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**TITLE:** CTS-1027, a potent MMP inhibitor, Protects Against TNF $\alpha$ - and  $\alpha$ -Fas-Induced liver Injury

**AUTHORS (LAST NAME, FIRST NAME):** Contreras, Patricia C.<sup>1</sup>; Valentino, Karen<sup>1</sup>

**INSTITUTIONS (ALL):** 1. Conatus Pharmaceutical, San Diego, CA, USA.

**ABSTRACT BODY: Background:** CTS-1027 is an orally bioavailable small molecule that is a potent inhibitor of MMP-2, 3, 8, 9, 12, 13 and 14, but not MMP-1. In the liver, in response to a variety of insults, excessive MMP activity may play a role in destruction of the extracellular matrix, and recruitment of inflammatory cells. CTS-1027 was previously evaluated in an extensive phase 2 clinical trial in which a well tolerated chronically administered dose was identified. Thus, it was of interest to evaluate a MMP inhibitor whose safety profile was known in models of acute liver injury in mice.

**Methods:** CTS-1027 (0.001-30 mg/kg) was administered PO to male mice (C57Bl/6), 30 minutes prior to treatment with TNF $\alpha$ /D-Galactosamine (D-Gln) or the Fas activating antibody ( $\alpha$ -Fas). Six hours later, animals were anesthetized with Nembutal and blood taken by cardiac puncture. Plasma ALT activity was determined using a commercially available kit. For survival studies, mice were observed up to 24 hours post-insult. Pharmacokinetic analysis of CTS-1027 was conducted in treatment-naive mice to determine plasma and liver levels.

**Results:** CTS-1027 dose-dependently decreased plasma ALT activity in the TNF $\alpha$  model. The average ED50 from 4 studies was  $0.26 \pm 0.08$  mg/kg. Twenty-four hour survival was also increased by CTS-1027 (10 mg/kg). The average 24 hour survival from 3 studies was  $27 \pm 7.3\%$  and  $55 \pm 7.6\%$  ( $p=0.03$ ) in the TNF $\alpha$ /D-Gln control mice and CTS-1027-treated mice, respectively. CTS-1027 (10 mg/kg; PO) was also protective against  $\alpha$ -Fas, significantly ( $p<0.05$ ) reducing the elevation in plasma ALT activity in 2 independent studies by an average of 49%. In a separate group of mice, PK analysis of CTS-1027 in plasma vs. liver indicated that CTS-1027 was rapidly absorbed with T<sub>max</sub> of 0.25-0.5 hour in liver and plasma. AUCs increased in a dose-dependent manner and were 1.7-fold greater in liver than plasma. The AUC in plasma at the ED50 dose in the TNF $\alpha$ /D-Gln model ( $\sim 0.3$  mg/kg) was 13-fold lower than the AUC at a dose previously determined to be well tolerated in man.

**Conclusions:** CTS-1027 potently antagonized the liver toxicity induced by treatment with TNF $\alpha$ /D-Gln or  $\alpha$ -Fas as indicated by reductions in plasma ALT and/or lethality/morbidity at doses lower than the well tolerated dose in man. CTS-1027 is an attractive candidate for further development and is expected to enter clinical trials in patients with liver disease by the end of 2007.