

1026 - Nonclinical Drug-Drug Interaction Profile of BCX4208, An Oral, Once-Daily, Novel Nonmetabolized Enzyme Inhibitor for Chronic Management of Gout

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Hall F2 - Poster Hall (McCormick Place West)

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Background/Purpose: Common comorbidities associated with gout, including obesity, hypertension, diabetes, and chronic kidney disease, may confer a greater risk of drug-drug interaction (DDI) through both polypharmacy and disease-associated alterations in drug absorption, distribution, metabolism, or excretion. Currently available antiinflammatory and urate-lowering therapies (such as colchicine, allopurinol, and probenecid) used for management of gout are associated with significant DDIs. BCX4208 is an oral, once-daily, novel enzyme inhibitor in clinical development for the chronic management of gout. In Phase 1 pharmacokinetic (PK) studies of BCX4208, a dose-dependent reduction in serum uric acid was related to inhibition of purine nucleoside phosphorylase. In this study, we characterized the potential for BCX4208 to (1) interact with cytochrome P450 enzymes, (2) interact with drug transporters, and (3) induce or act as a substrate of metabolizing enzymes.

Method: BCX4208 was incubated in gender-pooled human liver microsomes with marker substrates for CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5, and the catalytic activity of these isoforms was determined. BCX4208 was incubated with human primary hepatocytes from three donors, and induction of CYP1A2, CYP2B6, CYP2C9, CYP3A4/5, MDR1 (P-glycoprotein [P-gp]), and MRP2 was assessed.

Result: CYP isoforms: No significant inhibition of catalytic activity by BCX4208 was observed for CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 using gender-pooled human liver microsomal incubations. Additionally, BCX4208 was not shown to be a time-dependent inhibitor of CYP3A4/5. BCX4208 did not induce protein synthesis or enzyme activity for CYP1A2, CYP2B6, CYP2C9, and CYP3A4 in primary hepatocyte cultures from human donors. Drug transporters: BCX4208 did not induce protein synthesis of MDR1 or MRP2 in primary human hepatocytes, nor did the drug significantly inhibit OAT1 (kidney transport)-mediated uptake of p-aminohippuric acid, a substrate for OAT1. In addition, BCX4208 was not a substrate for the OAT1 transporter. BCX4208 was demonstrated to be a weak inhibitor of the kidney transporter OCT2 (11%-24% inhibition at 200 mM in CHP-OCT2 cells); however, BCX4208 is unlikely to mediate a DDI with compounds that are cleared by OCT2.

Conclusion: In summary, there is a low risk of DDIs between BCX4208 and coadministered medications. The potential for hepatic and/or renal DDIs is low given that BCX4208 does not induce or inhibit cytochrome P450 isoforms, has low potential as a P-gp substrate or inducer, and is not a substrate or inhibitor of renal organic anion and cation transporters. Furthermore, BCX4208 undergoes renal elimination and is not metabolized extensively; therefore, the clinical PK of BCX4208 will not be altered by inhibitors of drug metabolizing enzymes. These results provide good assurance in the clinical setting that drug interactions are not expected with BCX4208 in a chronic gout patient population. Indeed, in a Phase 2 trial of BCX4208 administered in combination with allopurinol, a first-dose PK assessment revealed no DDI with allopurinol or its active metabolite oxypurinol.

Keywords: drug interactions and gout

Disclosure: **P. G. Pearson**, Pearson Pharma Partners, 5 ; **S. Bantia**, BioCryst Pharmaceuticals, Inc, 3 ; **L. Harman**, BioCryst Pharmaceuticals, Inc, 3 .