

NASDAQ: PALI  
palisadebio.com



# palisade**bio**

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

Corporate Presentation  
September 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 commence human clinical trials of PALI-2018, the potential for PALI-2108 to transform the current standard of care, strategy, potential of PALI-2018 to be covered by a patient’s pharmacy benefit, 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 anticipated 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 a pre-clinical stage of 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.

The trademarks included herein are the property of the owners thereof and are used for reference purposes only.

# Investment Highlights

## *Our Mission:*

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

## *Our Vision:*

Advance early-stage product candidates that address efficacy, safety, and patient selection concerns associated with currently available drugs and those in development.

- Lead program targeting multi-billion-dollar IBD market
- Commercially proven PDE4 target with potential to address systemic safety concerns
- Rapidly advancing towards first patient dose in Phase 1 study of NHV and UC patients in 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             | IND/CTA-Enabling | IND/CTA-enabling tox studies completed and CTA submitted<br><br>Rapidly advancing towards first patient dosed in Phase 1 of healthy and UC patients in 2024 |
| PALI-1908 | Fibro Stenotic Crohn's Disease | Discovery        | Significant overlap with PALI-2108<br>IND/CTA filing in 2024<br><br>POC for fibrosis pathway engagement completed                                           |

# We Are in a Space Big Pharma is Active Spending Big Dollars for Earlier Stage Programs

| Company                                                                                                      | Acquirer                                                                                            | Date     | Lead Asset         | Phase at Deal | MOA                           | Upfront               | Total Deal            | Royalties           | Current Status      |
|--------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|----------|--------------------|---------------|-------------------------------|-----------------------|-----------------------|---------------------|---------------------|
|  Télavant                    |  Roche             | Oct 2023 | RVT-3101           | Phase 3 Ready | Anti-TL1A Mab                 | <b>\$7.1 Billion</b>  | <b>\$7.2 Billion</b>  | NA                  | Phase 3 Prep        |
|  teva                       |  sanofi            | Oct 2023 | TEV'574            | Phase 2b      | Anti-TL1A Mab                 | <b>\$500 Million</b>  | <b>\$1.5 Billion</b>  | 50/50 JV            | Active              |
|  Recludix Pharma            |  sanofi            | Jul 2023 | Pre-IND Candidates | Preclinical   | STAT6 Inhibitor (IL-4, IL-13) | <b>\$125 Million</b>  | <b>\$1.3 Billion</b>  | Potential for 50/50 | Active              |
|  Prometheus Biosciences     |  MERCK             | Apr 2023 | PRA023             | Phase 2       | Anti-TL1A Mab                 | <b>\$10.8 Billion</b> | <b>\$10.8 Billion</b> | NA                  | Phase 3 Prep        |
|  ARENA PHARMACEUTICALS    |  Pfizer          | Dec 2021 | Etrasimod          | Phase 3 Ready | Oral S1P                      | <b>\$6.7 Billion</b>  | <b>\$6.7 Billion</b>  | NA                  | Approved (Oct 2023) |
|  Protagonist Therapeutics |  Johnson&Johnson | May 2017 | JNJ-2113 (PN-235)  | Preclinical   | Oral IL-23 peptide            | <b>\$50 Million</b>   | <b>\$990 Million</b>  | 6-10%               | Phase 2/3 Ongoing   |



# **PALI-2108**

## **Initially Targeting Ulcerative Colitis (UC)**

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

# Ulcerative Colitis: A Significant Unmet Medical Need

The unmet need is for more effective at induction of remission, non-systemically immunosuppressive and less toxic, and precision medicine and tailored approaches to therapy to address the heterogeneity of the UC population

## Improved Remission Rates

### Need for improved rates of clinical remission despite increased treatment options

- Clinical remission rates are an average of ~16% on advanced therapies
- 30-40% fail to respond adequately to 1L biologic advanced therapies
- Disease-modifying agents are needed to prevent sequelae of disease e.g. colectomy

*“40-50% of patients getting 1L have no response, so unmet need of efficacy is huge.”*

*– IBD US KOL*

## Optimized & Tailored Treatment

### Need for patient stratification and predictive biomarkers to facilitate tailored therapies

- UC is a heterogeneous with location, activity, presentation and course, and current treatment algorithms suggest a generalized approach
- It can take several months to identify non-response and a stratified medicine approach may radically improve effectiveness and efficiency of outcomes

*“We are using a sort of best guess method right now to select patients and therapies and we need a way to predict what will work for the patient.”*

*– IBD US KOL*

## Novel Oral Treatments

### Need for oral options without significant limitations

- Black Box warnings for JAK inhibitors and risk of infection/liver dysfunction with S1P1
- No significant improvements in efficacy versus biologics

# Locally Delivered Oral Therapy for UC with Potential for Improved Efficacy and Safety

Novel Oral PDE4 Inhibitor Prodrug Therapy that Act Locally at Site of Disease

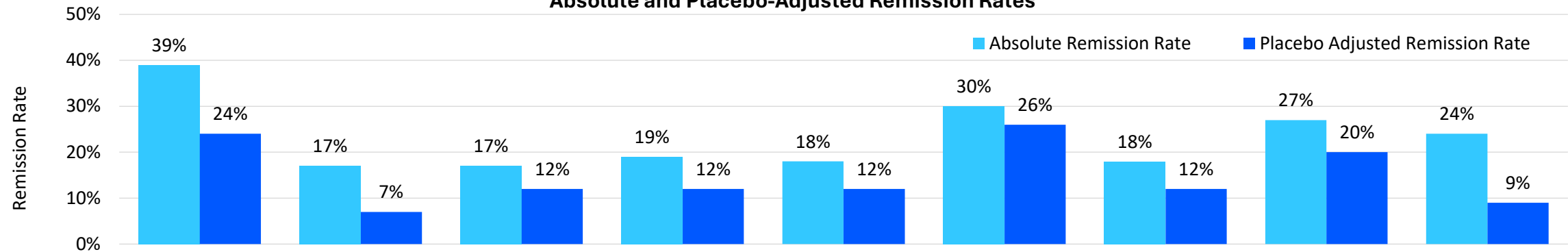
Leveraging innovative machine learning technology to identify PDE4 effectors, leading to selection of potential responders

- ✓ PDE4 target and pathway is validated in inflammatory and fibrotic disease and there are compelling Phase 2 UC data
- ✓ Limited systemic activity and potentially improved safety profile
- ✓ Oral dosing and locally active
- ✓ Demonstrated proof-of-concept efficacy
- ✓ Preclinical and *ex vivo* data suggest potential for superior efficacy and derisks program

# Current Therapies Have 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

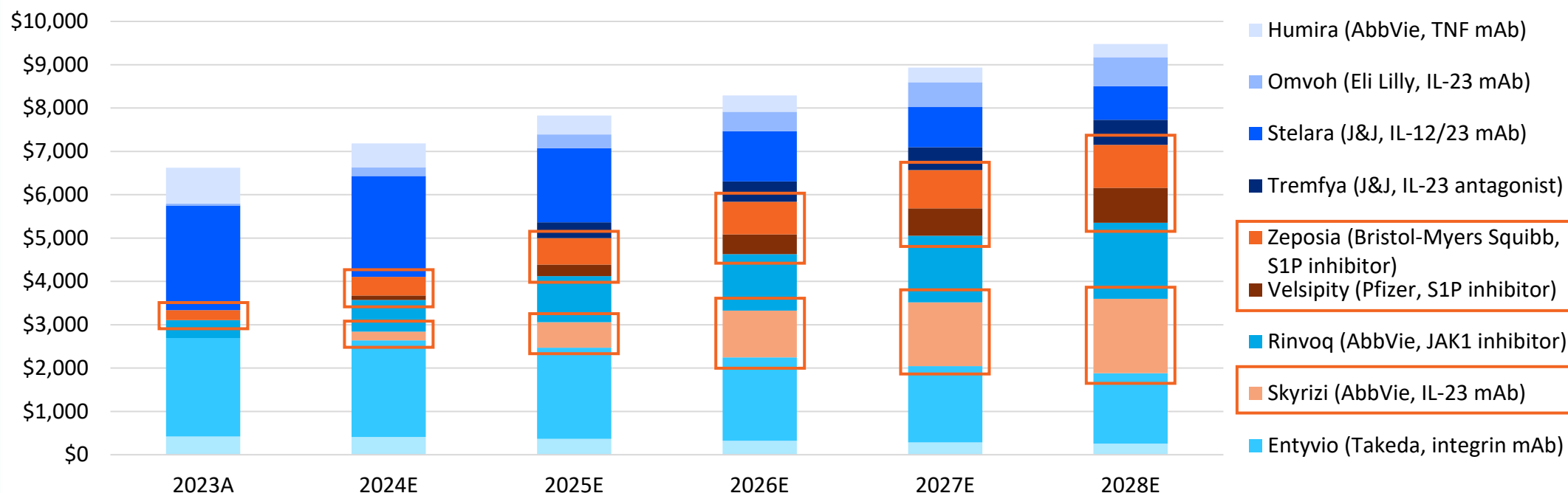


| Therapy           |  <b>Remicade</b><br>INFLIXIMAB |  <b>HUMIRA</b><br>adalimumab |  <b>Entyvio</b><br>vedolizumab |  <b>Stelara</b><br>(ustekinumab) |  <b>XELJANZ</b><br>(tofacitinib citrate) |  <b>RINVOQ</b><br>upadacitinib |  <b>ZEPOSIA</b><br>(ozanimod) |  <b>Velsipity</b><br>(etrasimod) 2mg tablets |  <b>omvoh</b><br>(mirikizumab-mrkz) |
|-------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Target            | TNF-α                                                                                                           | TNF-α                                                                                                         | α4β7                                                                                                            | IL-12/23                                                                                                            | JAK                                                                                                                         | JAK                                                                                                               | S1PR                                                                                                             | S1PR                                                                                                                            | IL-23p19                                                                                                               |
| RoA               | IV                                                                                                              | SC                                                                                                            | IV                                                                                                              | IV                                                                                                                  | Oral                                                                                                                        | Oral                                                                                                              | Oral                                                                                                             | Oral                                                                                                                            | IV/SC                                                                                                                  |
| Loss of Response* | ~10%                                                                                                            | ~13%                                                                                                          | ~39%                                                                                                            | ~36%**                                                                                                              | ~39%                                                                                                                        | ~52%                                                                                                              | ~14%                                                                                                             | 14%                                                                                                                             | 24%                                                                                                                    |
| Safety / Toxicity | <b>Black box warning:</b><br>increased risk of serious infection                                                | <b>Black box warning:</b><br>increased risk of serious infection                                              | Risk of PML                                                                                                     | Headache, risk of infection, including of the upper respiratory tract (URT)                                         | <b>Black box warning:</b><br>increased risk of serious infection and CV events                                              | <b>Black box warning:</b><br>increased risk of CV events                                                          | Back pain, elevated liver enzymes, risk of infection, including URT & urinary tract                              | Elevated liver function test and headache                                                                                       | Headache, risk of infection, including of the URT                                                                      |
| WAC               | <b>\$30K</b>                                                                                                    | <b>\$108K</b>                                                                                                 | <b>\$56K</b>                                                                                                    | <b>\$181K</b>                                                                                                       | <b>\$70K</b>                                                                                                                | <b>\$78K</b>                                                                                                      | <b>\$108K</b>                                                                                                    | <b>\$75K</b>                                                                                                                    | <b>\$67K</b>                                                                                                           |

# 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)



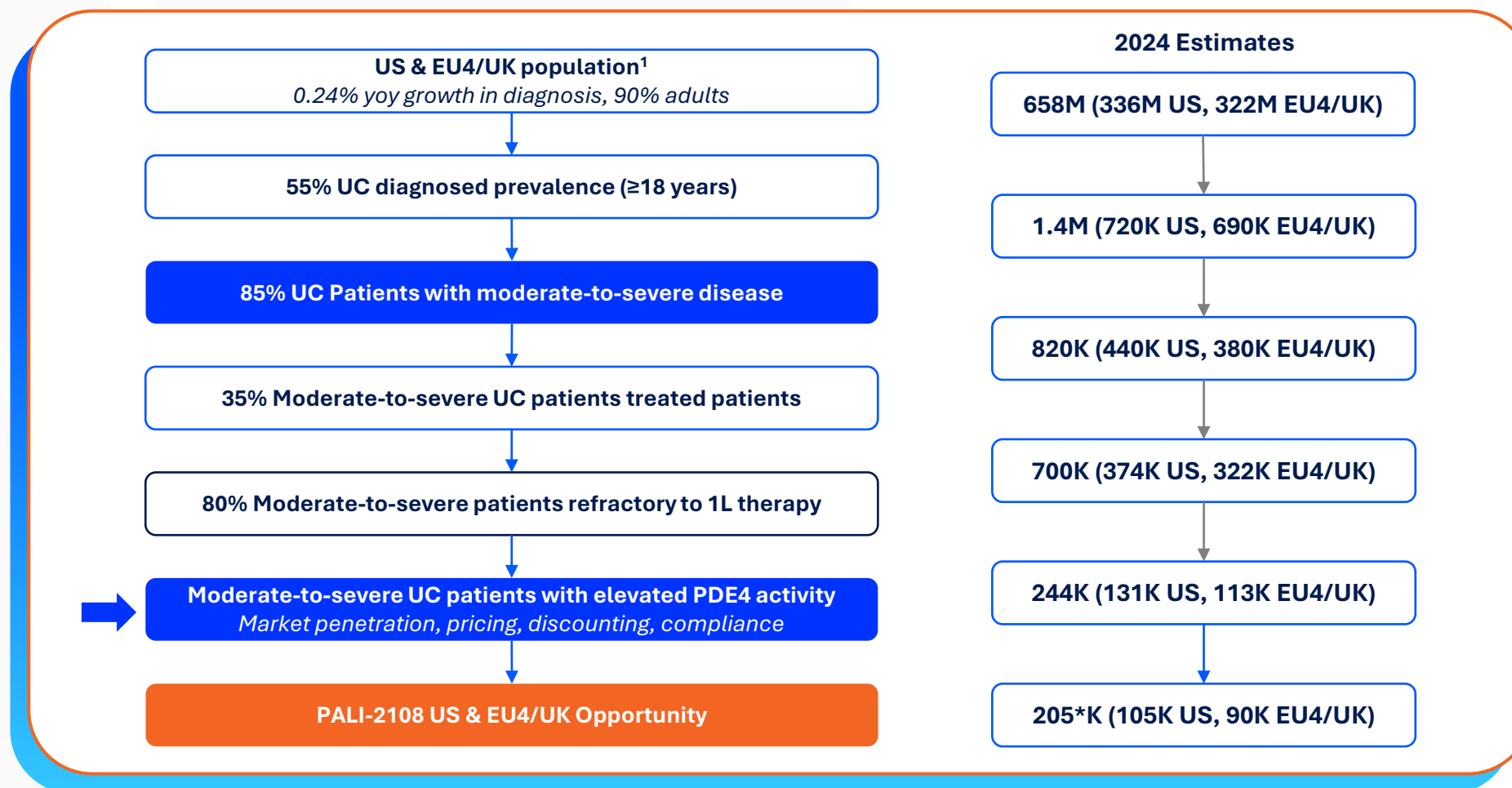
**Key market growth drivers coming primarily from oral drugs**

## Emergence of Oral Tx

- Oral options Rinvog 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

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



# Ulcerative Colitis: A Significant Opportunity

Strong rationale for developing a PDE4 inhibitor with a precision-medicine approach in moderate-to-severe ulcerative colitis (UC), with significant unmet need for new therapies and approaches for predicting patient response

**35%+**

refractory to 1L biologics

**Up to ~\$15B**

total US annual economic burden

**~70-80%**

of UC patients overexpress PDE4

**>\$2.7B**

worldwide revenue opportunity

## Unmet Need

- Patients experience **disease burden on all domains** relative to the US general population
- Current treatment options have **safety concerns and limited efficacy – remission rates ~16% (PBO adjusted)**
- **30-40% of patients fail** to respond adequately to first-line biologics therapy

## PDE4 Precision Medicine

- ~70-80% of patients express PDE4 in colon tissue, which **propagates inflammation and immune cell infiltration into inflamed tissues**
- PDE4 inhibitors have potent **anti-inflammatory capabilities** and anti-fibrotic effects, with a relatively benign safety profile
- **Limited ability to stratify patients/tailor treatment** is amongst the chief unmet needs identified by physicians

## Market Opportunity

- UC market forecast to grow to nearly \$10B by 2028, driven by growth of oral therapies
- Significant addressable population given epidemiology and refractory patient segment
- **Clear precedent for premium pricing in US, with most therapies priced \$70-100K/year, before discounting**

# Leveraging Commercially Proven PDE4

How We Compare to Systemic PDE4 inhibitors Currently Approved for the Treatment of COPD, Plaque Psoriasis and Psoriatic Arthritis

## Key OTEZLA® (Apremilast) Stats

### Systemically Active

Dose-limiting side effects include:

- Nausea
- Headache
- Vomiting

TNF-Alpha at IC50 (key inflammatory marker):  
0.41 $\mu$ M

## PALI-2108 Comparison

### Locally Delivered and Active Prodrug

Lack of systemic exposure potentially eliminates concerns for CNS adverse events

Improved therapeutic window enables maximal PDE4 inhibition supporting higher cAMP tissue levels

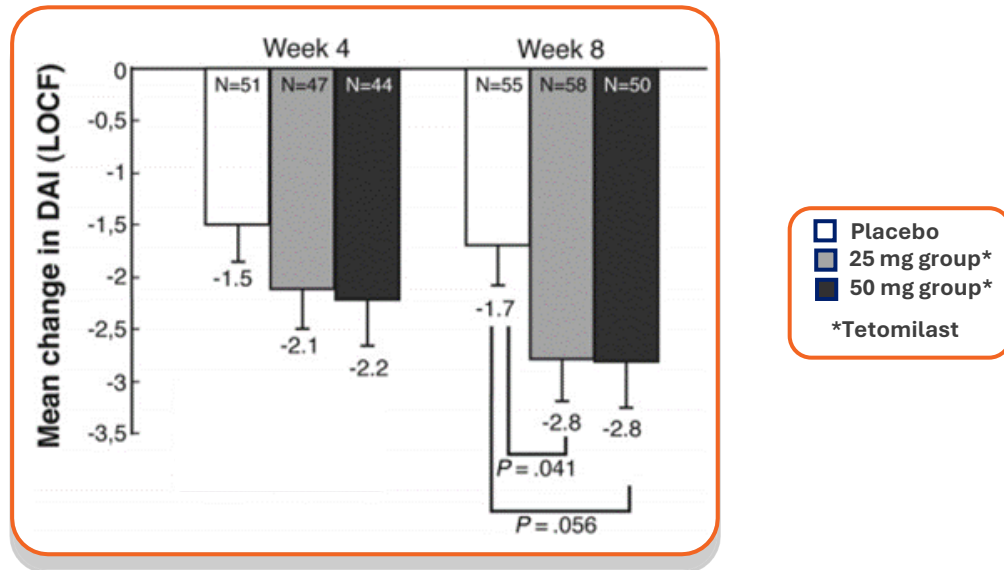
TNF-Alpha at IC50: 0.022 $\mu$ M (**~20x more potent**)

**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**

# Clear Systematic PDE4 Inhibitors Demonstrated Compelling Dose Response and Efficacy in Multiple Phase 2 UC Studies

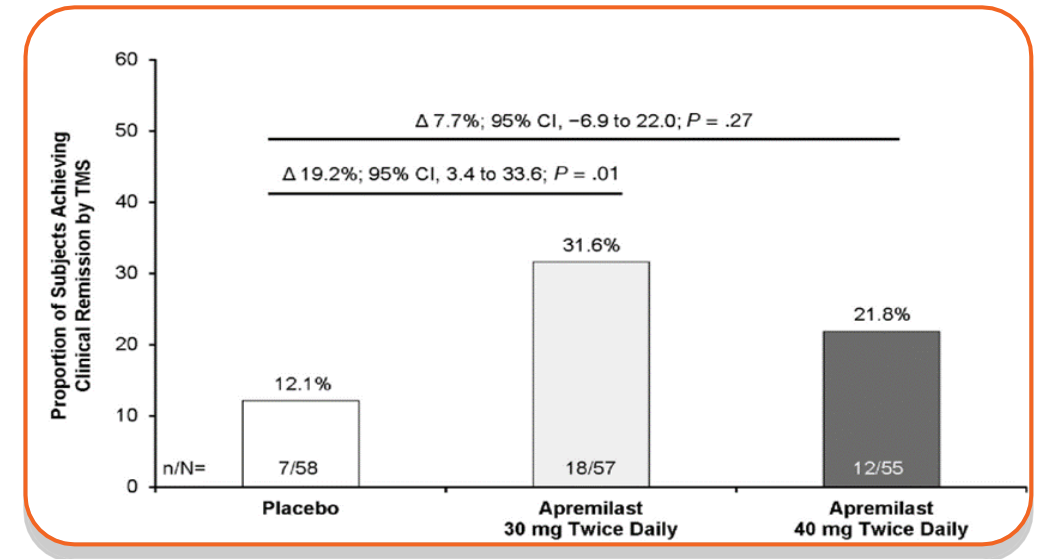
While Phase 2 Studies Validate PDE4 Target in UC, Adverse Events Limited Dose Selection and Complicated Potential Advancement in UC

## Mild-to-Moderate Active UC<sup>1</sup>



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

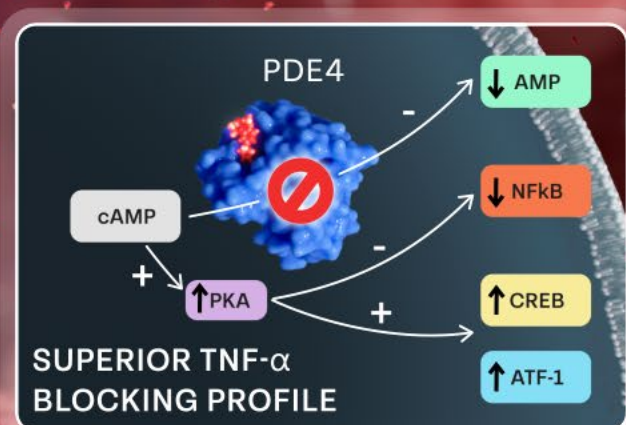
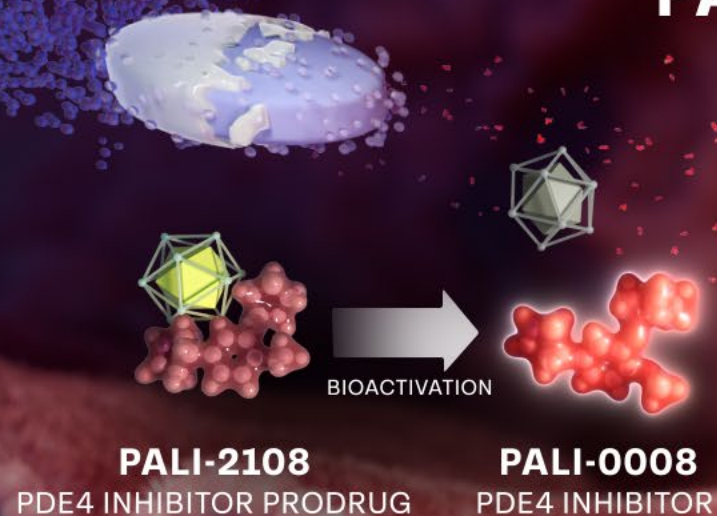
## Moderate-to-Severely Active UC<sup>2</sup>



Significant improvement in clinical remission rate of 19.2%  
Adverse Events (AEs) were most frequently headache and nausea

ORAL DELIVERY

# PALI-2108: Mechanism of Action



LOCAL ACTIVATION

↓ IL-13  
↓ IL-2  
↓ IFN-γ  
↓ IL-17  
↓ TNF-α  
↓ TGF-β

↑ IL-10

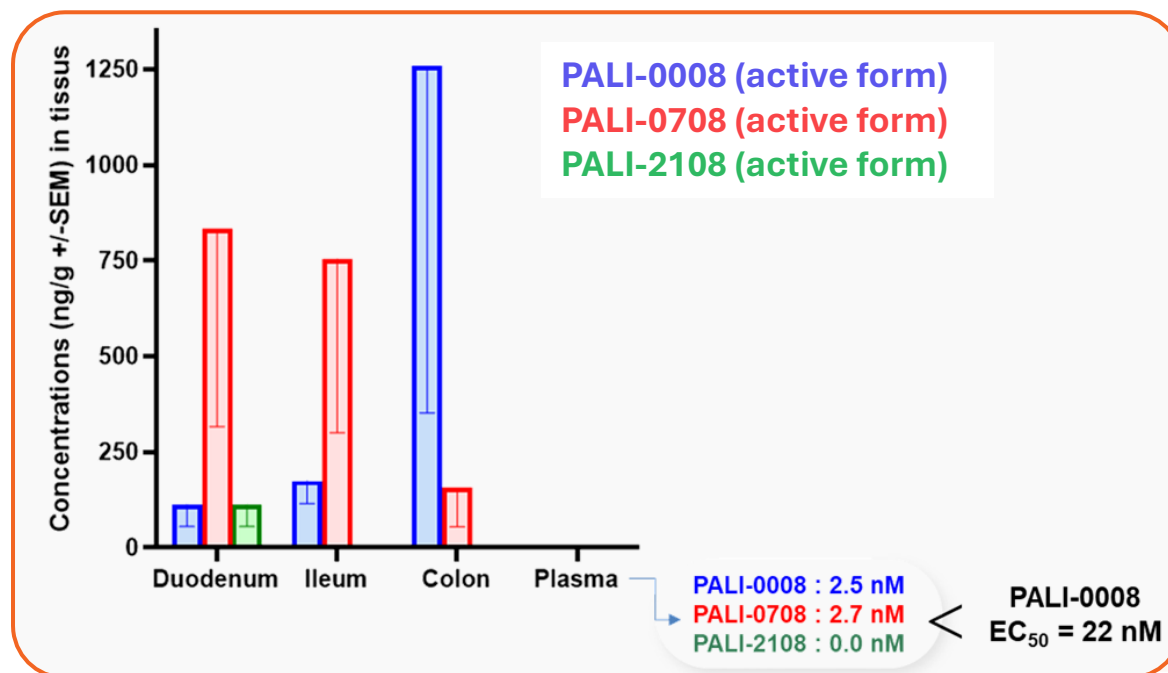
↓ TNF-α  
↓ TGF-β  
↓ IL-12  
↓ IFN-γ  
↓ chemokines

LIMITED SYSTEMIC  
BIOAVAILABILITY



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

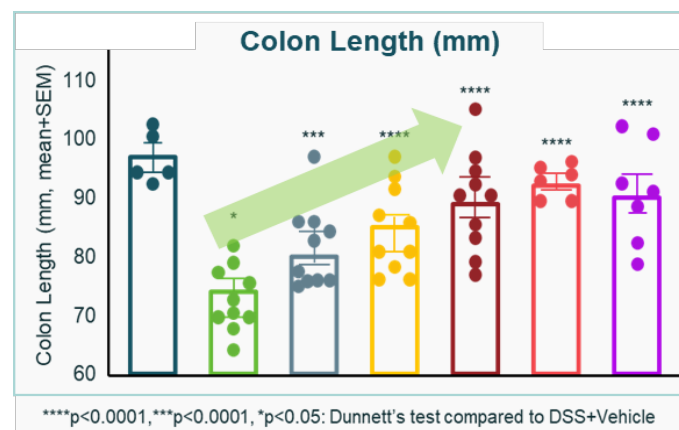
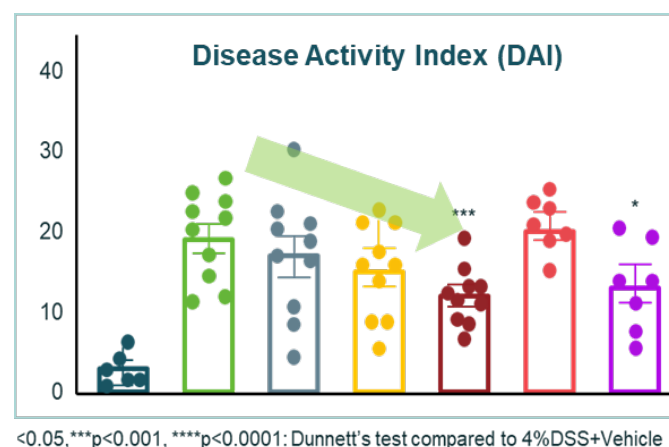
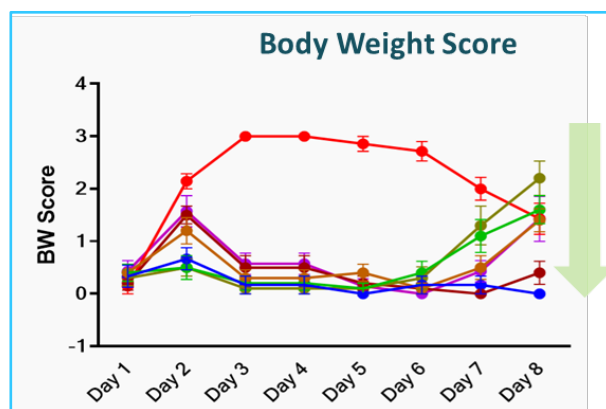
Lack of Plasma Activity is Believed to Mitigate CNS Side Effects, like Nausea, Which is Seen with Systemic PDE4 Inhibitors



- ✓ 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)

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

## Dose Dependent Efficacy Response in Two DSS Colitis Mouse Models



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

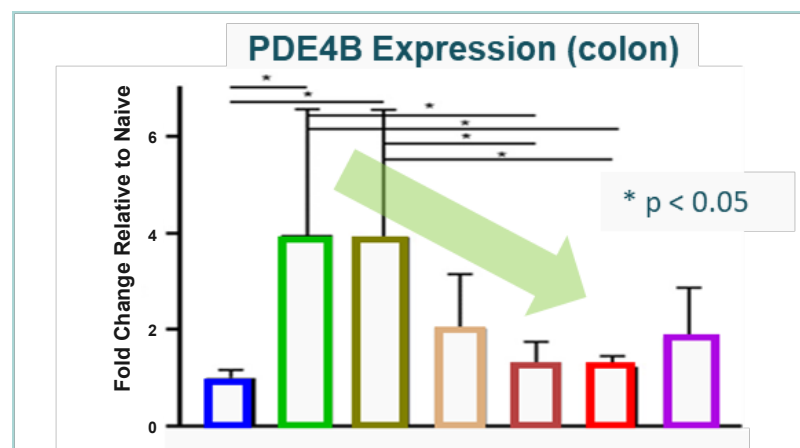
# Demonstrated Improved Efficacy Over Standard of Care and Systematic PDE4 Inhibitors in DSS Colitis Mouse Model

## Dose Dependent Efficacy Response in DSS Colitis Mouse Model

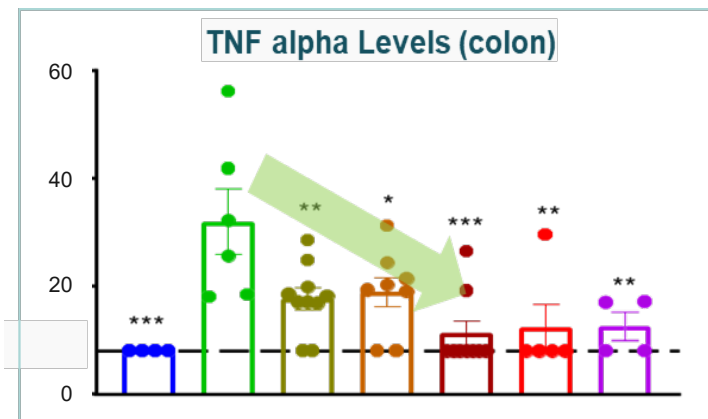
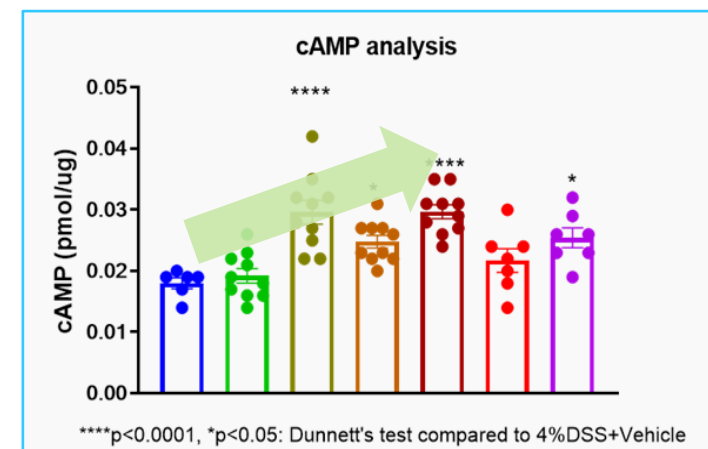
Colon tissue PDE4B Expression (mRNA) was reduced in response to PALI-2108 in a dose dependent manner together with local PDE4B inhibition and increased intracellular cAMP

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)



# 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

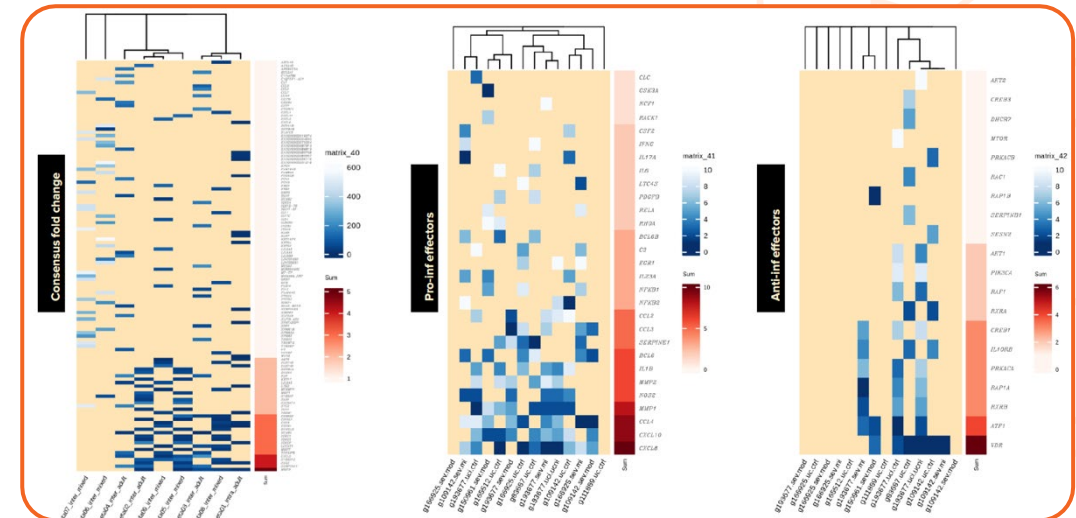
## Output

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

Developments Underscore Our Commitment to Leading the Field of Precision Medicine for UC and Driving Forward Personalized Treatment Strategies That May Transform Patient Care

## 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
- ✓ Robust finding supports the potential for an FDA-approved test
- ✓ Process may maximize efficacy of UC PDE4 prodrug therapeutic

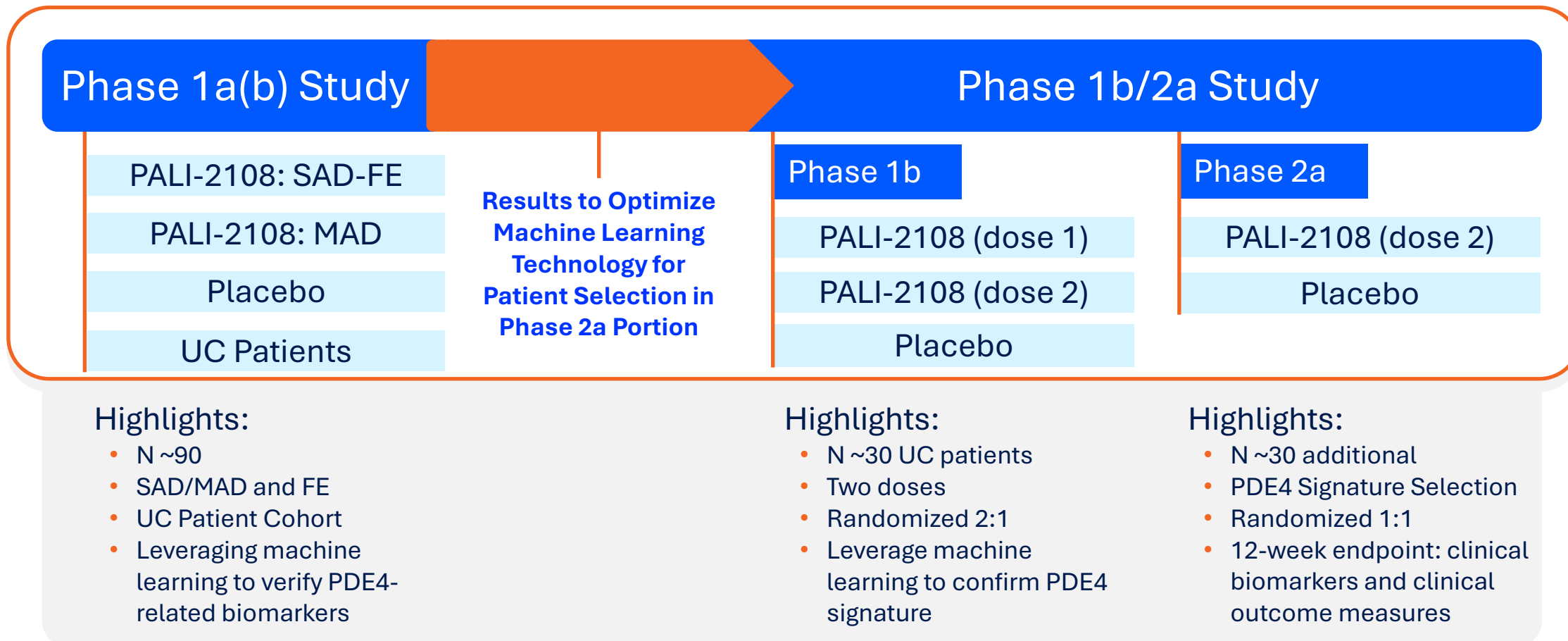
## Elevated PDE4B-Related Biomarkers:

- ✓ 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

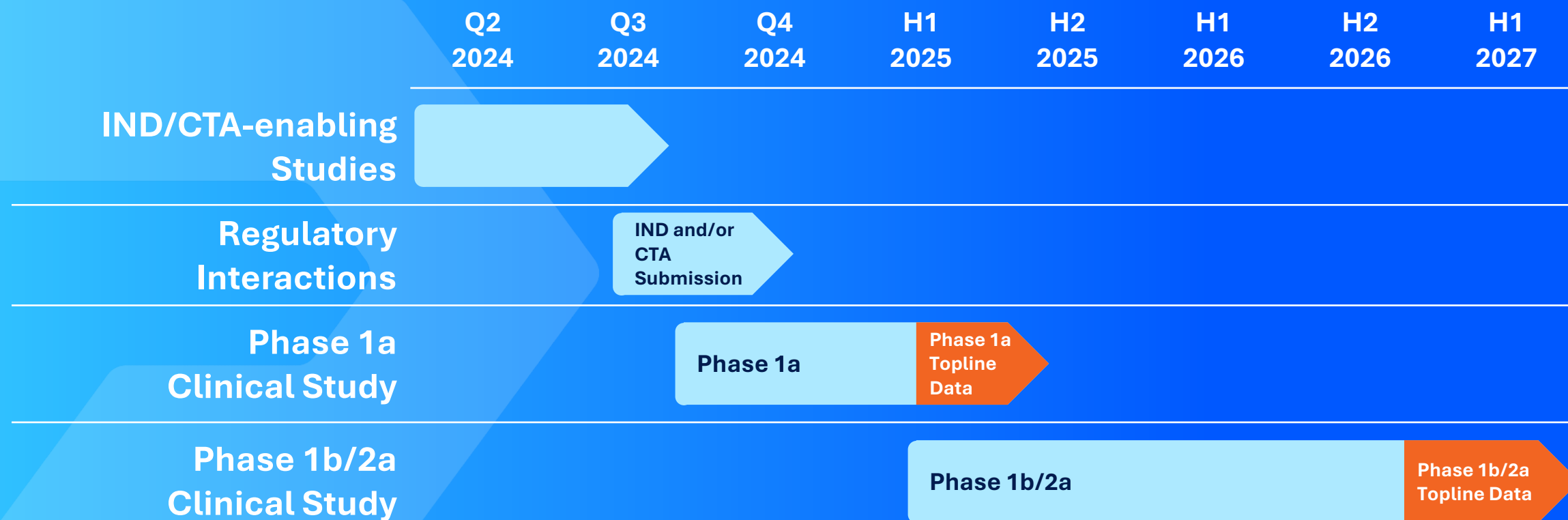
# Rapidly Advancing Toward Phase 1b/2a Study

Engaging with Key Opinion Leaders and FDA to Finalize Study Design

Targeting Moderate to Severe Ulcerative Colitis



# Development Plan Through Phase 1b/2a



# 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

- By 2028, the UC market is expected to reach \$10B, 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

- As of 2023, the global market for CD was estimated to be ~\$15B
  - + Emerging novel oral small molecules in CD are projected to generate at least \$2-3B at peak, commanding 7-10% market share
- The global IPF market is currently estimated to be ~\$4B
  - + In IPF, novel emerging oral small molecules are projected to garner up to 25% market share and generate \$1-2B revenue at peak

# Significant IP Portfolio Through 2042

- Composition of Matter  
Patent Family  
PCT/CA2012/050725
- 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 2042+
- FDA Regulatory Exclusivity  
Coverage for 8 Years
- Potential to File Additional  
Patents
  - Formulation patents
  - Methods of use
  - Platform

# 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**

# Financial Snapshot

Strong Financial Position with Cash to Fund Operations into First Quarter of 2025

**\$11.4M**

Cash

As of June 30, 2024

**~\$4.2M**

Market Cap<sup>1,2</sup>

**~65K**

Volume<sup>1</sup>

# Investment Summary

Strong Financial Position with Cash to Fund Operations into First Quarter of 2025

- Rapidly Advancing Towards First Patient Dosed in Phase 1 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
- Extensive IP Protection with CoM extending to 2042

**Building a Rich Pipeline in a Space that Has Seen Many High Value Acquisitions from Big Pharma, Even at Earlier Stages**

NASDAQ: PALI  
palisadebio.com



# palisadebio

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