

Introduction:

CTS-1027 is a hydroxamate sulfone designed to selectively inhibit the activity of key members of a class of proteases, the matrix metalloproteases or MMPs.

In the liver and in other solid organs, MMPs play an important role in regulating inflammation as well as in maintaining the integrity of the extracellular matrix. Excessive MMP activity has been demonstrated to occur in the liver in response to HCV infection.

MMPs are an attractive mechanism to target in the setting of HCV as:

- MMPs are directly involved in the inflammatory processes that perpetuate liver damage and fibrosis as a consequence of chronic HCV infection.
- MMP expression is up-regulated by HCV and therefore likely provides a survival advantage to the virus. This advantage could be through:
 - Degradation and inactivation of IFN, thereby facilitating or enabling a pro-viral state.
 - Facilitating viral spread to uninfected cells.
 - Prolonging lifespan of infected cells by blocking chemotaxis of and immune clearance by HCV specific CTLs.
- MMP inhibition may assist to reestablish an effective immune response in patients.

Study Objectives:

The objectives of the study were to assess the safety and efficacy of CTS-1027 administered orally in patients with chronic hepatitis C virus infection and its effects on aminotransferases.

Methodology:

This was a randomized, placebo-controlled, double-blind, parallel group, multicenter, dose response study of CTS-1027, administered orally once daily (qd), in outpatients with HCV infection. Patients were screened and had up to four weeks (Baseline period) to qualify for study entry. Eligible patients were randomized to one of four doses of CTS-1027 (2.5 mg, 5 mg, 10 mg or 30 mg) or placebo qd.

The study blind was broken after four weeks of treatment and all patients were given the option of receiving open-label treatment with CTS-1027 for eight weeks (open-label phase) at the same dose as the double-blind (placebo patients were assigned 10 mg qd). The protocol was amended to allow patients to receive an additional open-label treatment with CTS-1027 for a further 12 weeks (open-label extension phase) to explore further dosing regimens (10 mg bid, 10 mg tid, and 15 mg bid).

Patients were assessed every two weeks during the double-blind phase (Week 2, Week 4) and open-label phases (Weeks 6, 8, 10, and 12), and every four weeks during the open-label extension phase (Weeks 16, 20, and 24). At the end of treatment, patients were observed for a further four weeks.

Major entry criteria were:

- A history of chronic HCV infection
- Unsuccessful HCV treatment defined as one or more of the following criteria:
 - Failure to achieve a virologic response during previous therapy
 - Failure to tolerate therapy
 - Failure to maintain a sustained virologic response
 - Unsuitable candidate for interferon based therapy
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels 1.5 - 7 x ULN on at least two occasions, seven or more days apart, during the Baseline period.

Major exclusion criteria were:

- Decompensated or severe liver disease, including cirrhosis

- HCC
- Coinfection with HIV or HBV.

Evaluation was based on a series of laboratory and diagnostic tests and physical examinations for safety and efficacy. Adverse events (AE) were recorded and the medication was collected for assessment of compliance.

The serum markers CK18/M30, neopterin, and TIMP-1 were collected and analyzed in the study. The Enhanced Liver Fibrosis (ELF™ - a registered trademark of Siemens Healthcare Diagnostics) test*, which is comprised of a score based on the markers hyaluronic acid, procollagen III aminoterminal peptide (PIIINP) and TIMP-1, was utilized as a marker of liver fibrosis. MMP-2 mass and MMP-9 mass and activity were also analyzed in the study.

*The Immunot1 ELF Test is CE marked.

Results:

164 patients were screened and 87 patients were randomized at 19 centers in the US. Patient demographics and HCV genotype are presented in Tables 1 and 2.

Table 1: Patient Demographics

	N (%)	Treatment group					total (N = 87)
		placebo (N = 20)	2.5 mg qd (N = 21)	5 mg qd (N = 14)	10 mg qd (N = 16)	30 mg qd (N = 16)	
Male	13 (65.0)	13 (61.9)	8 (57.1)	13 (81.3)	10 (62.5)	57 (65.5)	
Female	7 (35.0)	8 (38.1)	6 (42.9)	3 (18.8)	6 (37.5)	30 (34.5)	
Age (years)	Median 52	53	54	55	54	54	
Range	34-60	44-72	43-67	42-65	44-62	34-72	
White	14 (70.0)	18 (85.7)	11 (78.6)	8 (50.0)	11 (68.8)	62 (71.3)	
Black / African American	4 (20.0)	2 (9.5)	3 (21.4)	7 (43.8)	3 (18.8)	19 (21.8)	
Hispanic / Latino	2 (10.0)	1 (4.8)	-	1 (6.3)	2 (12.5)	6 (6.9)	
Weight (lb)	Mean 196	189	207	213	181	196	
STD	37	53	53	41	34	45	
BMI (kg/m ²)	Mean 30	29	32	31	27	30	
STD	5	7	7.3	6	3	6	

BMI = body mass index, ITT = intention-to-treat analysis set, lb = pounds, N = number of patients, qd = once daily, STD = standard deviation.

Table 2: HCV Genotype

HCV genotype	N (%)	Number (%) of patients					total (N = 87)
		placebo (N = 20)	2.5 mg qd (N = 21)	5 mg qd (N = 14)	10 mg qd (N = 16)	30 mg qd (N = 16)	
1	79 (90.8)	16 (80.0)	18 (85.7)	11 (78.6)	13 (81.3)	11 (68.8)	79 (90.8)
1 other	4 (20.0)	1 (4.8)	-	-	1 (6.3)	1 (1.1)	4 (4.6)
1a	9 (45.0)	11 (52.4)	5 (35.7)	11 (68.8)	8 (50.0)	44 (50.6)	
1b	7 (35.0)	6 (28.6)	6 (42.9)	4 (25.0)	5 (31.3)	28 (32.2)	
2a	-	1 (4.8)	-	1 (6.3)	-	2 (2.3)	
2b	-	1 (4.8)	-	-	-	1 (1.1)	
3a	-	1 (4.8)	2 (14.3)	-	1 (6.3)	4 (4.6)	
3d	-	-	1 (7.1)	-	-	1 (1.1)	

The most common HCV genotype was genotype 1, detected in 79 out of 87 (90.8%) patients. Eight patients (9.2%) were infected with genotypes 2 or 3. Half of all patients (44 out of 87, 50.6%) were infected with the sub-genotype 1a, and 28 (32.2%) patients were known to be infected with sub-genotype 1b.

All but two patients had received prior therapy for HCV. Of the 85 patients who had previous therapy, 84 of these patients had been treated with both antiviral therapy (ribavirin and other analogues) and immunotherapy (various interferons). The two patients who had no prior therapy were randomized to the placebo group.

The relative % changes in ALT in each study phase are provided in Tables 3 to 5.

Table 3: Relative % Change in ALT from Pretreatment in Double-Blind Phase

Visit	N	ALT % change			
		placebo	2.5 mg qd	5 mg qd	10 mg qd
Week 2	18	21	14	16	16
median	-4.3	-7.6	-20.1	-5.4	-5.4
range	-50 - 52	-41 - 38	-79 - 11	-35 - 43	-23 - 30
mean	-4.1	-18.9	-1.5	-1.0	-1.0
SD	23.6	18.3	22.3	21.6	17.9
Week 4	21	21	14	16	16
median	-9.8	-1.0	-11.7	0.9	-4.2
range	-62 - 42	-53 - 48	-36 - 1	-31 - 68	-20 - 42
mean	-6.9	1.2	-14.7	6.6	1.1
SD	28.0	24.6	19.9	25.5	19.3

Pretreatment value was mean of Screening, Baseline 1, 2, 3, and Week 0 (Day 1). ALT = alanine aminotransferase, N = number of patients, qd = once daily, SD = standard deviation. Kruskal-Wallis test for overall difference between treatment groups, Week 2 p = 0.2245, Week 4 p = 0.0497.

Table 4: Relative % Change in ALT from Pretreatment in Open-Label Phase

Visit	N	ALT % change				
		2.5 mg qd	5 mg qd	10 mg qd	15 mg bid	30 mg qd
Week 6	7	7	14	45	6	79
median	-4.3	-18.3	-8.9	-12.1	-9.5	-13.4
range	-37 - 38	-48 - 6	-43 - 71	-57 - 42	-28 - 17	-57 - 71
mean	2.7	-19.3	-6.1	-8.4	-9.2	-8.0
SD	29.6	13.4	30.8	21.1	17.1	23.0
Week 8	7	6	14	45	5	77
median	-16.5	-19.6	-8.8	-5.0	-2.6	-8.3
range	-53 - 49	-35 - 10	-47 - 73	-50 - 173	-20 - 16	-53 - 173
mean	1.2	-19.9	-7.0	-3.2	-2.2	-4.7
SD	43.1	8.5	31.3	34.2	15.1	32.1
Week 10	6	6	13	42	5	72
median	6.0	-21.6	-14.5	-10.5	-3.8	-11.4
range	-26 - 37	-32 - 1	-38 - 128	-56 - 106	-19 - 17	-56 - 128
mean	5.4	-19.1	1.5	-6.2	1.6	-4.4
SD	32.0	11.3	45.3	27.4	14.0	30.2
Week 12	6	5	13	39	5	68
median	8.1	-13.0	-0.3	-12.6	-9.3	-10.9
range	-26 - 54	-20 - 20	-38 - 134	-62 - 42	-29 - 18	-62 - 134
mean	13.3	-8.4	6.7	-12.4	-6.6	-5.8
SD	33.4	16.2	46.1	20.0	19.1	28.6

Pretreatment value was mean of Screening, Baseline 1, 2, 3, and Week 0 (Day 1). ALT = alanine aminotransferase, bid = twice daily, N = number of patients, qd = once daily, SD = standard deviation. Kruskal-Wallis test for overall difference between treatment groups, Week 6 p = 0.6706, Week 8 p = 0.6239, Week 10 p = 0.4095, Week 12 p = 0.4208.

Table 5: Relative % Change in ALT from Pretreatment in Open-Label Extension Phase

Visit	N	ALT % change		
		10 mg bid	10 mg tid	15 mg bid
Week 16	7	7	36	50
median	-7.9	21.1	-9.8	-8.2
range	-33 - 45	-28 - 122	-55 - 49	-55 - 122
mean	-4.8	22.1	-10.4	-5.1
SD	25.9	49.5	23.6	30.1
Week 20	6	6	33	45
median	-14.2	28.4	-14.6	-12.7
range	-34 - 583	-22 - 121	-42 - 42	-42 - 583
mean	101.3	34.5	-11.7	9.5
SD	242.6	48.3	22.8	94.4
Week 24	6	5	33	44
median	-9.6	10.1	-9.4	-9.0
range	-14 - 255	-42 - 148	-49 - 66	-49 - 255
mean	39.1	-5.6	-4.1	4.1
SD	196.2	79.2	27.7	51.9

Pretreatment value was mean of Screening, Baseline 1, 2, 3, and Week 0 (Day 1). ALT = alanine aminotransferase, bid = twice daily, N = number of patients, qd = once daily, tid = thrice daily. Kruskal-Wallis test for overall difference between treatment groups, Week 16 p = 0.1483, Week 20 p = 0.0388, Week 24 p = 0.4204.

The CK18/M30 values generally increased from pretreatment in all treatment groups without any dose-dependent effect in any of the study phases. There was very little difference in neopterin values from pretreatment values at Week 4, with no difference between the treatment groups. Neopterin levels were not measured in all patients, and therefore at Week 12 and Week 24, no comparison can be made between the treatment groups.

There was no overall significant change in the ELF marker or TIMP-1 over time compared to the pretreatment value, and no difference was observed between the different treatment groups.

There was no dose dependent change in MMP-2 mass over time. An overall difference was observed between the treatment groups for the change from pretreatment to Week 24 (p = 0.0317), with a significant difference between the 10 mg bid and 15 mg bid treatment groups (p = 0.0275).

MMP-9 mass and MMP-9 activity slightly increased or decreased with no consistent trend across dose groups or visits. The greatest reductions were seen in the 10 mg tid dose at Week 24 with a significant overall difference between the 10 mg bid treatment group and the other groups for MMP-9 activity (p = 0.0295).

There was no clear linear dose-dependency on the frequency or nature of AEs, related AEs, or intolerable AEs (leading to premature study withdrawal of patients).

In the double-blind phase, the highest frequency of AEs was observed in the 10 mg and 30 mg groups followed by placebo. For related AEs, the highest frequency was seen in the 10 mg group, followed by the 30 mg and 2.5 mg groups.

The most frequently reported AEs were associated with musculoskeletal and connective tissue disorders, which was expected. The proportion of

CTS-1027-treated patients reporting such events varied between 14.3% and 52.2% across all study phases.

Two patients (4009 and 4040) evidenced a transient elevation in aminotransferase levels, followed by a transient fall in HCV-RNA. A third patient evidenced less clear-cut changes with a similar pattern (4041; see Figure 1). While these observations are anecdotal, they could indicate that CTS-1027 is playing a role in overcoming immune tolerance. Sentinel aminotransferase elevations have been reported in acutely infected HCV human patients who clear the virus spontaneously¹. It is also a phenomenon seen preceding viral clearance in human hepatitis B infection.

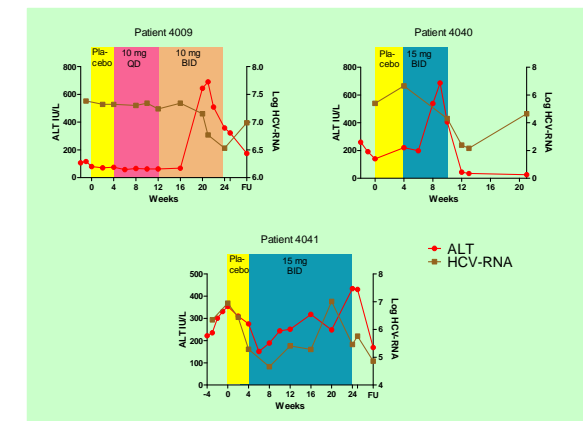


Figure 1: Pattern of ALT Flares and Reductions

Summary:

Overall, the three phases of the CTS-1027-01 study have demonstrated that:

- CTS-1027 was well tolerated in the HCV patient population.
- No clear dose-dependent changes in aminotransferases occurred.
- No significant changes in inflammation or liver fibrosis markers occurred.
- No significant safety issues were identified.
- No dose-dependent changes in HCV-RNA were seen.
- A total of six patients normalized ALT levels at least once.
- A total of 23 patients normalized AST levels at least once.
- 30 mg/day cumulative dose, given as 15 mg bid, appeared to be the maximum tolerated dose for chronic administration in HCV patients.
- Two patients experienced aminotransferase elevations followed by transient declines in HCV-RNA. These events may reflect innate efforts at viral clearance.

Institutions:

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11. FGK Clinical Research GmbH, Munich, Germany
12. Siemens Diagnostics, Tarrytown, NY, USA
13. iQur Ltd, London, UK
14. McGuire Veterans Administration Medical Center, Richmond, VA, USA

Reference:

1. Hoofnagle JH. Course and Outcome of Hepatitis C. Hepatology. 2002; 36: S21-S29.