

NASDAQ: PALI
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palisade**bio**

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

Corporate Presentation
December 2024

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 to address systemic safety concerns
- Two cohorts dosed in SAD of Phase 1 study of NHV subjects and UC patients (Nov 2024)
- 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	Two cohorts dosed in SAD of Phase 1 trial (Nov 2024) 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

- Phase 1 SAD-FE and MAD Complete
- Phase 2 GMP Drug Substance Complete

Q2 2025

- Phase 1 UC Complete
- Phase 1 Top Line Data Readout
- Pre IND-Meeting
- Phase 2 GMP Drug Product Complete

Q3 2025

- Phase 1 Final CSR
- IND Submission
- 3-month Safety and Tox Complete

Q4 2025

- IND Clearance
- Phase 1b/2a Site Initiation
- Phase 1b/2a First Subject Dosed



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
- ✓ Locally active (gut-restricted, colon-specific)
- ✓ Limited systemic exposure due to gut restriction and potentially 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
Adverse Event:	Central Nervous System: Nausea Headache Vomiting	Lack of systemic exposure potentially eliminates concerns for CNS adverse events
Results:	Suspension of treatment due to toxicities	Improved therapeutic window 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)

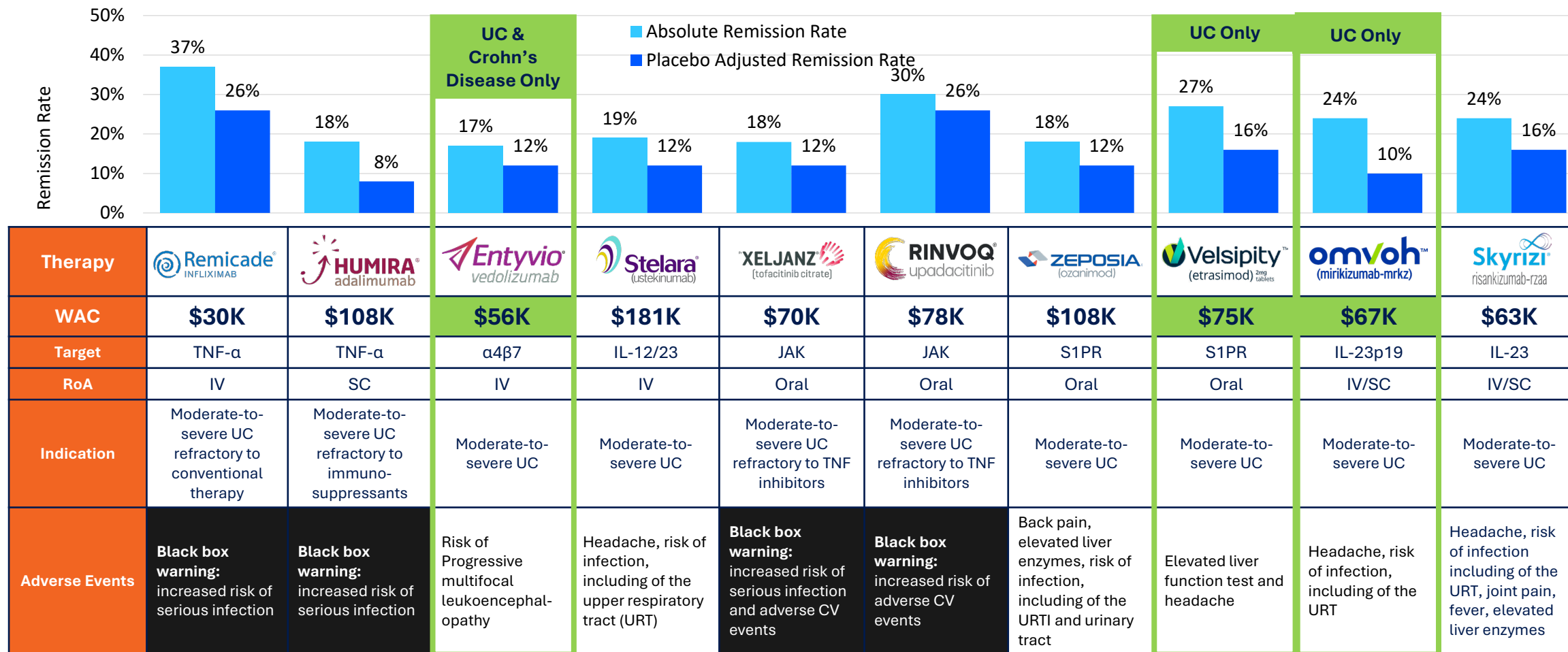
Apremilast demonstrated efficacy in a Phase 2 UC study, but selection of dose was limited by expected toxicities which prevented adequate dose ranging; the program was discontinued in IBD

Current Therapies for UC

Limited Efficacy with Significant Safety Concerns

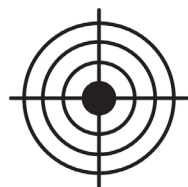
Though the number of available therapeutics for moderate-to-severe patients is growing, the placebo-adjusted remission rate remains low, ~10-20%, and many therapies have poor safety profiles

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



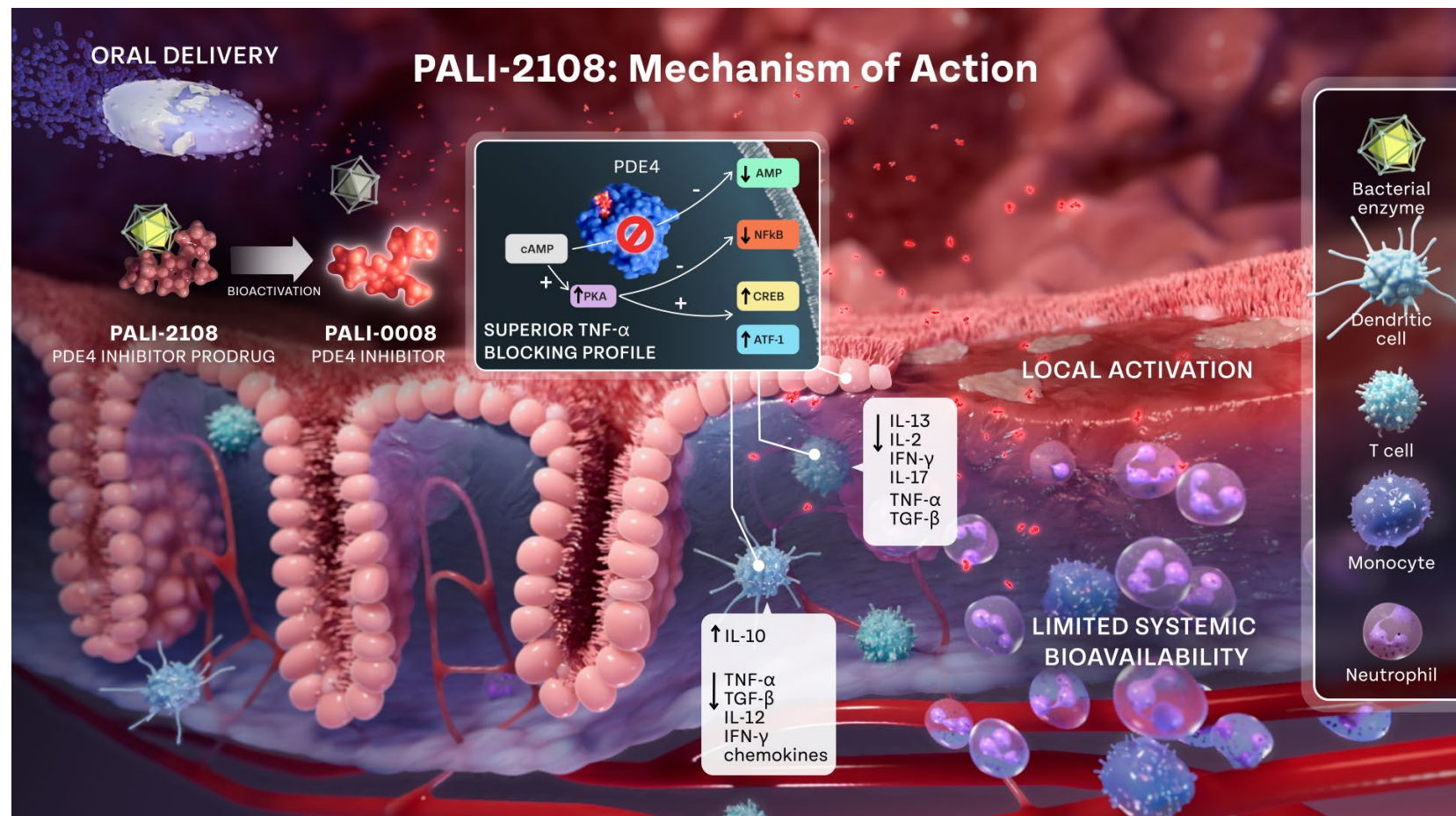
Prevent breaking down of cAMP molecules



Intracellular cAMP molecule levels become elevated



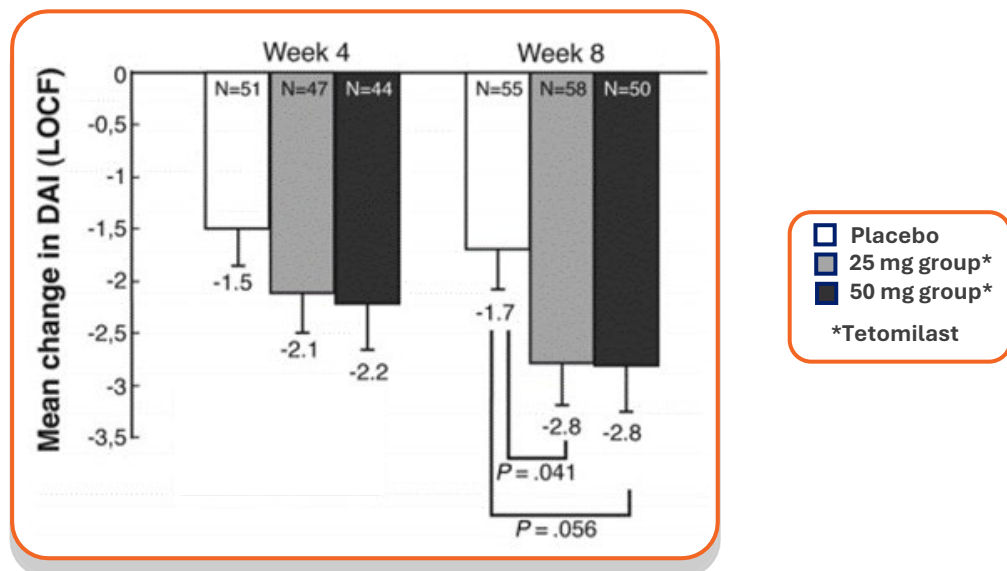
Reduction of inflammatory molecules and an increase of anti-inflammatory molecules within tissues of the colon



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



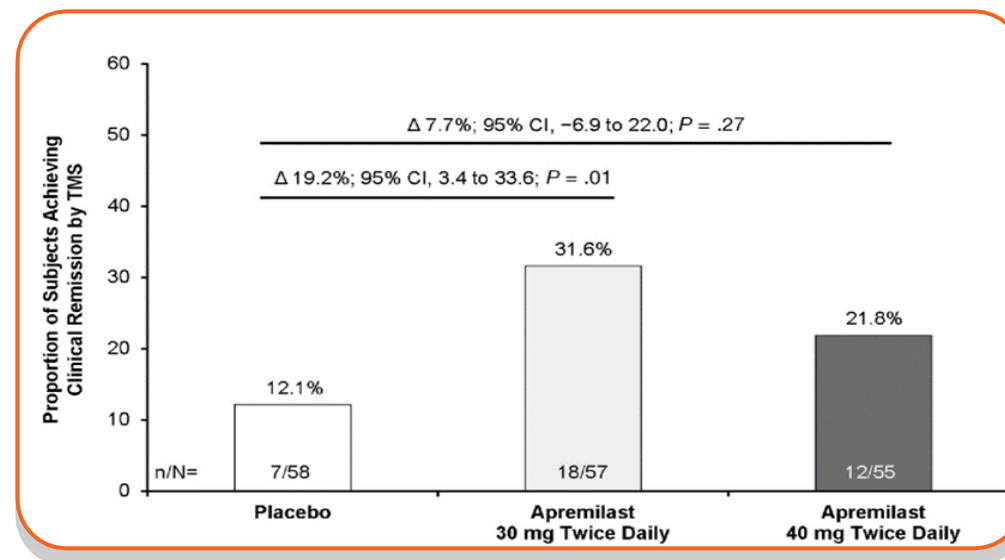
1. Schreiber et al. Gastroenterology. 2007 (not PALI data)

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

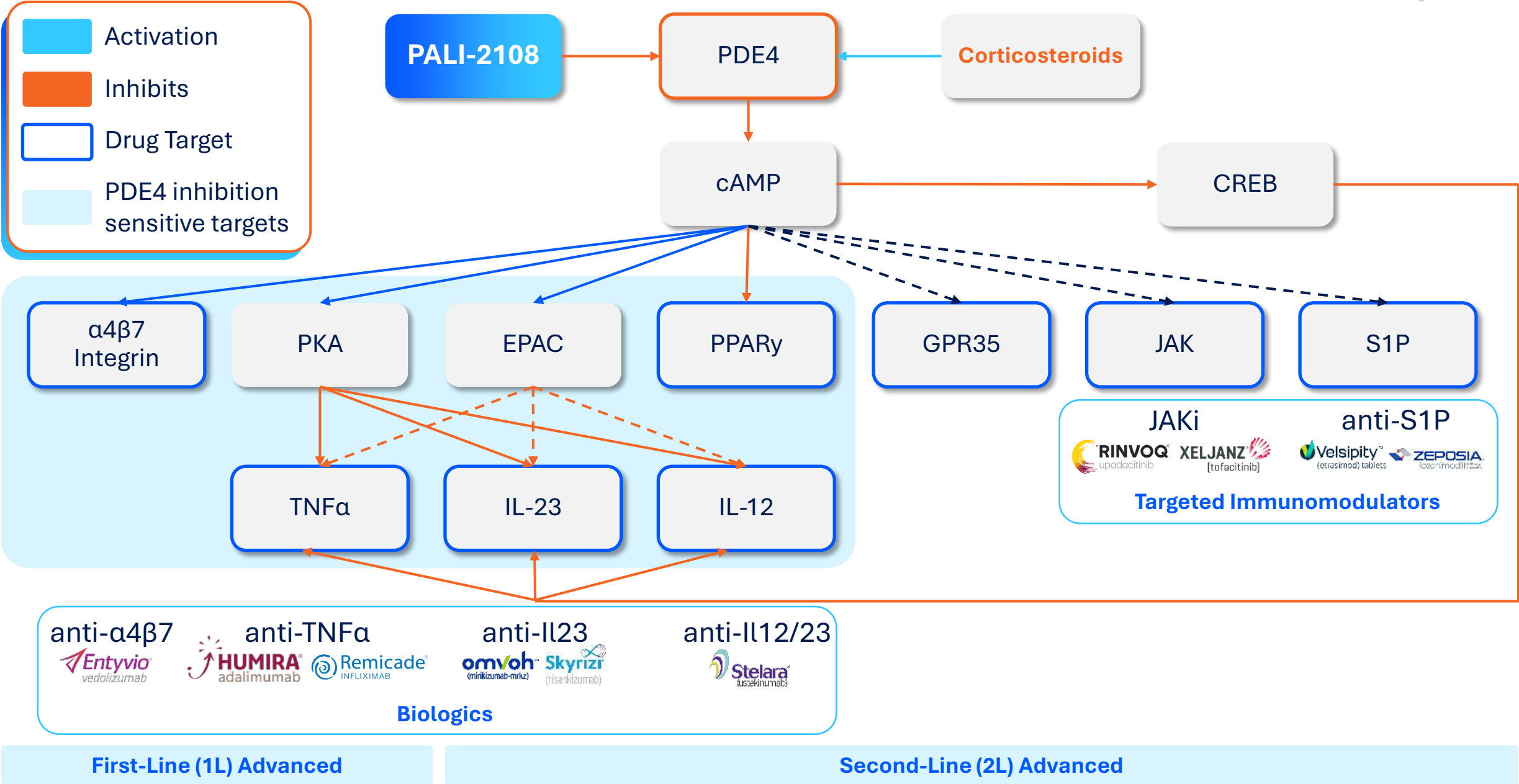


2. Danese et al. Clin Gastro and Hep. 2020 (not PALI data)

Significant improvement in clinical remission rate of 19.2%

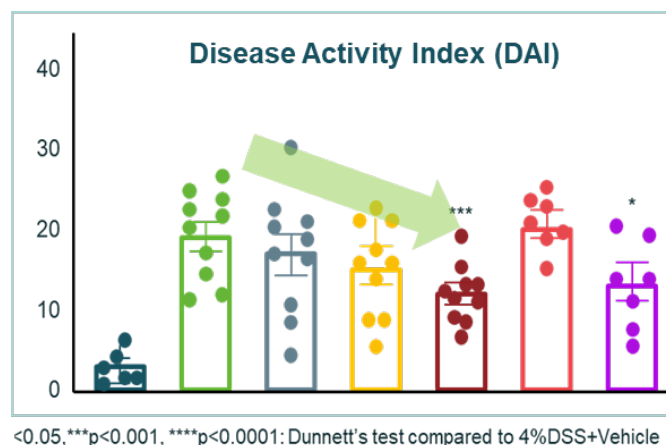
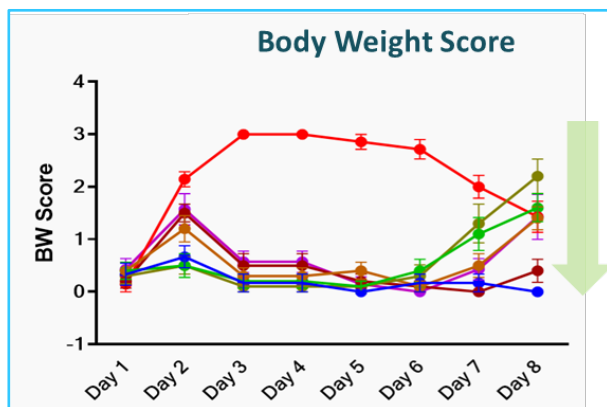
Adverse Events (AEs) were most frequently headache and nausea

How PDE4 Regulates the UC Therapeutic Targets

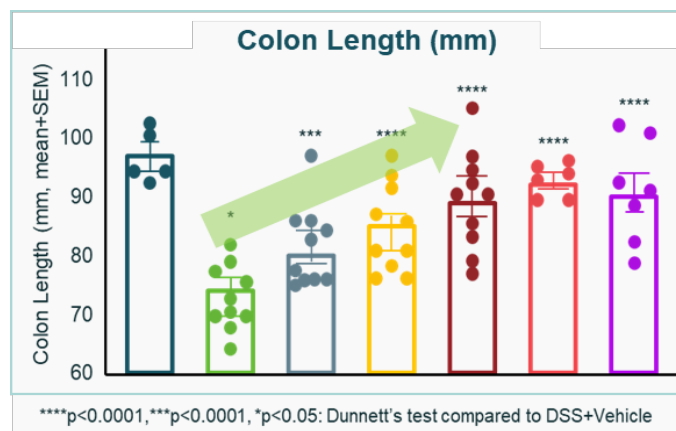


PALI-2108 Demonstrated Improved Efficacy Over Standard of Care and Systematic PDE4 Inhibitors in DSS Colitis Mouse Model

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

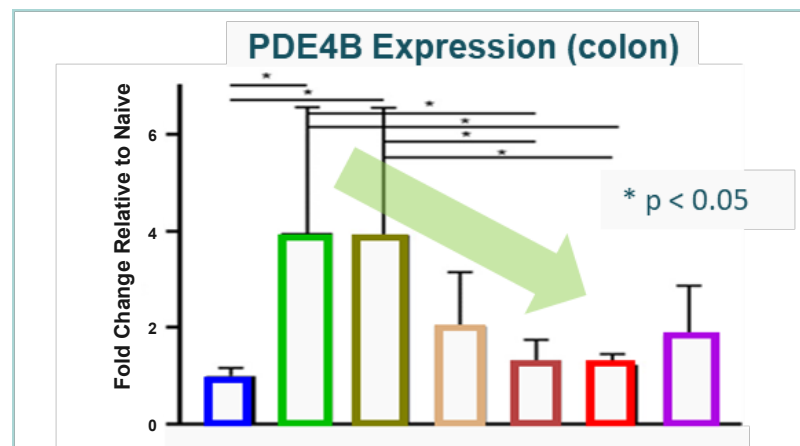
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Dose Dependent Efficacy Response in DSS Colitis Mouse Model

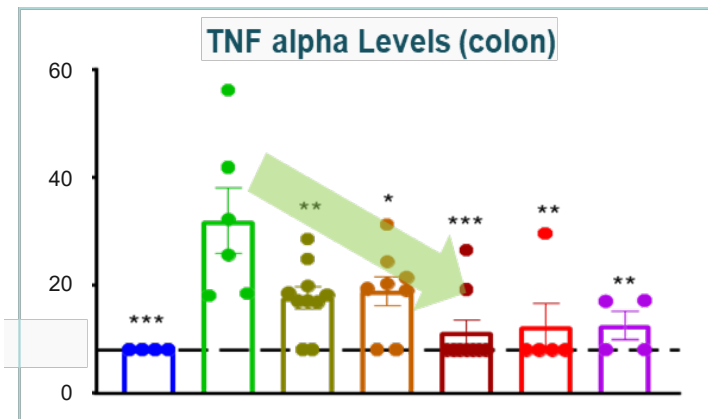
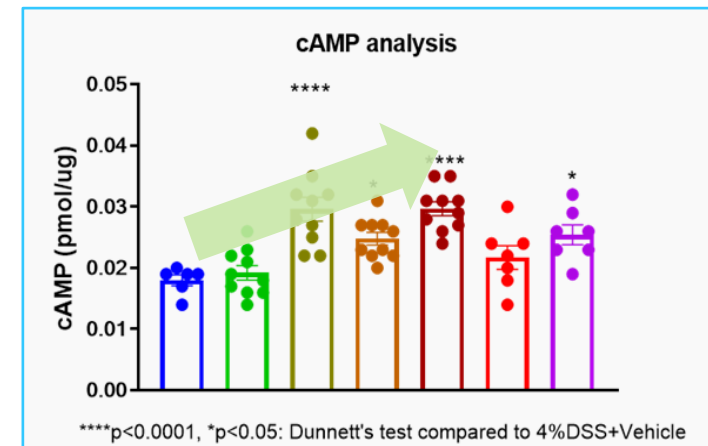
Colon tissue PDE4B Expression (mRNA) was reduced in response to PALI-2108 in a dose dependent manner together with local PDE4B inhibition and increased intracellular cAMP

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

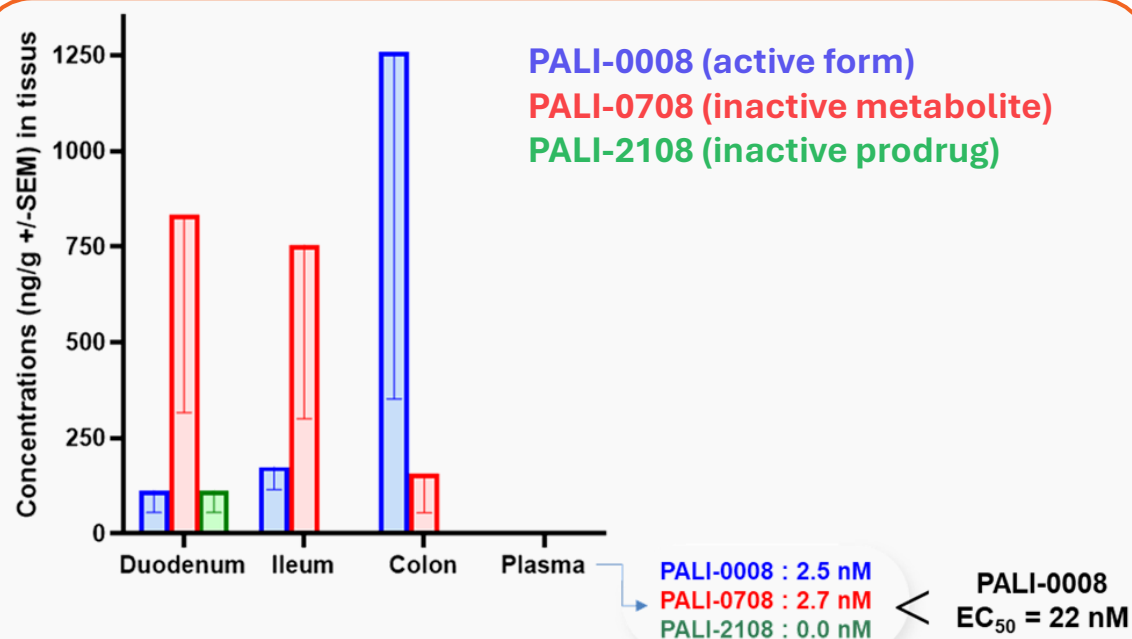


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- 4% DSS + Cyclosporin A 80mg/kg (PO)
- 4% DSS + Apremilast/ 25mg/kg (PO)



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 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

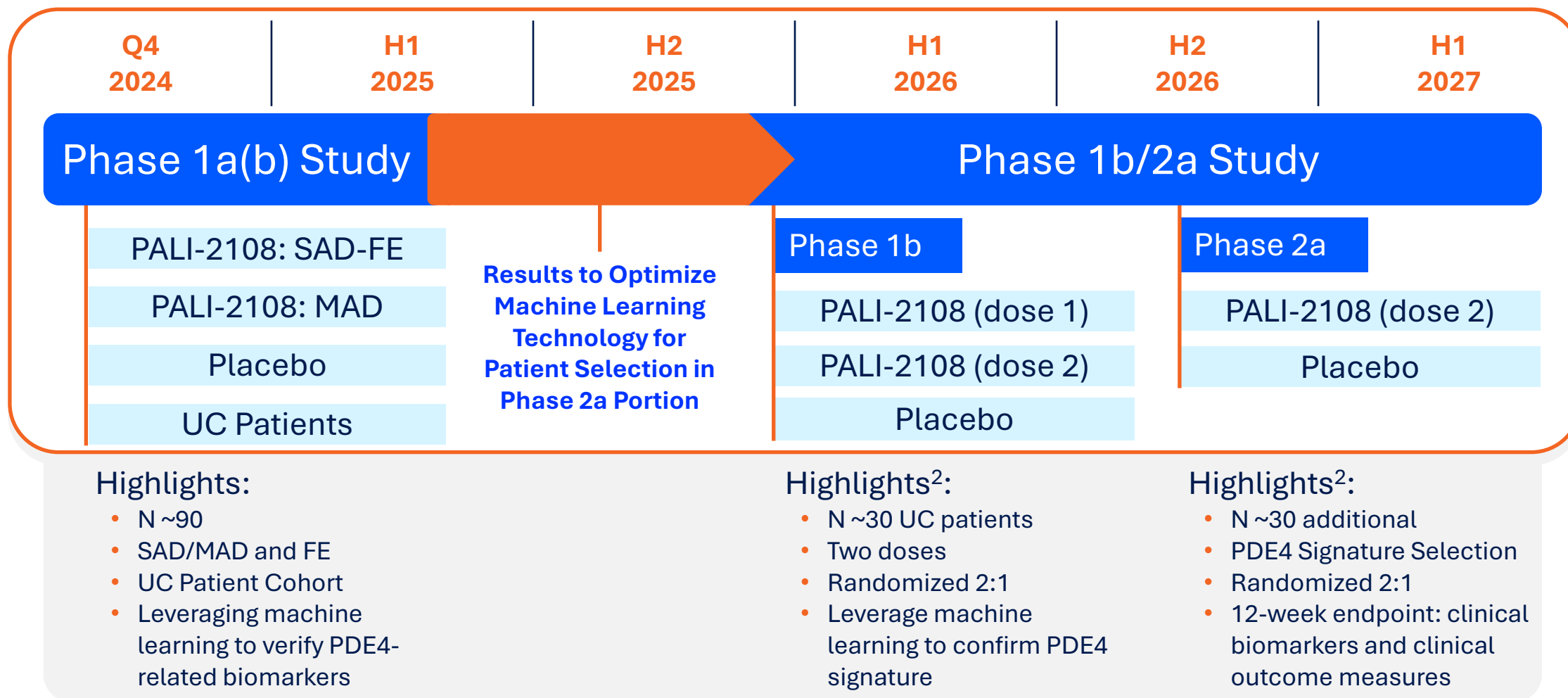
Elevated PDE4B-Related Biomarkers:

- ✓ 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.

Development Plan Through Phase 1b/2a¹



1. The timing of all events referenced herein are estimates and the actual timing of these events may differ than described herein.

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

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**

Corporate Summary

- Two Cohorts Dosed in SAD of Phase 1 Study of Healthy and UC Patients in 2024
- 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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Appendix

Additional Upside Potential

Expanding the Population into the Broad UC Population and Development in Additional Inflammatory and Fibrotic Indications



Broader UC Population

Opportunity

- Moderate-to-severe, 1L refractory UC population would bring a novel oral therapy to the market and expand the total addressable population by at least 25%

Rationale

- In inflamed colon tissue in chronic UC patients, PDE4 has been shown to be overexpressed compared to healthy tissue

Unmet Need

- 30-60% of UC patients have an inadequate response to current therapies, leaving a high unmet need for therapies with novel MoAs and better efficacy

Market Size

- The UC market for the 8 major markets is estimated to reach ~\$10B by 2031, with oral medicines anticipated to capture >40% of newly written prescription market share
- In 1L refractory moderate-to-severe PDE4+ UC patients determined by CDx, PALI-2108 is estimated to be a >\$2.7B opportunity, worldwide; development of PALI-2108 in the broad 1L refractory moderate-to-severe population expands the opportunity to ~\$3.4B



Additional Indications

Opportunity

- Additional indications: fibrostenotic Crohn's (CD) or ILD/IPF

Rationale

- PDE4 inhibition is associated with anti-inflammatory & anti-fibrotic effects that could address fundamental drivers of disease in patients with IPF and CD

Unmet Need

- Up to half of all CD patients develop disease complications related to ineffective management, one which is fibrostenosis, leading to GI tract obstruction and severe complications, which can only be treated by surgery
- IPF is ultimately fatal, and current therapies can slow, but not reverse or stop, disease progression and are associated with severe side-effects

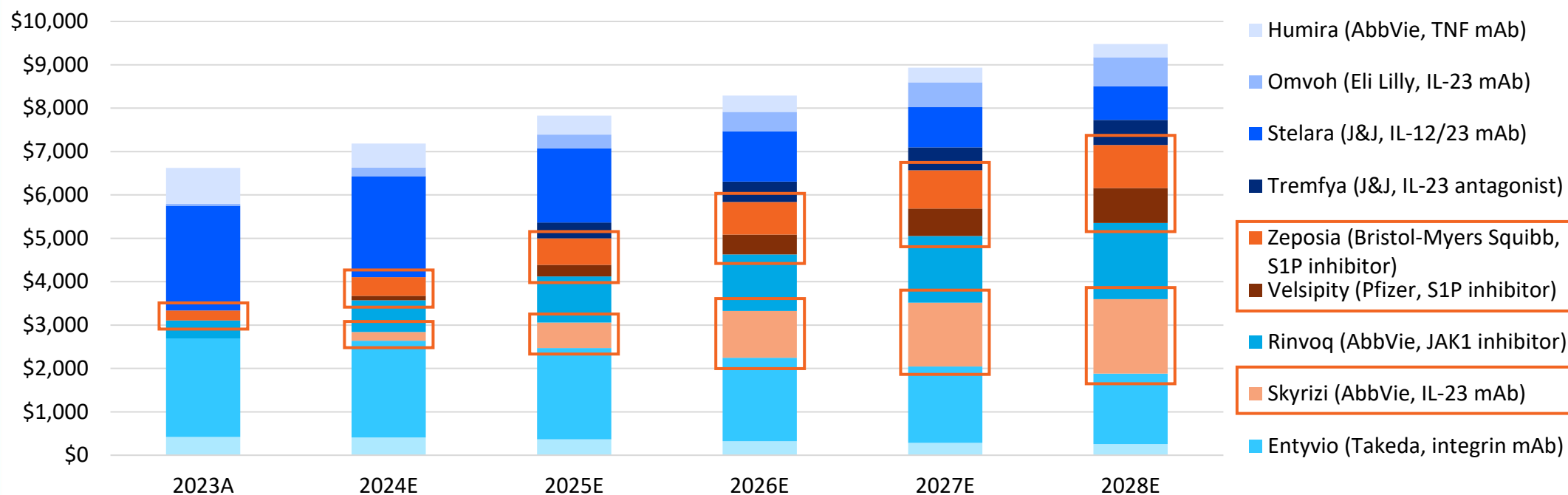
Market Size

- The CD market for the 8 major markets is estimated to reach ~\$15B by 2032
 - + Emerging novel oral small molecules in CD are projected to generate at least \$2-3B at peak, commanding 7-10% market share
- The IPF market for the 7 major markets is estimated to reach ~\$4B by 2029
 - + In IPF, novel emerging oral small molecules are projected to garner up to 25% market share and generate \$1-2B revenue at peak

UC Market Overview

Despite biosimilar entries for Humira and Stelara, the overall market will still grow to nearly \$10B across the top 10 products by 2028 driven by new entrants

WW UC Market – Top 10 Products (2023-2028)



Key market growth drivers coming primarily from oral drugs

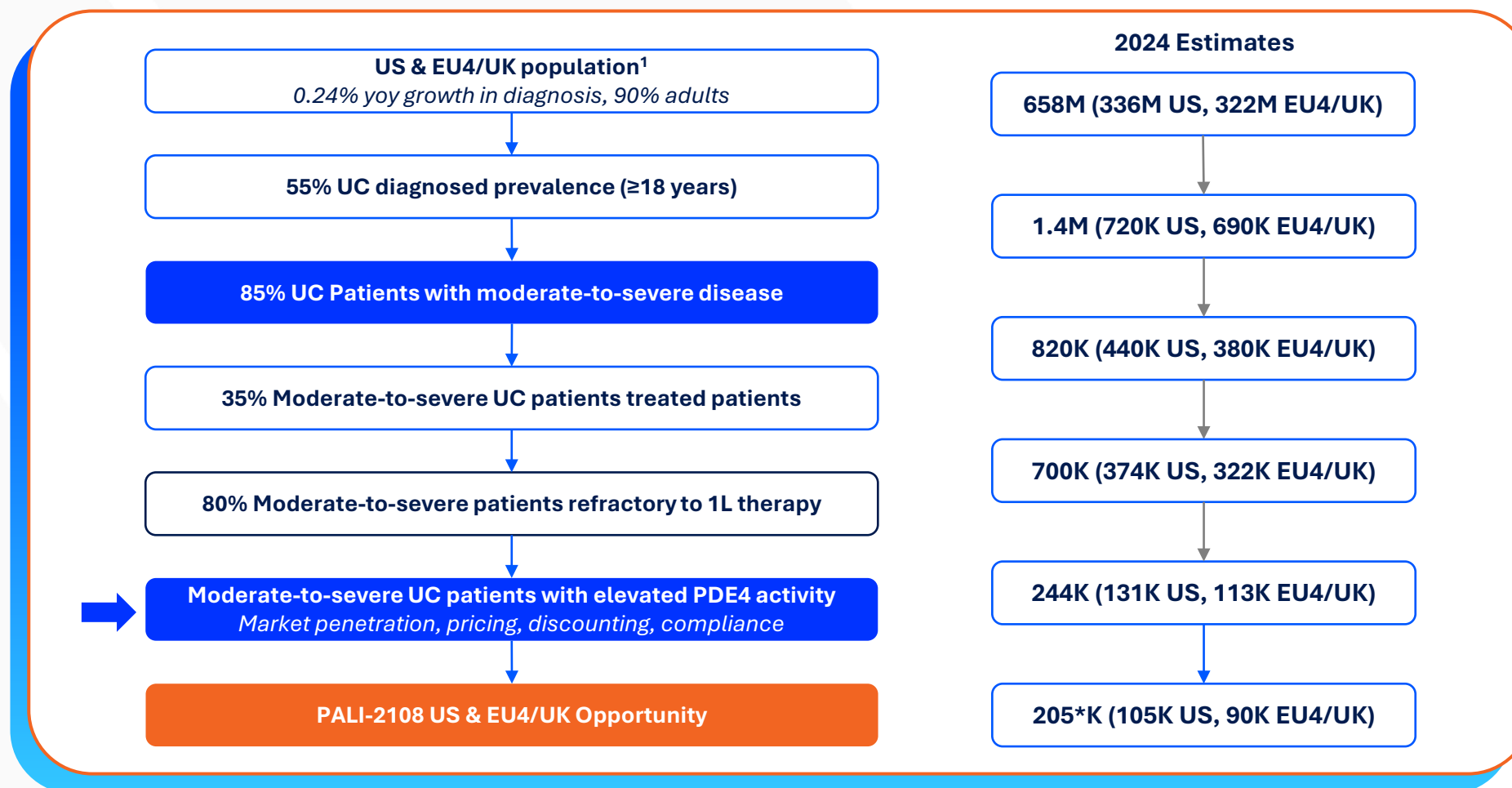
Emergence of Oral Tx

- Oral options Rinvoo and Zeposia were the main NWRx gainers in 2022-2023, with oral medicines as a class capturing a >40% NWRx share
- Patients are expected to continue to shift to newly launched drugs that offer novel mechanisms of action and convenient oral formulation

Addressable Population

PALI-2108

In moderate-to-severe UC patients overexpressing PDE4 and refractory to 1L therapy, there are currently >200K addressable patients across US and EU4/UK



IP Protection Through 2041+

- Composition of Matter patent family
PCT/CA2021/050725
- National phase entry of PCT
December 2022
- National phase entry
US, Canada, China, Japan,
Mexico, Australia, EU
(France, Germany, Italy,
Spain, UK, etc.), South
Korea

- Composition of Matter
coverage until 2041+
- Will seek FDA regulatory
exclusivity coverage for up
to 8 Years following new
drug approval
- Potential to file additional
patents
Formulation patents
Methods of use