# Rifaximin Monotherapy Is More Effective Than Lactulose Monotherapy for Reducing the Risk of Overt Hepatic Encephalopathy Recurrence and All-Cause Mortality: An Analysis of Two Randomized Trials

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ACG 2024
October 25-30, Philadelphia, PA

# Introduction

- Lactulose monotherapy is recommended as secondary prophylaxis after an initial OHE episode[1,2]
  - Rifaximin is recommended as add-on therapy when additional episodes occur[1,2]
- Nonadherence to lactulose therapy can precipitate HE recurrence[3-5]
- There are several potential barriers to lactulose adherence[5-7]
  - GI adverse effects
    - These can lead to dehydration or electrolyte imbalances—which are also OHE precipitating
  - Dosing and volume requirements
  - Unpleasant taste
- These lactulose-related issues indicate that alternative management strategies to reduce the risk of OHE recurrence may be required

- **Aim:** to compare the efficacy and safety of rifaximin monotherapy versus lactulose monotherapy for reducing the risk of OHE recurrence in patients with cirrhosis and a history of OHE

GI = gastrointestinal; HE = hepatic encephalopathy; OHE = overt hepatic encephalopathy.

**1.** European Association for the Study of the Liver. *J Hepatol.* 2022;77(3):807-824. **2.** Vilstrup H, et al. *Hepatology.* 2014;60(2):715-735. **3.** Bajaj JS, et al. *Aliment Pharmacol Ther.* 2019;49(12):1518-1527. **4.** Bajaj JS, et al. *Aliment Pharmacol Ther.* 2010;31(9):1012-1017. **5.** Chow KW, et al. *Dig Dis Sci.* 2023;68(6):2389-2397. **6.** Khungar V, et al. *Clin Liver Dis.* 2012;16(2):301-320. **7.** Bloom PP, et al. *Hepatol Commun.* 2023;7(11):e0295.

# Methods

- **Study design:** post hoc analysis of 2 randomized trials (phase 3 double-blind[1]; phase 4 open-label)
- **Population:** adults with cirrhosis and history of OHE during previous 6 months (in remission)*
- **Treatment**†
  - Rifaximin 550 mg BID for up to 6 months (phase 3 or 4 trials) *or*
  - Lactulose (titrated, 2-3 soft stools/d) plus placebo for up to 6 months (phase 3 trial)
- **Assessments**
  - Phase 3 trial: Day 0 (± 1); Days (± 2) 7, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, and 168; 14 ± 2 days after EOT
  - Phase 4 trial: Day 1; Days (± 2) 28, 56, 84, 112, 140, and 168; 14 ± 2 days after EOT
- **Statistics:** HR estimates were obtained using a Cox proportional hazards model with effect for treatment; *P* values based on score statistic
- **Primary efficacy endpoint:** time to first breakthrough OHE episode‡

*Conn score ≤1.
†In the phase 3 trial, rifaximin 550 mg BID or placebo was administered with optional lactulose; in the phase 4 trial, rifaximin 550 mg BID or rifaximin 550 mg BID plus lactulose was administered. Only patients receiving rifaximin alone or lactulose + placebo ("lactulose alone") were included in the current analysis.
‡Original primary endpoint in both trials (defined as Conn score ≥2).
BID = twice daily; EOT = end of treatment; HR = hazard ratio; OHE = overt hepatic encephalopathy.
**1.** Bass NM, et al. *N Engl J Med*. 2010;362(12):1071-1081.

# Inclusion/Exclusion Criteria

| Criteria | Phase 3 Double-Blind Trial[1] | Phase 4 Open-Label Trial |
|---|---|---|
| Inclusion | • Aged ≥18 y<br>• ≥2 episodes of OHE (Conn score ≥2) during previous 6 months<br>• Currently in HE remission (Conn score ≤1)<br>• MELD score ≤25 | • Aged ≥18 y<br>• ≥1 episode of OHE (Conn score ≥2) during previous 6 months<br>• Currently in HE remission (Conn score ≤1) |
| Exclusion | • Current GI bleeding or GI hemorrhage requiring hospitalization and transition of ≥2 units of blood ≤3 months before screening<br>• Chronic renal insufficiency (creatinine >2.0 mg/dL)<br>• Chronic respiratory insufficiency<br>• Anemia (hemoglobin <8 g/dL)<br>• Electrolyte abnormality<br>– Serum sodium <125 mmol/L<br>– Serum calcium >10 mg/dL (2.5 mmol/L)<br>– Potassium <2.5 mmol/L<br>• Intercurrent infection<br>• Active SBP<br>• Portosystemic shunt or TIPS placement ≤3 months before screening<br>• Liver transplantation anticipated ≤1 month after screening | • Current GI bleeding or GI hemorrhage requiring hospitalization and transfusion of ≥2 units of blood ≤3 months before screening<br>• Renal insufficiency requiring dialysis<br>• Chronic respiratory insufficiency<br>• Anemia (hemoglobin <8 g/dL)<br>• Hypovolemia or electrolyte abnormality<br>– Serum sodium <125 mmol/L<br>– Serum calcium >10 mg/dL<br>– Potassium <2.5 mmol/L<br>• Current infection for which oral or parenteral antibiotics are used<br>• Positive stool test for *Clostridium difficile* toxin at screening<br>• Active SBP or requires daily prophylactic antibiotics |

GI = gastrointestinal; HE = hepatic encephalopathy; MELD = Model for End-Stage Liver Disease; OHE = overt hepatic encephalopathy; SBP = spontaneous bacterial peritonitis; TIPS = transjugular intrahepatic portosystemic shunt.

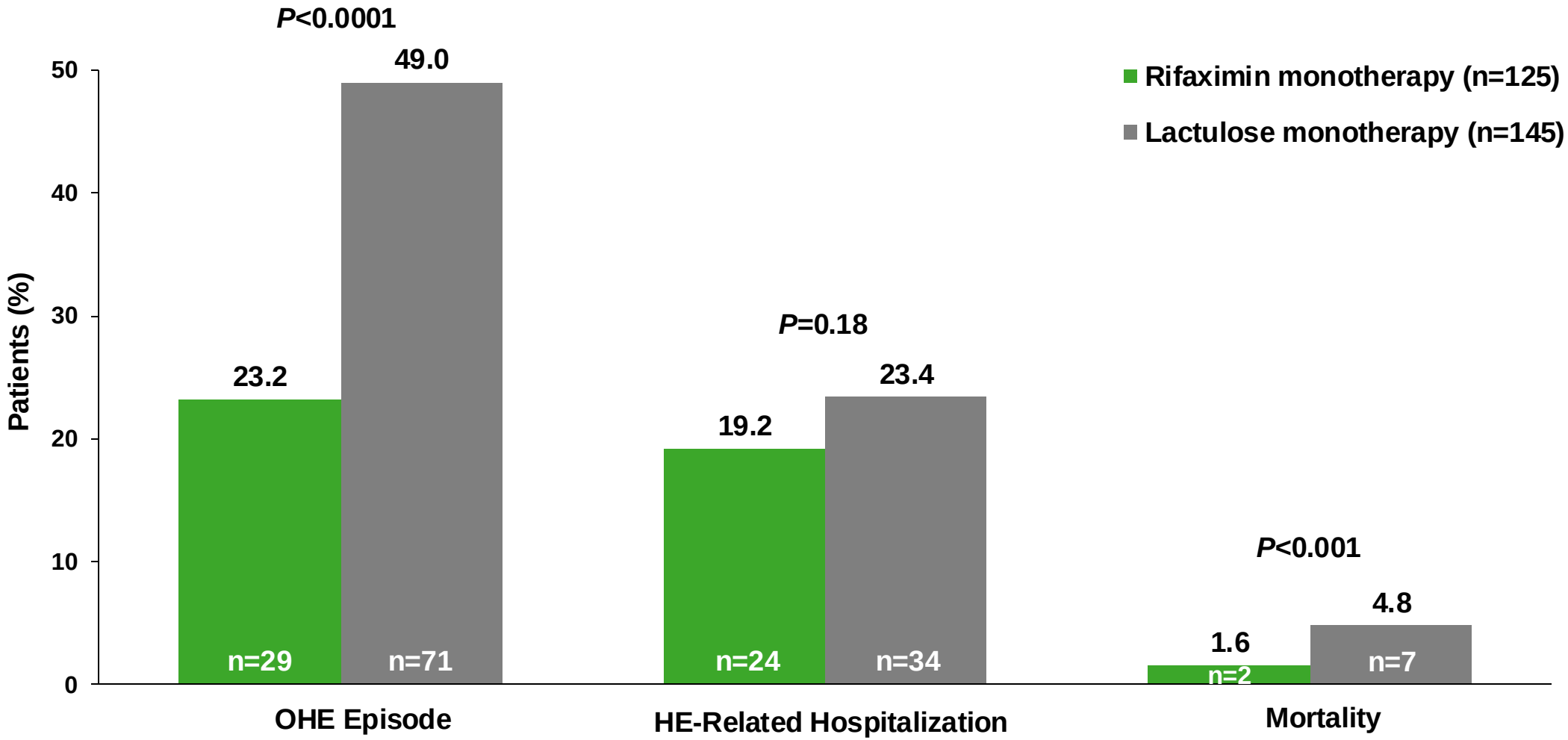
**1.** Bass NM, et al. *N Engl J Med*. 2010;362(12):1071-1081.

# Demographics and Baseline Characteristics

| Parameter | Patients, n (%) | |
|---|---|---|
| | Rifaximin Monotherapy (n=125) | Lactulose Monotherapy (n=145) |
| Age, y, mean (SD) | 58.2 (9.5) | 56.6 (9.3) |
| Male, n (%) | 75 (60.0) | 99 (68.3) |
| Race, n (%) | | |
| White | 113 (90.4) | 126 (86.9) |
| Black | 8 (6.4) | 5 (3.4) |
| Asian | 2 (1.6) | 7 (4.8) |
| Other | 2 (1.6) | 7 (4.8) |
| Baseline MELD score* | | |
| Mean (SD) | 12 (4) | 13 (4) |
| Median (range) | 12 (6-24) | 12 (6-23) |
| Child-Pugh class, n (%)† | | |
| A | 54 (43.2) | 49 (33.8) |
| B | 64 (51.2) | 67 (46.2) |
| C | 7 (5.6) | 13 (9.0) |
| Missing data | 0 | 16 (11.0) |
| Baseline Conn score, n (%) | | |
| 0 | 86 (68.8) | 98 (67.6) |
| 1 | 39 (31.2) | 47 (32.4) |
| Duration of current OHE remission, d, mean (SD) | 89.7 (56.0) | 73.6 (52.0)‡ |

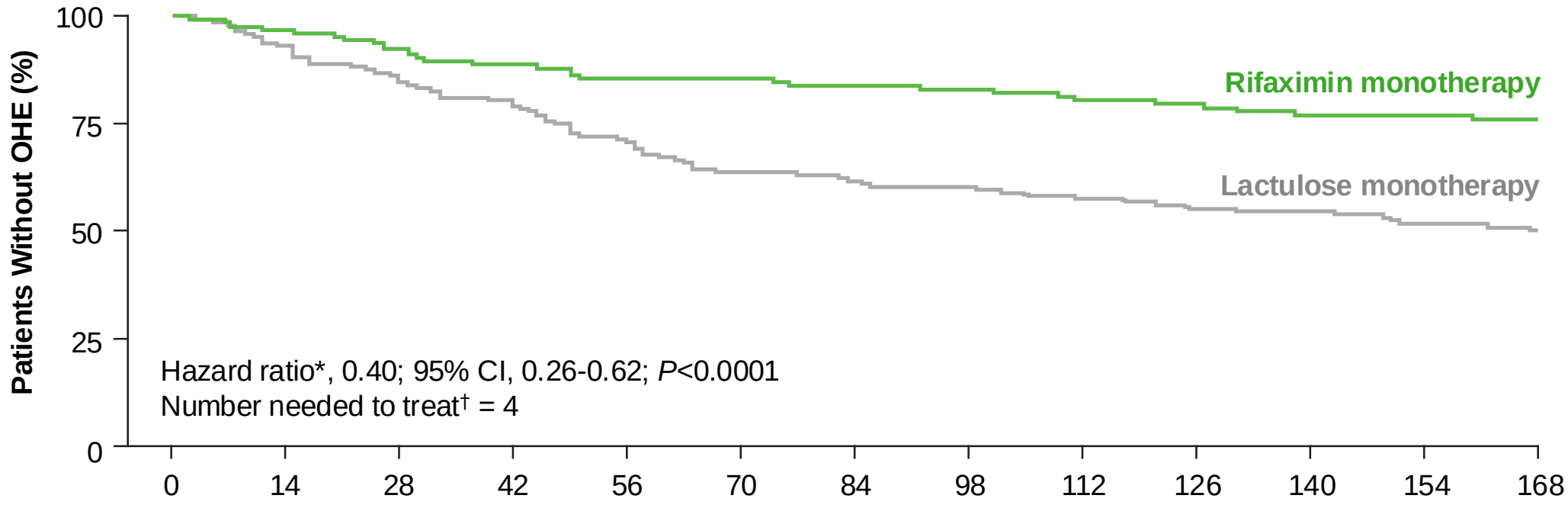
*$P$=0.09 comparing rifaximin and lactulose monotherapy data across MELD categories (≤10, 11-18, and 19-24; Chi-Square test).
†$P$=0.36 comparing rifaximin and lactulose monotherapy data across class categories (Chi-Square test).
‡Data missing for 1 patient.
MELD = Model for End-Stage Liver Disease; OHE = overt hepatic encephalopathy.

# Outcomes During 6 Months of Treatment*




*Through Day 168.
HE = hepatic encephalopathy; OHE = overt hepatic encephalopathy.

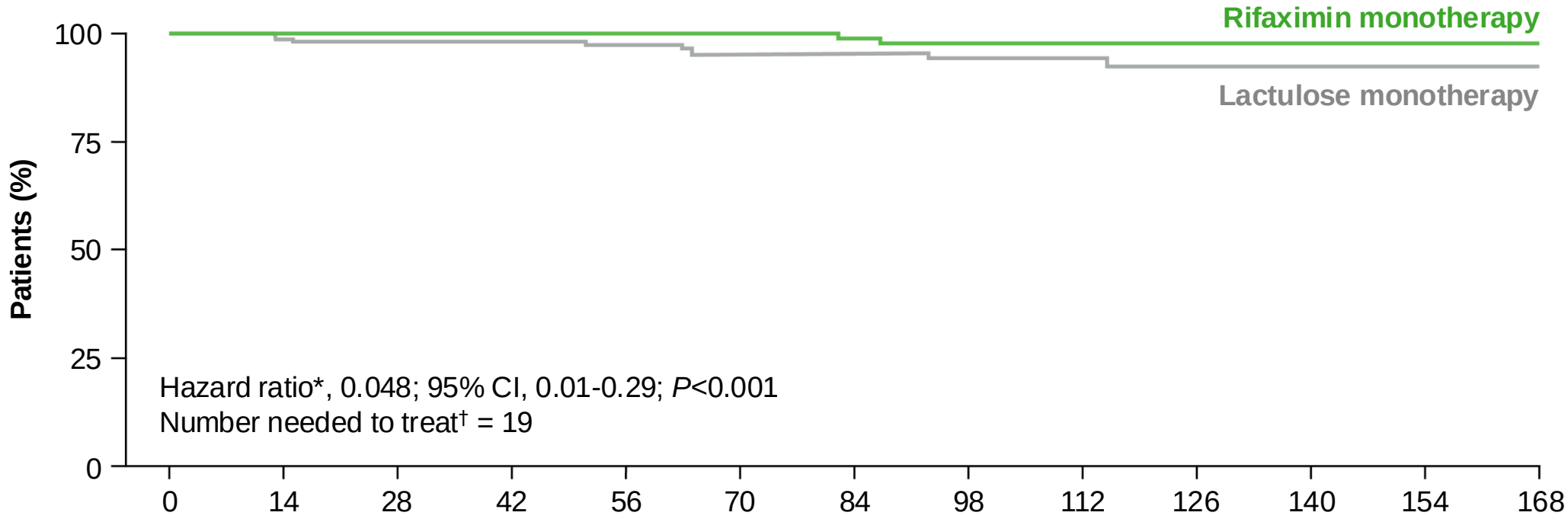
# Time to First Breakthrough OHE Episode




| PATIENTS | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rifaximin | 125 | 125 | 116 | 104 | 99 | 94 | 88 |
| Lactulose | 145 | 145 | 121 | 101 | 88 | 81 | 76 |

*Hazard ratio for the risk of a breakthrough OHE episode in the rifaximin group compared with the lactulose group. †Rifaximin group vs lactose group.
OHE = overt hepatic encephalopathy.

# Time to All-Cause Mortality




| PATIENTS | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rifaximin | 125 | 125 | 119 | 109 | 99 | 92 | 90 |
| Lactulose | 145 | 145 | 125 | 103 | 84 | 70 | 62 |

*Hazard ratio for the risk of all-cause mortality in the rifaximin group compared with the lactulose group. †Rifaximin group vs lactose group.
OHE = overt hepatic encephalopathy.

# Baseline Characteristics in Mortality Population*

| Baseline Characteristic | Rifaximin Monotherapy (n=2) | Lactulose Monotherapy (n=10) |
|---|---|---|
| MELD score | 14 (n=1)<br>22 (n=1) | 11 (n=1)<br>14 (n=3)<br>15 (n=2)<br>16 (n=2)<br>18 (n=1)<br>19 (n=1) |
| Child-Pugh class | B (n=2) | A (n=2)<br>B (n=7)<br>C (n=1) |
| Number of OHE episodes in previous 6 months | 1 (n=2) | 2 (n=5)<br>3 (n=5) |
| Conn score | 0 (n=1)<br>1 (n=1) | 0 (n=5)<br>1 (n=5) |
| Verified duration of current OHE remission | 14 days (n=1)<br>89 days (n=1) | 19-34 days (n=4)<br>45-67 days (n=3)<br>119-138 days (n=3) |

*Fatalities through follow-up (14 ± 2 days after end of treatment): 2 (1.6%) and 10 (6.9%) patients in rifaximin and lactulose monotherapy groups, respectively.
MELD = Model for End-Stage Liver Disease; OHE = overt hepatic encephalopathy.

# Safety Profile

| Parameter | Patients, n (%) | |
|---|---|---|
| | Rifaximin Monotherapy (n=125) | Lactulose Monotherapy (n=145) |
| Discontinuation from study | 45 (36.0)* | 90 (62.1) |
| ≥1 AE | 105 (84.0) | 126 (86.9) |
| ≥1 drug-related AE | 8 (6.4)* | 35 (24.1) |
| ≥1 serious AE | 44 (35.2) | 60 (41.4) |
| Discontinuation due to an AE | 25 (20.0)† | 57 (39.3) |
| Most common AEs‡ | | |
| Nausea | 17 (13.6) | 21 (14.5) |
| Fatigue | 16 (12.8) | 18 (12.4) |
| Peripheral edema | 20 (16.0) | 13 (9.0) |
| Constipation | 18 (14.4) | 10 (6.9) |
| UTI | 14 (11.2) | 14 (9.7) |
| Diarrhea | 6 (4.8)§ | 21 (14.5) |
| Headache | 9 (7.2) | 17 (11.7) |
| Insomnia | 14 (11.2) | 11 (7.6) |
| Ascites | 9 (7.2) | 15 (10.3) |
| Muscle spasms | 10 (8.0) | 10 (6.9) |
| Vomiting | 6 (4.8) | 14 (9.7) |
| Abdominal pain | 8 (6.4) | 11 (7.6) |
| Anemia | 12 (9.6) | 6 (4.1) |
| Asthenia | 6 (4.8) | 12 (8.3) |

*$P$<0.0001 vs lactulose. †$P$=0.0006 vs lactulose; patients with AE leading to study discontinuation may have chosen termination reason as due to AE, breakthrough hepatic encephalopathy, or liver transplant. ‡Ranked by the highest incidence in the overall population (≥6.7%), then alphabetically (excluding hepatic encephalopathy). §$P$=0.008 vs lactulose.

*P* values calculated using Fisher's exact test.

AE = adverse event; UTI = urinary tract infection.

# Conclusions

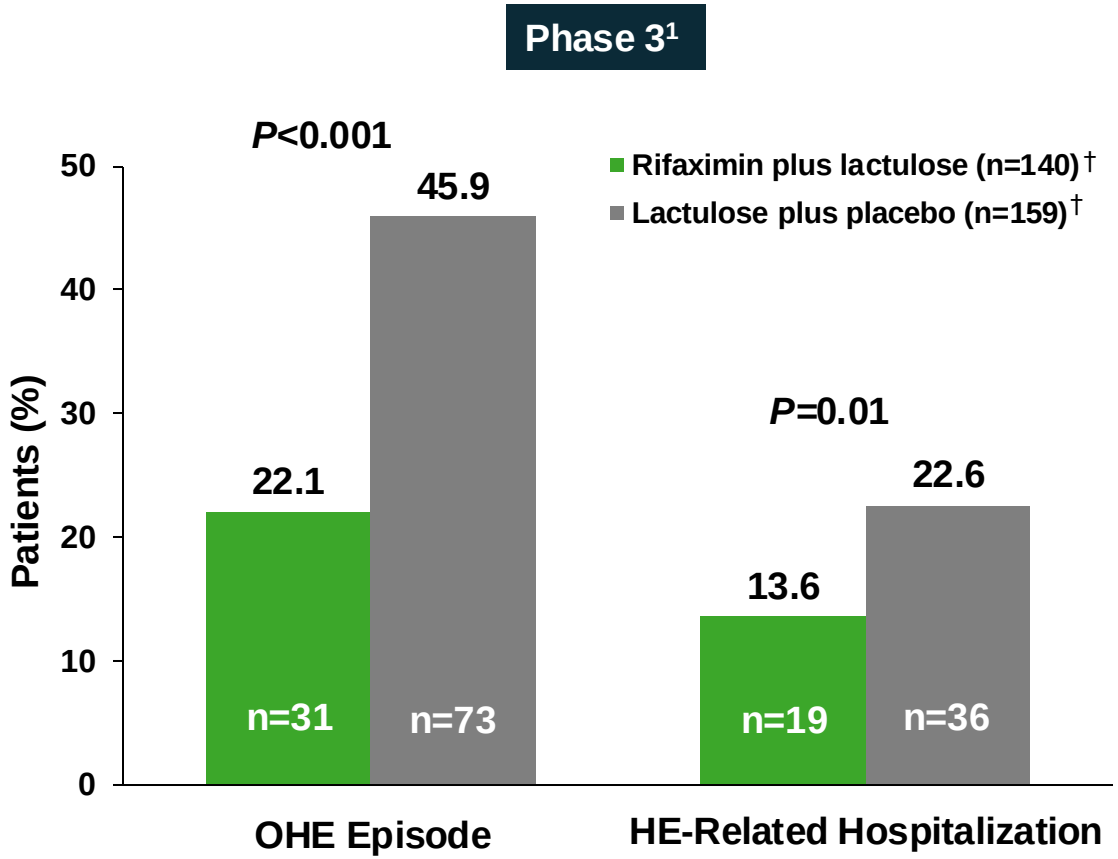
- Significantly fewer OHE recurrence episodes were reported with rifaximin monotherapy compared with lactulose monotherapy in patients with a history of OHE
  - Rifaximin treatment may also confer a survival benefit
  - Rifaximin was well tolerated
- Rifaximin monotherapy may be an appropriate management approach in select patient populations

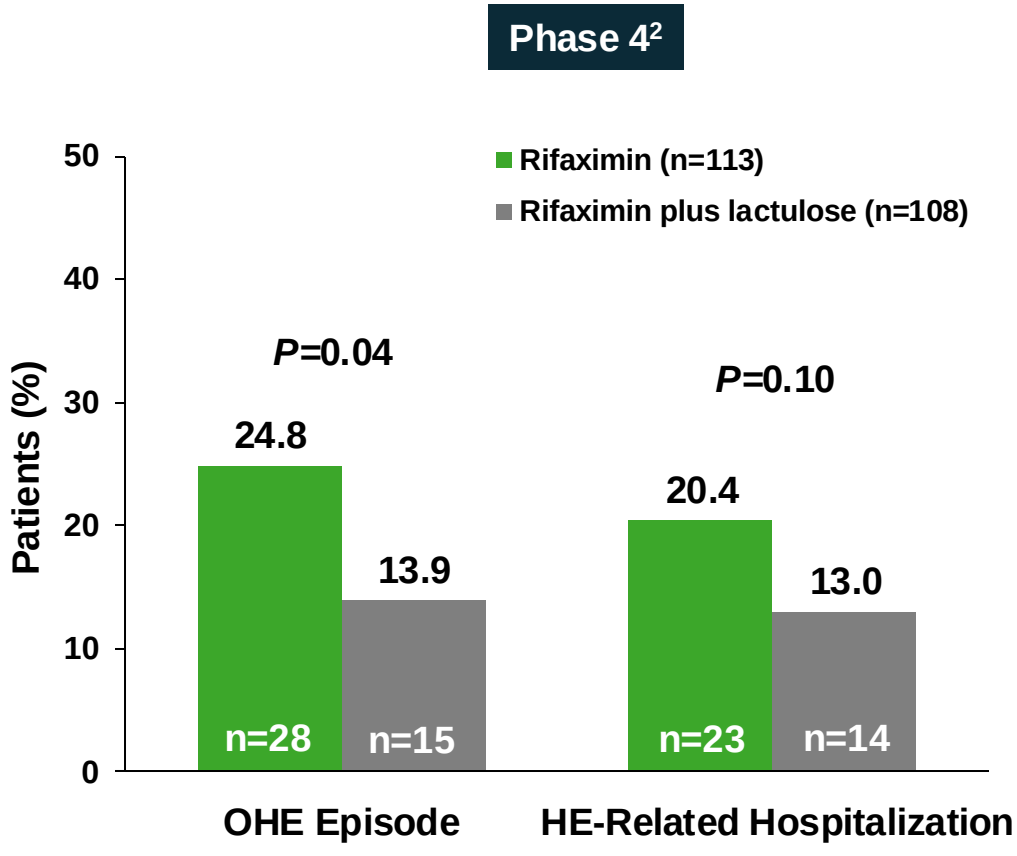
OHE = overt hepatic encephalopathy.

# Thank You

# Backup Slides

# Phase 3 and Phase 4 Trial Outcomes*




*Day 168 (phase 3) and Day 170 (phase 4).
†91.4% of 140 patients treated with rifaximin were taking concomitant lactulose, and 91.2% of 159 patients treated with placebo were taking concomitant lactulose.
HE = hepatic encephalopathy; OHE = overt hepatic encephalopathy.
**1.** Bass NM, et al. *N Engl J Med*. 2010;362(12):1071-1081. **2.** ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT01842581?term=RFHE4044&rank=1&tab=results. Accessed August 23, 2024.