PART 1

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

A. GENERAL INFORMATION

1. Details of notification

a) Member State of notification FRANCE
b) Notification number B/FR/13/GT03
c) Date of acknowledgement of notification 04/06/2013
d) Title of the project Phase I/II open-label randomized multicenter trial to assess immunogenicity and safety of 4 prime-boost combinations of HIV vaccine candidates (MVA HIV-B/LIPO-5; LIPO-5/MVA HIV-B; GTU-MultiHIV B/LIPO-5; GTU-MultiHIV B/MVA HIV-B) in healthy volunteers at low risk of HIV infection (ANRS VRI01)
e) Proposed period of release 56 weeks from the start of the clinical trial (December 2013)

2. Notifier

Name of institution or company Institut national de la santé et de la recherche médicale-Agence nationale de recherches sur le sida et les hépatites virales (Inserm-ANRS) 101 rue de Tolbiac 75013 PARIS

3. GMO characterization

a) Indicate whether the GMO is a:

- Viroid ☐
- RNA virus ☐
- DNA virus ☐
- bacterium ☐
- fungus ☐
- animal ☐
  - mammals ☐
  - insect ☐
  - fish ☐
  - other animal ☐ please specify phylum, class

other, please specify (kingdom, phylum and class): Naked plasmid DNA
b) Identity of the GMO (genus and species) GTU-MultiHIV B Naked Plasmid DNA Vaccine
c) Genetic stability – according to Annex IIIa, II, A(10) Donor: the gene inserts are derived from Han-2 isolate clade B HIV. The donor is not stable in the normal environment Concerning the GMP: Plasmid DNA is not stable in the normal environment

4. <u>Is the same GMO release planned elsewhere in the Community [in conformity with Article 6 (1)], by the same notifier</u>?

Yes ☐	No ☒
If yes, insert the country code(s):	

5. <u>Has the same GMO been notified for release elsewhere in the Community by the same notifier?</u>

Yes ☐	No ☒
If yes: – Member State of notification - Notification number	

6. <u>Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier</u>?

Yes ☐	No ☒
If yes: – Member State of notification - Notification number	

7. Summary of the potential environmental impact of the release of the GMOs

According to biodistribution data of the GTU®-MultiHIV B, its dissemination out off the injection site (in environment) is strongly limited.

Due to the low probability of dissemination of this plasmid, contamination of healthcare staff and family circle is highly unlikely. Besides, the intramuscular route of administration selected for the clinical trial minimizes the possibility of plasmid leakage.

B. INFORMATION RELATING TO THE RECIPIENT OR PARENTAL ORGANISMS FROM WHICH THE GMO IS DERIVED

1. Recipient or parental organism characterization:

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

Viroid	☐	
RNA virus	☐	
DNA virus	☐	
bacterium	☒	(Production organism)
fungus	☐	
animal	☐	
- mammals	☐	
- insect	☐	
- fish	☐	
-other animal	☐	(please specify phylum, class)

other, please specify The recipient in clinical trials: Homo Sapiens

2. Name (applicable for the Production Organism)

(i) Order and/or higher taxon (for animals)

Not applicable

(ii) Genus

Escherichia

(iii) Species

coli

(iv) Subspecies

Not applicable

(v) Strain AG-1
(vi) pathovar (biotype, ecotype, race, etc.) Not applicable
(vii) common name *Escherichia coli* AG-1 (Commercially available from Stratagene)

3. <u>Geographical distribution of the organism</u> – Not Applicable

a) Indigenous to, or otherwise established in, the country where the notification is made: Yes ☐ No ☐ 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 ☐ Mediterranean ☐ Arctic ☐ Alpine ☐ Continental ☐ (ii) No ☐ (iii) Not known ☐
c) Is it frequently used in the country where the notification is made? Yes ☐ No ☐
d) Is it frequently kept in the country where the notification is made? Yes ☐ No ☐

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 ☐ in association with animals ☐ other (specify) Not applicable
(b) If the organism is an animal: natural habitat or usual agroecosystem: Not applicable

5. a) Detection techniques

Donor genes can be identified with molecular detection methods (PCR based assays, northern blot and western blots).

5. b) Identification techniques

The identification techniques of the plasmid DNA product comprise: restriction enzyme analyses and sequencing analyses.

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

Yes ☐	No ☒
If yes, specify	

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

Yes ☐	No ☒	Not known ☐
If yes: a) to which of the following organisms: humans ☐ animals ☐ plants ☐ other ☐		
b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC Not applicable		

8. Information concerning reproduction – Not applicable

a) Generation time in natural ecosystems: Not applicable
b) Generation time in the ecosystem where the release will take place: Not applicable
c) Way of reproduction: Not applicable Sexual ☐ Asexual ☐
d) Factors affecting reproduction: Not applicable

9. Survivability

a) Ability to form structures enhancing survival or dormancy: Not applicable (i) endospores ☐ (ii) cysts ☐ (iii) sclerotia ☐ (iv) asexual spores (fungi) ☐ (v) sexual spores (fungi) ☐ (vi) eggs ☐ (vii) pupae ☐ (viii) larvae ☐ (ix) other, please specify
b) Relevant factors affecting survivability: Not applicable

10. a) Ways of dissemination

Not applicable

10. b) Factors affecting dissemination

Not applicable

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)

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	☐
(iii) Base substitution	☐
(iv) Cell fusion	☐
(v) Other, please specify	

2. Intended outcome of the genetic modification

The investigational vaccine developed by FIT Biotech is designed to induce immune responses to six proteins or protein fragments of HIV (three regulatory gene products Rev, Nef, Tat and structural gene products (Pol, Gag, Env).

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

Yes ☒	No ☐
If no, go straight to question 5.	

3. 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, please specify

b) Identity of the vector

GTU®-MultiHIV B

c) Host range of the vector

Not applicable

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

Yes ☐ No ☒

Antibiotic resistance ☐

Other, specify

The vector backbone contains the kanamycin resistance gene which primary role is only in the selection of the production organism (*E. coli* AG-1) and not active in the final investigational product intended to be administered to the recipient: *Homo sapiens*.

e) Constituent fragments of the vector

Donor genes: HIV-1 Han-2 isolate clade B regulatory genes Rev, Nef, Tat and structural genes p17 and p24 as well as more than 20 Th and CTL epitopes of protease, reverse transcriptase and gp160.

f) Method for introducing the vector into the recipient organism

(i) transformation ☐
(ii) electroporation ☐
(iii) macroinjection ☐
(iv) microinjection ☐
(v) infection ☐

(vi) other, please specify: Administration by intramuscular route using Biojector medical device and by intradermal route using sterile syringe.

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

(i) transformation ☐
(ii) microinjection ☐
(iii) microencapsulation ☐
(iv) macroinjection ☐

(v) other, please specify

6. Information on the insert

a) Composition of the insert

Donor genes: HIV-1 Han-2 isolate clade B regulatory genes Rev, Nef, Tat and structural genes p17 and p24 as well as more than 20 Th and CTL epitopes of protease, reverse transcriptase and gp160.

b) Source of each constituent part of the insert

HIV-1 HAN 2 isolate, clade B

c) Intended function of each constituent part of the insert in the GMO

The insert (synthetic fusion protein built up by full length polypeptides of Rev, Nef, Tat, p17 and p24 with more than 20 Th and CTL epitopes of protease, reverse transcriptase and gp160) functions as an immunogen

d) Location of the insert in the host organism

- on a free plasmid ☒
- integrated in the chromosome ☐

- other, please specify

e) Does the insert contain parts whose product or function are not known?

Yes ☐ No ☒

If yes, please specify

D. INFORMATION ON THE ORGANISM(S) FROM WHICH THE INSERT IS DERIVED (DONOR = GTU-MULTIHIV B CLADE INVESTIGATIONAL VACCINE)

1. Indicate whether it is a:

Viroid ☐
RNA virus ☐
DNA virus ☐
bacterium ☐
fungus ☐
animal ☐

- mammals ☐
- insect ☐
- fish ☐
- other animal ☐ (please specify phylum, class)

other, please specify: Naked plasmid DNA

2. Complete name

(i) order and/or higher taxon (for animals)
(ii) family name (for plants)
(iii) genus
(iv) species
(v) subspecies
(vi) strain Inserts derived from B clade Han-2 isolate
(vii) cultivar/breeding line Not applicable
(viii) pathovar Not applicable
(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*, please specify the following

a) 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 related to exposure to biological agents at work?

Yes ☐	No ☒

If yes, please specify:

5. Do the donor and recipient organism exchange genetic material naturally?

Yes ☐ (virus to human)	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 ☒	No ☐	Not known ☐

Please specify: GMO is plasmid, recipient is human

b) Is the GMO in any way different from the recipient as far as mode and/or rate of *reproduction* is concerned?

Yes ☒ No ☐ Not known ☐

Please specify: GMO is plasmid, recipient is human

c) Is the GMO in any way different from the recipient as far as *dissemination* is concerned?

Yes ☒ No ☐ Not known ☐

Please specify: GMO is plasmid, recipient is human

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

Yes ☒ No ☐ Not known ☐

Please specify: GMO is plasmid, recipient is human

2. Genetic stability of the genetically modified organism

In vitro genetic stability studies have been conducted with the plasmid DNA vaccine both in bacterial as well as in eukaryotic cells. The plasmid vector is stable in these cells and no-rearrangements nor integration could be observed. The plasmid vector is stable as an episomal genetic element in eukaryotic cells.

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

Yes ☐ No ☒ Not known ☐

If *yes*,

a) to which of the following organisms?: humans ☐
animals ☐
plants ☐
other ☐

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

The plasmid DNA vector is not pathogenic

4. Description of identification and detection methods

a) Techniques used to detect the GMO in the environment

Molecular detection techniques such as polymerase chain reactions, western and northern blots may be applied.

b) Techniques used to identify the GMO

Restriction enzyme and sequencing based assays.

F. INFORMATION RELATING TO THE RELEASE

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

Donor: **GTU-MultiHIV B**

Recipient: *Homo sapiens*

Parenteral organism: *E.coli* Ag-1 – this is the production organism

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 ☒	No ☐

If yes, please specify: The clinical studies using GTU®-MultiHIV B are conducted in limited hospital area in France.

3. Information concerning the release and the surrounding area

a) Geographical location (administrative region and where appropriate grid reference):

The clinical study using MVA HIV-B is conducted in Four clinical sites in France:

- Unité d'immunologie Clinique, Hôpital Henri Mondor (Créteil),
- CIC de Vaccinologie, Hôpital Cochin (Paris),
- CIC-UPCET, Hôpital de la Timone (Marseille),
- Service des Maladies Infectieuses et Tropicales, Hôpital Nord - CHU Saint-Etienne (Saint-Etienne)

b) Size of the site (m^2): Not applicable

(i) actual release site (m^2):

(ii) wider release area (m^2):

c) Proximity to internationally recognized 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:

46 healthy volunteers will receive the immunisation with the GTU vaccine candidate in two different routes of administration: 0,5 ml intradermally of GTU® MultiHIV B vaccine with appropriate sterile syringe and needle and 0.5 mL intramuscularly of GTU® MultiHIV B using the Biojector® 2000 injection system.

b) Duration of the operation:

The immunizations will occur in an outpatient setting and participants will be closely observed for 30 minutes after each administration.

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

Procedures are available to administer the vaccine.

The sponsor of the clinical trial will provide a procedure detailing the precautions for confinement and inactivation of waste in accordance with the GMO guidelines. All concerned hospital staff will receive appropriate information from the sponsor before the start of the trial. Gloves will be worn for GMO handling.

The vaccination will take place in level 1 confinement. Dressing will be placed over the site of injection for 30 minutes. All waste potentially in contact with the GMO will be inactivated according to the guidelines for level 1 confinement. Disposal of all waste shall be traced appropriately.

5. Short description of average environmental conditions (weather, temperature etc.)

Hospital conditions

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

Several clinical trials with previous GTU®-based vectors (GTU®-Nef) were conducted in HIV-infected and healthy volunteers. Several phase I and II clinical studies were also conducted with FIT Biotech's GTU®-MultiHIV B-clade that have been tested in in Finland and South Africa. All clinical trial studies conducted so far with GTU®-based vectors showed that the vaccines were safe and well tolerated.

G. INTERACTIONS OF THE GMO WITH THE ENVIRONMENT AND POTENTIAL IMPACT ON THE ENVIRONMENT, IF SIGNIFICANTLY DIFFERENT FROM THE RECIPIENT OR PARENT ORGANISM

NOT APPLICABLE

1. Name of target organisms (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

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

None

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?

Yes ☐	No ☒	Not known ☐
Please give details		

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established

Not applicable

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

7. **Likelihood of genetic exchange in vivo**

a) from the GMO to other organisms in the release ecosystem: Not applicable
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 simulated natural environments (e.g. microcosms, etc.):

Not applicable

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

The GMO is confined in the pharmacy in sealed vials. The product is only drawn at the time of injection. All waste is inactivated prior to disposal and all waste is traced. In absence of a specific accident (the breakage of a vial), no dispersal in the environment is envisaged during the procedure.

Data from biodistribution in the rat indicate that following intra-muscular injection, the GMO remains primarily at the injection site, it may propagate to the lymph nodes and is progressively eliminated from the organism. It appears extremely unlikely that the GMO is eliminated in its original state in excretions.

2. Methods for monitoring ecosystem effects

Not applicable

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms

PCR based techniques

4. Size of the monitoring area (m^2)

Not applicable

5. Duration of the monitoring

Not applicable

6. Frequency of the monitoring

Not applicable

I. INFORMATION ON POST-RELEASE AND WASTE TREATMENT

1. Post-release treatment of the site

Surfaces that have been used during vaccination will be cleaned using 2° chloride-solution or other disinfecting solution available at the hospital (i.e. Surfanios).

All materials used during vaccination (used GMO vials, syringue, gauze...) will be treated according to the instructions given by the sponsor (Inserm-ANRS) following the recommendations of the Haut conseil des biotechnologies.

2. Post-release treatment of the GMOs

At the end of the study, all unused vaccine vials will be destroyed according to procedures for hospital wastes. Previously, these vials will be decontaminated by autoclave (121°C, 20 min).

3. a) Type and amount of waste generated

Material: empty sealed vials, syringe, needle, gauze dressing,…
Gloves (single use)

3. b) Treatment of waste

Decontamination and destruction according to approved procedures for GMO given by the sponsor.

J. INFORMATION ON EMERGENCY RESPONSE PLANS

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

In case of broken vaccine vial, the hospital staff must clean the surface (GMO and broken glass) immediately using gloves, absorbent material and 2° chloride-solution or other commercial disinfectant solution (i.e. Surfanios).
Blood and vaccine that could go out from the injection site during any of the vaccination procedures will be recovered using adhesive gauze dressing which will be applied on the injection site during 30 minutes.

All materials (absorbent material, empty or broken vials, syringe, gauze...) used during the cleaning procedures will be decontaminated and/or destroyed according to procedures for the GMO destruction.

2. Methods for removal of the GMO(s) of the areas potentially affected

As described above (J.1).

3. Methods for disposal or sanitation of plants, animals, soils etc. that could be exposed during or after the spread

Not applicable

4. Plans for protecting human health and the environment in the event of an undesirable effect

Pre-clinical and clinical studies indicate that the GMO is well-tolerated and does not present any particular risk for human health.

The GMO, as is the case for all DNA, is UV-sensitive (and therefore to daylight). It is not stable in the environment and it does not replicate in humans.

All in all biomedical studies, patients will be monitored regularly by medical doctors throughout the clinical trial (14 visits in 48 weeks); all unexpected adverse event will be reported to the pharmacovigilance surveillance team of the sponsor and all SUSARs will be declared to the ANSM (the competent authority in France). All affected individuals will receive the appropriate treatment and care. In the case of a severe adverse event linked to the GMO, the ANSM may decide to suspend or stop vaccination with the GMO. This scenario is however estimated to be extremely unlikely considering the good tolerance results already determined in humans.