Gut-Targeted PDE4 Inhibition with PALI-2108 Demonstrates Rapid Clinical, Histologic, and Biomarker Improvement in Ulcerative Colitis: Translational Findings from a Phase 1 Study

Joerg Heyer PhD[1], Patrick Colin BPharm PhD[1], Gaetano Morelli MD[2], Florian Rieder MD[3] and Mitch Jones MD, PhD[1]
[1]Palisade Bio, Carlsbad, CA; [2]Altasciences, Montreal, QC; [3]Cleveland Clinic, Cleveland, OH

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon affecting approximately 5 million patients worldwide and remains associated with substantial morbidity despite the availability of advanced biologic and small-molecule therapies. Phosphodiesterase-4 (PDE4) inhibition is a clinically validated anti-inflammatory mechanism that suppresses multiple cytokine pathways central to UC pathophysiology through elevation of intracellular cyclic AMP (cAMP). However, the clinical utility of systemic PDE4 inhibitors has been limited by dose-limiting gastrointestinal and central nervous system adverse events driven by peak systemic exposure (Cmax).

PALI-2108 is a novel, orally administered PDE4 inhibitor prodrug designed for localized bioactivation in the terminal ileum and colon. The prodrug is cleaved by colonic bacterial β-glucuronidase, releasing the active PDE4 inhibitor (PALI-0008) selectively in lower gastrointestinal tissues. This approach is intended to expand the therapeutic window by minimizing upper GI exposure, reducing systemic Cmax, and limiting CNS toxicity while maintaining potent local PDE4 inhibition.

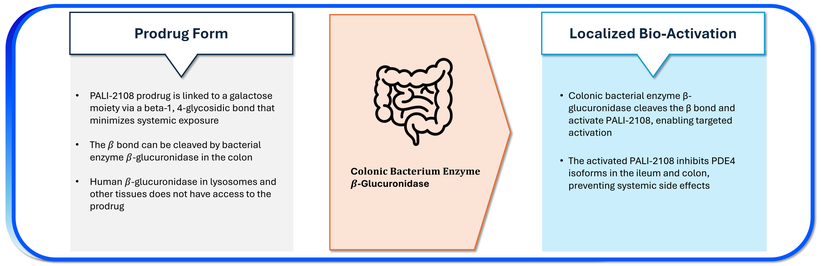


Figure 1: Localized bio-activation targets the ileum and colon, reducing the risk of GI and CNS adverse events with PALI-2108 vs. non-specific and non-localized PDE4 inhibitors.

Here, we report results from a first-in-human Phase 1a/1b study (NCT06663605) evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of PALI-2108 in healthy normal volunteers (NHVs) and patients with moderate-to-severe ulcerative colitis.

Methods

NCT06663605 was a single-center Phase 1 study comprising a randomized, double-blind, placebo-controlled Phase 1a component in healthy normal volunteers and an open-label Phase 1b cohort in patients with moderate-to-severe UC. In Phase 1a, subjects received ascending single and multiple oral doses of PALI-2108, including a food-effect cohort, to evaluate safety, tolerability, and pharmacokinetics. In Phase 1b, UC patients received PALI-2108 30 mg BID for 7 days following a 5-day dose titration. Safety assessments included adverse events, laboratory tests, vital signs, and ECGs. Pharmacokinetics were assessed in plasma and colon tissue, and pharmacodynamic endpoints included inflammatory biomarkers, colon tissue PDE4 expression, histology, and clinical disease activity.

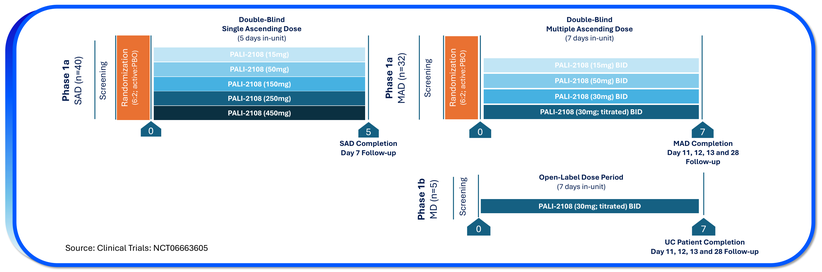
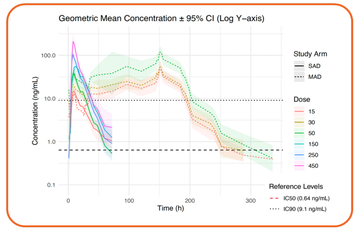


Figure 2: Phase 1a/b double-blind, placebo-controlled, safety, tolerability, PK, and PD study of PALI-2108 in NHV and an open-label study of UC patients (NCT06663605).

Results

Phase 1 SAD/MAD PK Demonstrates PK Characteristics and Superior Exposure to Other PDE4s

Dose Proportionality and Extended Half-Life Enabling Daily Dosing



Single Ascending Dose (SAD)

PALI-2108 (prodrug; NOT SHOWN)
- **Tmax:** ~3–4h → consistent with small intestinal dissolution (Eudragit + prodrug design)
- **Exposure (AUC):** Minimal, as intended (GI-restricted)

PALI-0008 (active PDE4 inhibitor)
- **Tmax:** ~8–9h → consistent with ileocolonic bioconversion
- **PK profile:** Extended release; ~2–3× longer half-life than other PDE4 inhibitors (usually BID)
- **Dose proportionality:** Cmax and AUC approximately dose-proportional

Multiple Ascending Dose (MAD

Bioconversion
- PALI-2108 converted locally to PALI-0008 in terminal ileum/colon

Steady State
- Reached within ~48h
- Stable pre-dose troughs with repeat dosing
- Pre-dose troughs ~20% higher than single-dose Cmax, above IC90

Dosing Implications
- Extended half-life supports **once-daily dosing**

Figure 3: Safety Results of the Phase 1a/1b. PALI2108 is safe and well tolerated.

Phase 1a Confirms PALI-2108 was Safe and Well Tolerated

SAD Safety and Tolerability

	15mg		50mg		150mg		250mg		450mg	
	Active	PBO	Active	PBO	Active	PBO	Active	PBO	Active	PBO
Number of subjects	6	2	6	2	6	2	6	2	6	2
TEAEs, possibly related (n)	0	0	0	0	0	0	0	0	22	1
Investigator defined TEAEs (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (100%)	1 (50%)
> Grade 1 TEAE (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severe Adverse Events (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Withdrawn b/c TEAE (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

MAD Safety and Tolerability

	15mg BID		30mg BID (titrated)		30mg BID		50mg BID	
	Active	PBO	Active	PBO	Active	PBO	Active	PBO
Number of subjects	6	2	6	2	6	2	6	2
TEAEs, possibly related (n)	0	0	1	0	21	0	18	0
Investigator defined TEAEs (n/%pts)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	4 (67%)	0 (0%)	4 (67%)	0 (0%)
> Grade 1 TEAE (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)	0 (0%)	1 (17%)	0 (0%)
Severe Adverse Events (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Withdrawn b/c of TEAE (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)

PALI-2108 Ph1a Findings:
- ✓ **84 patients treated and no SAEs and no AEs related to labs or EKGs**
- ✓ **Completed all SAD cohorts** demonstrating Safety and Tolerability of single dose PALI-2108 up to 450mg
- ✓ **Completed all MAD cohorts** demonstrating safety and tolerability of twice daily (BID) doses of 15mg, 30mg and 50mg with 15mg BID having zero (not even minor) TEAE in any subject
- ✓ **Completed FE cohort** demonstrating minimal changes, reduced Cmax, right shifted AUC and delayed Tmax due to colon bioactivation
- ✓ **Confirmed utility of titration** with 30mg BID like other PDE4s

Figure 4: Pharmacokinetic profile of the Phase 1 a multiple ascending dose (MAD) cohort.

- ✓ **Tissue cAMP was increased** in 4/5 patients (~27% individual mean increase) as expected due to inhibition of PDE4 enzyme
- ✓ **Tissue lymphocytes was decreased** in 4/4 (mean ~29% reduction; ~40% by individual mean approach)
- ✓ **Tissue PDE4B was decreased** in 5/5 patients (mwan ~71% reduction)
- ✓ **Fecal calprotectin was decreased** in 4/5 patients by a mean of ~70.3%
- ✓ **hsCRP was decreased** by a mean of ~15.2%

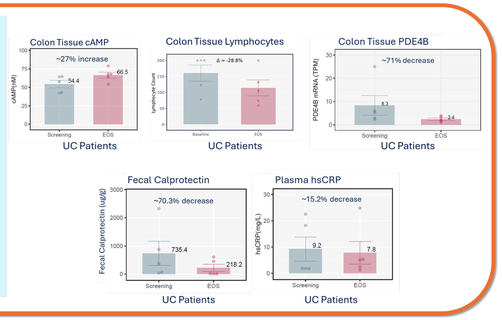
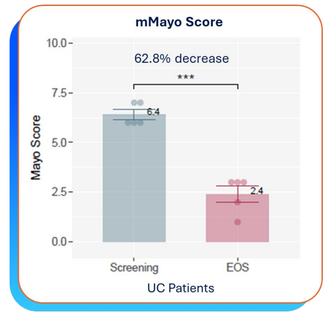


Figure 5: In Phase 1b study, improvements were seen in mechanistic and inflammatory markers, including cAMP, PDE4B and TLC, CalPro and hsCRP.



Patient	Screening (Baseline)	Day 7	Absolute Δ	% Change from Baseline
1701	6	2	-4	-66.7%
1702	6	1	-5	-83.3%
1703	6	3	-3	-50.0%
1704	7	3	-4	-57.1%
1705	7	3	-4	-57.1%

Mean Baseline = (6+6+6+7+7)/5 = **6.4**
Mean Day 7 = (2+1+3+3+3)/5 = **2.4**
Mean Absolute Change = **-4.0**
Mean % Change from Baseline = (**-62.8%**)

Modified Mayo Score was reduced in 5/5 patients with mean absolute reduction of 62.8% from baseline

Clinical Response was achieved in 5/5 (100%) of patients (≥30% or ≥3-point drop in modified Mayo score with rectal bleeding subscore of 0 or 1)

Clinical Remission was achieved 2/5 (40%) of patients

Figure 6: Clinical Response and Remission as demonstrated by Modified Mayo Score (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

Summary

In this Phase 1a/1b study (NCT06663605), PALI-2108 demonstrated a favorable safety, tolerability, PK, and PD profile in NHV and patients with moderate-to-severe UC. Across all cohorts (n=89), there were no SAEs, no treatment-related laboratory or ECG abnormalities, and no study discontinuations. PDE4-related adverse events were mild, transient, and occurred primarily during early titration, supporting the tolerability of the dosing strategy.

Pharmacokinetic analyses confirmed approximately dose-proportional exposure, delayed Tmax, and extended half-life of the active metabolite (PALI-0008), consistent with targeted ileocolonic bioactivation and extended-release characteristics. Colon tissue concentrations approached IC90 levels even up to 36 hours post-dose while maintaining >IC90 systemic exposures with very good tolerability, supporting once-daily dosing now used in our FSCD cohort study and an improved therapeutic index relative to systemic PDE4 inhibitors.

In the UC cohort, PALI-2108 treatment resulted in consistent pharmacodynamic target engagement and anti-inflammatory effects. Colon tissue PDE4B expression was reduced in all patients, accompanied by increased tissue cAMP levels, reduced lymphocyte infiltration, and improvements in inflammatory biomarkers including fecal calprotectin and plasma hsCRP. Histologic improvement was observed across multiple validated scoring systems, and all patients achieved clinical response by modified Mayo Score, with a subset achieving clinical remission after just one week of treatment.

Collectively, these results demonstrate that PALI-2108 achieves localized PDE4 inhibition with favorable tolerability, robust biomarker confirmation of mechanism, and early signals of clinical activity in ulcerative colitis. The data support continued clinical development of PALI-2108 as a differentiated, ileum and colon-targeted oral PDE4 inhibitor prodrug which is locally bioactivated for inflammatory bowel disease.