CRV431: An Optimized Cyclophilin Inhibitor with Multiple Anti-HBV Activities, High Selectivity Index, and Synergy with CMX157

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INTRODUCTION

Novel drug combinations targeting multiple HBV activities are needed to eliminate HBV.

CRV431
- CRV431, a novel cyclophilin inhibitor ("CPI"), designed to be layered on top of HBV therapeutic drugs including NUC backbone

CMX157
- CMX157, a nucleotide ("NUC") analogue of tenofovir, designed to reduce viral load and serve as backbone HBV therapy

IDEAL THERAPEUTIC DRUG COMBINATION
- Additive to synergistic, with wide in vitro Selective Index ("SI") to optimally position combination for wide Therapeutic Index ("TI") in clinic, while reducing exposures compared with monotherapy
- Targets multiple stages of the HBV lifecycle

CRV431 NON-VIRAL EFFECTS

CRV431 is a highly potent cyclophilin inhibitor

IC50

CRV431 blocks HBeAg and HBsAg production and/or secretion in infected and transfected cells, unlike entecavir

CRV431 blocks HBV DNA replication in AD38 cells

CRV431 inhibits NTCP-mediated HBV entry

Other studies show that NTCP inhibition by cyclophilin analogs results in synergistic inhibition of human hepatitis B virus replication, independent mechanism.

CRV431 has less cytotoxicity than other cyclophilin inhibitors

Comparisons

A. B. C.

CRV431 IN VIVO

CRV431 is suitable for oral dosing

Single oral dose of CRV431 at 10 mg/kg in 6 male and 6 female rats. Male and female rats showed similar responses.

CRV431 + CMX157 COMBINATION

CRV431 inhibits HBV synergistically with CMX157

AD38 cells treated with multiple combinations of CRV431 and CMX157 for 5 days. Measurement of intracellular HBV DNA.

CONCLUSIONS

- CRV431 has a wide SI, as defined by the ratio of CC50 to IC50 in vitro
- The SI of CRV431 is the widest of any known CPI, potentially offering a wide TI in patients
- Thus far, CRV431 addresses many of the identified endpoints relevant to HBV drug therapy including:
  - Reduction of HBV DNA
  - Suppression of HBeAg and HBsAg
  - Inhibition of viral entry via NTCP
- CRV431, in combination with CMX157, is synergistic (reduction of HBV DNA)
- CRV431 has potential beneficial effects on progression of liver fibrosis