Xifaxan® (rifaximin) Tablets 550 mg for Hepatic Encephalopathy

United States Food and Drug Administration
Gastrointestinal Drugs Advisory Committee

February 23, 2010

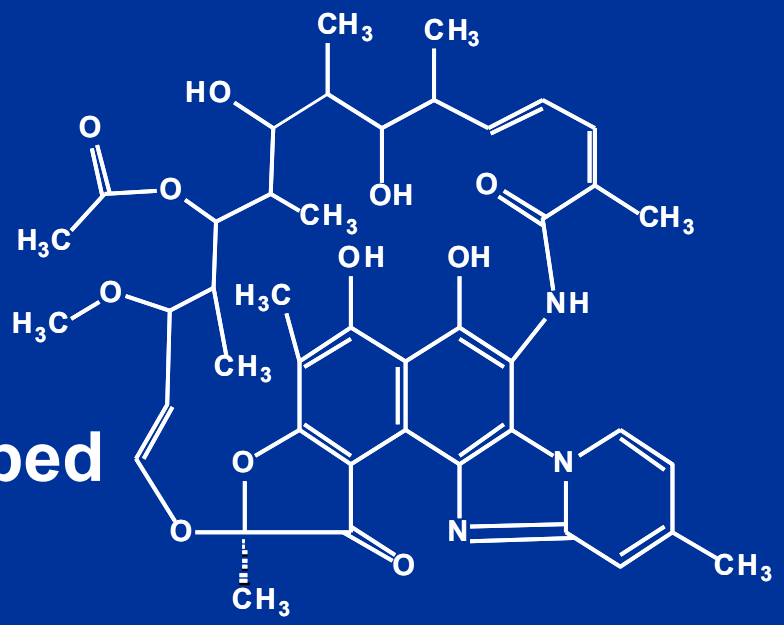
Xifaxan® (rifaximin) Tablets 550 mg for Hepatic Encephalopathy

Introduction

David Dobrowski

Director, Regulatory Affairs
Salix Pharmaceuticals, Inc.

Rifaximin
Product Characteristics



- Antibiotic of rifamycin class
- Gut targeted; minimally absorbed
- Low risk of drug interactions
- Broad spectrum in vitro antibacterial activity
- Low risk of antibiotic resistance

Proposed Indication

- **NDA 22-554 (550 mg tablet BID)**
  - **Xifaxan® (rifaximin) is indicated for the maintenance of remission of hepatic encephalopathy (HE) in patients ≥ 18 years of age**

Rifaximin Regulatory Overview

- Approved in 33 countries for various GI indications including
  - Hepatic encephalopathy and/or hyperammonemia
- 5 years US postmarketing experience

Major US development programs

Travelers' Diarrhea	NDA 21-361 *Approved May, 2004*	XIFAXAN® 200 mg tablets (TID)
Hepatic Encephalopathy	NDA 22-554 *PDUFA: March 24, 2010*	550 mg tablets (BID)
Hepatic Encephalopathy	Orphan drug status *Granted 1998*	n/a
Irritable Bowel Syndrome	Phase 3 complete NDA: 2Q 2010	550 mg tablets (TID)
Pediatric Acute Diarrhea	TBD	TBD

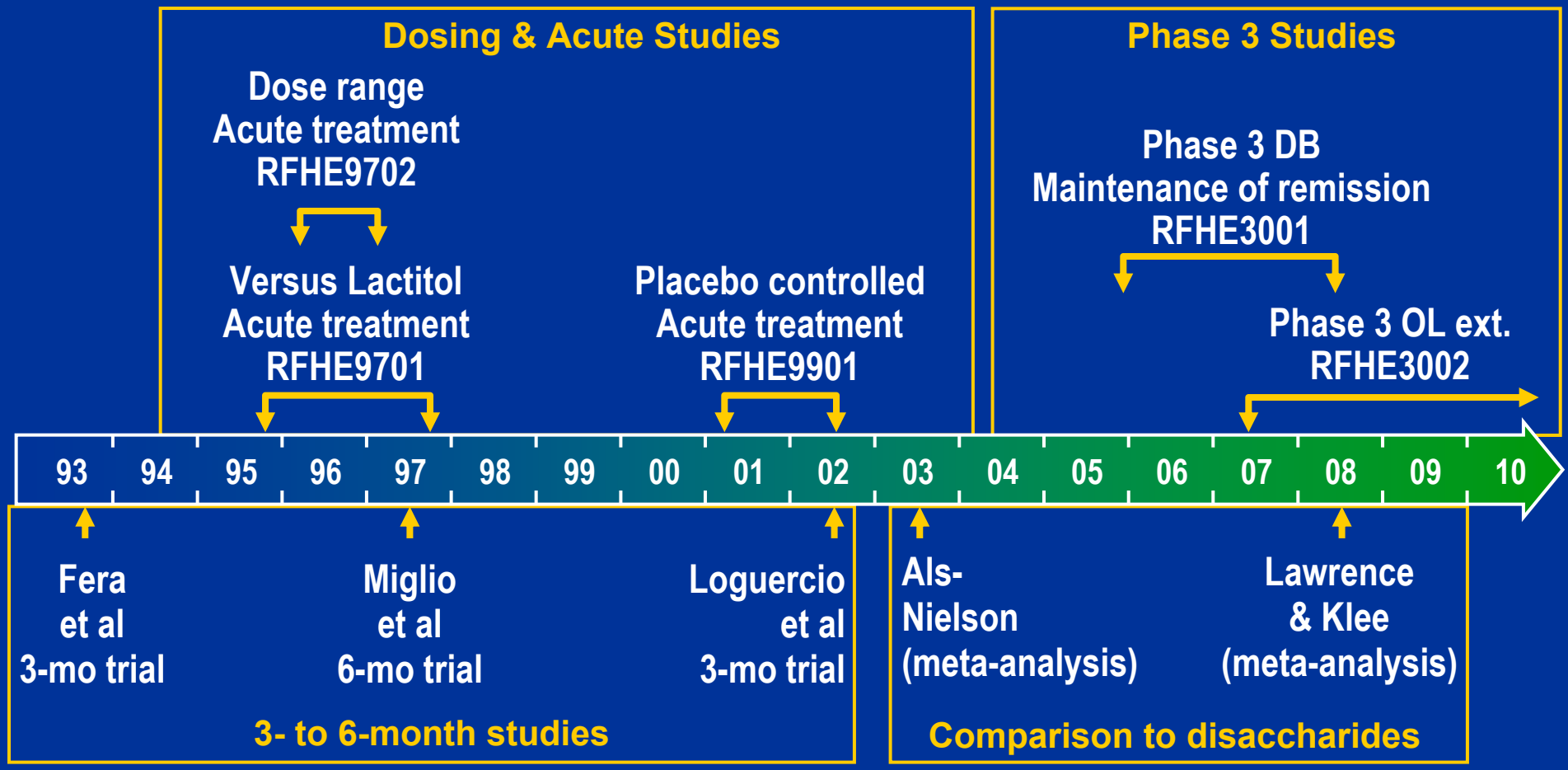
Rifaximin HE Development
US Regulatory History and Interactions

Initial FDA Interactions	• Orphan drug status granted 1998 • IND filed 1999
RFHE3001 Study Design	• Consultation with ~25 experts • 6 advisory boards
FDA Meeting 2004	• 19 studies in acute treatment and 1 meta-analysis • Proposed "maintenance of remission" indication • Need confirmatory trial for "maintenance" indication
Primary Endpoint Agreement	An increase in Conn score to ≥ 2 (ie, 0 or 1 to ≥ 2) OR An increase of 1 for both Conn score and asterixis grade for patients with a baseline Conn score 0
FDA Meeting 2007	• PK study design in patients with advanced liver disease
NDA 2009	• FDA Guidance (1998): "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" • Priority review granted

US Treatment Options for HE

- Lactulose (FDA approved 1976)
  - Prevention and treatment of portal-systemic encephalopathy including the stages of pre-coma and coma
- Neomycin (FDA approved 1970)
  - Adjunctive therapy in hepatic coma by reduction of the ammonia-forming bacteria in the intestinal tract. The subsequent reduction in blood ammonia has resulted in neurological improvement
- Metronidazole and Vancomycin (not approved)
- Rifaximin (FDA review 2010)
  - For the maintenance of remission of hepatic encephalopathy (HE)

Rifaximin Development Timeline
Hepatic Encephalopathy



Highlights for Advisory Committee Meeting

- HE is a serious, debilitating condition
- HE is an unmet medical need
- Criteria for determining HE breakthrough
  - Conn is clinically relevant and endorsed by World Congress of Gastroenterology
  - Agreed upon by FDA and Salix
- Rifaximin is a meaningful advancement for HE treatment
  - Results are significant, robust, and confirmatory
    - Reduced risk of HE episodes
    - Reduced HE-related hospitalizations
    - Benefit correlates to known prognostic variables associated with HE
  - Well tolerated with a favorable safety profile

Today's Agenda

Rifaximin Pharmacology	**Pamela L. Golden, PhD** Director, Development Salix Pharmaceuticals, Inc.
Hepatic Encephalopathy and Current Management	**Nathan M. Bass, MD, PhD** Professor of Medicine Assoc. Medical Director, UCSF Liver Transplant Program University of California, San Francisco, School of Medicine
Rifaximin Efficacy	**William P. Forbes, PharmD** Senior Vice President, R&D Chief Development Officer Salix Pharmaceuticals, Inc.
Rifaximin Safety	**Naga P. Chalasani, MD** Professor of Medicine, Director of Gastroenterology and Hepatology Indiana University School of Medicine
Benefit/Risk Profile	**Steven L. Flamm, MD** Professor of Medicine and Surgery, Liver Transplantation Northwestern University

Consultants

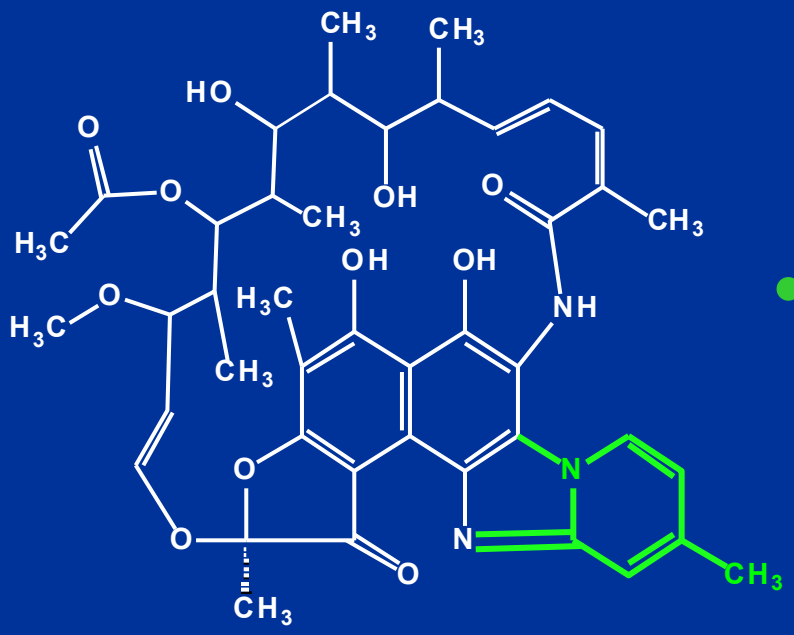
- **Roger Butterworth, PhD**
  Faculty of Medicine
  University of Montreal
  Quebec, Canada
- **Herbert L. DuPont, MD**
  St. Luke Hospital
  Houston, TX
- **Tarek Hassanein, MD**
  University of California San Diego
  San Diego, California
- **W. Ray Kim, MD**
  Mayo Clinic
  Division of Gastroenterology and Hepatology
  Rochester, MN
- **Colleen Johnson, MS, DABT**
  Reno Associates
  Hamilton, VA
- **Gary Koch, PhD**
  Professor of Biostatistics
  University of North Carolina
  Chapel Hill, NC
- **Kevin Mullen, MD**
  Metro Health Center
  Case Western Reserve University
  Cleveland, OH
- **Eugene R. Schiff, MD**
  MACP, FRCP, MACG, AGAF
  University of Miami
  Miami, FL

Rifaximin Pharmacology

Pamela L. Golden, PhD

Director, Development
Salix Pharmaceuticals, Inc.

Rifaximin ADMET Summary



- Poorly absorbed (< 0.4%)
  - Low solubility and permeability (BCS 4)
  - P-glycoprotein efflux
- Clearance pathways
  - > 99% excreted unchanged in feces
  - First-pass biliary clearance
  - One known metabolite (~2.5% of parent)
  - Minimal renal clearance (0.32%)
- No nonclinical safety signals
  - Doses up to 125 × human dose
  - Nonclinical studies show no QT prolongation risk

ADMET = Absorption, distribution, metabolism, excretion, toxicology

Rifaximin Microbiology

- Binds to β-subunit of bacterial DNA dependent RNA polymerase, resulting in inhibition of RNA synthesis
- In vivo
  - Ameliorates bacterial diarrheal symptoms
    - Achieves concentrations ~ 8000 µg/g of stool[a]
    - Modest alterations in normal intestinal flora and pathogen counts[b,c]
  - Reduced systemic exposure minimizes driving force for resistant bacteria

[a] Jiang et al. *Antimicrob Agents Chemother*. 2000;44:2205-2206.
[b] DuPont HL and Jiang ZD. *Clin Microbiol Infect*. 2004;10:1009-1011.
[c] DuPont HL, et al. *Clin Infect Dis*. 2001;33:1807-1815.

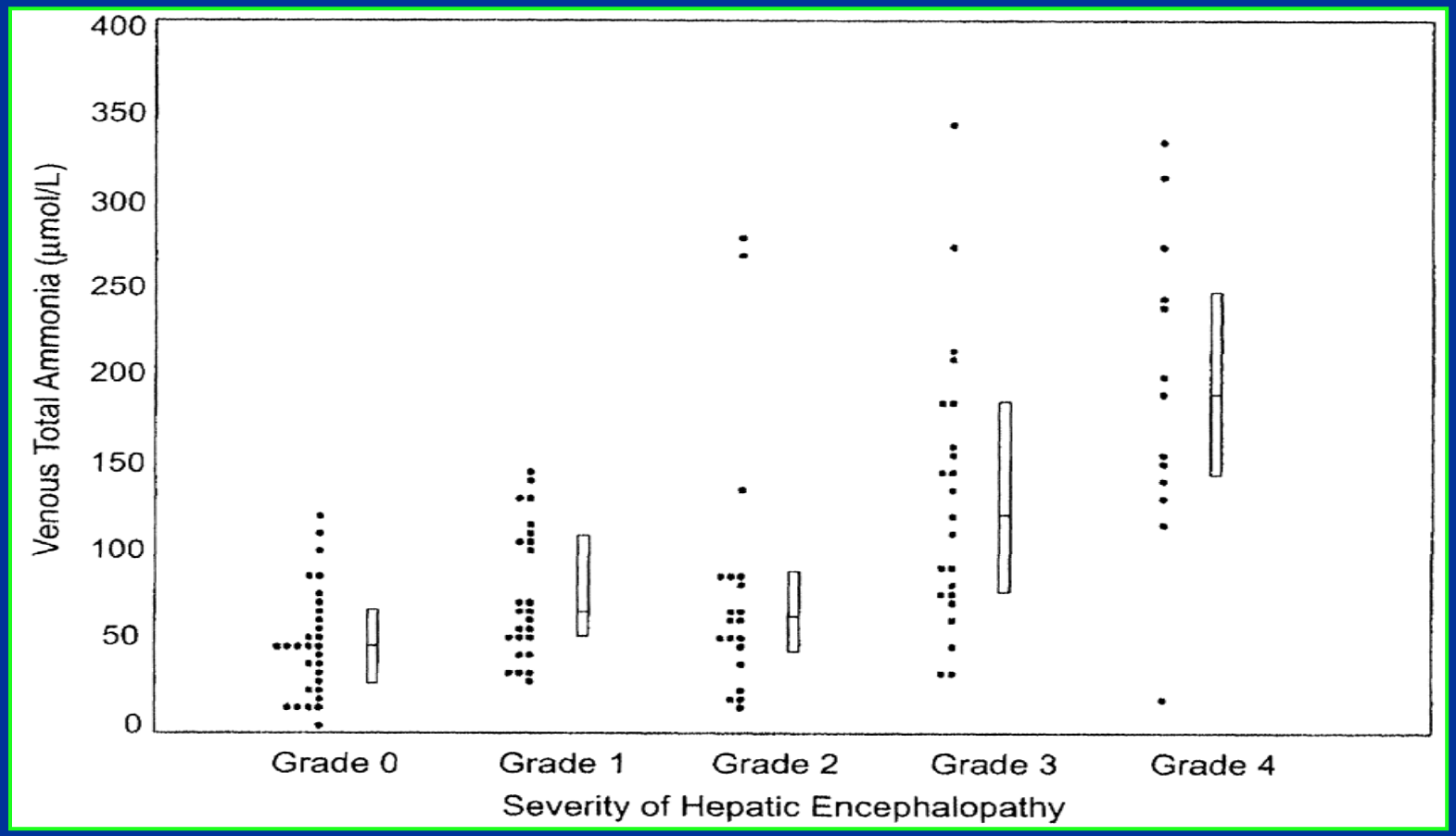
Rifaximin Microbiology and Pharmacology

- In vitro
  - Effects on bacteria at sub-MIC levels
    - Cured host cells of plasmids and reduced plasmid transfer[a]
    - Reduced virulence of enteric bacteria[b]
  - Effects on mammalian cells
    - Upregulates detoxification pathways in intestinal epithelial cells[c]
    - Stabilizes epithelial cells and inhibits subsequent bacterial attachment[d]

Reduces gut-derived neurotoxins (eg, ammonia) which lead to HE in liver-impaired patients

[a] Debbia EA, et al. *J Chemotherapy*. 2008;20:186-194; [b] Jiang ZD, et al. *Int J Antimicrob Agents*. 2009.
[c] Ma X, et al. *J Pharmacol Exp Ther*. 2007;322:391-398; [d] Brown EL, et al. *Antimicrob Agents Chemo*. 2010;54:388-396.

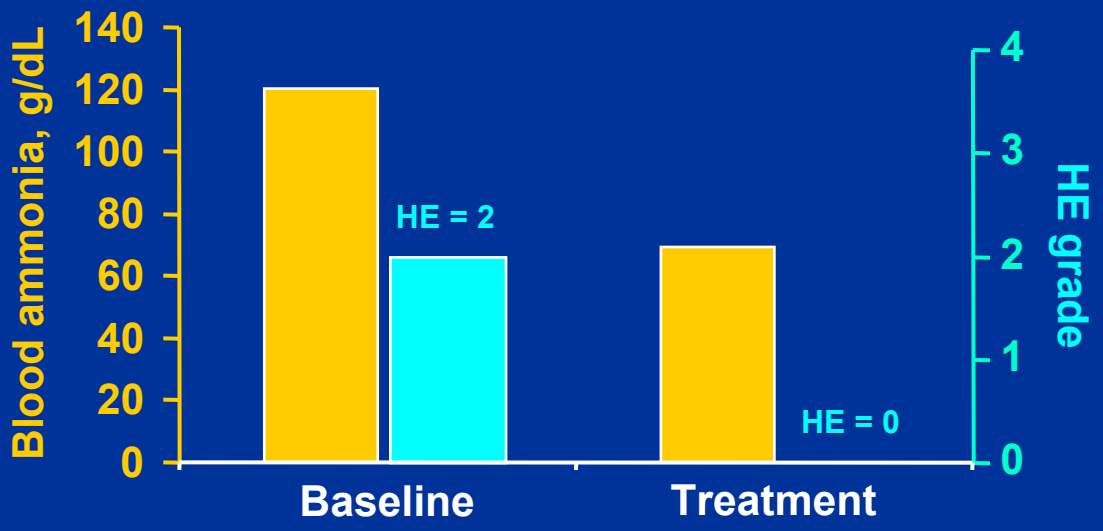
Single Venous Ammonia Measurements Correlate With HE Grade



HE Grade increases in the presence of increasing venous ammonia

Ong JP, et al. *Amer J Med*. 2003;114:188-193.

Rifaximin
Effect on Blood Ammonia Over 10 Days

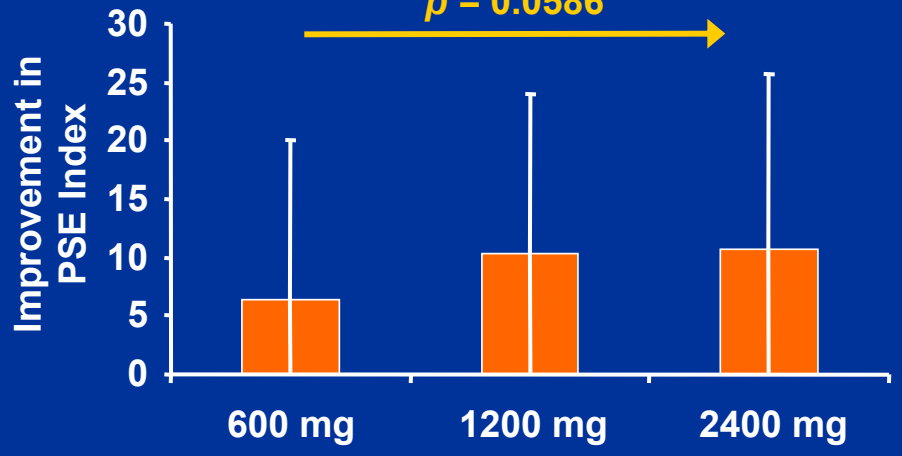


- Rifaximin 1200 mg/day decreased blood ammonia ($p < 0.0001$)
- Corresponding improvement in median HE grade ($p < 0.0001$)
- Correlation between ammonia and HE was examined in RFHE3001

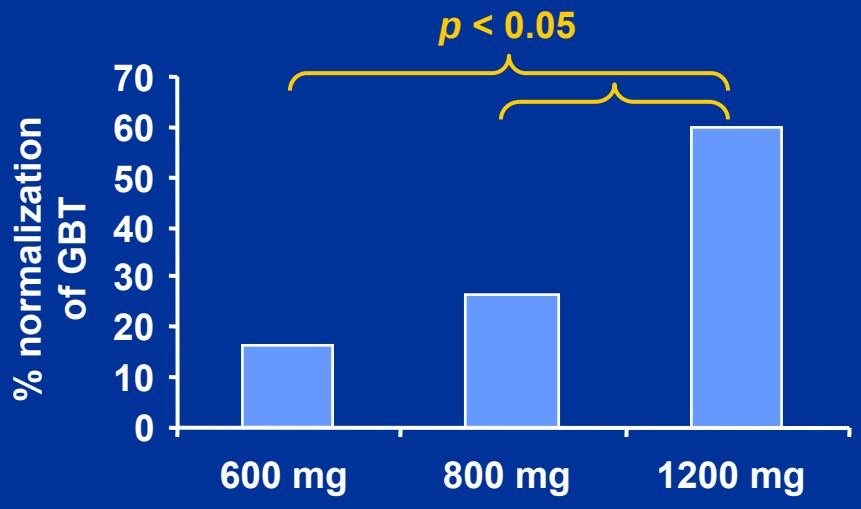
Mas A, et al. *J Hepatology*. 2003;38:51-58.

Rifaximin Pharmacodynamics
Dose Selection for Phase 3

- **RFHE9702: HE**
  - Double-blind, dose-ranging
  - Optimal dose of 1200 mg/day



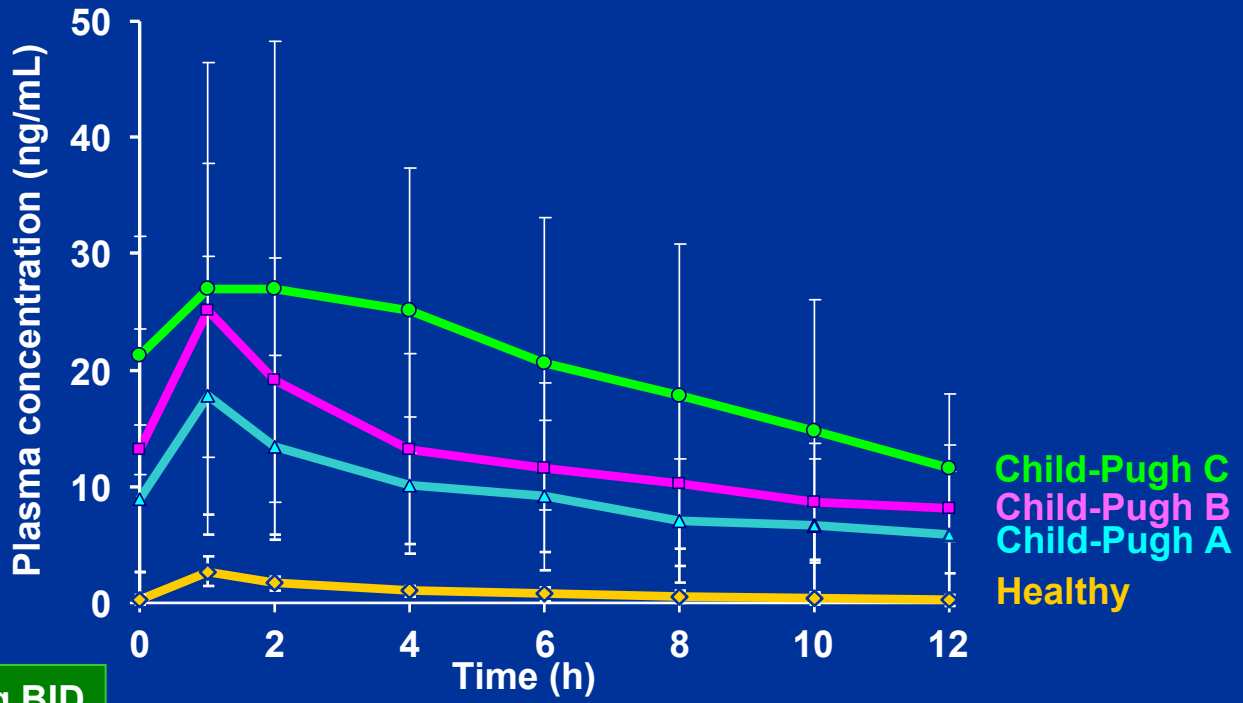
- **Lauritano *et al*: SIBO**
  - Dose-finding in treatment of small intestinal bacterial overgrowth
  - Optimal dose of 1200 mg/day



- **Dose selection: Phase 3 HE**
  - 550 mg maximizes dose and tablet size
  - BID regimen based on intestinal transit time and compliance

Lauritano et al. *Aliment Pharmacol Ther*. 2005;22:31-35.

Rifaximin PK in Liver Impairment

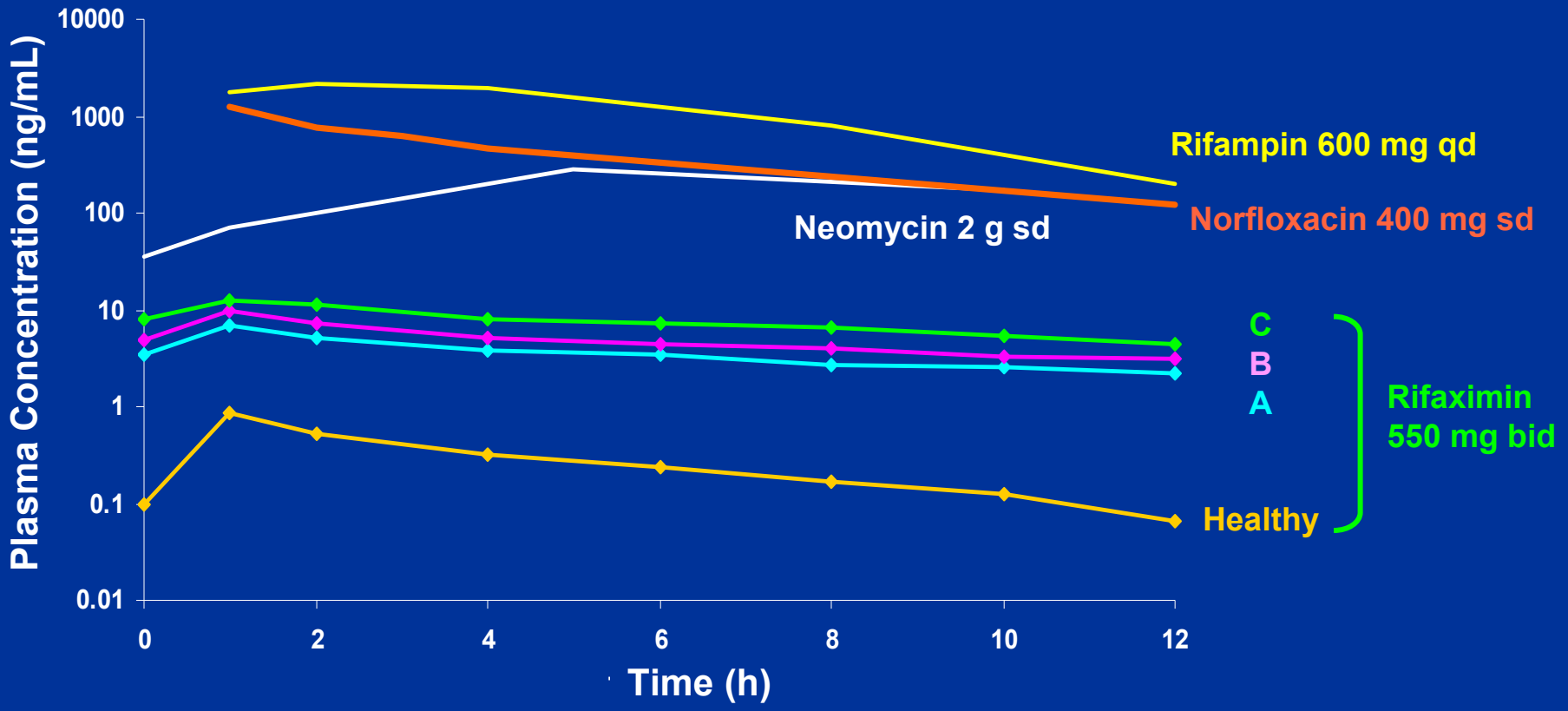


Rifaximin 550 mg BID

Mean (95% CI)	Healthy subjects N = 14	C-P A n = 18	C-P B n = 7	C-P C n = 4
AUC_{tau} (ng·h/mL)	12.3 (9.5-15.0)	118 (83.5-153.2)	161 (55.5-267)	246 (55.9-436)
C_{max} (ng/mL)	3.41 (2.47-4.34)	19.5 (13.8-25.2)	25.1 (13.4-36.8)	35.5 (15.6-55.5)
$t_{1/2}$ (h)	4.17 (2.44-5.90)	8.12 (6.25-10.0)	10.5 (9.20-11.8)	6.55 (4.94-8.16)
Protein binding (% bound)	67.5 (59.3-75.7)	62.6 (51.7-73.4)	60.9 (47.1-74.6)	

Rifaximin Exposure is Significantly Lower Than Other Antibiotics

- Rifaximin exposure in advanced liver disease
  - > 200-fold lower than rifampin exposure
  - ≥ 10-fold lower than neomycin exposure
  - > 35-fold lower than norfloxacin exposure



Well et al. *International Journal of Antimicrobial Agents*. 1998;10:31-38.

Low Risk of Drug Interactions

- **Inhibition**
  - **No inhibition of CYP enzymes, P-glycoprotein, or BSEP in vitro**
- **Induction**
  - **No clinically significant induction in vivo**

Midazolam parameters, mean (SD)	Midazolam alone N = 24	Midazolam with 7 days rifaximin N = 24	Midazolam with 14 days rifaximin n = 20
C_{max} (ng/mL)	10.8 (3.56)	10.1 (2.64)	10.1 (3.10)
$AUC_{0\text{-}t}$ (ng·h/mL)	22.5 (9.19)	21.0 (7.54)	20.5 (8.40)

No dose adjustments are recommended

Rifaximin Pharmacology Summary

- **Mechanisms**
  - Bacteriostatic activity and bacterial virulence reduction
    - Results in ammonia reduction in HE
- **ADMET**
  - Poor absorption, minimal metabolism, moderate protein binding
  - No clinically significant drug-drug interactions
  - No nonclinical safety signals
- **Important differences from rifampin**
  - Lower systemic exposure for rifaximin (100- to 1000-fold)
  - Lower induction potential for rifaximin (~10-fold)
  - Lower potential for antibacterial resistance (TB, *C. difficile*)

Overview of Hepatic Encephalopathy and Current Management Practices

Nathan Bass, MBChB, PhD

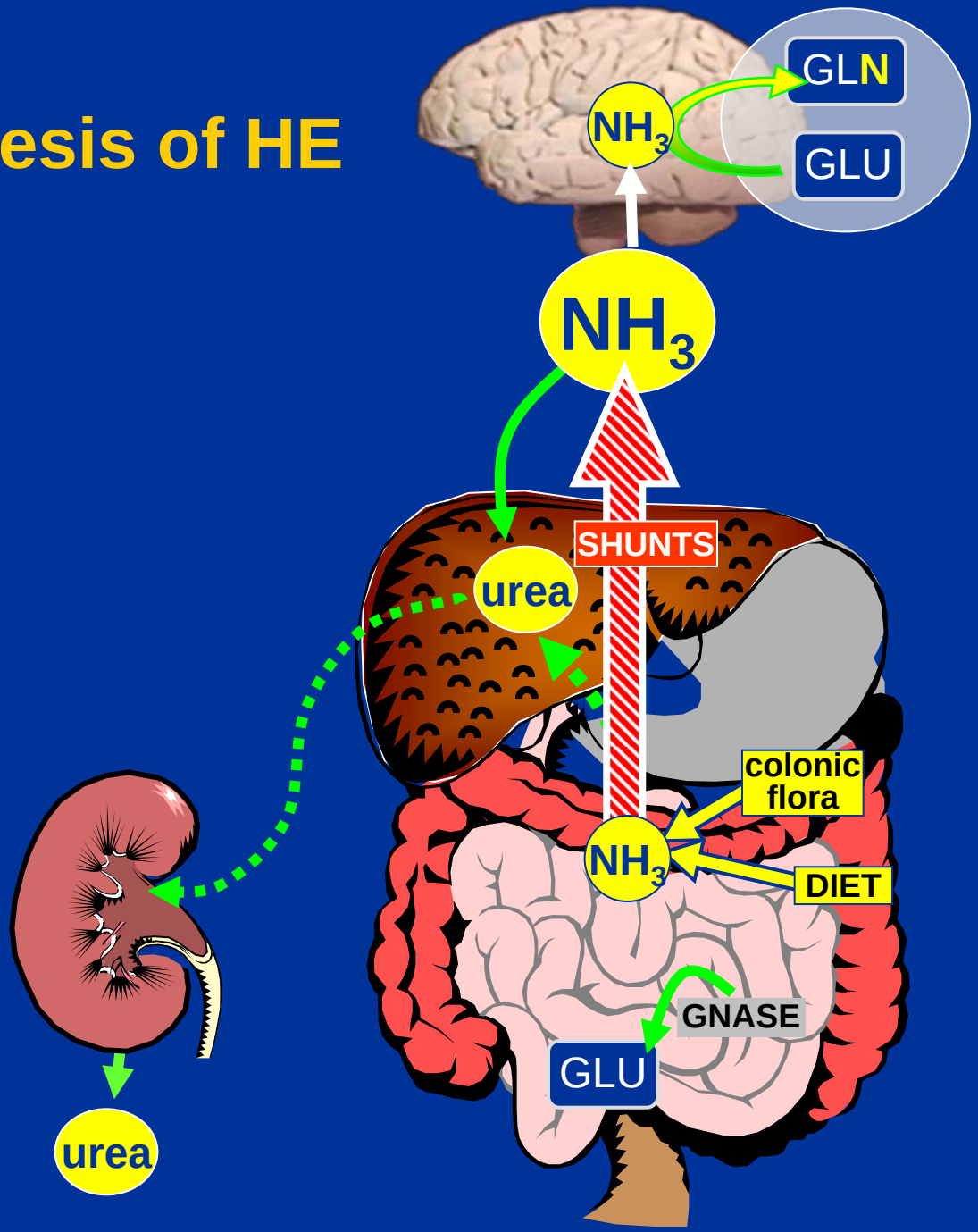
Professor of Medicine & Associate Medical Director,
UCSF Liver Transplant Program
University of California, San Francisco, School of Medicine

What is Hepatic Encephalopathy?

- Complication of advanced liver disease
- Exclusion of other known brain diseases
- HE affects 30% to 45% of cirrhosis patients
  - Cirrhosis is the 12th leading cause of death (27,555 deaths in 2006)
- Characterized by disturbance in personality, cognitive, intellectual, and neuromuscular function
- Ranges from minimal disturbances to coma

Abou-Assi S et al. *Postgrad Med*. 2001;109:52-70
Ferenci P et al. *Hepatology*. 2002;35:716-721.
Mas A et al. *J Hepatol*. 2003;38:51-58.
Heron MP et al. *National Vital Statistics Reports*. 2009; 57 no 14.

Pathogenesis of HE



Clinical Presentation of HE
Classification by 1998 WCOG Working Group

Type	HE Associated With	Category	Subcategory	
Acute liver failure	Acute liver failure			
Bypass	Portal-systemic Bypass and no intrinsic hepatocellular disease	Episodic	Precipitated Spontaneous Recurrent	Overt
Cirrhosis	Cirrhosis and portal hypertension or portosystemic shunts	Persistent	Mild Severe Treatment-dependent	Overt
		Minimal		

Diagnosis/Presentation of Episodic HE

- Episodic HE presents with impairment of
  - Consciousness
  - Intellectual function
  - Personality and behavior
  - Neuromuscular function
- Precipitating factors or spontaneous
- Reversible with treatment
- High rate of recurrence

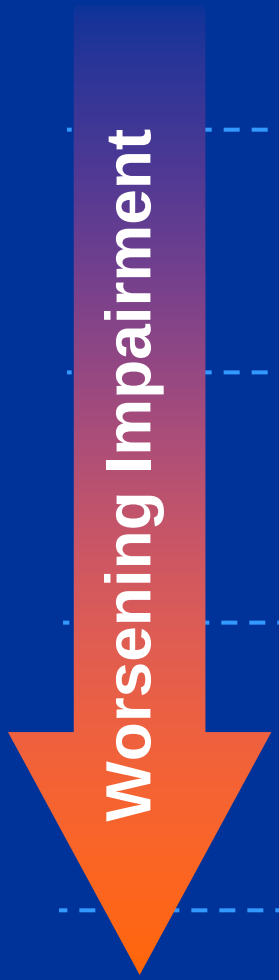
Ferenci P, et al. *Hepatology*. 2002;35:716-721; Mas A. *Digestion*. 2006;73(Suppl1):86-93; Amodio et al. *J Hepatol*. 2001; 35(1):37-45; Guevara et al. *Am J Gastroenterol*. 2009;104(6):1382-1389; Poordad FF. *Aliment Pharmacol Ther*. 2006;25(Suppl 1):3-9; Arguedas MR, et al. *Dig Dis Sci*. 2003;48(8):1622-1626; Bustamante J, et al. *J Hepatol*. 1999;30:890-895; Fichet et al. *J Crit Care*. 2009;24(3):364-370.

Key Diagnostic Strategies for HE

- Patient presentation
  - Advanced liver disease (PE, med Hx and clin labs)
  - Rule out unrelated neurologic and metabolic abnormalities
- Clinical assessment
  - West Haven (Conn) score
  - Asterixis grading
  - Clinical labs
    - Blood ammonia
  - Neurophysiological
    - Critical flicker frequency (CFF)
    - EEG

Blei AT, et al . *Am J Gastroenterol*. 2001 96:1968-1975; Hassanein TI, et al. *Dig Dis Sci*. 2008;53:529-538. Hassanein TI, et al. *Am J Gastroenterol*. 2009;104(6):1392-400; Conn HO, et al. *Gastroenterology.* 1977;72:573-583. Timmermann L, et al. *Clin Neurophysiol*. 2008;119:265-272.

Conn Score and Management Options



		Treatment approach
0	No abnormality detected	
1	Trivial lack of awareness Shortened attention span Impaired addition or subtraction Euphoria or anxiety	Outpatient intervention
2	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior	Medical intervention in ER/hospital
3	Somnolence to semi-stupor Responsive to stimuli Confusion Gross disorientation Bizarre behavior	
4	Coma, unable to test mental state	

HESA Mapping of Conn Score

	State of consciousness	Intellectual function	Personality/ behavior	Neuromotor function
Conn score = 0	• Alert and oriented X 3			
Conn score = 1	– Trivial lack of attention	– Shortened attn. span – Impaired addition	– Euphoria or depression	– Asterixis
HESA criteria	• Sleep disorder	• Impaired complex computations • Shortened attention span	• Euphoria or depression	• Tremor • Impaired construction
Conn score = 2	– Lethargy	– Minimal disorientation to time and place – Impaired subtraction	– Bizarre behavior	– Asterixis
HESA criteria	• Lethargy	• Disorientation to time • Mental control = 1 - 4 • Amnesia • Impaired simple computations	• Inappropriate behavior • Anxiety	• Slurred speech • Hyperactive reflexes
Conn score = 3	– Somnolence/stupor	– Confusion gross disorientation	– Bizarre behavior	– Clonus/rigidity
HESA criteria	• Somnolence	• Confusion • Disorientation to place • Mental control = 0	• Bizarre behavior/anger rage	• Clonus/rigidity
Conn score = 4	– Coma	– N/A	– N/A	– N/A
HESA criteria	• No eyes opening; No verbal responses; No reaction to simple commands			

Adapted. Reprinted by permission from Macmillan Publishers Ltd: American Journal of Gastroenterology.
Hassanein TI, et al. *Am J Gastroenterol*. 2009;104(6):1392-1400.

HESA Mapping of Conn Score

	State of consciousness	Intellectual function	Personality/ behavior	Neuromotor function
Conn score = 0	• Alert and oriented X 3			
Conn score = 1	– Trivial lack of attention	– Shortened attn. span – Impaired addition	– Euphoria or depression	– Asterixis
HESA criteria	• Sleep disorder	• Impaired complex computations • Shortened attention span	• Euphoria or depression	• Tremor • Impaired construction
Conn score = 2	– Lethargy	– Minimal disorientation to time and place	– Bizarre behavior	– Asterixis
HESA				
Conn				
HESA		• Mental control =0	rage	
Conn score = 4	– Coma	– N/A	– N/A	– N/A
HESA criteria	• No eyes opening, No verbal responses, No reaction to simple commands			

HESA neuropsych assessments

Arithmetic subtest of the Wide Range Achievement Test

Letter–Number Sequencing (Wechsler Adult Intelligence Scale)

7 point Likert scale

BVMT-R Copy Trial or can write name legibly

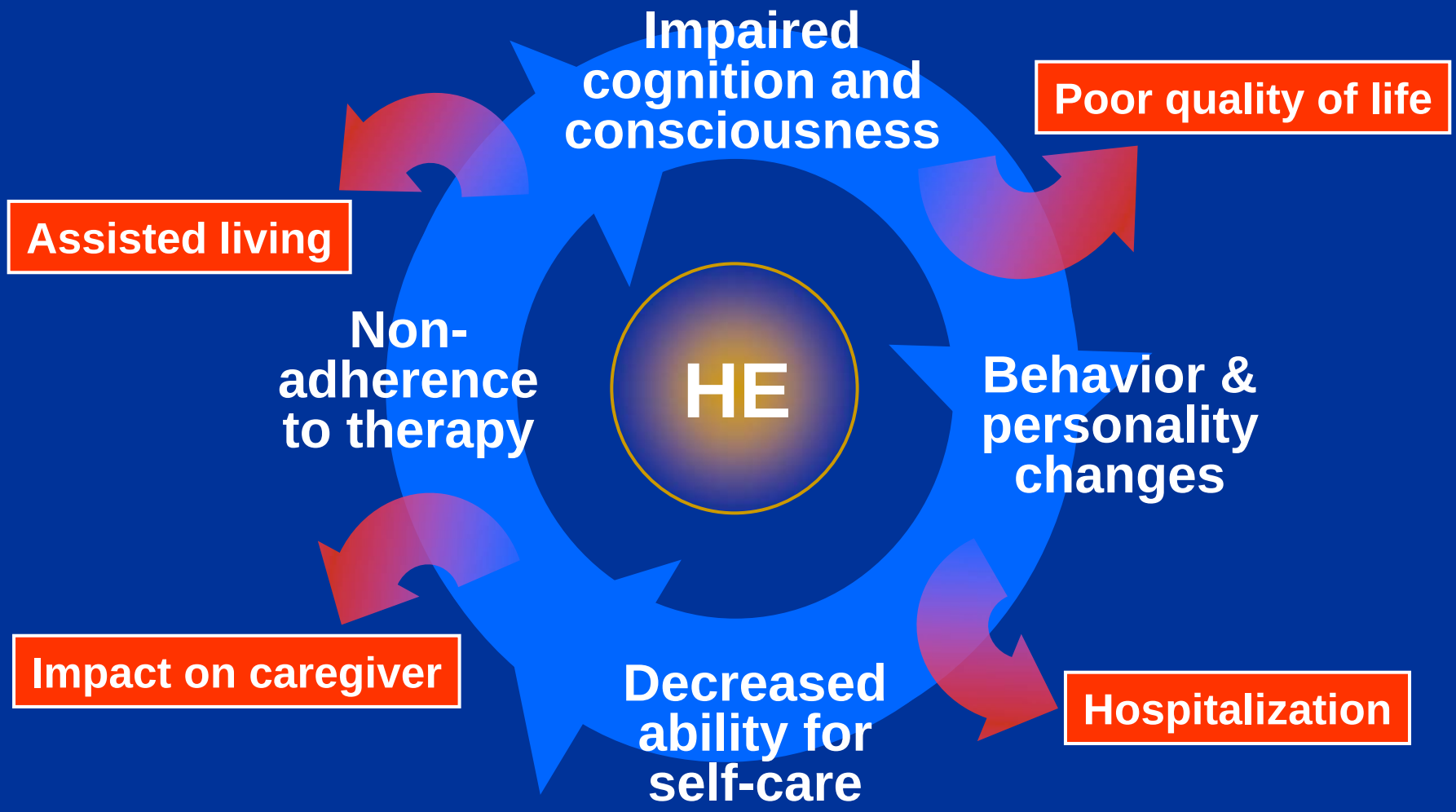
Adapted. Reprinted by permission from Macmillan Publishers Ltd: American Journal of Gastroenterology.
Hassanein TI, et al. *Am J Gastroenterol*. 2009;104(6):1392-1400. BVTM-R = Brief Visuospatial Memory Test-Revised

Asterixis Grading

Grade 0 =	No tremors
Grade 1 =	Rare flapping motions
Grade 2 =	Occasional, irregular flaps
Grade 3 =	Frequent flaps
Grade 4 =	Almost continuous flapping motions

Reprinted from Elsevier. Conn HO, et al. Gastroenterology. 1977;72;573-583.

Impact of HE on the Patient and Caregiver



Goals of Therapy for Episodic HE

- Resolve the acute episode
- Prevent recurrent HE episodes
  - Decrease the impact of HE on patient's health and quality of life
  - Decrease the impact of HE on the healthcare system

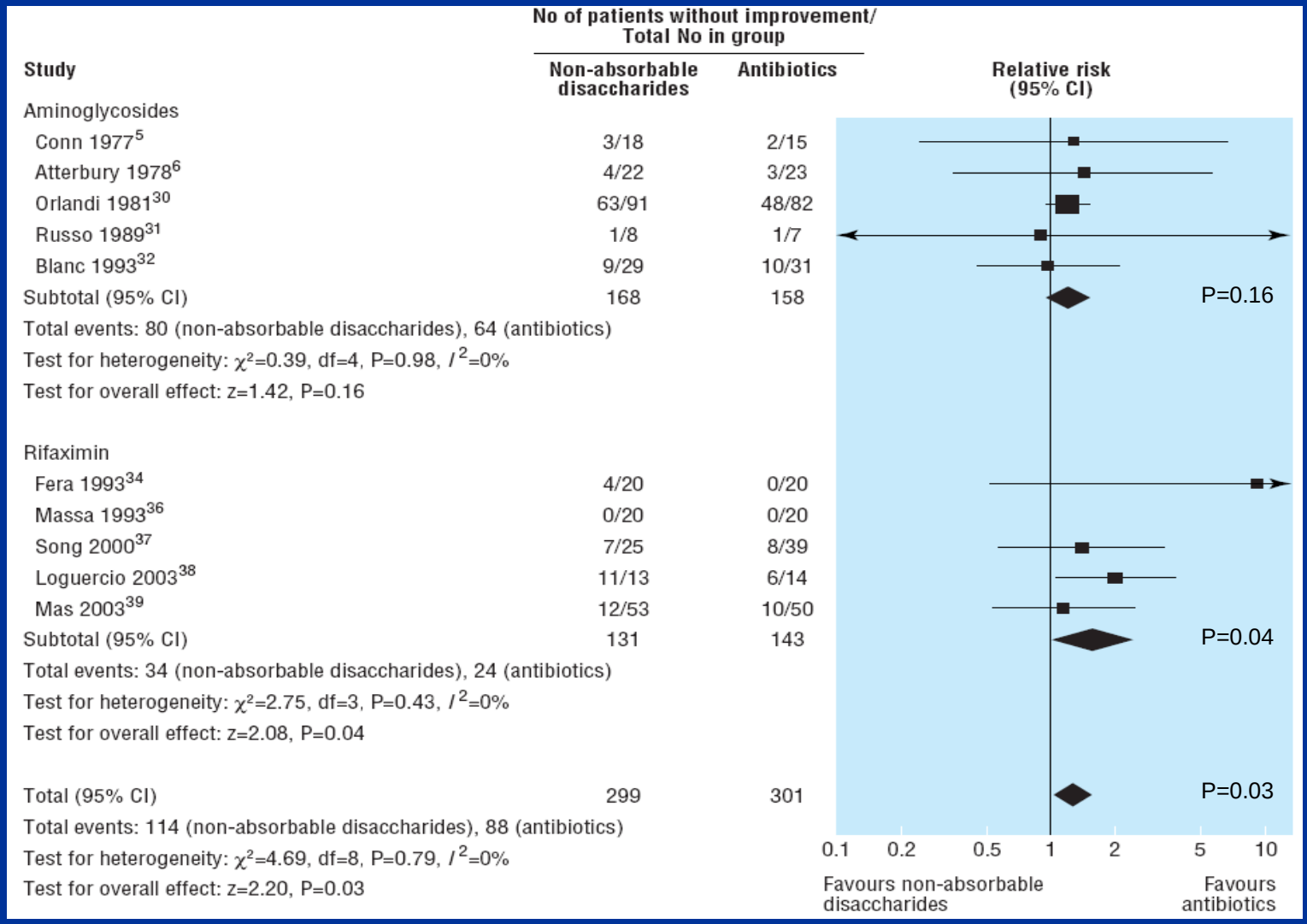
An effective, well-tolerated and safe therapy for long-term treatment

Currently Approved HE Therapies

	Lactulose	Neomycin
Mechanism	• Traps ammonia and inhibits production • Purging effect (frequent bowel movements)	• Antibacterial action • Prevention of bacterial ammonia production
Limitations	• Reliance on self-titration • Unpredictable, severe diarrhea • Dehydration and hypernatremia • Nausea, abdominal pain, flatulence	• Nephrotoxic and ototoxic • Increased risk in advanced liver disease
Long-term Limitations	• Poor tolerance, compliance and varying efficacy	• Toxicity

Rifaximin as a Treatment Option for Hepatic Encephalopathy

Antibiotics as a Treatment Option for HE
Cochrane Meta-Analysis

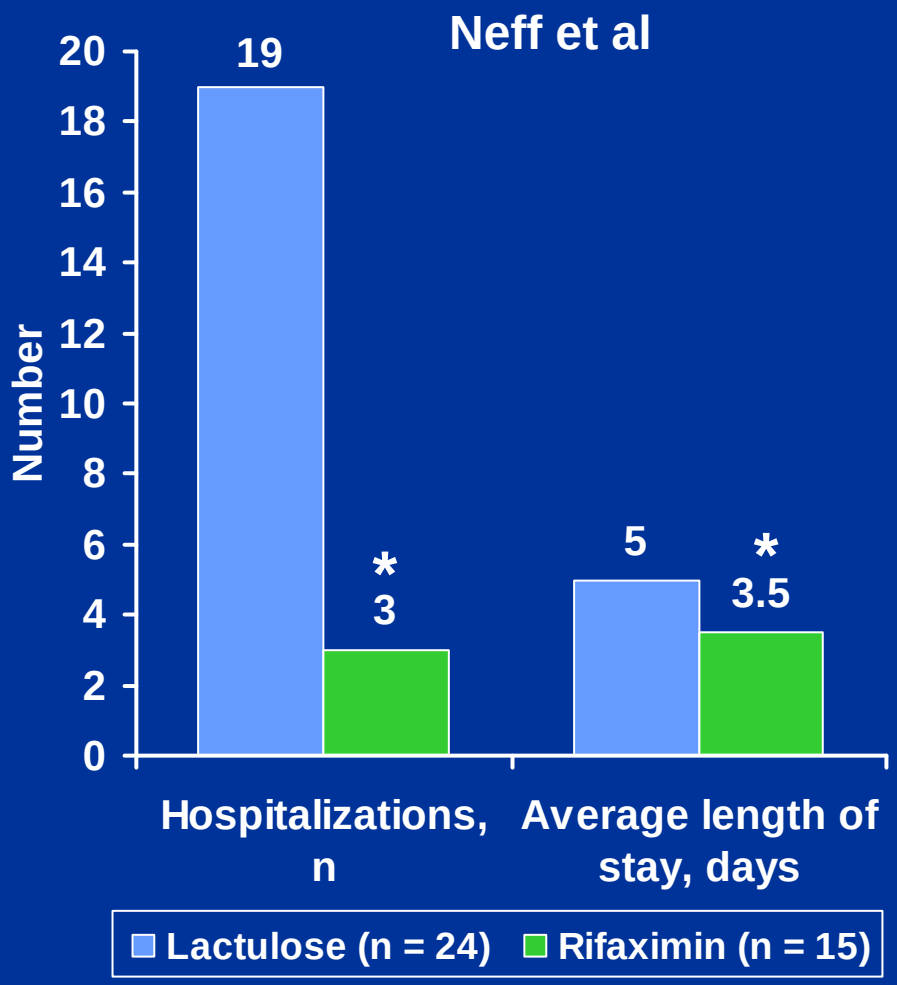


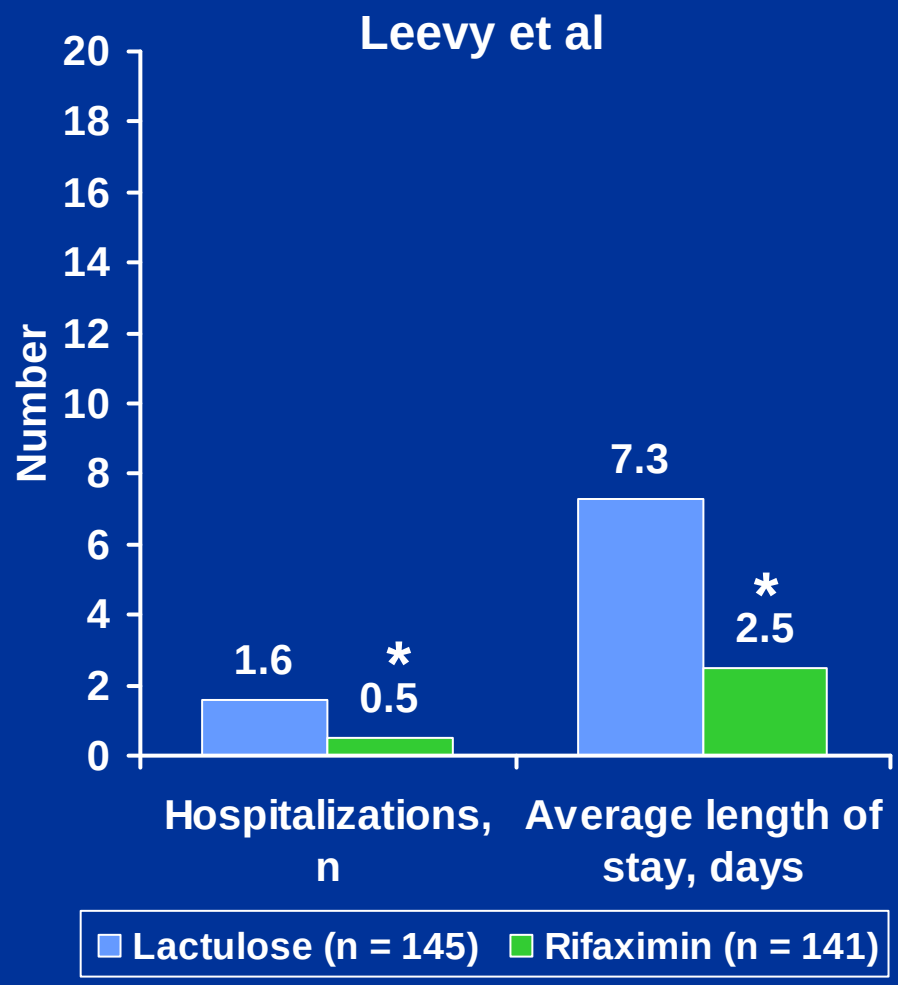
Efficacy of Rifaximin for the Treatment of HE Episodes

Study	Design	Results
RFHE9702 Williams, 2000 N = 54	• Double blind, 7 days • Dose ranging 600, 1200, 2400 mg/day	• Dose response ($p = 0.056$) for PSE Index • 1200 mg/day (400 mg TID) optimal dose
RFHE9701 Mas, 2003 N = 104	• Double blind, 10 days • Rfx (1200 mg/day) • Lactitol (60 g/day)	• Rfx vs lactitol ($p < 0.05$) for PSE index, HE grade, ammonia
RFHE9901 Bass, 2004 N = 93	• Double blind, PBO controlled, 14 days • Rfx (1200 mg/day)	• Rfx vs PBO for asterixis ($p < 0.01$)

Williams R, et al. *Eur J Gastroenterol Hepatol*. 2000;12:203-208. Mas A, et al. *J Hepatol*. 2003;38:51-58. Bass N, et al. Presented at: 55th Annual Meeting of the American Association for the Study of Liver Diseases; October 29-November 2, 2004; Boston, Mass.

Rifaximin Reduces Hospitalizations Compared With Lactulose





*$p < .0001$

[a] Neff GW, et al. *Transplant Proc*. 2006;38:3552-3555; [b] Leevy CB, Phillips JA. *Dig Dis Sci*. 2007;52:737-741.

Summary

- HE is a serious, debilitating condition resulting from advanced liver disease
- HE causes significant cognitive impairment that
  - Disrupts ability for self-care, compliance, and quality of life
  - Results in frequent intervention and hospitalization
- There remains an unmet medical need for effective, safe, and well-tolerated therapies
- Rifaximin represents a significant, therapeutic advancement in treatment of HE

Efficacy of Rifaximin for Treatment of Hepatic Encephalopathy

William P. Forbes, PharmD

Senior Vice President, Research & Development
Chief Development Officer
Salix Pharmaceuticals, Inc.

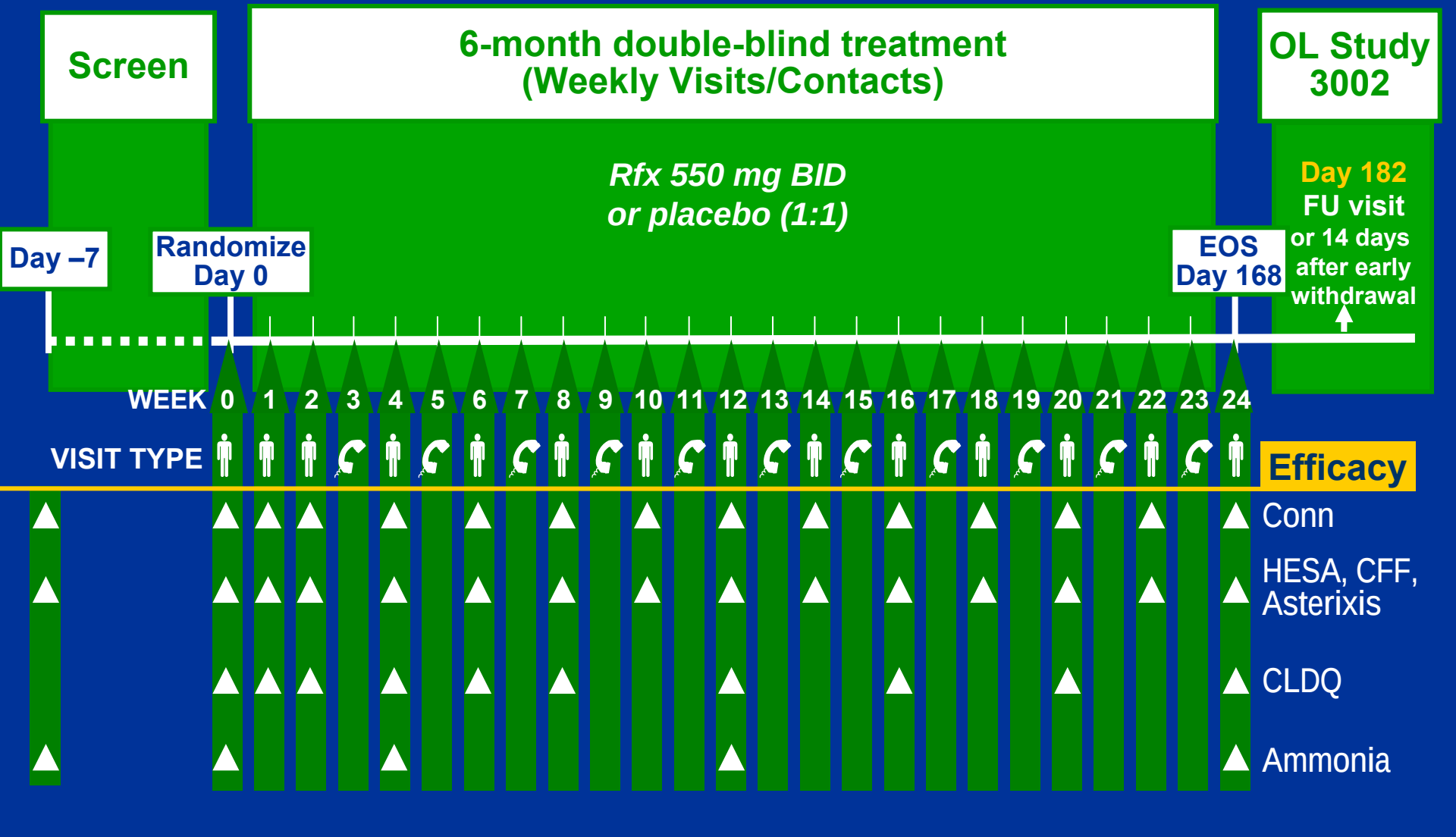
Overview of Topics Covered
Pivotal Study 3001

- Study design
  - Reliability of determining Conn at baseline (HESA)
  - Subject disposition and baseline characteristics
- Study results
  - Primary endpoint (time to breakthrough)
    - Subgroup analysis (consistency of effect)
    - FDA Issues: validity of endpoint
  - Key secondary endpoint (time to HE-related hosp)
  - Secondary and exploratory endpoints
    - Conn, asterixis, PRO, ammonia, CFF
  - Long-term efficacy
- Conclusion

Study 3001

- Design
  - Randomized, placebo-controlled, double-blind
- Study objective
  - Evaluate efficacy and safety of Rifaximin for 6 months in maintenance of remission in patients with documented episodic, overt HE as result of liver disease
- Dose: 550 mg BID
- 299 patients enrolled in 70 study centers in the US, Canada, and Russia

Study Design
Studies 3001 and 3002



Key Entry Criteria
Study 3001

- **Inclusion**
  - HE associated with advanced liver disease
  - ≥ 2 episodes of HE (Conn score ≥ 2) within 6 months of screening (1 documented in medical record)
  - Conn score 0 or 1 at screening and randomization
  - MELD score ≤ 25
  - Signed informed consent/assent of patient and caregiver
- **Exclusion**
  - Medical/psychiatric condition interfering with assessments
  - Use of alcohol within 14 days, sedatives within 7 days, current drug dependence
  - HE due to GI hemorrhage, CNS insult, medications, renal failure
  - TIPS placement or revision within 3 months prior to screening
  - Renal insufficiency, anemia, hypovolemia, electrolyte abnormality

Primary Efficacy Endpoint
Study 3001

Time to first breakthrough HE episode

Breakthrough HE episode:

- An increase in Conn score[a] to ≥ 2 (ie, 0 or 1 to ≥ 2)

OR

- An increase of 1 for both Conn score and asterixis grade for patients with a baseline Conn score 0

[a] Definition of Breakthrough HE mirrors Final Report of the Working Party at the 11th World Congresses of Gastroenterology, Vienna, 1998.

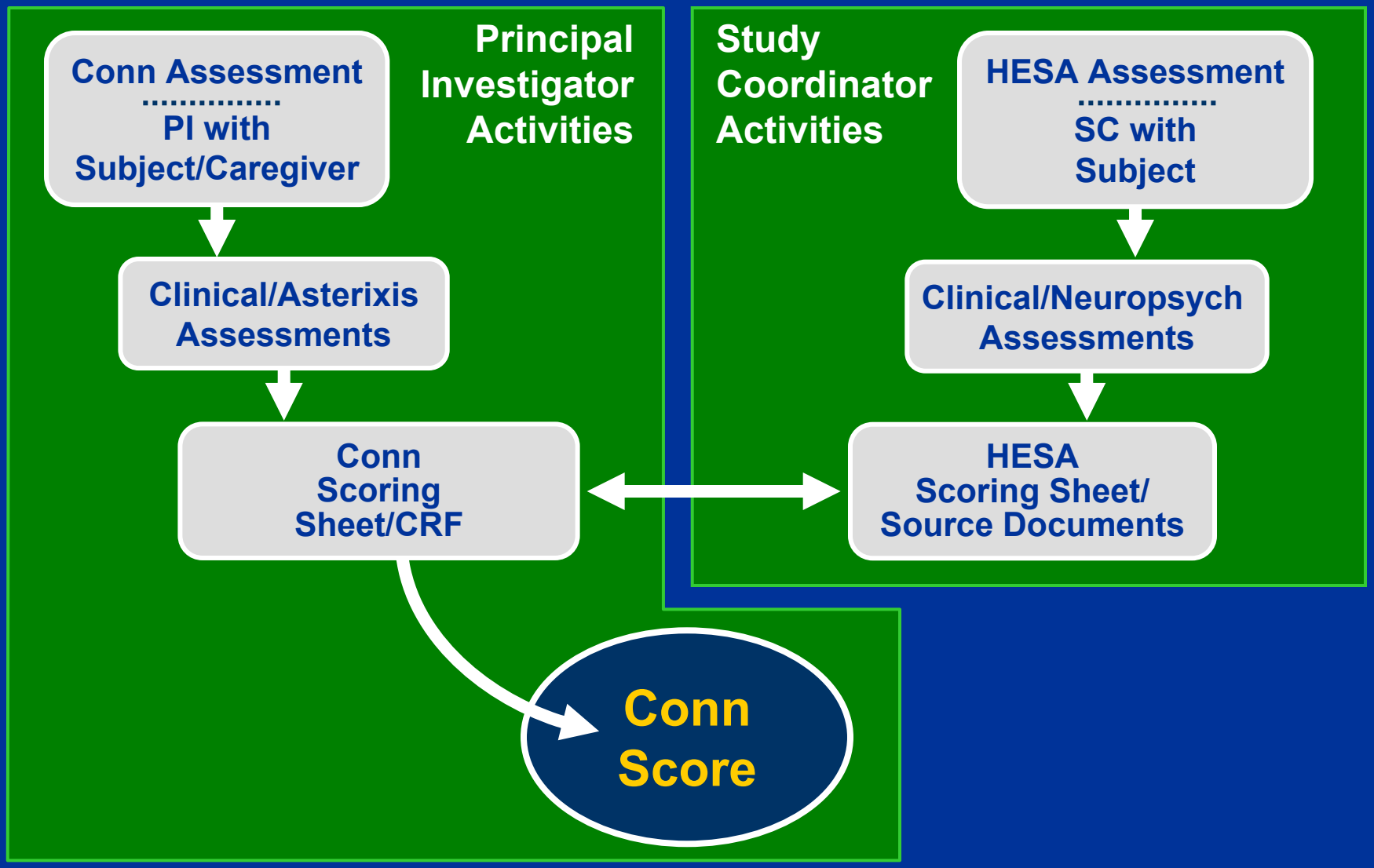
Breakthrough HE Surveillance
Study 3001

HE breakthrough always adjudicated by principal investigator

- During clinic visits
  - HESA
  - Conn and Asterixis
- Between clinic visits
  - Conn score only (no asterixis)
  - Weekly or unscheduled phone calls
    - Initiated by site/patient/caregiver
    - Changes in patient's routine, behavior or demeanor
    - Adverse events
    - Concomitant medication (including lactulose) changes
  - ER or hospitalization
    - Physician observed HE symptoms

Assessment at Baseline and Postbaseline Visits

Conn and HESA



The Conn (West Haven Criteria)

- Conn is the most widely used HE grading method
- Grading relies solely on clinical judgment

HE Grade	Conn Criteria
0	No personality or behavioral abnormality detected
1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction
2	Lethargy Disorientation for time Obvious personality change Inappropriate behavior
3	Somnolence to semistupor Responsive to stimuli Confused Gross disorientation Bizarre behavior
4	Coma (Unresponsive to verbal or noxious stimuli)

Atterbury, Maddey, & Conn, 1978; Conn et al., 1977; Huda et al., 1998; Quero Guillen et al., 2003; RFHE3001 protocol

Asterixis Grading

Grade 0 =	No tremors
Grade 1 =	Rare flapping motions
Grade 2 =	Occasional, irregular flaps
Grade 3 =	Frequent flaps
Grade 4 =	Almost continuous flapping motions

HESA Components Assessed by Study Coordinator

HESA Clinical Assessments REQUIRED

- Sleep disorder
- Tremor

- Lethargy
- Loss of time
- Slurred speech
- Hyperactive reflexes
- Inappropriate behavior

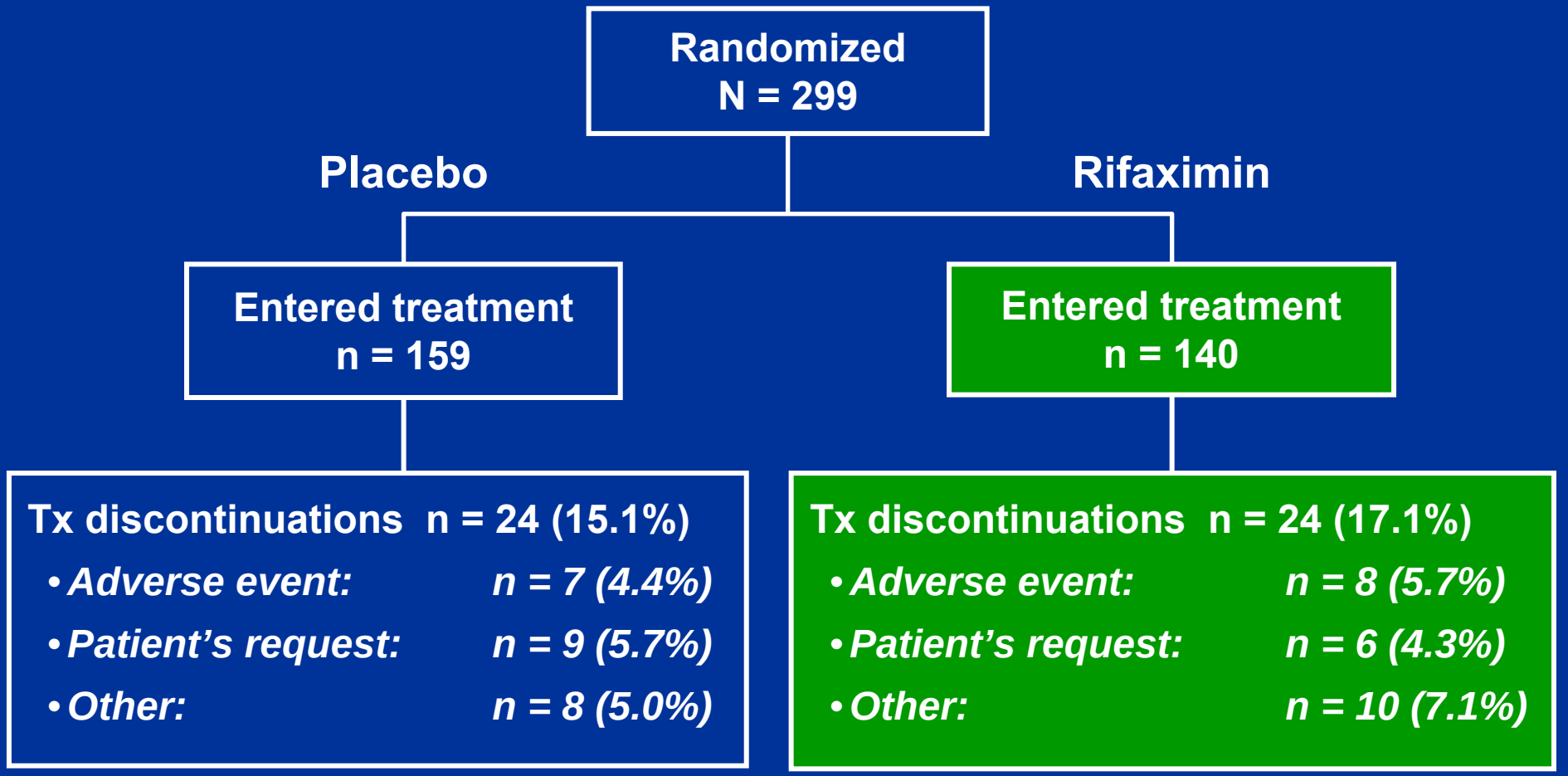
- Somnolence
- Confusion
- Disoriented to place
- Bizarre behavior/Anger/Rage
- Clonus/Rigidity/ Nystagmus/Babinsky

- No eyes opening
- No reaction to simple commands
- No verbal response

Neuropsychological testing REQUIRED

- Counting numbers and saying alphabet
  - Mental Control
- Word Recognition and Recall
  - Hopkins Verbal Learning Test (HVLT)
- Simple and complex computations
- Depression rating
- Anxiety rating
- # digits remembered
  - Digit span
- Analysis of ability to draw
  - Copy trial

Patient Disposition
Study 3001 - Intent-to-Treat Population



Demographics
Studies 3001 and 3002

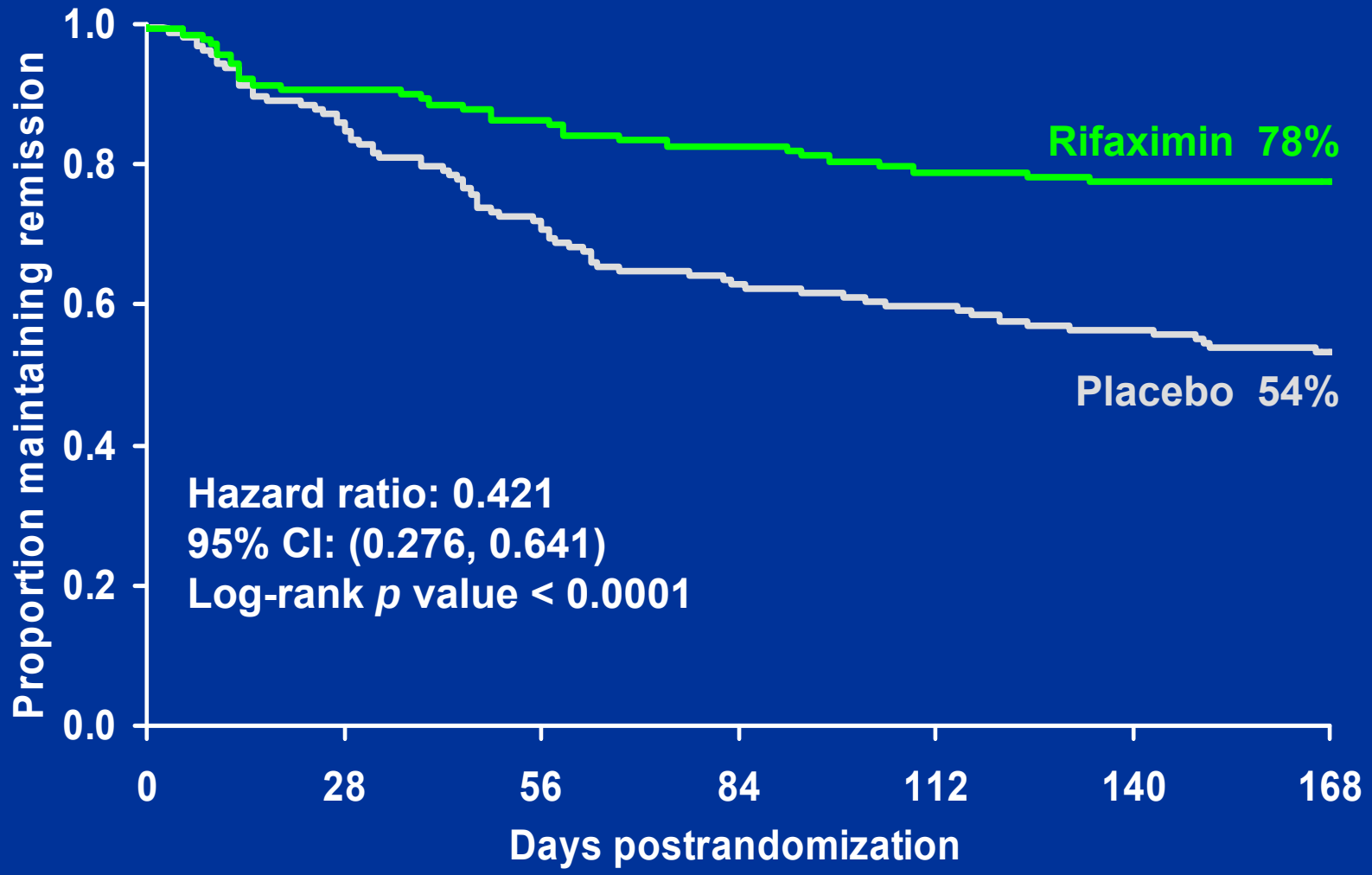
Category		Patients, n (%)		
		Study 3001		3001/3002
		Placebo n = 159	Rifaximin n = 140	All rifaximin n = 348
Sex	Male	107 (67)	75 (54)	203 (58)
	Female	52 (33)	65 (46)	145 (42)
Age	Mean (SD)	57 (9)	56 (10)	57 (9)
	< 65 yr	128 (81)	113 (81)	277 (80)
	≥ 65 yr	31 (19)	27 (19)	71 (20)
Race	White	139 (87)	118 (84)	310 (89)
	Non-White	20 (13)	21 (15)	37 (11)
Ethnicity	Hispanic or Latino	28 (18)	21 (15)	45 (13)
	Not Hispanic or Latino	131 (82)	119 (85)	303 (87)
Country	United States	112 (70)	93 (66)	269 (77)
	Canada	6 (4)	8 (6)	15 (4)
	Russia	41 (26)	39 (28)	64 (19)

Baseline Disease Characteristics
Study 3001

		Placebo n = 159	Rifaximin n = 140
Liver	Duration CLD, mo, mean (range)	61 (2.0 - 323.4)	51 (1.7 - 260.5)
	MELD, mean (range)	12.7 (6 - 23)	13.1 (6 - 24)
	TIPS, n (%)	20 (13)	12 (9)
HE	Time since last HE, days (range)	73 (12 - 205)	69 (8 - 222)
	HE episodes, past 6 mo, n (%)		
	n = 2	111 (70)	97 (69)
	n > 2	47 (30)	43 (31)
	Conn at baseline, n (%)		
	Score = 0	107 (67)	93 (66)
	Score = 1	52 (33)	47 (34)
	Ammonia, µg/dL, mean (range)	90.3 (20 - 465)	87.9 (20 - 290)
	CFF, Hz, mean (range)	37.4 (15 - 50)	36.9 (18 - 48)

Results RFHE3001

Primary Endpoint
Kaplan-Meier of Time to First HE Breakthrough
Study 3001 - ITT Population



Lactulose Use – Did Not Influence Study Outcome

Study 3001

Parameter	Placebo N = 159	Rifaximin N = 140
Lactulose at baseline		
Yes, n (%)	145 (91)	128 (91)
No, n (%)	14 (9)	12 (9)
Average daily lactulose use (cups/d [15 mL/cup])		
Mean ± SD	3.51 ± 2.59	3.14 ± 2.10
Median (min - max)	2.8 (0 - 11.8)	2.8 (0 - 9.0)

Components of Primary Endpoint Are Significant

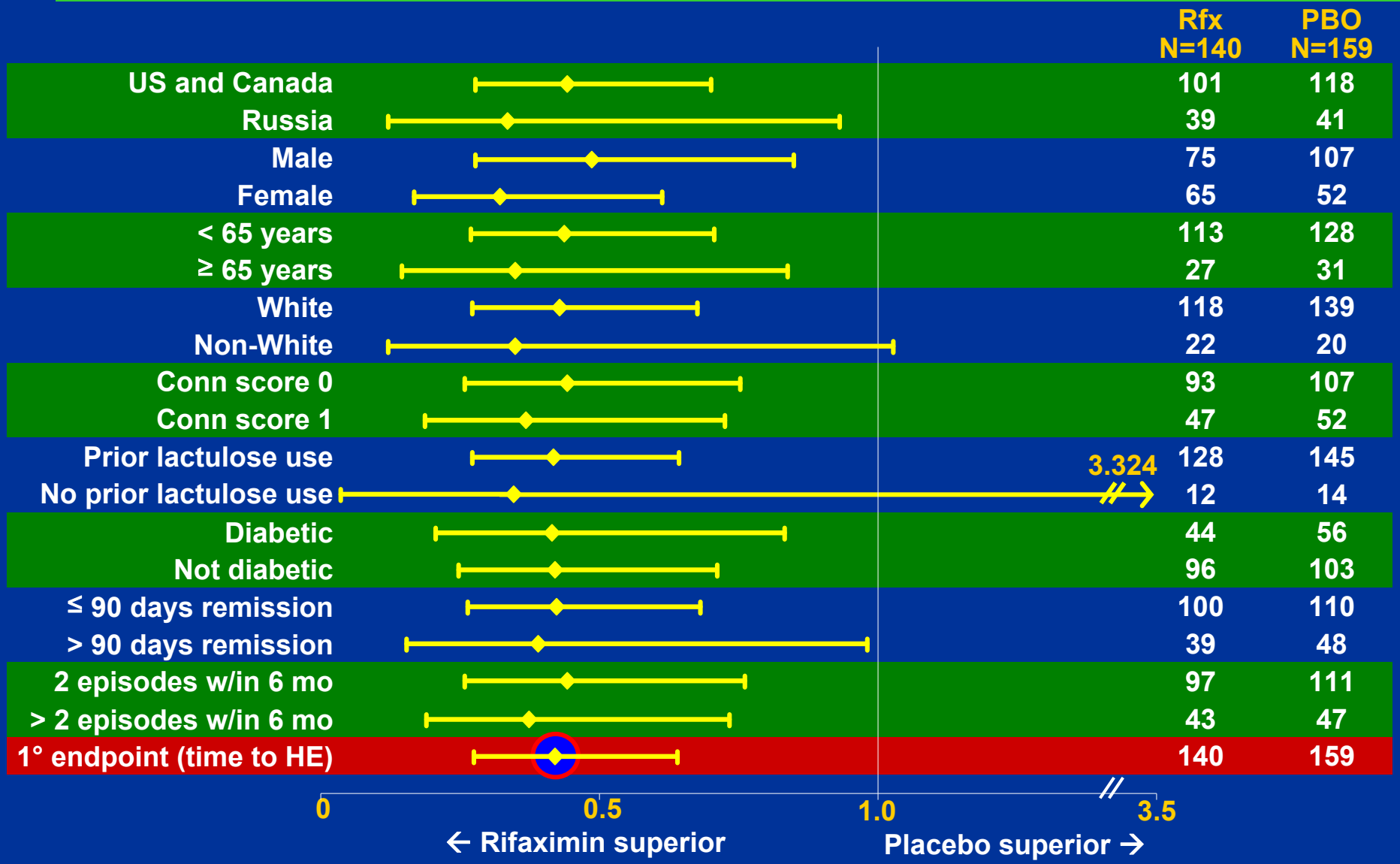
Study 3001 - ITT Population

	Patients, n (%)			
	Placebo N = 159	Rifaximin N = 140	Hazard ratio (95% CI)	*p* value
Conn score ≥ 2	57 (35.8)	28 (20.0)		0.0027[a]
Increase in Conn and asterixis of 1 each if baseline Conn score = 0	16 (10.1)	3 (2.1)		0.0055[a]
Primary endpoint	73 (45.9)	31 (22.1)	0.421 (0.28, 0.64)	< 0.0001[b]

[a] Cochran-Mantel-Haenszel Test
[b] Log rank test

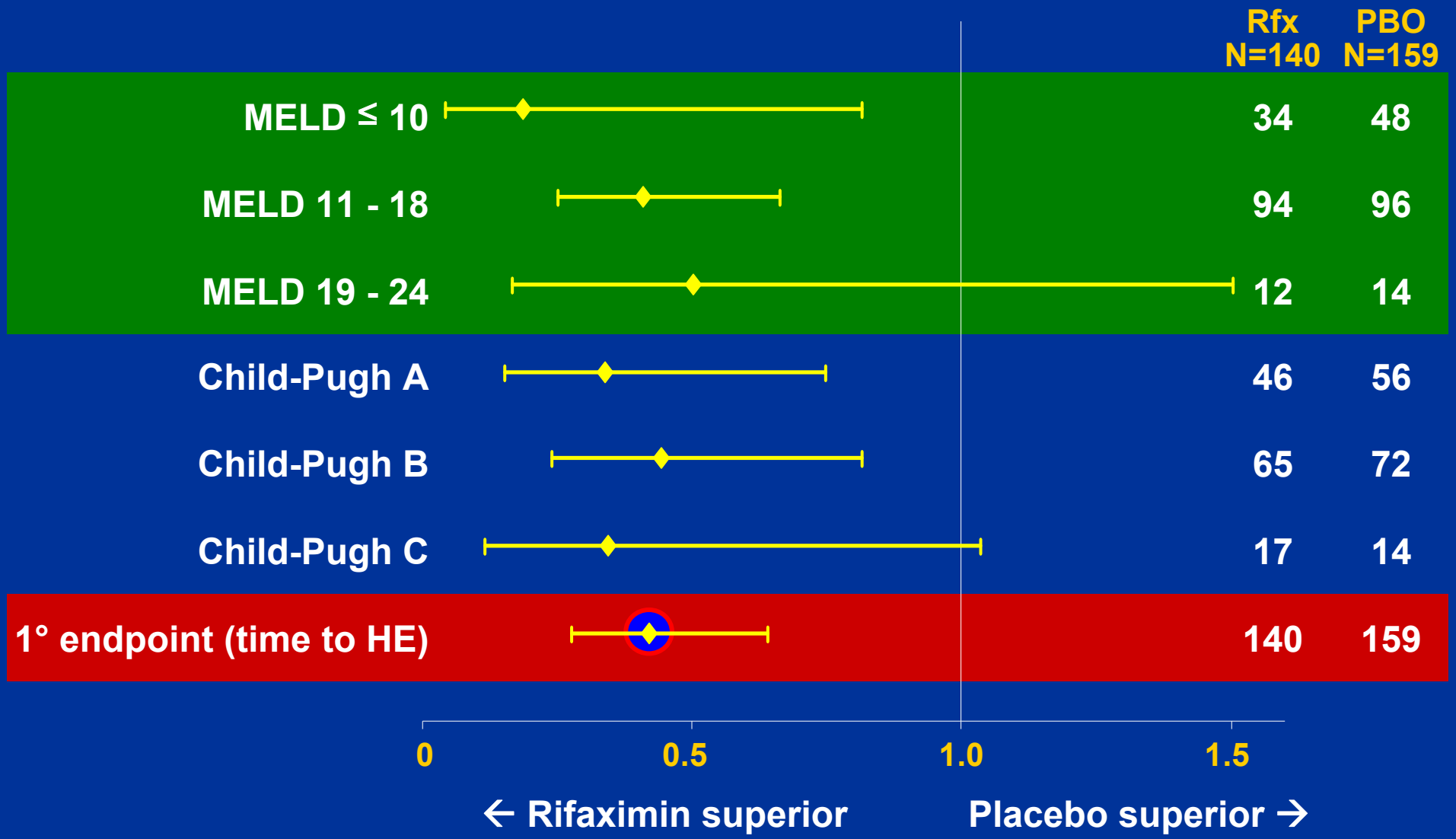
Consistency of Treatment Effect Across Subgroups

Study 3001 - Primary Endpoint



Consistency of Treatment Effect Across Subgroups

Study 3001 - Primary Endpoint



FDA Questions: Validity of Primary Endpoint
Study 3001

- Is Conn score a valid endpoint?
  - Standard assessment tool for over 30 years
  - Easily identifiable clinical changes
  - Endorsed by WCOG and medical experts?
  - Agreed upon endpoint between FDA and Sponsor
  - No substitute proposed
- Accuracy of Conn score at baseline?
  - HESA confirmation of Conn scoring
- Accuracy of Conn score at visits and breakthrough?
  - HESA confirmation of Conn scoring
  - Symptoms vs source (PI/Hospital/Caregiver)
- Correlation of primary endpoint with time dependent prognostic factors
  - Ammonia and CFF
  - Patient-reported outcome
  - All-cause mortality

Accuracy of Conn Score at baseline
HESA Confirmation of Conn Scoring

HESA category	HESA indicator	Patients, n (%) Conn score = 0 N = 129	Conn score = 1 N = 43	Conn score = 2 N = 0	*p value Conn 0 vs 1
Clinical	Sleep disorder/ Impaired sleep pattern	32 (25)	27 (63)	—	< 0.0001
Clinical	Tremor	17 (13)	21 (49)	—	< 0.0001
Clinical	Inappropriate/ Bizarre behavior	0	0	—	
Clinical	Disorientation to place	0	0	—	
Neuropsychological	Amnesia of recent events	64 (50)	32 (74)	—	0.0047
Neuropsychological	Impaired simple computations	4 (3)	6 (14)	—	0.0167
Neuropsychological	Impaired complex computations	31 (24)	18 (42)	—	0.0320
Neuropsychological	Depression	17 (13)	13 (30)	—	0.0186

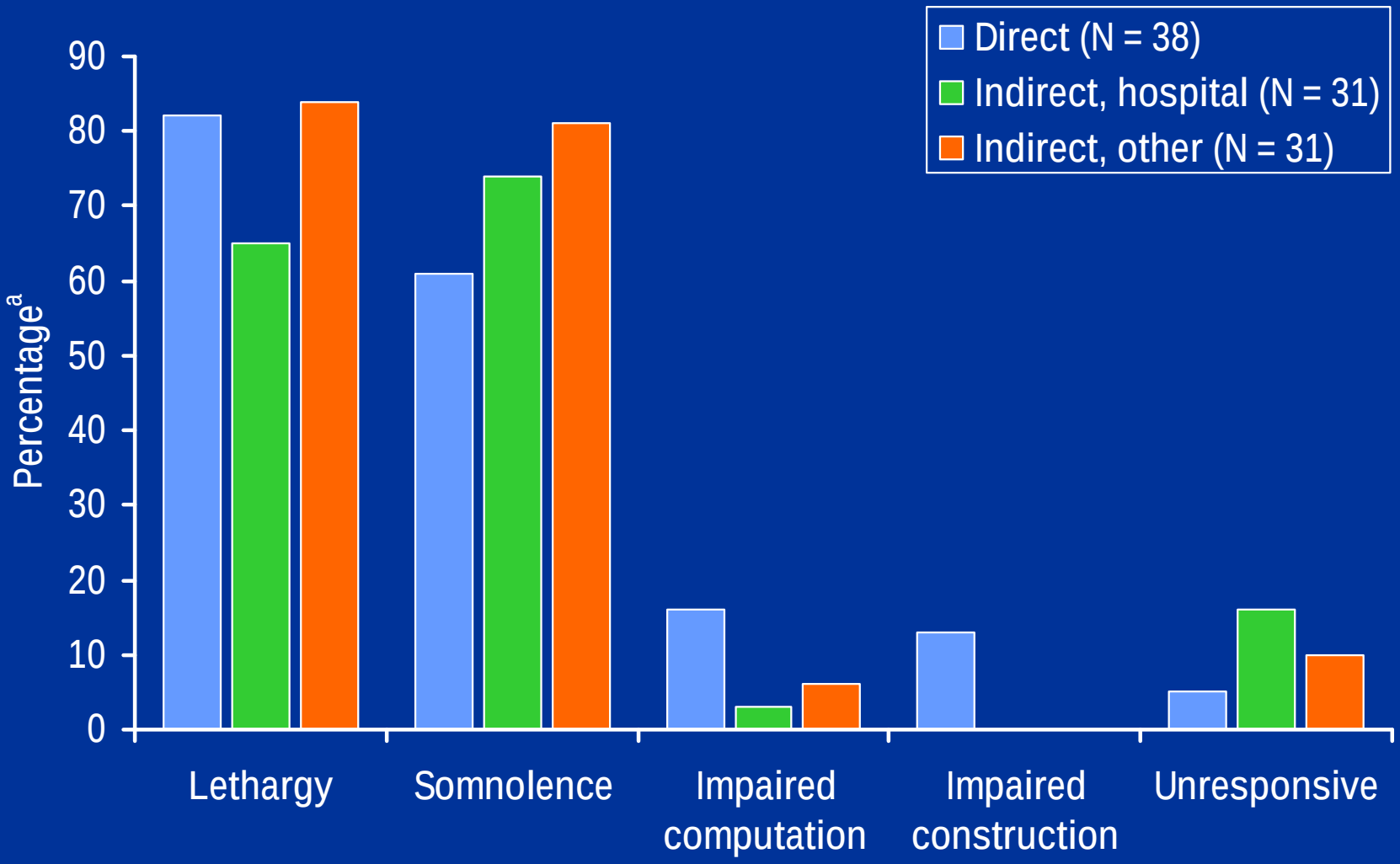
Method of Diagnosing Breakthrough HE

FDA Ad Comm Briefing Document, Tables 1, 9

	Patients, n / N (%)	
Category (% of 104)	Placebo N = 159 73 breakthrough HE	Rifaximin N = 140 31 breakthrough HE
Direct, at site (37)	30 / 73 (43)	8 / 31 (27)
Indirect, hospitalized (30)	19 / 73 (27)	12 / 31 (40)
Indirect, other ER or caregiver (30)	21 / 73 (29)	10 / 31 (32)
Post-study F/U (4) (168 days)	3 / 73 (4)	1 / 31 (3)

Symptoms Associated With Diagnostic Class

FDA Ad Comm Briefing Document

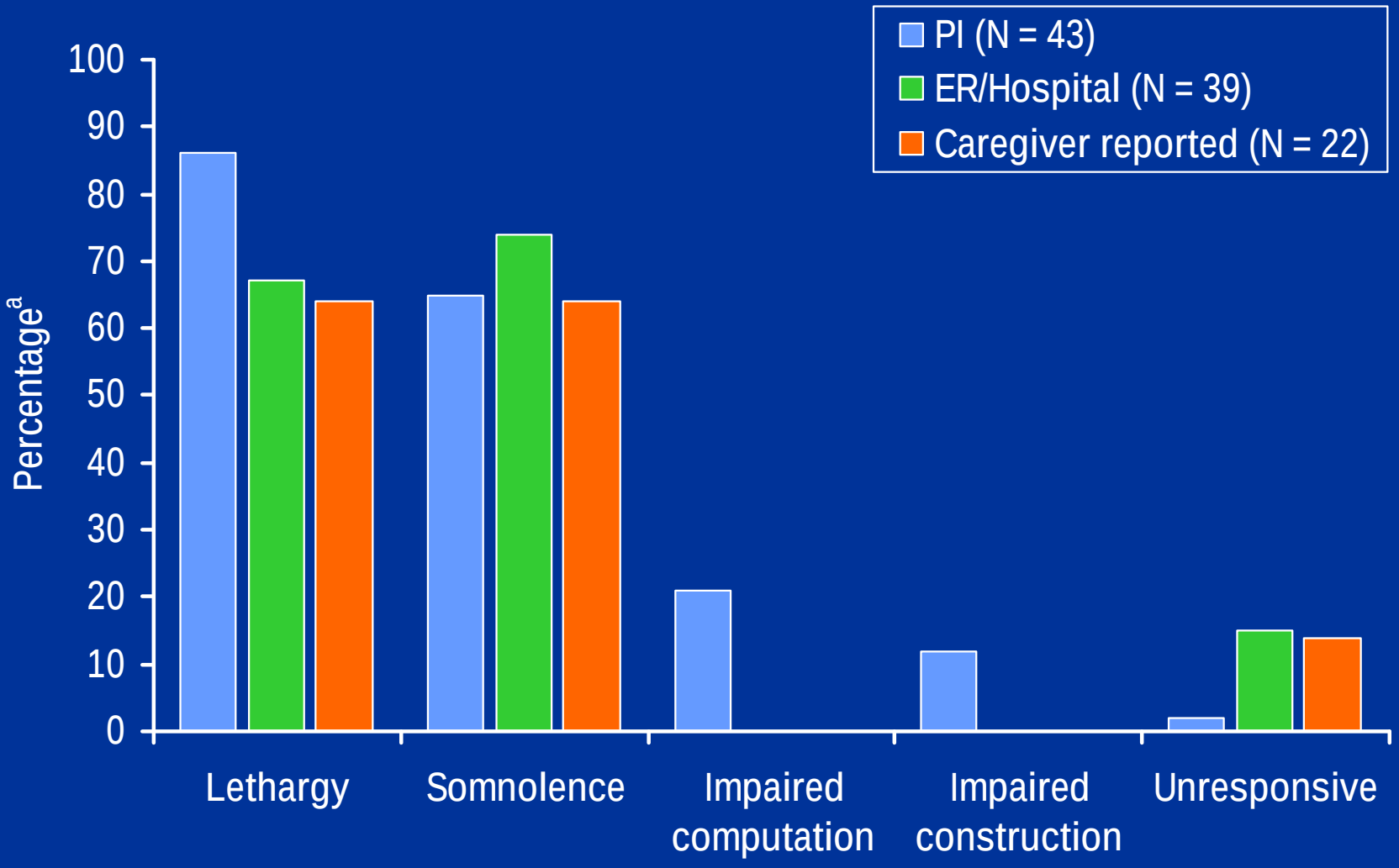


[a] % based on number of reported symptoms within a category.

Breakthrough HE
Basis of Information Used for PI Adjudication

Category (% of 104)	Patients, n / N (%)	
	Placebo N = 159 73 breakthrough HE n / n (%)	Rifaximin N = 140 31 breakthrough HE n / n (%)
PI (41) PI observed and adjudicated breakthrough HE in clinic or hospital	32 / 73 (44)	11 / 31 (35)
ER/Hospital (38) PI adjudicated breakthrough HE after review of medical records and caregiver testimony	26 / 73 (36)	13 / 31 (42)
Caregiver reported (21) PI adjudicated breakthrough HE based on caregiver / patient testimony	15 / 73 (21)	7 / 31 (23)

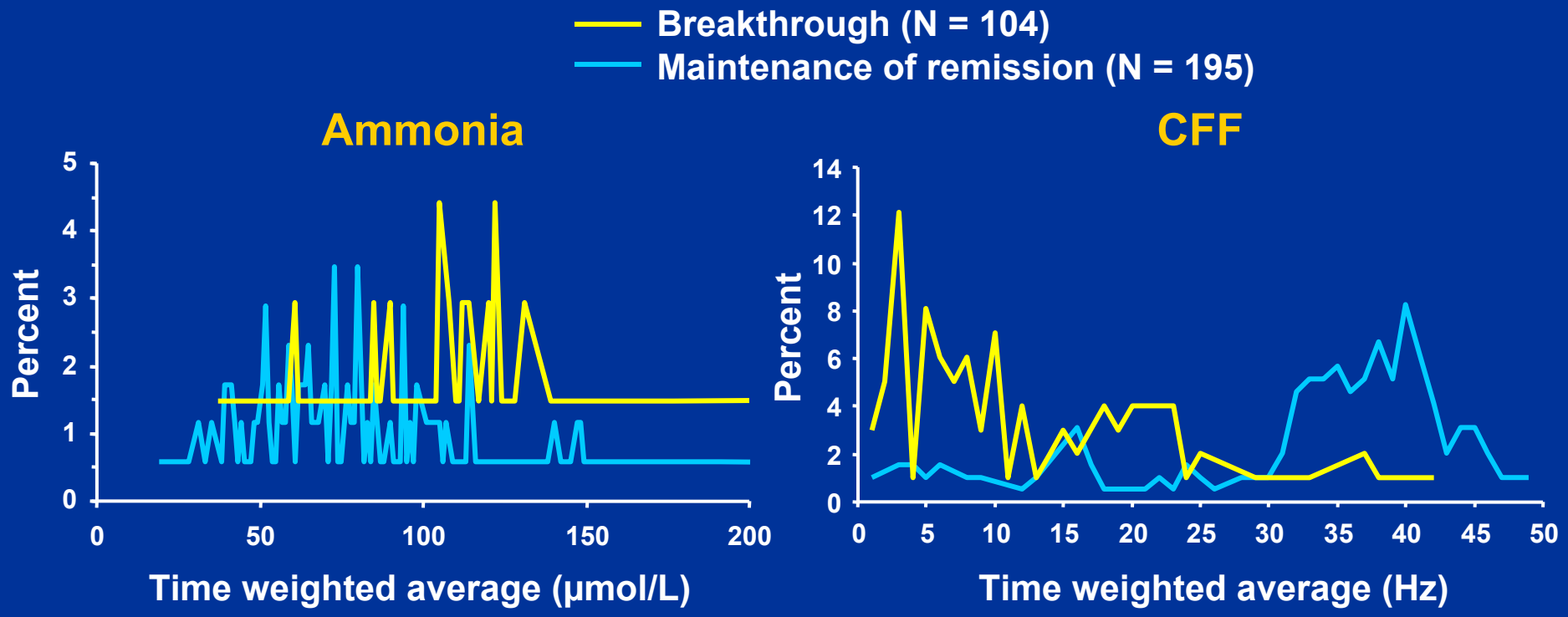
Breakthrough HE
Symptoms Used for PI Adjudication



[a] % based on number of reported symptoms within a category.

Correlation of Primary Endpoint With Time Dependent Prognostic Factors

Ammonia and CFF



	HE Breakthrough N	HE Breakthrough Mean	Remission N	Remission Mean	*p* value
Ammonia (μmol/L)	68	102.4	173	85.4	0.0079
CFF (Hz)	99	12.5	194	32.7	< 0.0001

Correlation of Primary Endpoint With Time Dependent Prognostic Factors

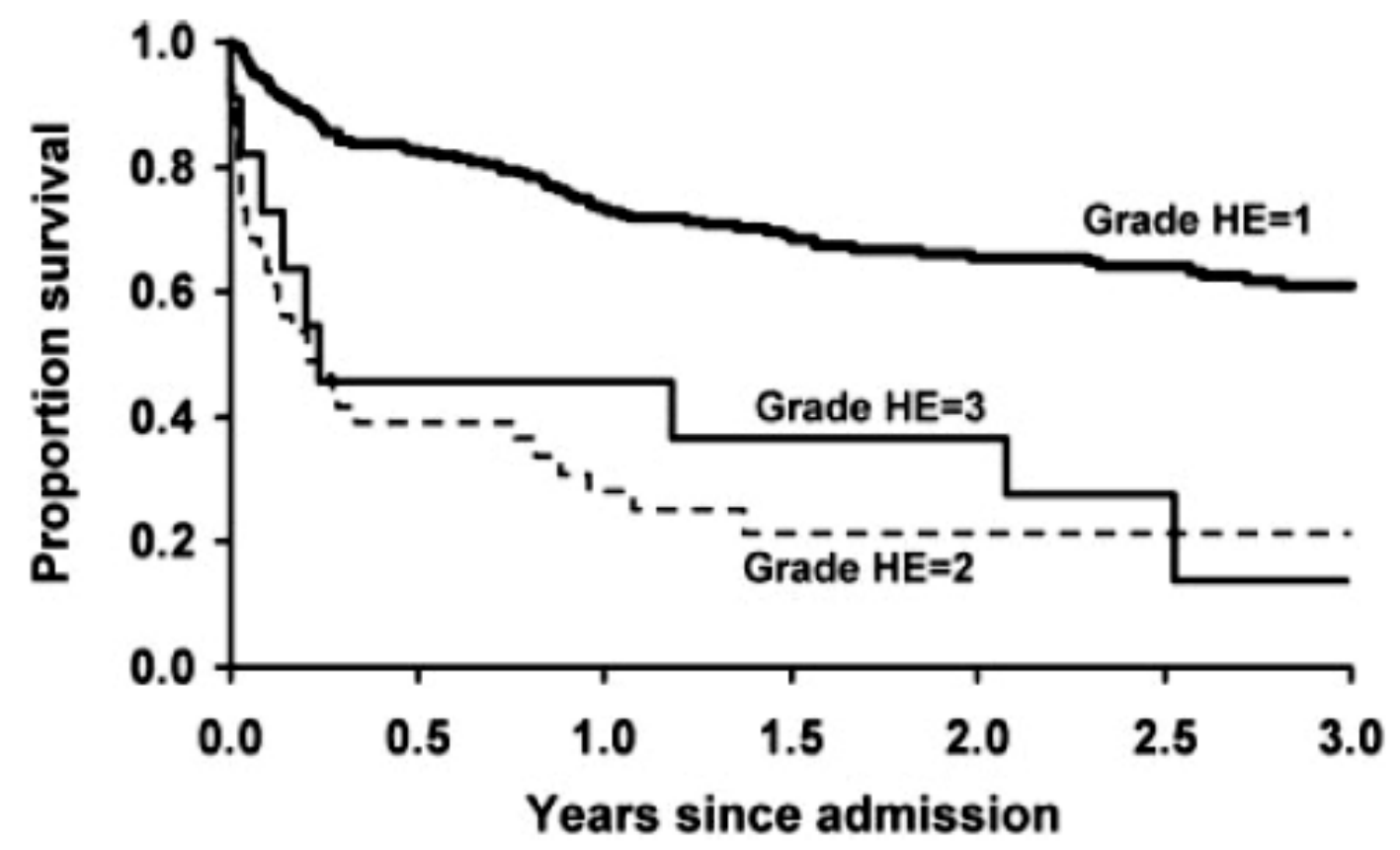
Patient Reported Outcomes

Maintenance of Remission
N=195

Breakthrough HE
N=104

Correlation of Primary Endpoint With Time Dependent Prognostic Factors

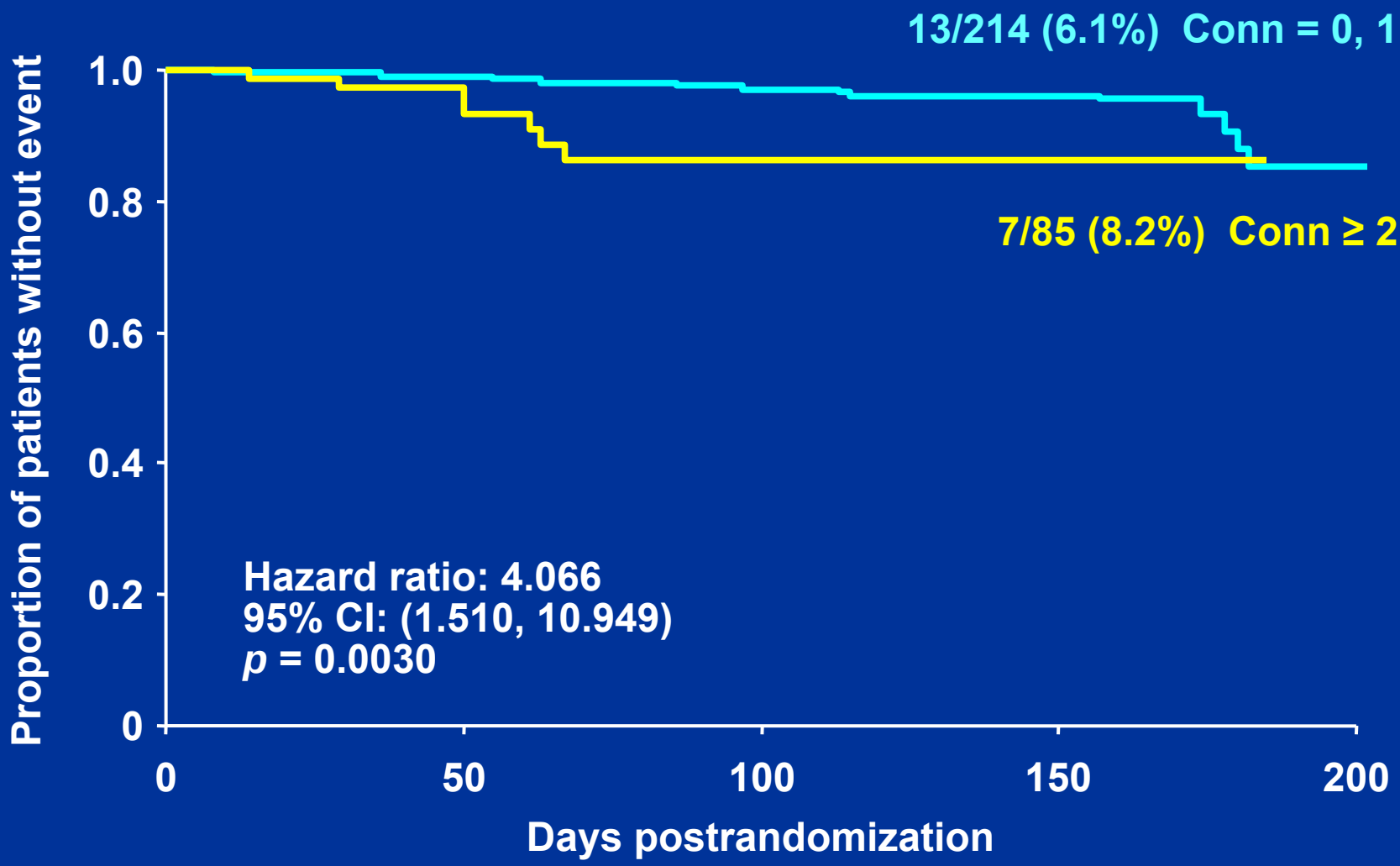
Association Between Conn and Mortality



Kaplan-Meier plot of survival estimates of hospitalized patients with cirrhosis according to grade of hepatic encephalopathy (HE)

Correlation of Primary Endpoint With Time Dependent Prognostic Factors

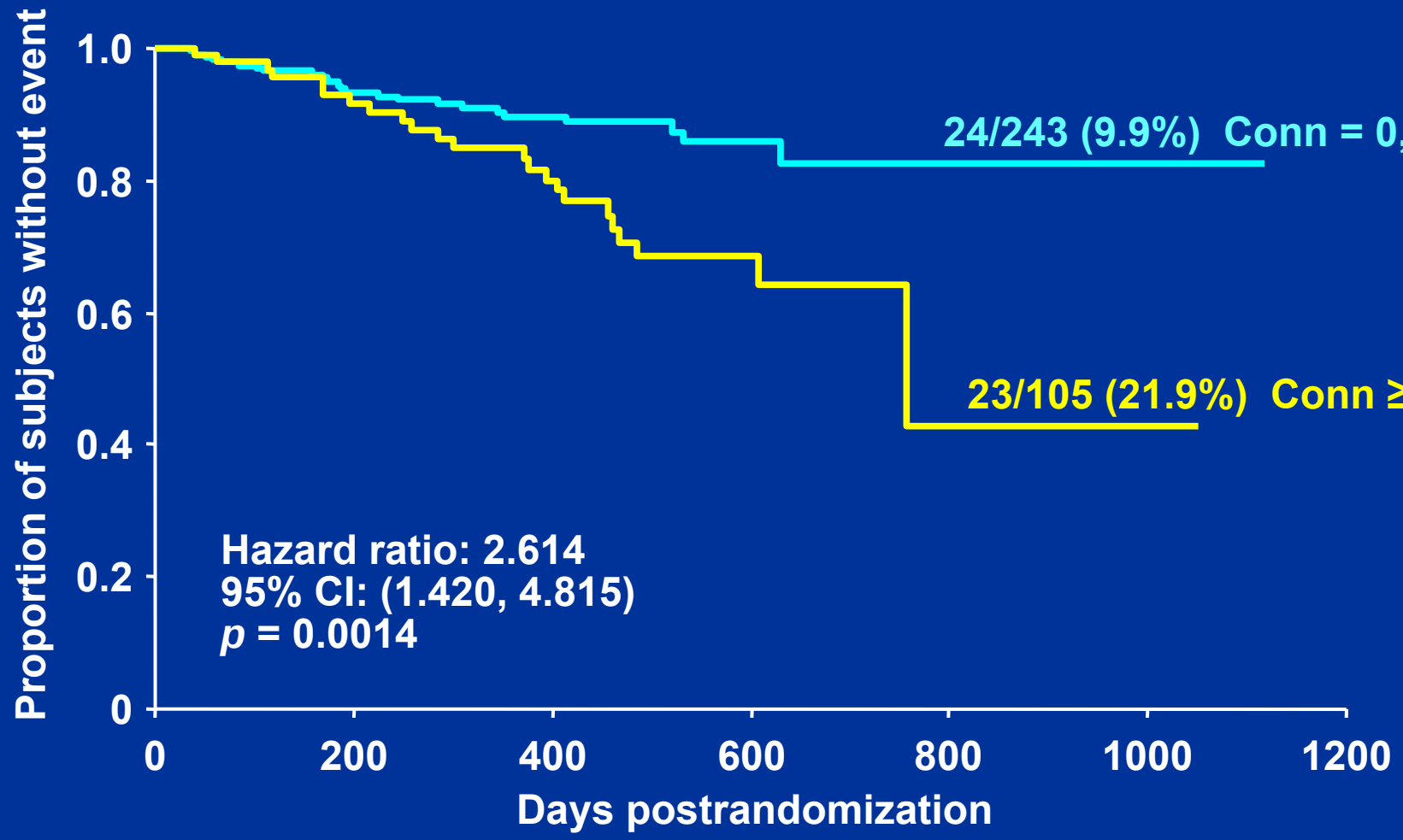
Study 3001 - Association Between Conn and Mortality



[a] Mortality within 30 days of last dose

Correlation of Primary Endpoint With Time Dependent Prognostic Factors

Studies 3001/3002 - Association Between Conn and Mortality



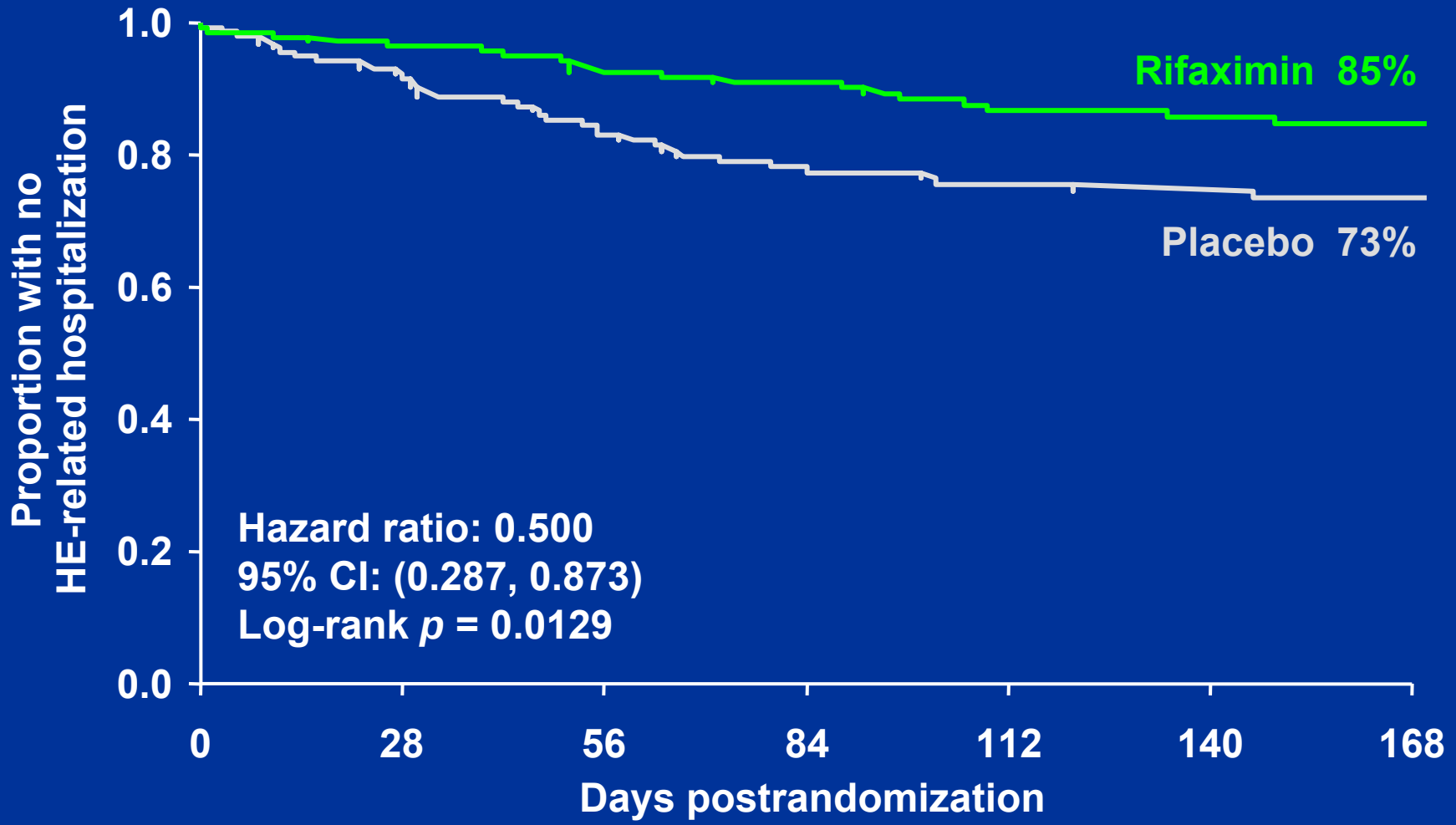
[a] Mortality within 30 days of last dose

Key Secondary Endpoint
Time to HE-Related Hospitalization
Study 3001 - ITT Population

- Time to HE-related hospitalization
  - Hospitalization directly resulting from HE

    OR
  - HE occurring during hospitalization

Key Secondary Endpoint
Time to HE-Related Hospitalization
Study 3001 - ITT Population



Supplementary Analyses of Time to HE-related Hospitalizations

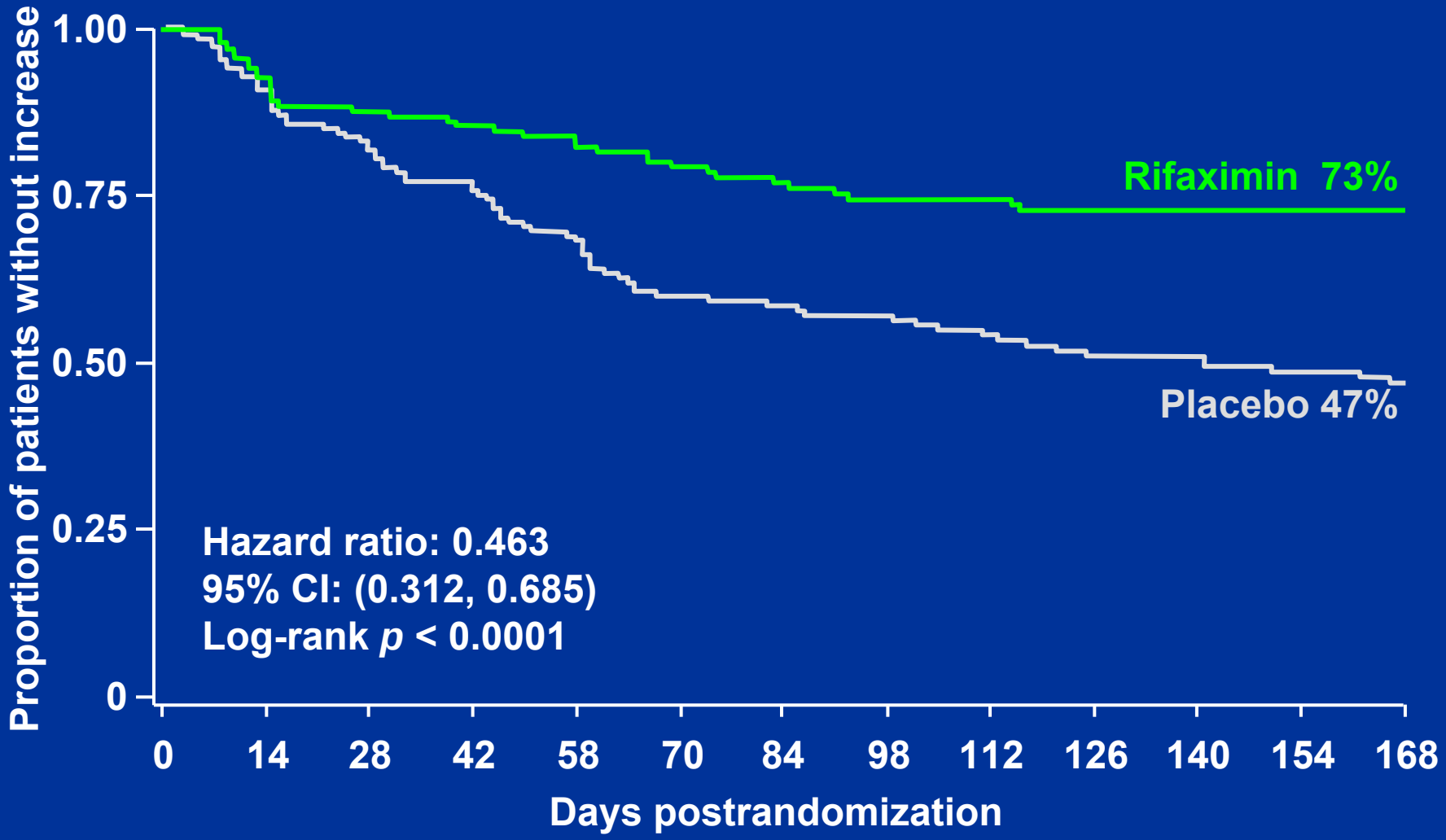
Study 3001 - ITT Population

- Time to HE-caused hospitalizations
  - 56% reduction in risk of first HE-caused hospitalization (HR = 0.436, 95% CI: 0.238, 0.807; *p* = 0.0064 rifaximin vs placebo)
- Time to all-cause hospitalizations
  - 30% reduction in risk of first all-cause hospitalization (HR = 0.706, 95% CI: 0.478, 1.044; *p* = 0.0793 rifaximin vs placebo)

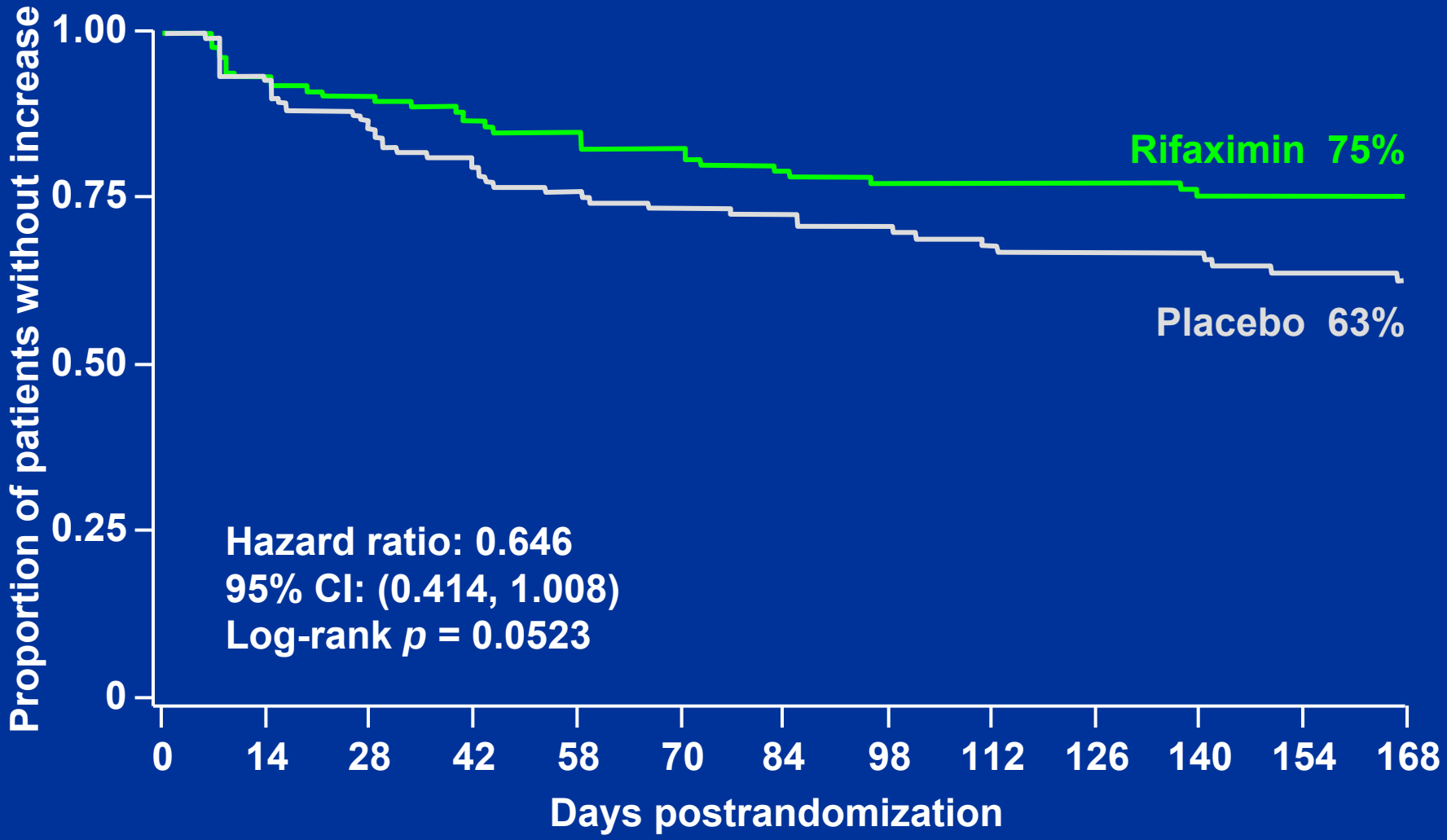
Prespecified Secondary Analyses
Study 3001 - ITT Population

- Other secondary endpoints in hierarchical order
  - Time to first worsening Conn score
  - Time to first worsening Asterixis grade
  - Patient Reported Outcome: fatigue
  - Blood ammonia

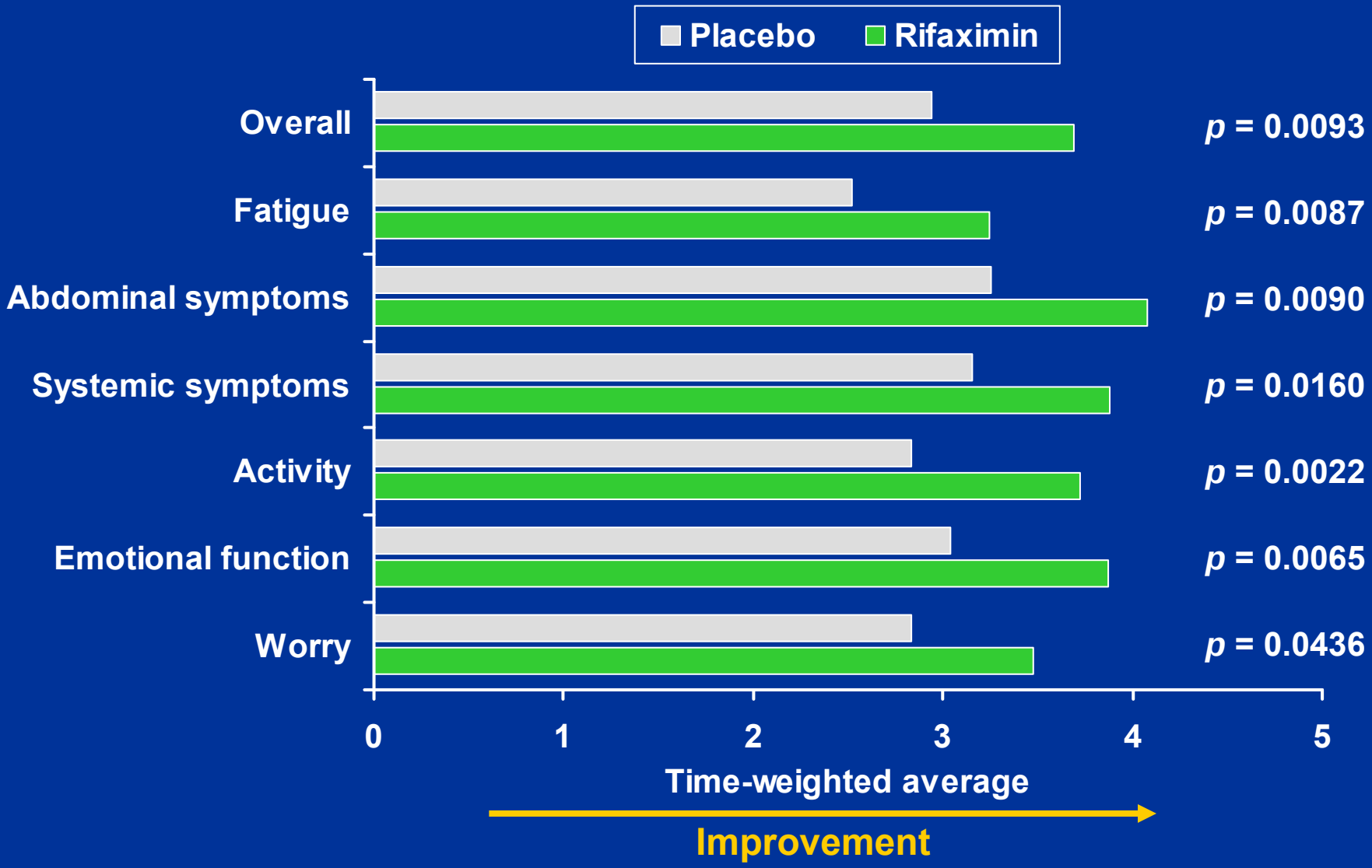
Secondary Endpoint
Time to Any Worsening Conn Score
Study 3001 - ITT Population



Secondary Endpoint
Time to Any Worsening Asterixis Grade
Study 3001 - ITT Population



Disease-Specific Patient Reported Outcome
Study 3001 - CLDQ



Ammonia and CFF
Study 3001

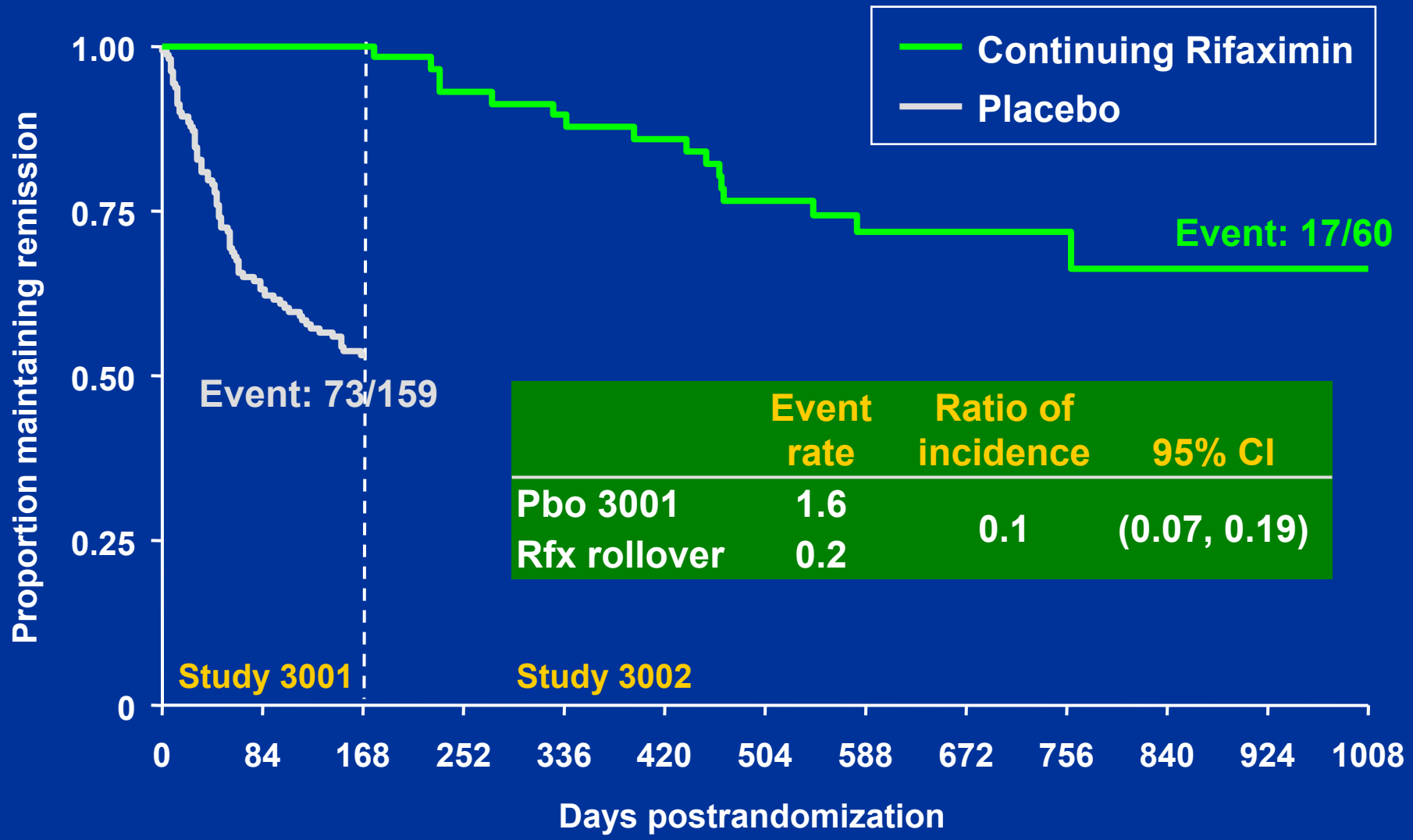
Changes from baseline to EOT	Placebo N = 159	Rifaximin N = 140	*p* value
Ammonia concentration, µmol/L	n = 131	n = 125	
Mean	–1.2	–5.7	0.0391
Min - max	–334 - 189	–156 - 236	
Critical flicker frequency, Hz	n = 155	n = 139	
Mean	0.355	0.945	0.0320
Min - max	–12.43 - 15.84	–13.88 - 11.30	

Support of Primary Endpoint: Long-Term Efficacy
Study 3002

- Long-term dosing in
  - Rifaximin-treated patients from Study 3001
  - Crossover placebo-treated patients from Study 3001
  - New HE patients

Support of Primary Endpoint: Durability of Treatment Effect

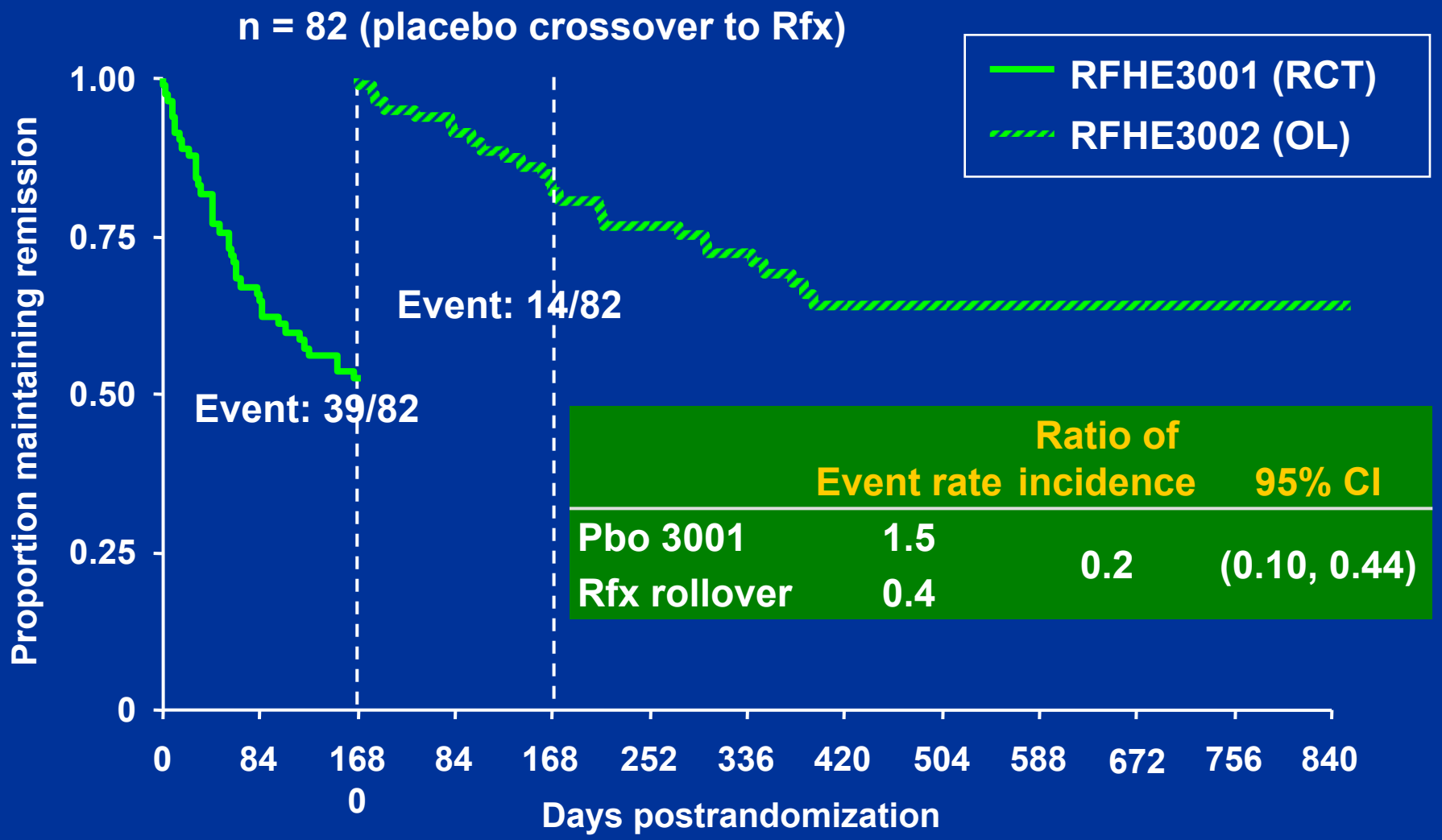
Studies 3001 and 3002



	Event rate	Ratio of incidence	95% CI
Pbo 3001	1.6	0.1	(0.07, 0.19)
Rfx rollover	0.2		

Support of Primary Endpoint: Repeatability of Treatment Effect

Studies 3001 and 3002



Efficacy Conclusions
Rifaximin 550 mg BID (1100 mg/day)

- Clinically meaningful benefit
  - Reduces risk of overt HE episode by 58%
  - Reduces risk of HE-related hospitalizations by 50%
  - Reduces risk of HE-caused hospitalization by 56%
  - Effect is consistent across subgroups and other secondary endpoints
- High degree of precision of breakthrough definition
  - Convergent results seen across all analyses: Subgroups, hospitalization, ammonia, CFF, PRO, all-cause mortality
- Long-term effect is durable and repeats 3001 result
- Rifaximin is effective in maintaining remission from HE breakthrough, the indication sought today

Safety of Rifaximin Treatment of Hepatic Encephalopathy

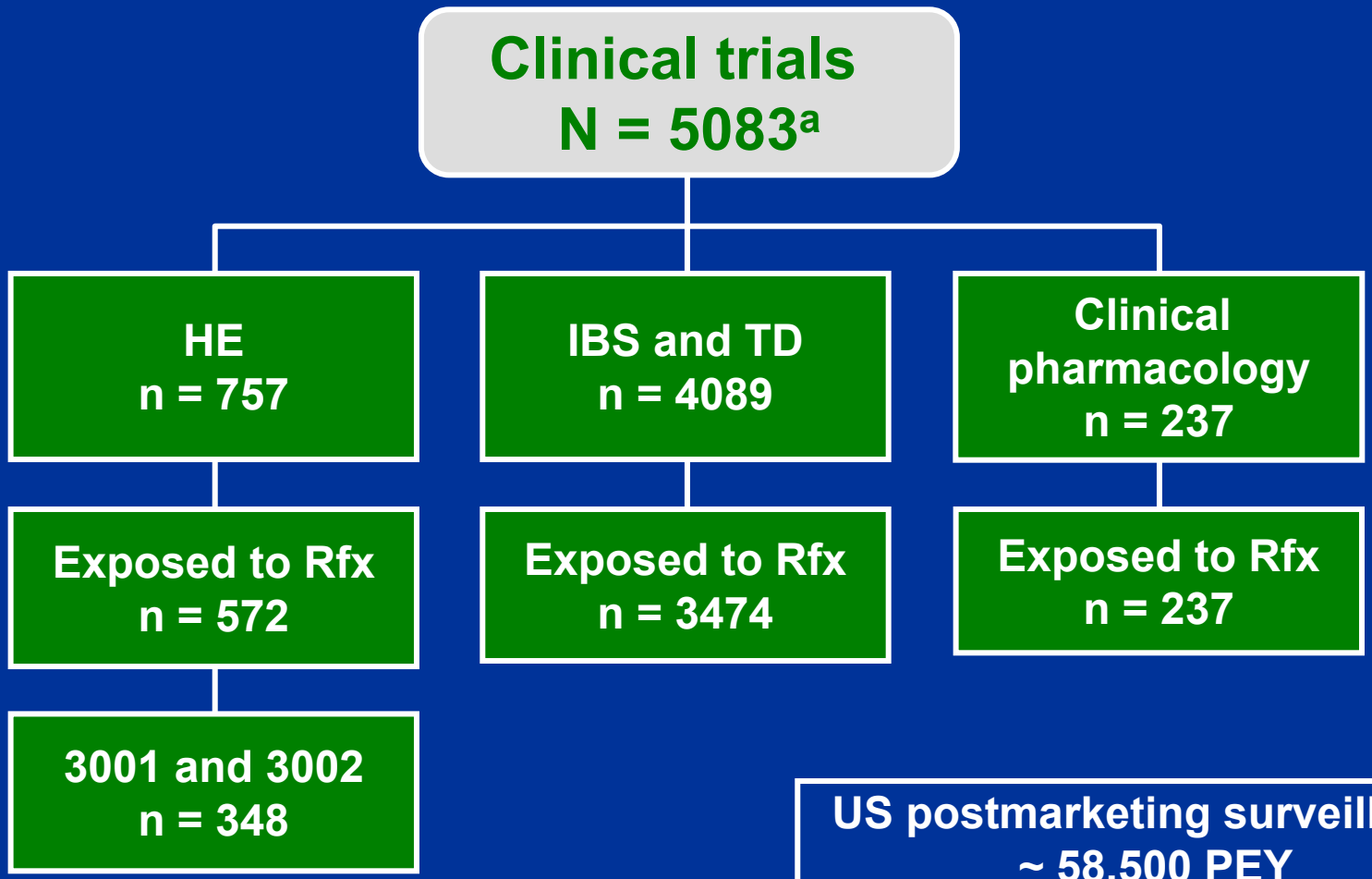
Naga P. Chalasani, MD, FACG

Professor & Director
Division of Gastroenterology and Hepatology
Indiana University School of Medicine

Presentation Overview

- Safety database
  - Exposure and follow-up
- Adverse events
  - Most Frequent AEs/SAEs
  - AEs by MELD
  - Infections
    - C. difficile
- All-cause mortality
- Conclusion

Rifaximin Safety Database



IBS = Irritable Bowel Syndrome; TD = Traveler's Diarrhea

[a] Rifaximin all doses or placebo as of September 14, 2009

HE Breakthrough Discontinuations: Follow-up

- Evaluated by investigator as soon as possible
- Phone follow-up in 2 weeks
- Patients remained under investigators care
- SAEs within 30 days after stopping study drug were captured
- ~ 50% were enrolled into Study 3002

Exposure to Study Medications
Studies 3001 and 3002

	Study 3001		3001/3002
	Placebo	Rifaximin	All Rifaximin
Patients, n	159	140	348
Person-years exposure[a]	46	50	347
Mean, days	106	130	364
Median, days (range)	110 (6 - 176)	168 (10 - 178)	403 (7 - 1008)

BID = Twice daily

[a] Person-years of exposure was computed as the sum of exposure days for all patients included in the analysis divided by 365.25.

Adverse Events Overview
Studies 3001 and 3002

Event[a]	Patients, n (%)		
	Study 3001		3001/3002
	Placebo PEY = 46 N = 159	Rifaximin PEY = 50 N = 140	All Rifaximin PEY = 347 N = 348
Any AEs	127 (80)	112 (80)	307 (88)
SAEs	63 (40)	51 (36)	190 (55)
AEs resulting in discontinuation	45 (28)	30 (21)	88 (25)
Deaths	11 (7)	9 (6)	47 (14)

[a] Events are defined on drug or within 30 days of last dose.

Most Frequent AEs: ≥ 10% in 3001
Studies 3001 and 3002

	Patients, n (%)		
	Study 3001		3001/3002
Preferred Term	Placebo PEY = 46 N = 159	Rifaximin PEY = 50 N = 140	All Rifaximin PEY = 347 N = 348
Any AEs	*127 (80)*	*112 (80)*	*307 (88)*
Peripheral edema	13 (8.2)	21 (15.0)	64 (18)
Nausea	21 (13.2)	20 (14.3)	66 (19)
Dizziness	13 (8.2)	18 (12.9)	39 (11)
Fatigue	18 (11.3)	17 (12.1)	40 (11)
Ascites	15 (9.4)	16 (11.4)	55 (16)
Diarrhea	21 (13.2)	15 (10.7)	41 (11.8)
Headache	17 (10.7)	14 (10.0)	31 (8.9)

Most Frequent SAEs: ≥ 2% in 3001
Studies 3001 and 3002

Preferred Term	Patients, n (%) Study 3001 Placebo PEY = 46 N = 159	Study 3001 Rifaximin PEY = 50 N = 140	3001/3002 All Rifaximin PEY = 347 N = 348
All SAEs	*63 (39.6)*	*51 (36.4)*	*190 (54.6)*
Anemia	0	4 (2.9)	16 (4.6)
Ascites	4 (2.5)	4 (2.9)	14 (4.0)
Esophageal variceal hemorrhage	2 (1.3)	4 (2.9)	8 (2.3)
Pneumonia	1 (0.6)	4 (2.9)	11 (3.2)
Vomiting	0	3 (2.1)	6 (1.7)
Generalized edema	2 (1.3)	3 (2.1)	6 (1.7)
Hepatic cirrhosis	6 (3.8)	3 (2.1)	15 (4.3)
Cellulitis	2 (1.3)	3 (2.1)	14 (4.0)
Acute renal failure	4 (2.5)	2 (1.4)	22 (6.3)

Hepatobiliary Serious Adverse Events
Studies 3001 and 3002

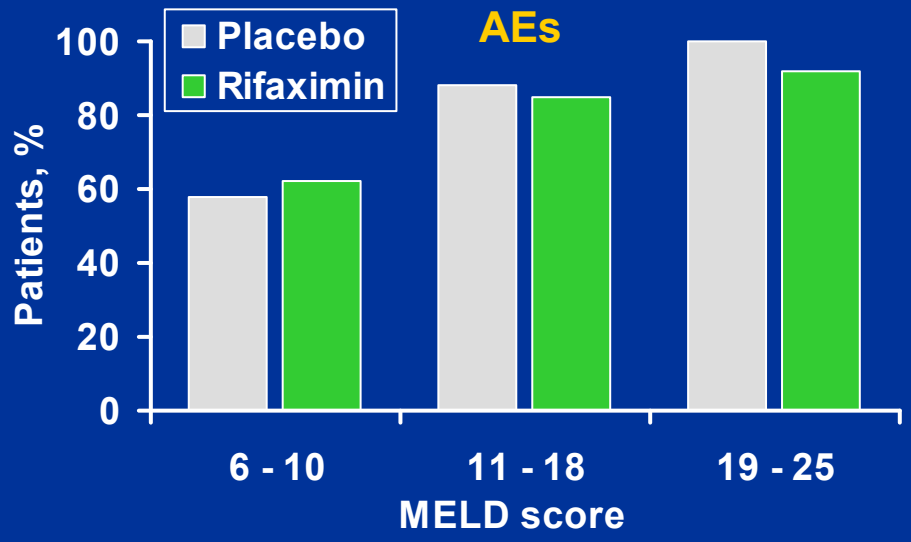
MedDRA system organ class Preferred term	Patients, n (%) Study 3001 Placebo PEY = 46 N = 159	Study 3001 Rifaximin PEY = 50 N = 140	3001/3002 All Rifaximin PEY = 347 N = 348
Hepatobiliary disorders	*10 (6.3)*	*7 (5.0)*	*46 (13.2)*
Hepatic failure	1 (0.6)	1 (0.7)	19 (5.5)
Hepatic cirrhosis	6 (3.8)	3 (2.1)	15 (4.3)
Hepatorenal syndrome	0	0	4 (1.1)
Cirrhosis alcoholic	0	1 (0.7)	2 (0.6)
Biliary cirrhosis primary	0	1 (0.7)	3 (0.9)
Cholecystitis acute	1 (0.6)	0	0
Cholecystitis chronic	1 (0.6)	0	0
Cholestasis	1 (0.6)	0	0
Portal hypertension	1 (0.6)	0	1 (0.3)
Portal vein thrombosis	0	1 (0.7)	1 (0.3)

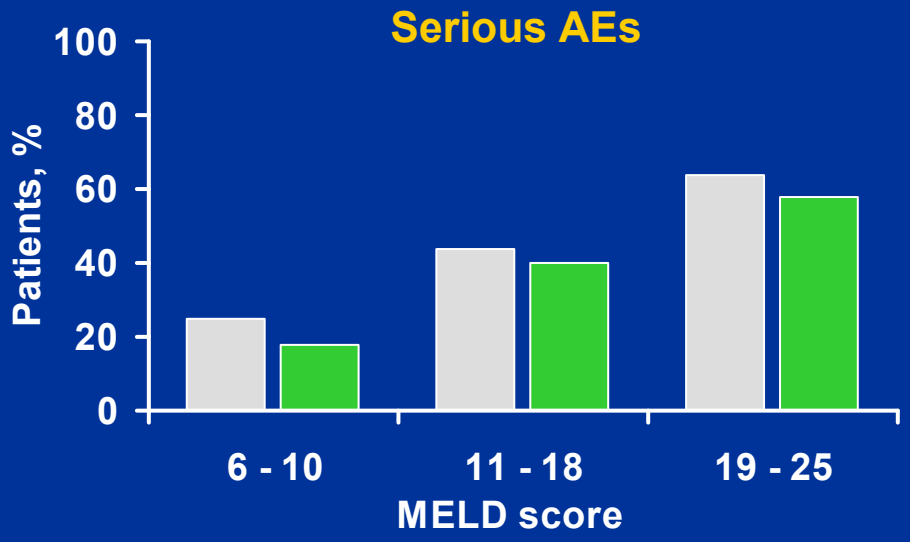
Hepatic Laboratory Changes
ALT/AST and Hy's Law

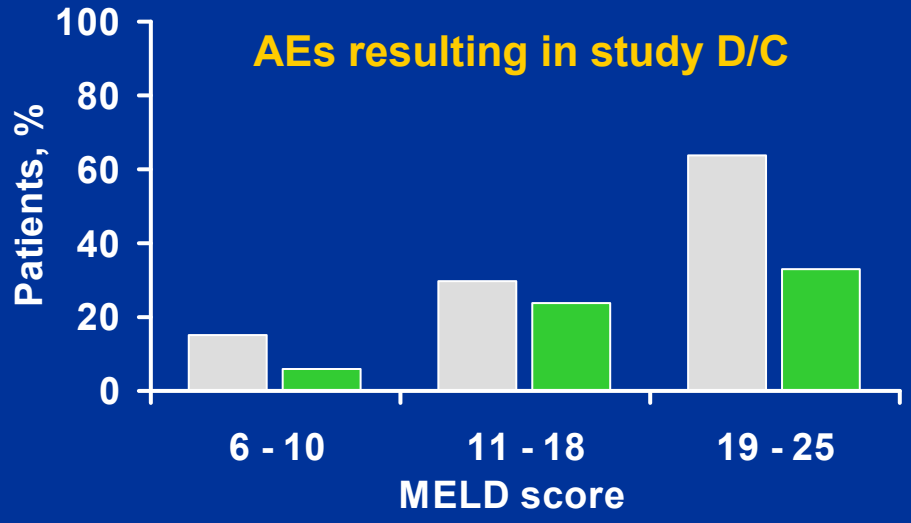
Laboratory variable limit		Patients, n (%) Study 3001 Placebo PEY = 46 N = 159	Rifaximin PEY = 50 N = 140
ALT	> 3 × ULN/BL	0/ 154	1/ 138 (1)
	> 5 × ULN/BL	0/ 154	0/ 138
	> 10 × ULN/BL	0/ 154	0/ 138
AST	> 3 × ULN/BL	1/ 154 (1)	6/ 138 (4)
	> 5 × ULN/BL	0/ 154	1/ 138 (1)
	> 10 × ULN/BL	0/ 154	1/ 138 (1)
Total bilirubin > 2 × ULN/BL		11/ 154 (7)	7/ 138 (5)
ALT > 3 × ULN/BL concurrent with total bilirubin > 2 × ULN/BL		0/ 154	0/ 138

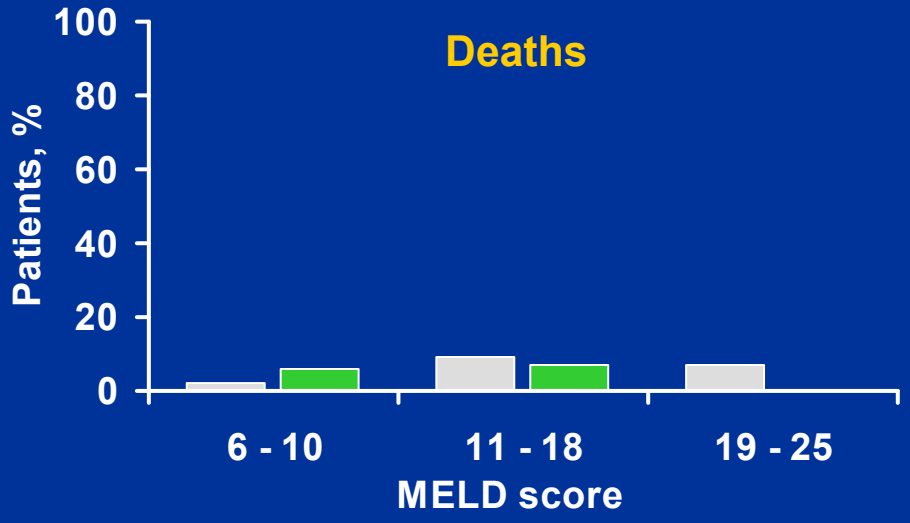
ULN: Upper Limit of Normal – BL: Baseline

Adverse Events by Baseline MELD Category









Infections

Infections - Serious Adverse Events
Studies 3001 and 3002

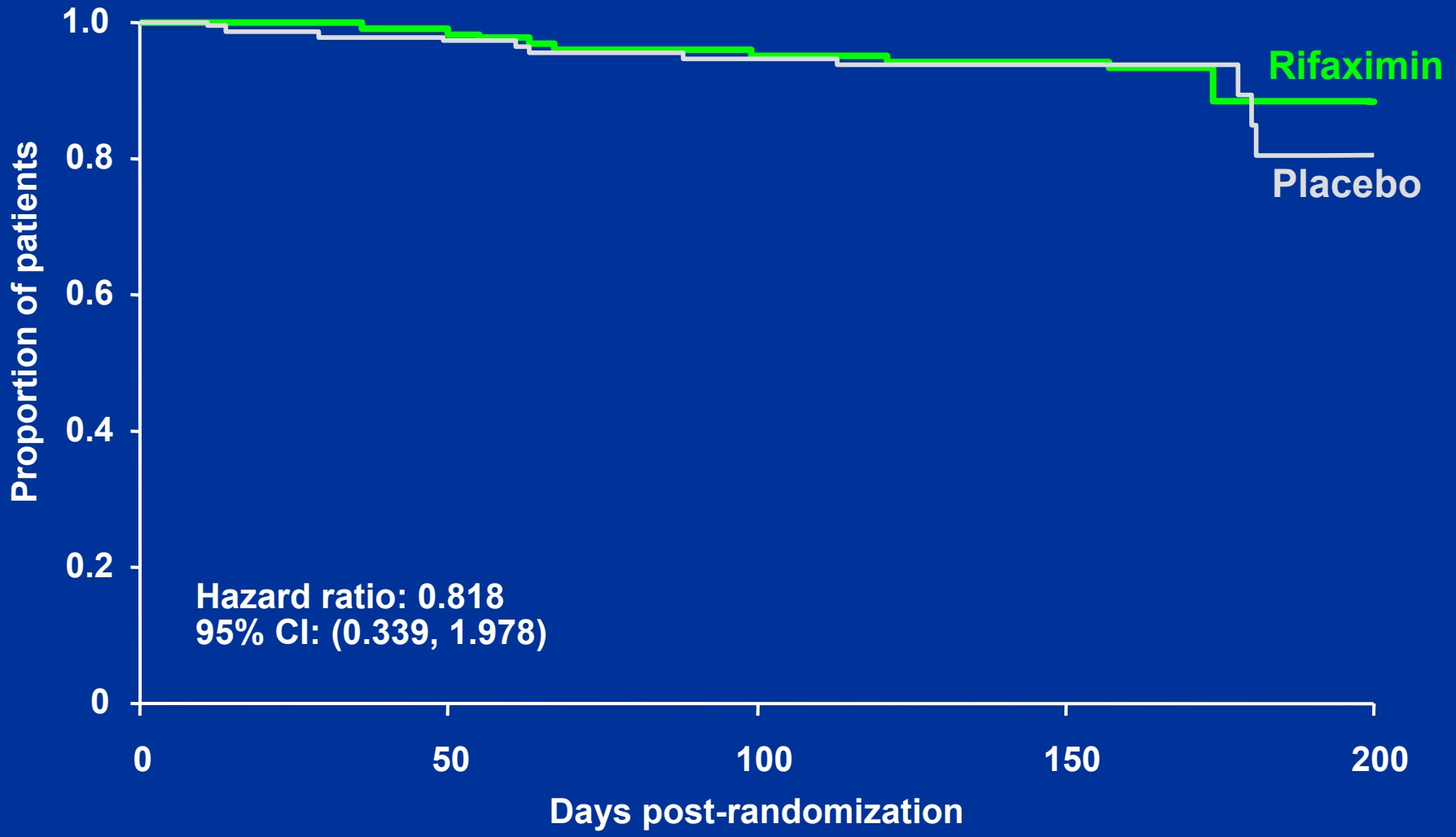
MedDRA system organ class Preferred term	Patients, n (%) Study 3001 Placebo PEY = 46 N = 159	Study 3001 Rifaximin PEY = 50 N = 140	3001/3002 All Rifaximin PEY = 347 N = 348
Infections	*9 (5.7)*	*11 (7.9)*	*59 (17.0)*
Pneumonia	1 (0.6)	4 (2.9)	11 (3.2)
Cellulitis	2 (1.3)	3 (2.1)	14 (4.0)
Urinary tract infection	1 (0.6)	2 (1.4)	10 (2.9)
Clostridium difficile infection	0	2 (1.4)	5 (1.4)
Bacterial peritonitis	3 (1.9)	1 (0.7)	7 (2.0)
Septic shock	0	0	5 (1.4)
Sepsis	2 (1.3)	0	2 (0.6)

Clostridium Difficile Infection
Studies 3001 and 3002

- 5 episodes: 2 in 3001 and 3 in 3002 (1.4%)
- C. diff in rifaximin
  - All were taking PPIs and other antibiotics
  - 3/5 occurred while on rifaximin
    - 2 continued study participation
  - 2/5 occurred within 30 days of stopping rifaximin
  - All resolved with traditional antibiotic therapy
- Xifaxan® (rifaximin 200 mg tablets) includes class labeling in Warnings and Precautions for antibiotic associated colitis

All-Cause Mortality

All-Cause Mortality Comparison
Study 3001



No Increased Mortality in Rifaximin Group
All Rifaximin vs 3001 Placebo Group

Analysis group	Death n	Patients N	Exposure person-yr	Event rate	Ratio of incidence (95% CI)
Placebo (3001)	11	159	46.0	0.2	
New Rifaximin (3002)	27	208	211.4	0.1	0.5858 (0.2833, 1.2112)
All Rifaximin (3001/3002)	47	348	346.7	0.1	0.5825 (0.3003, 1.1296)

Low MELD Deaths

Subj # Age Sex	Sc & BL MELD	TTO (Total Exp)	Day of Death	Relevant Med History	Event Detail and Autopsy Findings
351-0012 45 / F	17 & 11	Day 67 (67 d)	Day 67	HE, ESLD, HBV, Pul HTN, alcoholic cirrhosis, tricuspid valve regurgitation, esophageal varices, GI bleed, anxiety, depression, edema, smoker, alcohol abuse	Day 54: Gastroenteritis; Day 56: discharged; Day 57 readmitted N/V w/ abd pain in epigastric area; Day 62 band ligation for esoph varices. Autopsy Findings: alcoholic cirrhosis, pul HTN, dilated cardiomegaly. shock kidney, hemorrhagic ovaries & cystitis, atherosclerosis, cholelithiasis, diverticulosis
706-0002 69 / F	12	Last Dose +2 (48 d)	Last Dose +2	HE, cirrhosis, ESLD, myelodysplastic syndrome, ascites, breast cancer	Died at home; subject house-bound; refused doctor and hospital; palliative morphine treatment started on 8Feb06. No autopsy
679-0005 52 / M	11& 7	Last Dose +10 (29 d)	Last Dose +10	HE, cirrhosis, ESLD, HCV, alcohol abuse, esophageal varices, jaundice, ascites, HTN, H/A, diabetes, obesity	Day 27: Initiated Vicodin and tramadol for headaches; Day 29: Dc'd study due to Vicodin & tramadol use; 10 d after last dose died at home. No autopsy

Conclusions

- AE profile consistent with history of cirrhosis and HE
  - No unexpected SAEs
  - Hepatobiliary profile appears unaffected by rifaximin
  - Infections are comparable
    - C. diff - Xifaxan® includes class labeling
  - All-cause mortality comparable to placebo
- 5-year postmarketing experience in the US raised no safety issues (other than hypersensitivity)

Benefit/Risk Profile
Xifaxan® (rifaximin)

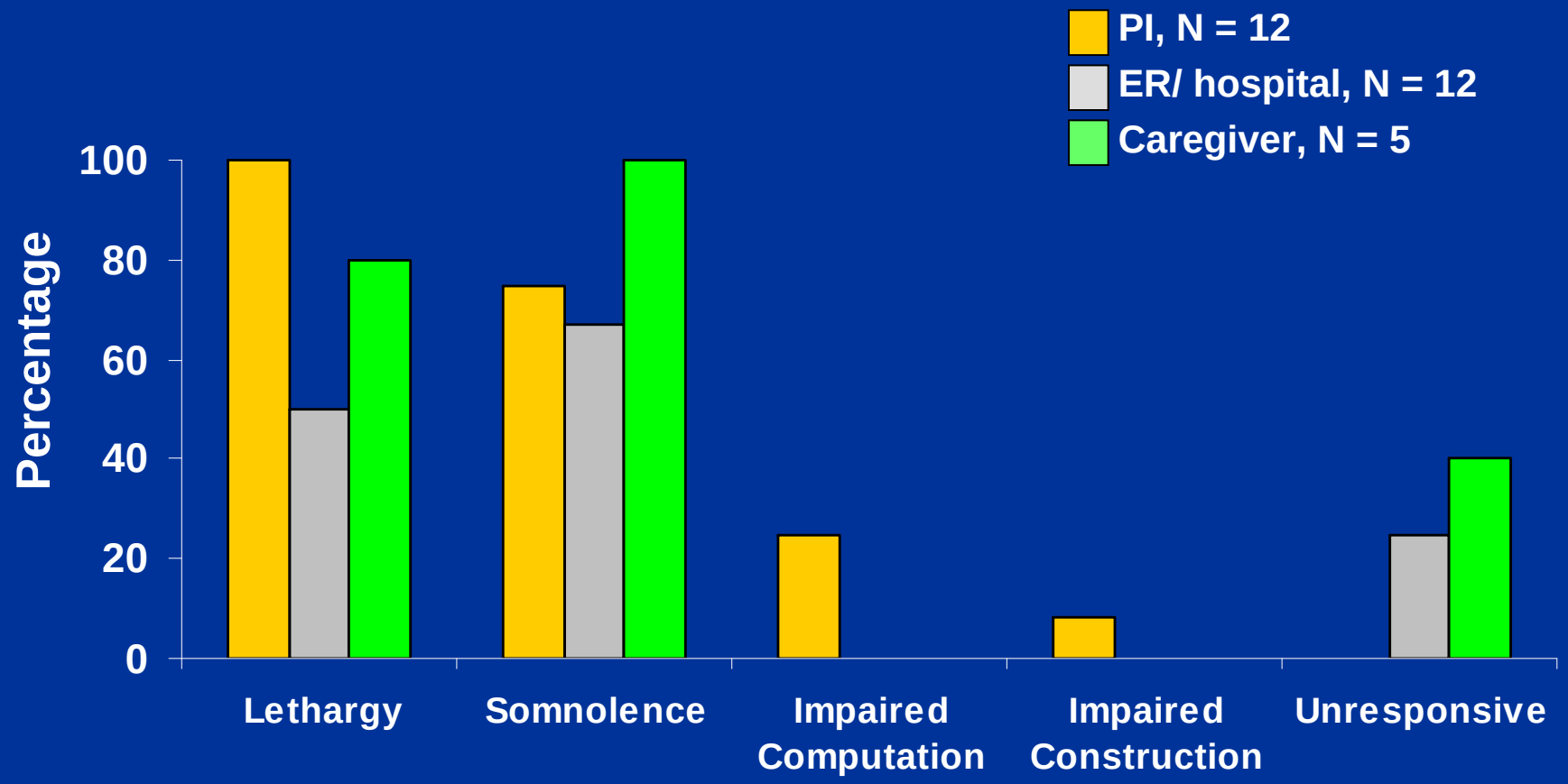
Steven L. Flamm, MD

Professor of Medicine and Surgery, Liver Transplantation
Northwestern University Feinberg School of Medicine

Clinician's Perspective on Hepatic Encephalopathy

- **Impact of HE**
  - Impact on patients
  - Impact caregivers
  - Impact on the medical team
- **Current treatment limitations**
  - Limitations of lactulose
  - Limitations of antibiotics (neomycin and metronidazole)
- **Rifaximin**
  - Favorable safety profile
  - Therapeutic benefit

Symptoms of Breakthrough for Sites[1] with Placebo Only Breakthrough



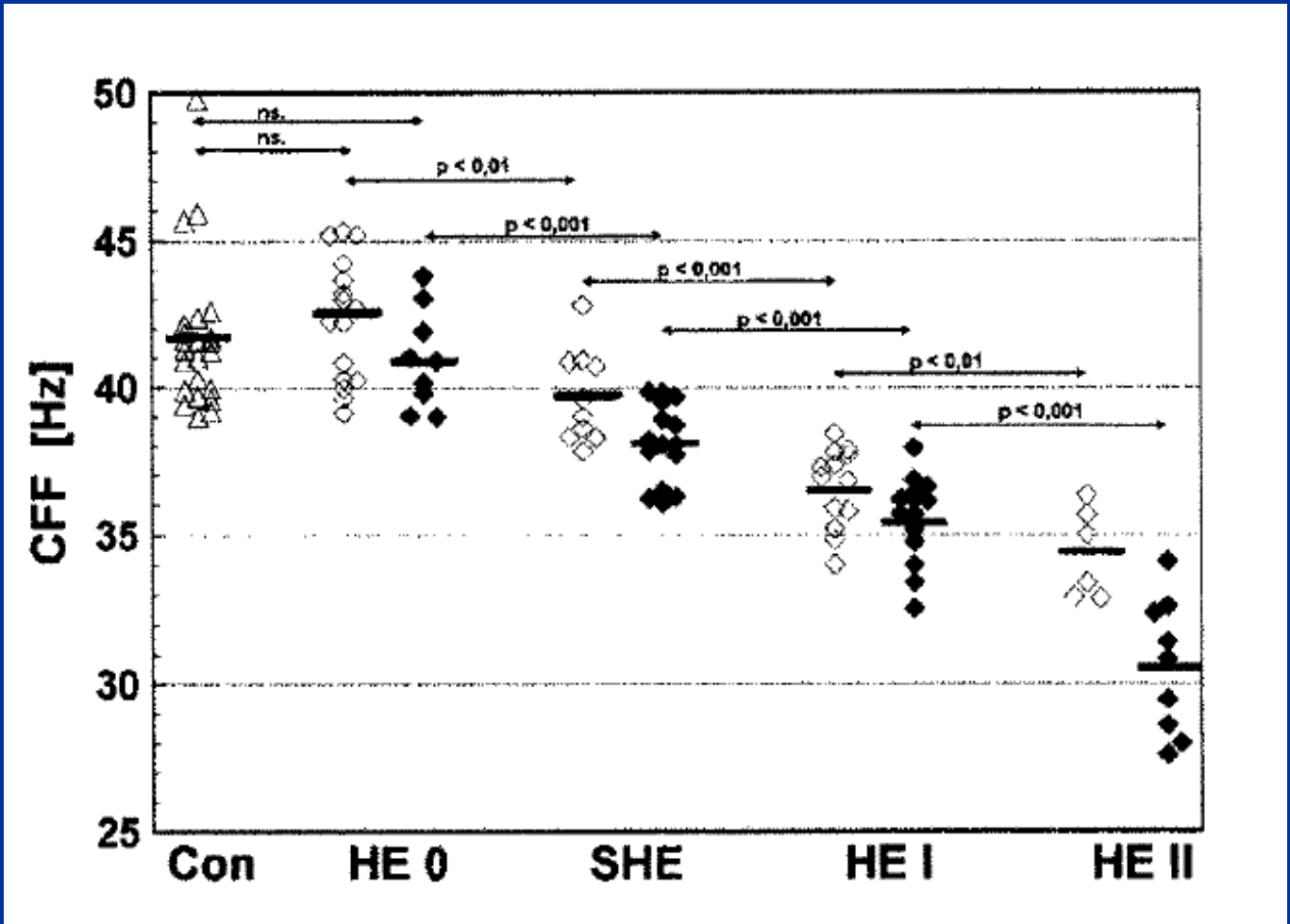
[1] Sites 106, 351, 547, 586, 743, 760, 761, 799, 876, 901, 938.

Critical Flicker Frequency (CFF) for Assessment of HE Grade

- **Basis: Retinal gliopathy (Muller cells) – cerebral cortical dysfunction**
- **Ability to discriminate flickering light as a function of frequency (Hz)**
- **Discriminates HE grades 0, 1, 2**
- **Correlation with Conn score**
- **Objective, sensitive, reproducible**

Kircheis et al. *Hepatology.* 2002:35(2):357-66

Correlation of CFF to HE



Kircheis et al., Hepatology, 35: 357, 2002

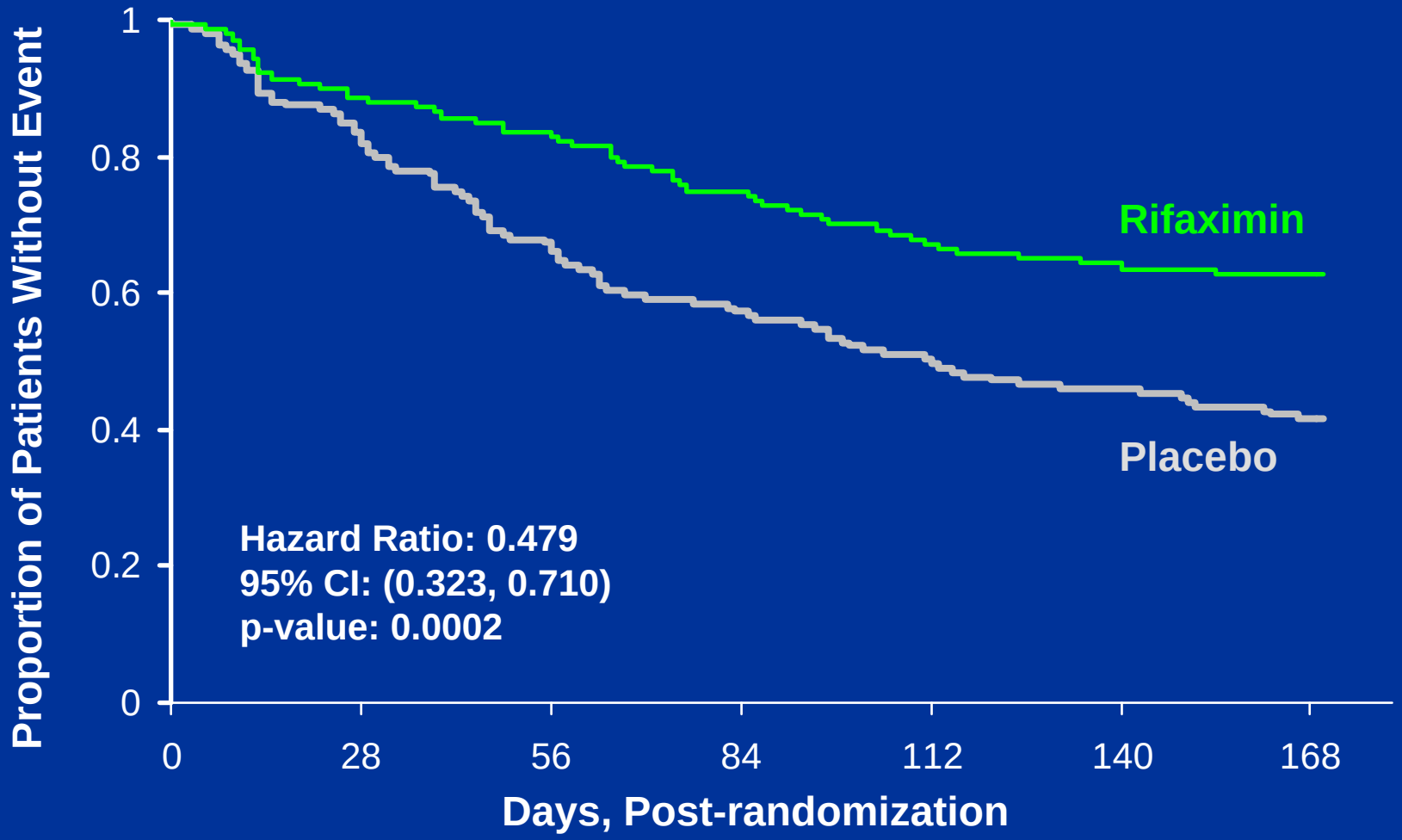
Caregiver Responsibilities MARC

Monitor, Assist, Remind & Contact

- **Monitor**
  - **changes in the subject's health and HE status.**
- **Assist**
  - **Subject attending scheduled and unscheduled study visits**
- **Remind**
  - **Study medication**
  - **Diary**
- **Contact the site**
  - **Significant changes in subject's health and HE**
  - **Increase lactulose to prevent possible decline in mental status**
  - **Lactulose > 60 g of lactulose per day**
- **Caregiver must attend at least screening visit (Amendment)**

K-M of Time to First HE Breakthrough or Death[1]

Study 3001 – ITT population



[1]HE include subjects who experienced HE or died

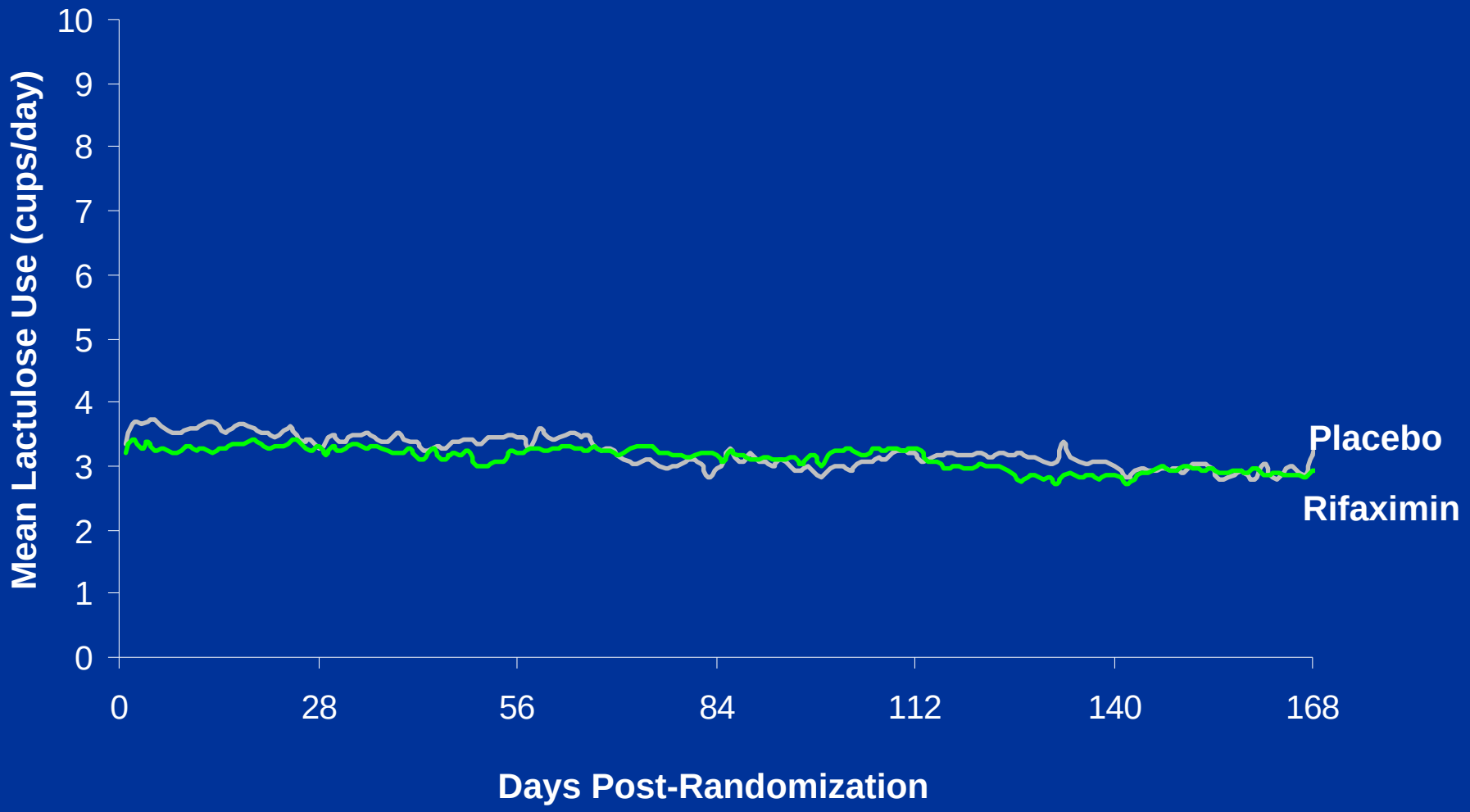
Rifaximin and Resistance

- Rifaximin does not induce rifaximin-resistant or rifampin-resistant mutants of *Mycobacterium tuberculosis*
- Three days and 7 or 14 days of rifaximin therapy does not alter counts of coliforms or *Enterococcus* and MICs change insignificantly
- Two studies showed small number of resistant strains after courses of rifaximin that disappeared with discontinuance of treatment

Rifaximin and *Clostridium difficile* Infection and Diarrhea

- All antibiotics can predispose to *C. difficile* diarrhea
- Rifaximin preserves colonic flora which protects against *C. difficile* infection
- Rifaximin MICs of most *C. difficile* strains averages .01 µg/mL (while coliform flora MICs average 16-32 µg/mL)
- Rifaximin has been successfully used to treat acute *C. difficile* diarrhea and *C. difficile* recurrences

Daily Lactulose Use
ITT Population



Multiple Breakthrough HE events
RFHE3002

Number of Breakthrough HE	Continuing Rifaximin N=70 n (%)	Placebo Crossover Rifaximin N=82 n (%)	New Rifaximin N=128 n (%)	All Subjects N=280 n (%)
Subjects with at least one Breakthrough HE	*25 (36)*	*26 (32)*	*42 (33)*	*93 (33)*
1	11 (16)	12 (15)	18 (14)	41 (15)
2	5 (7)	8 (10)	8 (6)	21 (8)
>2	9 (13)	6 (7)	16 (13)	31 (11)

MELD Score Change from Baseline
Study 3001

Assessment Time	Placebo (N = 159)	550mg Rifaximin BID (N = 140)	Total (N = 299)
Baseline			
n	158	140	298
Mean	12.70	13.08	12.88
SD	3.938	3.639	3.799
Median	12.35	13.08	12.56
Min	6.4	6.4	6.4
Max	23.2	23.5	23.5
EOT [1]			
n	146	131	277
Mean	12.80	13.05	12.92
SD	4.393	4.369	4.376
Median	12.79	12.63	12.76
Min	6.4	6.4	6.4
Max	33.2	27.0	33.2
Change from Baseline to EOT [1]			
n	145	131	276
Mean	0.20	0.06	0.14
SD	2.785	2.823	2.799
Median	0.00	-0.16	-0.11
Min	-7.1	-11.7	-11.7
Max	19.6	11.2	19.6

MELD Change Rate Over Time
Study 3001 3002

	RCT Study		
MELD Change Rate [1]	Placebo (N = 159)	550mg Rifaximin BID (N = 140)	All Rifaximin (N = 348)
n	156	136	343
Mean	0.0046	0.0055	0.0022
SD	0.06935	0.07910	0.04079
Median	0.0000	-0.0014	0.0000
Min	-0.317	-0.331	-0.324
Max	0.386	0.533	0.399
P-value [2]:		0.9177	

[1] MELD score change rate was estimated using linear regression model. MELD was dependent variable and assessment time (defined as sample collect date – first dose date of study drug + 1) was independent Variable.
[2] P-value was for test of treatment difference in RCT study (T-test).

Symptoms Consistency Across Pooled Centers
Study 3001