

The Microbiome-Activated Phosphodiesterase (PDE)-4 Inhibitor, PALI-2108 Leads to Rapid Clinical and Histologic Improvement in Moderate-to-Severe Ulcerative Colitis: A Phase1a/1b Study

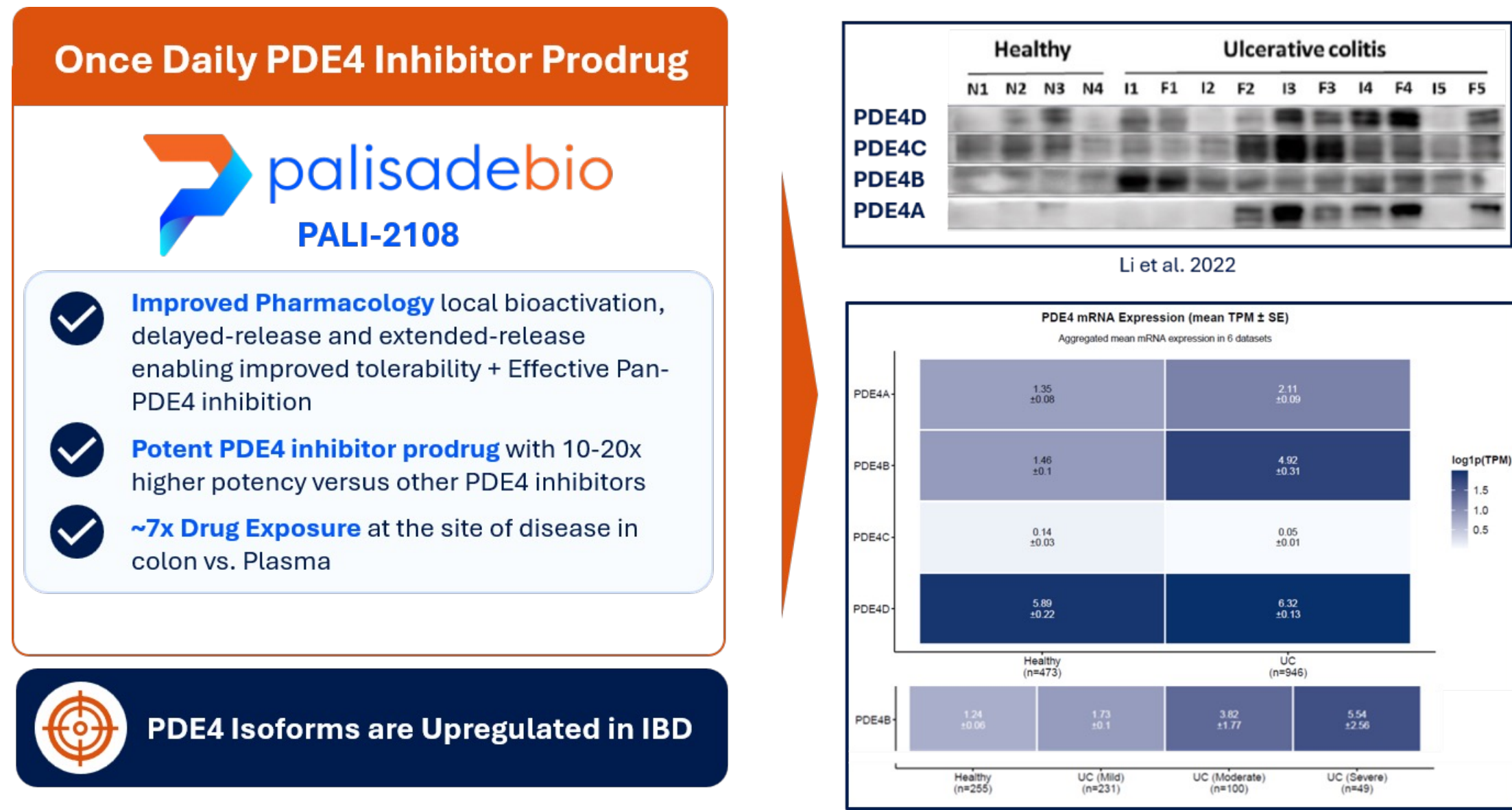


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Introduction and Aim

- Ulcerative colitis (UC)** is a chronic inflammatory disease affecting 5 million people worldwide. Although mortality is low, UC is associated with substantial morbidity and reduced quality of life despite available biological and small-molecule therapies.
- Systemic PDE4 inhibitors exert anti-inflammatory activity; however, their usage is limited by dose-dependent adverse events (AEs) driven by peak systemic exposure (C_{max}). **PALI-2108** is a microbiome-activated, once-daily oral PDE4 inhibitor designed to achieve localized PDE4 inhibition within ileocolonic tissues while minimizing systemic effects.
- This study evaluated the safety, pharmacokinetic (PK), pharmacodynamic (PD), and early clinical activity of PALI-2108 in normal healthy volunteers (NHVs) and patients with moderate-to-severe UC in an adaptive Phase 1a/b study.

Figure 1: Localized bioactivation of PALI-2108 prodrug results in improved PK characteristics, including delayed-release and extended-release of active PDE4 inhibitor targeting the diseased tissues of the colon overexpressing PDE4 A, B, C, and D (Western Blot above and mRNA Expression), and improving GI and CNS tolerability versus immediate release and non-localized PDE4 inhibitors.



Methods

Safety, tolerability and PK were assessed in NHVs receiving ascending single (n=40) and multiple (n=32) oral doses of PALI-2108, including a food-effect (FE) cohort 150 mg crossover (fed vs fasted; n=12). UC patients [n=5, modified Mayo (mMayo 5-9; endoscopic subscore ≥ 2)] received PALI-2108 30 mg BID for 7d, including a 5d dose titration. mMayo score, histologic indices (Nancy, Robarts, Geboes), colonic tissue lymphocyte density, fecal calprotectin (FCal), plasma hsCRP, and tissue PDE4B expression were evaluated at baseline and at 7d. Exploratory analyses evaluated PK/PD relationships and inflammatory signaling markers including cyclic adenosine monophosphate (cAMP) levels. We performed PathAI quantitative digital pathology to evaluate immune cell contribution in both tissue (lamina propria (LP) and mucosal) and plasma along with structural changes in mucosa (hematoxylin and eosin).

Phase 1a/b Studies with UC Cohort Study Design



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

Phase 1a SAD/MAD Cohorts Demonstrate Favorable PK and Superior Exposure Compared with Other PDE4 Inhibitors

Dose Proportionality and Extended Half-Life Enabling Daily Dosing

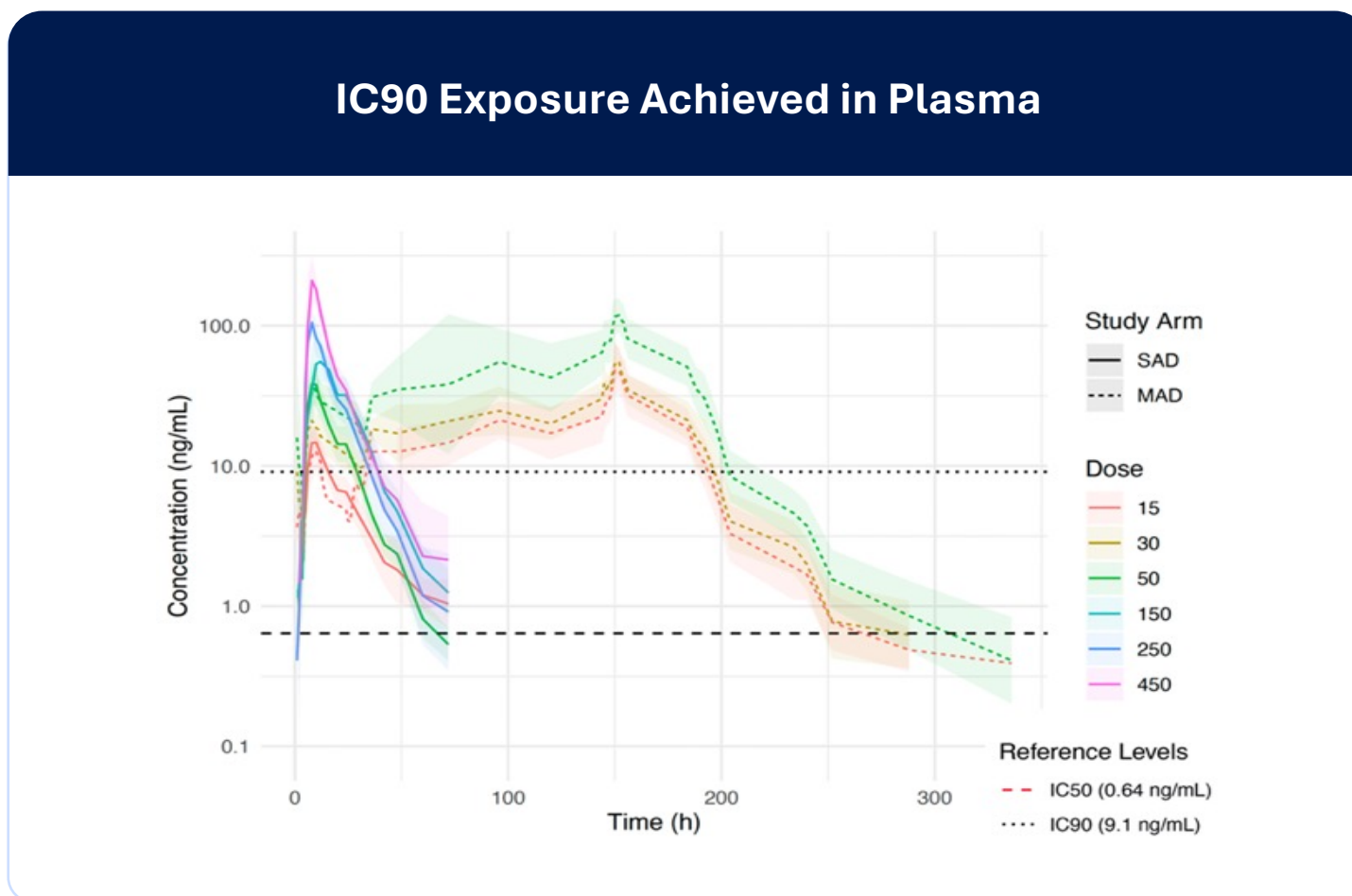


Figure 3: PK profile of the Phase 1a SAD/MAD cohort

Single Ascending Dose (SAD)

- PALI-2108 (prodrug; data not shown)**
 - T_{max} : ~3-4hr $\rightarrow$ consistent with small intestinal dissolution (Eudragit + prodrug design)
 - Exposure (AUC):** Minimal, as intended (GI-restricted)
- PALI-0008 (active PDE4 inhibitor)**
 - T_{max} : ~8-9hr $\rightarrow$ consistent with ileocolonic bioconversion
 - PK profile:** Extended release/ ~2-3x longer half-life than other PDE4 inhibitors (usually BID)
 - Dose proportionality:** C_{max} 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 ~48 hrs
 - Stable pre-dose troughs with repeat dosing
 - Pre-dose troughs ~20% higher than single-dose C_{max} above IC90
- Dosing Implications**
 - Extended half-life supports once-daily dosing

PALI-2108 Demonstrates Consistent PD and Biomarker Improvements in UC Patients

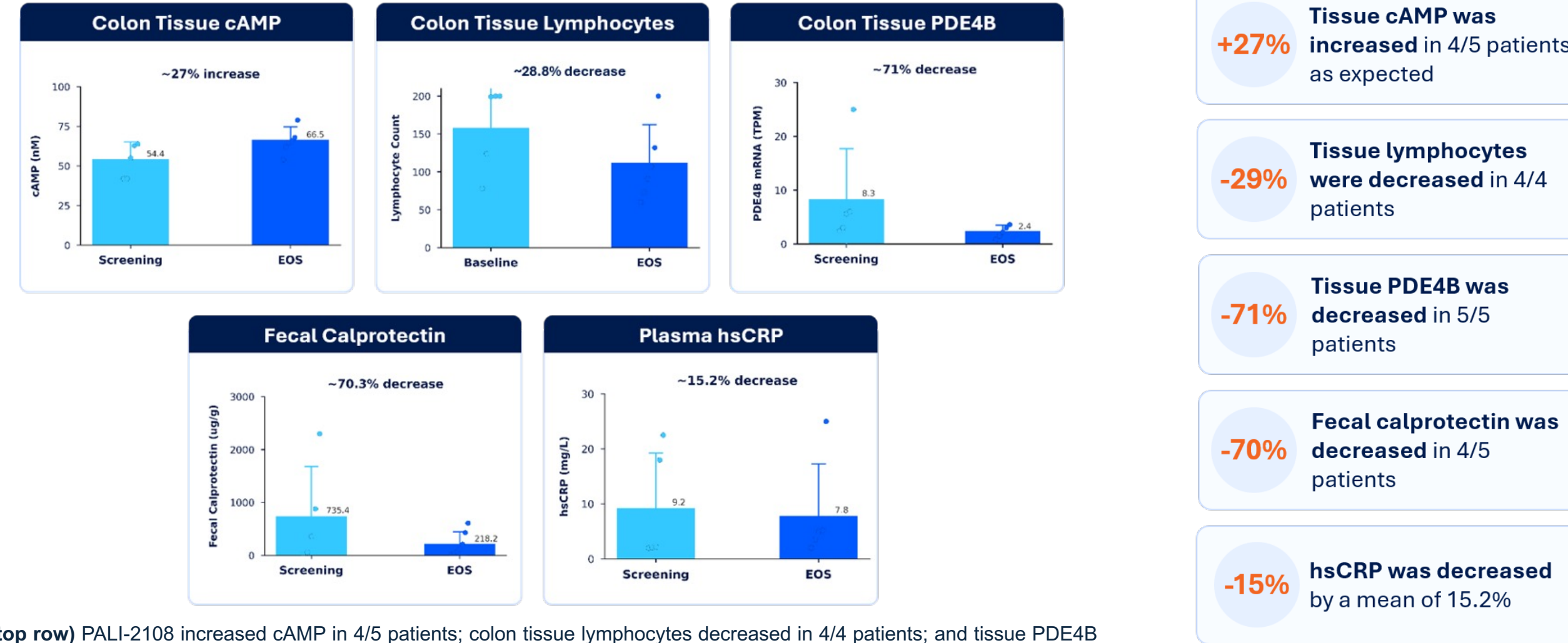


Figure 4: (top row) PALI-2108 increased cAMP in 4/5 patients; colon tissue lymphocytes decreased in 4/4 patients; and tissue PDE4B expression decreased in 5/5 patients. (bottom row) Fecal calprotectin decreased in 4/5 patients and plasma hsCRP decreased.

PALI-2108 Improves Histological Outcomes, Clinical Response, and Remission in UC Patients

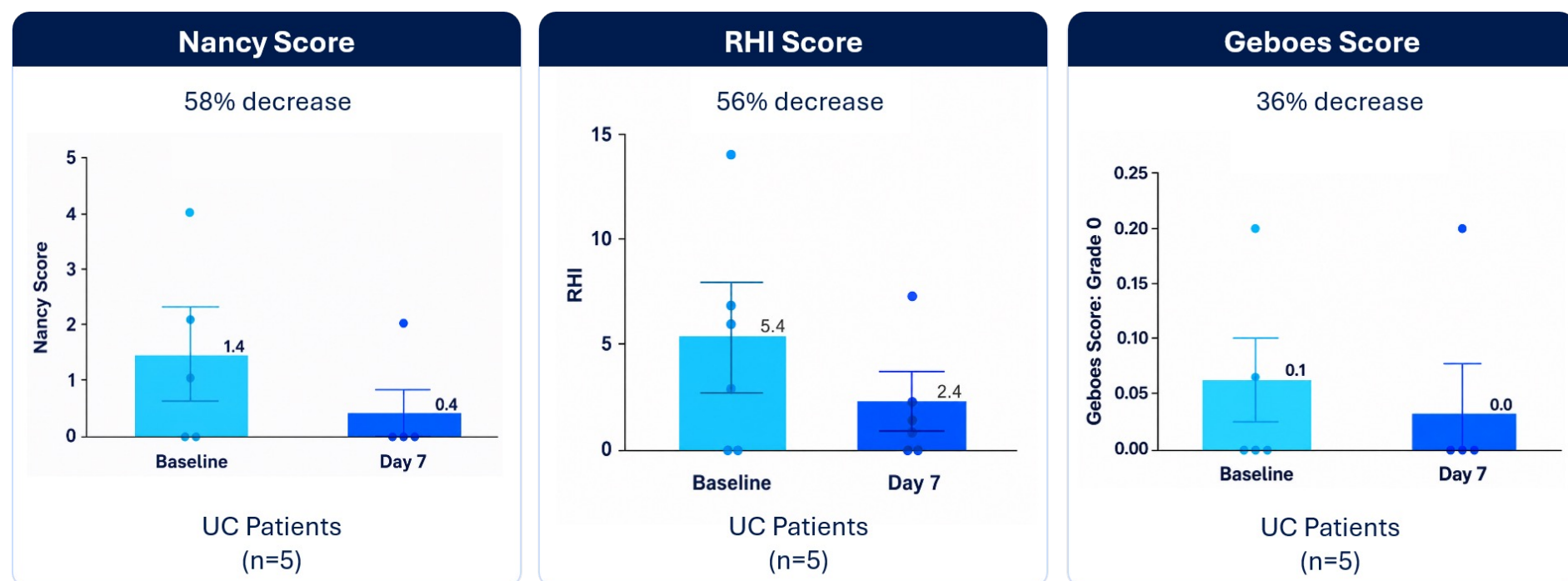
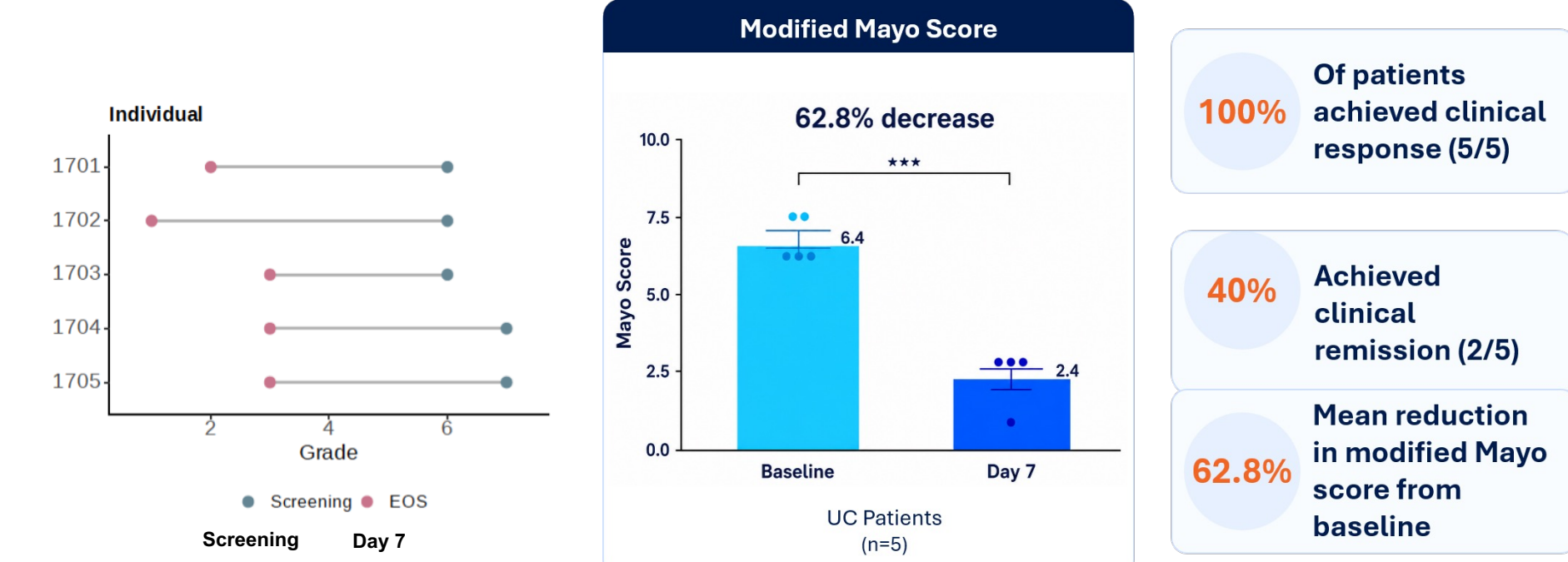


Figure 5: (upper panel) PALI-2108 shows reductions in Nancy score, RHI, and Geboes score. (lower panel) mMayo score significantly decreased (***P<0.001) with PALI-2108.



Results

PALI-2108 Reduces Tissue Inflammatory Cell Counts in UC Patients

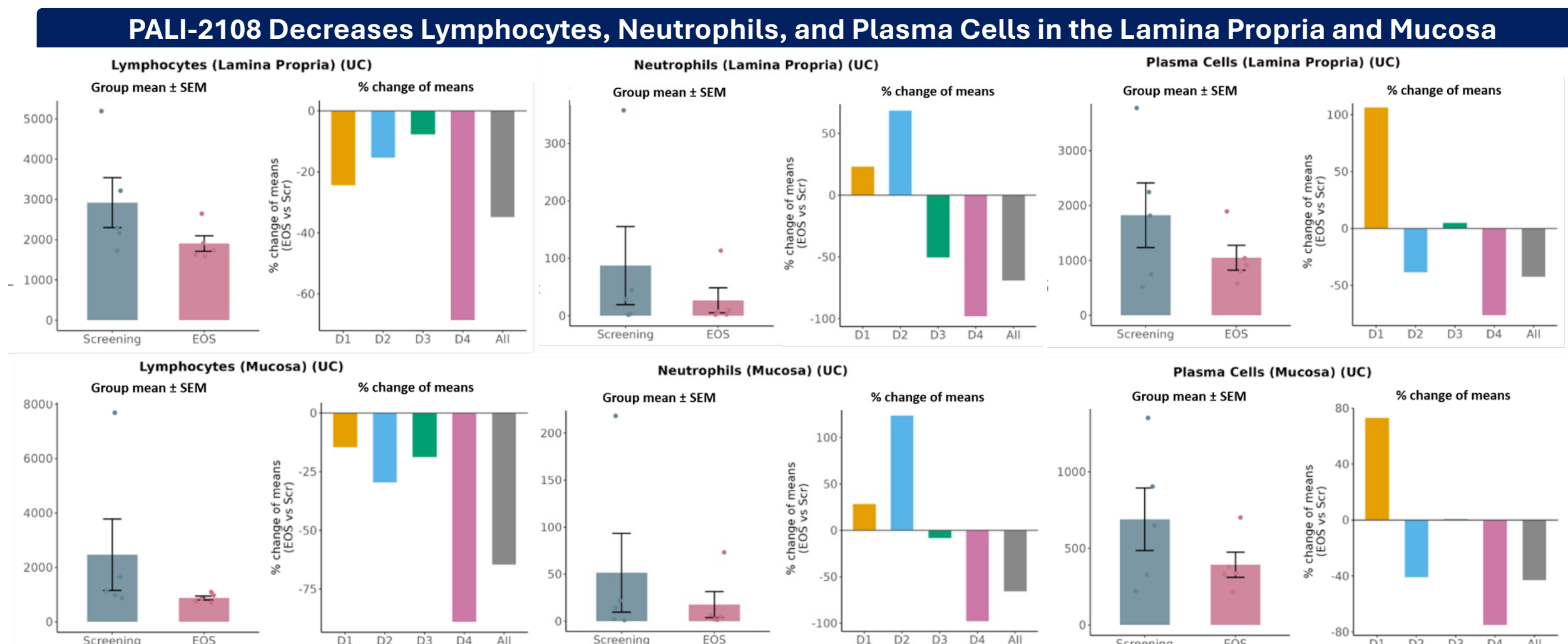


Figure 6: PathAI-enabled quantitative digital pathology analysis demonstrated reductions in inflammatory cell counts in LP and mucosal tissue in individual patients (n=5) over 1 week.

PALI-2108 Induces Early Histologic Features of Mucosal Healing in UC Patients

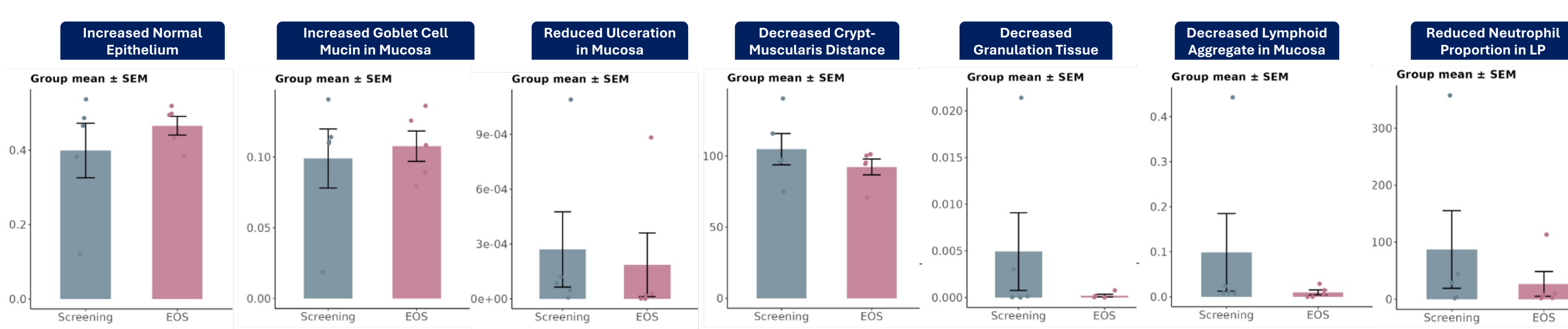


Figure 7: Representative histopathology showing PALI-2108-induced structural changes consistent with mucosal healing, including increased normal epithelium, goblet cells, and mucin, and reduced ulceration, crypt-to-mucosal distance, granulation tissue, lymphoid aggregates, and LP neutrophils.

Proposed Phase 2 Study Design in UC (Study Initiated)

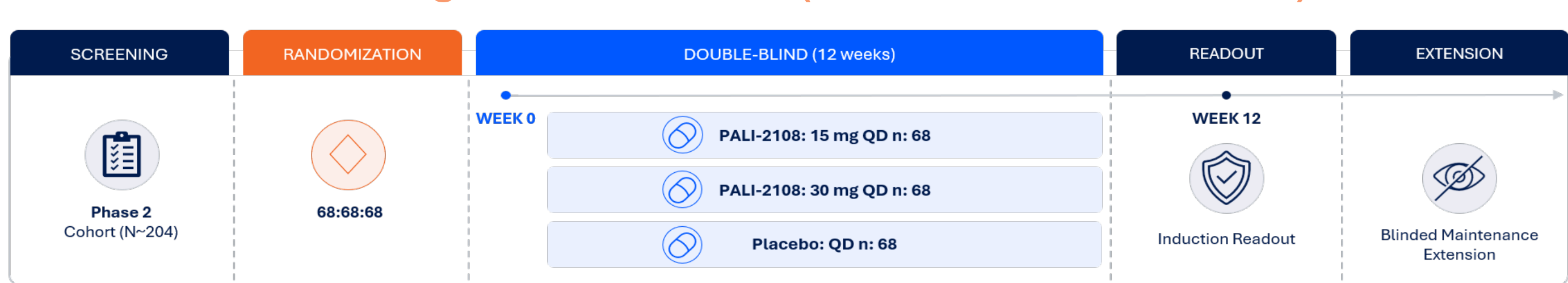


Figure 8: Phase 2: randomized, blinded long-term extension (remission maintenance) in UC patients; QD= once daily, HEM: Histologic-Endoscopy Improvement

Summary

- PALI-2108 demonstrated PK consistent with targeted ileocolonic delivery and once-daily dosing, with 30 mg QD maintaining PALI-0008 exposure above IC90 for 24 hours.
- PALI-2108 was well tolerated and demonstrated target engagement and early activity in UC, including $\downarrow$ PDE4B, $\uparrow$ cAMP, reduced inflammation, improved histology, 100% clinical response, and early remission.
- Early histologic features of mucosal healing were observed, including reductions in inflammatory cells in plasma and tissue.
- These findings support continued development of PALI-2108 as a differentiated, ileum- and colon-targeted oral PDE4 inhibitor prodrug for IBD.