GI-5005 THERAPEUTIC VACCINE PLUS PEG-IFN/RIBAVIRIN IMPROVES SUSTAINED VIROLOGIC RESPONSE VERSUS PEG-IFN/RIBAVIRIN IN PRIOR NON-RESPONDERS WITH GENOTYPE 1 CHRONIC HCV INFECTION

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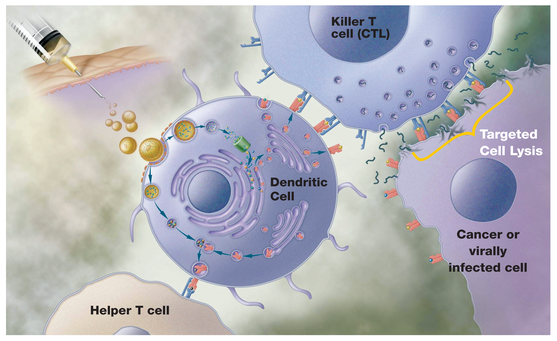
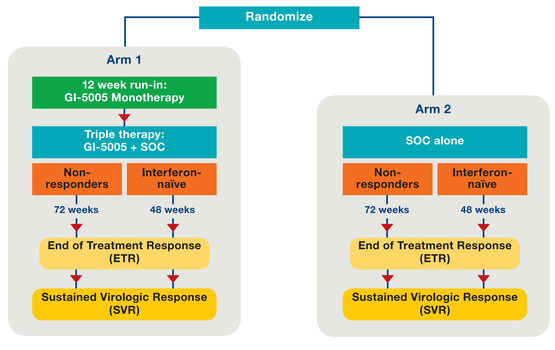
Introduction

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 (1). The current standard of care (SOC) is pegylated interferon (IFN) 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, ALT normalization and Fibrotest scores. Presented here are the complete virologic response at end of treatment (ETR) and sustained virologic response (SVR) data in naïve and non-responder (NR) patients grouped by *IL28B* genotype.





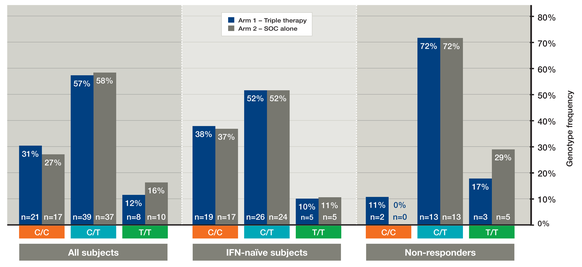
Phase 2 design

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 /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).

GI-5005-02 demographics

Variable	Treatment Group	
	SOC + GI-5005-02 (n=68)	SOC Alone (n=65)
Prior Treatment Status		
INF-naïve	50	46
INF-non-responder	18	19
Baseline HCV RNA (log_{10} IU/mL)[2]		
Mean	6.58	6.65
Race		
African American	5 (7.4%)	11 (16.9%)
Hispanic	6 (8.8%)	4 (6.2%)
Asian	6 (8.8%)	6 (9.2%)
Age		
Median (years)	48	49
Gender		
Male	38 (55.9%)	43 (66.2%)
Female	30 (44.1%)	22 (33.8%)

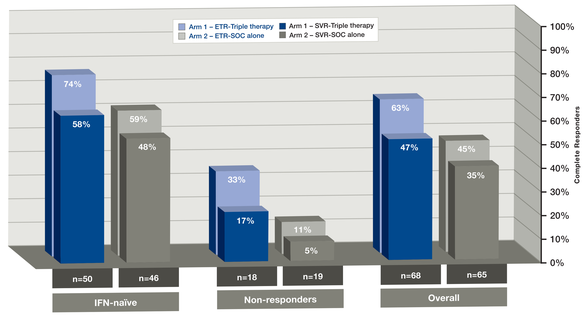
IL28B genotype is well balanced in GI-5005-02



IL28B genotype

IL28B genotypes predict spontaneous clearance of HCV (2), and response to pegIFN/ribavirin therapy (3). The role of *IL28B* in acute clearance of HCV strongly suggests that it is a marker of cellular immunity. *IL28B* testing in GI-5005-02 showed excellent balance between the GI-5005 triple therapy and SOC groups.

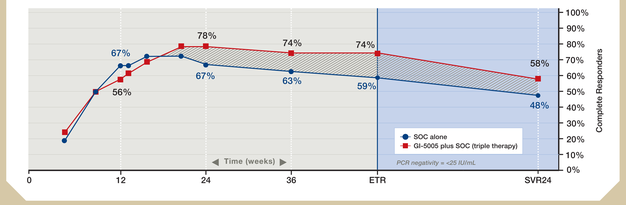
GI-5005-02



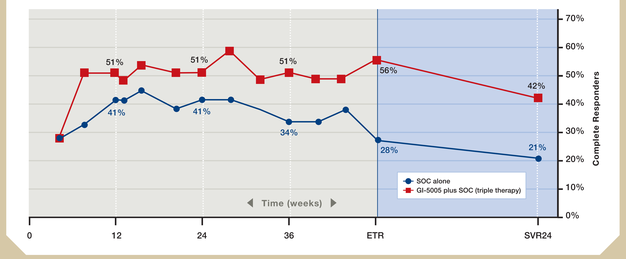
Virologic response / ETR and SVR

GI-5005 triple therapy improved virologic response at end or treatment (ETR) and 6 months after completion of therapy (SVR) overall and in naïve and NR subgroups as measured by PCR assay. ETR: Naïve triple 74% vs SOC 59%, NR triple 33% vs SOC 11%, All triple 63% vs SOC 45% (p=0.04). SVR: Naïve triple 58% vs SOC 48%, NR triple 17% vs SOC 5%, All triple 47% vs SOC 35%.

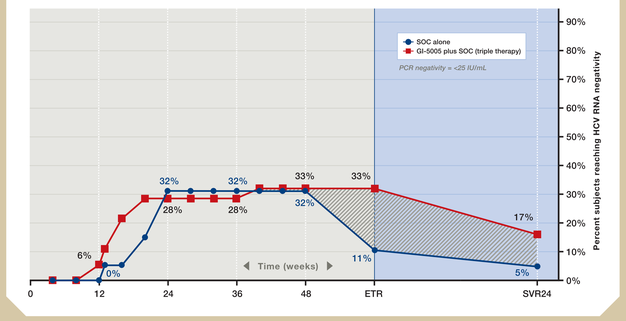
Complete response over time (IFN-naïve, ITT)



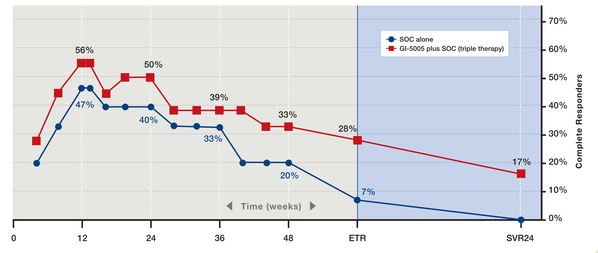
ALT normalization IFN-naïve (ITT)



Complete response over time (IFN-non-responder, ITT)



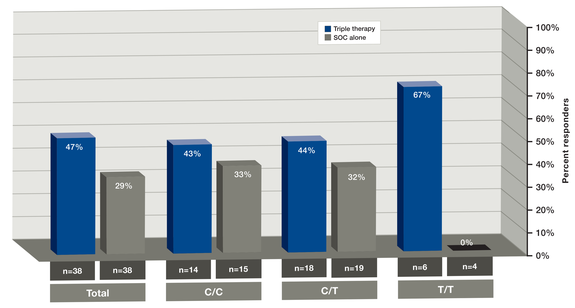
ALT normalization IFN-non-responders (ITT)



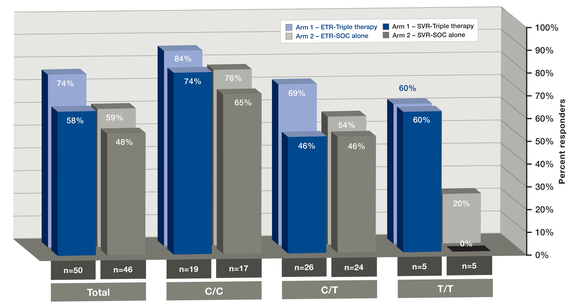
Virologic response and ALT normalization over time

The pattern of ALT normalization and virologic response in naïve and NR patients show that biochemical response favors GI-5005 triple therapy and precedes viral clearance. The advantage in ALT normalization is also sustained for 6 months after the completion of therapy in both the naïve and NR groups.

Categorical cellular immune response *IL28B* subgroups (naïve)



Virologic response *IL28B* subgroups (naïve)



Virologic response by *IL28B* genotype

Important differences were noted for the different *IL28B* genotypes related to the timing and magnitude of HCV specific cellular immunity as measured by IFNγ ELISpot assay. GI-5005 triple therapy improved HCV specific cellular immunity as measured by IFNγ ELISpot assay in all *IL28B* subgroups (C/C; 43% vs 33%, C/T; 44% vs 32%, T/T; 67% vs 0%) as well as end of treatment viral clearance (C/C; 84% vs 76%, C/T; 69% vs 54%, T/T; 60% vs 20%) and SVR in C/C (74% vs 65%) and T/T groups (60% vs 0%).

Conclusions

- GI-5005 triple therapy improved SVR by 12% overall, 10% in naïves, and 12% in NR subjects.
- GI-5005 triple therapy showed the greatest virologic (ETR +40% and SVR +60%) and immunologic response (+67%) in naïve *IL28B* T/T subjects.
- Low levels of HCV specific cellular immunity measured in the SOC naïve *IL28B* T/T group suggest that a poor cellular immune response may be the most significant deficit in these patients.
- GI-5005 showed improvements in ALT normalization that precede virologic clearance, suggesting that it may mitigate non-specific inflammation and hepatic injury.
- Differences of treatment response in *IL28B* subgroups indicate that distinct treatment strategies be developed on a genotype specific basis.
- These data suggest new models of pathogenesis that point to an important role for the GI-5005 therapeutic vaccine in combination with either IFN-based or DAA-(direct-acting antivirals) based therapies.

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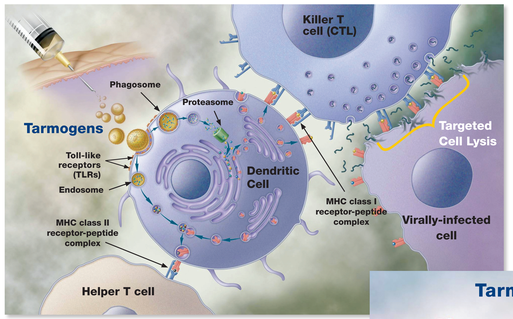
Active immunotherapy with yeast-based Tarmogens

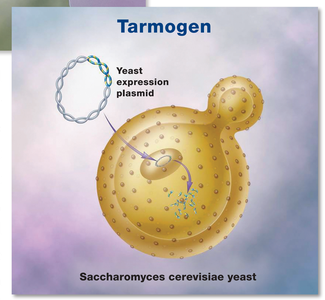
Tarmogens are whole, heat-killed recombinant *Saccharomyces cerevisiae* yeast modified to express one or more protein targets that stimulate the immune system against diseased cells. The target antigens are



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

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Background and aims: The GI-5005 therapeutic vaccine has been shown to improve sustained virologic response in naïve subjects with the greatest effect observed in *IL28B* T/T subjects. We now report the sustained virologic response (SVR) data from prior IFN/ribavirin non-responders (NR).

Methods: HCV genotype 1 patients were randomized 1:1, and stratified by prior treatment status; Arm 1 - GI-5005 monotherapy run-in of five weekly followed by 2 monthly subcutaneous (SC) doses of 40YU (1 YU = 10^7 yeast) GI-5005 over 12 weeks, followed by triple therapy of monthly 40YU GI-5005 doses plus 48 weeks pegIFN α-2a/ribavirin (SOC), Arm 2 - SOC alone. NRs received 72 weeks of triple therapy versus SOC. Prior NRs were defined as poor responders (> 1$\log_{10}$ and < 2 $\log_{10}$ reduction) or partial responders (> 2 $\log_{10}$ reduction without clearance at any time during therapy). Prior null response, relapse, and breakthrough were exclusionary.

Results: Triple therapy was well tolerated with an equivalent number of discontinuations due to adverse events in each group; Triple 8/68(11.8%) and SOC 8/65(12.3%). Improvement in end of treatment response (ETR) (Triple 6/18 [33%] vs SOC 2/19 [11%]) and SVR (Triple 3/18[17%] vs SOC 1/19[5%]) was observed in NR patients. Due to the small number of patients in each treatment arm, these differences were not statistically significant (see table). SVR in NRs occurred only in IL28B C/T subjects (Triple 3/13[23%] vs SOC 1/13[8%]). In summary, GI-5005 triple therapy delivered improved ETR and SVR (Δ ranging from 10-22%) in all patient subgroups (see table).

Population		GI-5005	SOC-alone	Δ=	p-value*
ETR	All	43/68 (63%)	29/65 (45%)	18%	p=0.024
	Naïve	37/50 (74%)	27/46 (59%)	15%	p=0.085
	Non-responder	6/18 (33%)	2/19 (11%)	22%	p=0.099
SVR	All	32/68 (47%)	23/65 (35%)	12%	p=0.117
	Naïve	29/50 (58%)	22/46 (48%)	10%	p=0.214
	Non-responder	3/18 (17%)	1/19 (5%)	12%	p=0.214

*Statistics by one-tailed Fisher's exact test; no adjustments were made for multiple analyses.

Conclusions: GI-5005 plus SOC is well tolerated and improved SVR rates compared to SOC in genotype 1 NR patients. ETR and SVR rates were improved by GI-5005 triple therapy for all subgroups (all, naïve, and NR). These data support further investigation of GI-5005 triple therapy in naïve and NR patients as well as novel combination strategies for GI-5005 with other HCV inhibitory agents in larger numbers of patients.

Poster references

1. Rehermann B, Chisari FV. Cell mediated immune response to the hepatitis C virus. Current Topics in Microbiology and Immunology (2000) 242: 299-325.
2. Thomas DL., et al. Genetic variation in *IL28B* and spontaneous clearance of hepatitis C virus. Nature (2009) 461: 798-801.
3. Ge D., et al. Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance. Nature. (2009) 461: 399-401.