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# Patience Is a Virtue: Evidence for Waiting Until Day 4 and After 12 Doses of Terlipressin Before Evaluating Treatment Response in Patients with HRS-AKI

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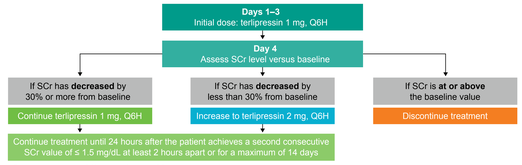
## INTRODUCTION

- Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a serious and potentially lethal, yet reversible, form of AKI in patients with decompensated cirrhosis[1]
- Terlipressin, a vasopressin analogue, demonstrated efficacy in improving renal perfusion and kidney function in 3 large Phase III, placebo-controlled clinical studies: OT-0401[2] (NCT00089570), REVERSE[3] (NCT01143246), and CONFIRM[1] (NCT02770716)
- Terlipressin is the only US Food and Drug Administration (FDA)-approved therapy for HRS-AKI[4]
- The FDA recommends treating adult patients with HRS and a rapid deterioration in kidney function with a 1 mg dose of terlipressin intravenously every 6 hours (Q6H), and making a decision regarding continuation of the same dose, a dose increase, or drug discontinuation on Day 4, based on changes in serum creatinine (SCr) from baseline, which is defined as the last available SCr value before treatment initiation[a] (**Figure 1**)
  - If SCr decreased by 30% or more from baseline, a patient should continue on the 1 mg dose of terlipressin Q6H
  - If SCr decreased by less than 30% from baseline, the terlipressin dose should be increased to 2 mg Q6H
  - Notably, a 30% reduction in SCr following terlipressin treatment is associated with a lower incidence of renal replacement therapy and a higher number of patients alive at Day 90[5]

**Figure 1. Terlipressin dosing chart per the FDA prescribing information**




FDA, Food and Drug Administration; Q6H, every 6 hours; SCr, serum creatinine.

- Among the pooled population from the OT-0401[2], REVERSE[3], and CONFIRM[1] Phase III studies, patients who achieved HRS reversal had a mean ± standard deviation (SD) time to HRS reversal of 6.3 ± 3.0 days in the terlipressin group and 6.7 ± 3.3 days in the placebo group[6]

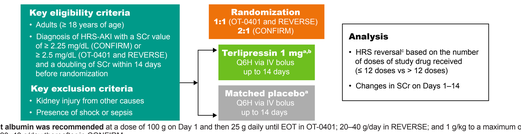
## AIM OF THE STUDY

- To evaluate the rationale for waiting until Day 4 (12 doses) before assessing treatment response to terlipressin, using a large, pooled database from 3 Phase III clinical studies

## METHODS

- Data were pooled from the OT-0401[2], REVERSE[3], and CONFIRM[1] Phase III studies (**Figure 2**)
- Eligible patients had HRS with a rapid deterioration in kidney function and a SCr ≥ 2.5 mg/dL (OT-0401 and REVERSE) or ≥ 2.25 mg/dL (CONFIRM)
- Patients received terlipressin or matched placebo at 1 mg Q6H initially, with an increase in dose to 2 mg Q6H on Day 4 if SCr had decreased, but by < 30% from baseline
- Responders were defined as those patients who had achieved HRS reversal, defined as ≥ 1 SCr value of ≤ 1.5 mg/dL while on treatment up to 24 hours after the last dose, by the end of treatment (EOT)
- SCr level and mean change in SCr from baseline (ΔSCr) were examined on Days 1–14 for responders versus nonresponders in the pooled safety population—defined as all patients randomly assigned to treatment who received at least 1 dose of study drug (terlipressin or placebo)

**Figure 2. Study design**




[a] **Concomitant albumin was recommended** at a dose of 100 g on Day 1 and then 25 g daily 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 levels had decreased—but by less than 30%—then the terlipressin dose could be increased to 2 mg Q6H.
[c] HRS reversal was defined as ≥ 1 SCr value of ≤ 1.5 mg/dL while on treatment up to 24 hours after the last dose, by the EOT.
AKI, acute kidney injury; EOT, end of treatment; HRS, hepatorenal syndrome; IV, intravenous; Q6H, every 6 hours; SCr, serum creatinine.

## RESULTS

### Baseline characteristics

- Baseline characteristics were similar in both treatment groups (terlipressin and placebo) (**Table 1**)

**Table 1. Baseline demographic and clinical characteristics by treatment group, pooled ITT population**

| Parameter | Terlipressin (n = 352) | Placebo (n = 256) | *P* value |
|---|---|---|---|
| **Age (years), mean ± SD** | 54.0 ± 10.55 | 54.0 ± 10.54 | .994 |
| **Sex, male** | 213 (60.5) | 165 (64.5) | .352 |
| **Race** | | | .162 |
| American Indian or Alaska Native | 3 (0.9) | 4 (1.6) | |
| Asian | 8 (2.3) | 1 (0.4) | |
| Black or African American | 24 (6.8) | 14 (5.5) | |
| Native Hawaiian or Pacific Islander | 0 | 1 (0.4) | |
| White | 313 (88.9) | 235 (91.8) | |
| **Alcohol-associated hepatitis** | 121 (34.4) | 84 (32.8) | .728 |
| **Baseline SCr (mg/dL), mean ± SD** | 3.6 ± 1.29 | 3.7 ± 1.11 | .421 |
| **SIRS subgroup (REVERSE and CONFIRM only)** | (n = 296) | (n = 200) | |
| | 112 (37.8) | 78 (39.0) | .794 |
| **MELD score** | (n = 312) | (n = 221) | |
| mean ± SD | 33.0 ± 6.39 | 33.1 ± 5.86 | .834 |
| **Prior midodrine and octreotide** | 147 (41.8) | 91 (35.5) | .130 |
| **Child-Pugh score** | | | |
| Class A [5–6] | 5 (1.4) | 3 (1.2) | |
| Class B [7–9] | 100 (28.4) | 71 (27.7) | |
| Class C [10–15] | 232 (65.9) | 168 (65.6) | .980 |
| **MAP, mm Hg** | (n = 352) | (n = 255) | |
| mean ± SD | 77.3 ± 11.97 | 76.6 ± 10.85 | .446 |
| **MAP < 65 mm Hg** | 49 (13.9) | 34 (13.3) | .905 |
| **Hepatocellular carcinoma** | 24 (6.8) | 24 (9.4) | .287 |
| **Etiology of cirrhosis** | | | |
| Alcohol-associated | 212 (60.2) | 150 (58.6) | .685 |
| Autoimmune hepatitis | 13 (3.7) | 9 (3.5) | 1.00 |
| MASLD | 52 (14.8) | 36 (14.1) | .907 |
| Viral hepatitis (B or C) | 51 (14.5) | 39 (15.2) | .798 |
| Primary biliary cholangitis | 11 (3.1) | 6 (2.3) | .564 |

Data are presented as the n (%) unless otherwise noted.
Data were pooled from the OT-0401, REVERSE, and CONFIRM studies.
ITT, intent-to-treat; MAP, mean arterial pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-Stage Liver Disease; SCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

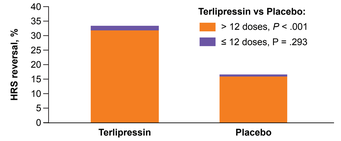
### Exposure to treatment

- In the pooled population, mean ± SD dose duration was 6.3 ± 4.4 days in the terlipressin group and 6.0 ± 3.9 days in the placebo group
- Mean ± SD number of doses was 21.1 ± 17.2 in the terlipressin group and 20.4 ± 15.4 in the placebo group

### Incidence of HRS reversal, baseline SCr, and the number of doses in the terlipressin versus placebo group

- In the pooled data set of patients assessed by dose (N = 598), the rate of HRS reversal by the EOT was 33.6% (117/348) in the terlipressin group and 16.8% (42/250) in the placebo group (**Figure 3**)
- A significantly higher incidence of HRS reversal was observed in the terlipressin group versus placebo among those who received > 12 doses (terlipressin: 54.7% [111/203], placebo: 32.0% [40/125], *P* < .001), but not among those who received ≤ 12 doses (terlipressin: 4.1% [6/145], placebo: 1.6% [2/125], *P* = .293) (**Figure 3**)
- On Day 4, the cumulative rate of HRS reversal was 10.5% in the terlipressin group and 3.5% in the placebo group

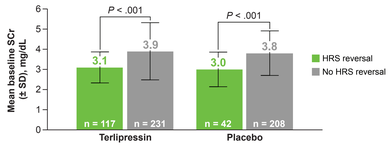
**Figure 3. HRS Reversal at the EOT by treatment group and total number of doses received, pooled ITT population**




Data were pooled from the OT-0401, REVERSE, and CONFIRM studies. Screened *P* values were generated using Chi-square or Fisher's Exact tests.
EOT, end of treatment; HRS, hepatorenal syndrome; ITT, intent-to-treat.

- The mean SCr at treatment initiation/baseline was significantly lower in patients who achieved HRS reversal compared with those who did not, regardless of treatment (terlipressin, 3.1 mg/dL versus 3.9 mg/dL, *P* < .001; placebo, 3.0 mg/dL versus 3.8 mg/dL, *P* < .001) (**Figure 4**)

**Figure 4. Mean SCr at initiation/baseline by HRS reversal status at the EOT, pooled safety population**

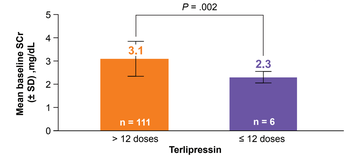



Data were pooled from the OT-0401, REVERSE, and CONFIRM studies. Screened *P* values were generated using ANOVA and Kruskal-Wallis tests following testing for normality.
HRS, hepatorenal syndrome; SCr, serum creatinine, SD, standard deviation.

### Baseline SCr and the number of terlipressin doses in patients who achieved HRS reversal

- Among patients who achieved HRS reversal in the terlipressin group, 94.9% (111/117) received > 12 doses, and only 5.1% (6/117) received ≤ 12 doses before discontinuation
- Among patients with HRS reversal, baseline SCr was significantly higher in those who received > 12 doses compared with those who received ≤ 12 doses of terlipressin, and the mean ± SD baseline SCr was 3.1 ± 0.8 mg/dL versus 2.3 ± 0.2 mg/dL, respectively, *P* = .002 (**Figure 5**)

**Figure 5. Baseline SCr in patients who received terlipressin and achieved HRS reversal based on the number of doses received, pooled ITT population**

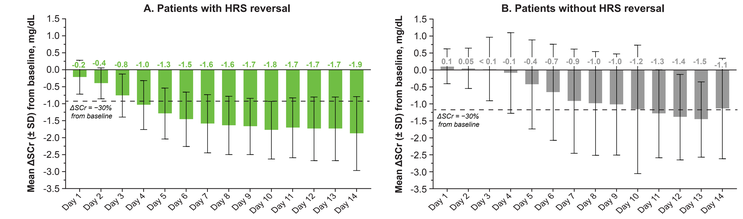



Data were pooled from the OT-0401, REVERSE, and CONFIRM studies. Screened *P* values were generated using ANOVA and Kruskal-Wallis tests following testing for normality.
HRS, hepatorenal syndrome; ITT, intent-to-treat; SCr, serum creatinine; SD, standard deviation.

### Changes in SCr level from baseline to Day 14 in the terlipressin group based on HRS reversal status

- Among patients with HRS reversal, mean SCr levels decreased from baseline in those who responded to terlipressin through Day 9 (**Figure 6A**)
  - On Days 1–3, the mean decrease (ΔSCr) was < 1 mg/dL
  - A mean decrease of > 30% (ie, ΔSCr > 0.93 mg/dL in this subgroup)—and the recommended ΔSCr cutoff point for a dose decision on Day 4—was only achieved on Day 4 and subsequent days thereafter
- On Day 4, the decrease in mean SCr from baseline was significantly greater among patients who achieved HRS reversal compared with those who did not (ΔSCr = −1.0 mg/dL [**Figure 6A**] versus ΔSCr = −0.1 mg/dL [**Figure 6B**], *P* < .001)
- Among patients who did not achieve HRS reversal, mean SCr did not decrease from baseline on Days 1–3 and only started to decrease minimally on Day 4 (**Figure 6B**)
  - Notably, a > 30% decrease in mean SCr (ie, ΔSCr > 1.16 mg/dL in this subgroup) was achieved on Day 10 in the group of patients without HRS reversal (**Figure 6B**)
    - Consequently, a > 30% mean decrease in SCr from baseline among some of the patients who did not achieve HRS reversal suggests a potential for a clinical benefit in some patients after additional days of treatment and possibly an increase in the dose of terlipressin after Day 4
      - However, this hypothesis merits further investigation

**Figure 6. Change in SCr from Day 1 to Day 14 in patients treated with terlipressin in (A) those who achieved HRS reversal, and (B) those who did not achieve HRS reversal by the EOT, pooled safety population**




Data were pooled from the OT-0401, REVERSE, and CONFIRM studies. The dotted line indicates a 30% decrease in SCr from the mean baseline value.
HRS, hepatorenal syndrome; ΔSCr, change in SCr; SCr, serum creatinine; SD, standard deviation.

## CONCLUSIONS

- **Among the patients who responded by achieving HRS reversal by the EOT, most needed continuation of therapy beyond Day 4**
- **Collectively, these results indicate that terlipressin should be used for an adequate amount of time (ie, 4 days) at the initial standard dose before a clinical decision for discontinuation is made**

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## DISCLOSURES

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