

NASDAQ: PALI
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**Next-Generation, Once Daily, Oral PDE4
Inhibitor Prodrugs for Inflammatory Disease**

April 2026
Precision Medicine in IBD – Phase 1b FSCD

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-2108, the ability of PALI-2108 to achieve market acceptance, the success of our development and business strategy, Insurance companies agreeing to reimburse patients for treatments utilizing PALI-2108, 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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Corporate Highlights

Our Mission:

Advancing next-generation, once daily, oral PDE4 inhibitor prodrugs for patients with inflammatory and fibrotic diseases

Lead program, PALI-2108, targeting multi-billion-dollar IBD market

Raised \$138 Million from Leading Fundamental Institutional Healthcare Investors to Fund Company Through Major Development Milestones

PALI-2108

- **Only PDE4 inhibitor prodrug in development targeting the terminal ileum and colon** for treatment of ulcerative colitis (UC) and Crohn's disease (CD)
- **Commercially proven PDE4 target** with potential for superior efficacy and greater tolerability with PDE4 inhibitor over systemic PDE4 inhibitors
- **Positive Phase 1a/b data** demonstrating safety, tolerability and PK supporting local bioactivation in UC and fibrostenotic Crohn's disease (FSCD)
- **First and only dual-acting anti-inflammatory and anti-fibrotic candidate in development for IBD**
- **Precision Medicine CDx test in development** to identify UC patient responders to PDE4 inhibitors, ensuring better treatment outcomes

Development Pipeline


Differentiated product candidate with potential to address shortcomings of existing therapies in established markets

PROGRAM	INDICATION	STAGE	HIGHLIGHTS
PALI-2108 PDE4 Inhibitor Prodrug, Once Daily	Ulcerative Colitis (UC)	Phase 1b	Completed and reported topline data for Ph1 IND and Ph2 expected to commence in 2026
	Crohn's Disease (CD) / Fibro stenotic Crohn's Disease (FSCD)	Phase 1b	Completed and reported topline data for Ph1 IND and Ph2 expected to commence in 2026

PALI-2108 Upcoming Milestones¹



(1) The timing of the milestones are estimated, and the actual timing of these milestones may differ than described herein.



PALI-2108

Differentiated asset with potential to address important unmet medical needs in large, established IBD market

PDE4 inhibitors are pleiotropic drugs with commercially proven anti-inflammatory and anti-fibrotic activity

Anti-Inflammatory

PDE4 inhibition → ↑ cAMP

- ↓ Pro-inflammatory cytokines (TNFα, IL-23, IL-6)
- ↓ Immune cell activation
- ↓ Immune cell trafficking
- ↓ Tissue inflammation

Result: Reduced inflammation

Inflammatory Indications:

- Psoriasis
- Psoriatic arthritis
- Behcet's disease
- COPD

AMGEN

Otezla[®]
(apremilast) tablets

AstraZeneca

Daliresp[®]
(roflumilast) tablets

Verona Pharma[®]

Ohtuvayre[®]
(ensalentine) tablets

Anti-Fibrotic

PDE4 inhibition → ↑ cAMP

- ↓ Fibroblast activation
- ↓ Collagen and ECM production
- ↓ Tissue remodeling and scarring

Result: Reduced fibrosis

Fibrosis Indications:

- Interstitial Pulmonary Fibrosis (IPF)

 **Boehringer Ingelheim**




JASCAYD[®]
(nerandomilast)
tablets 18 mg

PALI-2108's Highly Differentiated PDE4 Inhibitor Prodrug Improves PK and Tolerability, and Enables Daily Dosing


Pan-PDE4 Inhibitors

 AMGEN	Otezla (apremilast) tablets
 AstraZeneca	Daliresp (roflumilast) tablets
 Verona Pharma ⁽¹⁾	Ohtuvayre (ensifentrine) suspension 3 mg/25 mL ⁽²⁾
 ARCUTIS BIOTHERAPEUTICS	Z ZORYVE (roflumilast) cream
 HEMAY	Mufemilast

Selective PDE4 Inhibitors

 Boehringer Ingelheim	 JASCAYD (nerandomilast) tablets 18 mg
 UNION THERAPEUTICS	Orismilast

Once Daily PDE4 Inhibitor Prodrug

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PALI-2108

- ✓ PALI-2108 is a **potent PDE4 specific inhibitor prodrug** with 10x-20x potency level of other PDE4 inhibitors
- ✓ PALI-2108 **targets the terminal ileum and colon**

Effectively Improve Therapeutic Window and Minimize Adverse Events

(1) On July 9, 2025, Merck announced its plans to acquire Verona Pharma for \$10B, which will close in 4Q 25.

(2) In addition to targeting PDE4, OHTUVAYRE also targets PDE3.

PALI-2108 Only Bio-Activates in the GI System



Targets PDE4 enzymes



Prevents breakdown of intracellular cAMP



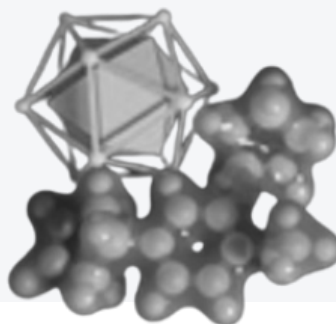
cAMP levels become elevated



Reduces inflammatory tone and prevents inflammatory cell infiltration within tissues of the ileum and colon

Prodrug Form

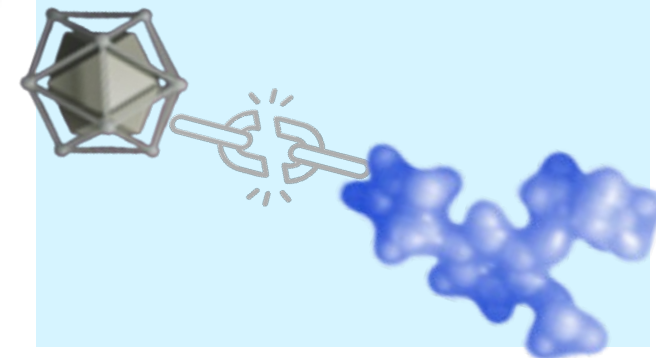
- PALI-2108 prodrug is linked to a galactose moiety via a beta-1, 4-glycosidic bond that minimizes systemic exposure
- The β bond can be cleaved by bacterial enzyme β -glucuronidase in the colon
- Human β -glucuronidase in lysosomes and other tissues does not have access to the prodrug



Colonic Bacterium Enzyme β -Glucuronidase

Localized Bio-Activation

- Colonic bacterial enzyme β -glucuronidase cleaves the β bond and activates PALI-2108, enabling targeted activation
- The activated PALI-2108 inhibits PDE4 isoforms in the ileum and colon, preventing systemic side effects



Localized bio-activation in combination with isoform specificity limits cAMP modulation to the ileum and colon, reducing the risk of GI and CNS adverse events with PALI-2108 vs. non-specific and non-localized PDE4 inhibitors

A Differentiated Approach to IBD – PALI-2108

Key Differentiation

- ✓ **Oral Dosing Once Daily**
Preferred by patients and clinicians and an important goal for large pharma
- ✓ **Novel Target**
First therapy designed to target PDE4 enzymes in treating inflammatory and fibrotic bowel diseases
- ✓ **Gut-Activated Prodrug**
Only PDE4 inhibitor prodrug being activated in the terminal ileum and colon with both high local tissue delivery and slow-release into the systemic bloodstream
- ✓ **Improved Tolerability**
Minimizes common PDE4 inhibitor-related side effects, such as CNS and GI toxicity
- ✓ **Dual-Action Mechanism**
Delivers both anti-inflammatory and anti-fibrotic effects, offering a novel treatment approach
- ✓ **Potential for Combination Therapies**
Safety profile supports future oral or IV/SQ combination therapies



PALI-2108 Phase 1a/b

SAD/MAD, FE and UC Cohort
Study Design and Findings

Summary of PALI-2108 Phase 1a/b in UC

Topline Data Summary

➤ GI-Restricted PDE4 Inhibitor Prodrug Targeting Inflammation and Fibrosis in UC and Crohn's Exceptional Safety & Tolerability


- 89 patients treated with **no SAEs, no lab or EKG abnormalities and no TEAE-related discontinuations**
- Completed all SAD cohorts: Single dose safe up to 450 mg
- Completed all MAD cohorts: BID dosing well tolerated up to 50 mg
- 15 mg BID had zero TEAEs, not even minor, in any subject
- Titration at 30 mg BID improved tolerability, with single minor TEAE, leveraging tachyphylaxis profile of PDE4s

➤ Robust PK/PD Profile Supporting Mucosal Targeting

- Localized GI delivery confirmed: SI release and colonic bioactivation demonstrated in humans and preclinical models
- High mucosal drug levels exceeded IC_{90} in colon, including 36h post-last dose
- Systemic exposure C_{max} delayed and exposure right shifted and long half-life
- **Long half-life and extended-release PK characteristics support QD dosing**

➤ Early Signals of Clinical Activity in UC

- **100% clinical response after 7 days of 30 mg BID (with titration) in UC patients ($\geq 30\%$ or ≥ 3 -pt drop in Modified Mayo + RBS ≤ 1)**
- **40% clinical remission after 7 days of 30 mg BID (with titration)**
- Modified Mayo \downarrow 62.8% (mean -4.0 pts)
- Tissue cAMP \uparrow $\sim 27\%$, Lymphocytes \downarrow $\sim 40\%$
- Histology improved: Nancy (58%), Robarts (56%), Geboes (36%)
- Fecal calprotectin \downarrow in 4/5

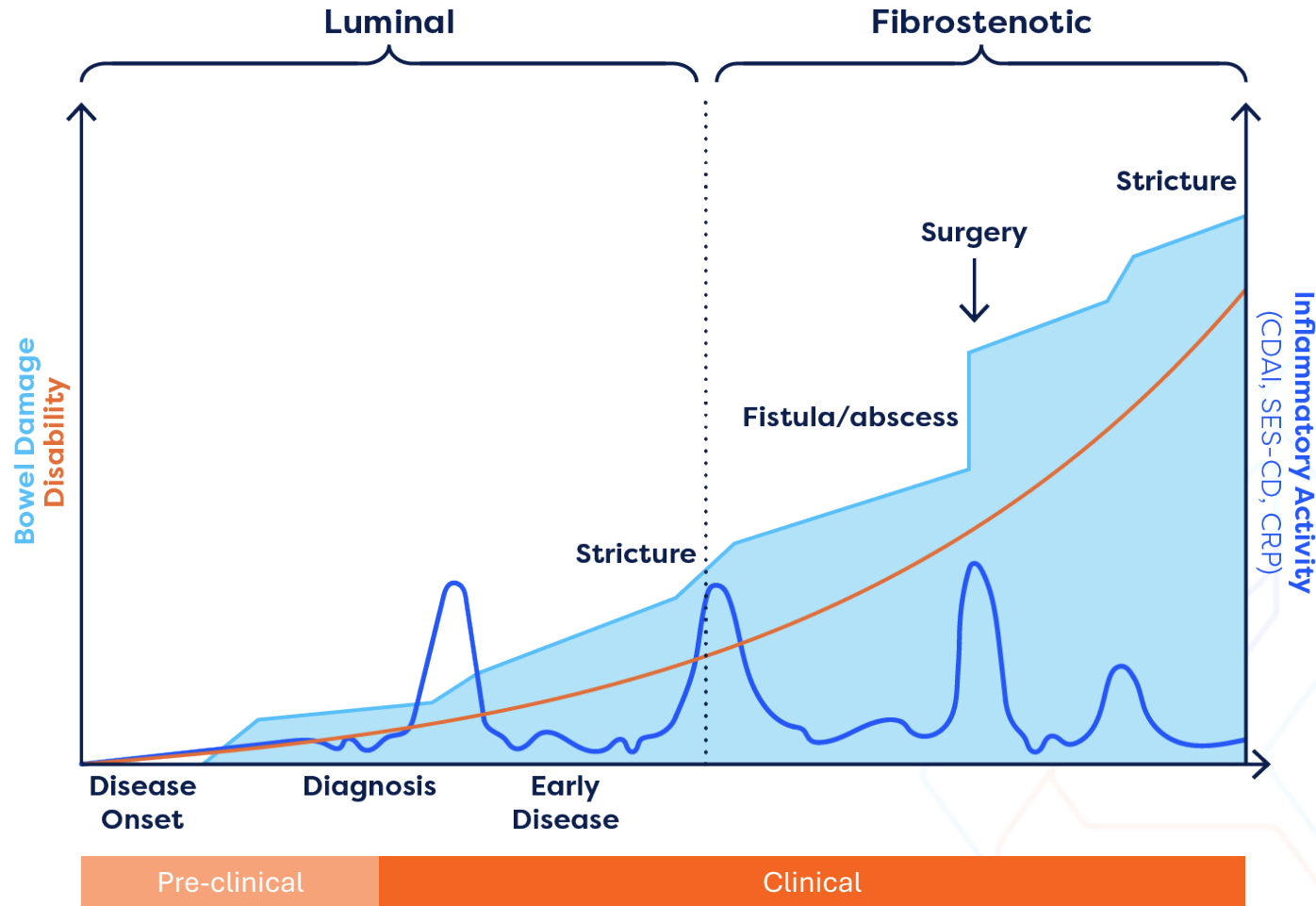


PALI-2108

**Fibrostenotic Crohn's
Disease (FSCD)**

The Progressive Nature of Crohn's Disease & Unmet Needs

Crohn's Disease Progression



Disease Progression to Fibrosis and Bowel Disability

Crohn's disease is a chronic, progressive condition where persistent inflammation drives irreversible tissue remodeling, leading to fibrosis and significant bowel disability.

Luminal: Efficacy Ceiling, Limited Orals

Current anti-inflammatory medications focus on luminal disease but have hit an "efficacy ceiling," with many patients failing to achieve long-term remission. There remains a critical lack of potent, convenient oral options also.

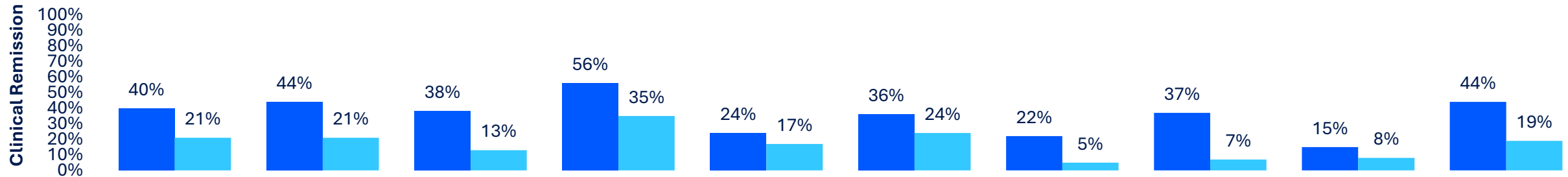
Fibrostenotic: No Approved Therapies





















Fibrostenotic disease (FSCD) represents the most severe manifestation of progression. There is an urgent medical need for dual-action therapeutics that provide both anti-inflammatory and anti-fibrotic benefits.

Approved Crohn's Disease Therapies have limited efficacy with only one oral option – which is not approved for first line use in US

Induction Therapy: Absolute and Placebo-Adjusted Clinical Remission Rates

■ Absolute Remission Rate ■ Placebo Adjusted Remission Rate



Therapy	Sponsor	Target	Inclusion Criteria	*Clinical Remission Data (pbo-adj)	Adverse Events	Black Box Warning	**Dosing and Administration
		IL-12/23	Failed conventional	<ul style="list-style-type: none"> UNITI-2 Trial (Wk8): 40% (21%) 	Infections	No	SC 90mg Q8W
		IL-23	Failed CD biologic	<ul style="list-style-type: none"> ADVANCE Trial (Wk12): 45% (20%) MOTIVATE Trial (Wk12): 42% (22%) 	Elevated liver function tests	No	SC 180/360mg Q8W
		IL-23p19	Failed conventional CD tx or biologic	<ul style="list-style-type: none"> VIVID-1 Trial (Wk12): 38% (13%) 	Infections (incl URTI)	No	SC 300mg Q4W
		IL-23	Failed conventional CD tx or biologic	<ul style="list-style-type: none"> GRAVITI Trial (Wk12): 56% (35%) 	Infections (incl URTI)	No	SC 400mg Q4W
		TNFα	Failed conventional tx (e.g. MTX)	<ul style="list-style-type: none"> ACCENT1 Trial (Wk12): 24% (17%) 	Infections (incl TB)	Yes; serious infections and malignancy	IV 5mg/kg, Q8W
		TNFα	Failed conventional tx (e.g. MTX)	<ul style="list-style-type: none"> CLASSIC I Trial (Wk4): 36% (24%) 	Infections (incl TB)	Yes; serious infections and malignancy	SC 40mg Q2W
		TNFα	Failed conventional tx	<ul style="list-style-type: none"> PRECISE 1 Trial (Wk6): 22% (5%) 	Infections (incl URTI)	Yes; serious infections and malignancy	SC 400mg Q4W
		α4β1 integrin	Failed TNFα or conventional tx	<ul style="list-style-type: none"> ENACT-1 Trial (Wk10): 37% (7%) 	Hepatotoxicity, PML risk	Yes; PML	IV 300mg Q4W
		α4β7 integrin	Failed TNFα or conventional tx	<ul style="list-style-type: none"> GEMINI 2 Trial (Wk6): 15% (8%) 	Headache, Infections	No	IV 300mg Q8W
		JAK	Failed Biologic	<ul style="list-style-type: none"> U EXCEL Trial (Wk12): 50% (20%) U EXCEED Trial (Wk12): 39% (18%) 	VTE/MACE Risk	Yes; Morality/MACE, serious infections, malignancy, thrombosis	Oral 15/30 mg QD

*For products where two trials are listed for clinical remission data, chart displays the average across two trials. **Reflects maintenance dosing and administration. MACE: major cardiovascular events, MTX: methotrexate, PML: progressive multifocal leukoencephalopathy, RR: remission rate, URTI: upper respiratory tract infection, VTE: venous thromboembolism.

Sources: FDA labels, Biomedtracker and trial results as published in *The New England Journal of Medicine*, *The Lancet*, *Gastroenterology*, *Clinical Medicine Therapeutics* and *Clinical and Experimental Gastroenterology*.

FSCD Phase 1b Study Design

Once-daily dosing

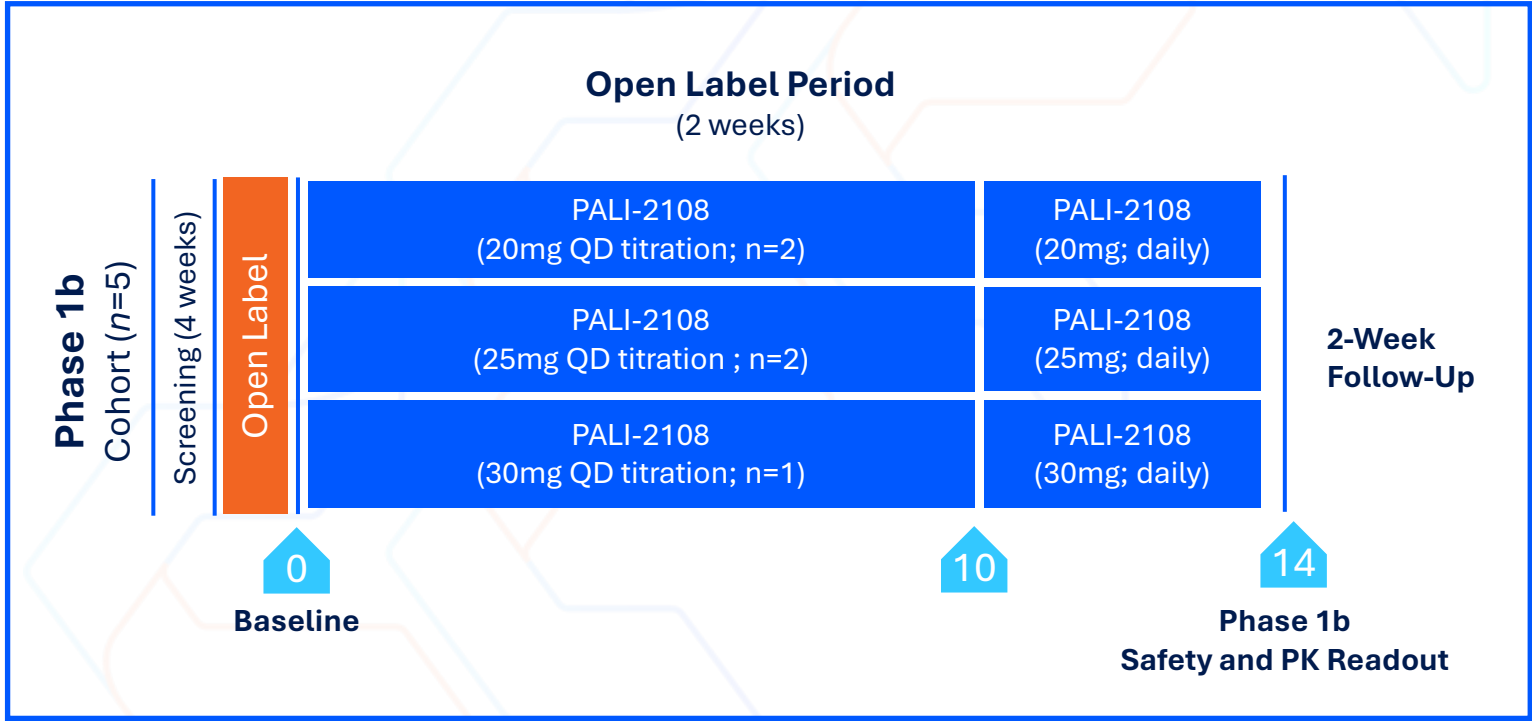
Ph1b Safety and PK Readout ($n=5$):

Key Objectives:

- Safety and tolerability
- Pharmacokinetics
- Pharmacodynamics
- Luminal Efficacy (SES-CD)

Key Endpoints:

- Safety and tolerability: AEs, Labs, and EKGs
- PK plasma and tissue (ileum, ascending, descending colon)
- PD plasma and ileal biopsy (RNAseq)
- Histology of ileal tissue
- Ileocolonoscopy (Change from baseline SES-CD, Endoscopic Remission and Response)
- Biomarkers (fecal calprotectin)



FSCD Patient Demographics and Clinical Profile

Parameter	All Subjects
Age (mean, SD)	39.6 (14.40)
Male (n, %)	5 (100%)
White (n, %)	5 (100%)
BMI (mean, SD)	26.6 (4.3)
Disease Duration (mean, SD)	15.4 (11.1)
Ileocolonic Disease (n, %)	5 (100%)
Intestinal Resection (n, %)	2 (40%)
FCAL (mean, SD)	267.8 (275.8)
SES-CD (mean, SD)	8 (1.2)
Prior Biologic Use (n, %)	4 (80%)
Concomitant Biologics (n, %)	4 (80%)
Concomitant Immunomodulators (n, %)	0 (0%)

Concomitant Biologic (n, %)	All Subjects
Adalimumab	2 (40%)
Infliximab	1 (20%)
Ustekinumab	1 (20%)

FSCD Patient Summary:

- ✓ Disease duration mean (years): 15.4
- ✓ SES-CD at baseline mean (score): 8.0
- ✓ Concomitant biologics (% patients): 80%
- ✓ Fecal Calpro baseline mean (ug/g): 267.8

Safety Profile of PALI-2108 in FSCD

Generally safe and well-tolerated

No serious adverse events

Consistent profile with Phase 1b UC study

No study or treatment discontinuations

All AE's mild in severity

One GI AE (abdominal discomfort) -
Possibly drug related

No nausea

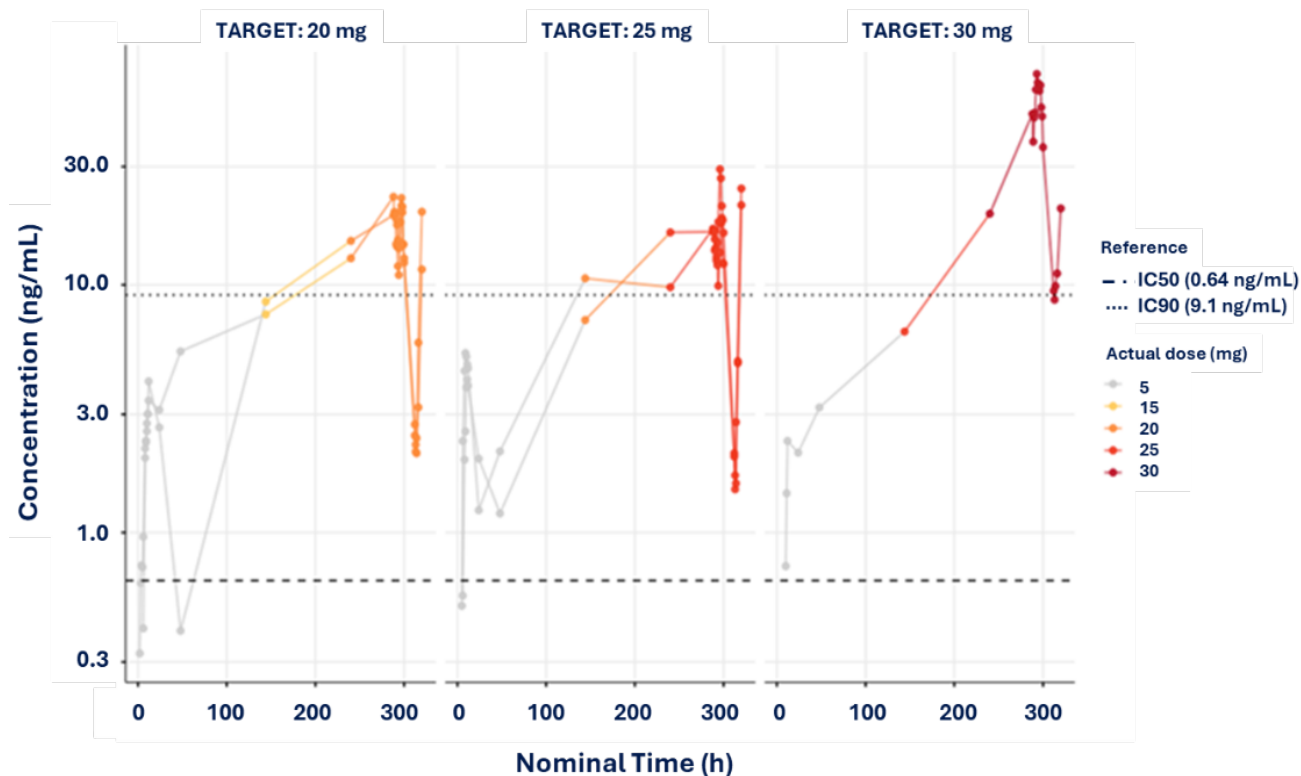
No vomiting

No diarrhea

Total number of subjects (n)	5
Subjects with TEAE, at least possibly related	2/5 (40%)
Subjects with > Grade 1 TEAE (n/%pts)	0
Subjects with Severe Adverse Events (n/%pts)	0
Subjects withdrawn because of TEAE (n/%pts)	0
TEAEs per SOC: GI system (>5%)	
- Nausea (n/%pts)	0
- Vomiting (n/%pts)	0
- Abdominal Discomfort / Cramps (n/%pts)	1/5 (20%)
- Diarrhea (n/%pts)	0
TEAEs per SOC: Nervous System (>5%)	
Headache (n/%pts)	0
TEAEs per SOC: Other (>5%)	
Fatigue (n/%pts)	1/5 (20%)

Phase 1 FSCD Demonstrates PK for Once Daily Dosing

- ✓ Once daily dosing confirmed as ideal dosing frequency
- ✓ Titration schedule successful in maintaining gradual plasma drug concentration increase over time at all doses
- ✓ Plasma pre-dose trough concentrations >IC90 at all doses (20mg, 25mg, and 30mg) and in all patients
- ✓ Ileum tissue active drug concentrations >>IC90 at Steady State
- ✓ Ileum tissue to plasma ratio was increased ~3x at steady state confirming preclinical findings

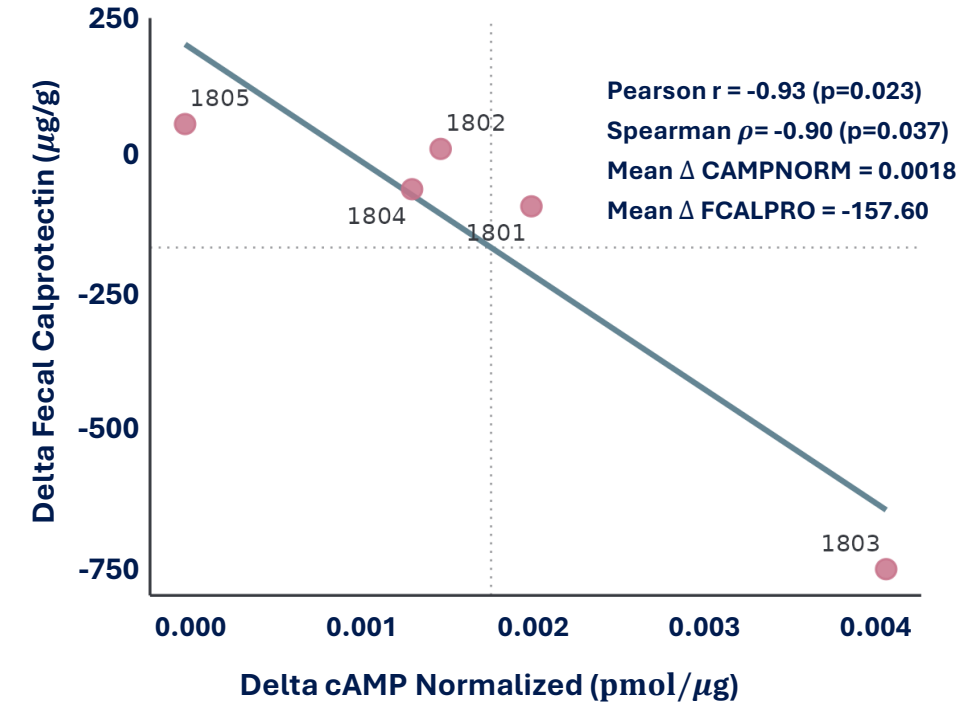
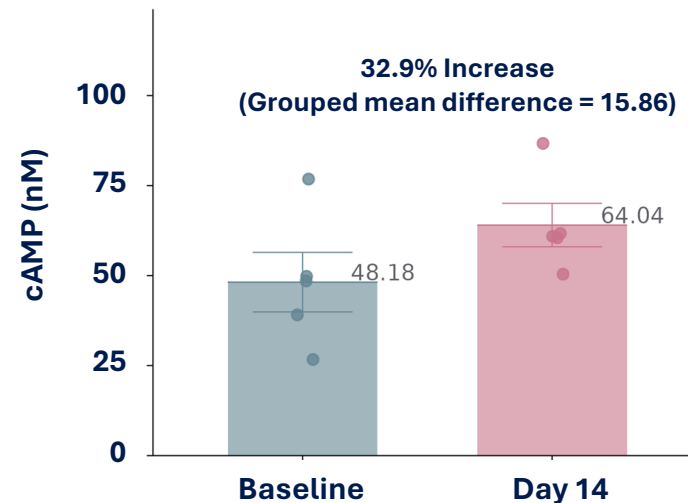
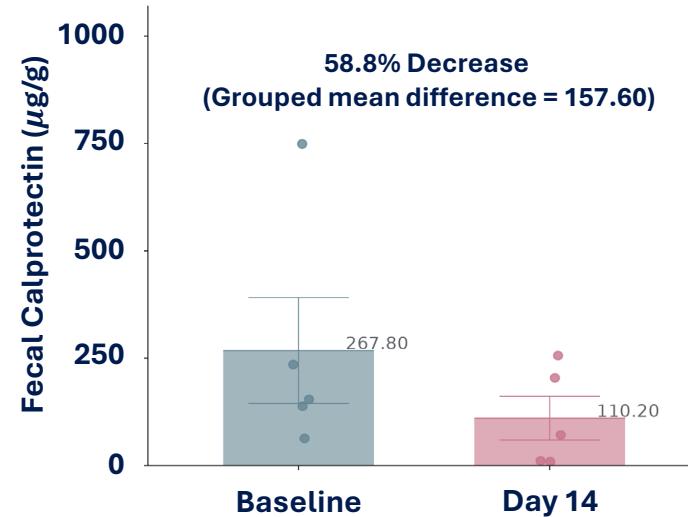


Tissue Concentration	Ascending colon (ng/mL)	Descending colon (ng/mL)	Ileum (ng/mL)	All segments (ng/mL)	Plasma Cmax (ng/mL)	Tissue/plasma ratio All segments
Mean	185.4	114.4	107.6	149.0	32.8	6.2

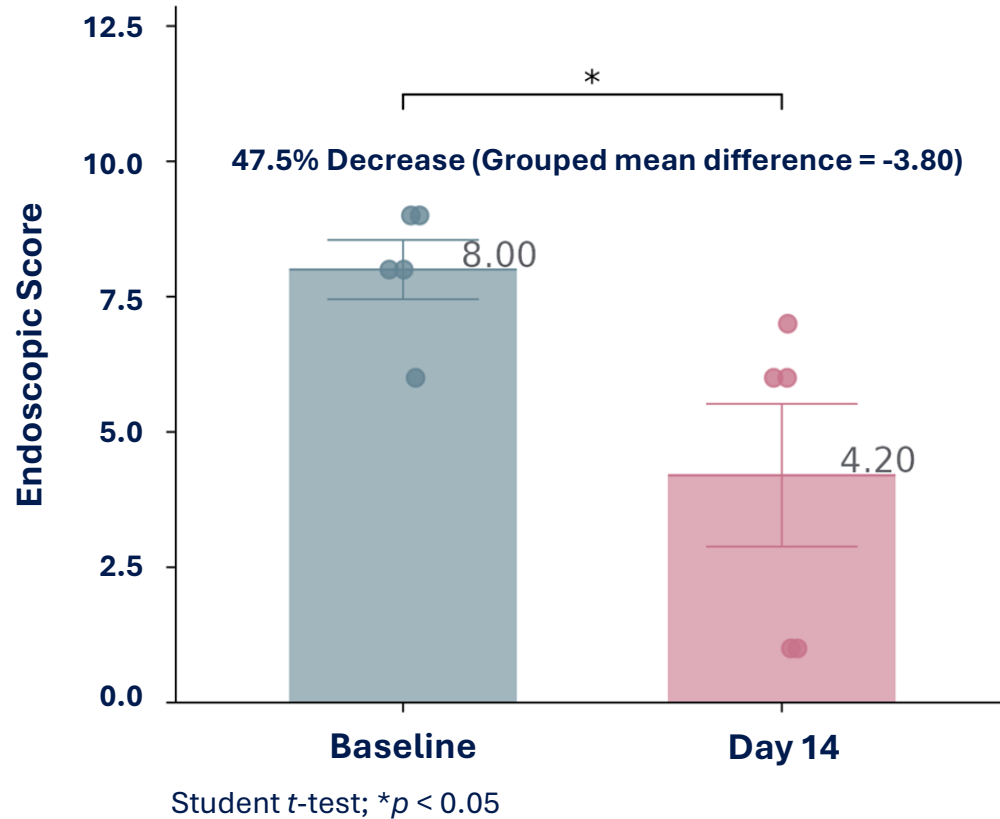
Using the peak plasma (Cmax) and tissue (4-8h post dose), there was a 6.2x average tissue/plasma ratio across all segments

Mechanistic and Inflammatory PD were Improved: cAMP and Fecal Calprotectin

- ✓ **Tissue cAMP was increased** in 4/5 patients (~41% individual mean increase) as expected due to inhibition of PDE4 enzyme
- ✓ **Tissue cAMP % change was greater** in ileum in FSCD (~41%) than in colon in Phase 1B UC patients (~27%)
- ✓ **Fecal calprotectin was decreased** by a mean ~59% of the course of the study and rebounded after drug withdrawal
- ✓ **Fecal calpro and cAMP were highly correlated** with $r^2=0.93$ and significant ($p<0.05$) suggesting a tight correlation between PD and inflammatory biomarkers



Endoscopic Response and Remission Were Demonstrated by Improvements in SES-CD



Patient	Screening (Baseline)	Day 14	Absolute Δ	% Change from Baseline
1801	9	1	-8	-88.8%
1802	6	6	0	0.0%
1803	8	6	-2	-25.0%
1804	8	1	-7	-87.5%
1805	9	7	-2	-22.2%

Mean Baseline = 8.0
Mean Day 14 = 4.2

Mean Absolute Change = -3.8
Mean % Change from Baseline = -47.5%

SES-CD was reduced in 4 of 5 patients over 2 weeks with mean absolute reduction of 47.5% from baseline

Endoscopic Response was achieved in 2/5 (40%) of patients ($\geq 50\%$ reduction of baseline SES-CD score)

Endoscopic Remission was achieved 2/5 (40%) of patients (SES-CD score of ≤ 2)

Compelling FSCD Phase 1b Signal Support Broader CD Development

Well-tolerated across all doses: 20–30 mg QD

Robust PK: plasma + ileal exposure >IC90 in all patients

Strong target engagement: ↑ Ileal cAMP (~41%), > UC colon signal

Clear MOA: cAMP correlates with ↓ inflammation (fecal calprotectin)

Clinical activity: Significant SES-CD reduction; 40% response / 40% remission

Supports expansion into broader luminal CD: no anatomical constraints

Established regulatory guidance in luminal CD: Acknowledged critical endpoints in SES-CD and corresponding symptomatic benefit

Phase 2 CD study: Assess efficacy in moderate to severe population including anti-fibrotic effects earlier in disease course

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