INFORMATION FOR THE PUBLIC

Nouscom Srl

An Open-Label, Multicenter, Non-Randomized, Dose-Confirmation and Cohort-Expansion Phase 1b Study to Evaluate the Safety, Tolerability, and Anti-Tumor Activity of Nous-PEV, with pembrolizumab, in Patients with Unresectable Stage III / IV Cutaneous Melanoma and with Stage IV NSCLC (PDL1≥ 50%)

European notification number
EudraCT N. 2019-004759-35

The release of genetically modified organisms (GMOs) in the environment is strictly regulated at European level by directive 2001/18/EC of 12 March 2001 repealing directive 90/220/EEC and at Belgian level by a new Royal Decree "regulating the deliberate release and/or marketing of GMOs or products that contain GMOs into the environment" repealing the Royal Decree of 18 December 1998. The transposition procedure is still ongoing for the moment.

To ensure the safe use of GMOs, the provisions of the Royal Decree above stipulate that the release of GMOs for experimental aims is prohibited without prior consent from the competent Minister. The decision is based on a thorough evaluation of the biosafety of the planned release, which is conducted by the Biosafety Advisory Council, composed of different Scientific Committees grouping independent experts from Belgian universities and governmental institutes.

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To acquire the necessary authorization from the competent Minister, **Nouscom Srl** submitted an application dossier to the competent authority. On the basis of the advice of the Biosafety Council, the competent minister could grant a permission to **Nouscom Srl** to conduct experiments with a candidate vaccine treatment as stipulated in the application EudraCT N. 2019-004759-35.

The release will take place at two hospitals in Flanders and Wallonia:

Universitair Ziekenhuis Leuven, Campus Gasthuisberg, Department of General Medical Oncology, Herestraat 49, 3001 Leuven, Belgium

Grand Hôpital de Charleroi, Department of Oncology and Hematology, Grand Rue 3, 6000 Charleroi, Belgium

The study is expected to start in Belgium in Feb-2021 and to be completed on 31-Mar-2023.

The planned number of patients in Belgium is 11.

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General Information

Description of the trial

The study NOUS-PEV-01 is a clinical trial that will take place in Belgium, Spain and United Kingdom, in several oncological hospitals: the study is aimed at experimenting in about 30 informed and selected cancer patients, along with a standard therapy with a commercial product, new Investigational Medicinal Products (IMPs).

This clinical trial (further on referred to as "trial") will evaluate a new therapy, Nous-PEV vaccine (formed by GAd-PEV and MVA-PEV IMPs), in combination with pembrolizumab (Keytruda®), for the treatment of skin and lung cancer types which cannot be cured by an operation alone.

The skin cancer type addressed by the trial is called unresectable stage III / IV cutaneous melanoma. This type of cancer starts in the pigment-producing skin cells. "Unresectable" means that it cannot be removed, at least not completely, by surgery. The lung cancer type is called stage IV non-small-cell lung carcinoma (NSCLC) in which at least 50% of the cancer cells carry a certain protein called PD-L1 (i.e., PDL1 ≥50%). PD-L1 is an abbreviation for "programmed death ligand 1" which denotes a protein that helps prevent immune cells from attacking healthy cells in patient's body.

Many cancer types are carrying PD-L1 and in doing so protect themselves against the patient immune system. In the last years, medicines have been approved which block the function of PD-L1 and similar molecules, so patients' immune system can start attacking tumor cells better. Such medicines are called "immune checkpoint inhibitors". One of them, pembrolizumab, will be given as a continuous treatment in this trial.

For the unresectable stage III / IV cutaneous melanoma or stage IV NSCLC (PDL1 ≥50%), the following alternative treatments are available, other than taking part in the trial: other immunotherapies, other targeted therapies, radiotherapy or chemotherapy, isolated or in combination. The trial investigators can discuss available alternatives with patients, including risks and benefits, and answer any questions they may have.

The trial will look at how well people tolerate taking Nous-PEV and if it is safe to take Nous-PEV together with pembrolizumab. It will also be observed if the IMP has certain effects on patients' immune cells, blood composition and tumor tissue, which are related to the function of the immune system.

Nous-PEV is a vaccine, which means it is given to initiate a response of the patients' immune system directed against a certain disease (e.g. like a flu vaccine which is directed against influenza). Nous-PEV is given against cancer with the intention to cure or alleviate an existing cancer. It is therefore called an anticancer therapeutic vaccine. It will be given in addition to pembrolizumab because it is hoped that the combination of the vaccine and an immune checkpoint inhibitor will be more effective in fighting the cancer than either of them alone. This is however subject to ongoing research and therefore cannot be guaranteed. This is the first trial in humans using Nous-PEV.

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This trial is being paid for by Nouscom Srl (the sponsor); Pharm-Olam is working with the sponsor to help manage this trial.

Treatment will begin with pembrolizumab of which the patient will receive 200 mg by vein infusion every 3 weeks, as per standard treatment of the kind of cancers included in the trial. This treatment will be repeated throughout the study as long as the patient tolerates it well.

Description of the GMO IMPs

Nous-PEV is the name of the personalized experimental vaccine that will be administered to trial participants. It is formed by two vaccines administered sequentially, GAd-PEV (priming vaccination) and MVA-PEV (boosting vaccination). The original GAd is a gorilla virus, the original MVA is an attenuated virus derived from the vaccinia virus after a long selection in cell culture of non-replicating variants.

Both GAd-PEV and MVA-PEV are recombinant viruses, that means that they are Genetically Modified Organisms (GMO). They are unable to replicate and to infect humans and animals, because they have been modified by different procedures eliminating part of their genome (DNA) that was responsible for replication functions in the original non-recombinant viruses. Moreover, in both non-replicating GMO viruses an extraneous DNA sequence has been inserted by molecular biology techniques that contains the information to produce patient-specific cancer 'neoantigens'. These are protein molecules that are not present in normal tissues but only in cancer tissues and are recognized as foreign target (non-self) by the immune system of the cancer patient that reacts against them. When the GMO products GAd-PEV and MVA-PEV, carrying a high amount of cloned personalized neoantigens, are administered to the patient, this immune reaction should be more potent and effective.

The vaccine to be tested, called Nous-PEV, is a personalized vaccine because it is produced for individual patients, based on specific features of the individual tumor. For this purpose, a sample of the tumor tissue is collected in the screening phase and is analyzed for characteristics in which the tumor differs from patient's healthy tissues, that is the identification of patient-specific neoantigens.

The genetic information (neoantigens sequence) from each patient tumor is then used to make the personalized vaccine. This process will take several weeks, during which the patient will receive only the standard treatment (pembrolizumab). The patient will receive the first dose of the individual tumor vaccine (GAd-PEV, vaccine prime) in week 9, on the same day as the 3rd dose of pembrolizumab. If the patient is tolerating the vaccine well, he/she will receive a 2nd, 3rd, and 4th dose of the individual vaccine (MVA-PEV, vaccine boost), each 3 weeks after the previous one.

The GMO vaccine is given as an intramuscular injection. To avoid that the GMOs contaminate the environment, even though they are not harmful and unable to replicate, the injection site is covered with a bandage for 30 min, and afterwards it is treated as biohazard waste. The patients

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are also requested not to touch the injection site and wash their hands should this unwillingly occur.

A deliberate release of the GMOs is not performed on purpose, but it cannot even be excluded referring to potential shedding of the GMO through body fluids of the treated patients inside and outside the clinical centers. Data are not available about that because the products will be used for the first time in the proposed study NOUS-PEV-01.

Research/Development Activities

Nature and goal of the foreseen deliberate release

Due to the fact that no deliberate release is proven from patients after IMPs administration but it only cannot be excluded, there are no goals for that and the deliberate release, if any, has to be considered an unavoidable consequence of the physiological elimination of the IMPs from the human body, for which the sponsor doesn't have direct evidence since the specific products will be used for the first time in the NOUS-PEV-01 clinical trial.

Framework of research and/or development

The IMPs have been produced through steps including cell culture and in vitro molecular biology operations in controlled conditions regarding the biohazard risks. Even though these GMO IMPs are classified as biological risk-1 and has to be managed in BSL-1 conditions, both Nouscom research labs and Reithera production labs (Good Manufaturing, GMP, type) are BSL-2, so the products were handled and, when the case, disposed of, by procedures exceeding those required for BSL-1. No deliberate release apply to these research/development/production stages, but only contained release.

Studies in animals with the Nous-PEV products have also been conducted under controlled conditions (Good Laboratory Practice, GLP), which are mandatory before starting the clinical stage of a medicine experimentation, to ascertain safety (toxicology studies) and distribution of the product in the body (pharmacokinetics). The studies were conducted by European CROs complying with all EU regulations, including those related to biohazard material disposal. All the organs and biological fluids, besides the sacrificed animals remains, have been disposed of according to biohazard waste regulations. Even in these studies deliberate release has not occurred.

Both pharmacokinetic and toxicology studies with the GMO IMPs have given very good results. The complete reports are part of the application package for the clinical study NOUS-PEV-01.

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Benefits

Potential advantages of the deliberate release

The potential advantage of using the Nous-PEV IMPs in humans is related to the improvement of the current therapy for melanoma and NSCLC type lung cancer. To ascertain that improvement is indeed the goal of the clinical program with Nous-PEV of which NOUS-PEV-01 is the first study that will be run.
Due to the fact that no deliberate release from patients after IMPs administration is known (in the NOUS-PEV-01 trial the products will be used for the first time in humans) but it only cannot be excluded, there are no advantage that can be forecast for deliberate release as a consequence of patients' participation to the NOUS-PEV-01 clinical trial.

Risks

Assessment of the potential risks for human health and the environment linked to the deliberate release

No deliberate release is known deriving from patients after IMPs administration (in the NOUS-PEV-01 trial the products will be used for the first time in humans) but it only cannot be excluded. Besides the fact that this is only a not demonstrated possibility, mainly replying on the hypothesis of a viral shedding through body fluids, it has also to be considered that the risks inherent to a hypothetical release of the IMPs in the environment are null or negligible. In fact, both IMPs have been genetically modified in order to lose the possibility to replicate outside specific laboratory cell lines (not fresh cells derived from animals or humans but selected cells that only can live and multiply in controlled laboratory conditions). Those IMPs are absolutely unable to grow in the environment and to infect any animal or in general living beings. Even in the hypothetical possibility that they would contaminate the environment, this will have no effect of flora and fauna, including the human population.
The function of the IMPs in the proposed clinical trial is not based on infection and replication (that they are unable to do) but on the mere entry in the human body by intramuscular administration and work as vectors of the cloned neoantigens DNA sequences that are translated into the corresponding proteins that in turn will boost the natural immune system against the specific tumor they derive.

Containment, Control Measures

Proposed measures to limit the potential risks, to control and to ensure follow-up of the deliberate release.

During the handling of the IMPs at the clinical sites BSL-1 conditions will be applied, as detailed below. Actually in non-clinical manipulations, since the facilities in which they were

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conducted were designed and run as BSL-2 ones, they have been handled accordingly (see also section Research/Development Activity section).

BSL-1 operating conditions, sufficient for GAd-PEV and MVA-PEV, also included in the Appendix 2 of CAF, included in the application package, are listed below:

Precautions appropriate for Risk-Group-1 virus are recommended for use of GAd-PEV and MVA-PEV IMP in labs and in the clinical practice (Biosafety level 1, BSL-1).

Biosafety level 1 applies to laboratory or clinical settings in which personnel work with low-risk microbes that pose little to no threat of infection in healthy adults.

This laboratory setting typically consists of research taking place on benches without the use of special contaminant equipment. A BSL-1 area, which is not required to be isolated from surrounding facilities, houses activities that require only standard microbial practices, such as:

- Mechanical pipetting only (no mouth pipetting allowed)
- Safe sharps handling
- Avoidance of splashes or aerosols
- Daily decontamination of all work surfaces when work is complete
- Hand washing
- Prohibition of food, drink and smoking materials in lab setting
- Personal protective equipment, such as; eye protection, gloves and a lab coat or white coat or gown
- BSL-1 biohazard signs
- Immediate decontamination after spills. Infection materials are also decontaminated prior to disposal, generally through the use of an autoclave or other decontaminating tools, and dispose of residual materials in agreement with national and local regulations for GMO waste.
    - For spills outside of a biological safety cabinet the following procedures may be used:
        i. Wearing gloves, splash guard and gown, cover the spill with paper towels and then pour freshly prepared disinfectant (usually 1:0 dilution of bleach or equivalents) on paper towels.
        ii. Leave disinfectant in contact with spill for at least 30 minutes.
        iii. Pick up paper towels and discard into biohazard waste container.
        iv. Any broken glass should be picked up with forceps and placed in sharps container.
        v. Wipe the spill area with disinfectant and then remove and dispose of gloves properly and wash hands with soap or suitable alternative.
    - All procedures associated with a high risk of aerosolization, such as centrifugation or sonication, should be performed in a biosafety cabinet.
- Any personnel who experience a splash or spray accident involving a mucous membrane,

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or who experience a puncture or needle stick injury that is potentially contaminated with virus, should immediately notify the Principal Investigator and Medical Monitor.

Due to the fact that no deliberate release is proved from patients after IMPs administration (in the NOUS-PEV-01 trial the products will be used for the first time in humans) but it only cannot be excluded. Hence it is not known - if deliberate release occurs - through which routes it might occur and for this reason it is not possible to apply a specific mitigation plan to steps following the product administration to patients. However, indications will be given to patients participating to the trial about the measures to take to minimize potential risks that can be forecast, for instance: do not touch the injection site; if it occurs, wash hands carefully (included in ICF and Pharmacy manual); apply with particular attention all the hygienic procedures for the care of the person and the environment.

References

- Summary of notification (SNIF) of the clinical study NOUS-PEV-01: website of the Joint Research Centre of the European Commission (http://gmoinfo.jrc.ec.europa.eu/).-

- NOUS-PEV-01 trial information in www.clinicaltrials.gov database (entry and accessibility will be implemented after trial will be authorized in at least one of the Countries to which it has been submitted).

Contact

If you have any comment on the public dossier or our activities, or wish to obtain additional information on the deliberate release, please contact us at the address reported below.

You can also have access to a summary of the notification (SNIF) on the website of the Joint Research Centre of the European Commission (http://gmoinfo.jrc.ec.europa.eu/). Comments can be addressed to the Commission via this website.

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