Results

GS-9256 is a potent and selective non-covalent HCV NS3 protease inhibitor – Genotype 1α and 2α, IC50 = 0.10-0.90 nM, IC50/IC50 = 20 nM
- Selectivity vs mammalian proteases of 1,000-28,500-fold
- In vitro, GS-9256 has additive antiviral activity with IFNα, ribavirin, and certain NS5B inhibitors
- In vitro DMPK profile:
  - No significant metabolism by CYP450 enzymes (for all tested CYP450s, GS-9256 metabolism was only 1-2% of controls)
  - Did not inhibit major CYP450 enzymes up to 25 μM
- May be a substrate for efflux transporters (Caco-2)
- A moderate inhibitor of P-gp and OATP2B1 and a weak inhibitor of MRP1; not an inhibitor of MRP2 at clinically relevant concentrations

Methods

- Study 1: Phase 1a, randomized, double-blind, placebo-controlled trial in healthy volunteers
  - Single ascending dose design
  - 150 mg, 300 mg, 600 mg or placebo under fasting conditions
  - N = 7 groups (1 group, GS-9256 placebo)
  - Outcome measures:
    - Safety & tolerability
    - Plasma pharmacokinetics
- Study 2: Phase 1b, randomized, double-blind, placebo-controlled trial in GT-1 HCV-infected subjects
  - Single-dose, parallel-group design
  - 150 mg, 300 mg, 450 mg or placebo under fasting conditions
  - N = 8 groups (including placebo)
  - Outcome measures:
    - Safety & tolerability
    - Plasma pharmacokinetics
    - Antiviral efficacy

Results

- GS-9256 was well-tolerated – No drug-related SAEs
- A moderate inhibitor of P-gp and BSEP and a weak inhibitor of MRP1; not an inhibitor of MRP2 at clinically relevant concentrations

Conclusions

- The pharmacokinetic profile of GS-9256 following single-dose administration is similar between healthy volunteers and HCV-infected subjects with plasma concentrations well above the protein-adjusted EC50 value of 10 μg/mL
- The potent antiviral activity observed following single-dose administration (1.0-2.8 log10 (IU/mL) HCV RNA reductions) in HCV-infected subjects supports continued development of GS-9256 for the treatment of chronic HCV infection
- The lack of cross resistance between GS-9256 and GS-9190 supports the combination therapy with these agents in genotype 1α or 1b HCV-infected subjects

Acknowledgements

Gilead gratefully acknowledges the contributions of the staff and subjects at the participating sites in Studies GS-US-208-0110 and GS-US-208-0103.