

# Gastrointestinal (GI) Locally-Activating JAK Inhibitor for Treatment of Ulcerative Colitis

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## OVERVIEW

A novel JAK inhibitor that successfully treats ulcerative colitis

- Minimal systemic absorption and therefore low risk of side effects
- Superior efficacy to existing agents that treat ulcerative colitis

## BACKGROUND

Inflammatory Bowel Disease (IBD) affects about one million people in the United States. The major types of inflammatory bowel disease (IBD) are ulcerative colitis (UC) and Crohn's disease, with the incidence of the former twice that of the latter. UC usually originates the rectum and extends proximally to the colon. The associated inflammation is restricted to the innermost, or mucosal, layer of the intestine and results in ulceration and bloody diarrhea. In addition, UC patients have up to 18% higher risk of developing colon cancer, depending on the severity and the duration of the disease. UC occurs widely in all age groups and large portion of patients relapse, thereby requiring life-long treatment.

Several treatment options exist for patients with UC, including anti-inflammatory medicines such as corticosteroids or 5-aminosalicylates, which unfortunately both suffer from both spotty usefulness and treatment-related toxicities. Generalized immune system suppressors like azathioprine and cyclosporin also have limited efficacy and create risks for systemic side effects. Anti-tumor necrosis factor (TNF) antibodies can work quite well, though they require lifelong injections. More recently, inhibition of the Janus Kinases (JAK1, JAK2, JAK3 and TYK2) has emerged as a new and better therapeutic approach for the treatment of UC<sup>12</sup>. However, JAK inhibitors are associated with side effects including major adverse cardiovascular events (MACE), thrombosis and pulmonary embolism, malignancies, and infections. A need exists for a method to deliver JAK inhibitors in a way that is more anatomically specific to the GI tract.

## INNOVATION

Researchers have discovered a GI locally activating JAK inhibitor for the treatment of colitis while minimizing systemic drug exposure to reduce the potential side effects. The compound MMT3-72 showed minimal inhibitory activities against all JAKs while also exhibiting minimal absorption into the systemic circulation. Subsequently, the local activation of MMT3-72 released the active form MMT3-72-M2 which does elicit potent JAK inhibitory activities in GI tissues. The drug was noted to be present in particularly high concentrations in the colon. And experiments in mouse models showed the agent to have superior efficacy compared to the existing drug tofacitinib as measured by disease activity incidence (DAI) scoring, length of affected colon, GI bleeding, and

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histologic examination of recovered colonic tissues. These data suggest that GI locally activating JAK inhibitor MMT3-72 provides advantage for superior efficacy and minimizes potential systemic side effects in treatment of IBD.