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

*Corresponding author: martin.sprinzl@unimedizin-mainz.de*

***Martin F. Sprinzl[2], Claire Fournier[3], Vincent Leroy[4], Stanislas Pol[5], François Habersetzer[6], Robert Thimme[7], Mang M. Ma[8], Benoit Sansas[1], Genevieve Inchauspe[1], Céline Halluard[1], Kaïdre Bendjama[1], Maud Brandely[1], Fabien Zoulim[9]***

*[1]**Transgene** SA, Illkirch-Graffenstaden, France - [2]**I. Medical Department, University Medical Center Mainz**, Mainz, Germany - [3]**Hepatology, St Luc Hospital**, Montreal, QC, Canada - [4]**Michallon Hospital**, Grenoble, France - [5]**Liver Unit, Paris Descartes University**, Cochin Hospital, Paris, France - [6]**University Hospital Strasbourg**, Strasbourg, France - [7]**Department of Medicine, University Hospital Freiburg**, Freiburg, Germany - [8]**Univ Alberta**, Edmonton, AB, Canada - [9]**Hospices Civils of Lyon**, Croix Rousse Hospital, Lyon, France*

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## 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 [1].

**Figure 1: Fusion protein encoded by TG1050 comprising truncated HBV Core fused to a deleted and mutated HBV polymerase and 2 selected domains of Envelope (genotype D)**


### Objective of TG1050

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

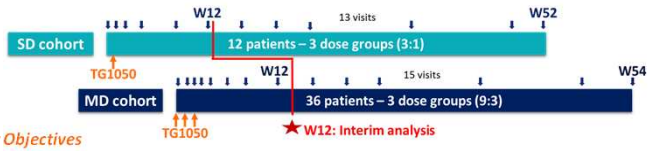
### Mechanism of Action (MoA)

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 in naïve 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[1] and, in some cases, by triggering anti-HBsAg antibodies.

## MATERIAL & 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 (DLs) of $10^9$, $10^{10}$, $10^{11}$ virus particles and then randomized 3:1 within each DL 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

Secondary Objectives
- To evaluate the antiviral activity of TG1050, e.g. HBsAg levels over time and loss 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 (ENT) for ≥2 years
- Undetectable level of anti-Ad5 nAb
- HBV DNA level below 20 IU/mL for at least 6 months
- HBsAg positive
- Compensated liver disease and no prior history of clinical hepatic decompensation
- ALT level below ULN
- No co-infections (HIV, HCV or HDV)
- No medical history or evidence of cirrhosis at baseline
- No history of immunodeficiency or autoimmune disease

## DEMOGRAPHICS

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

| | | $10^9$ vp N=4 | $10^{10}$ vp N=4 | $10^{11}$ vp N=4 | Overall N=12 |
|---|---|---|---|---|---|
| **Gender** | Male/Female | 2/2 (50%) | 3/1 (75%) | 2/2 (50%) | **7/5 (58.3%)** |
| **Age (years)** | Median | 48.0 | 48.0 | 45.0 | **48.0** |
| **Duration of HBV disease (years)** | Median | 25.5 | 19.7 | 14.4 | **19.7** |
| **Nucleo(s)tides treatment** | ENT | 2 (50%) | 2 (50%) | 1 (25%) | **5 (41.7%)** |
| **Duration of NUC therapy (years)** | Median | 4.9 | 5.5 | 3.2 | **4.1** |
| **HBeAg status** | Positive/Negative | 0/4 | 1/3 | 0/4 | **1/11** |

## SAFETY & TOLERABILITY

### Evaluation Criteria

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. Blinded safety data of SD cohort were reviewed by an independent Safety Review Committee before initiating the MD cohort, which is ongoing.

### Results

**Study treatment was well-tolerated**. No sign of hepatotoxicity was reported. 23 AEs were reported:
- 14 (61%) AEs were in SOC (System Organ Class) "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 according to NCI CTC AE. There was **no SAE** and no sign of immune related AE.

| Primary System Organ Class MedDRA Preferred Term | $10^9$ vp N=4 All | $10^9$ vp N=4 Grade 1 | $10^9$ vp N=4 Grade 2 | $10^{10}$ vp N=4 All | $10^{10}$ vp N=4 Grade 1 | $10^{10}$ vp N=4 Grade 2 | $10^{11}$ vp N=4 All | $10^{11}$ vp N=4 Grade 1 | $10^{11}$ vp N=4 Grade 2 |
|---|---|---|---|---|---|---|---|---|---|
| **Number of patients with at least one IMP or NUC-related AE** | **0** | **0** | **0** | **2** | **2** | **0** | **3** | **3** | **1** |
| **General disorders and administration site conditions** | **0** | **0** | **0** | **1** | **1** | **0** | **3** | **3** | **1** |
| Influenza like illness | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| Injection site erythema | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Injection site induration | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0 |
| Injection site pain | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 1 |
| Injection site pruritus | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| Pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| Pyrexia | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| **Nervous system disorders** | **0** | **0** | **0** | **1** | **1** | **0** | **0** | **0** | **0** |
| Dizziness | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Somnolence | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |

## HBV-SPECIFIC IMMUNOGENICITY

Besides safety endpoints, this study is backed by an extensive biomarker program aiming at further documenting the associated mechanism of action and antiviral effects.

### Evaluation Criteria

- Cell-mediated immune responses against HBV antigens were evaluated in patients by ELISpot IFNγ assay. PBMC were collected at Baseline, Week 2, Week 4 and Week 12 after administration of TG1050. Additional exploratory parameters are being analyzed.
- Patients were adjudicated as responders for one antigen when at least a doubling of response or an increase of ≥ 500 sfc from baseline was observed. Changes below the assay precision were not considered significant.

### Results

| | Number of responses $10^9$ vp | $10^{10}$ vp | $10^{11}$ vp | Overall |
|---|---|---|---|---|
| POL 1 | 0/3 | 2/4 | 2/3 | 4/10 |
| POL 2 | 2/3 | 3/4 | 2/3 | 7/10 |
| POL 3 | 1/3 | 1/4 | 2/3 | 4/10 |
| CORE | 0/2 | 4/4 | 2/3 | 6/9 |
| ENV | 0/2 | 2/4 | 2/3 | 4/9 |
| **At least one** | **2/3** | **4/4** | **3/3** | **9/10** |
| **At least two** | **1/3** | **3/4** | **2/3** | **6/10** |
| **At least three** | **0/3** | **2/4** | **2/3** | **4/10** |

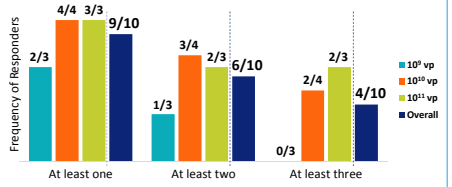



**Table 3 & Figure 2: Number of responses observed in the SD cohort for each antigen in each dose group and number of patients responding to at least 1, 2 or 3 antigens**

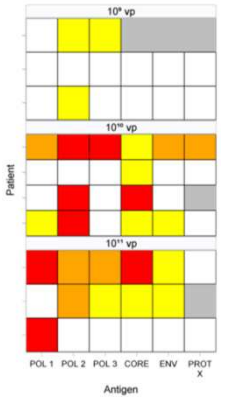



**Figure 3: Heatmap of ELISPOT responses. Patients are listed as lines and test conditions as columns**

Intensity of response in SFC/million cells: No response; <400; No data; 400 to 750; >750

- **10/12 patients were evaluable** by ELISpot assay. For all tested antigens patient exhibited a generally low response at baseline (median ~100 spots).
- **Robust responses** were observed against targeted antigens for the intermediate and high dose levels peaking between W2 and W4.
- A **dose-effect relationship** was observed in terms of number of patients developing responses against 2 or more pools of peptides (Table 3). Similarly, intensity of responses observed was higher in the intermediate and high dose level cohort. (Figure 2).
- One response was observed against protein X, an antigen that is not targeted by TG1050. This response occurred at late-time point and may result from epitope spreading.

*Note: This blinded analysis includes data from patients randomized 3:1 to receive TG1050 or placebo.*

## 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 after unblinding.

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.

## REFERENCES

[1] Martin et al., Gut, Dec 2015; 64(12):1961-71
[2] Dion et al., J Virol, May 2013; 87(10):5554-63
[3] ClinicalTrials.gov: NCT02428400

## DISCLOSURES

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