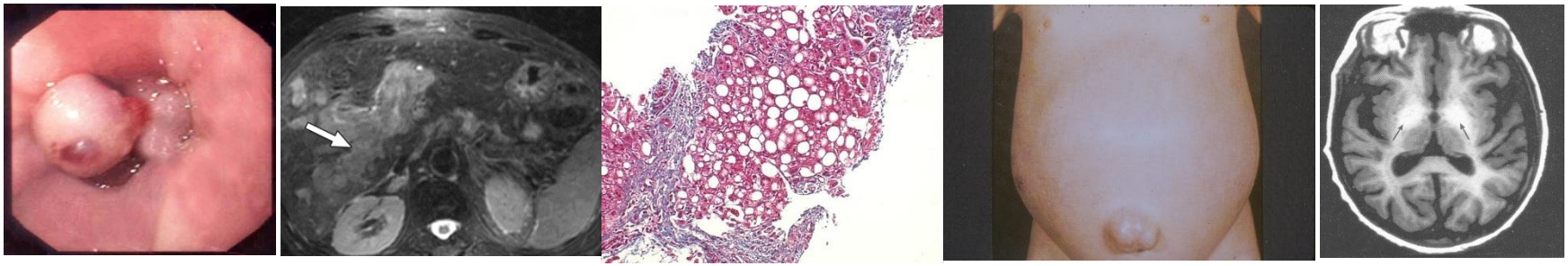
DECOMPENSATED CIRRHOSIS: ENDPOINTS AND EXPERIENCE IN US PHASE 2B/3 TRIALS



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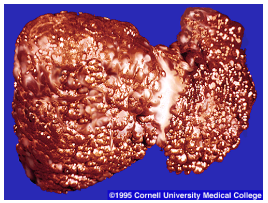
Conflicts of Interest

- President, Sanyal Biotechnologies
- Stock options: Genfit, Akarna, Tiziana, Indalo, Durect, Exhalenz, Hemoshear
- Advisor with compensation: Lilly, Pfizer, Novartis, Ardelyx, Salix, Hemoshear
- Advisor without compensation: Galectin, Intercept, Merck, Bristol Myers, Immuron, Gilead, Chemomab, Affimmune, Protalix, Nitto Denko, Novo Nordisk, Cirius, Boehringer Ingelhiem
- Grants to institution: Gilead, Tobira, Allergan, Merck, Bristol Myers, Astra Zeneca, Immuron, Intercept, Novo Nordisk, Shire, Boehringer Ingelhiem, Cirius

Clinical trial data has to be considered in the context of when interventions are made



Salix 2131

Rifaximin Pivotal trial

Terlipressin Pivotal trials

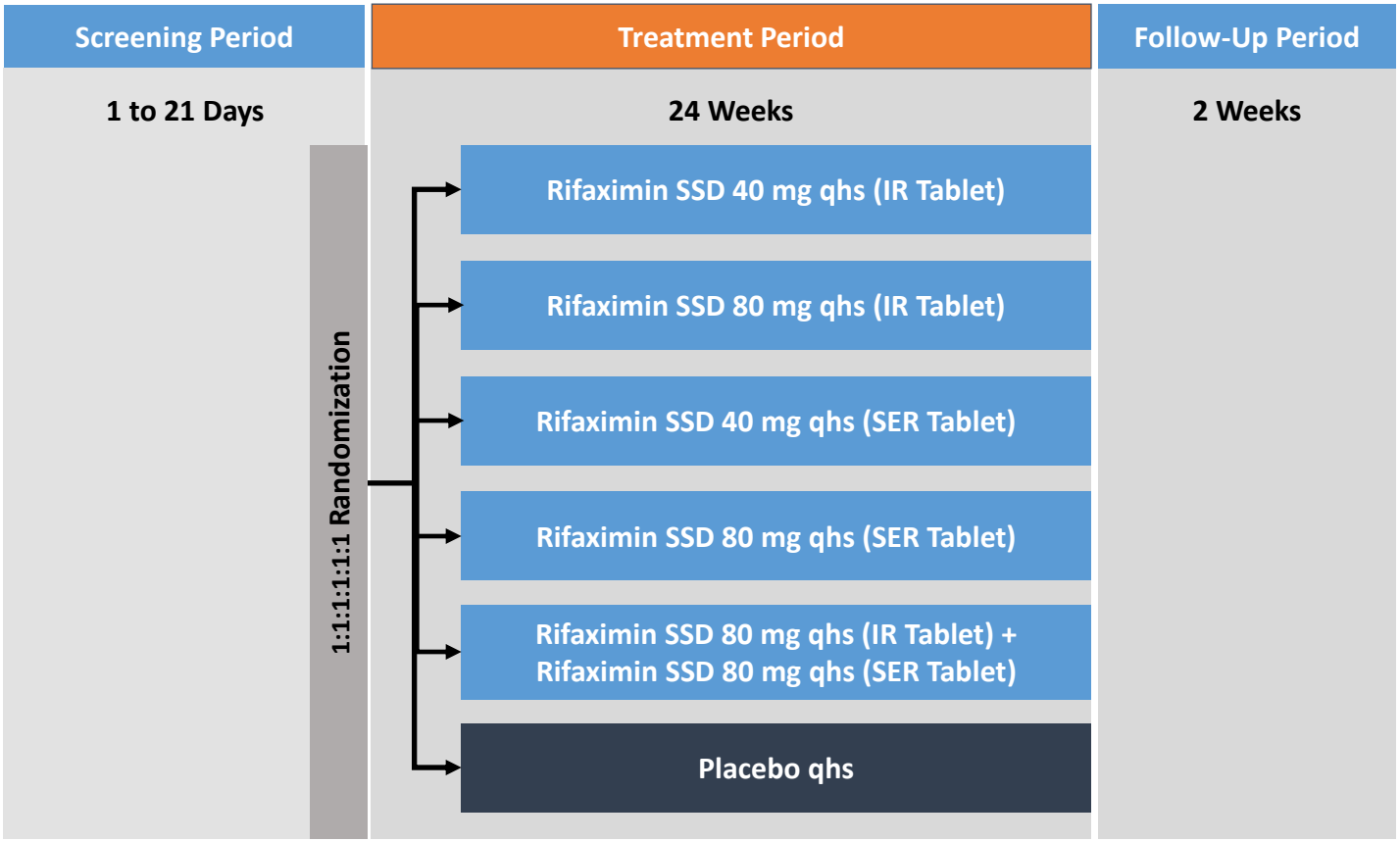
MELD: < 10 11-14 ≥ 15

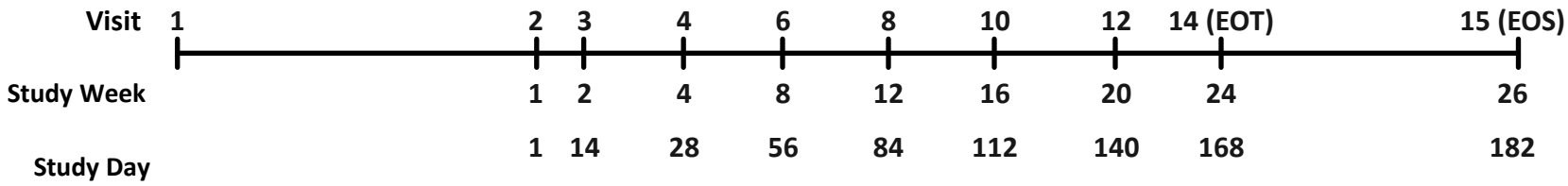
Clinically Significant Portal Hypertension (HVPG > 10 mm Hg)

LACE
- Ascites/SBP/HRS
- Encephalopathy
- HCC
- Variceal bleed

Sepsis
ACLF
MOD

Salix 2131: Phase 2 Study Design





EOS = end of study; EOT = end of treatment; IR = immediate release; qhs = once nightly at bedtime; SER = sustained extended release; SSD = soluble solid dispersion.

Key Inclusion Criteria

- Adults with diagnosis of liver cirrhosis with ascites (grade ≥1, by imaging or physical examination), without history of:
  - EVB (ie, clinically significant GI bleeding)
  - SBP (ie, >250 PMN cells/mm^3 and/or positive monomicrobial culture in ascites fluid)
  - Renal failure with ascites (ie, increase in serum creatinine of 0.5 mg/dL to level >1.5 mg/dL)
  - Development of medically refractory ascites
- MELD score ≥12 or MELD-Na score ≥12 or Child-Pugh B classification (score = 7-9)
- Resolution of any documented overt HE episode (ie, Conn score ≥2) within 30 days of screening

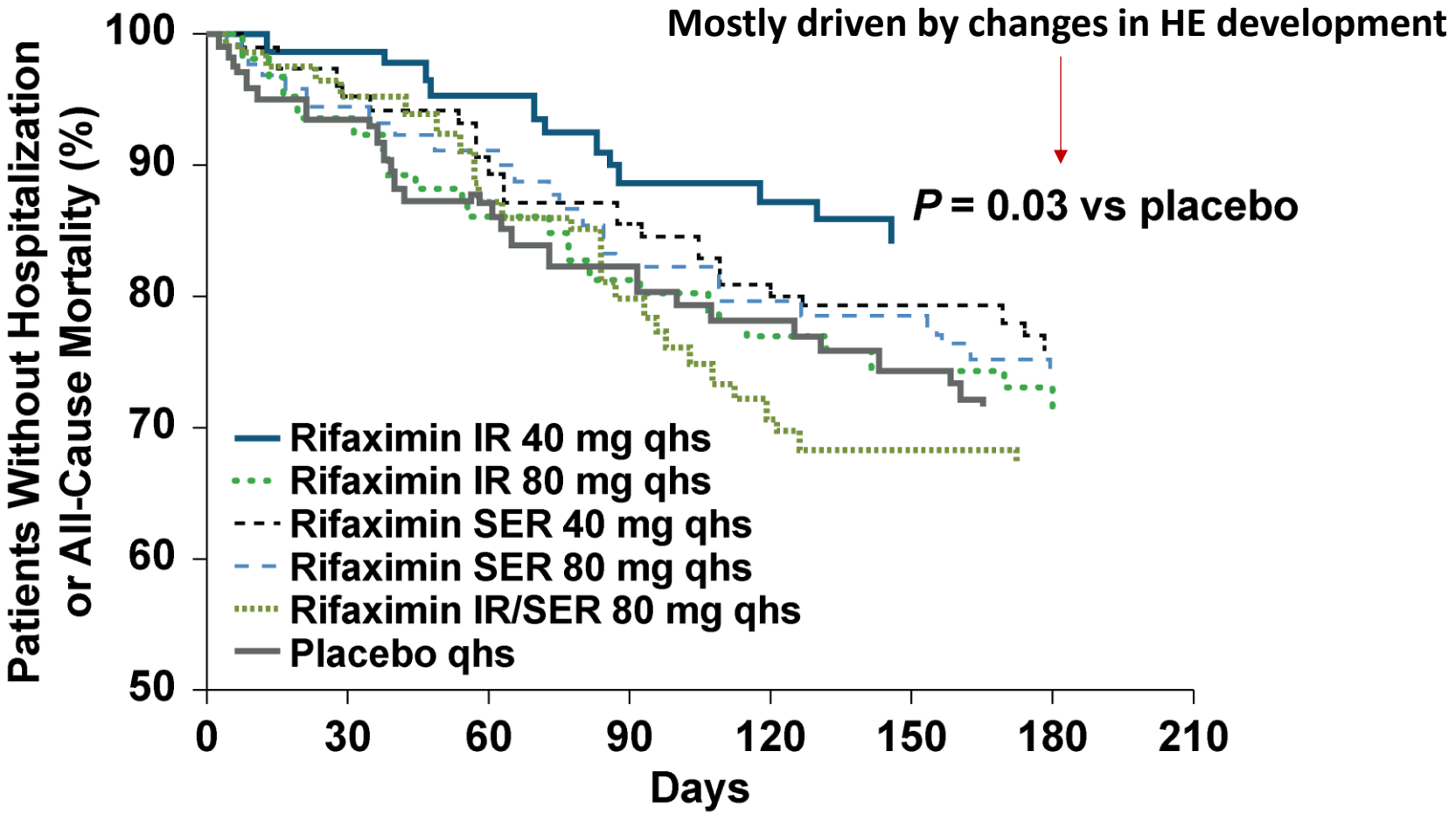
EVB = esophageal variceal bleeding; GI = gastrointestinal; HE = hepatic encephalopathy; MELD = model end-stage liver disease; MELD-Na = model end-stage liver disease with sodium; PMN = polymorphonuclear; SBP = spontaneous bacterial peritonitis.

Demographics and Baseline Disease Characteristics

Characteristic	Rifaximin IR		Rifaximin SER		Combo	Placebo (n = 94)
	40 mg (n = 78)	80 mg (n = 91)	40 mg (n = 84)	80 mg (n = 89)	80 mg IR + 80 mg SER (n = 80)	
Age, y, mean (SE)	56.4 (1.2)	56.9 (1.0)	57.4 (1.0)	57.5 (1.0)	57.2 (1.0)	57.4 (0.9)
Male sex, n (%)	52 (66.7)	52 (57.1)	43 (51.2)	56 (62.9)	51 (63.8)	61 (64.9)
MELD score, mean (SE)	11.5 (0.3)	11.6 (0.4)	10.9 (0.4)	11.5 (0.4)	12.1 (0.4)	11.5 (0.4)
MELD score, n (%)						
≤10	32 (41.0)	38 (41.8)	42 (50.0)	37 (41.6)	29 (36.3)	41 (43.6)
11-18	45 (57.7)	50 (54.9)	39 (46.4)	50 (56.2)	47 (58.8)	49 (52.1)
19-24	1 (1.3)	3 (3.3)	3 (3.6)	2 (2.2)	3 (3.8)	4 (4.3)
≥25	0	0	0	0	1 (1.3)	0
MELD-Na score, mean (SE)	12.9 (0.4)	13.0 (0.4)	12.5 (0.4)	12.6 (0.4)	13.8 (0.5)	12.8 (0.4)
Child–Pugh class						
Class A	10 (12.8)	11 (12.1)	16 (19.0)	6 (6.7)	8 (10.0)	10 (10.6)
Class B	64 (82.1)	74 (81.3)	62 (73.8)	77 (86.5)	62 (77.5)	77 (81.9)
Class C	4 (5.1)	6 (6.6)	6 (7.1)	6 (6.7)	10 (12.5)	7 (7.4)

IR = immediate release; MELD = model end-stage liver disease; MELD-Na = model end-stage liver disease with sodium; SE = standard error; SER = sustained extended release.

Time to Hospitalization or All-Cause Mortality

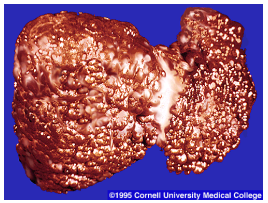


IR = immediate release; qhs = once nightly at bedtime; SER = sustained extended release.

Lessons learned from studies to prevent Liver-Associated Clinical Events (LACE)

- MELD > 10
- Early Child B

→ Outcome can not be present before entry
Outcomes should be MOA-specific



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Clinically Significant Portal Hypertension (HVPG > 10 mm Hg)

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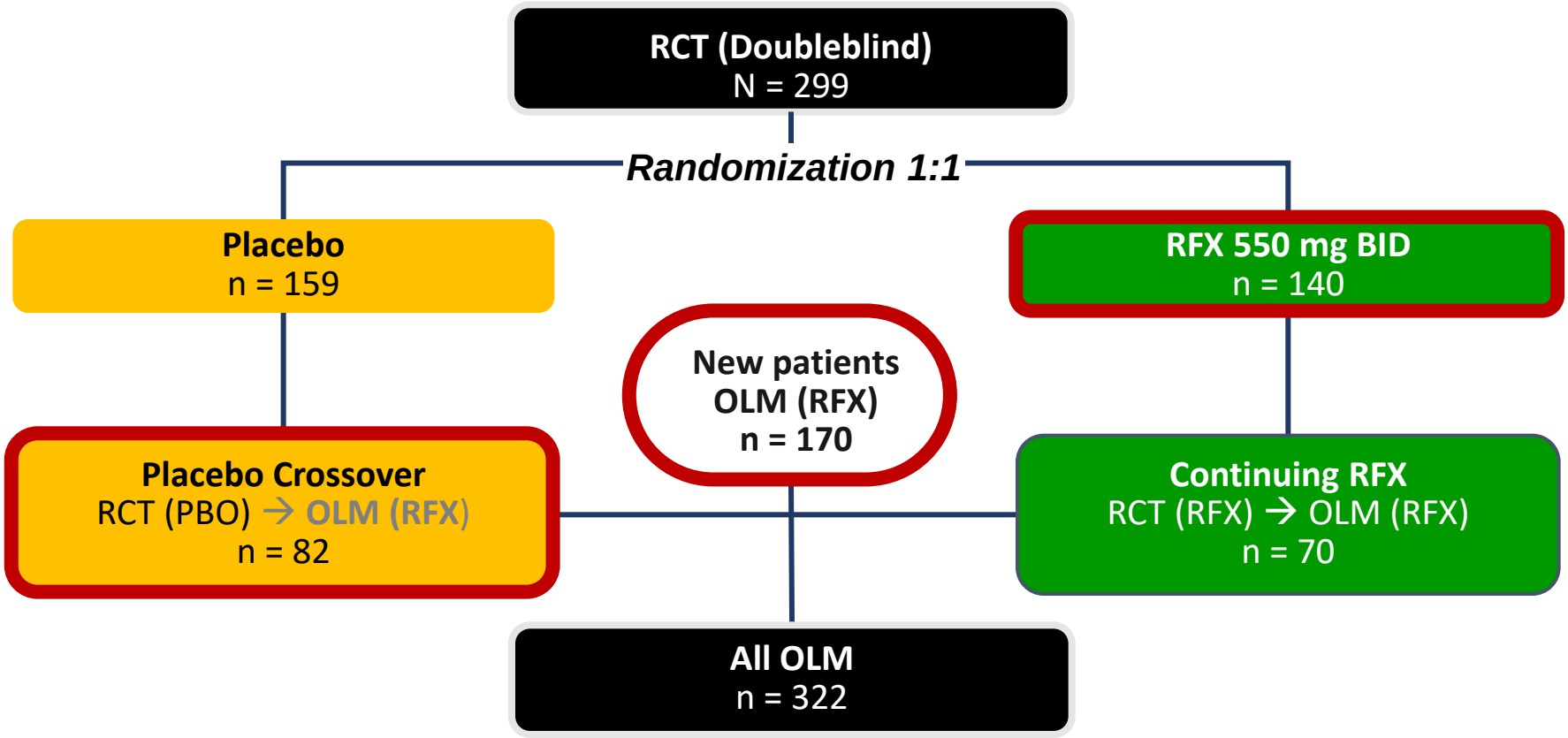
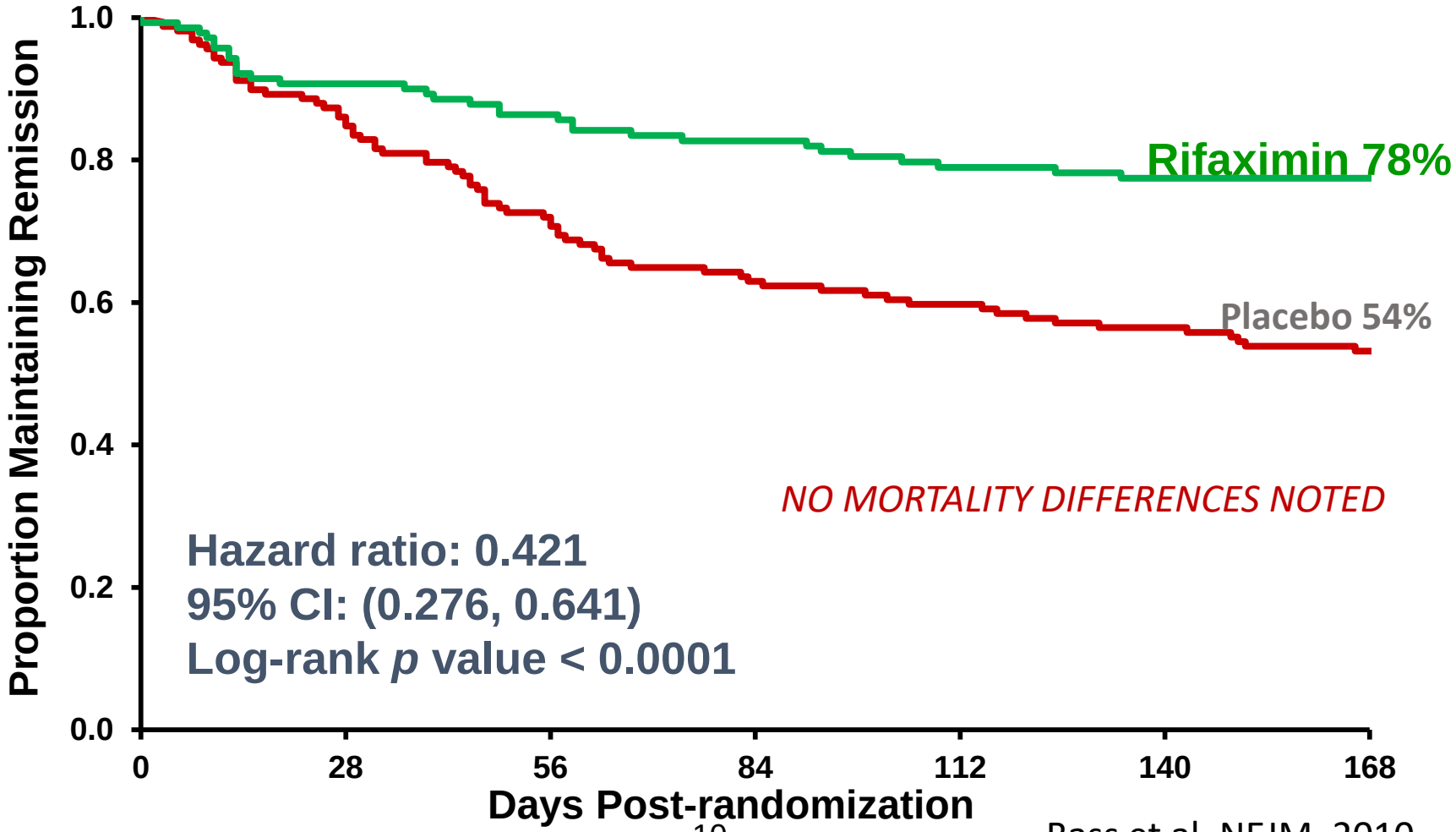
Rifaximin for HE: phase 3-4 experience
Patient Disposition



"All Rifaximin" Population = 392 (140+170+82)

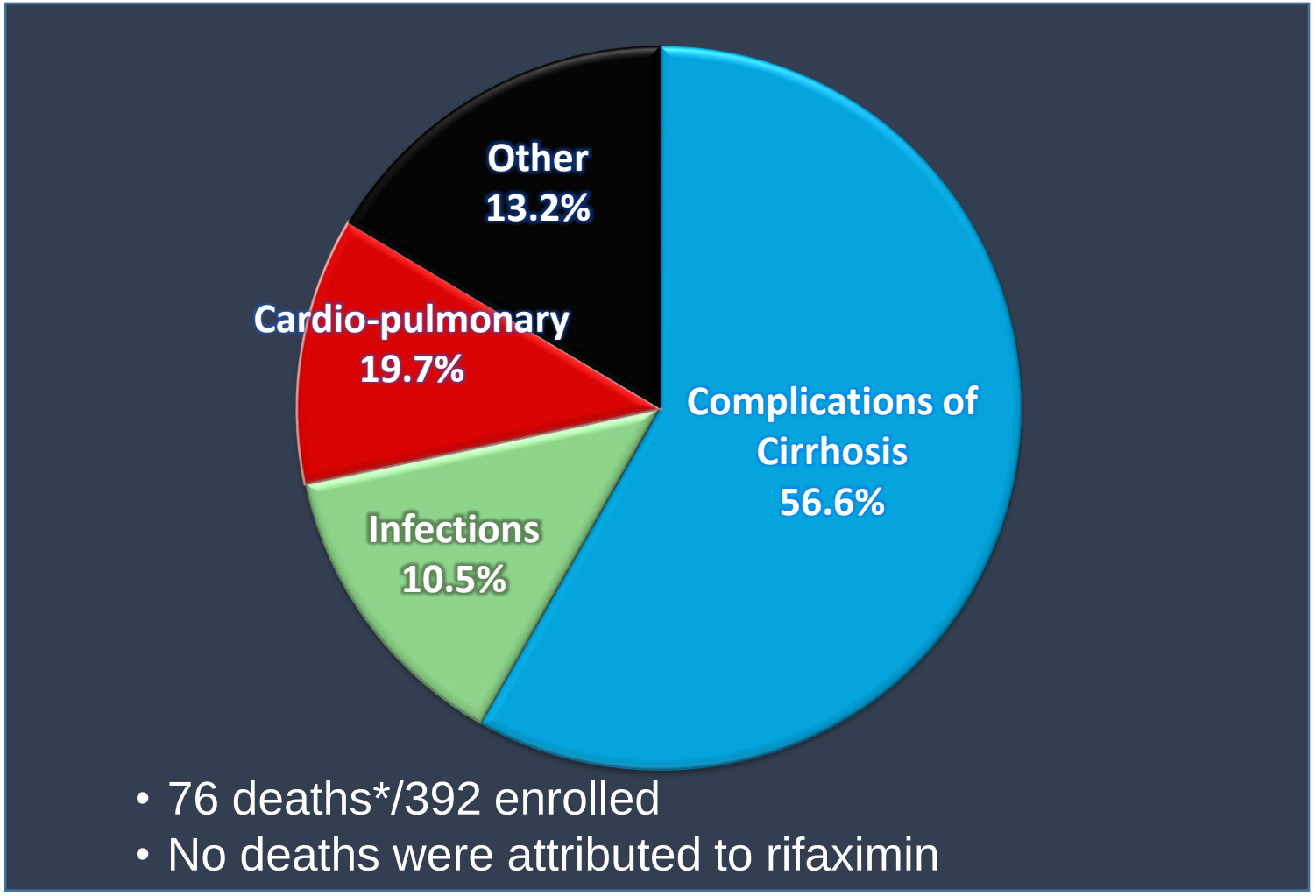
Primary Endpoint: RCT Population

Kaplan-Meier of Time to First HE Breakthrough



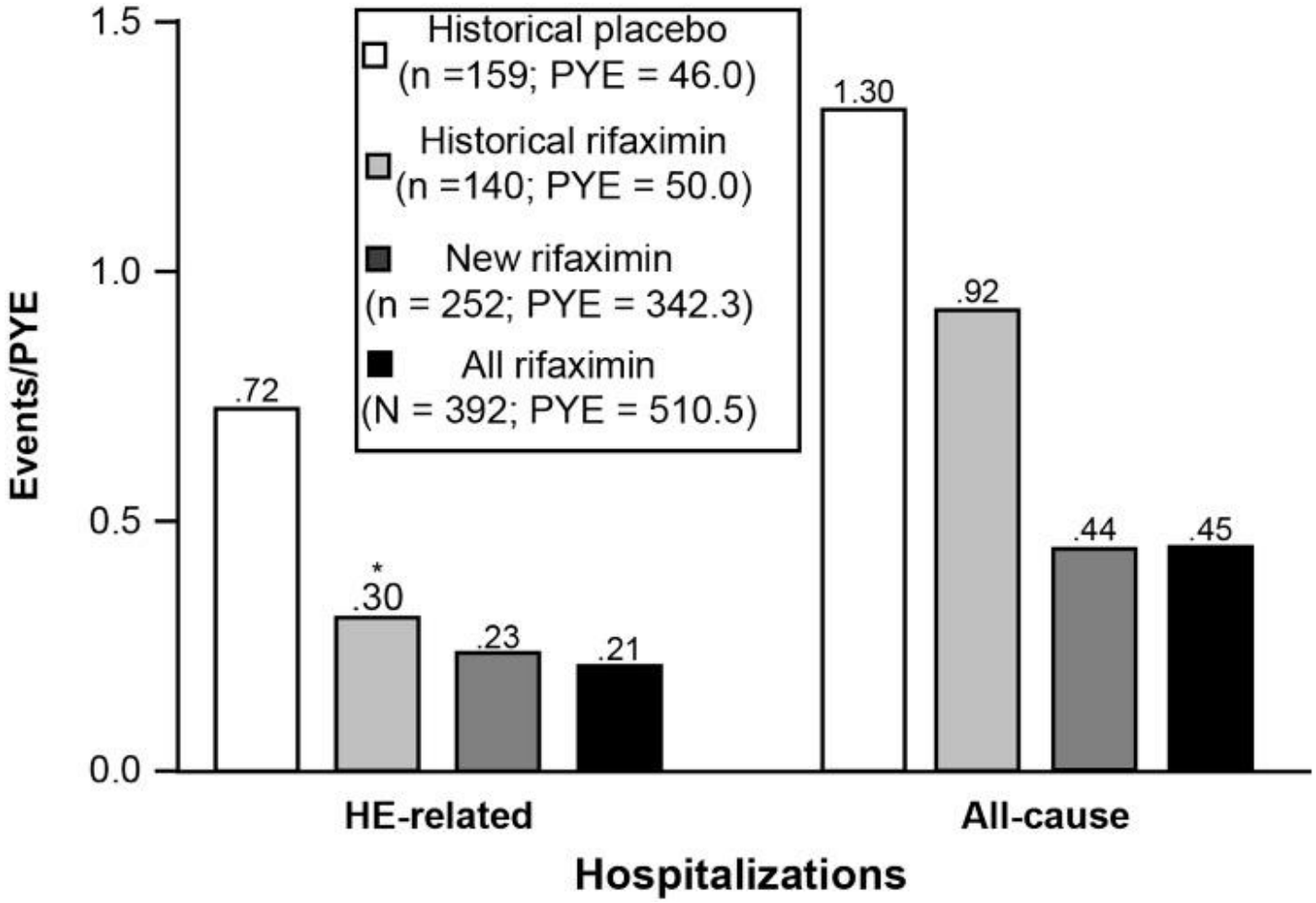
Bass et al, NEJM, 2010

Cause of Death in ALL Rifaximin Group



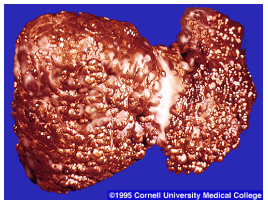
- 76 deaths*/392 enrolled
- No deaths were attributed to rifaximin

Rifaximin effects on LACE



Mullen et al, Clin Gastroenterol Hepatol. 2014 Aug;12(8):1390-7.e2.

Clinical trial data has to be considered in the context of when interventions are made



Terlipressin
Pivotal trials

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Clinically Significant Portal Hypertension (HVPG > 10 mm Hg)

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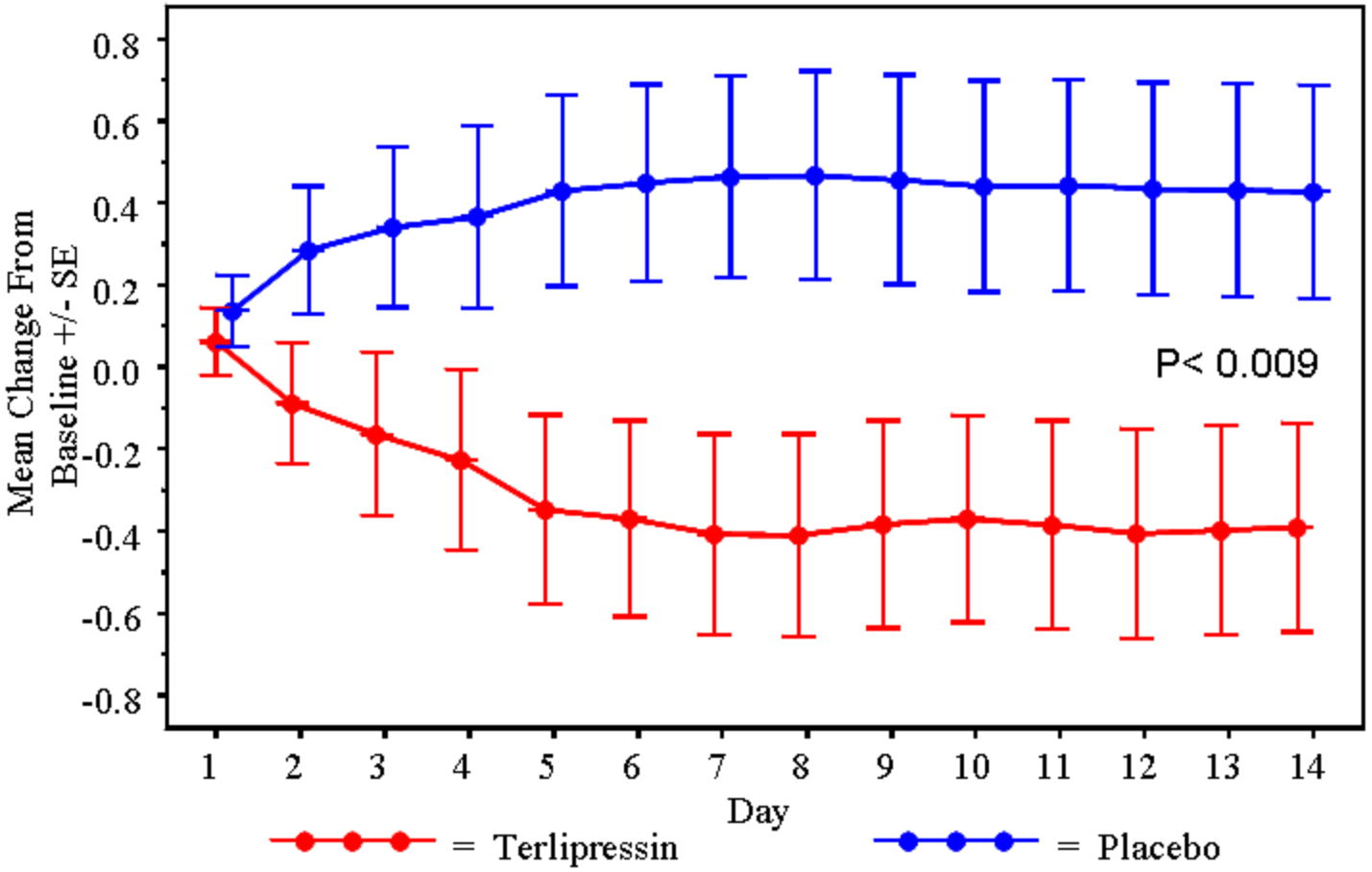
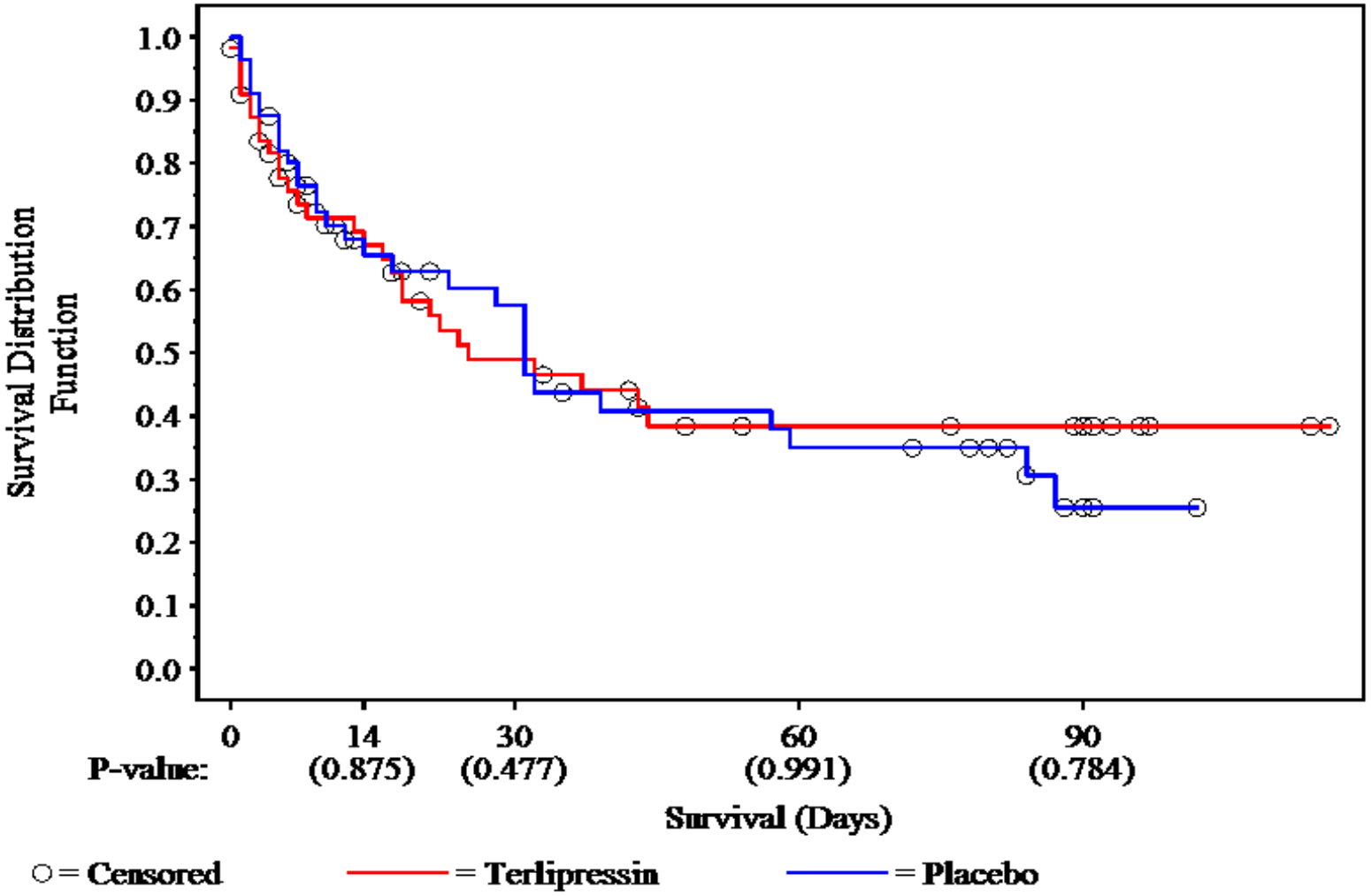
Terlipressin produced a significant improvement in serum creatinine (OT-0401 TRIAL)



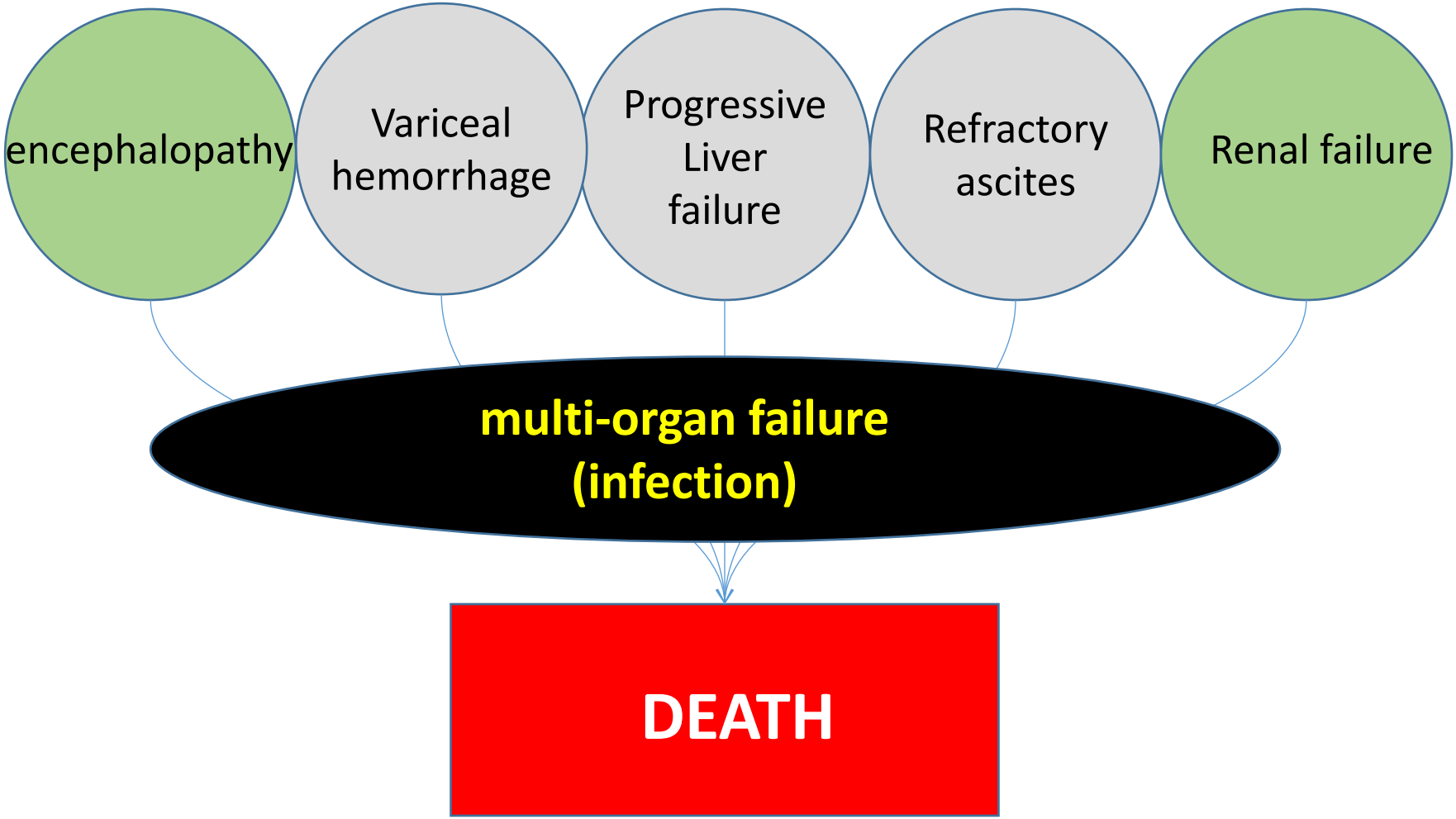
Sanyal et al, Gastroenterology 2008

Despite improvement in renal function transplant free mortality did not improve with terlipressin

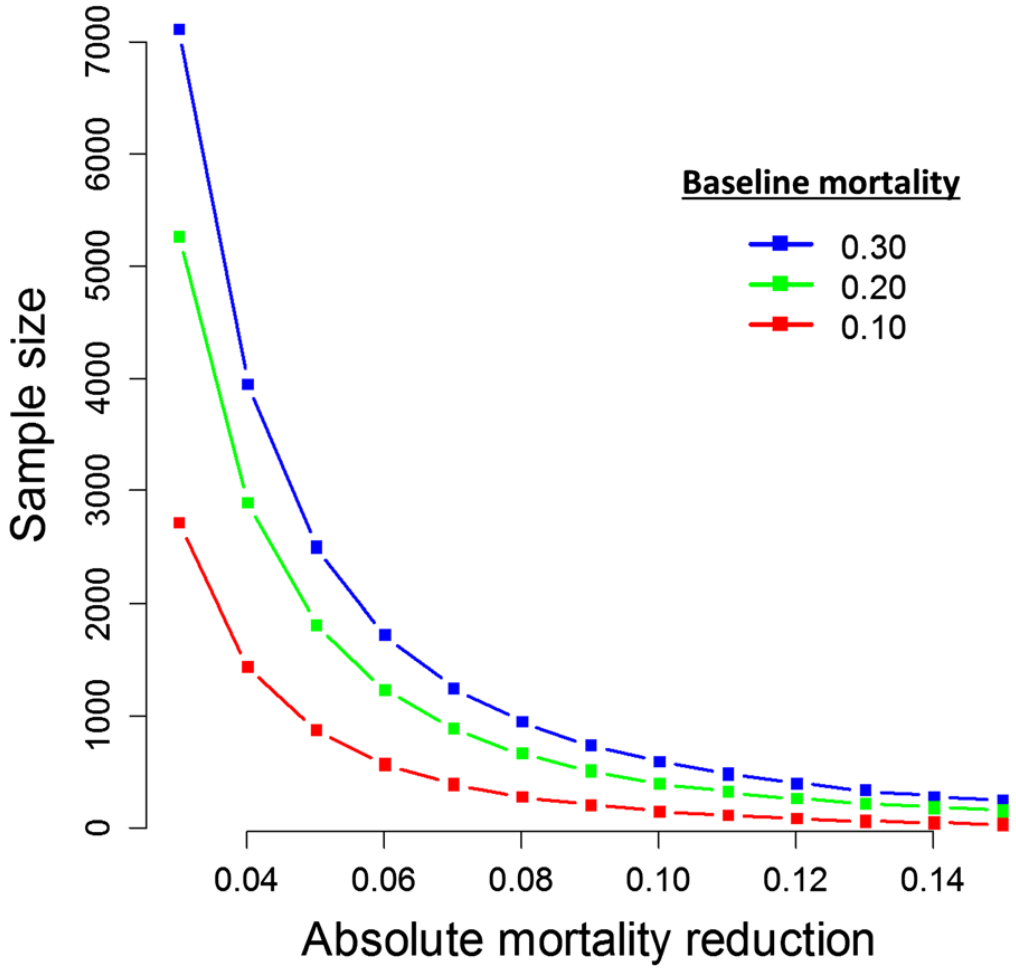


Sanyal et al, Gastroenterology 2008

All cause mortality is reasonable if the population is homogeneous in terms of drivers of mortality and there is a single primary driver of death- *THIS IS NOT THE CASE IN DECOMPENSATED CIRRHOSIS*



Sample size implications of mortality reduction



There is a need for new ways of thinking about primary endpoints in decompensated cirrhosis

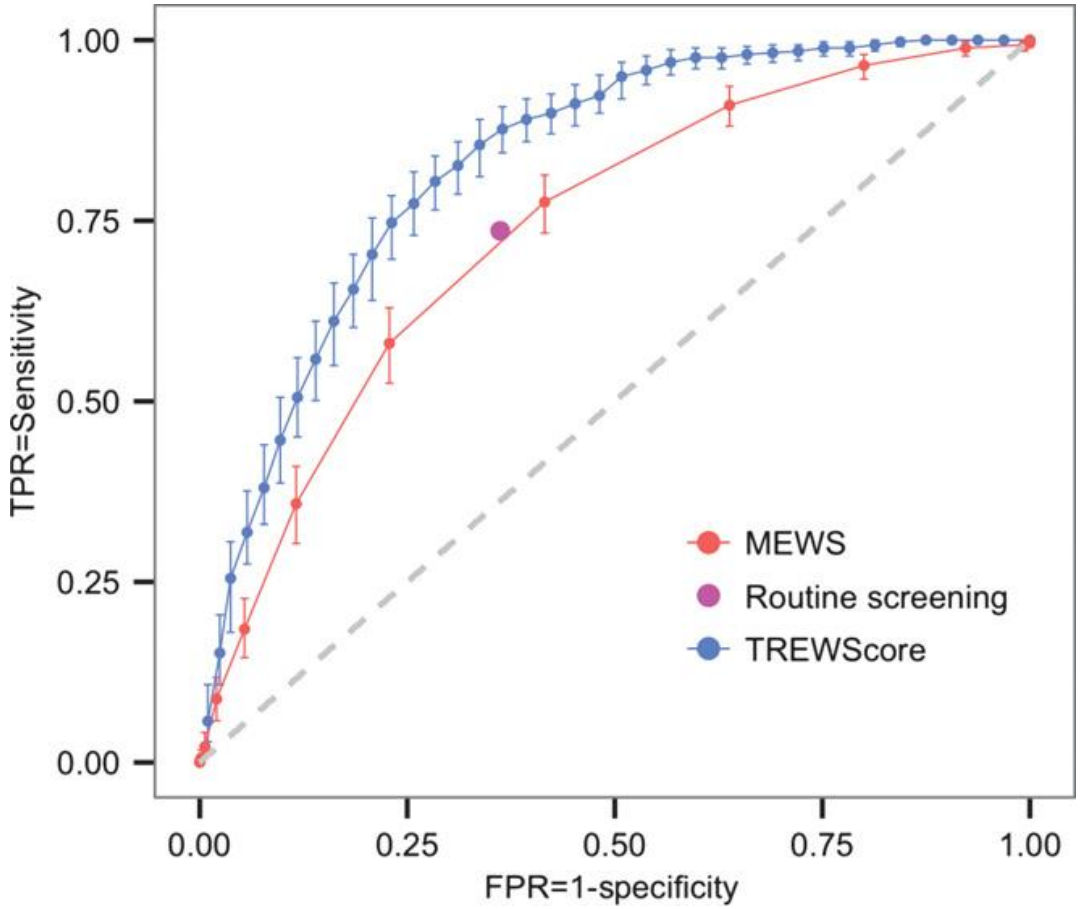
Regulatory agencies have recently agreed to a primary hierarchical clinical composite endpoint in an acute heart failure trial that combines a global assessment of symptoms, persistent or worsening heart failure requiring an intervention, and all-cause mortality assessed at 6, 24, and 48 h.

Mebazaa et al. Journal of Intensive Care (2016) 4:24 Page 6 of 11

Efficacy and Safety of Ularitide for the Treatment of Acute Decompensated Heart Failure
http://www.clinicaltrials.gov/ct2/show/NCT01661634..
Allen LA, Hernandez AF, O'Connor CM, Felker

TREW-SCORE FOR DETECTION OF SEPSIS BEFORE IT IS EVIDENT

Mews: modified early warning score
TREW- targeted realtime early warning

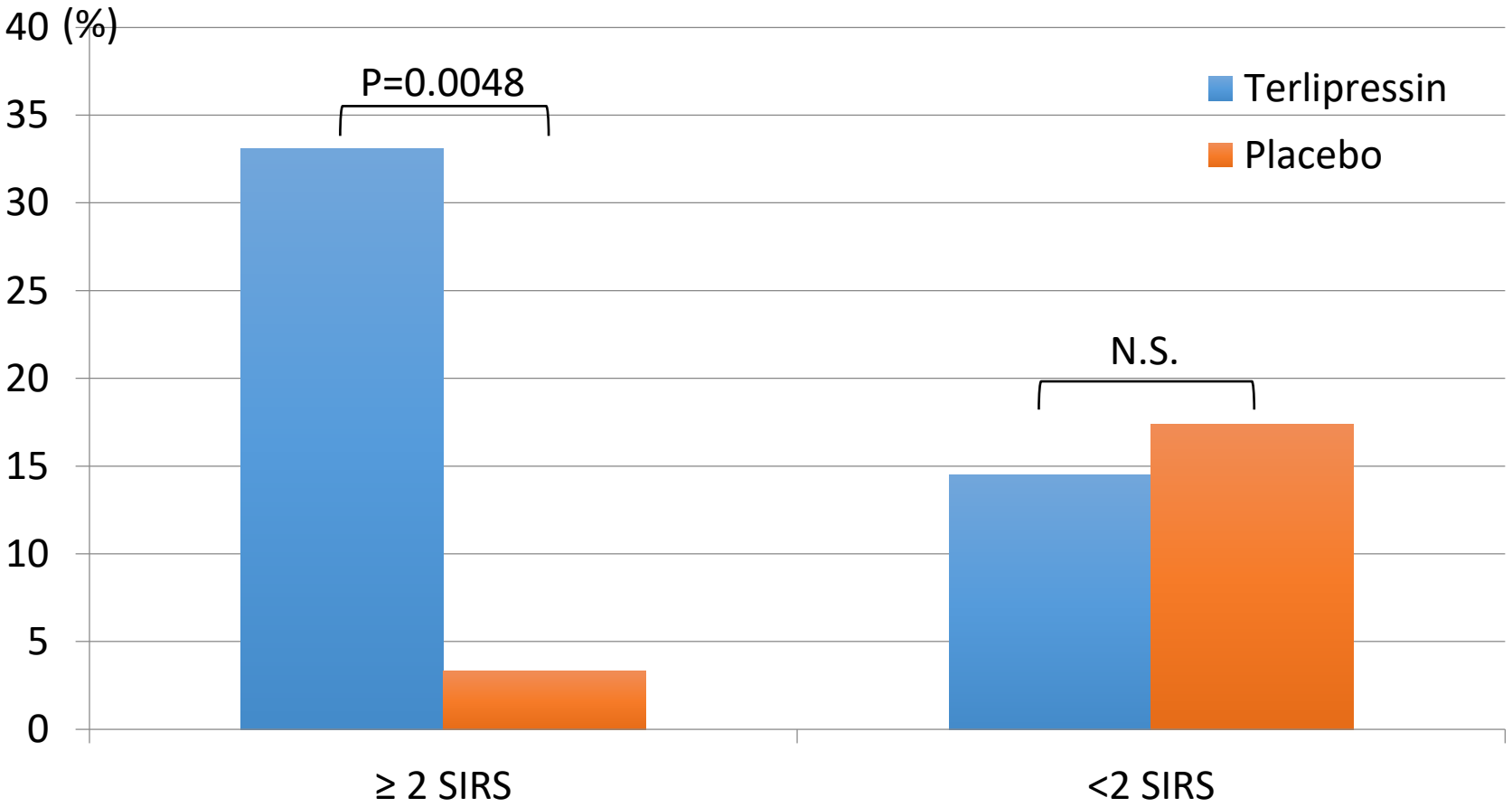


Katharine E. Henry et al., Sci Transl Med 2015;7:299ra122

Published by AAAS

SIRS as a predictor of outcomes for terlipressin

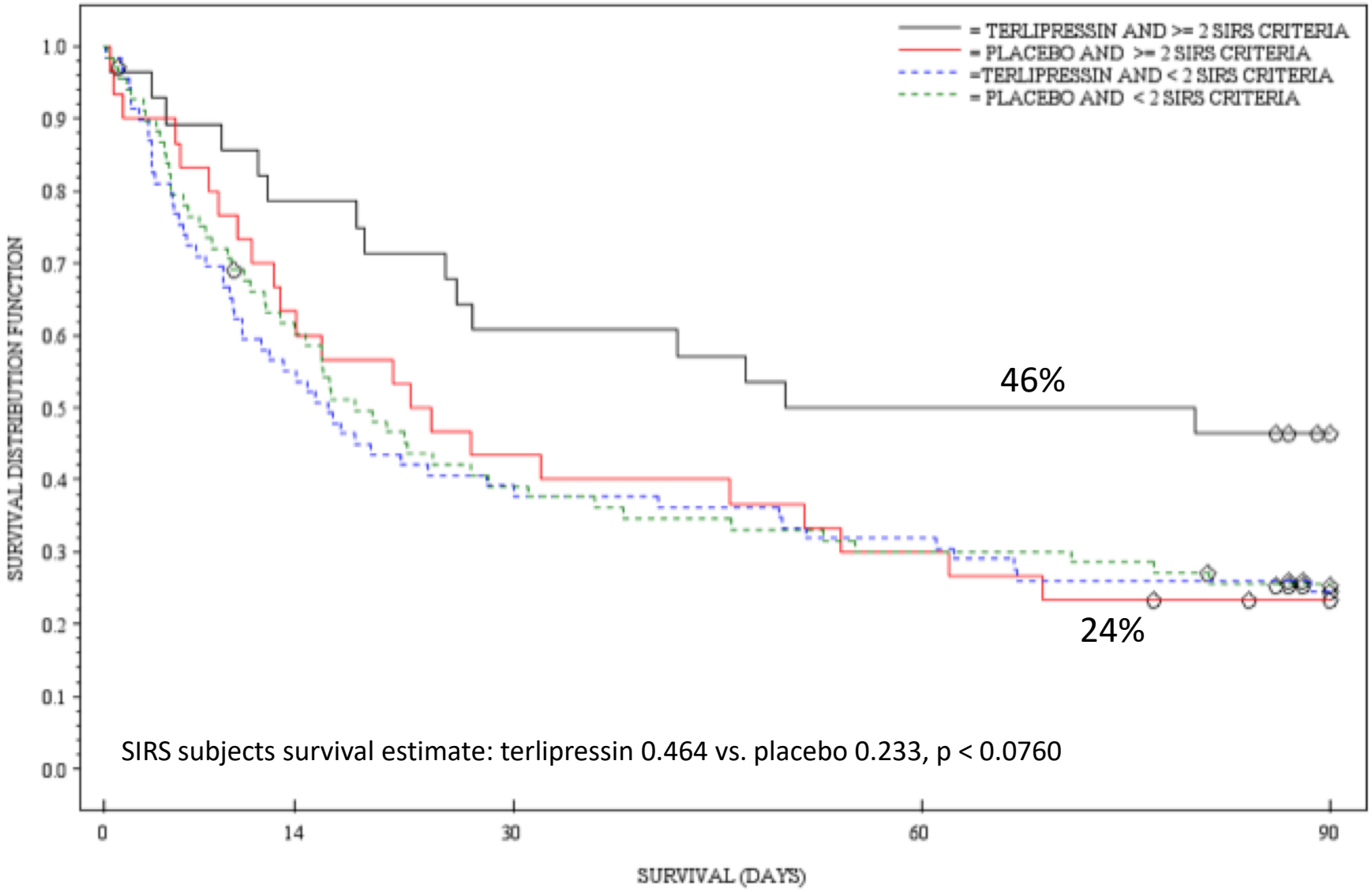
Confirmed HRS Reversal



Confirmed HRS Reversal (CHRSR): percentage of subjects with 2 SCr values of ≤1.5 mg/dL at least 48 hours apart, on treatment

Wong et al, Clin Gastroenterol Hepatol. 2017 Feb;15(2):266-272

Transplant Free Survival



Wong et al, Clin Gastroenterol Hepatol. 2017 Feb;15(2):266-272

Lessons learned in end-stage liver disease trials

- Population to be studied is related to goal of study and MOA of agent.
- Need to identify some key outcome drivers e.g. sepsis, sarcopenia, status of end-organs etc for better risk stratification- *these will inform case definitions*
- End-points: must re reconfigured for decompensated cirrhosis

THANKS TO SALIX , ORPHAN THERAPEUTICS AND MALINKRODT FOR SHARING DATA