Decision-Analytic Model to Project the Benefit of Terlipressin Treatment Among Patients With Alcohol-Related Cirrhosis and HRS

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Disclosures

Khalid Mumtaz, MBBS, MSc

- Speaker Bureau for Mallinckrodt Pharmaceuticals

Background

- Alcohol-related liver disease is a major cause of liver cirrhosis and has recently emerged as the most common indication for liver transplantation[1,2]
- HRS-AKI—a rapidly progressive renal failure—is a fatal complication of decompensated cirrhosis with ascites[3]
- Terlipressin—in combination with albumin—is the first and only US FDA-approved pharmacological therapy to improve kidney function in adult patients with HRS-AKI[4]
  - Per the FDA label, patients with SCr > 5 mg/dL are unlikely to experience a clinical benefit, and those with ACLF Grade 3 are at an increased risk of respiratory failure[4]
- Premier Healthcare Database (PHD) was used to develop decision analysis model to assess the efficacy of Terlipressin in HRS-AKI in US healthcare system
- Based on PHD, the annualized estimate of HRS-AKI cases in 2021 were over 60,000[5]
  - Approx. 60% of HRS-AKI cases were reported in alcohol-related cirrhosis[5]

ACLF, acute-on-chronic liver failure; FDA, Food and Drug Administration; HRS-AKI, hepatorenal syndrome-acute kidney injury; SCr, serum creatinine; US, United States.

1. Janicko M et al. *Biomedical papers,* 2014;159(4):661−665. **2.** Lee P et al. *JAMA Intern Med.* 2019;179(3):340−348. **3.** Wong F et al. *N Engl J Med*. 2021;384(9):818−828. **4.** TERLIVAZ® (Terlipressin). Full Prescribing Information. Mallinckrodt Pharmaceuticals; 2022. **5.** Wong RJ et al. *American College of Gastroenterology Annual Meeting*, Charlotte, NC, Oct 23−26, 2022.

Study Aim

- To assess the benefits of terlipressin therapy for adult patients with HRS-AKI and alcohol-related liver cirrhosis from the US hospital system perspective

HRS-AKI, hepatorenal syndrome-acute kidney injury; US, United States.

Methods

- A decision-analytic approach was used to create a model to estimate the effect of terlipressin on patients with HRS-AKI and alcohol-related cirrhosis from the US hospital system perspective
- The US annual projection for prevalence of HRS-AKI cases was derived from the Premier Healthcare Database among hospitalized patients
- Model inputs for treatment efficacy (i.e., HRS reversal) of terlipressin versus placebo were based on data from the CONFIRM RCT (NCT02770716)[1]
- Model inputs of the effect of HRS reversal on the likelihood of RRT, TFS, and duration of ICU stay were based on pooled data from 3 North American RCTs (CONFIRM [NCT02770716][1], REVERSE [NCT01143246][2], and OT-0401 [NCT00089570][3])

HRS-AKI, hepatorenal syndrome-acute kidney injury; ICU, intensive care unit; RRT, renal replacement therapy; RCT, randomized controlled trial; TFS, transplant-free survival; US, United States.

1. Wong F et al. *N Engl J Med*. 2021;384(9):818−828. **2.** Boyer TD et al. *Gastroenterology*. 2016;150(7):1579−589.
3. Sanyal AJ et al. *Gastroenterology*. 2008;134(5):1360−1368.

Model Assumptions and Projections

- Assumption: 80% of patients with HRS-AKI and alcohol-related cirrhosis would meet the US FDA label criteria for terlipressin use (i.e., SCr < 5 mg/dL and ACLF grade 0–2)
- Model projections for the outcomes:
  - Higher HRS reversal rate
  - Reduction in ICU stay
  - Reduction in the need for RRT
  - Increase in transplant-free survival (TFS)

ACLF, acute-on-chronic liver failure; FDA, Food and Drug Administration; HRS, hepatorenal syndrome; ICU, intensive care unit; RRT, renal replacement therapy; SCr, serum creatinine; US, United States.

Model Population: HRS-AKI and Alcohol-Related Cirrhosis

HRS-AKI per year in the US
(based on the Premier Healthcare Database)[1]
~50,000 cases

↓

60% of HRS-AKI cases are associated with alcohol-related cirrhosis
(based on RWE data)[2]
~30,000 cases

↓

80% of cases meet the US FDA label criteria (i.e., SCr < 5 mg/dL, and ACLF grade 0–2)
(based on CONFIRM data)
~24,000 cases

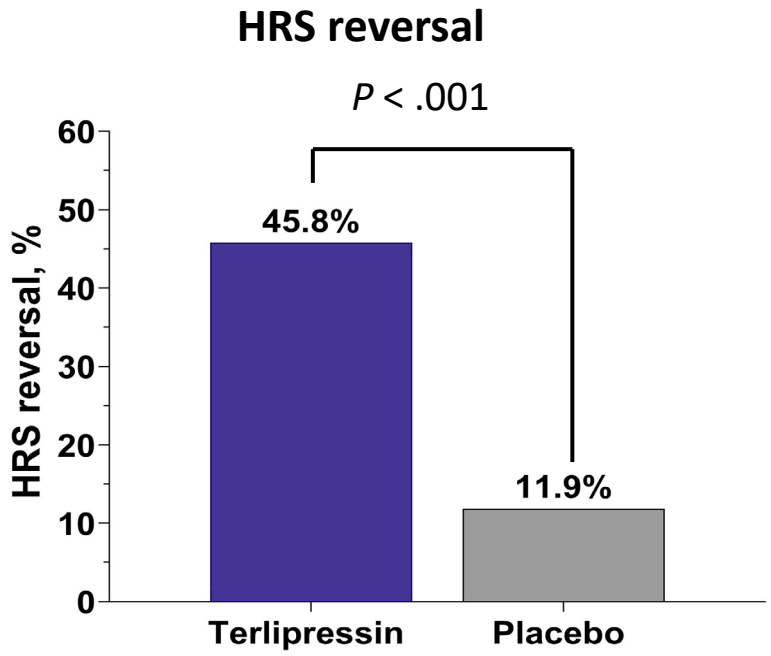
→ Patients with HRS-AKI and alcohol-related cirrhosis eligible for terlipressin treatment per year

ACLF, acute-on-chronic liver failure; FDA, Food and Drug Administration; HRS-AKI, hepatorenal syndrome-acute kidney injury; RWE, real-world evidence; SCr, serum creatinine; US, United States.

1. Wong RJ et al. *American College of Gastroenterology Annual Meeting*, Charlotte, NC, Oct 23–26, 2022.
2. Jamil K et al. *Curr Ther Res Clin Exp.* 2022;96:100663.

HRS Reversal Rate in CONFIRM

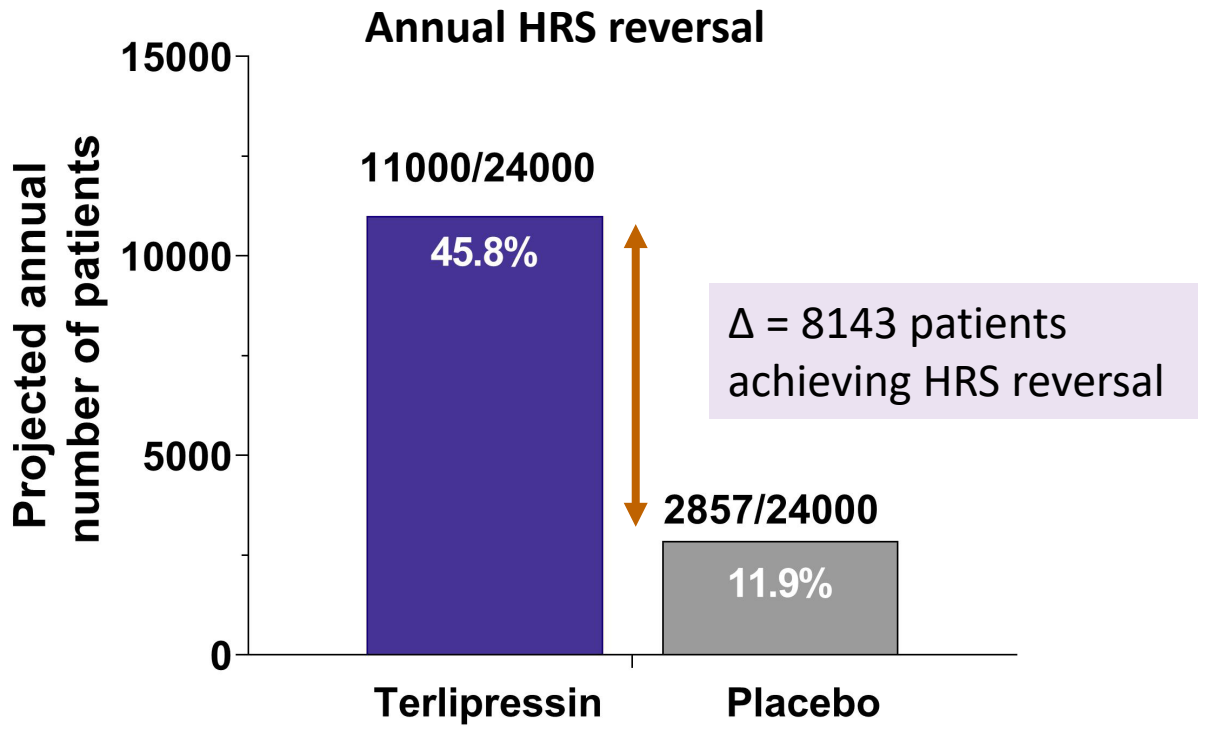
- HRS reversal was defined as at least 1 SCr value ≤ 1.5 mg/dL while on treatment (on treatment was defined as up to 24 hours after the final dose of study drug) by Day 14 or discharge
- Efficacy (i.e., HRS reversal) was evaluated among patients with alcohol-related cirrhosis, SCr < 5 mg/dL, and ACLF grade 0–2 from the CONFIRM study



ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome; SCr, serum creatinine.

1. Sanyal AJ et al. *Gastroenterology*. 2008;134(5):1360–1368. **2.** Boyer TD et al. *Gastroenterology*. 2016;150(7):1579–1589.
3. Wong F et al. *N Engl J Med*. 2021;384(9):818–828.

Model Projections for HRS Reversal in the PHD[a]



[a] **For patients with alcohol-related cirrhosis, SCr < 5 mg/dL, and ACLF grade 0–2.**

ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome; SCr, serum creatinine.

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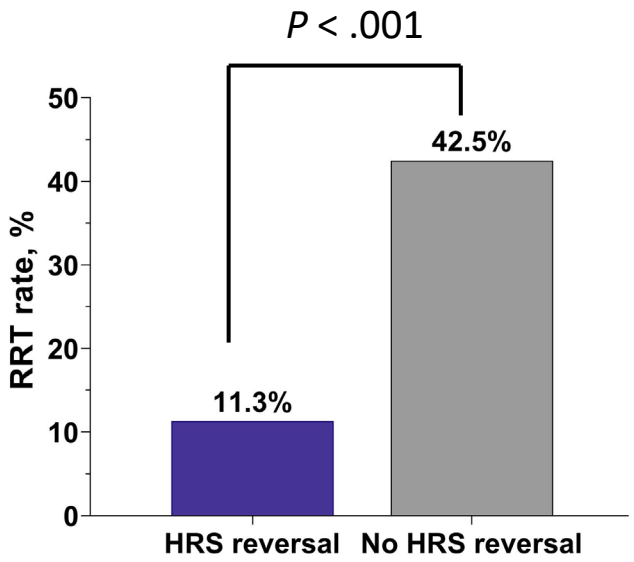
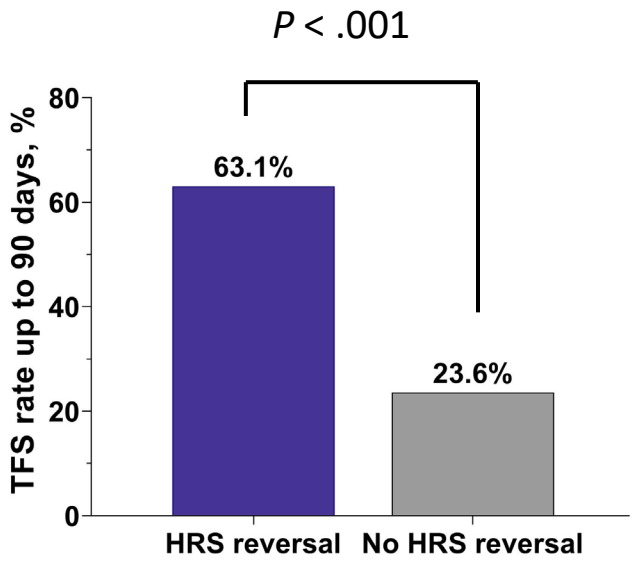
3. Wong F et al. *N Engl J Med*. 2021;384(9):818–828.

Impact of HRS Reversal on RRT, TFS, and ICU Stay in the Pooled Trials

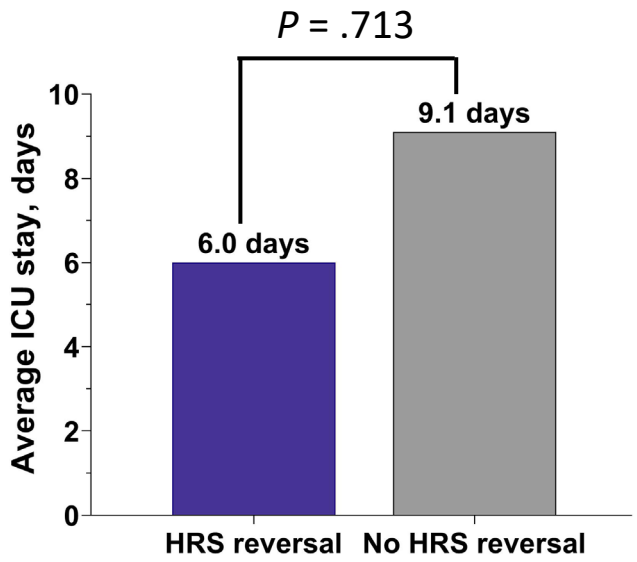
RRT rate[a]



TFS rate up to 90 days[a]



ICU stay [b]



[a] RRT and TFS effect estimates are based on the pooled data from OT-0401[1], REVERSE[2], and CONFIRM[3] for the overall population.
[b] ICU stay duration estimates are based on data from the CONFIRM study only for the overall population.

HRS, hepatorenal syndrome; ICU, intensive care unit; RRT, renal replacement therapy; TFS, transplant-free survival.

1. Sanyal AJ et al. *Gastroenterology*. 2008;134(5):1360–1368. **2.** Boyer TD et al. *Gastroenterology*. 2016;150(7):1579–1589.
3. Wong F et al. *N Engl J Med*. 2021;384(9):818–828.

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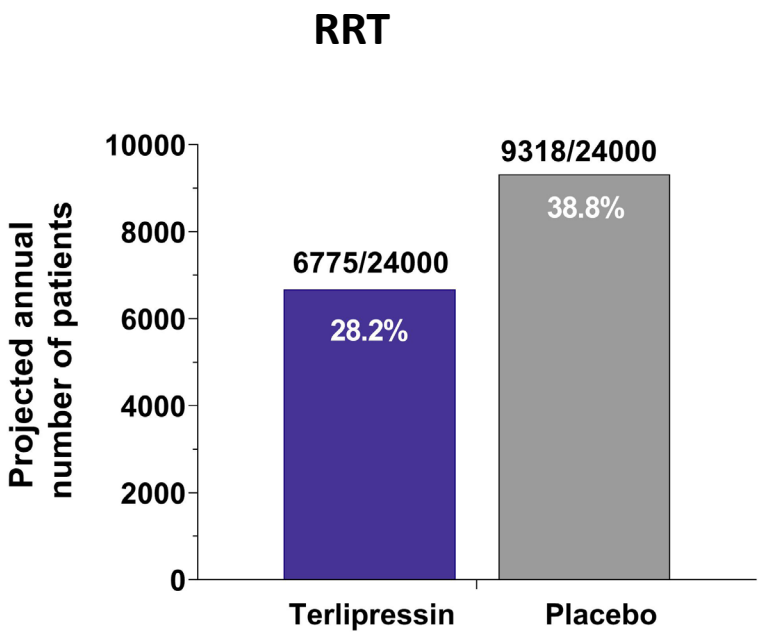
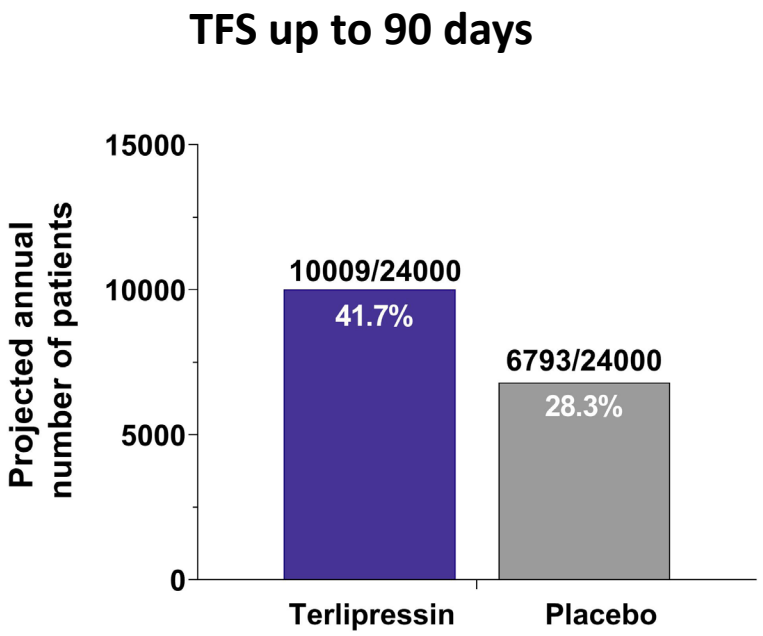
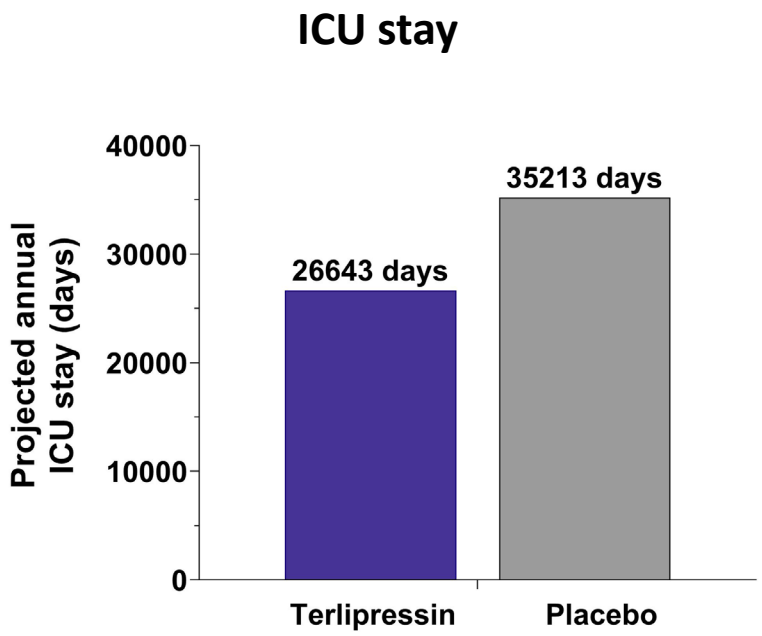
Model Projections for impact of HRS reversal on RRT, TFS, and ICU Stay in the PHD[a]







[a] For patients with alcohol-related cirrhosis, SCr < 5 mg/dL, and ACLF grade 0–2.

ACLF, acute-on-chronic liver failure; ICU, intensive care unit; RRT, renal replacement therapy; SCr, serum creatinine; TFS, transplant-free survival.

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Limitations

- Several assumptions were used in the analysis, including the proportion of patients with HRS-AKI and alcohol-related cirrhosis
- This analysis relied on efficacy data from the CONFIRM[1] RCT (for patients with alcohol-related cirrhosis), and the impact of HRS reversal on RRT, TFS and ICU stay based on data from the pooled analyses from 3 RCTs (ie, CONFIRM[1], REVERSE[2], and OT-0401[3])
- However, data from RCTs may not be generalizable to real-world clinical practice in different hospitals in the US healthcare system
- Not all variables of the pooled trial population were available from the Premier Healthcare Database

AKI, acute kidney injury; HRS, hepatorenal syndrome; ICU, intensive care unit; RCT, randomized control trial; RRT, renal replacement therapy; TFS, transplant-free survival; US, United States.

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Key Takeaways

The terlipressin trial results-based model projected on to the Premier Healthcare Database showed substantial improvements in pivotal clinical outcomes, including:

- Increased HRS reversal rates
- Increased rate of TFS (up to 90 days)
- Decreased need for RRT
- Reduced duration of ICU stay

- The expected benefits from terlipressin therapy may improve clinical outcomes in patients with alcohol-related cirrhosis and HRS-AKI in the US healthcare system
- Potentially, this improvement may translate into a decrease in the cost of care

AKI, acute kidney injury; HRS, hepatorenal syndrome; ICU, intensive care unit; RRT, renal replacement therapy; TFS, transplant-free survival; US, United States.

Acknowledgments

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GPP 2022, Good Publication Practice 2022 Update: ICMJE, International Committee of Medical Journal Editors.

Thank you!

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Backup slides

Demographics and Baseline Characteristics

Table 1. Demographics and baseline characteristics for patients with HRS-AKI and alcohol-related cirrhosis with ACLF grade 0–2 and SCr < 5 mg/dL in the CONFIRM[1] study

Parameter at baseline	Terlipressin (n = 89)	Placebo (n = 48)	*P* values[a]
Age (years)	53.5 ± 10.23	49.5 ± 10.10	.022
Male sex (n, %)	61 (68.5)	35 (72.9)	.593
SCr (mg/dL)	3.2 ± 0.68	3.3 ± 0.76	.528
MELD score	31.4 (6.39)	32.0 (5.97)	.364
MAP (mm Hg)	78.4 ± 12.01	77.9 ± 9.88	.977
Child-Pugh score (n, %)			.563
Class A [5-6]	2 (2.2)	2 (4.2)	
Class B [7-9]	31 (34.8)	17 (35.4)	
Class C [10-15]	54 (60.7)	26 (54.2)	
Bilirubin (mg/dL)	10.7 ± 11.85	15.0 ± 14.11	.081
BUN (mg/dL)	58.6 ± 25.47	59.9 ± 30.01	.950
Prior albumin use (n, %)	89 (100.0)	47 (97.9)	.350
Amount of prior albumin (g)	310.2 ± 161.24	378.5 ± 344.74	.364
Prior steroid use (n, %)	11 (12.36%)	5 (10.42%)	.736
Concomitant steroid use (n, %)	5 (5.62%)	3 (6.25%)	1.000

Data are presented as the mean ± SD unless otherwise noted.
[a] *P* values are calculated using Chi-square or Fisher's exact tests.

ACLF, acute-on-chronic liver failure; BUN, blood urea nitrogen; HRS-AKI, hepatorenal syndrome-acute kidney injury; MAP, mean arterial pressure; MELD, Model for End-stage Liver Disease; SCr, serum creatinine.

1. Wong F et al. *N Engl J Med*. 2021;384(9):818–828.