Hepatitis C virus (HCV) NS5B polymerase has emerged as a promising target for the treatment of HCV infection. The NS5B polymerase is responsible for the replication of the HCV genome and has been shown to be a target for nucleoside and nucleotide inhibitors. MIV-802 is a novel uridine nucleotide inhibitor of HCV NS5B polymerase that has shown high pan-genotypic activity and a high barrier to resistance. The mechanism of action for MIV-802-UTP was elucidated to be inhibition of NS5B-catalyzed RNA polymerization through chain termination. The EC50 was 0.71 µM for MIV-802-UTP and 2.10 µM for sofosbuvir-UTP (Figure 1).

**MATERIALS & METHODS**

- **Antiviral activity for MIV-802 was evaluated using HCV replicon systems expressing NS5B sequences from HCV genotypes 1-6, including variants conferring resistance to sofosbuvir.**
- **The antiviral profile of MIV-802 on a series of clinical isolates was also studied.** For each genotype, EC50 values obtained using MIV-802 were lower than those obtained using sofosbuvir, e.g., MIV-802 was 2.2-fold more potent than sofosbuvir against the GT1a* S282T variant.
- **MIV-802 was evaluated for inhibition of HCV replicons encoding sofosbuvir-associated resistance substitutions in NS5B.** The data revealed that, like sofosbuvir, MIV-802 confers a small change in susceptibility (Table 3).
- **The panel of replicons encompassing GTs 1 to 4 were selected for Virology and Specificity studies.** For each genotype, the EC50 values obtained using MIV-802 were lower than those obtained using sofosbuvir, e.g., MIV-802 was 2.2-fold more potent than sofosbuvir against the GT1a* S282T variant. The data showed that, like sofosbuvir, MIV-802 confers a small change in susceptibility (Table 3).

**RESULTS**

- **Formation of MIV-802-UTP in vitro and in vivo**
  - High levels of MIV-802-UTP (100-fold above its EC50 against HCV NS5B polymerase) were rapidly formed in primary human hepatocytes during incubation with 10 µM MIV-802. After 24h incubation with MIV-802, following removal of extracellular MIV-802, the MIV-802-UTP decayed with a T1/2 of 14 hours, supporting the viability of human primary cells for up to 14 days.
  - Hepatic MIV-802-UTP levels in dog, 4 hours post-dose (oral dosing 50 mg/kg, once daily for 4 days), were 40-fold above the HCV NS5B polymerase Ki. The mean T1/2 was estimated to be 12 hours.

**CONCLUSIONS**

- MIV-802 is a potent, pan-genotypic and selective nucleotide analogue with favorable resistance profile. MIV-802 displays high potency against replicons encoding NS5B sequences derived from HCV-infected patients with improved antiviral activity relative to sofosbuvir.
- MIV-802 shows good safety margins in vitro and in vivo and delivers pharmacologically relevant amounts of UTP to human hepatocytes, and to dog liver after oral administration.
- Given its favorable preclinical profile, MIV-802 is currently being advanced towards clinical development.

**REFERENCES**