Independent and Combinational Anti-HBV Effects of CRV431 and TXL in the HBV Transgenic Mouse Model

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**BACKGROUND**

- CRV431 is a cyclophilin inhibitor
- CRV431 reduces HBV DNA, HBsAg, and HBeAg in a variety of cell culture assays.

**Tenoforv Exalidex (TXL)**
- TXL is a pro-drug of the nucleotide analogue, tenofovir.
- TXL reduces serum HBV DNA in hepatitis B patients in Phase 2 clinical trials.

Combining drugs from different classes is believed to be necessary for eradicating HBV more effectively than current treatments.

**PURPOSE**

The purpose of this study was to investigate the effect(s) of CRV431 and TXL, administered alone and in combination, in the HBV transgenic mouse model.

**METHODS**

- Administer CRV431 and TXL by once-daily oral gavage for 16 days to HBV transgenic mice which replicate HBV from a 1.3x overlength HBV genome integrated into the mouse genome. Expression occurs mostly in hepatocytes.
- Treatment groups (n = 8/group):
  a) Vehicle
  b) CRV431 low dose – 10 mg/kg/day
  c) CRV431 high dose – 50 mg/kg/day
  d) TXL low dose – 5 mg/kg/day
  e) TXL high dose – 10 mg/kg/day
  f) CRV431 low dose (10) + TXL low dose (5)
- After 16 days of dosing, harvest livers and serum, and measure:
  a) HBV DNA by quantitative PCR (liver and serum)
  b) HBsAg by ELISA (liver and serum)
  c) HBeAg by ELISA (serum)
  d) CRV431 concentrations by liquid chromatography-mass spectrometry (serum)

**CONCLUSIONS**

- CRV431 and TXL were both highly efficacious as monotherapies at lowering HBV DNA in the livers of transgenic mice.
- Unlike nucleos(t)ide analog therapies (including TXL in the present study), CRV431 was able to lower serum HBsAg levels. This finding is consistent with previous in vitro observations and indicates a different mode of action for CRV431.
- Additive or greater reductions in HBV DNA achieved with CRV431 + TXL combination supports the possibility that CRV431 and TXL could be administered together and improve outcomes in antiviral treatment for hepatitis B.