A quantitative systems pharmacology (QSP) model to interrogate the underlying mechanisms of cholestatic pruritus (itch) in primary biliary cholangitis (PBC) and the impact of linerixibat treatment

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QSP analysis corroborated the heterogeneous nature of itch in patients with PBC, with IL-31 signaling identified as an important contributor to itch and a putative marker of linerixibat efficacy

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Background

- PBC is marked by impaired bile secretion in the liver, resulting in hepatic inflammation and pruritogen release into the blood[1–3]
- Several key mediators of cholestatic pruritus have been identified, including bile acids, ATX/LPA and IL-31;[1,4,5] however, the underlying pathophysiological mechanisms remain poorly understood[3,6,7]
- Data from the Phase 3 GLISTEN (NCT04950127) study, the largest ever symptom trial conducted in PBC evaluating linerixibat, a minimally absorbed IBAT inhibitor, demonstrated that linerixibat significantly reduced pruritus at Week 2 and over 24 weeks of treatment versus placebo[8]
- A QSP model was developed to elucidate the mechanisms underlying cholestatic pruritus in PBC and to provide insight for linerixibat's MoA, alone or in combination with a PPAR agonist

Methods

- Clinical data were leveraged from GLISTEN and the Phase 2b GLIMMER (NCT02966834) clinical datasets of linerixibat, as well as aggregate data from the Phase 3 ENHANCE study (NCT03602560) of seladelpar, a PPARδ agonist[8–10]
- The QSP model consists of 4 interconnected layers:

Treatment layer: Represents how linerixibat and seladelpar modulate bile acid reabsorption leading to downstream signaling in hepatocytes

Pruritus layer: Converts systemic biomarker concentrations into quantifiable pruritic signals

PBC layer: Includes mechanisms such as bile acid homeostasis and enterohepatic recirculation and the spillover of pruritogens into the systemic circulation

Output layer: Provides simulation outputs for key quantitative endpoints (e.g., WI-NRS* scores)
**Measures worst itch using an NRS, ranging from 0 to 10, where 0 represents no itching and 10 the worst imaginable itching.*

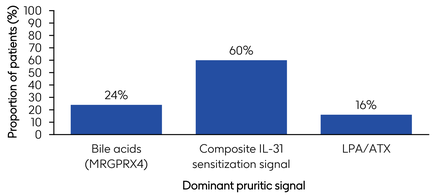
- The model was calibrated using a subset of participants in GLISTEN who took both placebo and linerixibat, for which all main pruritogen concentrations (ATX, IL-31 regulated by FXR activation, bile acids, and bilirubin) were measured; model behavior/outputs for biomarkers and WI-NRS under seladelpar were calibrated using ENHANCE data
- Calibration steps allowed reproduction of pruritogen concentrations and itch scores before and after treatment, yielding digital twins to represent each GLISTEN patient
- An *in silico* clinical trial was performed; each digital twin received placebo or linerixibat (thereby acting as its own control) to investigate the characteristics of the best responders

Results

Heterogeneity of pruritus mechanisms in PBC

- Model analysis revealed high heterogeneity of pruritus signal strengths, largely (60%) driven by a sensitization mechanism, which includes IL-31 as the dominant pruritic signal modulated by FXR signaling (**Figure 1**)

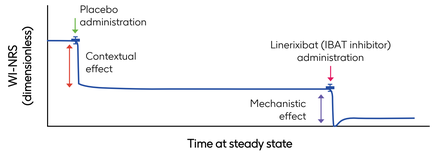
Figure 1: **Mechanistic insights into cholestatic pruritus: a composite IL-31 sensitization signal is a key mediator[3,5]**



Contribution of a contextual effect (caused by other non-mechanistic factors e.g. placebo effect) vs pruritogen-driven modulation to WI-NRS reduction

- The model predicted that linerixibat modulation of pruritogen-driven pathways accounted for ~50% of the median WI-NRS reduction, with the remaining ~50% attributed to the contextual effect (**Figure 2**)

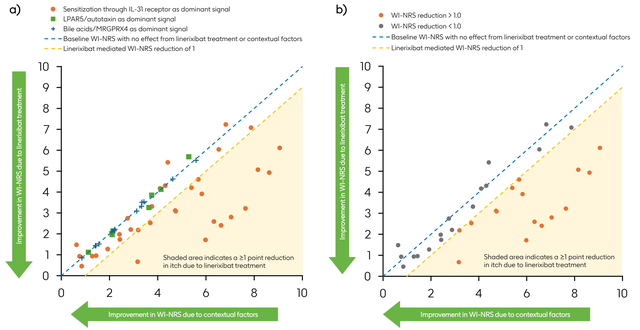
Figure 2: **Example of individual participant illustrating the impact of contextual vs linerixibat effect on WI-NRS**



The QSP model was used to interpret observed data and suggested that the reduction in pruritus is mainly driven by linerixibat-induced decreases in IL-31 levels through a sensitization mechanism

- Most participants (~60%) exhibited a dominant pruritic signal linked to IL-31 sensitization, particularly among those who experienced a reduction in the WI-NRS under linerixibat treatment by ≥1 point greater than the contribution due to contextual effect; those with pruritus driven solely by bile acids (MRGPRX4) or ATX/LPA (LPAR5) did not show significant improvement above the contextual effect (**Figure 3a**)
- Among participants whose pruritus was modulated by the IL-31 sensitization signal, the model predicted that ~52% exhibited a reduction in WI-NRS by ≥1 point greater than the contribution due to contextual effect, while ~48% did not (**Figure 3b**)

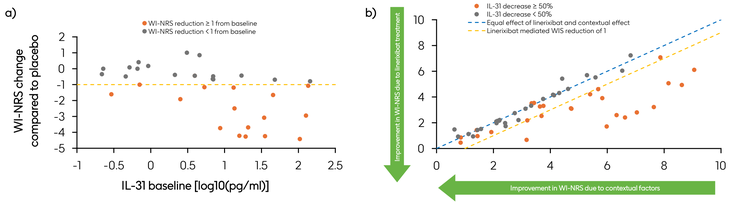
Figure 3: **(a) Classification of pruritus drivers; (b) Response stratification based on IL-31 sensitization**



QSP analysis suggested that baseline IL-31 levels are predictive of linerixibat-mediated treatment response

- Patients with a dominant sensitization signal showed a positive correlation between baseline IL-31 levels and WI-NRS reduction following linerixibat treatment (**Figure 4a**)
- A >50% post-treatment decrease from baseline in IL-31 was observed in patients achieving a WI-NRS reduction ≥1 under linerixibat treatment versus placebo (**Figure 4b**)

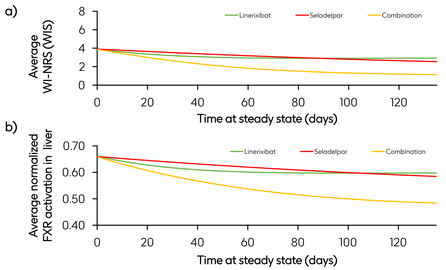
Figure 4: **(a) Baseline IL-31 levels and their link to linerixibat efficacy; (b) Post-treatment IL-31 level stratification by linerixibat-mediated response**



Model simulations of virtual patients demonstrated linerixibat provides a significant reduction of itch when combined with seladelpar

- Model predictions indicated that combining linerixibat with seladelpar would result in further reduction in WI-NRS (WIS)* compared to each treatment individually (**Figure 5a**)
- The increased efficacy appeared to be driven by a reduction in pruritogen levels, particularly IL-31, through an IBAT-mediated decrease in FXR activity, where the treatments demonstrated an enhanced effect (**Figure 5b**)

Figure 5: **Combination therapy with seladelpar. (a) Predicted average WI-NRS (WIS)*; (b) Predicted average FXR activation**



**WIS: The 7-day average of patients' WI-NRS daily scores.*

Conclusions

- QSP analysis corroborated the heterogeneous nature of itch in patients with PBC
- QSP modeling suggests that linerixibat-mediated reduction of IL-31 through a composite sensitization mechanism is a major contributor to itch reduction (please see poster #4393 also)
- Simulations predict further itch reduction when combining linerixibat with a PPAR agonist

Abbreviations

ATX, autotaxin; FXR, farnesoid X receptor; IBAT, ileal bile acid transporter; IL-31, interleukin 31; LPA, lysophosphatidic acid; LPAR5, lysophosphatidic acid receptor 5; MoA, mode of action; MRGPRX4, mas-related G protein-couple receptor X4; NRS, numerical rating scale; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; QSP, quantitative systems pharmacology; TSBA, total serum bile acids; vs, versus; WIS, Weekly Itch Score; WI-NRS, Worst Itch Numerical Rating Scale

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