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Gut-Targeted PDE4 Inhibition with Once-Daily PALI-2108 Demonstrates Early Clinical and Biomarker Improvements in Fibrostenotic Crohn's Disease: Results From a Phase 1b Study

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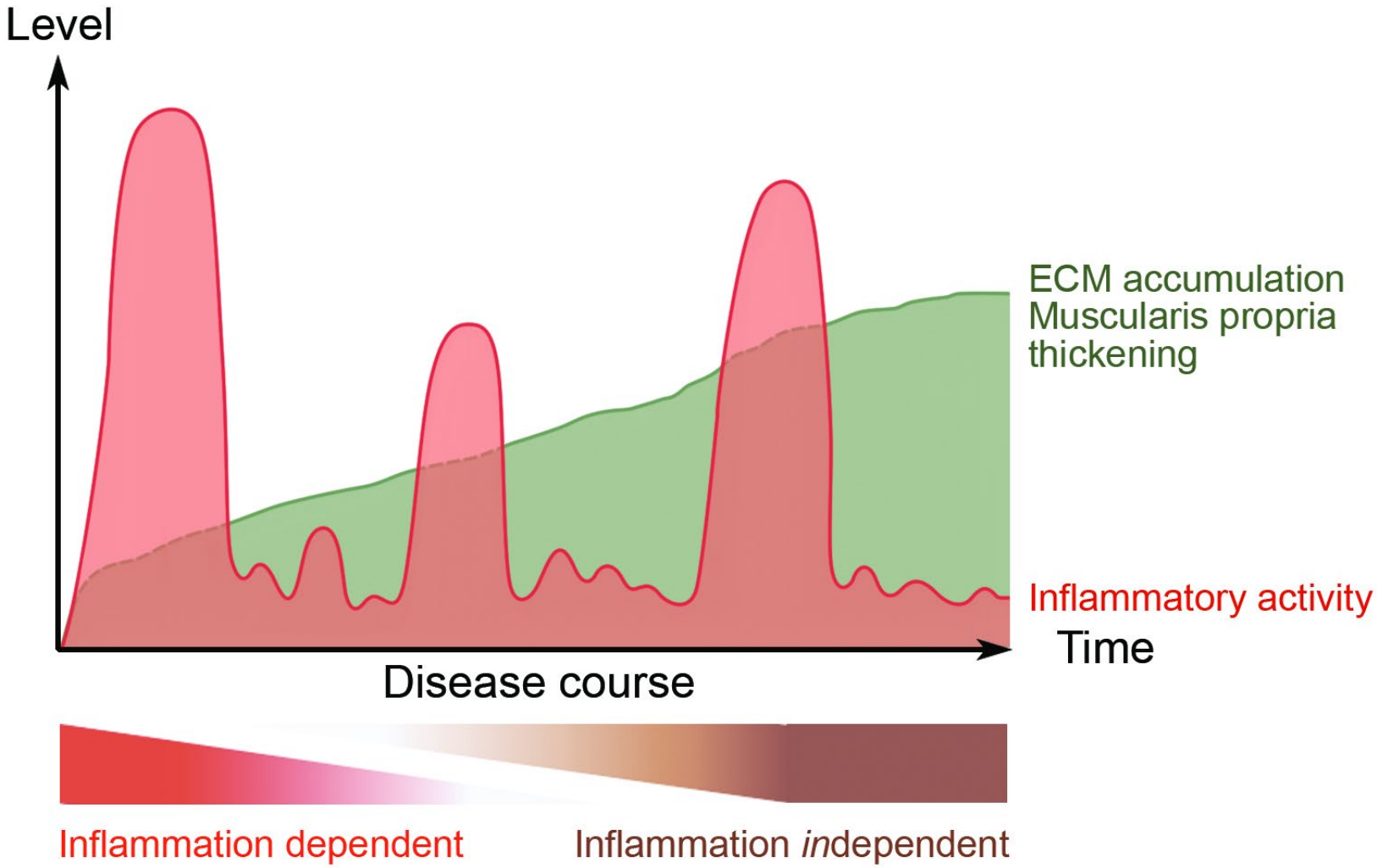
Disclosure of Conflicts of Interest

I herewith declare the following paid or unpaid consultancies, business interests, or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

Florian Rieder: AbbVie, Abivax, Adiso, Adnovate, Agomab, Allakos, Allergan, Anaptys, Arena, AstraZeneca, Bausch & Lomb, Boehringer-Ingelheim, Cabaletta, Cage (Advisory Committee/Board Member, Consultant), Cellarity, Celgene/BMS, Celltrion, CDISC, Celsius, Chemomab, Cowen, 89Bio, Enveda, Equillium, Eugit, Falk, Ferring, Frequency Therapeutics, Galapagos (Advisory Committee/Board Member, Consultant), Galmed, Genentech, Gilead, Gossamer, Granite, GSK, Guidepoint, Helios, Helmsley, Horizon Therapeutics, Image Analysis Limited, Imidomics, Index Pharma (Advisory Committee/Board Member, Consultant), Jannsen, Koutif, Landos, Lassen, Lilly, Medbiopharma, Merck, Mestag, Metacrine, Mirador, Mirum, Mobius, Mopac, Morphic, Myka Labs, Nxera, Ono (Advisory Committee/Board Member, Consultant), Organovo, Origo, Palisade, Pfizer, Pharvaris, Pliant, Prometheus Biosciences, Receptos, RedX, Roche, Samsung, Sanofi, Sironax, SRT, Surmodics (Advisory Committee/Board Member, Consultant), Surrozen, Takeda, Techlab, Tentarix, Teva, Thabor, Theravance, Thetis, Tillerts Tr1x Bio,UCB, Ventus, Versant, Viatris, Virgo, Xencor, Ysios (Advisory Committee/Board Member, Consultant)

Crohn's Disease is a Progressive Disorder



Rieder Gut 2024; Rieder Nat Rev Drug Discov 2025

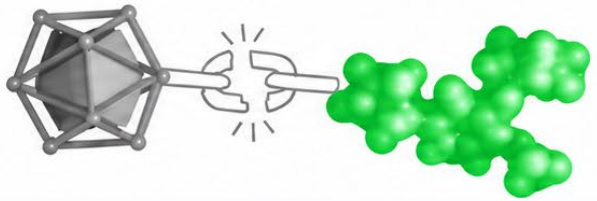
PALI-2108 Enables Localized PDE4 Inhibition and Demonstrates Early Clinical Activity in UC

Once-Daily PALI-2108

- 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: Localized Bio-Activation

- Galactose-linked prodrug designed to limit systemic exposure
- Activated in the colon by bacterial β-glucuronidase
- Restricted from activation by human enzymes outside the GI tract
- 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, potentially reducing systemic tolerability risk



Early Clinical Activity in UC

mMayo
–62.8%
mean reduction (from baseline)

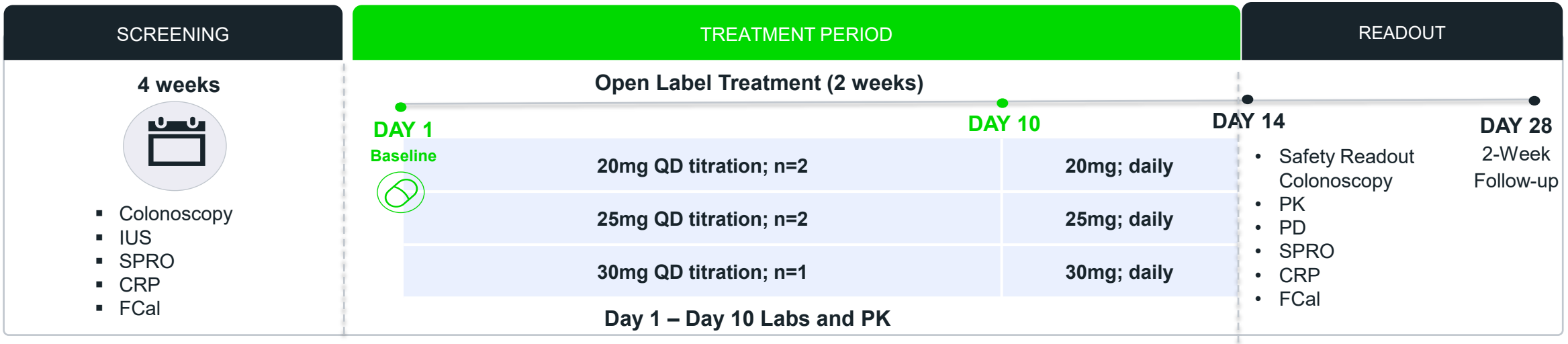
Clinical response
5/5 (100%)

Clinical remission
2/5 (40%)

Well tolerated
No SAEs
No discontinuations

Targeted, once-daily PDE4 inhibition with early evidence of clinical activity in UC, supporting further evaluation in FSCD

Methods: FSCD Phase 1b Open-Label Study Design



KEY INCLUSION / EXCLUSION CRITERIA

- **Clinically symptomatic fibrostenosing Crohn's disease, defined by ≥1 obstructive symptom attributable to the index ileal stricture within the prior 12 weeks**
- **Symptoms must be accompanied by an ileal stricture within reach of the endoscope (defined as SES-CD ileal narrowing sub score of ≥ 1)**
- **Screening IUS confirming the presence of at least 1 stricture in the terminal ileum (defined as wall thickness ≥ 3mm, luminal narrowing of ≤ 50% of normal bowel lumen, prestricture dilation of ≥ 2.5cm)**
- **Stable background therapy for CD and agree to maintain background therapy for the study duration)**

ENDPOINTS

- **Primary Endpoint**
  - Safety & tolerability
- **Secondary Endpoints**
  - PK: plasma and tissue (ileum, ascending, descending colon)
  - PD: Fecal calprotectin, cAMP, tissue lymphocytes
  - Histology of ileal tissue
  - Endoscopic Remission and Response (SES-CD)

IUS: Intestinal Ultrasound SPRO: Stricture Patient Reported Outcome CRP: C-Reactive Protein FCAL: 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%)
S-PRO severity (mean)	0.6
Stricture Location, Ileum (n, %)	5 (100%)
CRP (mean, SD)	3.4 (2.6)
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%)
Risankizumab	0 (0%)
Ustekinumab	1 (20%)
Vedolizumab	0 (0%)

FSCD Patient Summary:

- ✓ **Mean duration of disease 15.4 years**
- ✓ **Mean baseline SES-CD score: 8.0**
- ✓ **80% of patients on concomitant biologics** (adalimumab, infliximab, ustekinumab),
- ✓ **Mean baseline Fecal Calprotectin 267.8 ug/g**

PALI-2108 Was Well Tolerated in FSCD Patients, Consistent with UC Phase 1b Data

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

Generally safe and well-tolerated

No serious adverse events

- No biochemical, hematologic or ECG related AE's
- Consistent profile with Phase 1b UC study

No study or treatment discontinuations

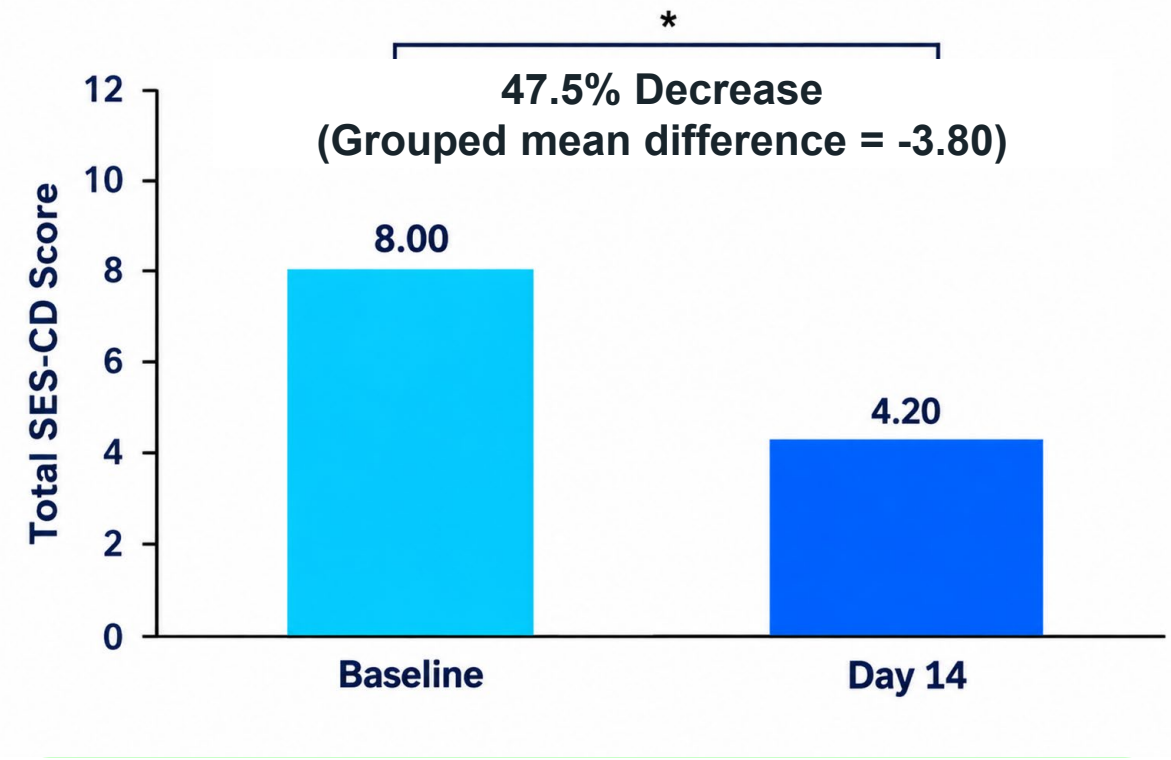
All AEs mild in severity

One GI AE (abdominal discomfort) – Possibly drug-related

- No nausea
- No headache
- No diarrhea

PALI-2108 Resulted in Significant Endoscopic Improvement in FSCD Patients

Simple Endoscopic Scoring (SES-CD)



1/1 Impassible stricture at baseline was passible at day 14

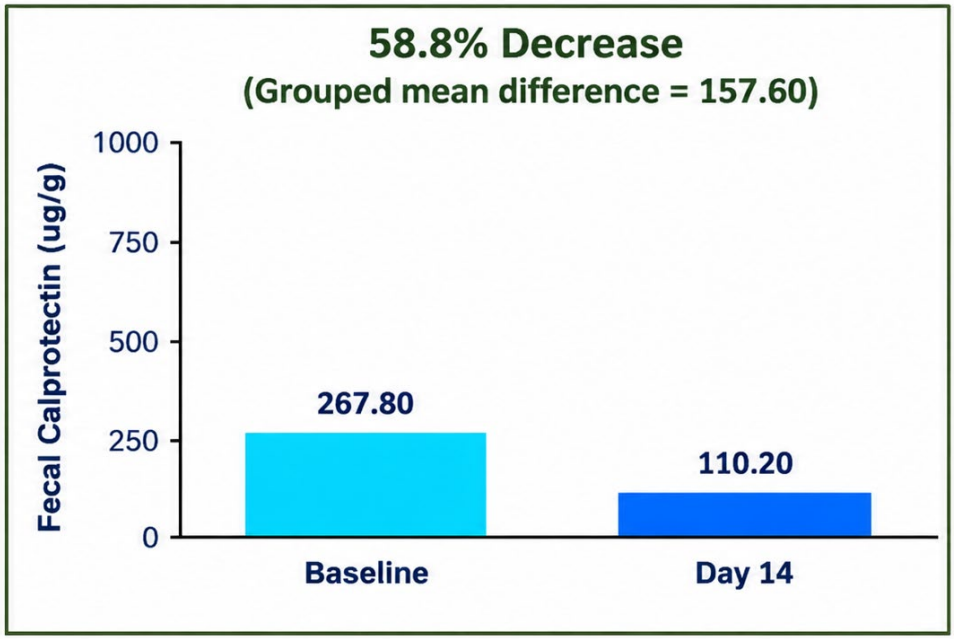
40% Endoscopic response achieved

40% Endoscopic remission achieved

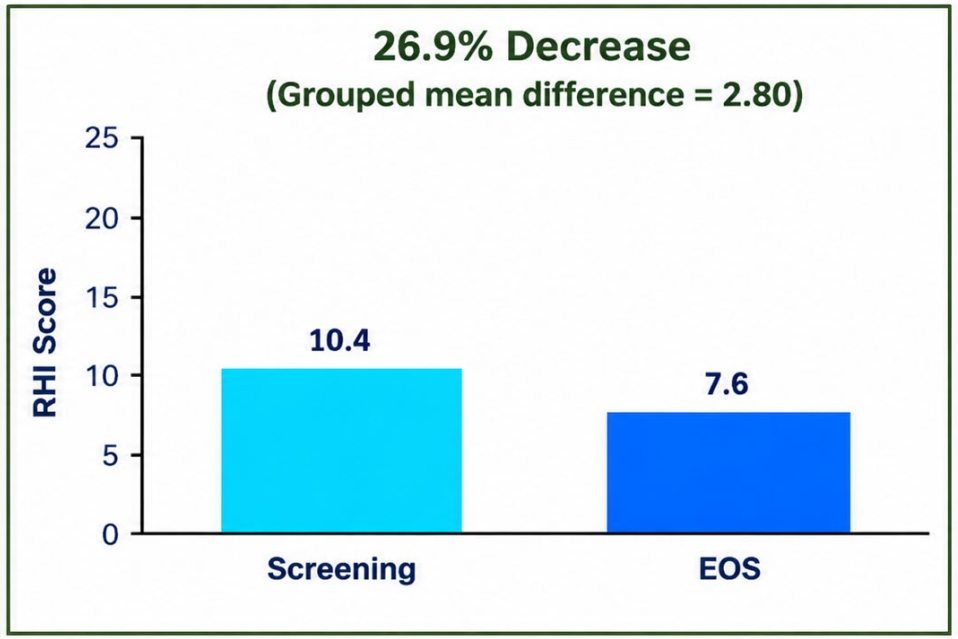
Endoscopic Response: 50 percent reduction from baseline SES-CD
Endoscopic Remission: SES-CD of 0 to 2

PALI-2108 Demonstrates Anti-Inflammatory Activity in FSCD Patients

Fecal Calprotectin

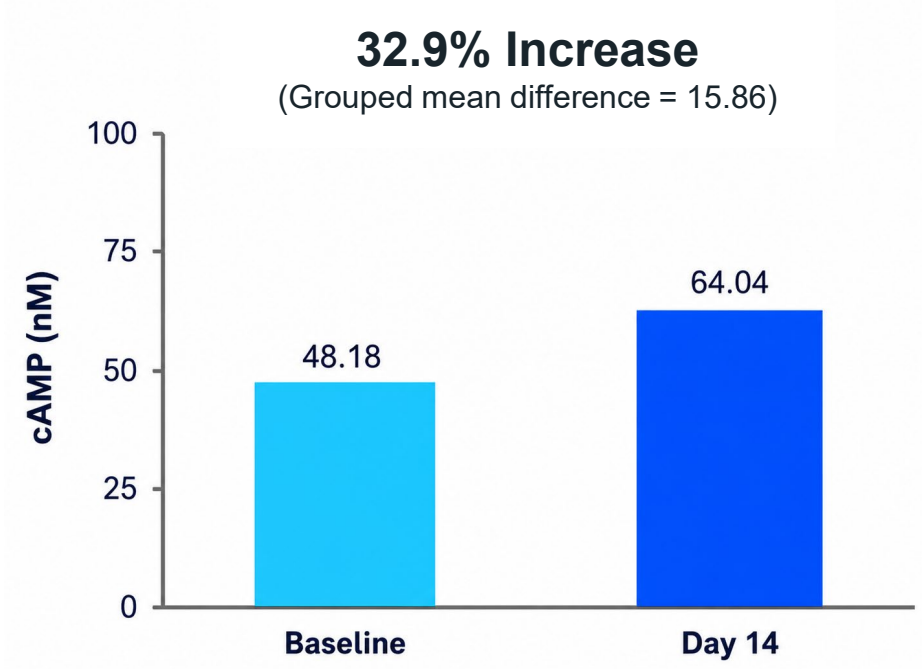


Robarts Histopathologic Index

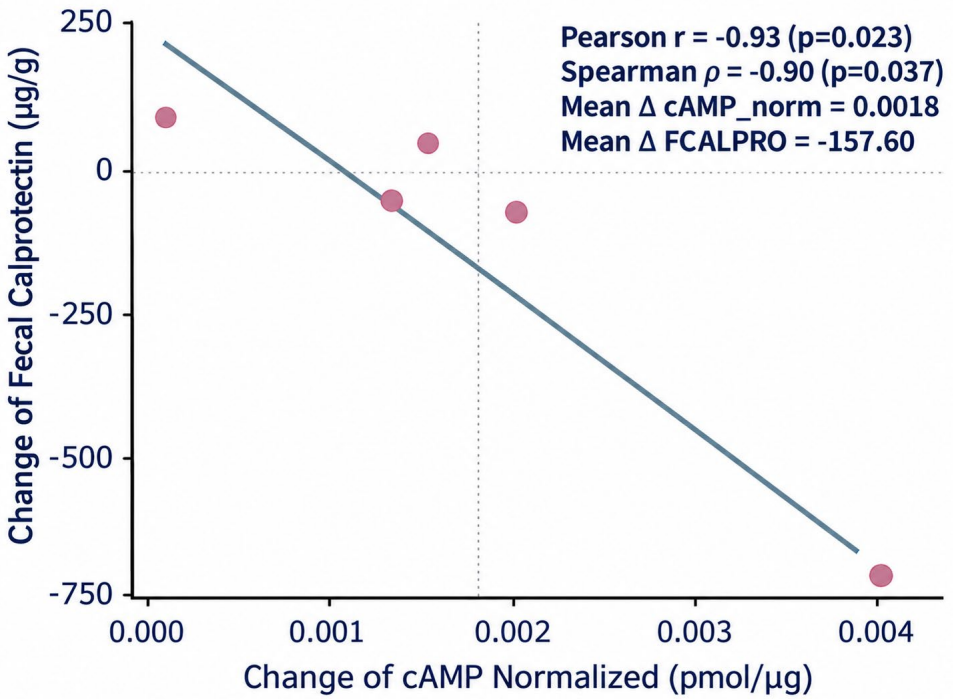


Target Engagement Correlates with Anti-Inflammatory Activity in FSCD Patients

cAMP

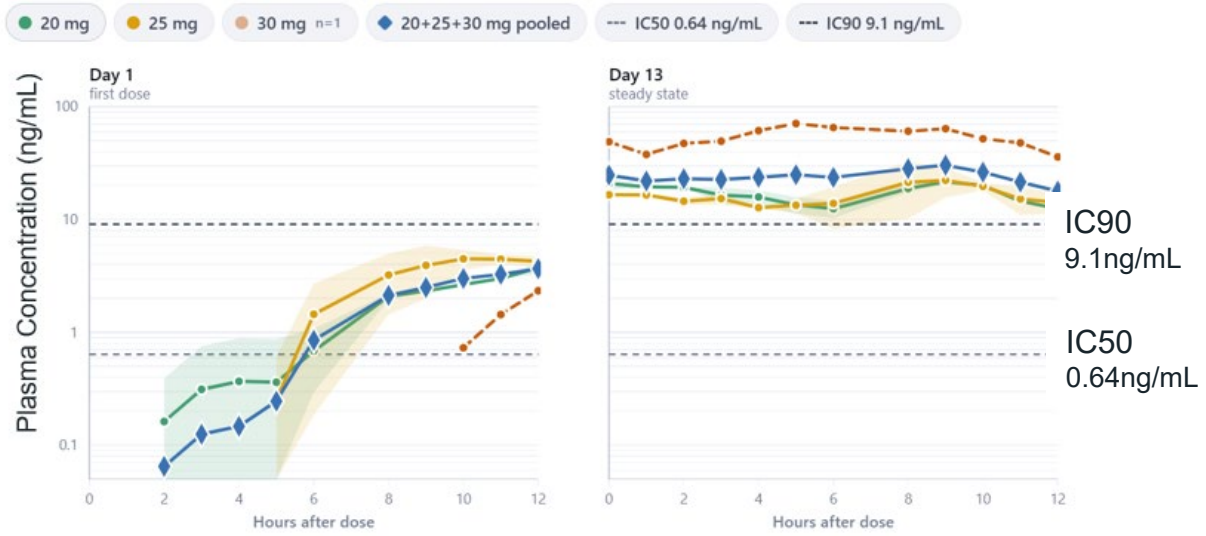


Correlation between cAMP and Fecal Calprotectin



PALI-2108 Achieves Efficient Plasma and Tissue PK, and All Patients Reached >IC90 in Plasma and Tissue, Including Ileum

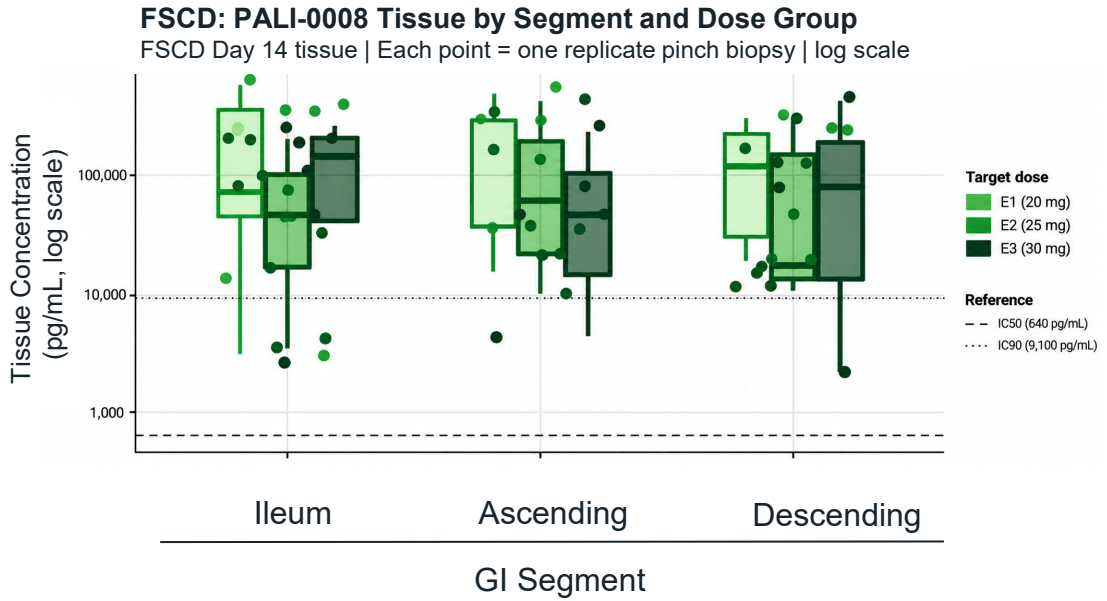
Plasma Concentration > IC90 at Steady State



Hours after dose

Data are mean ± SD; diamonds indicate pooled 20–30 mg means. Hollow markers indicate reduced n; 30 mg represents one participant. Zero values are not shown on the log scale.

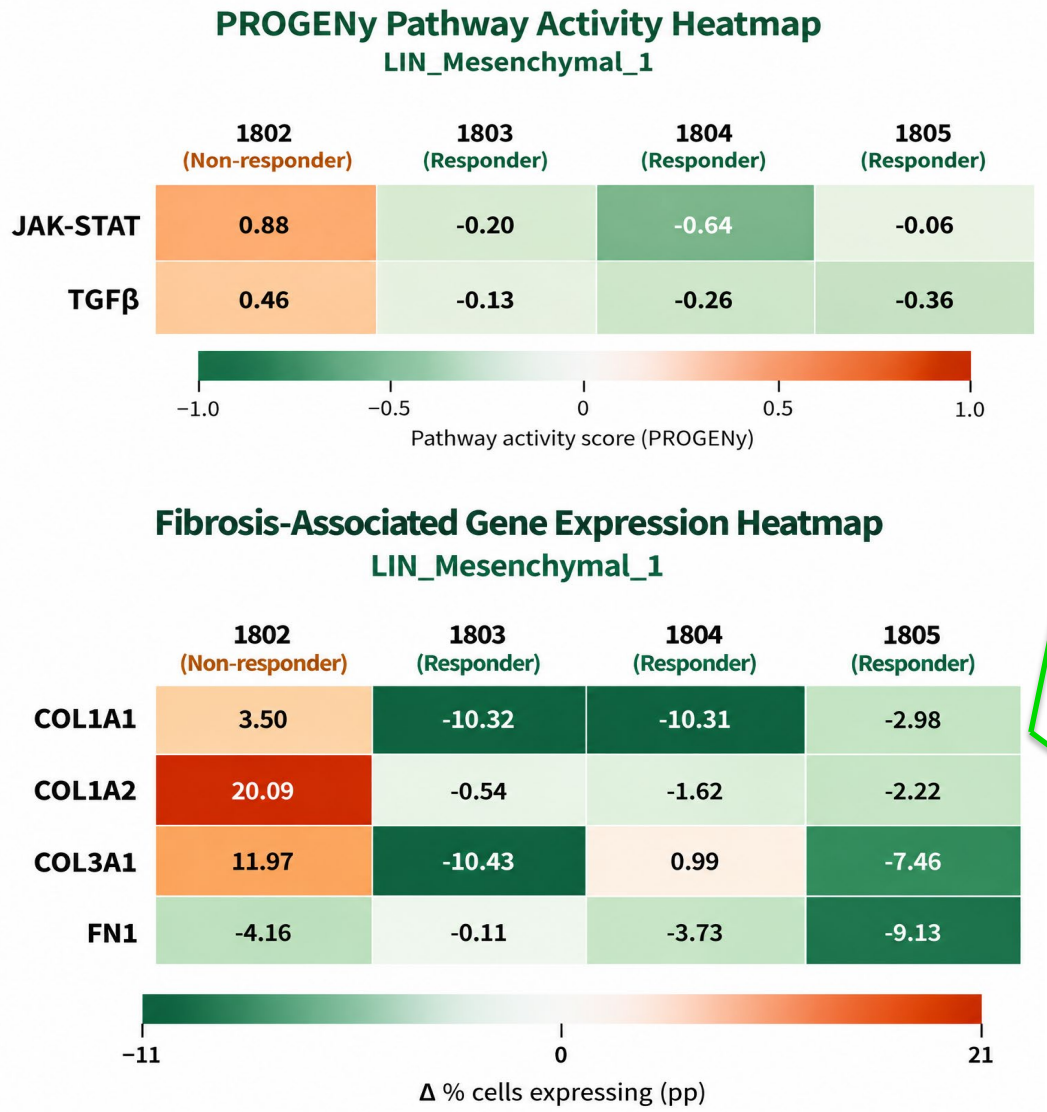
Tissue Concentration > IC90 in GI Segments



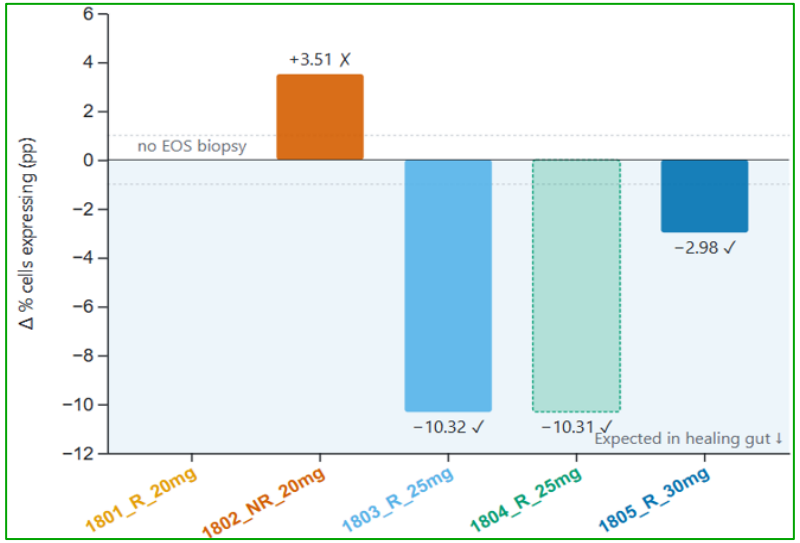
FSCD PALI-0008 tissue: individual concentrations by GI segment and target dose group (E1=20mg; E2=25mg; E3=30mg target dose). Replicate pinches (H1-H5) are shown as individual points.

PALI-2108 Steady State Tissue PK of PDE4 Active ~7x Higher in Tissues vs Plasma

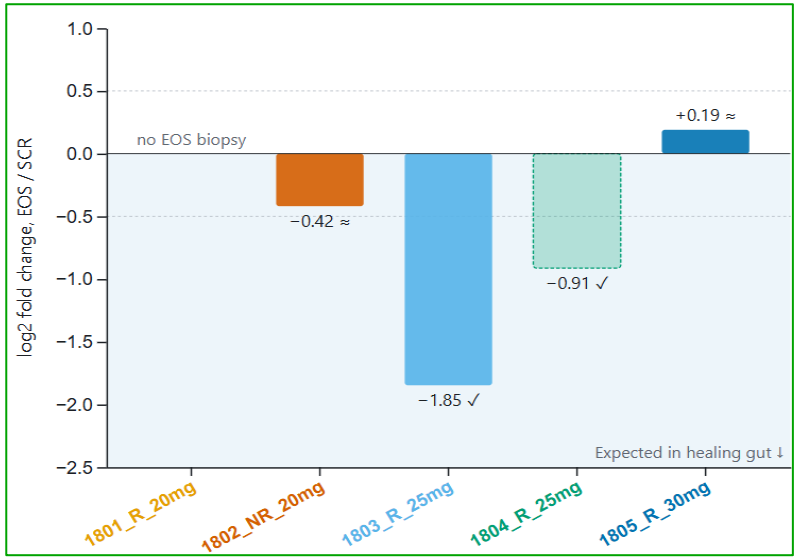
PDE4 Inhibition Reduces TGFβ Expression and Fibrosis-Associated Gene Expression in FSCD Lesions



COL1A1 % cells Expression (SCR → EOS)



COL1A1 Abundance (CPM), (SCR → EOS)



Conclusion

- Stricturing disease is an unmet need in the treatment of CD patients
- PDE4 inhibition has been shown to have anti-inflammatory and anti-fibrotic effects
- PALI-2108 is safe and well tolerated
- Favorable PK profile allowing once-daily dosing
- Exploratory efficacy analyses show reduction in SES-CD after 14 days of treatment, an increase in cAMP, and snRNA sequencing suggesting an anti-fibrotic effect on mesenchymal cells

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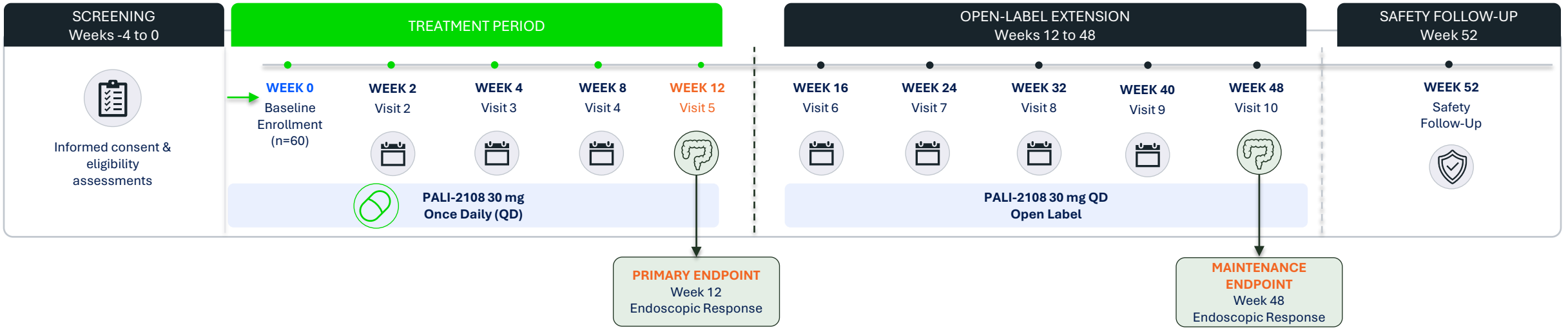
This study was sponsored by Palisade Bio

ASCENTRA-CD Potential Trial Design

Phase 2a Open-Label Study



KEY INCLUSION CRITERIA

- ✓ CDAI 220-450 and either mean daily SF ≥ 3 OR mean daily AP score > 1
- ✓ SES-CD of ≥ 6 (or ≥4 for isolated ileal disease
- ✓ ADT-naïve or ADT-experienced

SECONDARY CD ENDPOINTS AT WEEKS 12 and 48

- Clinical Remission
- Clinical Response
- Endoscopic Remission
- Histological Response

EXPLORATORY CD ENDPOINTS

- Fibrosis Biomarkers (tissue and plasma)
- RNAseq

COMPARATOR

Historic Control Arm

- Endoscopic Response
- Clinical Remission

PALI-2108 Phase 2 study to demonstrate clinical benefit and support local efficacy in **Crohn's disease** patients

ADT = advanced therapy | AP = abdominal pain | CD = Crohn's disease | CDAI = Crohn's Disease Activity Index | QD = once daily | SF = stool frequency | SES-CD = Simple Endoscopic Score for CD