# Impact of the United Network for Organ Sharing (UNOS) Region on Transplantation Rates for Patients with Hepatorenal Syndrome: A Pooled Retrospective Analysis

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## Introduction

► Hepatorenal syndrome (HRS) is a life-threatening but potentially reversible form of acute kidney injury, for which a liver transplant is necessary to cure the underlying liver disease¹

Adult patients with HRS and a rapid reduction in kidney function can be treated with terlipressin, an FDA-approved vasopressin analogue that improves kidney function<sup>2</sup>

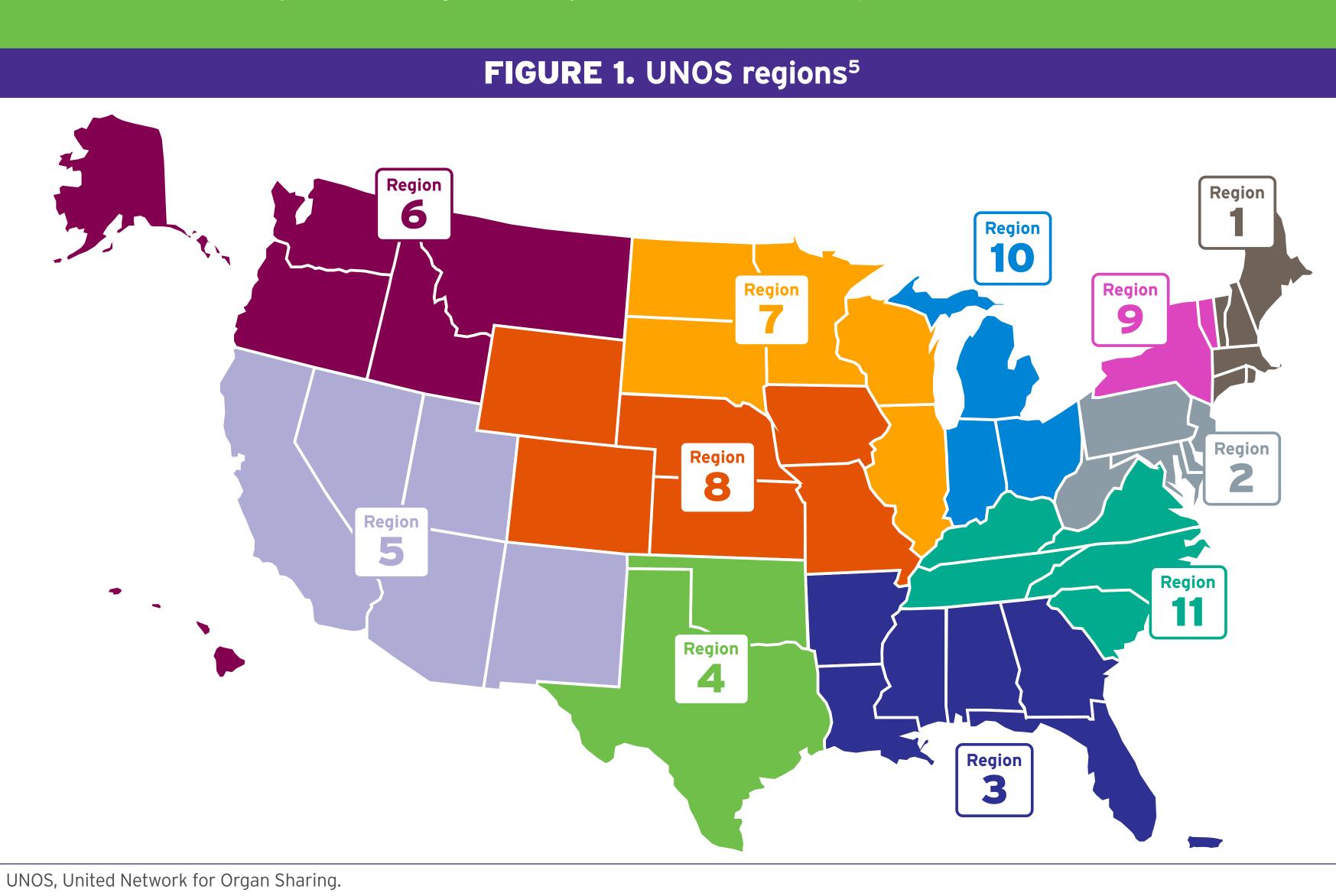
► Terlipressin treatment often decreases serum creatinine levels, which may ultimately result in a decrease in Model for End-stage Liver Disease (MELD) score¹-³

► MELD score is used in the prioritization of liver transplant recipients, and thus the lowering of MELD scores may lead to de-prioritization of transplant candidacy³

► The allocation of transplant organs in the United States (US) and Puerto Rico is performed by the United Network for Organ Sharing (UNOS)<sup>4</sup>

▶ UNOS is a non-profit organization contracted by the US federal government to serve as the Organ Procurement and Transplantation Network (OPTN), and thereby manages the nation's transplant waiting list⁴

▶ UNOS utilizes a system of regions (**Figure 1**) to facilitate optimal use of the OPTN<sup>4,5</sup>





## Aims

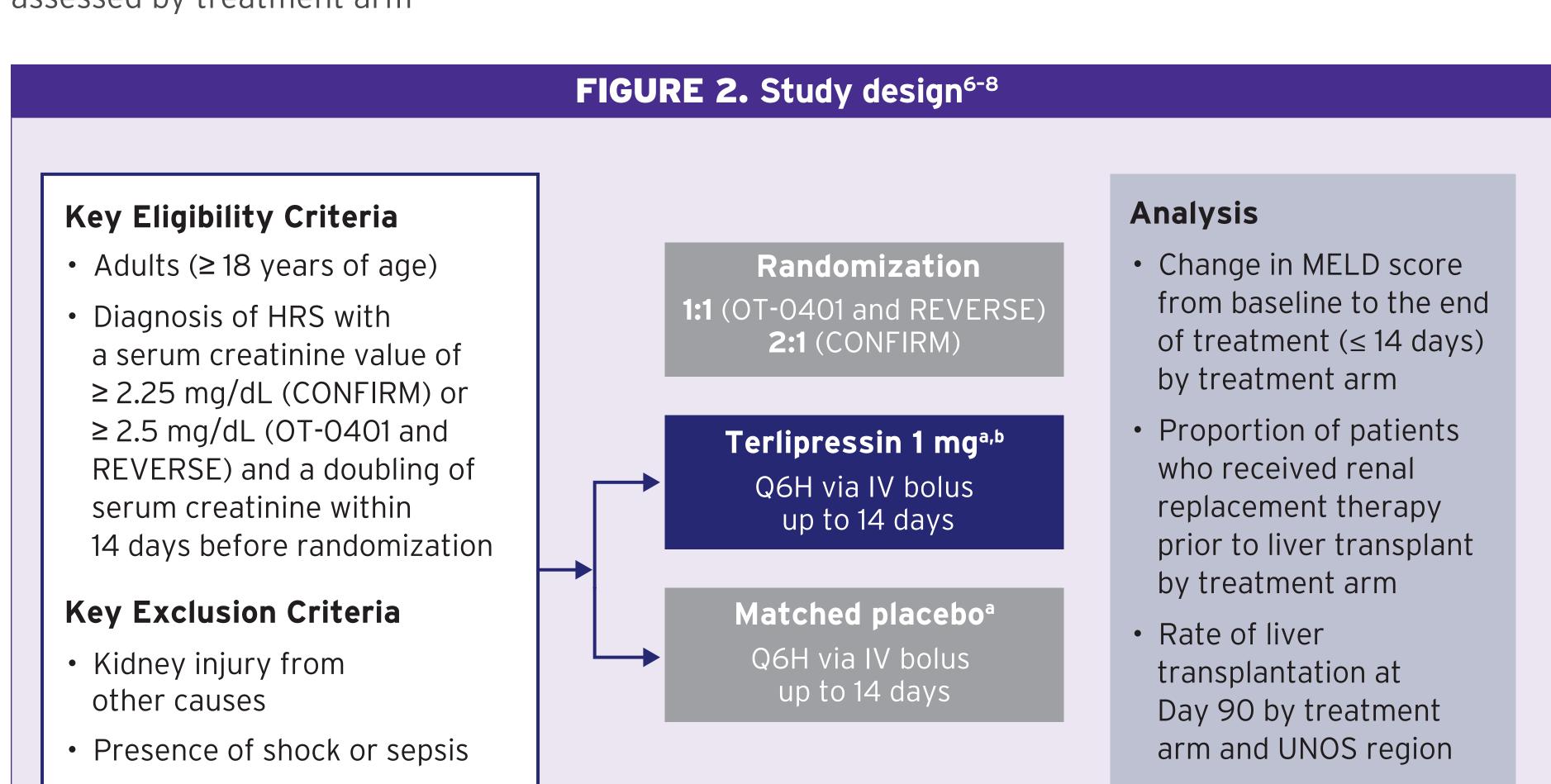
► This study retrospectively assessed the impact of UNOS region on liver transplant rates and timing among patients with HRS, by utilizing a large, pooled dataset of patients with HRS who were treated with terlipressin in 3 Phase III Placebo-Controlled clinical studies

## Methods

In the 3 Phase III studies that were pooled for this analysis (OT-0401 [ClinicalTrials.gov identifier: NCT00089570], REVERSE [NCT01143246], and CONFIRM [NCT02770716]), adult patients with HRS (defined as a serum creatinine value of  $\geq 2.5$  mg/dL [OT-0401, REVERSE] or  $\geq 2.25$  mg/dL [CONFIRM]) were treated with terlipressin or matched placebo at 1 mg every 6 hours for up to 14 days (**Figure 2**)

► Pooled data were retrospectively assessed for the proportion of patients who had undergone liver transplantation (LT), time of LT, and renal replacement therapy (RRT) prior to LT, by UNOS region and treatment arm

► Change in MELD ( $\Delta$ MELD) from baseline to the end of treatment (EOT; ie, up to Day 14) was also assessed by treatment arm



<sup>a</sup> **Concomitant albumin was recommended** at a dose of 1 g/kg body weight up to 100 g followed by 20–40 g/d.

<sup>b</sup> If, after Day 3, serum creatinine levels had decreased—but by less than 30%—then the terlipressin dose could be increased to 2 mg Q6H.

HRS, hepatorenal syndrome; IV, intravenous; MELD, Model for End-stage Liver Disease; Q6H, every 6 hours; UNOS, United Network for Organ Sharing.

# Results

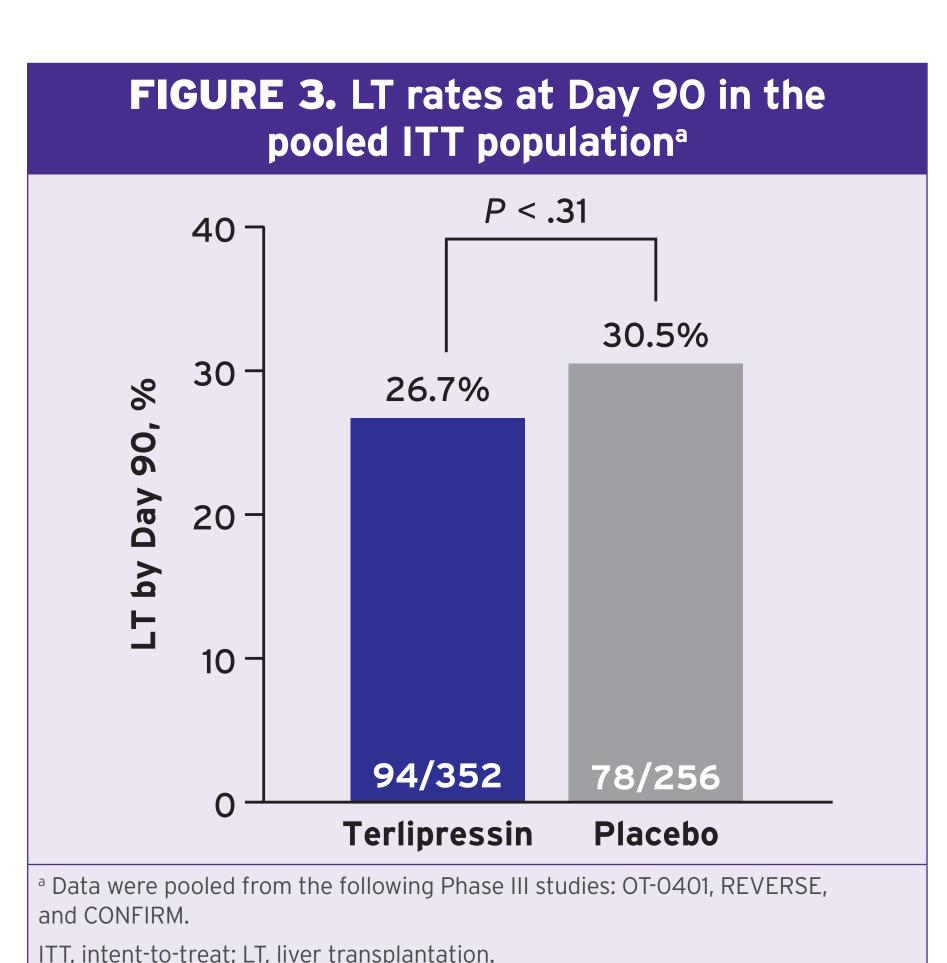
 $\triangleright$  Of the 608 patients in the pooled patient data set, MELD scores (at baseline and EOT) were available for 490 patients (terlipressin, n = 288; placebo, n = 202)

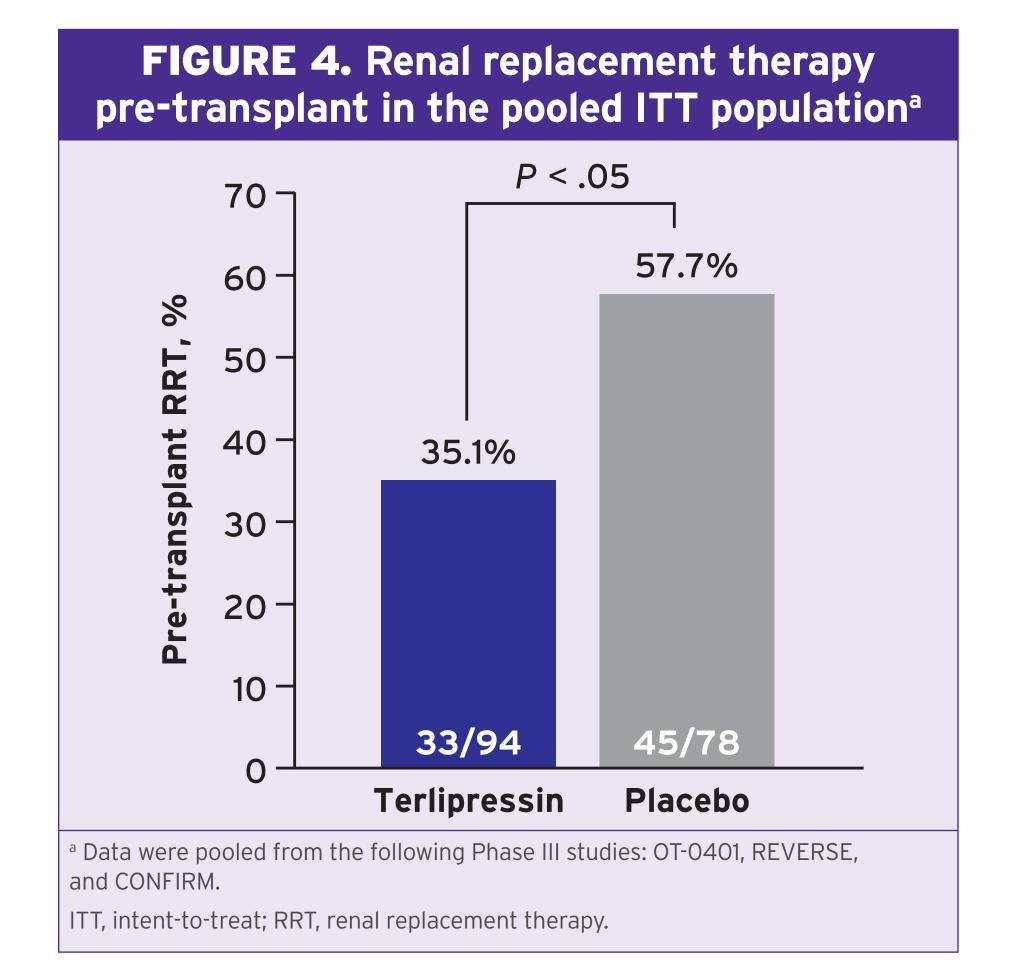
Across treatment arms, the baseline mean MELD score was 32.9 (mean  $\pm$  standard deviation [SD]: terlipressin, 32.9  $\pm$  6.38; placebo, 32.9  $\pm$  5.92)

At EOT, MELD scores decreased to  $30.0 \pm 8.08$  in the terlipressin arm and  $31.8 \pm 7.21$  in the placebo arm, resulting in the mean  $\Delta$ MELD  $\pm$  SD being significantly larger in the terlipressin arm versus placebo (-2.9  $\pm$  4.86 vs -1.1  $\pm$  4.43, P < .001)

▶ Despite these differences in mean  $\Delta$ MELD, LT rates at Day 90 were similar across treatment arms (terlipressin, 26.7% [94/352]; placebo, 30.5% [78/256], P = .31) (**Figure 3**)

Of note, significantly fewer patients in the terlipressin arm (versus placebo) received RRT prior to LT (35.1% [33/94] vs 57.7% [45/78], P < .05; **Figure 4**)





The rates of LT within treatment arms varied by UNOS region (Figure 5; Table 1)

Over half of the UNOS regions assessed had a LT rate > 30% across treatment arms (UNOS Regions: 2, 3, 7, 8, 9, 10), and UNOS Region 1 had the lowest LT rate (Figure 5; Table 1)

Some of the UNOS regions had similar rates of transplant between treatment arms (Regions 3, 5, and 8; **Figure 5**), whereas others had notable differences (≥ 12%) in the proportion of patients who received LT between the terlipressin and placebo arms (terlipressin vs placebo: Region 1 (11.8% [2/17] vs 0%

LT between the terlipressin and placebo arms (terlipressin vs placebo: Region 1 (11.8% [2/17] vs 0% [0/11]); Region 4 (16.7% [8/48] vs 34.8% [8/23]); Region 7 (34.3% [12/35] vs 52.6% [10/19]); and Region 9 (31.3% [5/16] vs 42.9% [6/14]) (**Figure 5**; **Table 1**)

► Mean day to LT also varied by UNOS region (**Table 1**)

The shortest time to LT (mean  $\pm$  SD) occurred in UNOS Region 8 for the terlipressin arm (10.0  $\pm$  7.7 days) and UNOS Region 3 for the placebo arm (7.0  $\pm$  4.0 days) (**Table 1**)

The longest mean ± SD time to LT was 49.2 ± 32.9 days in UNOS Region 9 for the terlipressin arm and 30.4 ± 25.1 days in Region 11 for the placebo arm (**Table 1**)

► Among the 454 patients listed for LT at baseline from the CONFIRM and REVERSE studies, the mean ± SD day for transplant was 21.2 ± 23.5 days for the terlipressin arm and 17.8 ± 18.5 days for the placebo arm (**Table 1**)

Total transplant rates were comparable for terlipressin and placebo, among those listed for LT at baseline (26.3% vs 29.9%, respectively) (**Table 1**)

# FIGURE 5. Liver transplantation rates for terlipressin versus placebo by UNOS region, pooled ITT population Region 11.8% vs 0% Region 34.3% vs 52.6% Region 35.0% vs 33.3% Region 39.4% vs 35.7% Region 39.4% vs 35.7% ITT, intent-to-treat; UNOS, United Network for Organ Sharing.

TABLE 1. Liver transplantation rates and mean time to transplant by UNOS region, pooled ITT population				
	Transplanted Patients, n/N (%)		Study Day of Transplant, mean ± SD	
UNOS Region	Terlipressin	Placebo	Terlipressin	Placebo
Region 1	2/17 (11.8)	0/11 (0)	48.0 ± 59.4	0
Region 2	13/35 (37.1)	10/33 (30.3)	10.5 ± 14.3	21.6 ± 20.5
Region 3	13/33 (39.4)	5/14 (35.7)	12.5 ± 15.5	7.0 ± 4.0
Region 4	8/48 (16.7)	8/23 (34.8)	25.0 ± 15.8	15.4 ± 15.6
Region 5	12/46 (26.1)	11/38 (28.9)	24.8 ± 31.8	22.5 ± 27.4
Region 6	1/11 (9.1)	1/6 (16.7)	45.0 ± NA	22.0 ± NA
Region 7	12/35 (34.3)	10/19 (52.6)	23.8 ± 21.1	14.3 ± 9.5
Region 8	7/20 (35.0)	7/21 (33.3)	10.0 ± 7.7	14.0 ± 6.3
Region 9	5/16 (31.3)	6/14 (42.9)	49.2 ± 32.9	9.7 ± 6.9
Region 10	7/19 (36.8)	7/16 (43.8)	18.0 ± 27.6	11.0 ± 3.3
Region 11	7/33 (21.2)	5/33 (15.2)	38.0 ± 16.7	30.4 ± 25.1
Total (US)	87/313 (27.8)	70/228 (30.7)		
Ex-US	7/39 (17.9)	8/28 (28.6)	44.1 ± 45.1	54.0 ± 32.2
Total	94/352 (26.7)	78/256 (30.5)		
otal transplanted / isted for LT <sup>a</sup> (US)	71/270 (26.3)	55/184 (29.9)	21.2 ± 23.5	17.8 ± 18.5

<sup>a</sup> Patients listed for LT at baseline for CONFIRM and REVERSE only.

Ex-US, outside the United States of America; ITT, intent-to-treat; LT, liver transplantation; NA, not applicable; SD, standard deviation; UNOS, United Network for Organ Sharing

# **Conclusions**

► MELD scores decreased by EOT and to a larger extent in the terlipressin arm; however, this did not appear to affect the overall LT rate at Day 90

RRT pre-transplant was significantly lower with terlipressin treatment than placebo

The time to LT and the rate of LT varied by UNOS region, with no clear trend in favor of either treatment arm

► Thus, this study suggests that UNOS region location appears to play a larger role in the actual receipt of a liver transplant, rather than a decreased MELD score or renal replacement therapy pre-transplant

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