PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

(a)	Member State of notification	Belgium
(b)	Notification number	B_BE_21_BVW2
(c)	Date of acknowledgement of notification	../April/2021
(d)	Title of the project	**Phase I, single-centre, randomized, double blind, placebo-controlled study to assess safety, tolerability and immunogenicity of hRVFV-4s vaccine in healthy subjects**
(e)	Proposed period of release	From 01/11/2021 until 24/10/2022

2. Notifier

Name of institution or company: Wageningen Bioveterinary Research

3. GMO characterisation

(a) Indicate whether the GMO is a:

viroid		(.)
RNA virus		(x)
DNA virus		(.)
bacterium		(.)
fungus		(.)
animal		
-	mammals	(.)
-	insect	(.)
-	fish	(.)
-	other animal	(.)

specify phylum, class:

Phylum: Negarnaviricota
Subphylum: Polyploviricotina
Class: Ellioviricetes

(b) Identity of the GMO (genus and species)

Order:	*Bunyavirales*
Family:	*Phenuiviridae* (formerly *Bunyaviridae*)
Genus:	*Phlebovirus*
Species:	*Rift Valley fever virus*
Strain:	*Clone 13*
Vaccine name:	*hRVFV-4s*

(c) Genetic stability – according to Annex IIIa, II, A(10)
The hRVFV-4s vaccine strain was passaged in Vero cells, to be used for manufacturing of the vaccine, after which the complete genome was sequenced using next-generation, full genome sequencing. The virus was found to be genetically stable upon repeated passage (>20 times) in these cells.
The parent virus (RVFV strain Clone 13) is not known to recombine and no homologous sequences are present that may facilitate recombination. Bunyaviruses can reassort their genome segments, but the risk of reassortment is considered negligible as hRVFV-4s, nor the Clone 13 parent strain, cause viremia. Furthermore, RVFV is not present in Belgium, where the clinical trial will be performed, further minimizing any hypothetical risk of genome reassortment with wild-type RVFV or dissemination of the vaccine virus via mosquitoes.

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?
Yes (.) No (x)
If yes, insert the country code(s) …

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?
Yes (.) No (x)
If yes:
- Member State of notification …
- Notification number B/../../…

Please use the following country codes:
Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?
Yes (.) No (x)
If yes:
- Member State of notification …
- Notification number B/../../…

7. Summary of the potential environmental impact of the release of the GMOs.
No environmental impact is foreseen. Based on the extensive non-clinical studies performed with the hRVFV-4s candidate vaccine in the most susceptible species naturally affected by

the wild-type virus, no untoward effects are expected in humans. Additionally no viremia, shedding or spreading to the environment is foreseen, either directly or via mosquitoes. The hRVFV-4s candidate vaccine was shown to be genetically stable and there is no environmental risk of reversion to virulence through recombination or reassortment.

B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

(a) Indicate whether the recipient or parental organism is a:

(select one only)

viroid	(.)
RNA virus	(x)
DNA virus	(.)
bacterium	(.)
fungus	(.)
animal	
- mammals	(.)
- insect	(.)
- fish	(.)
- other animal	(.)

(specify phylum, class):
Phylum: Negarnaviricota
Subphylum: Polyploviricotina
Class: Ellioviricetes

other, specify …

2. Name

(i)	order and/or higher taxon (for animals)	Bunyavirales
(ii)	genus	Phlebovirus
(iii)	species	Rift Valley fever virus
(iv)	subspecies	N.A.
(v)	strain	Clone 13
(vi)	pathovar (biotype, ecotype, race, etc.)	Veterinary vaccine strain
(vii)	common name	Clone 13

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes (.) No (x) Not known (.)

(b) Indigenous to, or otherwise established in, other EC countries:

(i) Yes (.)

If yes, indicate the type of ecosystem in which it is found:

Atlantic	..
Mediteranean	..
Boreal	..
Alpine	..
Continental	..
Macaronesian	..

(ii) No (x)
(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?
Yes (.) No (x)

(d) Is it frequently kept in the country where the notification is made?
Yes (.) No (x)

4. Natural habitat of the organism

(a) If the organism is a microorganism

water	(.)
soil, free-living	(.)
soil in association with plant-root systems	(.)
in association with plant leaf/stem systems	(.)
other, specify	

The parental organism is a naturally attenuated and highly attenuated virus and cannot be maintained in the environment.

(b) If the organism is an animal: natural habitat or usual agroecosystem:
Not applicable

5. (a) Detection techniques
The parental virus (Clone 13) can be detected by conventional reverse-transcriptase quantitative PCR (RT-qPCR) using RVFV-specific primers and probe and by Sanger- or next-generation sequencing. The viruses can also be detected using antibodies against the N, Gn or Gc protein in Western blots, immunoperoxidase monolayer assays (IPMA) or virus neutralization test (VNT).

(b) Identification techniques
The parental virus (Clone 13) can be identified by conventional reverse-transcriptase quantitative PCR (RT-qPCR) using RVFV-specific primers and probe. The virus can furthermore be identified by Sanger- or next-generation sequencing. The virus can also be identified using antibodies against the N, Gn or Gc protein in Western blots and IPMA.

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?

Yes (X) No (.)

If yes, specify The wild-type RVFV is classified as a biosafety level-3 organism in line with Directive 2000/54/EC of the European Parliament and of the Council on the protection of workers from risks related to exposure to biological agents at work. The German "Zentrale Kommission für die Biologische Sicherheit" (ZKBS) has classified Clone 13 as a risk class 2 organism.

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

Yes (x) No (x) Not known (.)

If yes:

(a) to which of the following organisms:

humans	(x) only relevant for wild-type RVFV
animals	(x) only relevant for wild-type RVFV
plants	(.)
other	(.)

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC

Rift Valley fever (RVF) is a disease that is caused by Rift Valley fever virus (RVFV). Humans can become infected via contact with tissues of diseased animals, although the virus is not contagious (transmission depends on mosquito vectors). Infected humans generally develop a self-limiting febrile illness, whereas up to 2% of patients develop encephalitis with occasionally severe neurological sequelae, or haemorrhagic icterus with a high case-fatality rate.

The parental organism of the hRVFV-4s vaccine, named Clone 13, is a natural isolate that lacks 69% (549 nucleotides) of the gene encoding NSs, which is the major virulence determinant of the virus. The Clone 13 strain is avirulent in animals that are naturally affected by the wild-type virus, although this attenuated virus can still cross the ovine placenta and is still pathogenic to the ovine fetus. The further attenuated hRVFV-4s vaccine was shown not to transmit to the ovine fetus and to be completely safe for young lambs, which are the most susceptible target animals. The vaccine was furthermore shown to be completely safe for (nude) mice, rats, and marmosets. The parent organism (Clone 13) as well as hRVFV-4s do not cause viremia in animals known to be the most susceptible to the wild-type virus, explaining that viremia is also not expected in vaccinated humans. This renders any theoretical risk of transmission via mosquitoes (to humans or non-target organisms) negligible. RVFV was never reported to induce a latent infection and the virus is not known to persist or colonize other organisms.

8. Information concerning reproduction

(a) Generation time in natural ecosystems:

Wild-type RVFV can survive in infected mosquitoes for weeks to months and potentially in dehydrated mosquito eggs. The virus can also be maintained in the environment in mosquito-vertebrate-mosquito transmission cycles. However, whereas

the parental virus (Clone 13) can infect mosquitoes, the virus cannot be transmitted from vertebrates by mosquitoes, as Clone 13 does not cause viremia in vertebrates. Similarly, the hRVFV-4s vaccine virus does not cause viremia in the most susceptible target species. The hRVFV-4s vaccine virus is therefore not able to survive or replicate in natural ecosystems.

(b) Generation time in the ecosystem where the release will take place:
Not applicable.

(c) Way of reproduction: Sexual .. Asexual ..
Not applicable.

(c) Factors affecting reproduction:
Not applicable

9. Survivability

(a) ability to form structures enhancing survival or dormancy:

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (funghi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify	

Not applicable

(b) relevant factors affecting survivability:
Wild-type RVFV and the parental organism (Clone 13) may survive on contaminated surfaces for a number of hours, but data on this is not available. However, neither wild-type RVFV nor Clone 13 was ever reported to be transmitted via contaminated surfaces.

10. (a) Ways of dissemination
The parental organism (Clone 13) was shown to disseminate in interferon deficient mice (albeit not between animals) and to be capable of transmitting to the ovine fetus, resulting in congenital malformations. The virus cannot spread between animals or to the environment as the virus does not cause viremia which is necessary for dissemination via mosquitoes. Importantly, the further attenuated hRVFV-4s vaccine was shown not to transmit across the ovine placenta.

(b) Factors affecting dissemination
The parental virus (Clone 13) can only disseminate in mice lacking a functional Type I interferon system, possibly in the placenta of pregnant ewes, and in the ovine foetus.

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)
…, B/../../…

Not applicable.

C. **Information relating to the genetic modification**

1. Type of the genetic modification

(i)	insertion of genetic material	(.)
(ii)	deletion of genetic material	(x)
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify	

Compared to the Clone 13 parent virus, the hRVFV-4s vaccine virus contains a split M genome segment, resulting in a four-segmented RVFV strain. Compared to wild-type RVFV, the hRVFV-4s vaccine virus additionally lacks 69% of the NSs gene.

2. Intended outcome of the genetic modification
The Clone 13 parental virus contains a deletion of 69% of the NSs gene, which is the only known virulence determinant of RVFV, functioning as an antagonist of host innate immune responses. The split M genome segment was shown to render an otherwise highly virulent RVFV strain completely avirulent in the mouse model. The 69% deletion in the NSs gene and the split M genome segment thereby independently contribute to the avirulent phenotype of hRVFV-4s for even the most susceptible target animals.

3. (a) Has a vector been used in the process of modification?

Yes (.) No (x)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?

Yes (.) No (.)

If no, go straight to question 5.

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

plasmid	(.)
bacteriophage	(.)
virus	(.)
cosmid	(.)
transposable element	(.)
other, specify …	

(b) Identity of the vector
…

(c) Host range of the vector
…

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes (.) No (.)

antibiotic resistance (.)
other, specify …

Indication of which antibiotic resistance gene is inserted
…

(e) Constituent fragments of the vector
…

(f) Method for introducing the vector into the recipient organism

(i) transformation (.)
(ii) electroporation (.)
(iii) macroinjection (.)
(iv) microinjection (.)
(v) infection (.)
(vi) other, specify …

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

(i) transformation (.)
(ii) microinjection (.)
(iii) microencapsulation (.)
(iv) macroinjection (.)
(v) other, specify:

The modification (the split M genome segment) was designed *in silico* and the resulting genome was synthesized (with cloning steps in *E. coli*) at the GenScript Corporation. The resulting plasmids were used to transfect cells, resulting in the production of the vaccine virus.

6. Composition of the insert

(a) Composition of the insert
Not applicable. There is no insert.

(b) Source of each constituent part of the insert
Not applicable. There is no insert.

(c) Intended function of each constituent part of the insert in the GMO
Not applicable. There is no insert.

(d) Location of the insert in the host organism

- on a free plasmid (.)

- integrated in the chromosome (.)
- other, specify: Not applicable. There is no insert.

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No (.)
If yes, specify …

Not applicable.

D. Information on the organism(s) from which the insert is derived

Not applicable. The hRVFV-4s vaccine virus does not contain any foreign gene sequences (there is no insert).

1. Indicate whether it is a:

viroid (.)
RNA virus (.)
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals (.)
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class) …

other, specify

Not applicable. There is no insert.

2. Complete name

(i) order and/or higher taxon (for animals) …
(ii) family name for plants …
(iii) genus …
(iv) species …
(v) subspecies …
(vi) strain …
(vii) cultivar/breeding line …
(viii) pathovar …
(ix) common name …

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (.) Not known (.)
If yes, specify the following:

(b) to which of the following organisms:

humans (.)
animals (.)
plants (.)
other ..

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism
Yes (.) No (.) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):
…

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?
Yes (.) No (.)
If yes, specify …

5. Do the donor and recipient organism exchange genetic material naturally?
Yes (.) No (.) Not known (.)

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?
Yes (x) No (.) Not known (.)
Specify

The hRVFV-4s vaccine virus is strongly attenuated when compared to the parental organism (Clone 13). This is expected to result in absent or lower dissemination in a vaccinated human. However, also the parental organism is not expected to survive in animals or humans, due to its high attenuation.

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
Yes (x) No (.) Unknown (.)
Specify
The hRVFV-4s vaccine virus replicates to lower levels as the parental organism.

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?
Yes (x) No (.) Not known (.)
Specify
Whereas the parental organism can still replicate in mosquito cells, the hRVFV-4s vaccine virus replicates very poorly in these cells. Both the GMO and the parental organism (Clone 13) cannot sustain replication in interferon-competent human cells.

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?

Yes (x) No (.) Not known (.)

Specify

The hRVFV-4s vaccine is strongly attenuated compared to the already largely avirulent parent strain. Whereas Clone 13 is still pathogenic to immunocompromised mice and the ovine fetus, hRVFV-4s was shown to be avirulent in (nude) mice and not to transmit the ovine placenta.

2. Genetic stability of the genetically modified organism

The virus is very stable, with no mutations accumulating during 20 passages in Vero cells, as demonstrated by full genome sequencing. The risk of recombination is considered negligible as no homologous sequences are present in the genome segments. The risk of recombination or reassortment with wild-type virus is considered negligible as wild-type RVFV does not occur in Belgium, where the clinical trial will be performed. Furthermore, even if recombination or reassortment would occur, the risk that this results in more pathogenic strains is considered negligible as further detailed in the Technical Dossier (B3a).

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?

Yes (.) No (x) Unknown (.)

(a) to which of the following organisms?

humans (.)
animals (.)
plants (.)
other …

Not applicable

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)

Annex III A, point II (A)(11)(d) addresses the "*pathogenicity: infectivity, toxigenicity, virulence, allergenicity, carrier (vector) of pathogen, possible vectors, host range including non-target organism. Possible activation of latent viruses (proviruses) and ability to colonise other organisms*". The Clone 13 strain is avirulent in laboratory animals and natural target species, although the virus is pathogenic for immunodeficient mice and the ovine fetus. The hRVFV-4s vaccine was however shown to be further attenuated and shown to be avirulent in nude mice and not to transfer the ovine placenta. The hRVFV-4s vaccine is not expected to be virulent, not toxic or allergenic in humans and does not colonize other organisms.

Annex III A, point II(C)(2)(i) addresses the "*considerations for human health and animal health, as well as plant health*". The strong attenuation of hRVFV-4s is

exemplified by being avirulent in nude mice (mice lacking T cells), suggesting that the vaccine can possibly be applied even in humans with immunodeficiencies. Neither Clone 13 or hRVFV-4s has a capacity of colonization.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
Although there are numerous methods that can be used to detect the virus in the environment, the vaccine virus cannot establish itself outside interferon-deficient cells. It is therefore not likely that the vaccine virus can ever be detected in environmental samples. However, if such analyses would be performed, the RVFV-specific RT-(q)PCR can be applied as the most sensitive method.

(b) Techniques used to identify the GMO
The GMO can be identified by RT-PCR followed by sequencing.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
The purpose of the release is the performance of a Phase I, single-centre, randomized, double-blind, placebo-controlled study to assess safety, tolerability and immunogenicity of the hRVFV-4s vaccine in healthy subjects. Upon successful completion of the study, stockpiling of the vaccine and a Phase II study are foreseen. The vaccine can subsequently be used in emergency situations.

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?
Yes (x) No (.)
If yes, specify:
The Phase I trial will be performed in Belgium, where RVFV is not present.

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):
Center for Vaccinology (CEVAC), University Hospital Ghent, Corneel Heymanslaan 10, 9000 Ghent, Belgium.

(b) Size of the site (m^2): … m^2
(i) actual release site (m^2): … m^2
(ii) wider release site (m^2): … m^2
Not applicable.

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
Not applicable.

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO

Not applicable.

4. Method and amount of release

(a) Quantities of GMOs to be released (injected in volumes of 500µl):
20 human subjects will be injected with a dose of $3x10^4$ +/- 0.5 log $TCID_{50}$ of hRVFV-4s
20 human subjects will be injected with a dose of $3x10^5$ +/- 0.5 log $TCID_{50}$ of hRVFV-4s
20 human subjects will be injected with a dose of $3x10^6$ +/- 0.5 log $TCID_{50}$ of hRVFV-4s

The optimal dose level will be identified based on the available safety and immunogenicity data and data on virus shedding and spreading.

(b) Duration of the operation:
The total duration of the study (First Patient In, Last Patient Out): 11-12 months.

(c) Methods and procedures to avoid and/or minimize the spread of the GMOs beyond the site of the release

After injection of the vaccine, the injection site is covered with a wound dressing to prevent dissemination from the injection site. Healthcare personnel administrating the vaccine will wear protective gloves. Also, the GMO could be introduced into an ecosystem via a spill. However, the Phase 1 clinical trial will be performed in a clinical trial centre and spill cleaning procedures are adopted. Therefore, introduction into an ecosystem outside the clinical trial centre setting is highly unlikely.

Exposure during contact with participants in follow-up visits or when handling of samples collected from the participant and preparing for shipment is not expected, as no multiplication or shedding is anticipated.

5. Short description of average environmental conditions (weather, temperature, etc.)
Belgium has a temperate climate characterized by mild winters and cool summers. In the summers it can be rainy, humid and cloudy. Average annual temperature is 10 degrees °C.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.
There was not previous release of this GMO.

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organism (if applicable)
(i) order and/or higher taxon (for animals) …
(ii) family name for plants …
(iii) genus …

(iv) species …
(v) subspecies …
(vi) strain …
(vii) cultivar/breeding line …
(viii) pathovar …
(ix) common name …
Not applicable

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)
Not applicable

3. Any other potentially significant interactions with other organisms in the environment
Not applicable

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
Yes (.) No (x) Not known (.)
Give details
The GMO was shown to be genetically stable in cells in which the virus replicates optimally, whereas very little, if any, replication is expected to occur in vaccinated humans. Competitiveness is not relevant and increase invasiveness is not expected.

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established
The parental virus, Clone 13, does not cause viremia in any animal species evaluated and hRVFV-4s is a further attenuated virus. Neither Clone 13, nor hRVFV-4s can therefore be taken up by mosquitoes upon feeding on a vaccinated subject. Therefore the vaccine virus cannot disseminate from the site of release.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

(i) order and/or higher taxon (for animals) …
(ii) family name for plants …
(iii) genus …
(iv) species …
(v) subspecies …
(vi) strain …
(vii) cultivar/breeding line …
(viii) pathovar …
(ix) common name …

Not applicable

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:

Bunyaviruses, RVFV and more specifically the Clone 13 strain are RNA viruses and are not known to exchange genetic information.

(b) from other organisms to the GMO:
Not applicable.

(c) likely consequences of gene transfer:
Not applicable.

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):
Studies have been performed with laboratory animals (mice, rats), lambs, pregnant ewes, and marmosets. In all species evaluated, the vaccine was completely avirulent, did not result in any clinical sign and did not result in viremia.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
Not applicable.

H. Information relating to monitoring

1. Methods for monitoring the GMOs
After vaccination, urine, saliva, semen and blood samples will be collected at regular intervals, which will be tested for the presence of vaccine virus RNA using the most sensitive reverse-transcriptase quantitive PCR.

2. Methods for monitoring ecosystem effects
No ecosystem effects are expected and will not be monitored.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
Bunyaviruses were never found to donate genetic material to other organisms.

4. Size of the monitoring area (m^2)
… m^2
Not applicable.

5. Duration of the monitoring
Monitoring of each group will continue until day 180.

6. Frequency of the monitoring
Two cohorts will be monitored on day -28 and on days 0, 1, 3, 7, 14, 28, and 180.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
The hRVFV-4s candidate vaccine can only infect the vaccinated individual and is not expected to survive in the environment. If needed, and depending on the affected area, chemical disinfection can be used. Chemical decontamination of surfaces or equipment

contaminated with hRVFV-4s and chemical inactivation of the GMO will be performed with hypochlorite (Javel) at 0.1% active chorine. For this 1 part of Javel (5.5% chlorine) will be diluted approximately 50-fold in water. Minimal decontamination time will be 60 minutes.

2. Post-release treatment of the GMOs
Not applicable.

3. (a) Type and amount of waste generated
Waste that can be expected to contain hRVFV-4s is limited to materials at the clinical trial centers that contain or have been exposed to the vaccine (*e.g.* residual doses, empty containers, equipment used during visits of and sampling of participants. The amount of waste generated at the clinical trial centers is not expected to be significant and will be within the normal handling capacity.

3. (b) Treatment of waste
After vaccine preparation and dosing, all medical hazardous waste will be removed in UN-approved yellow polyethylene containers, collected by an approved transporter of medical hazardous waste and transported directly to one of the approved incinerators in Belgium.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread
In the unexpected event that hRVFV-4s vaccination results in viremia, the risk of further dissemination is considered negligible, as transmission of RVFV from humans to other humans (or animals) via mosquitoes was never demonstrated. Humans are consequently considered dead-end hosts as they are not believed to develop sufficiently high viremia to enable transmission via mosquitoes. Accordingly, most human infections are attributed to contact with tissues of diseased animals (nosocomial transmission was also never reported).

2. Methods for removal of the GMO(s) of the areas potentially affected
The hRVFV-4s candidate vaccine can only infect the vaccinated individual and is not expected to survive in the environment. If needed, and depending on the affected area, chemical disinfection can be used. Chemical decontamination of surfaces or equipment contaminated with RVFV-4s and chemical inactivation of the GMO will be performed with hypochlorite (Javel) at 0.1% active chorine. For this 1 part of Javel (5.5% chlorine) will be diluted approximately 50-fold in water. Minimal decontamination time will be 60 minutes.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread
Not applicable. The hRVFV-4s vaccine virus cannot survive in the environment.

4. Plans for protecting human health and the environment in the event of an undesirable effect
Not applicable. In the event of an undesirable effect, the risk for humans not taking part of the clinical trial or the environment is considered negligible.