MK-3682, a HCV NS5B Inhibitor with a Broad Spectrum of HCV Genotypic Activity, Demonstrates Potent Antiviral Activity in Genotypes -1,-2, and -3 HCV-Infected Patients

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17th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy
June 10, 2016
Washington, DC

Disclosures and Acknowledgments

- [1]These authors are employees of Merck
- Disclosures: CS – advisory boards/speakers bureau for Abbvie, Gilead Sciences, and MSD; JSB – current employee of Contravir
- The design, study conduct, analysis, and financial support of the trial were provided by Merck.
- We extend our gratitude to SGS Life Sciences, and the patients, investigators, and site personnel who participated in this study.

Background

- MK-3682 is a potent pan-genotypic inhibitor of Hepatitis C Virus (HCV) non-structural protein 5B (NS5B) that is being developed for the treatment of HCV infection.
- MK-3682 is expected to exhibit a high barrier to resistance.
- MK-3682 has pharmacokinetics supportive of once-daily oral administration.
- Clinical studies are evaluating the pharmacokinetics of the parent prodrug (MK-3682) and its major circulating metabolite (M6) that may inform the efficacy and safety of MK-3682 in clinical development.

Objectives

- To evaluate the antiviral activity, pharmacokinetics, and safety of MK-3682 administered as 7 days of monotherapy in non-cirrhotic patients with genotype (GT) -1, -2, or -3, HCV infection.
- To evaluate the antiviral activity, pharmacokinetics, and safety of MK-3682 administered as 7 days of monotherapy in HCV GT1-infected patients with mild hepatic impairment (Child-Pugh A).

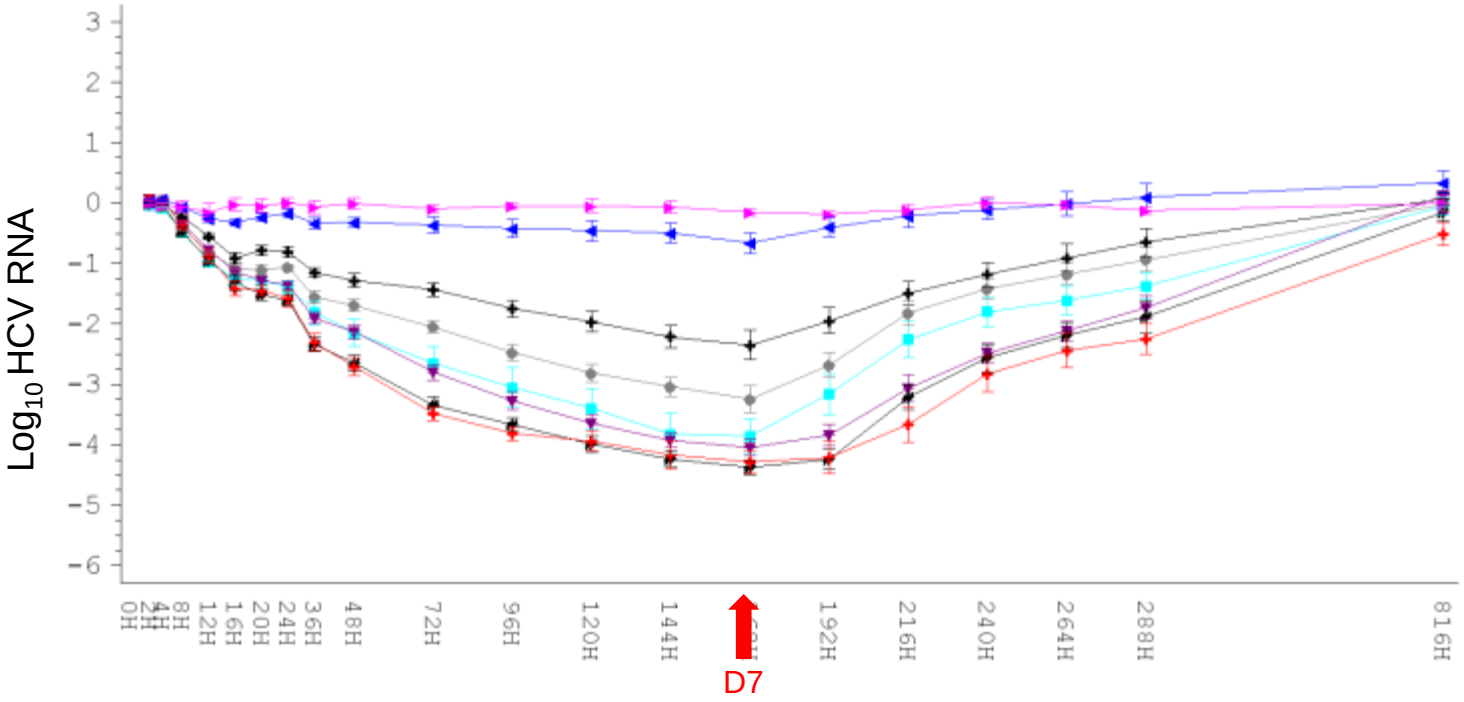
Methods

- Phase 1b, randomized, placebo-controlled study
- Eighty (80) adults, with HCV GT-1, -2, or -3 infection (HCV RNA ≥ 5.0 $\log_{10}$ IU/mL) without clinical evidence of cirrhosis, randomized to receive:
  - placebo or MK-3682 from 50 to 400 mg (GT1) (capsule)
  - open-label MK-3682 300 to 450 mg (GT1) (tablet) or 50 to 300 mg (GT2 or GT3) once daily for 7 days (capsule)
- Pharmacokinetic (PK) sampling for 12 days
- Viral load sampling for 35 days
- Safety and tolerability were evaluated using laboratory values, ECGs, and evaluation of adverse events (AEs)

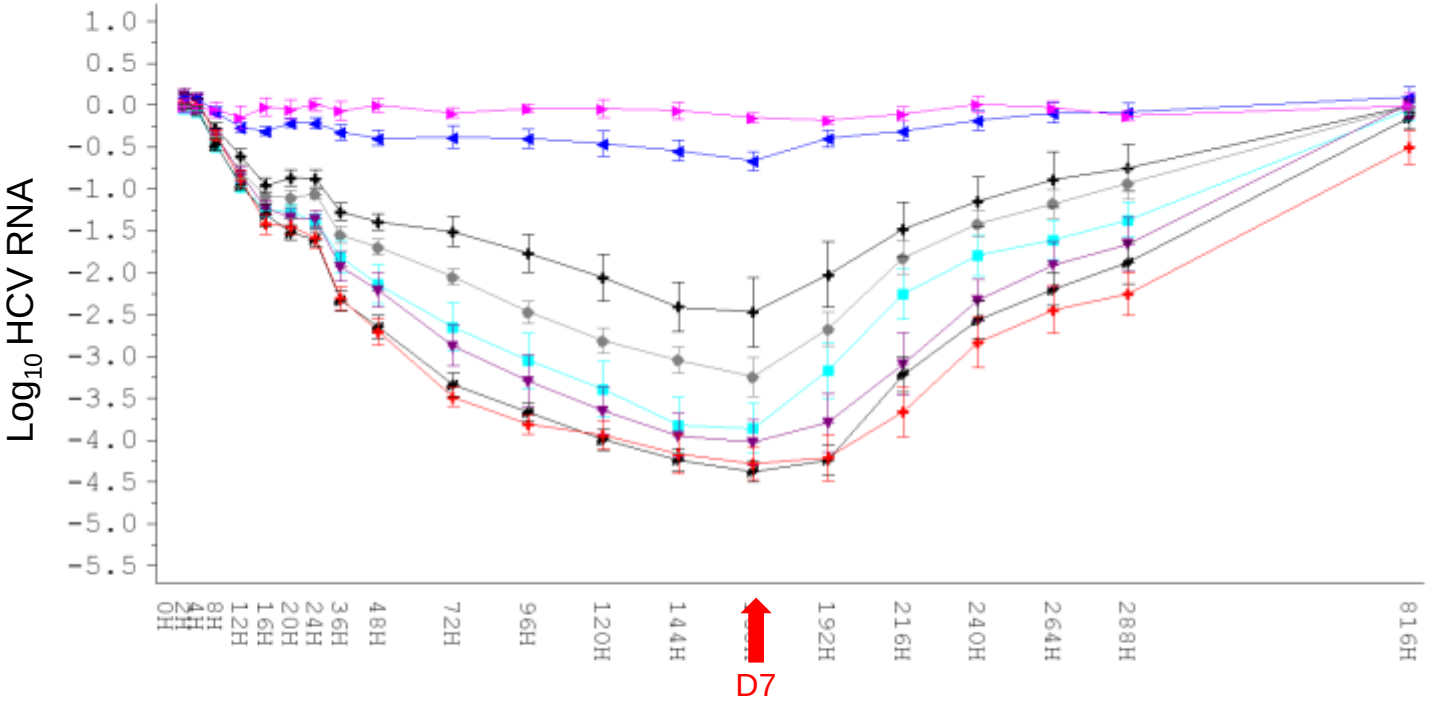
Methods

- Eleven (11) adults with HCV GT1 infection and mild hepatic impairment (Child-Pugh Score A) randomized to receive open-label MK-3682 300 or 450 mg once daily for 7 days
- Pharmacokinetic (PK) sampling for 12 days
- Viral load sampling for 35 days
- Safety and tolerability were evaluated using laboratory values, ECGs, and evaluation of adverse events (AEs)

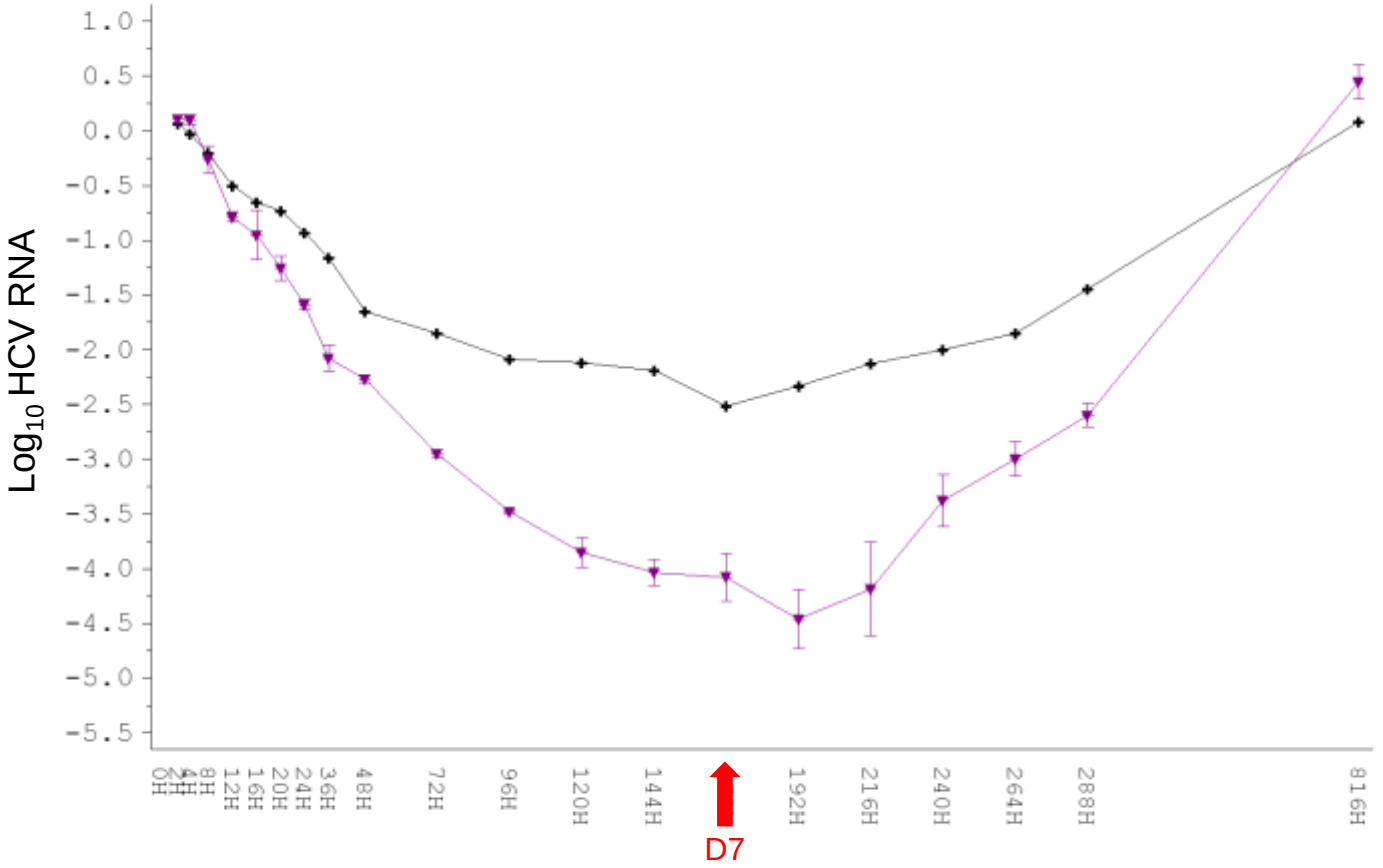
Change from baseline log_{10} HCV RNA over time after receiving multiple doses of MK-3682 or placebo for 7 days -- overall



Change from baseline log_{10} HCV RNA over time after receiving multiple doses of MK-3682 or placebo for 7 days – GT1



Change from baseline log_{10} HCV RNA over time after receiving multiple doses of MK-3682 for 7 days – GT2



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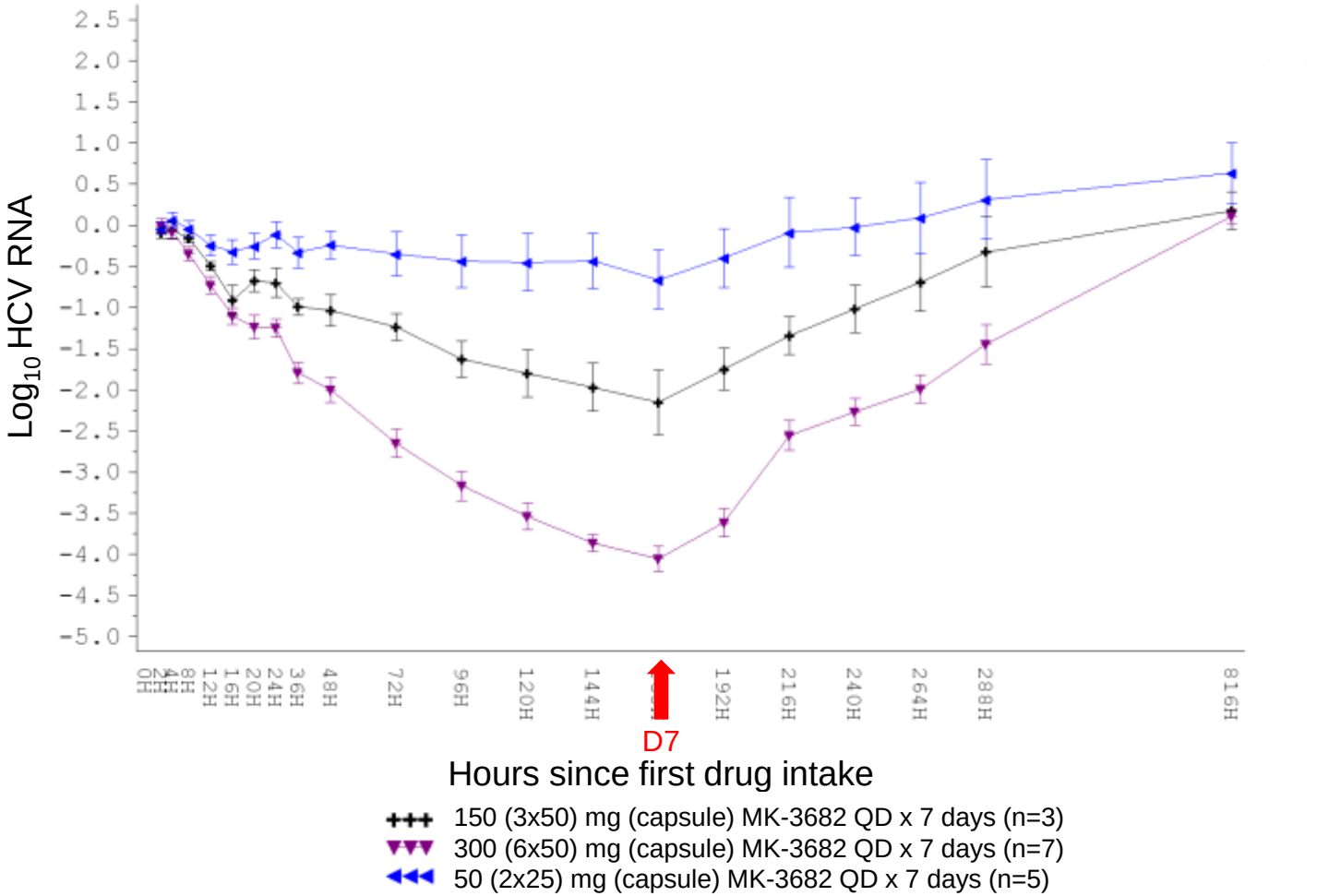
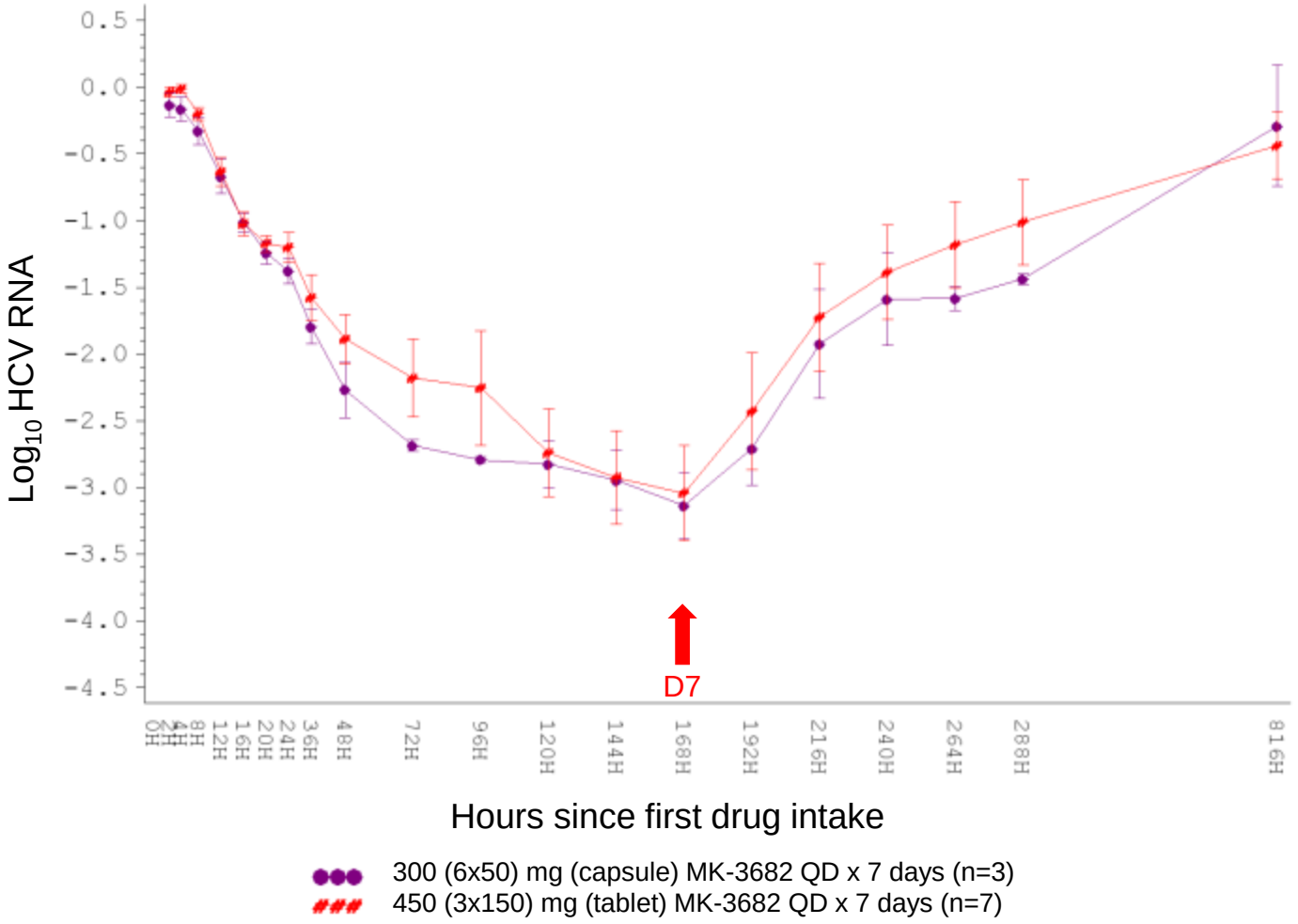
Be well

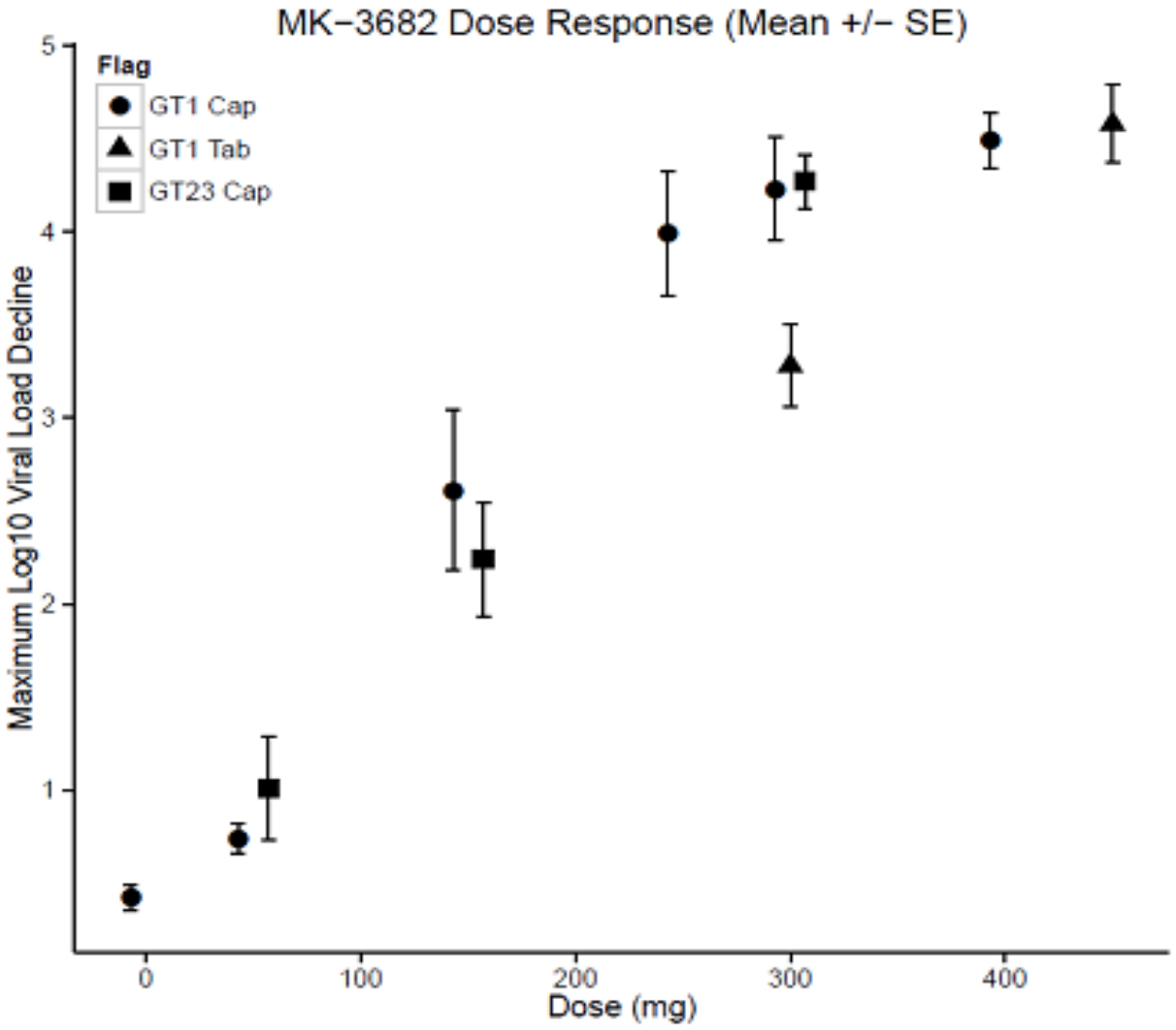
Change from baseline log_{10} HCV RNA over time after receiving multiple doses of MK-3682 for 7 days – GT3



Change from baseline log_{10} HCV RNA over time after receiving multiple doses of MK-3682 for 7 days – mild hepatic insufficiency, GT1



Dose-Response Relationship



Pharmacokinetics

- After QD administrations for 7 days in fasted state in HCV-infected patients, MK-3682 was rapidly absorbed (t_{max} <2h), with t_{max} for its major metabolite M6 <4h.
- $t_{1/2}$ for MK-3682 was <3h and $t_{1/2}$ for M6 were ~30h. Consistent with the $t_{1/2}$, MK-3682 exhibited no accumulation, and accumulation ratio for M6 was ~1.5 fold.
- MK-3682 PK were largely dose proportional while M6 PK were less than dose proportional.
- *tablet vs. capsule in HCV-infected patients:*
  - bioavailability of MK-3682 (both C_{max} and AUC) was lower with the tablet formulation, with C_{max} and AUC_{0-t} reduced by 60% and 34%.
  - M6 exposures were comparable between the tablet formulation and the reference capsule formulation.
  - The rate of absorption and the rate of elimination were similar.
- *Mild Hepatic impairment in HCV-infected patients:*
  - MK-3682 C_{max} and AUC_{0-t} increased by 29% and 22%, respectively
  - M6 steady-state C_{max} and AUC_{0-24h} were similar

Safety findings (1)

- MK-3682 was well-tolerated, with all AEs transient and mild in intensity
- In non-cirrhotic HCV-infected patients receiving multiple doses of MK-3682:
  - TEAEs occurred in 6 (67%) patients receiving placebo and 46 (65%) patients receiving MK-3682
  - headache was the most frequently observed TEAE
    - 3 patients (33%) receiving placebo, 2 patients (18%) receiving 50 mg capsules, 0 patients receiving 150 mg capsules, 4 patients (50%) receiving 250 mg capsules, 2 patients (11%) receiving 300 mg capsules, 4 patients (50%) receiving 400 mg capsules, 3 patients (38%) receiving 300 mg tablets, and no patients receiving 450 mg tablets

Safety findings (2)

- In HCV-infected patients with mild hepatic impairment receiving multiple doses of MK-3682, the most commonly reported TEAEs were headache (2 [18%] patients) and nasopharyngitis (2 [18%] patients)
- No clinically significant laboratory abnormalities or changes in vital signs or ECG readings in all groups

Conclusions

- MK-3682 exhibits potent antiviral activity during 7 days of monotherapy in non-cirrhotic patients with GT-1, -2, and GT-3 chronic HCV infection and in patients with mild hepatic impairment with GT-1 chronic HCV infection.
- Exposure-response analyses suggest that antiviral activity of MK-3682 at a 450 mg dose of the tablet formulation is largely maintained at the plateau level.
- The safety, pharmacokinetics, and antiviral data support the continued clinical investigation of MK-3682 at a dose of 450 mg as a once-daily component of an all-oral, interferon-free regimen for the treatment of chronic HCV-infection.