Public Information

Clinical trial BT-001.01

A Phase I/IIa study of intra-tumoral BT-001 (TG6030) administered alone and in combination with pembrolizumab in patients with cutaneous or, subcutaneous lesions or easily injectable lymph nodes of metastatic/advanced solid tumors.

Sponsor:

Transgene

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ABBREVIATIONS

CTLA-4	Cytotoxic T-Lymphocyte-Antigen 4
DNA	Deoxyribonucleic acid
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GMO	Genetically modified organism
IV	Intravenous
RR	Ribonucleotide Reductase
TK	Thymidine Kinase

Purpose of the release

The release is made in the context of the BT-001.01 clinical trial entitled « *A Phase I/IIa study of intra-tumoral BT-001 (TG6030) administered alone and in combination with pembrolizumab in patients with cutaneous or, subcutaneous lesions or easily injectable lymph nodes of metastatic/advanced solid tumors.* ».

BT-001 is a genetically modified organism (GMO); pembrolizumab is not GMO.

This clinical trial is split in three parts:

▪ The first part (Phase I, Part A): the purpose of this part is to assess the safety and tolerability of BT-001 repeatedly injected directly into tumors in patients with cutaneous (e.g., skin) or subcutaneous (e.g., just under the skin) lesions or easily injectable lymph nodes of metastatic/advanced solid tumors.

▪ The second part (Phase I, Part B): the purpose of this part is to assess the safety and tolerability of BT-001 in combination with intravenous (IV) infusions of pembrolizumab in patients with cutaneous (e.g., skin) or, subcutaneous (e.g., just under the skin) lesions or easily injectable lymph nodes of metastatic/advanced solid tumors.

▪ The third part (Phase IIa): the purpose of this part is to evaluate whether BT-001 in combination with IV infusions of pembrolizumab help patients with metastatic/advanced soft tissue sarcoma, Merkel cells carcinoma, melanoma, triple negative breast cancer or non-small cell lung cancer fight tumors.

Nature of the release

The release consists of administering to patients with solid cancer BT-001 directly into tumor(s), in a hospital room. Between 1 and 4 mL of BT-001 will be injected depending on the number and the size of the lesion(s) to be injected. Participating patients will receive repeated administration of BT-001: up to 4 administrations (Phase I, Part A) or until documented confirmed disease progression, unacceptable toxicity or patient refusal (Phase I, part B or Phase IIa). For a given patient, the dose of BT-001 will be the same throughout the trial among the three doses tested.

The BT-001.01 clinical trial is expected to start in Quarter (Q)4 2020 and to be completed by Q3 2024.

Sponsor

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Location of the release

In Belgium, one clinical site (Cliniques universitaires Saint-Luc (UCLouvain) - Brussels – Pr Baurain is planned to participate.

General description of the genetically modified organism (GMO)

Co-developed by Transgene and BioInvent, BT-001 is a genetically modified research treatment from the vaccinia virus which was used to vaccinate hundreds of millions of individuals against smallpox. The original vaccinia virus has been genetically modified in the laboratory by inactivation of its thymidine kinase (TK) and ribonucleotide reductase (RR) genes and by addition of genes encoding for the human granulocyte-macrophage colony-stimulating factor (hGM-CSF) cytokine and for a monoclonal antibody targeting the Cytotoxic T-Lymphocyte-Antigen 4 (CTLA-4).

Due to the inactivation of the TK and the RR genes, BT-001 preferably infects cells undertaking intense divisions (with high nucleotide pool) such as cancer cells and spares healthy cells. BT-001 then replicates (multiplication) in tumor cells which lead to kill them (oncolysis). Overall, these two inactivations attenuate the viral replication compared to vaccine virus strains used for smallpox eradication campaign.

BT-001 not only causes direct destruction of tumor cells by oncolysis but is designed to stimulate patient anti-tumor immune responses by production of the anti-CTLA4 antibody (named 4-E03) and human GM-CSF directly in the tumor site which should contribute to the destruction of tumor cells.

Potential advantages of the release

The administration of BT-001 may drive an anti-tumor response or a disease stabilization and possibly improve the survival of patients with metastatic or advanced solid cancer.

The assessment of the potential risks for human health and the environment linked to the release

Due to the inactivation of its TK and RR genes, BT-001 replicates preferentially in cancer cells. This limits the propagation of the recombinant virus. Apart from this difference and the insertion of the 4-E03 mAb and hGM-CSF transgenes, BT-001 is comparable to its parental vaccinia virus. As the vaccinia virus, BT-001 remains exclusively in the cytoplasm of infected cells thus eliminating any risk of integration of the viral DNA into the patient genome (no mix of viral genes with patient genes). The genetic modifications introduced in BT-001 are therefore not expected to increase dissemination and survival capacity of the GMO in the environment compared to the parental virus.

As BT-001 will be administered for the first time in Humans, there is no data available in terms of adverse reactions related to BT-001. The clinical experience gained with two other viruses derived from the vaccinia virus sponsored by TRANSGENE as medications against cancer has shown transient flu-like symptoms (e.g.: fever, nausea, headache) as the most common side effects which generally develop and resolve shortly and can be anticipated with BT-001.

The risk of contact transmission is rare as demonstrated with vaccinia-based smallpox vaccine experience (occurrence of secondary transmission for 5.4 cases of vaccinia secondary transmission per 100.000 vaccinees). The risk of transmission in the proposed clinical trial is reduced by the use of universal precautions by healthcare workers and the education of patients in meticulous hand hygiene and appropriate dressing of the injection site.

No adverse effect on the environment or human health had been reported further to the massive use of the non-attenuated virus during the smallpox eradication program, to the spread of an attenuated virus in oral rabies vaccination campaigns delivered by edible bait over the zones of rabies contamination or from clinical trial experience with other viruses derived from the vaccinia virus.

In the unlikely event of severe complication following vaccinia virus-based vaccination, some antiviral rescue therapies are available.

The probability of a BT-001 propagation in the environment is therefore very low and it is not expected that the release of BT-001 within the proposed BT-001.01 clinical trial conditions would result in any other environmental or human health risk.

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

A set of protective measures is set up in the BT-001.01 clinical trial setting to prevent potential risks with the release of the GMO and includes:

1. Proposed protective measures for BT-001 preparation and administration at clinical sites:

- BT-001 documentation and clinical site staff training

  Before being able to participate in any BT-001 operation (i.e.: preparation or administration) and in the care of patients receiving BT-001, the healthcare worker must attend training. A set of trial documents specific to BT-001 is provided and gives information related to the clinical lot of BT-001, the conditions and precautions of BT-001 use, instructions in case of incident or inadvertent exposure including accidental spillage and for waste management, step by step instructions for preparation and administration operations.

- Exclusion of "at risk" group of healthcare professionals for any BT-001 operations based on vaccinia virus-based vaccination
- Personal protective equipment (e.g.: gloves, mask, googles) requirements for all staff involved in handling of BT-001 or any material or linen potentially contaminated with BT-001
- Restricted access for all zones in which BT-001 is handled and administered to the patients or where the patients are located after BT-001 administration
- BT-001 transfer operations in hermetic transport box

2. Proposed protective measures following BT-001 administration and during the post discharge phase:

- Patient monitoring period at clinical site after BT-001 administrations
- Provision of antiviral rescue medications in case of serious infection due to BT-001
- Prevention of shedding risk from injection site

  At the end of each BT-001 administration procedure, a dry occlusive dressing will be put on each injection site. Once removed, the dressing(s) must be returned to the hospital for destruction.
  Specific instructions will be given to the patient in case of pustule appearance.

- BT-001.01 regular trial visits for safety monitoring

Shedding analysis are planned in BT-001.01 clinical trial assessing the virus concentration in different patient samples (blood, skin swabs, saliva, urine and feces) at different timepoints.

Long-term follow-up observations for a duration of five years after the last BT-001 administration are planned in the BT-001.01 trial.

Proposed protective measures and follow-up allows to mitigate potential BT-001 release risks in the BT-001.01 clinical trial setting.