PALI-2108, A COLON-SPECIFC PDE4B INHIBITOR PRODRUG IS ACTIVATED IN THE COLON AND REDUCES ULCERATIVE COLITIS SYMPTOMS IN AN ACUTE COLITIS DSS MOUSE MODEL

palisadebio

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Introduction

Ulcerative Colitis is a devastating inflammatory disease of the lower GI tract with an estimated incidence of 900,000 patients and an estimated prevalence of 5 million patients. Phosphodiesterase-4 (PDE4) inhibition leads to downregulation of inflammatory cytokines. Systemic PDE4 inhibitors exposure has resulted in Central Nervous System (CNS) toxicity such as nausea or vomiting, often leading to discontinuation of therapy limiting efficacy.

We developed PALI-2108, an orally-delivered, colon-activated PDE4 inhibitor prodrug. PALI-2108 gets converted by colonic bacterium enzyme β-glucuronidase to the active drug PALI-0008 and minimizes its systemic exposure, thereby reducing CNS toxicity as demonstrated in mice and dogs. Here we demonstrate:

- Target engagement of PDE4 inhibitor active (PALI-0008) released locally from PALI-2108.
- Significant PALI-2108 treatment effect on efficacy measures including colon length and DAI in an acute DSS-induced colitis mouse model in a dose dependent manner.
- Significant PALI-2108 treatment effect on biomarkers including reduced PDE4B expression, increased cAMP, and reduced TNF alpha in colon tissues.
- Model the predicted active inhibitor PALI-0008 plasma concentrations regarding efficacious doses in the DSS mouse model

Methods

Study 1: Colitis was induced in mice using a single 3% oxazolone (OXZ) intrarectal (i.r.) dose. Mice were then treated with PALI-2108 (4.2 mg/kg) twice daily (BID) for 3 days. Plasma, duodenum, ileum, and colon samples were collected at 72 hours to measure PALI-2108, -0708, and -0008 concentrations. A cellular thermal shift assay (CETSA) was developed to assess on-target PDE4 binding in colon tissue homogenates. Mice were dosed with apremilast, PALI-2108, or vehicle, and changes in thermal stability were measured to evaluate PDE4 binding.

Study 2: Acute colitis was induced using 2% DSS in drinking water from Day 0 (D0) to Day 7. Mice were treated with PALI-2108 BID (1.5 mg/kg) from D-1 to D6, while tacrolimus and apremilast were administered once daily (QD). Mice were sacrificed on Day 7. Disease activity index (DAI) scores were recorded based on body weight loss, stool consistency, and blood presence in feces.

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

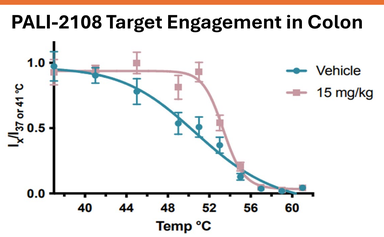


Figure 1. Thermal stabilization effect on PDE4 was observed confirming target engagement in vivo in OXZ mouse colon demonstrating target engagement.

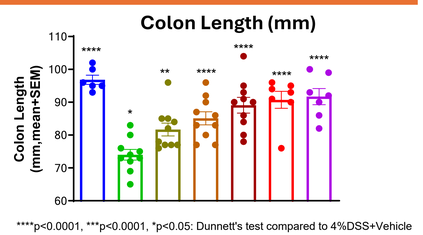


Figure 2. In the DSS acute colitis mouse model, PALI-2108 significantly prevented, in dose dependent manner, increased Body Weight Score, the colon length reduction on Day 8.

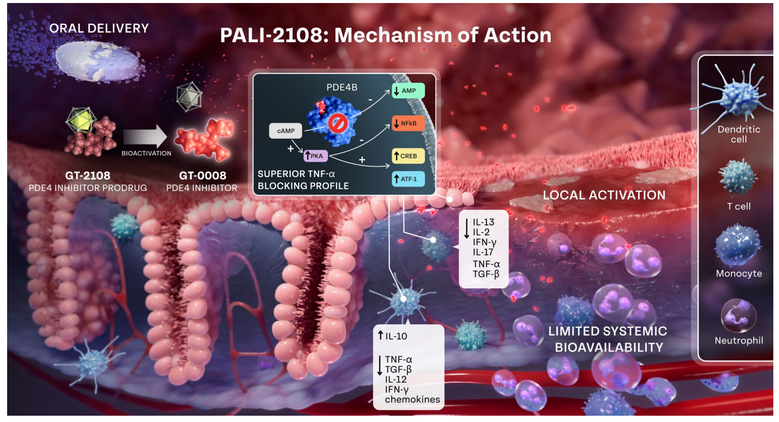


Figure 3. PALI-2108 Mechanism of Action

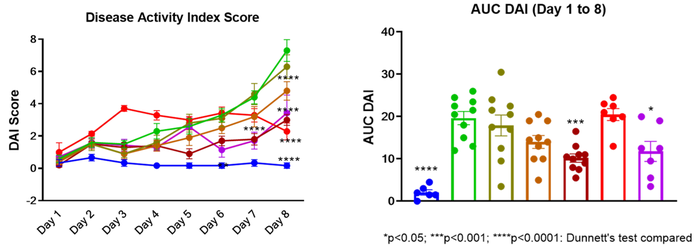


Figure 4. In the DSS acute colitis mouse model, PALI-2108 significantly showed dose dependent efficacy on disease activity index (DAI) score and AUC of DAI from day 1 to 8.

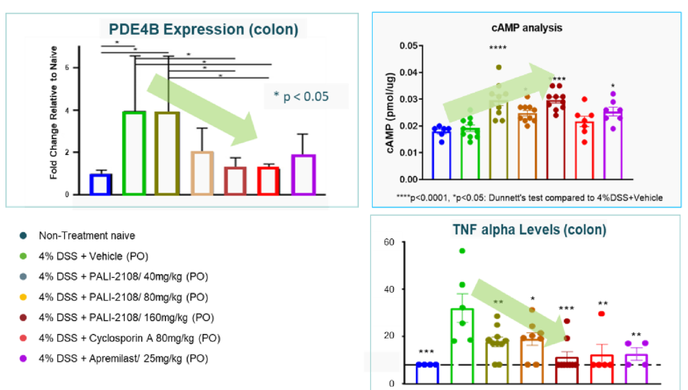
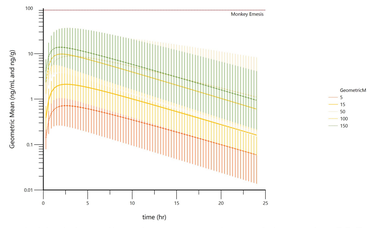


Figure 5. In the DSS acute colitis mouse model, PALI-2108 resulted in significantly reduced PDE4B expression (fold change relative to Naïve), increased levels of cAMP (pmol/ug), and reduced TNF alpha (fold change relative to Naïve) over the course of the study day 1 to 8.

Model predicted concentrations of PALI-0008 in human plasma



Model predicted concentration of PALI-0008 in human colon

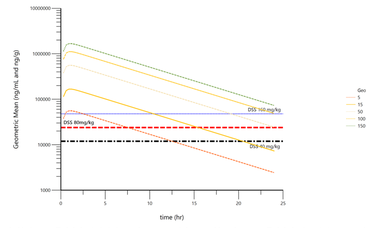


Figure 6. Model predicted concentrations of the active PDE4 inhibitor PALI-0008 released locally from PALI-2108 prodrug.

Clinical trial 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.

Summary

PALI-2108 is a novel, promising therapy for colonic inflammatory conditions such as ulcerative colitis (UC) and inflammatory bowel disease (IBD). Its localized bioactivation, expanded colonic therapeutic window, extended-release characteristics, and potent PDE4 inhibition result in superior efficacy compared to other PDE4 inhibitors. PALI-2108 is currently under evaluation in a Phase 1 study, with a favorable safety profile observed in ascending single-ascending-dose cohorts.

Key findings for PALI-2108 include:

- **Oral Administration and Prodrug Conversion:** PALI-2108 is effectively converted to the active PDE4 inhibitor, PALI-0008, in the colon following oral administration in mice, dogs, and humans in a dose-dependent manner.
- **Target Engagement and Potency:** PALI-2108 shows favorable target engagement and superior potency compared to other PDE4 inhibitors.
- **Dose-Dependent Efficacy:** Demonstrated dose-dependent efficacy in an induced mouse UC model (DSS) compared to standard-of-care and systemic PDE4 comparators.
- **Safety and Tolerability:** No systemic safety issues seen in mice, dogs, or monkey.
- **Pharmacokinetics (PK) Modeling:** Twice-daily (BID) dosing during induction and once-daily (QD) dosing during maintenance are supported by PK modeling, leveraging the drug's extended-release properties and the increased bowel movement frequency during active disease.

Unmet Need and Clinical Potential:

Better-tolerated oral PDE4 inhibitors remain an unmet need in IBD. PALI-2108, a colon-bioactivated PDE4 inhibitor with 20-30% bioavailability, effectively reduces colitis symptoms in the DSS mouse model without CNS toxicity associated with systemic exposure. This suggests it could be a novel alternative for UC patients. Safety and tolerability of PDE4 inhibitors are closely linked to peak drug concentrations (Cmax). The proposed BID dosing during induction minimizes Cmax, while the extended-release characteristics allow for effective QD dosing during maintenance. The pharmacokinetic modeling suggests a favorable therapeutic window, with PALI-2108 achieving higher tissue-to-plasma drug ratios and enhanced tissue inhibition compared to other PDE4 inhibitors.PALI-2108 has now entered a Phase 1 study to assess its tolerability in healthy volunteers and UC patients.