CLX-103

CLX-103: A NOVEL MOLECULAR CONJUGATE OF MESALAMINE WITH EICOSAPENTAENOIC ACID AND CAPRYLIC ACID FOR THE TREATMENT OF ULCERATIVE COLITIS AND INFLAMMATORY BOWEL DISORDERS

- **A Novel Next Generation 5-aminosalicylic acid (5-ASA) Prodrug Conjugate**
- **Designed for Slow Sustained Release of The Actives at the Target Site (Intestine/Colon)**
- **Host Intestinal Enzyme Mediated Release of the Actives; 5-ASA, Eicosapentaenoic Acid (EPA) and Caprylic Acid (CPA)**
- **All the Released Actives 5-ASA, EPA and CPA , expected to have Advantageous Synergistic Pharmacological Effects**
- **Expected to be More Efficacious than the Commercial Formulations of 5-ASA/ Sulphasalazine**
- **Safer than Suphasalazine and 5-ASA formulations; Reduced Systemic Exposure to 5-ASA, N-Acetyl 5-ASA, No Systemic Exposure to Sulphapyridine**
- **Preclinical Work Nearing Completion; Ready For GLP Tox And Clinical Development**
- **US Patent and other National Patents ISSUED/ALLOWED**

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1. Opportunity Overview

CLX-103 is a differentiated drug candidate for the treatment of inflammatory bowel disorders. CLX-103 has the potential to become "next-generation Aminosalisylate" with an incremental benefit in efficacy and safety than 5-ASA and sulfasalazine. CLX-103 is designed to exert its anti-inflammatory activity specifically at the intestinal target sites (ileum and colon). CLX-103 is expected to have a significantly improved activity in Ulcerative Colitis (UC) due to the synergistic effect from Eicosapentaenoic acid (EPA) and Caprylic acid (CPA) coupled with the improved delivery and tissue distribution of the actives at the target site.

CLX-103 is molecular conjugate of 5-ASA with EPA and CPA. In this molecular conjugate, 5-ASA is chemically linked with EPA and CPA utilizing CellixBio's proprietary patented Synergix platform technology. EPA and CPA are linked with 5-ASA through simple ester linkages, which undergoes hydrolytic cleavage by the host enzymes present in the small intestinal fluid and intestinal epithelium. The presence of two ester bonds in the molecule controls the release profile of 5-ASA in the intestine and ensure the effective delivery of the active moieties at the target site (intestine), while minimizing the systemic absorption.

CellixBio have completed biopharmaceutical assessment, pharmacokinetic study in the rats and *in-vivo* intestinal tissue distribution study and efficacy study in mice. Non-clinical studies indicate that CLX-103 should achieve a favorable target product profile (TPP) as given below:

- Oral/Rectal route of administration
- First line therapy for UC superior to 5-ASA/sulphasalazine in efficacy (improved response rate and remission incidence)
- Improved safety over marketed formulations of 5-ASA/Sulphasalazine
- Potential disease modification effects due to synergistic pharmacology with EPA and CPA

2. Market Description

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), represents disorders characterized by an uncontrolled autoimmune inflammatory response in the gut. In CD, inflammation primarily involves all layers of the intestinal wall (transmural inflammation) and can affect any area of the gastrointestinal tract, from mouth to anus. UC, on the other hand, is usually confined to the colonic mucosa, where it consistently affects the rectum and can variably extend proximally to affect portions of, or the entire, large intestine. An undetermined percentage of patients can experience a severe attack of UC that can potentially be life threatening, requiring hospitalization, intensive medical regimen, and in 25% of the cases, total colectomy. Long standing UC is an important risk factor for colorectal cancer, with its incidence increasing and dependent on the duration and extent of disease.

As the etio-pathogenesis of UC is still unclear, no known cure exists. Current therapeutic strategies are aimed to reduce/shut down the inflammatory response activated during relapse of the disease, as well as to prevent further disease flare-ups. However, several patients do not respond, or experience loss of response, to treatment leading to prolonged hospitalization and increased medical expenses that eventually leave surgery as the only therapeutic option.

The estimated yearly prevalence of UC is ~ 0.2% of the total North American population and seems to grow year after year in Western countries. Approximately 1.86 billion (20% of the world population) patients have been diagnosed with UC globally, with 1.54 billion patients currently receiving treatment. Traditional therapies have yielded $4.18 billion in annual sales around the world, a figure expected to increase to $6.85 billion by 2022 (Global Data, Ulcerative Colitis—Global Drug Forecast and Market Analysis to 2022, Pipeline plus, ulcerative colits and Crohn's disease, August 2012). The total annual estimated financial burden (adding direct and indirect costs) of IBD in the US is $14.6 billion to $31.6 billion.

High prevalence, young age of disease onset and the chronic and relapsing nature of UC, explain the elevated medical costs over the past several years resulting from this disease. Main

commercial drivers will be disease prevalence, improving diagnosis, better therapies and wider access to treatments.

3. Unmet Medical Need

The therapeutic management of UC has been divided into two main categories: i) treatments targeting the active phase of disease; and ii) treatments designed to maintain disease remission. The therapeutic algorithm is also dictated by the severity and extent of disease. Therefore, different compounds in various formulations are selected to fulfil these aforementioned criteria. Typically, the therapeutic approach to a disease flare-up consists of a 'step-up' strategy, starting with a first-line therapy, generally characterized by decreased toxicity, and climbing stepwise up the 'treatment pyramid' towards more potent (and potentially toxic) drugs if response to previous medications fails. The current artillery of drugs commonly used to treat UC are the aminosalicylates, the steroids, the immunomodulators and the biologics.

Aminosalicylate class of drugs represents the most diffuse first-line therapy for mild to moderate UC. Aminosalicylates are considered to be effective both for the induction as well as the maintenance of remission in mild to moderate disease. However, although obviously superior to placebo, aminosalicylate's capability to induce remission is quite low. Considering this, novel therapeutic options are extensively needed to treat reduce relapse rates in refractory patients. CLX-103 is expected to offer significant improvement in the therapeutic outcome over the current available aminosalicylate class of drugs.

4. Scientific Rationale

CLX-103 is molecular conjugate of 5-amino salicylic Acid (5-ASA) with EPA and CPA. 5-ASA is an approved agent for the induction and maintenance of remission for ulcerative colitis. The mechanism of action include, inhibition of mucosal production of arachidonic acid metabolites, both through the COX and LOX pathways and the potential to inhibit the activation of nuclear factor kappa B (NFκB).

The EPA and CPA were selected as the molecular partners of 5- ASA, considering their proven therapeutic effects in various inflammatory conditions and the availability of extensive human safety data (1-5). EPA is an Omega-3 fatty acid known to have broad spectrum of anti-inflammatory properties that include Inhibition of leucocyte chemotaxis, adhesion molecule expression, leucocyte-endothelial adhesive interactions and cytokines production, activation of the anti-inflammatory transcription factor NR1C3 and inhibition of the activation of the pro-inflammatory transcription factor NFK-B. CPA is a GRAS listed molecule with potential anti-inflammatory/anti-fungal (more specifically against candida) activity. CPA is an eight-carbon saturated fatty acid and is found naturally in the milk of various mammals, and as a constituent of coconut oil. CPA is found to suppress the secretion of IL-8, a key cytokine believed to involve in induction and progression of Inflammatory Bowel Disease (6). Additionally, recent studies showed that high level of Candida colonization occurs with diseases of the gastrointestinal tract such as gastritis and colitis and suggests that probiotic and even antifungal therapy should be considered in the treatment of chronic inflammatory bowel diseases (7).

Thus, CLX-103 has the ability to address multiple components involved in the pathogenesis of IBD and thus bring in an effective cure as well as longer remission than the currently used first line salicylate class of drugs.

5. Preclinical Summary

Several preclinical investigations were carried out with CLX-103 in order to assess the biopharmaceutical, pharmacokinetic and intestinal tissue uptake properties.

The biopharmaceutical properties (solubility, physicochemical and stability in various biological matrixes) of CLX-103 were quite acceptable for developing an oral/rectal dosage form that could ensure optimal delivery and retention of the active moieties in the intestine. The release of the actives is shown to be mediated by intestinal hydrolytic enzymes present in the small intestinal fluids and in the intestinal (small intestine and colon) epithelium. Notably, CLX-103 was stable in simulated gastric fluids, a condition ideal for the delivery of the actives to lower intestinal

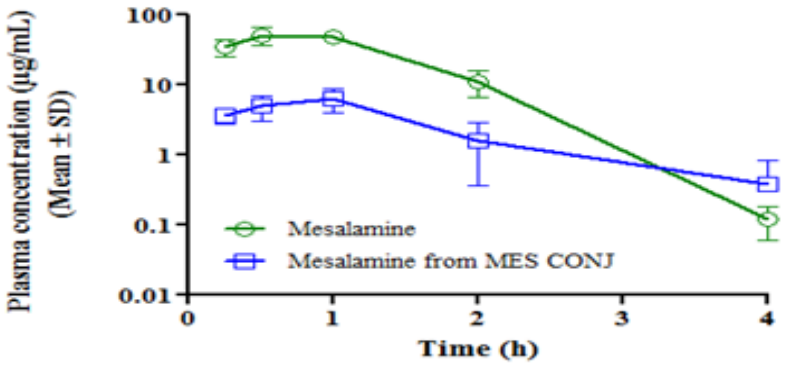
regions. The in-vitro release study of the actives from CLX-103 in the intestinal homogenate was close to 100% within the 4-hr incubation time.

Intestinal tissue distribution study in mice showed very low systemic concentration of mesalamine, but significant and sustained levels of mesalamine in the intestinal tissues (jejunum, ileum and colon) in the animals exposed to CLX-103 as compared to sulfasalazine. In addition, the inter-animal variability for the tissue levels of mesalamine was remarkably less with CLX-103 in comparison with that observed with sulfasalazine.

A comparative in vivo rat oral pharmacokinetic study was conducted at a dose equivalent to 100 mg/kg of 5-ASA. The plasma concentration vs time profile of mesalamine is shown in the fig below.

The systemic exposure to 5-ASA after oral dosing with CLX-103 was significantly low in relation to 5-ASA

Test animal: Male Sprague-Dawley rats
Dose: 100 mg/kg equivalent 5-ASA



Compound	Cmax (µg/mL)	Tmax (h)	AUC_{0-t} (µg.h/mL)
5-ASA	56.3 ± 9.32	0.70 ± 0.27	81.3 ± 8.83
CLX-103	6.39 ± 2.30	0.90 ± 0.22	10.4 ± 1.80

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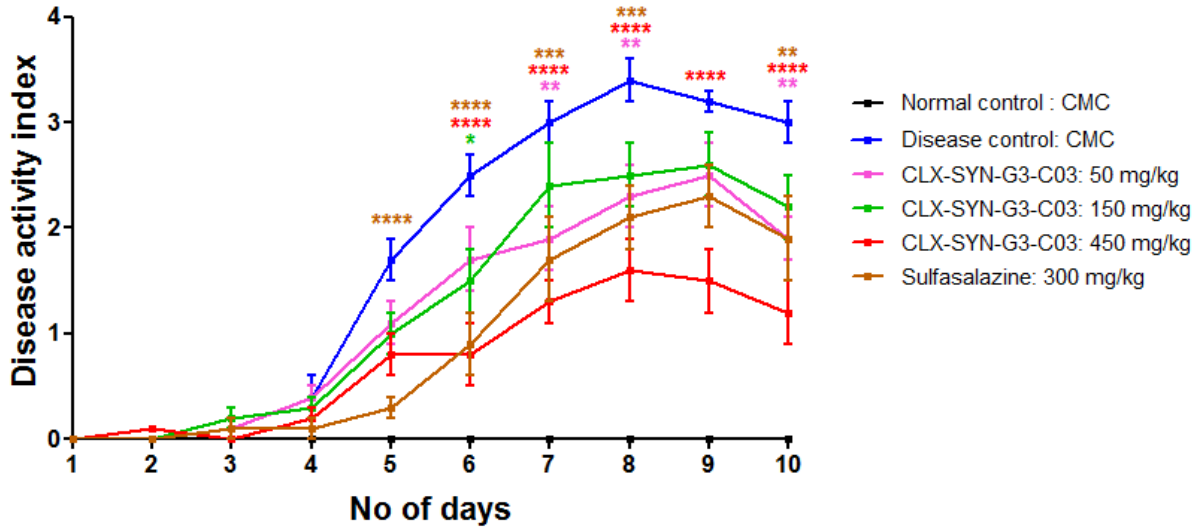
The in vivo data was consistent with the in-vitro release studies. There was no detectable level of CLX-103 in the plasma. The systemic exposure to 5-ASA and its metabolite were significantly lower with CLX-103 compared to an equivalent dose of 5-ASA. This data suggests the potential retention of the active components in the intestine, when dosed with CLX-103, which is an essential requirement for an IBD drug.

In an acute DSS induced colitis model in mice, once daily oral administration of CLX-SYN-G3-C03 at 50, 150 and 450 mg/kg/day showed statistically significant reduction in the Disease Activity Index (DAI) and colon weight/ length ratio ($p<0.05$ at 50 and 450 mg/kg). Additionally, CLX-SYN-G3-C03 showed lower mean MPO activity in colon tissue homogenates and decrease in histological scores at all the dose levels tested, when compared with disease control. The reference compound sulfasalazine at 300 mg/kg/day demonstrated significant efficacy in this model, as expected.

Effect of CLX-SYN-G3-C03 (CLX-103) on Disease Activity Index in DSS Induced Colitis in C57BL/6 Mice



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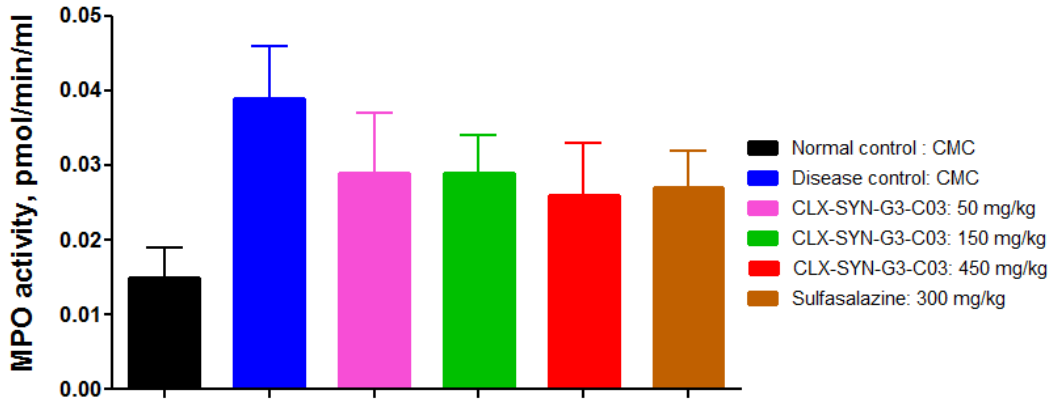
Note: Data shown as Mean ± SEM, * p<0.05, ** p<0.01, *** p<0.001 and **** p<0.0001 vs Disease control, Two way ANOVA followed by Bonforoni post test.

Effect of CLX-SYN-G3-C03 on MPO activity in colon in DSS Induced Colitis



Data shown as Mean ± SEM, One way ANOVA followed by Dunnett's post test

Chemistry Manufacturing Controls

- CMC Development : Ongoing
- A conventional or delayed or extended release oral dosage form or rectal dosage forms that can deliver the actives locally at the affected site of GIT could be easily developed

IND Filing with US-FDA / EMA / DCGI, India:

- Projected Schedule: 1Q 2017

Intellectual Property

- US Patent: US 933187 B1
- Australian Patent Issued
- Filed with 12 National Patent Offices

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