PALI-2108, A COLON-SPECIFIC PDE4 INHIBITOR PRODRUG, IS BIOACTIVATED IN THE COLON AND REDUCES COLON TISSUE PDE4B IN A DOSE-DEPENDENT MANNER, INCREASING cAMP AND SUPPRESSING TNF-α IN A MOUSE MODEL OF COLITIS

Joerg Heyer, PhD[1], Joie Bernard, PhD[1], Sonia Edaye, PhD[2], Florian Rieder, MD[3], Mitchell Jones, MD, PhD[1]
1. Palisade Bio, Carlsbad, CA; 2. Charles River Labs, Montreal, QC; 3. Cleveland Clinic, Cleveland, OH

Digestive Disease Week
San Diego 2025
#Mo1296

Introduction

Ulcerative Colitis (UC) is a chronic and debilitating inflammatory disease of the lower gastrointestinal (GI) tract, affecting approximately 5 million people worldwide. While current treatments for UC, such as phosphodiesterase-4 (PDE4) inhibitors, have shown efficacy in reducing key inflammatory mediators like TNF-α, these therapies often suffer from central nervous system (CNS) toxicity, limiting their overall therapeutic potential. PALI-2108 is an innovative, orally-delivered, lower GI-Tract-specific PDE4 inhibitor prodrug designed to activate locally in the lower GI-Tract, thus reducing systemic exposure and minimizing CNS-related side effects. This study evaluates the preclinical efficacy and safety profile of PALI-2108 in a mouse model of colitis, with a particular focus on its impact on PDE4B expression, cAMP levels, and TNF-α suppression as well as predicting efficacious PALI-0008 levels in patients.

Methods

DSS Model: Colitis was induced in mice using 4% dextran sulfate sodium (DSS) in drinking water. Mice were treated with PALI-2108 at 20, 40, or 80 mg/kg BID, cyclosporine A (40 mg/kg, BID), or apremilast (12.5 mg/kg, BID). Clinical disease progression was monitored through changes in body weight, stool consistency, and fecal blood scores, with the Disease Activity Index (DAI) calculated to quantify disease severity. Colon biopsies were collected for analysis of PDE4B expression, cAMP levels, and TNF-α expression. *Pharmacokinetic (PK) Modeling:* Population pharmacokinetic modeling was conducted using non-linear mixed-effect modeling. Human ex vivo fecal data from UC patients and healthy volunteers (HV) were used to construct the model, with consistent absorption rates observed in both groups. Bioavailability was set at 29%, and alternative bioavailability values (F) were considered for the CTS analysis.

Results

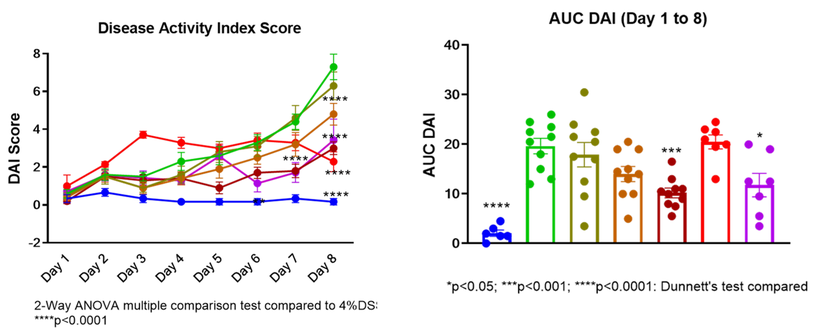

Figure 2 In the DSS acute colitis mouse model, PALI-2108 significantly showed dose dependent efficacy on disease activity index (DAI) score and AUC of DAI from day 1 to 8.

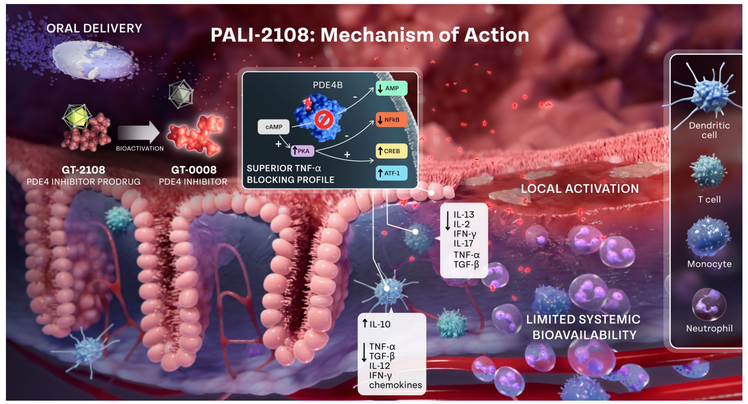

Figure 1. PALI-2108 Mechanism of Action

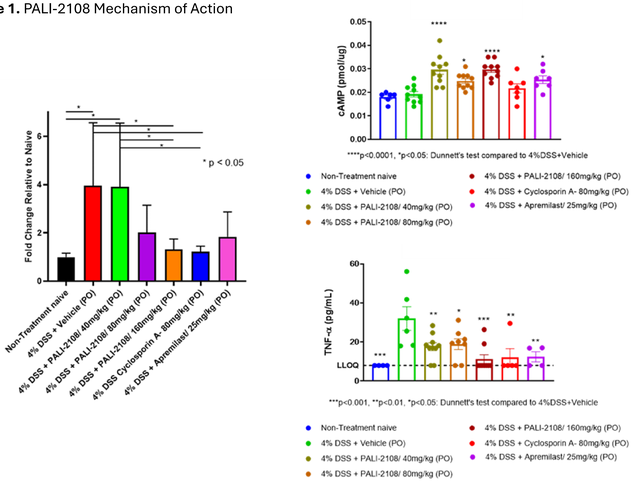

Figure 3: (Left) PDE4B expression (right top) cAMP levels, and (right bottom) TNFα levels in colon tissues in Naïve and groups treated with Vehicle, PALI-2108 and Apremilast.

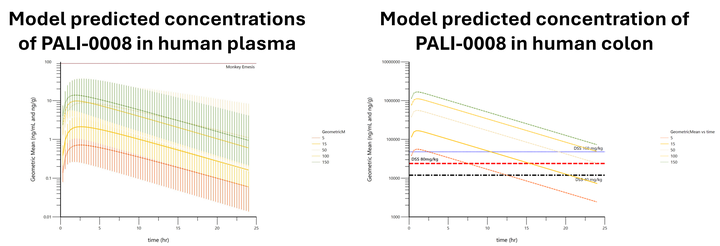

Figure 4: Clinical trial PK simulations suggested several feasible starting doses that adhere to safety thresholds defined by previous toxicological assessments. These doses have the potential to achieve tissue levels associated with efficacious mice levels from the DSS model, while maintaining plasma exposure below anticipated NOAELs and levels associated with emesis in monkeys.

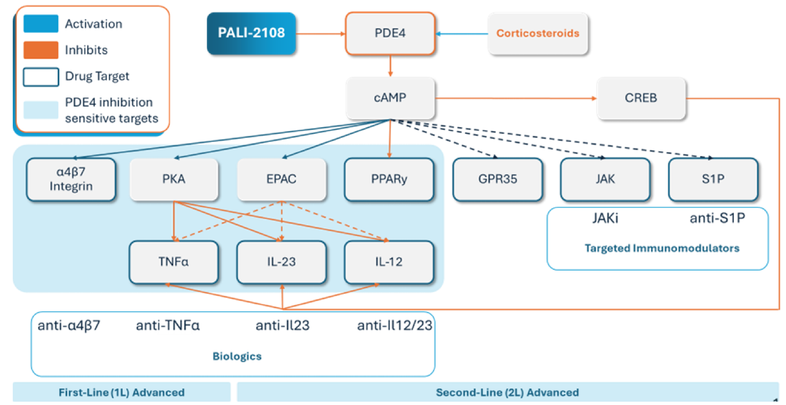

Figure 5. UC drug targets and their cAMP regulation.

PDE4 is directly or indirectly regulating multiple drug targets in Ulcerative Colitis, whereas other targets are not being regulated by cAMP levels. This allows for a rationale selection of drug combinations, with PALI2108 being uniquely placed for its combinability due to its benign tolerability profile.

Summary and Conclusions

Our previous studies demonstrated that PALI-2108 undergoes efficient bioconversion in the lower GI-Tract, leading to minimal systemic exposure and no evidence of CNS toxicity in both preclinical models and human-derived ex vivo data. In the present study, PALI-2108 treatment significantly improved clinical parameters of colitis, including the DAI, body weight, and colon length in a dose-dependent manner. Furthermore, PALI-2108 administration resulted in a marked dose-dependent reduction of PDE4B expression in colon tissues, with higher cAMP levels and a notable suppression of TNF-α compared to standard treatments like cyclosporine A and apremilast. These results indicate that PALI-2108 effectively modulates inflammatory pathways in the colon, promoting a more favorable immune response.

PALI-2108 is a promising colon-specific PDE4 inhibitor for the treatment of UC and other inflammatory bowel diseases (IBD). By increasing cAMP levels and modulating key inflammatory mediators such as TNF-α, PALI-2108 shows significant potential for reducing symptoms associated with UC. The preclinical data underscore its efficacy and safety profile, with minimal CNS toxicity and favorable dose-dependent effects. A Phase 1 clinical trial is currently underway to further assess the safety, tolerability, and pharmacokinetic properties of PALI-2108 in healthy volunteers and UC patients, offering hope for a more effective and better-tolerated alternative to existing treatments for UC.