GI-5005 IMMUNOTHERAPY PLUS PEG-IFN/RIBAVIRIN IN GENOTYPE 1 CHRONIC HEPATITIS C PATIENTS COMPARED TO PEG-IFN/RIBAVIRIN ALONE IN NAIVE AND NON-RESPONDER PATIENTS; PRELIMINARY RVR AND VIRAL KINETIC ANALYSIS FROM THE GI-5005-02 PHASE 2 STUDY

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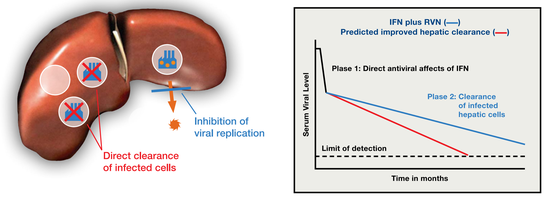
Introduction

Chronic hepatitis C virus (HCV) infection is a worldwide health problem that affects 4.8 million people in the US and approximately 180 million people worldwide. The majority of patients exposed to HCV develop chronic infection. However, approximately 20% of people exposed to hepatitis C virus (HCV) are able to clear their infection during the acute phase without medical intervention. A strong and broadly directed HCV-specific T cell response has been associated with these spontaneously resolving infections (B. Rehermann 2005 Nat. Rev. Immuno.). The current standard of care (SOC) for patients chronically infected with HCV is pegylated interferon plus ribavirin, which works primarily through the inhibition of viral replication. While SOC can often deliver substantial reductions in serum virus levels during the first days of therapy (first phase viral kinetic clearance), only 50% of HCV genotype 1 patients receiving SOC achieve a sustained virologic response (SVR defined as serum negativity for HCV RNA by PCR assay lasting 6 months after the completion of 48 weeks of therapy). Achievement of SVR depends on the patient's ability to clear infected cells from the liver and requires long periods of SOC treatment for a weak host immune response to completely eliminate HCV infected cells (second phase viral kinetic clearance). Therapies that improve the T cell immune response would be predicted to improve the rate of clearance of HCV infected liver cells and lead to improvement of early virologic markers as well as improved rates of remission (SVR). (Figure 1)

There are numerous products in development that aim to inhibit viral replication directly. However, these agents do not contribute significantly to increasing the clearance of HCV infected liver cells. Substantial gains in the treatment of HCV should be attainable through a combination approach that includes inhibition of viral replication (SOC or small molecule antivirals) with a product that generates an enhanced complementary HCV-specific cellular immune responses.

Figure 1.

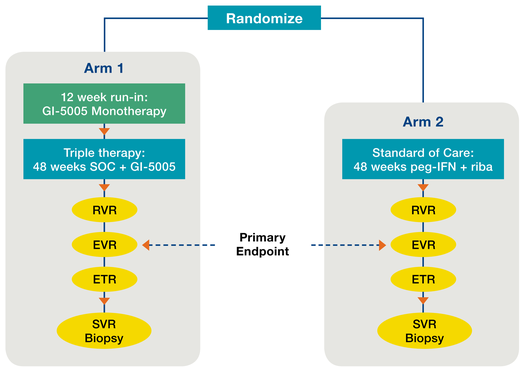


The objective of the GI-5005-02 study is to evaluate whether the ability of the GI-5005 Tarmogen® product to produce an HCV-specific T cell immune response will enhance the clearance of infected cells from the liver in the setting of inhibited viral replication. This will potentially improve established virologic endpoints, and ultimately, clinical outcomes. An HCV-specific T cell response, combined with lower rates of viral replication, should promote accelerated clearance of infected cells resulting in improved rapid virologic response (RVR), early virologic response (EVR), end of treatment response rates (ETR), and sustained virologic response (SVR) rates (considered cure) for patients.

The GI-5005 Tarmogen® product consists of recombinant *S. cerevisiae* yeast expressing a fusion protein of large conserved regions from the HCV NS3 and Core proteins. In a randomized, placebo-controlled phase 1b trial, GI-5005 monotherapy was well-tolerated, generated broadly targeted HCV-specific T cell responses and favorably impacted clinically relevant markers such as ALT (alanine aminotransferase, a marker of liver damage) and HCV RNA levels. The GI-5005-02 study, described herein, is the first clinical study evaluating GI-5005 in combination with SOC versus SOC alone.

Update

The GI-5005-02 dataset has evolved from the time of initial abstract submission to include the complete Arm 1 and Arm 2 cohorts through 4 weeks of therapy. The safety, viral kinetics, and RVR data using the complete dataset are described herein.



Phase 2 design

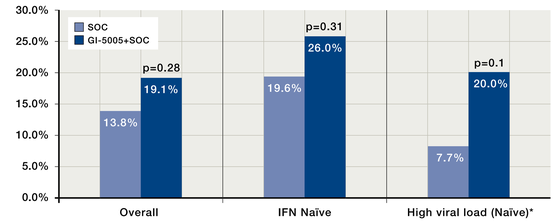
GI-5005-02 is a randomized, open-label phase 2 trial evaluating the efficacy, immunogenicity, and safety of GI-5005 in combination with standard of care Pegasys and ribavirin therapy (triple therapy) vs. standard of care (SOC) alone in subjects with genotype 1 HCV. Treatment naïve subjects in Arm 1 receive monotherapy GI-5005 for 12 weeks (5 weekly doses plus 2 monthly doses), followed by 48 weeks of triple therapy (GI-5005 administered monthly). Prior treatment failures in Arm 1 receive 12 week monotherapy run-in, followed by 72 weeks of triple therapy. Arm 2 patients receive Pegasys/ribavirin as per the product labels. Randomization was stratified by prior treatment therapy. The primary endpoint for the trial is early virologic response (EVR) at week 12. Secondary endpoints include viral kinetics, RVR, ETR, SVR, 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)	
HCV Genotype			
Type 1	7 (9.7)	11 (16.2)	18 (12.9)
Type 1a	39 (54.2)	37 (54.4)	76 (54.3)
Type 1b	26 (36.1)	20 (29.4)	46 (32.9)
Prior Treatment Status			
Naive	53 (73.6)	49 (72.1)	102 (72.9)
Non-response to prior treatment	19 (26.4)	19 (27.9)	38 (27.1)
Years Between Diagnosis of Chronic HCV Infection and Randomization			
Median	2.65	2.95	2.70
Range	0.5 to 31.9	0.5 to 28.3	0.5 to 31.9
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			
18 to <25 years	3 (4.2)	3 (4.4)	6 (4.3)
25 to <45	20 (27.8)	14 (20.6)	34 (24.3)
45 to <65	47 (65.3)	47 (69.1)	94 (67.1)
65 to <75	2 (2.8)	4 (5.9)	6 (4.3)
Median (years)	48.0	49.0	48.0
Range	20 to 74	20 to 68	20 to 74
ALT (U/L)			
Mean (SD)	76.3 (40.3)	64.7 (34.2)	70.7 (37.8)
Median	65.5	61.0	62.5
Range	21 to 199	23 to 214	21 to 214
HCV RNA (log_{10} IU/mL)			
Mean (SD)	6.71 (0.66)	6.74 (0.63)	6.72 (0.64)
Median	6.82	6.86	6.84
Range	4.55 to 7.64	4.89 to 7.80	4.55 to 7.80

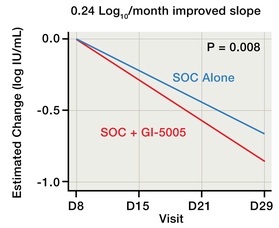
Rapid virologic response (RVR) rates

Rapid virologic response (RVR) is defined as HCV RNA negativity by PCR assay (<25IU/mL) by 4 weeks of therapy and is highly predictive of future sustained virologic response (SVR) for patients who go on to complete full duration of SOC. RVR rates at week 4 were assessed in the triple therapy and SOC groups in the current study. A 2.6-fold advantage was observed in naïve+high load patients with a trend favoring triple therapy (20.0% vs. 7.7%, p=0.1). The majority of naïve+low load patients achieved RVR in both treatment groups, contributing to the smaller observed advantage for triple therapy in the all naïve group (includes both high load and low load patients, 26.0% vs 19.6%). There were no observed RVRs in the non-responder patients from either treatment arm, thereby producing lower absolute RVR rates in the all patients analysis (19.1% vs 13.8%).

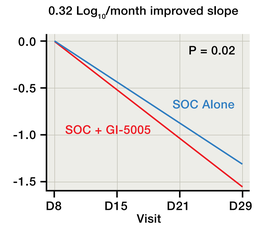


* Baseline viral load >600,000 IU/mL

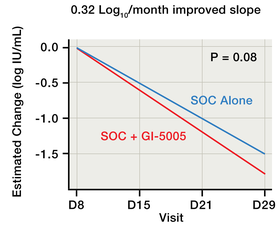
Prior non-responders



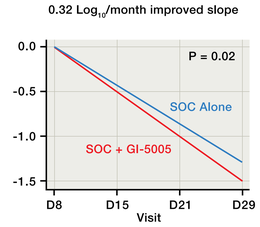
High viral load at baseline



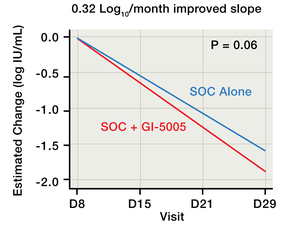
Interferon naïve



All treated



IFN naïve+high viral load at baseline



Viral clearance

Second phase viral kinetic clearance reflects the rate of clearance of the hepatic reservoir of infection. Day 8 was considered the baseline for the calculation of second phase viral kinetics, and samples from Day 15, Day 22, and Day 29 were used to establish the slope of clearance using a repeated measures linear mixed effects model to estimate the change from Day 8 to Day 29. Missing HCV RNA values at Day 8 were imputed by the value at Day 15 or Day 22. Analysis includes all patients with at least an HCV RNA value at Day 8 (actual or imputed) and Day 29. All major patient subgroups showed an increased rate of second phase viral clearance which favored triple therapy; 3 subgroups achieved statistical significance (All, NR, and High Load, with p=0.02, p=0.008, and p=0.02 respectively), and 2 subgroups showed strong trends (Naïve, and Naïve+high Load, with p=0.08 and p=0.06 respectively).

Safety

During the 12 week GI-5005 monotherapy phase no patients discontinued therapy due to adverse events. There have been no deaths to date in either the triple therapy or SOC alone arms. Five subjects had discontinuations of SOC due to adverse events in both treatment arms. Triple therapy: delirium and anemia (neither of these events were considered by the principal investigator to be possibly related to GI-5005); and SOC alone: 2 cases of fatigue, and seizure. Three discontinuations of GI-5005 occurred due to adverse events during triple therapy- anemia, CPK increase and delirium.

Three serious adverse events (SAE) occurred during triple therapy (delirium secondary to illicit drug use, chest pain secondary to anemia, and acute hemolytic anemia), and none of these events were considered by the principal investigator to be possibly related to GI-5005. One SAE occurring on SOC alone was considered possibly related to SOC (seizure).

The most commonly reported non-serious adverse events (defined as > 25% incidence) considered by the principal investigator to be related to SOC in each group included:

	Fatigue	Headache	Nausea	Pyrexia	Insomnia	Depression
SOC	57%	39%	32%	23%	28%	25%
Triple therapy	44%	32%	28%	25%	17%	13%

The most commonly reported non-serious adverse events (defined as > 5% incidence) considered by the principal investigator to be related to GI-5005 included injection site erythema (12%), fatigue (9%), and headache (9%).

Conclusions

- GI-5005 is well tolerated with no product-related SAEs or DLTs.
- GI-5005 plus SOC demonstrated 2.6-fold improvement in RVR rates compared to SOC alone in treatment naïve patients with high baseline HCV RNA levels (>600,000 IU/mL)
- GI-5005 plus SOC demonstrated a ~2-fold improvement over four weeks in the linear rate of viral clearance (0.24-0.32log_{10}/month) compared with SOC alone in all relevant subgroups, including prior non-responders to interferon-based therapy. This improved rate of clearance would project to a 3 to 4 log_{10} improved reduction of virus if sustained for the full 48-72 week regimen.
- The improvement in the rate of second phase viral kinetic clearance is consistent with the proposed mechanism of Tarmogen-induced improved elimination of infected hepatic cells.
- GI-5005 in combination with SOC may represent a novel triple therapy approach that could result in improved SVR rates and may also serve as an optimized backbone therapy to which other novel antiviral agents could be added.
- GI-5005 in combination with different inhibitors of viral replication, such as small molecule polymerase and protease inhibitors may result in the future ability to spare or eliminate components of the current standard of care (pegylated IFN or ribavirin).

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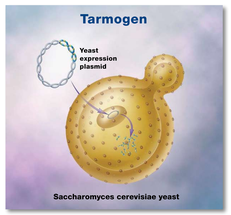
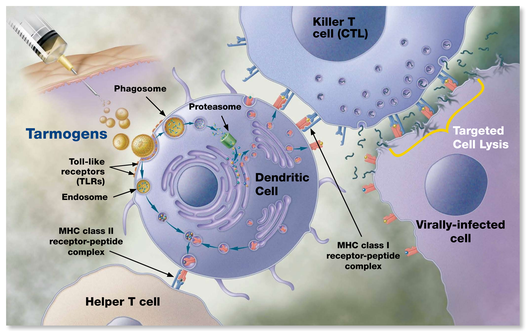
Active immunotherapy with yeast-based Tarmogens

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 final 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]

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]

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]

For more information, visit www.globeimmune.com.

[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] Wansley et al. “Vaccination with a Recombinant Saccharomyces cerevisiae Expressing a Tumor Antigen Breaks Immune Tolerance and Elicits Therapeutic Antitumor Responses” Clinical Cancer Research. July 2008.
[4] 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

Purpose – GI-5005 is a whole heat-killed *S. cerevisiae* immunotherapy expressing high levels of HCV NS3 and Core antigens. GI-5005 has been designed to elicit antigen-specific host CD4 and CD8 T-cell responses with the goal of improving the rate of immune clearance of HCV. The GI-5005-02 phase 2 study evaluates the efficacy and safety of GI-5005 plus peg-IFN/ribavirin (SOC) in subjects with genotype 1 chronic HCV infection.

Methods – Genotype 1 subjects with chronic HCV infection who were treatment naïve or non-responders to prior interferon (IFN) or pegylated interferon (pegIFN) based therapy were eligible (prior null responders and relapsers were excluded). Patients were randomized 1:1, and stratified by virologic response during their prior course of treatment in this open label trial; Arm 1- GI-5005 monotherapy run-in consisting of five weekly followed by 2 monthly subcutaneous (SC) doses of 40YU (1 YU = 10,000,000 yeast) GI-5005 over 12 weeks, followed by triple therapy consisting of monthly 40YU GI-5005 doses plus pegIFN/ribavirin (48 wks in naïve patients, 72 weeks in prior non-responders), Arm 2- treatment with SOC alone (without antecedent GI-5005 monotherapy).

Results – At this interim analysis 28 of 72 patients have completed the first 4 weeks of triple therapy, with a trend to improved rapid virologic response (RVR defined as HCV RNA < 25IU/mL by week 4) in the triple therapy group; overall (8/28 {29%} vs 9/65 {14%}; p=0.08), naïve (8/17 {47%} vs 9/46 {20%}; p=0.03), and baseline HCV RNA >600,000IU/mL (4/22 {18%} vs 5/60 {8%} p=0.19). There were no RVR responses in prior non-responders in either treatment arm. Second phase viral kinetic slopes (Day8-Day29) showed an advantage for triple therapy compared to SOC in prior IFN non-responders (-1.16 $\log_{10}$/mo. vs -0.88 $\log_{10}$/mo; p=0.02), and patients with HCV RNA >600,000 IU/mL at baseline (-1.92 $\log_{10}$/mo. vs -1.76 $\log_{10}$/mo; p= 0.36). Triple therapy has been well-tolerated to date, with no GI-5005 related serious adverse events, dose limiting toxicities or discontinuations due to adverse events.

Conclusion – Triple therapy with GI-5005 plus pegIFN/ribavirin was well tolerated and has generated preliminary data indicative of improved RVR rates compared to SOC in naïve patients with chronic genotype 1 HCV. Second phase viral clearance kinetics also indicates an early favorable effect of this strategy in prior IFN non-responders. These data are consistent with the HCV-specific cellular immune responses observed in the GI-5005-01 phase 1 trial. This therapeutic approach and the mechanism of action of GI-5005 support further investigation and development of combination therapy strategies in chronic HCV infection.

Update – The GI-5005-02 dataset has evolved from the time of initial abstract submission to include the complete Arm 1 and Arm 2 cohorts through 4 weeks of therapy. The safety, viral kinetics, and RVR data using the complete dataset are described herein.