



BRINCIDOFOVIR (BCV, CMX001) DELIVERS HIGH INTRACELLULAR CONCENTRATIONS OF CIDOFOVIR DIPHOSPHATE

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Background: Brincidofovir (BCV, CMX001) is a lipid conjugate nucleotide in Phase 3 development for the prevention of CMV infection in HCT recipients. BCV is administered orally, circulates as BCV, and is converted to the active antiviral cidofovir diphosphate (CDV-PP) within cells. BCV shares the broad-spectrum antiviral activity of CDV against all five families of dsDNA viruses which cause disease in humans. The 50 to 500-fold improved *in vitro* activity of BCV vs CDV has been hypothesized to result from more efficient transport of circulating BCV across the cell membrane, resulting in higher intracellular concentrations of CDV-PP. Five cell types used for determination of EC₅₀s were exposed to identical concentrations of BCV and CDV and evaluated to determine the intracellular concentration of CDV-PP.

Methods: Human foreskin fibroblast cells, MRC-5 cells, A549 cells, HepG2 cells and Vero cells were treated with 1 μ M of BCV or CDV for 72 hours. Cells were rinsed thoroughly to remove any residual BCV or CDV and immediately extracted in methanol/water (70:30). Intracellular levels of BCV, CDV and CDV-PP were determined by LC/MS/MS.

Results: BCV exposure resulted in 20 to 140-fold higher intracellular concentrations of CDV in the 5 cell types as compared to CDV-treated cells. The concentration of CDV-PP in BCV-treated cells was 33 to 450-fold higher than that measured in CDV-treated cells.

Conclusions: CDV-PP has been shown to act as an alternative substrate for viral DNA polymerases. Since the primary mechanism of viral growth inhibition involves CDV-PP as a competitive inhibitor of the natural substrate for viral polymerases, higher intracellular concentrations should be more effective and the EC₅₀ should be lower. These data demonstrate more efficient intracellular delivery of CDV and CDV-PP by BCV versus CDV as predicted. In addition to improved efficacy, BCV may provide an improved safety profile through lower plasma concentrations of CDV, a compound noted for its renal toxicity due to preferential uptake by human organic anion transporters (hOATs) and resulting high concentration in the proximal renal tubules. The significantly improved safety profile of BCV versus CDV is partly attributable to the inability of hOATs to recognize BCV.