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Role of High Versus Standard Dose of Terlipressin in Reversing HRS-AKI: Pooled Analysis from Phase III Clinical Trials

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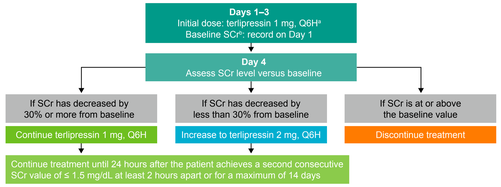
INTRODUCTION

- Terlipressin is a vasopressin receptor agonist approved for the management of hepatorenal syndrome-acute kidney injury (HRS-AKI)[1]—a rapidly progressive form of AKI that occurs in patients with cirrhosis and ascites[2,3]
- The US Food and Drug Administration (FDA) dosing information recommends an initial terlipressin dose of 1 mg every 6 hours (Q6H), which may be escalated on Day 4 to 2 mg Q6H if the serum creatinine (SCr) has decreased, but the improvement is < 30% from baseline[1] (**Figure 1**)

Figure 1. Terlipressin dosing regimen[1]



[a] **Concomitant albumin was strongly recommended** at a dose of 100 g on Day 1 and then 25 g/day until the EOT in OT-0401; 20–40 g/day in REVERSE; and 1 g/kg body weight to a maximum of 100 g on Day 1 and 20–40 g/day thereafter in CONFIRM.
[b] Baseline SCr is the last available SCr before treatment initiation.
EOT, end of treatment; Q6H, every 6 hours; SCr, serum creatinine.

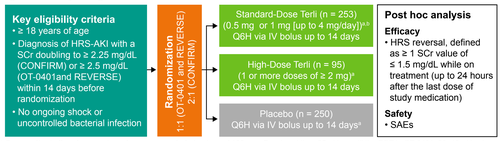
AIM OF THE STUDY

To assess the efficacy and safety profile of terlipressin in patients who had a dose escalation (high dose) versus those who did not (standard dose), compared to the placebo group

METHODS

- A pooled patient cohort from 3 Phase III, placebo-controlled clinical studies (OT-0401[3], REVERSE[4], and CONFIRM[5]) was retrospectively assessed
- A standard dose of terlipressin was defined as 0.5 mg or 1 mg per dose (up to 4 mg/day), and a high dose was defined as 1 or more doses of ≥ 2 mg per dose
- In each study, if on Day 4 of treatment SCr decreased—but by < 30% from the baseline value—the dose could be increased to 2 mg Q6H (ie, 8 mg/day)
  - For each Phase III study, baseline was defined as Day 0 of the study period, but a pre-study period value could be utilized instead if the Day 0 value was missing
- HRS reversal was defined as ≥ 1 SCr value of ≤ 1.5 mg/dL while on treatment (up to 24 hours after the last dose of study medication)
- Serious adverse events (SAEs) were assessed in all treated patients
- *P* values were generated for screening purposes
- The study design is shown in **Figure 2**

Figure 2. Study design



[a] **Concomitant albumin was strongly recommended** at a dose of 100 g on Day 1 and then 25 g/day until the EOT in OT-0401; 20–40 g/day in REVERSE; and 1 g/kg body weight up 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.
AKI, acute kidney injury; EOT, end of treatment; HRS, hepatorenal syndrome; IV, intravenous; Q6H, every 6 hours; SAE, serious adverse event; SCr, serum creatinine.

RESULTS

Baseline characteristics

- Baseline characteristics for the intent-to-treat (ITT) pooled population (terlipressin, n = 352; placebo, n = 256) are presented in **Table 1**
- Baseline demographics and clinical characteristics were comparable between the terlipressin and placebo groups across the pooled ITT population from all 3 studies

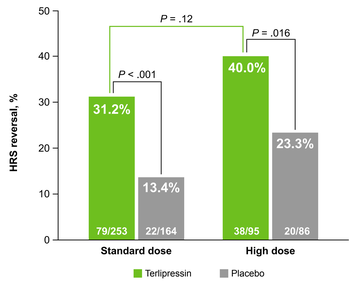
Table 1. Summary of baseline demographic and clinical characteristics; Pooled ITT population

Parameter	Terlipressin (n = 352)	Placebo (n = 256)
Age, years, mean ± SD	54.0 ± 10.55	54.0 ± 10.54
Sex, n (%)		
Male	213 (60.5)	165 (64.5)
Female	139 (39.5)	91 (35.5)
Geographic region, n (%)		
United States	313 (88.9)	228 (89.1)
Non-United States	39 (11.1)	28 (10.9)
Race, n (%)		
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 Other Pacific Islander	0	1 (0.4)
White	313 (88.9)	235 (91.8)
Baseline serum creatinine (mg/dL)		
mean ± SD	3.6 ± 1.29	3.7 ± 1.11
SIRS subgroup[a], n (%)	112 (37.8)	78 (39.0)
Baseline MELD score	(n = 312)	(n = 221)
mean ± SD	33.0 ± 6.39	33.1 ± 5.86
Baseline CPT class, n (%)		
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)
Missing	15 (4.3)	14 (5.5)
Baseline bilirubin, mg/dL	(n = 338)	(n = 249)
mean ± SD	12.8 ± 12.72	14.1 ± 14.58
Baseline MAP, mmHg	(n = 352)	(n = 255)
mean ± SD	77 ± 12	77 ± 11
Amount of prior albumin (g)[b]	(n = 330[c])	(n = 244)
mean ± SD	328.4 ± 187.67	313.3 ± 236.76

[a] Criteria to define the SIRS subgroup were not collected for OT-0401. Percentages are based on the number of patients in each treatment group, excluding OT-0401.
[b] Prior albumin use was during the 14 days prior to randomization.
[c] One terlipressin-treated patient with prior albumin use in OT-0401 was inadvertently excluded from the count in the OT-0401 clinical study report; however, this patient was included in the count for the pooled studies.
CPT, Child-Pugh-Turcotte; ITT, intent-to-treat; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

- In the pooled safety population (terlipressin, n = 349), most patients (72.8% [254/349]) received a standard dose of terlipressin (1 mg Q6H), while 27.2% (95/349) required a dose escalation to 2 mg Q6H (high dose)
- In the terlipressin group of the pooled ITT population (n = 348), the rate of HRS reversal was 31.2% (79/253) in the standard-dose group and 40.0% (38/95) in the high-dose group (*P* = .12)
- Among those who received terlipressin, significantly more patients achieved HRS reversal versus placebo (high dose: 40.0% [38/95] vs 23.3% [20/86], *P* = .016; standard dose: 31.2% [79/253] vs 13.4% [22/164], *P* < .001; **Figure 3**)

Figure 3. HRS reversal in patients with HRS-AKI who were treated with terlipressin standard or high dose; Pooled ITT population



AKI, acute kidney injury; HRS, hepatorenal syndrome; ITT, intent-to-treat.

- SAEs were observed in each treatment group as follows: 66.1% (168/254) in patients who received a standard dose of terlipressin; 62.1% (59/95) in patients in the high-dose group; and 59.8% (149/249) in patients in the placebo group
- SAEs in ≥ 2% of patients in any treatment group by system organ class and preferred term by terlipressin dose group are presented in **Table 2**
- Respiratory failure (standard vs high dose: 9.1% [23/254] vs 6.3% (6/95]) and multiple organ dysfunction syndrome (MODS; standard vs high dose: 6.3% [16/254] vs 10.5% [10/95]) were the most frequent SAEs observed in the standard- and high-dose groups, respectively

Table 2. Onset of SAEs in ≥ 2% of patients in any treatment group by system organ class and preferred term by terlipressin dose group; Pooled safety population

System Organ Class Preferred Term[a]	Terlipressin Standard[b] Dose (N = 254)		Terlipressin High[b] Dose (N = 95)		Placebo (N = 249)	
	Patients[c] n (%)	Events n	Patients[c] n (%)	Events n	Patients[c] n (%)	Events n
At least 1 SAE	168 (66.1)	305	59 (62.1)	115	149 (59.8)	248
Gastrointestinal disorders	34 (13.4)	48	14 (14.7)	21	18 (7.2)	20
Abdominal pain	9 (3.5)	11	6 (6.3)	8	2 (0.8)	2
Gastrointestinal hemorrhage	8 (3.1)	8	2 (2.1)	2	1 (0.4)	1
Lower gastrointestinal hemorrhage	0	0	2 (2.1)	2	0	0
Esophageal varices hemorrhage	7 (2.8)	8	0	0	4 (1.6)	4
General disorders and administration site conditions	19 (7.5)	19	11 (11.6)	11	14 (5.6)	15
Multiple organ dysfunction syndrome	16 (6.3)	16	10 (10.5)	10	8 (3.2)	8
Hepatobiliary disorders	61 (24.0)	63	13 (13.7)	13	63 (25.3)	63
Chronic hepatic failure	20 (7.9)	21	1 (1.1)	1	15 (6.0)	15
Hepatic cirrhosis	4 (1.6)	4	2 (2.1)	2	3 (1.2)	3
Hepatic failure	17 (6.7)	17	4 (4.2)	4	23 (9.2)	23
Hepatorenal syndrome	7 (2.8)	7	4 (4.2)	4	12 (4.8)	12
Infections and infestations	31 (12.2)	40	12 (12.6)	17	19 (7.6)	23
Pneumonia	6 (2.4)	6	3 (3.2)	3	8 (3.2)	8
Sepsis	15 (5.9)	16	3 (3.2)	3	4 (1.6)	4
Septic shock	8 (3.1)	9	1 (1.1)	1	2 (0.8)	2
Metabolism and nutrition disorders	5 (2.0)	5	6 (6.3)	7	4 (1.6)	4
Fluid overload	0	0	2 (2.1)	2	0	0
Metabolic acidosis	1 (0.4)	1	2 (2.1)	2	2 (0.8)	2
Nervous system disorders	11 (4.3)	11	7 (7.4)	7	14 (5.6)	17
Hepatic encephalopathy	5 (2.0)	5	5 (5.3)	5	9 (3.6)	10
Psychiatric disorders	2 (0.8)	2	2 (2.1)	2	2 (0.8)	2
Mental status changes	2 (0.8)	2	2 (2.1)	2	2 (0.8)	2
Renal and urinary disorders	15 (5.9)	16	10 (10.5)	10	14 (5.6)	14
Acute kidney injury	3 (1.2)	3	5 (5.3)	5	5 (2.0)	5
Renal failure	7 (2.8)	8	3 (3.2)	3	6 (2.4)	6
Renal impairment	2 (0.8)	2	2 (2.1)	2	0	0
Respiratory, thoracic and mediastinal disorders	43 (16.9)	54	14 (14.7)	15	26 (10.4)	32
Acute respiratory failure	10 (3.9)	10	1 (1.1)	1	5 (2.0)	5
Dyspnea	1 (0.4)	1	2 (2.1)	2	0	0
Pulmonary edema	4 (1.6)	4	3 (3.2)	3	3 (1.2)	3
Respiratory distress	0	0	2 (2.1)	2	4 (1.6)	4
Respiratory failure	23 (9.1)	24	6 (6.3)	6	6 (2.4)	6
Vascular disorders	13 (5.1)	14	2 (2.1)	2	9 (3.6)	9
Hypotension	6 (2.4)	6	1 (1.1)	1	4 (1.6)	4

Initial and retreatment periods were combined. N = number of patients in the treatment group; n for patients = number of patients in the category of patients in the treatment group; and n for events = number of events in the category of patients in the treatment group.
[a] Up to 30 days posttreatment.
[b] Patients in the standard-dose group received only 0.5 mg and 1 mg doses. Patients in the high-dose group received at least 1 dose ≥ 2 mg.
[c] Patients experiencing multiple episodes of a given adverse event are counted once within each preferred term and within each system organ class.
SAE, serious adverse event.

CONCLUSIONS

- **Terlipressin can be dose escalated to 2 mg Q6H in patients who do not achieve adequate improvement in SCr by Day 4**
  - **A dose escalation to 2 mg was required by 27.2% of terlipressin-treated patients**
- **The rate of HRS reversal was 40% among patients who had a terlipressin dose escalation compared with 23.3% among patients who received placebo**
- **The observed 40% incidence in HRS reversal among patients who needed a dose escalation suggests that dose escalation can be performed and lead to HRS reversal, even if the initial response is suboptimal**
- **The overall SAE and safety profiles were comparable between the standard- and high-dose terlipressin groups**

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