PUBLIC INFORMATION

ENGLISH VERSION

Study code #THV01-11-01

EudraCT #2011-006260-52

B/BE/12/BVW1

Sponsor:	THERAVECTYS Pasteur Biotop building 28 rue du Dr ROUX 75015 Paris - FRANCE
Investigational products:	Two lentiviral vectored vaccines
Products code:	THV01-1; THV01-2
Therapeutic indication:	HIV-1, clade B
Version number:	2.0 (Belgium)
Release date:	27/04/2012

Abbreviations

AIDS	Acquired immunodeficiency syndrome
GMO	Genetically modified organism
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
RCL	Replication competent lentivirus

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1. Purpose of the release

This public information is made in the context of the Phase I/II clinical trial THV01-11-01 entitled:

"A multi-center, randomized, double-blind, placebo-controlled Phase I/II trial to compare the safety, tolerability and immunogenicity of the therapeutic THV01 vaccination at 5.10^6 TU, 5.10^7 TU or 5.10^8 TU doses to placebo in HIV-1 clade B infected patients under highly active antiretroviral therapy (HAART)".

2. Regulatory framework

The release of genetically modified organisms (GMOs) in the environment is regulated at the European level by the European directive 2001/18/EC.

The dossier must contain a public information document (the present document) to inform the population.

3. Sponsor details

THERAVECTYS
Biotop building – Institut Pasteur
28 rue du Docteur ROUX
75015 Paris, France
Tel: + 33 1 44 38 93 13
Fax: + 33 1 45 68 86 57

4. Localisation of the release

The clinical sites in Belgium whose participation in the trial is confirmed are listed below:

- **CHU Liège**
  Pr. Michel MOUTSCHEN
  Service d'infectiologie et medicine générale
  Domaine universitaire du Stat Tilman
  B-400 Liège
- **CHU Saint-Pierre**
  Pr. Nathan CLUMECK
  Département des maladies infectieuses
  Rue Haute, 322
  B-1000 Bruxelles

5. Description of the products and mode of action

5.1. Products

Human Immunodeficiency Virus (HIV) is the etiologic agent of AIDS (Acquired Immunodeficiency Syndrome) during which the viral replication increases and opportunistic diseases develop because of the dramatic CD4+ T cell depletion.

The THV01 treatment is intended for therapeutic vaccination against HIV in HIV-1 clade B infected patients. It is comprised of two GMOs vaccines, THV01-1 and THV01-2. THV01-1 and THV01-2 are

lentiviral vectored vaccines derived from the HIV-1. They are however **non-pathogenic**, **non-replicative**, and self-inactivating vectors: **they cannot replicate and hence do not proliferate**. They are absolutely not virulent in humans. The antigen encoded by these vaccines is derived from the HIV-1, clade B. It is composed of clustered epitopes of the Gag, Pol and Nef proteins under the regulation of a THERAVECTYS patented human promoter. It is an artificially gene coding for a non-functional polyprotein.

THV01-1 and THV01-2 are supplied as frozen concentrated suspensions in PBS-Lactose (40mg L^{-1}), without adjuvant or preservative, individually packed.

5.2. Mode of action

Following injection of the THV01-1 or THV01-2 vaccine, it will enter into the host cell. Then, the antigen it encodes will be expressed and cleaved into epitopes that will be exposed at the cells' surface. The expected resulting effect is elicitation of a broad and long lasting cellular immune response against the epitopes. This will lead to elimination of the host of cells infected by the HIV. THV01-1 and THV01-2 are aimed at enabling the infected patients to stop taking their therapies because they have induced an efficient and sufficient immune response.

6. Information regarding the trial

6.1. Objectives

The objectives of this first in Human Phase I/II trial is to evaluate the safety and tolerability of the THV01 vaccine treatment and to compare its immunogenicity to placebo in HIV-1 infected patients under HAART.

6.2. Investigators' sites

The clinical trial THV01-11-01 will be held at the investigational sites listed in section 4. These are standard healthcare facilities (hospitals) with trained personnel, used to perform clinical trials, especially with GMOs investigational products.

6.3. Doses and patients

36 patients will be enrolled. They must be HIV-1 (clade B) infected patients, treated by HAART for more than 24 months.

Patients will be randomly allocated to one of the 4 groups:

- Group 1: patients will receive the THV01-1 and THV01-2 vaccines at 5.10^6 TU or placebo;
- Group 2: patients will receive the THV01-1 and THV01-2 vaccines at 5.10^7 TU or placebo;
- Group 3: patients will receive the THV01-1 and THV01-2 vaccines at 5.10^8 TU or placebo.

Twelve patients will be randomized in blocks of 4 in a 3:1 ratio (vaccine:placebo) for each dose group. The first 3 patients of each dose group will be injected within a minimum of 24 hours of each other. The 4^{th} patient and each subsequent patient in a dose group may receive the injection on the same day as the previous patient.

Trial is expected to start in Q2 2012. Recruitment will be competitive and is planned to end in Q3 2012. Trial is expected to be completed in Q2 2013.

6.4. Mode and schedule of administration

The THV01-1 and THV01-2 vaccines are to be administrated 8 weeks apart, via intramuscular injection. Volumes to be injected are approximately 1.6mL for THV01-1 and approximately 3mL for THV01-2, with extemporaneous dilutions to be performed for the two lowest doses of each vaccine (5.10^6 TU and 5.10^7TU).

7. Expected benefits and risks to human health

7.1. Expected benefits

Although efficient in slowing down progression to AIDS, none of the antiretroviral treatments cure or prevent HIV infection. Their high cost, limited ability and adverse reactions added to the drug resistance emergence call for the development of alternative preventive and therapeutic strategies. Vaccines would be less costly than antiretroviral treatments and an increased compliance is expected as only two injections will be required versus taking daily pills.

The THV01-1 and THV01-2 vaccines have a very good safety profile: no toxicity has been detected during nonclinical experiments performed to date whereas antiretroviral treatments still induce both short and long terms adverse events such as lipodystrophy, adverse events on the gastrointestinal tract, central nervous system, cardiovascular as well as hepatic and renal toxicities.

The expected effect of the THV01 vaccination is the induction of a cellular immune response against cells transduced by the lentiviral vectors and those infected by the HIV. This immune response should result in a long-lasting control of HIV replication **allowing the patients to stop taking their antiretroviral therapies for a sustainable period of time while controlling viral replication and maintaining normal CD4+ T cells count: a "functional cure".** In addition, this will increase their quality of life while reducing the secondary effects of antiretroviral treatments.

7.2. Potential risks to the patients enrolled in the trial

No relevant toxicity has been detected during nonclinical studies (performed prior Human injection in animals). THV01-1 and THV01-2 were injected at the maximal injectable dose either using the clinical chosen route of administration (intramuscular injection) or intravenously (to assess the systemic toxicity). The administration was well tolerated without triggering relevant macroscopic or microscopic toxicity (assessed by physical examination, observation of the behaviour, weight evolution and inflammation markers quantification).

In addition, biodistribution studies demonstrated that using the clinical administration route (intramuscular injection), the integrated vectors remained localized at the injection site and draining lymph nodes. Of note, **no vector sequence was detected in the gonads**.

The THV01-1 and THV01-2 are not competent for replication and the risk of recombination leading to replication-competent lentiviral vectors (RCL) is negligible. This has been assessed on the products to be used during this clinical trial. *In vivo*, this risk is also very low, as the vectors are depleted from the promoter sequence of the U3 region in the 3'- and 5'-LTRs, rendering the expression of the HIV transgene dependant of an internal promoter. Moreover, the probability for the vectors to encounter wild-type HIV particles circulating in the patient is low because the targeted population is patients that have an undetectable level of viraemia (<50copies mL^{-1} using standard commercially available assays). In addition, there is a very low sequences homology between the THV01-1 and THV01-2 and the wild-type virus.

The risk of insertional mutagenesis that could lead to oncogenesis is very low as the lentiviruses do not integrate preferentially into close proximity of transcription start sites and as the promoter selected by THERAVECTYS is a human promoter devoid of any enhancer sequence. In addition, the cellular immune response induced will lead to elimination of the transduced cells within a few weeks.

Based on these observations, **the two THV01 vaccines are considered to have a favourable safety profile**.

7.3. Patient monitoring

The patients will receive the THV01 vaccines in a conventional hospital room without requirement of containment. Nobody should be present, besides the hospital personnel, at the time of the injection of the product. The patient will remain in the hospital room for observation according to the protocol and then is free to leave the hospital (no hospitalization is required).

Monitoring will be performed according to the established flowchart and will include physical examination as well as haematological and biochemical tests.

7.4. Potential risks for the sexual partner

During the studies performed on animals (“nonclinical studies”), using intramuscular injection, which is the chosen route of administration during the clinical trial, no GMO was detected in blood or urine. These tests were performed using very sensitive methods (qPCR or RT-qPCR). No excretion is thus expected following vaccination during the trial (partly for this reason, patients are allowed to be treated on out-patient basis).

In addition and as requested by the protocol of the study, during the whole participation of the trial, all participants are requested to use two efficient contraception methods (one for the patient and one for the partner) such as preservative. This is anyway strongly advised for HIV patient, as it is the sole efficient protection against HIV.

In conclusion, the risk for the partner to receive incidentally the GMO is null.

7.5. Potential risks for the personnel

The GMOs are provided in hermetically closed vials, 0.65mL filling (0.5mL extractible volume). At all times except just prior injection, vials containing the GMOs will remain closed. To perform the injection, only the top of the lid should be removed and the syringe passed through the rubber cap.

Accidental exposure to the GMO is decreased to a minimum and personnel performing the preparation and/or injection of the GMO must wear at least one pair of gloves, a mask and a gown. Therefore, contamination could occur only if the person performing the injection accidentally jab himself with the needle. In that case, risks are similar to those of the patients; except that the risk of formation of replication competent lentivirus is even lower if personnel are not HIV-infected.

Another possibility of accidental contact with the GMO would be in the event of vial breakage. However, the GMOs presented here do not cross the skin spontaneously and can hence not penetrate within a body without a transcutaneous action (injection). In addition, they are susceptible to current disinfectants and a thorough cleaning of the contaminated surface with bleach for instance will destroy them.

8. Control of the GMO dissemination: potential risks to the environment

8.1. Storage

THV01-1 and THV01-2 are frozen suspensions, individually packed into closed vials, to be stored at -80°C +/- 10°C in a secure area with access limited to the investigator and authorized site staff, and must not be used for any purpose other than the study. Administration of the study treatment will be carried out only by authorized and trained site staff.

At all times, the GMOs will remain in closed containers (closed vials) except in syringes just prior injection.

8.2. Genetic stability of the GMO

THV01-1 and THV01-2 vectors derived from an HIV strain. However, such strain has been modified to render the GMO non-pathogenic, non-virulent, non-replicative and self-inactivating.

Control of the genetic stability is performed on the integrated proviral product by sequencing the full sequence. It guarantees that the sequence transmitted to the host (the "transgene") is consistent with the expected one.

Formation of RCL which would indicate instability of the sequence, is assessed at the penultimate step of the production process (just prior vials filling) to guaranty that no recombination leading to formation of RCL has occurred. *In vivo*, this risk is low (please refer to section 7.2).

Finally, stability studies demonstrated that the GMOs are stable at -80°C ±10°C for at least 12 months whereas at room temperature, the GMOs are stable for 8 hours. In addition, the GMOs are susceptible to common disinfectants or solutions used for decontamination (such as Hexanios G+R, bleach, ethanol) as well as irradiation, UV light, autoclaving and incineration.

8.3. Destruction of the GMO or material containing the GMO

All vials (either empty or containing remaining products) will be shipped back to the manufacturer for storage until completion of the study. Destruction will be performed by incineration and only upon order from the sponsor.

All materials that have been in contact with the products (needles, syringes, bandages, cotton) will be discarded into appropriate biohazard waste containers and destroyed according to the procedures in use at the investigational site.

8.4. Potential risks to the environment

It is anticipated that the **genetic exchange from the GMOs to other organisms in the release ecosystem is very unlikely**. Indeed, the GMOs will be released during a clinical trial. They will be stored in secured access area and will remain in hermetically closed containers and the volume per vial is 0.65mL (0.5mL extractable). In addition, biodistribution studies demonstrated localization only at the injection site and draining lymph node without dissemination in blood or urine.

The only identified exchange that could occur would be in HIV infected patients, with wild-type virus. However, as detailed above, the homologous sequences between the vaccine and the wild type virus are reduced to a minimum by design optimization and the patients eligible to this trial have undetectable viral load, thus minimizing the risk of recombination.

8.5. Training requirement

During the initiation visit organized by a CRO, all persons involved in the clinical trial (doctor, nurses, pharmacist) will be informed in detail of the objectives and the schedule of the clinical trial as well as the nature of product, any possible product-related risks, handling procedures required and measures to take in case of accidental propagation. All of these recommendations are also described in the protocol and in the data sheet distributed to the personnel involved in the trial.

8.6. Emergency situations

The patients receiving the THV01 vaccines will be biologically and clinically monitored by the medical team during their entire participation in the trial. An unexpected event may thereby be detected and handled immediately and managed on a case by case basis.

Concerning the product handling within hospitals, THERAVECTYS will provide recommendations concerning the accidental propagation of the product, skin contamination with or without wound, eye contamination or ingestion. This information will be provided in the study protocol and in a separate data sheet that will be delivered to the medical team and will be available on the sites where the product is handled.

9. Conclusions

The probability of the propagation of THV01-1 and THV01-2 vaccines in the environment is very low, considering the results of biodistribution studies and the fact that the GMOs will be released during a human clinical trial. In addition, they are self-inactivating and non-replicative and all safeguards have been put in place to unable reversion to wild type strain. They have a very good safety profile and would allow patients to stop taking their treatments for a sustainable period of time.