GI-5005 THERAPEUTIC VACCINE ENHANCES VIROLOGIC CLEARANCE BY PEG-IFN/RIBAVIRIN IN NAÏVE HCV GENOTYPE 1 PATIENTS WITH IL28B GENOTYPE T/T

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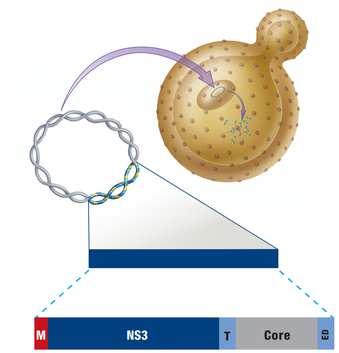
Introduction

Chronic HCV infection is a major health epidemic with up to 170 million people infected worldwide. Approximately 20% to 30% of all HCV patients will face life-threatening complications as a result of their disease. In industrialized countries, HCV accounts for 40% of cases of end-stage cirrhosis, 60% of cases of hepatocellular carcinoma and 30% of liver transplants. Historically, standard-of-care treatment of genotype 1 HCV has been weekly injections of pegylated interferon with twice-daily oral ribavirin, or pegIFN/ribavirin, for 48 weeks of therapy. A host genetic marker near the IL28B gene has been shown to be an important predictor of which patients in the acute setting will clear HCV without treatment and which patients with chronic infection are likely to achieve SVR24. The most difficult to treat patients have the IL28B T/T genotype. Unfavorable IL28B genotypes occur at a higher frequency in African Americans and correlate significantly to the poor SVR24 rates observed in this group. The consistency of the IL28B effect on viral clearance without treatment in the acute setting as well as SVR24 rates in the chronic setting suggests that the different genotypes mark a difference in the underlying immune response characteristics of the patients.

Recently, the addition of telaprevir or boceprevir to pegIFN/ribavirin has improved SVR24 to 65% to 75% using a shortened overall regimen. Despite these improvements, the addition of these agents adds toxicity to pegIFN/ribavirin therapy, which is associated with flu-like symptoms, depression, and decreased white and red blood cells. Future improvements to HCV treatment will likely include strategies to eliminate interferon entirely from the regimen.

Recent data suggests that an interferon-free treatment regimen may be effective in achieving higher SVR24 rates in certain treatment groups. Historically, genotype 2/3 HCV infected populations treated with interferon-based therapy have achieved higher SVR24 rates compared to genotype 1 HCV infected populations treated with interferon-based therapy. Recent studies have shown promising SVR24 rates in genotype 2/3 HCV infected patients using interferon-free treatment regimens. However, these studies have also shown that in genotype 1 HCV infected patients an interferon-free treatment regimen may be less effective than it is in patients with genotype 2/3 HCV, at least in difficult to treat subjects. We believe additional data from external ongoing clinical trials using interferon-free treatment regimens may help to identify difficult-to-treat subgroups within the genotype 1 HCV population, potentially those with the IL28B T/T genotype. As these data become available, we will evaluate the potential role of GI-5005 in the emerging landscape of interferon-free HCV treatment regimens.

GI-5005

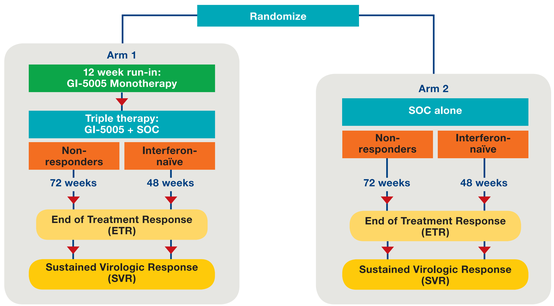


GI-5005 is a recombinant yeast-based biological product engineered to express NS3-Core HCV proteins. The Tarmogen product is a heat-killed yeast (*S. cerevisiae*) containing a fusion protein of NS3-Core suspended in PBS and vialed at 20 YU/mL.

M, MADEAP (Met-Ala-Asp-Glu-Ala-Pro) tag for enhanced metabolic stability; NS3, 262 amino acids of HCV Non-structural protein 3 (residues 1115 to 1376 of the HCV polyprotein); T, single threonine spacer; Core, 139 residues of HCV Core antigen (residues 2 to 140 of the HCV polyprotein); ED, C terminal hydrophilicity enhancer.

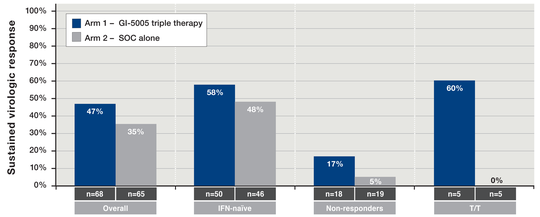
GI-5005-02: initial results

The GI-5005-02 trial, as originally designed, enrolled 140 genotype 1 subjects in a double-blind, open-label trial. Randomization was stratified by prior response to ensure balance with 74% of subjects treatment-naïve and 26% prior non-responders. Gender, race, age, baseline HCV viral load and IL28B genotype were balanced between arms.



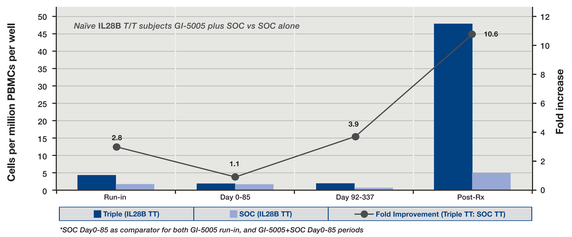
For the initial 140 subjects enrolled in the trial, GI-5005 plus pegIFN/ribavirin has demonstrated statistically significant improvement in complete virologic response (HCV RNA < 25IU/mL) at the end of treatment (ETR; 74% vs 59%, p=0.04), significant improvement in ALT normalization (ALT < ULN for at least 2 consecutive visits) at the end of treatment (61% vs 36%, p=0.02), and improved sustained virologic response for 24 weeks after completion of therapy (SVR) in treatment naïve subjects (58% vs 48%) with the most pronounced benefit seen in the most difficult to treat IL28B T/T subjects (60% SVR vs. 0%). See Figure 1a below:

Figure 1a: GI-5005 improves SVR in difficult to treat patients



Striking differences in HCV specific cellular immune responses were observed in immune testing of the T/T patients from the GI-5005 triple therapy group and SOC groups, with increases in the mean change from baseline in the number of HCV specific T cells ranging from 2.9 fold better for the GI-5005 group during the monotherapy run-in period compared to SOC alone, comparable increases during the first 12 weeks of therapy, 3.9 fold better for GI-5005 in the last 36 weeks of triple therapy compared to SOC alone, and > 10 fold better for GI-5005 in the post-treatment period. See Figure 1b below:

Figure 1b: Change from baseline of HCV specific T cells by ELISpot assay (IL28B T/T subjects; GI-5005+SOC vs. SOC alone)



*SOC Day0-85 as comparator for both GI-5005 run-in, and GI-5005+SOC Day0-85 periods

Safety

Of the 136 subjects that were included in the initial safety analyses (received at least one dose of study therapy), 98.6% of the triple therapy and 100.0% of the SOC subjects experienced at least 1 AE during the study. Additionally, over the course of the study, comparable proportions of subjects in the triple therapy and SOC groups discontinued treatment due to AEs (12.7% and 12.3%, respectively); See table 1.

Table 1: Discontinuations of study therapy due to adverse events

	Triple therapy	Standard of Care	Total
	n=71	n=65	n=136
Total therapy discontinuations	9 (12.7%)	8 (12.3%)	17 (12.5%)
Discontinued SOC only	1 (1.4%)	8 (12.3%)	9 (6.6)
Discontinued GI-5005 only	3 (4.2%)	n/a	3 (4.2)

No deaths were reported at any time during the study. During the treatment period, 19.7% of the subjects in the triple therapy group and 10.8% of the subjects in the SOC group experienced other serious AEs; see Table 9. Overall, there were no meaningful clusters of events in the triple therapy group and 5 of the serious events reported by subjects in this group were clearly unrelated to treatment (1 event each of cat bite, fall, and hemorrhage after biopsy; 2 events of substance abuse).

Table 2: Serious adverse events

	Triple therapy	Standard of Care
	(n=71)	(n=65)
Subjects reporting serious AEs (n [%])	14 (19.7%)	7 (10.8%)
Number of SAEs related to GI-5005	3	n/a
Number of SAEs related to SOC	5	1
Events occurring in >1 subject	2	0

IL28B T/T GI-5005-02 study expansion

Given the striking differences seen in both in HCV specific cellular immune responses and sustained virologic response in the IL28B T/T subjects from GI-5005-02, enrollment was expanded to increase the number of subjects with the IL28B T/T genotype.

An additional 17 treatment-naïve, genotype subjects with the IL28B T/T were treated.

Additional patients were randomized at a 2:1 ratio (GI-5005 triple:SOC alone)

Table 3: Baseline demographics – IL28B T/T subjects

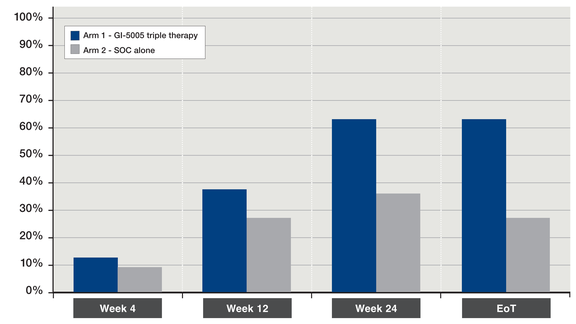
Variable	Treatment Group[3]		Total (n=27)
	SOC + GI-5005 (n=16)	SOC Alone (n=11)	
HCV Genotype			
1	0 (0.0%)	2 (18.2%)	2 (7.4%)
1a	10 (62.5%)	6 (54.5%)	16 (59.3%)
1b	6 (37.5%)	3 (27.3%)	9 (33.3%)
Sex			
Male	10 (62.5%)	5 (45.5%)	15 (55.6%)
Female	6 (37.5%)	6 (54.5%)	12 (44.4%)
Race			
White	8 (50.0%)	2 (18.2%)	10 (37.0%)
African American	8 (50.0%)	9 (81.8%)	17 (63.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hispanic	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age			
Mean	52.1	53.4	52.6
Range	34-74	45-65	34-74
ALT (U/L)[1]			
Median	49.5	39.5	46.5
Range	17-136	26-73	17-136
HCV RNA (log_{10} IU/mL)[2]			
Median	6.19	6.68	6.34
Range	3.1-7.09	5.6-7.72	3.1-7.72

[1] ALT baseline values taken on Day1 of study therapy [2] HCV baseline values taken on Day 1 of SOC
[3] Demographic population includes all T/T subjects enrolled (original 10 T/T subjects plus 17 additional subjects).

Figure 2: GI-5005 plus pegIFN/ribavirin improves end of treatment virologic response in IL28B T/T subjects compared to SOC alone

GI-5005 plus pegIFN/ribavirin improved virologic response in IL28B T/T subjects compared to pegIFN/ribavirin (SOC) alone. These data suggest that the GI-5005 therapeutic vaccine augments the immune response in subjects with the IL28B T/T genotype and may serve as a proxy for interferon replacement. GI-5005 may therefore serve as a component of emerging IFN-free regimens for use in difficult to treat chronic HCV populations such as IL28B T/Ts, African Americans, and prior pegIFN/ribavirin non-responders.

Figure 2: Virologic response through end of treatment in genotype 1 naïve subjects with the IL28B T/T genotype



	GI-5005 + SOC	SOC Alone
	n=16	n=11
Week 4	2 (13%)	1 (9%)
Week 12	6 (38%)	3 (27%)
Week 24	10 (63%)	4 (36%)
End of treatment	10 (63%)	3 (27%)

Conclusions

- GI-5005 is well tolerated and showed comparable rates of serious adverse events and discontinuations due to adverse events compared to SOC.
- In the original 140 subjects, GI-5005 plus pegIFN/ribavirin improved SVR in genotype 1 naïve, genotype 2/3 naïve and prior non-responders, with the greatest effect in genotype 1 naïve, IL28B T/T subjects.
- In the T/T study expansion, a benefit in complete virologic response was observed for the GI-5005 group compared to SOC alone (63% GI-5005+SOC vs. 27% SOC alone; p=0.12, by two tailed Fisher's exact test).
  - For the original 10 T/T subjects, SVR was 60% vs. 0%.
- GI-5005 in combination with different inhibitors of viral replication, such as small molecule polymerase and protease inhibitors may result in the ability to further improve response rates in difficult to treat HCV populations.

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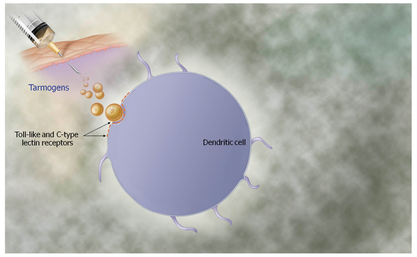
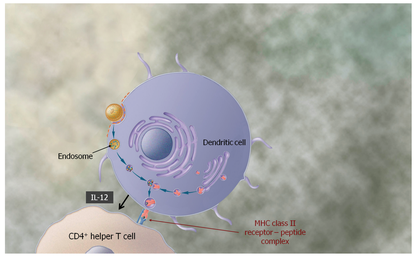
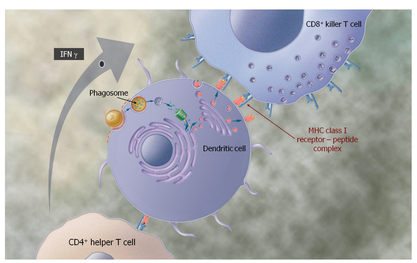
Active immunotherapy with yeast-based Tarmogens



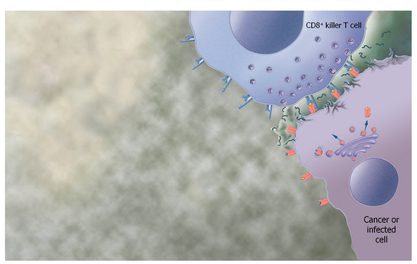
Administration of Tarmogens initially results in binding of the yeast to antigen-presenting cells, the most important of which are dendritic cells, near the injection site. The dendritic cells are activated as a result of the Tarmogens binding to Toll-like receptors and other receptor molecules on the surface of the dendritic cell, resulting in the activation of cytokine immune signaling molecules. The dendritic cell also engulfs the Tarmogen. Multiple Tarmogens may be taken up by the same dendritic cell.



The Tarmogen is processed by the dendritic cell in two ways. First, the Tarmogen is engulfed by endosomes and the protein inside the endosome is cut into shorter peptides fragments. These peptides are presented by Class II MHC molecules on the surface of the dendritic cell. In combination with IL-12, a cytokine that is produced by the dendritic cell, these MHC-peptide complexes on the surface of the dendritic cell are recognized by and activate cells involved in viral immunity called $CD4^+$ helper T cells.



Dendritic cells also process Tarmogens by engulfing them with phagosomes. This results in presentation of peptides, including the antigen from inside the Tarmogen, to $CD8^+$ killer T cells, via Class I MHC molecules on the surface of the dendritic cell, resulting in proliferation of identical antigen specific $CD8^+$ T cells. $CD4^+$ helper T cells are so named because one of their roles is to "help" activate killer T cells by expressing interferon gamma (IFNγ).



The newly activated $CD8^+$ killer T cells move throughout the body and identify any other cell that expresses the same disease protein as the one recognized by the $CD8^+$ killer T cells. Once the $CD8^+$ killer T cell finds another cell in the body containing the target protein, it can kill the cell using multiple mechanisms.

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Purpose: Background and aims: The IL28B T/T genotype predicts poor sustained virologic response (SVR) to PegIFN/ribavirin (P/R). GI-5005 is a therapeutic vaccine which enhanced HCV specific cellular immunity and improved SVR in response to P/R in naïve genotype 1 subjects with IL28B T/T [GI-5005 + P/R; 3/5 (60%) compared to P/R alone; 0/5 (0%)]. For this study, we have expanded the sample size by an additional 17 subjects with IL28B genotype T/T.

Methods: Peripheral blood mononuclear cells (PBMCs) were harvested from donors and stimulated over 3, 7-day rounds with autologous dendritic cells pulsed with SCore, XSCore, or empty vector (ctrl) yeast. Following this stimulation the conditioned PBMCs were incubated with HBV antigen-pulsed autologous PBMCs for 24h and evaluated by IFNγ ELISpot and by intracellular cytokine staining to measure markers of CD4 and CD8 T cell activation or function (IFNγ, IL-4, IL-17, and $CD10^7$a/LAMP1).

Results: GI-5005 in combination with P/R was well tolerated and had a higher virologic response rate, 63% (10/16) compared to P/R 27% (3/27) [ITT analysis; subjects received at least 1 dose of GI-5005 plus P/R or P/R alone]. Four subjects in the GI-5005 plus P/R group and 1 subject in the P/R group discontinued treatment early (prior to 48 weeks) while HCV RNA < 25IU/mL (*see table below). We continue to monitor subjects in the post-treatment period for SVR24, and these data will be reported when available.

Virologic Response in HCV Genotype 1, Naïve IL28B T/T Subjects During Treatment

HCV RNA < 25 IU/mL	GI-5005 plus PegIFN/Riba	PegIFN/Riba
	n=16	n=11
Week 4	2 (13%)	1 (9%)
Week 12	6 (38%)	3 (27%)
Week 24	10 (63%)	4 (36%)
End of treatment*	10 (63%)	3 (27%)

**# of subjects with HCV RNA < 25IU/ml when they completed study therapy. One subject in the PegIFN/Riba group experienced viral rebound prior to discontinuing therapy.*

Conclusions: GI-5005 plus P/R improved virologic response in IL28B T/T subjects compared to P/R alone. These data suggest that the GI-5005 therapeutic vaccine augments the immune response in subjects with the IL28B T/T genotype and may serve as a proxy for interferon replacement. GI-5005 may therefore serve as a component of emerging IFN-free regimens for use in difficult to treat chronic HCV populations such as IL28B T/Ts, African Americans, and prior P/R non-responders.