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## PUBLICATIONS

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#### Chronic diarrhoea - From bench to bedside

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Hall G

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OP345

#### **A NOVEL ORAL ADSORBENT, AST-120, SPECIFICALLY AND IRREVERSIBLY BINDS PRO-INFLAMMATORY MEDIATORS OF THE GUT IN VITRO AND IN VIVO.**

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Topics: 13.5 Functional gastrointestinal disorders (clinical, management)

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**INTRODUCTION:** AST-120 is currently in clinical trials for fistulizing Crohn's disease, hepatic encephalopathy, IBS and Pouchitis. AST-120 selectively binds low molecular weight organics and has optimized binding characteristics for known pro-inflammatory mediators. The properties of AST-120 provide for a well-tolerated, broad-spectrum, oral adsorbent that has application in chronic inflammatory bowel disease. This report details the binding capacity of AST-120 for a number of known gastro-intestinal stimulants as well as preclinical support for a mechanism-based approach in treatment of inflammatory diseases.

**AIMS & METHODS:** 10 mg/dL solutions of test compounds were prepared in pH 7.4 phosphate buffer. AST-120 was suspended in above buffer systems ranging from 10 - 50mg/mL and incubated for 3hr under constant agitation at 37°C. Residual analyte was detected by total organic carbon and quantitated against appropriate controls. AST-120 was further assessed vs. negative control for amelioration of symptoms in a preclinical Dextran Sulfate Sodium - induced inflammation rat model under increased bile acid load (n=10/group). AST-120 was administered oral gavage at a dose of 4g/kg in methylcellulose (MC) suspension qd for 12 days 30 min following a 200 mg/kg dose of deoxycholic acid. Food and water were provided ad libitum. The control group was administered MC suspension only.

**RESULTS:** Normalized results for removal of test compound from buffer systems in the presence of AST-120 were: high (> 80%) for DL-Beta-amino isobutyric acid, putrescine, aspartylglycine creatinine, indoleacetic acid, p-hydroxyphenylacetic acid, glycodeoxycholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid, histamine and very high (> 99%) for caffeine, serotonin, tyramine, tryptamine, n-formyl-Met-Leu-Phe, cholic acid, deoxycholic acid, taurodeoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, chenodeoxycholic acid. The control group had deterioration in general symptoms, inhibition of spontaneous motor activity, reduced feed intake and weight loss with petechial hemorrhages (colitis) detected at necropsy. In contrast, the AST-120 group exhibited marked improvement in all symptom scores with reduced evidence of intestinal petechial hemorrhage at necropsy.

**CONCLUSION:** AST-120 has demonstrated a strong, irreversible binding affinity for many pro-inflammatory mediators in the GI tract. Further, AST-120 has demonstrated efficacy for reduction in symptoms of colitis in a DSS-induced inflammatory rat model under bile acid load. Local sequestration of pro-inflammatory mediators in the GI tract appears to play a complimentary role in treatment of inflammatory disease processes.

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