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## **Late-Breaking Presentation at Liver Meeting Details Results of Phase 3 Study of terlipressin for Type 1 Hepatorenal Syndrome**

Lebanon, NJ (October 30, 2006) – At a late-breaking oral presentation today at the 57<sup>th</sup> Annual Meeting of the American Association for the Study of Liver Diseases, topline results of a Phase 3 clinical trial for terlipressin indicated positive trends in treatment for type 1 Hepatorenal Syndrome (HRS). The study, conducted by Orphan Therapeutics, was the first randomized, double-blind, placebo-controlled clinical trial of terlipressin in type 1 HRS in the United States. HRS is a life-threatening condition characterized by rapid kidney failure in patients with end-stage liver cirrhosis.

The findings were presented by Arun J. Sanyal, M.D., Chairman, Division of Gastroenterology, Hepatology and Nutrition at Virginia Commonwealth University. The study enrolled 112 patients at 30 liver disease centers in the United States and five centers outside the United States. Using the primary end-point, terlipressin improved outcome of type 1 HRS, but this narrowly failed to achieve statistical significance. However, using either improvement in serum creatinine or HRS reversal on treatment, terlipressin was significantly more effective than placebo. The overall safety profile of terlipressin was similar to placebo.

“We are encouraged by the results of this important clinical trial,” said Peter Teuber, PhD, President of Orphan Therapeutics. “We look forward to continuing our goal of developing terlipressin to treat this rare but serious condition.”

A full copy of the study’s abstract is on the following page of this document.

### **ABOUT ORPHAN THERAPEUTICS:**

Founded in 2003, Orphan Therapeutics, LLC is a privately-held, specialty pharmaceutical company dedicated to developing and commercializing treatments for rare but serious diseases. Its initial purpose is to develop and seek FDA approval for intravenous terlipressin for the treatment of hepatorenal syndrome (HRS) type 1 in the United States.

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**A PROSPECTIVE, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL OF TERLIPRESIN FOR TYPE 1 HEPATORENAL SYNDROME (HRS)** Arun Sanyal<sup>1</sup>, Thomas Boyer<sup>2</sup>, Guadalupe Garcia-Tsao<sup>3</sup>, Frederick Regenstein<sup>4</sup>, Lorenzo Rossaro<sup>5</sup>, Peter Teuber<sup>6</sup>, Study Group Hepatorenal<sup>6</sup>, <sup>1</sup>Internal Medicine, Virginia Commonwealth University, Richmond, VA; <sup>2</sup>Internal Medicine, University of Arizona, Tucson, AZ; <sup>3</sup>Internal Medicine, Yale, New Haven CT; <sup>4</sup>Internal Medicine, Tulane, New Orleans LA; <sup>5</sup>Internal Medicine, University of California Davis, Sacramento, CA; <sup>6</sup>Orphan Therapeutics, Newark, NJ

**Background:** Type I HRS is characterized by rapidly progressive functional renal failure in subjects with cirrhosis and is associated with a 90 day mortality exceeding 90%. Uncontrolled trials suggest that vasoconstrictor therapy plus albumin improve HRS. However, there are no phase III controlled trials of such agents in HRS. **Aims:** We report the preliminary analysis of a phase III prospective, randomized, double-blind, placebo-controlled trial of terlipressin, a vasopressin analog, for Type 1 HRS. **Methods:** Type 1 HRS was defined using the International Ascites club criteria (Hepatology: 1996, 23:164-176). Subjects were randomized (1:1) to receive Terlipressin (1mg/Q 6h) or placebo I.V. in addition to albumin until creatinine decreased to  $\leq 1.5$  mg/dl on 2 measurements 48 h apart or for up to 14 days (treatment stopped earlier for treatment failure or transplantation). If after 3 days, creatinine had not improved by  $\geq 30\%$  the dose was increased to 2 mg Q 6h. Failure was defined as death, dialysis or failure of creatinine to improve after 7 days. **Results:** 112 patients were enrolled, 56 Terlipressin (MELD =  $33 \pm 6.2$ ) and 56 Placebo (MELD =  $33 \pm 6.4$ ). The primary end-point (patient alive on day 14 with creatinine  $\leq 1.5$  mg/dl on 2 measurements 48 h apart without relapse of creatinine after the improvement) was reached in 27% of subjects receiving Terlipressin and 16% of those getting placebo ( $p = 0.059$ ). There was a significant reduction in serum creatinine those receiving terlipressin vs. placebo from baseline to day 14:  $-0.7$  vs  $0$  mg/dl,  $p < 0.009$ . In addition, the commonly used criterion for reversal of HRS in the literature of creatinine of  $\leq 1.5$  mg/dl on treatment was achieved in 34% (terlipressin) vs. 13% (placebo) ( $p = 0.008$ ). Overall survival and transplant free survival at 60 days were similar, 48% & 48% -terlipressin vs. 48% & 46% - placebo respectively. The incidence of adverse (93% terlipressin vs. 89% placebo) and serious adverse events (66%-terlipressin vs 66%-placebo) was similar in the two groups. Treatment related serious adverse events occurred in 5 patients on terlipressin and 1 on placebo and there were no treatment related deaths. **Summary:** Using the primary end-point, terlipressin improved outcome of type 1 HRS but this narrowly failed to achieve statistical significance. However, using either improvement in serum creatinine or HRS reversal on treatment, Terlipressin was significantly more effective than Placebo. The overall safety profile of terlipressin was similar to Placebo. **Conclusion:** Terlipressin is an effective and safe therapy for HRS type 1.

**Disclosures:**

Peter Teuber – President: Orphan Therapeutics

The following people have nothing to disclose: Arun Sanyal, Thomas Boyer, Guadalupe Garcia-Tsao, Frederick Regenstein, Lorenzo Rossaro, Study Group Hepatorenal

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**CORRECTIONS TO ORIGINAL ARTICLE:**

Please note due to a clerical error, several figures in the original abstract were printed incorrectly.

Highlighted below are the correct numbers and/or information:

- i. “The primary end-point (patient alive on day 14 with creatinine  $\leq 1.5$  mg/dl on 2 measurements 48 h apart without relapse of creatinine after the improvement) was reached in 27% of subjects receiving terlipressin and **13%** of those getting placebo ( $p=0.059$ ).”
- ii. "Overall survival and transplant free survival at 60 days were similar, 48% and **38%**-terlipressin vs. **46%** & **34%**-placebo respectively.”
- iii. Dr. Boyer, from the University of Arizona, is located in **Tucson**, not Tucson.
- iv. Orphan Therapeutics is located in **Lebanon**, not Newark.