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Summary

PALI-2108, A NOVEL, NEXT-GENERATION ORAL ONCE-DAILY PDE4 INHIBITOR EXHIBITS GUT-TARGETED DRUG EXPOSURE AND FAVORABLE SAFETY AND TOLERABILITY IN INFLAMMATORY BOWEL DISEASE

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PALI-2108, an oral once-daily PDE4 inhibitor prodrug with delayed ileocolonic bioactivation, demonstrated favorable safety, sustained tissue exposure, and early clinical activity in a Phase 1a/1b study of patients with inflammatory bowel disease.

KEY POINTS

- In 76 participants (healthy volunteers and patients with moderate-to-severe UC or fibrostenosing Crohn's disease), PALI-2108 showed no serious adverse events, no discontinuations, and predominantly mild, transient adverse events consistent with the PDE4 inhibitor class.
- All UC patients achieved clinical response with reductions in modified Mayo score and multiple histologic indices, and 40% achieved clinical remission after 7 days of treatment.
- PALI-2108 is engineered for enteric dissolution in the small intestine followed by microbiome-mediated ileocolonic bioactivation to PALI-0008, resulting in delayed plasma Tmax, sustained colonic tissue exposure, and controlled systemic peak concentrations.
- Tissue concentrations in the ileum and colon were approximately seven-fold higher than plasma, and PALI-2108 achieved the highest IC90-normalized daily exposure compared with other PDE4 inhibitors evaluated at 30 mg once daily.
- Pharmacodynamic effects in UC patients included increased tissue cyclic AMP and decreased PDE4B expression, tissue lymphocyte content, and fecal calprotectin, with tolerability improved by dose titration and food intake.

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