Dosing ileal bile acid transporter inhibitors in the fasted state minimises gastrointestinal adverse effects while maintaining pharmacodynamic effect

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Introduction

- Ileal bile acid transporter inhibitors (IBATis) interrupt enterohepatic circulation of bile acids (BAs) and increase faecal BA (fBA) excretion, thereby reducing serum BA.[1,2]
- IBATis, including maralixibat (MRX) and volixibat (VLX), decrease the toxic accumulation of BAs in the liver and mitigate cholestasis.[2,3]
- MRX is approved for the treatment of cholestatic pruritus in patients with Alagille syndrome 1 year of age and older.[4]
- Gastrointestinal (GI) adverse events (AEs), including diarrhoea and abdominal pain, are effects of IBATis due to increased excretion of fBA.[3,5]

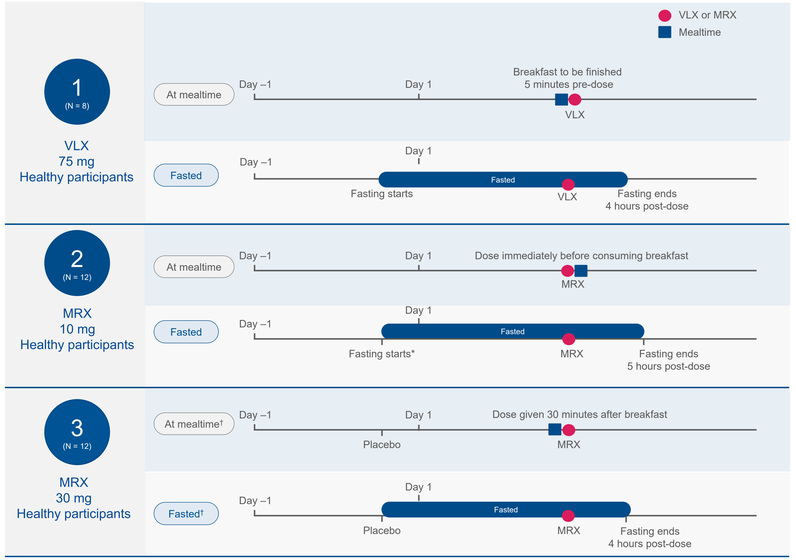
Aim

- To assess the impact of timing of IBATi dosing, relative to food, on GI AEs and pharmacodynamic (PD) effects to inform on the optimal dosing approach for IBATis.

Phase 1 clinical studies: Methods

- AE data from three Phase 1 clinical studies of MRX and VLX in healthy participants (**Figure 1**) were compiled to assess relative tolerability with different timing of IBATi dosing versus mealtime.

Figure 1. Study designs, drugs, doses and at mealtime/fasted timelines.



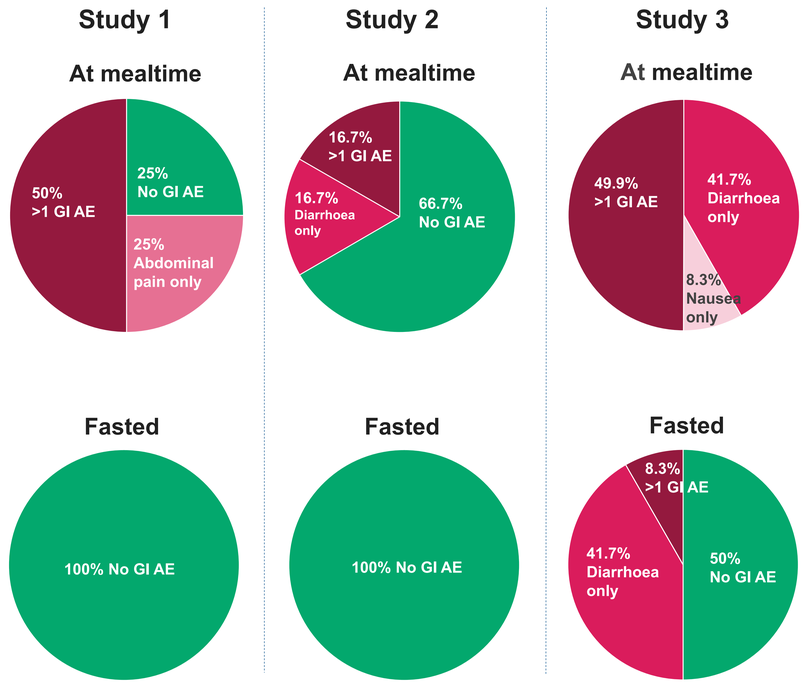
*Fasting was started ≥10–12 hours before MRX dosing. †Patients were randomised 1:1 to two cohorts and received sequentially fasted then at mealtime dosing, or at mealtime then fasted dosing.
MRX, maralixibat; VLX, volixibat.

- Patients were to adhere to certain timings of IBATi dosing, as well as a specific diet, consisting of high-fat, fixed-calorific content.
- AEs were monitored throughout the study period.

Clinical data demonstrate a lower rate of GI AEs when IBATis are dosed in the fasted state

- Across the three Phase 1 clinical studies, there was a lower rate of GI AEs when dosing with IBATis in the fasted state versus at mealtime (**Figure 2**).
- All AEs were mild or moderate in severity.
- GI AEs were most frequent overall, and included abdominal pain, diarrhoea and nausea.
- No deaths or serious AEs were reported and no AEs led to discontinuation.

Figure 2. Proportion of healthy participants who experienced GI treatment-emergent AEs following IBATi administration at mealtime versus in the fasted state.

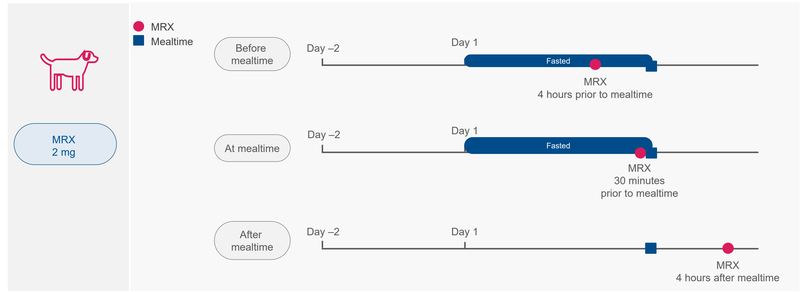


AE, adverse event; GI, gastrointestinal; IBATi, ileal bile acid transporter inhibitor.

Non-clinical PD data: Methods

- fBA excretion is a PD marker of efficacy but can be difficult to measure in clinical trials. The impact of fasted versus fed on fBA was measured in healthy dogs (**Figure 3**).

Figure 3. The effect of MRX on fBA excretion in dogs: study drug, and dosing/mealtime schedule.

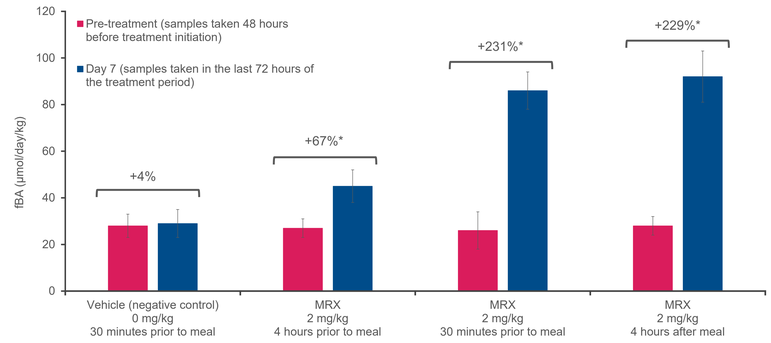


fBA, faecal bile acid; MRX, maralixibat.

Non-clinical PD data demonstrate that fasted versus fed dosing had no impact on fBA excretion

- MRX significantly increased fBA excretion across all dosing time schedules, relative to the daily meal.
- Maximal increases in fBA excretion were seen when dosing 30 minutes before to 4 hours after mealtime, indicating flexibility in the timing of IBATi dosing versus mealtime to maintain maximal PD effect (**Figure 4**).

Figure 4. The effect of MRX on fBA excretion in dogs: change in fBA excretion from pre-treatment to day 7.



Groups were dosed at the indicated times. Faecal samples were taken 48 hours before treatment initiation and for the last 72 hours of the 7-day treatment period and analysed for bile acid content.
*p<0.01 versus pre-treatment, by one-tail paired t-test. Data are presented as ±SEM (n = 7–8). % = change compared with pre-treatment value.
fBA, faecal bile acid; MRX, maralixibat; SEM, standard error of the mean.

Conclusions

- **In healthy human participants, GI tolerability was improved when dosing IBATis in the fasted state, versus dosing immediately before or at mealtime.**
- **Animal data showed that fBA excretion was maintained regardless of dosing time relative to mealtime, indicating that there is flexibility in the dosing of IBATis relative to food.**

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