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PALISADE BIO

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Advancing PALI-2108: Discovery to Strategic Positioning

Cristophe Mellon (Giiant Pharma) & Mitch Jones (Palisade Bio)

IBD Innovate
Boston, April 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.

Christophe Mellon, PhD

Chief Executive Officer, Giiant Pharma

Journey to PALI-2108

ORIGINALLY GT-0008

- Teams at Montreal Merck Campus
- 8+ years of development for COPD
- Highly selective to PDE4 enzyme
- 20x more potent than Apremilast
- Unsuitable properties to progress
- Merck closed Montreal site
- Chemist + Formulator found Giiant

REPURPOSED TOWARDS GI INDICATIONS

- IP created in 2021 by making a prodrug
- Money raised in tranches early 2021
- Proof of concepts experiments done
- Syndicate splits leading to slowing down
- US Crohn Colitis Foundation Support 2022
- Advances in key experiments
- License agreement with Palisade Bio 2023

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PALI-2108: Selectivity and Potency of its API

Against a panel of 209 enzymes and receptors PALI-0008 was found to be exclusively selective for PDE4

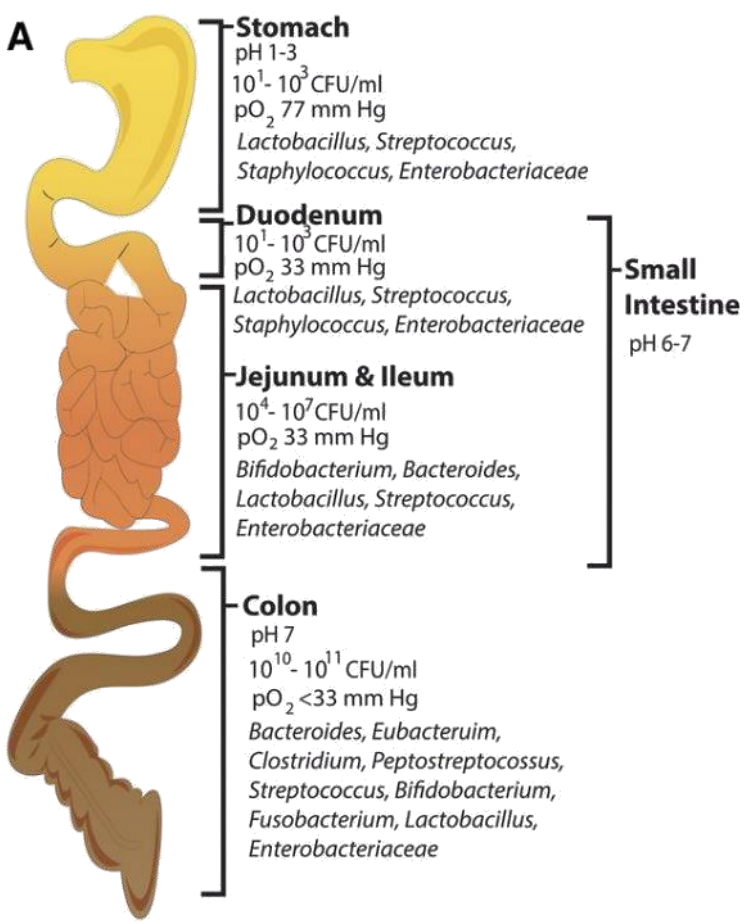
	PDEs Inhibition at 10 μM (%)								
	PDE1A	PDE3A	PDE5A1	PDE6C	PDE7A1	PDE8A1	PDE9A2	PDE10A1	PDE11A4
PALI-0008	0	4	0	0	0	16	1	0	0

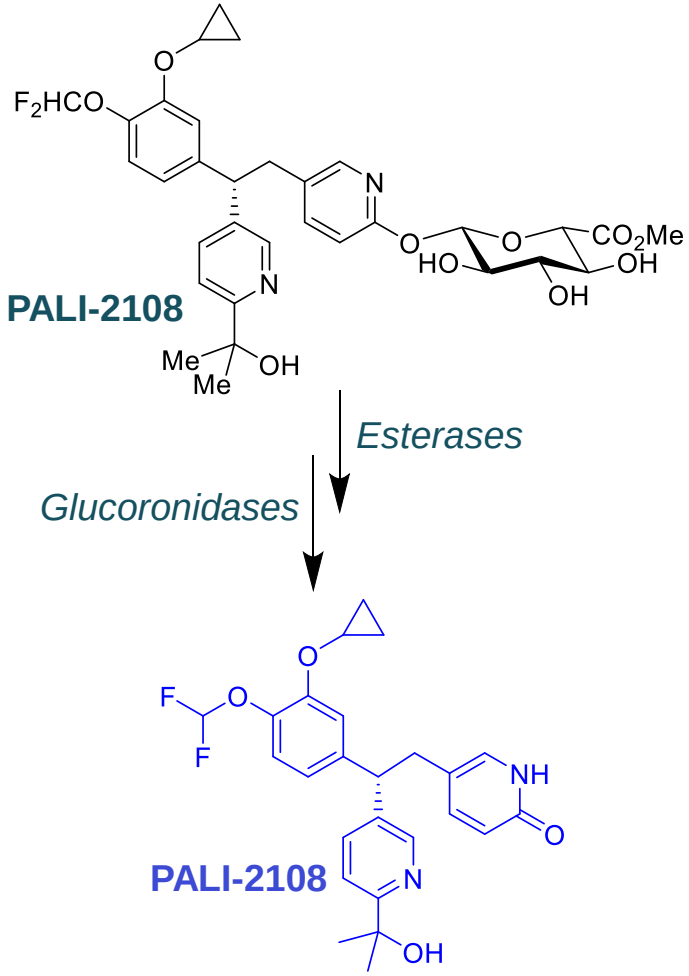
	PDE4 IC_{50} (nM)		
	PDE4A1	PDE4B1	PDE4D2
PALI-0008	1.5	1.4	0.40

	PDE4B IC_{50} (nM)	LPS-HWB TNF_{α} IC_{50} (nM)	Clinical Human Dose
Cilomilast	33	18 000	15 mg BID (failed)
Roflumilast	0.40	60	0.5 mg QD (COPD)
Apremilast	33	410	30 mg BID (Psoriasis, PA)
PALI-2108	**1.4**	**22**	N/A

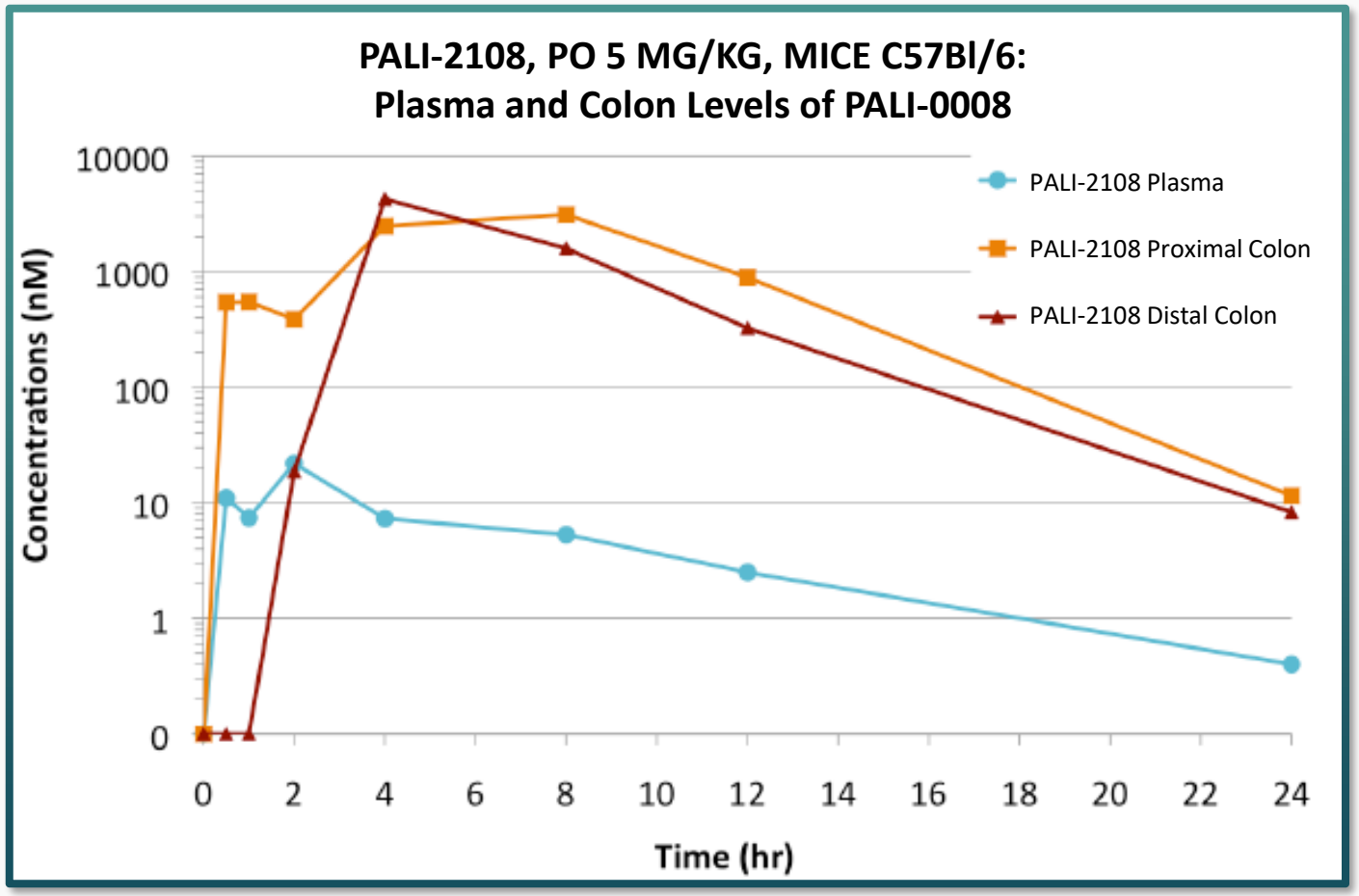
Concept: Precision Delivery Using Bacterial Gradient

We leverage connection between the bacterial metabolic capabilities along the GI tract to sugar structure to design prodrugs for ***site specific release***



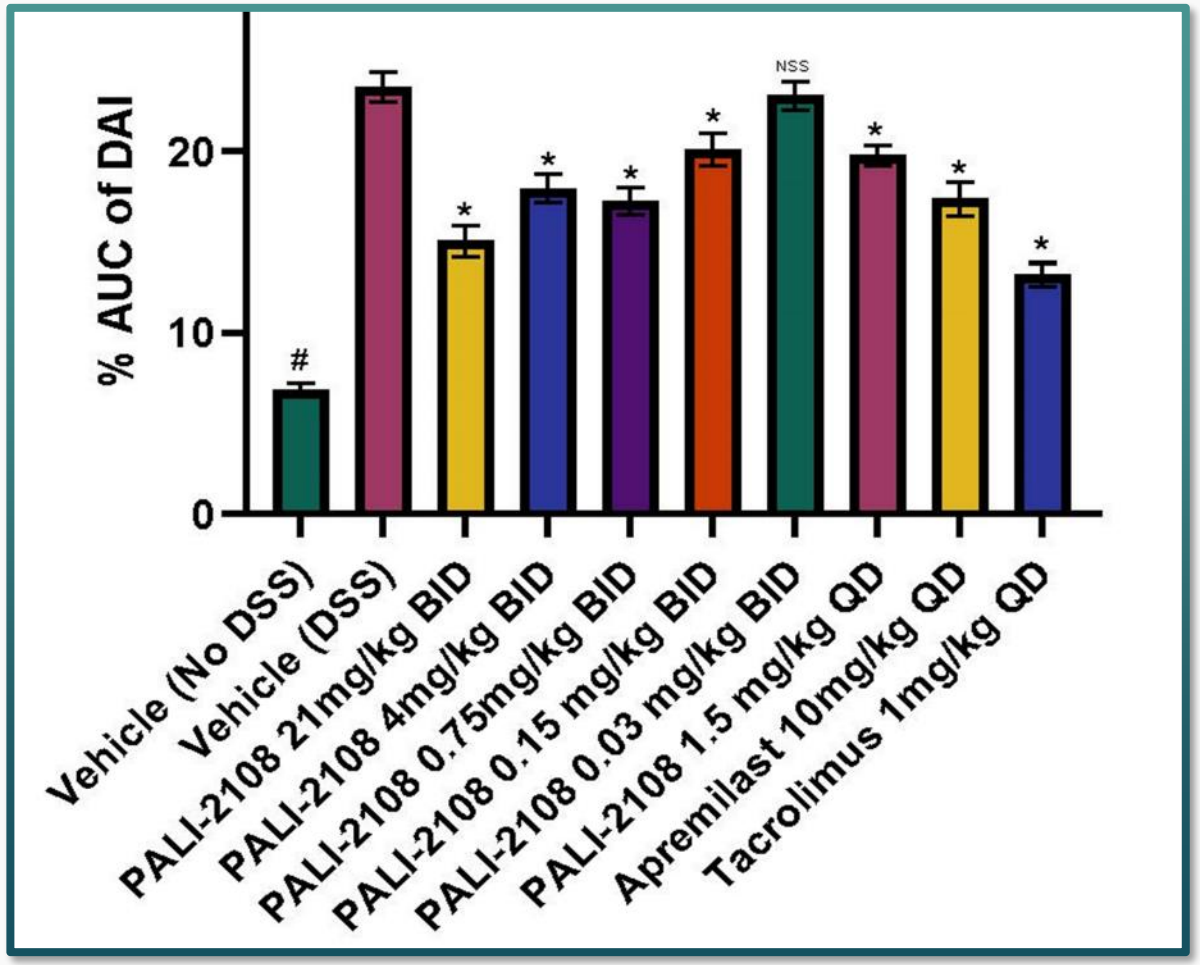


PALI-2108 Converts to PALI-0008 *In Vivo*, High in GI Tissues



PALI-0008 levels in healthy mice dosed PO with PALI-2108. PALI-0008 is favorably distributed to the colon as indicated by a colon/plasma AUC ratio of >200 and the bioavailability of PALI-0008 when delivered as the prodrug PALI-2108 is only 4%

Efficacy in 7-Day Colitis Model



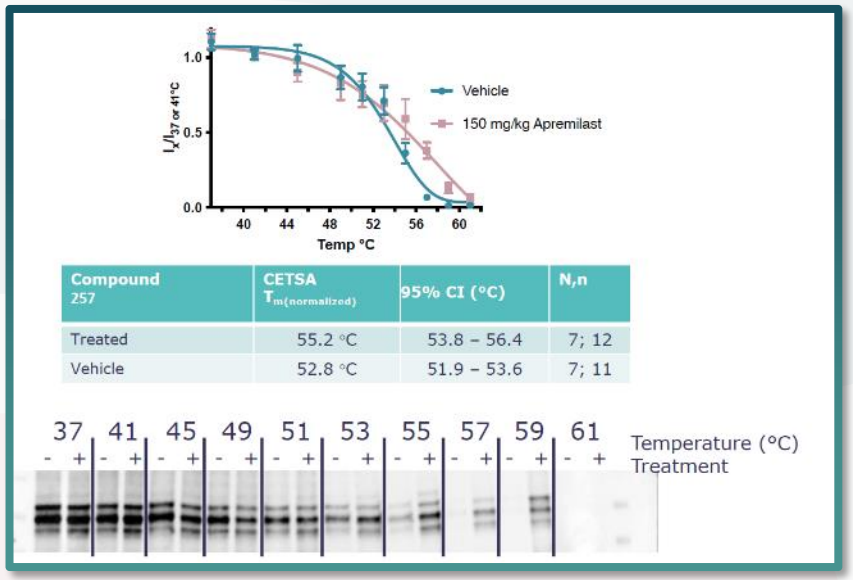
Cumulative Disease Activity Index (DAI) in DSS acute colitis mouse model showed that PALI-2108 at 21, 4 and 0.75 mg/kg BID as well as 1.5 mg/kg QD significantly decreased the mean DAI score compared to DSS control.

Superior to Apremilast which demonstrated efficacy in the clinic against Colitis.

In Vivo Target Engagement Demonstration in Mice

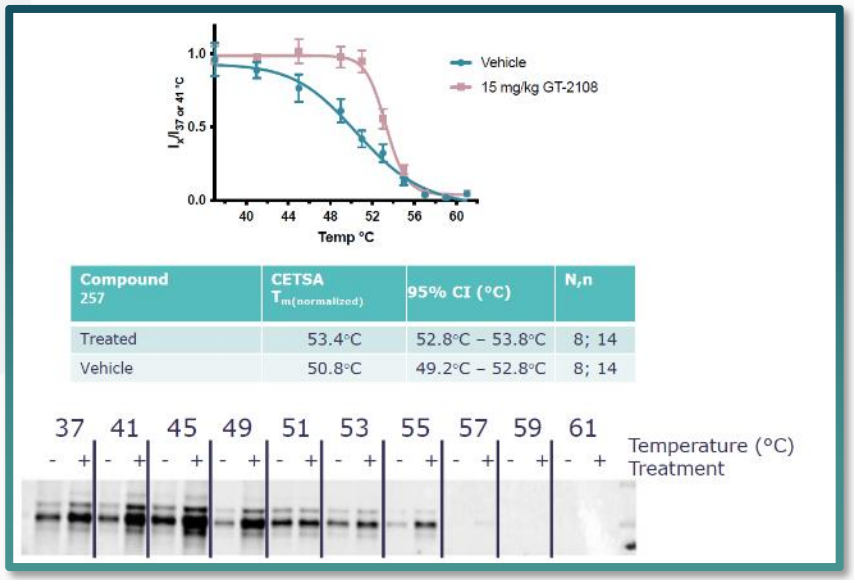
PO dosing of Apremilast (150 mg/kg, and PALI-2108 (15 mg/kg, 24 h) followed by Western on colon homogenates to demonstrate resistance to heat denaturation

Melt and shift curves for PDE4D of animals dosed with Apremilast



Compound 257	CETSA $T_{m(normalized)}$	95% CI (°C)	N,n
Treated	55.2 °C	53.8 – 56.4	7; 12
Vehicle	52.8 °C	51.9 – 53.6	7; 11

Melt and shift curves for PDE4D of animals dosed with PALI-2108



Compound 257	CETSA $T_{m(normalized)}$	95% CI (°C)	N,n
Treated	53.4°C	52.8°C – 53.8°C	8; 14
Vehicle	50.8°C	49.2°C – 52.8°C	8; 14

"A significant thermal stabilization could be observed for both treatment groups when compared to their vehicle control" Pelago.

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Prodrug Administration Curbs Side-Effects

PO administration of prodrug PALI-2108 at 43 mg/kg was well tolerated while PO administration of PALI-0008 resulted in emesis at 1 and 3 mg/kg, suggesting systemic toxicity only with administration of the active compound and not the prodrug

Species	Route of Admin	Compound	Dose (mpk)	Analysed Compound	C_{max} (nM)	Emesis
Dog	PO; QD	PALI-2108	43	PALI-2108	11	NO
				PALI-0008	28	
				PALI-0708	9	
Dog	PO; QD	PALI-0008	0.1	PALI-0008		NO
			0.3			NO
			1		139	Yes 2/3
			3		270	Yes 2/3

Mitch Jones, MD, PhD

Chief Medical Officer, Palisade Bio

Strategic Shift in Prioritization to Newly Licensed Assets for Treatment of Inflammatory Bowel Diseases

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We entered into an exclusive worldwide licensing agreement to develop and commercialize proprietary oral prodrug therapies that act locally targeting multi-billion-dollar IBD market

Company Secured Favorable Terms:

100% Exclusive Worldwide Rights	**Milestones Starting at Phase 1**	**Locally Acting PDE4 Inhibitor Developed by Merck Scientists**	**Prodrug Formulations to Locally Deliver the Active Ingredient**

Our Oral IBD Development Pipeline

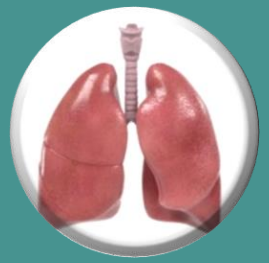
Oral Prodrug Therapies that Act Locally at Site of Disease

Program	Discovery	IND/CTA-Enabling	Phase 1	Phase 2	Phase 3	Highlights
PALI-2108	**Ulcerative Colitis**					Ongoing IND/CTA-enabling tox studies Rapidly advancing towards IND/CTA filing in 2024
PALI-1908	**Fibro Stenotic Crohn's Disease**					Lead optimization complete Significant overlap with PALI-2108 IND/CTA filing in 2024

Platform Technology Provides Opportunity to Grow Pipeline Organically and Target Additional High-Value Gastrointestinal Diseases

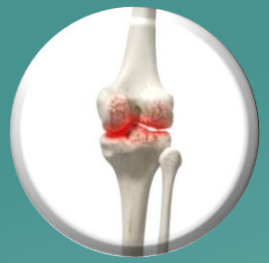
PDE4 is an Established Dual Acting (Pleiotropic) Anti-Inflammatory and Anti-Fibrotic Target

AstraZeneca



COPD (Roflumilast; AstraZeneca): Anti-fibrotic indications such as chronic obstructive pulmonary disease

AMGEN



Psoriasis and Psoriatic Arthritis (Apremilast; Amgen): Anti-inflammatory indications validated by approved drug Otezla

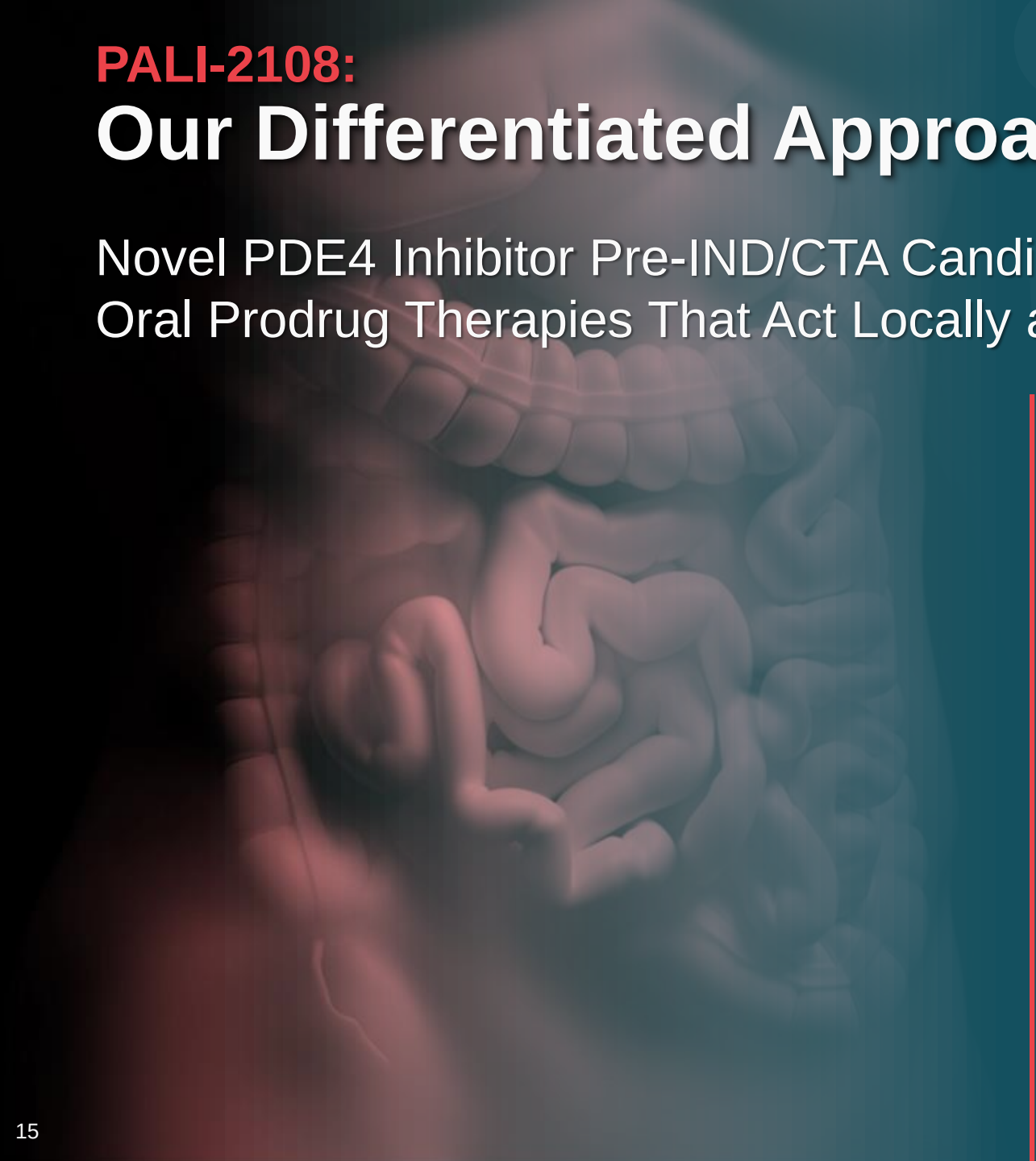
Boehringer Ingelheim

Idiopathic Pulmonary Fibrosis (BI 1015550; Boehringer Ingelheim): Under evaluation in global Phase 3 study (FIBRONEER) for idiopathic pulmonary fibrosis

PALI-2108:

Our Differentiated Approach to Ulcerative Colitis

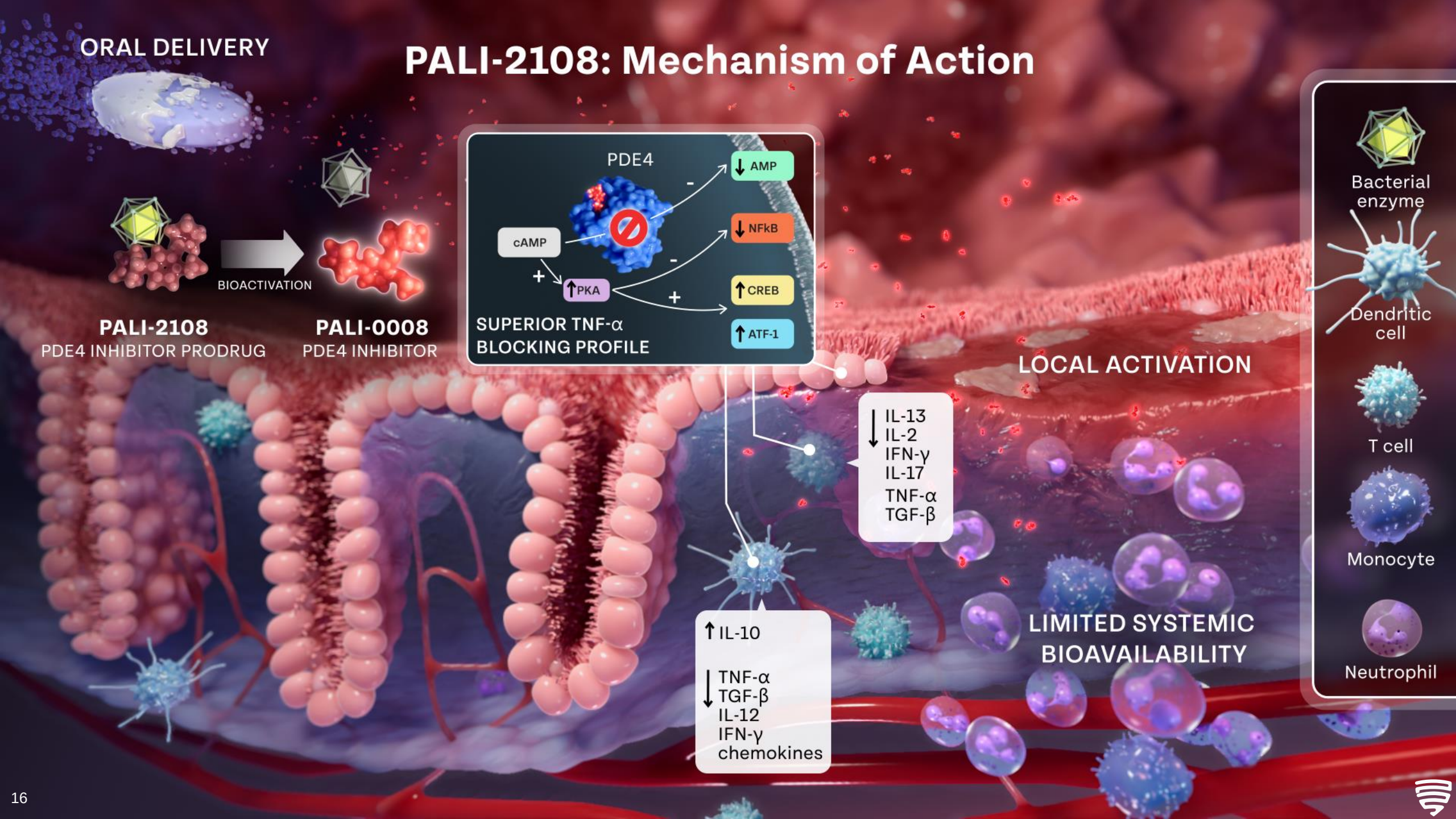
Novel PDE4 Inhibitor Pre-IND/CTA Candidate
Oral Prodrug Therapies That Act Locally at Site of Disease



KEY DIFFERENTIATION

- ✓ Oral Dosing
- ✓ Locally Active
- ✓ Limited Systemic Activity (improved safety)
- ✓ Superior Cytokine Blocking Profile
- ✓ Potential of Breakthrough Clinical Efficacy
- ✓ Potential for Precision Medicine Approach

PALI-2108: Mechanism of Action

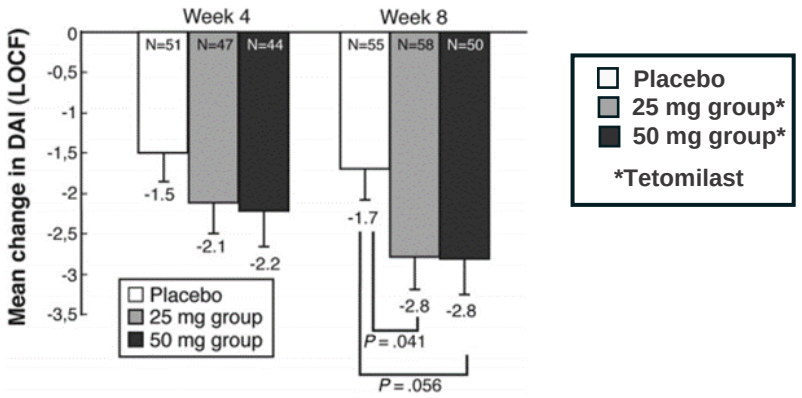


PALI-2108: Locally Active

Potential to overcome systemic PDE4 toxicities of nausea and vomiting

Compelling Efficacy Demonstrated in Multiple Phase 2 Studies with Systemic PDE4 Inhibitors but with Dose Limiting Toxicity

Mild-to-Moderate Active UC[1]

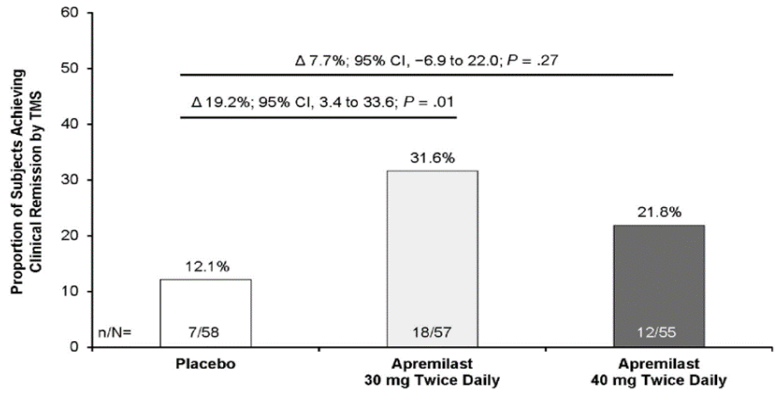


Significant improvement in disease activity index (DAI) at Week 8

Significant improvement in clinical remission rate

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

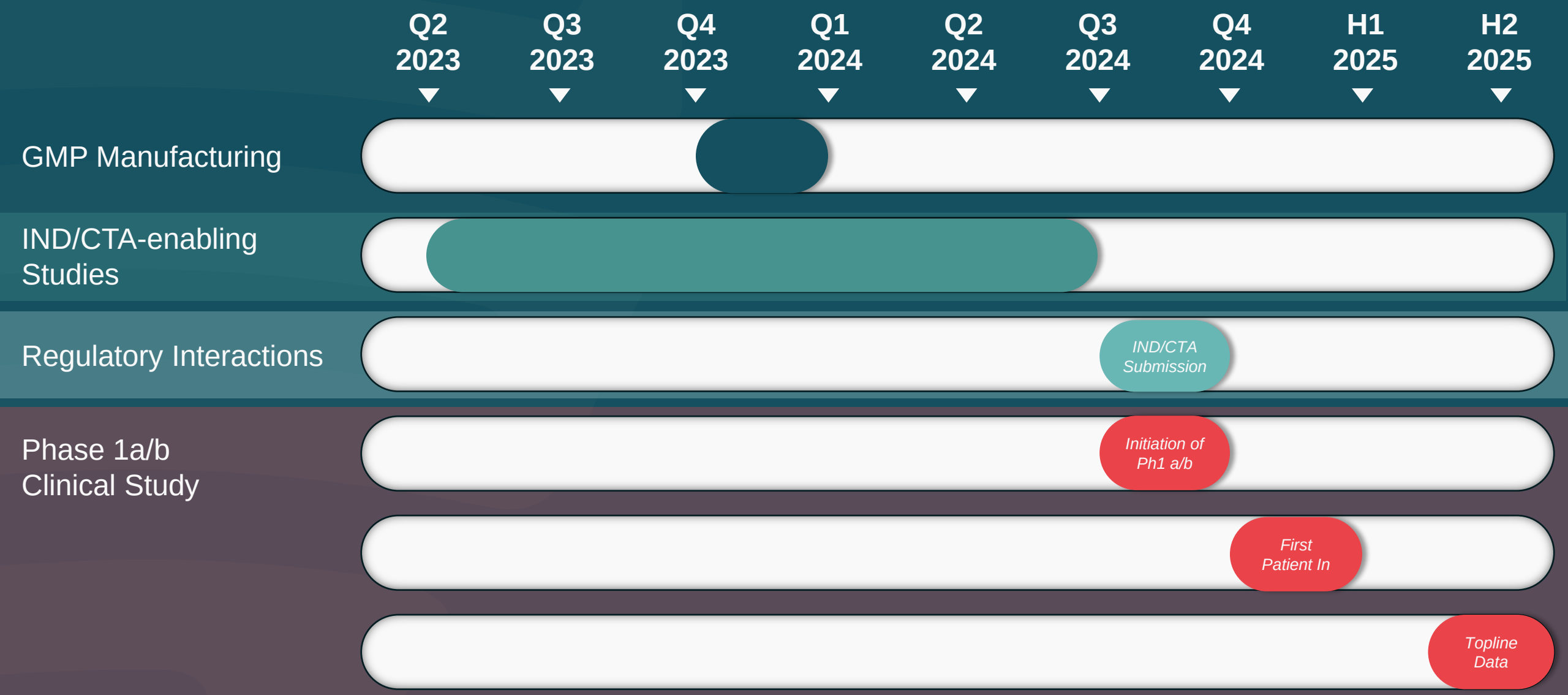
Moderate-to-Severely Active UC[2]



Significant improvement in clinical remission rate of 19.2%

Adverse Events (AEs) were most frequently headache and nausea

PALI-2108 Development Plan Through Phase 1a/b

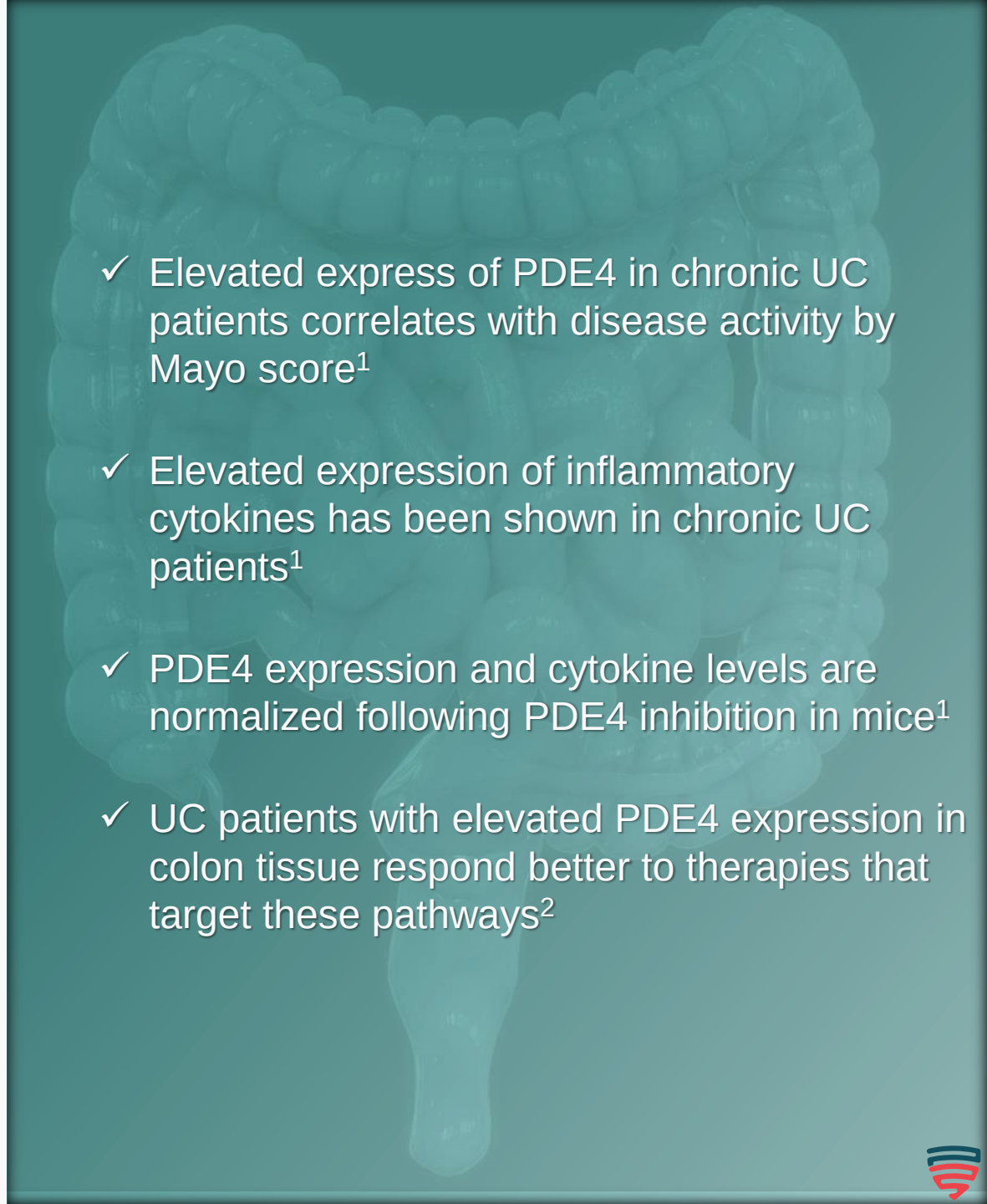


Precision Medicine Approach

Identifying Patients Likely to Respond to PDE4 Inhibitor Therapy in UC

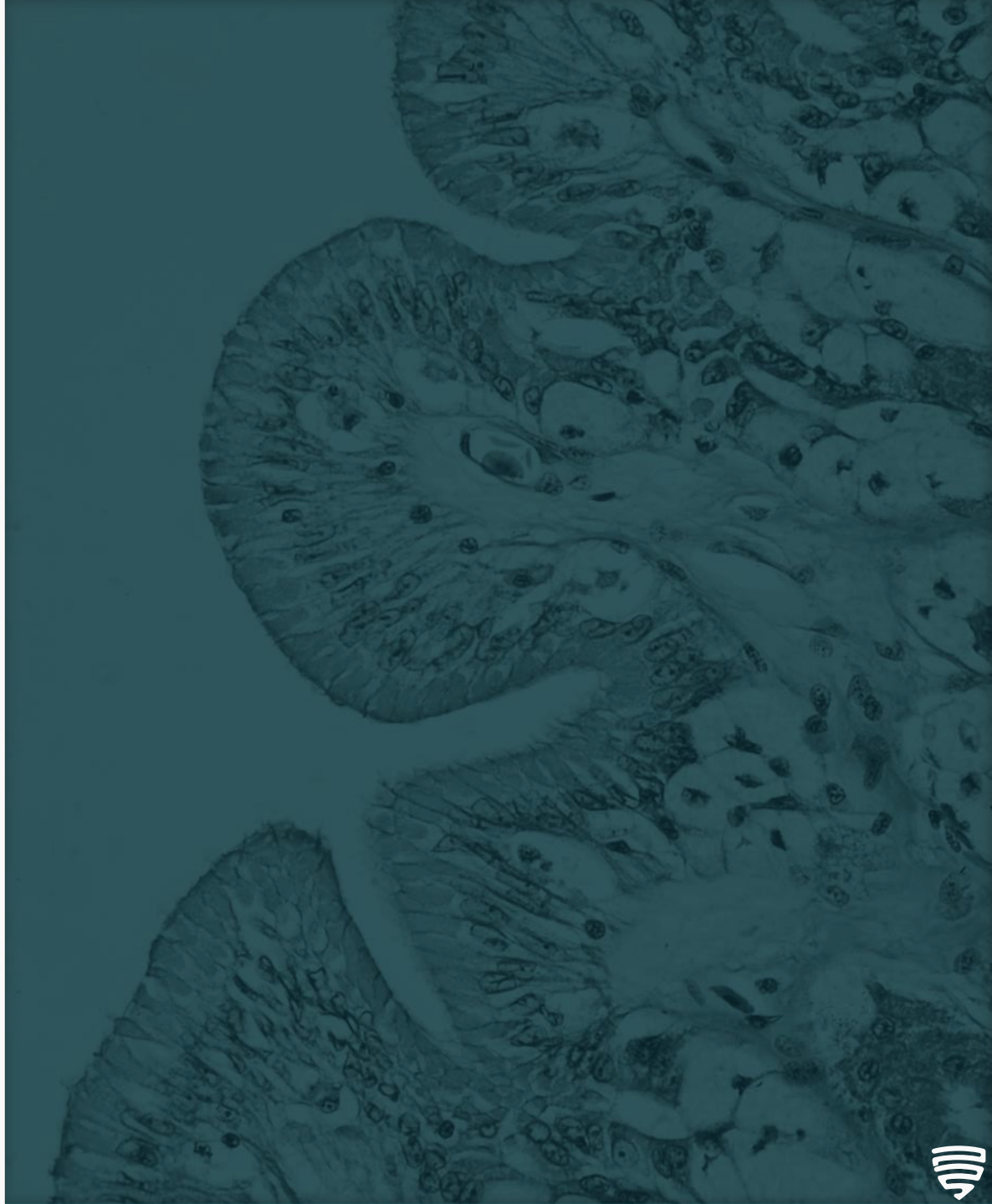
TRANSCRIPTOMICS

- **Expression-level changes from RNAseq of colon tissue**
- *Developed a Pipeline with 10 UC clinical studies including transcriptomics, clinical biomarkers, and outcomes data.*
- *Normalized the ten clinical datasets.*
- *Curated 7 optimal datasets, totaling 1600+ samples.*
- *Selected 7 datasets based on quality and completeness of data and sample sizes.*
- *Analyzed 7 datasets, totaling 1600 samples.*
- *Developed and used an in-house Pipeline for robust analysis.*
- *Included 2 curated PDE4 interventional studies.*
- *Identified downstream effectors that are PDE4-related.*



- ✓ Elevated express of PDE4 in chronic UC patients correlates with disease activity by Mayo score[1]
- ✓ Elevated expression of inflammatory cytokines has been shown in chronic UC patients[1]
- ✓ PDE4 expression and cytokine levels are normalized following PDE4 inhibition in mice[1]
- ✓ UC patients with elevated PDE4 expression in colon tissue respond better to therapies that target these pathways[2]

Thank you! Questions & Answers



The IBD Patient Journey

Patients and clinicians search out the most effective therapies with novel mechanism that are not systemically distributed to reduce side effects

__~10-35%__ of Patients Switch Due to Lack of Efficacy Typically Three to Six Months Following Treatment Indication

Only __50%__ of Patients Achieve Remission Within a Year; Often Requiring Several Different Treatments

Source: Crohn's & Colitis Foundation of America, The Facts About Inflammatory Bowel Diseases

ULCERATIVE COLITIS

~40-50%	Of patients have moderate-to-severely active disease
70%	Of patients with active disease will have active disease the next year
30%	Of patients in remission will have active disease the next year
40%	Of patients with long-lasting UC and extensive disease require colectomies

CROHN'S DISEASE

52%	Have uncontrolled active disease
70%	Of mod-severe patients cannot sustain remission on the same drug "patient churn"
15%	Require colectomies
~20-30%	Require surgery within 10 years of diagnosis

Current Standard-of-Care Therapies Have Limited Effectiveness

No Standard Regimen for Managing All IBD Patients
The Approach to Treatment Needs to Be Tailored for the Individual

CURRENT TREATMENT APPROACH

5-ASA is generally first line for ulcerative colitis but not as effective in Crohn's Disease

Corticosteroids: not for long-term use due to significant side effects

Immune-modulating therapies are considered second line for moderate-to-severely active disease

FACTORS THAT DETERMINE TREATMENT APPROACH

Disease severity

Anatomic location of disease

Previous response to medication

Side effects of medication

Comorbidities

Average **Clinical Remission Rate Only 16%** of Treated Patients After Induction Therapy

Ulcerative Colitis Competitive Landscape

Most Effective Therapies Have Black Box Warning, New Therapies Are Not as Effective

Drug	Company	Placebo-Adjusted Clinical Remission	Overall Remission Rate	Indication	FDA Approval	Route of Administration	Safety Considerations
Remicade® INFLIXIMAB	janssen	24% (ACT1)	38.8% (ACT1)	Moderate-to-severely active UC with inadequate response or intolerance to standard therapies	2005	Injectable	***BLACK BOX WARNING***
RINVOQ® upadacitinib	abbvie	21% (U-ACHIEVE)	26% (U-ACHIEVE)	Moderate-to-severely active UC with inadequate response to (TNF) blockers	2022	Oral	***BLACK BOX WARNING***
Entyvio® vedolizumab	Takeda	11.5% (GEMINI I)	16.9 (GEMIMI I)	Moderate-to-severely active UC with inadequate response to (TNF) blockers	2014	Injectable	Risk of PML
Skyrizi® risankizumab-rzaa	abbvie	14.1% (INSPIRE)	20.3% (INSPIRE)	Moderate-to-severely active UC with inadequate response to conventional or biologic	2023	Injectable	URTI, headache, fatigue
ZEPOSIA® (ozanimod) 0.92 mg capsules	Bristol Myers Squibb	10.3% (TOUCHSTONE)	16.3% (TOUCHSTONE)	Moderate-to-severely active UC	2021	Oral	URTI, UTI, back pain, liver enzymes
XELJANZ® (tofacitinib)	Pfizer	10.3% (OCTAVE 1)	18.5% (OCTAVE 1)	Moderate-to-severely active UC with inadequate response to (TNF) blockers	2018	Oral	***BLACK BOX WARNING***
HUMIRA® adalimumab	abbvie	9.3% (ULTRA I)	18.5% (ULTRA I)	Moderate-to-severely active UC with inadequate response or intolerance to standard therapies	2012	Injectable	***BLACK BOX WARNING***

Potential Future Ulcerative Colitis Competitive Landscape

UC Market is Expected to Evolve By 2028 with New Therapies

We Believe PALI-2108 Has a Significant Advantage Over Current Projections and has Potential to Take Significant Market Share

Drug	Company	Placebo-Adjusted Clinical Remission	Overall Remission Rate	Indication	FDA Approval	Route of Administration	Safety Considerations
Velsipity™ (etrasimod) tablets	abbvie	11% (ELEVATE UC 12)	26% (ELEVATE UC 12)	Moderate-to-severely active UC	2023	Oral	Elevated LFTs and headache
Tremfya® (guselkumab)	Johnson&Johnson	9.5% (QUASAR 1)	25.7% (QUASAR 1)	Moderate-to-severely active UC	Phase 3	Injectable	URTI, headache, infection
Stelara® (ustekinumab)	Johnson&Johnson	19.8% (UNIFI)	43.8% (UNIFI)	Moderate-to-severely active UC	2022	Injectable	URTI, headache, infection
omvoh™ (mirikizumab-mrkz) 300 mg/15 mL infusion 100 mg/mL injection	Lilly	15% (LUCENT)	24% (LUCENT)	Moderate-to-severely active UC	2023	Injectable	URTI, headache, infection

Big Pharma is Active in IBD and Spending Big Dollars for Earlier Stage Programs

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

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Cleveland Clinic