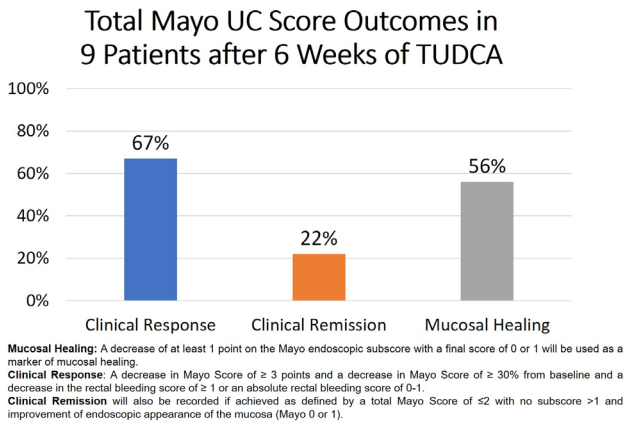
of tauroursodeoxycholic acid (TUDCA), a naturally occurring bile salt proven to reduce ER stress both in vitro and in vivo, dramatically decreases the clinical, histological and biochemical signs of inflammation in four different IBD mouse models through reducing ER stress in colonic epithelial cells.

Aim : Based on this, our aim was to test the efficacy and safety of TUDCA in an open label, Phase I trial for patients with symptomatic ulcerative colitis.

Methods: TUDCA was administered at 2000 mg divided TID for 6 weeks. Baseline and 6 week colonoscopy/flexible sigmoidoscopy with biopsy was performed. Outcome measures include safety, tolerability, Mayo score, and change in markers of ER stress from colon biopsies.

Results: To date, complete data is available on 9 of a planned 12 patients. TUDCA was well tolerated and safe with no Grade 3 or greater CTCAE adverse events and no Serious Adverse Events. A significant reduction of 4.6 points on the complete Mayo score was observed from baseline to week 6 (Avg. 8.6 ± 2.5 → 4.00 ± 2.7, P=0.004) with 100% of patients seeing a decrease. Clinical remission, clinical response and mucosal healing were observed in 22%, 67% and 56% respectively. Fecal calprotectin decreased in 67% of patients. As diarrhea can be a side effect of TUDCA treatment at these doses, we also assessed the Partial Mayo Score at two weeks after completion of the trial (8 weeks from baseline). At this time point the Partial Mayo Score significantly decreased by 3.8 points (Avg. 6.2 ± 2.1 → 2.4 ± 1.9, P=0.004) with 67% achieving clinical response and 56% remission. The Robarts Histopathology Index decreased in 8 of 9 patients with a mean reduction of 2.67 points (Avg. 6.4 ± 3.2 → 3.8 ± 2.9, P=0.003). Total serum bile acid profiles changed, but not significantly so, from Wk0 to Wk6. ER stress markers Bip, eIF2a and p-eIF2a were increased in inflamed colon tissue and were lowered post TUDCA treatment in a subset of patients.

Conclusions: Preliminary results from a Phase I clinical trial demonstrate that the dietary supplement TUDCA is safe, well tolerated and is associated with significant clinical improvement in a majority of patients with moderate to severely active ulcerative colitis. Mucosal healing and reductions in markers of ER stress were observed in a subset of patients. Study completion and analysis of gene expression and microbiome are underway.




## EFFECT OF OZANIMOD ON FECAL CALPROTECTIN AND FECAL LACTOFERRIN, BIOMARKERS OF INTESTINAL INFLAMMATION, IN THE PHASE 2 TOUCHSTONE STUDY OF PATIENTS WITH MODERATE-TO-SEVERE ULCERATIVE COLITIS

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Introduction: Efficacy and safety of ozanimod, an oral sphingosine-1-phosphate (S1P) receptor modulator selectively targeting $S1P_1$ and $S1P_5$, was previously demonstrated in the double-blind phase 2 TOUCHSTONE study (NCT01647516) in patients with moderate-to-severe ulcerative colitis. Here we report the effect of ozanimod on levels of fecal calprotectin (FCP) and fecal lactoferrin (FLF), two markers of intestinal inflammation.

Methods: Patients in TOUCHSTONE were randomized 1:1:1 to once daily oral ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg), ozanimod HCl 1.0 mg (equivalent to ozanimod 0.92 mg), or placebo for 8 weeks; responders at week 8 (based upon Mayo score) entered a maintenance phase through week 32. Stool collection occurred at baseline and weeks 8 and 32 to measure levels of FCP and FLF.

Results: A total of 197 patients were randomized and received treatment (n=65, placebo; n=65, ozanimod 0.5 mg; n=67, ozanimod 1 mg). Median baseline levels of FCP were 1272, 1477, and 1238 µg/g, respectively; baseline FCP levels were not associated with baseline Mayo score. Median baseline levels of FLF were 29.0, 30.6, and 29.9 µg/g, respectively; baseline FLF was related to week 8 Mayo score even after adjusting for baseline Mayo score. At week 8, FCP levels declined across treatment groups (median percent change from baseline, -53.4, -68.7, and -70.0 in placebo, ozanimod 0.5 mg and 1 mg groups, respectively); declines in FCP were maintained at week 32 (median percent change from baseline, -42.3, -72.6, and -80.6, respectively). At week 8, declines in FCP were greater in patients achieving clinical response (based on Mayo score) than in non-responders on ozanimod 1 mg. Declines in FCP at week 8 were also greater in patients achieving clinical remission than in those who did not, with greater declines with ozanimod 1 mg relative to 0.5 mg. FLF levels declined at weeks 8 and 32 across treatment groups, with greater changes in the ozanimod 1 mg group vs placebo (median percent change from baseline, week 8: -35.7, -61.0, and -84.7, respectively; week 32: -60.2, -62.5, -85.3, respectively, for placebo, ozanimod 0.5 mg, and ozanimod 1 mg). Reductions in FLF at week 8 were greater for treatment responders vs non-responders and for those achieving vs not achieving clinical remission in the ozanimod 1 mg group.

Conclusion: In TOUCHSTONE, treatment with ozanimod was associated with declines in FCP levels in treatment responders (for the 1 mg dose group) or those who achieved clinical remission (both doses). Ozanimod 1 mg was also associated with declines in FLF for treatment responders and those achieving remission.

## EFFECTIVENESS OF ANTIBIOTICS AS A TREATMENT OPTION FOR PATIENTS WITH CROHN'S DISEASE: A META ANALYSIS

Joshua Patterson

Crohn's Disease (CD) is an Inflammatory Bowel Disease (IBD) whose etiology has been suspected to include bacterial antigens. A treatment option, therefore, would be the usage of antibiotics. To that end, the purpose of this study was to perform a meta-analysis on the ability of antibiotics inducing remission or a favorable clinical response in Crohn's disease (CD) patients. Thirty-two randomized, double-blind, placebo-controlled trials of antibiotics for treatment of CD in adults, totaling 3269 patients, were reviewed. Log-odds ratio and probability difference were performed to estimate risk difference. The Number Needed to Treat (NNT) was also calculated for each antibiotic reviewed (rifaximin, metronidazole, clarithromycin, and ciprofloxacin). The analysis revealed that antibiotics greatly improved patients' Crohn's disease activity, with a total response (defined as clinical response plus remission) odds ratio of 0.715 (95% CI: 0.6319–0.7971), a clinical response odds-ratio of 0.7478 (95% CI: 0.6214–0.8715), and a remission odds-ratio of 0.6877 (95% CI: 0.5768–0.7987). The Number Needed to Treat for each of the antibiotics used in the clinical trials were 5.018 (Ciprofloxacin), 6.480 (Clarithromycin), 7.556 (Metronidazole), and 6.824 (Rifaximin). This is an important outcome because it not only opens up a new treatment option for those suffering from Crohn's Disease but it also leads credibility to the theory that Crohn's is caused, at least in part, by bacteria, such as Mycobacterium avium subspecies paratuberculosis and adherent invasive E. coli.

## LOW DOSE IL-2 FOR THE TREATMENT OF MODERATE TO SEVERE ULCERATIVE COLITIS

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Background: A significant proportion of patients with ulcerative colitis (UC) have suboptimal responses to medical therapy. Expansion of regulatory T cells (Tregs), but not conventional T cells (Tcons), through the use of low doses (LD) of the T cell growth factor Interleukin-2 (IL-2, Proleukin®), has been a promising approach in other immune-mediated diseases and pre-clinical humanized UC mouse models. We performed a phase 1b/2a clinical trial in patients with moderate-to-severe UC to determine if subcutaneously (SC) administered LD IL-2 is safe and results in a biological response.

Methods: An open-label single arm phase 1b/2a trial of LD SC IL-2 in moderate-to-severe UC patients involving 2 phases: (1) dose escalation phase, in which three sequentially increasing dose levels were tested: $0.3x10^6$ IU/m$^2$/day (Dose A), $1x10^6$ IU/m$^2$/day (Dose B) or $1.5x10^6$ IU/m$^2$/day (Dose C); (2) treatment at the maximum tolerated dose (MTD) phase, defined as the highest tolerated dose level at which fewer than 2 evaluable subjects experienced a dose limiting toxicity (DLT). Adult patients with UC and a Mayo score of 6–12 were included and received a daily

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