

Introduction:

CTS-1027 is a potent inhibitor of select members of a class of proteases known as matrix metalloproteases or MMPs. MMPs may be upregulated in chronic HCV and may interfere with the host immune response and facilitate viral spread. MMPs cleave and modulate the activity of numerous chemokines that are important to the host immune response.

We previously reported that CTS-1027, administered as a monotherapy, was safe and well tolerated in chronic HCV patients who had failed prior therapy¹. A subset of patients in this study demonstrated transient elevations in aminotransferases that were followed by declines in HCV-RNA. This observation suggested that CTS-1027 may facilitate innate efforts at viral clearance. We also reported that CTS-1027 in combination with ribavirin was safe and well tolerated in HCV treatment naïve patients for whom interferon-based therapy was deemed inappropriate². A similar profile of aminotransferase elevations accompanied by reductions in HCV-RNA was also observed in this study.

Null-responder patients, defined as failing to achieve at least a 2 log decline in HCV-RNA by week 12 following a standard course of pegylated interferon and ribavirin (SOC), are the most difficult to treat patient population. These patients are unable to launch an effective immune response to the HCV virus and are particularly unresponsive to the antiviral actions of interferon. Therefore, effective treatment of these patients represents an area of high unmet medical need. As CTS-1027 may facilitate the host immune response and potentially lower the barrier of resistance to interferon, it may offer a unique benefit to the null-responder patient as well as the broader HCV population.

Study Objectives:

The objectives of the study are:

- To assess the safety and tolerability of CTS-1027 in combination with pegylated interferon + ribavirin (SOC) in genotype 1 HCV patients who were null-responders to previous SOC therapy
- To assess the effects of SOC in combination with CTS-1027 on HCV-RNA levels

Methodology:

This is an open-label, single-arm, multicenter study utilizing SOC in combination with CTS-1027. All patients receive peginterferon alpha-2a and ribavirin (SOC), plus 15mg *bid* CTS-1027. Patients with ≥ 2 log decrease in HCV-RNA after 24 weeks of treatment will continue for an additional 24 weeks for a total of 48 weeks of treatment. Patients with < 2 log reduction in HCV-RNA at week 24 will stop treatment and enter the follow-up period of the study. The study schema is presented in Figure 1.

Major entry criteria were:

- HCV genotype 1 infected null-responder to prior therapy comprised of pegylated interferon and ribavirin defined as:
 - Failure to achieve a ≥ 2 log decline in HCV-RNA by week 12 or if week 12 was not obtained but week 24 was obtained, week 24 must be < 2 log decline
- The patient was compliant in prior SOC therapy as defined by the 80%/80%/80% rule: 80% of the doses, 80% of the dose size for at least 80% of the dose duration

Major exclusion criteria were:

- < 2 log decline in HCV RNA at week 12 but > 2 log decline at any time from week 12 to week 24 during prior therapy with pegylated interferon and ribavirin
- Decompensated or severe liver disease, including cirrhosis
- HCC
- Coinfection with HIV or HBV
- Prior triple treatment comprised pegylated interferon, ribavirin and protease or polymerase inhibitor

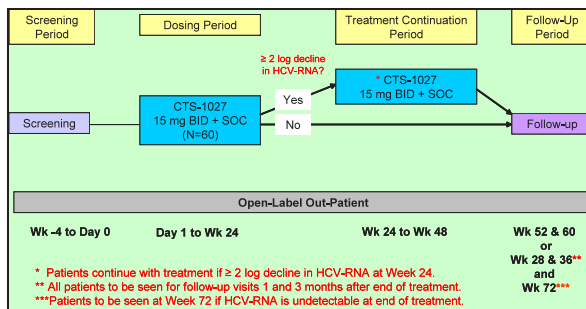


Figure 1: Study Schema

Results:

93 HCV genotype 1 patients were screened and 67 patients were randomized at 17 centers in the US. Patient demographics are presented in Table 1. All patients entering the study were defined as prior null-responders based on strict clinical criteria. The allelic variation at IL-28B was determined at week 24 or at the early termination visit. Data were collected on 61 patients, (91.0%, ITT). 58 patients carried either TT or CT alleles whereas 3 patients (4.5%) possessed a CC allele. These results are consistent with the IL-28B allelic distribution found in the null-responder patient population.

Table 1: Patient Demographics and Baseline Characteristics (ITT, N=67)

		Genotype 1 Null Responders CTS-1027+SOC (N = 67)	
Male	N (%)	49 (73.1)	
Female	N (%)	18 (26.9)	
Age (years)	Median	53	
	Range	25 - 67	
White	N (%)	35 (52.2)	
Black / African American	N (%)	13 (19.4)	
Hispanic/Latino	N (%)	18 (26.9)	
Pacific Islander	N (%)	1 (1.5)	
HCV-RNA	Mean	6.26	
(Log value)	Range	4.39-7.13	
IL-28B allelic distribution	TT N(%)	17 (25.4)	
	CT N(%)	41 (61.2)	
	CC N(%)	3 (4.5)	
	NA N(%)	6 (8.9)	
Weight (Kg)	Mean	83.2	
	SD	21.4	
BMI (kg/m ²)	Mean	29.9	
	SD	7.06	

BMI = body mass index, ITT = intention-to-treat analysis set, Kg = kilogram, N = number of patients, SD = standard deviation, NA = not available

The overall mean reduction in HCV-RNA over time to week 24 is presented in Figure 2. A steady decline in mean HCV-RNA was observed in the population with a slope of reduction of -0.14 log/week. The mean log reduction in HCV-RNA at week 12 and 24 was 2.1 and 3.3, respectively. The slow, apparently monophasic decline in viral load is consistent with primarily immune clearance of infected hepatocytes coupled with decreased frequency of new infections and not involving significant direct inhibition of viral replication.

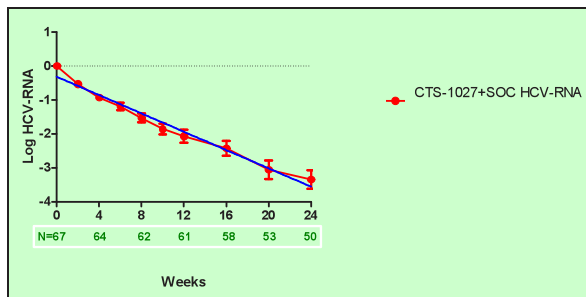


Figure 2: Mean Change over Time in HCV-RNA

The individual patient responses to treatment over time to week 24 are shown in Figure 3. By week 4 patients began achieving HCV-RNA levels below the quantification limit (BQL) of the assay (43 IU/mL, Roche Cobas Ampliprep/TaqMan™).

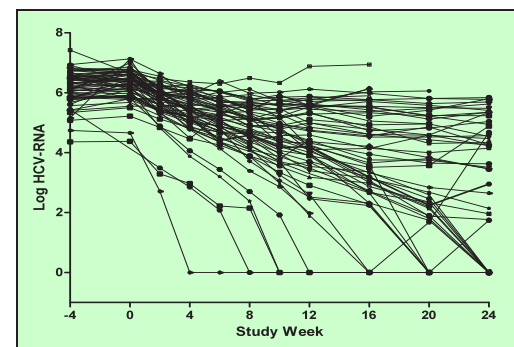


Figure 3: Individual Patient Reductions in HCV-RNA over Time

The categorical reduction HCV-RNA over time is shown in Table 2. At week 12, 31 patients (50.8%) experienced a ≥ 2 log decline in HCV-RNA. Of these patients, 5 were BQL; which represents 8.2% of the 61 patients at week 12. At week 24, 31 patients had a ≥ 2 log decline in HCV-RNA. Of these patients 17 were BQL; which represents 34% of the 50 patients at week 24.

Table 2: Absolute Number and Percentage of Patients and Log Decline in HCV-RNA over Time

Study Wk	N	Log HCV-RNA Decline			
		< 1	≥ 1 to < 2	≥ 2	BQL*
4	64	43 (67.2%)	16 (25.0%)	5 (7.8%)	1 (1.6%)
12	61	17 (27.9%)	13 (21.3%)	31 (50.8%)	5 (8.2%)
16	58	14 (24.1%)	13 (22.4%)	31 (53.4%)	7 (12.1%)
20	53	10 (18.9%)	11 (20.8%)	32 (60.4%)	11 (20.8%)
24	50	9 (18.0%)	10 (20.0%)	31 (62.0%)	17 (34.0%)

* BQL = 43 IU/mL, Roche Cobas Ampliprep/TaqMan™

IL-28B allelic analysis is available for 48 of the 50 patients who completed study week 24. Figure 4 shows the response to treatment within the three allelic populations. 11 of 12 (92%) of patients with TT allele exhibited a ≥ 2 log reduction in HCV-RNA and 5 of 12 (42%) of patients with TT allele were BQL at week 24. 19 of 33 (57%) of patients with CT allele exhibited a ≥ 2 log reduction in HCV-RNA and 11 of 33 (33%) of patients with CT allele were BQL by week 24. Of the 3 patients possessing the CC allele, 2 met the stopping criteria, having not achieved a ≥ 2 log decline in HCV-RNA at week 24, while HCV-RNA of 1 patient was BQL at week 24.

Interestingly, the 24 week response rate in this study was higher in patients possessing the TT allele. In addition, there were better responses in African American patients compared to Caucasians and in patients presenting with lower ALT levels at baseline. Taken together, these data suggest a pattern of improved response in patients most refractory to interferon-based therapy. These preliminary observations may suggest that CTS-1027 could potentially improve patients' responsiveness to interferon-based therapies.

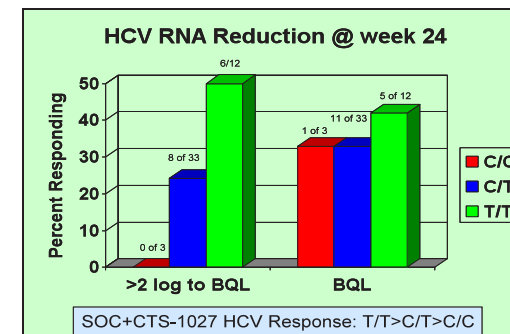


Figure 4: IL-28B Genotype and HCV-RNA Response at Week 24

CTS-1027 added to peginterferon alpha-2a and ribavirin (SOC) appears safe and has been well tolerated in this on going study. The addition of CTS-1027 does not appear to increase the side effect profile normally observed with SOC therapy in HCV patients.

Summary:

- CTS-1027 added to SOC appears to be well tolerated.
- A significant percentage (62%) of clinically defined prior null-responder patients achieved a ≥ 2 log decline in HCV-RNA at week 24.
- A significant percentage (34%) of patients were BQL at week 24
- The IL-28B allelic distribution of the patients in this study is consistent with expectation in the null-responder population.
- Patients with multiple risk factors associated with poor immune response to HCV, including possessing a TT allele, appear to be most responsive in this study.
- Addition of CTS-1027 to SOC resulted in a slow, constant reduction in HCV-RNA.

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References:

- Pockros PJ, Gordon SC, McCullough A, et al. Randomized, Placebo-Controlled, Double-Blind, Dose Response (RPCDBDR) Trial of CTS-1027, an Inhibitor of Matrix Metalloproteases (MMPs) in Patients with HCV who had Failed Prior Therapies. EASL: Abstract 1586, 2010.
- Chojkier M, Everson G, Muir A, et al. 24-Week Treatment with CTS-1027 in Combination with Ribavirin Reduces HCV-RNA in Treatment Naïve Genotype-1 Patients. EASL: Abstract 562, 2011.