NATIONAL BIOSAFETY AUTHORITY

Summary risk assessment report on the application for Confined Field Trial of a novel Rift Valley Fever Vaccine in sheep, goats, cattle and camels

Background information

The National Biosafety Authority (NBA) received an application for Confined Field Trial of a novel Rift Valley Fever Vaccine in sheep, goats, cattle and camels on 19th August, 2016. The application was administratively screened and acknowledged within the stipulated 30 days.

Rift Valley Fever (RVF) in livestock is characterized by high rates of mortality in newborn animals and abortions in those that are pregnant. Vaccination is an effective strategy for disease control in livestock, which also limits disease spillover into humans. Though highly immunogenic live RVF virus vaccines are available for livestock (e.g. Smithburn, Clone 13), these carry the risk of reversion to virulence and, as acknowledged by the Kenyan government's RVF contingency plan, make distinguishing infected from vaccinated animals (DIVA) difficult since they are based on whole RVF viruses. An RVF vaccine with DIVA capability is an urgent unmet need that would readily allow distinction between infected and susceptible animals, thus ensuring effective deployment of resources to high-risk areas during outbreaks. With approval from the NBA, ChAdOx1-GnGc, a DIVA vaccine composed of a replication-deficient simian adenovirus vector encoding RVF virus envelope glycoproteins was developed. Following its evaluation, ChAdOx1-GnGc showed that single-dose immunization is highly immunogenic and provides 100% protection from RVF virus challenge in sheep, goats and cattle sourced from local farms.

The objective of this confined use activity is to evaluate ChAdOx1-GnGc in a confined field trial to further assess its safety, and immunogenicity among sheep, goats, cattle and dromedary camels in Kenya. Specific objectives of the study are;

1. Screening for past exposure to RVF and random vaccination of 3-months old cattle, goats, sheep and camels with ChAdOx1-GnGc, the licensed live Smithburn vaccine (Riftvax™; made by KEVEVAPI) or placebo at the CFT.

2. General health monitoring of the animals throughout the study period, including assessment of rectal temperature over the first 3 days post-vaccination and monitoring for other systemic signs of ill health.

3. Serological analysis for virus neutralizing antibodies in sera collected pre-

vaccination, and at 1, 3, 6 and 12 months post-vaccination.

Results from this work will be used in a vaccine registration dossier for submission to the relevant Kenyan authorities to allow future use of ChAdOx1-GnGc in livestock in the country.

Summary details of the application

Title of application: Application for Confined Field Trial of a Novel Rift Valley Fever Vaccine in Sheep, Goats, Cattle and Camels

Applicant: International Livestock Research Institute (ILRI)

Collaborating Institutions: The Jenner Institute, University of Oxford, United Kingdom

Type of Application: Confined field trial (CFT)

Location of Research: ILRI - Kapiti Ranch, Machakos County, 1°38'00.6"S 37°08'46.1"E

Parental Organisms: ChAdOx1 is a replication-deficient vaccine vector derived from a **simian adenovirus**. It has been rendered replication-deficient by removal of the E1 gene.

Trait being modified: Animal vaccines rationally designed for the specific control and eradication of diseases, including the implementation of DIVA (differentiating infected from vaccinated animals) strategies.

Genetic modification method used: ChAdOx1-GnGc was prepared by Gateway® recombination between the ChAdOx1 vector and an entry plasmid containing the coding sequence for RVF virus envelope glycoproteins. After viral rescue, ChAdOx1-GnGc was propagated in the HEK293 cell line and subsequently purified by caesium chloride (CsCl) gradient ultracentrifugation.

Risk Assessment Summary Table

	Issues of concern	Potential adverse effects (Hazard)	Estimation of likelihood	Consequences if the adverse effect were to happen	Estimation of risk/consequences (HazardxLikelihood)	Risk management measures	Acceptable/ Manageable
1	Gene flow	Vertical gene transfer: Possibility of out-crossing	Unlikely	Minor	Risk of crossing with sexually compatible relatives is low	• ChAdOx1 has been rendered replication-deficient by removal of the E1 gene and can only replicate in cell lines that express E1 (e.g. HEK293 cell line). • ChAdOx1-Gn-Gc is not shed, has a low environmental stability and there are low incidences of viruses that present sequence homology with ChAdOx-1-Gn-Gc	Acceptable
		Horizontal gene transfer	Unlikely	Minor	Risk of transfer of ChAdOx1-Gn-Gc to unvaccinated animals is low	• ChAdOx1 is not capable of causing an infection in humans or animals, although it will transduce human and animal cells (i.e. the virus will enter a cell and express the recombinant protein, but no infectious viral particles can be produced). • The human or animal's immune response rapidly clears the vaccine vector from circulation • There is no vaccine shedding among the vaccinated animals.	Acceptable
2	GMO handling	Possibility of inadvertent loss of experimental material	Unlikely	Minor	Risk of escape of experimental material is low	• The imported vaccine will be stored in a designated secure -80 ^{o}C freezer at ILRI. • On the day of immunization, vaccine will be transported to the Kapiti ranch by means of an ILRI vehicle, accompanied by the PI and a representative from the DVS • Vaccinated animals (with unique ID no.) will be confined at the ranch, which is fully secured with fencing with 24-hour security. • Any remaining vaccine will be transported back to the ILRI and autoclaved and/or incinerated • All harvested animal samples will also be stored in secure -80 ^{o}C freezers and liquid nitrogen tanks at ILRI.	Acceptable
3	Persistence and invasiveness	Possibility of increased fitness or competitive advantage	Unlikely	Minor	Risk of wild uncontrolled growth is low	• During the contained use trial no shedding of ChAdOx1-GnGc was observed among vaccines. • The vaccine was not transmitted to co-housed sentinel animals, proof that ChAdOx1 vaccine vector is therefore not capable of persisting in the environment. • ChAdOx1-GnGc vaccine is not able to replicate outside of the laboratory environment and is therefore not capable of persisting in the environment.	Acceptable
4	Gene safety	Adverse effects on human and animal health	Unlikely	Marginal	The risk of Allergenicity, Toxicity and Pathogenicity occurring is negligible	• Replication-deficient simian adenoviruses (including ChAdOx1) have been used in previous and currently ongoing human clinical trials of vaccines against malaria, HIV, TB, human influenza, Ebola, among others, in many thousands of adults, children and infants in Europe	Acceptable

						and Africa. • They have also been used for livestock vaccines against TB and RSV, further reinforcing their • Despite their extensive use there has been no report of reversion to replication competency of any of these vaccine vectors • The Gn and Gc are non-toxic and non-allergenic (Kortekaas *et al*, .2014). They have been used in numerous pre-clinical and field trials either as DNA vaccines, protein vaccines or in other viral vectored systems.	
5	Stability of inserted gene	Gene disintegration	Unlikely	Minor	The risk of gene disintegration in subsequent generations is low	• ChAdOx1-GnGc was evaluated in a contained trial in sheep, goats and cattle at ILRI, Nairobi where no vaccine shedding was observed among the vaccinated animals.	Acceptable
6	Non target organisms	Adverse effect on other non-targeted organisms leading to loss of bio-diversity	Unlikely	Marginal	The risk of the inserted genes causing adverse effects on non-targets is negligible	• ChAdOx1 has been rendered replication-deficient by removal of the E1 gene and can only replicate in cell lines that express E1. • It is therefore not capable of causing an infection in humans or animals, although it will transduce human and animal cells (i.e. the virus will enter a cell and express the recombinant protein, but no infectious viral particles can be produced).	Acceptable

Overall conclusion on risk and risk management

The likelihood of risk arising from this research is low considering the scope of application. ChAdOx1 has been rendered replication-deficient and it is therefore not capable of causing an infection in humans or animals. During the contained use experiment, no shedding of ChAdOx1-GnGc was observed among the vaccinated animals and the vaccine was not transmitted to co-housed sentinel animals. The ChAdOx1 vaccine vector is not capable of persisting in the environment. Further, replication-deficient simian adenoviruses (including ChAdOx1) have been used in previous and currently ongoing human clinical trials of vaccines against malaria, HIV, tuberculosis, human influenza, Ebola, among others, in many thousands of adults, children and infants in Europe and Africa. They have also been used for livestock vaccines against tuberculosis and Respiratory Syncytial Virus in multiple livestock species. In this extensive use there has not been any report of reversion to replication competency of any of these vaccine vectors. The Gn and Gc envelope glycoproteins are non-toxic and non-allergenic and have been used in numerous pre-clinical and field trials either as DNA vaccines, protein vaccines or in other viral vectored systems.

Additionally, the vaccinated animals will be confined at the ILRI Kapiti ranch, which is fully secured with 24-hour security and restricted access. All study animals will have unique identification numbers by ear tag, and records kept of their arrival at the trial site till end of the study. No animal product is expected to be consumed either by humans or animals hence food/feed safety concerns at this stage are negligible.

Decision
The application is approved with the following conditions:

1. Import permit for ChAdOx1-Gn-Gc vaccine must be obtained from Directorate of Veterinary Services (DVS) who will ensure that the vaccine is well packaged and securely transported from the airport to ILRI.

2. The Confined Field Trial site must be inspected by NBA and DVS before the commencement of the trial.
3. Strict adherence to biosafety and biosecurity measures to avoid environmental contamination.
4. A representative from NBA and DVS to be present during the vaccination and the disposal of all unused vaccines.
5. A detailed schedule of activities and the experimental design must be provided both to NBA and DVS before commencement of the trial to aid in monitoring purposes.

6. Put and implement measures to ensure that no transgenic material from the laboratory and the CFT enters the human food or animal feed chain.

7. The trial animals shall be monitored for vaccine viraemia in milk, meat, blood and nasal secretions for the first month and subsequently on quarterly basis for 12 months post-immunization. The study animals selected for slaughter and having the ChAdOx1 vaccine shall be incinerated under the supervision of NBA and DVS. The data collected during the monitoring period shall be submitted to NBA and DVS who will make a determination on whether the experimental animals can be allowed back in to the food chain.

8. Provide quarterly and annual progress reports to NBA in the prescribed format. The reports should be discussed by and forwarded through ILRI Institutional Biosafety Committee (IBC).

Approval details

Approval number: NBA/GMO/C09/18/27

Approval Date: 25th November, 2016

Duration of approval: 5 years (Renewable)

Approved by,

Prof. Dorington O. Ogoyi **Date: 18th April 2020**
Chief Executive Officer
National Biosafety Authority - Kenya