Improved Mean Arterial Pressure From Baseline to the End of Treatment With Terlipressin is Associated With Hepatorenal Syndrome Reversal: A Pooled Analysis of 3 Phase III Studies

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Disclosures

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Background

- HRS-AKI is a rapidly progressive form of renal failure associated with a high mortality in patients with decompensated cirrhosis and ascites[1]
- The underlying cirrhosis causes vasodilatory factors to accumulate, which reduces the effective circulating blood volume and decreases MAP[2]
- Terlipressin, a vasopressin analogue, is the first and only US FDA-approved treatment for HRS-AKI[3]
- Terlipressin improves renal function in patients with HRS-AKI by reducing portal hypertension and increasing effective arterial volume and MAP—a marker of the hemodynamic response to treatment[1,4]
- The AASLD recommends terlipressin in combination with albumin as a first-line therapy for adult patients with HRS[5]

1. Boyer TD, et al. *J Hepatol*. 2011;55(2):315–321; **2.** Belcher JM, et al. *Am J Kidney Dis*. 2022;79(5):737–745; **3.** TERLIVAZ. Prescribing Information. Mallinckrodt Pharmaceuticals. September 19, 2022; **4.** Nazar A, et al. *Hepatology*. 2010;51(1):219–226; **5.** Biggins SW, et al. *Hepatology*. 2021;74(2):1014–1048.

AASLD, American Association for the Study of Liver Diseases; FDA, Food and Drug Administration; HRS-AKI, hepatorenal syndrome-acute kidney injury; MAP, mean arterial pressure.

Study Objective

- To evaluate the association of change in MAP from baseline (Day 0) to EOT with HRS reversal
  - HRS reversal was defined as a serum creatinine of ≤ 1.5 mg/dL while on treatment up to 24 hours after the last dose of study drug, by Day 14, or at discharge

Retrospective Analysis

Patients

- Patient data were pooled from the following Phase III studies: OT-0401[1], REVERSE[2], and CONFIRM[3]
- The pooled patient population included 598 treated patients with HRS-AKI
  - Terlipressin (n = 349)
  - Placebo (n = 249)

Methods

- For change in MAP assessments, MAP was averaged daily, before and 2 hours post-injection (4 per day) of terlipressin or placebo. If data were missing, the last observation was used

1. Sanyal AJ et al. *Gastroenterology*. 2008;134:1360–1368; **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.

EOT, end of treatment; HRS, hepatorenal syndrome; MAP, mean arterial pressure.

Patient Data Were Pooled From 3 Phase III Studies for this Retrospective Analysis: Overview of Clinical Study Designs

OT-0401[1]
(N = 112)
35 clinical study sites
US, Germany, and Russia

REVERSE[2]
(N = 196)
52 clinical study sites
US and Canada

CONFIRM[3]
(N = 300)
60 clinical study sites
US and Canada

Key Inclusion Criteria:
- Adults aged ≥ 18 years
- Diagnosis of cirrhosis, ascites, and HRS—defined as a SCr doubling to ≥ 2.5 mg/dL (OT-0401 and REVERSE) or ≥ 2.25 mg/dL (CONFIRM) within 14 days before randomization

Key Exclusion Criteria:
- SCr > 7 mg/dL (REVERSE and CONFIRM)
- Kidney injury or AKI from other causes
- Shock or sepsis

Randomization
1:1 (OT-0401 and REVERSE)
2:1 (CONFIRM)

Terlipressin 1 mg[a,b]
Q6H IV bolus up to 14 days

Placebo[a]
Q6H IV bolus up to 14 days

[a] **Concomitant albumin was strongly recommended** at a dose of 100 g on Day 1 and then 25 g/day until EOT in OT-0401; 20–40 g/day in REVERSE; and 1 g/kg to a maximum of 100 g on Day 1 and 20–40 g/day thereafter in CONFIRM.
[b] If after Day 3, SCr had decreased—but by less than 30%—then the terlipressin dose could be increased to 2 mg Q6H.

1. Sanyal AJ et al. *Gastroenterology*. 2008;134:1360–1368; **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.

AKI, acute kidney injury; EOT, end of treatment; HRS, hepatorenal syndrome;
IV, intravenous; Q6H, every 6 hours; MAP, mean arterial pressure; SCr, serum creatinine.

Baseline Demographics and Clinical Characteristics

Parameter	Terlipressin (n = 349)	Placebo (n = 249)
Age, years	54.0 ± 10.6	54.1 ± 10.5
Male sex, n (%)	211 (60.5)	160 (64.3)
Alcoholic hepatitis, n (%)	121 (34.7)	82 (32.9)
SIRS, n (%)[a]	110 (37.5)	77 (39.7)
MAP, mm Hg	77.4 ± 11.9	76.8 ± 10.9
MAP < 65 mm Hg, n (%)	48 (13.8)	32 (12.9)

Parameter	Terlipressin (n = 349)	Placebo (n = 249)
SCr, mg/dL	3.6 ± 1.3	3.6 ± 1.1
Total bilirubin, mg/dL	12.9 ± 12.8	14.0 ± 14.5
Child-Pugh score, n (%)		
Class A (5–6)	5 (1.4)	3 (1.2)
Class B (7–9)	101 (28.9)	69 (27.7)
Class C (10–15)	229 (65.6)	163 (65.5)
Missing	14 (4.0)	14 (5.6)
MELD score	33.0 ± 6.4	33.1 ± 5.8

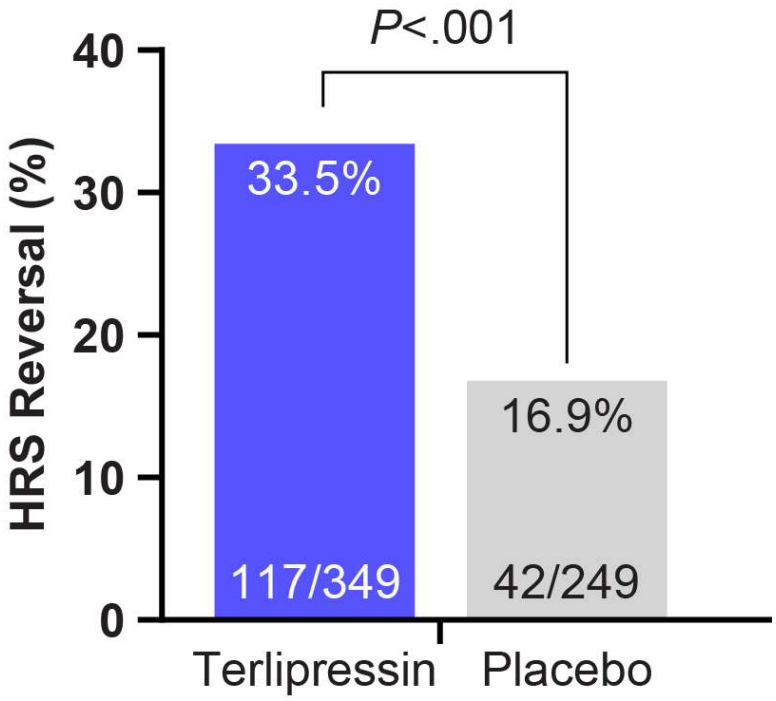
Data are presented as the mean ± SD unless otherwise noted.
[a] SIRS subgroup data were available for the CONFIRM and REVERSE studies only.
MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; SCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

Baseline characteristics were similar across treatment arms

Duration of Treatment

Duration of Treatment, Days	Terlipressin (N = 352)	Placebo (N = 256)
Mean ± SD	6.3 ± 4.39	6.0 ± 3.86
Median	5.0	4.0
Min, Max	1.0, 25.0	1.0, 19.0

Incidence of HRS Reversal



The *P* value was determined using a Chi-square test.

- HRS reversal was achieved by more patients who were treated with terlipressin than placebo

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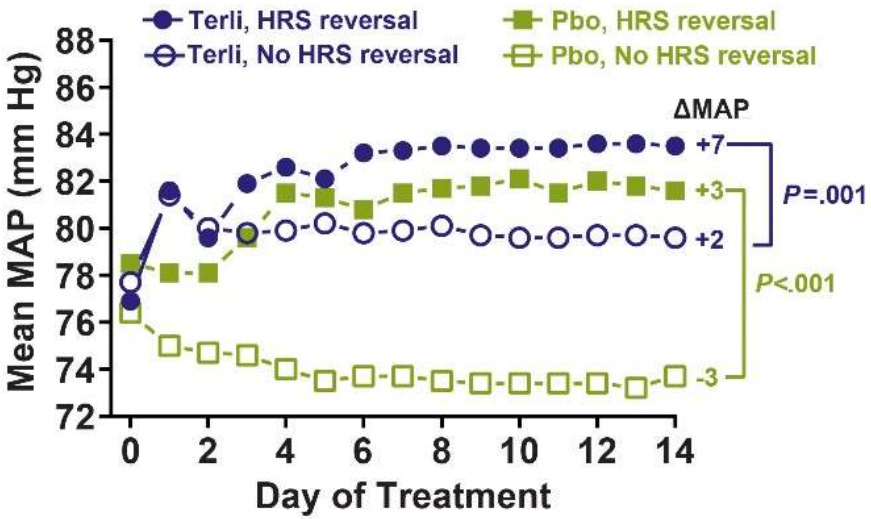
HRS, hepatorenal syndrome.

Daily MAP in Patients by Treatment and HRS Reversal Status



P values assessed change in MAP at Day 14 and were generated by ANOVA and Kruskal-Wallis tests.

- Patients who achieved HRS reversal had a greater increase in MAP from baseline to the EOT compared with those with no HRS reversal

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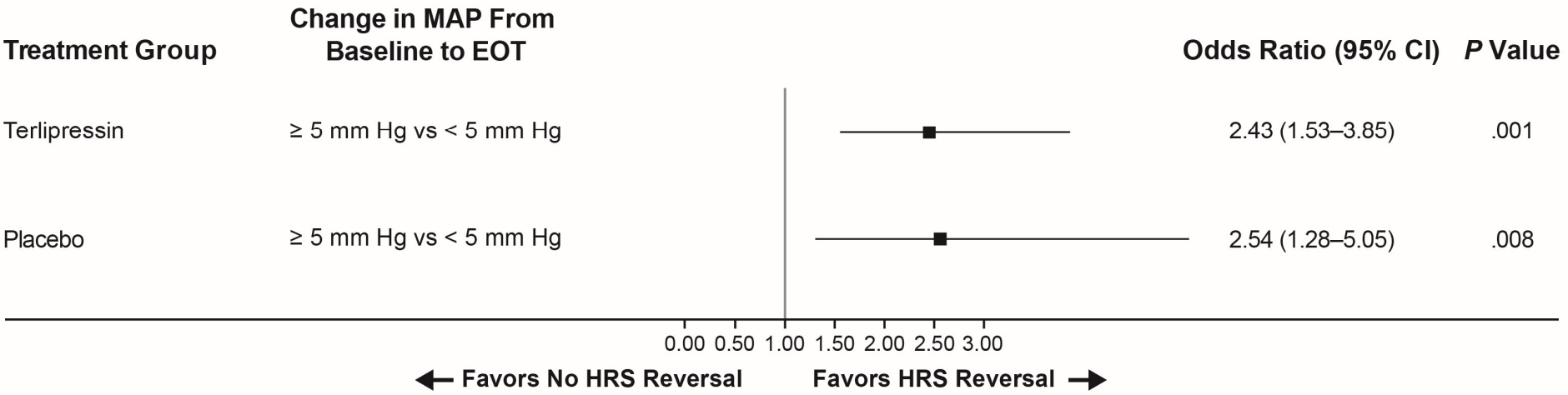
ANOVA, analysis of variance; EOT, end of treatment; HRS, hepatorenal syndrome; MAP, mean arterial pressure; ΔMAP, change in MAP from baseline (ie, Day 0) to Day 14; Pbo, placebo; Terli, terlipressin.

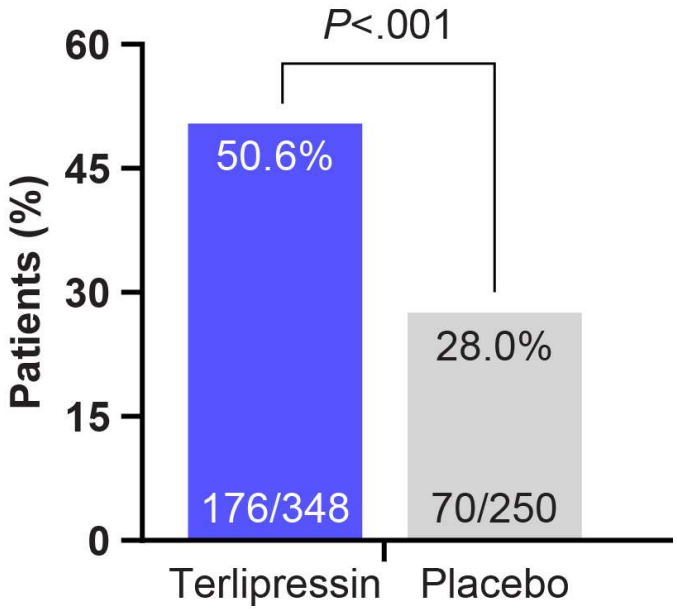
Association of Changes in MAP From Baseline to the EOT



Associations were assessed by a logistic regression analysis.
P values were generated using a Wald test.
CI, confidence interval; EOT, end of treatment; HRS, hepatorenal syndrome; MAP, mean arterial pressure.

A change in MAP of ≥ 5 mm Hg was significantly associated with HRS reversal, regardless of treatment

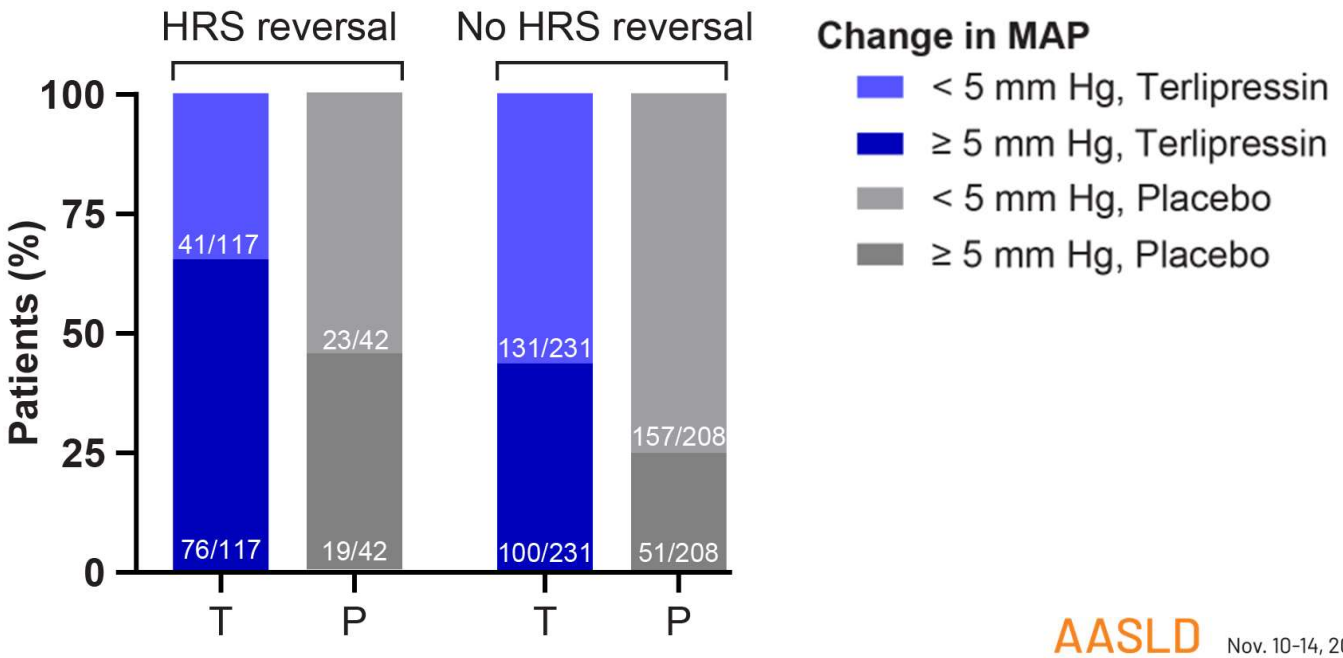
Changes in MAP From Baseline to the EOT of ≥ 5 mg/dL by Treatment Group



EOT, end of treatment; MAP, mean arterial pressure.

More patients in the terlipressin group had a change in MAP ≥ 5 mg/dL

HRS Reversal by Change in MAP from Baseline to EOT, ≥ or < 5 mm Hg



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EOT, end of treatment; HRS, hepatorenal syndrome; MAP, mean arterial pressure; P, placebo; T, terlipressin.

Daily MAP in Patients With HRS Reversal by Treatment Group

	Patients With HRS Reversal (N = 159)						
	Terlipressin (n = 117)			Placebo (n = 42)			
Time Point	N	**Mean MAP, mm Hg**	**Change from Baseline**	N	**Mean MAP, mm Hg**	**Change from Baseline**	***P* value**
Day 0 (Baseline)	117	76.9 ± 10.7		42	78.5 ± 10.46		
Day 1	113	83.9 ± 10.8	**7.1 ± 8.18**	42	78.4 ± 9.29	**-0.1 ± 6.87**	**<.001**
Day 2	115	79.7 ± 8.33	2.7 ± 8.93	42	78.3 ± 8.96	-0.2 ± 7.10	.059
Day 3	115	82.0 ± 9.1	**5.1 ± 9.18**	42	79.5 ± 8.37	**1.1 ± 7.51**	**.003**
Day 4	111	82.7 ± 9.77	5.9 ± 9.45	42	81.5 ± 8.33	3.1 ± 8.34	.090
Day 5	102	81.9 ± 9.54	5.2 ± 10.09	36	79.9 ± 9.50	2.9 ± 7.99	.223
Day 6	87	82.9 ± 9.56	**6.4 ± 9.46**	34	79.3 ± 10.35	**1.8 ± 7.98**	**.001**
Day 7	72	82.8 ± 9.34	6.2 ± 11.10	31	80.9 ± 9.01	3.1 ± 6.70	.148
Day 14	18	77.9 ± 9.34	2.2 ± 7.43	12	81.6 ± 5.18	3.6 ± 11.13	.668

Data are presented as the mean ± SD; *P* values were generated by ANOVA and Kruskal-Wallis tests. N indicates the number of patients with HRS reversal on that day.
ANOVA, analysis of variance; EOT, end of treatment; HRS, hepatorenal syndrome; MAP, mean arterial pressure; SD, standard deviation.

No significant changes in MAP were observed among patients with HRS reversal between treatment groups after Day 6

Prior and Concomitant Albumin Use by HRS Reversal Status and Treatment Group

	Terlipressin (n = 349)			Placebo (n = 249)		
	HRS Reversal (n = 117)	**No HRS Reversal (n = 232)**	***P* value**	**HRS Reversal (n = 42)**	**No HRS Reversal (n = 207)**	***P* value**
Total exposure of concomitant albumin, g	(n = 102)	(n = 197)		(n = 38)	(n = 189)	
Mean ± SD	253.9 ± 208.53	199.0 ± 186.64	.004	296.3 ± 184.56	232.2 ± 181.98	.019
Total exposure of prior albumin, g	(n = 103)	(n = 206)		(n = 37)	(n = 177)	
Mean ± SD	317.8 ± 186.55	333.8 ± 188.16	.411	291.4 ± 186.66	321.3 ± 248.61	.642

P values were generated by ANOVA and Kruskal-Wallis tests.
ANOVA, analysis of variance; HRS, hepatorenal syndrome.

Conclusions

- A greater increase in MAP from baseline to the EOT was noted among patients who achieved HRS reversal (vs those with no HRS reversal)
- An increase in MAP of ≥ 5 mm Hg, regardless of treatment, was significantly associated with achieving HRS reversal
- Significantly more patients in the terlipressin group had a change in MAP ≥ 5 mm Hg compared to placebo

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Thank you!

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