ALT normalization during treatment period for naive and prior non-responder patients

Triple therapy compared to SOC alone in patients who normalized ALT at the end of treatment (all subjects 61% vs 36%, p=0.018), and also showed a substantial advantage for sustained ALT normalization in the post-treatment period for 4 months after the completion of therapy (50% vs 10%, p=0.04).

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/RBV in treatment-naïve (Arm 1) vs. prior non-responder patients (Arm 2). 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 SOC alone. Patients who received GI-5005 monotherapy at week 12 were eligible for re-randomization to SOC plus GI-5005 as a triple therapy regimen (Arm 1) or SOC alone (Arm 2). The primary endpoint was achievement of SVR24 in the SOC group. Secondary endpoints included virologic response at all time points, normalization of ALT and HCV RNA levels in the SOC group. The study included 232 treatment-naïve HCV genotype 1 patients and was stratified by genotype, prior treatment response, and racial/ethnic characteristics.

Time course of viral clearance (IFN-naïve)

The proportion of subjects achieving viral clearance (PCR<25 IU/mL) is shown for the naive subjects from each treatment group during the treatment period and post-treatment period. Subjects achieving SVR in the treatment period and post-treatment period are shown.

ALT normalization over time for IFN-naïve and non responder patients

Alofi concentrations (ALT levels in the first period) a comprises real-time markers of liver injury in patients with chronic HCV infection. Marked reductions in ALT levels may predict a greater level of liver inflammation and recession and a more rapid progression to cirrhosis. Normalization of ALT levels for sustained periods of time may reflect an improvement in liver inflammation and fibrosis, and suggests better overall health, overall well-being, and reduced risk of progression to cirrhosis.

Liver biopsy: reduction in necro-inflammation scores

Periodic biopsies were collected from consenting subjects to assess hepatic necro-inflammatory scores (all subjects 61% vs 36%, p=0.018), and also showed a substantial advantage for sustained ALT normalization in the post-treatment period for 4 months after the completion of therapy (50% vs 10%, p=0.04).

Conclusions

- GI-5005 significantly improved ALT normalization (49% vs 10%, p=0.001) and was associated with a higher rate of treatment success compared to SOC.
- The achievement for ALT normalization in GI-5005 treated subjects precede the achievement observed for virologic response and justify the parallel treatment period of 24 weeks.
- A larger reduction in necro-inflammation was observed in the biopsied GI-5005 treated patients compared to SOC alone.
- These reductions in necro-inflammatory scores were well correlated to ALT reductions in the GI-5005 treated subjects but not in the SOC treated subjects.
- GI-5005 showed incremental advantages in ALT reduction and liver biopsy indication of better liver health independent of the favorable effects observed in virologic response.
- These data support further study of the influence of GI-5005 treatment as a marker of clinical benefit in addition to virologic response in patients with chronic HCV infection.
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, S. cerevisiae yeast, was coupled to the target antigens by a recombinant plasmid. The heat-inactivated yeast, S. cerevisiae, coupled to the target antigens by a recombinant plasmid. The heat-inactivated yeast, S. cerevisiae, coupled to the target antigens by a recombinant plasmid.

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 peptide-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 whole heat-killed Saccharomyces cerevisiae therapeutic vaccine expressing HCV NS3 and Core antigens. GI-5005 elicits antigen-specific T-cell responses (Hepatology 2007; 46: 836A) 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 4 weeks later by 1 dose of pegIFN-α2b/ribavirin. Arm 2: GI-5005, followed by triple therapy (TT) consisting of monthly doses of GI-5005 doses plus 48 weeks pegIFN-α2b/ribavirin (SOC) in naïve subjects (TT) and 48 weeks pegIFN-α2b/ribavirin (SOC) in naïve subjects (TT). These data along with the previously reported 15% treatment advantage for complete virologic response in naïve subjects (74% vs 59%) support further investigation of GI-5005 triple therapy and novel combination strategies for GI-5005 with STATC agents.

Conclusions: Triple therapy (GI-5005 plus pegIFN/ribavirin) improved week 48 biopsy necro-inflammatory scores compared to SOC alone in genotype 1 patients. Improvement in NI scores was observed in both groups by either Ishak or Knodell index (<0.1 point change). Higher rates of ALT normalization were observed at 48 weeks in TT compared to SOC: TT naive 24/44 (55%), SOC naive 9/29 (31%) p = 0.04, TT NR 6/18 (33%) vs SOC NR 3/15 (20%) p = 0.32. Pearson correlation of average ALT reduction and NI scores was greater for TT compared to SOC: correlation coefficient Knodell TT 0.47, p = 0.01 vs SOC 0.24, p = 0.07. Improvement in NI scores was observed in both groups by either Ishak or Knodell index (<0.1 point change). Higher rates of ALT normalization were observed at 48 weeks in TT compared to SOC: TT naive 24/44 (55%), SOC naive 9/29 (31%) p = 0.04, TT NR 6/18 (33%) vs SOC NR 3/15 (20%) p = 0.32. Pearson correlation of average ALT reduction and NI scores was greater for TT compared to SOC: correlation coefficient Knodell TT 0.47, p = 0.01 vs SOC 0.24, p = 0.07. Improvement in NI scores was observed in both groups by either Ishak or Knodell index (<0.1 point change). Higher rates of ALT normalization were observed at 48 weeks in TT compared to SOC: TT naive 24/44 (55%), SOC naive 9/29 (31%) p = 0.04, TT NR 6/18 (33%) vs SOC NR 3/15 (20%) p = 0.32. Pearson correlation of average ALT reduction and NI scores was greater for TT compared to SOC: correlation coefficient Knodell TT 0.47, p = 0.01 vs SOC 0.24, p = 0.07. Improvement in NI scores was observed in both groups by either Ishak or Knodell index (<0.1 point change). Higher rates of ALT normalization were observed at 48 weeks in TT compared to SOC: TT naive 24/44 (55%), SOC naive 9/29 (31%) p = 0.04, TT NR 6/18 (33%) vs SOC NR 3/15 (20%) p = 0.32. Pearson correlation of average ALT reduction and NI scores was greater for TT compared to SOC: correlation coefficient Knodell TT 0.47, p = 0.01 vs SOC 0.24, p = 0.07. Improvement in NI scores was observed in both groups by either Ishak or Knodell index (<0.1 point change). Higher rates of ALT normalization were observed at 48 weeks in TT compared to SOC: TT naive 24/44 (55%), SOC naive 9/29 (31%) p = 0.04, TT NR 6/18 (33%) vs SOC NR 3/15 (20%) p = 0.32. Pearson correlation of average ALT reduction and NI scores was greater for TT compared to SOC: correlation coefficient Knodell TT 0.47, p = 0.01 vs SOC 0.24, p = 0.07.