GI-5005 THERAPEUTIC VACCINE PLUS PEG-IFN/RIBAVIRIN SIGNIFICANTLY IMPROVES VIROLOGIC RESPONSE AND ALT NORMALIZATION AT END-OF-TREATMENT AND IMPROVES SVR24 COMPARED TO PEG-IFN/RIBAVIRIN IN GENOTYPE-1 CHRONIC HCV PATIENTS

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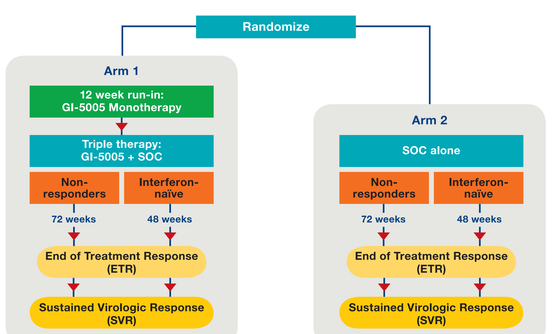
Introduction

Chronic hepatitis C virus (HCV) infection is a health problem that affects 4.8 million people in the U.S. and approximately 180 million people worldwide. The majority of patients exposed to HCV develop chronic infection. However, approximately 20% are able to clear their infection during the acute phase without medical intervention. A strong HCV-specific T cell response has been associated with those spontaneously resolving infections (B. Rehermann 2005 Nat. Rev. Immuno.). The current standard of care (SOC) is pegylated interferon plus ribavirin, which works primarily through the inhibition of viral replication. Only ~40% of HCV genotype 1 patients receiving SOC achieve a sustained virologic response (SVR). Achievement of SVR depends on the patient's ability to clear infected cells from the liver and requires long periods of antiviral suppression by SOC to allow a weak host immune response sufficient time to completely eliminate HCV infected cells.

Substantial gains in the treatment of HCV could be attained through a combination approach that inhibits viral replication (SOC or small molecule antivirals) and enhances HCV-specific cellular immune responses (GI-5005). The GI-5005 Tarmogen® product consists of recombinant *S. cerevisiae* yeast expressing large conserved regions from HCV NS3 and Core proteins. In a randomized, placebo-controlled, phase 1b trial, GI-5005 monotherapy was well tolerated, generated strong HCV-specific T cell responses, and favorably impacted ALT and HCV RNA levels. The GI-5005-02 phase 2 study, described herein, is the first clinical study evaluating GI-5005 in combination with SOC versus SOC alone. We have previously shown in this phase 2 study that GI-5005 plus SOC improved second phase viral kinetics, rapid virologic response (RVR) and early virologic response (EVR) rates, as well as ALT normalization and Fibrotest scores. Presented here are the end of treatment response (ETR) data for all subjects, as well as the sustained virologic response (SVR) and ALT normalization data for interferon-naïve subjects.



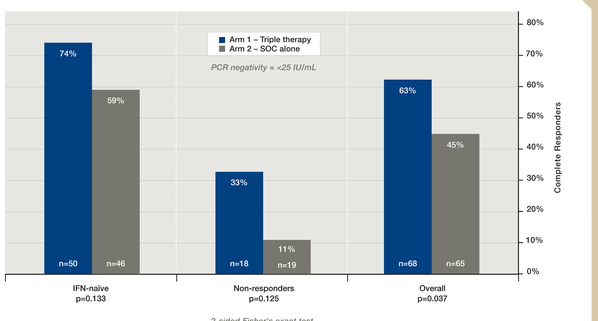
Phase 2 design

GI-5005-02 is a randomized, open-label phase 2 trial evaluating the efficacy, immunogenicity, and safety of GI-5005 in combination with standard of care (SOC) pegIFN-α2a/ribavirin therapy (triple therapy) vs. SOC alone in subjects with genotype 1 HCV. Treatment naïve subjects in Arm 1 receive GI-5005 monotherapy weekly from day 1 to week 4, a dose at week 8, followed four weeks later by monthly maintenance doses in combination with 48 weeks of SOC (triple therapy). In Arm 1 prior treatment failures receive 12 week monotherapy run-in, followed by 72 weeks of triple therapy. Arm 2 patients received SOC as per the product labels (72 week treatment duration for prior treatment failures). Randomization was stratified by response to prior therapy (interferon-naïve or non-responder). Efficacy endpoints for the trial include viral kinetics, RVR, EVR, ETR, SVR, Fibrotest, biochemical response by ALT reductions and normalization, and histologic improvement by liver biopsy assessment.

Demographics

Variable	Treatment Group		Total (n=140)
	SOC + GI-5005 (n=72)	SOC Alone (n=68)	
Prior Treatment Status			
Naïve	53 (73.6)	49 (72.1)	102 (72.9)
Non-response to prior treatment	19 (26.4)	19 (27.9)	38 (27.1)
Sex			
Male	42 (58.3)	45 (66.2)	87 (62.1)
Female	30 (41.7)	23 (33.8)	53 (37.9)
Race			
White	50 (69.4)	47 (69.1)	97 (69.3)
African American	7 (9.7)	11 (16.2)	18 (12.9)
Hispanic	6 (8.3)	6 (8.8)	12 (8.6)
Asian	6 (8.3)	4 (5.9)	10 (7.1)
Other	3 (4.2)	0 (0.0)	3 (2.1)
Age			
Median (years)	48.0	49.0	48.0
Range	20 to 74	20 to 68	20 to 74
ALT (U/L)[1]			
Mean (SD)	74.4 (41.2)	65.1 (47.3)	70.0 (44.3)
Median	63.0	53.5	57.0
Range	17 to 266	14 to 275	14 to 275
HCV RNA (log_{10} IU/mL)[2]			
Mean (SD)	6.58 (0.63)	6.65 (0.81)	6.61 (0.72)
Median	6.72	6.79	6.78
Range	4.64 to 7.48	3.01 to 7.72	3.01 to 7.72

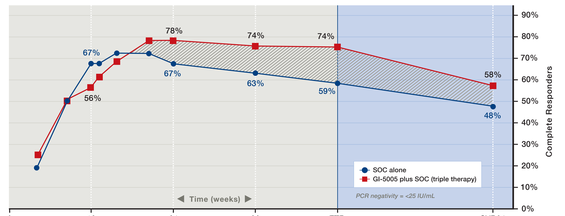
[1]ALT baseline values taken on Day1 of study therapy [2]HCV baseline values taken on Day 1 of SOC



2-sided Fisher's exact test

Complete virologic response at end of treatment

Triple therapy significantly improved the proportion of patients with undetectable HCV RNA using PCR assay (<25IU/mL) at the end of treatment (naïve, NR, and all subjects shown).



	SVR %	Absolute improvement	Relative improvement	p value
Arm 1 – Triple therapy	58%	10%	21%	0.32
Arm 2 – SOC alone	48%			

Sustained virologic response for IFN-naïve patients (ITT)

The proportion of subjects achieving viral clearance (PCR<25IU/mL) is shown for the naïve subjects from each treatment group during the treatment period and post-treatment periods. Naïve subjects receiving triple therapy showed a 15% advantage for complete virologic response at the end of treatment and a 10% advantage in SVR 6 months after the completion of therapy.

Safety

During the 12 week GI-5005 monotherapy period no patients discontinued therapy due to adverse events (AE). Comparable numbers of patients from the triple therapy group and SOC group discontinued therapy due to adverse events; 9/68 (13.2%) triple therapy group, 8/65 (12.3%) SOC group. During the treatment period 14/68 (20.6%) subjects experienced serious adverse events (SAE) in the triple therapy group compared to 7/65 (10.8%) in the SOC group. There was no significant clustering of SAE event type in the triple therapy group, and 5 of the serious adverse events in the triple therapy group were clearly unrelated to therapy (1 cat bite, hemorrhage after biopsy, fall, and 2 events of substance abuse). There was no increase in the frequency of common non-serious AEs in the triple therapy group compared to SOC. Trends for decreased frequency of common non-serious events in the triple therapy group were noted for fatigue, insomnia, depression, chills, myalgia, dizziness, and back pain.

Discontinuous due to adverse events

	SOC + GI-5005	SOC Alone
	n=68	n=65
Total discontinuations	9 (13.2%)	8 (12.3%)
Discontinued only SOC	1 (1.5%)	8 (12.3%)
Discontinued only GI-5005	3 (4.4%)	n/a
Discontinued both SOC and GI-5005	5 (7.3 %)	n/a

**Analysis of patients receiving at least 1 dose of any study drug*

Serious adverse events

SAEs	Triple (n=68)	SOC (n=65)
Number of subjects reporting an SAE	14 (20.6%)[¥]	7 (10.8%)
Number of SAEs related to GI-5005	3[†]	na
Number of SAEs related to SOC	5	1
Events occurring in >1 subject	2[*]	0

[¥] Five of the 14 events were clearly unrelated to therapy (1 cat bite, hemorrhage after biopsy, fall and 2 events of substance abuse)

[†] 1) Injection site reactions (considered related, but did not cause d/c of therapy), 2) Chest pain (considered possibly related to both GI-5005 and SOC, self limited on continued therapy), and 3) Flu-like symptoms (considered possibly related to both GI-5005 and SOC)

[*] Two events of non-cardiac chest pain

Common non-serious adverse events during treatment period

	SOC + GI-5005	SOC Alone
	n=68	n=65
Fatigue	35 (52%)	42 (65%)
Headache	26 (38%)	26 (40%)
Nausea	25 (37%)	25 (39%)
Pyrexia	19 (28%)	17 (26%)
Rash	18 (27%)	15 (23%)
Injection site reaction	18 (27%)	22 (34%)
Insomnia	17 (25%)	25 (39%)
Irritability	15 (22%)	17 (26%)
Depression	14 (21%)	21 (32%)
Cough	14 (21%)	13 (20%)
Chills	12 (18%)	15 (23%)
Diarrhea	11 (16%)	15 (23%)
Myalgia	10 (15%)	15 (23%)
Pruritus	9 (13%)	14 (22%)
Dizziness	8 (12%)	14 (22%)
Back pain	5 (7%)	13 (20%)

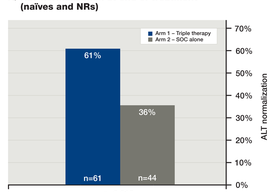
**Any adverse event preferred term with an incidence of >/= 20% in either group*
**Analysis of patients receiving at least 1 dose of GI-5005 and SOC or SOC alone*

Common laboratory-related AEs

	SOC + GI-5005	SOC Alone
	n=68	n=65
Neutropenia* (Grade 3/4)	29 (42.6%)	26 (40.0%)
GM-CSF use (all grades)	1 (1.5%)	0 (0.0%)
Anemia* (Grade 3/4)	1 (1.5%)	0 (0.0%)
Erythropoietin use (all grades)	5 (7.4%)	5 (7.7%)

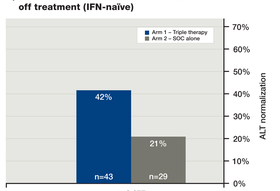
**Grade 1 and 2 anemias and neutropenias occurred at similar frequencies in both treatment groups*

A) ALT normalization at end of treatment (naïves and NRs)



2-sided Fisher's exact test

B) Sustained ALT normalization 24 weeks off treatment (IFN-naïve)



2-sided Fisher's exact test

ALT normalization* at the end of treatment and post-treatment

Triple therapy significantly improved the proportion of patients who normalized ALT at the end of treatment (all subjects), and also showed a substantial advantage for sustained ALT normalization in the post-treatment period (durable for 6 months after completion of therapy).

** ALT normalization defined as 2 consecutive visits <ULN at least 14 days apart for subjects with ALT>ULN at baseline.*

Conclusions

- GI-5005 is the first therapeutic vaccine to favorably impact meaningful clinical endpoints in a chronic infectious disease.
- GI-5005 triple therapy significantly improved end of treatment viral clearance (63% vs 45%, p= 0.037) and ALT normalization (61% vs. 36%, p=0.018) compared to SOC alone.
- GI-5005 triple therapy improved end of treatment viral clearance in naïves after 48 weeks of therapy (74% vs 59%) and improved SVR (58% vs 48%) compared to SOC alone.
- Other GI-5005 data being presented at EASL 2010:
  - McHutchison et al. GI-5005 improves ALT normalization and necro-inflammation in chronic genotype 1 HCV (Thursday, April 15, 7:00-8:30pm; session: *Viral hepatitis: hepatitis C-clinical/therapy*)
  - McHutchison et al. GI-5005 improves viral clearance in all *IL-28* B genotypes in chronic genotype 1 HCV (Saturday, April 17, 11:15-2:00pm; session: *IL-28 B polymorphism*)

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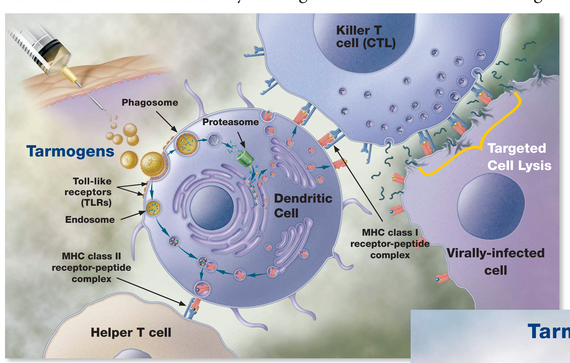
Active immunotherapy with yeast-based Tarmogens

Tarmogens are whole, heat-killed recombinant *Saccharomyces cerevisiae* yeast modified to express one or more protein targets that stimulate the immune system against diseased cells. The target

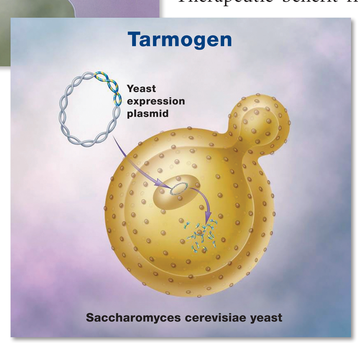


antigens are markers of diseased cells and can be conserved viral proteins, mutated proteins unique to cancer cells, or proteins over-expressed in cancer. To create a new Tarmogen, DNA encoding target protein antigens is engineered into a yeast expression plasmid. The heat-inactivated yeast, with the target protein inside, is administered as the Tarmogen product. Tarmogens stimulate the innate and antigen-specific immune system to produce a highly specific and potent T cell response against the diseased cell, with little or no impact on healthy cells.[1]

Tarmogens are administered subcutaneously and are avidly taken up by antigen presenting cells (APCs), such as dendritic cells and macrophages in a process mediated by Toll-like receptors (TLRs) found on the cell surface. Uptake of Tarmogens activates the APCs and results in their migration to lymph nodes and their production of immune-stimulating cytokines.[2,3]

Tarmogens are degraded inside APCs within hours and the target antigens are presented by MHC class I and II receptors on the APC surface. Tarmogens are initially digested in phagosomes, whereupon the antigens are delivered to the cytosol, and these proteins are cleaved by proteasomes into small peptides. These small peptides are loaded into newly folded MHC class I receptors in the secretory pathway of the APC. The peptide-MHC I receptor complex is shuttled to the surface of the APC, where the antigenic peptides are presented to CD8+ killer T cells (causing activation of these cells). Tarmogens are also digested in endosomes, and the product-associated peptides are loaded into MHC class II receptors for antigen presentation to CD4+ helper T cells (causing activation of these cells).[2,3]

Therapeutic benefit from the Tarmogen is driven by the targeted activation of the immune system. Tarmogens activate killer T cells capable of locating and destroying the target cancer or virally-infected cells. Repeated dosing with Tarmogens further increases the number of T cells available to eliminate diseased cells. In summary, Tarmogens couple the innate immune response to yeast with potent activation of antigen-specific cellular immune responses against cancer cells or virally infected cells.[3-4]



[1] Munson et al. "Coupling Innate and Adaptive Immunity with Yeast-Based Cancer Immunotherapy" Chapter 9; Cancer Vaccines and Tumor Immunity. January 2008

[2] Bernstein et al. "Recombinant Saccharomyces cerevisiae (yeast-CEA) as a potent activator of murine dendritic cells." Vaccine (2008) 26, 509-521.

[3] Remando et al. "Human Dendritic Cell Maturation and Activation by a Heat-Killed Recombinant Yeast Vector Encoding Carcinoembryonic Antigen." Vaccine (2009) 27, 987-994.

[4] Wansley et al. "Vaccination with a Recombinant Saccharomyces cerevisiae Expressing a Tumor Antigen Breaks Immune Tolerance and Elicits Therapeutic Antitumor Responses" Clinical Cancer Research. Clin Can Res (2008) 14,4316-4325.

[5] Haller et al. "Whole recombinant yeast-based immunotherapy induces potent T cell responses targeting HCV NS3 and Core proteins" Vaccine (2007) 25, 1452-1463.

Abstract

GI-5005 THERAPEUTIC VACCINE PLUS PEG-IFN/RIBAVIRIN SIGNIFICANTLY IMPROVES VIROLOGIC RESPONSE AND ALT NORMALIZATION AT END-OF-TREATMENT AND IMPROVES SVR24 COMPARED TO PEG-IFN/RIBAVIRIN IN GENOTYPE-1 CHRONIC HCV PATIENTS

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Background and aims: GI-5005 is a therapeutic vaccine expressing HCV NS3 and Core antigens. GI-5005 elicits antigen-specific T-cell responses with the goal of improving the rate of immune-mediated elimination of HCV-infected hepatocytes.

Methods: Naïve and non-responder (NR) chronic HCV genotype 1 patients were randomized 1:1, and stratified by prior treatment status. Arm 1: GI-5005 monotherapy for 5 weekly doses (day 1 through week 4) followed 4 weeks later by 1 dose at week 8, then monthly GI-5005 plus 48 weeks pegIFN α-2a/ribavirin (SOC) in Naives or 72 weeks triple therapy in NRs. Arm 2: SOC alone (48 weeks in naives and 72 weeks in NRs).

Results: All patients have completed GI-5005 triple therapy, and naïve patients have completed 24 weeks of post-treatment follow up. Triple therapy was well tolerated with no increase in discontinuations due to adverse events (10% in each group), related serious adverse events, or growth factor use for anemia or neutropenia. ETR*, SVR**, and ALT normalization*** are described at right.

Endpoints	Triple	SOC	p-value(ITT)#
ETR* all (nt= 68, nsoc= 65)	63%	45%	0.037
ETR naives (nt=50 , nsoc= 46)	74%	59%	0.133
ETR NRs (nt= 18, nsoc=19)	33%	11%	0.125
SVR naives** (nt= 50, nsoc=46)	58%	48%	0.32
Relapse (nt= 36, nsoc= 26) missing censored	19%	15%	ND
On-treatment breakthrough (nt= 36, nsoc= 28)	8%	11%	ND
SVR naives IL28 T/T (nt=5 , nsoc=5)	60%	0%	0.166
ALT nl EOT *** all (nt=61 , nsoc= 44)	61%	36%	0.018

ETR= % patients HCV RNA neg by PCR at end of treatment, ** SVR=% with HCV RNA < 25IU/mL 24 weeks after completion of therapy, *% patients with ALT >ULN at baseline (Day 1 of Run-In for Arm 1 and Day 1 of SOC for Arm 2) and at least 2 consecutive visits <ULN, # Fisher's 2 sided analysis for ITT includes all patients who received at least 1 dose of triple therapy or SOC*

Conclusions: Triple therapy significantly improved ETR and ALT normalization compared to SOC alone. An improvement of 10% in SVR was observed in naïve patients 24 weeks after the completion of therapy. SVR in *IL-28* genotype TT patients was greater for triple therapy compared to SOC or historical controls, suggesting a potentially greater treatment effect in this high risk patient group. These data support further development of GI-5005 in combination with SOC and novel combination use with direct acting antiviral agents.