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

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## BACKGROUND

### CRV431

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

### Tenofovir 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

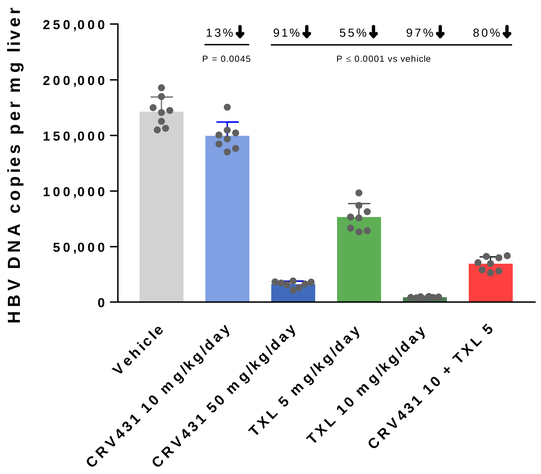
The purpose of this study was to investigate the effect(s) of CRV431 and TXL, administered alone and in combination, in the HBV transgenic mouse model.

## 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)

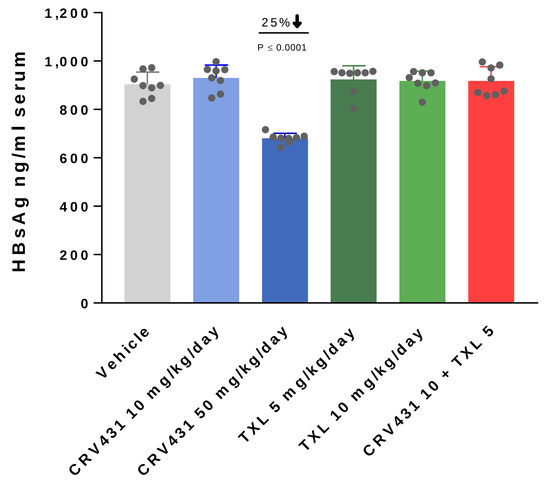
## Liver HBV DNA

- **CRV431 administered alone decreases liver HBV DNA**
- **TXL administered alone decreases liver HBV DNA**
- **Combination CRV431 + TXL decreases HBV DNA more than either drug alone**



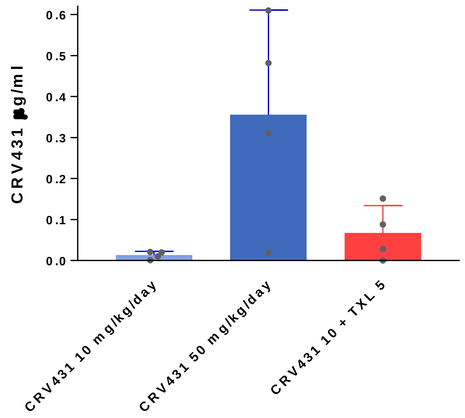

## Serum HBsAg

- **High-dose CRV431 decreases serum HBsAg**
- **TXL administered alone or in combination with low-dose CRV431 does not affect serum HBsAg**




## Serum CRV431

**Serum CRV431 concentration at 3-hr post-dose on Day 16 of dosing correlates with the effects of CRV431 on HBV DNA and HBsAg**

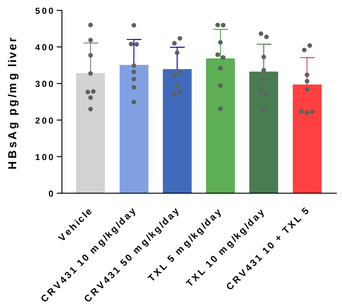


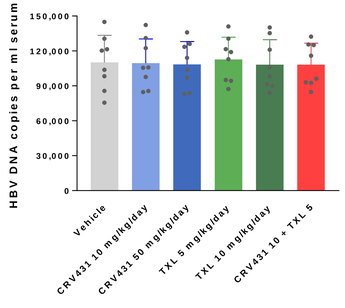

## Liver HBsAg

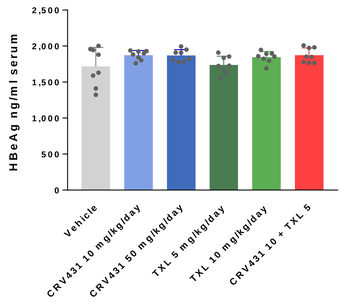
## Serum HBV DNA

## Serum HBeAg

**CRV431 and TXL, alone or in combination, do not affect levels of liver HBsAg, serum HBV DNA, or serum HBeAg**




## 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.