Phase 1b clinical trial of TG1050, a novel HBV-targeted immunotherapy, in NUC suppressed chronic B patients: safety and early immunological data following single administration.

**RATIONALE AND PRODUCT DESCRIPTION**

**Product Description**

TG1050 is based on a recombinant non-replicative Adenovirus 5 vector encoding for a large fusion protein comprising sequences of truncated Core, an almost full-length Polymerase and domains of Envelope.

**Objective of TG1050**

To increase the functional cure rate in chronic HBV patients in combination with SOC and/or novel antivirals.

**Mechanism of Action (MoA)**

Following s.c. injection, the expected MoA of TG1050 is transduction of APC at injection site and priming of HBV-specific T cells. These T-cells, following migration to the liver, will exert antiviral activity through non-cytolytic and cytolytic mechanisms. This MoA was demonstrated in preclinical experiments and persistent mouse models: TG1050 demonstrated the induction of functional HBV-specific T cells and an antiviral effect by decreasing both HBV viremia and circulating HBsAg and, in some cases, by triggering anti-HBs antibodies.

**MATERIALS & METHODS**

**Study Design**

Randomized, double blind, placebo-controlled and dose finding study. The study includes 2 sequential phases: one single dose (SD) cohort and one multiple dose (MD) cohort.

In the SD cohort, 12 patients were randomized 1:1:1 across 3 dose levels (ELs) of 10^10, 10^11, 10^12 virus particles and then randomized 1:1 within each EL to placebo (4 patients in each dose group included 1 placebo). The study is ongoing in 12 investigational centers in France, Germany and Canada. Patients received the allocated randomized product as a single subcutaneous injection.

**Study Objectives**

- **Primary Objectives**
  - To evaluate the safety and tolerability of TG1050 administered as single or multiple doses in patients who are currently being treated for chronic hepatitis B virus (HBV) infection
  - To determine the dose and schedule of TG1050 administration
  - To evaluate the antiviral activity of TG1050, e.g. HBsAg levels over time and level of HBsAg
  - To evaluate the cellular and humoral immune responses to TG1050

- **Selection Criteria**
  - Chronic hepatitis B (CHB) patients were eligible when they met the following criteria:
    - NUC treatment: tenofovir (TDF) or entecavir (ETV) for ≥2 years
    - Undetectable level of anti-HBs ≤100 mIU/mL
    - HBV DNA level below 20 IU/ml for at least 6 months
    - HBV/HBV positive
    - Compensated liver disease and no prior history of chronic hepatitis decompensation
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- **Secondary Objectives**
  - To assess the cellular and humoral immune response to TG1050
  - To determine the level and kinetics of anti-HBs antibodies

**Study endpoints**

- **Safety & Tolerability**
  - Adverse events were collected and graded according to Common Terminology Criteria for Adverse Events (CTCAE) versions 4.0.
  - Hepatitis flares were monitored by ALT, AST and bilirubin levels.
  - Lymphocyte and CD8+ T-cell counts were monitored.

**Demographics**

A total of 12 patients were randomized and received a single dose of TG1050 or placebo.

**Evaluation Criteria**

- **Cell-mediated immune responses**
  - HBV-specific T-cell responses were evaluated in patients by a cytotoxic T-cell assay.
  - ELISpot IFNγ assay was performed for cell-mediated immune responses against HBV antigens.

**Study duration**

- **Patients enrolled in the SD cohort underwent 13 visits, including screening, baseline, and end-of-study visit at week 52.**
  - Visits comprised clinical evaluation, full laboratory evaluation, ECG, FibroScan® or Fibrosure®/FibroTest®.
  - Incidence of AEs and standard laboratory parameters were evaluated according to NCI Common Toxicity Criteria for Adverse Events.

**Results**

- **Safety and tolerability**
  - No sign of hepatotoxicity was reported.
  - 23 AEs were reported: 14 (61%) AEs were in SOC “General disorders and administration site conditions”, mostly injection site reactions.
  - 12 (52%) AEs were related to IMP or NUC.
  - 5 patients (41.7%) had drug-related adverse events (AEs) which were mainly injection site reactions such as erythema, induration, and pain.
  - All AEs were of grade 1 or 2 except one NCI CTC AE. There was no SAE and no sign of immune related AE.

**DISCLOSURES**

All authors affiliated to Transgene SA or were employees of Transgene SA or the manufacturer of TG1050. Other authors do not have competing interest.

**REFERENCES**

1. Martin F. et al., Gut 2015; 64(12):1963-71
2. Olen et. al., J. Virol, May 2013, 87(10):5544-63
3. ClinicalTrials.gov. NCT02438400

**CONCLUSION**

- **Safety:** A subcutaneous SD of TG1050 in NUC suppressed CHB patients was safe over the 3 DLs and did not have any negative impact on disease control. This observation, in a particularly sensitive population (no pre-immunity against the adenoviral vector), demonstrated a robust safety profile of TG1050.
- **Immunogenicity:** Early analysis indicated that TG1050 induced a robust cell-mediated immune response against the HBV Polymerase, the CORE protein and the Envelope protein. A dose-effect relationship was observed across the 3 DLs in terms of number of responders.
- **Perspective:** Additional immune and HBV related markers are being assessed and will be published later under unblinding.

**Hepatitis B and AASLD Liver Meeting – Washington, DC – October 2017**

**Recruitment**

Recruitment has been completed in the ongoing MD cohort. 36 CHB patients were randomized regardless of anti-Adenovirus serology status: 27 patients received 3 doses of TG1050 at the 3 DLs and 9 patients received matching placebo.

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