DDW2024 Digestive Disease Week®

MAY 18-21, 2024 | WASHINGTON, D.C.

EXHIBIT DATES: MAY 19-21, 2024

LOCAL BIOACTIVATION AND EFFICACY OF PALI-2108: A PROMISING PDE4 INHIBITOR PRODRUG FOR ULCERATIVE COLITIS TREATMENT

Authors: Joie Bernard[1] PhD, Christophe Mellon[2] PhD, Maxime Ranger[2], Bernard Cote[2] PhD, and Mitchell Jones[1] MD PhD

1. Palisade Bio, Carlsbad, CA. United States; 2. Giiant Pharma, Montreal, Quebec.

PURPOSE / OBJECTIVES

Phosphodiesterase-4 (PDE4) is a key enzyme in cAMP hydrolysis and its inhibition elevates intracellular cAMP, downregulates inflammatory cytokines, and reduces the expression of cell adhesion molecules, thereby preventing local infiltration and activation of inflammatory cells. Approved PDE4 inhibitors include roflumilast for use in chronic obstructive pulmonary disease (COPD) and apremilast for psoriasis/psoriatic arthritis. Despite the development of subtype specific PDE4 inhibitors, oral administration and systemic distribution has resulted in central nervous system (CNS) toxicity, such as headaches, nausea or vomiting, leading to discontinuation of therapy and limiting potential efficacy. Targeted and better-tolerated oral PDE4 inhibitors hence remain an unmet need in IBD.

We investigated PALI-2108, an orally delivered, intestinally activated PDE4 inhibitor prodrug designed with a D-glucoronic sugar moiety. PALI-2108 minimizes systemic exposure until cleaved by the colonic bacterium enzyme β-glucuronidase, producing active drug PALI-0008, therefore reducing potential CNS toxicity. PALI-2108 proposed mechanism of action is outlined in figure 7.

MATERIAL & METHODS

First, a classic cellular thermal shift assay (CETSA) was developed to assess on-target PDE4 binding within colon tissue homogenates dosed with apremilast, PALI-2108 or Vehicle and detecting changes in thermal stability (Figure 2 and 3).

To test the efficacy of PALI-2108 across a range of doses, we utilized an acute colitis model in mice with disease induction from 4% DSS in drinking water administered from D1 to D8. Mice were treated BID with PALI-2108 at 20, 40, 80 mg/kg/dose, while cyclosporin A and apremilast were administered at 40, and 12.5 mg/kg/dose respectively (Figure 1). DSS-induced colitis was assessed by measuring in-life endpoints including Body Weight score, Stool Consistency score and Fecal Blood score from Day 1 through Day 8. On days of dosing, evaluations were performed 1 to 2 hours after dosing. Scoring for overall disease state (Disease Activity Score) was measured by pooling the three in-life scores. DAI was assessed on Days 1 to 8 (Figure 4).

Finally, a single PO dose of prodrug PALI-2108 at 43 mg/kg and active PALI-0008 at 0.1,0.3,1, and 3 mg/kg was administered to dogs and monitored for key clinical adverse events including emesis (Figure 6).

RESULTS

Figure 1. DSS study treatment groups and dosing schedule.

Group No.	Treatment	Test Items Dosing: Dose Level mg/kg/day	Dose Level mg/kg/dose	Dose volume mL/kg[a]	Concentration mg/mL	Route/ Frequency
1	Non-treatment naive	-	-	-	-	-
2	DSS + Vehicle	0	0	10	0	PO/ BID
3	DSS + PALI-2108 Low dose	40	20	10	2	PO/ BID
4	DSS + PALI-2108 Mid Dose	80	40	10	4	PO/ BID
5	DSS + PALI-2108 High Dose	160	80	10	8	PO/ BID
6	DSS + Cyclosporin A	80	40	10	4	PO/ BID
7	DSS + Apremilast	25	12.5	10	1.25	PO/ BID

RESULTS

Figure 2. Diagram depicting how CETSA assesses on-target binding by detecting changes in protein thermal stability upon ligand binding.

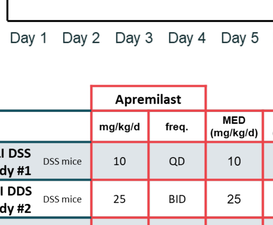


Figure 3. Mouse colon homogenate with 10 µM of apremilast resulted in a stable assay for PDE4D where the target protein was thermally stabilized by the compound. Target engagement was validated in tissue from animals that were in vivo dosed with apremilast, PALI-2108 or Vehicle controls. For both compounds a thermal stabilization effect on PDE4 was observed confirming target engagement in vivo.

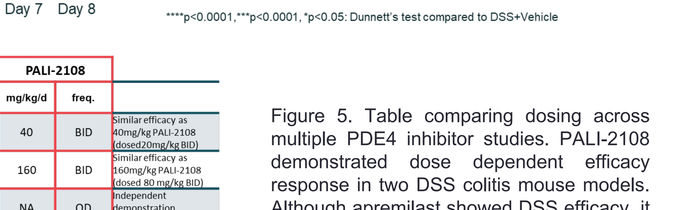


Figure 4. In the DSS acute colitis mouse model, PALI-2108 significantly prevented, in dose dependent manner, the colon length reduction on Day 8, showed dose dependent efficacy on body weight score, disease activity index (DAI) score and AUC of DAI from day 1 to 8.

		Apremilast mg/kg/d	Apremilast freq.	MED (mg/kg/d)	HED (mg/kg)	PALI-2108 mg/kg/d	PALI-2108 freq.	
PALI DSS Study #1	DSS mice	10	QD	10	0.81	40	BID	Similar efficacy as 40mg/kg PALI-2108 (dosed20mg/kg BID)
PALI DDS Study #2	DSS mice	25	BID	25	2.03	160	BID	Similar efficacy as 160mg/kg PALI-2108 (dosed 80 mg/kg BID)
Li et al.	DSS mice	25	QD	25	2.03	NA	QD	Independent demonstration of efficacy
Danese et al.	Phase 2	60	BID	12.3	1.00	NA	BID	Clinical remission >31%
Danese et al.	Phase 2	80	BID	16.4	1.33	NA	BID	AEs leading to discontinuation and loss of efficacy

Conversions based on FDA guidance for FIH studies:
Mouse wt = 0.03 | Human wt = 60 | MED to HED = 12.3

Figure 5. Table comparing dosing across multiple PDE4 inhibitor studies. PALI-2108 demonstrated dose dependent efficacy response in two DSS colitis mouse models. Although apremilast showed DSS efficacy, it was at a dose that translates to an intolerable human dose in UC patients, with dose limiting toxicities, including nausea (Danese et al).

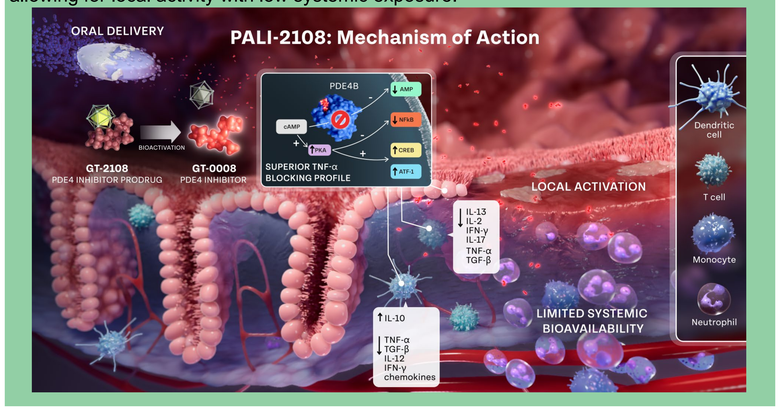
RESULTS

Figure 6. A single PO dose of prodrug PALI-2108 at 43 mg/kg and active PALI-0008 at 0.1,0.3,1, and 3 mg/kg was administered to dogs and monitored for key clinical adverse events including emesis. PALI-2108 was well tolerated, while 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 3/3

PALI-2108 MECHANISM OF ACTION

Figure 7. PDE4 is highly expressed in immune and proinflammatory cells. The inhibition of PDE4 prevents transcription factors, such as NF-κB, from inducing the expression of various proinflammatory mediators involved in IBD, such as TNF-α and various interleukins. The PDE4 inhibitor PALI-2108 is orally delivered and colon activated allowing for local activity with low systemic exposure.



SUMMARY / CONCLUSION

Novel orally delivered, intestinally activated PDE4 inhibitor prodrug, PALI-2108:

- Similar target engagement to PDE4 inhibitor, apremilast
- Dose-dependent efficacy in a mouse UC model, including stool consistency score, fecal blood score, and overall DAI score
- Significantly prevented, in dose dependent manner, colon length reduction on Day 8
- No clinical signs were associated with twice daily dosing of PALI-2108 at any of the doses and showed comparable efficacy to apremilast at a dose that translates to a know intolerable human dose
- No systemic toxicity in dog and large therapeutic window due to local activation

PALI-2108 is in development for moderate-to-severe UC and is advancing toward regulatory filing for first-in-human studies.

Joie Bernard PhD
Palisade Bio
Carlsbad, CA
joie.bernard@palisadebio.com