

Oral Locally Bioactivated PDE4 Inhibitor Prodrug PALI-2108 Demonstrates Rapid Clinical, Histologic, and Biomarker Improvement in Ulcerative Colitis: Ph1b Translational Findings

Joerg Heyer PhD¹, Patrick Colin BPharm PhD¹, Gaetano Morelli MD², Florian Rieder MD³ and Mitch Jones MD, PhD¹

¹Palisade Bio, Carlsbad, CA; ²Altasciences, Montreal, QC; ³Cleveland Clinic, Cleveland, OH

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon affecting ~5 million patients worldwide. Phosphodiesterase-4 (PDE4) inhibition suppresses pro-inflammatory cytokine production but has been clinically limited by CNS- and upper GI-mediated adverse effects. PALI-2108 is an oral, ileum and colon-activated PDE4 inhibitor prodrug designed to maximize local efficacy and improve tolerability. It is selectively converted by bacterial β -glucuronidase to the active inhibitor, resulting in limited systemic Cmax, reduced CNS liability, and minimized upper GI absorption, thereby improving tolerability.

Methods

An adaptive Phase 1a/1b study evaluated PALI-2108 in NHV and UC patients. NHV cohorts included SAD (n=40), MAD (n=32), and food-effect (n=12) studies. In the Phase 1b cohort, 5 adults with UC (modified Mayo 5-9; endoscopy ≥ 2) received titrated PALI-2108 30 mg BID for 7 days. Baseline and Day 7 assessments included modified Mayo Score (mMS), histology, fecal calprotectin, hsCRP, and colonic tissue pharmacodynamic biomarkers (cAMP, lymphocytes, and RNAseq). PK and safety were contextualized using pooled data from 89 NHV and UC patients across cohorts.

Results

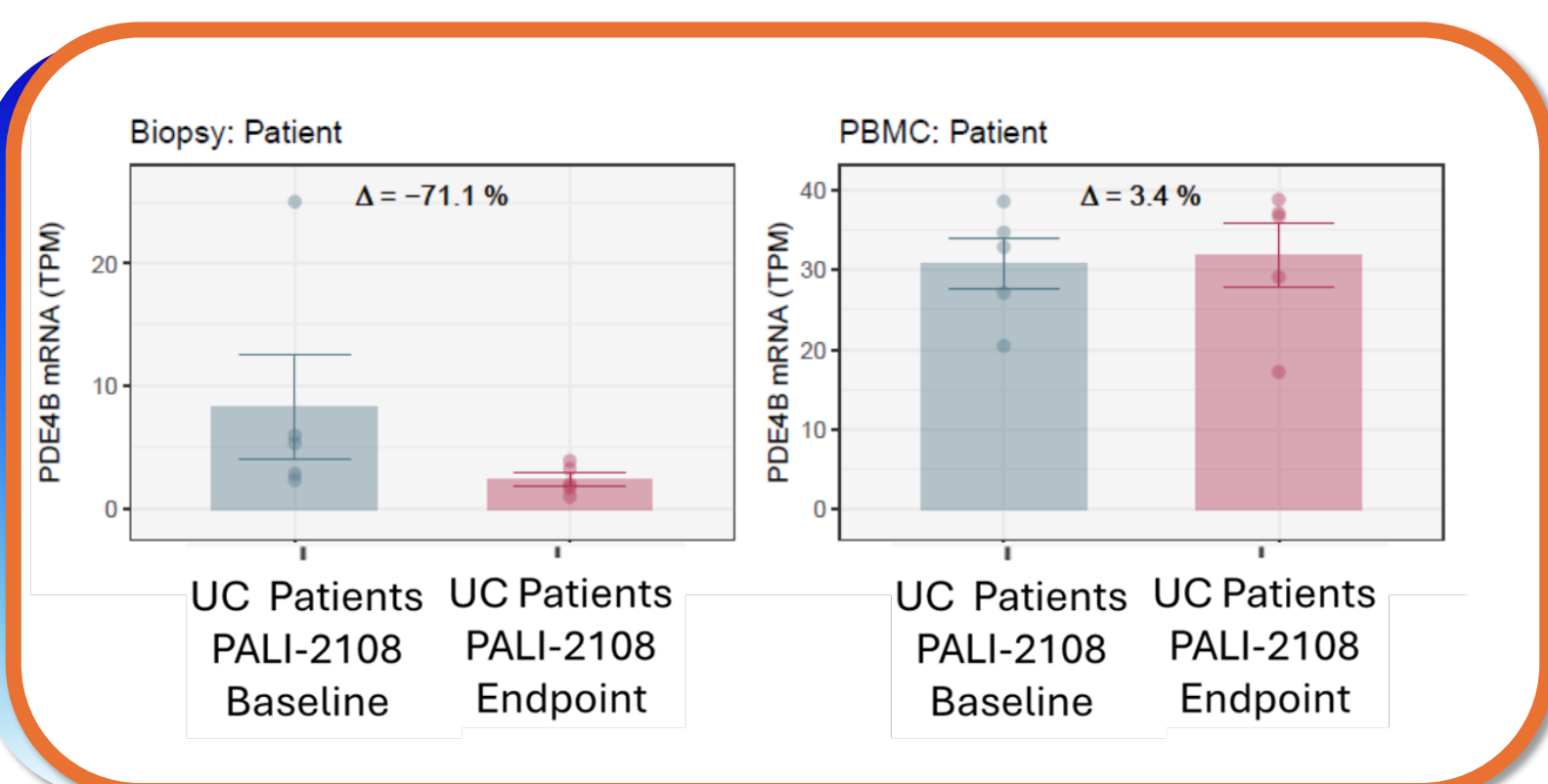


Figure 1. PALI-2108 reduces elevated mucosal PDE4B expression in colon tissue (left) whereas the PBMC compartment is unchanged in UC patients. mRNA expression shown in transcripts per million (TPM) and individual data points are shown with group means.

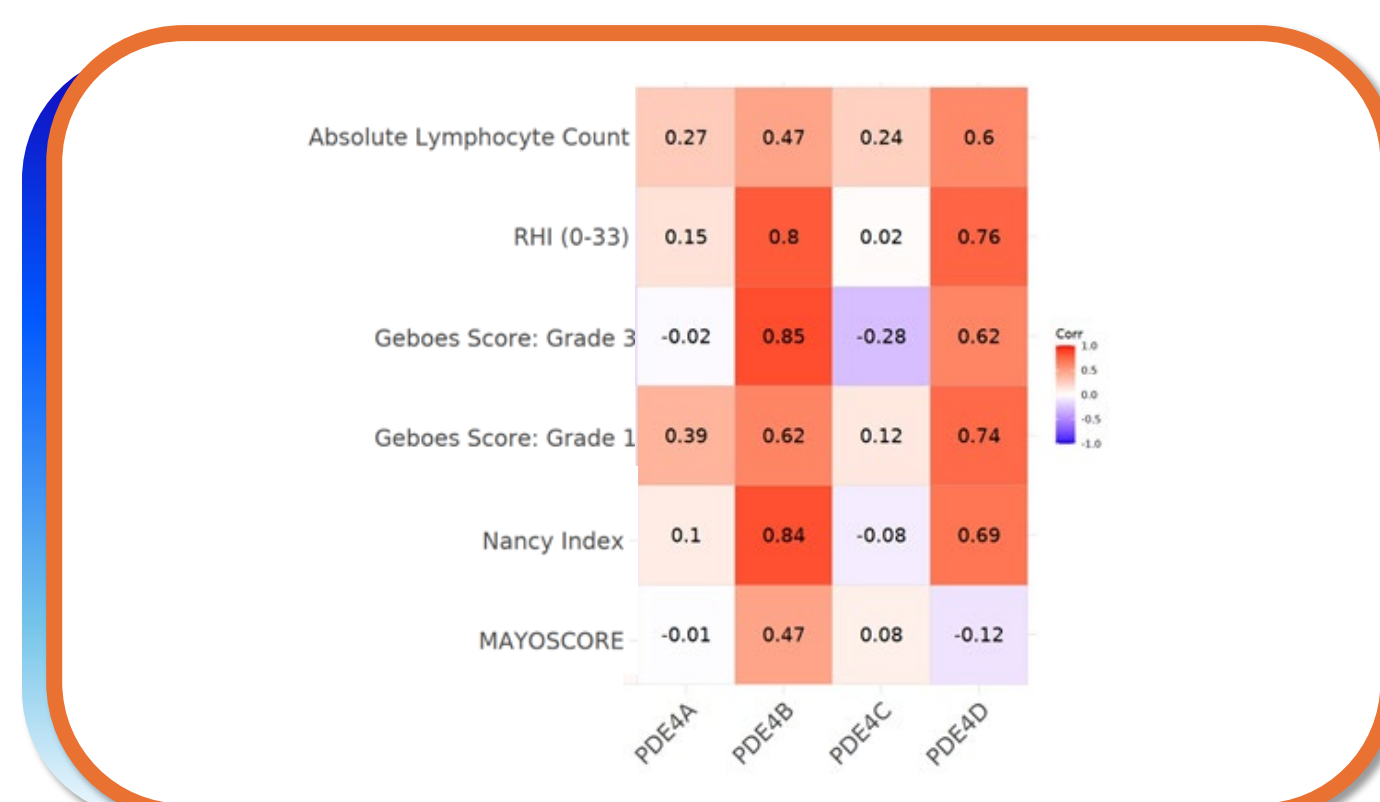


Figure 2. PDE4B and PDE4D expression correlates with histologic disease severity in ulcerative colitis. Heatmap depicts correlations between mucosal PDE4 isoform expression and clinical/histologic activity scores.

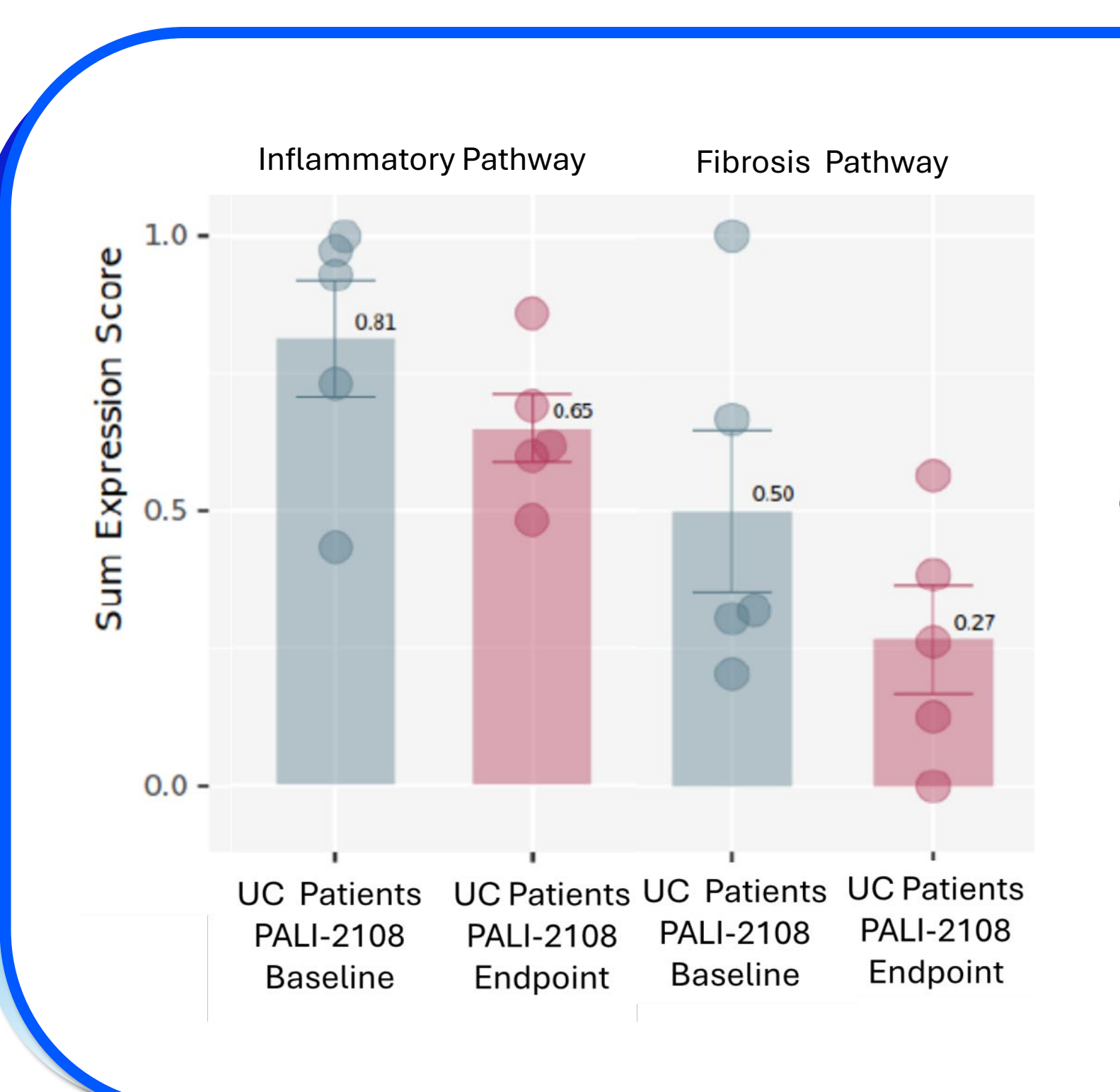


Figure 3. PALI-2108 reduces mucosal inflammatory gene expression (left) and fibrosis gene expression (right) in UC patients. The Sum Expression Score (aggregate gene expression) is shown in colon biopsies for UC patients at Baseline and Endpoint (Day 7) following PALI-2108 treatment. Individual data points are shown with group means.

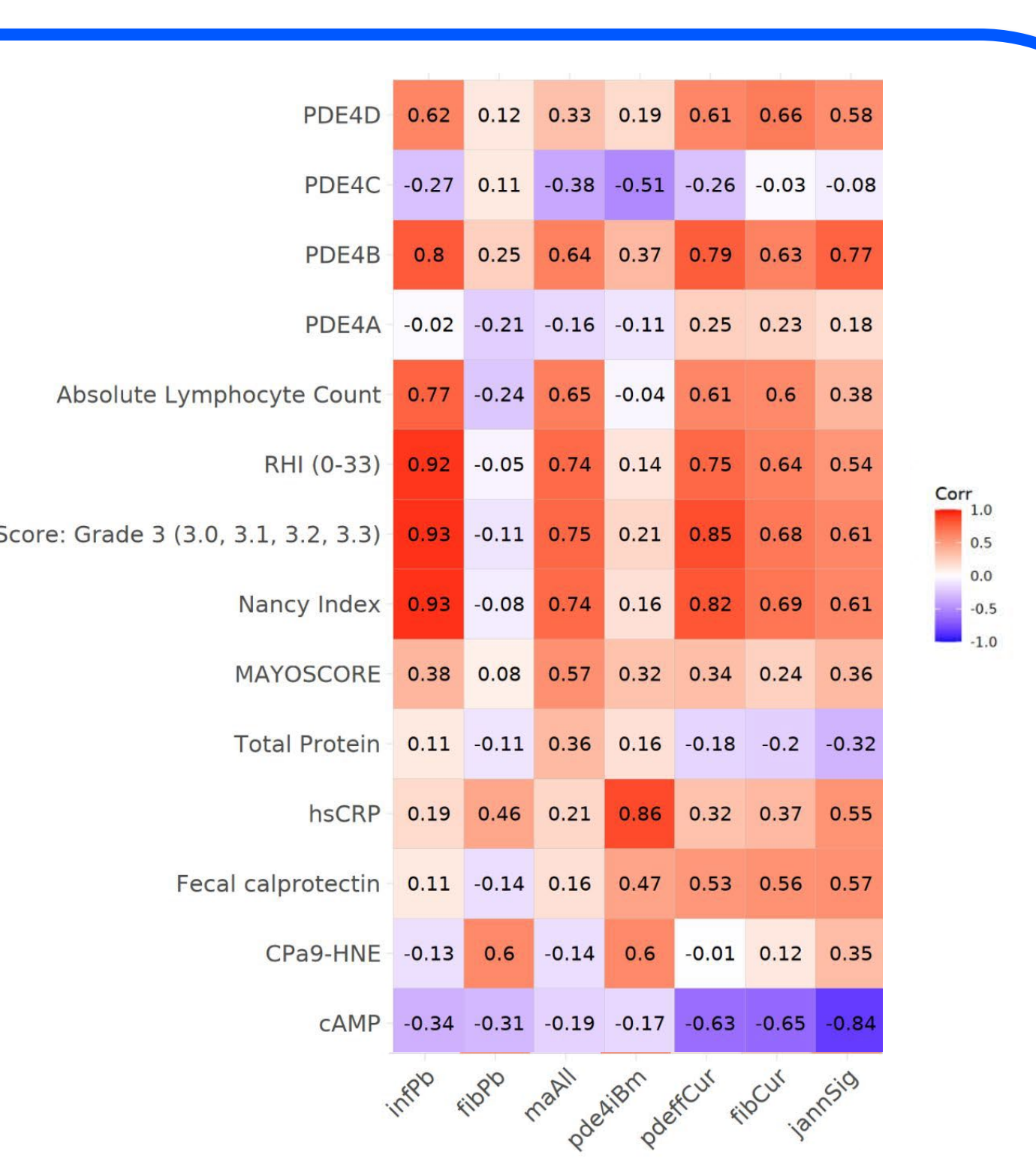


Figure 4. Correlation of RNA sequencing expression level data GSEA grouped markers with clinical markers of severity and metabolite markers of IBD. Inflammatory gene panel = InfPB; fibrotic gene panel = fibPB; Meta of diff expression = maAll; PDE4 effectors = pdeffCur; fibrotic gene panel 2 = fibCur; Jansen 130 gene PM gene signature = jannSig.

Conclusion	Observations
Inflammation down signal	Neutrophils were reduced in relative abundance in colon tissue. This is classic "active colitis" signature (cryptitis/abscesses, IL-12/CCL chemokines, S100A8/A9, etc.). A drop is directionally consistent with mucosal improvement.
Decreased abundance of B cells	Immature Plasma cells and naive B- cells decrease. In UC tissue, "plasma cell / plasmablast" modules often track with inflammatory activity in many datasets.
Increased resting/less-activated T cells	CD4 naive cells increase. CD4 naive "functions as a proxy for a more resting/less-activated T cell transcriptional state"
Myeloid compartment increases	Monocyte increase. Could be a shift from neutrophil-dominant acute inflammation toward monocyte/macrophage-mediated resolution/repair.
Hypothesis	PDE inhibition leads to increase in cAMP in immune cells leading to broad dampening of inflammatory programs. Reduced production of pro-inflammatory cytokines (TNF- α , IL-12/23, IL-17/IFN γ -associated tone). Reduced chemokine driven recruitment and reduced neutrophil activation/tracking

Figure 5. Interpretation of cellular deconvolution of RNA sequencing of colon tissue lesion samples after treatment with PALI-2108 and the effects of PDE4 inhibition. Lymphocyte populations and inflammatory response reveals reduced inflammatory cells in UC colon tissue lesions.

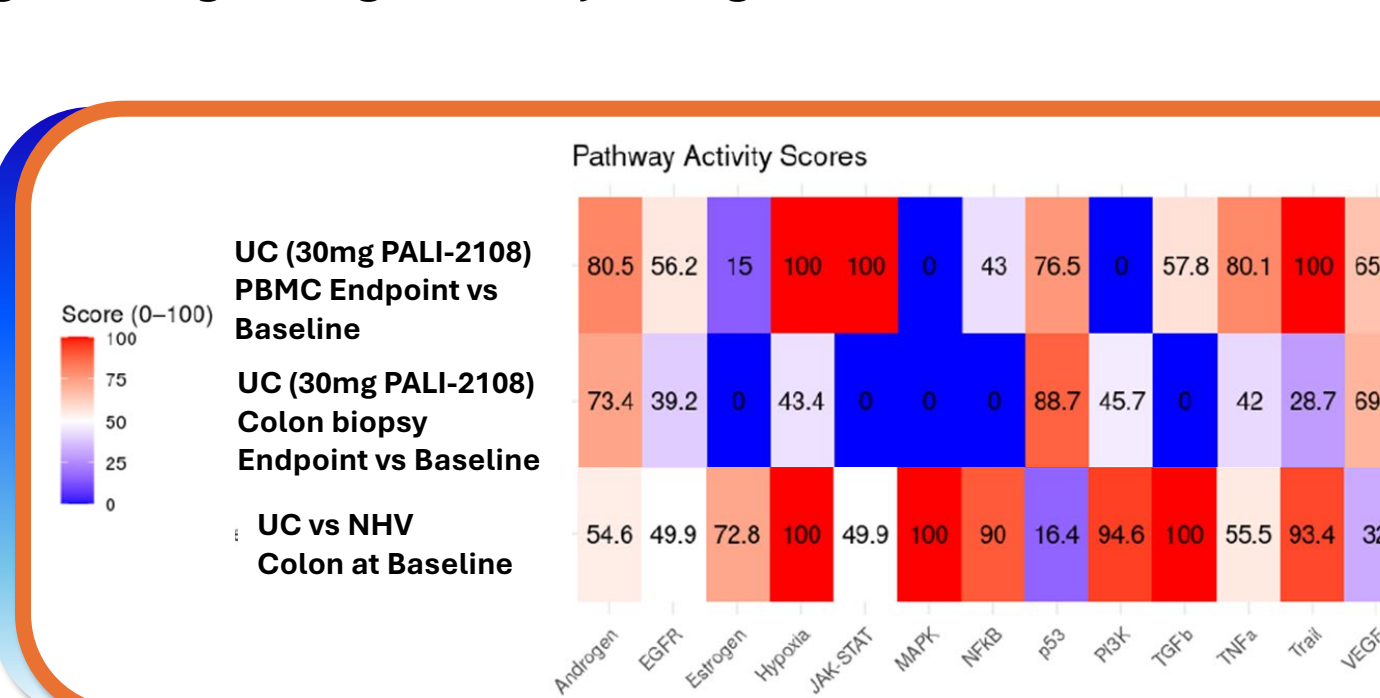
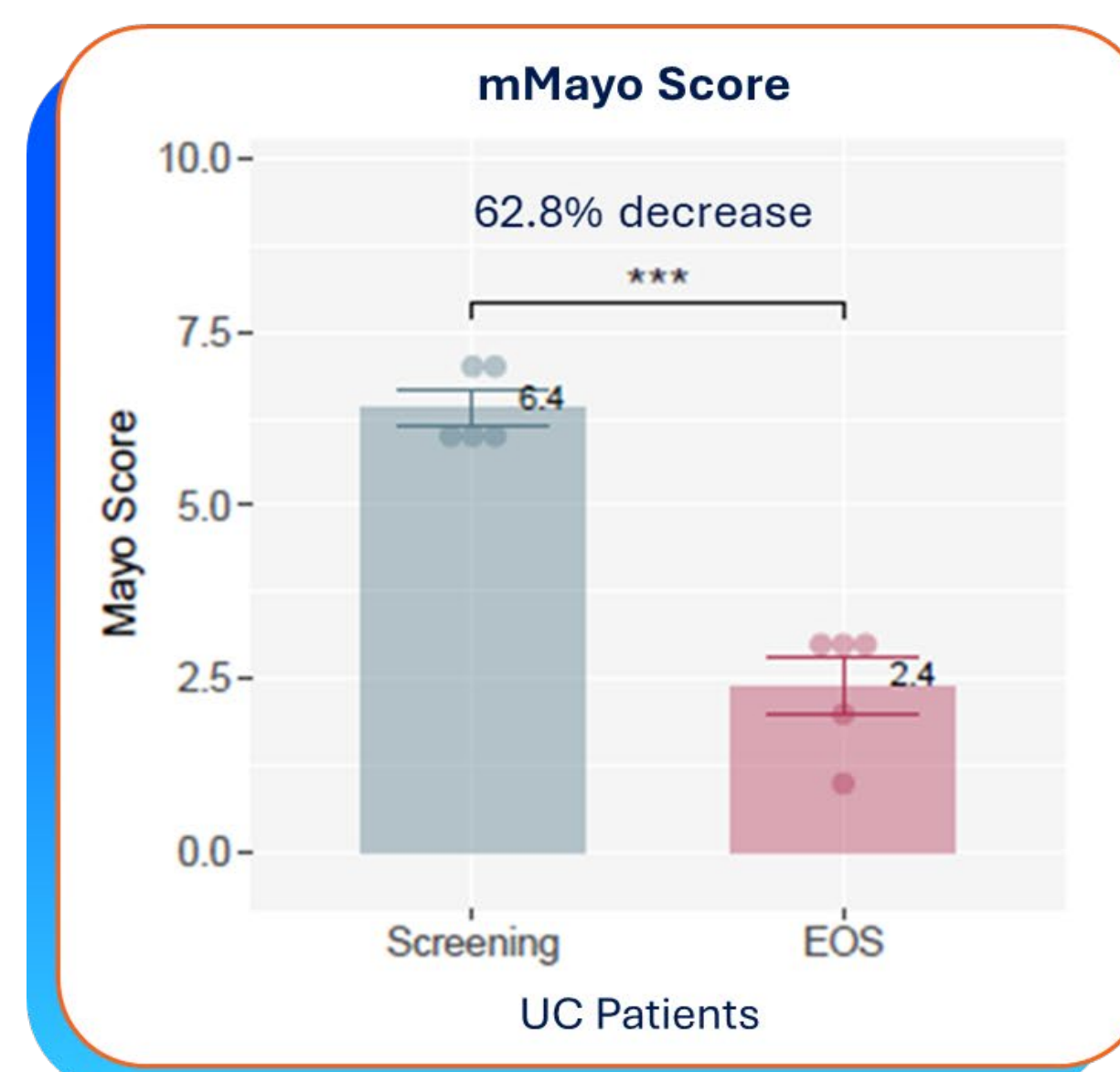


Figure 6. PALI-2108 preferentially modulates inflammatory pathway activity in colonic tissue relative to peripheral blood. PROGENY-derived Pathway Activity Scores (0-100) (Schubert et al., Nat Commun 2018) are shown for UC patients treated with 30 mg PALI-2108, comparing Day 7 versus baseline in PBMCs and colonic biopsies, alongside baseline UC versus NHV differences in colon tissue. Notable reductions in JAK-STAT, MAPK, NF- κ B, TGF- β , and TNF- α pathway activity are observed in colon biopsies, consistent with localized pharmacologic activity.



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 ($\geq 30\%$ 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 < 0.001.

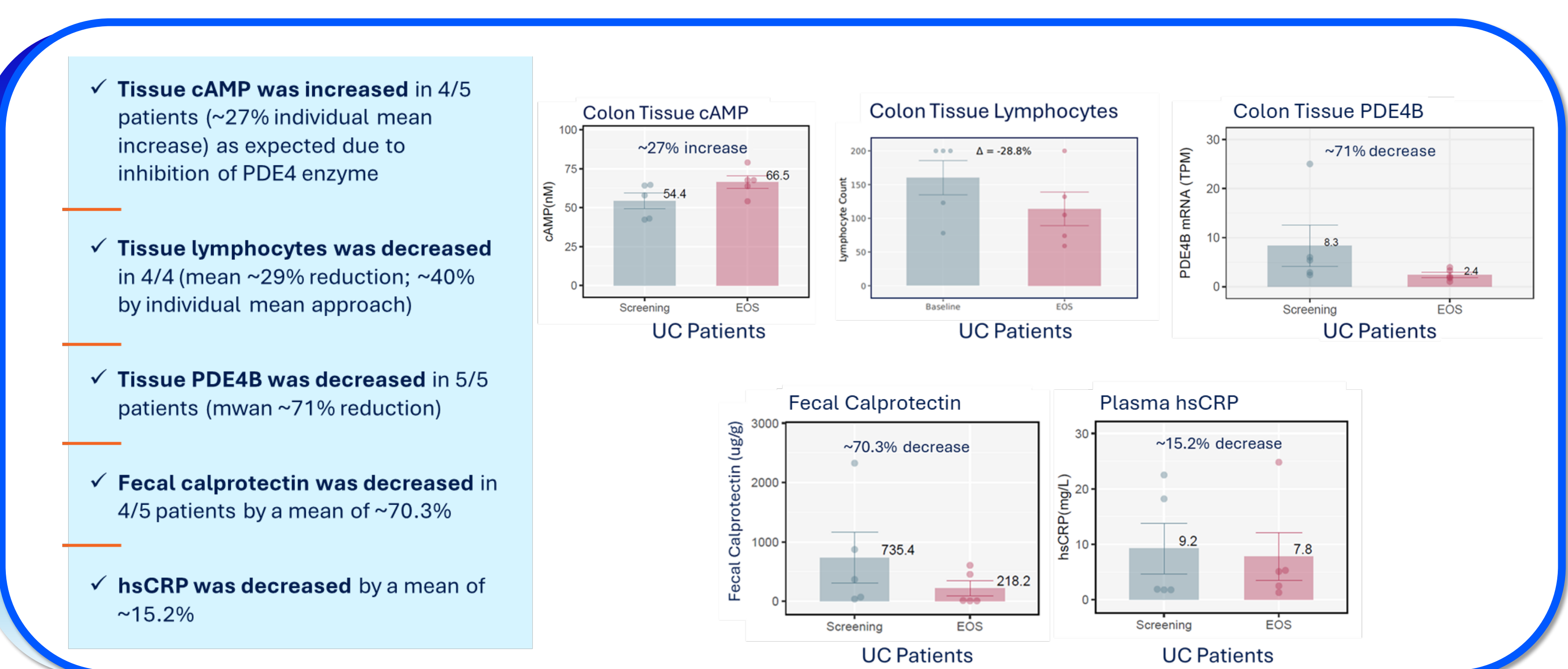


Figure 7. In Phase 1b study, improvements were seen in mechanistic and inflammatory markers, including cAMP, PDE4B and TLC, CalPro and hsCRP.

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 in UC patients. 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 PDE4 inhibitor (PALI-0008), consistent with targeted ileocolonic bioactivation and extended-release characteristics. Plasma concentrations were >IC90 at Steady State (SS) and colon tissue concentrations approached IC90 even 36 hours post-dose with very good tolerability, supporting once-daily dosing now used in our FSCD cohort study. This is a greatly 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 UC. The data support continued clinical development of PALI-2108 as a differentiated, ileum and colon-targeted once-daily oral PDE4 inhibitor prodrug which is locally bioactivated for inflammatory bowel disease.