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UEGW 2008 - Abstract Database

[« back to listing](#)

Nerve gut and motility: Functional gastrointestinal disorders (clinical, management)

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ABSENCE OF PHARMACOKINETIC DRUG-DRUG INTERACTIONS IN HEALTHY VOLUNTEERS BETWEEN AST-120, A NOVEL ORAL ADSORBENT AND CONCOMITANT MEDICATIONS : CIPROXR[®] (CFXR) AND AZATHIOPRINE (AZA)

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Topics: 13.5 Functional gastrointestinal disorders (clinical, management)

INTRODUCTION: AST-120 is a novel oral adsorbent currently under investigation for fistulizing Crohn's disease, Pouchitis, IBS, and Hepatic Encephalopathy. AST-120 has a high specific surface area (>1600 m²/g) and retains large, selective binding capacity for many low molecular weight organic compounds, such as pro-inflammatory mediators and GI stimulants. A series of drug-drug interaction studies has been initiated to investigate the potential for AST-120 to impact the pharmacokinetics of concomitant therapies. This report details the PK of CFXR and AZA administered with AST-120.

AIMS & METHODS: 60 healthy volunteers were randomized between CFXR or AZA; "active treatment". Treatment groups were divided into 15-subject cohorts randomly assigned to be treated with a single dose of active treatment followed by either 2 g AST-120 TID or 2 g placebo TID in a crossover design. The initial dose of placebo or AST-120 was given 30 minutes after the active treatment dose then followed at regular intervals during waking hours. After 48 hours of observation, subjects were released to undergo 7 days of washout before returning to the clinic where each subject received the crossover treatment and was observed for 48 hours. Seventeen blood samples were collected during the 48 hours for quantifying CFX or AZA in plasma using validated LC/MS/MS bioanalytical methods.

RESULTS: Plasma concentrations of CFX and AZA were similar between the active treatment test and control reference groups. The mean ratios of the test versus reference comparisons confirm that the 90% geometric confidence intervals for the primary pharmacokinetic parameters AUC_{last}, AUC(0-inf), and C_{max} were within the 80-125% bioequivalence range for both CFX and AZA. The geometric mean ratios (test/reference) for AUC_{last}, AUC(0-inf), and C_{max} were 101.9%, 101.8% and 100.6% respectively for CFX and 88.4%, 89.8%, and 101.4% respectively for AZA.

CONCLUSION: Results confirm that concomitant administration of AST-120 with CFXR or AZA has no impact on the PK and bioavailability of these compounds. AST-120 has been demonstrated to specifically bind pro-inflammatory mediators in the GI tract. The maximal binding kinetics for compounds to AST-120 typically ranges from 4-6 hr, which matches well with typical small intestinal transit times. Due to the inherent features of the product, capacity is retained for many organic compounds (< 10 kD) that continually evolve as a product of, e.g., sustained inflammatory processes. A distinguishing feature is that this data support that AST-120 does not interfere with the absorption of other commonly used concomitant medication for chronic IBD, including sustained release medications, such as CFXR.

[« back to listing](#)