

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

Corporate Presentation
February 2025

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.

This presentation discusses product candidates that are at an early stage of clinical and pre-clinical development , and which have not been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of these product candidates. Caution should be exercised when interpreting results from the Company’s pre-clinical and anticipated clinical trials. This presentation includes statistical and other industry and market data obtained from industry publications, third-party research, surveys and studies. The information has been obtained from sources believed to be reliable, although there is no guarantee regarding the accuracy or completeness of such information.

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Corporate Highlights

Our Mission:

Develop differentiated product candidates targeting immune, inflammatory and fibrotic diseases in established commercial markets where there is significant unmet medical need.

- Lead program targeting multi-billion-dollar IBD market
- Commercially proven PDE4 target with potential for superior safety and efficacy over systemic PDE4 inhibitors
- All five cohorts dosed in SAD of Phase 1 study of NHV subjects and UC patients (Nov 2024); MAD portion initiated
- Leveraging innovative machine learning technology for Precision Medicine approach to responder selection
- Multiple pipeline expansion opportunities across immune, inflammatory and fibrotic diseases

Development Pipeline

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

PROGRAM	INDICATION	STATUS	HIGHLIGHTS
PALI-2108	Ulcerative Colitis “UC”	Phase 1	All five cohorts dosed in SAD of Phase 1 trial (Nov 2024); MAD portion initiated Topline data expected H1-2025
PALI-1908	Fibro Stenotic Crohn’s Disease	Discovery	Significant overlap with PALI-2108 CTA filing in 2024 POC for fibrosis pathway engagement completed

Upcoming Milestones¹

Q1 2025	Q2 2025	Q3 2025	Q4 2025	Q1 2026
• Phase 1 MAD Complete • Phase 2 GMP Drug Substance Complete	• Phase 1 UC Complete • Phase 1 Top Line Data Readout • Pre IND-Meeting	• Phase 2 GMP Drug Product Complete • Phase 1 Final CSR	• 3-month Safety and Tox Complete • IND Submission • IND Clearance	• Phase 1b/2a Site Initiation • Phase 1b/2a First Subject Dosed

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



PALI-2108

Initially Targeting Ulcerative Colitis (UC)

Lead differentiated program with potential to address important unmet medical needs in large, established IBD market

PALI-2108

A Differentiated Approach to Ulcerative Colitis

An oral prodrug designed to treat UC by targeting the key enzyme PDE4 locally in colon tissues

Key Differentiation

- ✓ Oral Dosing
- ✓ Gut-restricted prodrug is bioactivated locally in the colon resulting in a longer apparent half-life and greater exposure
- ✓ Greater colonic tissue and lesser systemic exposure due to local bioactivation with the potential for greater efficacy and an improved safety profile
- ✓ Demonstrated proof-of-concept efficacy
- ✓ Preclinical and *ex vivo* data suggest potential for superior efficacy and derisks program

Apremilast: A Well Known PDE4 Inhibitor with Demonstrated Efficacy in UC but Systemic Toxicities



Active:	Systemic	Local and Extended-Release
Adverse Event:	Central Nervous System: Nausea Headache Vomiting	Increased local colon tissue to blood drug ratio enables lower systemic exposures and potential concerns for CNS tolerability
Results:	Suspension of treatment due to toxicities	Improved therapeutic window with greater exposures and extended-release characteristics enables maximal PDE4 inhibition supporting higher cAMP tissue levels
TNF-Alpha at IC50 (key inflammatory marker):	0.41 μ M	0.022 μ M (~20x more potent)

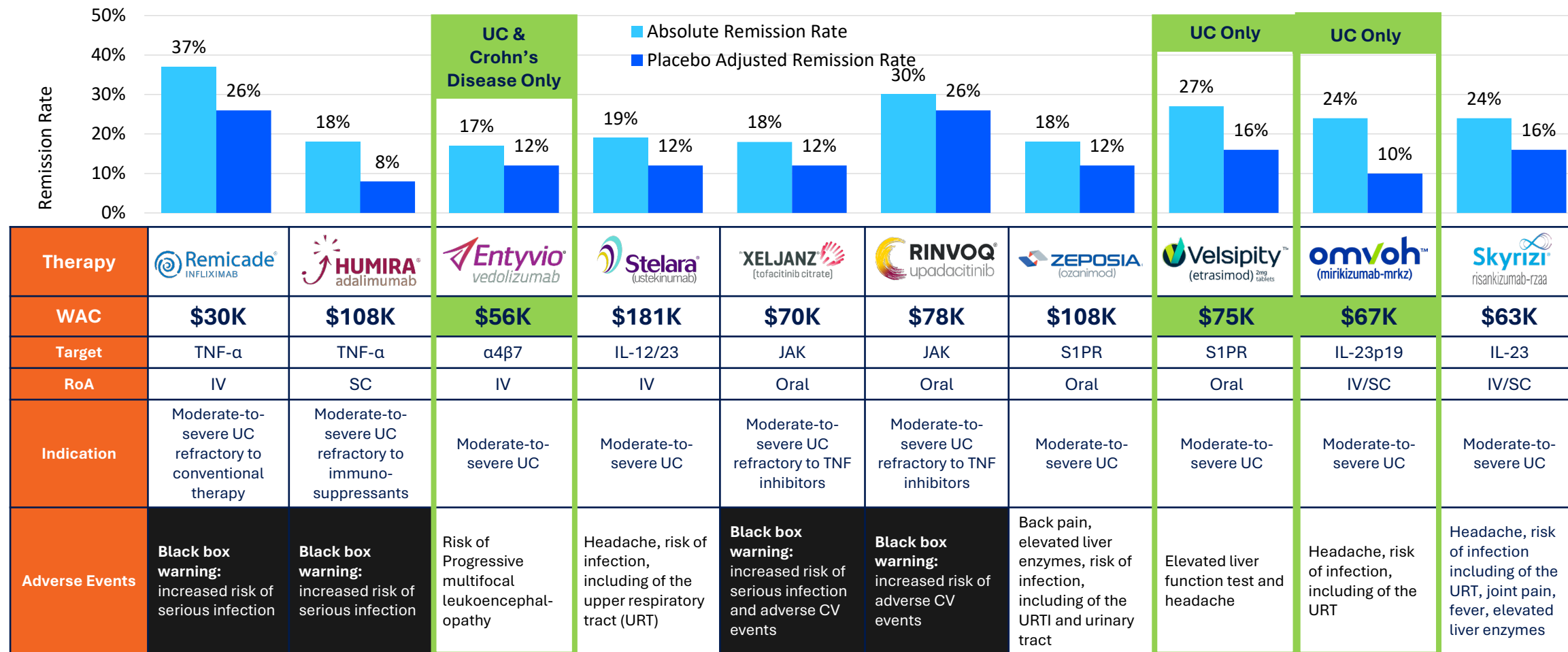
Apremilast demonstrated efficacy in a Phase 2 UC study, but selection of dose was limited by expected toxicities which prevented adequate dose ranging; the program was discontinued in IBD

Current Therapies for UC

Limited Efficacy with Significant Safety Concerns

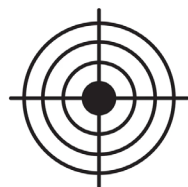
Though the number of available therapeutics for moderate-to-severe patients is growing, the placebo-adjusted remission rate remains low, ~10-20%, and many therapies have poor safety profiles

Absolute and Placebo-Adjusted Remission Rates at Completion of Induction (8 to 12 Weeks)



Tx's = treatments, SC = subcutaneous, IV = intravenous, Bio = biologic, TNF = tumor necrosis factor, JAK = janus kinase, S1PR = sphingosine-1-phosphate; SAE: serious adverse event; CV: cardiovascular, *based on clinical remission at one year, **at 31 weeks, ^45% 180mg and 41% 360mg; Sources: Back Bay analysis and prior work, Morgan Stanley 5May2023, Stifel 16Mar2023, Inflamm Bowel Dis. 2023 Oct 3;29(10):1633-1647, Inflamm Bowel Dis. 2018 Oct 12;24(11):2461-2467, J Crohns Colitis. 2021 Nov 8;15(11):1846-1851, company press releases for [Rinvoq](#) and [Zeposia](#).

PALI-2108 Only Bio-Activates in the GI System



Target PDE4 Enzyme



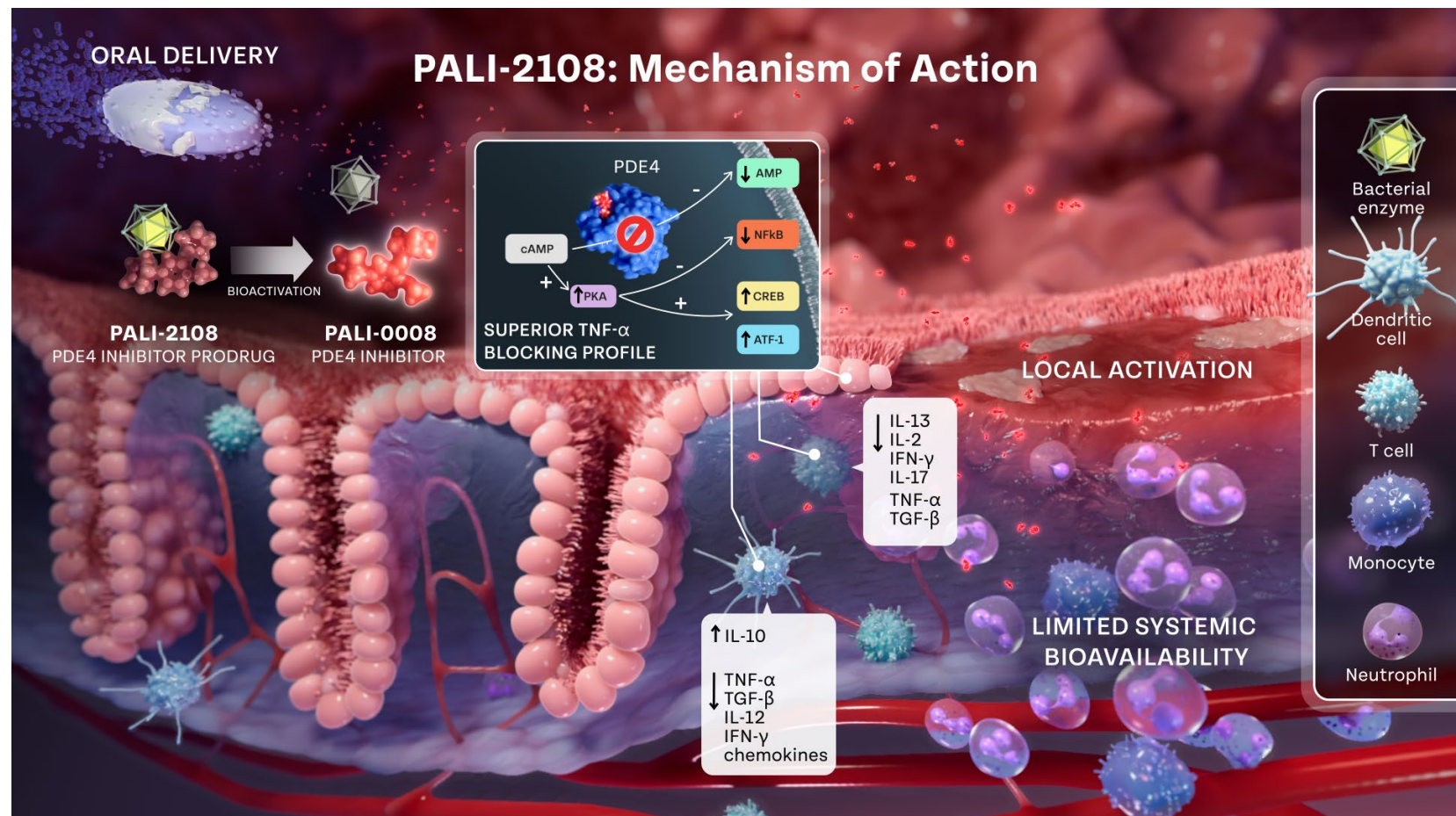
Prevent breaking down of cAMP molecules



Intracellular cAMP molecule levels become elevated



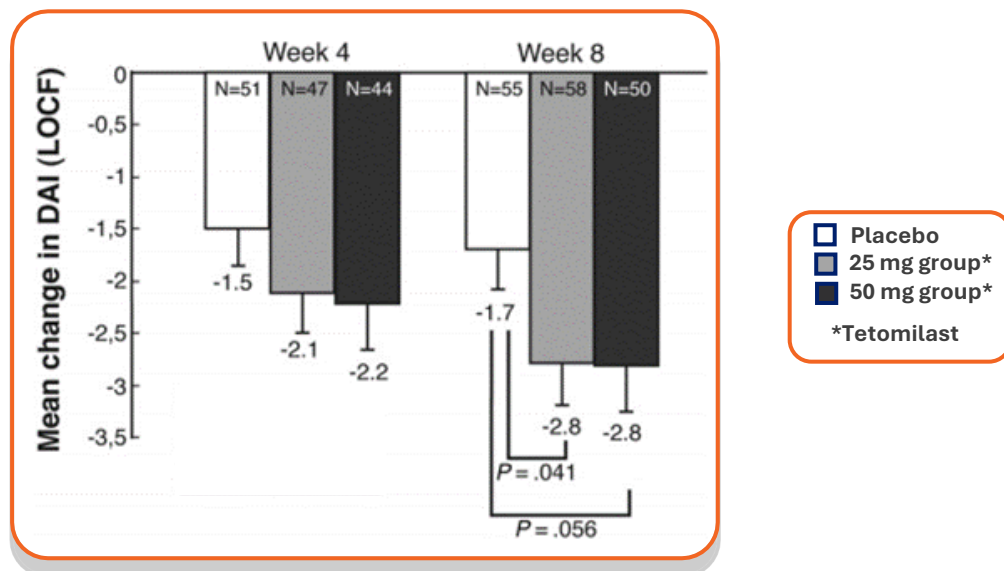
Reduction of inflammatory molecules and an increase of anti-inflammatory molecules within tissues of the colon



Previously Published Ph2 Studies of Systemic PDE4 Inhibitors Demonstrate Compelling Dose Response and Efficacy

While Phase 2 Studies Validate PDE4 Target in UC, Adverse Events Limited Dose Selection and Complicated Potential Advancement in UC

Mild-to-Moderate Active UC¹



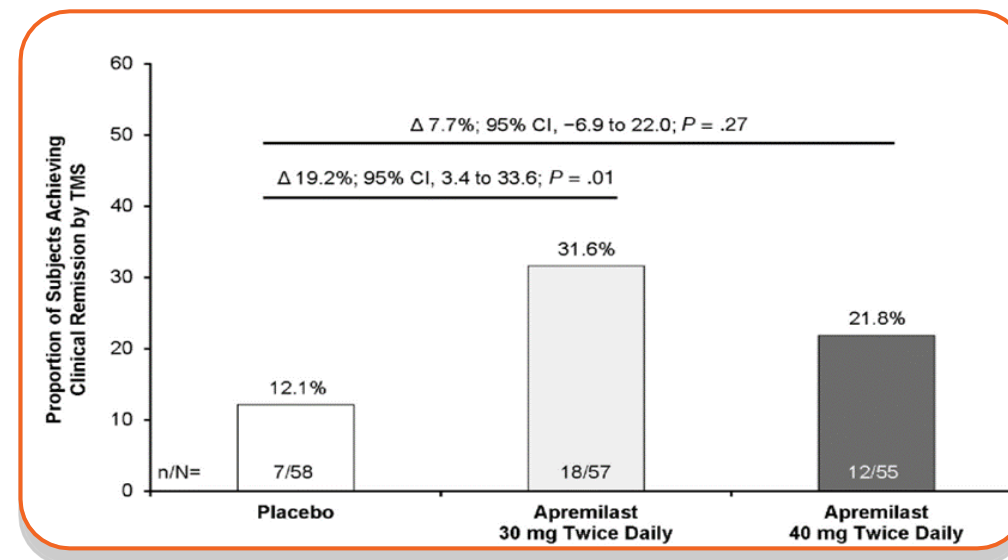
1. Schreiber et al. Gastroenterology. 2007 (not PALI data)

Significant improvement in disease activity index (DAI) at Week 8

Significant improvement in clinical remission rate

Adverse Events (AEs) were most frequently nausea, headache, and vomiting

Moderate-to-Severely Active UC²

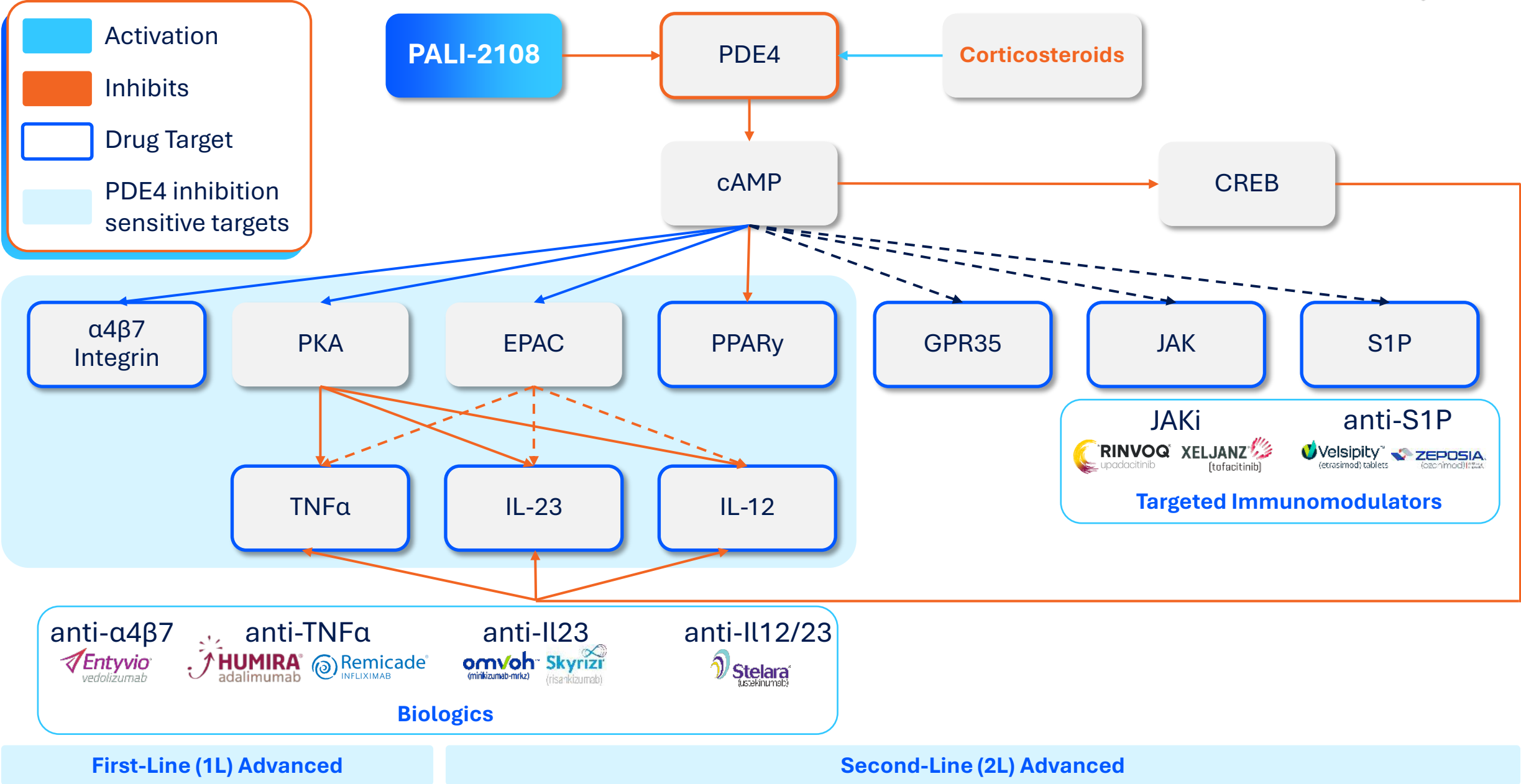


2. Danese et al. Clin Gastro and Hep. 2020 (not PALI data)

Significant improvement in clinical remission rate of 19.2%

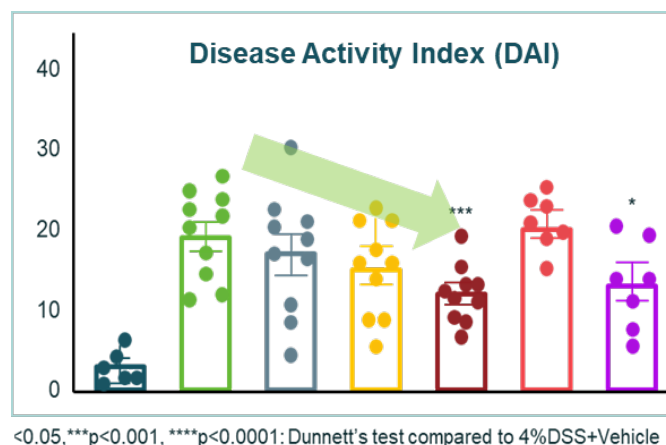
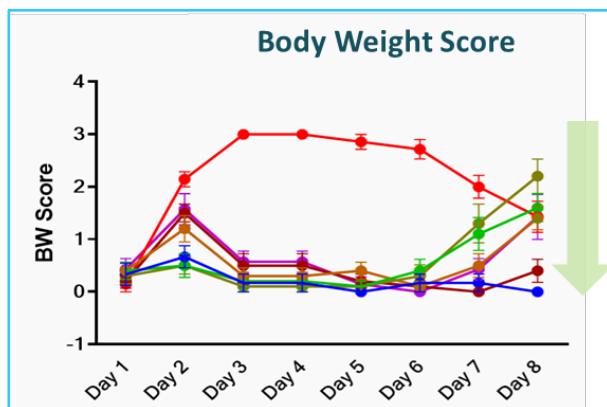
Adverse Events (AEs) were most frequently headache and nausea

How PDE4 Regulates the UC Therapeutic Targets

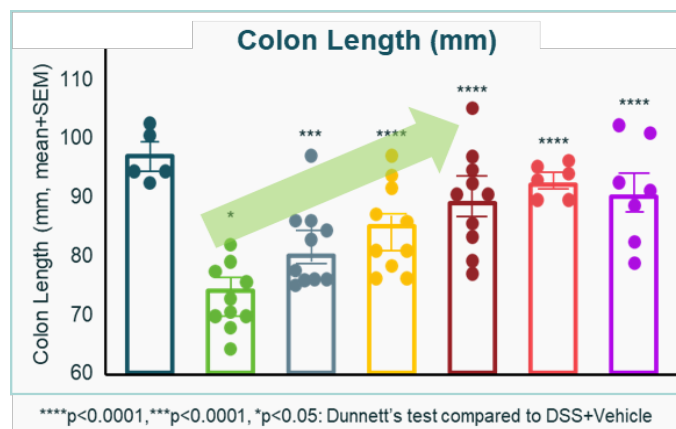


PALI-2108 Demonstrated Improved Efficacy Over Standard of Care and Systematic PDE4 Inhibitors in DSS Colitis Mouse Model

Dose Dependent Efficacy Response in DSS Colitis Mouse Model



- Non-Treatment naive
- 4% DSS + Vehicle (PO)
- 4% DSS + PALI-2108/ 40mg/kg (PO)
- 4% DSS + PALI-2108/ 80mg/kg (PO)
- 4% DSS + PALI-2108/ 160mg/kg (PO)
- 4% DSS + Cyclosporin A 80mg/kg (PO)
- 4% DSS + Apremilast/ 25mg/kg (PO)



PALI-2108 demonstrated clear dose dependent improvements in clinical outcome measures and was better than SOC in DSS colitis mouse model

While apremilast showed efficacy, it was at a dose not well tolerated when translated to human, including nausea*

Danese et al. evaluated 60mg and 80mg daily doses in UC patients which is ~1mg/kg; whereas we used the HED of ~2mg/kg in this study

*Danese et al

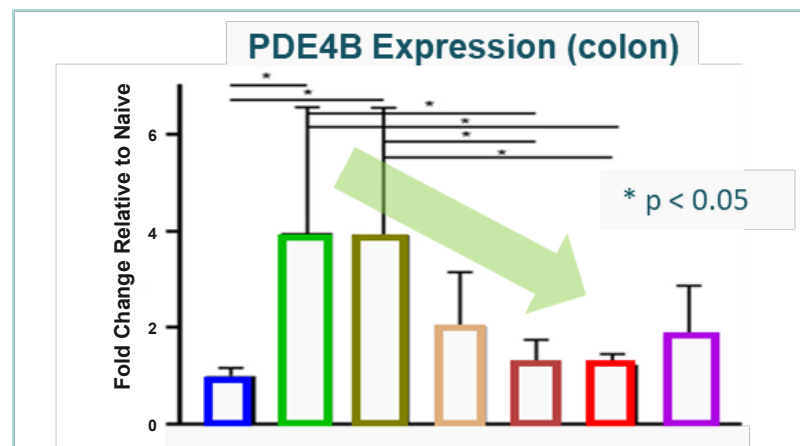
PALI-2108 Demonstrated Improved Efficacy Over Standard of Care and Systematic PDE4 Inhibitors in DSS Colitis Mouse Model

Dose Dependent Efficacy Response in DSS Colitis Mouse Model

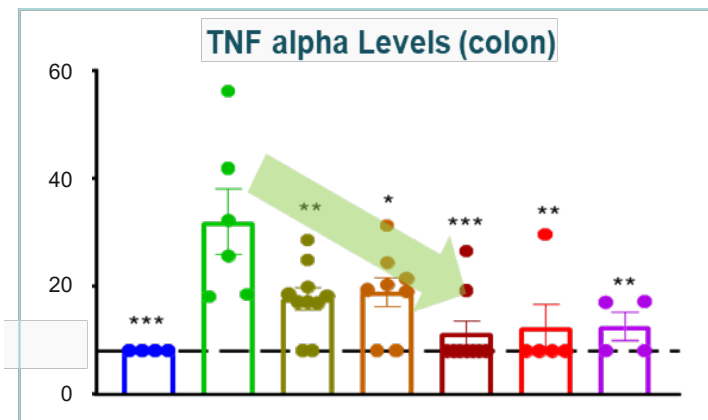
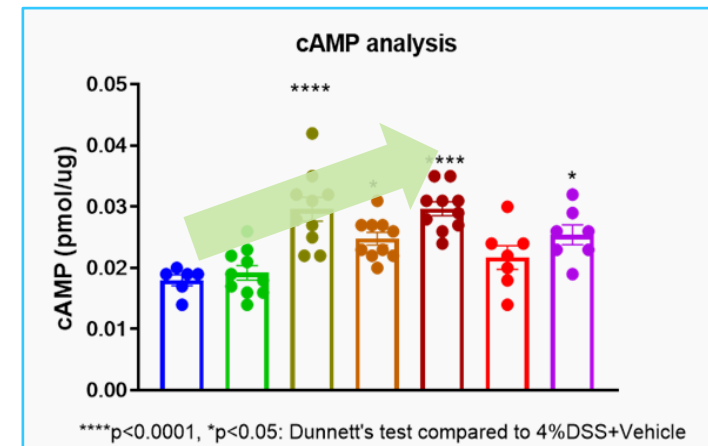
Colon tissue PDE4B Expression (mRNA) was reduced in response to PALI-2108 in a dose dependent manner together with local PDE4B inhibition and increased intracellular cAMP

cAMP levels were increased more with PALI-2108 and TNF-alpha levels in colon tissue are normalized on average an in most animals

*Danese et al

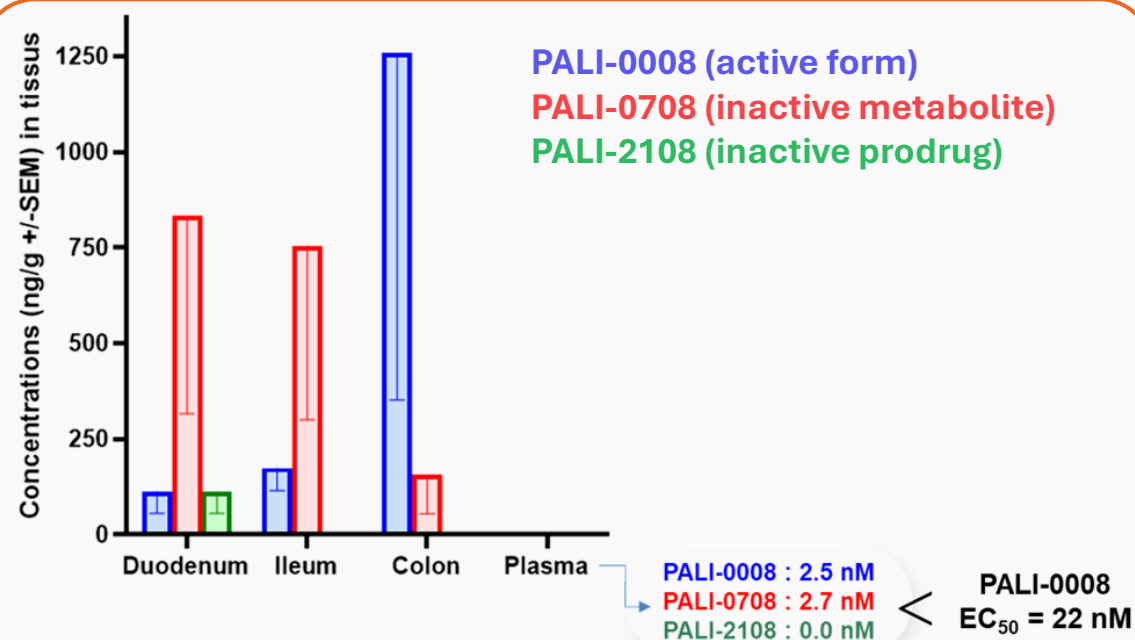


- Non-Treatment naive
- 4% DSS + Vehicle (PO)
- 4% DSS + PALI-2108/ 40mg/kg (PO)
- 4% DSS + PALI-2108/ 80mg/kg (PO)
- 4% DSS + PALI-2108/ 160mg/kg (PO)
- 4% DSS + Cyclosporin A 80mg/kg (PO)
- 4% DSS + Apremilast/ 25mg/kg (PO)



Limited Systematic Activity in Preclinical Model Provides Potential for Improved Safety Profile

Lack of Plasma Activity is Believed to Mitigate CNS Side Effects, like Nausea, Which is Seen with Systemic PDE4 Inhibitors



- ✓ Prodrug is released within the ileum and bio-converted by bacterial enzymes in the colon
- ✓ Prodrug is locally absorbed and inhibits PDE4 enzyme intracellularly
- ✓ Improved therapeutic window enables maximal PDE4 inhibition supporting higher cAMP tissue levels (supporting data in next slide)

Precision Medicine-Based Approach

Machine Learning Technology For Patient Selection

Targeting Patients with Elevated PDE4 Activity (PDE4-Related Biomarkers) to Potentially Enhance Responder Population

Process

Identify Markers of Colitis

RNAseq DiffExp

Top Ranked Genes (U or D)

Top Ranked in Multiple Studies

Relation with PDE4

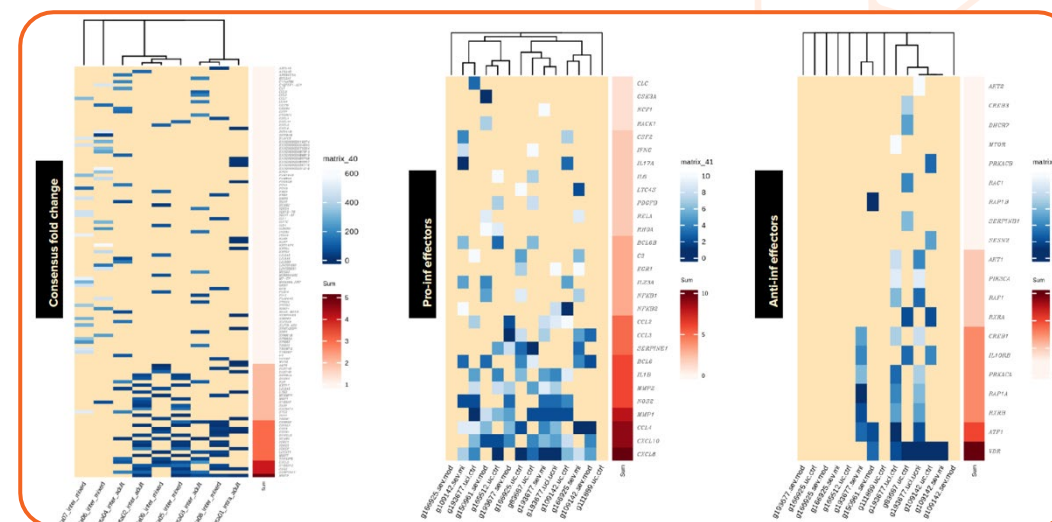
Output

Identified pool of PDE4-effector genes predictive of potential patient response to PDE4 inhibitor

Genes ranked by weights were selected from meta-analysis, pro-inflammatory and anti-inflammatory

Generate a weighted sum DAS score

Meta-Analysis



Precision Medicine Test with PDE4-Related Biomarkers Could be a Breakthrough for UC Treatment

We are developing a biomarker-based patient selection approach to aid clinicians in identifying patients who may better respond to PALI-2108

Elevated PDE4B Expression:

- ✓ Identified measurable threshold of elevated PDE4B expression across >1,600 patients and 10 studies
- ✓ Enabling the identification of over-expressing patients in over 70% of cases
- ✓ Findings support the potential for an FDA-approved test
- ✓ Process may maximize efficacy of UC PDE4 prodrug therapeutic

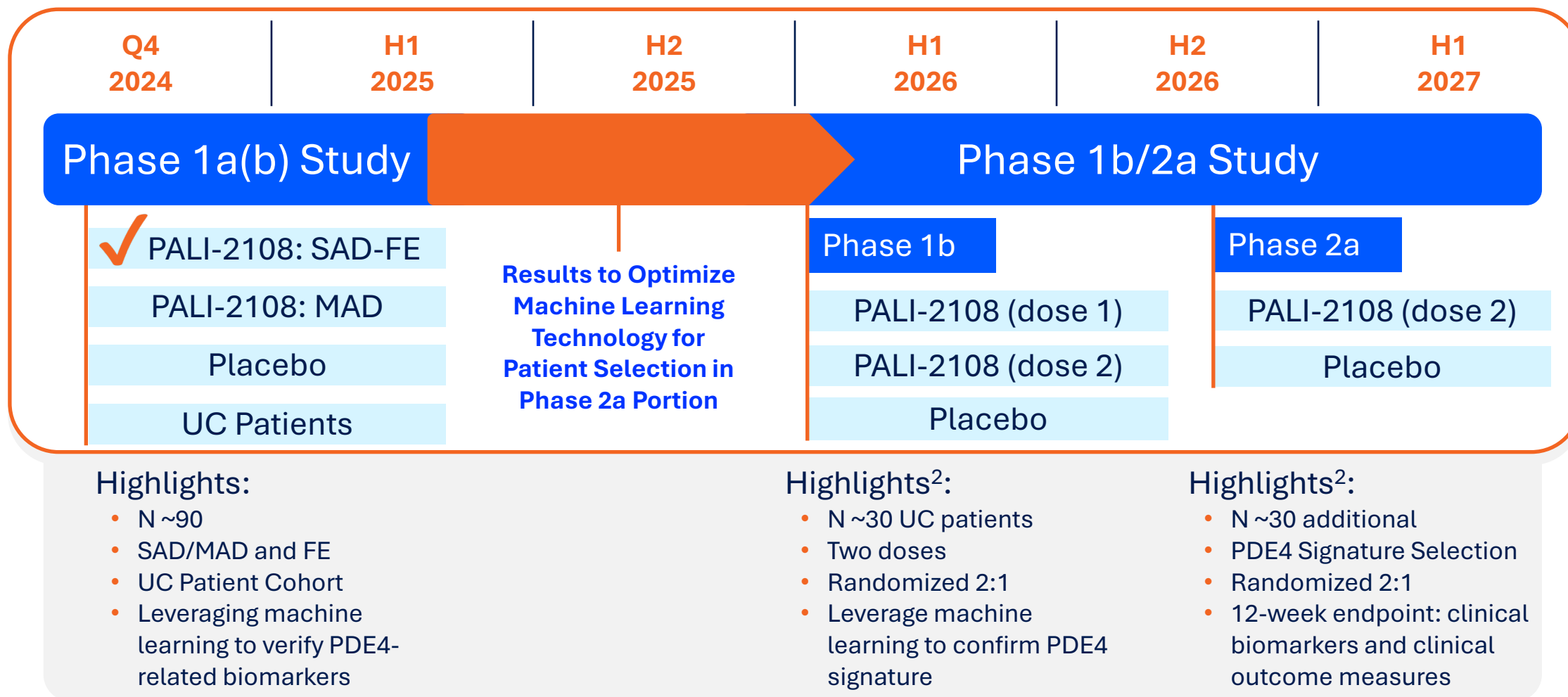
Elevated PDE4-Related Biomarkers:

- ✓ Advanced a second approach featuring 6 PDE4B-related biomarkers
- ✓ Shown superior performance compared to benchmark
- ✓ Tailored for PDE4 inhibition, providing a targeted solution for enhancing therapeutic outcomes
- ✓ PCR-based assays aimed at potential FDA approval may ensure precision in patient targeting

Advancing Toward US Phase 1b/2a Study¹

Engaging with Key Opinion Leaders and FDA to Finalize Study Design

Targeting Moderate to Severe Ulcerative Colitis



1. The timing of all events referenced herein are estimates and the actual timing of these events may differ than described herein.
 2. Trial design are anticipated/subject to change.

Capitalization

Capitalization (As of Nov. 18, 2024)

Common Stock Equivalents

Common Stock	1,329,516
Warrants (WAEP \$27.04) ¹	1,245,470
Pre-Funded Warrants (WAEP \$0.0001)	184,000
Stock Options (WAEP \$164.61)	51,269
RSUs	776
PSUs	2,952
Preferred Stock ²	8
Total Fully Diluted	2,813,991

\$8.0M*

Cash

As of September 30, 2024

**Cash Position Does Not Include Proceeds from the
\$5M Public Offering That Closed on December 13, 2024*

Program Team



JD Finley, MT
CEO



Mitch Jones, MD, PhD
CMO



Joerg Heyer, PhD
Head of Translational Science
and Medicine



Adarsh Patel, MS, MBA
Assoc. Director, Technical Operations



Christophe Mellon, PhD
CMC & Medicinal Chemistry



Jon Daniels, PhD
Safety & Tox & Reg (Consultant)



Patrick Colin, B. Pharm, PhD
Clinical Dev/Ops (Consultant)

Clinical Advisory Board



Bruce Sands MD, MS

Dr. Burrill B. Crohn Professor of Medicine, Icahn School of Medicine at Mount Sinai and System Chief, Division of Gastroenterology, Mount Sinai Health System

 Icahn School of Medicine
at **Mount Sinai**



Florian Rieder, MD

Associate Staff in the Department of Gastroenterology, Hepatology, and Nutrition, as well as an Investigator in the Department of Pathobiology at the Cleveland Clinic

 **Cleveland Clinic**



Brian Feagan, MD, FRCPC

Professor of Medicine at the Schulich School of Medicine & Dentistry at the University of Western Ontario, gastroenterologist at London Health Sciences Centre in Ontario, Canada.

 **Schulich**
MEDICINE & DENTISTRY

Corporate Summary

- PALI-2108 has improved therapeutic window, greater exposures and extended-release characteristics which enable maximal PDE4 inhibition in UC patient population
- Five cohorts dosed in SAD of Phase 1 study of healthy and UC patients in 2024; MAD portion initiated
- Precision medicine approach developed and leverages machine learning for selection of patient responders
- PDE4 inhibitors are proven in multiple indications with Phase 2 derisking data
- IP protection with composition of matter extending to 2042

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