NASDAQ: PALI
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Next-Generation Precision Therapies for Immune, Inflammatory and Fibrotic Diseases

September 2025

STAR Annual Meeting

Forward Looking Statements

Statements in this presentation that are not statements of historical fact are forward-looking statements. Such forward-looking statements include, without limitation, statements regarding our research and pre-clinical and clinical development plans, expected near and long-term milestones, hypothesis related to PALI-2108, the potential of PALI-2108 to treat inflammatory bowel disease ("IBD"), our ability to successfully complete our current and planned human clinical trials of PALI-2018, the ability of PALI-2108 to achieve market acceptance, the success of our development and business strategy, Insurance company's agreeing to reimburse patients for treatments utilizing PALI-2018, ability to leverage certain regulatory pathways, timing of studies, competitors, regulatory matters, market size and opportunity and our ability to complete certain milestones, including completion of subject enrollment. Words such as "believe," "anticipate," "could," "estimate," "aim," "target," "plan," "expect," "intend," "will," "may," "goal," "potential" and similar expressions are intended to identify forward-looking statements, though not all forward-looking statements necessarily contain these identifying words. These forward-looking statements are based on the beliefs of management of Palisade Bio, Inc. (the "Company") as well as assumptions that may never materialize or prove to be incorrect. Such statements reflect the current views of the Company with respect to future events and are subject to known and unknown risks, including business, regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company, including, without limitation, risks inherent in developing pharmaceutical products, future results from the Company's ongoing pre-clinical studies and clinical trials, the Company's ability to obtain adequate financing to fund its operations and planned studies and other expenses, trends in the industry, changes in the competitive landscape, delays or disruptions due to the pandemics, the legal and regulatory framework for the industry and future expenditures. In light of these risks and uncertainties, the events or circumstances referred to in this presentation may not occur. The actual results may vary from the anticipated results and the variations may be material. Other factors that may cause the Company's actual results to differ from current expectations are discussed in the Company's filings with the Securities and Exchange Commission, including the section titled "Risk Factors" contained therein. These forward-looking statements should not be taken as forecasts or promises, nor should they be taken as implying any indication, assurance or guarantee that the assumptions on which such forward-looking statements have been made are correct or exhaustive or, in the case of the assumptions, fully stated in this presentation. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date this presentation is given. Except as required by law, the Company assumes no obligation to update any forward-looking statements contained herein to reflect any change in expectations, even as new information becomes available.

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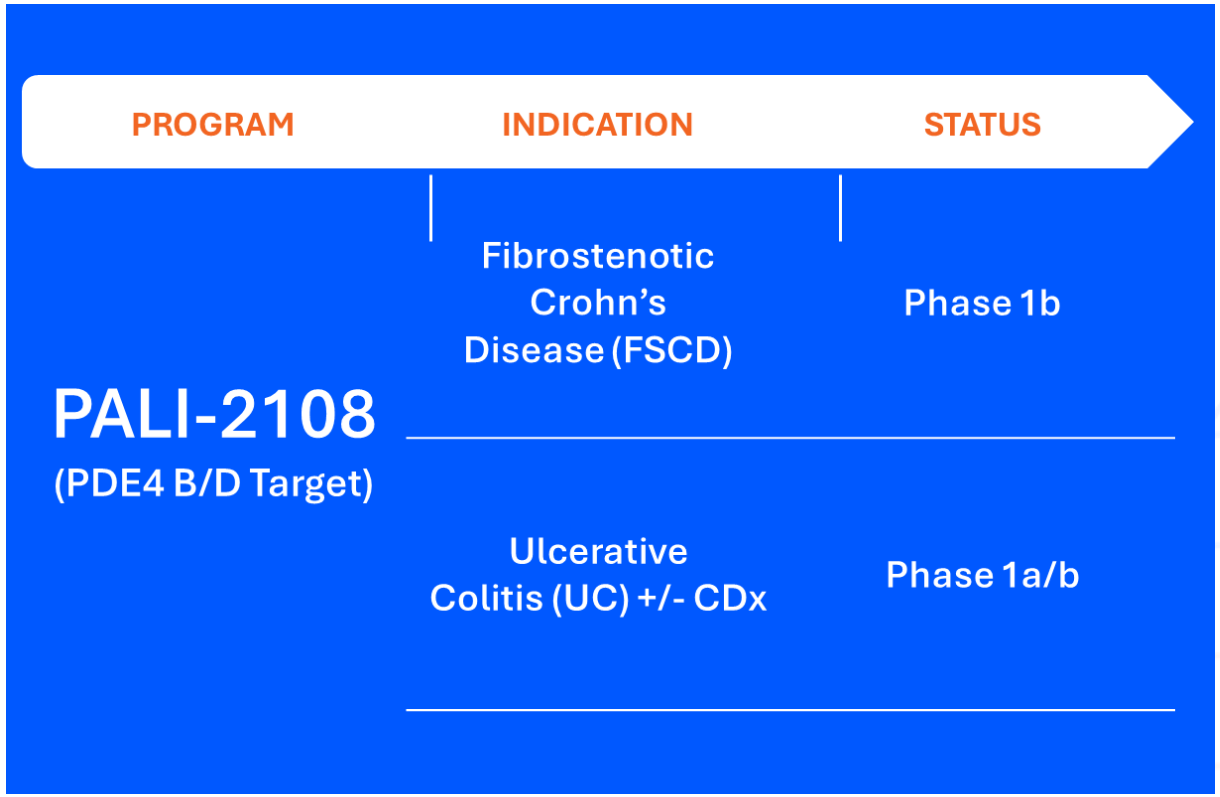
PALI-2108 - Lead Program Targeting FSCD

Advancing Toward IND Submission for Phase 2 study in H1 2026



- **Only PDE4 inhibitor in development targeting the terminal ileum and colon** for treatment of fibrostenotic Crohn's disease (FSCD) and ulcerative colitis (UC)
- **Only extended release once daily PDE4 inhibitor in development**
- **Only clinically proven dual-acting anti-inflammatory and anti-fibrotic candidate in development for FSCD** where there are currently no approvals
- **Demonstrated Safety and Tolerability with no serious adverse events**
- **Demonstrated 100% Clinical Response and 40% Clinical Remission in Phase 1b UC cohort over one week**
- **Precision Medicine test in development** to identify UC patient responders to PDE4 inhibitors, ensuring better treatment outcomes.

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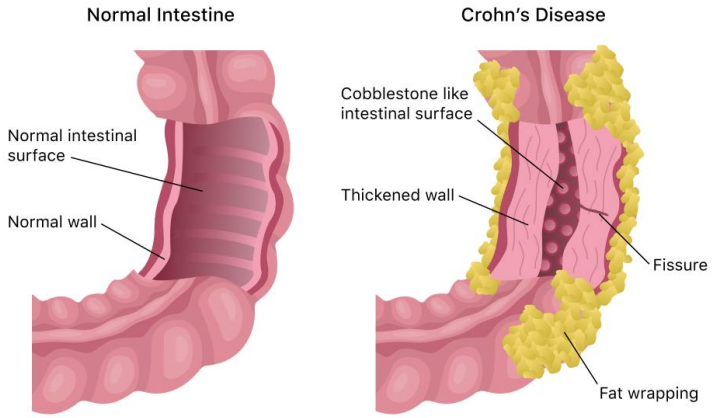
FSCD One of the Largest Unmet Medical Needs in IBD

Strictures are a driven by interplay of **inflammatory *and* fibrotic** pathways



Stricture formation occurs most commonly in the terminal ileum and colon, causing obstructive symptoms

FSCD patients experience higher health and economic burden (1) (2)

4x Hospitalization rate

2x Need for Endoscopic procedures

2x Need for IBD-related surgery

1.5x Steroid Dependency

The current standard of care (SOC) is inadequate

- **Corticosteroids -** lead to high recurrence.
- **Anti-inflammatory drugs -** don't address fibrosis.
- **Endoscopic balloon dilation has limited durability -**
  - > 70% of patients needing repeat dilation within two years,
  - > 40% of patients require surgery.
- **Surgery itself isn't curative** –
  - 75% of patients eventually require surgery
  - > 50% experience recurrence of fibrosis and strictures afterwards.

As highlighted by the STAR Consortium just last year: "the ultimate goal is still the development of selective anti-fibrotic therapies for FSCD."- STAR Consortium, July 2024

(1) https://pmc.ncbi.nlm.nih.gov/articles/PMC8689124/
(2) https://pmc.ncbi.nlm.nih.gov/articles/PMC10387957/
(3) Solitano, et al. (2023). FSCD: What is new and what is next? *Journal of Clinical Medicine*, *12*(9), 3052. https://doi.org/10.3390/jcm12093052
(4) Mak et al, Epidemiology of fibrostenosing inflammatory bowel disease, J Dig Dis. 2020 Jun;21(6):332-335

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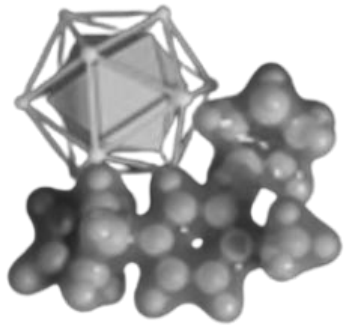
PALI-2108 Designed to Bio-Activate Locally and Deliver Clinically Proven Anti-Inflammatory and Anti-Fibrotic Effects of PDE4s

- Targets PDE4 B/D enzymes
- Prevents break down of intracellular cAMP
- cAMP levels become elevated
- **Reduces inflammatory tone and prevents inflammatory cell infiltration within tissues of the ileum and colon**

Prodrug Form

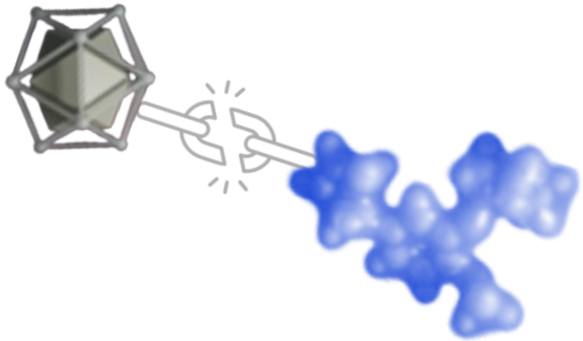
- *It is an oral prodrug that bio-activates locally in the distal gut, where bacterial activity is highest.*
- *Once activated, it selectively inhibits PDE4B and PDE4D.*



Colonic Bacterium Enzyme β-Glucuronidase

Localized Bio-Activation

- *This raises cAMP levels, reduces inflammatory tone, and prevents inflammatory cell infiltration into tissues.*
- *By combining selectivity with local activation, we max cAMP modulation locally in tissue lymphocytes and fibroblasts*

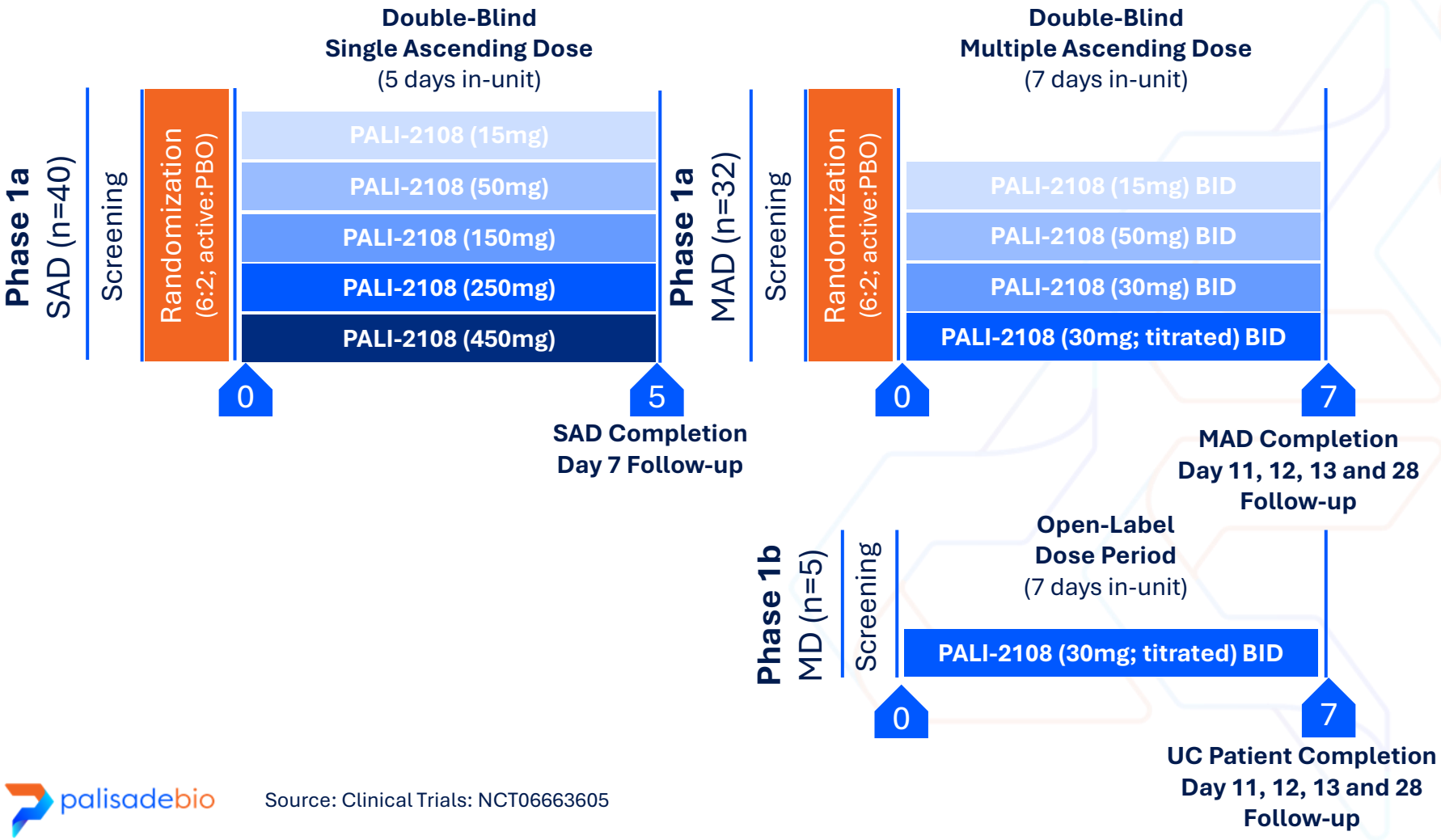


The combination of selectivity and local bioactivation helps to avoid the GI and CNS side effects typically seen with non-specific, systemically distributed PDE4 inhibitors.

Completed Phase 1a/b Study with NHV and UC Patients

Double-Blind, Placebo-Controlled, Safety, Tolerability, PK and PD Study of PALI-2108 in NHV and Open-Label Study of a Patient Cohort with UC

Topline Data Expected Q2 2025



Single Ascending Dose (n~40)

- Primary Endpoint
  - Safety and tolerability
- Secondary Endpoints
  - PK including Tmax, Cmax and T1/2

Multiple Ascending Dose (n~32)

- Primary Endpoint
  - Safety and tolerability
- Secondary Endpoints
  - PK including plasma and tissue C SS and colon : plasma ratio

Multiple Dose UC Cohort (n~5)

- Pharmacokinetic Endpoints
  - Plasma, colon tissue, urine, stool including plasma and tissue C SS and colon : plasma ratio
- Pharmacodynamic Endpoints
  - Fecal calpro, calpro epitope, hsCRP, colon tissue PDE4s, cAMP, TLC, and histology

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Source: Clinical Trials: NCT06663605

Phase 1a Confirms PALI-2108 was Safe and Well Tolerated

SAD Safety and Tolerability

	15mg		50mg		150mg		250mg		450mg	
	Active	PBO	Active	PBO	Active	PBO	Active	PBO	Active	PBO
Number of subjects	6	2	6	2	6	2	6	2	6	2
TEAEs, possibly related (n)	0	0	0	0	0	0	0	0	22	1
Investigator defined TEAEs (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (100%)	1 (50%)
> Grade 1 TEAE (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severe Adverse Events (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Withdrawn b/c TEAE (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

MAD Safety and Tolerability

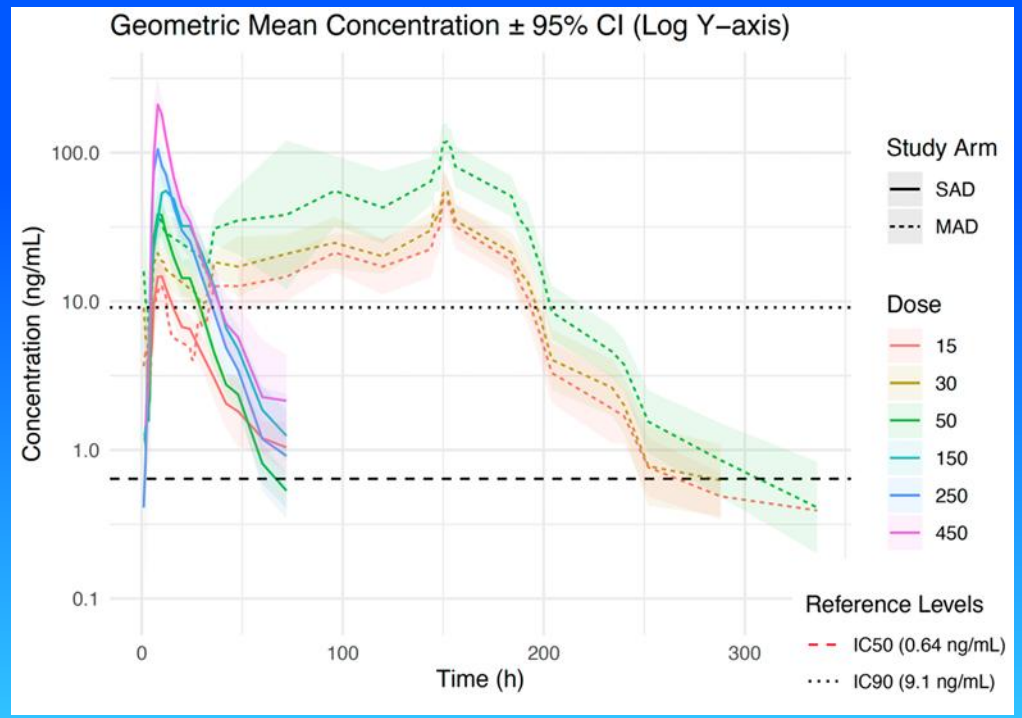
	15mg BID		30mg BID (titrated)		30mg BID		50mg BID	
	Active	PBO	Active	PBO	Active	PBO	Active	PBO
Number of subjects	6	2	6	2	6	2	6	2
TEAEs, possibly related (n)	0	0	1	0	21	0	18	0
Investigator defined TEAEs (n/%pts)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	4 (67%)	0 (0%)	4 (67%)	0 (0%)
> Grade 1 TEAE (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)	0 (0%)	1 (17%)	0 (0%)
Severe Adverse Events (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Withdrawn b/c of TEAE (n/%pts)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)

PALI-2108 Ph1a Findings:

- ✓ **84 patients treated and no SAEs and no AEs related to labs or EKGs**
- ✓ **Completed all SAD cohorts** demonstrating Safety and Tolerability up to 450mg
- ✓ **Completed all MAD cohorts** demonstrating safety and tolerability of twice daily (BID) doses up to 50mg with 15mg BID having zero TEAE in any subject and 30mg titrated with one.
- ✓ **Completed FE cohort** demonstrating beneficial changes, reduced Cmax, right shifted AUC and delayed Tmax due to colon bioactivation
- ✓ **Confirmed utility of titration** with 30mg BID like other PDE4s

Phase 1 SAD/MAD PK Demonstrates PK Characteristics and Superior Exposure to Other PDE4s

Dose Proportionality and Extended Half-Life Enabling Daily Dosing



- **Single Ascending Dose (SAD)**
- **PALI-2108 (prodrug; NOT SHOWN)**
  - **Tmax:** ~3–4h → consistent with small intestinal dissolution (Eudragit + prodrug design).
  - **Exposure (AUC):** Minimal, as intended (GI-restricted).
- **PALI-0008 (active PDE4 inhibitor)**
  - **Tmax:** ~8–9h → consistent with ileocolonic bioconversion.
  - **PK profile:** Extended release; ~2–3× longer half-life than other PDE4 inhibitors (usually BID).
  - **Dose proportionality:** Cmax 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 ~48h.
  - Stable pre-dose troughs with repeat dosing.
  - Pre-dose troughs ~20% higher than single-dose Cmax, above IC90.
- **Dosing Implications:**
  - Extended half-life supports **once-daily dosing**.

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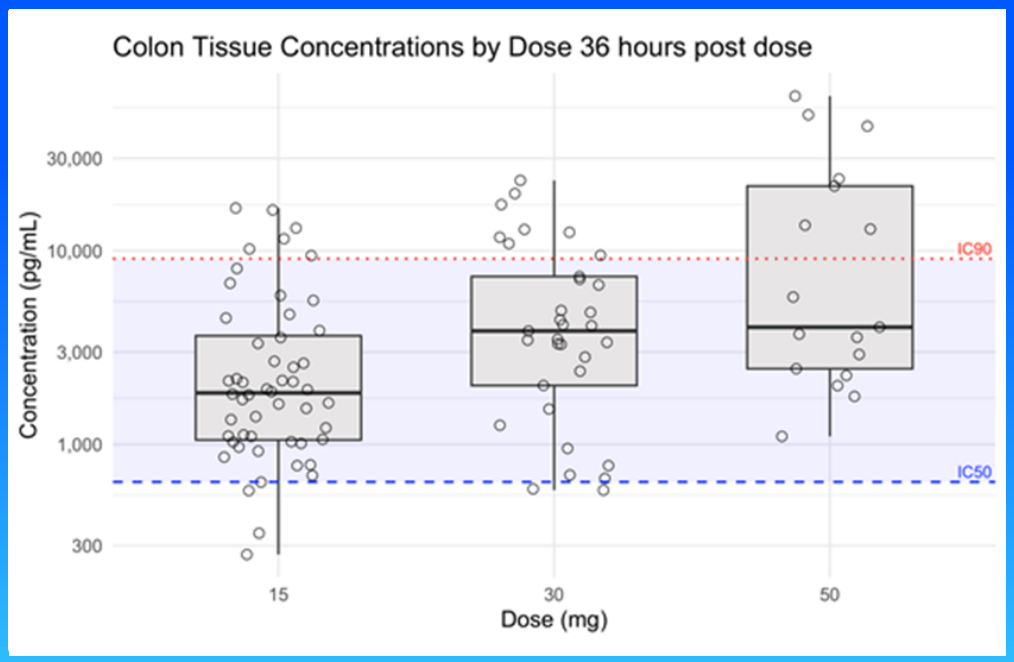
Phase 1 MAD Colon Tissue Pharmacokinetics

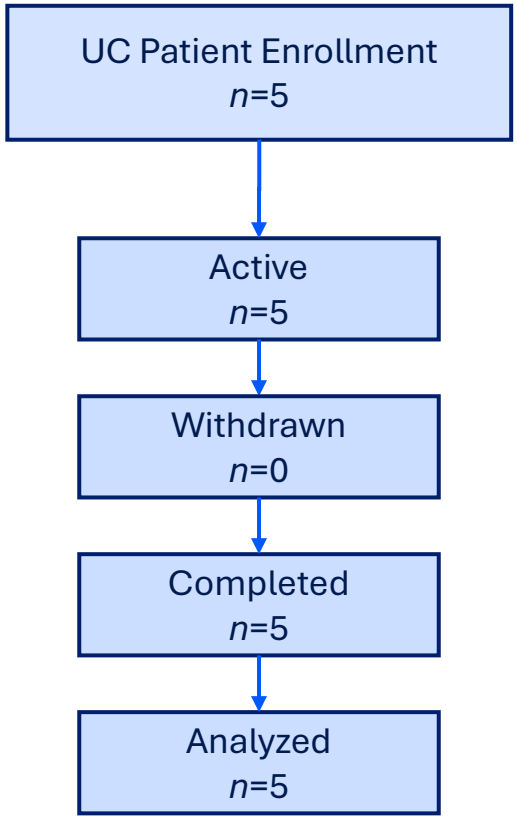
Tissue PK 36 Hours Post Dose Demonstrates Extended-Release PK and Potential for Daily Dosing



Tissue PK Observations from MAD:

- ✓ **Colon Tissue Concentrations approached IC90 36h post dose -** demonstrating therapeutic concentrations and extended-release tissue PK at multiple dose levels supporting a daily dosing regimen

Phase 1b UC Cohort Patient Disposition and Safety



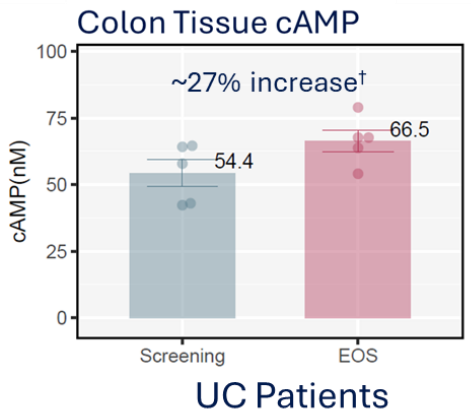
UC Patient Cohort Details

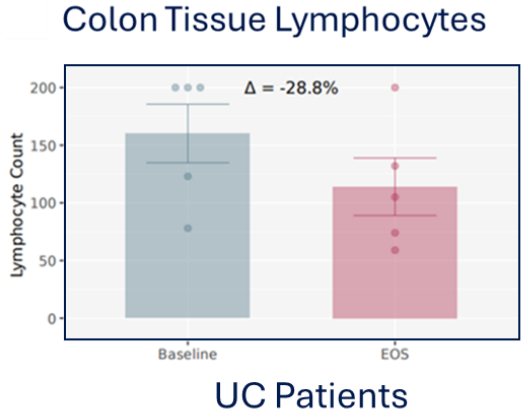
- 5 patients with moderate to severe ulcerative colitis enrolled
- All patients received 30 mg (titrated) BID PALI-2108 for 7 days (open-label design)
- All patients completed the study and there were no withdrawals

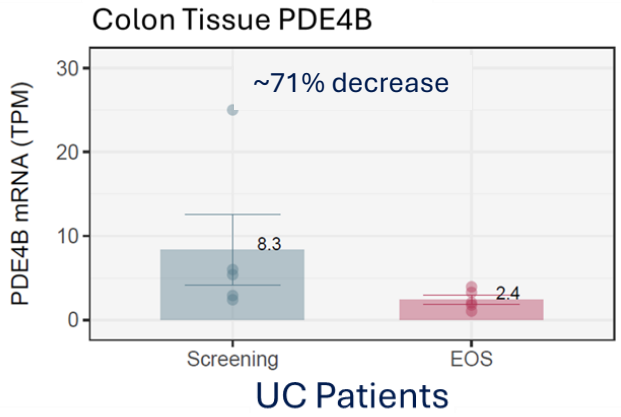
- **Safe and Well-Tolerated:**
  - No clinically significant change in PE, vital signs, safety lab tests and EKG
  - PDE4-related TEAEs were mild and quickly resolved
- **Successful Titration Strategy:**
  - Using a 5-day dose titration regimen led to good tolerability
  - With few TEAEs by end of titration related to Cmax and BID dosing
- **Time-Limited Adverse Events:**
  - TEAEs occurred within 2-3 days of treatment, with reduction in frequency and severity over time.
- **Extended-Release PK:**
  - PK suggests daily dosing and lower initial titration expected to achieve plasma and tissue IC50/90 goals with excellent Day 7 tolerability

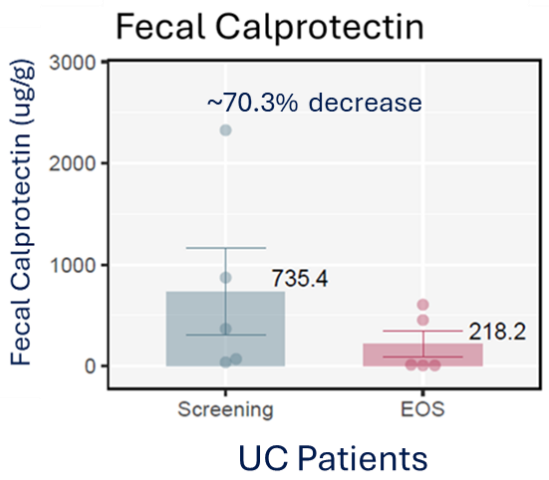
BID = Twice daily; hsCRP = highly sensitive C-reactive protein; PDE4 = phosphodiesterase type 4

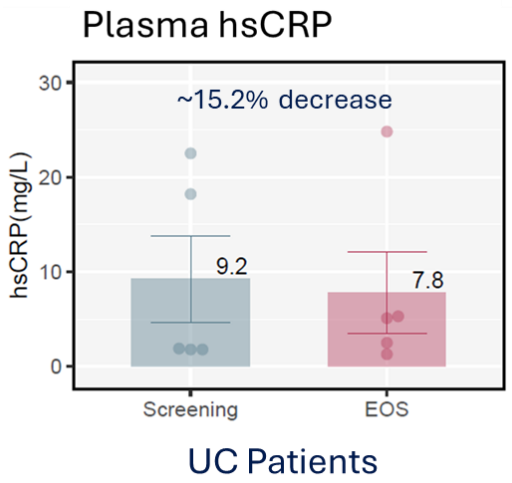
Mechanistic and Inflammatory PD were Improved cAMP, PDE4B and TLC, CalPro and hs CRP











- ✓ **Tissue cAMP was increased** in 4/5 patients (~27% mean increase) as expected due to inhibition of PDE4 enzyme
- ✓ **Tissue lymphocytes was decreased** in 4/5 (mean ~29% reduction; ~40% by individual mean approach)
- ✓ **Tissue PDE4B was decreased** in 5/5 patients (mean ~71% reduction)
- ✓ **Fecal calprotectin was decreased** in 4/5 patients by a mean of ~70.3%.
- ✓ **hsCRP was decreased by** a mean of ~15.2%.

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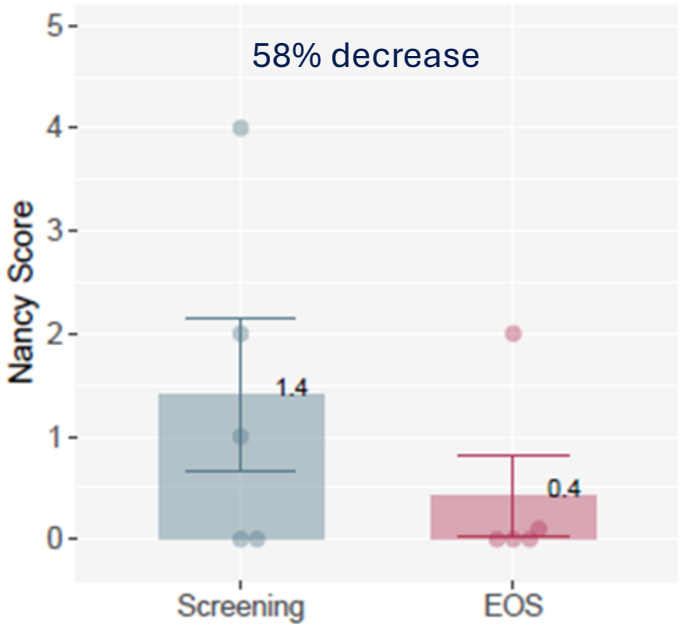
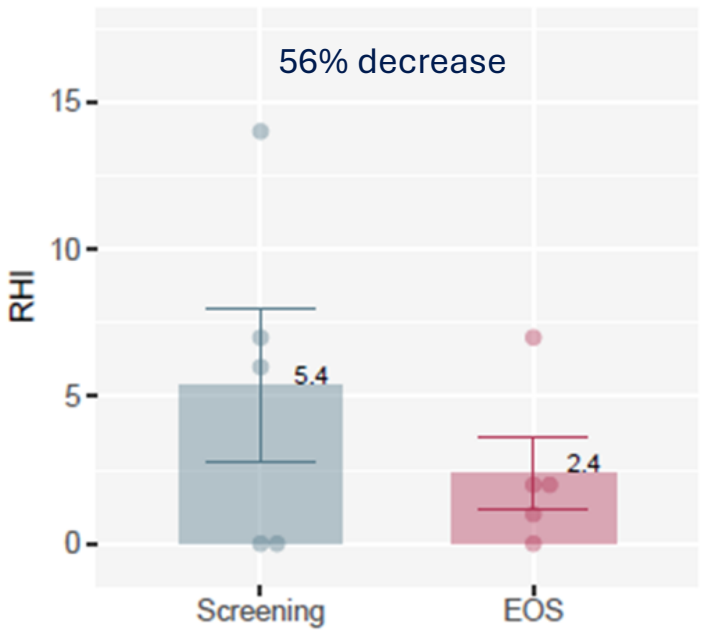
Colon Tissue Histologic Scores were Improved

Nancy Score



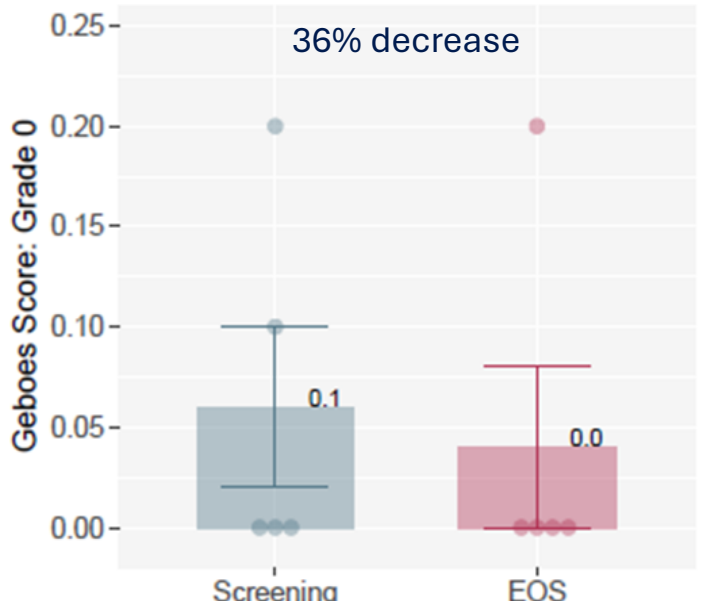
UC Patients

RHI Score



UC Patients

Geboes Score



UC Patients

✓ **Tissue Histology: Improvements observed in:**

- ✓ **Nancy Index** was decreased ~58%
- ✓ **Robarts Histopathology Index** was decreased ~56%.
- ✓ **Geboes Score was decreased** ~36%.

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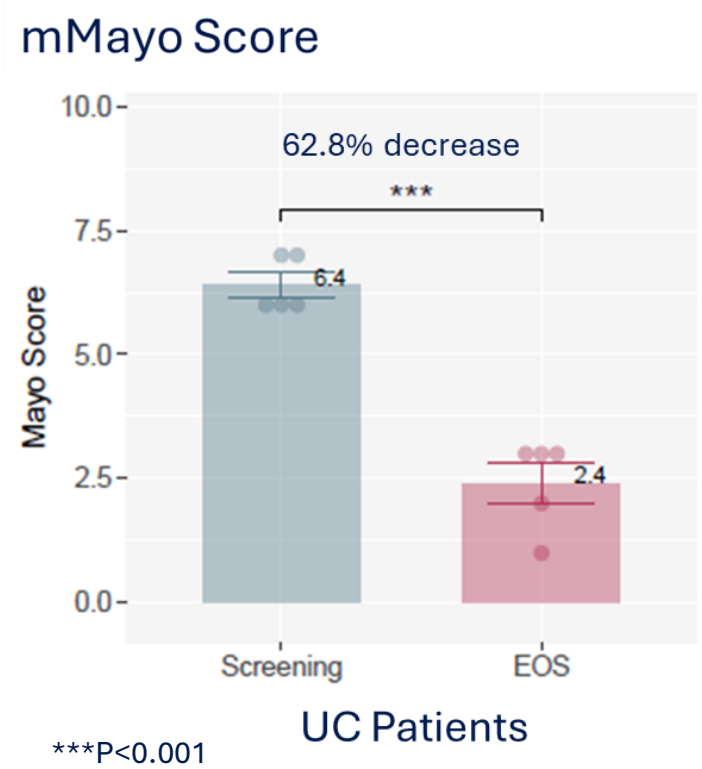
Clinical Response and Remission was Demonstrated by Modified Mayo Score



***P<0.001

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%**

- ✓ **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** (≥30% or ≥3-point drop in modified Mayo score (with rectal bleeding subscore of 0 or 1)
- ✓ **Clinical Remission was achieved in 2/5 (40%) of patients**

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%**)

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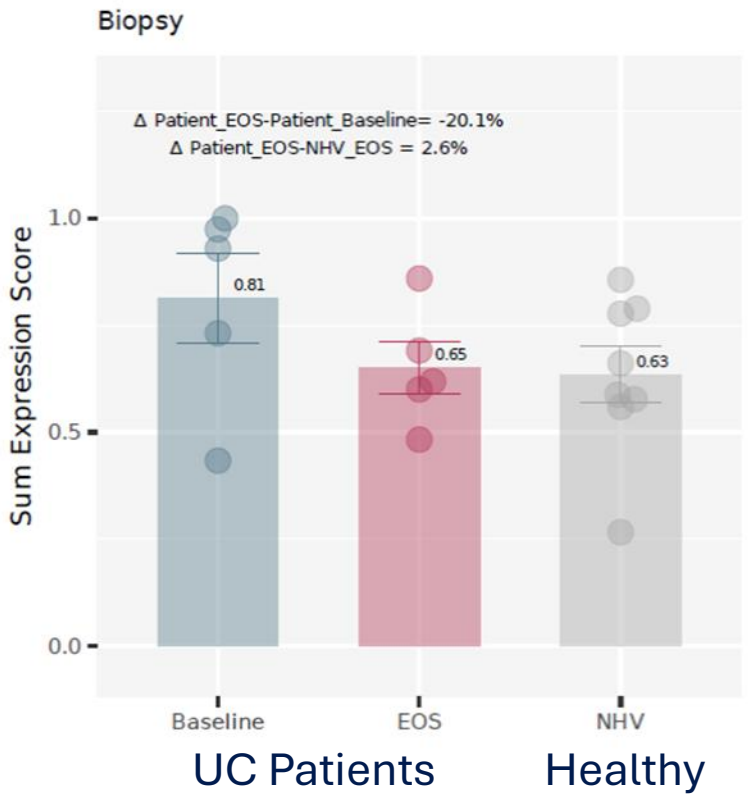
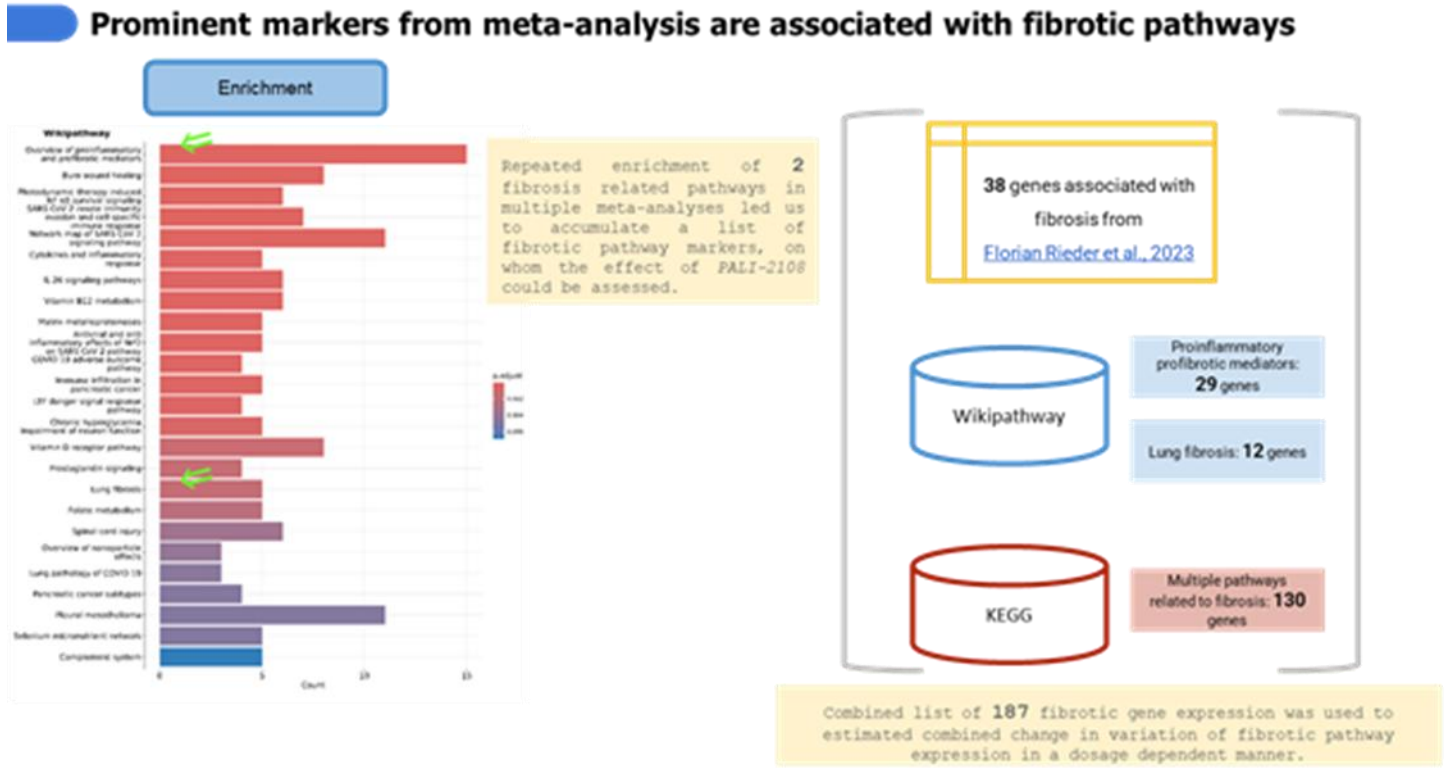
Key Colon Tissue Fibrosis Pathways for Fibrostenotic Crohn's Disease (FSCD) were Engaged





Sum Colon Tissue Fibrosis Biomarkers (186 fibrotic gene markers) were elevated in UC patients at Baseline compared to Normal Healthy Volunteers (NHV) and reduced by the study endpoint (EOS)

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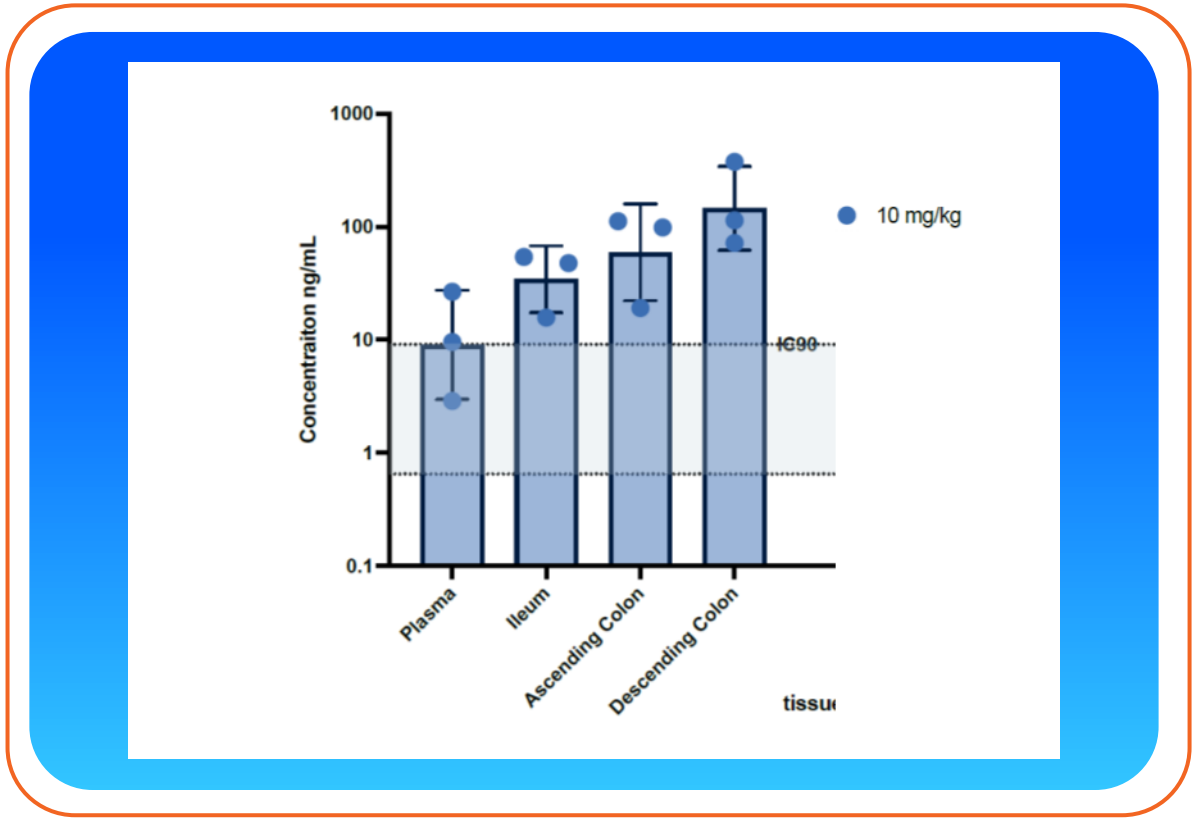
Summary PALI-2108
Phase 1b UC Cohort Topline Data Summary

- ✓Clinical Response was achieved in 100% of patients
- ✓Mean mMayo Score reduction of 62.8% or ~4 points
- ✓Clinical Remission was achieved in 40% of patients
- ✓Histologic improvement was achieved across multiple indices
- ✓Inflammatory biomarkers were reduced including fecal calprotectin and plasma hsCRP
- ✓Mechanistic biomarkers demonstrated a consistent increase in colon tissue cAMP, decrease in Tissue Lymphocyte Count, and reduction in tissue PDE4B
- ✓Colon tissue expression of biomarkers representing key Fibrostenotic Crohn's Disease (FSCD) pathways were engaged

PALI-2108: Sustained Tissue Concentration of PDE4 active (PALI-0008) Across the Ileum and Colon

Tissue Levels of Active Bioactivated PALI-2108 (PALI-0008) and Shows Drug Concentration in Ileum Ascending and Descending Colon 12 hours After Twice Daily (BID) Dosing in Dog

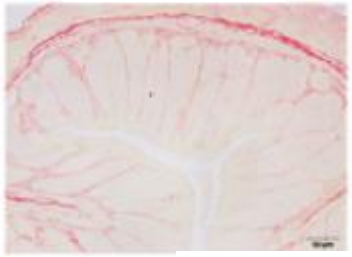


PALI-2108 Demonstrated Dose Response on Fibrotic Pathways In DSS Mouse Model

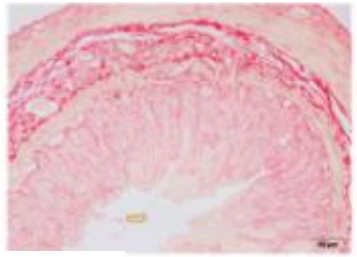
PDE4 Inhibitor Effect on Fibrotic Pathways

PDE4 Inhibitor Attenuates Collagen Deposition and Reverses Activation of Mucosal Fibroblasts

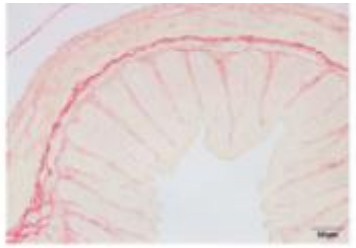
Normal



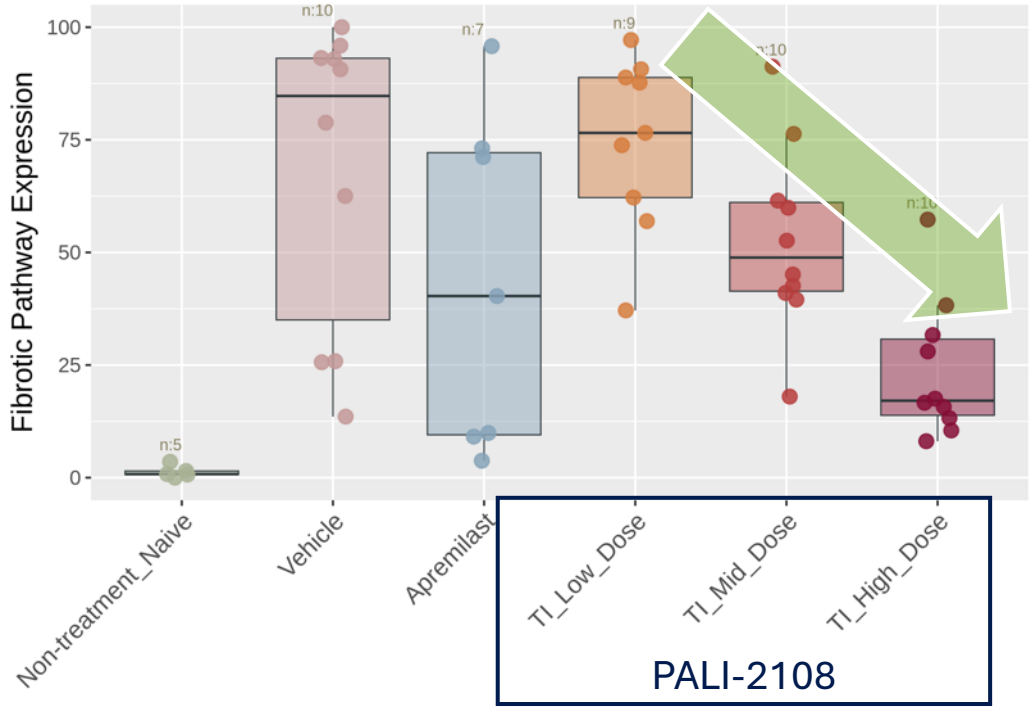
DSS Mice + Vehicle



DSS Mice + Apremilast



PALI-2108 Demonstrated Greater Antifibrotic Effect Compared to Apremilast



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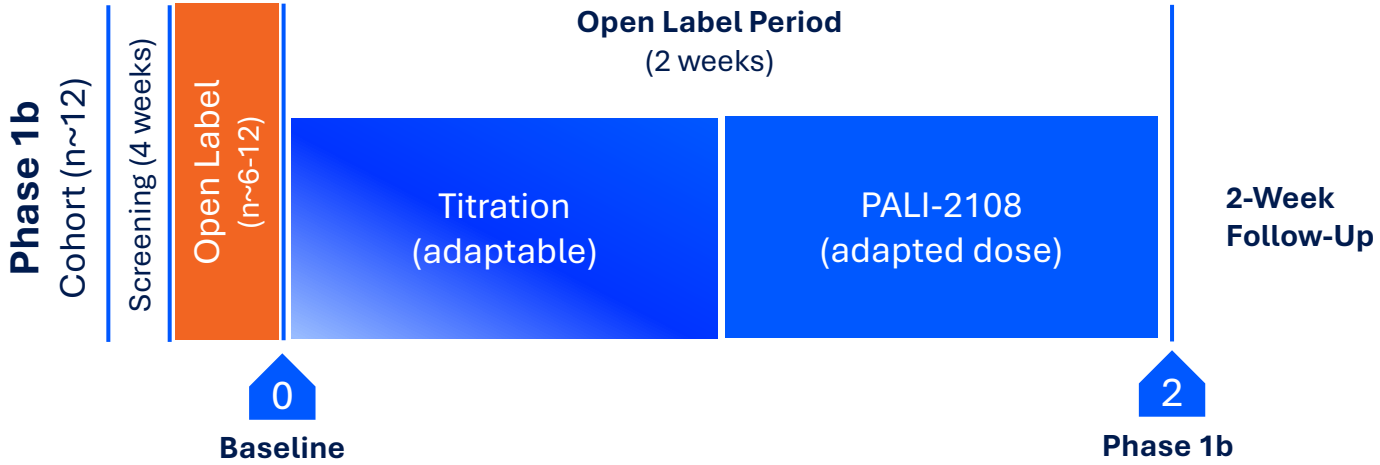
*Li et al.

FSCD Phase 1b Study Design (Ongoing)

Study Designed for First Fibrostenotic Crohn's Disease (FSCD) Safety, Tolerability, PK and PD



- Safety and tolerability: AEs, Labs, and EKGs
- PK plasma and tissue (ileum, ascending, descending colon)
- PD plasma and ileal biopsy (RNAseq)
- Patient reported outcomes (SPROs)
- Histology and staining
- Intestinal ultrasound (IUS)

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Ph1b Safety and PK Readout (n~6-12)

- Safety and tolerability: AEs, Labs, and EKGs
- PK plasma and tissue ileum, ascending, descending colon
- PD plasma and ileum biopsy (RNAseq)
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