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.

Promoter: **Transgene**
400 Boulevard Gonthier d'Andernach
Parc d'Innovation
CS80166
67405 Illkirch Graffenstaden cedex
France

Co-developer: **BioInvent International AB**
Ideon Science Park
SE-223 70 Lund,
Sweden

Version 1.0; - October 30, 2020

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
VV	Vaccinia Virus

1. Study overview

Investigational medicinal products studied in BT-001.01 study are **BT-001** and **pembrolizumab.**

BT-001 is a **virus genetically modified** and pembrolizumab is a **monoclonal antibody**. They stimulate the immune system to fight cancer. Pembrolizumab (Keytruda®) is approved in multiple countries including the US and in the European Union for use in a variety of solid tumors.

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.

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).

2. BT-001 overview

Co-developed by Transgene and BioInvent, BT-001 is a **virus genetically modified** use as **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 the human granulocyte-macrophage colony-stimulating factor (hGM-CSF) cytokine and a monoclonal antibody targeting a protein present on the surface of cytotoxic T lymphocytes, the human CTLA-4 protein (Cytotoxic T-Lymphocyte-Antigen 4).

Due to the inactivation of the TK and the RR genes, the virus 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.

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.

3. Potential risks

3.1 Wild type vaccinia virus

Vaccinia virus (VV) is a linear, double-stranded DNA virus that is a member of the Poxviridae family. VV is not known to have serious health effects in humans, although it can cause disease of the skin when used to inoculate against the smallpox virus. Vaccinia virus is usually injected in the dermis where a localized lesion appears (a "take"), and then scabs over and heals in about 10-14 days. The vaccination is accompanied by fever, rash, enlarged lymph nodes, fatigue, muscles pain and headaches in some patients.

Accidental infection with the virus can occur through contact between the vaccination lesion (localized lesion that appeared on the skin after injection of the vaccine) and broken skin (inadvertent inoculation). Serious complications such as ocular vaccinia, myopericarditis, eczema vaccinatum (a papular, vesicular and pustular rash that is very infectious, 38 cases per million doses), progressive vaccinia (progressive necrosis at the vaccination site, 3 cases per million doses), postvaccinial Central Nervous System disease (headache, lethargy, seizures and coma, 12 cases per million doses), foetus malformations and abortion (very rare) sometimes occur after vaccination.

Contraindications to vaccine are their use in immunocompromised individuals, individuals with certain skin conditions (e.g., eczema) and cardiac diseases, pregnant and breastfeeding women.

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.

3.2 BT-001

Due to the inactivation of its TK and RR genes, BT-001 replicates (multiplies) preferentially in cancer cells. This limits the propagation of the genetically modified 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 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, fatigue) as the most common side effects which generally develop and resolve shortly and can be anticipated with BT-001.

3.3 Risks of transmission of vaccinia virus to healthcare staff

Transmission of vaccinia virus (wild type or BT-001) is only possible through direct contact with infectious material (e.g., superficial skin lesions, exudate, contaminated bandages, etc.). Contact transmission is the only documented mode of spread for vaccinia virus (no airborne transmission has been reported so far).

Secondary transmission of BT-001 to healthcare workers has not been reported to date.

4. Measures to limit the potential risks of contamination

4.1 Universal precautions*

Individuals who are / have:

- **possibly pregnant,**
- **breast feeding,**
- **less than 12 months old,**
- **active skin condition** (eczema or psoriasis lesions in areas potentially in contact with the product, psoriasis requiring a systemic treatment, etc.),
- **immunocompromised** (HIV positives, organ transplant recipients, etc.),

are considered as "**at risk population**" that **MUST**

- **Not handle BT-001** (prepare, administer, etc.)**,
- **Avoid physical contact** with patients receiving BT-001 **during the seven days after each administration** or in case of the **occurrence of pustule(s)** (small swelling on the skin),
- **Avoid any contact with dressings, clothing, linen and equipment including medical devices contaminated** by contact with injection sites or skin lesions.

* These recommendations have been established for wild type vaccinia virus and applied without modification to attenuated vaccinia viruses according to the precautionary principle.

** Only trained hospital staff are authorized to handle the BT-001

4.2 At the hospital:

4.2.1 Protective measures for BT-001 preparation and administration

- Universal measures apply to all hospital staff who prepare and administer BT-001
- 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 product 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.

- Personal protective equipment (e.g.: gloves, mask, googles) requirements for all staff involved in *preparation an administration of* BT-001.
- BT-001 transfer operations in hermetic transport box.

4.2.2 Protective measures to apply for any direct physical contact with patient receiving BT-001 within seven days after each administration or in case of the occurrence of pustule(s)

- Universal measures apply to all hospital staff in direct physical contact with patient receiving BT-001 within seven days after each administration or in case of the occurrence of pustule(s)
- For direct contact with patient and/or contaminated material, it is highly recommended to wear non-sterile gloves and then observe strict hand hygiene using hot soapy water or a hydro-alcoholic solution/gel containing at least 60% alcohol.
- Contaminated disposal material must be discarded into a biohazard bag and disposed according to country-specific requirements and/or regular hospital procedure for infectious waste (e.g. autoclaving or treatment with bleach solution before incineration).
- Contaminated non-disposable material must be cleaned/treated according to regular hospital procedure for infectious material.
- All equipment must be cleaned with a disinfectant active on BT-001:
    - Solution of bleach at 0.6% of active chlorine:
        - 4 tablets [if 1.5 g/tablet of active chlorine] per litre of water, or
        - 1 volume of bleach at 2.6%Cl [i.e. 26 g/l of active chlorine] for 4 volumes of water, or
        - 1 volume of bleach at 9.6%Cl [i.e. 96 g/l of active chlorine] for 17 volumes of water.
    - Aniospray Quick® and Aseptanios Terminal Spore® (tested by Transgene), and Aniospray SF IP sterile®, Surfa'Safe Premium®, Anios Oxy'Floor®, Virkon®, Incidin®, Aldekol Des Acid®, Aldekol Desaktiv®, Aldekol Des 03®, Viruzidal Extra®, Fermacidal®, Pursept-FD®, Perform classic concentrate Q-Plus®, Terralin protect®.

4.3 At Home:

- After each administration, before returning home, patients receive a **hygiene kit** which contains all of the materials they may need at home as antiseptic, sterile compress, protective dressings, a mask and a waterproof pocket with a zip-lock to put in potentially contaminated material as for example removed dressing.
- Patients must indicate in the hospital or health center at which they are taken in charge that they are participating or have participated in this clinical trial and show their trial **emergency card** to any health professional they may consult.
- In case of appearance of pustule(s) on the skin or in the mouth, patients should contact the

trial staff as soon as possible to receive the guidelines to be followed.

During the period of 7 days following each BT-001 administration or in case of appearance of lesions (pustule) on the skin or in the mouth up to the scab has fallen off, patients have to:

- **Wash hands** frequently with soap and hot water, or with a hand sanitizer containing at least 60% alcohol (hydro-alcoholic solution).
- **Avoid sharing personal items**: toiletries, eating tableware items.
- **Avoid intimate contacts** (kissing, sex).
- **Avoid any physical contact with "at risk" population**:
  - children less than 12 months old,
  - possibly pregnant or breastfeeding women,
  - people with active skin condition (eczema, psoriasis, atopic dermatitis, etc.),
  - immunocompromised persons (e.g., organ transplant recipients, patients with AIDS or chronically treated with immunosuppressive drugs).
- **Avoid contact with any animals.**
- **Cover pustule with protective dressing(s)** included in the kit provided and not allow other persons or any animals to have a direct contact either with the pustule or with potentially contaminated surfaces (e.g., the bandage covering the pustule, a piece of cloth, or linen). Care givers have to wear gloves should be worn, and hands be washed with soap and hot water, or with a hand sanitizer containing at least 60% alcohol.
- **Wear a mask in the presence of other people** in case of pustule(s) in the mouth.
- **Avoid any contact with other parts of his body** (e.g., the eyes, the nose, etc.) after having touched a pustule or any other potentially contaminated surface (e.g., after having changed a bandage).
- **Dispose all non-washable contaminated materials** (bandages, gauze) in a hermetically closed container or in the **waterproof bag with a zip-lock** included in the hygiene kit supplied by the hospital. **Store the bag in a safe place** so as to avoid any unwanted contact by individuals other than the patient or animals **and bring it back to the hospital for destruction** at the next visit.
- **Laundry** (e.g., sheets, clothes, towels) **can be washed with hot water and detergent**. Bleach can also be used (one cup per wash load) for decontamination.