SAFETY, TOLERABILITY, AND PHARMACOKINETICS

DISCOVERY OF POTENT, BIOAVAILABLE HCV NS3/4A INHIBITORS THAT DISPLAY UNIMPAIRED ACTIVITY AGAINST AN NS3 SEQUENCE VARIANT ASSOCIATED WITH RESISTANCE TO LINEAR TETRAPEPTIDES AND MACROCYCLIC INHIBITORS

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Background: Agents that inhibit serine protease activity of HCV NS3/4A have emerged as potentially significant components of regimens targeting HCV virus. ITMN-191 is a highly potent and selective macrocyclic inhibitor of the HCV NS3/4A serine protease. In short duration human clinical studies, administration of ITMN-191 has demonstrated multi-log10 reductions in circulating HCV RNA and a very favorable safety profile. As with linear tetrapeptide telaprevir, a fraction of patients receiving ITMN-191 monotherapy experience virologic rebound driven by the emergence of drug resistant mutations. The NS3 escape mutation R155K is the only NS3 substitution that is common to both classes of structurally diverse inhibitors in monotherapy. While the clinical significance of escape mutations is yet to be defined, it would be valuable to identify chemical matter with unimpaired activity against NS3 with R155K.

Methods: Structure-guided rational drug design employed both molecular modeling and protein-inhibitor complex x-ray structures of both WT and R155K NS3. Biochemical and replicon assays were used to determine activity against NS3 variants. Pharmacokinetics performance was examined by standard procedures that were IACUC approved.

Results: We have discovered inhibitors with no reduction in potency against R155K-bearing NS3. The best compounds display an equivalent, sub-nanomolar potency against WT or R155K replicons. These compounds also display a slow-binding mechanism that is associated with slow dissociation and persistent inhibition of protease activity. Pharmacokinetics and plasma AUC following PO dosing in monkeys is equivalent or better than ITMN-191, a compound with robust virologic effect in q12 h dosing regimens.

Conclusion: The overlap in NS3 escape mutations observed with linear tetrapeptides and macrocyclic compounds indicates that multiple drug resistant strains of HCV may develop. Using structure-based drug design, we have discovered potent, bioavailable inhibitors that show equal activity against WT and R155K-bearing NS3; the NS3 variant observed in monotherapy with telaprevir and a macrocyclic compound. The favorable pharmacokinetic profile of these compounds in monkeys suggests that their exposure would support a q12 h schedule for both WT and drug resistant strains. Further investigation of these compounds is warranted.

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INTRODUCTION

MK-3281 is a novel non-nucleoside hepatitis C virus polymerase inhibitor with potent and selective in vitro activity against genotype 1 hepatitis C viruses (genotype 1b replicon assay, EC50 = 241 nM in 50% human serum). Pharmacokinetic and safety data after single-dose (SD) and multiple-dose (MD) administration in healthy subjects were collected.

METHODS: SD: Alternating panel, multiple period, dose escalation study in 16 healthy males who received 25 to 2250 mg single doses of MK-3281 or placebo in the fed or fasted state; MD: Ongoing serial-panel study in 24 healthy males who received 100 to 400 mg MK-3281 or placebo q12 hr for 10 days. Safety evaluations were performed throughout the studies. Plasma samples for MK-3281 concentration determination and pharmacokinetics were collected.

RESULTS: There were no serious adverse experiences reported and no discontinuations due to adverse experiences. SD: Following oral administration, MK-3281 increased in plasma with median Tmax values of 2.5–3.5 hours. Thereafter, concentrations declined in a biphasic manner with mean terminal t1/2 ≈ 14.3–18.6 hours. Administration of 800 mg with a high-fat meal had no clinically meaningful effect on the pharmacokinetic parameters. Mean AUC0–∞, Cmax and C12hr values appeared to increase in a dose proportional fashion through 200 mg and in a less than dose proportional manner at doses greater than 200 mg. MD: Steady state was achieved after 4–5 days. Accumulation over the 10-day period occurred in all subjects for AUC0–12hr (geometric mean ratio (GMR) 2.3–2.8), Cmax (GMR 1.7–2.8) and C12hr (GMR 2.5 to 2.7). In general, AUC0–∞, Cmax and C12hr appear to increase less than dose proportionally on Day 1 and on Day 10. The apparent terminal half-life on Day 10 following multiple twice daily doses in the present study (e.g., ~17 hours) was consistent with values from the SD study.

CONCLUSIONS: MK-3281 is generally well tolerated and exhibits a pharmacokinetic profile supportive of twice daily dosing.
were evaluated in vitro in systems derived from human and/or animal species.

Results: In rats and dogs, VCH-222 displayed low total body clearance with excellent oral bioavailability (greater than 30%). The exposure of VCH-222 in rat liver was 5-fold higher than in plasma. Excretion studies in bile-duct cannulated rats indicated that, upon oral and iv administration, [14C]-VCH-222 was excreted mainly intact in bile or as glucuronide adducts. VCH-222 was metabolically stable in human microsomes and hepatocytes. Both oxidation and glucuronidation pathways were observed. Phenotyping studies indicated that several enzymes were involved in the biotransformations of VCH-222 (CYP1A1, 2A6, 2B6, 2C8, CYP 3A4, UGT1A3). In vivo studies, VCH-222 demonstrated limited potential to cause human CYP inhibition or CYP induction. The absorption potential of VCH-222 was shown to be acceptable based on its good permeability in Caco-2 cell monolayer and minimal recognition by intestinal efflux proteins. In addition, VCH-222 had no significant effect of digoxin permeability. Based on sandwich-cultured hepatocyte studies, VCH-222 is predicted to be actively transported in liver and to have a low biliary clearance in humans.

Conclusion: VCH-222 has a good oral bioavailability and ADME properties in terms of permeability, metabolic behaviours and distribution in hepatic tissue/cell. VCH-222 is neither a CYP inhibitor/inducer nor a Pgp inhibitor reducing the likelihood of VCH-222 to be involved in drug interactions. From these data, a favorable pharmacokinetic profile is expected in humans.

**SAFETY, TOLERABILITY AND PHARMACOKINETICS OF THE HCV POLYMERASE INHIBITOR VCH-222 FOLLOWING SINGLE DOSE ADMINISTRATION IN HEALTHY VOLUNTEERS AND ANTIVIRAL ACTIVITY IN HCV-INFECTED INDIVIDUALS**

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Background and Aims: VHC-222 is a novel non-nucleoside inhibitor of the HCV NS5B polymerase. It has demonstrated potent in vitro antiviral activity in genotype 1a and 1b replicon systems with IC50 values of 65 and 41 nM (29 and 18 ng/mL), respectively.

Methods: A Phase 1, randomized, double-blind, ascending, single dose trial was conducted to evaluate the safety, tolerability, pharmacokinetics and food effect of VCH-222. Healthy subjects were randomized into four treatment cohorts (250, 500, 1000 and 1500 mg). All doses were administered in the fasted state with the exception of the 500 mg-fed group. An open cohort of 6 subjects with HCV genotype-1 infection was dosed with 750 mg bid for 3 days.

Results: VCH-222 was well tolerated at all doses tested. There have been no serious adverse events and all adverse events observed were classified as mild to moderate with no apparent dose relationship. There have been no clinically significant changes in other safety assessments. Under fasted condition, the rate and extent of absorption (Cmax and AUC) appeared relatively proportional between the doses of 250 and 1500 mg. The half-life was approximately 4 hours and the plasma levels observed at 24 h (C24 h) were above the IC50 replicon values in all cohorts. In the subjects treated for 3 days with 750 mg bid there was a 2-fold increase in Cmax and AUC observed between Day 1 and Day 3. Preliminary efficacy results on the first 4 treatment-naïve subjects dosed for 3 days reveal a mean log10 reduction of 3.2 (range 3.0−3.3) within 24 hours of dosing and of 3.7 (range 3.2−4.2) on Day 4.

Conclusions: VCH-222 was safe and well tolerated up to 1,500 mg administered as a single dose or at 750 mg bid for 3 days. In terms of exposure versus in vitro potency, excellent pharmacokinetic properties were exhibited. In vivo, high HCV virological potency was demonstrated.