Hepatorenal Syndrome-Acute Kidney Injury Reversal and Liver Transplant Rates in Patients Treated with Terlipressin

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Background

- Hepatorenal syndrome-acute kidney injury (HRS-AKI), a form of AKI, occurs in patients with advanced cirrhosis and ascites[1]
- HRS-AKI has a poor prognosis and without treatment, median survival is between 7 and 10 days[2]
- Liver transplantation (LT) is the definitive treatment for the underlying disease[3,4]; and first-line treatment is with albumin and terlipressin[4]
- Terlipressin, a vasopressin analogue, is US Food and Drug Administration (FDA)-approved to treat adult patients with HRS and a rapid reduction in kidney function[5]
- Treatment with terlipressin can reverse HRS-AKI, leading to improved renal function that is associated with better clinical outcomes after LT[2,6]
- However, there are concerns that HRS-AKI reversal and the consequent decrease in serum creatinine (SCr) levels may reduce Model for End-Stage Liver Disease (MELD) score and thereby negatively affect LT prioritization[7,8]
- The FDA recommends the use of terlipressin in patients with SCr < 5 mg/dL, acute-on-chronic liver failure grade 0–2, and a MELD score < 35 (if transplant listed)[5]
  - The subgroup of patients who met these criteria will subsequently be referred to as the "label-specific population"

Objective

- To assess the rates of HRS-AKI reversal, durable HRS-AKI reversal, renal replacement therapy (RRT), and LT up to 90 days in patients from the label-specific population who were LT listed at baseline in 2 Phase III, placebo-controlled studies of terlipressin in patients with HRS-AKI

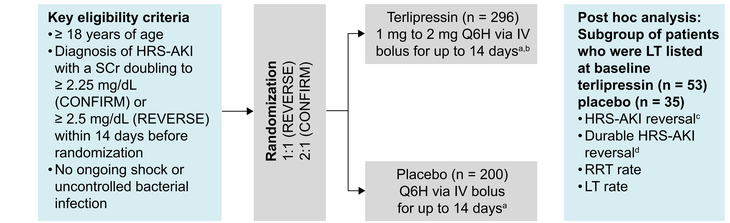
Methods

- Data from patients from 2 Phase III studies (ie, REVERSE [NCT01143246][9] and CONFIRM [NCT02770716][2]), who were LT listed at baseline and met the FDA criteria for terlipressin use (ie, the label-specific population), were pooled for the analysis
  - This retrospective analysis of pooled data was based on a mitigation strategy that reduced the risk of adverse events by identifying the subpopulation of patients who would have a more favorable risk-to-benefit profile
- In these studies, patients with HRS-AKI were treated with terlipressin at 1–2 mg every 6 hours via intravenous bolus or matched placebo; concomitant albumin administration was also strongly recommended[2,9]
- The study design is shown in **Figure 1**

Statistical analyses

- *P* values were derived from a Fisher's Exact test or a Chi-square test
- *P* values were generated for screening purposes

Figure 1. Study design



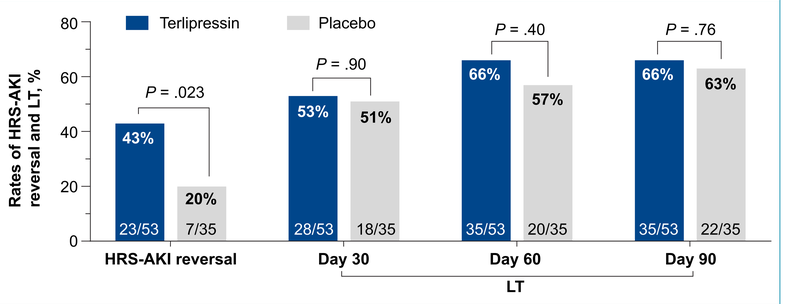
[a] **Concomitant albumin was strongly recommended** at a dose of 20–40 g/day in REVERSE; and 1 g/kg of body weight to a maximum of 100 g on Day 1 and 20–40 g/day thereafter in CONFIRM. [b] If after Day 3, SCr had decreased, but by less than 30%, then the terlipressin dose could be increased to 2 mg Q6H. [c] HRS-AKI reversal was defined as the percentage of patients who achieved a SCr value ≤ 1.5 mg/dL while on treatment up to 24 hours after the final dose of study drug, by Day 14, or discharge. [d] Defined as HRS-AKI reversal without RRT up to Day 30.

AKI, acute kidney injury; HRS, hepatorenal syndrome; IV, intravenous; LT, liver transplantation; Q6H, every 6 hours; RRT, renal replacement therapy; SCr, serum creatinine.

Results

- In LT-listed patients in the pooled intent-to-treat (ITT) label-specific population (terlipressin: n = 53; placebo: n = 35), the rate of HRS-AKI reversal was significantly higher in the terlipressin group compared with the placebo group (43% vs 20%, *P* = .023) (**Figure 2**)

Figure 2. Incidence of HRS-AKI reversal and LT rate among patients listed for LT at baseline; subgroup of patients who met US FDA treatment criteria from the pooled ITT population in CONFIRM and REVERSE



P values were derived from a Fisher's Exact test or a Chi square test.

FDA, Food and Drug Administration; HRS-AKI, hepatorenal syndrome-acute kidney injury; ITT, intent-to-treat; LT, liver transplantation; US, United States.

- The rate of RRT in the terlipressin group compared with the placebo group was 28% versus 46% (*P* = .094) by Day 30; 32% versus 54% (*P* = .038) by Day 60; and 36% versus 54% (*P* = .087) by Day 90 (**Table 1**)
- However, the LT rate was similar in the terlipressin and placebo groups, respectively, at all time points assessed: 53% versus 51% (*P* = .90) by Day 30; 66% versus 57% (*P* = .40) by Day 60; and 66% versus 63% (*P* = .76) by Day 90 (**Figure 2**)

Table 1. The incidence of RRT through Day 90 for patients who were LT listed at baseline; pooled (CONFIRM + REVERSE) ITT label-specific population

Parameter	Terlipressin (n = 53)	Placebo (n = 35)	Total (N = 88)	*P* value[a]
RRT by Day 14, n (%)	6 (11.3)	5 (14.3)	11 (12.5)	.681
RRT by Day 30, n (%)	15 (28.3)	16 (45.7)	31 (35.2)	.094
RRT by Day 60, n (%)	17 (32.1)	19 (54.3)	36 (40.9)	.038
RRT by Day 90, n (%)	19 (35.9)	19 (54.3)	38 (43.2)	.087

[a] *P* values were derived from a Fisher's Exact test or a Chi square test.

The label-specific population included patients with an ACLF grade 0–2 and SCr < 5 mg/dL at baseline and excludes patients who were LT listed at baseline with a baseline MELD score of ≥ 35.

ACLF, acute-on-chronic liver failure; ITT, intent-to-treat; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; RRT, renal replacement therapy.

Conclusions

- Compared with placebo, terlipressin increased the rate of HRS-AKI reversal in LT-listed patients in the pooled ITT label-specific population and reduced the need for RRT in patients with HRS-AKI at Days 30, 60, and 90
- Importantly, the increase in HRS-AKI reversal in the terlipressin group did not negatively impact the LT rate in patients listed for LT at baseline in the subgroup of patients who met the FDA label criteria for terlipressin treatment

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