SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Global Development, Inc. (formerly Astellas Pharma US, Inc.)		
Name of Finished Product: Vaprisol®		
Name of Active Ingredient: Conivaptan hydrochloride (YM087)		
Title of Study: A phase 2 randomized, double blind, placebo controlled, dose escalation study to assess the safety and effects of intravenous conivaptan on the hepatic hemodynamic response in stable euvolemic or hypervolemic cirrhotic patients		
Responsible Medical Officer: [redacted] MD, [redacted] **Investigator:** [redacted] MD		
Study Center(s): 1 study center in [redacted] Spain		
Publication (reference): None		
Study Period: 8 days (6.5-hour treatment; 17.5-hour post-treatment, and 7-day follow-up) **Date of first enrollment:** 17 December 2007 **Date of last evaluation:** 6 November 2008	**Phase of Development:** 2	
Objectives: The objectives of this study were to evaluate the safety of 2 different doses of IV conivaptan in stable euvolemic or hypervolemic cirrhotic patients with serum sodium levels of 115 – 140 mEq/L and to characterize the effects of IV conivaptan on hepatic hemodynamic response in patients with cirrhosis.		
Methodology: This was a randomized, double-blind, placebo-controlled sequential dose escalation study in adult stable euvolemic or hypervolemic cirrhotic patients who had clinical evidence of portal hypertension and who had a serum sodium level between 115 mEq/L and 140 mEq/L. Twenty patients were randomized in a 3:1 dose-escalation fashion (active:placebo) into one of 2 dosing regimens. The first 8 patients (6 active and 2 placebo) were randomized within group 1 (10 mg conivaptan or placebo 30-minute loading dose followed by 2.5 mg conivaptan or placebo 6-hour continuous infusion). The next 12 patients (9 active and 3 placebo) were randomized within group 2 (20 mg conivaptan or placebo 30-minute loading dose followed by 5 mg conivaptan or placebo 6-hour continuous infusion). Hemodynamic parameters were the primary variables examined in the study. Serum sodium measurements were collected at various time points to assess efficacy as a secondary variable. Adverse events, laboratory measurements, urinalysis and ECGs were assessed.		

Number of Patients (enrolled and analyzed):

Enrolled: 20 patients

Number of patients in safety analysis set (SAF); full analysis set (FAS); and pharmacokinetic analysis set (PKAS):

Conivaptan 12.5 mg – 6 patients (SAF, FAS, PKAS)
Conivaptan 25 mg – 9 patients (SAF, FAS, PKAS)
Placebo – 5 patients (SAF, FAS)

Diagnosis and Main Criteria for Inclusion:

Male and female adult patients were eligible for the study who had a serum sodium value between 115 and 140 mEq/L prior to 24 hours of study drug administration. Patients also had to be euvolemic or hypervolemic (edematous) secondary to cirrhosis and had to display clinical evidence of portal hypertension by the presence of esophageal varices, ascites or both. Criteria for exclusion included clinical evidence of volume depletion or dehydration; supine systolic blood pressure <85 mmHg or uncontrolled hypertension; bradyarrhythmias or tachyarrhythmias requiring emergent pacemaker or treatment; untreated severe hypothyroidism or adrenal insufficiency; estimated creatinine clearance <40 mL/min, WBC <2000/mcL or platelets <30,000/mcL documented during the 7 days prior to study drug administration; hepatic encephalopathy or fulminant hepatic failure within 30 days prior to the start of study drug administration; and fasting blood glucose level ≥180 mg/dL (10.0 mmol/L) at baseline.

Test Product, Dose and Mode of Administration, Batch Numbers:

Conivaptan (20mg/4mL) ampoules were given as a 30-minute 10-mg loading dose followed by a 2.5 mg conivaptan 6-hour continuous infusion; or as a 20 mg conivaptan 30-minute loading dose followed by a 5 mg conivaptan 6-hour continuous infusion. The drug was administered in D5W via a dedicated peripheral intravenous line.

Batch numbers: [redacted]

Duration of Study:

After a screening period that lasted up to 7 days, the study duration was 8 days including a treatment period that lasted 6.5 hours

Reference Product, Dose and Mode of Administration, Batch Numbers:

Placebo for conivaptan injection was provided in 4 mL ampoules given as a 30-minute loading dose followed by a 6-hour continuous infusion via a dedicated peripheral intravenous line

Batch number: [redacted]

Criteria for Evaluation:

Hepatic venous pressure gradient (HVPG), hepatic blood flow (HBF), mean arterial pressure (MAP); heart rate; systolic and diastolic blood pressure, physical examination, electrocardiogram (ECG), laboratory measurements, urinalysis and adverse events were assessed. The hemodynamic parameters (HVPG, HBF, MAP, heart rate, and systolic and diastolic blood pressure) were the primary variables examined in the study. Serum sodium measurements were collected at various time points to assess efficacy as a secondary variable.

Statistical Methods: Descriptive statistics were used to summarize continuous variables. Number and percentage of patients in each category were used to summarize categorical variables. Percentages by categories were based on the number of patients with no missing data, ie, added up to 100%.

All statistical comparisons were made using two-sided tests at the alpha=0.05 significance level unless specifically stated otherwise. All null hypotheses were of no treatment difference. All alternative hypotheses were two-sided.

Patients receiving placebo in the 2 dosing regimens were pooled for statistical summaries and analyses. The patients who did not have hyponatremia (ie, patients with serum sodium levels of 136-140 mEq/L) were analyzed in the same way as those who did have hyponatremia.

Summary

Demographics: Most patients (78%) in the conivaptan 25 mg arm and all patients in the placebo arm were male, while 50% of patients in the conivaptan 12.5 mg arm were male. Patients in the placebo arm were younger than in the active arms, with a median age of 52 years for the placebo arm and 62 and 59 years for the conivaptan 12.5 mg and conivaptan 25 mg arms, respectively. All patients in the study were white.

All patients in the study had cirrhosis of the liver, caused by alcoholism, hepatitis C, or both. Eleven of the 20 patients in this study (55%) had hyponatremia due to cirrhosis and 2 patients (10%) had hyponatremia due to diuretic treatment. Hyponatremia was defined as a serum sodium level ≤135 mEq/L. Seven of the patients (35%) had a serum sodium level of 135 to 140 mEq/L 24 hours prior to the start of treatment and consequently did not have hyponatremia but were euvolemic or hypervolemic.

Drug Administration: All patients in the study received the 30-minute loading dose of study drug and the 6-hour continuous infusion of study drug.

Pharmacokinetic/Pharmacodynamic Results: Mean plasma conivaptan concentrations reached a peak of 500 ng/mL in the conivaptan 12.5 mg group and 901 ng/mL in the conivaptan 25 mg group at the end of the loading dose (hour 0.5). Mean concentrations had decreased at hour 6.5 to 53.1 ng/mL in the conivaptan 12.5 mg group and 98.9 ng/mL in the conivaptan 25 mg group. The greater increase in the conivaptan 25 mg group compared with the 12.5 mg group appeared to be approximately dose proportional.

The maximum median plasma concentration was observed in the conivaptan 25 mg group at 0.5 hours (894 ng/mL). The highest individual concentration was observed in the conivaptan 25 mg group at 0.5 hours (1550 ng/mL).

At 0.5 hours there was greater variation in the concentrations observed in the conivaptan 25 mg group (with a 37% coefficient of variation [CV]) compared with the conivaptan 12.5 mg group (16% CV). At 6.5 hours, the variations were similar with 29% CV in the conivaptan 12.5 mg group and 27% CV in the conivaptan 25 mg group.

Efficacy Results: Little change from baseline was observed in serum sodium levels in any treatment arm. Both active treatment arms demonstrated a stronger increase from baseline than placebo.

Safety Results: Statistical analyses found no significant mean percent change from baseline in HBF or in heart rate in any treatment group at any time point. Results were similar when treatment groups were pooled.

Slight mean increases in HPVG were observed in the active treatment groups at each time point, while decreases were observed in the placebo group. Statistical analysis of percent increase in mean HPVG found none of these increases to be statistically significant in the conivaptan 12.5 mg and 25 mg groups. The increases were not considered to be clinically meaningful.

Wide individual variations were observed in MAP in the active and placebo groups. In the conivaptan 25 mg group, mean MAP values consistently increased over time. The magnitude of the changes was not considered to be clinically significant.

Wide individual variations were observed in systolic blood pressure in the active and placebo groups. These results along with statistical analyses indicate that systolic blood pressure did not show notable treatment-related changes.

For diastolic blood pressure, mean percent change from baseline was significantly increased at all time points in the conivaptan 25 mg group and in the pooled groups, and at the hour 1 and hour 1.5 time points in the conivaptan 12.5 mg group. The clinical significance of the results must be assessed further.

No treatment-emergent adverse events were reported in the placebo arm; treatment-emergent adverse events were reported for 1 patient (16.7%) in the conivaptan 12.5 mg arm and 7 patients (77.8%) in the conivaptan 25 mg arm. All treatment-emergent adverse events were considered by the investigator to be either mild or moderate in intensity.

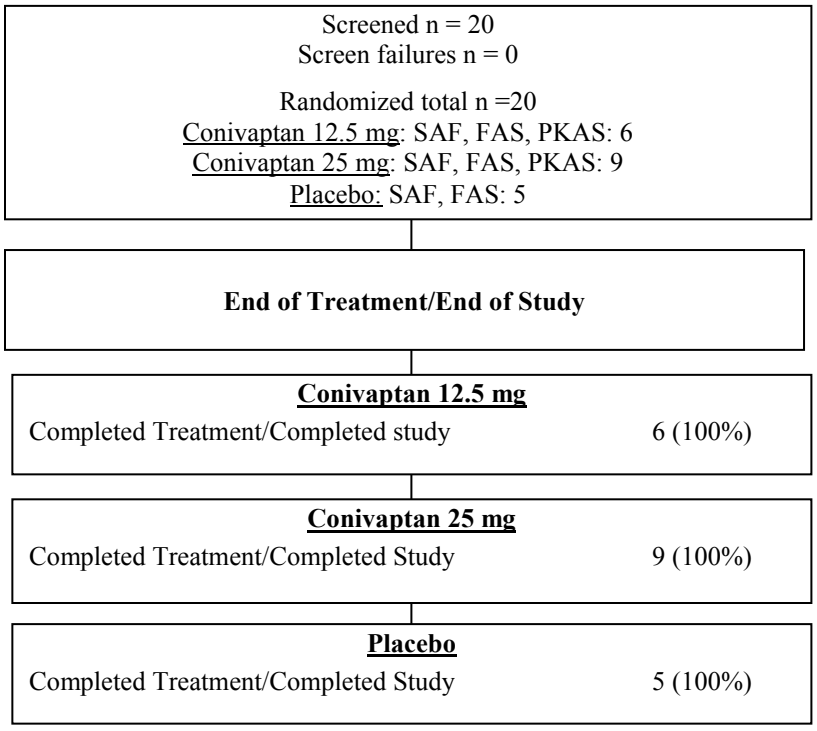
The only treatment-emergent adverse event experienced by more than 1 patient in any treatment arm was phlebitis in the conivaptan 25 mg arm (2 patients, 22.2%).

Three serious adverse events were reported for 2 patients in the conivaptan 25 mg group: mild atrial tachycardia, moderate hepatic encephalopathy, and moderate urinary tract infection. Both patients recovered from the events. The atrial tachycardia was considered by the investigator to be possibly related to study drug. The other adverse events were considered unrelated.

CONCLUSIONS: Conivaptan was generally found to be safe and well-tolerated in cirrhotic patients with clinically significant portal hypertension and mild- to moderate-hepatic impairment using the dosing regimens tested in this study.

Date of Report: 25 June 2009

Synopsis Figure 1 Analysis Sets and Patient Disposition



Conivaptan 12.5 mg: 30-minute infusion of 10 mg conivaptan plus 6-hour continuous infusion of 2.5 mg of conivaptan; conivaptan 25 mg: 30-minute infusion of 20 mg conivaptan plus 6-hour continuous infusion of 5 mg of conivaptan

SAF (safety analysis set): all randomized patients who received at least 1 dose of study medication; FAS (full analysis set): all randomized patients who received at least 1 dose of study medication and who had hepatic venous pressure gradient data at baseline; PKAS (pharmacokinetic analysis set): all randomized patients who received at least 1 dose of study drug and who had at least 1 observable drug concentration value.

Synopsis Table 1 Summary of Demographics

Parameter	Conivaptan 12.5 mg n=6	Conivaptan 25 mg n=9	Placebo n=5
Sex (number of patients)			
Male	3 (50%)	7 (77.8%)	5 (100%)
Female	3 (50%)	2 (22.2%)	0
Race (number of patients)			
White	6 (100%)	9 (100%)	5 (100%)
Age (years)			
Mean (SD)	63.7 (8.52)	60.0 (9.72)	55.2 (7.19)
Median	61.5	59.0	52.0
Min, Max	53, 77	45, 77	47, 65

Patient base: Safety analysis set (all randomized patients who received at least 1 dose of study medication)

Conivaptan 12.5 mg: 30-minute infusion of 10 mg conivaptan plus 6-hour continuous infusion of 2.5 mg of conivaptan; conivaptan 25 mg: 30-minute infusion of 20 mg conivaptan plus 6-hour continuous infusion of 5 mg of conivaptan

Synopsis Table 2 Summary of Target Disease History

Parameter	Conivaptan 12.5 mg n=6	Conivaptan 25 mg n=9	Placebo n=5
Euvolemic/Euvolemic Hyponatremia Patients			
Underlying Cause of Hyponatremia			
Cirrhosis	1 (16.7%)	1 (11.1%)	1 (20%)
Not hyponatremia†	2 (33.3%)	1 (11.1%)	1 (20%)
Other	1 (16.7%)‡	0	0
Hypervolemic/Hypervolemic Hyponatremia Patients			
Underlying Cause of Hyponatremia			
Cirrhosis	2 (33.3%)	3 (33.3%)	3 (60%)
Not hyponatremia†	0	3 (33.3%)	0
Other	0	1 (11.1%)‡	0

Patient base: Safety analysis set (all randomized patients who received at least 1 dose of study medication)

Conivaptan 12.5 mg: 30-minute infusion of 10 mg conivaptan plus 6-hour continuous infusion of 2.5 mg of conivaptan; conivaptan 25 mg: 30-minute infusion of 20 mg conivaptan plus 6-hour continuous infusion of 5 mg of conivaptan

†Had serum sodium levels of 135-140mEq/L

‡Diuretic treatment

Synopsis Table 3 Statistical Analysis of Change From Baseline in Serum Sodium Levels (mEq/L)

Parameter	Conivaptan 12.5 mg n=6	Conivaptan 25 mg n=9	Placebo n=5
Hour 0.5			
LSM-Difference (95% CI)	–1.33 (–3.7, 1.0)	–1.11 (–3.0, 0.8)	–0.80 (–3.4, 1.8)
P-value (active arm vs placebo)	0.7646	0.8496	
P-value (12.5 mg vs 25 mg)		0.8860	
Hour 1.0			
LSM-Difference (95% CI)	–0.33 (–2.7, 2.0)	0.89 (–1.0, 2.8)	–1.80 (–4.4, 0.8)
P-value (active arm vs placebo)	0.4108	0.1029	
P-value (12.5 mg vs 25 mg)		0.4310	
Hour 2.5			
LSM-Difference (95% CI)	1.83 (–0.5, 4.2)	0.22 (–1.7, 2.2)	0 (–2.6, 2.6)
P-value (active arm vs placebo)	0.3042	0.8923	
P-value (12.5 mg vs 25 mg)		0.2996	
Hour 4.0			
LSM-Difference (95% CI)	–2.17 (–4.5, 0.2)	–1.00 (–2.9, 0.9)	–3.60 (–6.2, –1.0)
P-value (active arm vs placebo)	0.4215	0.1147	
P-value (12.5 mg vs 25 mg)		0.4521	
Hour 6.5			
LSM-Difference (95% CI)	–1.17 (–3.5, 1.2)	1.33 (–0.6, 3.3)	–2.40 (–5.0, 0.2)
P-value (active arm vs placebo)	0.4890	0.0242	
P-value (12.5 mg vs 25 mg)		0.1085	

Patient base: Full analysis set (all randomized patients who received at least 1 dose of study medication and who had hepatic venous pressure gradient data at baseline)

Conivaptan 12.5 mg: 30-minute infusion of 10 mg conivaptan plus 6-hour continuous infusion of 2.5 mg of conivaptan; conivaptan 25 mg: 30-minute infusion of 20 mg conivaptan plus 6-hour continuous infusion of 5 mg of conivaptan

Statistical analysis used ANOVA (analysis of variance) on change from baseline serum sodium level, with treatment, time, and time by treatment interaction as main effect and patient as random effect.

ANOVA: analysis of variance; CI: confidence interval; LSM: least squares mean

Synopsis Table 4 Statistical Analysis of Percent Change From Baseline in Hepatic Venous Pressure Gradient (mmHg)

Parameter	Conivaptan 12.5 mg n=6	Conivaptan 25 mg n=9	Placebo n=5
Hour 0.5			
LSM-Difference (95% CI)	3.25 (–4.4, 10.9)	–0.07 (–6.3, 6.2)	–0.43 (–8.8, 7.9)
P-value (difference)	0.3937	0.9822	0.9166
P-value (treatment vs placebo)	0.5135	0.9437	
P-value (12.5 mg vs. 25 mg)		0.4990	
Hour 1.0			
LSM-Difference (95% CI)	4.25 (–3.4, 11.9)	3.05 (–3.2, 9.3)	–3.61 (–12.0, 4.8)
P-value (difference)	0.2654	0.3263	0.3865
P-value (treatment vs placebo)	0.1672	0.2028	
P-value (12.5 mg vs. 25 mg)		0.8062	
Hour 1.5			
LSM-Difference (95% CI)	7.57 (–0.1, 15.2)	4.64 (–1.6, 10.9)	–1.43 (–9.8, 6.9)
P-value (difference)	0.0517	0.1396	0.7296
P-value (treatment vs placebo)	0.1152	0.2449	
P-value (12.5 mg vs. 25 mg)		0.5491	

Patient base: Full analysis set (all randomized patients who received at least 1 dose of study medication and who had hepatic venous pressure gradient data at baseline)

Conivaptan 12.5 mg: 30-minute infusion of 10 mg conivaptan plus 6-hour continuous infusion of 2.5 mg of conivaptan; conivaptan 25 mg: 30-minute infusion of 20 mg conivaptan plus 6-hour continuous infusion of 5 mg of conivaptan

ANOVA on percent change from baseline hemodynamic parameter with treatment, time and time by treatment interaction as main effects and patient as a random effect.

ANOVA: analysis of variance; CI: confidence interval; LSM: least squares mean

Synopsis Table 5 Statistical Analysis of Percent Change From Baseline in Hepatic Blood Flow (mL/min)

Parameter	Conivaptan 12.5 mg n=6	Conivaptan 25 mg n=9	Placebo n=5
Hour 0.5			
LSM-Difference (95% CI)	7.31 (–19.9, 34.5)	–4.46 (–22.6, 13.7)	4.26 (–20.1, 28.6)
P-value (difference)	0.5871	0.6188	0.7230
P-value (treatment vs placebo)	0.8657	0.5614	
P-value (12.5 mg vs. 25 mg)		0.4677	
Hour 1.0			
LSM-Difference (95% CI)	–2.32 (–29.5, 24.9)	–2.39 (–20.5, 15.8)	–4.05 (–30.8, 22.7)
P-value (difference)	0.8626	0.7894	0.7590
P-value (treatment vs placebo)	0.9269	0.9172	
P-value (12.5 mg vs. 25 mg)		0.9966	
Hour 1.5			
LSM-Difference (95% CI)	2.31 (–24.9, 29.5)	–5.55 (–23.7, 12.6)	8.40 (–15.9, 32.7)
P-value (difference)	0.8635	0.5368	0.4860
P-value (treatment vs placebo)	0.7354	0.3553	
P-value (12.5 mg vs. 25 mg)		0.6271	

Patient base: Full analysis set (all randomized patients who received at least 1 dose of study medication and who had hepatic venous pressure gradient data at baseline)

Conivaptan 12.5 mg: 30-minute infusion of 10 mg conivaptan plus 6-hour continuous infusion of 2.5 mg of conivaptan; conivaptan 25 mg: 30-minute infusion of 20 mg conivaptan plus 6-hour continuous infusion of 5 mg of conivaptan

ANOVA on percent change from baseline hemodynamic parameter with treatment, time and time by treatment interaction as main effects and patient as a random effect.

ANOVA: analysis of variance; CI: confidence interval; LSM: least squares mean

Synopsis Table 6 Statistical Analysis of Percent Change From Baseline in Mean Arterial Pressure (mmHg)

Parameter	Conivaptan 12.5 mg n=6	Conivaptan 25 mg n=9	Placebo n=5
Hour 0.5			
LSM-Difference (95% CI)	–6.19 (–16.1, 3.7)	5.83 (–2.4, 14.1)	3.58 (–7.3, 14.4)
P-value (difference)	0.2123	0.1602	0.5064
P-value (treatment vs placebo)	0.1850	0.7391	
P-value (12.5 mg vs. 25 mg)		0.0666	
Hour 1.0			
LSM-Difference (95% CI)	–4.43 (–14.3, 5.5)	6.11 (–2.0, 14.2)	10.92 (0.1, 21.8)
P-value (difference)	0.3694	0.1340	0.0485
P-value (treatment vs placebo)	0.0410	0.4740	
P-value (12.5 mg vs. 25 mg)		0.1031	
Hour 1.5			
LSM-Difference (95% CI)	0.54 (–9.4, 10.4)	9.76 (1.7, 17.8)	4.65 (–6.2, 15.5)
P-value (difference)	0.9124	0.0195	0.3896
P-value (treatment vs placebo)	0.5731	0.4473	
P-value (12.5 mg vs. 25 mg)		0.1516	

Patient base: Full analysis set (all randomized patients who received at least 1 dose of study medication and who had hepatic venous pressure gradient data at baseline)

Conivaptan 12.5 mg: 30-minute infusion of 10 mg conivaptan plus 6-hour continuous infusion of 2.5 mg of conivaptan; conivaptan 25 mg: 30-minute infusion of 20 mg conivaptan plus 6-hour continuous infusion of 5 mg of conivaptan

ANOVA on percent change from baseline hemodynamic parameter with treatment, time and time by treatment interaction as main effects and patient as a random effect.

ANOVA: analysis of variance; CI: confidence interval; LSM: least squares mean

Synopsis Table 7 Statistical Analysis of Percent Change From Baseline in Blood Pressure and Heart Rate

Parameter	Conivaptan 12.5 mg n=6	Conivaptan 25 mg n=9	Placebo n=5
Systolic Blood Pressure (mmHg)			
Hour 0.5			
LSM-Difference (95% CI)	4.22 (–8.0, 16.4)	4.57 (–5.4, 14.5)	12.37 (–1.0, 25.7)
P-value (difference)	0.4870	0.3578	0.0685
P-value (treatment vs placebo)	0.3663	0.3482	
P-value (12.5 mg vs. 25 mg)		0.9642	
Hour 1.0			
LSM-Difference (95% CI)	4.72 (–7.5, 16.9)	12.46 (2.5, 22.4)	7.57 (–5.8, 20.9)
P-value (difference)	0.4371	0.0158	0.2575
P-value (treatment vs placebo)	0.7507	0.5553	
P-value (12.5 mg vs. 25 mg)		0.3251	
Hour 1.5			
LSM-Difference (95% CI)	6.63 (–5.6, 18.8)	5.76 (–4.2, 15.7)	1.79 (–11.6, 15.2)
P-value (difference)	0.2771	0.2484	0.7869
P-value (treatment vs placebo)	0.5903	0.6319	
P-value (12.5 mg vs. 25 mg)		0.9108	
Diastolic Blood Pressure (mmHg)			
Hour 0.5			
LSM-Difference (95% CI)	8.29 (–0.5, 17.0)	7.25 (0.1, 14.4)	3.01 (–6.6, 12.6)
P-value (difference)	0.0626	0.0469	0.5270
P-value (treatment vs placebo)	0.4147	0.4764	
P-value (12.5 mg vs. 25 mg)		0.8530	
Hour 1.0			
LSM-Difference (95% CI)	12.08 (3.3, 20.8)	8.15 (1.0, 15.3)	5.59 (–4.0, 15.2)
P-value (difference)	0.0082	0.0266	0.2443
P-value (treatment vs placebo)	0.3161	0.6664	
P-value (12.5 mg vs. 25 mg)		0.4833	
Hour 1.5			
LSM-Difference (95% CI)	15.23 (6.5, 24.0)	8.78 (1.6, 15.9)	5.80 (–3.8, 15.4)
P-value (difference)	0.0012	0.0175	0.2269
P-value (treatment vs placebo)	0.1490	0.6159	
P-value (12.5 mg vs. 25 mg)		0.2539	
Pulse (Heart) Rate (beats per minute)			
Hour 0.5			
LSM-Difference (95% CI)	3.31 (–6.7, 13.3)	–5.17 (–13.3, 3.0)	–2.28 (–13.2, 8.7)
P-value (difference)	0.5053	0.2064	0.6746
P-value (treatment vs placebo)	0.4485	0.6698	
P-value (12.5 mg vs. 25 mg)		0.1904	
Table continued on next page			

Parameter	Conivaptan 12.5 mg n=6	Conivaptan 25 mg n=9	Placebo n=5
Hour 1.0			
LSM-Difference (95% CI)	6.72 (–3.3, 16.7)	–5.50 (–13.7, 2.7)	–3.00 (–13.9, 7.9)
P-value (difference)	0.1805	0.1795	0.5811
P-value (treatment vs placebo)	0.1913	0.7120	
P-value (12.5 mg vs. 25 mg)		0.0625	
Hour 1.5			
LSM-Difference (95% CI)	6.21 (–3.8, 16.2)	–3.50 (–11.7, 4.7)	–3.71 (–14.7, 7.2)
P-value (difference)	0.2148	0.3891	0.4956
P-value (treatment vs placebo)	0.1824	0.9755	
P-value (12.5 mg vs. 25 mg)		0.1350	

Patient base: Full analysis set (all randomized patients who received at least 1 dose of study medication and who had hepatic venous pressure gradient data at baseline)

Conivaptan 12.5 mg: 30-minute infusion of 10 mg conivaptan plus 6-hour continuous infusion of 2.5 mg of conivaptan; conivaptan 25 mg: 30-minute infusion of 20 mg conivaptan plus 6-hour continuous infusion of 5 mg of conivaptan

ANOVA on percent change from baseline hemodynamic parameter with treatment, time and time by treatment interaction as main effects and patient as a random effect.

ANOVA: analysis of variance; CI: confidence interval; LSM: least squares mean

Synopsis Table 8 Summary of Treatment-Emergent Adverse Events

MedDRA (v. 9.1) Primary System Organ Class Preferred Term	Number of Patients (%)		
	Conivaptan 12.5 mg n=6	Conivaptan 25 mg n=9	Placebo n=5
Any Adverse Event	**1 (16.7%)**	**7 (77.8%)**	**0**
Cardiac disorders	**0**	**1 (11.1%)**	**0**
Atrial Flutter	0	1 (11.1%)	0
Atrial Tachycardia	0	1 (11.1%)	0
Gastrointestinal disorders	**0**	**1 (11.1%)**	**0**
Nausea	0	1 (11.1%)	0
Vomiting	0	1 (11.1%)	0
Infections and Infestations	**0**	**1 (11.1%)**	**0**
Urinary Tract Infection	0	1 (11.1%)	0
Metabolism and nutrition disorders	**0**	**1 (11.1%)**	**0**
Polydipsia	0	1 (11.1%)	0
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (11.1%)**	**0**
Back Pain	0	1 (11.1%)	0
Nervous System Disorders	**1 (16.7%)**	**1 (11.1%)**	**0**
Dizziness	1 (16.7%)	0	0
Hepatic Encephalopathy	0	1 (11.1%)	0
Respiratory, Thoracic and Mediastinal Disorders	**0**	**1 (11.1%)**	**0**
Productive Cough	0	1 (11.1%)	0
Skin and Subcutaneous Disorders	**0**	**1 (11.1%)**	**0**
Dry Skin	0	1 (11.1%)	0
Vascular disorders	**0**	**2 (22.2%)**	**0**
Phlebitis	0	2 (22.2%)	0

Patient base: Safety analysis set (all randomized patients who received at least 1 dose of study medication)

Conivaptan 12.5 mg: 30-minute infusion of 10 mg conivaptan plus 6-hour continuous infusion of 2.5 mg of conivaptan; conivaptan 25 mg: 30-minute infusion of 20 mg conivaptan plus 6-hour continuous infusion of 5 mg of conivaptan

Within a system organ class patients may have reported more than 1 adverse event.

Treatment-emergent: an adverse event that occurred after the first dose of study drug through 24 hours after the last dose of study drug