sup>   | N <sup>b</sup>      | Study Status |
|----------|--|---|---|---------------------|--------------|
| TB034    | Phase I<br>open<br>label<br>non-<br>randomi<br>sed | Healthy BCG-<br>vaccinated UK<br>adults | Starter: $5 \times 10^9$ vp ChAdOx1 85A at D0<br>A: $2.5 \times 10^{10}$ vp ChAdOx1 85A at D0<br>B: $2.5 \times 10^{10}$ vp ChAdOx1 85A at D0 followed by $1 \times 10^8$ pfu MVA85A at D56<br>C: $2.5 \times 10^{10}$ vp ChAdOx1 85A at D0 followed by $2.5 \times 10^{10}$ vp ChAdOx1 85A at D28 and $1 \times 10^8$ pfu MVA85A at D119 | 6<br>12<br>12<br>12 | Completed    |

a. Intramuscular route of administration unless otherwise stated

b. Number of subjects is actual number enrolled

Table 3. TB034 trial design

### Safety profile

There have been no SAEs to date with ChAdOx1 85A. In TB034 the majority of local AE's were mild to moderate in nature in all 4 groups. Two volunteers in Group B reported severe pain at vaccination site however this was following MVA85A vaccination at D56. Local redness and swelling across all vaccinations were comparable with no significant difference seen using one-way Anova with Tukey's test for multiple comparisons ( $p > 0.05$ ). The majority of systemic, solicited AE's, were also mild/moderate in nature. Those who reported a severe AE included 1 volunteer in Group A and 1 in Group B (following D0 ChAdOx1 85A) with severe feverishness and fatigue, and 1 Group A volunteer who reported a severe headache. One Group B volunteer reported severe feverishness and headache following D56 MVA85A vaccination. Of unsolicited AE's considered to be possibly, probably or definitely related to vaccination, of note 1 volunteer in Group A reported axillary lymphadenopathy which was transient. There were 12 haematological laboratory AE's considered to be possibly, probably or definitely related to vaccination. Of those with a temporal relationship to ChAdOx1 85A vaccination, there were 3 lymphopenias, 2 neutropenias, 1 leukopenia, 2 eosinophilias (both in same volunteer) and 1 thrombocytopenia. All fully resolved. There was 1 Group C volunteer with a lymphopenia possibly related to MVA85A D119 vaccination which was ongoing at the end of the study. All others were transient.

### Dosing

As TB034 was a first in man trial for ChAdOx1 85A a lower dose of  $5 \times 10^9$  vp was administered initially, with dose escalation post safety review as follows. The first six volunteers in the study received  $5 \times 10^9$  vp of ChAdOx1 85A. Their data was deemed to have an acceptable AE profile at review, and so the dose was escalated to  $2.5 \times 10^{10}$  vp ChAdOx1 85A.

### Immunogenicity

A single dose of  $2.5 \times 10^{10}$  vp of ChAdOx1 85A induced significant Ag85A-specific IFN- $\gamma$  responses following vaccination in the three study groups, these responses peaked 14 days post-vaccination (Wilcoxon test,  $p = 0.0005$  for Groups A (ChAdOx1 85A alone), B (ChAdOx1 85A – MVA85A) and C (ChAdOx1 85A – ChAdOx1 85A – MVA85A), and remained significantly higher than baseline at the end of follow-up (D168) in Group A ( $p = 0.003$ ). A second dose of ChAdOx1 85A did not boost these IFN- $\gamma$  responses in Group C, however they were significantly boosted with MVA85A vaccination at D56 (Group B) and D119 (Group C) ( $p = 0.0005$  at D63 (Group B) and D126 (Group C), IFN- $\gamma$  responses remained significantly higher than at baseline at the end of the study ( $p = 0.005$  for Group B D224 and  $p = 0.001$  for Group C D287). No differences were detected in the magnitude of the MVA85A-boosted IFN- $\gamma$  responses between Group B and Group C one week post-MVA85A ( $p = 0.31$ ). Polyfunctional CD4 and CD8 + T cells are detectable after ChAdOx1 85A and MVA85A vaccinations.



## 5.2. Goal

Our goal is to identify a TB vaccination regimen that will induce strong protective immune responses against tuberculosis in a tropical endemic setting.

## 5.3. Hypothesis

Our hypothesis is that a prime-boost regimen of ChAdOx1 85A – MVA85A will have greater immunogenicity than BCG revaccination among Ugandan adolescents who were BCG vaccinated at birth, and comparable immunogenicity to that observed in European adults.

## 5.4. Risks and Benefits

### 5.4.1. Potential risks

The potential risks to volunteers in this trial include risks associated with:

#### 1. Venepuncture

Localised bruising and discomfort can occur at the site of venepuncture. Infrequently fainting may occur. The total volume of blood drawn over a 6-month period will be 143mL, which should not compromise these otherwise healthy volunteers.

#### 2. Vaccination

ChAdOx1 85A has been administered to 42 healthy UK adults with no SAEs or safety concerns. MVA85A has now been administered to over 2500 healthy human individuals with one possible serious adverse reaction (SAR). BCG is a licensed vaccine which has been administered to millions of people. The potential known adverse events associated with vaccination are:

##### *Local reaction from IM vaccination*

The typical local reaction as a result of IM injection is temporary pain, redness and swelling at the site of the injection.

##### *Local reaction for intradermal (ID) vaccination*

BCG vaccination or revaccination usually causes local scarring and occasionally an abscess and regional lymphadenopathy [52].

##### *Systemic reactions*

Constitutional influenza-like symptoms such as fatigue, headache, malaise, feverishness, and muscle aches can occur with any vaccination and last for 2-3 days. In the case of MVA85A, and ChAdOx1 85A these are usually mild to moderate in severity, and transient. Following ChAdOx1 85A vaccination in TB034, transient lymphopenia and neutropenia was seen in some volunteers; all spontaneously resolved. Similar mild to moderate transient abnormalities of leukocyte parameters have been previously noted in other adenovectored vaccine studies [24, 53].

Presyncopal and syncopal episodes may occur at the time of vaccination which rapidly resolve. As with any other vaccine, immune mediated reactions that can lead to organ damage may occur. For influenza vaccines an excess of approximately 1 Guillain-Barré syndrome case per million persons immunised has been observed. No cases were observed in people under 45 years of age. However, this has never been seen with the ChAdOx1 85A or MVA85A vaccines or vaccines containing any of its components. In immunocompromised people, BCG vaccination can cause disseminated disease [54, 55].

##### *Allergic reactions*

Allergic reactions from mild to severe may occur in response to any constituent of a medicinal product's preparation. Anaphylaxis is extremely rare (less than 1 in 1000 people) but can occur in response to any vaccine or medication.

#### **5.4.2. Potential benefits**

Volunteers are not expected to benefit directly from participation in this trial. Volunteers will gain some information about their general health as a result of the screening history, examination, blood tests, and urine tests. Volunteers found to have a previously undiagnosed condition thought to require further medical attention will be referred appropriately for further investigation and treatment, with their permission.

It is hoped that their contribution will further the development of a safe and successful vaccine for TB and our knowledge about TB infection and protection.

## 6. OBJECTIVES AND OUTCOME MEASURES

| Objectives  | Outcome Measures   | Timepoint(s) of evaluation of this outcome measure  |
|---|--|---|
| <b>Primary Objective</b><br>To evaluate the safety and immunogenicity of ChAdOx1 85A – MVA85A prime-boost vaccination in Ugandan adolescents  | Actively and passively collected data on adverse events  | All Adverse Events (AEs) from day 0-28 post vaccination<br>Serious Adverse Events (SAEs) throughout follow up   |
|   | T-cell Interferon- $\gamma$ ELIspot response to antigen 85A  | ELIspot spot-forming counts per $1 \times 10^6$ peripheral blood mononuclear cells (PBMCs) at day 14 for groups 1-4<br><br>ELIspot spot-forming counts per $1 \times 10^6$ peripheral blood mononuclear cells (PBMCs) at day 63 for groups 5 and 6<br><br>Area under the curve (AUC) analysis of immunogenicity (days 0-168 for groups 1-4; days 0-365 for groups 5 and 6)                                  |
| <b>Secondary Objective</b><br>To further characterise immunogenicity of ChAdOx1 85A – MVA85A prime-boost vaccination in Ugandan adolescents   | Antibody response to antigen 85A<br><br>Exploratory immunology including ELIspot response to BCG, flow cytometry, gene expression, and mycobacterial killing assays  | Screening and follow up visits as shown in Schedule of Visits, section 3  |
| <b>Tertiary Objectives</b><br>1. To compare the response to ChAdOx1 85A – MVA85A prime-boost vaccination with the response to BCG revaccination in Ugandan adolescents<br><br>2. To compare the response to ChAdOx1 85A – MVA85A prime-boost vaccination in Ugandan adolescents with the response in Oxford adults<br><br>3. To investigate pre-immunisation epidemiological and immunological characteristics associated with the immune response induced by ChAdOx1 85A – MVA85A prime-boost vaccination in Ugandan adolescents | T-cell Interferon- $\gamma$ ELIspot response to antigen 85A<br><br>Antibody response to antigen 85A, exploratory immunology including T cell ELIspots, flow cytometry, gene expression, and mycobacterial killing assays | Primary outcomes for these analyses will be antigen 85A specific ELIspot spot-forming counts per $1 \times 10^6$ peripheral blood mononuclear cells (PBMCs) at day 63 from the first vaccination and ELIspot AUC analysis<br><br>Additional outcomes using data from follow up visits as shown in Schedule of Visits, section 3<br>Screening and follow up visits as shown in Schedule of Visits, section 3 |

Table 4. Objectives and Outcome Measures

## 7. TRIAL DESIGN

We will commence with a dose-escalation and age de-escalation study in healthy adults and adolescents in Uganda, focussing on ChAdOx1 85A, to provide safety data for ChAdOx1 85A in this population. These measures are not required for MVA85A since this vaccine has been more widely used, including among adolescents in Uganda, and the dose has been standardised (as described above).

ChAdOx1 85A dose escalation and age de-escalation will be followed by a Phase IIa randomised trial comparing the immunogenicity of ChAdOx1 85A and MVA85A with the immunogenicity of BCG revaccination. ChAdOx1 85A and MVA85A will be administered via the intramuscular route. The target dose for the Phase IIa trial is  $2.5 \times 10^{10}$  vp because the lower dose is expected to have lower immunogenicity, based on the Oxford study, TB034 (Table 3, above). Data from the Oxford study suggest that this dose will be well tolerated. However, if this dose is not tolerated then the lower dose will be used. The dose of MVA85A will be  $1 \times 10^8$  pfu in the groups in which it is given.

There will be 6 study groups with 3 to 30 volunteers in each group (Table 5).

### *Dose escalation for ChAdOx1 85A in adults*

Group 1. The first three adults will receive ChAdOx1 85A at  $5 \times 10^9$  vp.

Group 2. The next three adults will be enrolled after safety data has been reviewed by the trial management team to one week after ChAdOx1 85A vaccination in group 1. These adults will receive ChAdOx1 85A at  $2.5 \times 10^{10}$  vp.

### *Age de-escalation and dose escalation for ChAdOx1 85A in adolescents*

Group 3. The first three adolescents will be enrolled after safety data has been reviewed to one week after ChAdOx1 85A vaccination in group 2. These three adolescents will receive ChAdOx1 85A at  $5 \times 10^9$  vp

Group 4. The next three adolescents will be enrolled after safety data has been reviewed to one week after ChAdOx1 85A vaccination in group 2. These three adolescents will receive ChAdOx1 85A at  $2.5 \times 10^{10}$  vp

### *Randomised comparison of ChAdOx1 85A-MVA85A versus BCG revaccination*

Once safety data has been reviewed for groups 1 to 4 to one week post ChAdOx1.85A vaccination, recruitment to the randomised trial will commence. Sixty adolescents will be randomised, 30 (group 5) to receive ChAdOx1 85A at  $2.5 \times 10^{10}$  vp followed by MVA85A boost and 30 (group 6) to receive BCG revaccination.

BCG will be obtained from the Serum Institute of India, an approved provider for Uganda, and used at the standard dose of 0.1mL. BCG will be given intradermally.

### 7.1. Trial Numbers and Groups

| Group | Sample size    | Intervention  |
|-------|----------------|---|
| 1     | 3 adults       | ChAdOx1 85A at $5 \times 10^9$ vp   |
| 2     | 3 adults       | ChAdOx1 85A at $2.5 \times 10^{10}$ vp  |
| 3     | 3 adolescents  | ChAdOx1 85A at $5 \times 10^9$ vp   |
| 4     | 3 adolescents  | ChAdOx1 85A at $2.5 \times 10^{10}$ vp  |
| 5     | 30 adolescents | ChAdOx1 85A at $2.5 \times 10^{10}$ vp followed by MVA85A $1 \times 10^8$ pfu |
| 6     | 30 adolescents | BCG revaccination, Serum Institute of India, 0.1 mL intradermally             |

Table 5. Trial groups

## 7.2. Recruitment

### *The Entebbe Mother and Baby Study.*

This project will be undertaken within the Entebbe Mother and Baby Study (EMaBS) cohort [56]. Between 2003 and 2005, 2,507 pregnant women were recruited to the cohort at the antenatal clinic of Entebbe General Hospital, Uganda. The study area was Entebbe Municipality and the neighbouring Katabi sub-county. The original objective was to investigate the effects of prenatal exposure to helminth infection on the infant response to vaccines, and on infant susceptibility to infectious diseases [56]. Children were born between April 2003 and April 2006. In 2018, they will be aged 11 to 15 years. The cohort has unique value for this study because extensive data are available on factors relevant to this trial including date of birth, date and strain of infant BCG immunisation, immune responses to TB antigens at age one and five years, and exposure to infectious diseases including TB, malaria, helminths and viral infections. Genetic data are also available for this cohort. Field workers regularly visit the participants at home and record the location of the home by global positioning systems (GPS) in order to facilitate follow up, and to allow adjustment for potential confounding related to location of residence in the analysis of results. The EMaBS archived data will contribute to investigation of factors that impact vaccine immunogenicity (tertiary aim 3).

### *Stakeholder engagement.*

Before initiating the study, we will hold a series of meetings to engage relevant stakeholders, including vaccine and tuberculosis programmes at the Ministry of Health, district health officials, local council leaders and hospital staff. Also, we will hold meetings for community representatives, and for EMaBS participants and their families. The proposed work will be explained, and questions about it will be addressed. A consultative group of selected parents will be set up; this group will advise us on issues such as the timing of activities in relation to the school year.

### *Recruitment of volunteers*

Using the EMaBS databases, we will identify participants who have no known chronic illness (such as HIV infection or sickle cell disease), who are still resident in the original study catchment area and who received immunisation within two weeks of birth with BCG Russia (BCG-I strain from Moscow, Serum Institute of India, India; the strain used for most EMaBS infants). A randomised list of these participants will be generated and they will be approached sequentially until the enrolment is complete.

Potential adolescent volunteers and their parents or guardians will be invited to attend the clinic for the screening processes.

To recruit the six adults, parents or guardians of EMaBS children will be approached until the target number have been enrolled. Only one parent or guardian will be enrolled from each family.

## 7.3. Informed Consent

All volunteers will sign and date the informed assent form before any study specific procedures are performed, and a parent or guardian will sign a consent form (except in the case of adult volunteers, when only a consent form will be signed). The information sheet will be made available to the volunteer and their parents/ guardians at least 24 hours prior to the screening visit. At the screening visit, the volunteer and their parent/guardian will be fully informed of all aspects of the trial, the potential risks and their obligations. The following general principles will be emphasised:

- Participation in the study is entirely voluntary
- Refusal to participate involves no penalty or loss of medical benefits

- The volunteer may withdraw from the study at any time
- The volunteer is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved
- The study involves research of investigational vaccines
- There is no direct benefit from participating
- The volunteer's EMaBS clinic file will be reviewed to corroborate their medical history
- The volunteer's blood samples taken as part of the study will be stored indefinitely and samples may be sent outside of Uganda to collaborating laboratories in the UK. These will be anonymised.

The aims of the study and all tests to be carried out will be explained. The volunteer will be given the opportunity to ask about details of the trial, and will then have time to consider whether or not to participate. If they do decide to participate, they will sign and date two copies of the assent and consent forms, one for them to take away and keep, and one to be stored in the case report form (CRF). Separate information and consent forms will be provided for consent for storage of samples for future studies, and for anonymous sharing of data from this study. These forms will also be signed and dated by the Investigator.

#### **7.4. Inclusion Criteria**

Volunteers must meet all of the following criteria to enter the trial:

- Resident within the study area and planning to be resident in the study area for the duration of the study
- Participant in the Entebbe Mother and Baby Study; healthy; aged 11 to 14 [or, for adults, a parent or guardian of a participant; healthy; aged 18 to 49]
- Documented immunisation within two weeks of birth with BCG Russia (BCG-I strain from Moscow, Serum Institute of India, India) [adolescents only]
- BCG scar or documented previous BCG immunisation [adults only]
- No relevant findings in medical history or on physical examination
- Written informed consent by parent or guardian [or by the volunteer themselves, for adults]
- Written informed assent by subject [for adolescents]
- Agreed to refrain from blood donation during the trial [adults only; adolescents under age 18 are not eligible to give blood]
- Agree to avoid pregnancy for the duration of the trial (female only)
- Able and willing (in the Investigator's opinion) to comply with all the study requirements

#### **7.5. Exclusion Criteria**

Volunteers must meet none of the following criteria to enter the trial:

- Clinical, radiological, or laboratory evidence of current active TB disease<sup>a</sup>
- Laboratory evidence at screening of latent *M.tb* infection as indicated by a positive ELISPOT response to ESAT6 or CFP10 antigens<sup>b</sup>
- Previous treatment for active or latent tuberculosis infection
- Shared a residence with an individual who has started on anti-tuberculosis treatment, or been diagnosed with culture or smear-positive pulmonary tuberculosis, within six months prior to day 0
- Received a TST within 90 days prior to day 0

- Clinically significant history of skin disorder, allergy, immunodeficiency (including HIV), cancer, cardiovascular disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness, drug or alcohol abuse
- History of serious psychiatric condition or disorder
- Concurrent oral or systemic steroid medication or the concurrent use of other immunosuppressive agents within 2 months prior to enrolment
- History of anaphylaxis to vaccination or any allergy likely to be exacerbated by any component of the study vaccine, including eggs
- Any abnormality of screening blood or urine tests that is deemed to be clinically significant or that may compromise the safety of the volunteer in the study<sup>a</sup>
- Positive HBsAg, HCV or HIV antibodies<sup>a</sup>
- Use of an investigational medicinal product or non-registered drug, live vaccine, or medical device other than the study vaccine for 30 days prior to dosing with the study vaccine, or planned use during the study period
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned trial vaccination date
- Female currently lactating, confirmed pregnancy or intention to become pregnant during the trial period
- Screening blood sample positive for malaria by microscopy

<sup>a</sup>Subjects who are excluded from the trial because they have been discovered during screening procedures to be suffering from a previously undiagnosed condition thought to require further medical attention will be referred appropriately for further investigation and treatment.

<sup>b</sup>Subjects discovered to have evidence of latent *M.tb* infection as defined by a positive ELISPOT test will be referred for a plain chest X-ray and reviewed by a physician and considered for chemoprophylaxis. If there is any evidence of active TB disease either on clinical or radiological grounds, further investigation and treatment will be offered in collaboration with the National Tuberculosis Control Programme.

### **Effective contraception for female volunteers**

Adolescent female volunteers will need to agree not to become pregnant during the course of the trial. The introduction of formal methods of contraception in the young adolescent age group to be enrolled in this study would not be appropriate in Uganda.

Adult female volunteers will be required to use an effective form of contraception during the course of the trial. There is no information about the effect of ChAdOx1 85A on a fetus. Previous investigations looking at excretion of viral vectors after vaccination in urine for males, demonstrated no detectable virus; therefore males are not required to use barrier contraception whilst taking part in this study as the risk of excretion of the virus is very low.

Acceptable forms of contraception for female volunteers include:

- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Permanent sterilisation or bilateral tubal occlusion
- Barrier methods of contraception (condom; or occlusive cap with spermicide)
- Male sterilisation, if the vasectomised partner is the sole partner for the subject
- True abstinence, when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence and withdrawal are not acceptable methods of contraception)

## 7.6. Screening and Eligibility Assessment

Once the informed consent process has been completed, and consent (and assent) given, a baseline medical history (including concomitant medication) and history relating to risk of prior TB exposure will be collected. Vital signs will be checked and a physical examination will be performed. Inclusion and exclusion criteria will be checked using a tabulated format.

Subjects will undergo pre- and post-test counselling for HIV, hepatitis B and C testing and (for girls) pregnancy testing by a trained and experienced nurse- or clinician-counsellor. Blood, urine and stool samples will be obtained, for tests as specified in the schedule of procedures. These tests are planned in order to exclude major, immunomodulating co-infections (HIV, malaria) or conditions that might impact safety, or the assessment of safety-related parameters (hepatitis, pregnancy). The total duration of the screening visit will be approximately one and a half hours.

Subjects with abnormal findings on screening will be counselled, managed and referred as appropriate.

- Any volunteers found to be HIV positive will be offered a CD4 T cell count and treated with antiretroviral therapy under the auspices of the EMaBS clinic, or referred to another provider, if preferred.
- Any volunteers with evidence of hepatitis C infection, or of active hepatitis B infection (surface antigen positive) will be supported to undergo further serology and viral load testing (available, for example, at MBN laboratory, Nakasero, Kampala) and abdominal ultrasound. They will then be referred to Mulago Hospital (the national referral hospital) for further follow up and care.
- Volunteers found to have a positive ELISPOT for *M. tuberculosis*-specific antigens (suggesting *M.tb* infection) will be examined by a physician, have a sputum examination (if they have a productive cough) and will be offered a chest x-ray. If there is evidence of active tuberculosis they will be referred to the nearest treatment centre of the National Tuberculosis Control Programme for further management.
- Volunteers found to be positive for malaria will be treated.
- Asymptomatic helminth infection (with normal full blood count, biochemistry and liver function tests) will not be an exclusion criterion. These will be treated after data on the primary outcomes have been collected since it is possible that helminth co-infection contributes to the “normal” baseline immunological status in African populations, and treatment of helminths can result in sudden changes in immunological parameters [57]. Volunteers with asymptomatic helminth infection will be treated according to the schedules in section 3.
- Volunteers found to have helminth infections that require immediate treatment (hookworm and haemoglobin level below 8 g/dl; *Schistosoma mansoni* with egg counts >2000 per gram (a level at which intensity is associated with hepatosplenic morbidity [58]) will be treated immediately.
- Volunteers found to be pregnant will be counselled and referred to the most convenient antenatal care clinic of their choice.

## 7.7. Enrolment

Subjects who complete the screening processes, satisfy all the inclusion criteria, and meet none of the exclusion criteria will be enrolled into the trial and their visits scheduled in the calendar. The ongoing eligibility of the subject will be reviewed on the day of enrolment and any new events, medications, or changes to the screening documents recorded. Subjects will be enrolled on the vaccination visit (day 0). The vaccination visit will last approximately two hours, which includes a 60 minute follow up period in the clinic for observation after vaccination.



## **7.8. Randomisation and blinding**

After completion of the dose escalation and age de-escalation components, enrolment to the randomised trial of ChAdOx1 85A-MVA85A versus BCG revaccination will commence. This will be an open label trial as it will not be possible to blind either volunteers or clinic staff to the allocation. However, laboratory staff will be blinded to the allocation of the volunteers as they undertake the immunological assays.

The randomisation code will be generated by the trial statistician, using a block size of 6. Eligible volunteers will be sequentially allocated to a randomisation number by the screening interviewer. Sealed envelopes, labelled with the code, will contain instructions on which vaccines should be given.

## **7.9. Timepoints**

### *Screening – trial enrolment time window*

Enrolment should take place no longer than 90 days following the date of screening appointment. If more than 90 days elapse, the screening visit should be repeated in full prior to enrolment in order to minimise the risk to volunteers of any new unidentified health problems having arisen during that period.

### *Vaccination of first volunteer – subsequent vaccination time window*

The first volunteer, who will be allocated to Group 1, will be vaccinated with ChAdOx1 85A by the intramuscular route at least 7 days before any subsequent volunteers in this group. After safety review by the clinical team and the Chief Investigator of the three Group 1 volunteers, the first volunteer in Group 2 will be vaccinated at least 7 days prior to further volunteer enrolment into Group 2. After similar safety review of the three Group 2 volunteers, the first volunteer in Group 3 will be vaccinated at least 7 days prior to further enrolment into Group 3. After similar safety review of the three Group 3 volunteers, the first volunteer in Group 4 will be vaccinated at least 7 days prior to further enrolment into Group 4. After review by the clinical team and the Chief Investigator of the safety data from groups 1-4, enrolment into the randomised trial will commence. The data and safety monitoring board (DSMB) will be consulted if there are any issues of concern.

### *Follow up period*

The follow up period will be 24 weeks for groups 1-4, one year for groups 5 and 6, after first vaccination in accordance with findings from previous studies in which adequate safety data and reliable markers of immunogenicity have been obtained in this time interval. All follow up visits will last approximately 15 to 30 minutes.

## **7.10. Sample handling**

Details regarding samples, volume and frequency of sampling are listed in the Schedule of Trial Visits and Procedures (section 3.2). Blood and other samples will be processed according to local laboratory SOPs. All samples will be in anonymised form.

Volunteers will be informed that there may be leftover samples of their blood. With the volunteers' informed consent, any leftover cells and serum, or plasma samples will be frozen for future analysis of *M.tb* and/or BCG-related responses. This may include human DNA and RNA analysis to search for correlates of TB risk and/or protection. Samples may be shipped to other parties involved in our research in anonymised form for immunological analysis. Volunteers will be able to decide if they will permit such future use of any leftover samples. If they elect not to permit this, all of those leftover samples will be discarded after the required period of storage to meet GCP and regulatory requirements.

### **7.11. Vaccination Postponement Criteria**

The following adverse events constitute contraindications to administration of vaccine at that point in time; if any one of these adverse events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, or withdrawn at the discretion of the Investigator. The subject must be followed until resolution of the event as with any adverse event:

- Acute disease at the time of vaccination. (Acute disease is defined as the presence of a moderate or severe illness with or without fever). All vaccines can be administered to persons with a minor illness such as diarrhoea, mild upper respiratory infection with or without low-grade febrile illness, i.e. temperature of  $\leq 37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$ .
- Temperature of  $>37.5^{\circ}\text{C}$  ( $99.5^{\circ}\text{F}$ ) at the time of vaccination.

### **7.12. Discontinuation / Withdrawal Criteria**

In accordance with the principles of the current revision of the Declaration of Helsinki and any other applicable regulations, a volunteer has the right to withdraw from the study at any time and for any reason, and is not obliged to give his or her reasons for doing so. The Investigator may withdraw the volunteer at any time in the interests of the volunteer's health and well-being. In addition the volunteer may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the Investigator.
- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening).
- Significant protocol deviation.
- Volunteer non-compliance with study requirements.
- An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures.

Any volunteer who becomes pregnant during the trial will be followed up as per the protocol and until the end of the pregnancy. The babies will also be followed up and examined for any adverse effects. We will not routinely perform venepuncture in a pregnant volunteer.

The reason for withdrawal will be recorded in the CRF. If withdrawal is due to an AE, appropriate follow-up visits or medical care will be arranged, with the agreement of the volunteer, until the AE has resolved, stabilised or a non-trial related causality has been assigned. Any volunteer who is withdrawn from the study may be replaced, if that is possible within the specified time frame. Any volunteer who fails to attend for two or more follow-up visits during the study will be deemed to have withdrawn from the study.

If a volunteer withdraws from the study, blood samples collected before their withdrawal from the trial will be used/ stored unless the volunteer specifically requests otherwise.

In all cases of subject withdrawal, excepting those of complete consent withdrawal, long-term safety data collection, including some procedures such as safety bloods, will continue as appropriate if subjects have received one or more vaccine doses.

### **7.13. Discontinuation of the trial**

The trial will be discontinued in the event of any of the following:

- New scientific information is published to indicate that volunteers in the trial are being exposed to undue risks as a result of administration of the IMPs, or as a result of the trial procedures or follow-up schedule.

- Serious concerns about the safety of either of the IMPs arise as a result of one or more IMP-related SAE(s) occurring in the volunteers enrolled in this or any other ongoing trial of these IMPs.
- For any other reason at the discretion of the Investigator.

#### 7.14. End of Study Definition

The trial will be completed when the last volunteer enrolled into the trial has completed their final follow up visit.

## 8. CLINICAL PROCEDURES

This section describes the clinical procedures for evaluating study volunteers and follow-up after administration of study vaccine.

### 8.1. Schedule of Attendance

All volunteers will have the same schedule of clinic attendances and procedures as indicated in the Schedules of Visits and Procedures (section 3). The total volume of blood donated during the study will be 143mL. Additional visits or procedures may be performed at the discretion of the investigators, e.g., further medical history and physical examination, or urine microscopy in the event of positive urinalysis.

### 8.2. Observations

Pulse, blood pressure and temperature will be measured at the time-points indicated in the Schedule of Visits and Procedures (section 3) and may also be measured as part of a physical examination if indicated at other time-points.

### 8.3. Blood tests, urine and stool analysis

Blood will be drawn for the following laboratory tests and processed at the EMaBS clinic laboratory, or in laboratories at the Uganda Virus Research Institute (UVRI), using standard procedures:

- **Haematology and haemoparasitology:** full blood count, malaria slide, *Mansonella perstans* (using modified Knott's method [59]); malaria PCR will be conducted for sub-microscopic parasitaemia.
- **Biochemistry:** Sodium, Potassium, Urea, Creatinine, Albumin, Liver Function Tests (ALT, AST, ALP, GGT)
- **Diagnostic serology:** HBsAg, HCV antibodies, HIV antibodies (specific consent will be gained prior to testing blood for these blood-borne viruses)
- **Exploratory Immunology:** Immunogenicity will be assessed by a variety of immunological assays. This includes *ex vivo* ELISpot assays for interferon gamma and flow cytometry assay. Other exploratory immunological assays including cytokine analysis and gene expression studies amongst others may be performed at the discretion of the Investigators. Immunological assays will be conducted according to local SOPs.
- **Urinalysis:** Urine will be tested for protein, blood and glucose at screening. For female volunteers only, urine will be tested for beta-human chorionic gonadotropin ( $\beta$ -HCG) at screening and immediately prior to vaccination. Urine will also be examined for circulating cathodic antigen of *Schistosoma* species.
- **Stool:** stool samples will be examined for helminths by the Kato Katz method, and by PCR [60]. A sample will be stored for possible analysis of the microbiome in future.

**Genetic studies**, including a genome wide association analysis and work on HLA typing, have already been undertaken among EMaBS participants, based on prior ethical approval and consent. Genetic analyses relevant to vaccine responses were the primary motivation for the work. This will provide the opportunity for genetic analyses using immunological data generated under this new protocol also.

Collaboration with other specialist laboratories in the UK, Europe and outside of Europe for further exploratory tests may occur. This would involve the transfer of serum, urine or plasma and/or PBMC to these laboratories, but these would remain anonymised. Informed consent for this will be gained from volunteers. A Material Transfer Agreement will be submitted for review and approval before any samples are sent to collaborating institutions.

#### **8.4. Study visits**

The study visits and procedures will be undertaken by one of the clinical trials team. The procedures to be included in each visit are documented in the Schedule of Visits and Procedures (Section 3). Each visit is assigned a time-point and a window period, within which the visit will be conducted.

##### **8.4.1. Screening visit**

All potential volunteers will have a screening visit, which may take place up to 120 days prior to vaccination. Informed consent will be taken before screening, as described in section 7. **Error! Reference source not found.** If consent is obtained, the procedures indicated in the Schedule of Visits and Procedures (section 3) will be undertaken including a medical history, physical examination and blood tests.

The subject's EMaBS study file will be reviewed to ascertain any significant medical history. Abnormal clinical findings from the urinalysis or blood tests at screening will be assessed according to normal ranges defined locally by Lugada and colleagues for haematology [61], and those provided by the ISO accredited Clinical Diagnostic Laboratory at UVRI for biochemistry. Any abnormal test result deemed clinically significant may be repeated to ensure it is not a single occurrence. If an abnormal finding is deemed to be clinically significant, the volunteer will be informed and appropriate medical care arranged with the permission of the volunteer.

The eligibility of the volunteer will be reviewed at the end of the screening visit and again when all results from the screening visit have been considered. Decisions to exclude the volunteer from enrolling in the trial or to withdraw a volunteer from the trial will be at the discretion of the Investigator. If eligible, a day 0 visit will be scheduled for the volunteer to receive the vaccine.

##### **8.4.2. Day 0: Enrolment and vaccination visit**

Volunteers will not be considered enrolled in the study until they have received a vaccine. Before vaccination, the eligibility of the volunteer will be reviewed. Pulse, blood pressure and temperature will be observed and if necessary, a medical history and physical examination may be undertaken to determine need to postpone vaccination depending on criteria listed in section 7.11. A pregnancy test will be repeated for female volunteers. Vaccinations will be administered as described below.

##### **8.4.3. Vaccination (D0)**

Group 1 adults will be given ChAdOx1 85A at  $5 \times 10^9$  vp intramuscularly

Group 2 adults will be given ChAdOx1 85A at  $2.5 \times 10^{10}$  vp intramuscularly

Group 3 adolescents will be given ChAdOx1 85A at  $5 \times 10^9$  vp intramuscularly

Group 4 adolescents will be given ChAdOx1 85A at  $2.5 \times 10^{10}$  vp intramuscularly

Group 5 adolescents will be given ChAdOx1 85A at  $2.5 \times 10^{10}$  vp intramuscularly

Group 6 adolescents will be given BCG revaccination, Serum Institute of India, 0.1 mL intradermally  
Following vaccination the following procedures will be undertaken:

In all groups, volunteers will be given a thermometer, tape measure and paper diary card, with instructions on use, along with the emergency 24 hour telephone number to contact the on-call study physician if needed. Volunteers will be instructed on how to self-assess the severity of these AEs. There will also be space on the diary card to self-document unsolicited AEs, and whether medication was taken to relieve the symptoms. Diary cards will collect information on the timing and severity of the following solicited AEs:

| Local solicited AEs           | Systemic solicited AEs |
|-------------------------------|------------------------|
| Pain                          | Fever                  |
| Redness                       | Feverishness/Chills    |
| Warmth                        | Joint pains            |
| Itch                          | Muscle pains           |
| Blistering or ulceration      | Fatigue                |
| Swelling of local lymph nodes | Headache               |
|                               | Malaise                |
|                               | Abdominal pain         |
|                               | Chills                 |

*Table 6. Solicited AEs as collected on post vaccination diary cards*

#### **8.4.1. Subsequent visits**

All volunteers will be asked to attend as per the Schedule of Visits and Procedures in section 3. On visits other than for vaccination the volunteers will be assessed for local and systemic adverse events, using paper diary cards, interim history, physical examination and blood tests at the time-points indicated in the Schedule of Visits and Procedures (Section 3). Blood will also be taken for assessments of immunogenicity and exploratory immunology analysis.

#### **8.4.2. MVA85A booster immunisation.**

Volunteers in group 5 will be asked to attend on day 56 for booster immunisation with MVA85A [volunteers in group 6 will also be asked to attend on this date, but only to provide the samples indicated].

For group 5, before the MVA85A vaccination, the health of the volunteer will be reviewed. Pulse, blood pressure and temperature will be observed and if necessary, a medical history and physical examination may be undertaken to determine need to postpone booster vaccination. For girls, a pregnancy test will be repeated. If the volunteer is well and the pregnancy test is negative MVA vaccination will be administered at  $1 \times 10^8$  pfu.

Group 5 volunteers will be provided with a diary card and instructed in its use as described above.

Diary cards will be collected two weeks after ChAdOx1 85A and one week after MVA85A as these intervals correspond to the optimal time points for assessing the initial response to the two vaccines.

## 9. INVESTIGATIONAL PRODUCTS

### 9.1. ChAdOx1 85A

#### 9.1.1. ChAdOx1 85A Description

ChAdOx1 85A is a new adenoviral vaccine vector (ChAdOx1) based on a chimpanzee adenovirus isolate Y25 expressing M. tb antigen 85A. ChAdOx1 85A is a replication defective adenovirus where the E1 locus, required for viral replication has been deleted. This virus can therefore be propagated easily with good yields in cell lines expressing E1 from AdHu5 such as human embryonic kidney cells 293 (HEK 293). ChAdOx1 85A also encodes almost the complete M. tb gene for Ag85A.

#### 9.1.2. Supply and Storage of ChAdOx1 85A

ChAdOx1 85A is manufactured under Good Manufacturing Practice conditions at the Clinical Biomanufacturing Facility (CBF), University of Oxford. The vaccine is supplied as a liquid in glass vials for intramuscular administration and is stored at -80°C, in a locked, alarmed, temperature monitored freezer at the CCVTM, University of Oxford.

ChAdOx 85A will be shipped from CBF directly to the UVRI on dry ice and in the presence of a temperature logger. The vaccine will be certified and labelled for use in trial TB042 by a qualified person (QP) at CBF.

The vaccine will be stored at -80°C (nominal temperature) in a secure, temperature-monitored freezer at UVRI.

All movements of the study vaccine between the CBF and UVRI will be documented. Vaccine accountability, storage, shipment and handling will be in accordance with our vaccine related SOPs and associated forms.

#### 9.1.3. Formulation of ChAdOx1 85A

The ChAdOx1 85A vaccine is formulated in formulation buffer at a concentration of  $1.74 \times 10^{11}$  vp/mL. The formulation buffer consists of 10mM Histidine, 7.5% sucrose, 35mM NaCl, 1mM MgCl<sub>2</sub>, 0.1% PS80, 0.1mM EDTA, 0.5% EtOH, pH 6.6. The fill volume is 0.5 mL.

#### 9.1.4. Dispensing and administration of ChAdOx1 85A

All movements of vials of the trial vaccine between the CBF and UVRI, and in or out of the locked freezers, will be documented. On vaccination day, vaccines will be allowed to thaw to room temperature and will be administered within 1 hour. The vaccine will be administered intramuscularly over the deltoid region of the non-dominant upper arm, according to the standardized SOP. Subjects will stay in the unit for 60 minutes ( $\pm 10$  minutes) after vaccination. During the administration of the vaccine, monitoring equipment, oxygen, medicines including bronchodilators and resuscitation equipment will be immediately available for the management of anaphylaxis and bronchospasm.

In order to minimise dissemination of the recombinant vectored vaccine virus into the environment, a number of measures will be instituted during and following vaccination:

- The intramuscular injection site will be covered with a dressing after vaccination to absorb any virus that may leak out through the needle track. The dressing will be removed from the injection site after 30 minutes.
- The dilution process will be carried out in a sealed vial in accordance with the standardized SOP.

- All disposable items including needles, vials, dressings, and protective clothing will be disposed of as GMO waste by autoclaving, in accordance with the current approved SOPs and standard practice.

## **9.2. MVA85A**

### **9.2.1. MVA85A Description**

The MVA85A vaccine consists of the attenuated vaccinia virus MVA vector with a 1176 base-pair insert, which is almost the complete *M.tb* gene for Ag85A, with the tissue plasminogen activator (TPA) signal sequence preceding the N terminus and a monoclonal antibody tag (pk) at the C terminus. Expression of the antigen 85A DNA sequence is regulated by the vaccinia P7.5 early/late promoter. MVA85A is manufactured under Good Manufacturing Practice conditions by IDT Biologika GmbH (IDT), Germany.

### **9.2.2. Formulation of MVA85A**

MVA85A is supplied as a sterile liquid in glass vials. Each vial of lot 0050811 contains 400 µL of vaccine at a concentration of  $8.4 \times 10^8$  pfu/mL in 10mM Tris buffer 140 mM NaCl; pH 7.7. The dose of MVA85A to be used is  $1 \times 10^8$  pfu.

### **9.2.3. Storage of MVA85A**

MVA85A will be shipped from IDT directly to the UVRI on dry ice and in the presence of a temperature logger. The vaccine will be certified and labelled for use in trial TB042 by a qualified person (QP) at IDT.

The vaccine will be stored at -80°C (nominal temperature) in a secure, temperature-monitored freezer at UVRI.

All movements of the study vaccine between IDT and UVRI will be documented. Vaccine accountability, storage, shipment and handling will be in accordance with our vaccine related SOPs and associated forms.

### **9.2.4. Dispensing and administration of MVA85A**

All movements of vials of the trial vaccine between IDT/CBF and UVRI and in or out of the locked freezer will be documented. Vaccine accountability, storage, shipment and handling will be in accordance with local SOPs and other relevant local forms.

On vaccination day, vaccines will be allowed to thaw to room temperature and will be administered within 1 hour. The vaccine will be administered IM over the deltoid region of the non-dominant upper arm, according to the site-specific SOP. Volunteers will stay in the unit for 60 minutes ( $\pm 10$  minutes) after vaccination. During the administration of the vaccine, monitoring equipment, oxygen, medicines including bronchodilators and resuscitation equipment will be immediately available for the management of anaphylaxis and bronchospasm according to the site-specific SOP.

In order to minimise dissemination of the recombinant vectored vaccine virus into the environment, a number of measures will be instituted during and following vaccination:

- The dilution process will be carried out in a sealed vial in accordance with the vaccine dilution SOP.
- The IM injection site will be covered with a dressing after vaccination to absorb any virus that may leak out through the needle track. The dressing will be removed from the injection site after 30 minutes and will be disposed as GMO waste by autoclaving.

- All disposable items including nebuliser parts, needles, vials, dressings, and protective clothing will be disposed of as GMO waste by autoclaving, in accordance with the current approved SOP and standard practice.

### 9.3. Vaccine accountability and disposal

On completion of the trial and of close-out monitoring visits to check vaccine accountability, at the request of the CI, any remaining vials of investigational vaccines held in Uganda will either be shipped back to the Sponsor or will be destroyed by the National Drug Authority, and a certificate of shipment or destruction will be obtained as applicable.

## 10. ASSESSMENT OF SAFETY

Safety will be assessed by the frequency, incidence and nature of adverse events and serious adverse events arising during the trial.

### 10.1. Interim Safety Review

Prior to dose escalation of the IMP or age de-escalation, the clinical team and Chief Investigator will review the safety data and adverse events in volunteers before proceeding to the next group.

Dose escalation or age de-escalation will not take place in the event of any of the holding criteria being met. In addition, the Phase IIa randomised trial will be held, and the DSMB will be consulted, if any of the following holding criteria occurs.

#### 10.1.1. Holding criteria

Safety holding rules would be activated by any of the following:

- **A serious adverse event considered possibly, probably or definitely related to vaccination occurs**
- **Death occurs**
- **A life-threatening reaction occurs**
- **Solicited systemic adverse events:**  
If 2 or more vaccinations in group 1, 2, 3 or 4; or more than 25% of doses of the vaccine in group 5; is followed by the same Grade 3 solicited systemic adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at Grade 3 for >48hrs.
- **Unsolicited adverse events:**  
If 2 or more vaccinations in group 1, 2, 3 or 4; or more than 25% of doses of the vaccine in group 5; develop the same Grade 3 unsolicited adverse event beginning within 7 days after vaccination that is considered related to vaccination and persists at Grade 3 for > 48 hours.
- **Laboratory adverse event:**  
If 2 or more vaccinations in group 1, 2, 3 or 4; or more than 25% of doses of the vaccine in group 5; develop the same Grade 3 laboratory adverse event beginning within 7 days after vaccination and persists at Grade 3 for > 48 hours.

If a holding rule has been met, the internal safety review will consider:

- The relationship of the AE or SAE to the vaccine.
- The relationship of the AE or SAE to the vaccine dose, or other possible causes of the event.
- If appropriate, additional screening or laboratory testing for other volunteers to identify those who may develop similar symptoms and alterations to the current Volunteer Information Sheet (PIS).



- New, relevant safety information from ongoing research programs on the various components of the vaccine.

The local ethics committee and vaccine manufacturers will also be notified if a holding rule is activated or released.

All vaccinated volunteers will be followed for safety until the end of their planned participation in the study or until resolution or stabilisation (if determined to be chronic sequelae) of their AEs, providing they consent to this.

In addition to these pre-defined criteria, the study can be put on hold upon advice of the Chief Investigator, Principal Investigator, Study Sponsor, Regulatory Authority, Ethical Committee(s) or DSMB, for any single event or combination of multiple events which, in their professional opinion, jeopardise the safety of the volunteers or the reliability of the data.

## **10.2. Definitions**

### **10.2.1. Adverse Event (AE)**

An AE is any untoward medical occurrence in a volunteer, which may occur during or after administration of an Investigational Medicinal Product (IMP) and does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study intervention, whether or not considered related to the study intervention.

### **10.2.2. Adverse Reaction (AR)**

An AR is any untoward or unintended response to an IMP. This means that a causal relationship between the IMP and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by the reporting medical Investigator as having a reasonable suspected causal relationship to an IMP (i.e. possibly, probably or definitely related to an IMP) will qualify as adverse reactions.

### **10.2.3. Unexpected Adverse Reaction**

An adverse reaction, the nature or severity of which is not consistent with the applicable product information in the Investigator Brochure (IB).

### **10.2.4. Serious Adverse Event (SAE)**

An SAE is an AE that results in any of the following outcomes, whether or not considered related to the study intervention.

- Death
- Life-threatening event (i.e., the volunteer was, in the view of the Investigator, at immediate risk of death from the event that occurred). This does not include an AE that, if it occurred in a more severe form, might have caused death.
- Persistent or significant disability or incapacity (i.e., substantial disruption of one's ability to carry out normal life functions).
- Hospitalisation, regardless of length of stay, even if it is a precautionary measure for continued observation. Hospitalisation (including inpatient or outpatient hospitalisation for an elective procedure) for a pre-existing condition that has not worsened unexpectedly does not constitute a serious AE.
- An important medical event (that may not cause death, be life threatening, or require hospitalisation) that may, based upon appropriate medical judgment, jeopardise the

volunteer and/or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic reaction requiring intensive treatment in an emergency room or clinic, blood dyscrasias, or convulsions that do not result in inpatient hospitalisation.

- Congenital anomaly or birth defect.

#### 10.2.5. Serious Adverse Reaction (SAR)

An adverse event (expected or unexpected) that is both serious and, in the opinion of the reporting Investigator or Sponsors, believed to be possibly, probably or definitely due to an IMP or any other study treatments, based on the information provided.

#### 10.2.6. Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the IB.

NB: To avoid confusion or misunderstanding the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

### 10.3. Expected Serious Adverse Events

No serious adverse events are expected in this trial.

### 10.4. Causality Assessment

For every AE, an assessment of the relationship of the event to the administration of the vaccine will be undertaken by the CI-delegated clinician. An intervention-related AE refers to an AE for which there is a probable or definite relationship to administration of a vaccine. An interpretation of the causal relationship of the intervention to the AE in question will be made, based on the type of event; the relationship of the event to the time of vaccine administration; and the known biology of the vaccine therapy (Table 7). Alternative causes of the AE, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination will be considered and investigated. Causality assessment will take place during planned safety reviews, interim analyses (e.g. if a holding or stopping rule is activated) and at the final safety analysis, except for SAEs, which should be assigned by the reporting investigator.

|   |                        |  |
|---|------------------------|--|
| 0 | <b>No Relationship</b> | No temporal relationship to study product <b>and</b><br>Alternate aetiology (clinical state, environmental or other interventions);<br><b>and</b><br>Does not follow known pattern of response to study product                                |
| 1 | <b>Unlikely</b>        | Unlikely temporal relationship to study product <b>and</b><br>Alternate aetiology likely (clinical state, environmental or other interventions) <b>and</b><br>Does not follow known typical or plausible pattern of response to study product. |
| 2 | <b>Possible</b>        | Reasonable temporal relationship to study product; <b>or</b><br>Event not readily produced by clinical state, environmental or other interventions; <b>or</b><br>Similar pattern of response to that seen with other vaccines                  |
| 3 | <b>Probable</b>        | Reasonable temporal relationship to study product; <b>and</b><br>Event not readily produced by clinical state, environment, or other interventions <b>or</b><br>Known pattern of response seen with other vaccines                             |

|   |                 |  |
|---|-----------------|--|
| 4 | <b>Definite</b> | Reasonable temporal relationship to study product; <b>and</b><br>Event not readily produced by clinical state, environment, or other interventions; <b>and</b><br>Known pattern of response seen with other vaccines |
|---|-----------------|--|

Table 7. Guidelines for assessing the relationship of vaccine administration to an AE

### 10.5. Reporting Procedures for All Adverse Events

All local and systemic AEs occurring in the 28 days following each vaccination observed by the Investigator or reported by the volunteer, whether or not attributed to study medication, will be recorded. Recording and reporting of all AEs will take place as detailed in the study’s SOP. All AEs that result in a volunteer’s withdrawal from the study will be followed up until a satisfactory resolution occurs, or until a non-study related causality is assigned (if the volunteer consents to this). Serious adverse events (SAEs) will be collected throughout the entire trial period.

|                 | <b>Adverse event</b>                     |
|-----------------|--|
| <b>Local</b>    | Pain/tenderness at the injection site    |
|                 | Swelling at injection site               |
|                 | Warmth at the injection site             |
|                 | Itch at the injection site               |
|                 | Scaling/pustules at the injection site   |
| <b>Systemic</b> | Documented fever (temperature > 37.5° C) |
|                 | Myalgia                                  |
|                 | Arthralgia                               |
|                 | Feverishness                             |
|                 | Headache                                 |
|                 | Fatigue                                  |
|                 | Nausea                                   |
|                 | Malaise                                  |

Table 8. Routinely solicited adverse events

#### 10.5.1. Reporting Procedures for Serious AEs

In order to comply with current regulations on serious adverse event reporting to regulatory authorities, the event will be documented accurately and notification deadlines respected. SAEs will be reported on the SAE forms to members of the study team immediately the Investigators become aware of their occurrence, as described in the study’s SOP. Copies of all reports will be forwarded for review to the Chief Investigator (as the Sponsor’s representative) within 24 hours of the Investigator being aware of the suspected SAE. The data and safety monitoring board (DSMB) will be notified of SAEs that are deemed possibly, probably or definitely related to study interventions; the DSMB will be notified immediately (within 24 hours) of the Investigators’ being aware of their occurrence. SAEs will be reported to the Research Ethics Committee (REC) at UVRI within 7 calendar days of the Investigator becoming aware of them, and a full report (if the initial report is not complete) will be made within 7 calendar days of the initial report. SAEs will not normally be reported immediately to the Oxford or LSHTM ethical committee(s) unless there is a clinically important increase in occurrence rate, an unexpected outcome, or a new event that is likely to affect safety of trial volunteers, at the discretion of the Chief Investigator and/or DSMB. In addition to the expedited reporting above, the Investigator shall include all SAEs in the annual Development Safety Update Report (DSUR) report.

### 10.5.2. Reporting Procedures for SARs

These will be reported as per any SAE.

### 10.5.3. Reporting Procedures for SUSARs

The Principal Investigator will report all SUSARs to the UVRI REC within 7 calendar days of the Investigator becoming aware of them, and a full report (if the initial report is not complete) will be made within 7 calendar days of the initial report. The Chief Investigator will report all SUSARs to the MHRA and Oxford and LSHTM ethical committee(s) within required timelines (15 days for all SUSARs, unless life threatening in which case 7 days, with a final report within a further 8 days (total 15)). The Chief Investigator will also inform all Investigators concerned of relevant information about SUSARs that could adversely affect the safety of volunteers. All SUSARs and deaths occurring during the study will be reported to the Sponsor. For all deaths, available autopsy reports and relevant medical reports will be made available for reporting to the relevant authorities.

### 10.5.4. Development Safety Update Report

A Development Safety Update Report (DSUR) will be submitted by the Sponsor to the UK competent authority and ethical committee on the anniversary of the first approval date from the regulatory authority for each IMP, in accordance with UK regulatory requirements.

### 10.6. Assessment of Severity

The severity of clinical and clinical laboratory adverse events will be assessed according to the scales in Table 9-11. Clinical laboratory adverse events will be assessed as grade 1 if 1.1 to 2.4 times the limit of normal, grade 2 if 2.5 to 4.9 times, and 3 if greater than 5 times the limit of normal, in accordance with FDA guidance for toxicity grading. Normal ranges will be based on those defined locally by Lugada and colleagues for haematology [61], and those provided by the ISO accredited Clinical Diagnostic Laboratory at UVRI for biochemistry.

| Adverse Event               | Grade | Intensity                                |
|-----------------------------|-------|--|
| Pain at injection site      | 1     | Pain that is easily tolerated            |
|                             | 2     | Pain that interferes with daily activity |
|                             | 3     | Pain that prevents daily activity        |
| Erythema at injection site* | 1     | >3 - ≤50 mm                              |
|                             | 2     | >50 - ≤100 mm                            |
|                             | 3     | >100 mm                                  |
| Swelling at injection site  | 1     | >1 - ≤20 mm                              |
|                             | 2     | >20 - ≤50 mm                             |
|                             | 3     | >50 mm                                   |

Table 9. Severity grading criteria for local adverse events

\*erythema ≤3mm is an expected consequence of skin puncture and will therefore not be considered an adverse event

|                    | Grade 1<br>(mild) | Grade 2<br>(moderate) | Grade 3<br>(severe) |
|--------------------|-------------------|-----------------------|---------------------|
| Fever              | 37.6°C - 38.0°C   | 38.1°C – 39.0°C       | >39.0°C             |
| Tachycardia (bpm)* | 101 - 115         | 116 – 130             | >130                |

|                                |           |           |      |
|--------------------------------|-----------|-----------|------|
| Bradycardia (bpm)**            | 50 – 54   | 40 – 49   | <40  |
| Systolic hypertension (mmHg)   | 141 - 159 | 160 – 179 | ≥180 |
| Diastolic hypertension (mmHg)  | 91 - 99   | 100 – 109 | ≥110 |
| Systolic hypotension (mmHg)*** | 85 - 89   | 80 – 84   | <80  |

Table 10. Severity grading criteria for physical observations [appropriate adjustments will be made for age, gender and height percentiles]

\*Taken after ≥10 minutes at rest; \*\*When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterising bradycardia among some healthy volunteer populations, for example, conditioned athletes; \*\*\*Only if symptomatic (e.g. dizzy/ light-headed)

|                |  |
|----------------|--|
| <b>GRADE 0</b> | None   |
| <b>GRADE 1</b> | Mild: Transient or mild discomfort (< 48 hours); no medical intervention/therapy required  |
| <b>GRADE 2</b> | Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required   |
| <b>GRADE 3</b> | Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisation possible |

Table 11. Severity grading criteria for respiratory and systemic AEs

### 10.7. Procedures to be followed in the event of abnormal findings

Eligibility for enrolment in the trial in terms of laboratory findings will be assessed as detailed in Section 7. Abnormal clinical findings from medical history, examination or blood tests will be assessed as to their clinical significance throughout the trial. Laboratory adverse events will be assessed using the normal ranges based on those defined locally by Lugada and colleagues for haematology [61], and those provided by the ISO accredited Clinical Diagnostic Laboratory at UVRI for biochemistry. If a test is deemed clinically significant, it may be repeated, to ensure it is not a single occurrence. If a test remains clinically significant, the volunteer will be informed and appropriate medical care arranged as appropriate and with the permission of the volunteer. Specific details regarding findings, discussion with volunteers and resulting actions will be recorded in the CRF. Decisions to exclude the volunteer from enrolling in the trial or to withdraw a volunteer from the trial will be at the discretion of the Investigator.

### 10.8. Data and Safety Monitoring Board (DSMB)

A data and safety monitoring board (DSMB) will be appointed to provide real-time safety oversight. The DSMB will be notified within 24 hours of the Investigators' being aware of the occurrence of SAEs. The DSMB has the power to place the trial on hold if deemed necessary following a trial intervention-related SAE. The DSMB will be chaired by clinician experienced in early-phase clinical trials. There will be a minimum of two other appropriately qualified committee members. Membership will include a statistician, and at least one Ugandan member. All correspondence between Investigator and DSMB will be conveyed by the Chief Investigator to the trial Sponsor. The Chair of the DSMB will be contacted for advice and independent review by the Investigator or trial Sponsor in the following situations:

- Following any SAE deemed to be possibly, probably, or definitely related to the trial challenge agent.

- Any other situation where the Investigator or trial Sponsor feels independent advice or review is important.

Reports will be provided to the DSMB on completion of recruitment to groups 1 and 2 (adult dose escalation) before proceeding to group 3; and on completion of recruitment to groups 3 and 4 (adolescent dose escalation), before proceeding to the randomised trial (groups 5 and 6).

## 11. STATISTICS

This is primarily an exploratory immunogenicity and safety trial with descriptive endpoints.

Adverse events will be listed and summarised by type of AE, frequency, severity and trial group.

The sample size (12 participants for dose escalation and age de-escalation, 60 participants [30 in each arm] for the randomised trial) has been determined by the number of doses of ChAdOx1 85A available for this study. The following are the considerations regarding sample size for the randomised component of the trial. The primary outcome is the IFN- $\gamma$  ELISpot response to antigen 85A at week 9 which is measured in spot forming counts per  $1 \times 10^6$  peripheral blood mononuclear cells (PBMCs). Assuming a standard deviation of  $0.4 \log_{10} \text{ sfc}/1 \times 10^6 \text{ PBMC}$  (spot forming counts/ $1 \times 10^6$  peripheral blood mononuclear cells) in the peak Ag85A response, our study will have over 80% power to detect a difference of  $0.29 \log_{10}$  in  $\text{sfc}/10^6 \text{ PBMC}$  with  $p < 0.05$ . This is comparable to the difference that was observed between the response to human adenovirus vectored TB vaccine candidate Aeras 402 alone (Day 14 post Aeras) and Aeras 402 with MVA85A boost (Day 7 post MVA boost) [21], or between BCG (Day 28) and MVA85A alone (Day 7) in UK subjects [62], and hence a reasonable difference to expect between BCG and ChAdOx1 85A-MVA85A (aim 2).

For outcomes that are approximately normally distributed or normalised by log-transformation, differences in means will be presented together with 95% confidence intervals and p-values from unpaired t-tests. For non-normally distributed outcomes, the difference in medians between the two groups will be presented along with its 95% confidence intervals, and p-values from Wilcoxon ranksum tests.

## 12. DATA MANAGEMENT

### 12.1. Source Data

Source documents are where data are first recorded, and from which volunteers' CRF data are obtained. These include the CRF itself (history and examination), the volunteer consent form, blood and microbiology results, and any further correspondence relating to the volunteer regarding medical/clinical issues. The CRF will be electronic and/or paper together with paper diary cards.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the volunteer will be referred to by the trial volunteer number/code, not by name.

### 12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. All information relating to the trial and its volunteers will be held in strict confidence, and in accordance with GCP and institutional requirements.

### **12.3. Data Recording and Record Keeping**

The PI will be responsible for collecting, recording, analysing, and storing all the data accruing from the trial. These tasks may be delegated to other Investigators. Paper CRFs will be stored in a key-locked cabinet at the EMaBS clinic and MRC/UVRI archives, and electronic CRFs on the OpenClinica™ database, which is stored electronically on secure servers that are outsourced by OpenClinica™. Data from paper CRFs will be transcribed onto the OpenClinica™ database. Lab data will be transferred into Stata datasets and then stored on the secure servers at the MRC/UVRI.

Trial records will be held by the Investigator for as long as required by legislation as a minimum (currently until at least 2 years after the last marketing authorisation for the product) and in order to enable dissemination of trial results after publication, and to enable decoding and destruction of anonymised samples if subsequently requested by a volunteer. Data will subsequently be transferred to a secure archive in accordance with the UK Data Protection Act. Volunteers will be assigned individual unique trial numbers for identification on all trial records, except where the use of identifiable information is unavoidable (including on registration documents and consent forms). Documents with identifying information will be stored securely and separately from the other participant data.

## **13.QUALITY ASSURANCE PROCEDURES**

### **13.1. Quality Assurance**

#### **Investigator procedures**

Approved site-specific SOPs will be used.

#### **Modification to protocol**

No substantial amendments to this protocol will be made without consultation with, and agreement of, the Sponsor. Any substantial amendments to the trial that appear necessary during the course of the trial must be discussed by the Investigator and Sponsor concurrently. If agreement is reached concerning the need for an amendment, it will be produced in writing by the CI and will be made a formal part of the protocol following ethical and regulatory approval.

An administrative change to the protocol is one that modifies administrative and logistical aspects of a protocol but does not affect the volunteers' safety, the scientific value of the trial, the conduct of the trial or safety of the challenge agent. An administrative change is a non-substantial amendment and does not require REC approval. The CI is responsible for ensuring that changes to an approved trial, during the period for which REC approval has already been given, are not initiated without REC review and approval except to eliminate apparent immediate hazards to the volunteer.

#### **Protocol deviation**

All deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file and site file accordingly.

### **13.2. Monitoring**

Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The trial will be conducted in accordance with procedures identified in the protocol. Regular monitoring will be performed according to ICH GCP. According to applicable SOPs, the Monitors will verify that the clinical trial is initiated, conducted and completed, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

## **14.SERIOUS BREACHES AND PROTOCOL VIOLATIONS**

In Uganda, protocol violations will be reported to the UVRI REC within 14 calendar days of the Investigator recognising them. A protocol violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data.

In the UK, the Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach. A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree:

- the safety or physical or mental integrity of the volunteers of the trial
- the scientific value of the trial"

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory Authority and the NHS host organisation within 7 calendar days.

## **15.ETHICAL AND REGULATORY CONSIDERATIONS**

### **15.1. Declaration of Helsinki**

The Chief and Principal Investigators will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki as agreed by the World Medical Association General Assembly (Washington 2002).

### **15.2. Good Clinical Practice**

The Investigator will ensure that this trial is conducted in accordance with ICH Good Clinical Practice (GCP), and local regulatory requirements.

### **15.3. Approvals**

A copy of the protocol, proposed informed consent form, other written volunteer information and the proposed advertising material will be submitted to an independent REC for written approval. The Investigators will submit and, where necessary, obtain approval from the REC for all subsequent substantial amendments to the protocol and informed consent document. The Investigators will notify deviations from the protocol or SAEs occurring at the site to the Sponsor and will notify the REC of these in accordance with local procedures.

The Ethics Committees and Regulatory Authorities for this trial comprise the Research Ethics Committee of the UVRI, the Oxford Tropical Research Ethics Committee, the Ethics Committee of the London School of Hygiene & Tropical Medicine, the Uganda National Council for Science and Technology and the Uganda National Drug Authority.

### **15.4. Reporting**

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor. An annual DSUR will be submitted to the Regulatory Authority, if required by the MHRA.



### **15.5. Volunteer Confidentiality**

All data will be anonymised: volunteer data will be identified by a unique study number in the CRF and database. A separate confidential file containing identifiable information will be stored in a secured location in accordance with the UK Data Protection Act 1998. Only the Sponsor representative, Investigators, the clinical monitor, the REC and the Regulatory Agency will have access to the records.

### **15.6. Expenses and Benefits**

Volunteers will be compensated *pro rata* for their time, travel and for trial procedures while participating in the trial, amounting to a total of approximately £70, depending on the exact number of visits, site of recruitment and whether any repeat or additional visits are necessary.

## **16. FINANCE AND INSURANCE**

### **16.1. Funding**

This trial will be financed by a research grant from Medical Research Council, held by Professor Pontiano Kaleebu (as director of the MRC/UVRI Research Unit) and by Professor Alison Elliott (as head of the Immunomodulation and Vaccines Programme).

### **16.2. Indemnity**

If any volunteer is harmed as a result of this trial, medical care will be provided by Entebbe Hospital, or a referral hospital in Uganda if required.

#### *Negligent Harm*

Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the University is legally liable as the Research Sponsor will be covered by the University of Oxford.

#### *Non-Negligent Harm*

Indemnity and/or compensation for harm arising specifically from an accidental injury, and occurring as a consequence of the Research volunteers' participation in the trial for which the University is the Research Sponsor will be covered by the University of Oxford.

### **16.3. Insurance**

The University of Oxford has a specialist insurance policy in place which would operate in the event of any volunteer suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

## **17. PUBLICATION POLICY**

When the trial is complete, a manuscript describing the primary trial results will be written and published in a peer-reviewed, open access journal. International guidelines will be followed regarding authorship. There may also be secondary publications on more exploratory results.

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