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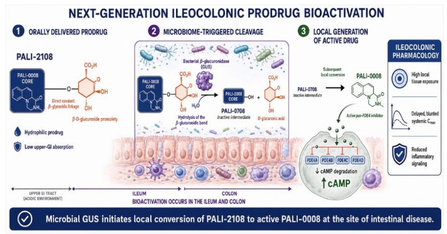
Fira Gran Via
October 17 – 20, 2026

PALI-2108, a Novel, Next-Generation Oral Once-Daily PDE4 Inhibitor Exhibits Gut-Targeted Drug Exposure and Favorable Safety and Tolerability in Inflammatory Bowel Disease

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INTRODUCTION AND AIM

Inflammatory bowel disease (IBD) is a debilitating disease with limited and unsatisfactory treatment options, highlighting the urgency for therapies that deliver potent anti-inflammatory effects and minimize systemic side effects. PALI-2108, an oral once-daily PDE4 inhibitor prodrug, is engineered as a delayed-release, locally targeted formulation combining enteric dissolution in the small intestine with microbiome-mediated ileocolonic bioactivation into its active form, PALI-0008, enabling high mucosal drug exposure while limiting systemic peak concentrations (C_{max}). This locally targeted design enables high mucosal exposure to PALI-0008 while limiting systemic peak concentrations (C_{max}), with the potential to improve the therapeutic profile of PDE4 inhibition in IBD (**Figure 1**).



Aim: We assessed pharmacokinetics (PK), pharmacodynamics (PD), safety, tolerability, and early clinical activity of PALI-2108, linking localized drug exposure and IC90 target coverage to PD effects and tolerability.

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

METHODS



In a Phase 1a/1b study, healthy volunteers (HVs) and patients with either moderate-to-severe ulcerative colitis (UC) or Fibrostenotic Crohn's disease (FSCD) received single ascending doses (SAD) of PALI-2108 or multiple ascending BID/QD doses, including dose titration and food-effect assessments (**Figure 2**).

We assessed plasma and ileocolonic tissue concentrations of PALI-0008 relative to PDE4 inhibitory thresholds along with treatment-emergent AEs (TEAEs), serious AEs (SAEs), ECGs, vitals, labs, exams, and drug discontinuation. UC end points included modified Mayo (mMayo) score, histologic indices (Nancy, Robarts, and Geboes),and inflammatory biomarkers. PD assessments included PDE4B expression, tissue cAMP, absolute tissue lymphocyte content (TLC), fecal calprotectin (Fcal), and plasma hsCRP. In FSCD patients, mean simple endoscopic score (SES)-CD, ileal tissue cAMP, FCal and the correlation between cAMP and FCal was evaluated. IC90-normalized daily exposure (AUC_{0-24}hr/IC90) was measured with PALI-2108 versus approved PDE4 inhibitors.

References: 1. FDA CDER. *Apremilast Clinical Pharmacology Review, NDA 205437*. 2014; 2. Li X, et al. Mufemilast first-in-human phase 1 study. *Clin Pharmacol Drug Dev*. 2026;15:e70005. doi:10.1002/cpdd.70005. 3. Maher TM, et al. Phase I studies of BI 1015550 in healthy males and patients with IPF. ERJ Open Res.2022;8:00240-2022. doi:10.1183/23120541.00240-2022.

RESULTS

Phase 1a Multiple Daily Dose (QD) PK Demonstrates Favorable Steady State Profile at Target Ph2 Doses



Figure 3: Plasma concentration–time profiles on Days 1 and 9. Lines and markers show arithmetic means for each dose cohort; shaded bands indicate ±1 SD. Dashed lines represent the IC_{50} (0.64 ng/mL) and IC90 (9.1 ng/mL). The Day 9 tissue reference was 22.3 ng/mL at 8 hours post-dose.

PALI-2108 Dosed at 30mg/QD Achieved Lower C_{trough} Variability

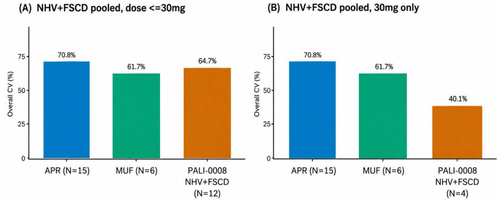


Figure 4: C_{trough} CV%: Apremilast (APR) vs. Mufemilast (MUF) vs. PALI-2108. APR 30mg BID Day 7 SS PsA (N=15)[1], MUF 60mg BID Day 9 SS HV fasted (N=6)[2] compared with **(A)** PALI-0008 (N=12) <=30mg: NHV F1 15mg Day 10 (n=4), NHV F2 30mg Day 10 (N=3), FSCD E1 20mg Day 11 (n=2), FSCD E2 25mg Day 11 (N=2), FSCD E3 30mg Day 11 (N=2), FSCD E3 30mg Day 11 (N=1); **(B)** PALI-0008 (N=4)= 30mg: NHV F2 30mg Day 10 (N=3), FSCD E3 30mg Day 11 (N=1)

PALI-2108 Increases Tissue cAMP and Reduces Intestinal Inflammation Resulting in Endoscopic Improvement and Response and Remission in FSCD

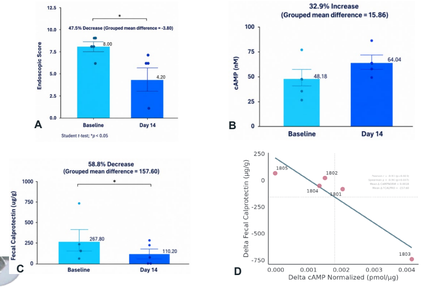


Figure 5: In FSCD patients following treatment with PALI-2108, (**A**) mean SES-CD significantly declined ($P < 0.05$), with 40% of patients achieving endoscopic remission and 40% achieving endoscopic response; (**B**) ileal tissue cAMP concentrations increased following treatment; (**C**) FCal levels decreased and (**D**) correlation analysis demonstrated a strong inverse relationship between tissue cAMP and FCal (Pearson $r = -0.93$, $P = 0.023$; Spearman $\rho = -0.90$, $P = 0.037$).

PALI-2108 Improves Tissue Histology Resulting in Clinical Response, and Remission in UC Patients

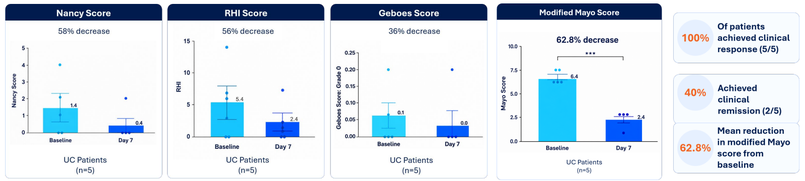


Figure 6. Changes in histologic disease activity scores from screening to end of study (Day 7) in colon tissue show reductions in the Nancy score; RHI; and Geboes score.

Figure 7. Mean mMayo score decreased (***P<0.001 versus screening patients).

PALI-2108 Steady State Tissue PK of PDE4 Active ~7x Higher in Tissues vs Plasma

Tissue Concentration	Ascending colon (ng/mL)	Descending colon (ng/mL)	Ileum (ng/mL)	All segments (ng/mL)	Plasma Cmax (ng/mL)	Tissue/ plasma ratio All segments
Mean	185.4	114.4	107.6	149.0	19.4	7.3

High concentrations observed across all target intestinal segments, including the ileum, ascending colon, and descending colon

Mean tissue concentrations were approximately **7.3-fold higher than peak plasma concentrations**, supporting targeted intestinal delivery

Strong tissue distribution supports the potential for localized PDE4 inhibition **while limiting systemic exposure**

Table 1: Tissue/plasma ratio for segments of bowel at 4-8h after dosing 20-30mg daily (QD) in FSCD patients.

PALI-2108 Achieved Higher Daily Exposure Compared to Approved PDE4 Inhibitors

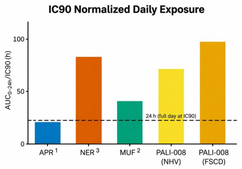


Figure 8: IC90-normalized daily exposure (AUC_{0-24}hr/IC90). PALI-0008 (30 mg QD) achieved the highest IC90-normalized exposure indicating the greatest total fold-over-IC90 exposure over 24 hr compared to other PDE4 inhibitors. The dashed line (24 hr) represents continuous exposure at IC90 (similar results were found for C_{avg} relative to IC90 (not shown). APR, apremilast; NER, nerandomilast ; MUF, mufemilast.

SUMMARY

PALI-2108 demonstrated PK consistent with delayed ileocolonic release and localized bioactivation, producing sustained PALI-0008 exposure in colonic tissue while maintaining attenuated systemic C_{max} and favorable steady-state tissue:plasma ratios in FSCD patients.

PALI-0008 exhibited low PK variability, with lower steady-state C_{trough} CV% in FSCD patients compared with published variability for apremilast and mufemilast. PALI-2109 achieved higher daily exposure compared to approved PDE4 inhibitors.

PALI-2108 was well tolerated across all study cohorts (n=76); TEAEs in FSCD were mild, transient, and improved with dose titration and administration with food.

PALI-2108 demonstrated early PD and clinical activity in UC and FSCD, cohorts including improved clinical/endoscopic outcomes, increased tissue cAMP, and reduced inflammatory biomarkers.

These data support continued development as a once-daily oral, gut-targeted therapy for patients with IBD.

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