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Title of study:
TG4040.02 HCVac study:
A phase II randomized, multicenter, open label study of TG4040 (MVA-HCV) in combination with pegylated interferon alfa-2a and ribavirin versus pegylated interferon alfa-2a and ribavirin in treatment-naïve patients with chronic genotype 1 hepatitis C.

Coordinating Investigator:
Pr. Heiner Wedemeyer (Hannover)

Study center(s):
A total of 26 centers, based in 7 countries, randomized patients into the study. These centers were in France, Germany, Israel, Poland, Romania, Spain and United States of America (USA).

Publications (reference):
-Wedemeyer H., Janczewska Kazek E., Mazur W. *et al.* HCVac study: Antiviral activity of TG4040 therapeutic vaccine in genotype-1 chronic HCV patients. Poster presentation at the 62nd Annual Meeting of the American Association for the Study of the Liver Diseases, San Francisco, Nov 2011.
-Wedemeyer H, Janczewska Kazek H, Mazur W, *et al*. Significant improvement of complete EVR in HCVac phase II clinical trial when adding TG4040 therapeutic vaccine to PegIFN and ribavirin. Oral presentation at the European Association for the Study of Liver Meeting, Barcelona, Apr 2012.
-Wedemeyer H, Janczewska Kazek E, Mazur W,*et al*. Phase II HCVac Study of TG4040 immunotherapeutic in combination with PegIFNα2a and ribavirin in genotype 1 CHC treatment naïve patients: SVR24 Final Results. Oral presentation at the European Association for the Study of Liver Meeting, Amsterdam, Apr 2013.
- Di Bisceglie AM, Janczweska-Kazek E, Habersetzer F *et al*. TG4040 Immunotherapeutic with Peginterferon/Ribavirin in Chronic HCV Infection: a Randomized Phase II Study. In review in Gastroenterology.

Studied period:	**Phase of development:** II
Start date (first patient randomized): 07-Oct-2010 Completion date (last patient last visit): 31-Oct-2012	

Objectives:
Primary: To evaluate the efficacy of TG4040 combined with pegylated interferon alfa-2a and ribavirin (PegIFN/RBV) in treatment-naïve patients with chronic genotype 1 hepatitis C infection as measured by the proportion of patients who achieved complete early virologic response (cEVR: was defined as undetectability of the Hepatitis C Virus [HCV] ribonucleic acid [RNA] after 12 weeks of PegIFN/RBV).

Secondary:
- To determine the effects of TG4040 alone and in combination with PegIFN/RBV on viral load, over time, relative to baseline.
- To evaluate the safety of TG4040 alone and in combination with PegIFN/RBV.
- To determine the immunogenicity of TG4040 alone and in combination with PegIFN/RBV.
- To identify molecular biomarkers related to TG4040 efficacy in combination with PegIFN/RBV by gene-expression profiling.

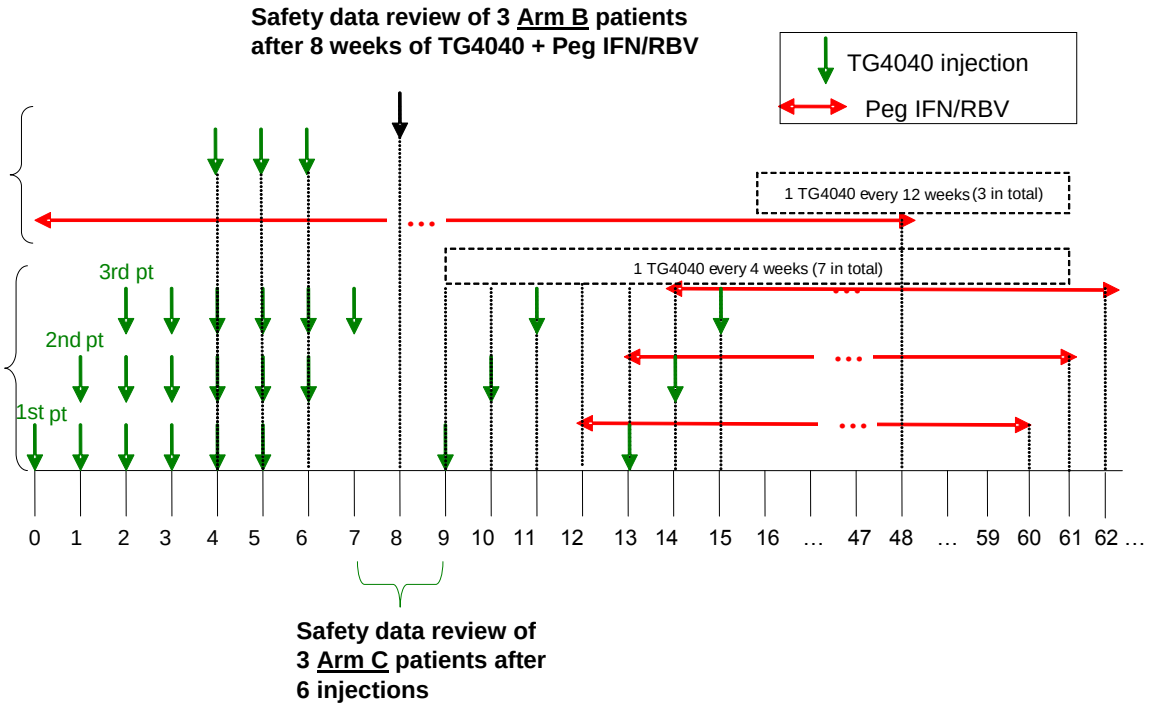
Methodology:
This was a randomized, open-label study in treatment-naïve HCV genotype 1-infected patients. It was planned to evaluate 123 patients in 3 treatment arms. All treatment arms received PegIFN/RBV. Patients were randomized in a 1:2:2 ratio to Arms A, B and C:
- **Arm A, Control arm** (n= 25 patients planned):
  PegIFN/RBV was to be administered for 48 weeks.
- **Arm B** (n= 49 patients planned):
  PegIFN/RBV was to be administered for 48 weeks and after 4 weeks of PegIFN/RBV,

3 subcutaneous (SC) weekly injections of TG4040 at the dose of 10^7 plaque forming unit (pfu) were to be performed, followed by 3 single injections, every 12 weeks.

- **Arm C** (n= 49 patients planned):
  TG4040 was to be administered SC at the dose of 10^7 pfu once-weekly for 6 weeks followed by 7 TG4040 SC single injections done every 4 weeks. Twelve weeks after first TG4040 injection, PegIFN/RBV was to be introduced and administered for 48 weeks.

All the patients were to receive 48 weeks of PegIFN/RBV. Patients in Arms B and C were to receive 36 and 33 weeks of TG4040, respectively.
The enrolment started at the same time in all 3 arms.
The first 3 patients enrolled in Arm C were sequentially enrolled and treated: there was a 1-week safety interval between enrollments of the 3 first patients followed by a review of safety data (by the Data Safety Monitoring Committee [DSMC]) after these 3 patients had received 6 injections.
A safety review of 3 Arm B patients was to be done at Week 8, and if no safety issue was raised, all patients were to continue treatment according to planned schedules of administration.
During the study, the DSMC reviewed the safety data of Arms A, B and C on a regular basis.
Follow-up was planned for all patients 24 weeks after the end of treatment or treatment discontinuation. Follow-up included safety, immune parameters evaluation and HCV-RNA monitoring.
On 10-Oct-2011, Investigators were informed to stop all TG4040 injections due to 3 events of severe blood toxicity. This decision was taken after DSMC meetings held on 05-Oct-2011 and 07-Oct-11. The halt in administration of TG4040 occurred after patients had received at least 12 weeks of PegIFN/RBV and corresponding TG4040 injections.

The sequential enrolment is summarized in the following scheme:



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Number of patients (planned and analyzed):

A minimum of 140 patients were planned to be enrolled to reach 123 evaluable patients.

Number of patients planned, randomized and analyzed:

Arm	Planned	Randomized	Evaluable (after 12 week PegIFN/RBV)	Intention-to-treat (ITT)	mITT	Interim Per Protocol (PP)	Final PP	Safety
Arm A	25	31	30	31	31	30	26	31
Arm B	49	63	61	63	63	60	58	63
Arm C	49	59	53	59	55	55	51	59
Total	123	153	144	153	149	145	135	153

mITT= modified intention-to-treat

All the randomized patients received at least one dose of investigational medicinal product (IMP)

Diagnosis and criteria for inclusion:

- Male or female patients, age ≥18 to ≤70 years;
- Chronically infected patients with Hepatitis C virus genotype 1 (1a or 1b) with detectable viremia (HCV RNA in blood) for more than 6 months and naïve to treatment;
- Patients had to have compensated liver disease, with no history of ascites, jaundice, hepatic encephalopathy or bleeding from esophageal or gastric varices requiring beta-blockers;
- No histological evidence of hepatic cirrhosis (including compensated cirrhosis) based on a liver biopsy taken within 24 months prior to baseline; or on a FibroScan® performed within 6 months prior to treatment which indicated the absence of liver cirrhosis, i.e., stage <F4 (METAVIR) or 12 kPa; in case of no available results, a liver biopsy or a FibroScan® was to be performed prior to treatment;
- All laboratory parameters had to be grade 0 or 1 (as per Common Terminology Criteria for Adverse Events [CTCAE] and Common Toxicity Criteria [CTC] CTCAE criteria of the National Cancer Institutes of the USA) except for alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) for which a grade 2 was allowed if stated non clinically significant;
- No co-infection with human immunodeficiency virus (HIV) or hepatitis B virus (Hepatitis B surface antigen [HBsAg] positive);
- No intravenous (IV) drug or alcohol abuse;
- Serum thyroid stimulating hormone (TSH) levels within normal ranges, regardless of treatment with L-thyroxin;
- Normal electrocardiogram (ECG);
- Normal retinal examination (eye fundus) within last 12 months for diabetic patients or patients suffering from high blood pressure;
- Negative pregnancy test in women of childbearing potential (a woman who was 2 years post-menopausal or surgically sterile was not considered to be of childbearing potential);
- Female patients and female partners of male patients (if childbearing potency) had to agree to use 2 effective methods of birth control during the study and for 6 months after the end of treatment. One of the methods needed to be a 'barrier' method (condom or diaphragm);
- Provided written informed consent.

Criteria for exclusion:

Patients were excluded from the study for any of the following reasons:

- Prior treatment for hepatitis C;

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- Malignancy within the last 5 years (except for history of squamous cell skin cancer or basal cell skin cancer, unless the skin cancer was at the vaccination site);
- Diagnosed or suspected hepatocellular carcinoma;
- History of psychiatric conditions (at Investigator's opinion);
- Serious concomitant medical disorder (including active systemic infection and proven or suspected immunosuppressive disorder, or any other condition that, in the Investigator's opinion, could have compromised the safety or compliance of the patient);
- History of immunodeficiency or autoimmune disease (including autoimmune hepatitis, allogenic transplant, or pre-existing autoimmune or antibody-mediated disease);
- Administration of any vaccine or immunoglobulin within 30 days before the first dose of TG4040 /PegIFN/RBV;
- Significant cardiovascular disease;
- Systemic corticosteroid therapy or other immunosuppressive/immunomodulating drugs (e.g. Cyclosporine) within 2 months prior to first TG4040/PegIFN/RBV administration (corticosteroid nasal sprays, inhaled steroids for asthma and/or topical steroids are allowed);
- Any known allergy or medical contraindications to interferon (IFN), RBV and/or their excipients, any known allergy to gentamycin, bovine serum albumin or eggs;
- Breastfeeding (women);
- Participation in another experimental therapeutic protocol;
- Patient unable or unwilling to comply with the protocol requirements.

Test product, dose and mode of administration, lot number:

Product: TG4040 is a viral suspension of Modified Virus of Ankara (MVA) virus containing sequences of the HCV (genotype 1b) coding for the non-structural (NS) proteins NS3, NS4 and NS5B.

Doses: SC injections of TG4040 at the dose 10^7 pfu:

- One cycle of 3 SC injections of TG4040 once-weekly followed by 3 single injections every 12 weeks (Arm B); OR
- SC injection once-weekly for 6 weeks followed by 7 single TG4040 SC injections every 4 weeks (Arm C).

Mode of administration: SC injections were done on thighs or arms, left and right, alternately.

Lot numbers: Z637 and Z692

Reference therapy, dose and mode of administration, lot number:

PegIFN/RBV

- SC injection of Peg-IFN alfa2a (Pegasys®) 180 µg once-weekly;
- Tablets of RBV (Copegus®) 1000-1200 mg/day (weight-based) taken orally.

Lot numbers: (expiry dates)

- Peg-IFN alfa2a: B1151 and B1191 (30-Jun-2012 and 30-Jun-2013);
- RBV: 130337, 119986, 134975 and 899755 (30-Apr-2012, 30-Apr-2012, 30-Jun-2014, and 30-Nov-2014).

Duration of treatment:

Arm A: PegIFN/RBV was to be given for 48 weeks:

After 12 weeks of PegIFN/RBV:

- patients who achieved early virologic response (EVR, defined as a viral load decrease ≥2 $\log_{10}$ IU/mL) continued PegIFN/RBV for 36 weeks;
- patients who experienced no EVR stopped treatment.

At any time, patients who discontinued PegIFN/RBV due to intolerance were proposed to start TG4040 alone once-weekly for 6 weeks followed by a single SC injection every 4 weeks for up to 48 weeks (based on Arm C schedule).

Arm B: Four weeks after PegIFN/RBV initiation, 3 SC weekly injections of TG4040 were performed, followed by 3 single TG4040 SC injections every 12 weeks:

- 12 weeks after PegIFN/RBV initiation, patients continued TG4040 plus PegIFN/RBV whether they achieved cEVR or not.

At any time, patients who discontinued PegIFN/RBV due to intolerance were proposed to continue TG4040 alone every 12 weeks for up to 48 weeks.

Arm C: SC injections of TG4040 were administered once-weekly for 6 weeks followed by 7 single SC injections every 4 weeks. Twelve weeks after TG4040 initiation (corresponding to 7 TG4040 injections), PegIFN/RBV was added:

- 12 weeks after PegIFN/RBV initiation, patients continued TG4040 plus PegIFN/RBV whether they achieved cEVR or not.

At any time, patients who discontinued PegIFN/RBV due to intolerance were proposed to continue TG4040 alone every 4 weeks for up to 48 weeks.

Stopping rule: whatever the arm, if HCV RNA was detectable and above limit of quantification (≥15 IU/mL) after 24 weeks of PegIFN/RBV, all treatments were stopped.

Criteria for evaluation:

Primary endpoints:

Efficacy:

- Percentage of patients who achieved cEVR, defined as undetectable HCV RNA (less than 10 IU/mL, as measured by the Roche TaqMan® assay) 12 weeks after the start of PegIFN/RBV.

Secondary endpoints:

Efficacy:

- Percentage of patients who achieved rapid virologic response (RVR), extended RVR (eRVR), EVR, end of treatment response (ETR), sustained virologic response (SVR), relapse rate, viral breakthrough, change in HCV RNA over time and at specific endpoints, and slope of the regression line of viral load.
- HCV and MVA-specific cellular immune responses from circulating blood cells were assessed by ELISpot IFN-gamma (IFN-γ) assay.
- Serum humoral total and neutralizing antibodies, responses to MVA were respectively assessed by Enzyme Linked Immunosorbent Assay (ELISA) and biological assay.
- The concentration of 89 soluble mediators in serum was measured by LUMINEX.
- Transcriptomic analysis by full genome gene expression profiling were initially planned by the protocol but collected samples were not analyzed.

Safety:

- Overall incidence of adverse events (AEs) and serious AEs (SAEs) as well as laboratory assessments, vital signs, physical examination and ECGs were evaluated for each arm and for the study as a whole.

Polymorphism analysis:

Some genetic polymorphisms identified in the literature, including IL28B polymorphism, were analyzed.

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Statistical methods:

Efficacy data

The primary endpoint was the percentage of responders, i.e. the percentage of patients achieving cEVR, defined as undetectable HCV-RNA 12 weeks after the start of PegIFN/RBV. The study was designed by using a hypothesis testing framework that allows 3 possible outcomes, the so-called three-outcome one-stage design for the cEVR response rate in Arms B and C separately.

The null hypothesis in terms of response rate (r) was: H_0: r <40%.

The alternative hypothesis was: H_A: r >60%.

The analysis of this variable was performed for the ITT, mITT, Evaluable patients, and final PP sets, but the ITT set was the main set used for analysis.

The analyses of secondary efficacy endpoints was also performed for the ITT, mITT, Evaluable patients, and final PP sets, for the endpoints available after 1, 2, 4, 5 and 12 weeks of PegIFN/RBV, and at the end of the study, after the data for the entire follow-up period had been obtained for all patients, for all parameters. Change in HCV RNA versus baseline was summarized using descriptive statistics overall and by treatment arm. Graphical displays of the summary statistics were used to present the evolution of the endpoints in time.

Safety data

Descriptive summary statistics were provided for safety data using the Safety set.

Immunologic and transcriptomic data

Although the study was not powered to detect differences between the randomized arms, comparisons between arms were performed for some biomarkers. In all cases, these comparisons were considered exploratory and required confirmation in larger patient samples.

For immunological parameters, no between arms statistical comparisons were performed.

Demographic data

Demographic and baseline data were summarized using the ITT, mITT and final PP sets.

Summary – Conclusions:

Efficacy results:

After 12 weeks of PegIFN/RBV, in the ITT set, the percentage of patients achieving cEVR was 29%, 44% and 58% in Arms A, B and C, respectively. For the Evaluable patients set, the corresponding values were 30%, 46% and 64%. For the mITT, the corresponding values were 29%, 44% and 62%. The interim PP set also showed similar results. In all sets of patients, the response rate was higher in the 2 arms receiving TG4040 injections and PegIFN/RBV compared with the arm receiving PegIFN/RBV alone. In addition, of the 2 arms receiving TG4040, a higher percentage of patients achieved cEVR in Arm C, leading to the achievement of the primary objective. Indeed, in Arm C, based on the number of patients achieving cEVR (Evaluable set), and as per hypothesis testing, the null hypothesis was rejected in favor of the alternative which means that for Arm C treatment the proportion of responders is considered equal or higher than 40%. The percentage of responders was indeed 64.2% [50.7%; 75.7%] which was statistically greater than 40% (p=0.0003) using a binomial test and the primary endpoint was achieved in Arm C. For Arm B, the testing provided either a rejection of the alternative (ITT set) or inconclusive results (all Evaluable patients) and the percentage of responders was 45.9% [31%; 58.3%] which was not statistically greater than 40% (p=0.3468); the primary endpoint was not achieved.

As an exploratory analysis, percentage of responders was compared between the three arms. To take into account the two factors of stratification (Age and Viral Load at Baseline), a CMH test was performed with a p-value below 2.5% considered as significant. Statistically significant differences were observed when comparing Arm A and C, in all 3 patient sets. Conclusions should however be considered cautiously due to the fact that this study was not designed to compare the treatment arms.

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To evaluate the impact of baseline parameters and PegIFN/RBV response prognostic factors on cEVR, a logistic regression stratified by Age (≤50y or >50y) and Viral Load at Baseline (log values ≤5.6 or >5.6) was performed for each arm independently with no major finding. Analyzed parameters were IL28B (C-C vs non C-C), HCV genotype (1b vs 1a), ALT (≥2ULN vs <2ULN), BMI (≥25 vs <25), Sex, Fibrosis (F2--F3 vs F0-F1). Similarly all cEVR analysis performed in sub-groups of patients according to baseline and prognosis factors failed to establish any notable trend. In conclusion, with such numbers of patients, the response to TG4040 does not seem to be influenced by PegIFN/RBV response known prognosis factors or any of the evaluated baseline parameters.
The association with IL28B polymorphism was studied more deeply and interesting observations can however be made as a higher response rate in the Arm C non C-C patients (60.0% versus 27.3% and 36.6% in Arms B and C), expected to be PegIFN/RBV bad responders.

Another important conclusion is the early benefit of TG4040 pre-treatment on the response to PegIFN/RBV. Indeed, Arm C TG4040 monotherapy only induced transient >0.5 $\log_{10}$ IU/mL viral load decreases in 27 out of 59 (46%) patients experienced, however one week after PegIFN/RBV initiation (Week 13 in Arm C), the mean decrease was 1.38 $\log_{10}$ in Arm C compared to 0.89 $\log_{10}$ in Arm A and 1.07 $\log_{10}$ in Arm B. Similar differences were observed 2 weeks after PegIFN/RBV initiation (Week 14 in Arm C). As at Week 1, the treatment received by Arm A and B patients was the same (PegIFN/RBV only), these two arms data were pooled for a t-test showing a significant difference between Arm C and the pooled Arms A and B data with a p=0.04 (ITT set).
This tendency can also be seen when considering the percentages of patients reaching ≥1 log10 IU/mL reduction in HCV-RNA after 1 week and 2 weeks of PegIFN/RBV with 35%, 43%, 55% after 1 week in Arms A, B, C and 58%, 59%, 73% after 2 weeks (mITT sets). At RVR evaluation (<10 IU/mL), the corresponding percentages were 6%, 10% and 24% and when including the patients below the limit of quantification (<15 IU/mL) percentages were 13%, 14% and 38%.

At later endpoints, the benefit is always seen in Arm C, with 68%, 62% and 76% (as above respectively in Arms A, B and C) at Week 24 response evaluation, with 68%, 67% and 76% at ETR and with 68%, 56% and 67% at ETR48 (mITT set).
At SVR12, corresponding results were 42%, 48% and 56% and at SVR24, 48%, 51% and 58%. Corresponding results for the final PP set at SVR24 were 50%, 53% and 61%. The final PP set excludes the patients who took HCV medication out of the protocol, who were maintained in the study after positive HCV RNA 24 weeks after PegIFN/RBV, who took less than 4 weeks of PegIFN/RBV and who took prohibited longterm immunostimulatory treatments; importantly, no inbalance was observed between arms regarding those deviations. Among the patients who completed their treatments, 66.7% (14/21), 76.3% (29/38) and 80% (32/40) respectively reached an SVR24 response in Arms A, B and C. To evaluate the impact of baseline parameters and of PegIFN/RBV known response prognostic factors on SVR24, the same logistic regression as for cEVR was applied with no significant association found. Additional exploratory analyses were performed to study more into details the impact of IL28B polymorphism on the SVR24 rates showing higher SVR24 rates in both experimental arms (46.3% and 51.4% in Arms B and C) compared to Arm A (36.4%).

Relapse after a full treatment schedule was lower and comparable in both experimental arms with respectively 10% and 13% in Arms B and C compared to 19% in Arm A (mITT set). Viral breakthough rates are very close between arms with 0%, 5% and 2% in Arms A, B and C.

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Efficacy results (immunology): Immune response analysis demonstrated specific TG4040-induced T cell responses predominantly detected in Arm C and mainly against NS3 in 46% of patients with a peak at Week 12, i.e. at the end of TG4040 pre-treatment phase. Similarly, regardless of the TG4040-administration schedule, robust MVA-specific T cell responses could be detected in both Arms B and C. PegIFN/RBV treatment significantly increased PBMC mortality prior to ELISpot analyses across all treatment Arms and interpretations have to be made with caution. In addition, TG4040 significantly increased total and neutralizing anti-MVA antibodies regardless of the administration schedule. Overall these data confirm the immunogenicity of TG4040 but no statistical correlation was observed between TG4040-specific T-cell responses and virological response (RVR, cEVR or SVR24). Similarly, no correlation was observed between the induction of total or neutralizing anti-MVA antibodies and virological response, demonstrating the absence of a negative impact of vector-specific antibodies on the response.

In addition, although the Luminex analyses did not identify any TG4040-specific signature several baseline and treatment-induced cytokines were significantly associated with the presence of an SVR24 response to either PegIFN/RBV alone or in combination with TG4040 treatment, some of them had already been associated with the response to PegIFN/RBV in the literature and some of them are new. Main categories include pro-inflammatory mediators, Th1/Th2 cytokines and cirrhosis or hepatocarcinoma markers. Of note, in Arm C, a significant increase in some pro-inflammatory mediators was associated with the induction of an ELISpot IFN-γ T cell response specific to NS3.

Safety results:

All the 153 randomized patients were treated with an IMP. One patient in Arm B did not receive treatment with TG4040. All 59 patients in Arm C received treatment with TG4040. One patient in Arm A was PegIFN/RBV intolerant and as permitted by the protocol, TG4040 monotherapy was given as an alternative treatment according to the Arm C scheme of administration. Four patients in Arm C did not receive PegIFN/RBV and were discontinued during the TG4040 monotherapy period. One patient in Arm C was PegIFN/RBV intolerant and continued with TG4040 monotherapy.

The overall mean (SD) treatment duration was 266.10 (108.15) days in Arm A, 270.02 (89.12) days in Arm B, and 347.95 (119.91) days in Arm C. Few patients had at least 1 IMP interruption (less than 5.5% in any arm).

Nineteen (19/153, 12.4%) patients experienced a total of 29 pre-drug AEs. All were mild or moderate and none were serious.

A total of 144/153 (94.1%) patients experienced 1739 treatment-emergent AEs (TEAEs). At least one TEAE was reported by 90.3%, 92.1% and 98.3% patients in Arms A, B and C, respectively Most of the reported TEAEs were of mild (68.1%) or moderate (24.1%) intensity. Forty-seven (47/153, 30.7%) patients presented a total of 120 grade 3 TEAEs and 7 (4.6%) patients experienced 12 (0.7%) grade 4 (life-threatening) TEAEs. Occurrence was similar in all arms.

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Safety results (continued):

A total of 139/153 (90.8%) patients experienced 1390/1739 (79.9%) TEAEs assessed by the investigator to be probably/possibly related to any IMP. Overall, 87.6% of patients experienced a TEAE assessed as 'at least related to PegIFN/RBV' (frequencies similar in all arms) and 38.6% had a TEAE at least related to TG4040 (36.5% of patients in Arm B and 61.0% in patients of Arm C). Among patients who experienced adverse drug reactions (ADRs) 'at least related to PegIFN/RBV', overall 41/153 (26.8%) patients had a total of 109 severe ADRs and 7/153 (4.6%) patients experienced 12 life-threatening ADRs (frequencies similar in all arms). When considering patients with ADRs 'at least related to TG4040', 5/59 (8.5%) patients in Arm C had a total of 22 severe ADRs (none in Arm B). Two (2) patients in Arm B (3.2%) experienced 2 life-threatening events and 2 patients in Arm C (3.4%) experienced 6 life-threatening TEAEs.

The system organ classes (SOCs) in which were reported the highest numbers of events (above 10% of patients overall) were general disorders and administration site conditions (75.8%), blood and lymphatic system disorders (55.6%), skin and subcutaneous tissue disorders (45.1%), infections and infestations (39.2%), nervous system disorders (36.6%), gastrointestinal disorders (34.6%), musculoskeletal and connective tissue disorders (30.1%), metabolism and nutrition disorders (26.1%), psychiatric disorders (25.5%), respiratory, thoracic and mediastinal disorders (24.2%) and investigations (11.1%). Of these SOCs, there were generally no differences >10% between treatment arms, with the exception of investigations where the frequencies were 16.1%, 4.8% and 15.3% for Arms A, B and C respectively, and of metabolism and nutrition disorders where the frequencies were 19.4%, 22.2% and 33.9% for Arms A, B and C respectively.

The most frequent preferred terms within TEAEs, observed in more than 20% of patients overall, were fatigue (54.2%), neutropenia (35.3%), pyrexia (28.1%), anemia (28.1%), headache (25.5%) and injection site erythema (20.3%). The frequencies of these preferred terms were generally similarly distributed between treatment groups, although there was slightly more pyrexia in Arm C compared to Arms A and B (35.6%, 22.6% and 23.8% of patients, respectively) and more injection site erythema in Arm C (30.5%) and Arm B (19.0%) compared to 1 (3.2%) patient in Arm A who was PegIFN/RBV intolerant and received TG4040 monotherapy as an alternative treatment.

In Arm C during the monotherapy period (i.e., TG4040 only, until Week 12 study visit) 66.1% (39/59) of patients experienced at least a TEAE. The SOC in which was reported the highest numbers of events was general disorders and administration site conditions (45.8% [27/59] of patients) with injection site erythema in 22.0% (13/59) of patients. Other SOCs or preferred terms were reported in less than 20% of patients, though other injection site events (less frequent than the injection site erythema) were also reported.

Among the patients with any ADRs, the most frequent SOCs and preferred terms were generally similar to the overall profile of TEAEs. Exceptions were the infections and infestations SOC (17.0% of patients with treatment-related TEAEs compared to 39.2% in the overall profile) and metabolism and nutritional disorders SOC (15.0% of patients with treatment-related TEAEs compared to 26.1% in the overall profile). As expected, for TG4040 the most frequent ADRs were injection site reactions, which were more frequent in Arm C possibly due to a higher number of injections in this arm. For ADRs related to Peg-IFN alfa2a (formulated as injectable solution), the most frequently reported ADRs were neutropenia (115 episodes in 31.4% [48/153] patients), pyrexia (42 episodes in 22.9% [35/153] patients), fatigue (34 episodes in 18.3% [28/153] patients), influenza-like illness (32 episodes in 15.7% [24/153] patients) and headache (28 episodes in 15.7% [24/153] patients), generally similarly distributed across arms.

Safety results (continued):

In addition to the occurrence of the most frequently expected ADRs related to Peg-IFN alfa2a the following events were observed: lymphopenia (45 episodes in 7.8% [12/153] patients), leukopenia (38 episodes in 11.1% [17/153] patients), injection site erythema (20 episodes in 9.2% [14/153] patients), myalgia (28 episodes in 13.1% [20/153] patients), insomnia (13 episodes in 7.8% [12/153] patients), alopecia (16 episodes in 9.8% [15/153] patients), arthralgia (11 episodes in 4.6% [7/153] patients), headache (28 episodes in 15.7% [24/153] patients).

For ADRs related to RBV (formulated as tablets), the most frequent ADR was anemia (62 episodes in 20.9% [32/153] patients), which was similarly distributed across arms. In addition to the occurrence of the most frequently expected ADRs related to RBV events of pruritus were also observed: 14 episodes in 7.2% [11/153] patients).

In Arm C during the monotherapy period (i.e. TG4040 only, until Week 12 study visit) 3.4% (2/59) of patients experienced 3 severe TEAEs related to TG4040 (none was life-threatening). These events were 1 episode of each of the following: cellulitis, myalgia and leukocytoclastic vasculitis.

The most frequent severe/life-threatening TEAEs were neutropenia (22.2% of patients overall and 25.8%, 25.4%, and 16.9% of patients in Arms A, B and C, respectively) and leukopenia (7.8% of patients overall and 9.7%, 4.8% and 10.2% of patients in Arms A, B and C, respectively)

Among patients who experienced grade 3 and 4/5 ADRs at least related to TG4040, events were most commonly reported in the SOC blood and lymphatic disorders (24 episodes in 4.6% [7/153] patients).

Among patients who experienced grade 3 and 4/5 ADRs at least related to PegIFN/RBV (Pegasys® or Copegus®), events were most commonly reported in the SOC blood and lymphatic disorders (107 episodes in 28.8% [44/153] patients), and the most frequent severe ADR was neutropenia (20.3% [31/153] overall and 22.6% [7/31], 23.8% [15/63], and 15.3% [9/59] in Arms A, B and C, respectively).

Twenty-one (21/153, 13.7%) patients had a total of 61 TEAEs that led to any IMP withdrawal: 2/31 (6.5%) in Arm A, 9/63 (14.3%) in Arm B and 10/59 (16.9%) in Arm C. Two patients (2/59, 3.4%) in Arm C experienced 4 TEAEs leading to TG4040 permanent withdrawal in the monotherapy period. These 2 discontinuations were related to severe skin reactions: a leukocytoclastic vasculitis associated with myalgia and arthralgia in 1 patient, and a cellulitis in 1 patient. Of note, these events were reversible and for the patient with leukocytoclastic vasculitis associated with myalgia and arthralgia, the reactions were not restricted to the administration site in accordance with a history of cryoglobulinemia.

Fourteen (14/153, 9.2%) patients discontinued from the study due to AEs: 1/31 (3.2%) patient in Arm A, 7/63 (11.1%) patients in Arm B and 6/59 (10.2%) patients in Arm C.

A total of 14/153 (9.2%) patients experienced 19 serious TEAEs, with 12 serious TEAEs in 9/153 (5.9%) patients, assessed as probably/possibly related to at least 1 IMP. One patient in Arm A experienced a serious TEAE of cryoglobulinemia considered related to Peg-IFN alfa2a. Two patients in Arm B reported a serious TEAE considered related to Peg-IFN alfa2a: one event of atrial fibrillation and one event of depression. One serious TEAE of thrombocytopenia was reported in Arm B and was related to both TG4040 and Peg-IFN alfa2a. One patient in Arm B experienced 3 serious TEAEs (anemia, acute pyelonephritis, and acute renal failure), all related to Peg-IFN alfa2a and RBV. One patient in Arm B experienced a serious TEAE of pancytopenia related to all 3 IMPs. One patient in Arm C experienced a serious TEAE of psoriatic arthropathy related to Peg-IFN alfa2a and one patient in Arm C experienced a serious TEAE of autoimmune thrombocytopenia related to Peg-IFN alfa2a and TG4040.

Safety results (continued):

One patient in Arm C experienced 2 serious TEAEs (aplastic anemia and purpura) considered to be related to all 3 IMPs. No serious TEAE related to TG4040 only or RBV only was reported.

No serious TEAEs were reported in Arm C during the monotherapy period (i.e. TG4040 only, until Week 12 study visit).

Four SUSARs of hematological disorders were reported in patients 10213, 10303, 10501 and 30302. As a result of these cases, additional safety monitoring was specified for all patients, including additional visits and examinations. Additionally, a decision was made to stop all further TG4040 injections, although PegIFN/RBV treatment continued.

All investigations performed to better understand the etiology of those four cases are summarized in the related safety report (See Module IV, Appendix 16.4.9). At this stage, considering similarities in the severity, the evolution and the treatment outcome of the 3 SUSARs with thrombopenia as main blood manifestation (Patients 10213, 10303 and 10501), the main hypothesis is the possible participation of the immune system. Severe thrombopenia, a known interferon immune side effect, could possibly be potentialized by the addition of TG4040 vaccinations via immune mechanisms. Interestingly, an HLA type II allele group known to be associated with a predisposition to auto-immune disease (HLA-DRB1*04 allele) is shared by these 3 patients with severe thrombopenia. The case of aplastic anemia (Patient 30302) could be of possible immuno-allergic mechanism of a toxic or medicated origin as per the results of the bone marrow central review. This event was atypical as immediately combined with a rash and several months later with arthritis.

More generally, as the immune system participation is considered at this stage as the main hypothesis to explain some hematologic SUSARs through a potentialization of known interferon immune side effects by the addition of TG4040 vaccination, this combination could also have an effect on an activation or re-activation of auto-immune diseases, more particularly in patients with autoimmune predisposition. In that context, it cannot be excluded that the case of serious severe (grade 3) psoriatic arthritis negative for the rheumatoid factor reported in an Arm C patient and evaluated as unlikely related to TG4040 by the investigator (it occurred 9 months after last injection of TG4040) but possibly related to Peg-IFN alfa2a administered for 48 weeks, could also be partially due to the combination of TG4040 to Peg-IFN alfa2a. Interestingly also, this patient is followed in the same Israelian site as the patient with the aplastic anemia and those 2 patients share 2 type I HLA-B alleles; B13 and B38. Those 2 alleles are known to be associated with psoriatic arthritis in Israeli patients and also support the hypothesis of the immune participation by the combination of treatments. Of note, the patient with the aplastic anemia is still treated with cyclosporine and developed arthritic like symptoms in a second time.

No deaths were reported during the study.

All measured hematology parameters tended to decrease over time about 1 week after start of PegIFN/RBV in a similar way in all treatment arms. Values tended to regain baseline levels at follow-up visits. These changes over time, similar between groups when looking from start of PegIFN/RBV, suggest a role of the PegIFN/RBV. However, hematology parameters did not show any clear decrease during the TG4040 monotherapy period of Arm C, except a slight decrease for hemoglobin which could be indicative of an inflammatory anemia. There were mild ALT/AST increases during the TG4040 monotherapy period of Arm C but with no signs of liver cytolysis.

A majority of individual laboratory values changes were from CTCAE grade 0 at baseline to grade 0 or 1 for the worst post-baseline CTCAE grade. Notable exceptions were changes in leucocytes, neutrophils, lymphocytes and platelets from grade 0 to grade 2, 3 or even 4.

Name of Sponsor/Company: Transgene S.A.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product:		
Name of Active Ingredient: TG4040 (MVA-HCV)		

Safety results (continued):

The proportions of clinically significant laboratory values were similar across treatment arms for most of the laboratory parameters. The only notable between arm differences were less clinically significant hematocrit, leucocyte, lymphocyte and red blood cell (RBC) values in Arm B. The majority of clinically significant laboratory values were reported for hematology parameters, which was expected due to the known safety profile of the PegIFN/RBV.

Biochemistry abnormalities were reported as TEAEs but not in more than 5% of patients in any treatment arm except VitD deficiency. There was >5% difference in the number of patients with abnormal and clinically significant ALT in Arm C compared to Arms A or B.

There were fewer clinically significant abnormal TSH values in Arm A (3.3%) than in Arm B (9.7%) or Arm C (88%). Among them, 9 patients had both clinically significant abnormal TSH values and AEs of hypo and/or hyperthyroidism: 1 patient in Arm A, 5 patients in Arm B, and 3 in Arm C.

At screening, 11.8% of patients were positive for antinuclear antibodies (ANA) (6.5% in Arm A, 19.0% in Arm B, and 6.8% in Arm C). The percentage of patients who were positive at the end of study was 9.7%, 17.5% and 11.9%, respectively.

The proportions of patients positive to antithyroid peroxidase antibodies (anti-TPO) were lower than those observed for ANA, especially in Arms A and B with no positive patients at screening. In Arm C, 6.8% of patients were positive at screening. At the end of study, 6.5%, 4.8% and 15.3% of patients in Arms A, B and C, respectively were positive for anti-TPO antibodies.

During the treatment period, no clinically significant changes in systolic or diastolic blood pressures, heart rate, respiratory, body temperature or physical examination were observed. There was one clinically significant ECG result, observed in Arm C at Week 4.

Conclusions:

The safety and efficacy of the immunotherapeutic TG4040 were evaluated alone and in combination with PegIFN/RBV for the treatment of genotype 1 HCV infection.

Since it is well established that failure to achieve EVR accurately predicts a subsequent lack of SVR, the study was designed to evaluate the proportion of patients with a cEVR to determine the possible added benefit of combining TG4040 with PegIFN/RBV. Treatment with the combination of TG4040 and PegIFN/RBV in Arm C met the study primary objective with a percentage of responders of 64.2% [50.7%; 75.7%] statistically greater than 40% (p=0.0003) using a binomial test. The Arm B with the PegIFN/RBV lead-in dosing and the less frequent TG4040 injections had an intermediate response. Arm C also produced a statistically significant steeper initial slope of decline of the viral load, a greater proportion of patients achieving undetectable HCV RNA 5 weeks following PegIFN/RBV introduction and a greater proportion of patients achieving ETR, SVR12 and SVR24 but also less relapser patients with however no statistical difference compared to Arm A. Overall, a numerically greater proportion of patients pretreated with TG4040 achieved SVR24; 58.2% (32/55) in Arm C versus 48.4% (15/31) in Arm A and 50.8% (32/63) in Arm B. Relapse after a full treatment schedule was lower and comparable in both experimental arms with respectively 10% and 13% in Arms B and C compared to 19% in Arm A. This supports that Arm C pre-treatment has potentiated the subsequent response to PegIFN/RBV. However, TG4040 pre-treatment by itself only led to transient >0.5 $\log_{10}$ IU/mL viral load decreases in about half of Arm C patients with no association with later immunological or viral responses. Also, no baseline or PegIFN/RBV response known prognosis parameter was significantly associated with the viral response (cEVR or SVR24) in any arm.

While a number of other immunotherapy-based products have been evaluated for HCV treatment, none have documented the striking effects observed in Arm C regardless of the endpoint, ie, RVR, cEVR, ETR, or SVR. Because Arm C included both TG4040 pretreatment and a higher frequency and longer duration of TG4040 treatment it is difficult to conclude which of these parameters was most important, possibly both.

Immune response analysis demonstrated specific TG4040-induced T cell responses predominantly detected in Arm C and mainly against NS3 in 46% of patients with a peak at Week 12, i.e. at the end of TG4040 pre-treatment phase. Similarly, regardless of the TG4040-administration schedule, robust MVA-specific T cell responses could be detected in both Arms B and C. Of note, PegIFN/RBV treatment significantly increased PBMC mortality prior to ELISpot analyses across all treatment Arms and interpretations have to be made with caution. Up to 44% of PBMC samples were not available to allow for full efficacy evaluation and this negative effect of PegIFN could be due to its known pro-apoptotic and anti-proliferative properties. It could also explain the minimal MVA- and HCV-specific cellular immune responses in this study following the introduction of PegIFN/RBV suggesting that this combination may have had a negative effect on induction and/or detection of T-cell responses thus potentially decreasing TG4040 efficacy.

Overall these data confirm the immunogenicity of TG4040 and support an immunotherapeutic role for TG4040 but we were unable to detect a correlation between the induction of total or neutralizing anti-MVA antibodies or the induced T-cell responses and virologic responses (RVR, cEVR or SVR24). Given the higher response rates in the TG4040 pretreated arm, TG4040 may be influencing the T-cell response in the liver to a much greater extent than what was detected in circulating PBMCs and/or might activate other unspecific innate immune effects. The significant loss of PBMC samples may also have underestimated T-cell responses.

In addition, although the Luminex analyses did not identify any TG4040-specific signature, several baseline and treatment-induced cytokines were significantly associated with an SVR24 response to PegIFN/RBV treatment alone or in combination with TG4040 treatment, some of them have been previously reported to be associated with the response to PegIFN/RBV in the literature and some of them are new. Main categories include pro-inflammatory mediators, Th1/Th2 cytokines and cirrhosis or hepatocarcinoma markers. Of note, in Arm C, a significant increase in predominantly circulating pro-inflammatory mediators was associated with the induction of an ELISpot IFN-γ T cell response specific to NS3.

TG4040 in combination with PegIFN/RBV was relatively well tolerated with the majority of patients experiencing AEs consistent with the known safety profile of both PegIFN/RBV and MVA-based vaccines. As expected both from other studies with MVA-based products and from TG4040 phase I, during the Arm C monotherapy period, the SOC in which the highest number of events was reported was general disorders and administration site conditions (45.8%) with injection site erythema in 22.0% of patients. Overall, 94.1% patients reported a total of 1739 TEAEs during the course of the study, and the percentage of patients who experienced any TEAE was similar between groups. Most of the reported TEAEs were mild or moderate and assessed by the investigator to be probably/possibly related to any IMP. Fourteen (9.2%) patients experienced a total of 19 serious TEAEs, with 12 serious TEAEs in 9 patients (5.9% [9/153]) deemed related to at least 1 IMP.

In three patients, an apparently autoimmune-like thrombocytopenia associated with the use of TG4040 and PegIFN/RBV was observed; these events resolved with corticosteroid treatment with or without the use of intravenous immunoglobulins, a consistent pattern of HCV patients with immune thrombocytopenia. Both severe thrombocytopenia and thrombocytopenic purpura have also been reported with PegIFN/RBV alone. Interestingly, the HLA-DRB1*04 allele was identified in the three patients with the severe thrombocytopenia. This allele has been associated not only with thrombocytopenic purpura but also other auto-immune disorders such as multiple sclerosis, arthritis, alopecia areata, and autoimmune gastritis. In general, some HLA alleles have been found to be associated with autoimmune and infectious diseases with different mechanisms to explain the associations (eg, linkage disequilibrium with the relevant disease susceptibility gene; preferential presentations of the pathogenic peptide by specific HLA molecules; and molecular mimicry between pathogenic peptides and host-derived peptides). Notably, grade 3 hematological events were observed

neither during the first 12 weeks of TG4040 monotherapy prior to the addition of PegIFN/RBV nor in previous phase I studies.

In addition, one patient developed an aplastic anemia. This case was related to both TG4040 and PegIFN/RBV by the investigator but after several investigations, it was concluded that a toxic reaction following to the intake of other drugs including Dypirone may also be causative of this event. Interestingly, at the same Israelian site, one patient developed psoriatic arthritis (not related to TG4040). Those 2 patients share 2 type I HLA-B alleles; B13 and B38, known to be associated with psoriatic arthritis in Israeli patients and also support the hypothesis of the immune participation by the combination of treatments. The patient with the aplastic anemia is still treated with cyclosporine and developed arthritic like symptoms in a second time.

Altogether, these data support the hypothesis that TG4040 could have potentiated a PegIFN-associated auto-immune response possibly favored by a shared HLA group predisposing to auto-immune disorders.

To conclude:

- The combination of TG4040 with PegIFN/RBV provides additional benefits to patients with HCV in terms of viral response rates.
- The immunogenicity of TG4040 was confirmed using several methods: HCV and MVA-specific ELISpot, anti-MVA specific antibodies and large scale Luminex assays. There was no specific immune signature associated with virological response to IFNα-based therapy but this needs to be re-evaluated in the context of IFN-free therapies.
- TG4040 was safe and well tolerated. The most frequent ADRs related to general disorders and administration site conditions. The most common ADRs were fatigue, neutropenia, pyrexia, anemia, headache and injection site erythema. In addition, TG4040 could have potentiated a PegIFN-associated auto-immune response possibly favored by a shared HLA group predisposing to auto-immune disorders in 4 patients.
- Both because of the current competition in HCV field and the auto-immune side effects, TG4040 will probably not be combined with PegIFN/RBV in the future. The potential long term advantage of an immunotherapeutic such as TG4040 in achieving high SVR and preventing relapse would have to be demonstrated in combination with direct-acting antivirals. This study is the first large-scale trial showing improved virological response rate with an immunotherapy combined with PegIFN/RBV in chronic hepatitis C. This proof-of-concept study may warrant further evaluation in the context of IFN-free regimens.

Date of the report: 11 February 2014