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


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**Sustained virologic response for IFN-naïve patients (ITT)**

The proportion of subjects achieving a sustained virologic response (SVR) from each treatment group during the treatment period and post-treatment periods. In all subjects, cumulative virologic response (%) is shown for the treatment period and end-of-treatment periods. Days are shown for the time at which the response was achieved. Only 15% advantage for complete virologic response at the end of treatment and a 9% advantage in SVR at 12 months after the completion of therapy.

**Conclusions**

- GI-5005 therapy for the first time improved virologic response at clinically meaningful endpoints in a phase 2 trial in patients with advanced fibrosis.
- GI-5005 triple therapy significantly improved end of treatment viral clearance (93% vs 86%), p=0.037; and ALT normalization (50% vs 67%) compared to SOC alone.
- GI-5005 triple therapy improved end of treatment viral clearance in naïve after 48 weeks of therapy (93% vs 86%) and improved SVR (90% vs 67%) compared to SOC alone.

**Safety**

During the 12 week GI-5005 monotherapy period no patients discontinued therapy due to adverse events (AEs). Comparative numbers of patients from the triple therapy group and SOC group discontinued therapy due to adverse events: SOC (13/59; 22%) triple therapy (6/67; 9%) SOC group. During the treatment period (10/44; 23%) subjects experienced serious adverse events (SAEs): in the SOC group 3 events of non-cardiac chest pain (2 events in the SOC subgroup) and 1 case of anaphylaxis. There were no significant differences in AE profile across the SOC group. There were no significant differences in AE profile across the SOC group. There were no significant differences in AE profile across the SOC group. There were no significant differences in AE profile across the SOC group.

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

ALT normalization (%) occurred in patients with advanced fibrosis (F3/4) at the end of treatment (all subjects), and also showed a substantial advantage in ALT normalization at the end of the post-treatment period (months after treatment; after completion of therapy).

**Phases 2 design**

Phase 2a/ribavirin therapy (triple therapy) vs. SOC alone, n=140 SOC + GI-5005 (n=72) SOC Alone (n=68) Statistical significance achieved if p<0.05, 2-sided Fisher’s exact test.

**Demographics**

<table>
<thead>
<tr>
<th>SOC Alone</th>
<th>SOC + GI-5005</th>
<th>SOC + GI-5005 (n=72)</th>
<th>SOC Alone (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean (SD)</td>
<td>74.4 (41.2)</td>
<td>65.1 (47.3)</td>
<td>70.0 (44.3)</td>
</tr>
<tr>
<td>African American</td>
<td>7 (9.7)</td>
<td>11 (16.2)</td>
<td>18 (12.9)</td>
</tr>
<tr>
<td>White</td>
<td>50 (69.4)</td>
<td>47 (69.1)</td>
<td>97 (69.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6 (8.3)</td>
<td>6 (8.8)</td>
<td>12 (8.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (8.3)</td>
<td>4 (5.9)</td>
<td>10 (7.1)</td>
</tr>
</tbody>
</table>

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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 the target protein inside, is administered as an expression plasmid. The heat-inactivated yeast, with the target protein antigens is engineered into a yeast cell. Tarmogens couple the innate immune response to eliminate diseased cells. In summary, Tarmogens activate the immune system. Tarmogens destroy the target cancer or virally-infected hepatocytes.

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). 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.

Background and aims: GI-5005 is a therapeutic vaccine expressing HCV NS3 and Core antigens. GI-5005 dicists 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 by 4 weeks later by 1 dose at week 8, then monthly GI-5005 plus 48 weeks pegIFN/Riba VIRIN in genotype-1 chronic HCV patients. 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), and ALT normalization compared to SOC alone. An improvement of 10% in SVR was observed in naive patients 24 weeks after the completion of therapy. 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.

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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Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SOC</th>
<th>GI-5005</th>
<th>SOC vs GI-5005 p-value(ITT)</th>
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</thead>
<tbody>
<tr>
<td>ETR</td>
<td>11%</td>
<td>33%</td>
<td>0.125</td>
</tr>
<tr>
<td>SVR**</td>
<td>16%</td>
<td>50%</td>
<td>ND</td>
</tr>
<tr>
<td>On-treatment breakthrough</td>
<td>6%</td>
<td>17%</td>
<td>ND</td>
</tr>
<tr>
<td>ALT at EOT*</td>
<td>41%</td>
<td>81%</td>
<td>ND</td>
</tr>
</tbody>
</table>

* ETR= % patients HCV RNA neg by PCR at end of treatment, ** SVR=%  with HCV RNA < 25IU/mL 24 weeks follow up.

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. 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.