**Meta-analysis of two phase 1b randomized, double-blind, placebo controlled clinical trials of the HBV therapeutic vaccines TG1050 and T101 developed in Europe/Canada or China**

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**BACKGROUND**

Two HBV therapeutic vaccines, TG1050 and T101, derived from a single design (Core, Polymersome, Envelope domains) and delivered by an adenovirus 5 (Ad5) have completed phase 1b in CHB patients with NUC. Both trials reached their primary endpoint (safety and evidence of immunogenicity and preliminary antiviral activity) as documented in Figure 1.

A meta-analysis was performed to evaluate the change over time of circulating HBsAg observed at the two highest treatment doses based on results from the two trials.

**DESCRIPTION OF PRODUCTS & OBJECTIVE**

Description of products

TG1050 and T101 are based on a recombinant non-expansive Adenovirus 5 vector encoding for a large fusion protein comprising sequences of latently core, an almost full-length Polymersome and domains on envelope 

Figure 1: Fusion protein encoded by TG1050 and T101 comprising truncated HBc Core fused to a deleted and modified HBV polymersome and 2 selected domains of Envelope (genotype D)

**Objective of TG1050 & T101**

To increase the functional cure rate in chronic HBV patients in combination with SOC and/or novel antivirals by triggering antiviral activity of T cells through non-cytolytic and cytolytic mechanisms 1,2,3.

**FIM STUDIES WITH TG1050 & T101**

The two FIM studies TG1050 F0812 & T101-002 evaluating respectively TG1050 & T101 were randomized, double blind, placebo-controlled and dose finding studies. They included 2 sequential phases: one single dose (SD) cohort and one multiple dose (MD) cohort.

84 patients were enrolled: 48 in TG1050 study (Europe/Canada) and 36 for in T101 study (China). Patients were randomized to receive: (1) single dose (SD cohort) or (2) multiple (x6) doses (MD cohort) across 3 or 2 dose levels (Dx) of 105, 106, 107 or 108 particles (µg) at the ratio of 2:1:2 with 6 placebo patients in each dose group included 3 placebo in SD cohort; 12 patients in each dose group included 3 placebo in MD cohort.

**Key Inclusion Criteria**

Chronic Hepatitis B (CHB) patients eligible when they met the following criteria:

- NUC treatment
- Compensated liver disease and no prior history of clinical hepatic decompensation
- ALT level <1.5 x ULN
- HBsAg positive
- DNA viral load <20 IU/mL

**Results of studies evaluating TG1050 & T101 have been reported 1,2,3**

**SAFETY & TOLERABILITY**

No AE, no sign of immune related AE and sign of hepatotoxicity were reported.

According to NCI-CTCAE, all AEs were of grade 1 or 2.

Most of AEs were in SOC (System Organ Class) “General disorders and administration site conditions”, mostly injection site reactions.

**HBV-SPECIFIC IMMUNOGENICITY**

**Evaluation Criteria**

Collimated immune responses against HBV antigens were evaluated in patients by ELISPOT if NUC assay. Peptide pools of HB Ag targets by the vaccines were tested: Pol, Pol3, Pol9, Core & Env + a HB Ag not targeted by the vaccine: Protein X + Ad virus to assess response to the vaccine vector.

**Results**

- TG1050 & T101 induced HBV-specific cellular immune responses 1,2,3,4,5

- In both studies, the dose 10⁸ µg was the most immunogenic 1,2,3,4,5

**DEMOGRAPHICS**

A total of 48 patients were randomized and received a multiple dose of 10⁶ or 10⁷ virus particles (µg) of TG1050 or T101 versus placebo.

**Table 1: Demographic characteristics at baseline in 10⁶ & 10⁷ µg MD cohorts of TG1050-02 & TC-2017-001 study**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male/Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.5/33.0</td>
</tr>
<tr>
<td>Duration of Hepatitis B virus (years)</td>
<td>10.0/10.0</td>
</tr>
<tr>
<td>Nucleoside analog treatment</td>
<td>60/60</td>
</tr>
<tr>
<td>Duration of NUC therapy (years)</td>
<td>3.5/2.0</td>
</tr>
<tr>
<td>HBV DNA level</td>
<td>6.3/6.7</td>
</tr>
</tbody>
</table>

**DISCUSSIONS**

All authors affiliated to Transgene SA are or were employees of Transgene the manufacturer of T101. All authors affiliated to Tsaly or are or were employees of Tsaly the manufacturer of TG101. Other authors do not have competing interest.

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**HBsAg evolution:** This exploratory meta-analysis shows a significant decline of HBsAg at the treatment dose 10⁷ µg, the dose received by all responders. Furthermore, no significant impact of NUC treatment, NUC duration and pre-existing ADV neutralizing Abs was found.

**CONCLUSION**

**A meta-analysis was performed to evaluate the change over time of HBsAg at two highest treatment doses based on the two trials**

**Evaluation Criteria**

- Reproducibility: defined as showing circulating HBsAg decrease of at least 6 log units over 1 or more time points.
- The analysis was performed on data generated from 10⁵ and 10⁶ µg cohorts of TG1050 & T101 studies in MD cohorts.

- Impact of baseline characteristics was evaluated using a mixed model considering the following parameters: age, gender, fibrosis, NUC, duration of treatment, ADV neutralizing (anti-ADV) and HBsAg dosage at baseline. Time and interaction between both fixed effects and the study in linear effect with ADV duration of treatment correlation coefficient.

A new meta-analysis was built in both studies to compare the impact on the doses 10⁵ and 10⁶ versus placebo.

**Figure 3: HBsAg log decrease in Responders of in MD cohorts of TG1050-02 & TC-2017-001 study**

**Table 2: Characteristics of responders of TG1050-02 & TC-2017-001 studies**

**Impact of baseline characteristics on HBsAg decrease**

**Figure 4: Meta-analysis of HBsAg evolution at each dose level**

**HBsAg decrease observed by: (1) timepoints in TC-2017-001 study: **

**Table 3: Mixed models on baseline characteristics**

**Mixed models using baseline characteristics as potential predictors:**

- Model 1: No significant impact of NUC, duration of NUC or baseline level of HBsAg was observed.
- Model 2: Significant impact of HBsAg score was identified.
- Model 3: Significant interaction HBsAg and fibrosis at baseline.

**Results**

- All these exploratory results should be interpreted cautiously and are only avenues of development for further studies given the differences of baseline characteristics between the 2 studies and the few number of patients.

- A total of 7 responders (3 in 5 in TG1050 and T101 coherently respectively) with HBsAg decreases ranging from 0.4 to 1.14 log was identified.

- Results of the mixed models indicate:

  - Significant interaction Time x Dose (p-value = 0.026) indicating HBsAg evolution over time depends on the vaccine dose injected;
  - Significant interaction was found with an antagonist effect meaning that patient with high level of HBsAg at baseline will benefit from the vaccine and present a higher decrease of HBsAg;
  - No significant impact of NUC, duration of NUC or baseline level of ADV Abs was found; and
  - Significant impact of T0/T101/01 at dose 10⁷ µg (p=0.029)

**Figure 5: HBsAg evolution at each dose level**

**Meta-analysis was done using a fixed effect model by weighting estimation with the inverse variance.**

**Figure 6: Meta-analysis of HBsAg evolution at each dose level**

**HBsAg evolution:** This exploratory meta-analysis shows a significant decline of HBsAg at the treatment dose 10⁷ µg, the dose received by all responders. Furthermore, no significant impact of NUC treatment, NUC duration and pre-existing ADV neutralizing Abs was found.