



**Clinical Study Protocol**  
Sponsor:  
**GlaxoSmithKline Biologicals**  
Rue de l'institut 89,  
1330 Rixensart, Belgium

<b>Primary Study vaccine and number</b>	<ul style="list-style-type: none"> <li>GlaxoSmithKline (GSK) Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (ChAd3-EBO-Z) (GSK3390107A)</li> </ul>
<b>Other Study vaccine</b>	<ul style="list-style-type: none"> <li>GSK Biologicals' meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate (MenACWY-TT) vaccine (GSK134612A)</li> </ul>
<b>eTrack study number and Abbreviated Title</b>	202090 (EBOLA Z CHAD3-004)
<b>Investigational New Drug (IND) number</b>	<i>16300</i> <i>(Amended 06 May 2015.)</i>
<b>EudraCT number</b>	2014-004714-28
<b>Date of protocol</b>	Final Version 1: 09 December 2014
<b>Date of protocol amendment</b>	Amendment 1 Final: 29 December 2014 Amendment 2 Final: 06 May 2015
<b>Title</b>	Safety and immunogenicity study of GSK Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (GSK3390107A) in children in Africa.
<b>Detailed Title</b>	A Phase 2, randomised, observer-blind, controlled, multi-country study to assess the safety and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (ChAd3-EBO-Z) (GSK3390107A), in children 1 to 17 years of age in Africa.
<b>Co-ordinating author</b>	PPD [redacted] Quintiles, Medical Writing

**CONFIDENTIAL**


202090 (EBOLA Z CHAD3-004)  
Protocol Amendment 2 Final

<b>eTrack study number and Abbreviated Title</b>	202090 (EBOLA Z CHAD3-004)
<b>Investigational New Drug (IND) number</b>	<i>16300</i> <i>(Amended 06 May 2015.)</i>
<b>EudraCT number</b>	2014-004714-28
<b>Title</b>	Safety and immunogenicity study of GSK Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (GSK3390107A) in children in Africa.
<b>Detailed Title</b>	A Phase 2, randomised, observer-blind, controlled, multi-country study to assess the safety and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (ChAd3-EBO-Z) (GSK3390107A), in children 1 to 17 years of age in Africa.
<b>Contributing authors</b>	<ul style="list-style-type: none"><li>• PPD [REDACTED], PPD [REDACTED] and PPD [REDACTED], Clinical Research and Development Leads</li><li>• PPD [REDACTED], Quintiles Medical Expert</li><li>• PPD [REDACTED], Vice President, Clinical Research and Translational Science</li><li>• PPD [REDACTED], Project Statistician</li><li>• PPD [REDACTED], Lead Statistician</li><li>• PPD [REDACTED] and PPD [REDACTED], Safety Representatives</li><li>• PPD [REDACTED], Project Delivery Lead</li><li>• PPD [REDACTED], Study Delivery Lead</li><li>• PPD [REDACTED] (CVO-Europe for GSK Biologicals) <i>and Laurent Glesner (CROMSource for GSK Biologicals)</i>, Vaccine Supply Coordinator <i>(Amended 06 May 2015.)</i></li><li>• PPD [REDACTED] (Aixial Pharma for GSK Biologicals), Study Data Manager</li><li>• PPD [REDACTED], GVCL Project Manager</li><li>• PPD [REDACTED] <i>and</i> PPD [REDACTED] (Business &amp; Decision Life Sciences for GSK Biologicals), GVCL Study Manager <i>(Amended 06 May 2015.)</i></li><li>• PPD [REDACTED], Global Regulatory Representative</li><li>• PPD [REDACTED], Global Patent Representative</li><li>• PPD [REDACTED] <i>and</i> PPD [REDACTED] (XPE Pharma &amp; Science for GSK Biologicals), Scientific Writer <i>(Amended 06 May 2015.)</i></li></ul>

*GSK Biologicals' Protocol DS v 14.1*

Copyright 2014 – 2015 the GlaxoSmithKline group of companies. All rights reserved.  
Unauthorised copying or use of this information is prohibited.

**Protocol Amendment 2 Sponsor Signatory Approval**

<b>eTrack study number and Abbreviated Title</b>	202090 (EBOLA Z CHAD3-004)
<b>IND number</b>	16300
<b>EudraCT number</b>	2014-004714-28
<b>Date of protocol amendment</b>	Amendment 2 Final: 06 May 2015
<b>Detailed Title</b>	A Phase 2, randomised, observer-blind, controlled, multi-country study to assess the safety and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (ChAd3-EBO-Z) (GSK3390107A), in children 1 to 17 years of age in Africa.
<b>Sponsor signatory</b>	Ripley Ballou Vice President Clinical Research and Translational Science
<b>Signature</b>	PPD 
<b>Date</b>	18 MAY 2015

**Protocol Amendment 2 Rationale**

Amendment number	Amendment 2
<p><b>Rationale/ background for changes:</b></p> <ul style="list-style-type: none"> <li> <p>In the on-going Phase 1 studies with the investigational ChAd3-EBO-Z vaccine in the United States (US), United Kingdom (UK), Switzerland and Mali, transient decreases in thrombocyte counts were observed. These decreases occurred mostly on Day 1 after vaccination and generally returned to baseline by Day 7. Although most of these decreases remained within the normal range, the as per protocol criteria for thrombocytopenia (thrombocyte count of <math>&lt; 150 \times 10^3/\mu\text{L}</math>) were met for 2.6% (7 out of 270) of the vaccinated subjects. None of the decreases in thrombocyte counts or the cases of thrombocytopenia were clinically significant, <i>i.e.</i>, no clinical signs or symptoms suggestive of increased tendency to bleed were reported in any of the subjects. Please refer to the Investigator's Brochure (IB) for more information.</p> <p>In the current study, a more vulnerable population (children) will be enrolled and the acceptable limit for the thrombocyte count for study eligibility (thrombocyte count of <math>\geq 100 \times 10^3/\mu\text{L}</math> is acceptable) will be lower as compared to the Phase 1 studies. In addition, in order to ensure enhanced vigilance from the Investigators, clinical bleeding events (according to the Standardised Medical Dictionary for Regulatory Activities [MedDRA] Query clinical haemorrhage) within 7 days after vaccination at Day 0 will be recorded and reported as adverse events (AEs) of specific interest (clinical symptoms of thrombocytopenia).</p> </li> <li> <p>Based on safety and immunogenicity data from the on-going Phase 1 studies, the <math>1 \times 10^{11}</math> viral particles (vp) dose was selected for further assessment in Phase 2 and Phase 3 clinical studies in adults. This dose was determined using a high performance liquid chromatography (HPLC) analytical method for the vaccine lots used in the Phase 1 studies. The same dose will also be used in this paediatric study. However, depending on the recommendation of the independent data monitoring committee (IDMC), a lower dose may be selected based on safety and reactogenicity data accrued during the age de-escalation process for children in younger age strata. In addition, because a different analytical method was used to determine the vp concentration for the lots used in this study (quantitative polymerase chain reaction [qPCR]) as compared to the lots used in the Phase 1 studies (HPLC), a dose of <math>2 \times 10^{11}</math> vp, as determined by qPCR, will be used in this study, to administer the equivalent of the <math>1 \times 10^{11}</math> vp dose, that was determined by HPLC and shown to be optimal in Phase 1 studies. This information was added in the protocol.</p> </li> <li> <p>Demographic data collection was updated to allow the full date of birth in the subject's eSource, but only month and year of the date of birth will be exported to GlaxoSmithKline's (GSK's) clinical database to guarantee subject confidentiality. The age as calculated in eSource will be used for analysis purposes as the full date of birth will not be exported.</p> </li> <li> <p>The IDMC highlighted that the study is conducted in Malaria endemic countries and that the presence of malarial infection may adversely affect the safety and</p> </li> </ul>	



immunogenicity evaluations of the investigational ChAd3-EBO-Z vaccine. In order to prevent subjects with Malaria from entering the study, all subjects who provide informed consent for study participation will be tested for Malaria infection at the time of Screening, using a rapid diagnostic test (RDT) procedure. Subjects who are diagnosed with Malaria, will receive antimalarial treatment according to local/ national standards during the Screening period (e.g., a 3-day treatment course of artemisinin-based combination therapy). Hence, only subjects for whom the RDT was negative, or for whom the RDT was positive and who received a complete course of antimalarial treatment during the Screening period can be considered for study participation. Procedures for Malaria Screening and treatment, as well as eligibility criteria specific for these procedures were adapted in the protocol.

- The scope of re-screening subjects has been clarified during the investigator's meeting, i.e., re-screening of subjects must be avoided and redrawing blood from the subject is only permitted during the Screening period if, for technical reasons, test results are not available or if they are non-interpretable. To comply with this recommendation and avoid the risk of inadequate re-screening, footnote 11 under [Table 5 \(List of study procedures\)](#) has been removed.
- After consultation with the Principal Investigators and the IDMC, the exclusion criterion "Maternal death" was removed. Instead the following exclusion criterion was included:

*Any condition that in the Investigator's opinion may potentially compromise subject safety or interfere with subject assessment or compliance.*

This will allow the investigator also to consider, on a case by case basis, whether the family circumstances of the child may allow participation to the study in compliance with local regulations, when applicable.

- Blood sample volumes for haematology and biochemistry testing were corrected.
- Some minor editorial updates were made.

## Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational vaccine and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance Procedure Manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written/ thumb printed informed consent of the subject and/or the subject's legally acceptable representative (LAR).
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the Investigator's ownership interest in the sponsor or the investigational vaccine, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

**CONFIDENTIAL**

202090 (EBOLA Z CHAD3-004)  
Protocol Amendment 2 Final

<b>eTrack study number and Abbreviated Title</b>	202090 (EBOLA Z CHAD3-004)
<b>IND number</b>	16300
<b>EudraCT number</b>	2014-004714-28
<b>Date of protocol amendment</b>	Amendment 2 Final: 06 May 2015
<b>Detailed Title</b>	A Phase 2, randomised, observer-blind, controlled, multi-country study to assess the safety and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (ChAd3-EBO-Z) (GSK3390107A), in children 1 to 17 years of age in Africa.
<b>Investigator name</b>	<hr/>
<b>Signature</b>	<hr/>
<b>Date</b>	<hr/>

## **Sponsor Information**

### **Sponsor**

GlaxoSmithKline Biologicals  
Rue de l'institut 89,  
1330 Rixensart, Belgium

## Contracted Research Organisation (Quintiles) Information

### 1. Medical Expert for the Study

PPD [REDACTED], MD  
Senior Medical Director  
*Allergy, Respiratory, Infectious Diseases & Vaccines*  
*Medical Strategy & Science*  
*Therapeutic Science & Strategy Unit*  
(Amended 06 May 2015.)

### 2. Study Contact for Reporting of a Serious Adverse Event

Primary method of reporting is via eSource. If eSource is not available, please refer to SAE /Pregnancy back-up reporting instructions in the Investigator binder.

#### Back-up Study Contact for Reporting SAEs and pregnancies:

Quintiles Lifecycle Safety

Email: PPD [REDACTED]

Phone: PPD [REDACTED]

Fax: PPD [REDACTED]

## SYNOPSIS

<b>Detailed Title</b>	A Phase 2, randomised, observer-blind, controlled, multi-country study to assess the safety and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (ChAd3-EBO-Z) (GSK3390107A), in children 1 to 17 years of age in Africa.
<b>Indication</b>	<p>Primary immunisation against Ebolavirus Zaire (EBOV):</p> <p>The investigational recombinant chimpanzee adenovirus type 3-vectored EBOV vaccine (ChAd3-EBO-Z) is developed for prevention of Zaire Ebola virus disease (EVD).</p>
<b>Rationale for the study and study design</b>	<ul style="list-style-type: none"><li>• Rationale for the study</li></ul> <p>On 7 August 2014, the World Health Organisation (WHO) requested that GlaxoSmithKline (GSK) “fully engages in WHO-coordinated efforts to test, license and make available safe and effective Ebola interventions” to assist in the control of the outbreak in Western Africa. Given the severity of the situation, time to vaccine deployment was an important aspect of the WHO request. In response to this call, an accelerated Phase 1, dose-finding vaccine development effort was initiated mid-August that involved WHO, GSK, Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (VRC/NIAID), the University of Oxford, the University of Maryland and the University of Lausanne and the Centre for Vaccine Development in Mali.</p> <p>Although health care workers will be priority vaccination targets, mass vaccination strategies may be developed as one of the ways to protect populations and contain the epidemics. In this context, children will need to be vaccinated too. The present Phase 2, randomised, controlled trial will aim at collecting safety and immunogenicity data following a single intramuscular dose of the investigational ChAd3-EBO-Z vaccine. In parallel with the current study, the safety and immunogenicity of the investigational ChAd3-EBO-Z vaccine will be assessed in healthy adults living in countries adjacent to the current Ebola outbreak (study EBOLA Z CHAD3-005). Study EBOLA Z CHAD3-005 will start before the current study as to collect safety and</p>

reactogenicity data in 100 adults, after 1 week of follow-up, living in countries adjacent to the current Ebola outbreak before proceeding to vaccination of children.

- Rationale for the study design

- Investigational ChAd3-EBO-Z vaccine dose

Dose selection for paediatric use *was* based on information derived from dose-range studies conducted with the ChAd3-EBO-Z vaccine candidate in adults and on past experience with other recombinant adenovirus-based candidate vaccines. *(Amended 06 May 2015.)*

While investigational ChAd3-based candidate vaccines have not been administered to children before, other recombinant adenovirus-based candidate vaccines have been administered to children without safety concerns. A recombinant chimpanzee adenovirus Type 63 vaccine expressing the *Plasmodium falciparum* pre-erythrocytic antigen ME-TRAP (multiple epitope string with thrombospondin-related adhesion protein) (ChAd63 ME-TRAP) malaria candidate vaccine has been safely administered to healthy adults in United Kingdom (UK) and Kenya, and to healthy infants and children in The Gambia and Burkina Faso. The intramuscular (IM) dose of  $5 \times 10^{10}$  viral particles (vp) was determined to be optimal in both adults and children [Afolabi, 2012; Ogwang, 2013; O'Hara, 2012; ClinicalTrials.gov NCT01635647; ClinicalTrials.gov NCT02083887; A. Hill, *personal communication*]. In the tuberculosis vaccine research field, up to two dose of  $1 \times 10^{11}$  vp of AERAS-402, a recombinant, replication-defective adenovirus type 35 expressing tuberculosis antigens, the highest dose evaluated, showed favourable safety in infants 6 to 9 months old [Kagina, 2014]. This dose is also used in adults [ClinicalTrials.gov NCT01683773].

Importantly, dose ranging in terms of vp is classically done on a logarithmic scale while arithmetic scales are usually used to describe weight differences between adults and children. In other words, the variability in weight between adults and children is small as compared to classical dose ranging in terms of number of vp, and inherent imprecision/variability in number of vp.

Four different investigational vaccine doses are currently being evaluated for safety, reactogenicity and immunogenicity in adults in Phase 1 studies. ***Based on data from these studies, the  $1 \times 10^{11}$  vp dose was selected for further assessment in Phase 2 and Phase 3 clinical studies in adults. This dose was determined using a high performance liquid chromatography (HPLC) analytical method for the vaccine lots used in the Phase 1 studies. The same dose will be used in this paediatric study. However, depending on the recommendation of the independent data monitoring committee (IDMC), a lower dose may be selected based on safety and reactogenicity data accrued during the age de-escalation process for children in younger age strata. It should be noted that the analytical method (quantitative polymerase chain reaction [qPCR]) that measures the concentration of virus particles per mL (vp/mL) present in the ChAd3-EBO-Z vials used in the current paediatric study is different from the analytical method (HPLC) used for the Phase 1 studies. As a result, a dose of  $2 \times 10^{11}$  vp will be used in this study, to administer the equivalent of the  $1 \times 10^{11}$  vp dose that was shown to be optimal in Phase 1 studies.*** As for other recombinant adenovirus-based vaccine candidates which showed adequate safety upon the use of adult doses in children as explained above, it is currently proposed that the same vaccine dose will be assessed ***in children 1 to 17 years of age*** in this study. However, a lower vaccine dose may be selected for children of younger age groups based on the safety and reactogenicity data accrued during the age de-escalation process. ***(Amended 06 May 2015.)***

- Administration of the investigational ChAd3-EBO-Z vaccine

Considering the risk of exposure to Ebola and the potential (based on animal data) for the investigational ChAd3-EBO-Z vaccine to afford at least partial protection, all children in the study will receive the investigational ChAd3 EBO-Z vaccine. The children in the Group EBO-Z/ MENACWY-TT will receive the investigational ChAd3-EBO-Z vaccine at Day 0 of the study, whereas the children in the Group MENACWY-TT/ EBO-Z will receive *Nimenrix* at Day 0 (as a control). At Month 6, the children in the Group MENACWY-TT/ EBO-Z will



receive the investigational ChAd3-EBO-Z vaccine (provided that no safety concerns are raised), whereas the children in the Group EBO-Z/ MENACWY-TT will receive *Nimenrix*.

In case the geographic range of EBOV transmission expands to encompass any of the regions where this trial is conducted, earlier administration of the investigational ChAd3-EBO-Z vaccine to the children in the Group MENACWY-TT/ EBO-Z will be considered in that region.

- Control vaccine

GSK Biologicals' meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate (MenACWY-TT) vaccine (*Nimenrix*) will be used as control.

*Nimenrix* is indicated for the active immunisation against invasive meningococcal diseases caused by *Neisseria meningitidis* (meningococcus) serogroups A, C, W-135 and Y. Invasive meningococcal disease, including meningitis and meningococcal septicaemia, often follows invasive infection by *Neisseria meningitidis* and is a major cause of death and morbidity throughout the world.

*Neisseria meningitidis* serogroups A, B, C, W-135 and Y are the most common causes of invasive meningococcal disease worldwide: serogroup A is most common in Africa and Asia, while serogroups B and C account for more than 90% of the cases in Europe and Latin America [[Anderson, 1998](#); [Connolly, 1999](#); [Harrison, 2009](#); [Peltola, 1998](#)].

*Nimenrix* is licensed in 50 countries (first approval in April 2012) and is currently available in at least 23 countries.

Using *Nimenrix* as a control vaccine in this study will provide a theoretical benefit to the children in the study and adequately support safety comparison.

- Stratification for age and staggered vaccination

In order to ensure equal distribution of the population, enrolment will be stratified by age so that an equal number of children are enrolled in each age stratum (1 to 5 years, 6 to 12 years and 13 to 17 years of age).

In order to ensure maximum safety for the subjects in this study, vaccination at Day 0 will be done in a staggered manner, starting with vaccination of the children in the oldest age stratum. For each age

stratum, an IDMC will conduct a review of all available safety data once data is available up to at least 7 days after vaccination of at least 50 subject (25/ group) in that age stratum. The start of vaccination in the younger age stratum, possibly with a lower vaccine dose, depends on the outcome of this IDMC review.

- Human immunodeficiency virus testing

There will be no routine testing for human immunodeficiency virus (HIV) in this trial. Tests will be performed when clinically indicated to guide subject management. Voluntary counselling and testing, highly active anti-retroviral therapy (HAART) and prevention of mother to child transmission (PMTCT) will be available at all study centres according to national policies.

- *Malaria Screening and treatment*

*As this study is conducted in Malaria endemic regions and the presence of malaria infection may adversely affect the safety and immunogenicity evaluations of the investigational ChAd3-EBO-Z vaccine, all subjects will be tested for Malaria infection using a rapid diagnostic test (RDT) procedure during Screening and all subjects diagnosed with Malaria will receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period. Hence, only subjects for whom the RDT was negative, or for whom the RDT was positive and who received a complete course of antimalarial treatment during the Screening period can be considered for study participation.*

*(Amended 06 May 2015.)*

## Objectives

### Primary

- To assess the safety and reactogenicity of a single IM dose of the ChAd3-EBO-Z vaccine, overall and in children aged 1 to 5, 6 to 12, and 13 to 17 years separately.

**Secondary**

- To assess the humoral immunogenicity of a single IM dose of the ChAd3-EBO-Z vaccine, in terms of anti-glycoprotein (GP) EBOV antibody responses, overall and in children aged 1 to 5, 6 to 12, and 13 to 17 years separately.

**Tertiary**

- To assess the persistence of the humoral immune response induced by a single IM dose of the ChAd3-EBO-Z vaccine, in terms of anti-GP EBOV antibody responses, overall and in children aged 1 to 5, 6 to 12, and 13 to 17 years separately.
- To assess EBOV-specific cell-mediated immunity (CMI) of a single IM dose of the ChAd3-EBO-Z vaccine, overall and in children aged 1 to 5, 6 to 12, and 13 to 17 years separately.
- To assess the pre-existing immunity to the ChAd3 virus vaccine vector prior vaccination, ChAd3-specific immune responses after vaccination and explore its potential impact on Ebola-specific immune responses, overall and in children aged 1 to 5, 6 to 12, and 13 to 17 years separately.
- If deemed necessary, to further characterise the immune response to/ the safety profile of the investigational ChAd3-EBO-Z vaccine.

**Study design**

- **Experimental design:** Phase 2, randomised, observer-blind, controlled, multi-country study with 2 groups and 3 age strata.
- **Duration of the study:** for each subject enrolled will be approximately 12 months from the Day 0 visit.
  - Epoch 001: Primary starting at Screening and ending at the Month 12 visit.
- **Study groups:**
  - **Group EBO-Z/ MENACWY-TT:** approximately 300 children in total; approximately 100 children per age stratum (1 to 5 years, 6 to 12 years, and 13 to 17 years of age).
  - **Group MENACWY-TT/ EBO-Z:** approximately 300 children in total; approximately 100 children per age stratum (1 to 5 years, 6 to 12 years, and 13 to 17 years of age).

17 years of age).

**Synopsis Table 1 Study groups and epochs foreseen in the study**

Study group	Number of subjects	Age	Epochs
			Epoch 001
EBO-Z/ MENACWY-TT	~300	~100 children per age stratum: 13 to 17, 6 to 12, 1 to 5 years	x
MENACWY-TT/ EBO-Z	~300	~100 children per age stratum: 13 to 17, 6 to 12, 1 to 5 years	x

~ = approximately

**Synopsis Table 2 Treatments foreseen in the study**

Treatment name	Vaccine/Product name	Study Groups	
		EBO-Z/ MENACWY-TT	MENACWY-TT/ EBO-Z
ChAd3-EBO-Z	ChAd3-EBO-Z	x (Day 0)	x (Month 6)
<i>Nimenrix</i>	MenACWY-TT ----- NaCl	x (Month 6)	x (Day 0)

**ChAd3-EBO-Z** = investigational recombinant chimpanzee adenovirus type 3-vectored Ebola virus Zaire (EBOV) vaccine; **MenACWY-TT** = meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine; **NaCl** = sodium chloride

- **Control:** Active control (*Nimenrix*).
- **Vaccination schedule:** All subjects will receive 2 vaccinations, 1 at the Day 0 visit and 1 at the Month 6 visit. All subjects will receive 1 dose of the investigational ChAd3-EBO Z vaccine and 1 dose of *Nimenrix*:
  - Subjects in Group EBO-Z/ MENACWY-TT will receive the investigational ChAd3-EBO-Z vaccine at the Day 0 visit and *Nimenrix* at the Month 6 visit.
  - Subjects in Group MENACWY-TT/ EBO-Z will receive *Nimenrix* at the Day 0 visit and the investigational ChAd3-EBO-Z vaccine at the Month 6 visit.

- **Treatment allocation:** Subjects will be randomised (1:1) at Day 0. In order to ensure equal distribution of the population, enrolment will be stratified by age so that an equal number of children are enrolled in each age stratum (1 to 5 years, 6 to 12 years, and 13 to 17 years of age). In addition, the randomisation will use a minimisation procedure accounting for gender and centre.
- **Staggered vaccination:** Vaccination at Day 0 will be done in a staggered manner, starting with vaccination of the children in the oldest age stratum (13 to 17 years of age). In order to proceed to vaccination of the subjects in the younger age stratum (6 to 12 years of age), possibly with a lower vaccine dose, a favourable outcome of the IDMC review of safety data up to at least 7 days after vaccination from at least 50 subjects (25/ group) in the oldest age stratum needs to be obtained. The same will be done for moving from the 6 to 12 years of age stratum to vaccination of the youngest children (1 to 5 years of age).
- **Blinding:**
  - **Observer-blind** from study start until the interim analysis that will be conducted when safety, reactogenicity and immunogenicity (including at least anti-GP EBOV data at Day 30) data is available from all subjects up to 30 days after vaccination at Day 0.
  - **Single-blind** as of the interim analysis *at Day 30*.  
(Amended 06 May 2015.)
- **Sampling schedule:**
  - *A blood sample (fingerprick) will be taken at Screening for Malaria RDT.*  
(Amended 06 May 2015.)
  - Blood samples for **haematology/ biochemistry** assessment will be taken from all subjects at Screening, at the Day 3, Day 6, the Day 30, the Month 6, the Month 6 + 6 days, the Month 6 + 30 days, and the Month 12 visits.
  - Blood samples for **humoral immunity** will be taken from all subjects at the Day 0, the Day 30, the Month 6, the Month 6 + 30 days, and the Month 12 visits.
  - Blood samples for **CMI** will be taken from a sub-cohort of 90 subjects per group (30 children per age stratum per group) at the Day 0, the Day 30, the

Month 6, the Month 6 + 30 days, and the Month 12 visits.

- **Safety monitoring:** An IDMC will be appointed to monitor the safety and tolerability of the investigational ChAd3-EBO-Z vaccine. The IDMC will consist of clinical experts and a statistician who are not involved in the conduct of the study.

**Number of subjects** The target is to enrol approximately 600 eligible children (approximately 300 per group and approximately 200 per age stratum).

## Endpoints

### Primary

- Occurrence of each solicited local and general adverse event (AE), during a 7-day follow-up period after each vaccination (*i.e.*, the day of vaccination and 6 subsequent days), in all subjects, in both groups.
- Occurrence of any unsolicited AE, during a 30-day follow-up period after each vaccination (*i.e.*, the day of vaccination and 29 subsequent days), in all subjects, in both groups.
- Occurrence of haematological (complete blood count [CBC], including differential count and platelet count) and biochemical (alanine aminotransferase [ALT], creatinine) laboratory abnormalities at Screening, Day 3, Day 6, Day 30, Month 6, Month 6 + 6 days, Month 6 + 30 days and Month 12 in all subjects in both groups.
- ***Occurrence of clinical symptoms of thrombocytopenia (AE of specific interest), during a 7-day follow-up period after vaccination at Day 0 (*i.e.*, Day 0 up to Day 6), in all subjects, in both groups.***  
***(Amended 06 May 2015.)***
- Occurrence of any serious adverse event (SAE), in all subjects, in both groups.

### Secondary

- Anti-GP EBOV antibody titres, as measured by enzyme-linked immunosorbent assay (ELISA):
  - At Day 0 and Day 30, in all subjects, in both groups.
  - At Month 6 and Month 6 + 30 days, in all subjects in the Group MENACWY-TT/ EBO-Z.

### Tertiary

- Anti-GP EBOV antibody titres, as measured by ELISA:
  - At Month 6 and Month 6 + 30 days, in all subjects, in the Group EBO-Z/ MENACWY-TT.
  - At Month 12, in all subjects, in both Group.
- Magnitude, responder rate and cytokine co-expression profile of ChAd3-EBO-Z-specific CD4<sup>+</sup> or CD8<sup>+</sup> T-cell responses, as assessed by intracellular cytokine staining (ICS) after stimulation with EBOV GP antigens:
  - At Day 0, Day 30, Month 6, Month 6 + 30 days and Month 12, in a sub-cohort of 30 subjects per age stratum, per group.
- ChAd3 neutralising antibody titres, as measured by a neutralisation assay:
  - At Day 0, Day 30, Month 6, and Month 6 + 30 days, in a subset of 30 subjects per age stratum, per group.

## TABLE OF CONTENTS

	PAGE
SPONSOR INFORMATION .....	8
CONTRACTED RESEARCH ORGANISATION (QUINTILES) INFORMATION .....	9
SYNOPSIS .....	10
LIST OF ABBREVIATIONS ( <i>AMENDED 06 MAY 2015</i> ) .....	29
GLOSSARY OF TERMS .....	33
TRADEMARKS .....	37
1. INTRODUCTION .....	38
1.1. Background .....	38
1.1.1. Ebola virus Zaire outbreak 2014 .....	38
1.1.2. Ebola virus and Zaire Ebola virus disease .....	38
1.1.3. GlaxoSmithKline Biologicals' investigational ChAd3-EBO-Z vaccine .....	39
1.2. Rationale for the study and study design .....	39
1.2.1. Rationale for the study .....	39
1.2.2. Rationale for the study design .....	40
1.2.2.1. Investigational ChAd3-EBO-Z vaccine dose .....	40
1.2.2.2. Administration of the investigational ChAd3-EBO-Z vaccine .....	41
1.2.2.3. Control vaccine .....	41
1.2.2.4. Stratification for age and staggered vaccination .....	42
1.2.2.5. Human immunodeficiency virus testing .....	42
1.3. Benefit : Risk assessment .....	42
1.3.1. Risk Assessment .....	43
1.3.2. Benefit assessment .....	44
1.3.3. Overall Benefit : Risk conclusion .....	45
2. OBJECTIVES .....	45
2.1. Primary objective .....	45
2.2. Secondary objective .....	45
2.3. Tertiary objectives .....	45
3. STUDY DESIGN OVERVIEW .....	46
4. STUDY COHORT .....	49
4.1. Number of subjects/centres .....	49
4.2. Sub-cohort for cell-mediated immunity .....	49
4.3. Inclusion criteria for enrolment .....	49
4.4. Exclusion criteria for enrolment .....	50
5. CONDUCT OF THE STUDY .....	51
5.1. Regulatory and ethical considerations, including the informed consent process .....	51



5.2.	Subject identification and randomisation of treatment .....	52
5.2.1.	Subject identification .....	52
5.2.2.	Randomisation of treatment .....	53
5.2.2.1.	Randomisation of supplies.....	53
5.2.2.2.	Treatment allocation to the subject .....	53
5.2.2.2.1.	Study group and treatment name allocation at Day 0 .....	53
5.2.2.2.2.	Treatment name allocation at Month 6 .....	54
5.2.3.	Allocation of subjects to assay subsets.....	54
5.3.	Method of blinding .....	54
5.4.	General study aspects .....	55
5.5.	Outline of study procedures .....	56
5.5.1.	List of study procedures .....	56
5.5.2.	Intervals between study visit .....	58
5.6.	Detailed description of study procedures .....	58
5.6.1.	Informed consent .....	58
5.6.2.	<i>Malaria Screening and treatment (Amended 06 May 2015)</i> .....	58
5.6.3.	Check inclusion and exclusion criteria .....	60
5.6.4.	Collect demographic data .....	60
5.6.5.	Medical history.....	60
5.6.6.	Physical examination .....	60
5.6.7.	Pregnancy test.....	61
5.6.8.	Check contraindications to vaccination .....	61
5.6.9.	Assess pre-vaccination body temperature .....	61
5.6.10.	Study group and treatment number allocation.....	61
5.6.11.	Sampling.....	61
5.6.12.	Study vaccine administration .....	62
5.6.13.	Check and record concomitant medications/ products/ vaccinations.....	62
5.6.14.	Recording of adverse events, serious adverse events, and pregnancies.....	62
5.6.14.1.	Diary Card for follow-up adverse events occurring from day 0 to day 6 after vaccination.....	63
5.6.14.2.	Unsolicited adverse events occurring from day 0 to day 29 after vaccination and serious adverse event data collection during the entire study duration.....	63
5.6.15.	Study conclusion.....	64
5.7.	Biological sample handling and analysis .....	64
5.7.1.	Use of specified study materials .....	64
5.7.2.	Biological samples .....	66
5.7.3.	Laboratory assays .....	67
5.7.3.1.	Haematology/ biochemistry .....	67
5.7.3.2.	Immune response against Ebola .....	67
5.7.3.3.	Immune response against ChAd3.....	67
5.7.4.	Biological samples evaluation .....	68
5.7.4.1.	Immunological read-outs .....	68
5.7.4.2.	Haematology/biochemistry .....	68
5.7.5.	Immunological correlates of protection.....	68

6.	STUDY VACCINES/ <i>PRODUCTS</i> AND ADMINISTRATION (AMENDED 06 MAY 2015.) .....	68
6.1.	<i>Malaria treatment (Amended 06 May 2015.)</i> .....	68
6.2.	Description of study vaccines.....	69
6.3.	Storage and handling of study vaccines.....	69
6.4.	Dosage and administration of study vaccines .....	70
6.5.	Replacement of unusable vaccine doses .....	70
6.6.	Contraindications to vaccination .....	70
6.7.	Concomitant medications/products and concomitant vaccinations .....	71
6.7.1.	Recording of concomitant medications/products and concomitant vaccinations .....	71
6.7.2.	Concomitant medications/ products/ vaccines that may lead to the elimination of a subject from according-to-protocol analyses.....	71
6.8.	Intercurrent medical conditions that may lead to elimination of a subject from according-to-protocol analyses .....	72
7.	OCCURRENCE OF SUSPECTED OR CONFIRMED EBOLA VIRUS DISEASE.....	72
8.	HEALTH ECONOMICS .....	73
9.	SAFETY .....	73
9.1.	Safety definitions .....	73
9.1.1.	Definition of an adverse event.....	73
9.1.2.	Definition of a serious adverse event .....	74
9.1.3.	Solicited adverse events .....	75
9.1.3.1.	Solicited local (injection-site) adverse events.....	75
9.1.3.2.	Solicited general adverse events .....	75
9.1.4.	Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events .....	75
9.1.5.	<i>Adverse events of specific interest</i> .....	76
9.1.5.1.	<i>Clinical bleeding within 7 days post-vaccination at Day 0</i> .....	76
9.2.	Events or outcomes not qualifying as adverse events or serious adverse events (pregnancy).....	76
9.3.	Detecting and recording adverse events, serious adverse events and pregnancies .....	77
9.3.1.	Time period for detecting and recording adverse events, serious adverse events and pregnancies.....	77
9.3.2.	Post-Study adverse events and serious adverse events .....	78
9.3.3.	Evaluation of adverse events and serious adverse events .....	79
9.3.3.1.	Active questioning to detect adverse events and serious adverse events.....	79
9.3.3.2.	Assessment of adverse events .....	80
9.3.3.2.1.	Assessment of intensity .....	80
9.3.3.2.2.	Assessment of causality .....	82
9.3.3.3.	Assessment of outcomes.....	83
9.3.3.4.	Medically attended visits.....	84
9.4.	Reporting of serious adverse events, pregnancies, and other events .....	84

9.4.1.	Prompt reporting of <i>adverse events of specific interest (clinical symptoms of thrombocytopenia)</i> , serious adverse events, and pregnancies to the contracted research organisation (Quintiles) ( <i>Amended 06 May 2015</i> ) .....	84
9.4.2.	Contact information for reporting <i>adverse events of specific interest (clinical symptoms of thrombocytopenia)</i> , serious adverse events, and pregnancies ( <i>Amended 06 May 2015</i> ).....	85
9.4.3.	<i>Reporting of adverse events of specific interest (clinical symptoms of thrombocytopenia) to the contract research organisation (Quintiles) (Amended 06 May 2015)</i> .....	85
9.4.4.	Completion and transmission of serious adverse events reports to the contracted research organisation (Quintiles) .....	86
9.4.4.1.	Back-up system in case the electronic reporting system does not work .....	86
9.4.5.	Completion and transmission of pregnancy reports to the contracted research organisation (Quintiles).....	87
9.4.6.	Updating of <i>adverse events of specific interest (clinical symptoms of thrombocytopenia)</i> , serious adverse events, and pregnancy information after removal of write access to the subject's eSource ( <i>Amended 06 May 2015</i> ).....	87
9.4.7.	Regulatory reporting requirements for serious adverse events .....	87
9.5.	Follow-up of adverse events, serious adverse events, and pregnancies .....	88
9.5.1.	Follow-up of adverse events and serious adverse events .....	88
9.5.1.1.	Follow-up during the study.....	88
9.5.1.2.	Follow-up after the subject is discharged from the study.....	88
9.5.2.	Follow-up of pregnancies .....	88
9.6.	Treatment of adverse events .....	89
9.7.	Unblinding.....	89
9.8.	Emergency unblinding .....	89
9.9.	Subject card.....	89
9.10.	Safety monitoring by the independent data monitoring committee .....	90
10.	SUBJECT COMPLETION AND WITHDRAWAL .....	92
10.1.	Subject completion .....	92
10.2.	Subject withdrawal.....	92
10.2.1.	Subject withdrawal from the study.....	92
10.3.	Extension study .....	93
10.4.	Screen failures.....	93
11.	STATISTICAL METHODS .....	93
11.1.	Primary endpoints.....	93
11.2.	Secondary endpoint.....	94
11.3.	Tertiary endpoints .....	94
11.4.	Determination of sample size .....	94
11.5.	Cohorts for Analyses.....	95
11.5.1.	Total vaccinated cohort.....	95
11.5.2.	According-to-protocol cohort for analysis of immunogenicity.....	95

11.6.	Derived and transformed data.....	96
11.7.	Analysis of demographics .....	96
11.8.	Analysis of safety .....	97
11.9.	Analysis of immunogenicity .....	98
11.10.	Interpretation of analyses.....	98
11.11.	Conduct of analyses .....	99
11.11.1.	Sequence of analyses.....	99
11.11.2.	Statistical considerations for interim analyses.....	99
12.	ADMINISTRATIVE MATTERS .....	99
12.1.	Electronic case report form instructions (eSource).....	99
12.2.	Study monitoring by the contracted research organisation.....	100
12.3.	Record retention .....	100
12.4.	Quality assurance .....	101
12.5.	Posting of information on publicly available clinical trial registers and publication policy.....	101
12.6.	Provision of study results to Investigators .....	101
13.	COUNTRY SPECIFIC REQUIREMENTS.....	102
14.	REFERENCES.....	102

## LIST OF TABLES

	<b>PAGE</b>
Table 1	Study groups and epochs foreseen in the study ..... 47
Table 2	Treatments foreseen in the study ..... 47
Table 3	Sub-cohort for cell-mediated immunity ..... 49
Table 4	Number of subjects required for enrolment..... 53
Table 5	List of study procedures during visits to the vaccination centre ( <i>Amended 06 May 2015</i> ) ..... 56
Table 6	Intervals between study visits ..... 58
Table 7	Biological samples ( <i>Amended 06 May 2015.</i> ) ..... 66
Table 8	Humoral immunity against Ebola ( <i>Amended 06 May 2015</i> ) ..... 67
Table 9	Cell-mediated immunity against Ebola ..... 67
Table 10	Humoral immunity against ChAd3 ..... 67
Table 11	Immunological read-outs (humoral immunity) ..... 68
Table 13	Haematology/ biochemistry readouts ..... 68
Table 14	Study vaccines ( <i>Amended 06 May 2015</i> ) ..... 69
Table 15	Dosage and administration ( <i>Amended 06 May 2015</i> ) ..... 70
Table 16	Solicited local adverse events ..... 75
Table 17	Solicited general adverse events ( <i>Amended 06 May 2015</i> ) ..... 75
Table 18	Reporting periods for collecting safety information ( <i>Amended 06 May 2015</i> ) ..... 78
Table 19	Intensity scales for solicited symptoms in infants/toddlers and children less than 6 years of age ( <i>Amended 06 May 2015</i> ) ..... 80
Table 20	Intensity scales for solicited symptoms in children of 6 years of age or more ( <i>Amended 06 May 2015</i> ) ..... 81
Table 21	Timeframes for submitting <i>adverse events of specific interest (clinical symptoms of thrombocytopenia)</i> , serious adverse events, and pregnancies to the contracted research organisation (Quintiles) ( <i>Amended 06 May 2015</i> ) ..... 85
Table 22	95% exact confidence intervals for the true AE rate at different possible observed AE rates within a group (300 subjects)..... 95

Table 23	True proportions associated with a 90% probability to observe a certain number of events.....	95
Table 24	Outsourced laboratories .....	106
Table 25	Acceptable limits/normal ranges for eligibility determination (Amended 06 May 2015).....	107
Table 26	Toxicity grading scales for hematology/ biochemistry parameters .....	107
Table 27	Acceptable limits/normal ranges for eligibility determination .....	108
Table 28	Toxicity grading scales for hematology/ biochemistry parameters .....	108

LIST OF FIGURES

		PAGE
Figure 1	Study design overview .....	46
Figure 2	Screening procedures .....	59
Figure 3	Overview of staggered design and independent data monitoring committee (IDMC) safety evaluations .....	91

LIST OF APPENDICES

	PAGE
APPENDIX A LABORATORY ASSAYS .....	104
APPENDIX B CLINICAL LABORATORIES ( <i>Amended 06 May 2015</i> ).....	106
APPENDIX C ACCEPTABLE LIMITS FOR ELIGIBILITY AND TOXICITY GRADING SCALES FOR HAEMATOLOGY/ BIOCHEMISTRY PARAMETERS ( <i>Amended 06 May 2015</i> ).....	107
APPENDIX D AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL.....	109



**LIST OF ABBREVIATIONS (*Amended 06 May 2015*)**

<b>AD5:</b>	Adenovirus Type 5
<b>AE:</b>	Adverse Event
<b>AIDS:</b>	Acquired Immune Deficiency Syndrome
<b>ALT:</b>	Alanine Aminotransferase
<b>ATP:</b>	According-To-Protocol
<b>BDBV:</b>	Ebola Virus Bundibugyo
<b>BNITM:</b>	Bernhard Nocht Institute for Tropical Medicine
<b>CBC:</b>	Complete Blood Count
<b>CDC:</b>	Centers for Disease Control
<b>ChAd3:</b>	Chimpanzee Adenovirus Type 3
<b>ChAd3-EBO-Z:</b>	Investigational Recombinant Chimpanzee Adenovirus Type 3-vectored EBOV Vaccine
<b>ChAd63 ME-TRAP:</b>	Recombinant Chimpanzee Adenovirus Type 63 Vaccine Expressing the <i>Plasmodium falciparum</i> Pre-erythrocytic Antigen ME-TRAP (Multiple Epitope String with Thrombospondin-related Adhesion Protein)
<b>CI:</b>	Confidence Interval
<b>CLIA:</b>	Clinical Laboratory Improvement Amendments
<b>CMI:</b>	Cell-mediated Immunity
<b>CRO:</b>	Contract Research Organisation
<b>EBOV:</b>	Ebola Virus Zaire
<b>EDD:</b>	Estimated Date of Delivery
<b>EENT:</b>	Eyes/ Ears/ Nose/ Throat
<b>EGA:</b>	Estimated Gestational Age
<b>ELISA:</b>	Enzyme-linked Immunosorbent Assay
<b>EU:</b>	European Union

**CONFIDENTIAL**

202090 (EBOLA Z CHAD3-004)  
Protocol Amendment 2 Final

<b>EUA:</b>	Emergency Use Authorization
<b>EVD:</b>	Ebola Virus Disease
<b>FDA:</b>	Food and Drug Administration
<b>GCP:</b>	Good Clinical Practice
<b>GMT:</b>	Geometric Mean Titre
<b>GP:</b>	Glycoprotein
<b>GSK:</b>	GlaxoSmithKline
<b>HAART:</b>	Highly Active Anti-retroviral Therapy
<b>HIV:</b>	Human Immunodeficiency Virus
<b>HPLC:</b>	<i>High Performance Liquid Chromatography</i>
<b>IAF:</b>	Informed Assent Form
<b>IB:</b>	Investigator Brochure
<b>ICF:</b>	Informed Consent Form
<b>ICH:</b>	International Conference on Harmonisation
<b>ICS:</b>	Intracellular Cytokine Staining
<b>IDMC:</b>	Independent Data Monitoring Committee
<b>EC:</b>	Independent Ethics Committee
<b>IM:</b>	Intramuscular
<b>IND:</b>	Investigational New Drug
<b>IRB:</b>	Institutional Review Board
<b>IVRS:</b>	Interactive Voice Response System
<b>IWRS:</b>	Interactive Web Response System
<b>LAR:</b>	Legally Acceptable Representative
<b>LMP:</b>	Last Menstrual Period
<b>MACDP:</b>	Metropolitan Atlanta Congenital Defects Program
<b>MedDRA:</b>	Medical Dictionary for Regulatory Activities

**CONFIDENTIAL**

202090 (EBOLA Z CHAD3-004)  
Protocol Amendment 2 Final

<b>MenACWY-TT:</b>	Meningococcal Serogroups A, C, W-135, Y Tetanus Toxoid Conjugate vaccine
<b>NA:</b>	<i>Not Applicable</i>
<b>NaCl:</b>	Sodium Chloride
<b>NVITAL:</b>	NIAID Vaccine Immune T-cell and Antibody Laboratory (NIH)
<b>PBMCs:</b>	Peripheral Blood Mononuclear Cells
<b>PSA:</b>	<i>Neisseria meningitidis</i> Serogroup A Polysaccharide
<b>PSC:</b>	<i>Neisseria meningitidis</i> Serogroup C Polysaccharide
<b>PSRI:</b>	Periodic Safety Report Information
<b>PSW:</b>	<i>Neisseria meningitidis</i> Serogroup W-135 Polysaccharide
<b>PsY:</b>	<i>Neisseria meningitidis</i> Serogroup Y Polysaccharide
<b>qPCR:</b>	<i>Quantitative Polymerase Chain Reaction</i>
<b>RDT:</b>	<i>Rapid Diagnostic Test</i>
<b>RESTV:</b>	Ebola Virus Reston
<b>RNA:</b>	Ribonucleic Acid
<b>SAE:</b>	Serious Adverse Event
<b>SmPC:</b>	Summary of Product Characteristics
<b>SOP:</b>	Standard Operating Procedure
<b>SUDV:</b>	Ebola Virus Sudan
<b>TAFV:</b>	Ebola Virus Taï Forest
<b>TVC:</b>	Total Vaccinated Cohort
<b>US:</b>	United States
<b>UK:</b>	United Kingdom
<b>vp:</b>	Viral Particles
<b>VRC/NIAID:</b>	Vaccine Research Center of the National Institute of Allergy and Infectious Diseases

**WHO:**

World Health Organisation

## GLOSSARY OF TERMS

- Adequate contraception:** Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:
- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
  - oral contraceptives, either combined or progestogen alone,
  - injectable progestogen,
  - implants of etenogestrel or levonorgestrel,
  - estrogenic vaginal ring,
  - percutaneous contraceptive patches,
  - intrauterine device or intrauterine system,
  - male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject,
- The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),
  - male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).
- Adequate contraception does not apply to subjects of childbearing potential with same sex partners, when this is their preferred and usual lifestyle.

- Adverse event:** Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of

efficacy), abuse or misuse.

**Blinding:**

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes.

Observer-blind means that the subject and the vaccination centre and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment.

Single-blind means that vaccination centre and sponsor personnel are aware of the treatment assignment but the subject is not.

**Child in care:**

A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.

**Eligible:**

Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

**Epoch:**

An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.

**eTrack:**

GlaxoSmithKline's (GSK's) tracking tool for clinical trials.

**Evaluable:**

Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see [Sections 6.7.2](#) and [11.5](#) for details on criteria for evaluability).

<b>Investigational vaccine:</b>  <b>(Synonym of Investigational Medicinal Product)</b>	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
<b>Menarche:</b>	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1 to 2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
<b>Protocol amendment:</b>	The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
<b>Protocol administrative change:</b>	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
<b>Randomisation:</b>	Process of random attribution of treatment to subjects in order to reduce bias of selection.
<b>Self-contained study:</b>	Study with objectives not linked to the data of another study.
<b>Solicited adverse event:</b>	Adverse events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
<b>Sub-cohort:</b>	A group of subjects for whom specific study procedures are planned as compared to other subjects.
<b>Subject:</b>	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine or as a control.

<b>Subject number:</b>	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
<b>Subset:</b>	A subset is defined as a group of subjects for which additional assays are planned as compared to other subjects.
<b>Treatment:</b>	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
<b>Treatment number:</b>	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.
<b>Unsolicited adverse event:</b>	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.



**TRADEMARKS**

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ® and in *italics*.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Nimenrix®	Meningococcal A, C, W-135 & Y vaccine

## 1. INTRODUCTION

### 1.1. Background

#### 1.1.1. Ebola virus Zaire outbreak 2014

The EVD outbreak in West Africa was first recognised on 22 March 2014 in Guinea. By 02 December 2014, the epidemic had spread to Sierra Leone and Liberia, with a total of 17 256 cases in those 3 countries (including 6 113 deaths). Travel-associated cases were observed in Mali, Senegal, Nigeria, Spain and United States (US), with localised transmission in Nigeria, Spain and US. The outbreaks of EVD in Senegal and Nigeria were declared over on 17 October and 19 October 2014, respectively. While children have been described as being less at risk of contracting of EVD [McElroy, 2014], it has been estimated that about 18% of cases in the current outbreak were people under 15 years of age [World Health Organisation (WHO) Ebola Response Team, 2014].

#### 1.1.2. Ebola virus and Zaire Ebola virus disease

The genus Ebola virus is one of 3 genera in the family Filoviridae, which along with the genera, Marburgvirus and Cuevavirus, are known to induce viral haemorrhagic fever. The 5 distinct species included in the genus Ebola virus are Bundibugyo (BDBV), Reston (RESTV), Sudan (SUDV), Taï Forest (TAFV), and Zaire (EBOV).

Ebola virus is a large, negative-strand ribonucleic acid (RNA) virus composed of 7 genes encoding viral proteins, including a single glycoprotein (GP). The virus is responsible for causing EVD in humans. In particular, BDBV, EBOV, and SUDV have been associated with large outbreaks of EVD in Africa and reported case fatality ratios of up to 90% (WHO, 2014a). Transmission of Ebola virus to humans is not yet fully understood, but is likely due to incidental exposure to infected animals. EVD then spreads through human-to-human transmission, with infection resulting from direct contact with blood, secretions, organs or other bodily fluids of infected people, and indirect contact with environments contaminated by such fluids.

EVD has an incubation period of 2 to 21 days (mean 4 to 10) which is followed by an abrupt onset of non-specific symptoms such as fever, chills, malaise, and myalgia. The subsequent signs and symptoms indicate multisystem involvement and include systemic (prostration), gastrointestinal (anorexia, nausea, vomiting, abdominal pain, diarrhoea), respiratory (chest pain, shortness of breath, cough, nasal discharge), vascular (conjunctival infection, postural hypotension, oedema), and neurological (headache, confusion, coma) manifestations. Haemorrhagic manifestations consistent with disseminated intravascular coagulation arise during the peak of the illness and include petechiae, ecchymoses, uncontrolled oozing from venepuncture sites, mucosal haemorrhages, and post-mortem evidence of visceral haemorrhagic effusions. A macropapular rash associated with varying severity of erythema and desquamate can often be noted by day 5 to 7 of the illness; this symptom is a valuable differential diagnostic feature and is usually followed by desquamation in survivors. Abdominal pain is sometimes associated with hyperamylasaemia and true pancreatitis. In later stages, shock, convulsions, severe metabolic disturbances, and, in more than half the cases,

diffuse coagulopathy supervene. Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes. In general, the symptoms last for about 7 to 14 days, after which recovery may occur. Death can occur 6 to 16 days after the onset of symptoms [Feldmann, 2011]. People are infectious as long as their blood and secretions contain the virus; the virus was isolated from semen 61 days after onset of illness in a man who was infected in a laboratory [WHO, 2014b].

### **1.1.3. GlaxoSmithKline Biologicals' investigational ChAd3-EBO-Z vaccine**

The replication-defective investigational EBOV vaccine encoded by chimpanzee-derived adenovirus (ChAd3-EBO-Z) was developed by the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (VRC/NIAID) in the US using the ReiThera (formerly known as Okairos) adenovirus vaccine platform technology, which was acquired by GSK Biologicals in May 2013. The DNA fragment inserted in the chimpanzee adenovirus type 3 (ChAd3) vector encodes the EBOV GP, which is expressed on the virion surface and is critical for attachment to host cells and catalysis of membrane fusion. A single dose of  $10^{10}$  viral particles (vp) of ChAd3-EBO-Z provided 100% protection 4 to 5 weeks after vaccination in cynomolgous macaques [Stanley, 2014].

Serological studies showed a low seroprevalence in human sera for antibodies to ChAd3, and when present, antibody titres were low [Colloca, 2012]. Adenovirus type 5 (Ad5; a common adenovirus infection of humans) pre-existing immunity did not appear to cross-react with ChAd3 in mice [Peruzzi, 2009]. ChAd3-based vaccines were capable of inducing an immune response and protection comparable to human Ad5 vectored vaccine even in those with pre-existing immunity against Ad5.

Please refer to the current Investigator Brochure (IB) for information regarding the pre-clinical and clinical studies of ChAd3-EBO-Z.

## **1.2. Rationale for the study and study design**

### **1.2.1. Rationale for the study**

On 7 August 2014, the WHO requested that GSK “fully engages in WHO-coordinated efforts to test, license and make available safe and effective Ebola interventions” to assist in the control of the outbreak in Western Africa. Given the severity of the situation, time to vaccine deployment was an important aspect of the WHO request. In response to this call, an accelerated Phase 1, dose-finding vaccine development effort was initiated mid-August that involved WHO, GSK, VRC/NIAID, the University of Oxford, the University of Maryland and the University of Lausanne and the Centre for Vaccine Development in Mali.

Although health care workers will be priority vaccination targets, mass vaccination strategies may be developed as one of the ways to protect populations and contain the epidemics. In this context, children will need to be vaccinated too. The present Phase 2, randomised, controlled trial will aim at collecting safety and immunogenicity data following a single intramuscular (IM) dose of the investigational ChAd3-EBO-Z vaccine.

The study will be conducted in healthy children living in countries adjacent to the current Ebola outbreak zones. In parallel with the current study, the safety and immunogenicity of the investigational ChAd3-EBO-Z vaccine will be assessed in healthy adults living in countries adjacent to the current Ebola outbreak (study EBOLA Z CHAD3-005). Study EBOLA Z CHAD3-005 will start before the current study as to collect safety and reactogenicity data in 100 adults, after 1 week of follow-up, living in countries adjacent to the current Ebola outbreak before proceeding to vaccination of children.

## 1.2.2. Rationale for the study design

### 1.2.2.1. Investigational ChAd3-EBO-Z vaccine dose

Dose selection for paediatric use *was* based on information derived from dose-range studies conducted with the ChAd3-EBO-Z vaccine candidate in adults and on past experience with other recombinant adenovirus-based candidate vaccines. ***(Amended 06 May 2015.)***

While investigational ChAd3-based candidate vaccines have not been administered to children before, other recombinant adenovirus-based candidate vaccines have been administered to children without safety concerns. A ChAd63 ME-TRAP malaria candidate vaccine has been safely administered to healthy adults in United Kingdom (UK) and Kenya, and to healthy infants and children in The Gambia and Burkina Faso. The IM dose of  $5 \times 10^{10}$  vp was determined to be optimal in both adults and children [Afolabi, 2012; Ogwang, 2013; O'Hara, 2012; ClinicalTrials.gov NCT01635647; ClinicalTrials.gov NCT02083887; A. Hill, *personal communication*]. In the tuberculosis vaccine research field, up to two dose of  $1 \times 10^{11}$  vp of AERAS-402, a recombinant, replication-defective adenovirus type 35 expressing tuberculosis antigens, the highest dose evaluated, showed favourable safety in infants 6 to 9 months old [Kagina, 2014]. This dose is also used in adults [ClinicalTrials.gov NCT01683773].

Importantly, dose ranging in terms of vp is classically done on a logarithmic scale while arithmetic scales are usually used to describe weight differences between adults and children. In other words, the variability in weight between adults and children is small as compared to classical dose ranging in terms of number of vp, and inherent imprecision/ variability in number of vp.

Four different investigational vaccine doses are currently being evaluated for safety, reactogenicity and immunogenicity in adults in Phase 1 studies. ***Based on data from these studies, the  $1 \times 10^{11}$  vp dose was selected for further assessment in Phase 2 and Phase 3 clinical studies in adults. This dose was determined using a high performance liquid chromatography (HPLC) analytical method for the vaccine lots used in the Phase 1 studies. The same dose will be used in this paediatric study. However, depending on the recommendation of the independent data monitoring committee (IDMC), a lower dose may be selected based on safety and reactogenicity data accrued during the age de-escalation process for children in younger age strata. It should be noted that the analytical method (quantitative polymerase chain reaction [qPCR]) that measures the concentration of virus particles per mL (vp/mL) present in the ChAd3-EBO-Z vials used in the current paediatric study is different***

*from the analytical method (HPLC) used for the Phase 1 studies. As a result, a dose of  $2 \times 10^{11}$  vp will be used in this study, to administer the equivalent of the  $1 \times 10^{11}$  vp dose that was shown to be optimal in Phase 1 studies.* As for other recombinant adenovirus-based vaccine candidates which showed adequate safety upon the use of adult doses in children as explained above, it is currently proposed that the same vaccine dose will be assessed *in children 1 to 17 years of age* in this study. However, a lower vaccine dose may be selected for children of younger age groups based on the safety and reactogenicity data accrued during the age de-escalation process. *(Amended 06 May 2015.)*

*As this study is conducted in Malaria endemic regions and the presence of Malaria infection may adversely affect the safety and immunogenicity evaluations of the investigational ChAd3-EBO-Z vaccine, all subjects will be tested for Malaria infection using a rapid diagnostic test (RDT) procedure during Screening. Subsequently, all subjects diagnosed with Malaria will receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period. Hence, only subjects for whom the RDT was negative, or for whom the RDT was positive and who received a complete course of antimalarial treatment during the Screening period can be considered for study participation. (Amended 06 May 2015.)*

#### **1.2.2.2. Administration of the investigational ChAd3-EBO-Z vaccine**

Considering the risk of exposure to Ebola and the potential (based on animal data) for the investigational ChAd3-EBO-Z vaccine to afford at least partial protection, all children in the study will receive the investigational ChAd3 EBO-Z vaccine. The children in the Group EBO-Z/ MENACWY-TT will receive the investigational ChAd3-EBO-Z vaccine at Day 0 of the study, whereas the children in the Group MENACWY-TT/ EBO-Z will receive *Nimenrix* at Day 0 (as a control). At Month 6, the children in the Group MENACWY-TT/ EBO-Z will receive the investigational ChAd3-EBO-Z vaccine (provided that no safety concerns are raised. Refer to [Section 9.10](#) for more information on the IDMC) whereas the children in the Group EBO-Z/ MENACWY-TT will receive *Nimenrix*.

In case the geographic range of EBOV transmission expands to encompass any of the regions where this trial is conducted, earlier administration of the investigational ChAd3-EBO-Z vaccine to the children in the Group MENACWY-TT/ EBO-Z will be considered in that region.

#### **1.2.2.3. Control vaccine**

GSK Biologicals' meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate (MenACWY-TT) vaccine (*Nimenrix*) will be used as control.

*Nimenrix* is indicated for the active immunisation against invasive meningococcal diseases caused by *Neisseria meningitidis* (meningococcus) serogroups A, C, W-135 and Y. Invasive meningococcal disease, including meningitis and meningococcal septicaemia, often follows invasive infection by *Neisseria meningitidis* and is a major cause of death and morbidity throughout the world. *Neisseria meningitidis* serogroups A, B, C, W-135

and Y are the most common causes of invasive meningococcal disease worldwide: serogroup A is most common in Africa and Asia, while serogroups B and C account for more than 90% of the cases in Europe and Latin America [Anderson, 1998; Connolly, 1999; Harrison, 2009; Peltola, 1998]. *Nimenrix* is licensed in 50 countries (first approval in April 2012) and is currently available in at least 23 countries.

Using *Nimenrix* as a control vaccine in this study will provide a theoretical benefit to the children in the study and adequately support safety comparison.

#### **1.2.2.4. Stratification for age and staggered vaccination**

In order to ensure equal distribution of the population, enrolment will be stratified by age so that equal number of children are enrolled in each age stratum (1 to 5 years, 6 to 12 years and 13 to 17 years of age).

In order to ensure maximum safety for the subjects in this study, vaccination at Day 0 will be done in a staggered manner, starting with vaccination of the children in the oldest age stratum. For each age stratum, an IDMC will conduct a review of all available safety data once data is available up to at least 7 days after vaccination of at least 50 subject (25/ group) in that age stratum. The start of vaccination in the younger age stratum, possibly with a lower vaccine dose, depends on the outcome of this IDMC review. For more detailed information on the staggered design of the study and on the safety monitoring, refer to [Section 9.10](#).

#### **1.2.2.5. Human immunodeficiency virus testing**

There will be no routine testing for human immunodeficiency virus (HIV) in this trial. Tests will be performed when clinically indicated to guide subject management. Voluntary counselling and testing, highly active anti-retroviral therapy (HAART) and prevention of mother to child transmission (PMTCT) will be available at all study centres according to national policies.

### **1.3. Benefit : Risk assessment**

All subjects in the study will receive a single dose of the investigational ChAd3-EBO-Z vaccine (either at Day 0 or at Month 6 of the study) and a single dose of *Nimenrix* (at Day 0 or at Month 6 of the study).

For general information on the risks and benefits of the investigational ChAd3-EBO-Z vaccine and *Nimenrix*, please refer to the current Investigator Brochure (IB), Periodic Safety Report Information (PSRI) and to the approved summary of product characteristics (SmPC)/ Prescribing Information/ package insert, as applicable.

The following section outlines the risk assessment and mitigation strategy for this study protocol.

**1.3.1. Risk Assessment**

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
<b>Both study vaccines</b>		
As with all injectable vaccines, allergic reactions to vaccination can occur.	Acute allergic reactions such as a rare case of anaphylactic event may occur with any vaccine administration. These are serious, but rare occurrences estimated in the range of 1 to 10 cases per million of vaccinations, depending on the vaccine studied [Rüggeberg, 2007]. No such event has been observed as of 14 November 2014 in the on-going Phase 1 trials with the investigational ChAd3-EBO-Z vaccine.	Warnings regarding allergic reactions. Anaphylaxis following vaccine administration is an exclusion criterion for study participation and a contraindication to vaccination. The onset of vaccine-related allergic symptoms is typically quite prompt. In order to treat subjects with a serious allergic reaction to vaccination, all subjects will need to remain under observation ( <i>i.e.</i> , visibly followed; no specific procedure) at the vaccination centre for at least 30 minutes after vaccination.
Syncope	Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the injection needle (also outlined in the <i>Nimenrix</i> Reference Safety Information). This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery.	It is important that procedures are in place to avoid injury from faints. All subjects will need to remain under observation ( <i>i.e.</i> , visibly followed; no specific procedure) at the vaccination centre for at least 30 minutes after vaccination.
<b><i>Nimenrix</i></b>		
Extensive limb swelling	The active ingredients of <i>Nimenrix</i> are conjugated to a tetanus toxoid carrier protein and exaggerated local (Arthus-like) reactions are occasionally reported following receipt of a diphtheria- or tetanus-containing vaccine. These reactions present as extensive painful swelling, often from shoulder to elbow. They generally begin from 2 to 8 hours after vaccination and are reported most often in adults, particularly those who have received frequent doses of diphtheria or tetanus toxoid.	Subjects' parent(s)/ LAR(s) should report any untoward symptoms experienced by the child after receiving the vaccine immediately to the Investigator.

**ChAd3-EBO-Z** = investigational recombinant chimpanzee adenovirus type 3-vectored Ebola virus Zaire (EBOV) vaccine; **GSK** = GlaxoSmithKline



### 1.3.2. Benefit assessment

#### **Benefits linked to the investigational ChAd3-EBO-Z vaccine**

The subjects in this study may not directly benefit from vaccination with the investigational ChAd3-EBO-Z vaccine as the vaccine has not been assessed in subjects exposed to EVD yet and it is hence not known whether it is effective in protecting against EVD. Moreover, this study will be conducted in countries adjacent to the current Ebola outbreak zone and the subjects in this study possibly may never come in contact with EBOV.

An indirect benefit is that the information obtained in this study will aid the development of a vaccine against EVD.

#### **Benefits linked to *Nimenrix***

Meningococcal disease continues to be endemic in both industrialised regions (such as North America and Europe) and developing regions and is associated with high case fatality even where adequate medical services and antibiotics are available. However, a significant decline in the incidence of confirmed meningococcal disease has been observed in those countries that include meningococcal vaccination in their routine immunisation schedule. Overall, clinical trial data and post-marketing experience continue to demonstrate the substantial benefit and acceptable safety profile of *Nimenrix* vaccination.

#### **Other benefits**

***All subjects who provide informed consent for study participation will be tested for Malaria infection using an RDT procedure at the time of Screening. Subjects who are diagnosed with Malaria will receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period, to clear the infection prior to vaccination. (Amended 06 May 2015.)***

Another benefit for the subjects may include the gaining of information about their general health status through the medical evaluations/ assessments associated with this study (physical examination, blood testing [haematology and biochemistry data]). All subjects participating to the Screening Visit of this study will be medically examined including testing for haematological (complete blood count [CBC], including differential count and platelet count) and biochemical (alanine aminotransferase [ALT] and creatinine) parameters. Those subjects with clinically significant disease who are not eligible for study participation will be referred for medical care to local facilities. Those subjects who are eligible and participate in the study will receive medical follow-up during the study.



**1.3.3. Overall Benefit : Risk conclusion**

The investigational ChAd3-EBO-Z vaccine is currently in an early stage of clinical development and no vaccine efficacy has been demonstrated. Measures are taken to minimise the risk to subjects participating in this study.

**2. OBJECTIVES****2.1. Primary objective**

- To assess the safety and reactogenicity of a single IM dose of the ChAd3-EBO-Z vaccine, overall and in children aged 1 to 5, 6 to 12, and 13 to 17 years separately.

Refer to [Section 11.1](#) for the definition of the primary endpoints.

**2.2. Secondary objective**

- To assess the humoral immunogenicity of a single IM dose of the ChAd3-EBO-Z vaccine, in terms of anti-GP EBOV antibody responses, overall and in children aged 1 to 5, 6 to 12, and 13 to 17 years separately.

Refer to [Section 11.2](#) for the definition of the secondary endpoint.

**2.3. Tertiary objectives**

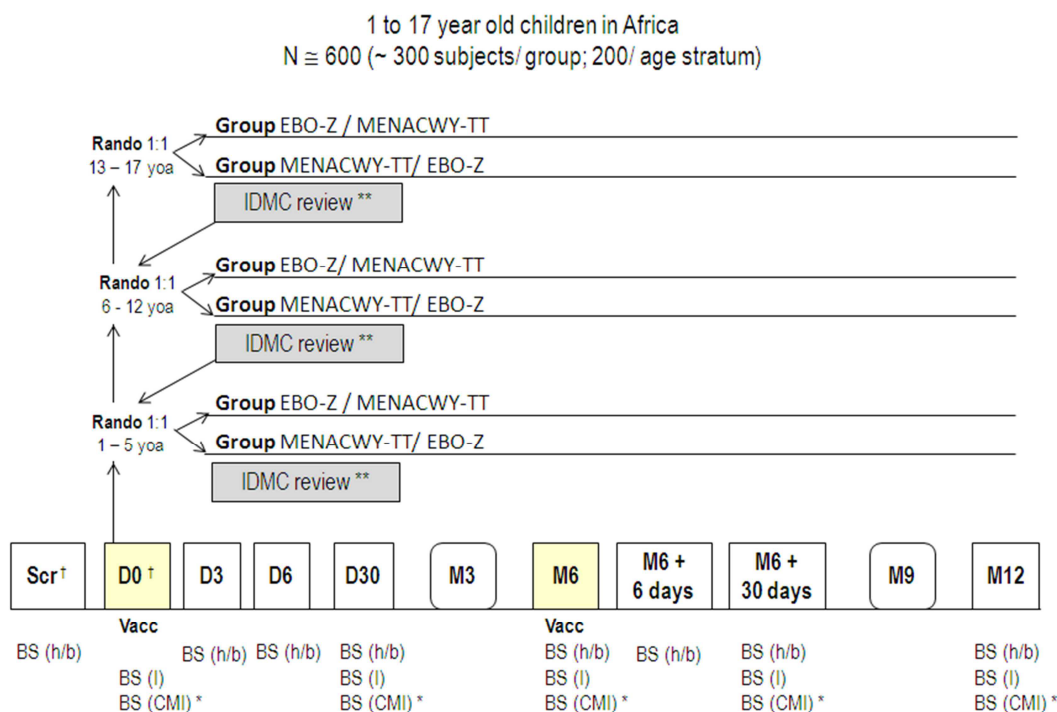
- To assess the persistence of the humoral immune response induced by a single IM dose of the ChAd3-EBO-Z vaccine, in terms of anti-GP EBOV antibody responses, overall and in children aged 1 to 5, 6 to 12, and 13 to 17 years separately.
- To assess EBOV specific cell-mediated immunity (CMI) of a single IM dose of the ChAd3-EBO-Z vaccine, overall and in children aged 1 to 5, 6 to 12, and 13 to 17 years separately.
- To assess the pre-existing immunity to the ChAd3 virus vaccine vector prior vaccination, ChAd3-specific immune responses after vaccination and explore its potential impact on Ebola-specific immune responses, overall and in children aged 1 to 5, 6 to 12, and 13 to 17 years separately.
- If deemed necessary, to further characterise the immune response to/ the safety profile of the investigational ChAd3-EBO-Z vaccine.

Refer to [Section 11.3](#) for the definition of the tertiary endpoints.

### 3. STUDY DESIGN OVERVIEW

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures ([Section 5.5](#)), are essential and required for study conduct.

**Figure 1 Study design overview**



**Rando** = randomisation; **yoa** = years of age; **Scr** = Screening; **D** = Day; **M** = Month; **BS (h/b)** = blood sample for haematology/ biochemistry parameters; **BS (I)** = blood sample for humoral immunity; **BS (CMI)** = blood sample for cell-mediated immunity.

Squares indicate visits to the vaccination centre. Rounded rectangles indicate study contacts (home visit or phone call).

Yellow-coloured visits indicate vaccination visits. At the Day 0 visit, subjects in the Group EBO-Z/ MENACWY-TT receive the investigational ChAd3-EBO-Z vaccine and subjects in Group MENACWY-TT/ EBO-Z receive *Nimenrix*. At the Month 6 visit, subjects in Group EBO-Z/ MENACWY-TT receive *Nimenrix* and subjects in the Group MENACWY-TT/ EBO-Z receive the investigational ChAd3-EBO-Z vaccine.

**Subjects will be followed-up for adverse events (AEs) on a daily basis during the 7-day follow-up period after vaccination (day 0 to 6). During this period, AEs will be recorded on a Diary Card. On those days that no study visit is planned, a home visit will be scheduled.**

† The Screening Visit and the Day 0 visit may take place on the same day (allowed interval 0 - 30 days).

\* Only for subjects in the sub-cohort for CMI.

\*\* IDMC review on all available safety data, which will include the safety data up to 7 days after vaccination at Day 0, from at least 50 children (25 per group) in an age stratum before proceeding to vaccination in the next (younger) age stratum (if applicable).

- **Experimental design:** Phase 2, randomised, observer-blind, controlled, multi-country study with 2 groups and 3 age strata.
- **Duration of the study:** For each subject enrolled it will be approximately 12 months from the Day 0 visit
  - Epoch 001: Primary starting at Screening and ending at the Month 12 visit.
- **Study groups:**
  - **Group EBO-Z/ MENACWY-TT:** approximately 300 children in total; approximately 100 children per age stratum (1 to 5 years, 6 to 12 years, and 13 to 17 years of age).
  - **Group MENACWY-TT/ EBO-Z:** approximately 300 children in total; approximately 100 children per age stratum (1 to 5 years, 6 to 12 years, and 13 to 17 years of age).

**Table 1 Study groups and epochs foreseen in the study**

Study group	Number of subjects	Age	Epochs
			Epoch 001
EBO-Z/ MENACWY-TT	~300	~100 children per age stratum: 13 to 17, 6 to 12, 1 to 5 years	x
MENACWY-TT/ EBO-Z	~300	~100 children per age stratum: 13 to 17, 6 to 12, 1 to 5 years	x

~ = approximately

**Table 2 Treatments foreseen in the study**

Treatment name	Vaccine/Product name	Study Groups	
		EBO-Z/ MENACWY-TT	MENACWY-TT/ EBO-Z
ChAd3-EBO-Z	ChAd3-EBO-Z	x (Day 0)	x (Month 6)
<i>Nimenrix</i>	MenACWY-TT NaCl	x (Month 6)	x (Day 0)

**ChAd3-EBO-Z** = investigational recombinant chimpanzee adenovirus type 3-vectored Ebola virus Zaire (EBOV) vaccine; **NaCl** = sodium chloride

- **Control:** Active control (*Nimenrix*).
- **Vaccination schedule:** All subjects will receive 2 vaccinations, 1 at the Day 0 visit and 1 at the Month 6 visit. All subjects will receive 1 dose of the investigational ChAd3-EBO Z vaccine and 1 dose of *Nimenrix*:
  - Subjects in Group EBO-Z/ MENACWY-TT will receive the investigational ChAd3-EBO-Z vaccine at the Day 0 visit and *Nimenrix* at the Month 6 visit.
  - Subjects in Group MENACWY-TT/ EBO-Z will receive *Nimenrix* at the Day 0 visit and the investigational ChAd3-EBO-Z vaccine at the Month 6 visit.

- **Treatment allocation:** Subjects will be randomised (1:1) at Day 0. In order to ensure equal distribution of the population, enrolment will be stratified by age so that an equal number of children are enrolled in each age stratum (1 to 5 years, 6 to 12 years, and 13 to 17 years of age). In addition, the randomisation will use a minimisation procedure accounting for gender and centre.
- **Staggered vaccination:** Vaccination at Day 0 will be done in a staggered manner, starting with vaccination of the children in the oldest age stratum (13 to 17 years of age). In order to proceed to vaccination of the subjects in the younger age stratum (6 to 12 years of age), possibly with a lower vaccine dose, a favourable outcome of the IDMC review of safety data up to at least 7 days after vaccination from at least 50 subjects (25/ group) in the oldest age stratum needs to be obtained. The same will be done for moving from the 6 to 12 years of age stratum to vaccination of the youngest children (1 to 5 years of age). Refer to [Section 9.10](#) for more information.
- **Blinding:**
  - **Observer-blind** from study start until the interim analysis that will be conducted when safety, reactogenicity and immunogenicity (including at least anti-GP EBOV data at Day 30) data is available from all subjects up to 30 days after vaccination at Day 0 (refer to [Section 11.11.1](#) for more information on this interim analysis).
  - **Single-blind** as of the interim analysis *at Day 30. (Amended 06 May 2015.)*
- **Sampling schedule:**
  - *A blood sample (fingerprick) will be taken at Screening for Malaria RDT. (Amended 06 May 2015.)*
  - Blood samples for **haematology/ biochemistry** assessment will be taken from all subjects at Screening, at the Day 3, Day 6, the Day 30, the Month 6, the Month 6 + 6 days, the Month 6 + 30 days, and the Month 12 visits.
  - Blood samples for **humoral immunity** will be taken from all subjects at the Day 0, the Day 30, the Month 6, the Month 6 + 30 days, and the Month 12 visits.
  - Blood samples for **CMI** will be taken from a sub-cohort of 90 subjects per group (30 children per age stratum per group) at the Day 0, the Day 30, the Month 6, the Month 6 + 30 days, and the Month 12 visits.
- **Type of study:** self-contained.
- **Data collection:** eSource.
- **Safety monitoring:** An IDMC will be appointed to monitor the safety and tolerability of the investigational ChAd3-EBO-Z vaccine. The IDMC will consist of clinical experts and a statistician who are not involved in the conduct of the study. Refer to [Section 9.10](#) for detailed description of the safety monitoring.

## 4. STUDY COHORT

### 4.1. Number of subjects/centres

The target is to enrol approximately 600 eligible children (approximately 300 per group and approximately 200 per age stratum). Refer to [Section 11.4](#) for a detailed description of the criteria used in the estimation of sample size. This study will be conducted in West and Central Africa.

### 4.2. Sub-cohort for cell-mediated immunity

A sub-cohort is defined as a group of subjects for whom specific procedures are planned as compared to other subjects. For each group, the first approximately 30 children enrolled in each age stratum will be part of the sub-cohort for CMI (*i.e.*, approximately 90 children per group and approximately 180 children in total; possibly at selected vaccination centres only). A blood sample for assessment of CMI should be taken from these subjects at certain study visits.

**Table 3 Sub-cohort for cell-mediated immunity**

Sub-cohort name	Description	Estimated number of subjects
Sub-cohort for CMI	A blood sample for assessment of CMI will be taken from these subjects at certain study visits.	~30 subjects per age stratum per group (~90 subject per group and ~180 subjects in total)

~ = approximately; CMI = cell-mediated immunity

A subset is defined as a group of subjects for which additional assays are planned as compared to other subjects. Refer to [Section 5.2.3](#) for the description of the subset for additional humoral immunogenicity assays.

### 4.3. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subject's parent(s)/ legally acceptable representative(s) (LAR[s]) who, in the opinion of the Investigator, can and will comply with the requirements of the protocol (*e.g.*, availability for Diary Card completion, return for follow-up visits, availability for clinical follow-up throughout the study period).
- Written/ thumb printed informed consent obtained from the subject' parent(s)/ LAR(s) prior to performing any study specific procedure. In addition, written/ thumb printed informed assent should be obtained if appropriate (from all subjects aged 13 to 17 years and from younger subjects as per local requirements).
- A male or female child aged 1 to 17 years inclusive at the time of **Screening**.  
(Amended 06 May 2015.)

- ***Subjects with a negative RDT test for Malaria within 30 days prior to randomisation into the study.***

***OR***

***Subjects with a positive RDT test for Malaria who completed antimalarial treatment at least 5 days prior to randomisation into the study.***

***(Amended 06 May 2015.)***

- Healthy subjects as per Investigator judgement, as established by medical history, clinical examination and haematology/ biochemistry laboratory parameters screening before entering into the study.
- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche or ovariectomy.

Please refer to the [glossary of terms](#) for the definition of menarche.

- Female subjects of childbearing potential may be enrolled in the study, if the subject:
  - has practiced adequate contraception for 30 days prior to the Day 0 visit, and
  - has a negative pregnancy test at the Day 0 visit, and
  - has agreed to continue adequate contraception until 30 days after the Month 6 visit.

Please refer to the [glossary of terms](#) for the definition of adequate contraception.

#### **4.4. Exclusion criteria for enrolment**

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Child in care.

Please refer to the [glossary of terms](#) for the definition of child in care.

***(Amended 06 May 2015.)***

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the period starting 30 days before the Day 0 visit, or planned use during the study period.
- Previous vaccination with an investigational EBOV or Marburg vaccine, or previous vaccination with a chimpanzee adenoviral vectored investigational vaccine.
- Known prior EBOV or SUDV disease.
- Travel to country affected by the EBOV epidemic or direct contact with person with EVD within 21 days prior to the Day 0 visit.

- History of any reaction or hypersensitivity (such as anaphylaxis, urticaria [hives], respiratory difficulty, angioedema, or abdominal pain) likely to be exacerbated by any component of the study vaccine.
- Planned administration/ administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after each vaccination visit.
- Acute or chronic illness determined by medical history, clinical examination and laboratory screening tests including, but not limited to:
  - Clinically significant immunosuppressive or immunodeficient condition (*e.g.*, clinical acquired immune deficiency syndrome [AIDS]).
  - Major congenital defects.
  - Malnutrition (defined as weight for age Z-score less than -3, or other clinical signs of malnutrition).
  - Any clinically significant haematological or biochemical laboratory abnormality (see [APPENDIX C](#) for acceptable limits for eligibility determination).
- Pregnant female.
- *Any condition that in the Investigator's opinion may potentially compromise subject safety or interfere with subject assessment or compliance.*

*(Amended 06 May 2015.)*

## **5. CONDUCT OF THE STUDY**

### **5.1. Regulatory and ethical considerations, including the informed consent process**

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

GSK Biologicals/ the contracted research organisation (CRO) engaged to conduct the study will obtain favourable opinion/ approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a vaccination centre initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.



- Subject's parent(s)/ LAR(s) informed consent and subject informed assent, as appropriate.
- Investigator reporting requirements as stated in the protocol.

GSK/ the CRO will provide full details of the above procedures to the Investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed informed consent from each subject's parent(s)/ LAR(s) and subject informed assent, as appropriate, must be obtained prior to participation in the study.

GSK Biologicals/ the CRO will prepare a model informed consent form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

In accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, subjects who can only be enrolled in the study with the consent of their parent(s)/ LAR(s) (*e.g.*, minors), should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date a written informed assent form (IAF). It should be assessed whether an assent is required depending of the age of the study population and the local requirements. In this study, written/ thumb printed informed assent should be obtained from all subjects in the oldest age category (13 to 17 year olds) and from younger subjects as per local requirements in addition to the informed consent that is to be signed/ thumb printed by their parent(s)/ LAR(s).

GSK Biologicals strongly recommends that if a subject reaches the age of consent during the study, he/ she will be asked to provide consent at the next study visit (if applicable). This procedure should be applied according to local laws and regulations.

The Investigator has the final responsibility for the final presentation of the ICF and IAF, respecting the mandatory requirements of local regulations. The ICF and IAF generated by the Investigator with the assistance of the sponsor's/ the CRO's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/ IEC.

## **5.2. Subject identification and randomisation of treatment**

### **5.2.1. Subject identification**

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study. The subject numbers will be assigned as a combination of the centre number and a sequential number.



**5.2.2. Randomisation of treatment****5.2.2.1. Randomisation of supplies**

The ChAd3-EBO-Z vaccine and *Nimenrix* will be numbered sequentially and packed separately.

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multi-centre study and to thus reduce the overall study recruitment period, an over-packaging of supplies will be prepared.

**5.2.2.2. Treatment allocation to the subject**

The treatment name will be allocated by dose to each subject.

**5.2.2.2.1. Study group and treatment name allocation at Day 0**

The target will be to enrol approximately 600 eligible children who will be randomly assigned to 2 study groups in a (1: 1) ratio (approximately 300 per group and approximately 200 per age stratum).

The enrolment will be performed to ensure equal distribution of the population across the 3 age strata (1 to 5 years, 6 to 12 years, and 13 to 17 years of age). Therefore the expected distribution of subjects is as shown in Table 4.

**Table 4 Number of subjects required for enrolment**

Age Stratum	Group	N
1 to 5 years	EBO-Z/ MENACWY-TT	100
	MENACWY-TT/ EBO-Z	100
6 to 12 years	EBO-Z/ MENACWY-TT	100
	MENACWY-TT/ EBO-Z	100
13 to 17 years	EBO-Z/ MENACWY-TT	100
	MENACWY-TT/ EBO-Z	100

N = number of subjects to be enrolled

Allocation of the subject to a study group at the vaccination centre will be performed using a central Interactive Web Response System (IWRS). In addition to the IWRS, an Interactive Voice Response System (IVRS) will be available in case of possible connectivity issues with the IWRS. Within each age stratum (1 to 5 years, 6 to 12 years, and 13 to 17 years of age), the randomisation algorithm will use a minimisation procedure accounting for gender and centre. The minimisation is a dynamic allocation method that will ensure that, within each age stratum, there is a good balance between groups in the number of subjects by gender and centre. Both minimisation factors will have equal weight in the minimisation algorithm.

After obtaining the signed/ thumb printed and dated ICF from the subject's parent(s)/ LAR(s) and signed/ thumb printed and dated IAF from the subject (if applicable) and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access IWRS/ IVRS. Upon providing the subject's age (1 to 5 years *versus* 6 to 12 years *versus* 13 to 17 years of age), gender, centre and the subject

identification number, the randomisation system will determine the study group and will provide the treatment name to be administered. Access to the IVRS/ IWRS ***unblinded treatment information*** will be limited to unblinded site staff. (*Amended 06 May 2015.*)

After vaccine administration, the treatment number of the vaccine administered (indicated on the label) should be recorded in IWRS/ IVRS, and for drug supply management purposes, by the unblinded study staff preparing and administering the vaccine. The applicable screen will only be available for unblinded staff in order to maintain the study blind.

When IWRS is not available, please refer to the relevant user guide for instructions for the use of the IVRS.

Note that as soon as the target number of 200 subjects in a specific age group has been reached, the enrolment will be frozen for this age group.

#### **5.2.2.2. Treatment name allocation at Month 6**

At Month 6, the study staff in charge of the vaccine administration will access IWRS/ IVRS, provide the subject identification number, and the system will provide a treatment name consistent with the allocated study group.

The number of the administered treatment should be recorded in the IWRS/IVRS by study staff preparing the vaccine.

#### **5.2.3. Allocation of subjects to assay subsets**

A subset is defined as a group of subjects for which additional assays are planned as compared to other subjects. Approximately 90 subjects per group (approximately 30 children per age stratum per group) will be part of the subset for additional humoral immunogenicity assays. These will be the same subjects as the subjects in the sub-cohort for CMI (refer to [Section 4.2](#)).

### **5.3. Method of blinding**

The blinding level will change in the course of the study:

- **Observer-blind** from study start until the interim analysis that will be conducted when safety, reactogenicity and immunogenicity (including at least anti-GP EBOV data at Day 30) data is available from all subjects up to 30 days after vaccination at Day 0 (refer to [Section 11.11.1](#) for more information on this interim analysis). By observer-blind, it is meant that the vaccine recipient and those responsible for the evaluation of any study endpoint will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration at Day 0 will be done by authorised medical personnel who will not participate in any of the study clinical evaluation assays.

*To ensure blinding of the site staff when preparing and administering the study vaccine details of vaccine management will be defined in a site vaccine management plan before site initiation.*

*(Amended 06 May 2015.)*

- **Single-blind** as of the interim analysis. At the time of the interim analysis, the study will become single-blind to ensure full data availability. By single-blind, it is meant that vaccination centre and sponsor personnel are aware of the treatment assignment but the subject is not.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

#### **5.4. General study aspects**

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying manuals. The manuals provide the Investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

**5.5. Outline of study procedures****5.5.1. List of study procedures****Table 5 List of study procedures during visits to the vaccination centre (Amended 06 May 2015)**

Type of contact	Visit	Visit	Visit	Visit	Visit	Contact *	Visit	Visit	Visit	Contact *	Visit
Timepoint	Screening <sup>1</sup>	Day 0 <sup>1</sup>	Day 3	Day 6	Day 30	Month 3	Month 6	Month 6 + 6 days	Month 6 + 30 days	Month 9	Month 12
Informed consent	•										
Informed assent <sup>10</sup>	•										
<b>RDT for Malaria</b>	•										
<b>Malaria treatment <sup>11</sup></b>	•										
Inclusion/exclusion criteria <sup>12</sup>	•	•									
Demographic data	•										
Medical history <sup>12</sup>	•	•									
Physical examination (including vital signs <sup>2</sup> )	• <sup>12</sup>	• <sup>3</sup>	0	0	0		•	0	0		0
Pregnancy test <sup>4</sup>	•	• <sup>5</sup>					•				
Pre-vaccination body temperature		•					•				
Check contraindications to vaccination		0					0				
Study group and treatment name allocation <sup>6</sup>		0					0				
Vaccination		•					•				
Recording of administered treatment number		0					0				
30 minutes post-vaccination observation		0					0				
<b>Blood sampling:</b>											
Blood for haematology/ biochemistry	• <sup>12</sup>		•	•	•		•	•	•		•
Blood for humoral immunity		•			•		•		•		•
Blood for CMI <sup>7</sup>		•			•		•		•		•
<b>Safety assessment:</b>											
Record solicited AEs (day 0 to day 6)		•	•	•			•	•			
Record unsolicited AEs (day 0 to day 29)		•	•	•	•		•	•	•		
<b>Record AEs of specific interest (clinical symptoms of thrombocytopenia)</b>			•	•							
Record SAEs	• <sup>8</sup>	•	•	•	•	•	•	•	•	•	•
Record pregnancies		•	•	•	•	•	•	•	•		

**CONFIDENTIAL**

202090 (EBOLA Z CHAD3-004)  
Protocol Amendment 2 Final

Type of contact	Visit	Visit	Visit	Visit	Visit	Contact *	Visit	Visit	Visit	Contact *	Visit
Timepoint	Screening <sup>1</sup>	Day 0 <sup>1</sup>	Day 3	Day 6	Day 30	Month 3	Month 6	Month 6 + 6 days	Month 6 + 30 days	Month 9	Month 12
Record concomitant medications/ products/ vaccinations <sup>9</sup>		•	•	•	•	•	•	•	•	•	•
Screening Conclusion	•										
Study Conclusion											•

~ = approximately; **AE** = adverse event; **CMI** = cell-mediated immunity; **CRO** = Contract research organisation; **EVD** = Ebola virus disease; **GSK** = GlaxoSmithKline; **RDT** = *Rapid*

**Diagnostic Test**; **SAE** = serious adverse event

• is used to indicate a study procedure that requires documentation in eSource.

○ is used to indicate a study procedure that does not require automatic transfer of the study data fields from the source database into the study database at the CRO.

\* Home visit by field worker or phone call.

<sup>1</sup> The Screening visit and the Day 0 visit may take place on the same day (allowed interval 0 to 30 days).

<sup>2</sup> Refer to [Section 5.6.6](#) for the specific assessments included in the physical examination.

<sup>3</sup> Only if Visit 1 and Screening take place on a different day.

<sup>4</sup> Only for women of childbearing potential.

<sup>5</sup> Only if Visit 1 takes place more than 1 week after the Screening Visit.

<sup>6</sup> Treatment name allocation with randomisation at Day 0; treatment name allocation without randomisation at Month 6.

<sup>7</sup> Only for subjects in the sub-cohort for cell-mediated immunity (CMI).

<sup>8</sup> From Screening to Day 0, only those SAEs that are considered related to study participation or to concurrent use of GlaxoSmithKline (GSK) medication/ vaccine need to be recorded.

<sup>9</sup> Concomitant medications/ products/ vaccinations as described in [Section 6.7.1](#) and [6.7.2](#) need to be recorded in eSource.

<sup>10</sup> Only for subjects in the oldest age stratum (13 to 17 year olds) and younger subjects as per local requirements.

<sup>11</sup> **Subjects diagnosed with Malaria at Screening must receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period.**

<sup>12</sup> **Study procedure must be performed at least 5 days after completion of Malaria treatment for all subjects diagnosed with Malaria at Screening.**

**5.5.2. Intervals between study visit****Table 6 Intervals between study visits**

Interval	Allowed interval
Screening → Visit Day 0	0 to 30 days
Visit Day 0 → Visit Day 3	3 days
Visit Day 0 → Visit Day 6	6 to 8 days
Visit Day 0 → Visit Day 30	30 to 44 days <sup>1</sup>
Visit Day 0 → Contact Month 3	3 months ± 30 days
Visit Day 0 → Visit Month 6	6 months ± 30 days <sup>1</sup>
Visit Month 6 → Visit Month 6 + 6 days	6 to 8 days
Visit Month 6 → Visit Month 6 + 30 days	30 to 44 days <sup>1</sup>
Visit Month 6 → Contact Month 9	3 months ± 30 days
Visit Month 6 → Visit Month 12	6 months ± 30 days <sup>1</sup>

<sup>1</sup> Subjects will not be eligible for inclusion in the according-to-protocol cohort for immunogenicity if they make the study visit outside this interval.

**5.6. Detailed description of study procedures****5.6.1. Informed consent**

The signed/witnessed/thumb printed informed consent of the subject's parent(s)/ LAR(s) must be obtained before study participation. For subjects in the oldest age stratum (13 to 17 years) and for younger subjects as per local requirements, the signed informed assent of the subject should be obtained in addition to the signed informed consent by his/her parent(s)/ LAR(s). Refer to [Section 5.1](#) for the requirements on how to obtain informed consent as appropriate.

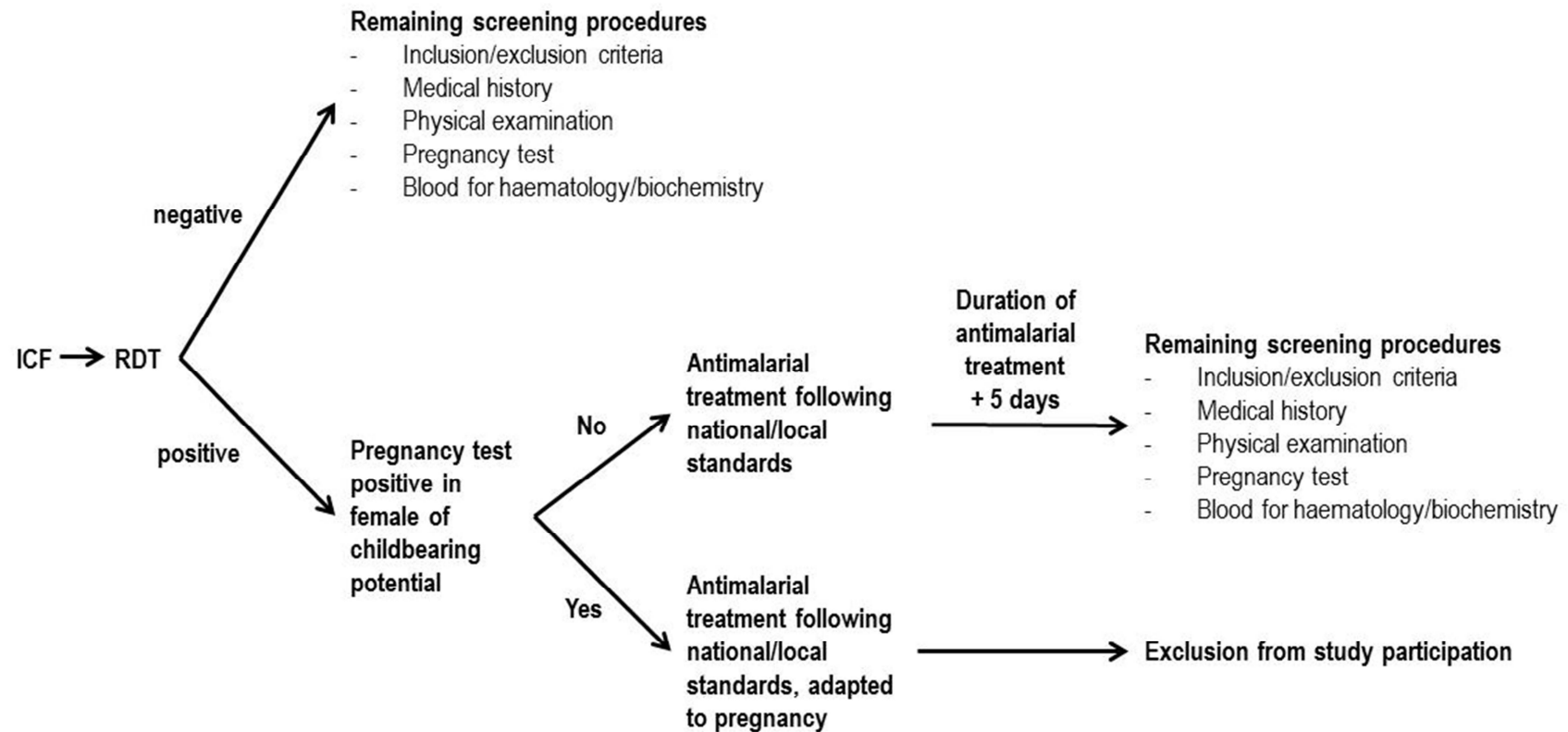
**5.6.2. Malaria Screening and treatment (Amended 06 May 2015)**

*After obtaining the informed consent of the subject's parent(s)/ LAR(s), all subjects should first be tested for Malaria infection using the WHO pre-qualified RDT.*

*All subjects diagnosed with Malaria using the RDT must receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period. In addition, a pregnancy test should be performed for women of childbearing potential in case the RDT is positive, so that an antimalarial treatment alternative to artemisinin-based combination therapy (e.g., quinine plus clindamycin) is proposed in case the pregnancy test is positive. For subjects whose RDT is positive, the following Screening procedures should be postponed until at least 5 days after completion of the Malaria treatment (Figure 2):*

- *Blood sampling for haematology and biochemistry testing.*
- *Physical examination.*
- *Review of eligibility criteria.*
- *Completion of the medical history.*

**Figure 2 Screening procedures**



ICF = Informed Consent Form; RDT = Rapid Diagnostic Test

***The outcome of the Malaria RDT and completion of Malaria treatment needs to be recorded in eSource.***

***(Amended 06 May 2015.)***

### **5.6.3. Check inclusion and exclusion criteria**

Check all inclusion and exclusion criteria as described in [Sections 4.3](#) and [4.4](#) before enrolment.

***For subjects diagnosed with Malaria at Screening, a full eligibility check should be postponed until at least 5 days after completion of Malaria treatment.***

***(Amended 06 May 2015.)***

### **5.6.4. Collect demographic data**

Record demographic data such as date of birth (***full date of birth will be collected in eSource, but only month and year of the date of birth will be exported to GSK's clinical database. The age as calculated in eSource will be used for analysis purposes as the full date of birth will not be exported***), gender, geographic ancestry, and ethnicity, in the subject's eSource.

***(Amended 06 May 2015.)***

### **5.6.5. Medical history**

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination in eSource.

***For subjects diagnosed with Malaria at Screening, completion of medical history should be postponed until at least 5 days after completion of Malaria treatment.***

***(Amended 06 May 2015.)***

### **5.6.6. Physical examination**

Perform a complete physical examination of the subject at the Screening, the Day 0, and the Month 6 visit, including assessment of height, weight, body temperature and resting vital signs: heart rate, respiratory rate after at least 10 minutes of rest, and an assessment of the following systems: head/ neck/ thyroid; eyes/ ears/ nose/ throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. Collected information needs to be recorded in eSource (height only needs to be recorded at Screening).



***For subjects diagnosed with Malaria at Screening, physical examination should be postponed until at least 5 days after completion of Malaria treatment.***

***(Amended 06 May 2015.)***

During all other study visits, perform a physical examination only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

***(Amended 06 May 2015.)***

Treatment of any abnormality observed during physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

#### **5.6.7. Pregnancy test**

Female subjects of childbearing potential are to have a pregnancy test prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative. Note: The pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

#### **5.6.8. Check contraindications to vaccination**

Contraindications to vaccination must be checked at the beginning of each vaccination visit. Refer to [Sections 6.6](#) for more details.

#### **5.6.9. Assess pre-vaccination body temperature**

The axillary body temperature of all subjects needs to be measured prior to any study vaccine administration. If the subject has fever [fever is defined as temperature  $\geq 37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$  on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see [Table 6](#)).

#### **5.6.10. Study group and treatment number allocation**

Study group and treatment name allocation will be performed as described in [Section 5.2.2](#).

#### **5.6.11. Sampling**

Refer to the Laboratory Manual for detailed instructions for the collection, handling and processing of the samples.

Blood samples will be taken during certain study visits as specified in [Section 5.5 List of Study Procedures](#).

- ***A blood sample (fingerprick) will be taken at Screening for Malaria RDT.***

***(Amended 06 May 2015.)***

- A volume of approximately 1 mL of whole blood (to provide at least 300 µL of serum) should be drawn from the children in the youngest age stratum (1 to 5 years of age) and a volume of approximately 2.5 mL of whole blood (to provide at least 800 µL of serum) should be drawn from the children in the other age strata (6 to 17 years of age) for each analysis of humoral immune response at each pre-defined timepoint. Refer to the Laboratory Manual for more details on sample storage conditions.
- Among the children in the sub-cohort for CMI, a volume of approximately 4 mL of whole blood should be drawn from the children in the youngest age stratum (1 to 5 years of age), a volume of approximately 6 mL of whole blood should be drawn from the children in the middle age stratum (6 to 12 years of age), and a volume of approximately 10 mL of whole blood should be drawn from the children in the oldest age stratum (13 to 17 years of age), at each pre-defined timepoint. Refer to the Laboratory Manual for more details on sample storage conditions.
- A volume of approximately **0.5 to 1.5 mL (*depending on the age of the child*)** of whole blood should be drawn from all subjects for each analysis of haematology **and each analysis of** biochemistry parameters at each pre-defined timepoint.

*(Amended 06 May 2015.)*

#### **5.6.12. Study vaccine administration**

- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered IM in the deltoid, or for small children, in the thigh (refer to [Section 6.4](#) for detailed description of the vaccine administration procedure). If the Investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to [Table 6](#)).
- The subjects will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.

#### **5.6.13. Check and record concomitant medications/ products/ vaccinations**

Concomitant medication/ products/ vaccinations must be checked and recorded in eSource as described in [Section 6.7](#).

#### **5.6.14. Recording of adverse events, serious adverse events, and pregnancies**

- Refer to [Section 9.3](#) for procedures for the Investigator to record AEs, serious adverse events (SAEs), and pregnancies. Refer to [Section 9.4](#) for guidelines and how to report *AEs of specific interest (clinical symptoms of thrombocytopenia)*, SAEs, and pregnancies to the CRO (Quintiles).

*(Amended 06 May 2015.)*

- The subjects and/ or the subjects' parent(s)/ LAR(s) will be instructed to contact the Investigator immediately should he/ she/ the subjects manifest any signs or symptoms they perceive as serious.

**5.6.14.1. Diary Card for follow-up adverse events occurring from day 0 to day 6 after vaccination**

Subjects will be followed up for AEs on a daily basis during the 7-day follow-up period after vaccination. During this period, AEs *with the exception of AEs of specific interest (clinical symptoms of thrombocytopenia)* will be recorded on a Diary Card, which will be managed/ completed by the Investigator (at study visits during the 7-day follow-up period), or by a field worker (at home visits during the 7-day follow-up period; on those days that no study visit is planned).

*(Amended 06 May 2015.)*

The home visits will be conducted by a trained field worker under the supervision of the Investigator. In the event that the field worker finds any Grade 3 AE, the child will be brought to the vaccination centre for examination by a study clinician. Any further clinical data, including treatment provided, will be documented on the paper Diary Card and on specific clinic forms and transcribed in eSource. If the physician finds that the child has experienced a SAE, the appropriate measures will be taken to report this (refer to [Section 9.4](#) for instructions on reporting SAEs).

Diary Cards will be checked and verified by the Investigator or his/ her designate before transcription in eSource. The Investigator has a primary responsibility for the data transcribed in eSource. Unresolved AEs will be followed-up by field workers until resolution under the supervision of the Investigator and data will be entered in eSource.

The procedures and frequency of visits will be outlined in an SOP at the vaccination centre.

**5.6.14.2. Unsolicited adverse events occurring from day 0 to day 29 after vaccination and serious adverse event data collection during the entire study duration**

Subjects will be advised to present when unwell. All unsolicited AEs will be captured by passive detection from day 0 up to day 29 after vaccination. All SAEs will be captured during the entire study duration. In order to maximise data completeness, occurrence of events will be discussed and reviewed during the planned study visits.

**5.6.15. Study conclusion**

The Investigator will:

- review data collected to ensure accuracy and completeness
- complete the Study Conclusion screen in eSource.

**5.7. Biological sample handling and analysis**

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject.

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects' parent(s)/ LAR(s), in countries where this is allowed, will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an Independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject's parents/ LAR(s).

Refer also to the [Amendment 2 Investigator Agreement](#), where it is noted that the Investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in [Section 5.7.4.1](#) may be changed.

Collected samples will be stored for a maximum of 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

**5.7.1. Use of specified study materials**

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those

materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the according-to-protocol (ATP) analysis (See [Section 11.5](#) for the definition of cohorts to be analysed). The Investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the Investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the Pharmacy Manual.

**5.7.2. Biological samples****Table 7 Biological samples (Amended 06 May 2015.)**

Sample type	Quantity	Unit	Age strata	Timepoint	Sub-cohort *	Number of subjects
<b>Blood for Malaria Screening</b>	<b>Fingerprick</b>	<b>NA</b>	<b>1 to 17 years</b>	<b>Screening</b>	<b>All screened subjects</b>	<b>&gt; 600</b>
Blood for haematology	<b>0.5 to 1.5</b>	mL	1 to 17 years	Screening Day 3 Day 6 Day 30 Month 6 Month 6 + 6 days Month 6 + 30 days Month 12	All screened subjects All enrolled subjects	> 600 ~600
<b>Blood for biochemistry</b>	<b>0.5 to 1.5</b>	<b>mL</b>	<b>1 to 17 years</b>	<b>Screening</b> <b>Day 3</b> <b>Day 6</b> <b>Day 30</b> <b>Month 6</b> <b>Month 6 + 6 days</b> <b>Month 6 + 30 days</b> <b>Month 12</b>	<b>All screened subjects</b> <b>All enrolled subjects</b>	<b>&gt; 600</b> <b>~600</b>
Blood for humoral immunity	~1 ~2.5 ~1 ~2.5 ~1 ~2.5 ~1 ~2.5 ~1 ~2.5	mL mL mL mL mL mL mL mL mL mL	1 to 5 years 6 to 17 years 1 to 5 years 6 to 17 years 1 to 5 years 6 to 17 years 1 to 5 years 6 to 17 years 1 to 5 years 6 to 17 years	Day 0  Day 30  Month 6  Month 6 +30 days  Month 12	All enrolled subjects  All enrolled subjects  All enrolled subjects  All enrolled subjects  All enrolled subjects	~600  ~600  ~600  ~600  ~600
Blood for CMI	~4 ~6 ~10 ~4 ~6 ~10 ~4 ~6 ~10 ~4 ~6 ~10 ~4 ~6 ~10	mL mL mL mL mL mL mL mL mL mL mL mL mL mL mL	1 to 5 years 6 to 12 years 13 to 17 years 1 to 5 years 6 to 12 years 13 to 17 years 1 to 5 years 6 to 12 years 13 to 17 years 1 to 5 years 6 to 12 years 13 to 17 years 1 to 5 years 6 to 12 years 13 to 17 years	Day 0  Day 30  Month 6  Month 6 +30 days  Month 12	Sub-cohort for CMI  Sub-cohort for CMI  Sub-cohort for CMI  Sub-cohort for CMI  Sub-cohort for CMI	~180  ~180  ~180  ~180  ~180

~ = approximately; **CMI** = cell-mediated immunity; **NA** = **not applicable**\* Refer to [Section 4.2](#) for the description of the sub-cohorts for CMIs.

**5.7.3. Laboratory assays**

Please refer to [APPENDIX A](#) for a detailed description of the assays performed in the study. Please refer to [APPENDIX B](#) for the address of the clinical laboratories used for sample analysis.

In addition to the assays described below, other tests to characterise the safety and/ or the immunogenicity of the investigational ChAd3-EBO-Z vaccine may be performed if deemed necessary for accurate interpretation of the data and/ or should such test(s) become available.

***Screening for Malaria infection will be performed using the WHO pre-qualified RDT at the site.***

*(Amended 06 May 2015.)*

**5.7.3.1. Haematology/ biochemistry**

Haematology (CBC, including differential count and platelet count) and biochemistry (ALT and creatinine) assessments will be performed at a local laboratory.

**5.7.3.2. Immune response against Ebola**

**Table 8 Humoral immunity against Ebola (Amended 06 May 2015)**

System	Component	Method	Kit/ Manufacturer	Laboratory *
Serum	anti-GP EBOV	ELISA	<i>In-house</i>	Quest Diagnostics

**EBOV** = Ebola virus Zaire; **ELISA** = enzyme-linked immunosorbent assay; **GP** = glycoprotein; **GSK** = GlaxoSmithKline;

\* Refer to [APPENDIX B](#) for the laboratory addresses.

**Table 9 Cell-mediated immunity against Ebola**

System	Component	Challenge	Method	Kit/ Manufacturer	Laboratory *
PBMCs	ChAd3-EBO-Z-specific CD4 <sup>+</sup> or CD8 <sup>+</sup> T-cell responses	EBOV GP antigens	ICS	In-house	NVITAL

**ChAd3-EBO-Z** = investigational recombinant chimpanzee adenovirus type 3-vectored Ebolavirus Zaire (EBOV) vaccine; **EBOV** = Ebola virus Zaire; **ICS** = intracellular cytokine staining; **NVITAL** = NIAID Vaccine Immune T-cell and Antibody Laboratory (NIH); **PBMCs** = peripheral blood mononuclear cells

\* Refer to [APPENDIX B](#) for the laboratory addresses.

**5.7.3.3. Immune response against ChAd3**

**Table 10 Humoral immunity against ChAd3**

System	Component	Method	Kit/ Manufacturer	Laboratory *
Serum	ChAd3 neutralising antibody	neutralisation	In-house	NVITAL

**NVITAL** = NIAID Vaccine Immune T-cell and Antibody Laboratory (NIH)

\* Refer to [APPENDIX B](#) for the laboratory addresses.

**5.7.4. Biological samples evaluation****5.7.4.1. Immunological read-outs****Table 11 Immunological read-outs (humoral immunity)**

Timepoints	Component	Subset/ Sub-cohort *	No. subjects	Priority rank
Day 0, Day 30, Month 6, Month 6 + 30 days,	Anti-GP EBOV	All subjects	~600	1
	ChAd3 neutralising antibody	Subset for additional humoral immunogenicity assays	~180	2
Month 12	Anti-GP EBOV	All subjects	~600	1

~ = approximately; **EBOV** = Ebolavirus Zaire; **GP** = glycoprotein

\* Refer to [Section 5.2.3](#) for the description of the subset for additional humoral immunogenicity assays.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 11.

**Table 12 Immunological read-outs (cell-mediated immunity)**

Timepoints	Component	Subset/ Sub-cohort *	No. subjects
Day 0, Day 30, Month 6, Month 6 + 30 days, Month 12	ChAd3-EBO-Z-specific CD4 <sup>+</sup> or CD8 <sup>+</sup> T-cell responses	Sub-cohort for CMI	~180

~ = approximately; **ChAd3-EBO-Z** = investigational recombinant chimpanzee adenovirus type 3-vectored Ebolavirus Zaire (EBOV) vaccine; **CMI** = cell-mediated immunity

\* Refer to [Section 4.2](#) for the description of the sub-cohort for CMI.

**5.7.4.2. Haematology/biochemistry****Table 13 Haematology/ biochemistry readouts**

Timepoints	Component	Subset/ Sub-cohort	No. subjects
Screening	CBC (including differential count and platelet count), ALT and creatinine	All screened subjects	> 600
Day 3, Day 6, Day 30, Month 6, Month 6 + 30 days, Month 12	CBC (including differential count and platelet count), ALT and creatinine	All enrolled subjects	~ 600

~ = approximately; **ALT** = alanine aminotransferase; **CBC** = complete blood count

**5.7.5. Immunological correlates of protection**

No generally accepted immunological correlate of protection has been demonstrated so far for the antigen used in the candidate vaccine, ChAd3-EBO-Z.

**6. STUDY VACCINES/ PRODUCTS AND ADMINISTRATION (AMENDED 06 MAY 2015.)****6.1. Malaria treatment (Amended 06 May 2015.)**

*All subjects diagnosed with Malaria during Screening will receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period.*



## 6.2. Description of study vaccines

The investigational ChAd3-EBO-Z vaccine has been developed by the VRC/NIAID using the ReiThera (formerly known as Okairos) adenovirus vaccine platform technology, which was acquired by GSK Biologicals in May 2013.

The Quality Control Standards and Requirements for the investigational vaccines are described in separate Quality Assurance documents (*i.e.*, release protocols, certificate of analysis) and the required approvals have been obtained.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's SmPC.

**Table 14 Study vaccines (Amended 06 May 2015)**

Treatment name	Vaccine/Product name	Formulation	Presentation	Volume to be administered	Number of doses
ChAd3-EBO-Z	ChAd3-EBO-Z	ChAd3-EBO-Z= $2 \times 10^{11}$ vp/mL*	Liquid in vial	0.25 mL to 1 mL**	1
Nimenrix	MenACWY-TT	PSA=5 µg TT; PSC=5 µg TT; PSW <sub>135</sub> =5 µg TT; PsY=5 µg TT; TT~44 µg	Powder in vial	0.5 mL***	1
	NaCl	NaCl=150 mM	Liquid in monodose, prefilled syringe		

**ChAd3-EBO-Z** = investigational recombinant chimpanzee adenovirus type 3-vectored Ebolavirus Zaire (EBOV) vaccine; **MenACWY-TT** = meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate; **NaCl** = sodium chloride; **PSA** = *Neisseria meningitidis* serogroup A polysaccharide; **PSC** = *Neisseria meningitidis* serogroup C polysaccharide; **PSW** = *Neisseria meningitidis* serogroup W-135 polysaccharide; **PsY** = *Neisseria meningitidis* serogroup Y polysaccharide; **TT** = tetanus toxoid; **vp** = viral particles

\* **The dose used in this study, labelled  $2 \times 10^{11}$  vp corresponds to the dose, labelled  $1 \times 10^{11}$  vp, used in the Phase I studies that was selected for further clinical development. The difference in vp concentration on the labels of the lots used in this study and the Phase I studies is the result of a different analytical method that was used to determine the vp concentration.**

\*\* The volume to be administered **to children in younger age strata** will depend on **the recommendation of the independent data monitoring committee as a lower vaccine dose may be selected based on safety and reactogenicity data accrued during the age de-escalation process (Refer to Section 1.2.2.1).**

\*\*\* Refer to the Pharmacy Manual for the volume **to be injected** after reconstitution.

## 6.3. Storage and handling of study vaccines

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorised study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the CRO study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Pharmacy Manual for more details on storage of the study vaccine(s).

Temperature excursions must be reported in degree Celsius.

Refer to the Pharmacy Manual for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccine.

## 6.4. Dosage and administration of study vaccines

**Table 15 Dosage and administration (Amended 06 May 2015)**

Type of contact and timepoint	Volume to be administered	Treatment name	Study group	Route	Site *
Visit Day 0	0.25 mL to 1 mL **	ChAd3-EBO-Z	Group EBO-Z/ MENACWY-TT	IM	Deltoid
	0.5 mL	<i>Nimenrix</i>	Group MENACWY-TT/ EBO-Z	IM	Deltoid
Visit Month 6	0.5 mL	<i>Nimenrix</i>	Group EBO-Z/ MENACWY-TT	IM	Deltoid
	0.25 mL to 1 mL **	ChAd3-EBO-Z	Group MENACWY-TT/ EBO-Z	IM	Deltoid

**ChAd3-EBO-Z** = investigational recombinant chimpanzee adenovirus type 3-vectored Ebolavirus Zaire (EBOV) vaccine; **IM** = intramuscular; **vp** = *viral particles*

\* For small children, the vaccine may be given in the thigh.

\*\* The volume to be administered *to children in younger age strata* will depend on *the recommendation of the independent data monitoring committee as a lower vaccine dose may be selected based on safety and reactogenicity data accrued during the age de-escalation process (Refer to [Section 1.2.2.1](#)).*

## 6.5. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 20% additional vaccine doses will be supplied to replace those that are unusable.

Staff responsible for preparing the vaccine will provide to the Investigator the next available vaccine vial for the relevant treatment as assigned by the IWRS/ IVRS in case of a replacement. Replacement vaccine vial numbers will be recorded in the IWRS/IVRS by the staff preparing the vaccine. In addition, the original unusable vaccine vial number will be reported in the IWRS/ IVRS as such.

## 6.6. Contraindications to vaccination

The following event constitutes a contraindication to study vaccination at that point in time; if this event occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the allowed time window:

- Acute disease and/ or fever at the time of vaccination.
  - Fever is defined as temperature  $\geq 37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$ . Body temperature will be measured axillary.

The following events constitute absolute contraindications to subsequent vaccination. If any of these events are applicable at Month 6 the subject must not be vaccinated, but may continue other study procedures at the discretion of the Investigator:

- Anaphylaxis following vaccine administration.
- Clinically significant immunosuppressive or immunodeficient condition (*e.g.*, AIDS).
- Pregnancy (see [Section 9.2](#)).

## **6.7. Concomitant medications/products and concomitant vaccinations**

At each study visit, the Investigator should question the subject and/ or the subject's parents/ LAR(s) about any medications/ products taken and vaccinations received by the subject, with a focus on the medications listed in the Section 6.7.1 and 6.7.2, which need to be recorded in eSource.

### **6.7.1. Recording of concomitant medications/products and concomitant vaccinations**

The following concomitant medications/ products/ vaccinations must be recorded in eSource:

- All concomitant medications/ products, except vitamins and dietary supplements, administered as of study vaccination up to 29 days after (30-day follow-up period).
- Any concomitant vaccination administered as of the Day 0 visit up to study conclusion (Day 0 to Month 12).
- Prophylactic medication (*i.e.*, medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).  
*E.g.*, an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring (fever is defined as temperature  $\geq 37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$ ).
- Any concomitant medications/products/vaccines relevant to an SAE to be reported as per protocol or administered at any time during the study period for the treatment of a SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the electronic AE/ SAE form in eSource.
- Any concomitant medications/products/vaccines listed in Section 6.7.2 during the period specified in that section.
- Any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination.

### **6.7.2. Concomitant medications/ products/ vaccines that may lead to the elimination of a subject from according-to-protocol analyses**

The use of the following concomitant medications/ products/ vaccinations will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis. See [Section 11.5](#) for cohorts to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
- A vaccine\* not foreseen by the study protocol administered within 30 days of each vaccination visit.

\*In case an emergency mass vaccination for an unforeseen public health threat (*e.g.*, a pandemic) is organised by the public health authorities, outside the routine

immunisation programme, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its SmPC or Prescribing Information and according to the local governmental recommendations and provided a written approval of the sponsor is obtained.

- Any immunosuppressive medication used during the study period.
- Any immunoglobulins and/ or any blood products administered during the study period.

#### **6.8. Intercurrent medical conditions that may lead to elimination of a subject from according-to-protocol analyses**

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or if they are diagnosed with an immunological disorder.

### **7. OCCURRENCE OF SUSPECTED OR CONFIRMED EBOLA VIRUS DISEASE**

This study is planned to be conducted in areas free of Ebola transmission. However, consideration has been given to the unlikely occurrence of a suspected EVD case. EVD will be considered in subjects who have travelled to a country affected by the EBOV epidemic, or have had direct contact with a person with EVD in the last 21 days, presenting with compatible symptoms.

In case of a suspected EVD, the following steps will be taken:

- All precautions will be taken to preserve the safety of the subject and Investigator, and anybody with potential exposure to biohazard.
- Public health authorities, regulatory authorities and IRBs/ IECs will be alerted.
- Case details will be captured as part of SAE reporting. ***In the case of a confirmed negative result, the event may be downgraded to non-serious.***  
***(Amended 06 May 2015.)***
- While sampling will be organised to support diagnostic confirmation (refer to the Laboratory Manual), all safety precautions will be taken to prevent any biohazard. Samples at risk already collected from the subject will be destroyed and no further samples will be taken in case of biohazard.
- If transmission in the community is suspected, the ability to preserve study integrity will be considered but if needed the study will be interrupted, with due consideration for investigational ChAd3-EBO-Z vaccination of all participants, considering potential risks and benefits upon review of available data.
- Care to infected subjects, and isolation of suspected/ confirmed cases will be organised according to best local medical standards in collaboration with organisations involved in outbreak control.

## 8. HEALTH ECONOMICS

Not applicable.

## 9. SAFETY

The Investigator or vaccination centre staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each subject and/ or the subjects' parent(s)/ LAR(s) will be instructed to contact the Investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

### 9.1. Safety definitions

#### 9.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (*i.e.*, lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/ or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational vaccine or a concurrent medication (overdose per se should not be reported as an AE/ SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (*e.g.*, invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in [Section 9.1.3](#). All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (*i.e.*, endoscopy, appendectomy); the condition that leads to the procedure is an AE/ SAE.
- Situations where an untoward medical occurrence did not occur (*i.e.*, social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to study vaccination. These events will be recorded in the medical history section of eSource.

### 9.1.2. Definition of a serious adverse event

An SAE is any untoward medical occurrence that:

- a. Results in death,
- b. Is life-threatening,

Note: The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

- c. Requires hospitalisation or prolongation of existing hospitalisation,

Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether ‘hospitalisation’ occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

- d. Results in disability/ incapacity, OR

Note: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (*i.e.*, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other

outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

### 9.1.3. Solicited adverse events

Solicited local and general AEs occurring during a 7-day follow-up period after vaccination (*i.e.*, the day of vaccination and 6 subsequent days) will be recorded via paper Diary Cards, which will be completed by a trained field worker/ the Investigator (see [Section 5.6.14.1](#)).

#### 9.1.3.1. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

**Table 16 Solicited local adverse events**

Pain at injection site
Redness * at injection site
Swelling at injection site

\* In case it is not possible to determine the extent of redness on darkly pigmented skin, it will be reported as uninterpretable on the Diary Card and in eSource.

#### 9.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

**Table 17 Solicited general adverse events (Amended 06 May 2015)**

Infant/ Toddler/ Child (< 6 years)	Child/ Adult (≥ 6 years)
Drowsiness	Fatigue
Fever *	Fever *
Irritability/Fussiness	Gastrointestinal symptoms **
Loss of appetite	Headache

\* Fever is defined as temperature  $\geq 37.5^{\circ}\text{C}$  /  $99.5^{\circ}\text{F}$ . Body temperature *may* be measured axillary (*preferred*), *oral*, *tympanic*, or *rectal*.

\*\* Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/ or abdominal pain.

### 9.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (*e.g.*, clinical chemistry, haematology) or other abnormal assessments (*e.g.*, vital signs measurements) that are judged by the Investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to [Sections 9.1.1](#) and [9.1.2](#)). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.

The Investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

**9.1.5. Adverse events of specific interest****9.1.5.1. Clinical bleeding within 7 days post-vaccination at Day 0**

*In the Phase 1 studies with the investigational ChAd3-EB0-Z vaccine in healthy adults, transient decreases in thrombocyte counts were observed. These decreases occurred mostly on Day 1 after vaccination and generally returned to baseline by Day 7. Although most of these decreases remained within the normal range, the as per protocol criteria for thrombocytopenia (thrombocyte count of  $< 150 \times 10^3/\mu\text{L}$ ) were met for 2.6% (7 out of 270) of the vaccinated subjects. None of the decreases in thrombocyte counts or the cases of thrombocytopenia were clinically significant, i.e., no clinical signs or symptoms suggestive of increased tendency to bleed were reported in any of the subjects. Please refer to the IB for more information.*

*In the current study, a more vulnerable population (children) will be enrolled and the acceptable limit for the thrombocyte count for study eligibility (thrombocyte count of  $\geq 100 \times 10^3/\mu\text{L}$  is acceptable) will be lower as compared to the Phase 1 studies. In addition, in order to ensure enhanced vigilance from the Investigators, clinical bleeding events (according to the Standardised MedDRA Query clinical haemorrhage) within 7 days after vaccination at Day 0 will be recorded and reported as AEs of specific interest (clinical symptoms of thrombocytopenia).*

*(Amended 06 May 2015.)*

**9.2. Events or outcomes not qualifying as adverse events or serious adverse events (pregnancy)**

Female subjects who become pregnant after completion of study vaccination may continue the study at the discretion of the Investigator.

Female subjects who are pregnant at the time of the vaccination at Month 6 must not be vaccinated, but may continue other study procedures at the discretion of the Investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on an electronic pregnancy form in eSource.

The following should always be considered as SAE:

- Spontaneous pregnancy loss, including:
  - Spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation).
  - Ectopic and molar pregnancy.
  - Stillbirth (intrauterine death of foetus after 22 weeks of gestation).



Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognised that national regulations might be different.

- Any early neonatal death (*i.e.*, death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the Investigator to be reasonably related to the investigational vaccine will be reported. While the Investigator is not obligated to actively seek this information from former study participants, he/ she may learn of a pregnancy through spontaneous reporting.

### **9.3. Detecting and recording adverse events, serious adverse events and pregnancies**

#### **9.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies**

An overview of the protocol-required reporting periods for AEs, SAEs and pregnancies is given in [Table 18](#).

#### **Adverse events**

All AEs starting in the 30-day follow-up period following administration of each dose of study vaccine must be recorded into the appropriate section of eSource, irrespective of intensity or whether or not they are considered vaccination-related.

#### ***Adverse events of specific interest***

***All AEs of specific interest (clinical symptoms of thrombocytopenia) starting in the 7-day follow-up period following vaccination at Day 0 must be recorded in the appropriate section of eSource.***

***(Amended 06 May 2015.)***

#### **Serious adverse events**

The time period for collecting and recording SAEs will begin at study vaccination at Day 0 and will end at study conclusion for each subject.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (*i.e.*, protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/ vaccine will be collected and recorded from the

time the subject's parent(s)/ LAR(s) consents to participation of the subject in the study until she/he is discharged from the study.

See [Section 9.4](#) for instruction on reporting SAEs.

### Pregnancies

The time period for collecting and recording pregnancies will begin at study vaccination and will end at the Month 6 + 30 days visit. See [Section 9.4](#) for instruction on reporting pregnancies.

**Table 18 Reporting periods for collecting safety information (Amended 06 May 2015)**

Event Timepoint	Scree- ning*	Vacc D0	end 7-day follow-up D6	end 30-day follow-up D29	Vacc M6	end 7-day follow-up M6 + 6 days	end 30-day follow-up M6 + 29 days	Study Conclusion M12
Solicited local and general AEs								
Unsolicited AEs								
<i><b>AEs of specific interest (clinical symptoms of thrombocyto- penia)</b></i>								
SAEs								
SAEs related to study participation or concurrent GSK medication/vaccine								
Pregnancies								

**AE** = adverse event; **D** = Day, **GSK** = GlaxoSmithKline; **M** = Month; **SAE** = serious adverse event; **Vacc** = vaccination

\* i.e., consent obtained.

### 9.3.2. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 18. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the

event reasonably related to the investigational vaccine, the Investigator will promptly notify the Study Contact for Reporting SAEs.

### **9.3.3. Evaluation of adverse events and serious adverse events**

#### **9.3.3.1. Active questioning to detect adverse events and serious adverse events**

As a consistent method of collecting AEs, the subject and/ or the subject's parent(s)/ LAR(s) should be asked a non-leading question such as:

*'Have you felt different in any way since receiving the vaccine or since the previous visit?'**'Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?'*

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) relative to the event. The Investigator will then record all relevant information regarding an AE/ SAE in eSource. The Investigator is not allowed to send photocopies of the subject's medical records instead of appropriately completing in eSource. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission.

The Investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/ symptoms.

**9.3.3.2. Assessment of adverse events****9.3.3.2.1. Assessment of intensity**

The intensity of the following solicited AEs will be assessed as described below.

**Table 19 Intensity scales for solicited symptoms in infants/toddlers and children less than 6 years of age (*Amended 06 May 2015*)**

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Redness * at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever **		Record temperature in °C/°F
Irritability/Fussiness	0	Behaviour as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behaviour as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all

\* In case it is not possible to determine the extent of redness on darkly pigmented skin, it will be reported as uninterpretable on the Diary Card and in eSource.

\*\* Fever is defined as temperature  $\geq 37.5^{\circ}\text{C}$  /  $99.5^{\circ}\text{F}$ . Body temperature *may* be measured axillary (*preferred*), *oral tympanic*, or *rectal*.

**Table 20 Intensity scales for solicited symptoms in children of 6 years of age or more (Amended 06 May 2015)**

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness * at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever **		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

\* In case it is not possible to determine the extent of redness on darkly pigmented skin, it will be reported as uninterpretable on the Diary Card and in eSource.

\*\* Fever is defined as temperature  $\geq 37.5^{\circ}\text{C}$  /  $99.5^{\circ}\text{F}$ . Body temperature *may* be measured axillary (*preferred*), *oral tympanic*, or *rectal*.

The maximum intensity of local injection site redness/swelling will be scored as follows:

1. Children 1 to 5 years of age:

0	:	None
1	:	> 0 mm to $\leq 10$ mm
2	:	> 10 mm to $\leq 30$ mm
3	:	> 30 mm

2. Children 6 to 12 years of age:

0	:	None
1	:	> 0 mm to $\leq 20$ mm
2	:	> 20 mm to $\leq 50$ mm
3	:	> 50 mm

## 3. Children 13 to 17 years of age:

0	:	$\leq 20$ mm
1	:	$> 20$ mm to $\leq 50$ mm
2	:	$> 50$ mm to $\leq 100$ mm
3	:	$> 100$ mm

The maximum intensity of fever will be scored as follows:

0	:	$< 37.5$ °C
1	:	$\geq 37.5$ °C to $\leq 38.5$ °C
2	:	$> 38.5$ °C to $\leq 39.5$ °C
3	:	$> 39.5$ °C

The Investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the Investigator's clinical judgement.

The intensity should be assigned to one of the following categories:

- |              |   |  |
|--------------|---|--|
| 1 (mild)     | = | An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.   |
| 2 (moderate) | = | An AE which is sufficiently discomforting to interfere with normal everyday activities.  |
| 3 (severe)   | = | An AE which prevents normal, everyday activities. In a young child, such an AE would, for example, prevent attendance at school/ kindergarten/ a day-care centre and would cause the parent(s)/ LAR(s) to seek medical advice. In an older child, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy. |

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in [Section 9.1.2](#).

#### **9.3.3.2.2. Assessment of causality**

The Investigator is obligated to assess the relationship between the study vaccination and the occurrence of each AE/ SAE. The Investigator will use clinical judgement to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccine will be considered and investigated.

There may be situations when a SAE has occurred and the Investigator has minimal information to include in the initial report to the CRO (Quintiles). However, it is very important that the Investigator always makes an assessment of causality for every event prior to submission of the electronic AE/ SAE form (eSource) to the CRO (Quintiles). The Investigator may change his/ her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccine administered. The Investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the Investigator using the following question:

*Is there a reasonable possibility that the AE may have been caused by the study vaccine?*

- YES : There is a reasonable possibility that the study vaccine contributed to the AE.
- NO : There is no reasonable possibility that the AE is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as ‘serious’ (see [Section 9.1.2](#)), additional examinations/tests will be performed by the Investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (specify).

#### **9.3.3.3. Assessment of outcomes**

The Investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.

- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

#### **9.3.3.4. Medically attended visits**

For each solicited and unsolicited symptom the subject experiences, the subject/ subject's parent(s)/ LAR(s) will be asked if he/she received medical attention defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in eSource.

### **9.4. Reporting of serious adverse events, pregnancies, and other events**

#### **9.4.1. Prompt reporting of adverse events of specific interest (*clinical symptoms of thrombocytopenia*), serious adverse events, and pregnancies to the contracted research organisation (Quintiles) (Amended 06 May 2015)**

*Adverse events of specific interest (clinical symptoms of thrombocytopenia) that occur in the time period defined in [Section 9.3.1](#) will be reported promptly to the CRO (Quintiles) within the timeframes described in [Table 21](#), once the Investigator becomes aware of the event.*

*(Amended 06 May 2015.)*

SAEs that occur in the time period defined in [Section 9.3](#) will be reported promptly to the CRO (Quintiles) within the timeframes described in [Table 21](#), once the Investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in [Section 9.3](#) will be reported promptly to the CRO (Quintiles) within the timeframes described in [Table 21](#), once the Investigator becomes aware of the pregnancy.



**Table 21** Timeframes for submitting *adverse events of specific interest (clinical symptoms of thrombocytopenia)*, serious adverse events, and pregnancies to the contracted research organisation (Quintiles) (Amended 06 May 2015)

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
<i>AEs of specific interest (clinical symptoms of thrombocytopenia)</i>	24 hours*	electronic AE/ SAE form in eSource	24 hours*	electronic AE/ SAE form in eSource
SAEs	24 hours*, ‡	electronic AE/ SAE form in eSource	24 hours*	electronic AE/ SAE form in eSource
Pregnancies	2 weeks*	electronic pregnancy form in eSource	2 weeks*	electronic pregnancy form in eSource

AE = adverse event; SAE = serious adverse event

\* Timeframe allowed after receipt or awareness of the information.

‡ The Investigator will **always provide an assessment of causality** within 24 hours of submission of the SAE.

**9.4.2. Contact information for reporting *adverse events of specific interest (clinical symptoms of thrombocytopenia)*, serious adverse events, and pregnancies (Amended 06 May 2015)**

Study Contact for Reporting <i>AEs of specific interest</i> , SAEs, and pregnancies
Primary method of reporting is via eSource.
If eSource is not available, please refer to SAE/ Pregnancy back-up reporting instructions in the Investigator binder.
Back-up Study Contact for Reporting <i>AEs of specific interest</i> , SAEs, and pregnancies
24/24 hour and 7/7 day availability:
Quintiles Lifecycle Safety
Email : PPD [REDACTED]
Phone : PPD [REDACTED]
Fax : PPD [REDACTED]

**9.4.3. Reporting of adverse events of specific interest (clinical symptoms of thrombocytopenia) to the contract research organisation (Quintiles) (Amended 06 May 2015)**

Once an Investigator becomes aware that an AE of specific interest (clinical symptoms of thrombocytopenia) has occurred in a study subject, the Investigator (or designate) must complete the information in the electronic AE/ SAE form in eSource WITHIN 24 HOURS. The AE and SAE form in eSource is the same form. When an AE of specific interest (clinical symptoms of thrombocytopenia) is indicated on the electronic AE/ SAE form, additional follow-up questions will become available, for completion by the Investigator (or designee). The report will always be completed as thoroughly as

*possible with all available details of the event. Even if the Investigator does not have all information regarding an AE of specific interest (clinical symptoms of thrombocytopenia), the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.*

*The Investigator will always provide an assessment of causality at the time of the initial report.*

*Refer to Section 9.4.4.1 for the back-up system in case the electronic reporting system does not work.*

#### **9.4.4. Completion and transmission of serious adverse events reports to the contracted research organisation (Quintiles)**

Once an Investigator becomes aware that a SAE has occurred in a study subject, the Investigator (or designate) must complete the information in the electronic AE/ SAE form in eSource WITHIN 24 HOURS. The AE and the SAE form in eSource is the same form. When the user indicates that an AE meets the definition of 'serious', the rest of the form related to SAE information unlocks and the user is required to enter the SAE information. The report will always be completed as thoroughly as possible with all available details of the event. Even if the Investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The Investigator will always provide an assessment of causality within **24** hours of submission of the SAE.

*(Amended 06 May 2015.)*

##### **9.4.4.1. Back-up system in case the electronic reporting system does not work**

If the electronic reporting system does not work, the Investigator (or designate) must complete, then date and sign a paper *AE of specific interest (clinical symptoms of thrombocytopenia)*/ SAE form and fax it to the Back-up Study Contact for Reporting SAEs within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the Investigator (or designate) must complete the electronic AE/ *AE of specific interest (clinical symptoms of thrombocytopenia)*/ SAE form in eSource within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic *AE of specific interest (clinical symptoms of thrombocytopenia)*/ SAE reporting system.

*(Amended 06 May 2015.)*

**9.4.5. Completion and transmission of pregnancy reports to the contracted research organisation (Quintiles)**

Once the Investigator becomes aware that a subject is pregnant, the Investigator (or designate) must complete the required information onto the electronic pregnancy form in eSource WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

**9.4.6. Updating of adverse events of specific interest (clinical symptoms of thrombocytopenia), serious adverse events, and pregnancy information after removal of write access to the subject's eSource (Amended 06 May 2015)**

When additional *AE of specific interest (clinical symptoms of thrombocytopenia)*, SAE, or pregnancy information is received after removal of the write access to the subject's eSource, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the Investigator. The updated report should be faxed to the Back-up Study Contact for Reporting *AE of specific interest (clinical symptoms of thrombocytopenia)*, SAEs, and pregnancy information within the designated reporting time frames specified in [Table 21](#).

*(Amended 06 May 2015.)*

**9.4.7. Regulatory reporting requirements for serious adverse events**

The Investigator will promptly report all SAEs to the CRO (Quintiles) in accordance with the procedures detailed in [Section 9.4.1](#). The sponsor (GSK Biologicals) has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the Investigator to the Study Contact/ Back-up Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the CRO's (Quintiles) policy and are forwarded to Investigators as necessary. An Investigator safety report is prepared for an SAE that is both attributable to the Investigational vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

## **9.5. Follow-up of adverse events, serious adverse events, and pregnancies**

### **9.5.1. Follow-up of adverse events and serious adverse events**

#### **9.5.1.1. Follow-up during the study**

After the initial AE/ *AE of specific interest (clinical symptoms of thrombocytopenia)*/ SAE report, the Investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to the CRO (Quintiles) (within 24 hours for *AEs of specific interest (clinical symptoms of thrombocytopenia)* and SAEs; refer to [Table 21](#)).

All *AEs of specific interest (clinical symptoms of thrombocytopenia)* and SAEs documented at a previous visit/ contact and designated as not recovered/ not resolved or recovering/ resolving will be reviewed at subsequent visits/ contacts until the end of the study.

All AEs documented at a previous visit/ contact and designated as not recovered/ not resolved or recovering/resolving will be reviewed at subsequent visits/ contacts until 30 days after the last vaccination.

*(Amended 06 May 2015.)*

#### **9.5.1.2. Follow-up after the subject is discharged from the study**

The Investigator will follow subjects with *AEs of specific interest (clinical symptoms of thrombocytopenia)* and SAEs until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the Investigator receives additional relevant information on a previously reported *AE of specific interest (clinical symptoms of thrombocytopenia)* or SAE, he/ she will provide this information to the CRO (Quintiles) using an electronic AE/ *AE of specific interest (clinical symptoms of thrombocytopenia)*/ SAE form in eSource.

The sponsor (GSK Biologicals) may request that the Investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the *AE of specific interest (clinical symptoms of thrombocytopenia)* or SAE. The Investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, the CRO (Quintiles) will be provided with any available post-mortem findings, including histopathology.

*(Amended 06 May 2015.)*

### **9.5.2. Follow-up of pregnancies**

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother

and child will be forwarded to the CRO (Quintiles) using the electronic pregnancy form and the electronic AE/ SAE form, both in eSource, if applicable. Generally, the follow-up period doesn't need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

## **9.6. Treatment of adverse events**

Treatment of any AE is at the sole discretion of the Investigator and according to local standard of care. Any medication administered for the treatment of an SAE should be recorded in the subject's eSource (refer to [Section 6.7](#)).

## **9.7. Unblinding**

GSK Biologicals' policy (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the investigational vaccine, prior to regulatory reporting. The Investigator is responsible for unblinding the treatment assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to [Section 9.4.1](#)).

## **9.8. Emergency unblinding**

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the treatment is essential for the clinical management or welfare of the subject, as judged by the Investigator.

The emergency unblinding process consists of the automated system IWRS/ IVRS that allows the Investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

The Investigator has the option of contacting the CRO's (Quintiles) Medical Expert if he/ she needs medical advice or needs the support of the CRO prior to performing the unblinding.

Any emergency unblinding must be recorded in IWRS/ IVRS and eSource by the Investigator within 24 hours.

## **9.9. Subject card**

Study subjects and/ or subjects' parent(s)/LAR(s) must be provided with the address and telephone number of the main contact for information about the clinical study.

The Investigator (or designate) must therefore provide a "Subject Card" to each subject/ subjects' parent(s) /LAR(s). In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the Investigator.

Subjects/ subjects' parent(s)/ LAR(s) must be instructed to keep Subject Cards in their possession at all times.

#### **9.10. Safety monitoring by the independent data monitoring committee**

An IDMC will be appointed to monitor the safety and tolerability of the investigational ChAd3-EBO-Z vaccine. The IDMC will consist of clinical experts and a statistician who are not involved in the conduct of the study.

The IDMC will review, in an unblinded manner, safety and reactogenicity data from the current study, and from the study EBOLA Z CHAD3-005, which will be conducted in parallel with the current study. In the study EBOLA Z CHAD3-005, the safety, reactogenicity and immunogenicity of the investigational ChAd3-EBO-Z vaccine will be assessed when administered to adults. Recommendations will be provided to the sponsor following each IDMC meeting.

Unblinded IDMC reports including all available safety and reactogenicity data will be produced by an independent statistician according to an agreed pre-defined Report and Analysis Plan. All data provided to the IDMC that will monitor the data from the above described Phase 2 studies, will also be made available to the IDMC that will be set up to monitor data from the Phase 3 programme with the investigational ChAd3-EBO-Z vaccine.

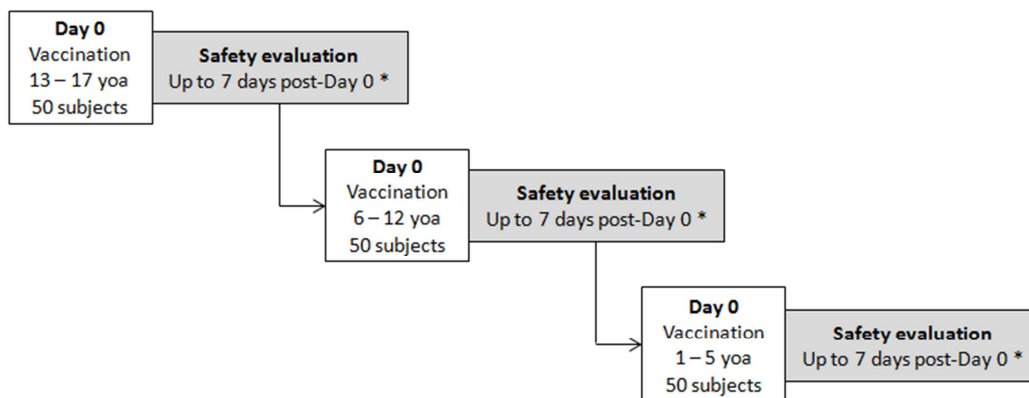
If, during an IDMC meeting, any safety concern is raised, continuation of vaccination and the start of vaccination of subjects in the younger age stratum (if applicable) will be put on hold. Vaccination will only resume, and age de-escalation will only proceed if GSK Biologicals agrees to it, following discussions with the IDMC. All IECs/ IRBs will be notified as applicable.

Refer to the IDMC Charter for more information.

#### **Staggered design and IDMC meetings**

No safety concerns have been raised from vaccination with different dosages of the investigational ChAd3-EBO-Z vaccine in healthy adults in the ongoing Phase 1 studies. However, the investigational vaccine has never been administered to children yet. In order to ensure maximum safety for the subjects in this study, vaccination in the study will only start after a favourable outcome of an IDMC review of the safety and reactogenicity data from 100 adults after 1 week follow-up in the study EBOLA Z CHAD3-005. In addition, vaccination at Day 0 will be done in a staggered manner, starting with vaccination of the children in the oldest age stratum. For each age stratum, the IDMC will conduct a review of all available safety data once data is available up to at least 7 days after vaccination of at least 50 subjects (25/ group) in that age stratum. In order to proceed to vaccination of the subjects in the younger age stratum (6 to 12 years of age), possibly with a lower vaccine dose, a favourable outcome of the IDMC review of safety data up to at least 7 days after vaccination from at least 50 subjects (25/ group) in the oldest age stratum needs to be obtained. The same will be done for moving from the 6 to 12 years of age stratum to vaccination of the youngest children (1 to 5 years of age).

**Figure 3 Overview of staggered design and independent data monitoring committee (IDMC) safety evaluations**



\* Safety evaluation on all available safety data from the entire study, which will include the safety data up to 7 days after vaccination at Day 0 from at least 50 subjects (25 subjects/ group) in the respective age stratum.

### Holding rules

During the IDMC meetings depicted in Figure 3, study holding rules will be assessed. If any of these holding rules are met (or if any other safety concern is raised), vaccination will be put on hold.

The holding rules will be assessed per age stratum and the frequency of events described in the holding rules apply to the Group EBO-Z/ MENACWY-TT only.

- Solicited local AEs:
  - More than 30% of doses are followed by Grade 3 solicited local AE beginning within 7 days after vaccination (day of vaccination and 6 subsequent days) and persisting at Grade 3 for > 2 consecutive days.
- Solicited general AEs:
  - More than 30% of doses are followed by any Grade 3 solicited general AE considered to be related to vaccination beginning within 7 days after vaccination (day of vaccination and 6 subsequent days) and persisting at Grade 3 for > 2 consecutive days.
  - More than 30% of doses are followed by Grade 3 fever considered to be related to vaccination beginning within 7 days after vaccination (day of vaccination and 6 subsequent days) and persisting at Grade 3 for > 2 consecutive days.
- Unsolicited AEs:
  - More than 30% of subjects develop any Grade 3 unsolicited AE considered to be related to vaccination and persisting at Grade 3 for > 2 consecutive days.
  - An SAE considered related to vaccination.



**Other IDMC meetings**

In addition to the IDMC meeting that will be held before the first vaccination and the meetings depicted in [Figure 3](#), the following IDMC evaluations will take place:

- IDMC review of all safety and reactogenicity data included in the interim analysis that will be conducted when data is available from all subjects up to 30 days after vaccination at Day 0 (refer to [Section 11.11.2](#) for more information on this interim analysis).
- An *ad hoc* IDMC meeting will be held in case of an SAE considered related to vaccination at any time during the study.
- *Ad hoc* IDMC meetings may be held if any safety concern is raised.

**10. SUBJECT COMPLETION AND WITHDRAWAL****10.1. Subject completion**

A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

**10.2. Subject withdrawal**

Withdrawals will not be replaced.

**10.2.1. Subject withdrawal from the study**

From an analysis perspective, a ‘withdrawal’ from the study refers to any subject who did not come back for the concluding visit foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a ‘withdrawal’ from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in eSource. The Investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself, by the subject’s parent(s)/LAR(s), or by the Investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious AE.
- Protocol violation (specify).
- Consent withdrawal, not due to an AE\*.



- Moved from the study area.
- Lost to follow-up.
- Other (specify).

\*In case a subject is withdrawn from the study because he/she/ the subject's parent(s)/LAR(s) has withdrawn consent, the Investigator will document the reason for withdrawal of consent, if specified by the subject/ subject's parent(s)/LAR(s) in eSource.

Subjects who are withdrawn from the study because of SAEs/ AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see [Section 9.5.1.2](#)).

### **10.3. Extension study**

At the end of the study (study conclusion visit), the Investigator will ask each subject/ subject's parent(s)/ LAR(s) if they are interested to participate/ to allow the subject to participate in a booster study/long-term follow-up study. If a subject/ subject's parent(s)/ LAR(s) is/ are not interested in participating/ allowing subject participation in the booster study/ long-term study, the reason for refusal will be documented in eSource.

### **10.4. Screen failures**

Screen failures are defined as subjects who are withdrawn from the study after giving informed consent, but who do not meet the inclusion and exclusion criteria.

The following information will be collected for screen failures:

- Informed consent.
- Inclusion/ exclusion criteria.
- Demographic data.
- Any SAEs related to study participation, to concomitant use of GSK products, or any fatal SAEs.
- Screening conclusion.

## **11. STATISTICAL METHODS**

### **11.1. Primary endpoints**

- Occurrence of each solicited local and general AE, during a 7-day follow-up period after each vaccination in all subjects, in both groups.
- Occurrence of any unsolicited AE, during a 30-day follow-up period after each vaccination (*i.e.*, the day of vaccination and 29 subsequent days), in all subjects, in both groups.

- Occurrence of haematological (CBC, including differential count and platelet count) and biochemical (ALT, creatinine) laboratory abnormalities at Screening, Day 3, Day 6, Day 30, Month 6, Month 6 + 6 days, Month 6 + 30 days and Month 12 in all subjects in both groups.
- ***Occurrence of clinical symptoms of thrombocytopenia (AE of specific interest), during a 7-day follow-up period after vaccination at Day 0 (i.e., Day 0 up to Day 6), in all subjects, in both groups.***  
***(Amended 06 May 2015.)***
- Occurrence of any SAE, in all subjects, in both groups.

### 11.2. Secondary endpoint

- Anti-GP EBOV antibody titres, as measured by enzyme-linked immunosorbent assay (ELISA):
  - At Day 0 and Day 30, in all subjects, in both groups.
  - At Month 6 and Month 6 + 30 days, in all subjects, in the Group MENACWY-TT/ EBO-Z.

### 11.3. Tertiary endpoints

- Anti-GP EBOV antibody titres, as measured by ELISA:
  - At Month 6 and Month 6 + 30 days, in all subjects, in the Group EBO-Z/ MENACWY-TT.
  - At Month 12, in all subjects, in both groups.
- Magnitude, responder rate and cytokine co-expression profile of ChAd3-EBO-Z-specific CD4<sup>+</sup> or CD8<sup>+</sup> T-cell responses, as assessed by intracellular cytokine staining (ICS) after stimulation with EBOV GP antigens:
  - At Day 0, Day 30, Month 6, Month 6 + 30 days and Month 12, in a sub-cohort of 30 subjects per age stratum, per group.
- ChAd3 neutralising antibody titres, as measured by a neutralisation assay:
  - At Day 0, Day 30, Month 6, and Month 6 + 30 days, in a subset of 30 subjects per age stratum, per group.

### 11.4. Determination of sample size

The primary objective of this study is to assess the safety of the investigational ChAd3-EBO-Z vaccine.

Considering the target sample size of approximately 300 subjects to be enrolled in the Group EBO-Z/ MENACWY-TT and approximately 300 subjects to be enrolled in the Group MENACWY-TT/ EBO-Z, [Table 22](#) below illustrates the 95% confidence intervals (CI) for different possible observed number of AEs within a group before vaccination at Month 6 (administration of the investigational ChAd3-EBO-Z vaccine to the children in the Group MENACWY-TT/ EBO-Z).

**Table 22 95% exact confidence intervals for the true AE rate at different possible observed AE rates within a group (300 subjects)**

Observed number of adverse events	Observed adverse event proportion	95% Exact Confidence Interval	
		Lower Bound	Upper Bound
0	0.0000	0.0000	0.0122
1	0.0033	0.0001	0.0184
5	0.0167	0.0054	0.0385
15	0.0500	0.0283	0.0811
50	0.1667	0.1263	0.2138
100	0.3333	0.2802	0.3898
150	0.5000	0.4420	0.5580

Another way to present the design is to show the true rates associated with a 90% probability to observe a certain number of events (Table 23).

**Table 23 True proportions associated with a 90% probability to observe a certain number of events**

True proportion	Number of adverse events observed with > 90% probability
0.008	> 0
0.013	> 1
0.018	> 2
0.022	> 3
0.027	> 4
0.031	> 5
0.070	> 15
0.126	> 30

## 11.5. Cohorts for Analyses

### 11.5.1. Total vaccinated cohort

The total vaccinated cohort (TVC) will include all subjects with at least one vaccine administration documented:

- A safety analysis based on the TVC will include all vaccinated subjects.
- An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available.

The TVC will be performed per treatment actually administered.

### 11.5.2. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will include all evaluable subjects:

- Who meet all eligibility criteria.
- Who have received at least one dose of study vaccine according to protocol procedures and to their random assignment.
- For whom the randomisation code has not been broken for vaccination at Day 0.

- Who comply with the procedures and intervals defined in the protocol (refer to [Table 6](#)).
- Who did not receive a concomitant medication/ product/ vaccination leading to elimination from an ATP analysis as listed [Section 6.7.2](#).
- Who did not present with a medical condition leading to elimination from an ATP analysis as listed [Section 6.8](#).
- For whom data concerning immunogenicity endpoint measures are available.

## 11.6. Derived and transformed data

### Immunogenicity

- The cut-off value will be defined by the laboratory before the analysis.
- A seronegative subject is a subject whose titre is below the cut-off value.
- A seropositive subject is a subject whose titre is greater than or equal to the cut-off value.
- Seroconversion is defined as the appearance of antibodies (*i.e.*, titre greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.
- The Geometric Mean Titres (GMTs) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT calculation.
- Handling of missing data: for a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

### Reactogenicity and Safety

- Handling of missing data: subjects who missed reporting symptoms (unsolicited or concomitant medications) will be treated as subjects without symptoms (unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be reassessed to ensure more accurate reporting of study data by further analysis.
- For the analysis of solicited symptom, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only subjects/doses with documented safety data.

## 11.7. Analysis of demographics

Demographic characteristics (age at study vaccination in years, gender, and ethnicity) and withdrawal status will be summarised by group in the TVC, using descriptive statistics:

- Frequency tables will be generated for categorical variable such as centre.
- Mean, median, standard deviation will be provided for continuous data such as age.

Analyses will be performed by age stratum (1 to 5 years, 6 to 12 years, and 13 to 17 years) and overall.

### **11.8. Analysis of safety**

The analysis will be performed on the TVC.

All analyses will be descriptive. Analyses will be performed by age stratum (1 to 5 years, 6 to 12 years, 13 to 17 years) and overall.

In a first step, the safety results will be presented by treatment administered at Day 0 (ChAd3-EBO-Z vaccine [300 subjects] versus *Nimenrix* [300 subjects]). In a second step, all **available** data post-vaccination with the investigational ChAd3-EBO-Z vaccine (ChAd3-EBO-Z vaccine at Day 0 [300 subjects] and ChAd3-EBO-Z vaccine at Month 6 [300 subjects]) will be pooled (600 subjects). The latter aggregated data cannot be presented versus control because of the administration of the investigational ChAd3-EBO-Z vaccine to the children in the Group MENACWY-TT/ EBO-Z, who initially received *Nimenrix* (population overlap).

**(Amended 06 May 2015.)**

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be performed for symptoms rated as Grade 3.

The percentage of subjects reporting each individual solicited local and general AE during the solicited follow-up period will be tabulated with exact 95% CI. The same tabulation will be performed for Grade 3 AEs and for AEs with relationship to vaccination.

Duration and prevalence of fever will be presented.

The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The percentage of subjects with at least one report of unsolicited AE classified by the MedDRA and reported up to 29 days after vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for Grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination.

At each haematology/ biochemistry sampling time point, by study group, individual haematological and biochemical values will be presented as number of subjects out of range (above and below normal range) and tabulated by toxicity grading (refer to [APPENDIX C](#)). In addition, changes from baseline (median/ interquartile range) will be presented.

SAEs *and AEs of specific interest (clinical symptoms of thrombocytopenia)* will be described in detail.

*(Amended 06 May 2015.)*

### **11.9. Analysis of immunogenicity**

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. If, in any study group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC will be performed to complement the ATP analysis.

All analyses will be descriptive. Analyses will be performed by age stratum (1 to 5 years, 6 to 12 years, 13 to 17 years) and overall.

In a first step, the immunogenicity results will be presented by treatment administered at Day 0 (ChAd3-EBO-Z vaccine [300 subjects] versus *Nimenrix* [300 subjects]). In a second step, all data post-vaccination with the investigational ChAd3-EBO-Z vaccine (ChAd3-EBO-Z vaccine at Day 0 [300 subjects] and ChAd3-EBO-Z vaccine at Month 6 [300 subjects]) will be pooled (600 subjects). The latter aggregated data cannot be presented versus control because of the administration of the investigational ChAd3-EBO-Z vaccine to the children in the Group MENACWY-TT/ EBO-Z, who initially received *Nimenrix* (population overlap).

#### **Humoral immune response**

For each study group, each antigen, at each timepoint where a blood sample result is available:

- Seropositivity rates (with exact 95% CI) will be calculated by group.
- GMTs with 95% CI will be tabulated.
- Vaccine responses to the antigen (with exact 95% CI) will be calculated.
- Reverse cumulative distribution curves will display antibody titres distributions

The same analyses will be done by baseline anti-GP EBOV serological status.

#### **Cell-mediated immune response**

For each study group, at each timepoint where a blood sample result is available, the frequency of specific CD4<sup>+</sup>/ CD8<sup>+</sup> T-cells will be summarised (descriptive statistics).

If numbers allow, the same analysis will be done by baseline anti-GP EBOV serological status.

### **11.10. Interpretation of analyses**

Comparative analyses will be descriptive with the aim to characterise the difference in reactogenicity/ safety/ immunogenicity between groups.

## 11.11. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

### 11.11.1. Sequence of analyses

All analyses (including the interim analysis) will be conducted on data as clean as possible.

The analyses will be performed stepwise:

- Analyses of safety and reactogenicity data will be performed for the IDMC. Access to individual treatment codes will be restricted to the IDMC support statistician in charge of the analyses and IDMC members.
- An interim analysis will be performed when safety, reactogenicity and immunogenicity (including at least anti-GP EBOV data at Day 30) data from all subjects are available up to 30 days after vaccination at Day 0.
- A final analysis of all data will be performed when all data up to study conclusion are available.

### 11.11.2. Statistical considerations for interim analyses

In order to obtain early data on the investigational ChAd3-EBO-Z vaccine, an interim analysis will be performed when safety, reactogenicity and immunogenicity (including at least anti-GP EBOV data at Day 30) data is available from all subjects up to 30 days after vaccination at Day 0. The interim analysis will be conducted on all safety, reactogenicity and immunogenicity data available at that time. This analysis will present a descriptive summary of safety, reactogenicity and immunogenicity. As the study does not include any confirmatory objective, no statistical adjustment will be made.

## 12. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

### 12.1. Electronic case report form instructions (eSource)

The data collection method used will be electronic source data collection, where the Investigator collects all source data electronically using a tablet device. Edit checks are run at the time of data capture and the data are stored in the source database. Automatic transfer of the study data fields will occur from the source database into the study database at the CRO. This method of data capture eliminates the need for site staff to transcribe data into a case report form from the source data, and therefore eliminates the need for on-site checking of the case report form data against the source data to identify transcription errors.

In all cases, subject initials will be collected *in eSource, but will not be* transmitted to GSK. Subject data necessary for analysis and reporting will be entered/ transmitted into a

validated database or data system. Clinical data management will be performed in accordance with applicable CRO standards and data cleaning procedures.

While completed eSource forms are reviewed by a CRO Site Monitor, omissions or inconsistencies detected by subsequent eSource review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the Investigator or appropriately qualified designee. In all cases, the Investigator remains accountable for the study data.

*(Amended 06 May 2015.)*

The Investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

Refer to the SureSource completion Manual for more information on completion of eSource.

## **12.2. Study monitoring by the contracted research organisation**

The CRO Site Monitor will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The Investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eSource review.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the Investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

## **12.3. Record retention**

Following closure of the study, the Investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (*i.e.*, audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format



other than hard copy (*i.e.*, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the Investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the Investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures.

The Investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the Investigator leaves the site.

#### **12.4. Quality assurance**

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

#### **12.5. Posting of information on publicly available clinical trial registers and publication policy**

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

Summaries of the results of GSK interventional studies (Phase 1 to 4) are posted on publicly available results registers within 6 months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit. At the time of publication, this protocol will be fully disclosed.

#### **12.6. Provision of study results to Investigators**

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study subjects, as appropriate.

### 13. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

### 14. REFERENCES

Afolabi, Muhammed, Adetifa, *et al.* Heterologous prime-boost vaccination with candidate malaria vaccines ChAd63 ME-TRAP and MVA.ME-TRAP is safe and highly immunogenic for effector T-cell induction in healthy Gambian infants. *61<sup>st</sup> Annual Meeting of the American Society of Tropical Medicine and Hygiene (ASTMH) (Atlanta, GA; USA)*. 2012.

Anderson MS, Glode MP, Smith AL. Meningococcal disease. In: Feigin RD, Cherry JD, editor. *Textbook of Pediatric Infectious Diseases*. Philadelphia:WB Saunders, 1998: 1143-1156.

Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (CDC MACDP) guidelines. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies;  
<http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf>

Colloca S, Barnes E, Folgori A, *et al.* Vaccine vectors derived from a large collection of simian adenoviruses induce potent cellular immunity across multiple species. *Sci Transl Med*. 2012; 4: 115ra2.

Connolly M, Noah N. Is group C meningococcal disease increasing in Europe? A report of surveillance of meningococcal infection in Europe 1993-6. *Epidemiol Infect*. 1999; 122: 41-49.

EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data (Doc. Ref. EMEA/CHMP/313666/2005 ) ‘adopted at Community level in May 2006);  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/11/WC500011303.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf). Last accessed 08 October 2014.

Feldmann H and Geisbert TW. Ebola haemorrhagic fever. *Lancet*. 2011; 377: 849-62.

Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine*. 2009; 27S: B51-B63.

Kagina BM, Tameris MD, Geldenhuys H, *et al.* The novel tuberculosis vaccine, AERAS-402, is safe in healthy infants previously vaccinated with BCG, and induces dose-dependent CD4 and CD8T cell responses. *Vaccine*. 2014; 32: 5908-17.

- McElroy AK, Erickson BR, Flietstra TD, *et al.* Biomarker correlates of survival in pediatric patients with ebola virus disease. *Emerg Infect Dis.* 2014 ; 20.
- Ogwang C, Afolabi M, Kimani D, *et al.* Safety and immunogenicity of heterologous prime-boost immunisation with Plasmodium falciparum malaria candidate vaccines, ChAd63 ME-TRAP and MVA ME-TRAP, in healthy Gambian and Kenyan adults. *PloS One.* 2013; 8: e57726.
- O'Hara GA, Duncan CJ, Ewer KJ, *et al.* Clinical assessment of a recombinant simian adenovirus ChAd63: a potent new vaccine vector. *J Infect Dis.* 2012; 205: 772-81.
- Paris R, Kuschner RA, Binn L, *et al.* Adenovirus type 4 and 7 vaccination or adenovirus type 4 respiratory infection elicits minimal cross-reactive antibody responses to nonhuman adenovirus vaccine vectors. *Clin Vaccine Immunol.* 2014; 21: 783-6.
- Peltola H. Meningococcal vaccines. Current status and future possibilities. *Drugs.* 1998; 55: 347-366.
- Peruzzi D, Dharmapuri S, Cirillo A, *et al.* A novel chimpanzee serotype-based adenoviral vector as delivery tool for cancer vaccines. *Vaccine.* 2009; 27: 1293-300.
- Rüggeberg JU, Gold MS, Bayas JM, *et al.* Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine.* 2007; 25: 5675-84.
- Sprangers MC, Lakhai W, Koudstaal W, *et al.* Quantifying adenovirusneutralizing antibodies by luciferase transgene detection: addressing preexisting immunity to vaccine and gene therapy vectors. *J. Clin. Microbiol.* 2003; 41: 5046–5052.
- Stanley DA, Honko AN, Asiedu C, *et al.* Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge. *Nat Med.* 2014 Sep 7 (*epub ahead of print*).
- WHO. Ebola virus disease. Fact sheet N°103. Updated September 2014. <http://www.who.int/mediacentre/factsheets/fs103/en/>. Last accessed 09 October 2014.
- WHO. Ebola virus disease, West Africa – update. Disease outbreak news. 27 July 2014. [http://www.who.int/csr/don/2014\\_07\\_27\\_ebola/en/](http://www.who.int/csr/don/2014_07_27_ebola/en/). Last accessed 09 October 2014.
- WHO Ebola Response Team. Ebola Virus Disease in West Africa – The First 9 Months of the Epidemic and Forward Projections. *N Engl J Med.* 2014 (*Epub ahead of print*).

## APPENDIX A    LABORATORY ASSAYS

### Anti-EBOV GP IgG ELISA

Blood samples for antibody determination will be collected at indicated timepoints and serum will be separated and frozen at  $-20^{\circ}\text{C}$ .

Antibody level will be determined by evaluating antibody (IgG) responses specific for Zaire Ebola Virus Glycoprotein (EBOV GP) using the ELISA developed by Battelle and JVAP/USAMRIID and transferred to Quest (Focus) laboratory.

Briefly, microtiter plates are coated with the purified recombinant Zaire GP (rGP) specific to the Kikwit-95 strain (the Non-Human Primates (NHP) challenge strain). This strain is 98.5% identical to the vaccine Mayinga EBOV strain (11 aa mismatched) and is 97.5% identical to the isolated Guinea 2014 virus strain (17 aa mismatched). Serial diluted test samples, 2 serial-diluted controls (one QC-high and one QC-low) and a negative sample control (composed of pooled normal human serum purchased from a commercial source) are allowed to incubate in the GP coated wells allowing GP specific antibodies to bind. Additionally, a two-fold serial diluted reference standard, obtained from a vaccinated donor, is included in duplicate. Each well is then incubated with goat anti-human IgG horseradish peroxidase conjugate (HRP). TMB substrate is added to each well and the enzymatic reaction is stopped with a sulfuric acid solution. The color change is then read in a plate reader and sample titers are based on the standard curve calculated using a 4 parameter logistic curve fit. Results are reported in ELISA units/ml (EU/ml). A 2<sup>nd</sup> generation human standard (microgram/mL) will be evaluated and bridged to the current standard.

This assay will be qualified at Quest Diagnostics laboratories before starting the clinical testings.

### ChAd3-EBO-Z specific CD4<sup>+</sup> or CD8<sup>+</sup> T-cells

T-cell response will be measured by ICS. In brief, peripheral blood mononuclear cells (PBMCs) are prepared by standard Ficoll-Paque Plus centrifugation and stored frozen in heat-inactivated foetal calf serum containing 10% dimethylsulfoxide. *In vitro* re-stimulation of the PBMCs is performed using a pool of peptides corresponding to the open reading frames of the vaccine GP insert. CD4<sup>+</sup> and CD8<sup>+</sup> T-cells expressing immune markers such as IFN- $\gamma$  and/or TNF- $\alpha$  and/or IL-2 are detected by flow cytometry. The method has been qualified at NVITAL laboratories.

### ChAd3 neutralising antibodies

In the process of evaluation of the pre-existing or vaccine-induced antibody response against ChAd3, it is of interest to quantify the neutralising antibody concentrations. Neutralising antibodies are antibodies with a capacity to block functional epitopes on the adenovirus, thereby blocking the entry of the virus to the target cells.

This method utilizes serotype-specific, replication incompetent adenovirus, which has an inserted luciferase reporter gene, as described [Paris, 2014; Sprangers, 2003]. Briefly, A549 human lung carcinoma cells are plated in 96-well plates and infected with E1-deleted replication-incompetent rAd-luciferase reporter construct. For each sample, a

total of seven 2-fold serial dilutions are tested in triplicate. Following a 24-hour incubation, the luciferase activity in the cells is measured using the Steady-Glo luciferase reagent system (Promega). 90% neutralisation titres are defined as the maximum serum dilution that neutralised 90% of luciferase activity. GMTs are calculated at pre- and/or post-vaccination and a positive response is defined as any increase in ChAd3 post-vaccination. The exceptions are those with pre-vaccination titres at the upper limit of quantitation (8748). The assay has been qualified for Ad5 and adapted for ChAd3 at NVITAL laboratories.

**APPENDIX B      CLINICAL LABORATORIES (*Amended*  
*06 May 2015*)****Table 24      Outsourced laboratories**

<b>Laboratory</b>	<b>Address</b>
NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL)	Suite 150 9 West Watkins Mill Road Gaithersburg, MD 20878 <b><i>United States</i></b>
Quest Diagnostics	Focus Diagnostics Clinical Trials, Inc. (d/b/a Quest Diagnostics) 33608 Ortega Highway San Juan Capistrano, CA 92675-2042, United States

## APPENDIX C ACCEPTABLE LIMITS FOR ELIGIBILITY AND TOXICITY GRADING SCALES FOR HAEMATOLOGY/ BIOCHEMISTRY PARAMETERS (*Amended 06 May 2015*)

ADULTS AND ADOLESCENTS > 12 YEARS OLD

Table 25 outlines the acceptable limits for eligibility when considering laboratory Screening values.

**Table 25 Acceptable limits/normal ranges for eligibility determination (*Amended 06 May 2015*)**

Haemoglobin (g/dL)	≥ 11 (males) or ≥ 9.5 (females)
Platelet count (x10 <sup>3</sup> /μL)	≥ 100
Total white cell count (x10 <sup>3</sup> /μL)	≥ 2.75
Creatinine (mg/dL)	< 1.5
ALT (IU/L)	< 60 (males) or < 40 (females)

ALT = alanine aminotransferase

Blood safety results at each planned timepoint will be presented per study group according to the toxicity grading scale presented in Table 26. In addition, for haematological values, changes at post vaccination timepoints relative to baseline will be presented per study group.

**Table 26 Toxicity grading scales for hematology/ biochemistry parameters**

Test	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin, male (g/dL)	10 to 10.9	9 to 9.9	8 to 8.9	< 8
Haemoglobin, female (g/dL)	8.5 to 9.4	7.5 to 8.4	6.5 to 7.4	< 6.5
Platelets (x10 <sup>3</sup> /μL)	75 to 100	50 to 74.999	25 to 49.999	< 25
WBC – decrease (x10 <sup>3</sup> /μL)	2 to 2.749	1.50 to 1.999	1 to 1.499	<1
Creatinine (mg/dL)	1.5 to 1.7	> 1.7 to 2	> 2.0 to 2.5	> 2.5
ALT increase by factor	1.1 to 2.5xULN	> 2.5 to 5.0xULN	> 5.0 to 10xULN	> 10xULN

ALT = alanine aminotransferase; ULN = upper limit of the normal range; WBC = white blood cells

Note: acceptable limits for eligibility and grading scale adapted from Division of AIDS table for grading severity of adult and pediatric adverse events December 2004; WHO Toxicity Grading Scale for Determining Severity of Adverse Events, February 2003; Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Guidance for Industry, 2007.

**CHILDREN  $\leq$  12 YEARS OLD**

Table 27 outlines the acceptable limits for eligibility when considering laboratory Screening values.

**Table 27 Acceptable limits/normal ranges for eligibility determination**

Haemoglobin (g/dL)	$\geq 8.5$
Platelet count ( $\times 10^3/\mu\text{L}$ )	$\geq 100$
Total white cell count ( $\times 10^3/\mu\text{L}$ )	$\geq 4$
Creatinine (mg/dL)	$< 1.2$
ALT (IU/mL)	$< 60$ (males) or $< 40$ (females)

ALT = alanine aminotransferase

Blood safety results at each planned timepoint will be presented per study group according to the toxicity grading scale presented in Table 28. In addition, for haematological values, changes at post vaccination timepoints relative to baseline will be presented per study group.

**Table 28 Toxicity grading scales for hematology/ biochemistry parameters**

Test	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin (g/dL)	7.5 to 8.49	6.5 to 7.49	5 to 6.49	$< 5$
Platelets ( $\times 10^3/\mu\text{L}$ )	75 to 99.999	50 to 74.999	25 to 49.999	$< 25$
WBC ( $\times 10^3/\mu\text{L}$ )	2.5 to 3.999	1.50 to 2.499	1 to 1.499	$< 1$
Creatinine (mg/dL)	1.2 to 1.7	$> 1.7$ to 2.1	$> 2.1$ to 2.5	$> 2.5$
ALT increase by factor	1.1 to 2.5xULN	$> 2.5$ to 5.0xULN	$> 5.0$ to 10xULN	$> 10\text{xULN}$

ALT = alanine aminotransferase; ULN = upper limit of the normal range; WBC = white blood cells

Note: acceptable limits for eligibility and grading scale adapted from Division of AIDS table for grading severity of adult and paediatric adverse events December 2004; WHO Toxicity Grading Scale for Determining Severity of Adverse Events, February 2003; Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Guidance for Industry, 2007.



**APPENDIX D AMENDMENTS AND ADMINISTRATIVE  
CHANGES TO THE PROTOCOL**

<b>GlaxoSmithKline Biologicals</b>	
Vaccine Value & Health Science (VVHS)	
<b>Protocol Amendment 1</b>	
<b>eTrack study number and Abbreviated Title</b>	202090 (EBOLA Z CHAD3-004)
<b>IND number</b>	<i>To be decided</i>
<b>EudraCT number</b>	2014-004714-28
<b>Amendment number</b>	Amendment 1
<b>Amendment date</b>	29 December 2014
<b>Co-ordinating author</b>	PPD [REDACTED], Quintiles, Medical Writing
<p><b>Rationale/background for changes:</b></p> <ul style="list-style-type: none"> <li>• For robustness of safety monitoring, the GSK Biologicals' internal safety review committee (iSRC) was replaced by an independent data monitoring committee (IDMC).</li> <li>• Indicate that safety and reactogenicity data will be collected in 100 adults after 1 week of follow-up (study EBOLA Z CHAD3-005) before commencing the current study.</li> <li>• Indicate that safety and reactogenicity data obtained in the context of the age de-escalation process may lead to the selection of a lower ChAd3-EBO-Z vaccine dose in the younger age groups.</li> <li>• Clarify that informed assent will be asked from all subjects in the oldest age stratum (13 to 17 years of age) and from younger subjects as per local requirements.</li> <li>• Define grading scales for local injection site redness/ swelling per age stratum.</li> <li>• Clarify that analysis of safety will be done on the total vaccinated cohort (TVC) and that no according-to-protocol (ATP) cohort for safety will be defined.</li> <li>• Include information on the anti-GP ELISA testing (laboratory, test description).</li> </ul> <p>In addition, some minor modifications/ clarifications were made.</p>	

Amended text has been included in ***bold italics*** and deleted text in ~~striketrough~~ in the following sections:

## SYNOPSIS

### Rationale for the study and study design

- Rationale for the study

...

Although health care workers will be priority vaccination targets, mass vaccination strategies may be developed as one of the ways to protect populations and contain the epidemics. In this context, children will need to be vaccinated too. The present Phase 2, randomised, controlled trial will aim at collecting safety and immunogenicity data following a single intramuscular dose of the investigational ChAd3-EBO-Z vaccine. In parallel with the current study, the safety and immunogenicity of the investigational ChAd3-EBO-Z vaccine will be assessed in healthy adults living in countries adjacent to the current Ebola outbreak (study EBOLA Z CHAD3-005). ***Study EBOLA Z CHAD3-005 will start before the current study as to collect safety and reactogenicity data in 100 adults, after 1 week of follow-up, living in countries adjacent to the current Ebola outbreak before proceeding to vaccination of children. (Amended 29 December 2014.)***

- Rationale for the study design

- Investigational ChAd3-EBO-Z vaccine dose

Dose selection for paediatric use will be based on information derived from dose-range studies ***conducted with the ChAd3-EBO-Z vaccine candidate*** in adults and ***on*** past experience with other recombinant adenovirus-based candidate vaccines. ***(Amended 29 December 2014.)***

...

Four different investigational vaccine doses are currently being evaluated for safety, reactogenicity and immunogenicity in adults in Phase 1 studies. As for other recombinant adenovirus-based vaccine candidates which showed adequate safety upon the use of adult doses in children as explained above, ***it is currently proposed that*** the same vaccine dose as the dose selected for adults will be assessed in this study.

*However, a lower vaccine dose may be selected for children of younger age groups based on the safety and reactogenicity data accrued during the age de-escalation process.  
(Amended 29 December 2014.)*

...

- Stratification for age and staggered vaccination

...

In order to ensure maximum safety for the subjects in this study, vaccination at Day 0 will be done in a staggered manner, starting with vaccination of the children in the oldest age stratum. For each age stratum, an ~~iSRC~~ **independent data monitoring committee (IDMC)** will conduct a review of all available safety data once data is available up to at least 7 days after vaccination of at least 50 subject (25/ group) in that age stratum. ~~Continuation of vaccination and the~~ **The** start of vaccination in the younger age stratum ~~will be put on hold if any safety concerns are raised by the iSRC,~~ **possibly with a lower vaccine dose, depends on the outcome of this IDMC review. (Amended 29 December 2014.)**

## Study design

- **Staggered vaccination:** Vaccination at Day 0 will be done in a staggered manner, starting with vaccination of the children in the oldest age stratum (13 to 17 years of age). In order to proceed to vaccination of the subjects in the younger age stratum (6 to 12 years of age), **possibly with a lower vaccine dose**, a favourable outcome of the ~~iSRC~~ **IDMC** review of safety data up to at least 7 days after vaccination from at least 50 subjects (25/ group) in the oldest age stratum needs to be obtained. The same will be done for moving from the 6 to 12 years of age stratum to vaccination of the youngest children (1 to 5 years of age). **(Amended 29 December 2014.)**

...

- **Safety monitoring:** An ~~iSRC~~ **IDMC** will be appointed to monitor the safety and tolerability of the investigational ChAd3-EBO-Z vaccine. ~~The iSRC will be authorised by the GSK Biologicals' Vaccine Safety Monitoring Board (VSMB). Core members of the iSRC will include a GSK Biologicals' Safety Physician, a Clinical Research and Development Lead (CRDL) and a Biostatistician who are not otherwise involved in the conduct of the project.~~ **The IDMC will consist of clinical experts and a statistician who are not involved in the conduct of the study.**

*(Amended 29 December 2014.)*

## LIST OF ABBREVIATIONS

<del>CRDL:</del>	<del>Clinical Research and Development Lead</del>
<del>iSRC</del>	<del>Internal Safety Review Committee</del>
<del>VSMB:</del>	<del>Vaccine Safety Monitoring Board</del>

### 1.2.1 Rationale for the study

...

The study will be conducted in healthy children living in countries adjacent to the current Ebola outbreak zones. In parallel with the current study, the safety and immunogenicity of the investigational ChAd3-EBO-Z vaccine will be assessed in healthy adults living in countries adjacent to the current Ebola outbreak (study EBOLA Z CHAD3-005). ***Study EBOLA Z CHAD3-005 will start before the current study as to collect safety and reactogenicity data in 100 adults, after 1 week of follow-up, living in countries adjacent to the current Ebola outbreak before proceeding to vaccination of children. (Amended 29 December 2014.)***

#### 1.2.2.1 Investigational ChAd3-EBO-Z vaccine dose

Dose selection for paediatric use will be based on information derived from dose-range studies ***conducted with the ChAd3-EBO-Z vaccine candidate*** in adults and ***on*** past experience with other recombinant adenovirus-based candidate vaccines. ***(Amended 29 December 2014.)***

...

Four different investigational vaccine doses are currently being evaluated for safety, reactogenicity and immunogenicity in adults in Phase 1 studies. As for other recombinant adenovirus-based vaccine candidates which showed adequate safety upon the use of adult doses in children as explained above, ***it is currently proposed that*** the same vaccine dose as the dose selected for adults will be assessed in this study. ***However, a lower vaccine dose may be selected for children of younger age groups based on the safety and reactogenicity data accrued during the age de-escalation process. (Amended 29 December 2014.)***

#### 1.2.2.2 Administration of the investigational ChAd3-EBO-Z vaccine

Considering the risk of exposure to Ebola and the potential (based on animal data) for the investigational ChAd3-EBO-Z vaccine to afford at least partial protection, all children in the study will receive the investigational ChAd3 EBO-Z vaccine. The children in the

Group EBO-Z/ MENACWY-TT will receive the investigational ChAd3-EBO-Z vaccine at Day 0 of the study, whereas the children in the Group MENACWY-TT/ EBO-Z will receive *Nimenrix* at Day 0 (as a control). At Month 6, the children in the Group MENACWY-TT/ EBO-Z will receive the investigational ChAd3-EBO-Z vaccine (provided that no safety concerns are raised. Refer to Section 9.10 for more information on the ~~internal safety review committee [iSRC]~~ ***independent data monitoring committee [IDMC]***) whereas the children in the Group EBO-Z/ MENACWY-TT will receive *Nimenrix*. ***(Amended 29 December 2014.)***

...

#### **1.2.2.4 Stratification for age and staggered vaccination**

...

In order to ensure maximum safety for the subjects in this study, vaccination at Day 0 will be done in a staggered manner, starting with vaccination of the children in the oldest age stratum. For each age stratum, an ~~iSRC~~ ***IDMC*** will conduct a review of all available safety data once data is available up to at least 7 days after vaccination of at least 50 subject (25/ group) in that age stratum. ~~Continuation of vaccination and the~~ ***The*** start of vaccination in the younger age stratum ~~will be put on hold if any safety concerns are raised by the iSRC,~~ ***possibly with a lower vaccine dose, depends on the outcome of this IDMC review.*** For more detailed information on the staggered design of the study and on the safety monitoring, refer to Section 9.10. ***(Amended 29 December 2014.)***

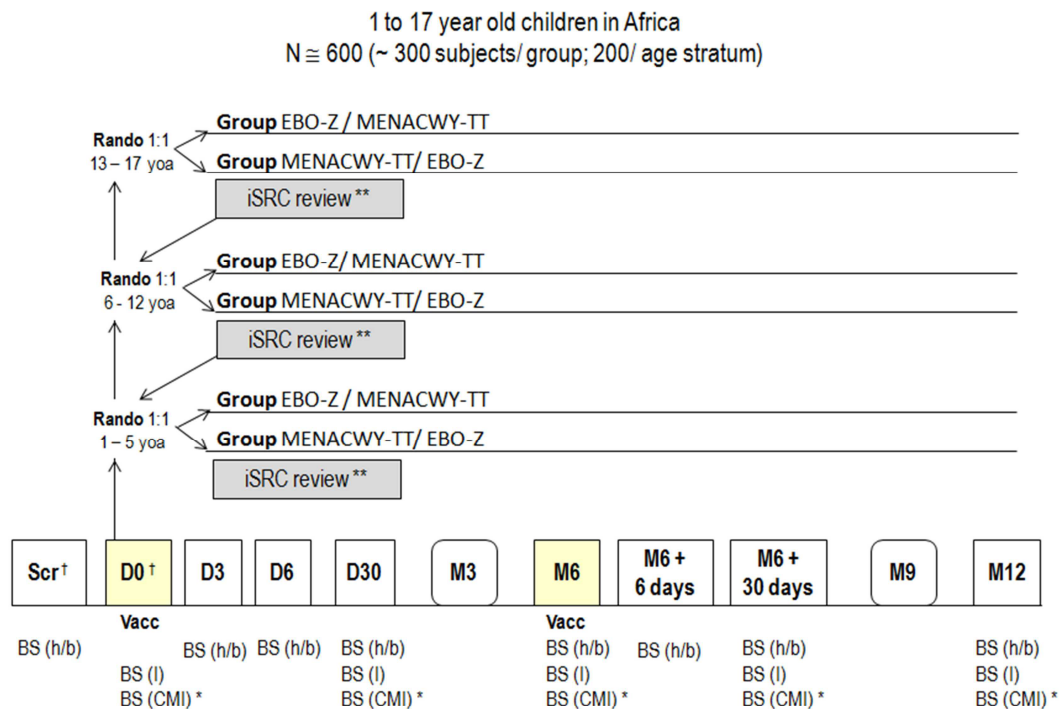
## **2.3 Tertiary objectives**

...

Refer to Section 11.3 for the definition of the tertiary endpoint(s). ***(Amended 29 December 2014)***

### 3. Study Design Overview

**Figure 1 Study design overview (Amended 29 December 2014.)**



**Rando** = randomisation; **yoa** = years of age; **Scr** = Screening; **D** = Day; **M** = Month; **BS (h/b)** = blood sample for haematology/ biochemistry parameters; **BS (I)** = blood sample for humoral immunity; **BS (CMI)** = blood sample for cell-mediated immunity.

Squares indicate visits to the vaccination centre. Rounded rectangles indicate study contacts (home visit or phone call).

Yellow-coloured visits indicate vaccination visits. At the Day 0 visit, subjects in the Group EBO-Z/ MENACWY-TT receive the investigational ChAd3-EBO-Z vaccine and subjects in Group MENACWY-TT/ EBO-Z receive *Nimenrix*. At the Month 6 visit, subjects in Group EBO-Z/ MENACWY-TT receive *Nimenrix* and subjects in the Group MENACWY-TT/ EBO-Z receive the investigational ChAd3-EBO-Z vaccine.

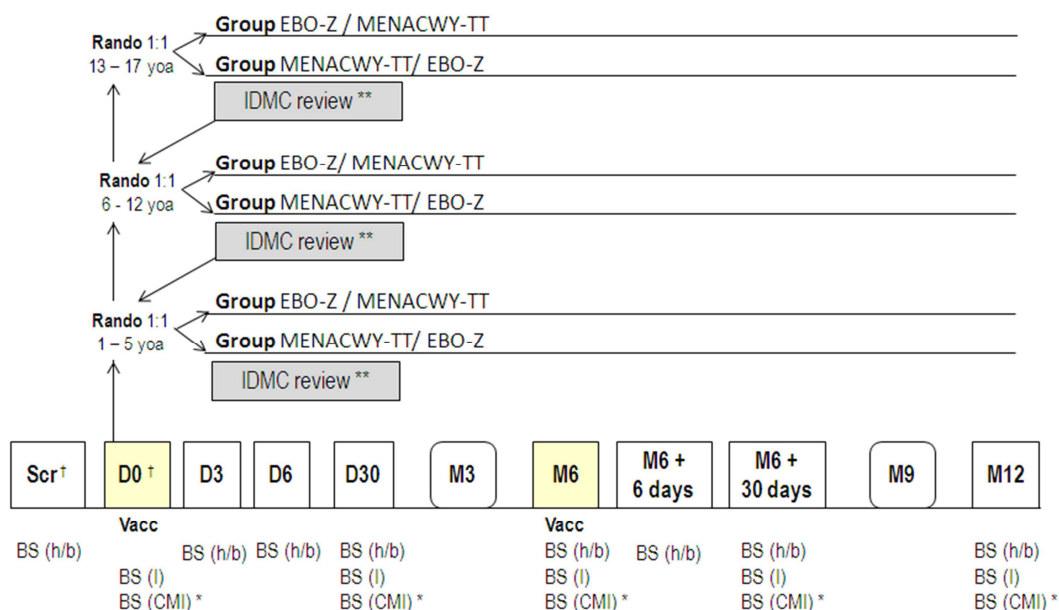
**Subjects will be followed-up for adverse events (AEs) on a daily basis during the 7-day follow-up period after vaccination (day 0 to 6). During this period, AEs will be recorded on a Diary Card. On those days that no study visit is planned, a home visit will be scheduled.**

<sup>†</sup>The Screening Visit and the Day 0 visit may take place on the same day (allowed interval 0 - 30 days).

\* Only for subjects in the sub-cohort for CMI.

\*\* iSRC review on all available safety data, which will include the safety data up to 7 days after vaccination at Day 0, from at least 50 children (25 per group) in an age stratum before proceeding to vaccination in the next (younger) age stratum (if applicable).

1 to 17 year old children in Africa  
N  $\approx$  600 (~ 300 subjects/group; 200/ age stratum)



**Rando** = randomisation; **yoa** = years of age; **Scr** = Screening; **D** = Day; **M** = Month; **BS (h/b)** = blood sample for haematology/ biochemistry parameters; **BS (I)** = blood sample for humoral immunity; **BS (CMI)** = blood sample for cell-mediated immunity.

Squares indicate visits to the vaccination centre. Rounded rectangles indicate study contacts (home visit or phone call). Yellow-coloured visits indicate vaccination visits. At the Day 0 visit, subjects in the Group EBO-Z/ MENACWY-TT receive the investigational ChAd3-EBO-Z vaccine and subjects in Group MENACWY-TT/ EBO-Z receive *Nimenrix*. At the Month 6 visit, subjects in Group EBO-Z/ MENACWY-TT receive *Nimenrix* and subjects in the Group MENACWY-TT/ EBO-Z receive the investigational ChAd3-EBO-Z vaccine.

**Subjects will be followed-up for adverse events (AEs) on a daily basis during the 7-day follow-up period after vaccination (day 0 to 6). During this period, AEs will be recorded on a Diary Card. On those days that no study visit is planned, a home visit will be scheduled.**

† The Screening Visit and the Day 0 visit may take place on the same day (allowed interval 0 - 30 days).

\* Only for subjects in the sub-cohort for CMI.

\*\* IDMC review on all available safety data, which will include the safety data up to 7 days after vaccination at Day 0, from at least 50 children (25 per group) in an age stratum before proceeding to vaccination in the next (younger) age stratum (if applicable).

- **Staggered vaccination:** Vaccination at Day 0 will be done in a staggered manner, starting with vaccination of the children in the oldest age stratum (13 to 17 years of age). In order to proceed to vaccination of the subjects in the younger age stratum (6 to 12 years of age), **possibly with a lower vaccine dose**, a favourable outcome of the ~~ISRC~~ **IDMC** review of safety data up to at least 7 days after vaccination from at least 50 subjects (25/ group) in the oldest age stratum needs to be obtained. The same will be done for moving from the 6 to 12 years of age stratum to vaccination of the youngest children (1 to 5 years of age). Refer to Section 9.10 for more information. *(Amended 29 December 2014.)*

...

- **Safety monitoring:** An ~~iSRC~~ **IDMC** will be appointed to monitor the safety and tolerability of the investigational ChAd3-EBO-Z vaccine. ~~The iSRC will be authorised by the GSK Biologicals' Vaccine Safety Monitoring Board (VSMB). Core members of the iSRC will include a GSK Biologicals' Safety Physician, a Clinical Research and Development Lead (CRDL) and a Biostatistician who are not otherwise involved in the conduct of the project.~~ **The IDMC will consist of clinical experts and a statistician who are not involved in the conduct of the study.** Refer to Section 9.10 for detailed description of the safety monitoring. (*Amended 29 December 2014.*)

#### 4.3 Inclusion criteria for enrolment

...

- Written/ thumb printed informed consent obtained from the subject' parent(s)/ LAR(s) prior to performing any study specific procedure. In addition, written/ thumb printed informed assent should be obtained *if appropriate* (from *all* subjects aged 13 to 17 years *and from younger subjects as per local requirements*). (*Amended 29 December 2014.*)

...

#### 5.1 Regulatory and ethical considerations, including the informed consent process

...

In accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, subjects who can only be enrolled in the study with the consent of their parent(s)/ LAR(s) (e.g., minors), should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date a written informed assent form (IAF). It should be assessed whether an assent is required depending of the age of the study population and the local requirements. In this study, written/ thumb printed informed assent should be obtained from ~~the~~ *all* subjects in the oldest age category (13 to 17 year olds) *and from younger subjects as per local requirements* in addition to the informed consent that is to be signed/ thumb printed by their parent(s)/ LAR(s). (*Amended 29 December 2014.*)

...

##### 5.2.2.2.1 Study group and treatment name allocation at Day 0

...

~~At Day 0, after~~ **After** obtaining the signed/ thumb printed and dated ICF from the subject's parent(s)/ LAR(s) and signed/ thumb printed and dated IAF from the subject (if applicable) and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access IWRS/ IVRS. Upon providing the subject subject's age (1 to 5 years *versus* 6 to 12 years *versus* 13 to 17 years of age), gender, centre and the subject identification number, the randomisation system will determine the study group



and will provide the treatment name to be administered. Access to the IVRS/ IWRS system will be limited to unblinded site staff. *(Amended 29 December 2014.)*

### 5.5.1 List of study procedures

**Table 5 List of study procedures during visits to the vaccination centre**

Footnotes:

...

<sup>10</sup> Only for subjects in the oldest age stratum (13 to 17 year olds) *and younger subjects as per local requirements.*  
*(Amended 29 December 2014.)*

...

### 5.6.1 Informed consent

The signed/witnessed/thumb printed informed consent of the subject's parent(s)/ LAR(s) must be obtained before study participation. For subjects in the oldest age stratum (13 to 17 years) *and for younger subjects as per local requirements*, the signed informed assent of the subject should be obtained in addition to the signed informed consent by his/her parent(s)/ LAR(s). Refer to Section 5.1 for the requirements on how to obtain informed consent as appropriate. *(Amended 29 December 2014.)*

### 5.7.3.2 Immune response against Ebola

**Table 8 Humoral immunity against Ebola (Amended 29 December 2014)**

System	Component	Method	Kit/ Manufacturer	Laboratory *
Serum	anti-GP EBOV	ELISA	TBD	Laboratory designated by GSK Biologicals <b>Quest Diagnostics</b>

**EBOV** = Ebola virus Zaire; **ELISA** = enzyme-linked immunosorbent assay; **GP** = glycoprotein; **GSK** = GlaxoSmithKline;  
**TBD** = to be determined

\* Refer to **APPENDIX B** for the laboratory addresses.

## 6.1 Description of study vaccines

...

**Table 14 Study vaccines (Amended 29 December 2014)**

Treatment name	Vaccine/ Product name	Formulation	Presentation	Volume to be administered	Number of doses
ChAd3-EBO-Z	ChAd3-EBO-Z	ChAd3-EBO-Z= 5*10 <sup>10</sup> vp/mL or 1*10 <sup>11</sup> vp/mL	Liquid in vial	0.5 0.25 mL to 1 mL *	1
<i>Nimenrix</i>	MenACWY-TT	PSA=5µg TT; PSC=5µg TT; PSW <sub>135</sub> =5µg TT; PsY=5µg TT; TT=44µg	Powder in vial	0.5 mL **	1
	NaCl	NaCl=150mM	Liquid in monodose, prefilled syringe		

**ChAd3-EBO-Z** = investigational recombinant chimpanzee adenovirus type 3-vectored Ebolavirus Zaire (EBOV) vaccine; **MenACWY-TT** = meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate; **NaCl** = sodium chloride; **PSA** = *Neisseria meningitidis* serogroup A polysaccharide; **PSC** = *Neisseria meningitidis* serogroup C polysaccharide; **PSW** = *Neisseria meningitidis* serogroup W-135 polysaccharide; **PsY** = *Neisseria meningitidis* serogroup Y polysaccharide; **TT** = tetanus toxoid; **vp** = viral particles

\* The volume to be administered will depend on the dosage ChAd3-EBO-Z selected based on Phase 1 data and on the concentration of the investigational ChAd3-EBO-Z vaccine and will be described in the Pharmacy Manual.

\*\* Refer to the Pharmacy Manual for the volume after reconstitution.

## 6.3 Dosage and administration of study vaccines

**Table 15 Dosage and administration (Amended 29 December 2014)**

Type of contact and timepoint	Volume to be administered	Treatment name	Study group	Route	Site *
Visit Day 0	0.5 0.25 mL to 1 mL **	ChAd3-EBO-Z	Group EBO-Z/ MENACWY-TT	IM	Deltoid
	0.5 mL	<i>Nimenrix</i>	Group MENACWY-TT/ EBO-Z	IM	Deltoid
Visit Month 6	0.5 mL	<i>Nimenrix</i>	Group EBO-Z/ MENACWY-TT	IM	Deltoid
	0.5 0.25 mL to 1 mL **	ChAd3-EBO-Z	Group MENACWY-TT/ EBO-Z	IM	Deltoid

**ChAd3-EBO-Z** = investigational recombinant chimpanzee adenovirus type 3-vectored Ebolavirus Zaire (EBOV) vaccine; **IM** = intramuscular

\* For small children, the vaccine may be given in the thigh.

\*\* The volume to be administered will depend on the dosage ChAd3-EBO-Z selected based on Phase 1 data on the concentration of the investigational ChAd3-EBO-Z vaccine and will be described in the Pharmacy Manual.

### 9.1.4 Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g., clinical chemistry, haematology, ~~urinalysis~~) or other abnormal assessments (e.g., vital signs measurements) that are judged by the Investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 9.1.1 and 9.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that

are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. *(Amended 29 December 2014.)*

### 9.3.3.2.1 Assessment of intensity

...

The maximum intensity of local injection site redness/swelling will be scored as follows:

#### 1. Children 1 to 5 years of age:

0	:	None
1	:	> 0 mm to ≤ 10 mm
2	:	> 10 mm to ≤ 30 mm
3	:	> 30 mm

#### 2. Children 6 to 12 years of age:

0	:	None
1	:	> 0 mm to ≤ 20 mm
2	:	> 20 mm to ≤ 50 mm
3	:	> 50 mm

#### 3. Children 13 to 17 years of age:

0	:	≤ 20 mm
1	:	> 20 mm to ≤ 50 mm
2	:	> 50 mm to ≤ 100 mm
3	:	> 100 mm

*(Amended 29 December 2014.)*

...

## 9.10 Safety monitoring by the ~~internal safety review committee~~ *independent data monitoring committee*

### 9.10.1 ~~Staggered vaccination and internal safety review committee~~

An ~~iSRC~~ *IDMC* will be appointed to monitor the safety and tolerability of the investigational ChAd3-EBO-Z vaccine. ~~The iSRC will be authorised by the GSK Biologicals' Vaccine Safety Monitoring Board (VSMB). Core members of the iSRC will include a GSK Biologicals' Safety Physician, a CRDL and a Biostatistician who are not otherwise involved in the conduct of the project.~~ *The IDMC will consist of clinical experts and a statistician who are not involved in the conduct of the study.*

The ~~iSRC~~ *IDMC* will review, in an unblinded manner, safety and reactogenicity data from the current study, and from the study EBOLA Z CHAD3-005, which will be conducted in parallel with the current study. In the study EBOLA Z CHAD-005, the safety, reactogenicity and immunogenicity of the investigational ChAd3-EBO-Z vaccine

will be assessed when administered to adults. ***Recommendations will be provided to the sponsor following each IDMC meeting.***

~~Interim~~ ~~Unblinded~~ ~~iSRC~~ **IDMC** reports including all available safety and reactogenicity data will be produced by an independent statistician according to an agreed pre-defined Report and Analysis Plan. All data provided to the ~~iSRC~~, which **IDMC** that will monitor the data from the above described Phase 2 studies, will also be made available to the independent data monitoring committee (IDMC) that will be set up to monitor data from the Phase 3 programme with the investigational ChAd3-EBO-Z vaccine.

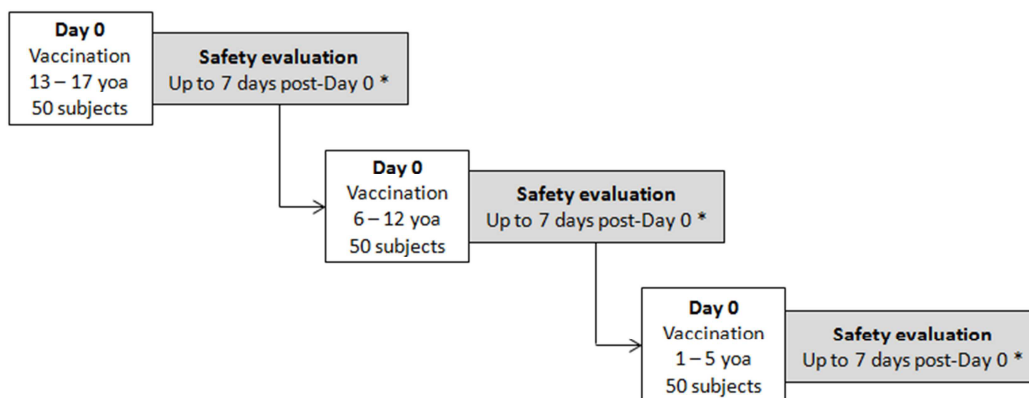
~~If, during an iSRC meeting, any safety concern is raised, continuation of vaccination and the start of vaccination of subjects in the younger age stratum (if applicable) will be put on hold and the VSMB will decide during an ad hoc meeting whether to suspend, modify or continue the conduct of the study(ies) in all age strata or in selected age strata.~~

***If, during an IDMC meeting, any safety concern is raised, continuation of vaccination and the start of vaccination of subjects in the younger age stratum (if applicable) will be put on hold. Vaccination will only resume, and age de-escalation will only proceed if GSK Biologicals agrees to it, following discussions with the IDMC. All IECs/ IRBs will be notified as applicable.***

Refer to the ~~iSRC~~ **IDMC** Charter for more information.

#### **Staggered design and ~~iSRC~~ IDMC meetings**

No safety concerns have been raised from vaccination with different dosages of the investigational ChAd3-EBO-Z vaccine in healthy adults in the ongoing Phase 1 studies. However, the investigational vaccine has never been administered to children yet. In order to ensure maximum safety for the subjects in this study, ***vaccination in the study will only start after a favourable outcome of an IDMC review of the safety and reactogenicity data from 100 adults after 1 week follow-up in the study EBOLA Z CHAD3-005.*** In addition, vaccination at Day 0 will be done in a staggered manner, starting with vaccination of the children in the oldest age stratum. For each age stratum, the ~~iSRC~~ **IDMC** will conduct a review of all available safety data once data is available up to at least 7 days after vaccination of at least 50 subjects (25/ group) in that age stratum. In order to proceed to vaccination of the subjects in the younger age stratum (6 to 12 years of age), ***possibly with a lower vaccine dose***, a favourable outcome of the ~~iSRC~~ **IDMC** review of safety data up to at least 7 days after vaccination from at least 50 subjects (25/ group) in the oldest age stratum needs to be obtained. The same will be done for moving from the 6 to 12 years of age stratum to vaccination of the youngest children (1 to 5 years of age).

**Figure 2 Overview of staggered design and iSRC IDMC safety evaluations**

\* Safety evaluation on all available safety data from the entire study, which will include the safety data up to 7 days after vaccination at Day 0 from at least 50 subjects (25 subjects/ group) in the respective age stratum.

### ***Holding rules***

During the iSRC IDMC meetings depicted in Figure 2, study holding rules will be assessed. If any of these holding rules are met (or if any other safety concern is raised), vaccination will be put on hold and the VSMB will be consulted.

The holding rules will be assessed per age stratum and the frequency of events described in the holding rules apply to the Group EBO-Z/ MENACWY-TT only.

### ***Holding rules***

...

### ***Other iSRC IDMC meetings***

In addition to the iSRC IDMC meeting that will be held before the first vaccination and the meetings depicted in Figure 2, the following iSRC IDMC evaluations will take place:

- iSRC IDMC review of all safety and reactogenicity data included in the interim analysis that will be conducted when data is available from all subjects up to 30 days after vaccination at Day 0 (refer to Section 11.11.2 for more information on this interim analysis).
- An *ad hoc* iSRC IDMC meeting will be held in case of an SAE considered related to vaccination at any time during the study.
- *Ad hoc* iSRC IDMC meetings may be held if any safety concern is raised.

*(Amended 29 December 2014.)*

## 11.4 Determination of sample size

The primary objective of this study is to assess the safety of the investigational ChAd3-EBO-Z vaccine. (*Amended 29 December 2014.*)

...

## 11.5 Cohorts for Analyses (*Amended 29 December 2014*)

### ~~11.5.2 According to protocol cohort for analysis of safety~~

~~The ATP cohort for analysis of safety will include all vaccinated subjects:~~

- ~~• Who meet all eligibility criteria.~~
- ~~• Who have received at least one dose of study vaccine according to protocol procedures and to their random assignment.~~
- ~~• Who have not received a concomitant medication/ product/ vaccination that may lead to elimination from an ATP analysis as listed in Section 6.7.2.~~
- ~~• For whom the randomisation code has not been broken for vaccination at Day 0.~~

### 11.5.32 According to protocol cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will include all evaluable subjects ~~from the ATP cohort for analysis of safety:~~

- Who meet all eligibility criteria.
- *Who have received at least one dose of study vaccine according to protocol procedures and to their random assignment.*
- *For whom the randomisation code has not been broken for vaccination at Day 0.*
- Who comply with the procedures and intervals defined in the protocol (refer to Table 6).

...

## 11.8 Analysis of safety

The ~~primary~~ analysis will be performed on the TVC. ~~If in any study group, 5% or more of the vaccinated subjects are eliminated from the ATP cohort for analysis of safety, a second analysis will be performed on the ATP cohort for analysis of safety.~~ (*Amended 29 December 2014.*)

...

**11.11.1 Sequence of analyses**

...

The analyses will be performed stepwise:

- Analyses of safety and reactogenicity data will be performed ~~by~~ *for* the ~~iSRC~~ *IDMC*. Access to individual treatment codes will be restricted to the ~~independent iSRC~~ *IDMC* support statistician in charge of the analyses and ~~iSRC~~ *IDMC* members. *(Amended 29 December 2014.)*

...

**APPENDIX A LABORATORY ASSAYS (Amended 29 December 2014)****~~Anti-GP EBOV~~ *Anti-EBOV GP IgG ELISA***

~~Information on these assays was not available yet at the time of protocol finalisation.~~

*Blood samples for antibody determination will be collected at indicated timepoints and serum will be separated and frozen at -20°C.*

*Antibody level will be determined by evaluating antibody (IgG) responses specific for Zaire Ebola Virus Glycoprotein (EBOV GP) using the ELISA developed by Battelle and JVAP/USAMRIID and transferred to Quest (Focus) laboratory.*

*Briefly, microtiter plates are coated with the purified recombinant Zaire GP (rGP) specific to the Kikwit-95 strain (the Non-Human Primates (NHP) challenge strain). This strain is 98.5% identical to the vaccine Mayinga EBOV strain (11 aa mismatched) and is 97.5% identical to the isolated Guinea 2014 virus strain (17 aa mismatched). Serial diluted test samples, 2 serial-diluted controls (one QC-high and one QC-low) and a negative sample control (composed of pooled normal human serum purchased from a commercial source) are allowed to incubate in the GP coated wells allowing GP specific antibodies to bind. Additionally, a two-fold serial diluted reference standard, obtained from a vaccinated donor, is included in duplicate. Each well is then incubated with goat anti-human IgG horseradish peroxidase conjugate (HRP). TMB substrate is added to each well and the enzymatic reaction is stopped with a sulfuric acid solution. The color change is then read in a plate reader and sample titers are based on the standard curve calculated using a 4 parameter logistic curve fit. Results are reported in ELISA units/ml (EU/ml). A 2<sup>nd</sup> generation human standard (microgram/mL) will be evaluated and bridged to the current standard. This assay will be qualified at Quest Diagnostics laboratories before starting the clinical testings.*

## APPENDIX B      CLINICAL LABORATORIES (*Amended 29 December 2014*)

**Table 24      Outsourced laboratories**

Laboratory	Address
NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL)	Suite 150 9 West Watkins Mill Road Gaithersburg, MD 20878
<i>Quest Diagnostics</i>	<i>Focus Diagnostics Clinical Trials, Inc. (d/b/a Quest Diagnostics) 33608 Ortega Highway San Juan Capistrano, CA 92675-2042, United States of America</i>

## APPENDIX C      ACCEPTABLE LIMITS FOR ELIGIBILITY AND TOXICITY GRADING SCALES FOR HAEMATOLOGY/ BIOCHEMISTRY PARAMETERS (*Amended 29 December 2014*)



<b>GlaxoSmithKline Biologicals</b>	
Vaccine Value & Health Science (VVHS)	
<b>Protocol Amendment 2</b>	
<b>eTrack study number and Abbreviated Title</b>	202090 (EBOLA Z CHAD3-004)
<b>IND number</b>	16300
<b>EudraCT number</b>	2014-004714-28
<b>Amendment number</b>	Amendment 2
<b>Amendment date</b>	06 May 2015
<b>Co-ordinating author</b>	PPD [REDACTED], Quintiles, Medical Writing
<b>Rationale/background for changes:</b>	
<ul style="list-style-type: none"> <li>In the on-going Phase 1 studies with the investigational ChAd3-EBO-Z vaccine in the United States (US), United Kingdom (UK), Switzerland and Mali, transient decreases in thrombocyte counts were observed. These decreases occurred mostly on Day 1 after vaccination and generally returned to baseline by Day 7. Although most of these decreases remained within the normal range, the as per protocol criteria for thrombocytopenia (thrombocyte count of <math>&lt; 150 \times 10^3/\mu\text{L}</math>) were met for 2.6% (7 out of 270) of the vaccinated subjects. None of the decreases in thrombocyte counts or the cases of thrombocytopenia were clinically significant, <i>i.e.</i>, no clinical signs or symptoms suggestive of increased tendency to bleed were reported in any of the subjects. Please refer to the Investigator's Brochure (IB) for more information. In the current study, a more vulnerable population (children) will be enrolled and the acceptable limit for the thrombocyte count for study eligibility (thrombocyte count of <math>\geq 100 \times 10^3/\mu\text{L}</math> is acceptable) will be lower as compared to the Phase 1 studies. In addition, in order to ensure enhanced vigilance from the Investigators, clinical bleeding events (according to the Standardised Medical Dictionary for Regulatory Activities [MedDRA] Query clinical haemorrhage) within 7 days after vaccination at Day 0 will be recorded and reported as adverse events (AEs) of specific interest (clinical symptoms of thrombocytopenia).</li> <li>Based on safety and immunogenicity data from the on-going Phase 1 studies, the <math>1 \times 10^{11}</math> viral particles (vp) dose was selected for further assessment in Phase 2 and Phase 3 clinical studies in adults. This dose was determined using a high performance liquid chromatography (HPLC) analytical method for the vaccine lots used in the Phase 1 studies. The same dose will also be used in this paediatric study. However, depending on the recommendation of the independent data monitoring committee (IDMC), a lower dose may be selected based on safety and reactogenicity data accrued during the age de-escalation process for children in younger age strata. In addition, because a different analytical method was used to determine the vp concentration for the lots used in this study (quantitative</li> </ul>	

polymerase chain reaction [qPCR]) as compared to the lots used in the Phase 1 studies (HPLC), a dose of  $2 \times 10^{11}$  vp, as determined by qPCR, will be used in this study, to administer the equivalent of the  $1 \times 10^{11}$  vp dose, that was determined by HPLC and shown to be optimal in Phase 1 studies. This information was added in the protocol.

- Demographic data collection was updated to allow the full date of birth in the subject's eSource, but only month and year of the date of birth will be exported to GlaxoSmithKline's (GSK's) clinical database to guarantee subject confidentiality. The age as calculated in eSource will be used for analysis purposes as the full date of birth will not be exported.
- The IDMC highlighted that the study is conducted in Malaria endemic countries and that the presence of malarial infection may adversely affect the safety and immunogenicity evaluations of the investigational ChAd3-EBO-Z vaccine. In order to prevent subjects with Malaria from entering the study, all subjects who provide informed consent for study participation will be tested for Malaria infection at the time of Screening, using a rapid diagnostic test (RDT) procedure. Subjects who are diagnosed with Malaria, will receive antimalarial treatment according to local/ national standards during the Screening period (e.g., a 3-day treatment course of artemisinin-based combination therapy). Hence, only subjects for whom the RDT was negative, or for whom the RDT was positive and who received a complete course of antimalarial treatment during the Screening period can be considered for study participation. Procedures for Malaria Screening and treatment, as well as eligibility criteria specific for these procedures were adapted in the protocol.
- The scope of re-screening subjects has been clarified during the investigator's meeting, *i.e.*, re-screening of subjects must be avoided and redrawing blood from the subject is only permitted during the Screening period if, for technical reasons, test results are not available or if they are non-interpretable. To comply with this recommendation and avoid the risk of inadequate re-screening, footnote 11 under Table 5 (List of study procedures) has been removed.
- After consultation with the Principal Investigators and the IDMC, the exclusion criterion "Maternal death" was removed. Instead the following exclusion criterion was included:

*Any condition that in the Investigator's opinion may potentially compromise subject safety or interfere with subject assessment or compliance.*

This will allow the investigator also to consider, on a case by case basis, whether the family circumstances of the child may allow participation to the study in compliance with local regulations, when applicable.

- Blood sample volumes for haematology and biochemistry testing were corrected.
- Some minor editorial updates were made.

Amended text has been included in ***bold italics*** and deleted text in ~~strike through~~ in the following sections:

## TITLE PAGE

**Investigational New Drug  
(IND) number**

~~*To be decided 16300*~~  
***(Amended 06 May 2015.)***

**Contributing authors**

- ...
- PPD [redacted] (CVO-Europe for GSK Biologicals) and PPD [redacted] (***CROMSource for GSK Biologicals***), Vaccine Supply Coordinator  
***(Amended 06 May 2015.)***
  - ...
  - PPD [redacted] and PPD [redacted] (Business & Decision Life Sciences for GSK Biologicals), GVCL Study Manager  
***(Amended 06 May 2015.)***
  - ...
  - PPD [redacted] and PPD [redacted] (XPE Pharma & Science for GSK Biologicals), Scientific Writer  
***(Amended 06 May 2015.)***

## Contracted Research Organisation (Quintiles) Information

### 4. Medical Expert for the Study

PPD [redacted], MD  
Senior Medical Director  
~~Pediatric Center of Excellence~~  
~~Allergy, Respiratory, ID & Vaccines TDU~~  
***Allergy, Respiratory, Infectious Diseases & Vaccines***  
***Medical Strategy & Science***  
***Therapeutic Science & Strategy Unit***  
  
***(Amended 06 May 2015.)***

## SYNOPSIS

**Rationale for the study and study design**

- Rationale for the study design

- Investigational ChAd3-EBO-Z vaccine dose

Dose selection for paediatric use ~~will be~~ **was** based on information derived from dose-range studies conducted with the ChAd3-EBO-Z vaccine candidate in adults and on past experience with other recombinant adenovirus-based candidate vaccines.  
*(Amended 06 May 2015.)*

...

Four different investigational vaccine doses are currently being evaluated for safety, reactogenicity and immunogenicity in adults in Phase 1 studies. ***Based on data from these studies, the  $1 \times 10^{11}$  vp dose was selected for further assessment in Phase 2 and Phase 3 clinical studies in adults. This dose was determined using a high performance liquid chromatography (HPLC) analytical method for the vaccine lots used in the Phase 1 studies. The same dose will be used in this paediatric study. However, depending on the recommendation of the independent data monitoring committee (IDMC), a lower dose may be selected based on safety and reactogenicity data accrued during the age de-escalation process for children in younger age strata. It should be noted that the analytical method (quantitative polymerase chain reaction [qPCR]) that measures the concentration of virus particles per mL (vp/mL) present in the ChAd3-EBO-Z vials used in the current paediatric study is different from the analytical method (HPLC) used for the Phase 1 studies. As a result, a dose of  $2 \times 10^{11}$  vp will be used in this study, to administer the equivalent of the  $1 \times 10^{11}$  vp dose that was shown to be optimal in Phase 1 studies.*** As for other recombinant adenovirus-based vaccine candidates which showed adequate safety upon the use of adult doses in children as explained above, it is currently proposed that the same vaccine dose ~~as the dose selected for adults~~ **will be assessed in children 1 to 17 years of age** in this study. However, a lower vaccine dose may be selected for children of younger age groups based on the safety and reactogenicity data accrued during the age de-escalation process.

*(Amended 06 May 2015.)*

...

- ***Malaria Screening and treatment***

*As this study is conducted in Malaria endemic regions and the presence of malaria infection may adversely affect the safety and immunogenicity evaluations of the investigational ChAd3-EB0-Z vaccine, all subjects will be tested for Malaria infection using an RDT procedure during Screening and all subjects diagnosed with Malaria will receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period. Hence, only subjects for whom the RDT was negative, or for whom the RDT was positive and who received a complete course of antimalarial treatment during the Screening period can be considered for study participation.*

*(Amended 06 May 2015.)***Study design**

...

- **Blinding:**

...

**Single-blind** as of the interim analysis *at Day 30.*  
*(Amended 06 May 2015.)*

- **Sampling schedule:**

- *A blood sample (fingerprick) will be taken at Screening for Malaria RDT.*

*(Amended 06 May 2015.)*

– ...

**Endpoints****Primary**

...

- Occurrence of haematological (complete blood count [CBC], including differential count and platelet count) and biochemical (alanine aminotransferase [ALT], creatinine) laboratory abnormalities at Screening, Day 3, Day 6, Day 30, Month 6, Month 6 + 6 days, Month 6 + 30 days and Month 12 in all subjects in both groups.
- ***Occurrence of clinical symptoms of thrombocytopenia (AE of specific interest), during a 7-day follow-up period after vaccination at Day 0 (i.e., Day 0 up to***

*Day 6), in all subjects, in both groups.*

*(Amended 06 May 2015.)*

- Occurrence of any serious adverse event (SAE), in all subjects, in both groups.

## LIST OF ABBREVIATIONS *(Amended 06 May 2015)*

<b>HPLC:</b>	<i>High Performance Liquid Chromatography</i>
<b>NA:</b>	<i>Not Applicable</i>
<b>qPCR:</b>	<i>Quantitative Polymerase Chain Reaction</i>
<b>RDT:</b>	<i>Rapid Diagnostic Test</i>
<b>SDV:</b>	Source Document Verification
<b>TBD:</b>	<del>To Be Determined</del>

### 1.2.2.1 Investigational ChAd3-EBO-Z vaccine dose

Dose selection for paediatric use ~~will be~~ *was* based on information derived from dose-range studies conducted with the ChAd3-EBO-Z vaccine candidate in adults and on past experience with other recombinant adenovirus-based candidate vaccines. *(Amended 06 May 2015.)*

...

Four different investigational vaccine doses are currently being evaluated for safety, reactogenicity and immunogenicity in adults in Phase 1 studies. *Based on data from these studies, the  $1 \times 10^{11}$  vp dose was selected for further assessment in Phase 2 and Phase 3 clinical studies in adults. This dose was determined using a high performance liquid chromatography (HPLC) analytical method for the vaccine lots used in the Phase 1 studies. The same dose will be used in this paediatric study. However, depending on the recommendation of the independent data monitoring committee (IDMC), a lower dose may be selected based on safety and reactogenicity data accrued during the age de-escalation process for children in younger age strata. It should be noted that the analytical method (quantitative polymerase chain reaction [qPCR]) that measures the concentration of virus particles per mL (vp/mL) present in the ChAd3-EBO-Z vials used in the current paediatric study is different from the analytical method (HPLC) used for the Phase 1 studies. As a result, a dose of  $2 \times 10^{11}$  vp will be used in this study, to administer the equivalent of the  $1 \times 10^{11}$  vp dose that was shown to be optimal in Phase 1 studies.* As for other recombinant adenovirus-based vaccine candidates which showed adequate safety upon the use of adult doses in children as explained above, it is currently proposed that the same vaccine dose

~~as the dose selected for adults~~ will be assessed *in children 1 to 17 years of age* in this study. However, a lower vaccine dose may be selected for children of younger age groups based on the safety and reactogenicity data accrued during the age de-escalation process. *(Amended 06 May 2015.)*

*As this study is conducted in Malaria endemic regions and the presence of Malaria infection may adversely affect the safety and immunogenicity evaluations of the investigational ChAd3-EBO-Z vaccine, all subjects will be tested for Malaria infection using a rapid diagnostic test (RDT) procedure during Screening. Subsequently, all subjects diagnosed with Malaria will receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period. Hence, only subjects for whom the RDT was negative, or for whom the RDT was positive and who received a complete course of antimalarial treatment during the Screening period can be considered for study participation. (Amended 06 May 2015.)*

### 1.3.2 Benefit assessment

...

#### Other benefits

*All subjects who provide informed consent for study participation will be tested for Malaria infection using an RDT procedure at the time of Screening. Subjects who are diagnosed with Malaria will receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period, to clear the infection prior to vaccination. (Amended 06 May 2015.)*

...

## 3. STUDY DESIGN OVERVIEW

...

- **Blinding:**

- ...

- Single-blind as of the interim analysis *at Day 30. (Amended 06 May 2015.)*

- **Sampling schedule:**

- *A blood sample (fingerprick) will be taken at Screening for Malaria RDT. (Amended 06 May 2015.)*

- ...

### 4.3 Inclusion criteria for enrolment

...

- A male or female child aged 1 to 17 years inclusive at the time of **Screening**.  
(Amended 06 May 2015.)
- *Subjects with a negative RDT test for Malaria within 30 days prior to randomisation into the study.*

**OR**

*Subjects with a positive RDT test for Malaria who completed antimalarial treatment at least 5 days prior to randomisation into the study.*

(Amended 06 May 2015.)

...

### 4.4 Exclusion criteria for enrolment

...

- ~~Maternal death.~~ (Amended 06 May 2015.)

...

- *Any condition that in the Investigator's opinion may potentially compromise subject safety or interfere with subject assessment or compliance.*

(Amended 06 May 2015.)

#### 5.2.2.1 Diary Card for follow-up adverse events occurring from day 0 to day 6 after vaccination

...

Access to the IVRS/ IWRS system ~~unblinded treatment information~~ will be limited to unblinded site staff. (Amended 06 May 2015.)

...

### 5.3 Method of blinding

The blinding level will change in the course of the study:

- **Observer-blind** from study start until the interim analysis that will be conducted when safety, reactogenicity and immunogenicity (including at least anti-GP EBOV data at Day 30) data is available from all subjects up to 30 days after vaccination at Day 0 (refer to Section 11.11.1 for more information on this interim analysis). By observer-blind, it is meant that the vaccine recipient and those responsible for the evaluation of any study endpoint will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration at Day 0 will be done



by authorised medical personnel who will not participate in any of the study clinical evaluation assays.

***To ensure blinding of the site staff when preparing and administering the study vaccine details of vaccine management will be defined in a site vaccine management plan before site initiation.***

***(Amended 06 May 2015.)***

## 5.5.1 List of study procedures

Table 5 List of study procedures during visits to the vaccination centre (*Amended 06 May 2015*)

Type of contact	Visit	Visit	Visit	Visit	Visit	Contact *	Visit	Visit	Visit	Contact *	Visit
Timepoint	Screening <sup>1</sup>	Day 0 <sup>1</sup>	Day 3	Day 6	Day 30	Month 3	Month 6	Month 6 + 6 days	Month 6 + 30 days	Month 9	Month 12
Informed consent	•										
Informed assent <sup>10</sup>	•										
<b>RDT for Malaria</b>	•										
<b>Malaria treatment <sup>11</sup></b>	•										
Inclusion/exclusion criteria <sup>12</sup>	•	•									
Demographic data	•										
Medical history <sup>12</sup>	•	•									
Physical examination (including vital signs <sup>2</sup> )	• <sup>12</sup>	• <sup>3</sup>	0	0	0		•	0	0		0
...											
Study group and treatment name allocation <sup>6</sup>		0					0				
...											
<b>Blood sampling:</b>											
Blood for haematology/ biochemistry	• <sup>12</sup>		•	•	•		•	•	•		•
Blood for humoral immunity		•			•		•		•		•
Blood for CMI <sup>7</sup>		•			•		•		•		•
<b>Safety assessment:</b>											
Record solicited AEs (day 0 to day 6)		•	•	•			•	•			
Record unsolicited AEs (day 0 to day 29)		•	•	•	•		•	•	•		
<b>Record AEs of specific interest (clinical symptoms of thrombocytopenia)</b>			•	•							
...											
Screening Conclusion <sup>14</sup>											
...											

... RDT = Rapid Diagnostic Test; ...

<sup>14</sup> Subjects who are Screening failures for a reason that is expected to be temporary may be re-Screened once. A different subject identification number will be assigned to such subject at re-Screening.<sup>11</sup> Subjects diagnosed with Malaria at Screening must receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period.<sup>12</sup> Study procedure must be performed at least 5 days after completion of Malaria treatment for all subjects diagnosed with Malaria at Screening.

**5.6.2 Malaria Screening and treatment (Amended 06 May 2015)**

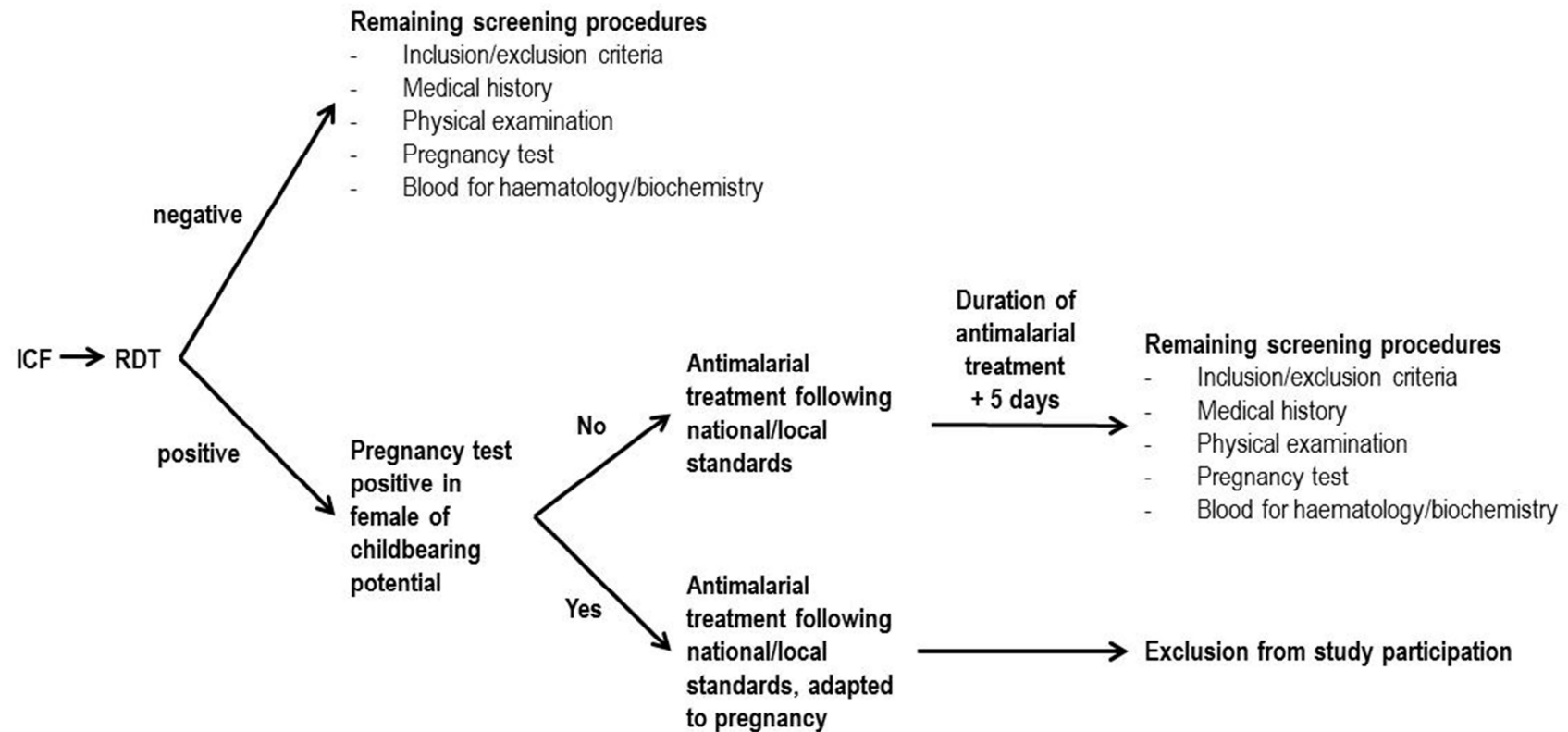
*After obtaining the informed consent of the subject's parent(s)/ LAR(s), all subjects should first be tested for Malaria infection using the WHO pre-qualified RDT.*

*All subjects diagnosed with Malaria using the RDT must receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period. In addition, a pregnancy test should be performed for women of childbearing potential in case the RDT is positive, so that an antimalarial treatment alternative to artemisinin-based combination therapy (e.g., quinine plus clindamycin) is proposed in case the pregnancy test is positive.*

*For subjects whose RDT is positive, the following Screening procedures should be postponed until at least 5 days after completion of the Malaria treatment (Figure 2):*

- *Blood sampling for haematology and biochemistry testing.*
- *Physical examination.*
- *Review of eligibility criteria.*
- *Completion of the medical history.*

**Figure 2 Screening procedures**



ICF = Informed Consent Form; RDT = Rapid Diagnostic Test

*The outcome of the Malaria RDT and completion of Malaria treatment needs to be recorded in eSource.*

#### **5.6.2 5.6.3 Check inclusion and exclusion criteria**

Check all inclusion and exclusion criteria as described in Sections 4.3 and 4.4 before enrolment.

*For subjects diagnosed with Malaria at Screening, a full eligibility check should be postponed until at least 5 days after completion of Malaria treatment.*

*(Amended 06 May 2015.)*

#### **5.6.3 5.6.4 Collect demographic data**

Record demographic data such as date of birth (~~month and year only~~ *full date of birth will be collected in eSource, but only month and year of the date of birth will be exported to GSK's clinical database. The age as calculated in eSource will be used for analysis purposes as the full date of birth will not be exported*), gender, geographic ancestry, and ethnicity, in the subject's eSource.

*(Amended 06 May 2015.)*

#### **5.6.4 5.6.5 Medical history**

...

*For subjects diagnosed with Malaria at Screening, completion of medical history should be postponed until at least 5 days after completion of Malaria treatment.*

*(Amended 06 May 2015.)*

#### **5.6.5 5.6.6 Physical examination**

...

*For subjects diagnosed with Malaria at Screening, physical examination should be postponed until at least 5 days after completion of Malaria treatment.*

*(Amended 06 May 2015.)*

During all other study visits, perform a physical examination only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate. ~~If a physical examination is performed during one of these visits, collected information will not need to be recorded in eSource.~~

*(Amended 06 May 2015.)*

...

**5.6.11 Sampling**

...

- *A blood sample (fingerprick) will be taken at Screening for Malaria RDT.*  
*(Amended 06 May 2015.)*
- ...
- A volume of approximately  $\pm 0.5$  to  $\pm 1.5$  mL (*depending on the age of the child*) of whole blood should be drawn from all subjects for each analysis of haematology<sup>†</sup> *and each analysis of* biochemistry parameters at each pre-defined timepoint.  
*(Amended 06 May 2015.)*

**5.6.14 Recording of adverse events, serious adverse events and pregnancies**

- Refer to Section 9.3 for procedures for the Investigator to record AEs, serious adverse events (SAEs), and pregnancies. Refer to Section 9.4 for guidelines and how to report *AEs of specific interest (clinical symptoms of thrombocytopenia)*, SAEs, and pregnancies to the CRO (Quintiles).  
*(Amended 06 May 2015.)*

...

**5.6.14.1 Diary Card for follow-up adverse events occurring from day 0 to day 6 after vaccination**

Subjects in the sub-cohort for follow-up of AEs and assessment of humoral immunity will be followed up for AEs on a daily basis during the 7-day follow-up period after vaccination. During this period, AEs *with the exception of AEs of specific interest (clinical symptoms of thrombocytopenia)* will be recorded on a Diary Card.

*(Amended 06 May 2015.)*

...

**5.7.2 Biological samples****Table 7 Biological samples (Amended 06 May 2015.)**

Sample type	Quantity	Unit	Age strata	Timepoint	Sub-cohort *	Number of subjects
<b>Blood for Malaria Screening</b>	<b>Fingerprick</b>	<b>NA</b>	<b>1 to 17 years</b>	<b>Screening</b>	<b>All screened subjects</b>	<b>&gt; 600</b>
Blood for haematology/ biochemistry	1 to 2 0.5 to 1.5	mL	1 to 17 years	Screening Day 3 Day 6 Day 30 Month 6 Month 6 + 6 days Month 6 + 30 days Month 12	All screened subjects    All enrolled subjects	> 600    ~600
<b>Blood for biochemistry</b>	<b>0.5 to 1.5</b>	<b>mL</b>	<b>1 to 17 years</b>	<b>Screening</b> <b>Day 3</b> <b>Day 6</b> <b>Day 30</b> <b>Month 6</b> <b>Month 6 + 6 days</b> <b>Month 6 + 30 days</b> <b>Month 12</b>	<b>All screened subjects</b>    <b>All enrolled subjects</b>	<b>&gt; 600</b>    <b>~600</b>
...						

... NA = not applicable

**5.7.3 Laboratory assays**

...

In addition to the assays described below, other tests to characterise the safety and/ or the immunogenicity of the investigational ChAd3-EBO-Z vaccine may be performed if deemed necessary for accurate interpretation of the data and/ or should such test(s) become available.

***Screening for Malaria infection will be performed using the WHO pre-qualified RDT at the site.***

***(Amended 06 May 2015.)***

**5.7.3.2 Immune response against Ebola****Table 8 Humoral immunity against Ebola (Amended 06 May 2015)**

System	Component	Method	Kit/ Manufacturer	Laboratory *
Serum	anti-GP EBOV	ELISA	TBD In-house	Quest Diagnostics

... TBD = to be determined ...

## 6. STUDY VACCINES/ PRODUCTS AND ADMINISTRATION (AMENDED 06 MAY 2015.)

### 6.1 Malaria treatment (Amended 06 May 2015.)

*All subjects diagnosed with Malaria during Screening will receive antimalarial treatment according to local/ national standards (e.g., a 3-day treatment course of artemisinin-based combination therapy), during the Screening period.*

### 6.2 Description of study vaccines

...

**Table 14 Study vaccines (Amended 06 May 2015)**

Treatment name	Vaccine/ Product name	Formulation	Presentation	Volume to be administered	Number of doses
ChAd3-EBO-Z	ChAd3-EBO-Z	ChAd3-EBO-Z= $4.2 \times 10^{11}$ vp/mL*	Liquid in vial	0.25 mL to 1 mL **	1
Nimenrix	MenACWY-TT	PSA=5 µg TT; PSC=5 µg TT; PSW <sub>135</sub> =5 µg TT; PsY=5 µg TT; TT~44 µg	Powder in vial	0.5 mL ***	1
	NaCl	NaCl=150 mM	Liquid in monodose, prefilled syringe		

...

\* The dose used in this study, labelled  $2 \times 10^{11}$  vp corresponds to the dose, labelled  $1 \times 10^{11}$  vp, used in the Phase I studies that was selected for further clinical development. The difference in vp concentration on the labels of the lots used in this study and the Phase I studies is the result of a different analytical method that was used to determine the vp concentration.

\*\* The volume to be administered to children in younger age strata will depend on the dosage ChAd3-EBO-Z selected based on Phase 1 data on the concentration of the investigational ChAd3-EBO-Z vaccine and will be described in the Pharmacy Manual. the recommendation of the independent data monitoring committee as a lower vaccine dose may be selected based on safety and reactogenicity data accrued during the age de-escalation process (Refer to Section 1.2.2.1).

\*\*\* Refer to the Pharmacy Manual for the volume to be injected after reconstitution.

### 6.3 6.4 Dosage and administration of study vaccines

**Table 15 Dosage and administration (Amended 06 May 2015)**

...
-----

... IM = intramuscular; vp = viral particles

...

\*\* The volume to be administered to children in younger age strata will depend on the dosage ChAd3-EBO-Z selected based on Phase 1 data on the concentration of the investigational ChAd3-EBO-Z vaccine and will be described in the Pharmacy Manual. the recommendation of the independent data monitoring committee as a lower vaccine dose may be selected based on safety and reactogenicity data accrued during the age de-escalation process (Refer to Section 1.2.2.1).



## 7. OCCURRENCE OF SUSPECTED OR CONFIRMED EBOLA VIRUS DISEASE

...

- Case details will be captured as part of SAE reporting. *In the case of a confirmed negative result, the event may be downgraded to non-serious.*  
(Amended 06 May 2015.)

...

### 9.1.3.2 Solicited general adverse events

...

**Table 17** Solicited general adverse events (Amended 06 May 2015)

...
-----

\* Fever is defined as temperature  $\geq 37.5^{\circ}\text{C}$  /  $99.5^{\circ}\text{F}$ . Body temperature ~~will~~ **may** be measured axillary (*preferred*), oral, tympanic, or rectal.

...

### 9.1.5 Adverse events of specific interest

#### 9.1.5.1 Clinical bleeding within 7 days post vaccination at Day 0

*In the Phase 1 studies with the investigational ChAd3-EB0-Z vaccine in healthy adults, transient decreases in thrombocyte counts were observed. These decreases occurred mostly on Day 1 after vaccination and generally returned to baseline by Day 7. Although most of these decreases remained within the normal range, the as per protocol criteria for thrombocytopenia (thrombocyte count of  $< 150 \times 10^3/\mu\text{L}$ ) were met for 2.6% (7 out of 270) of the vaccinated subjects. None of the decreases in thrombocyte counts or the cases of thrombocytopenia were clinically significant, i.e., no clinical signs or symptoms suggestive of increased tendency to bleed were reported in any of the subjects. Please refer to the IB for more information.*

*In the current study, a more vulnerable population (children) will be enrolled and the acceptable limit for the thrombocyte count for study eligibility (thrombocyte count of  $\geq 100 \times 10^3/\mu\text{L}$  is acceptable) will be lower as compared to the Phase 1 studies. In addition, in order to ensure enhanced vigilance from the Investigators, clinical bleeding events (according to the Standardised MedDRA Query clinical haemorrhage) within 7 days after vaccination at Day 0 will be recorded and reported as AEs of specific interest (clinical symptoms of thrombocytopenia).*

(Amended 06 May 2015.)

**9.3.1 Time period for detecting and recording adverse events, serious adverse events and pregnancies**

...

**Adverse events**

...

***Adverse events of specific interest***

***All AEs of specific interest (clinical symptoms of thrombocytopenia) starting in the 7-day follow-up period following vaccination at Day 0 must be recorded in the appropriate section of eSource.***

***(Amended 06 May 2015.)***

...

**Table 18 Reporting periods for collecting safety information (Amended 06 May 2015)**

Event Timepoint	Screening*	Vacc D0	end 7-day follow-up D6	end 30-day follow-up D29	Vacc M6	end 7-day follow-up M6 + 6 days	end 30-day follow-up M6 + 29 days	Study Conclusion M12
...								
Unsolicited AEs								
<b><i>AEs of specific interest (clinical symptoms of thrombocytopenia)</i></b>								
SAEs								
...								

**9.3.3.2.1 Assessment of intensity**

...

**Table 19 Intensity scales for solicited symptoms in infants/toddlers and children less than 6 years of age (Amended 06 May 2015)**

...
-----

...

**\*\* Fever is defined as temperature  $\geq 37.5^{\circ}\text{C}$  /  $99.5^{\circ}\text{F}$ . Body temperature ~~will~~ **may** be measured axillary (**preferred**), oral tympanic, or rectal.**

**Table 20 Intensity scales for solicited symptoms in children of 6 years of age or more (Amended 06 May 2015)**

...

...

\*\* Fever is defined as temperature  $\geq 37.5^{\circ}\text{C}$  /  $99.5^{\circ}\text{F}$ . Body temperature ~~will~~ **may** be measured axillary (**preferred**), oral tympanic, or rectal.

...

**9.4.1 Prompt reporting of adverse events of specific interest (clinical symptoms of thrombocytopenia), serious adverse events and pregnancies to the contracted research organisation (Quintiles) (Amended 06 May 2015)**

*Adverse events of specific interest (clinical symptoms of thrombocytopenia) that occur in the time period defined in Section 9.3.1 will be reported promptly to the CRO (Quintiles) within the timeframes described in Table 18, once the Investigator becomes aware of the event.*

*(Amended 06 May 2015.)*

...

**Table 21 Timeframes for submitting adverse events of specific interest (clinical symptoms of thrombocytopenia), serious adverse events, and pregnancies to the contracted research organisation (Quintiles) (Amended 06 May 2015)**

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
<b>AEs of specific interest (clinical symptoms of thrombocytopenia)</b>	<b>24 hours*</b>	<b>electronic AE/ SAE form in eSource</b>	<b>24 hours*</b>	<b>electronic AE/ SAE form in eSource</b>
<b>SAEs</b>	<b>24 hours*, †</b>	electronic AE/ SAE form in eSource	<b>24 hours*</b>	electronic AE/ SAE form in eSource
...				

...

† The Investigator will **always provide an assessment of causality** ~~be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic AE/ SAE form in eSource within 72-24~~ hours of submission of the SAE.

**9.4.2 Contact information for reporting adverse events of specific interest (clinical symptoms of thrombocytopenia), serious adverse events, and pregnancies (Amended 06 May 2015)**

<b>Study Contact for Reporting AEs of specific interest, SAEs, and pregnancies</b>
...
<b>Back-up Study Contact for Reporting AEs of specific interest, SAEs, and pregnancies</b>
...

**9.4.3 Reporting of adverse events of specific interest (clinical symptoms of thrombocytopenia) to the contract research organisation (Quintiles) (Amended 06 May 2015)**

*Once an Investigator becomes aware that an AE of specific interest (clinical symptoms of thrombocytopenia) has occurred in a study subject, the Investigator (or designee) must complete the information in the electronic AE/ SAE form in eSource WITHIN 24 HOURS. The AE and the SAE form in eSource is the same form. When an AE of specific interest (clinical symptoms of thrombocytopenia) is indicated on the electronic AE/ SAE form, additional follow-up questions will become available, for completion by the Investigator (or designee). The report will always be completed as thoroughly as possible with all available details of the event. Even if the Investigator does not have all information regarding an AE of specific interest (clinical symptoms of thrombocytopenia), the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.*

*The Investigator will always provide an assessment of causality at the time of the initial report.*

*Refer to Section 9.4.4.1 for the back-up system in case the electronic reporting system does not work.*

**9.4.4 Completion and transmission of serious adverse events reports to the contracted research organisation (Quintiles)**

...

The Investigator will always provide an assessment of causality ~~at the time of the initial report. The Investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic AE/ SAE form in eSource within 72~~ 24 hours of submission of the SAE.

*(Amended 06 May 2015.)*

**9.4.4.1 Back-up system in case the electronic reporting system does not work**

If the electronic reporting system does not work, the Investigator (or designate) must complete, then date and sign a paper *AE of specific interest (clinical symptoms of thrombocytopenia)*/SAE form and fax it to the Back-up Study Contact for Reporting SAEs within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the Investigator (or designate) must complete the electronic AE/ *AE of specific interest (clinical symptoms of thrombocytopenia)*/SAE form in eSource within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic *AE of specific interest (clinical symptoms of thrombocytopenia)*/SAE reporting system.

*(Amended 06 May 2015.)*

**9.4.6 Updating of adverse events of specific interest (clinical symptoms of thrombocytopenia), serious adverse events, and pregnancy information after removal of write access to the subject's eSource (Amended 06 May 2015)**

When additional *AE of specific interest (clinical symptoms of thrombocytopenia)*, SAE, or pregnancy information is received after removal of the write access to the subject's eSource, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the Investigator. The updated report should be faxed to the Back-up Study Contact for Reporting *AE of specific interest (clinical symptoms of thrombocytopenia)*, SAEs, and pregnancy information within the designated reporting time frames specified in Table 21.

*(Amended 06 May 2015.)*

**9.5.1.1 Follow-up during the study**

After the initial AE/ *AE of specific interest (clinical symptoms of thrombocytopenia)*/SAE report, the Investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to the CRO (Quintiles) (within 24 hours for *AEs of specific interest (clinical symptoms of thrombocytopenia)* and SAEs; refer to Table 21).

All *AEs of specific interest (clinical symptoms of thrombocytopenia)* and SAEs documented at a previous visit/ contact and designated as not recovered/ not resolved or recovering/ resolving will be reviewed at subsequent visits/ contacts until the end of the study.

...

*(Amended 06 May 2015.)*

#### **9.5.1.2 Follow-up after the subject is discharged from the study**

The Investigator will follow subjects with *AEs of specific interest (clinical symptoms of thrombocytopenia)* and SAEs until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the Investigator receives additional relevant information on a previously reported *AE of specific interest (clinical symptoms of thrombocytopenia)* or SAE, he/ she will provide this information to the CRO (Quintiles) using an electronic AE/ *AE of specific interest (clinical symptoms of thrombocytopenia)* / SAE form in eSource and/or pregnancy report as applicable.

The sponsor (GSK Biologicals) may request that the Investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the *AE of specific interest (clinical symptoms of thrombocytopenia)* or SAE. The Investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, the CRO (Quintiles) will be provided with any available post-mortem findings, including histopathology.

*(Amended 06 May 2015.)*

### **11.1 Primary endpoints**

...

- Occurrence of haematological (CBC, including differential count and platelet count) and biochemical (ALT, creatinine) laboratory abnormalities at Screening, Day 3, Day 6, Day 30, Month 6, Month 6 + 6 days, Month 6 + 30 days and Month 12 in all subjects in both groups.
- *Occurrence of clinical symptoms of thrombocytopenia (AE of specific interest), during a 7-day follow-up period after vaccination at Day 0 (i.e., Day 0 up to Day 6), in all subjects, in both groups.*

*(Amended 06 May 2015.)*

...

## 11.8 Analysis of safety

...

All analyses will be descriptive. Depending on the endpoint, data will be presented overall or for a sub-cohort of subjects. In a first step, the safety results will be presented by treatment administered at Day 0 (ChAd3-EBO-Z vaccine versus Placebo). In a second step, all **available** data post-vaccination with the investigational ChAd3-EBO-Z vaccine (ChAd3-EBO-Z vaccine at Day 0 and ChAd3-EBO-Z at Month 6) will be pooled. The latter aggregated data cannot be presented versus Placebo subjects because of the administration of the investigational ChAd3-EBO-Z vaccine to the subjects in the Group Placebo/ChAd3-EBO-Z, who initially received Placebo (population overlap).

*(Amended 06 May 2015.)*

...

SAEs *and AEs of specific interest (clinical symptoms of thrombocytopenia)* will be described in detail.

*(Amended 06 May 2015.)*

## 12.1 Electronic Case Report Form instructions (eSource)

...

In all cases, subject initials will ~~not~~ be collected **in eSource**, ~~not~~ **but will not be** transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable CRO standards and data cleaning procedures.

While completed eSource forms are reviewed by a CRO Site Monitor ~~at the study site~~, omissions or inconsistencies detected by subsequent eSource review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the Investigator or appropriately qualified designee. In all cases, the Investigator remains accountable for the study data.

*(Amended 06 May 2015.)*

...

## APPENDIX B      CLINICAL LABORATORIES (*Amended 06 May 2015*)

**Table 24      Outsourced laboratories**

Laboratory	Address
NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL)	Suite 150 9 West Watkins Mill Road Gaithersburg, MD 20878 <b>United States</b>
Quest Diagnostics	Focus Diagnostics Clinical Trials, Inc. (d/b/a Quest Diagnostics) 33608 Ortega Highway San Juan Capistrano, CA 92675-2042, United States of America

## APPENDIX C      ACCEPTABLE LIMITS FOR ELIGIBILITY AND TOXICITY GRADING SCALES FOR HAEMATOLOGY/ BIOCHEMISTRY PARAMETERS (*Amended 06 May 2015*)

...


**Table 25      Acceptable limits/normal ranges for eligibility determination  
(*Amended 06 May 2015*)**

...	...
ALT (IU/mL)	< 60 (males) or < 40 (females)

...



**Protocol Amendment 2 Sponsor Signatory Approval**

<b>eTrack study number and Abbreviated Title</b>	202090 (EBOLA Z CHAD3-004)
<b>IND number</b>	16300
<b>EudraCT number</b>	2014-004714-28
<b>Date of protocol amendment</b>	Amendment 2 Final: 06 May 2015
<b>Detailed Title</b>	A Phase 2, randomised, observer-blind, controlled, multi-country study to assess the safety and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (ChAd3-EBO-Z) (GSK3390107A), in children 1 to 17 years of age in Africa.
<b>Sponsor signatory</b>	Ripley Ballou Vice President Clinical Research and Translational Science
<b>Signature</b>	PPD 
<b>Date</b>	18 MAY 2015