Pharmacokinetics of CTS-1027, a Novel Matrix Metalloproteinase (MMP) Inhibitor, and Its Main Metabolites Following Once and Twice Daily Oral Dosing of CTS-1027 in Healthy Volunteers

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ABSTRACT

Objective: To compare the pharmacokinetics of CTS-1027 and its metabolites, CTS-1027-2 and CTS-1027-6, during QD and BID oral dosing in healthy volunteers.

Introduction: Excessive matrix metalloproteinase (MMP) activity has been implicated in the pathogenesis of acute and chronic liver injury including hepatitis C virus (HCV) (Ellington et al., 2005; Roderfeld et al., 2007). Liver disease and HCV represent major worldwide health problems.

Materials & Methods

Study: A healthy volunteer, open-label, multiple-dose, ascending frequency, tolerability and pharmacokinetic study of oral CTS-1027 administered once and twice daily.

Dose: Eight subjects received CTS-1027 as QD oral 30 mg dose on Days 1 and 2, 1.5 mg BID on Days 3 and 4, and a 15 mg dose on the morning of Day 5. Plasma samples were analyzed for CTS-1027 and its metabolites using a validated HPLC-MS/MS assay and the PK was determined by standard model-independent methods based on the plasma concentration-time data of each subject using WinNonlin Professional 4.1 (Pharsight Corp., Mountain View, CA).

Results & Discussion: Pharmacokinetic parameters for CTS-1027 and its metabolites for QD and BID oral dosing at Days 1 and 2 were determined for each subject. The metabolites have apparently reached the steady state on Day 5. The dose-normalized Cmax and AUC values were equal for all dosing.

Conclusion: Both metabolites were rapidly produced in plasma and their Cmax and AUC increased over study days with the highest exposure observed on Day 5. Exposures for CTS-1027-6 was ~4x CTS-1027-2. Both metabolite concentrations were apparently reaching steady state on Day 5.

RESULTS & DISCUSSION

CTS-1027

For both QD and BID dosing, CTS-1027 was absorbed rapidly (median Tmax = 1.5 h) and had similar Cmax and AUC0-12 on Days 1 and 2 (0 mg) and on Days 3 and 5 (15 mg).

The dose-normalized Cmax and AUC0-12 were equal for all days.

CTS-1027 was apparently approaching a steady state on study Day 2 and exhibited no accumulation following repeated dosing.

CTS-1027-2 and CTS-1027-6 were rapidly produced in plasma and their Cmax and AUC increased over study days with the highest exposure observed on Day 5. Cmax values for CTS-1027-2 and CTS-1027-6 ranged from 7.03% to 21.2% and 12.0% to 106% of the parent compound values, respectively. AUC0-12 ranged from 11.8% to 61.1% and 10.8% to 217%, respectively. Exposure of CTS-1027-6 was ~4x CTS-1027-2.

Both metabolite concentrations were apparently reaching steady state on Day 5.

Mean PK Parameters of CTS-1027 and its Metabolites in Human Subjects Following QD and BID Oral Administration of CTS-1027

CONCLUSION

CTS-1027 and its metabolites CTS-1027-2 and CTS-1027-6 exhibited favorable PK in humans.

CTS-1027 was absorbed rapidly; its PK for QD and BID dosing was comparable, but it did not accumulate due to repeated dosing and reached a steady-state within two days.

CTS-1027-2 and CTS-1027-6 were rapidly measurable in plasma with CTS-1027-6 ~4x CTS-1027-2 and both metabolites have apparently reached a steady-state at the end of study.

REFERENCES


