

Gut-Targeted Inhibition of Phosphodiesterase 4 with PALI-2108 Demonstrates Early Endoscopic and Biomarker Improvements in Fibrostenotic Crohn’s Disease: Results From a Phase 1b Study



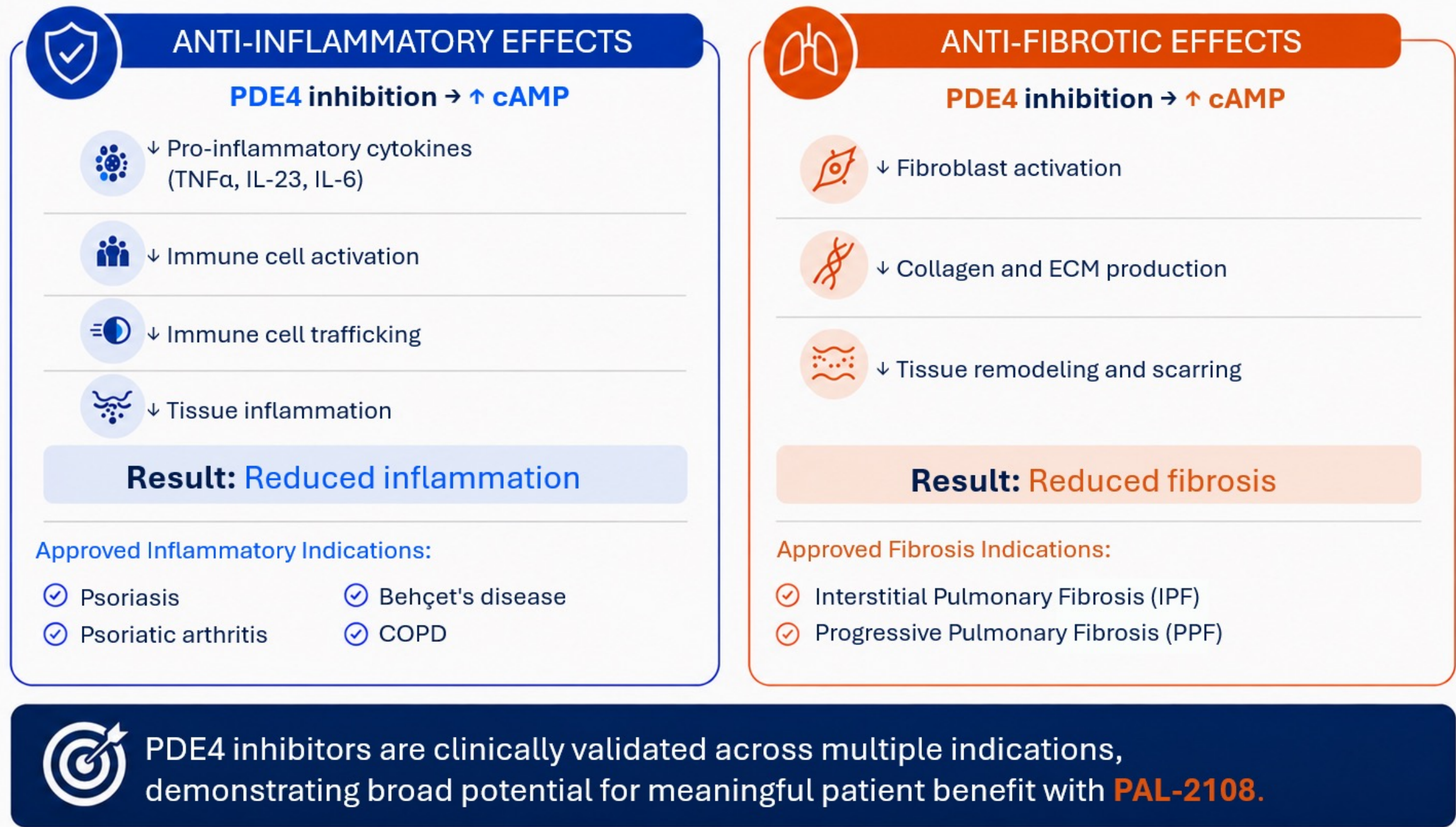
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Introduction and Aim

- Fibrostenotic Crohn’s disease (FSCD)** affects up to half of patients with Crohn’s disease and arises from persistent, dysregulated inflammation that promotes intestinal fibrosis, stricture formation, and obstruction. No approved pharmacologic therapy directly addresses FSCD.
- PALI-2108** is a once-daily oral phosphodiesterase-4 inhibitor prodrug engineered for ileocolonic delivery and localized conversion to its active metabolite, PALI-0008, with encouraging early clinical activity demonstrated in ulcerative colitis and here we report study results in FSCD patients.
- This study evaluated the **safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of PALI-2108 in patients with FSCD.**

PDE4 Inhibitors are Pleiotropic Drugs with Commercially Proven Anti-Inflammatory and Anti-Fibrotic Activity



Methods

In this adaptive Phase 1b multiple-dose study, adults with symptomatic endoscopically confirmed ileal FSCD (n=5) were assessed. Patients received once-daily oral PALI-2108 with food for 14 days, including a 10-day dose-escalation period followed by 4 days at target dose (20mg, n=2; 25mg, n=2; 30mg, n=1). Safety/tolerability, plasma and ileal/colonic PK, PD analyses (plasma and ileal RNA sequencing), ileal histopathology, endoscopic outcomes (SES-CD, response, remission), tissue cyclic adenosine monophosphate (cAMP), and fecal calprotectin (Fcal) were assessed. We performed PathAI quantitative digital pathology to assess (i) the role of inflammatory cells in both lamina propria (LP) and mucosal tissue; (ii) extracellular matrix (ECM) biomarker analysis (Nordic Biosciences); (iii) net fibrinolysis and; (iv) macrophage activation at baseline and end of study (EOS).

Phase 1b FSCD Clinical Study Design

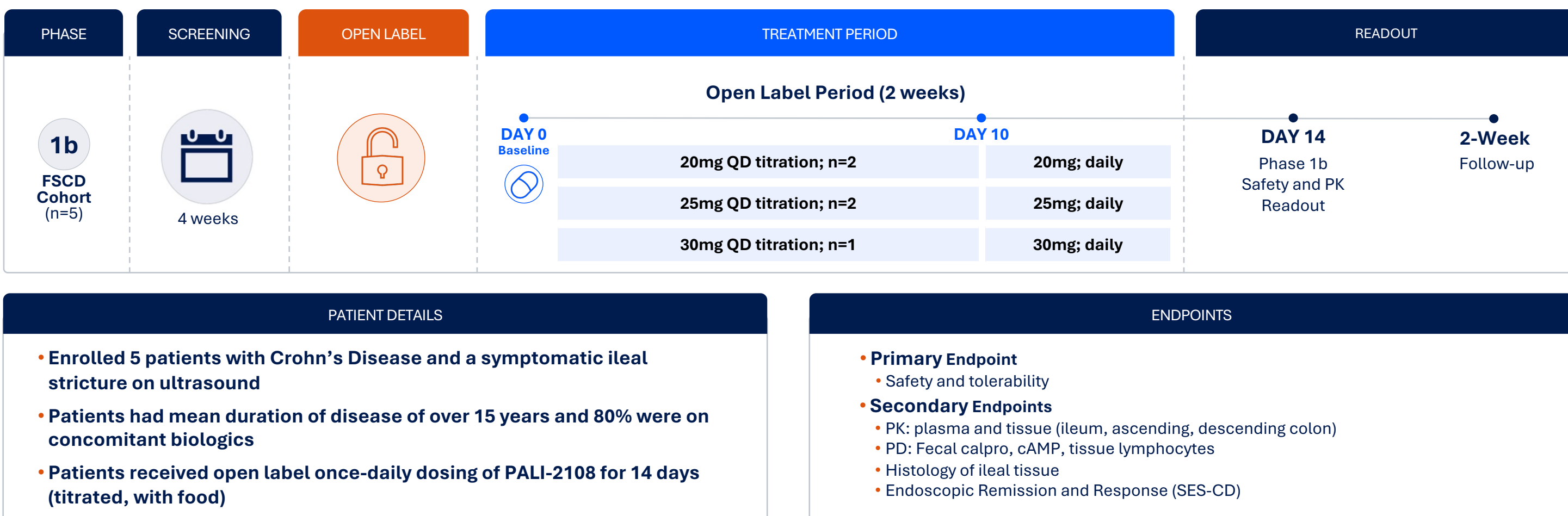


Figure 1: Phase 1b study of PALI-2108 in FSCD patients (NCT06663605).

PALI-2108 Demonstrates a Favorable Safety Profile in Phase 1b of Symptomatic FSCD Patients with Proven Ileal Stenosis

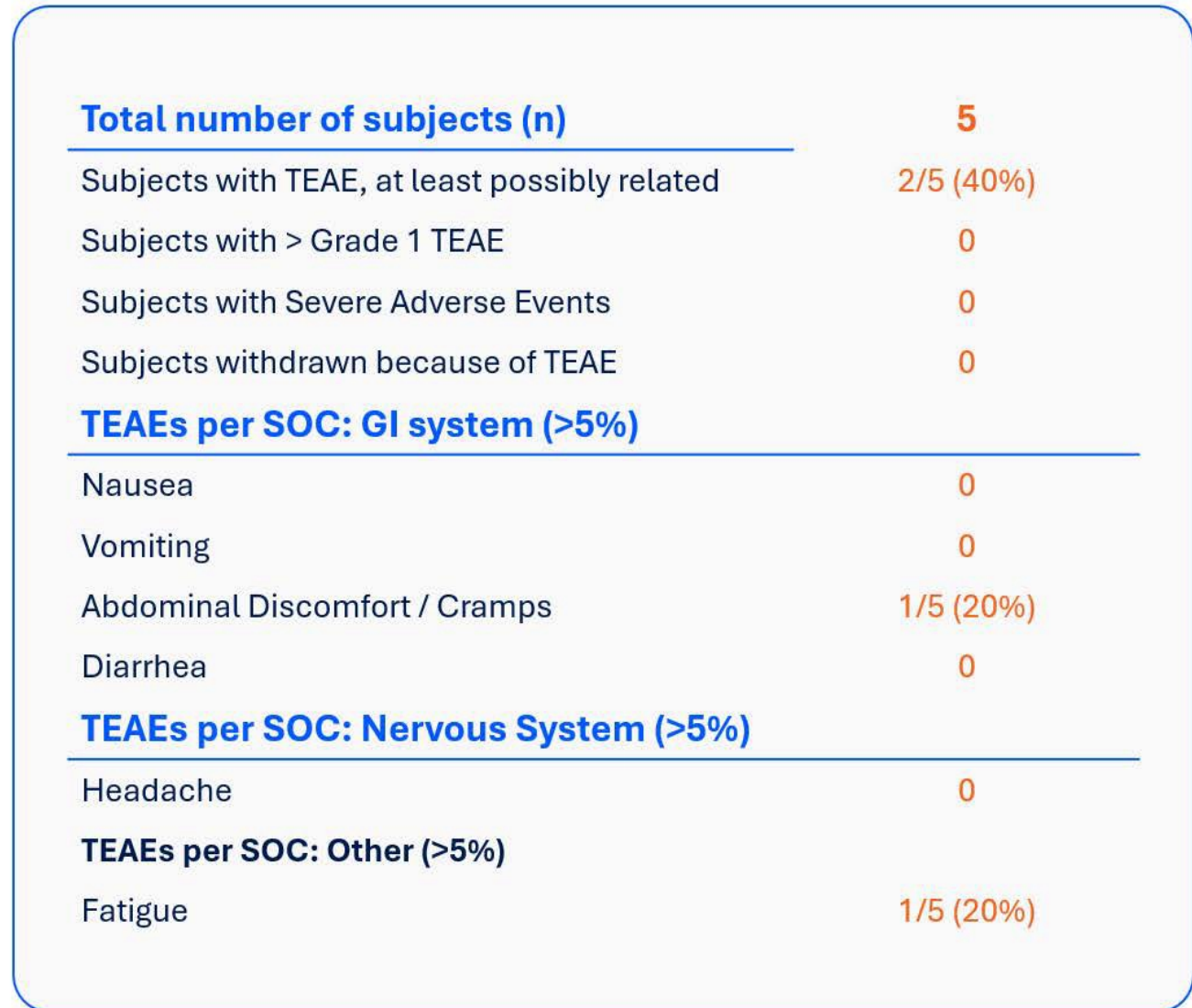


Figure 2: Safety profile in FSCD patients.

PALI-2108 Demonstrates Favorable Plasma and Tissue PK and All Patients Achieve >IC90 in Plasma and Tissue, Including Ileum

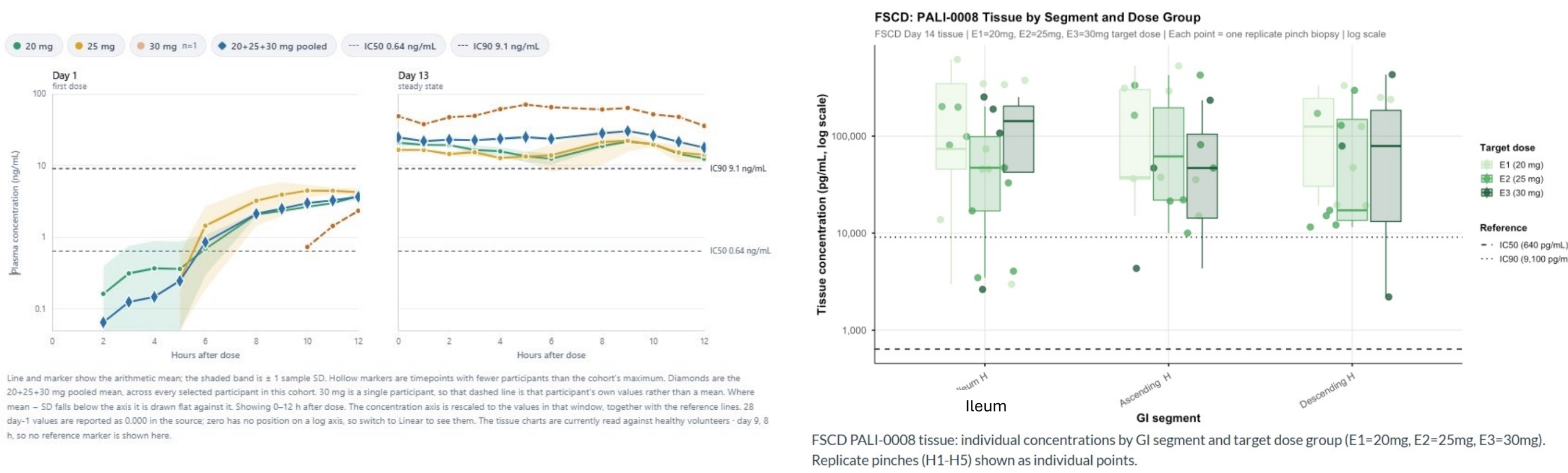


Figure 3: Plasma PK after oral once-daily PALI-2108 prodrug titrated to 20, 25, and 30mg with all patients achieving >IC90 active PDE4 inhibitor PALI-0008 in plasma over the course of the study.

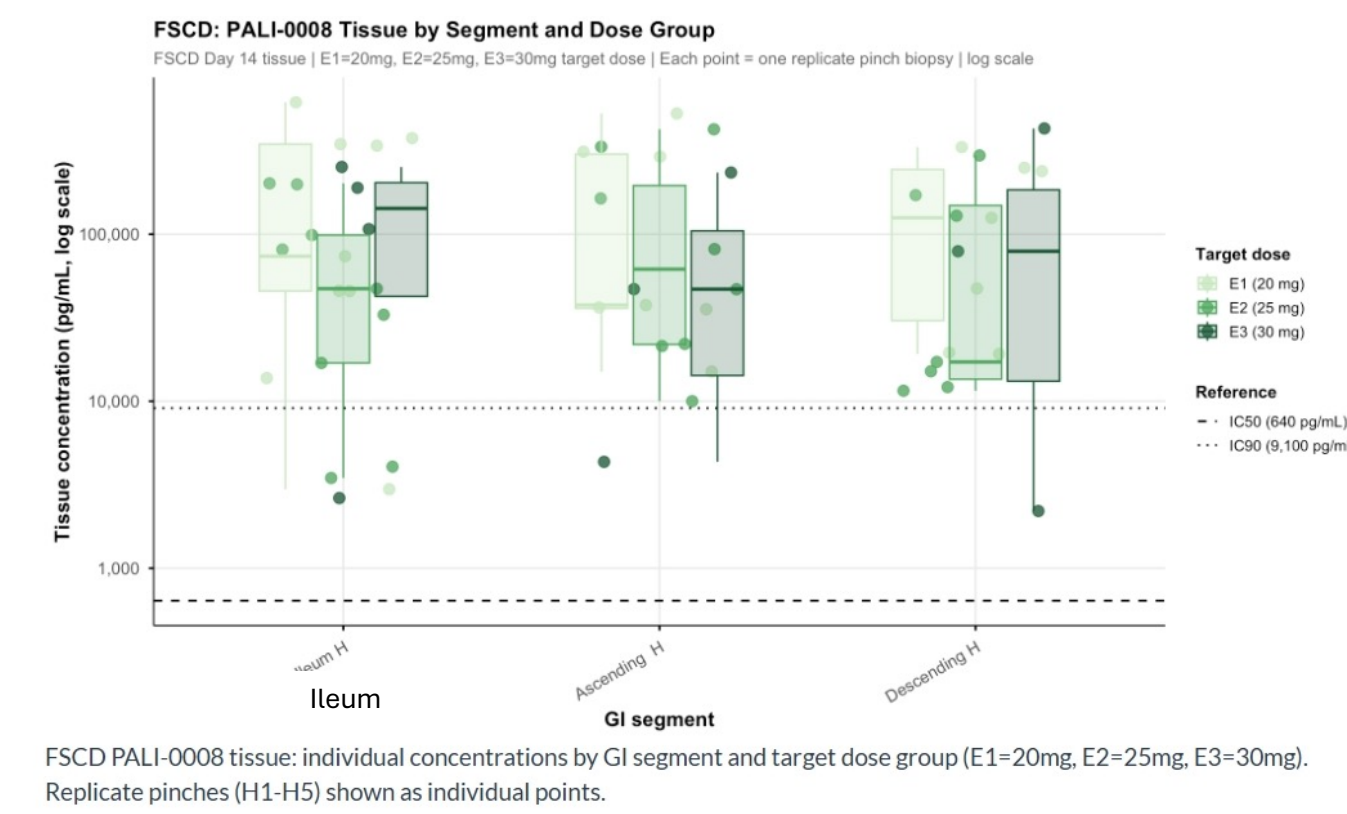


Figure 4: Tissue PK after oral once-daily PALI-2108 prodrug titrated to 20, 25, and 30mg with all patients achieving >IC90 active PDE4 inhibitor PALI-0008 in ileum, ascending and descending colon tissues over the course of the study.

Translational Biomarkers in Tissue and Plasma Demonstrate PALI-2108 Reduces Inflammatory Cell Counts and Initiates Fibrinolysis in FSCD

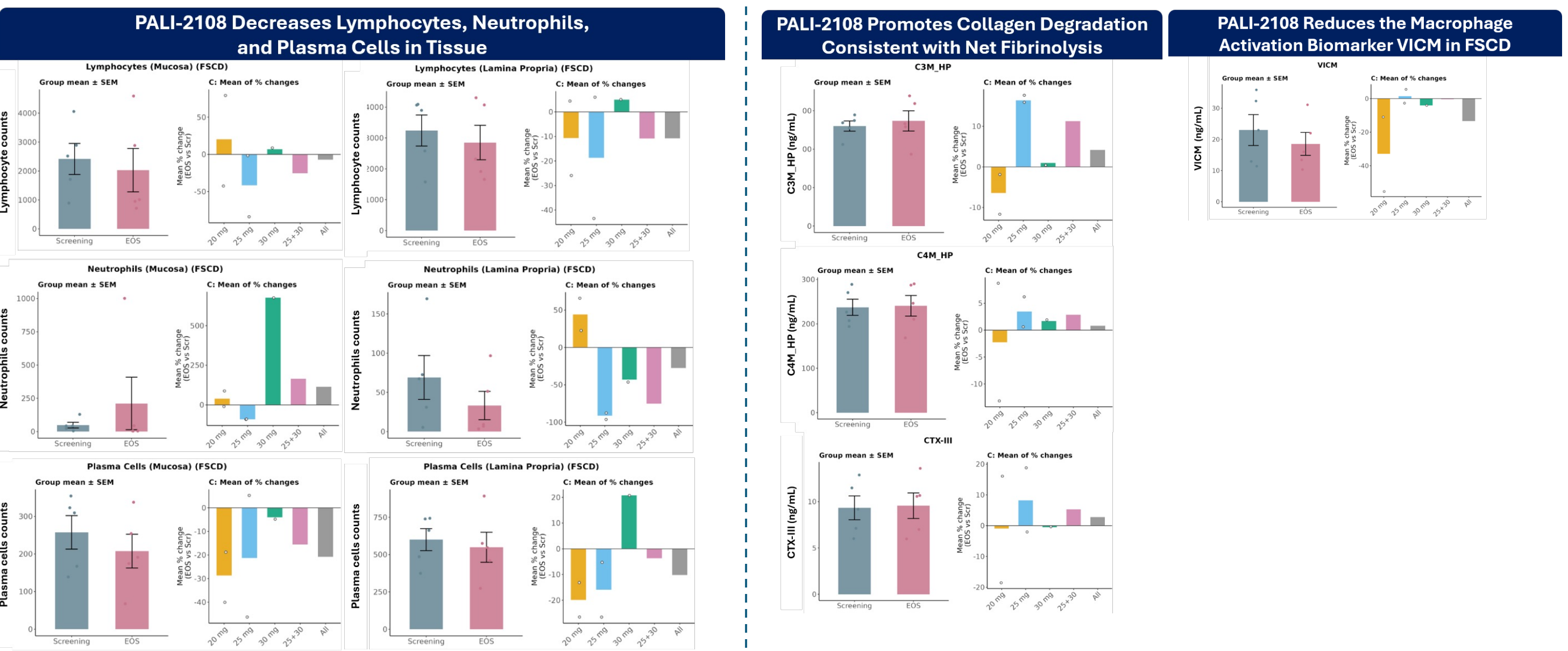


Figure 5: PALI-2108 treatment in paired biopsy specimens collected at screening and EOS demonstrated reduced lymphocyte, neutrophil, and plasma cell densities in the mucosa and LP.

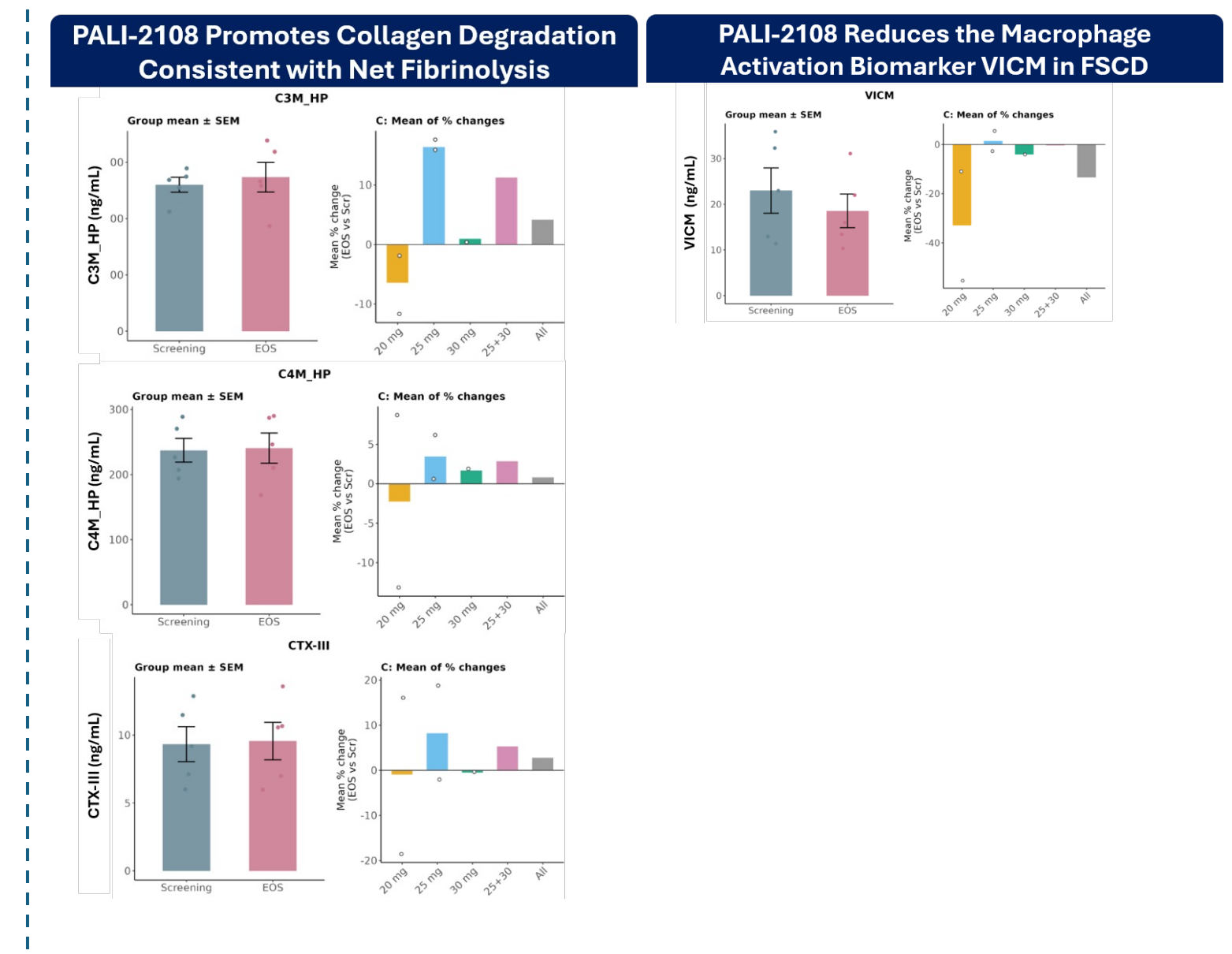


Figure 6: Plasma ECM biomarkers evaluated at screening and EOS demonstrated a profile consistent with increased collagen degradation and net fibrinolysis, accompanied by reduced macrophage activation. VICM: citrullinated and matrix metalloproteinase degraded vimentin fragment

Results

PALI-2108 Demonstrates Target Engagement Correlated with Anti-Inflammatory Activity in FSCD

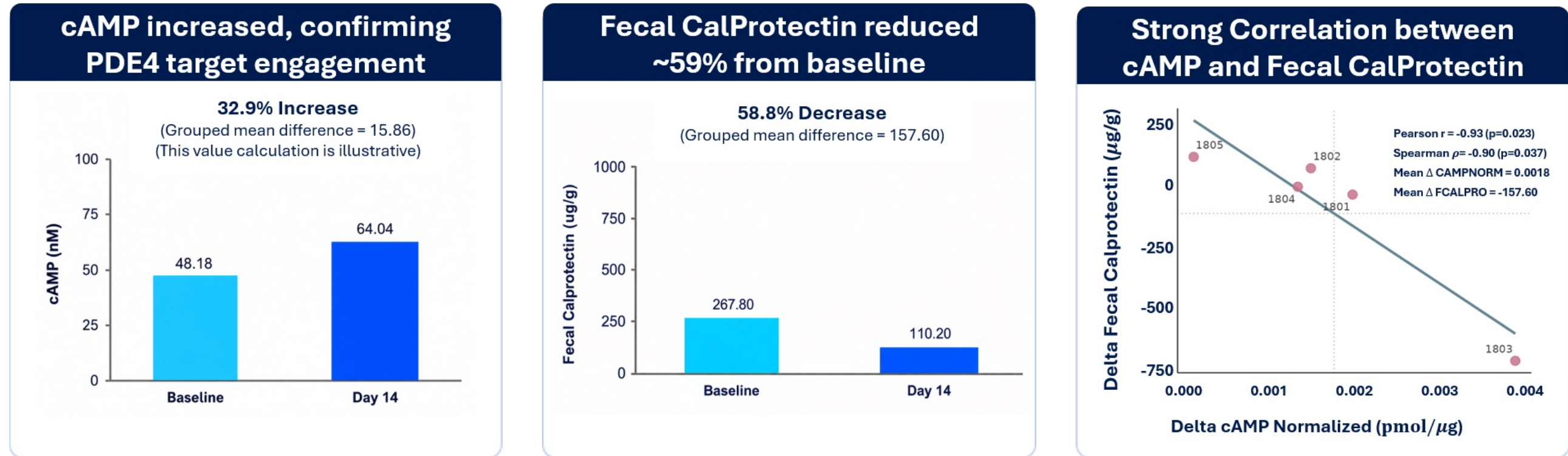


Figure 7: Increased PD biomarker cAMP and reduced fecal calprotectin (Fcal), and correlation of protein normalized biomarkers.

PALI-2108 Demonstrates Endoscopic Response and Remission in FSCD

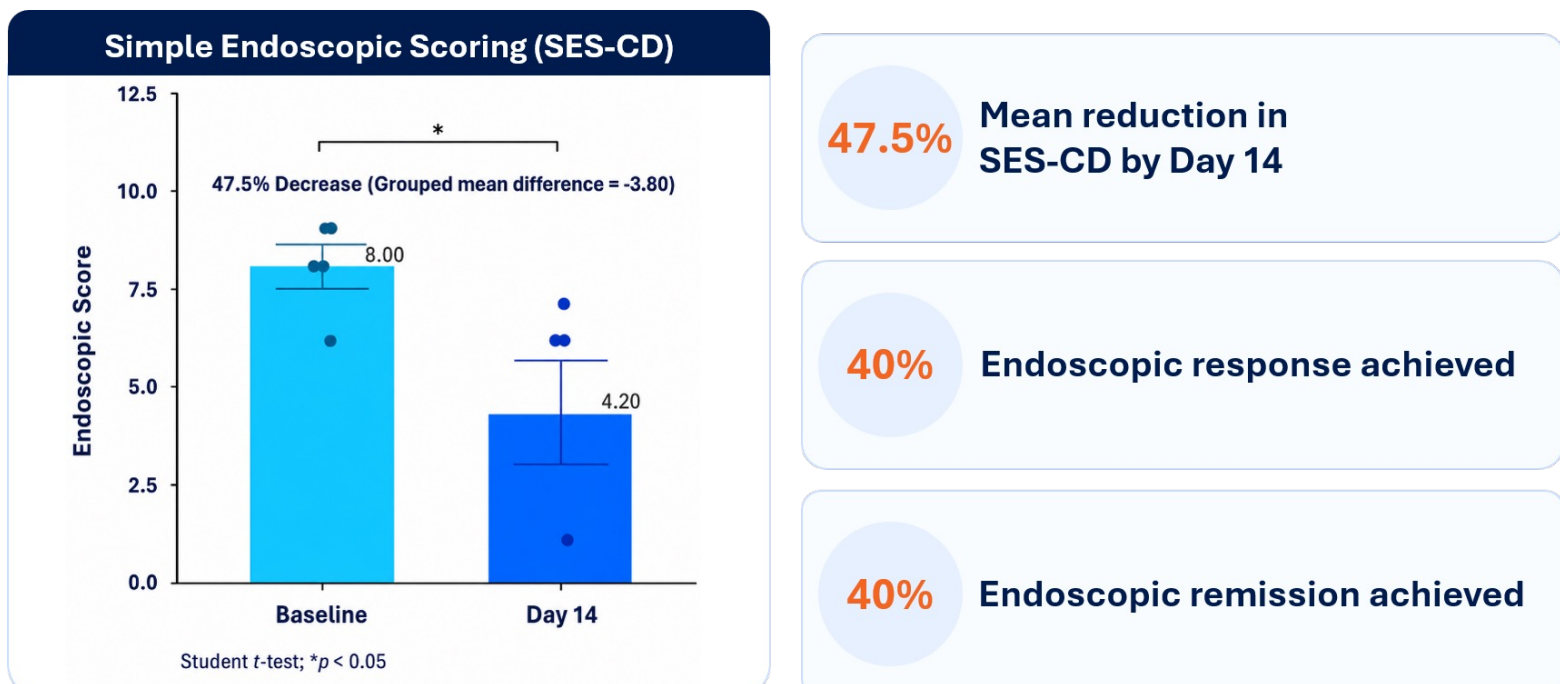


Figure 8: Improved SES-CD and proportion of patients achieving endoscopic response and endoscopic remission.

Proposed Phase 2a Open-label, Single Arm Moderate-to-Severe Crohn’s Disease Clinical Study Design (Study Initiated)

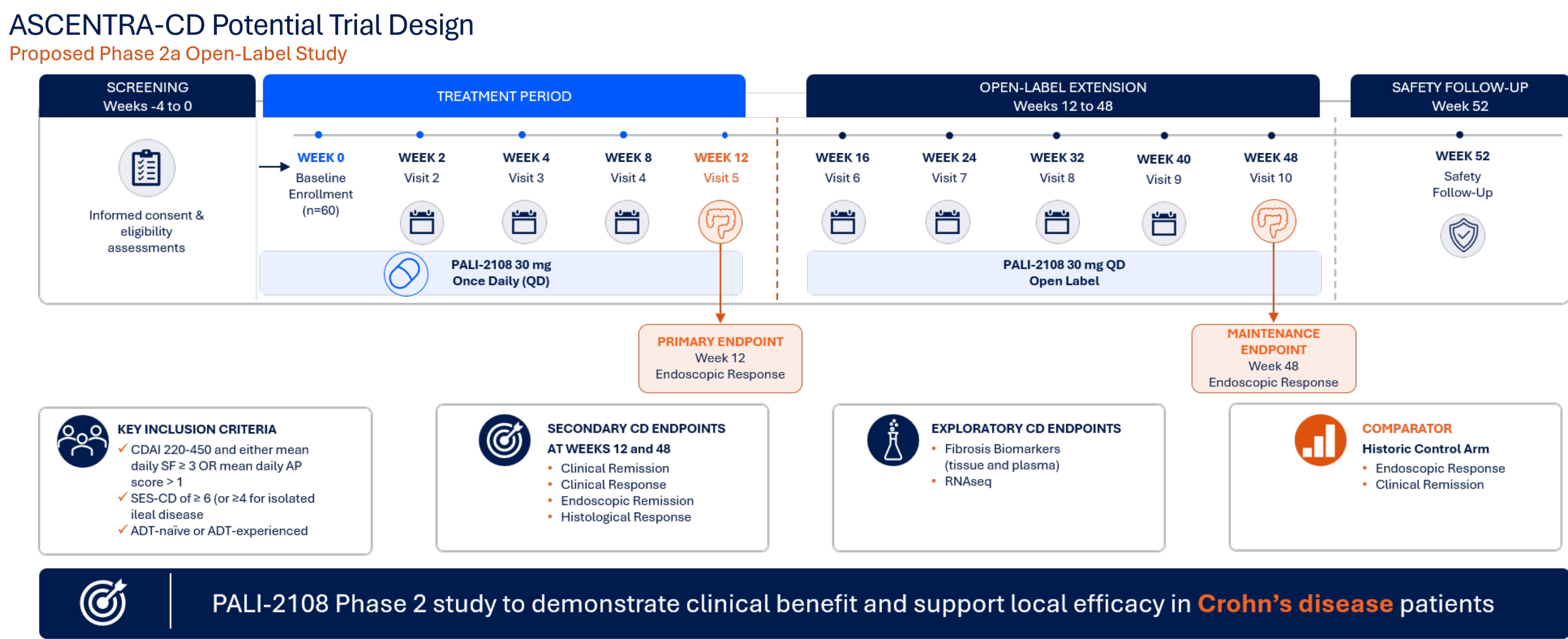


Figure 9: Proposed Phase 2a open-label, single arm moderate-to-severe Crohn’s Disease clinical study schema.

Summary

- In this exploratory **Phase 1b study**, once-daily oral PALI-2108 demonstrated favorable tolerability, evidence of target engagement, and early biologic and endoscopic and biomarker improvements in FSCD patients.
- Multimodal tissue analyses demonstrated that treatment with PALI-2108 reduced LP and mucosal inflammation and ECM remodeling consistent with fibrinolysis.
- Collectively, these findings demonstrate that **PALI-2108** enables localized **PDE4 inhibition** with favorable tolerability, robust biomarker confirmation of mechanism, and early signals of clinical efficacy, supporting continued clinical development as a differentiated, ileum- and colon-targeted oral PDE4 inhibitor prodrug for inflammatory bowel disease.

