Safety and Immunogenicity of Single and Multiple Injections of the Therapeutic Vaccine TG1050 in NUC-Suppressed Chronic Hepatitis B (CHB) Patients: Unblinded Analysis of a Double-Blind, Placebo-Controlled Phase 1b Study

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PRODUCT DESCRIPTION AND OBJECTIVE

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].

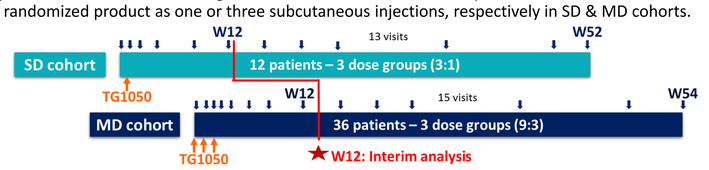
Figure 1: Fusion protein encoded by TG1050 comprising truncated HBV Core fused to a deleted and mutated HBV polymerase and 2 selected domains of Envelope (genotype D)

Objective of TG1050

To increase the functional cure rate in chronic HBV patients in combination with SOC and/or novel antivirals by triggering antiviral activity of T-cells through non-cytolytic and cytolytic mechanisms[1, 4].

STUDY DESIGN

It was a randomized, double blind, placebo-controlled and dose finding study. It included 2 sequential phases: one single dose (SD) cohort and one multiple dose (MD) cohort.
In SD & MD cohorts, 12 & 36 patients were randomized 1:1:1 across 3 dose levels (DLs) of 10^9, 10^{10}, 10^{11} virus particles (vp) and then randomized 3:1 within each DL to placebo (4 patients in each dose group included 1 placebo in SD cohort; 9 patients in each dose group included 3 placebo in MD cohort).
The study was conducted in 12 investigational centers in France, Germany and Canada. Patients received the allocated randomized product as one or three subcutaneous injections, respectively in SD & MD cohorts.



Study Objectives

Primary Objectives:
- Safety and tolerability
- Dose and schedule of administration

Secondary Objectives:
- Antiviral activity
- 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
- HBV DNA level below 20 IU/mL for at least 6 months
- HBsAg positive
- Undetectable level of anti-Ad5 nAb (for patients of SD cohort only)
- 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 48 patients were randomized and received a single or a multiple dose of TG1050 or placebo.

Table 1: Demographic characteristics at baseline in SD & MD cohorts

		Placebo		10^9 vp		10^{10} vp		10^{11} vp		Overall	
		SD N=4	MD N=9	SD N=4	MD N=9	SD N=4	MD N=9	SD N=4	MD N=9	SD N=12	MD N=36
Gender	Female/Male	0/3	0/9	2/1	2/7	1/2	1/8	2/1	3/6	**5/7**	**6/30**
Age (years)	Median	53	52	44	45	48	52	41	52	**48**	**49.5**
Duration of HBV disease (years)	Median	20.2	12.8	26.8	14.9	19.3	12.8	11.9	20.1	**19.7**	**14.6**
Nucleo(s)tides treatment	ETV/TDF	1/2	3/6	1/2	4/5	2/1	2/7	1/2	5/4	**5/7**	**14/22**
Duration of NUC therapy (years)	Median	6.2	5.1	3.2	4.9	4.8	6	3.4	5.6	**4.1**	**5.7**
HBeAg status	Neg/Positive	3/0	8/1	3/0	9/0	2/1	8/1	3/0	9/0	**11/1**	**34/2**

SAFETY & TOLERABILITY

Evaluation Criteria

Patients enrolled in SD & MD cohorts underwent 13 & 15 visits respectively, including screening, baseline, and end-of-study visit at week 52/54. 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

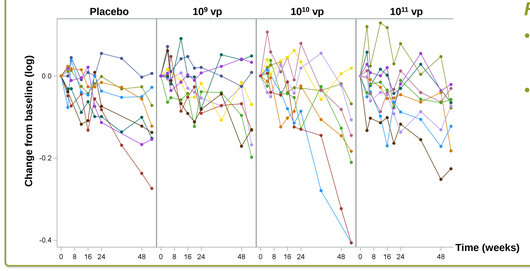
Study treatment was well-tolerated.
- **No SAE**, no sign of immune related AE and sign of hepatotoxicity were reported.
- Overall 23 patients (59 events) exhibited IMP or NUC-related AEs. Most of AEs (74%) were in SOC (System Organ Class) "General disorders and administration site conditions", mostly injection site reactions.
- According to NCI-CTCAE, all AEs were of grade 1 or 2 except 1 grade 3 which was not related to IMP or NUC.

Table 2: Number (%) of patients with IMP-related adverse events in SD & MD cohorts

	10^9 vp		10^{10} vp		10^{11} vp		Overall	
	SD (N=4) N(%)	MD (N=9) N(%)	SD (N=4) N(%)	MD (N=9) N(%)	SD (N=4) N(%)	MD (N=9) N(%)	SD (N=9) N(%)	MD (N=27) N(%)
Patient with at least one IMP or NUC-related adverse events	**0 (0.0%)**	**5 (55.6%)**	**1 (33.3%)**	**8 (88.9%)**	**3 (100.0%)**	**6 (66.7%)**	**4 (44.4%)**	**19 (70.4%)**
Blood and lymphatic system disorders				**1 (11.1%)**				**1 (3.7%)**
Ear and labyrinth disorders						**2 (22.2%)**		**2 (7.4%)**
Gastrointestinal disorders	**1 (11.1%)**			**1 (11.1%)**				**2 (7.4%)**
General disorders and administration site conditions	**3 (33.3%)**	**1 (33.3%)**	**5 (55.6%)**	**3 (100.0%)**	**5 (55.6%)**	**4 (44.4%)**	**13 (48.1%)**	
Influenza like illness				1 (33.3%)		1 (11.1%)		
Chills					1 (11.1%)		1 (3.7%)	
Fatigue			2 (22.2%)		1 (11.1%)		3 (11.1%)	
Feeling hot			1 (11.1%)				1 (3.7%)	
Injection site reaction	2 (22.2%)	1 (33.3%)	4 (44.4%)	3 (100.0%)	6 (66.6%)	4 (44.4%)	12 (44.4%)	
Pain	1 (11.1%)			1 (33.3%)			1 (3.7%)	
Pyrexia			1 (11.1%)	1 (33.3%)			1 (3.7%)	
Infections and infestations	**2 (11.1%)**		**1 (11.1%)**				**3 (11.1%)**	
Investigations (Body T° increased, WBC in urine)			**1 (11.1%)**		**1 (11.1%)**		**2 (7.4%)**	
Met and nutrition disorders (hypophosphatemia)			**1 (11.1%)**		**2 (22.2%)**		**3 (11.1%)**	
Musculoskeletal and connective tissue disorders	**1 (11.1%)**		**1 (11.1%)**				**2 (7.4%)**	
Nervous system disorders	**2 (22.2%)**				**1 (11.1%)**		**3 (11.1%)**	
Respiratory, thoracic and mediastinal disorders					**1 (11.1%)**		**1 (3.7%)**	
Skin & subcutaneous tissue disorders	**1 (11.1%)**				**1 (11.1%)**		**2 (7.4%)**	
Vascular disorders (Hot flush)			**1 (11.1%)**				**1 (3.7%)**	

ANTIVIRAL ACTIVITY

Figure 2: Individual HBsAg evolution over time in MD cohort



Results

- HBsAg decline reaches 0.4 log over time, observed in 2 patients of 10^{10} vp group.
- No statistically significant difference was observed across treatment groups*.

* Exploratory analysis. This study was not powered for this test.

HBV-SPECIFIC IMMUNOGENICITY

Evaluation Criteria

- Cell-mediated immune responses against HBV antigens were evaluated in patients by ELISpot IFNγ assay (10 day stimulation, 7 peptide pool: HBV Ag targeted by the vaccine: Pol1, Pol2, Pol3, Core & Env + HBV Ag not targeted by the vaccine: Protein X & vaccine vector: Ad5).
- PBMC were collected in SD cohort at baseline, week 2, 4 & 12 and in MD cohort at baseline, week 4, 6 & 12. As no consensus exists on threshold of anti-Ad5 neutralizing antibody (nAb) potentially affecting vaccine immunogenicity, we defined arbitrarily 2 sub-groups using median value of anti-Ad5 nAb: (1) < Median: anti-Ad5 low ; (2)> Median: anti-Ad5 high pre-immunity.
- Pre-existing seropositivity is known to potentially affect immunogenicity of Ad5 based vectors: All patients of SD cohort were anti-Ad5 seronegative. In MD cohort, patients with anti-Ad5 high pre-immunity, similar or stronger signals were observed in some placebo-treated patients compared with vaccinees, which led to the impossibility of data interpretation in this sub-group. Hence, all reported analyses focus on data from patients with no or anti-Ad5 low pre-immunity.
- Patients were adjudicated as responders for one antigen when at least a doubling of response or an increase of ≥ 500 spots from baseline was observed on the ELISpot assay. Changes below the assay precision were not considered significant.

Results

Figure 3: Number of patients with low anti-Ad5 pre-immunity per dose group responding to at least 1, 2 or 3 antigens

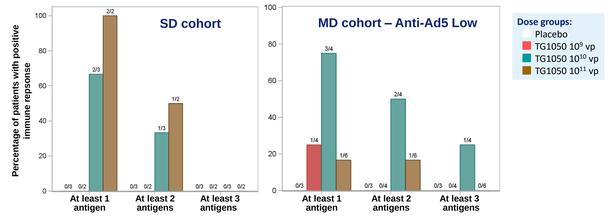


Figure 4: Heatmap of ELISpot responses. Patients with low anti-Ad5 pre-immunity are listed as lines and test conditions as columns
- HBV-specific responses detected in SD & MD cohorts mainly in 10^{10} & 10^{11} vp dose groups

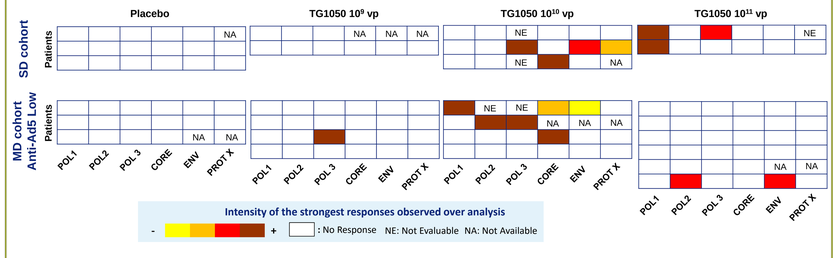
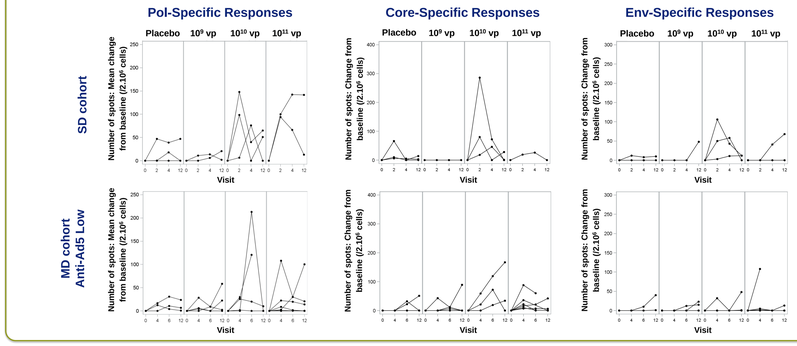


Figure 5: Individual evolution of ELISpot responses over time in patients with low anti-Ad5 pre-immunity
- Detectable responses in both SD & MD cohorts at 10^{10} & 10^{11} vp doses
- Env-specific responses detected despite TG1050 encoding for only small domains of Env/HBsAg as well as the very high tolerance against HBsAg characterizing CHB carriers.



CONCLUSION

***Safety:* Clinical trial primary end-point reached.** Subcutaneous SD & MD injections of TG1050 in NUC-suppressed CHB patients is well tolerated over the 3 DLs. No negative impact on disease control, especially in the sensitive part of patients with no pre-immunity against the adenoviral vector, reinforces the robust safety profile of TG1050.
Immunogenicity: TG1050 induces HBV-specific cellular immunity (IFN-g cells) in NUC-suppressed CHB patients without or with low anti-Ad5 pre-immunity. Background signals precluded interpretation in patients with high anti-Ad5 titers. Induced responses are specific of single or multiple antigens expressed by TG1050 (Core/Pol & Env). Detection of Env-specific responses is encouraging in a highly tolerogenic context for this antigen. Responses are detected following single and multiple injections: Intermediate dose 10^{10} vp is consistently immunogenic (~70% of patients).
HBsAg evolution: HBsAg decline reaches ≈0.4 log over time in 2 patients of 10^{10} vp group.

REFERENCES

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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.