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Linerixibat and the Future of Pruritus Therapy in Primary Biliary Cholangitis

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Abstract: Cholestatic pruritus significantly impairs quality of life in Primary Biliary Cholangitis (PBS) and is often refractory to ursodeoxycholic acid. This review explores Linerixibat, a gut-restricted ileal bile acid transporter (IBAT) inhibitor, as a targeted therapy for PBC-associated pruritus. By selectively blocking IBAT in the terminal ileum, Linerixibat reduces systemic bile acid (BA) accumulation—a key driver of itch via MAS-related G protein-coupled receptor X4 (MRGPRX4) activation on sensory neurons. Clinical trials demonstrate Linerixibat's efficacy in lowering serum BAs and alleviating pruritus, with a safety profile characterized primarily by manageable, mechanism-driven diarrhea. Unlike IBAT inhibitors developed for paediatric cholestatic disorders (e.g., odevixibat for PFIC), Linerixibat is optimized for adult PBC. Future therapeutic strategies may involve combining Linerixibat with agents targeting BA homeostasis (e.g., dual FXR/TRG5 agonists like INT-767) or pruritus signaling (e.g., MRGPRX4 antagonists). Ongoing Phase III trials will further define its long-term role in PBC management.

Keywords: Linerixibat; Primary biliary cholangitis; Cholestatic pruritus; Ileal Bile Acid Transporter (IBAT) inhibitor; Bile acids; MRGPRX4; Targeted therapy

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1. Introduction

PBC is an autoimmune liver disease characterised by progressive intrahepatic bile duct destruction, leading to cholestasis, fibrosis, and eventual cirrhosis [1]. Advanced stages often necessitate liver transplantation, a resource-intensive intervention demanding lifelong immunosuppression due to rejection risk [2]. Among PBC's debilitating symptoms, cholestatic pruritus severely impairs patient's quality of life, causing sleep deprivation, fatigue, and in extreme cases, suicidal ideation [3–5]. First-line therapy with ursodeoxycholic acid (UDCA) slows disease progression but often fails to relieve pruritus [6,7]. This treatment gap reflects the complex pathophysiology of PBC-associated pruritus, where bile acid (BA) accumulation activates specific pruritogenic pathways [8–10]. These insights have led to drugs such as Linerixibat, a selective ileal bile acid transporter (IBAT) inhibitor that reduces systemic BA overload.

2. BA accumulation and pruritus in PBC: The role of IBAT

Cholestatic pruritus in PBC results from systemic BA accumulation due to impaired bile flow, leading to elevated

cytotoxic BAs such as deoxycholic acid (DCA), taurochenodeoxycholic acid (TCDCA) and chenodeoxycholic acid (CDCA) [11,12]. These BAs bind and activate the Mas-related G protein-coupled receptor X4 (MRGPRX4) on dorsal root ganglion (DRG) neurons [12]. Upon activation, MRGPRX4 couples to Gq proteins and stimulate phospholipase C (PLC), hydrolysing phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol trisphosphate (IP3). IP3 induces intracellular calcium release, depolarising DRG neurons and triggering action potentials that transmit itch signals to the central nervous system [12–14] (**Figure 1**). This mechanism is supported by findings that intradermal BA injection induces scratching in MRGPRX4-humanised mice [15]. In humans, BAs or MRGPRX4 agonists elicit histamine-independent pruritus [12]. Moreover, plasma BA levels positively correlate with itch severity in PBC patients, and pathological BA mixtures selectively activate MRGPRX4, implicating MRGPRX4 in cholestatic itch [12].

Central to this process is IBAT, which mediates sodium-dependent reabsorption of conjugated BAs in the terminal ileum, returning them to the liver via the portal vein to support digestion and lipid absorption, maintaining enterohepatic circulation [16,17]. IBAT activity relies on a sodium gradient generated by basolateral Na^+/K^+-ATPase to co-transport Na^+ and BA from the intestinal lumen into enterocytes against their concentration gradient [18].

Structurally, IBAT contains seven transmembrane helices with an extracellular N- terminus and intracellular C-terminus [19,20]. Transmembrane helix 3 (TM3) contains critical aspartate residues (D122, D124) for Na+ and BA transport [21]. In PBC, IBAT is upregulated to compensate for low intestinal BA, as the body attempts to preserve enterohepatic circulation, which paradoxically increases systemic BA, sustaining MRGPRX4 activation and pruritus [12,22].

Beyond pruritus, excess BAs contribute to hepatic inflammation, fibrosis, and PBC progression [12,23–26], reinforcing BA reduction as a therapeutic strategy.

Figure 1. Bile Acid-Induced Itch Signalling via MRGPRX4 Activation

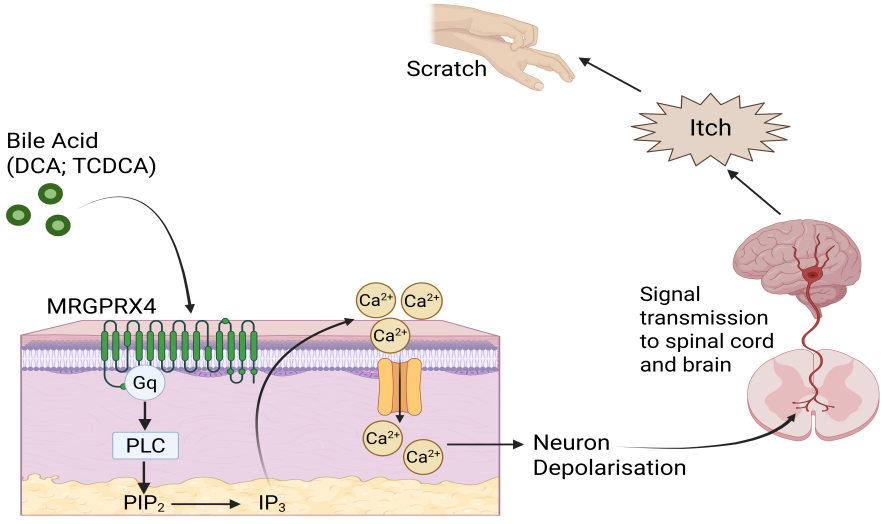

Figure 1. Bile acids such as deoxycholic acid (DCA) and taurochenodeoxycholic acid (TCDCA) activate the Mas-related G protein-coupled receptor X4 (MRGPRX4) on dorsal root ganglion (DRG) neurons. Upon ligand binding, MRGPRX4 couples with Gq proteins to activate phospholipase C (PLC), which hydrolyses PIP_2 into IP_3. IP_3 stimulates intracellular Ca^{2+} release, leading to neuronal depolarisation and transmission of itch signals to the spinal cord and brain. This cascade ultimately results in the itch sensation and the scratching response. Created in Biorender.com. Information from Yue et al. (2019 & 2021) [12,14].

3. Structure and mechanism of Linerixibat

Linerixibat (GSK2330672) is a potent, non-absorbable small molecule that selectively inhibits IBAT. Its structure features two terminal carboxylic acid groups and a zwitterionic structure (combining an ionizable amine linker with negatively charged carboxylates), which mimics the physicochemical properties of conjugated BAs [27,28]. These

polar, ionised groups confer high aqueous solubility while preventing passive diffusion across intestinal membranes, restricting Linerixibat to the intestinal lumen and minimising systemic absorption [28]. Linerixibat achieves high-affinity binding to sodium-coordinating aspartates in IBAT's TM3 [20,21]. By blocking BA reabsorption at the ileal brush border, Linerixibat diverts BAs to the colon for faecal excretion, disrupting enterohepatic circulation and reducing the BAs available for pruritogenic activation [29,30] (**Figure 2**).

Figure 2. Mechanism of Linerixibat in Disrupting Enterohepatic Circulation of Bile Acids

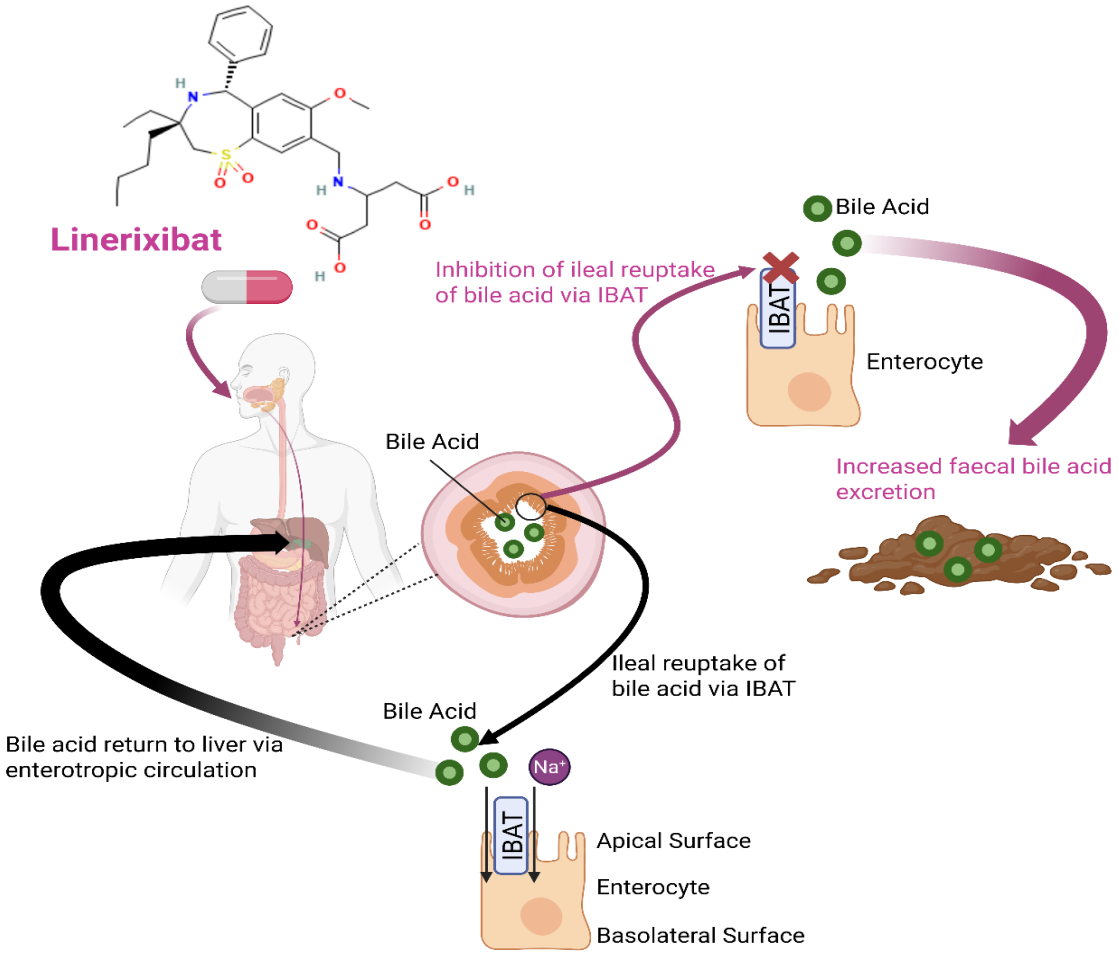

Figure 2. Linerixibat competitively inhibits IBAT on enterocytes in the terminal ileum. The black arrows represent the normal enterohepatic circulation, where bile acids (BA) are reabsorbed in the ileum and returned to the liver. The pink arrows represent the altered pathway following Linerixibat administration, where inhibition of IBAT blocks BA reuptake, leading to increased faecal BA excretion and reduced systemic BA levels. Created in Bioreder.com. Information from Hegade et al. (2016) and Hegade et al. (2017) [29,30]; Linerixibat chemical structure taken from PubChem (2025) [27].

4. Selectivity and therapeutic precision of Linerixibat

Linerixibat's selectivity arises from structural differences between IBAT and related transporters. Although the hepatic sodium-taurocholate co-transporting polypeptide (NTCP) shares moderate homology with IBAT, it lacks the TM3 aspartates required for sodium-coupled transport, making it insensitive to Linerixibat [21]. Moreover, Linerixibat doesn't interfere with basolateral organic solute transporter OSTα/β, which exports BAs from enterocytes into the circulation. These selective interactions reduce intestinal BA reabsorption while preserving systemic BA homeostasis, providing therapeutic effects with minimal off-target activities [28,31,32].

5. Clinical application of Linerixibat and other IBAT inhibitors

Linerixibat's gut-restricted action, non-absorbable design ensures localised action in the terminal ileum, minimising systemic effects while effectively reducing BA reabsorption via selective IBAT blockade [28,32–34]. Clinical trials consistently support its efficacy, with Phase II data showing significant serum BA and pruritus reduction without significant systemic toxicity [33,34,35]. The ongoing Phase III GLISTEN trial (NCT04950127) aims to optimise long-term dosing. So far, results demonstrate pruritus relief with consistent safety profiles [36,37].

The main side effect is colonic BA-induced diarrhoea. Unabsorbed BAs activate the Takeda G-protein-coupled receptor 5 (TGR5) on enterochromaffin cells and enteric neurons, promoting serotonin and calcitonin gene-related peptide release, accelerating colonic motility and reducing water reabsorption [38]. Additionally, high luminal BA concentration disrupts colonic epithelial tight junctions, enabling BA to reach the basolateral membrane and increasing fluid secretion [38]. These effects overwhelm colonic reabsorptive capacity, causing diarrhoea.

Elevated serum 7α-hydroxy-4-cholesten-3-one (C4), a biomarker of BA malabsorption, further confirms Linerixibat's action, and is a hallmark of BA malabsorption syndrome, where impaired BA uptake similarly causes diarrhoea [11,39,40]. This indicates diarrhoea is a mechanism-driven, non-toxic adverse effect. Diarrhoea is generally mild and self-limiting, consistent with Linerixibat's intestinal specificity [29,33,41].

Among IBAT inhibitors, therapeutic applications vary by age and pathology. Odevixibat is formulated for paediatric use in progressive familial intrahepatic cholestasis (PFIC), showing serum BA reduction and pruritus relief in infants as young as 3 months [42,43]. Maralixibat reduces serum BAs and pruritus in children with Alagille syndrome [44,45], but offers limited benefit in adult PBC [46]. Linerixibat is optimised for adult PBC, addressing ductal destruction rather than developmental defects, highlighting the importance of disease-specific therapy design.

6. Further directions: Combination therapies and novel targets

Linerixibat's potential may be enhanced by combining it with agents targeting hepatic inflammation and fibrosis. Preclinical studies demonstrate the efficacy of INT-767, a dual Farnesoid X receptor (FXR)/TGR5 agonist, in reducing BA toxicity while modulating inflammatory and fibrotic pathways [47] (**Figure 3**).

FXR activation suppresses hepatic BA synthesis via ileal small heterodimer partner (SHP) and intestinal fibroblast growth factor 15 (Fgf15) induction, both of which inhibit cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme in BA production, reducing BA production [48,49]. FXR also promotes bicarbonate-rich bile secretion through carbonic anhydrase 14 (CA14) upregulation, neutralising residual BA and protecting hepatocytes [50]. BA excretion is enhanced by bile salt export pump (BSEP) upregulation triggered by INT-767, further reducing hepatocellular BA accumulation [47]. Moreover, FXR-mediated reduction in IL-1β levels reduces autoimmune cholangiocyte damage [47,51].

Simultaneously, TGR5 activates cAMP signalling to supress NF-κB activation and downregulate proinflammatory cytokines (TNF-α, IL-6, MCP-1) in macrophages and Kupffer cells, promoting an anti-inflammatory hepatic environment [52–55]. INT-767 also inhibits hepatic stellate cell activation and collagen deposition, attenuating fibrosis and slowing cirrhosis [47].

Dual FXR/TGR5 agonism provides synergistic benefits not achievable with selective activation of either receptor alone [56]. However, human trials are needed to assess pharmacodynamic interactions, safety, and optimal dosing. Meanwhile, MRGPRX4 antagonist such as EP547, currently under Phase II trials (NCT04510090), offering a complementary strategy for pruritus relief in PBC [57,58].

Figure 3. Dual FXR and TGR5 Activation by INT-767 Reduces Bile Acid Toxicity and Hepatic Inflammation

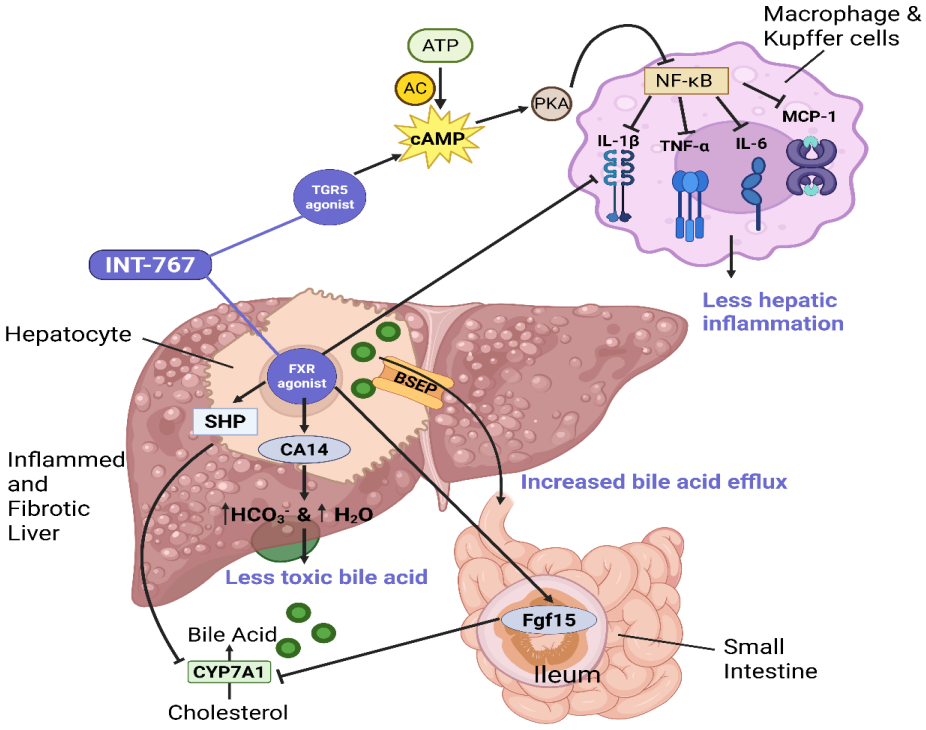

Figure 3. INT-767, a dual agonist of FXR and TGR5, reduces bile acid (BA)-induced toxicity and liver inflammation. FXR activation in hepatocytes induces small heterodimer partner (SHP) and intestinal fibroblast growth factor 15 (Fgf15), both of which suppress CYP7A1, the rate-limiting enzyme in BA synthesis. FXR also promotes bicarbonate-rich bile production via carbonic anhydrase 14 (CA14), and enhances bile acid excretion by upregulating the bile salt export pump (BSEP). These changes decrease intracellular bile acid accumulation and reduce toxicity. Simultaneously, TGR5 activation on macrophages and Kupffer cells increases cAMP via adenylyl cyclase (AC), activating PKA, which inhibits NF-κB signaling. This leads to downregulation of pro-inflammatory cytokines including IL-1β, TNF-α, IL-6, and MCP-1, creating an anti-inflammatory hepatic environment.Created in Biorender.com. Information from Baghdasaryan et al. (2011) and Pols et al. (2011) [47,55].

7. Conclusion

Linerixibat is a promising targeted therapy for cholestatic pruritus in PBC, leveraging selective IBAT inhibition to reduce systemic BA levels while avoiding systemic toxicity. Its gut-restricted mechanism ensures a favourable safety profile, with mild, mechanism-driven diarrhoea that could be mitigated through dose titration or adjunctive therapies targeting colonic BA effects. Compared to other IBAT inhibitors, Linerixibat is uniquely optimised for adult PBC. Further strategies may combine Linerixibat with agents such as INT767 or MRGPRX4 antagonists to address pruritus, inflammation, and fibrosis synergistically. Further research into the molecular mechanisms cholestatic pruritus is essential to fully understood and more effectively treat this complex and debilitating symptom.

Disclosure statement

The author declares no conflict of interest.

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