CRV431 and CMX157 (TXL; tenofovir exalidex): Anti-HBV combination effects in vitro between a cyclophilin inhibitor and a nucleotide prodrug

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INTRODUCTION
It is expected that a cure for HBV will require drug combinations that interact at more than one stage of viral replication and propagation. Our lead drug, tenofovir exalidex (TXL; formerly CMX157), a tenofovir (TFV) prodrug, is a novel lipid acyclic nucleoside (NUC) phosphonate designed to deliver high intranuclear concentrations of TFV, while minimizing off-target effects caused by high levels of circulating TFV. CRV431, our earlier-stage molecule, is a host targeting antiviral that exploits the complementary modes of action of the two drugs, which allows for suppression of HBV DNA, HBsAg, HBeAg, inhibition of viral entry, and blocking of cyclophilin A binding to HBx. The complementary actions of CRV431 with CMX157 may reasonably extend to drugs with other modes of activity including, for example, core inhibitors.

AIM
The aim of the current study was to investigate the combination anti-HBV effects of CMX157 and CRV431 by measuring HBV DNA levels.

METHOD
The current study measured inhibition of intracellular HBV DNA at concentrations of CRV431 ranging from 0-320 nM alone, and in combination with CMX157 ranging from 0-640 nM. Both drugs were tested in vitro in AD38, DE19, and DES19 cells. Cells were each exposed twice, in triplicate wells, using DMSO as control. Drug concentration versus effect was evaluated using Prichard-Shipman MacSynergy.

RESULTS
CRV431 and TXL independently inhibit HBV replication in HepAD38, DE19, and DES19 cells

Combination treatment with CRV431 and TXL inhibits HBV synergistically (Prichard-Shipman MacSynergy)

CONCLUSIONS
CRV431 and CMX157, tested in combination, represents a viable therapeutic drug strategy towards the cure of HBV. This strategy exploits the complementary modes of action of the two drugs, which allows for suppression of HBV DNA, HBsAg, HBeAg, inhibition of viral entry, and blocking of cyclophilin A binding to HBx. The complementary actions of CRV431 with CMX157 may reasonably extend to drugs with other modes of activity including, for example, core inhibitors.

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REFERENCES
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Prichard-Shipman MacSynergy – manual and spreadsheet: https://www.usab.edu/med/ext/peds/macsynergy

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