

PALI-2108, a Next-Generation Oral PDE4 Inhibitor Prodrug, Demonstrates Localized Ileocolonic Exposure with Favorable Tolerability in IBD

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Introduction and Aim

- Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, relapsing inflammatory gastrointestinal (GI) disease associated with substantial morbidity. Despite available biologic and small-molecule therapies, many patients do not achieve sustained remission or experience treatment-limiting adverse events (AEs), highlighting the need for effective, better-tolerated therapies.
- PALI-2108 is a novel, once-daily, colon-targeted oral phosphodiesterase-4 (PDE4) prodrug engineered for delayed ileocolonic release and microbiome-mediated conversion to active PALI-0008. This approach is designed to maximize local drug exposure at sites of inflammation while limiting systemic exposure and peak plasma concentrations (C_{max}) to improve tolerability.
- Phase 1a/b studies evaluated PALI-2108 tissue exposure, 90% inhibitory concentration (IC_{90}) coverage, pharmacokinetic/pharmacodynamic (PK/PD) effects, preliminary clinical activity, and safety/tolerability.

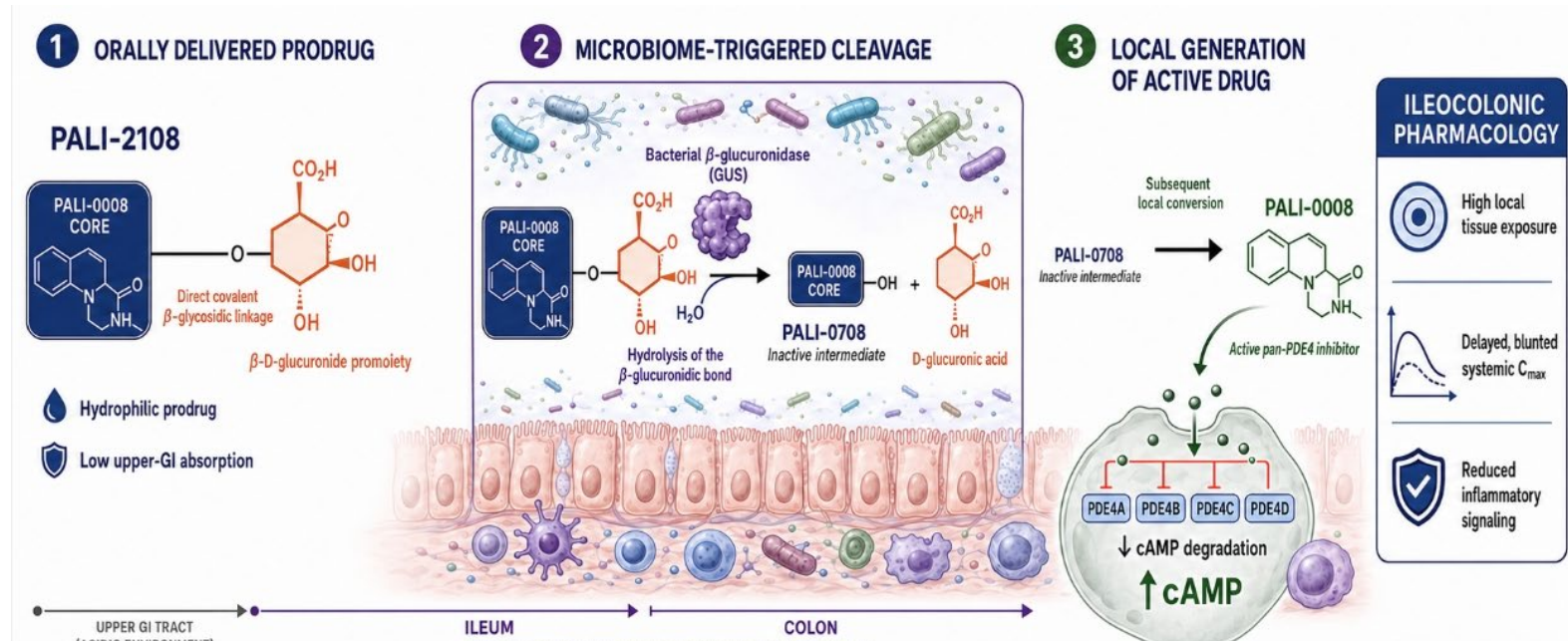


Figure 1: Localized bio-activation of PALI-2108 targets the ileum and colon, reducing the risk of GI and CNS AEs versus non-specific and non-localized PDE4 inhibitors.

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 (15–450 mg) or multiple ascending BID/QD doses (MAD, 15–30 mg), including dose titration and food-effect assessments.
- 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 endpoints 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.
- IC_{90} -normalized daily exposure ($AUC_{0-24}hr/IC_{90}$) was measured with PALI-2108 versus approved PDE4 inhibitors.



Phase 1a/b Study: UC and FSCD Cohort Study Design

Figure 2: Phase 1a/b double-blind, placebo-controlled study of PALI-2108 in NHV and an open-label study of UC and FSCD patients (NCT0663605).

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 IC_{90} (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

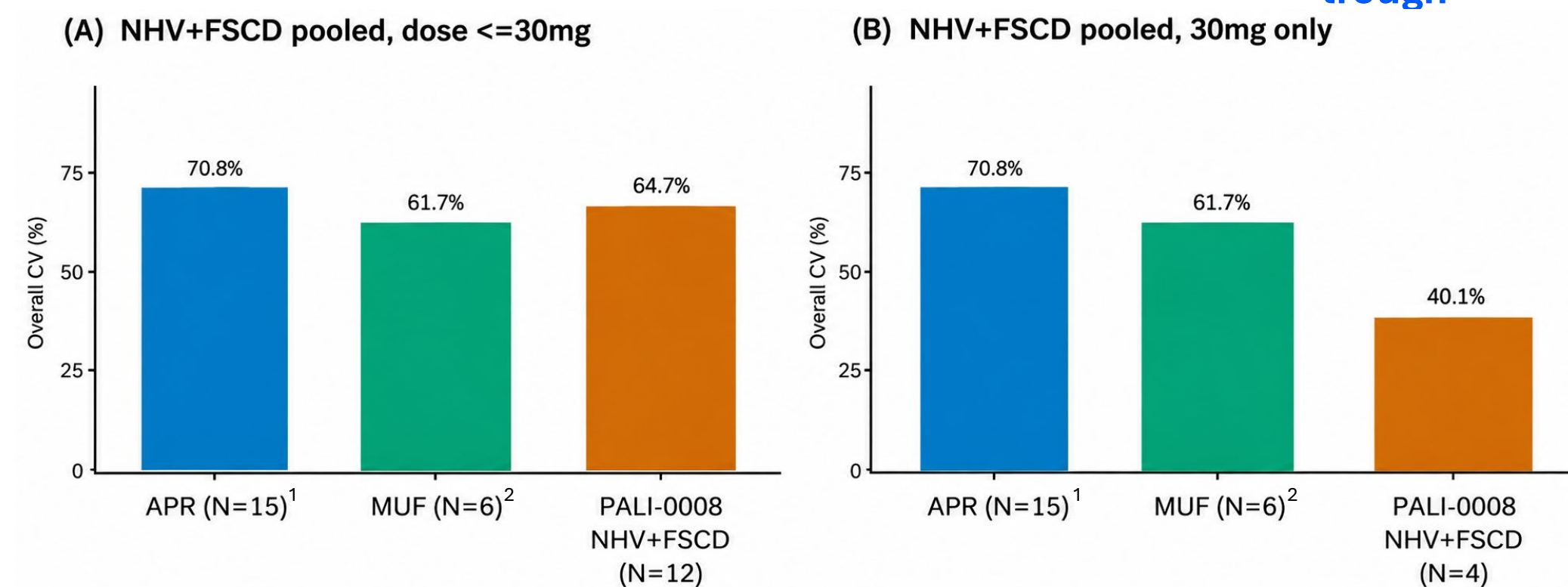


Figure 4: C_{trough} CV%: Apremilast (APR) vs. Mufemilast (MUF) vs. PALI-2108. APR 30mg BID Day 7 SS PsA (N=15), MUF 60mg BID Day 9 SS HV fasted (N=6) compared with (A) PALI-0008 (N=12) ≤ 30 mg: NHV F1 15mg Day 10 (n=4), NHV F2 30mg Day 10 (N=3), FSCD E1 20mg Day 11 (n=2), FSCD E2 25mg Day 11 (N=2),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

- FDA CDER, Apremilast Clinical Pharmacology Review, NDA 205437, 2014.
- Li X, et al. Mufemilast first-in-human phase 1 study. Clin Pharmacol Drug Dev. 2026;15:e70005. doi:10.1002/cpdd.70005.

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

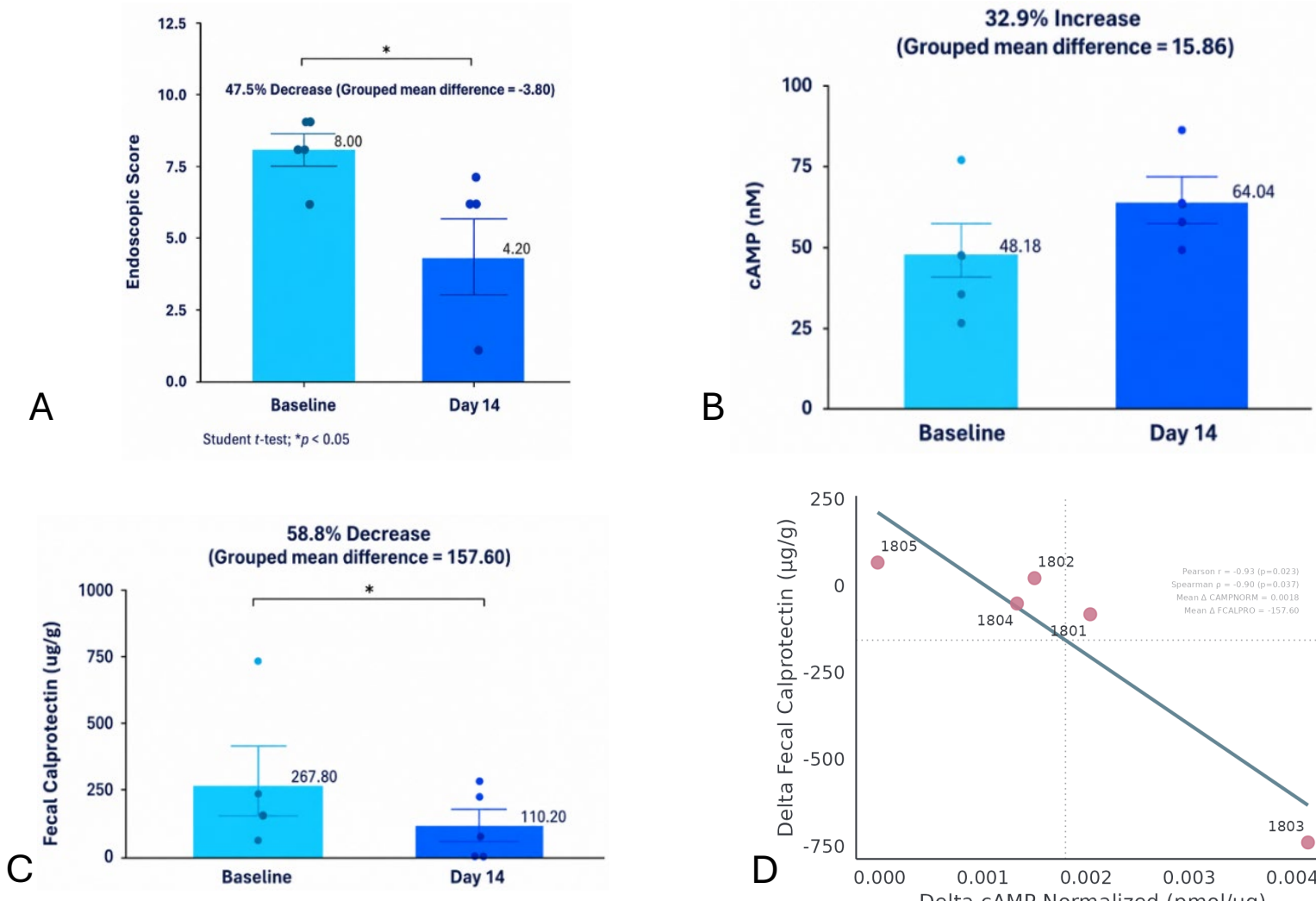


Figure 5: In FSCD patients following treatment with PALI-2108, (A) mean SES-CD significantly declined ($P < 0.05$), with 40% of patients achieving endoscopic remission and 40% achieving endoscopic response; (B) ileal tissue cAMP concentrations increased following treatment; (C) Fcal levels decreased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

Results

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

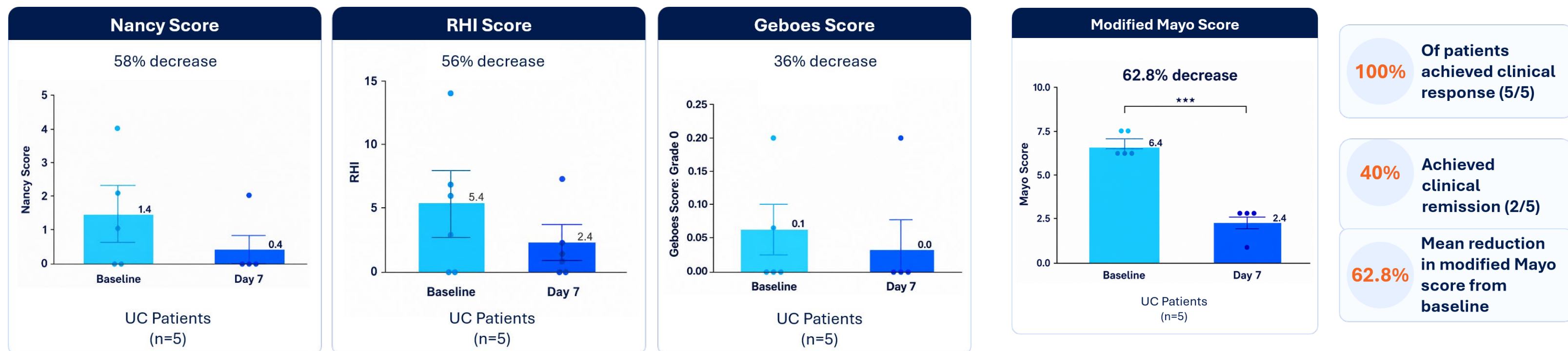


Figure 6: Changes in histologic disease activity scores from screening to end of study (Day 7) in colon tissue show reductions in the Nancy score; RHI; and Geboes score.

Figure 7: Mean mMayo score decreased by 62.8% ($***P < 0.001$ versus screening patients). Clinical response was achieved in 100% of patients and clinical remission was achieved in 40% of 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 C_{max} (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

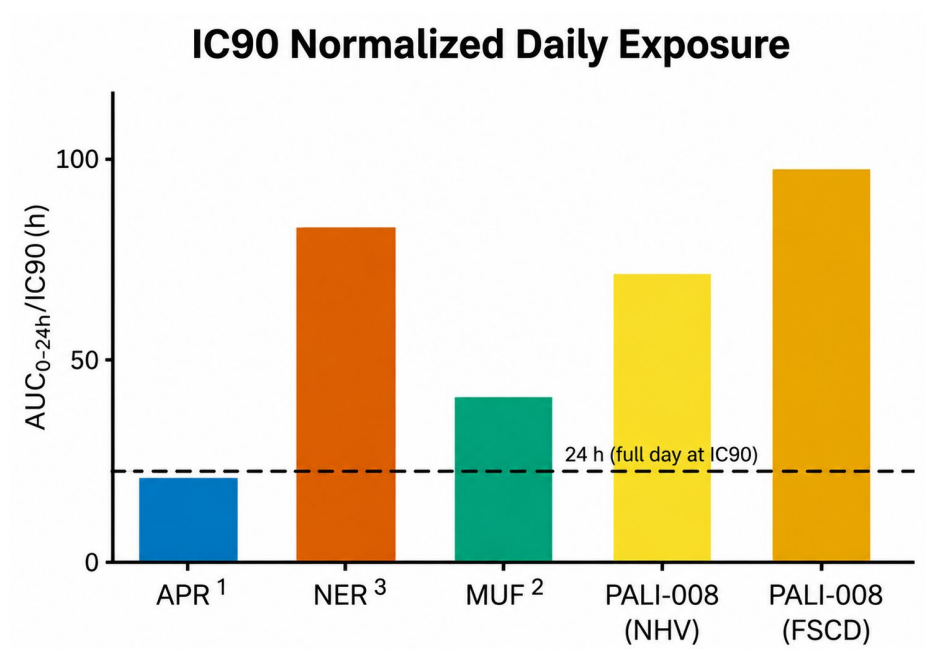


Figure 8: IC_{90} -normalized daily exposure ($AUC_{0-24}hr/IC_{90}$). PALI-0008 (30 mg QD) achieved the highest IC_{90} -normalized exposure indicating the greatest total fold-over- IC_{90} exposure over 24 hr compared to other PDE4 inhibitors. The dashed line (24 hr) represents continuous exposure at IC_{90} (similar results were found for C_{90} relative to IC_{90} (not shown). APR, apremilast; NER, nerandomilast; MUF, mufemilast.

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

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, nerandomilast, and mufemilast. PALI-2108 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.