Comparative effectiveness of odevixibat vs maralixibat in Alagille syndrome: A modeling-based analysis of pruritus response, durability, and long-term patient-relevant outcomes

Oyinkan Solanke,[1] Emmanuelle Kaltenbach,[1,*] Vicki Laskier-Owens,[2] Laurence Tilley[2]

[1]Ipsen, London, UK; [2]Acumetis, London, UK

*Affiliation at time of study.

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KEY LEARNINGS

Model-based projections in patients with ALGS suggest higher and more durable estimated pruritus response with ODX vs MRX. These symptom improvements may translate into reduced progression to advanced liver disease and lower LT rates over time, supporting the potential long-term clinical value of ODX.

BACKGROUND

- ALGS is a rare, multisystem, genetic cholestatic liver disease associated with elevated sBA and severe pruritus that can disrupt sleep and impair QoL.[1,2]
- Many patients with ALGS and cholestasis require surgical intervention or an LT before adulthood due to progressive liver damage and debilitating pruritus. However, these approaches are invasive and carry high risk of morbidity.[1,2]
- Two IBATis are approved for cholestatic pruritus in patients with ALGS:
  - ODX produced rapid, significant improvements in pruritus and reductions in sBA vs placebo in the phase III ASSERT study (NCT04674761), which were sustained with long-term treatment in ASSERT-EXT (NCT05035030).[3,4]
  - MRX demonstrated efficacy and safety in the phase IIb randomized drug withdrawal ICONIC study (NCT02160782).[5]
- A population-adjusted ITC reported statistically significant differences favoring ODX vs MRX for selected HRQoL and tolerability, and numerical trends favoring ODX for efficacy outcomes.[6]
- However, comparative evidence on IBATi outcomes beyond symptom control remains limited, highlighting the need for further long-term data to inform treatment decisions.

CONCLUSIONS

- In patients with ALGS, ODX had a higher estimated Week 48 pruritus response rate than MRX.
  - The model projected that a greater proportion of patients would remain in the pruritus-responder state over time with ODX vs MRX.
- Over 20 years, the model projected less progression to advanced liver disease and lower cumulative LT rates for ODX vs MRX.
- These findings suggest that achieving and maintaining pruritus response may have important implications for long-term outcomes in ALGS.
- Together with previous comparative analyses, these findings support a differentiated clinical profile for ODX vs MRX.[6]

OBJECTIVES

- Sustained pruritus control is clinically meaningful in ALGS; however, its potential implications for longer-term disease outcomes are not well characterized. This study addresses the lack of evidence comparing outcomes between ODX vs MRX.
- We compared the projected clinical effectiveness of ODX vs MRX in patients with ALGS, focusing on pruritus response and durability, and downstream clinical outcomes, including disease progression and LT.

METHODS

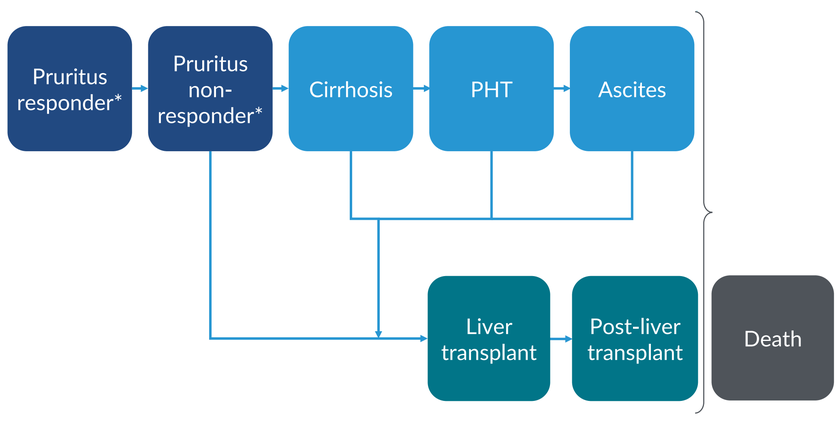
Data source

- A comparative effectiveness analysis was conducted using data from ASSERT/ASSERT-EXT for ODX and an unanchored population-adjusted ITC informed by ICONIC for MRX, adjusting for observed cross-trial differences in baseline characteristics.[3–6]

Model structure

- Pruritus response (≥1-point reduction in morning pruritus score) vs no response was modeled across disease progression states.
- A Markov state-transition model simulated disease progression across ALGS health states with 12-week cycles, aligned with the previous MRX NICE model[7] (**Figure 1**).

Figure 1. Markov model structure



* Response defined as ≥1-point reduction in morning pruritus score

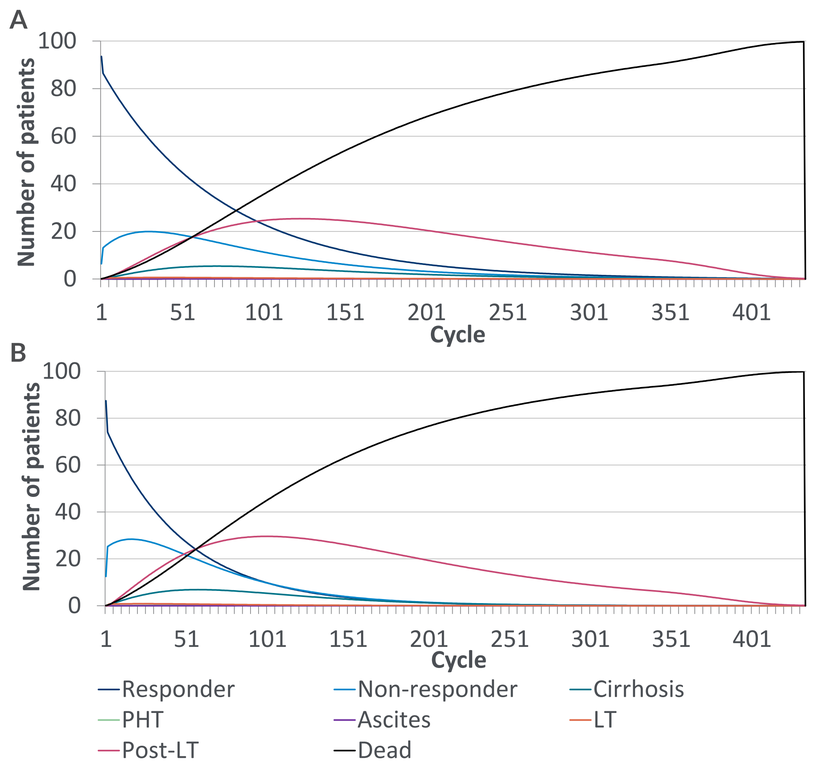
- Transition probabilities between advanced liver disease states and state-specific mortality inputs were informed by published literature.[8–12]
- In the base case, patients were assumed not to progress to advanced liver disease while remaining in the pruritus-responder state.
- Week 48 pruritus response estimates were used to allocate patients to the initial pruritus-responder and non-responder states for both treatments, aligning the comparative response-assessment timepoints.
  - ODX demonstrated a higher pruritus response rate compared with MRX at Week 48 (87.2% vs 75.0%).

RESULTS

Durability of pruritus response

- The model projected a more durable pruritus response with ODX than with MRX, with a greater proportion of patients remaining pruritus responders over time (**Figure 2**).

Figure 2. Modeled health-state occupancy over time for patients receiving (A) ODX and (B) MRX*



* Values represent the number of patients occupying each health state in a modeled cohort of 100 patients and should not be interpreted as cumulative incidence

Long-term modeled outcomes

- Model projections indicated lower cumulative LT incidence with ODX vs MRX at 5 years (12.1% vs 19.2%), 10 years (25.2% vs 36.4%), and 20 years (47.5% vs 60.8%; **Table 1**).
- Modeled health-state occupancy also indicated fewer patients in advanced liver disease states over time with ODX (**Figure 2**).

Table 1. Long-term modeled outcomes with ODX vs MRX

Outcome	Timepoint, years	ODX	MRX
Cumulative incidence of ≥1 LT, %*	5	12.1	19.2
	10	25.2	36.4
	20	47.5	60.8
Patients alive and transplant-free, %†	5	88.0	80.5
	10	80.9	61.4
	20	45.9	18.1
Patients remaining event-free, %‡	5	84.5	75.9
	10	61.7	54.6
	20	40.3	24.8

* Assumes a cohort of 100 patients; † Events include first LT or death; ‡ State occupancy based. Events include cirrhosis, PHT, ascites, LT, post-LT, and death

Limitations

- The model assumes that pruritus responders do not experience disease progression; limited long-term evidence and the need to extrapolate disease progression beyond available clinical data introduce uncertainty into projected long-term outcomes.
- MRX efficacy was informed by an unanchored population-adjusted ITC of separate studies with different designs; although adjustment was made for key baseline characteristics, residual confounding due to unmeasured cross-study differences cannot be excluded.

Abbreviations: ALGS, Alagille syndrome; HRQoL, health-related quality of life; IBATi, ileal bile acid transporter inhibitor; ITC, indirect treatment comparison; LT, liver transplantation; MRX, maralixibat; NICE, National Institute for Health and Care Excellence; ODX, odevixibat; PHT, portal hypertension; QoL, quality of life; sBA, serum bile acid; SBD, surgical biliary diversion.

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