TG4010

Public Information

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ABBREVIATIONS

DNA	Deoxyribonucleic acid
GMO	Genetically modified organism
IL2	Interleukin-2
IM	Intramuscular
IT	Intratumoral
IV	Intravenous
MUC1	Mucine 1
MVA	Modified virus ankara
MVATG9931	Recombinant vector
aNK	Activated natural killer
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFU	Plaque forming unit
Q	Quarter
SC	Subcutaneous
TG4010 or MVA-MUC1-IL2	Viral suspension of MVATG9931
ULN	Upper limit of normal

Purpose of the release

The release is made in the context of the Phase IIb/III clinical trial TG4010.14 entitled « *A Phase IIb/III randomized, double-blind placebo-controlled study comparing first-line therapy with or without TG4010 immunotherapy product in patients with stage IV non-small cell lung cancer (NSCLC)* ».

The purpose of this study is to determine whether the therapeutic vaccine TG4010 improves the benefit of the standard treatment of lung cancer.

Name and address of the sponsor

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Information relating to the release

Approximately 65 centers in the Europe, in the United States and in Israel will enroll patients in the Phase IIb part of the study. Additional centers (up to a total of around 200 and including other regions of the world) will be opened as soon as the results of the final efficacy analysis of the Phase IIb part become available.

The study is planned to include a minimum of 1018 patients (206 in Phase IIb and 812 in Phase III). It is planned that 30 subjects will be recruited at 4 centers in Belgium. The following centers are considered for the proposed study:

Investigator	**Institution**
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Dr. Frederic Forget	Centre Hospitalier de l'Ardenne

This study is expected to start in Quarter (Q)4 2011 with recruitment to be completed by Q2 2015. The study is expected to be completed by Q4 2015.

This study is conducted in double-blind. The treatment will be randomly allocated to one of the following treatment groups:

- **Group 1**: standard treatment (including chemotherapy) plus TG4010.
- **Group 2**: standard treatment (including chemotherapy) plus placebo.

There is a one in two chance probability of being allocated to either group.

The administration of the TG4010 consists of a sub-cutaneous (SC) injection of a small volume of liquid (~ 0.5 ml) under the skin alternately in the thigh or the arm. Patients will receive the injection once a week for the first 6 weeks then once every 3 weeks until progression of the disease or premature discontinuation of the study treatment due to any reason (e.g., adverse event). The same dose of TG4010 will be injected every time i.e. $1.0x10^8$ plaque forming unit (PFU).

General description of the genetically modified organism (GMO)

TG4010 is a suspension of the recombinant viral vector MVATG9931. The vector MVATG9931, the active substance of TG4010, is a GMO. It is derived from a highly attenuated strain of the modified vaccinia virus Ankara (MVA), in which the nucleotide sequences coding for the human mucine 1 (MUC1) antigen and human interleukin-2 (IL2) were inserted.

TG4010 has been developed for use as an immunotherapy in cancer patients whose tumors express the MUC1 antigen. Advanced NSCLC is the current lead indication.

TG4010 is intended to induce a MUC1-specific cellular immune response and to produce a non-specific activation of several components of the immune system.

Benefits

Despite the progressive improvement of the standard of care, the medical need in NSCLC still remains enormous and new approaches are necessary to significantly change the outcome of this disease. By modifying the host/tumor relations, immunotherapy products like TG4010 may achieve such a result.

The desired therapeutic benefit of the TG4010 vaccine is to enhance the beneficial effect of standard treatments in cancer patients whose tumors express the MUC1 antigen.

The previous Phase II studies in advanced NSCLC, TG4010.05 and TG4010.09 studies, both met their primary endpoint and suggested a clinical benefit of adding TG4010 to first-line chemotherapy with cisplatin + vinorelbine or cisplatin + gemcitabine, respectively, especially in patients with a level of activated natural killer (aNK) cells $\leq$ the upper limit of normal (ULN) at baseline as shown in the TG4010.09 study. These observations therefore warrant further investigation into the efficacy of TG4010 in this add-on setting, with an increased number of patients and different first-line therapy regimens.

In order to test the hypothesis that the addition of TG4010 improves the results of first-line therapy in stage IV NSCLC patients with MUC1 expressing tumor cells, depending on their pre-treatment level of aNK cells, the current Phase IIb/III study has been designed to compare the combination of TG4010 + first-line therapy versus placebo + first-line therapy in this population. This analysis will be performed independently in each subgroup of patients according to their pre-treatment level of aNK cells.

Risks

The parental virus of the MVATG9931 vector, MVA, is a highly attenuated viral strain, obtained from the Ankara strain of the vaccine that is only able to infect a reduced series of hosts (Mayr, Hochstein-Mintzel et al. 1975), (Mayr, Stickl et al. 1978), (Carroll and Moss 1997). MVA was specifically developed to immunize high risk patients (children under the age of 3 years and

patients presenting nervous disorders, allergies or skin diseases, chronic diseases) against smallpox. It was tested in many animal species and used in the primo vaccination of over 120,000 children and adults (Mayr, Hochstein-Mintzel et al. 1975), (Mayr, Stickl et al. 1978), (Stickl, Hochstein-Mintzel et al. 1974). No major problems were observed during the vaccination campaigns (apart from slight redness at the site of injection and fever over 38°C and/or general malaise in a small percentage of subjects) or any serious complications (such as encephalitis or septicaemia observed after the injection of other strains of the virus for the vaccine) (Mahnel and Mayr 1994), (Stickl, Hochstein-Mintzel et al. 1974).

Until now, TG4010 has been injected by intramuscular (IM) or SC route to 270 patients suffering from various type of cancer. To date, more than 800 patients were administered by SC, IM or intratumoral (IT) route with Transgene MVA based vectors with acceptable safety profiles. The most frequent adverse events attributed to TG4010 were mild to moderate vaccine-related reactions like injection site and /or skin reactions (erythema, pain, induration and inflammation), fatigue, pyrexia, influenza-like illness and myalgia.

In addition, animal toxicology studies have been conducted with TG4010 in mice, rat and in rabbit following single and/or repeated administrations by intravenous (IV), IM or SC routes. The administration of TG4010 was well tolerated and no significant and specific adverse reactions to TG4010 were observed, except for some minor local reactions at the injection sites frequently observed following administration of vaccines.

Based on these observations, TG4010 is considered to have a favorable safety profile.

Monitoring methods and plans for the operations and interventions in case of an emergency

Control of the GMO and gene dissemination

Conditions for storage and use:
TG4010 is a frozen preparation and should be stored in hospital centers at a temperature not exceeding -20°C, in a freezer with controlled access, under the responsibility of the investigator and/or pharmacist. Access to the place of storage of the TG4010 is restricted to authorized parties, in accordance with in-house hospital procedures.

Preparation for administration:
A preparation protocol containing detailed instructions for the preparation is provided by Transgene for the trial pharmacist/investigator.

The viral suspension is administered by SC route using a syringe with an adapted needle within an hour of the preparation.

Patient monitoring:
The patients receive TG4010 in a conventional hospital room. 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 for several minutes and then return at home.

The vector MVA is non propagative, poorly replicative (replication aborts at a late stage of the virus life cycle, after deoxyribonucleic acid [DNA] replication including the transgene coding sequence; virion morphogenesis is interrupted) and non integrative (the DNA of the virus remains localized in the cell cytoplasm and does not integrate the DNA of the host cell). Considering these properties, the virus most likely remains in the skin, thereby avoiding the dissemination of

the virus in the body fluids and the environment.

Viral shedding data collected up to now from previous clinical studies with TG4010 and other Transgene's recombinant MVA vectors confirmed the absence of dissemination. More than 100 patients (n=148) were monitored for the presence of viral DNA in blood and urine after the injection of the recombinant MVA vectors administered either by IM or SC routes at equivalent dose levels. There was no detection of viral DNA in the samples. These results confirms the non propagative property of the MVA vector.

Genetic stability of the GMO

The genetic modifications on the MVA virus, underlying its non-propagative and poorly replicative properties in mammal cells, prevent and reduce its propagation in the environment. The repair of several genes would be required in order to fully restore the ability of the MVA virus to replicate in human cells (Wyatt, Carroll et al. 1998). This is highly unlikely since it would require genetic recombinations with the wild smallpox virus, which is not naturally found in the environment and is non endemic in human.

The production of recombinant MVA particles occurs on specific laboratory cells. Each batch made for clinical trials involves controls of the production different steps to guarantee the integrity and functionality of the recombinant MVA genome and thereby the maintenance of its non-propagative and poorly replicative properties. The expression of genes coding for proteins MUC1 and IL2 is also controlled for each batch.

The possibility of controlling the genetic stability of TG4010 in patients is limited. However, assessment of the immune response to the virus at different times during the trial enables control of its biological efficacy and indirectly its genetic stability.

Destruction of material containing the GMO

In hospital units where patients are treated with TG4010, a technical sheet of the product is provided to the personnel trained for product handling. All materials in contact with TG4010 will be decontaminated and/or destroyed according to regular hospital procedure for infectious wastes.

Training requirements

During the initiation visit organized by a Transgene service provider, all persons involved in the clinical trial (doctor, nurses, pharmacist) are 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 a document summarizing all the product information called « Investigator Brochure » and in the data sheets distributed to the personnel involved in the trial.

Emergency situations

The patients receiving TG4010 will be biologically and clinically monitored by the medical team during their entire participation in the trial. An unexpected event may thereby be detected quickly, handled immediately and managed on a case by case basis.

Concerning the product handling within hospitals, Transgene will provide recommendations

concerning the accidental propagation of the product, skin contamination with or without wound, eye contamination or ingestion in a data sheet. This data sheet will be delivered to the medical team and will be available on the sites where the product is handled.

Summary of the assessment of the effects and environmental risks

The probability of the propagation of TG4010 in the environment is very low, considering the previous clinical experience with this product and other recombinant MVA vectors developed by Transgene. The MVA vector has non propagative and poor replicative properties, highly limiting the risks of propagation. In addition, a wild type vaccinia virus, with intact propagation ability would be required to allow for the propagation of the GMO in the environment. This is highly unlikely considering that no wild type vaccinia virus is currently endemic in the human population. It is also highly unlikely that all of the independent mutations required for the restoration of the genome of the (wild) parental virus occur. This phenomenon has never been observed during the smallpox vaccination in man and a mechanism capable of triggering and selecting an event of this extent is not likely.

In addition, studies have shown that the repair of several genes would be required in order to fully restore the ability of the MVA to effectively reproduce in human cells (Wyatt, Carroll et al. 1998). These results are consistent with the inability to detect spontaneous revertants of the MVA virus and are in favor of the safety of the use of the MVA virus as a vaccine and gene therapy vector.

References

Carroll, M. W. and B. Moss. "Poxviruses as expression vectors." *Current Opinion in Biotechnology*. (1997) 8(5): 573-577.

Mahnel, H. and A. Mayr. "Erfahrung bei der Schutzimpfung gegen Orthopocken von Mensch und Tier mit dem Impstamm MVA." *Berliner und Munchener Tierarztliche Wochenschrift*. (1994) 107: 253-256.

Mayr, A., V. Hochstein-Mintzel, et al. "Abstammung, Eigenschaften und Verwendung des attenuirten Vaccinia-Stammes MVA." *Infection*. (1975) 3(1): 6-14.

Mayr, A., H. Stickl, et al. "Der Pockenimpfstamm MVA: Marker, genetische Struktur, Erfahrung mit der parenteralen Schutzimpfung und Verhalten im abwehrgeschwächten Organismus." *Zentralblatt fur Bakteriologie, Mikrobiologie und Hygiene.1. Abt. Originale. B: Umwelthygiene. Krankenhaushygiene. Arbeitshygiene. Praventive Medizin*. (1978) 167: 375-390.

Stickl, H., V. Hochstein-Mintzel, et al. "MVA-Stufenimpfung gegen Pocken. Klinische Erprobung des attenuierten Pocken-Lebendimpfstoffes, Stammes MVA." *Deutsche Medizinische Wochenschrift*. (1974) 99: 2386-2392.

Wyatt, L. S., M. W. Carroll, et al. "Marker rescue of the host range restriction defects of modified vaccinia virus Ankara." *Virology*. (1998) 251(2): 334-342.