Terlipressin Overview

- Indications
  - Terlipressin for injection has been approved since the 1980s in more than 60 countries for Hepatorenal Syndrome Type 1 (HRS-1) and Esophageal Variceal Hemorrhage (EVH)
  - Globally, medical guidelines list terlipressin as first line treatment for HRS-1
  - In the U.S., Mallinckrodt is initiating a phase 3 trial of terlipressin for the treatment of HRS-1

- HRS-1 is a rare, life-threatening complication of cirrhosis that affects up to 20,000 patients annually in the U.S.

- Unresolved HRS-1 impacts post-transplant outcomes and leads to higher overall resource utilization and morbidity
  - 5.7 times higher rate of dialysis compared to patients without HRS-1
  - 12.1 times higher rate of renal failure compared to patients without HRS-1
  - 4.7 times more days spent in the Intensive Care Unit (ICU)

- HRS-1patients are managed in hospital settings across multiple specialties, including hepatology, nephrology, gastroenterology and critical care, with most patients requiring ICU care

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Reversal of Hepatorenal Syndrome Type 1 (HRS-1) with Terlipressin plus Albumin versus Placebo plus Albumin - Not All Responses Are Created Equal: An Analysis of the REVERSE and OT-0401 Trials

Arun J. Sanyal[1], Thomas D. Boyer[2], R. Todd Frederick[3], Fredric Regenstein[4], Lorenzo Rossaro[5], Victor Araya[6], Hugo E. Vargas[7], K. Rajender Reddy[8], Khurram Jamil[9], Stephen Chris Pappas[10]

[1]Virginia Commonwealth University, Richmond, VA; [2]University of Arizona, Tucson, AZ; [3]California Pacific Medical Center, San Francisco, CA; [4]St. Luke's Hospital, Kansas City, MO; [5]University of California, Davis Medical Center, Sacramento, CA; [6]Albert Einstein Medical Center, Philadelphia, PA; [7]Mayo Clinic, Scottsdale, AZ; [8]University of Pennsylvania, Philadelphia, PA; [9]Ikaria, Hampton, NJ; [10]Orphan Therapeutics, Lebanon, NJ

BACKGROUND

- Renal function affects outcomes in patients with decompensated liver disease and acute kidney injury, including hepatorenal syndrome Type 1 (HRS-1)[1]
- Terlipressin plus albumin has been shown to improve renal function in HRS-1 to a greater degree than placebo plus albumin[2-4]
- Improvement in renal function correlates with survival[2]
- However, it is unclear whether outcomes following reversal of HRS-1 are the same when reversal is achieved by terlipressin plus albumin vs albumin alone

OBJECTIVES

- The aim of this study was to review pooled data from 2 pivotal, Phase 3 trials in HRS-1 and evaluate outcomes of those subjects who achieved reversal of HRS-1
  - Survival and survival without renal replacement therapy (RRT) were evaluated

MATERIALS & METHODS

- Serum creatinine (SCr), RRT, and survival data from the REVERSE and OT-0401 trials, both randomized, placebo-controlled trials of terlipressin and albumin vs placebo plus albumin, with similar designs and patients enrolled (**Table 1**), were pooled to analyze: incidence of confirmed HRS reversal (CHRSR), use of RRT, overall survival, and survival at Day 90 without RRT. CHRSR was defined as 2 SCr values ≤1.5 mg/dL, at least 48 hours apart, on treatment, without RRT or liver transplant

***Table 1.* Study Design: REVERSE and OT-0401 Trials**

Study	Design and Patient Selection	Treatment	HRS Subjects / Number Exposed to Terlipressin	Key Endpoints
OT-0401	Multicenter, double-blind, randomized, placebo-controlled Patients with HRS-1 based on modified IAC criteria, 1996	Terlipressin: 4-8 mg/d (IV q6h) Placebo Albumin (100 g on Day 1, then 25 g/d): recommended for both groups Up to 14 d	112/56	Treatment success at Day 14; HRS reversal; change in SCr Survival
REVERSE	Multicenter, double-blind, randomized, placebo-controlled Patients with HRS-1 based on modified IAC criteria, 2007	Terlipressin: 4-8 mg/d (IV q6h) Placebo Albumin (up to 100 g on Day 1, then 20-40 g/d): recommended for both groups Up to 14 d (15-16 d if initial response on Day 13 or 14)	196/97	Confirmed HRS reversal; HRS reversal; change in SCr Survival

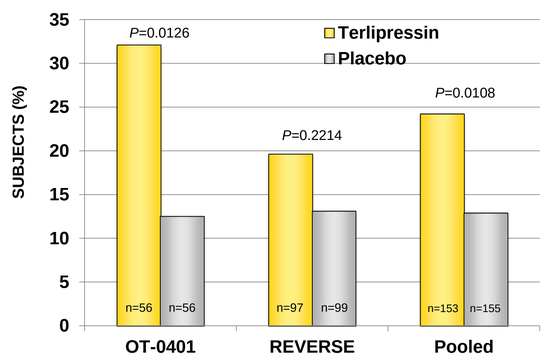
RESULTS

- Data from 308 subjects were analyzed; 153 were randomized to terlipressin, 155 to placebo
- Baseline characteristics were similar across the 2 studies and between treatment groups (**Table 2**)

***Table 2.* Baseline Demographics**

Demographics – OT-0401 and REVERSE	OT-0401		REVERSE	
	Terlipressin n = 56	Placebo n = 56	Terlipressin n = 97	Placebo n = 99
Age, mean (SD), y	50.6	52.9	55.8	54.8
Gender (n, %)				
Male	41 (73.2)	39 (69.6)	52 (53.6)	67 (67.7)
Female	15 (26.8)	17 (30.4)	45 (46.4)	32 (32.3)
Alcoholic hepatitis (n, %)	20 (35.7)	20 (35.7)	20 (20.6)	25 (25.3)
MELD Score (Mean)	33.4	33.4	33.5	32.6
Serum creatinine at baseline (mg/dL) (Mean)	3.96	3.85	3.6	3.7
Total bilirubin at baseline (mg/dL) (Mean)	15.0	15.8	11.2	12.1

***Figure 1.* Confirmed HRS Reversal (CHRSR)**



- Rates of RRT at Day 90 in subjects with and without CHRSR are shown in **Table 3**

***Table 3.* RRT at Day 90, Subjects with and without CHRSR**

STUDY	CHRSR-YES (n)	CHRSR-RRT (%)	CHRSR–NO (n)	No CHRSR–RRT (%)
OT-0401 †	25	1(4.0)	87	34(39.1)
REVERSE *	32	3(9.4)	164	75(45.7)
POOLED *	57	4(7.0)	251	109(43.4)

***P*<0.0001, CHRSR-RRT vs. No CHRSR-RRT, Fisher's exact test**
†P<0.0005, CHRSR-RRT vs. No CHRSR-RRT, Fisher's exact test

***Figure 2.* Survival by CHRSR Status and Treatment Arm**

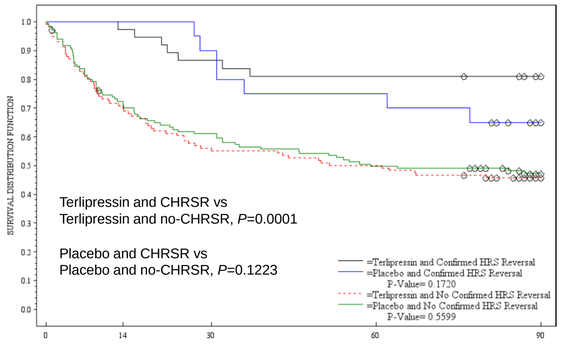
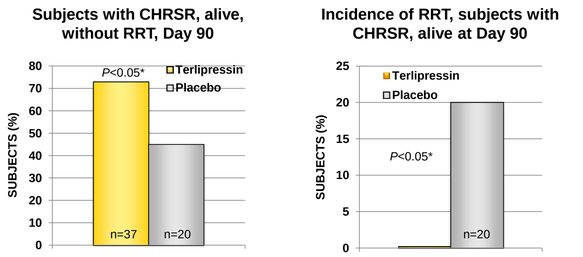


***Figure 3.* Survival, Incidence of RRT, at Day 90**



*Fisher's exact test.

No subject with CHRSR in the terlipressin group, alive at Day 90, received RRT

SUMMARY

- Pooled data from 2 large trials show that terlipressin plus albumin treatment was associated with an increased frequency of CHRSR compared with placebo and albumin (**Figure 1**)
- Survival in subjects with CHRSR was significantly higher (**Figure 2**), and use of RRT significantly lower (**Table 3**), than in subjects without CHRSR
- There were significantly more subjects in the terlipressin group with CHRSR alive at Day 90 without RRT compared with placebo (**Figure 3**)

CONCLUSIONS

- Reversal of HRS-1 following treatment with terlipressin plus albumin occurs significantly more frequently than with placebo plus albumin
- Achieving CHRSR reduces the need for RRT and improves survival
- Patients treated with terlipressin and albumin who achieve CHRSR appear to have a better outcome at Day 90 (survival and less need for RRT) compared with patients achieving CHRSR with albumin alone

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A Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Confirm Efficacy and Safety of Terlipressin in Subjects With Hepatorenal Syndrome Type 1 (CONFIRM Study)

Mallinckrodt Pharmaceuticals

Background

- Hepatorenal Syndrome Type 1 (HRS-1) is a serious, rapidly progressing yet potentially reversible renal failure in patients with chronic liver disease
- HRS -1 is a devastating disease impacting ~20,000 patients annually in US
- Mortality in HRS-1 is high, with only half of patients surviving past first 2 weeks
- There is no FDA-approved pharmacological therapy for treatment of HRS-1
- OUS[1], terlipressin is the most widely studied and clinically accepted pharmacological therapy for patients with HRS-1
- OUS, terlipressin has been approved since 1980s and is currently available in > 60 countries for treatments of a number of critical care indications

Purpose

To evaluate the efficacy and safety of intravenous terlipressin versus placebo in the treatment of adult subjects with HRS-1 receiving standard of care albumin therapy

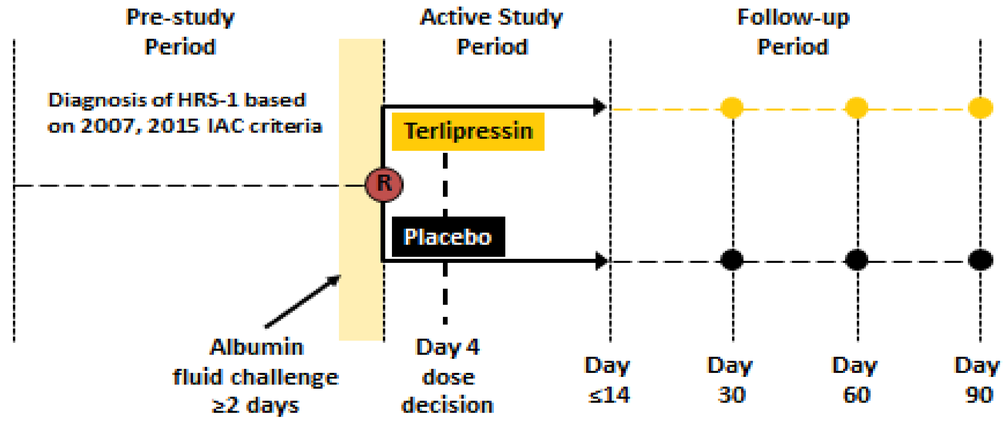
Objective

- The primary objective of this study is to assess the difference in HRS-1 reversal for subjects with terlipressin versus placebo
- HRS-1 reversal is defined as the percentage of subjects with at least one dose of study medication and a SCr value ≤ 1.5 mg/dL by Day 14 or discharge

Study Population

- Adult patients with cirrhosis, ascites & HRS-1 diagnosis
- Rapidly progressive worsening in renal function to SCr ≥ 2.25 mg/dL
- No sustained improvement in renal function at least 48 hours after diuretic withdrawal and beginning of plasma volume expansion with albumin

Study Design



2:1 Randomization for Terlipressin vs. placebo
Initial Treatment up to 14 days.

Study Endpoints

Primary Endpoint

- HRS-1 reversal by day 14

Key Secondary Endpoints

- Durability of HRS-1 reversal, defined as percentage of subjects with HRS-1 reversal without RRT to Day 14
- Incidence of HRS-1 reversal in systemic inflammatory response syndrome (SIRS) subgroup
- Transplant-free survival up to 90 days, defined as time (in days) subject survives without liver transplantation from day of randomization

[1]OUS: Outside United States