PHARMACOGENOMIC ANALYSIS REVEALS IMPROVED VIROLOGIC RESPONSE IN ALL IL-28 B GENOTYPES IN NAÏVE GENOTYPE 1 CHRONIC HCV PATIENTS TREATED WITH GI-5005 THERAPEUTIC VACCINE PLUS PEG-IFN/RIBAVIRIN


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Introduction
 Chronic hepatitis C virus (HCV) infection is a health problem that affects 4.6 million people in the US and approximately 180 million people worldwide. The majority of patients present with chronic disease and do not appear to be at risk during the acute phase without medical intervention. A strong HCV specific T cell response has been associated with these spontaneously resolving infections. B cells induce long-lasting neutralizing antibodies. The current standard of care (SOC) is pegylated interferon plus ribavirin, which works primarily through the induction of viral replication. Only ~10% of genotype 1 naive patients receiving SOC achieve a sustained virologic response (SVR). Advancement of SVR depends on the patient’s ability to clear infected cells from the liver and requires long periods of antiviral suppression for 48 weeks to allow a weak host immune response sufficient to completely eliminate HCV infected cells. Substantial gains in the treatment of HCV could be attained through a combination approach that inhibits viral replication (SOC or small molecule antivirals) and enhances HCV specific, cellular immune responses (GI-5005). The GI-5005 Tarmogen® product consists of recombinant MHC class 1 alpha and beta chains. In a randomized, placebo-controlled, phase II trial, GI-5005 monotherapy was well tolerated, generated strong HCV specific T cell responses, and favorably impacted ALT and HCV RNA levels. The GI-5005-02 phase 2 study, described herein, is the first clinical study evaluating GI-5005 in combination with SOC versus SOC alone. We have previously published a study demonstrating that GI-5005 as monotherapy has dose dependent, rapid virologic response (RVR) and early virologic response (EVR) rates, as well as ALT normalization and different rates. Potential places for the complete virologic response and end of trial ALT were described.

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) pegylated interferon/ribavirin therapy (triple therapy) vs. SOC alone in subjects with genotype 1 HCV. Treatment naïve subjects in Arm 1 receive SOC alone. Treatment naïve subjects in Arm 2 receive GI-5005 monotherapy weekly from week 1 to week 4, a dose in week 5, followed by monthly maintenance doses in combination with SOC for 24 weeks. In Arm 1, 3 treatment failure scores 0 (0.97), 2 (1.16), and 3 (1.23) weeks after treatment failure. Randomization was stratified by response to prior therapy (interferon naïve vs. non-responders). 3D efficacy analysis for the total trial endpoints: SVR, RVR, ETR, ITT. For SVR, Baseline naïvety response by ALT reductions and normalization, and baseline response by late-life mutagenesis

Historical IL-28 B data predicts response to IFN therapy

GI-5005-02 study published by Li et al. 2009 genome wide response analysis revealed that genetic variation at a single locus (rs12979860 located 3kb upstream of the IL-28B gene) was associated with virologic response to IFN therapy. These differences were described. The discovery of the IL-28B gene and its variants in acute clearance of HCV strongly suggests that it is a marker of the immune capacity of the patient, and influences responses to interferon therapy based on the amino acid differences in the B genotype.

• The immune based mechanism of GI-5005 may offer unique treatment advantages in B defined populations.

Discussion
 The discovery of the IL-28 B gene variants (Li et al 2009) and their predictive value for spontaneous clearance of HCV (Thomas et al 2006) and responses to pegylated interferon therapy (Li et al 2009) are supporting evidence for the development of the molecule (HCV). The discovery of genetic variation in acute clearance of HCV strongly suggests that it is a marker of the immune capacity of the patient, and influences responses to interferon therapy based on the amino acid differences in the B genotype. The benefit of GI-5005 triple therapy over SOC alone was noted for the different IL-28 B genotype related to the timing and magnitude of viral clearance and SVR. GI-5005 triple therapy improved end of treatment viral load in all IL-28 B genotypes (C/C: 89% vs 56%; C/T: 49% vs 20%; T/T: 16% vs 0%) and improved SVR in the C/C (96% vs 78%) and T/T groups (16% vs 0%). The pattern of response in the C/T group supports an important role for response guided therapy due to the fact that an advantage of 15% in response was observed at end of treatment but not at 6 months post-treatment. The majority of GI-5005 treated C/T patients who relapsed in the post-treatment period showed GI-5005 virus activity after 12 weeks of treatment, therefore they would benefit from a prolonged duration of treatment. The greatest sustained treatment effect for GI-5005 was observed in the T/T group with an advantage in end of treatment viral load reduction of 89% and an advantage in SVR of 36%. This may reflect an immune deficiency inherent in the T/T group, and suggests that GI-5005 can stimulate HCV specific immunity in a manner that compensates for this defect.

Conclusions
• GI-5005 has the potential to lead to the IL-28B locus predict spontaneous clearance of HCV as well as response to pegIFN/ribavirin.

• GI-5005 improved end of treatment (ETR) responses in all IL-28 B genotypes, with the greatest effect in T/T subjects (69% vs 25%).

• GI-5005 improved SVR in C/C and T/T patients, with the greatest effect in T/T subjects (48% vs 1%).

• IL-28B screening will be a critical baseline demographic to consider in future trial design.

• The immune based mechanism of GI-5005 may offer unique treatment advantages in different IL-28 B genotypes, with the greatest impact observed in the T/T responding population.

• These data support further study of GI-5005 in combination with pegIFN/ribavirin as well as direct acting antivirals in IL-28 B defined populations.

IL-28 B genotype is well balanced in GI-5005-02

GI-5005-02 demographics

EtR/ SVR by IL-28 B genotype (IFN-naïve)
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 vector. The heat-inactivated yeast, Saccharomyces cerevisiae, is administered as a vaccine for disease eradication. Virally-infected cells or proteins over-expressed in cancer. To create a new Tarmogen, DNA encoding target protein antigens is engineered into a yeast vector. The heat-inactivated yeast, Saccharomyces cerevisiae, is administered as a vaccine for disease eradication.

**Active immunotherapy with yeast-based Tarmogens**


**Background and aims:** IL-2B genotypes (CC/CT/TT) predict sustained virologic response (SVR) to standard of care (SOC) PegIFN/ribavirin and spontaneous clearance of acute HCV. Since GL-5005 generates HCV-specific T-cell responses in spontaneous HCV clearance, we assessed the influence of IL-2B on end-of-treatment (ETR) and SVR responses to GL-5005 plus SOC in naive genotype-1 chronic HCV patients.

**Methods:** Patients were randomized 1:1:1, and stratified by prior treatment status. Arm i: Triple (n=50): GI-5005 monotherapy for 5 weekly doses (day 1 through week 4) followed 4 weeks later by 1 dose at week 8. Arm ii: GI-5005 plus SOC (n=46) 48 weeks SOC. The IL-2B locus was PCR amplified from patient genomic DNA by primers specific for IL-2B genotypes (CC,CT,TT) predict sustained virologic response (SVR) to standard of care (SOC) PegIFN/ribavirin and spontaneous clearance of acute HCV. Since GL-5005 generates HCV-specific T-cell responses in spontaneous HCV clearance, we assessed the influence of IL-2B on end-of-treatment (ETR) and SVR responses to GL-5005 plus SOC in naive genotype-1 chronic HCV patients.

**Results:** IL-2B genotypes were balanced in both arms. Results shown in Tables 1 and 2.

**Conclusions:** Pharmacogenomic analyses can provide valuable insights into therapeutic trial results. Triple therapy improved ETR regardless of IL-2B genotype; delivering more CC and CT BVs and more CC and CT slow responders. The effect of GL-5005 on SVR is greatest in patients with the poorest genotype (TT). IL-2B genotyping suggests that the GL-5005 therapeutic vaccine augments response in those with unfavorable IL-2B types.