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, Polymerase, Envelope domains) and delivered by an adenovirus 5 (Ad5) have completed phase 1b in CHB patients receiving NUC. Both trials reached their primary endpoint (safety) and evidence of immunogenicity and preliminary antiviral activity (HBsAg evolution) was documented [1,2,3].

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-replicative Adenovirus 5 vector encoding for a large fusion protein comprising sequences of truncated Core, an almost full-length Polymerase and domains of Envelope [4].

Figure 1: Fusion protein encoded by TG1050 and T101 comprising truncated HBV Core fused to a deleted and mutated HBV polymerase 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 [4,5].

MATERIAL & METHOD

For these statistical analyses, only MD cohorts were used for comparisons and the two doses 10^{10} and 10^{11} vp. Circulating HBsAg (ng/mL) was used in this statistical analysis to evaluate TG1050/T101 activity, data were log-transformed for quantitative statistical analyses. The evolution over time was evaluated using a repeated mixed model and the statistical unit was the baseline delta after log-transformation. The evolution over time as a quadratic or polynomial function was studied.

A qualitative analysis was done by comparing the percentage of responders: a patient was considered as "Responder" if he presented a HBsAg decrease superior to 0.4 log compared with baseline value in one or more timepoints during the study.

To evaluate impact of covariates, a first mixed model was built including time, dose (placebo, 10^{10} and 10^{11} vp) and the interaction between time and dose.

A second global mixed model was used including all baseline characteristics: age, gender, Fibroscan, NUC, duration of treatment, Ad5 neutralizing (N) Antibodies (Abs) levels and HBsAg value and time, dose and interaction of both as fixed effects and study as random effect.

For the meta-analysis, a new model was done by estimating for each study the interaction term time*treatment (TG1050/T101 vs placebo) and the associated standard error. Then a meta-analysis using a fixed effect model was done by weighting estimation with the inverse-variance. The R package *metafor* was used. Results were presented using a Forest plot representation. Analyses were conducted using SAS® 9.4 and R version 3.2.2. Tests were performed at the level of 5%.

FIM STUDIES with TG1050 & T101

The two FIM studies TG1050.02 & TC-2017-001 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 (x3) doses (MD cohort) across 2 or 3 dose levels (DLs) of 10^9, 10^{10}, 10^{11} virus particles (vp) at the ratio of 3:1 within each DL to placebo (4 patients in each dose group included 1 placebo in SD cohort; 12 patients in each dose group included 3 placebo in MD cohort).

Primary objectives

- Safety and tolerability
- Dose and schedule of administration

Secondary objectives

- Antiviral activity
- Cellular & humoral immune responses

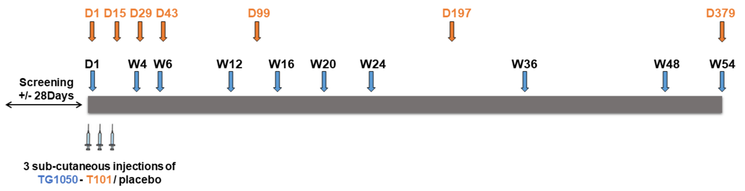
Key Inclusion Criteria

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

- NUC treatment
- HBsAg positive
- HBV DNA level < 20 IU/mL
- Compensated liver disease and no prior history of clinical hepatic decompensation
- ALT level < ULN or 1.5 ULN
- No co-infections (HIV, HCV or HDV)

Results of both studies evaluating TG1050 & T101 have been reported [1,2,3]

Figure 2: HBsAg sampling (⇩: timepoints in TC-2017-001 study, ⇩: timepoints in TG1050.02 study)



SAFETY & TOLERABILITY

TG1050 & T101 were well-tolerated and exhibited a similar safety profile.

- **No SAE**, 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

Cell-mediated immune responses against HBV antigens were evaluated in patients by ELISpot IFNγ assay. Peptide pools of HBV Ag targeted by the vaccines were tested: Pol1, Pol2, Pol3, Core & Env + a HBV Ag not targeted by the vaccine: Protein X as well Ad virus to assess response to the vaccine vector).

Results

- TG1050 & T101 induced HBV-specific cellular immune responses [1,2,3]
- In both studies, the dose 10^{10} vp was the most immunogenic [1,2,3]

DEMOGRAPHICS

A total of 48 patients were randomized and received a multiple dose of 10^{10} or 10^{11} virus particles (vp) of TG1050 or T101 versus placebo.

Table 1: Demographic characteristics at baseline in 10^{10} & 10^{11} vp MD cohorts of TG1050.02 & TC-2017-001 studi

		T101			TG1050		
		Placebo n=6	10^{10} vp n=9	10^{11} vp n=9	Placebo n=6	10^{10} vp n=9	10^{11} vp n=9
Gender	Female/Male	4/2	3/6	3/6	0/6	1/8	3/6
Age (years)	Median	37.5	30.0	33.0	51.5	52.0	52.0
Duration of HBV disease (years)	Median	10.0	5.0	10.0	12.6	12.8	20.1
Nucleo(s)tides treatment	ETV/TDF/LMV	6/0/0	8/1/0	6/1/2	2/4/0	2/7/0	5/4/0
Duration of NUC therapy (years)	Median	3.5	2.0	4.0	6.2	6.0	5.6
HBsAg (IU/ml)	Median – log	2.8	3.5	3.7	3.3	2.7	3.1
Fibroscan score	Median	5.1	5.3	4.7	7.4	4.1	5.5
Ad5 NAbs	Median	243	344	453	114	112	67

HBSAG

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

- Responders were defined as showing circulating HBsAg decrease of at least 0.4 log over 1 or more time points.
- The meta-analysis was performed on data generated from 10^{10} vp and 10^{11} vp cohorts of TG1050 & T101 studies in MD cohorts.
- Impact of baseline characteristics was evaluated using a mixed model considering the following parameters: age, gender, Fibroscan, NUC, duration of treatment, Ad5 neutralizing Antibodies (Abs) levels and HBsAg values at baseline), Time, Dose and interaction between both as fixed effects and the study as random effect with AR(1) variance-covariance matrix.
- A new model was built in each study to perform the meta-analysis on the doses 10^{10} and 10^{11} versus placebo.

Figure 3: HBsAg log decreases in Responders of in MD cohorts of TG1050.02 & TC-2017-001

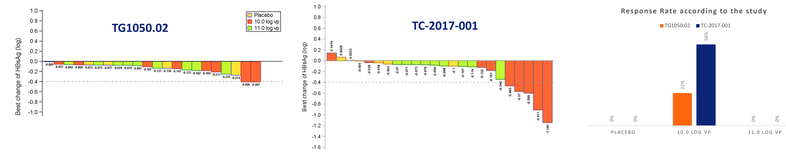


Figure 4: Individual HBsAg evolution over time in MD cohorts of TG1050.02 & TC-2017-001

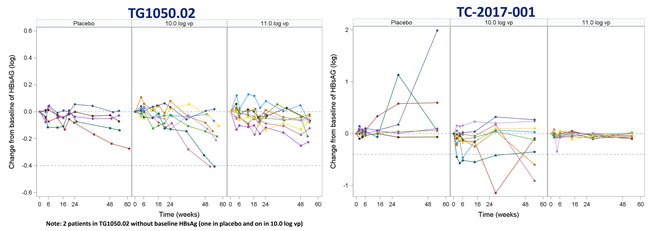


Table 2: Characteristics of responders of TG1050.02 & TC-2017-001 studies

Patient Id	Study	Age (years) / Gender	HBV disease duration (years)	NUC treatment	Treatment duration (years)	Fibroscan score at baseline	Baseline Ad5 Abs	Baseline HBsAg	HBsAg at last visit (W52-54)	Best HBsAg change (log)
401	TC-2017-001	37 / M	30.0	Entecavir	3.0	3.3	3179	323	345	-0.47
402	TC-2017-001	28 / M	12.0	Tenofovir	1.0	6.7	<30	3542	435	-0.91
403	TC-2017-001	28 / M	5.0	Entecavir	3.0	5.8	<30	17721	4458	-0.60
411	TC-2017-001	27 / F	6.0	Entecavir	2.0	5.3	513	12236	9919	-1.14
412	TC-2017-001	48 / F	5.0	Entecavir	5.0	5.3	59	212	94	-0.57
0103004	TG1050.02	52 / M	26.0	Tenofovir	6.0	6.8	112	172	67	-0.41
4103003	TG1050.02	41 / M	5.3	Entecavir	3.4	6.6	<10	196	77	-0.41

Impact of baseline characteristics

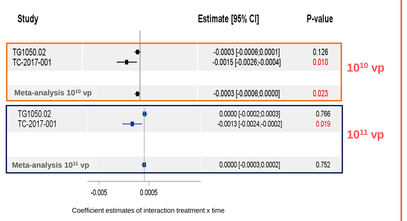
Table 3: Mixed models on baseline characteristics

Effect | P-value	M1	M2	M3
Time	0.999	0.999	0.741
Time²	0.080	0.081	0.113
Gender	0.987	0.818	
Age	0.266	0.208	
Dose	0.129	0.174	**0.020**
Time*Dose	**0.029**	**0.030**	**0.026**
Fibroscan score at Baseline	**0.017**	**0.012**	**0.002 (β=-0.113)**
Log(HBsAg) at BL	0.107	0.170	**0.008 (β=-0.164)**
Ad5 Abs at baseline (log)	0.831		
Treatment duration (years)	0.978		
Disease duration	0.300		
NUC	0.745		
HBsAg x Fibroscan			**0.007 (β=0.029)**

Mixed models using baseline characteristics as potential predictors:
Model 1 (M1): No significant impact of NUC, duration of NUC or baseline level of Ad5 Abs was found.
Model 2 (M2): Significant impact of Fibroscan score was identified (p=0.012, β=-0.027).
Model3 (M3): significant interaction HBsAg and Fibroscan at baseline.

Meta-analysis

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



Meta-analysis was done using a fixed effect model by weighting estimation with the inverse-variance. Significant impact of treatment was found at dose 10^{10} vp (p=0.023) with a higher decrease of HBsAg in patients treated with T101/TG1050 than patients treated with placebo.

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 (2 and 5 in TG1050 and T101 cohorts 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 that 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 or high Fibroscan score at baseline would present a higher decrease of HBsAg;
  - ✓ No significant impact of NUC, duration of NUC or baseline level of Ad5 Abs was found;
  - ✓ Significant impact of TG1050/T101 at dose 10^{10} vp (p=0.023)

CONCLUSION

HBsAg evolution: This exploratory meta-analysis shows a significant decline of HBsAg at the treatment dose 10^{10} vp, the dose received by all responders. Furthermore, no significant impact of NUC treatment, NUC duration and pre-existing Ad5 neutralizing Abs was found.

Status: T101 vaccine is being evaluated in a phase 2 clinical study

REFERENCES

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DISCLOSURES

All authors affiliated to Transgene SA are or were employees of Transgene the manufacturer of TG1050. All authors affiliated to Tasly are or were employees of Tasly the manufacturer of T101. Other authors do not have competing interest.