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


GI-5005 is a recombinant protein-based biological product engineered to express NS3-CORE HCV proteins. The Tarmaxx product is a heat-killed (≥ 60°C) containing a fusion protein of NS3-Core-HCV (pre- and folded) and IL28B.

Introduction

Chronic HCV infection is a major health epidemy with up to 170 million people infected worldwide. Approximately 20% to 50% of HCV patients will face liver-damaging cirrhosis, as a result of their disease. In uncontrolled cirrhosis, HCV accounts for 48% of cases of end-stage cirrhosis, 46% of cases of hepatocellular carcinoma, and 30% of liver transplants. Historically, standard-of-care treatment of genotype 1 HCV has been largely ineffective with null or low-dose activities, pegylated interferon, for 48-72 weeks of a fixed-dose regimen and pegylated interferon without treatment and with which patients infected with genotype 1 HCV are likely to achieve SVR28. The most difficult to treat patients have the HCV-1b genotype. Umbilical HCV-1b genotype occurs in a higher frequency in African Americans and correlates significantly to the pegylated interferon observed in this group. The consistency of the IL28B effect on viral clearance without treatment in the acute setting as well as pegylated interferon therapy do not account for 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 outcomes to 60% 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 fatigue, depression, and decreased white and red blood cells. Future improvements to HCV therapy will likely include strategies to eliminate interferon entirely from the regimen.

For the initial 160 subjects enrolled in the trial, GI-5005 plus pegIFN/ribavirin has demonstrated statistically significant improvements in virologic response (HCV RNA < 100IU/mL) at the end of therapy (41% vs 36%, p=0.02), statistically significant improvement in complete virologic response (HCV RNA < 25IU/mL) at week 12 (58% vs 48%, p=0.02), and statistically significant improvement in SVR24 (58% vs 48%, p=0.02).

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GI-5005-02: initial safety

Of the 136 subjects included in the initial safety analysis (received at least one dose of study therapy), 94% of the triple therapy and 95% of the SOC subjects experienced at least 1 AE during the study. Additionally, across the 2 arms, comparable proportions of subjects in the triple therapy and SOC groups discontinued treatment due to AEs (12% and 15%, respectively) (see table 1).

Table 1: Discontinuance of study therapy due to adverse events

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total (n=136)</th>
<th>Discontinuation of study therapy due to adverse events (% (n=136))</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI-5005+SOC</td>
<td>114</td>
<td>GI-5005-related AEs 4 (3.5%)</td>
</tr>
<tr>
<td>GI-5005 only</td>
<td>22</td>
<td>SOC-related AEs 8 (36.4%)</td>
</tr>
</tbody>
</table>

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

For the initial 140 subjects enrolled in the trial, GI-5005 plus pegIFN/ribavirin has demonstrated statistically significant improvements in virologic response (HCV RNA < 100IU/mL) at the end of therapy (41% vs 36%, p=0.02), statistically significant improvement in complete virologic response (HCV RNA < 25IU/mL) at week 12 (58% vs 48%, p=0.02), and statistically significant improvement in SVR24 (58% vs 48%, p=0.02).

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Conclusions

- GI-5005 is well tolerated and showed comparable rates of serious adverse events and discontinuations due to adverse events compared to SOC.

- For the original 140 subjects, GI-5005 plus pegIFN/ribavirin improved SVR24 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/T, African Americans, and prior pegIFN-naive non-responders.

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Purpose: Background and aims: The IL28B T/T genotype predicts poor sustained virologic response (SVR) to PegIFN/Riba.

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% (3/11) [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 < 25 IU/mL (*see table below). We continue to monitor subjects in the post-treatment period for efficacy and safety.

Conclusions: GI-5005 plus P/R improved virologic response in HCV 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.

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 peptide 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+ 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 (IFN-γ).

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.

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

<table>
<thead>
<tr>
<th>HCV RNA &lt; 25 IU/mL</th>
<th>GI-5005 plus PegIFN/Riba</th>
<th>PegIFN/Riba</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=16</td>
<td>n=11</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>2 (13%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Week 12</td>
<td>6 (38%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Week 24</td>
<td>10 (63%)</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>End of treatment*</td>
<td>10 (63%)</td>
<td>3 (27%)</td>
</tr>
</tbody>
</table>

*4 of subjects with HCV RNA > 250 IU/mL when they completed study therapy. One subject in the PegIFN/Riba group experienced viral rebound prior to discontinuing therapy.