

ORIGINAL ARTICLE

# Tolvaptan, a Selective Oral Vasopressin V<sub>2</sub>-Receptor Antagonist, for Hyponatremia

Robert W. Schrier, M.D., Peter Gross, M.D., Mihai Gheorghiu, M.D., Tomas Berl, M.D., Joseph G. Verbalis, M.D., Frank S. Czerwiec, M.D., Ph.D., and Cesare Orlandi, M.D., for the SALT Investigators\*

## ABSTRACT

### BACKGROUND

Hyponatremia (serum sodium concentration, <135 mmol per liter) is a predictor of death among patients with chronic heart failure and cirrhosis. At present, therapy for acute and chronic hyponatremia is often ineffective and poorly tolerated. We investigated whether tolvaptan, an orally active vasopressin V<sub>2</sub>-receptor antagonist that promotes aquaresis — excretion of electrolyte-free water — might be of benefit in hyponatremia.

### METHODS

In two multicenter, randomized, double-blind, placebo-controlled trials, the efficacy of tolvaptan was evaluated in patients with euvolemic or hypervolemic hyponatremia. Patients were randomly assigned to oral placebo (223 patients) or oral tolvaptan (225) at a dose of 15 mg daily. The dose of tolvaptan was increased to 30 mg daily and then to 60 mg daily, if necessary, on the basis of serum sodium concentrations. The two primary end points for all patients were the change in the average daily area under the curve for the serum sodium concentration from baseline to day 4 and the change from baseline to day 30.

### RESULTS

Serum sodium concentrations increased more in the tolvaptan group than in the placebo group during the first 4 days ( $P < 0.001$ ) and after the full 30 days of therapy ( $P < 0.001$ ). The condition of patients with mild or marked hyponatremia improved ( $P < 0.001$  for all comparisons). During the week after discontinuation of tolvaptan on day 30, hyponatremia recurred. Side effects associated with tolvaptan included increased thirst, dry mouth, and increased urination. A planned analysis that combined the two trials showed significant improvement from baseline to day 30 in the tolvaptan group according to scores on the Mental Component of the Medical Outcomes Study 12-item Short-Form General Health Survey.

### CONCLUSIONS

In patients with euvolemic or hypervolemic hyponatremia, tolvaptan, an oral vasopressin V<sub>2</sub>-receptor antagonist, was effective in increasing serum sodium concentrations at day 4 and day 30. (ClinicalTrials.gov numbers, NCT00072683 [SALT-1] and NCT00201994 [SALT-2].)

From the University of Colorado, Denver (R.W.S., T.B.); Universitätsklinikum Carl Gustav Carus, Dresden, Germany (P.G.); Feinberg School of Medicine, Northwestern University, Chicago (M.G.); Georgetown University, Washington, DC (J.G.V.); and Otsuka Maryland Research Institute, Rockville, MD (F.S.C., C.O.). Address reprint requests to Dr. Schrier at the Division of Renal Diseases and Hypertension, University of Colorado Health Sciences Center, 4200 E. 9th Ave., Denver, CO 80262, or at robert.schrier@uchsc.edu.

\*Investigators and institutions participating in the Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 (SALT-1 and SALT-2) trials are listed in the Appendix.

N Engl J Med 2006;355:2099-112.

Copyright © 2006 Massachusetts Medical Society.

**H**YPONATREMIA, THE MOST COMMON electrolyte derangement occurring in hospitalized patients,<sup>1,2</sup> is usually classified as hypovolemic, euvoletic, or hypervolemic. The secretion of arginine vasopressin appears to be of central importance in the decline of serum sodium concentrations in all these conditions.<sup>1,2</sup> Hyponatremia is reported to be associated with increased morbidity and mortality among patients with heart, liver, or neurologic disease.<sup>3-8</sup> Even mild chronic hyponatremia has been associated with subtle neurologic defects, manifested as impairments in balance and attention that can increase the incidence of falls.<sup>9</sup> These deficits may be reversed with the correction of the hyponatremia.

Tolvaptan, a novel, orally active, selective, non-peptide antagonist that blocks arginine vasopressin from binding to V<sub>2</sub> receptors of the distal nephron, induces the excretion of electrolyte-free water without changing the total level of electrolyte excretion.<sup>10</sup> In patients with heart failure, tolvaptan appears to decrease body weight and edema and increase serum sodium concentrations without adversely affecting serum electrolyte levels, vital signs, or renal function.<sup>11-14</sup>

We report the results of two randomized, placebo-controlled, double-blind phase 3 studies (Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 [SALT-1 and SALT-2]) examining the effect of tolvaptan on hypervolemic and euvoletic hyponatremia of diverse causes. These trials assessed the outpatient use of a vasopressin V<sub>2</sub>-receptor antagonist for hyponatremia of diverse origin, including assessments of reversibility and safety.

## METHODS

### PATIENTS

Eligible patients were 18 years of age or older and had euvoletic or hypervolemic hyponatremia (defined as a nonartifactual serum sodium concentration of <135 mmol per liter). Patients had chronic heart failure, cirrhosis, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in association with the hyponatremia. Persons with psychogenic polydipsia, head trauma, postoperative conditions, uncontrolled hypothyroidism or adrenal insufficiency, or any hyponatremic condition associated with the use of medications that could have been safely withdrawn were ineligible. The study protocols required a

serum sodium concentration of less than 130 mmol per liter at baseline in 50% of those enrolled and also required that no single disease entity be represented in more than half the total study population. Mild hyponatremia was defined as 130 to 134 mmol of sodium per liter and marked hyponatremia as less than 130 mmol of sodium per liter.

Patients were ineligible if they had clinically evident hypovolemic hyponatremia (a state in which normal plasma sodium concentrations could be reestablished through the restoration of plasma volume). Other exclusion criteria were recent cardiac surgery, myocardial infarction, sustained ventricular tachycardia or fibrillation, severe angina, cerebrovascular accident, or multiple strokes; systolic blood pressure of less than 90 mm Hg, central venous pressure of less than 5 cm of water, pulmonary-capillary wedge pressure of less than 5 mm Hg, a serum creatinine concentration of more than 3.5 mg per deciliter (309 μmol per liter), a Child-Pugh score of more than 10 (unless approved by the study's medical monitor), or a serum sodium concentration less than 120 mmol per liter in association with neurologic impairment; and the presence of severe pulmonary hypertension, urinary tract obstruction, uncontrolled diabetes mellitus, or progressive or episodic neurologic disease. Patients who were judged to have little chance of short-term survival or who might not tolerate sudden shifts in fluid volumes or pressures were ineligible.

### STUDY DESIGN

The two trials were identical prospective, multicenter, randomized, double-blind, placebo-controlled efficacy studies that were conducted at 42 sites in the United States between April 11, 2003, and December 20, 2005, and at 50 international sites between November 20, 2003, and July 6, 2005. The identical study designs of the two trials assessed reproducibility and were intended to ensure comparability. The institutional review board or ethics committee at each site approved the study protocols and ensured that written informed consent was obtained from all patients.

Patients meeting the eligibility requirements underwent central randomization with the use of random permuted blocks and stratification according to whether hyponatremia was mild or marked and whether or not it was associated with chronic heart failure. Patients were assigned in a

**Table 1. Demographic and Baseline Characteristics of Patients in the SALT-1 and SALT-2 Trials.\***

Characteristic	SALT-1		SALT-2		P Value	
	Tolvaptan (N = 102)	Placebo (N = 103)	Tolvaptan (N = 123)	Placebo (N = 120)	SALT-1	SALT-2
Age — yr						
Mean	60±14	60±13	62±15	63±14	0.94	0.66
Range	18–86	35–90	27–92	28–100		
Female sex — no. (%)	50 (49)	41 (40)	48 (39)	47 (39)	0.21	1.00
Race — no. (%)					0.26	0.47
White	71 (70)	76 (74)	118 (96)	109 (91)		
Black	13 (13)	17 (17)	1 (1)	3 (2)		
Hispanic	13 (13)	9 (9)	3 (2)	6 (5)		
Other	5 (5)	1 (1)	1 (1)	2 (2)		
Mean body weight — kg	78±23	75±22	73±19	75±21	0.44	0.39
Mean height — cm	167±10	170±11	168±11	167±9	0.02	0.42
Fluid status — no. (%)					0.38	0.80
Euvolemic	61 (60)	67 (65)	63 (51)	60 (50)		
Hypovolemic	41 (40)	34 (33)	58 (47)	60 (50)		
Cause of hyponatremia — no. (%)					0.63	0.96
Chronic heart failure	35 (34)	33 (32)	36 (29)	34 (28)		
Cirrhosis	25 (25)	21 (20)	38 (31)	36 (30)		
SIADH and other	42 (41)	49 (48)	49 (40)	50 (42)		
Mean serum sodium — mmol/liter	128.7±4.5	128.8±4.1	129.5±3.5	129.1±4.5	0.85	0.37
Degree of hyponatremia — no. (%)					0.89	1.00
Mild	49 (48)	51 (50)	64 (52)	62 (52)		
Mean serum sodium — mmol/liter	132.4±1.5	132.1±1.3	132.3±1.6	132.4±1.3	0.37	0.56
Marked	53 (52)	52 (50)	59 (48)	58 (48)		
Mean serum sodium — mmol/liter	125.4±3.5	125.5±3.2	126.6±2.5	125.5±3.8	0.84	0.07
Mean score on SF-12 Health Survey†						
Physical Component Summary	33.4±10.7	33.9±10.5	33.0±10.6	33.1±10.8	0.78	0.95
Mental Component Summary	42.4±11.6	44.7±11.9	44.3±11.9	44.9±11.6	0.15	0.89

\* Mild hyponatremia was defined as a baseline serum sodium concentration of 130 to 134 mmol per liter. Marked hyponatremia was defined as a serum sodium concentration of less than 130 mmol per liter. SIADH denotes syndrome of inappropriate antidiuretic hormone secretion. Race was self-reported. Plus-minus values are means ±SD.

† Scores on the Physical Component Summary of the SF-12 range from 5 to 69, and those on the Mental Component Summary range from 8 to 73, with higher scores indicating better functioning.

1:1 ratio to receive oral tolvaptan (a 15-mg tablet) or matching placebo once daily for up to 30 days. Study drugs were administered in the morning in either an inpatient or outpatient setting as an adjunct to the patient's standard therapy. Fluid restriction was not mandatory according to the study protocol. Treatment of hyponatremia with demeclocycline, lithium chloride, or urea was not permitted.

During the initial 4 days of therapy, the dose of the study drug could be increased from 15 to 30 mg or from 30 to 60 mg according to a regimen designed for slow correction of serum sodium concentrations to 135 mmol per liter or more. If the serum sodium concentration remained below 136 mmol per liter and had increased by less than 5 mmol per liter during the prior 24 hours, the dose was increased. If the serum sodium concentration rose above 145 mmol per liter or increased at too great a rate (by more than 12 mmol per liter during 24 hours or by more than 8 mmol per liter during 8 hours on the first day of therapy), the investigator either withheld or decreased the next dose or increased the patient's fluid intake. Patients were hospitalized for the first day of the study; the majority were discharged by day 4.

#### STUDY ASSESSMENTS

Patients were evaluated at baseline, 8 hours after the first administration of the study drug (tolvaptan or placebo), and on days 2, 3, 4, 11, 18, 25, 30, and 37. Study drugs were withheld after day 30, and the effect of discontinuation of the study drug was assessed on day 37.

The assessments included the two primary end points of the study: the change in the average daily area under the curve (AUC) for the serum sodium concentration from baseline to day 4 and from baseline to day 30. Prespecified secondary end points included the change in the AUC for the serum sodium concentration in patients with marked hyponatremia, the absolute serum sodium concentration at each visit, the time to normalization of the serum sodium concentration, the percentages of patients with serum sodium concentrations that had normalized at day 4 and day 30, and the categorical serum sodium concentration on day 4 and day 30 (normal value, >135 mmol per liter; mild hyponatremia, 130 to

#### Figure 1 (facing page). Enrollment, Randomization, and Follow-up of Patients in the SALT-1 (Panel A) and SALT-2 (Panel B) Trials.

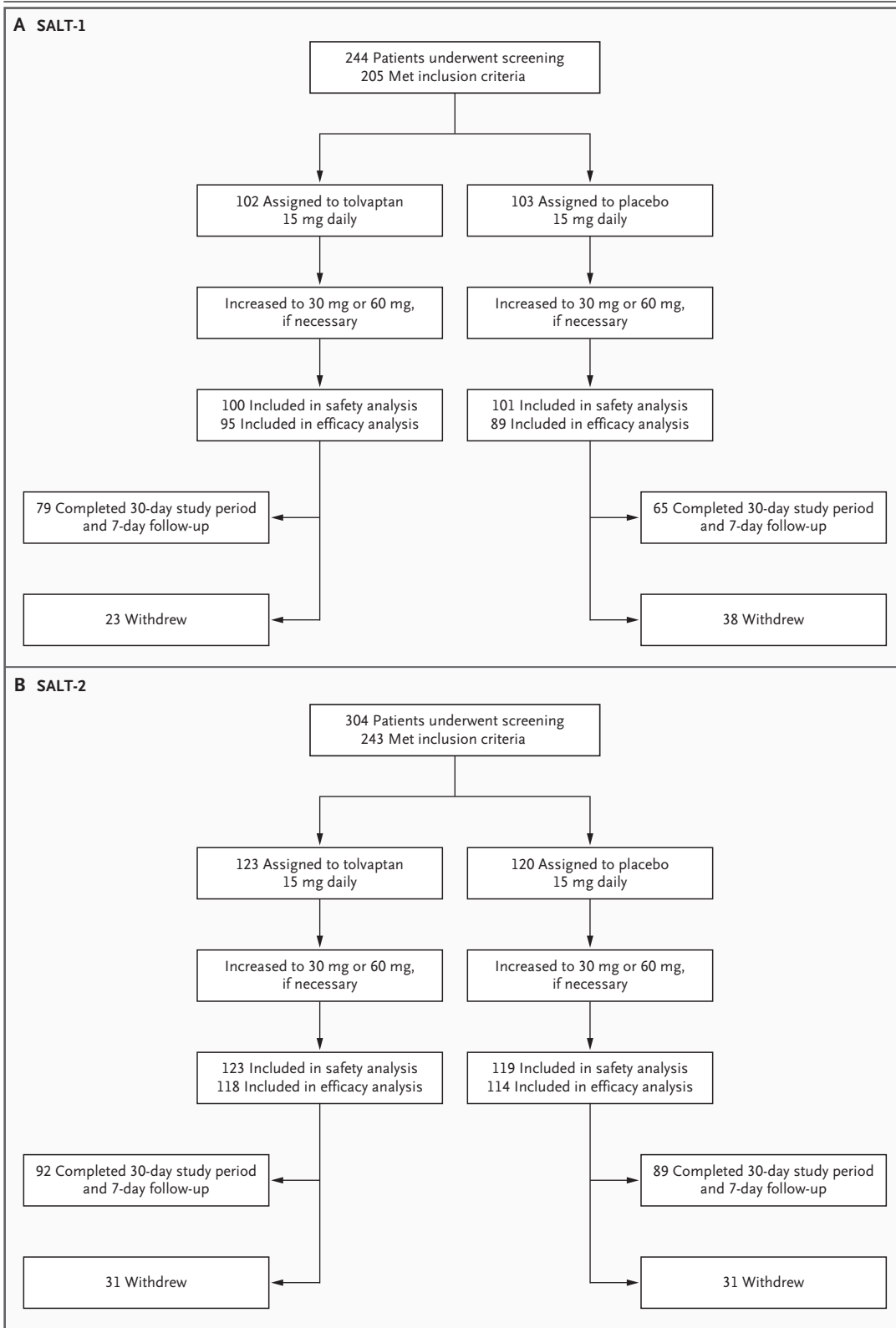
Patients who received at least one dose of the study medication (tolvaptan or placebo) were included in the safety analysis. Patients whose serum sodium concentrations were evaluated at baseline and one or more times after baseline were included in the efficacy analysis.

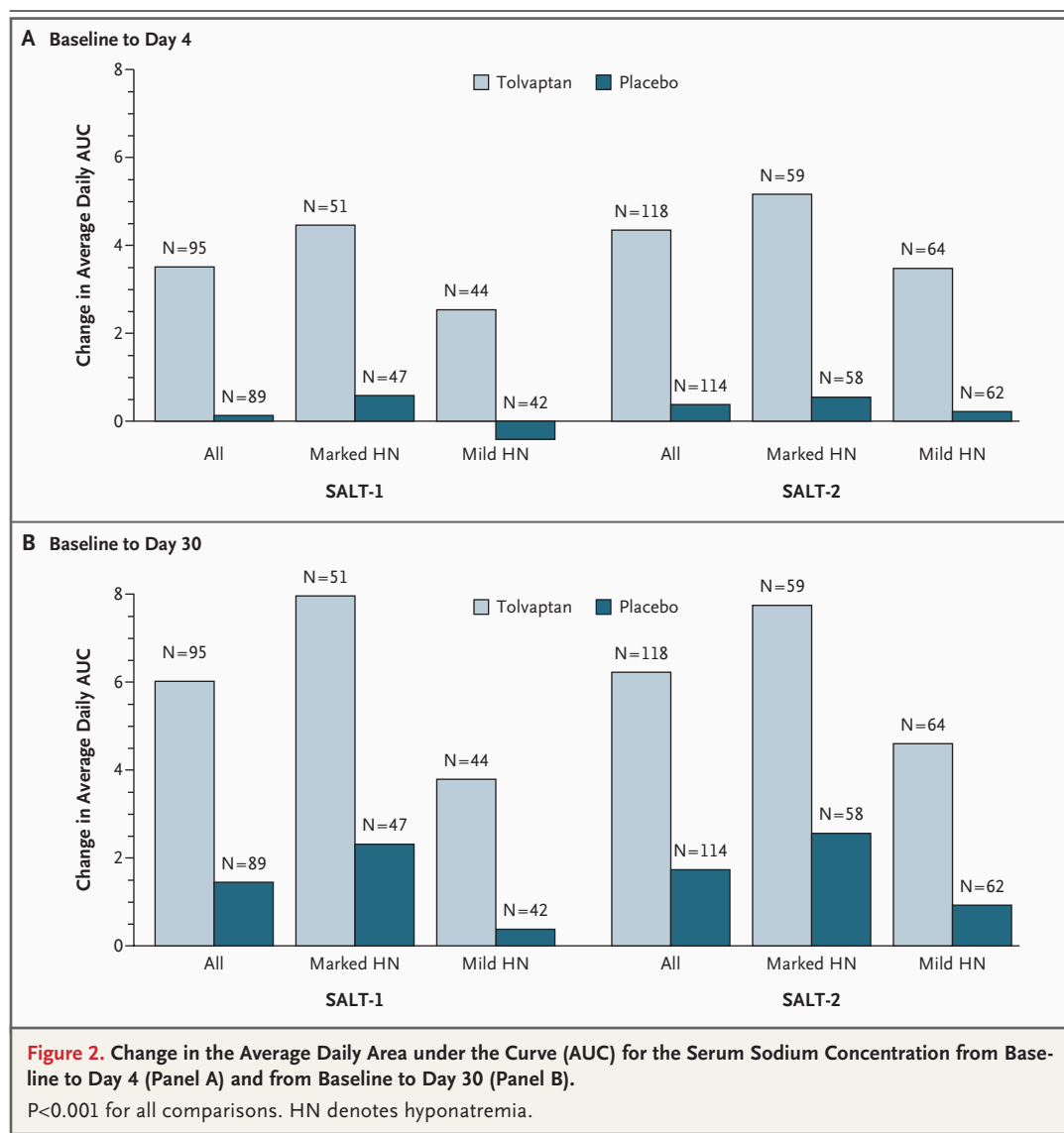
135 mmol per liter as conservatively extended for the analysis of categorical change; or marked hyponatremia, <130 mmol per liter) for patients with mild or marked hyponatremia at baseline. Other secondary end points were fluid intake and output on day 1, change in body weight in patients with hypervolemic hyponatremia on day 1, fluid restriction or use of intravenous saline as rescue therapy, and the change from baseline in scores on the Physical Component Summary and Mental Component Summary of the Medical Outcomes Study 12-item Short-Form (SF-12) General Health Survey.

Adverse events were defined as any new medical problem or exacerbation of an existing medical problem in a patient enrolled in the study. Patients could spontaneously report such events to an investigator. In addition, at each visit, investigators asked patients the nonleading question, "How have you felt since your last visit?" Each investigator was required to assess and report to the sponsor the seriousness and severity of each event and whether the event was probably associated with the study drug. The sponsor then reported such events to the appropriate regulatory authorities and to the study's independent safety oversight committee.

#### STATISTICAL ANALYSIS

The change in the average daily AUC for the serum sodium concentration from baseline to day 4 and from baseline to day 30 (the two primary end points) was calculated as the AUC for each patient, divided by the observation period (4 or 30 days), minus the baseline value. The sodium changes in the two study groups were compared with an analysis of covariance (ANCOVA) model in which the group assignment and baseline stratification factors were covariates. We calculated that a sample of 100 patients per group would yield more than 90% power (with a two-sided





significance level of 0.025) to detect a mean ( $\pm$ SD) between-group difference of  $1.99 \pm 2.7$  mmol of sodium per liter in the change from baseline to day 4 and of  $3.00 \pm 3.28$  mmol of sodium per liter from baseline to day 30. With similar assumptions, we calculated that the inclusion of 50 patients with marked hyponatremia in each group would yield 90% power (with a two-sided significance level of 0.05). To preserve an overall nominal significance level of 0.05 for each of the primary end points, the Hochberg procedure was prespecified.<sup>15</sup>

Serum sodium concentrations were compared between study groups with the use of the ANCOVA model and the covariates noted above. The per-

centage of patients in whom serum sodium concentrations normalized ( $>135$  mmol per liter) or fluid restriction was used was analyzed with the Cochran–Mantel–Haenszel test and the baseline stratification factors. We compared shifts in the categorical change in hyponatremia in the two groups with the use of the Cochran–Mantel–Haenszel mean score test, using a modified ridit score (van Elteren test), with cause as a stratification factor. This analysis was performed separately for subgroups of patients classified at baseline as having mild hyponatremia (a serum sodium concentration of 130 to 134 mmol per liter) or marked hyponatremia ( $<130$  mmol per liter). Categories after treatment were defined as normal,

**Table 2. Results of Efficacy Analysis.\***

Variable	SALT-1			SALT-2		
	Tolvaptan (N=102)	Placebo (N=103)	P Value	Tolvaptan (N=123)	Placebo (N=120)	P Value
<b>Primary end point: change in average AUC for serum sodium — mmol/liter</b>						
All patients						
Day 4	3.62±2.68	0.25±2.08	<0.001	4.33±2.87	0.42±2.56	<0.001
Day 30	6.22±4.10	1.66±3.59	<0.001	6.20±3.92	1.84±3.83	<0.001
Mild hyponatremia						
Day 4	2.52±1.95	-0.32±2.27	<0.001	3.59±2.34	0.18±2.01	<0.001
Day 30	3.87±3.01	0.68±2.78	<0.001	4.68±2.91	0.94±2.89	<0.001
Marked hyponatremia						
Day 4	4.56±2.88	0.76±1.77	<0.001	5.06±3.16	0.7±2.99	<0.001
Day 30	8.24±3.84	2.54±4.01	<0.001	7.60±4.31	2.72±4.41	<0.001
<b>Absolute change in serum sodium — mmol/liter</b>						
Baseline	128.5±4.5	128.7±4.1		129.±3.5	128.9±4.5	
Day 4						
Mean	133.9±4.8	129.7±4.9	<0.001	135.3±3.6	129.6±5.2	<0.001
No. of patients	95	88		115	112	
Day 30						
Mean	135.7±5.0	131.0±6.2	<0.001	135.9±5.9	131.5±5.7	<0.001
No. of patients	95	89		114	98	
<b>Categorical change in hyponatremia — no./total no. (%)</b>						
Baseline						
Mild hyponatremia	49/102 (48)	51/103 (50)		64/123 (52)	62/120 (52)	
Marked hyponatremia	53/102 (52)	52/103 (50)		59/123 (48)	58/120 (48)	
Day 4						
Normal	38/95 (40)	12/89 (13)	<0.001	65/118 (55)	12/114 (11)	<0.001
Marked hyponatremia	12/95 (13)	44/89 (49)	<0.001	12/118 (10)	46/114 (40)	<0.001
Day 30						
Normal	50/95 (53)	22/89 (25)	<0.001	69/118 (58)	28/114 (25)	<0.001
Marked hyponatremia	7/95 (7)	31/89 (35)	<0.001	18/118 (15)	37/114 (32)	0.002
<b>Fluid status</b>						
Urine output on day 1 — ml	3218±1646	2076±1534	<0.001	3185±2543	1914±1366	<0.001
Fluid intake on day 1 — ml	1825±1057	1492±945	0.04	2129±2110	1705±1396	0.09
Difference on day 1 — ml	-1533±1429	-636±1275	<0.001	-1059±1877	-185±870	<0.001
Patients requiring fluid restriction — %	9.3	17.5	0.08	9.2	16.8	0.08

\* The range for mild hyponatremia, defined as a baseline serum sodium concentration of 130 to 134 mmol per liter, was conservatively extended to 130 to 135 mmol per liter for the analysis of categorical change. Marked hyponatremia was defined as a serum sodium concentration of less than 130 mmol per liter. Patients whose serum sodium concentrations were evaluated at baseline and one or more times after baseline were included in the efficacy analysis. P values are for the comparison of the change in serum sodium concentrations from baseline to day 4 and from baseline to day 30 between the placebo group and the tolvaptan group. Plus-minus values are means ±SD. AUC denotes area under the curve.

mild, and marked, as described above, with the range for mild conservatively extended to a serum sodium concentration of 135 mmol per liter for this analysis.<sup>16</sup>

The time to normalization of the serum sodium concentration was analyzed with the use of a log-rank test. Fluid loss, fluid intake, and fluid balance (total intake minus total output) on day 1 were evaluated with the use of an analysis-of-variance model, with the assigned study group and baseline stratification factors as covariates.

The Physical Component Summary and Mental Component Summary scales of the SF-12 Health Survey (ranges, 5 to 69 for the physical component and 8 to 73 for the mental component, with higher scores indicating better functioning) were derived with the use of weights provided in the SF-12 Health Survey manual.<sup>17</sup> The SF-12 Health Survey was chosen as a patient-reported outcome for overall health status because it has been validated in numerous clinical studies. The physical component assesses physical functioning, bodily pain, physically limited accomplishment, and general health, and the mental component assesses vitality, social functioning, emotionally limited accomplishment, calmness, and sadness. The absolute shift from baseline of 5 units was considered a clinically important difference.<sup>18</sup> Changes from baseline scores were analyzed in the pooled database of the SALT-1 and SALT-2 trials with an ANCOVA model, with the assigned study group, baseline stratification factors, and baseline scores as covariates. All reported P values are two-sided.

The development of the protocol and the data analysis were undertaken jointly by the sponsor, the investigators, and the authors. Dr. Schrier assumes responsibility for the overall content and integrity of the manuscript, with substantial contributions from the coauthors; all authors vouch for the accuracy and completeness of the reported data. There was no interim analysis. The sponsor holds the data, which are freely available.

## RESULTS

In the SALT-1 and SALT-2 trials, 102 and 123 patients, respectively, were assigned to tolvaptan and 103 and 120, respectively, were assigned to placebo. The demographic and baseline characteristics of the patients were similar in the study

**Figure 3 (facing page).** Mean Serum Sodium Concentrations According to the Day of Patient Visit.

Asterisks indicate  $P < 0.001$  for the comparison between tolvaptan and placebo. Daggers indicate  $P < 0.01$  for the comparison between tolvaptan and placebo. Tolvaptan was discontinued on day 30. Circles denote patients receiving tolvaptan, and squares denote patients receiving placebo. Horizontal lines indicate the lower limit of the normal range for the serum sodium concentration. Vertical lines indicate the end of the treatment period. HN denotes hyponatremia.

groups in both trials (with the exception of a significant difference in height in SALT-1). Patients enrolled in the trials had similar diverse causes of hyponatremia (Table 1).

In SALT-1, 79 (77.5%) of the 102 patients assigned to tolvaptan and 65 (63.1%) of the 103 patients assigned to placebo completed the 30-day study period and the 7-day follow-up (Fig. 1A). In SALT-2, 92 (74.8%) of the 123 patients assigned to tolvaptan and 89 (74.2%) of the 120 patients assigned to placebo completed the trial (Fig. 1B).

### EFFICACY

The increase in the average daily AUC for the serum sodium concentration was significantly greater in the tolvaptan group than in the placebo group from baseline to study day 4 as well as during the entire 30-day study period (Fig. 2A and 2B and Table 2). Tolvaptan was also associated with a significantly greater increase in the average daily AUC for the serum sodium concentration in subgroups stratified according to whether hyponatremia was mild or marked at baseline.

Serum sodium concentrations over the course of the trial are shown in Figure 3. Within 8 hours after the first administration of tolvaptan, the serum sodium concentrations were significantly higher in the tolvaptan group than in the placebo group for both the total patient population and the subgroups stratified according to the degree of hyponatremia at baseline. This statistical superiority was maintained at all subsequent visits during the study period within all stratification subgroups. The serum sodium concentration approached the normal range more rapidly in the tolvaptan group than in the placebo group. During the follow-up week after discontinuation of the study drug, there was no statistical difference in the decline in serum sodium concentrations between the two groups.

In both SALT-1 and SALT-2, significantly more

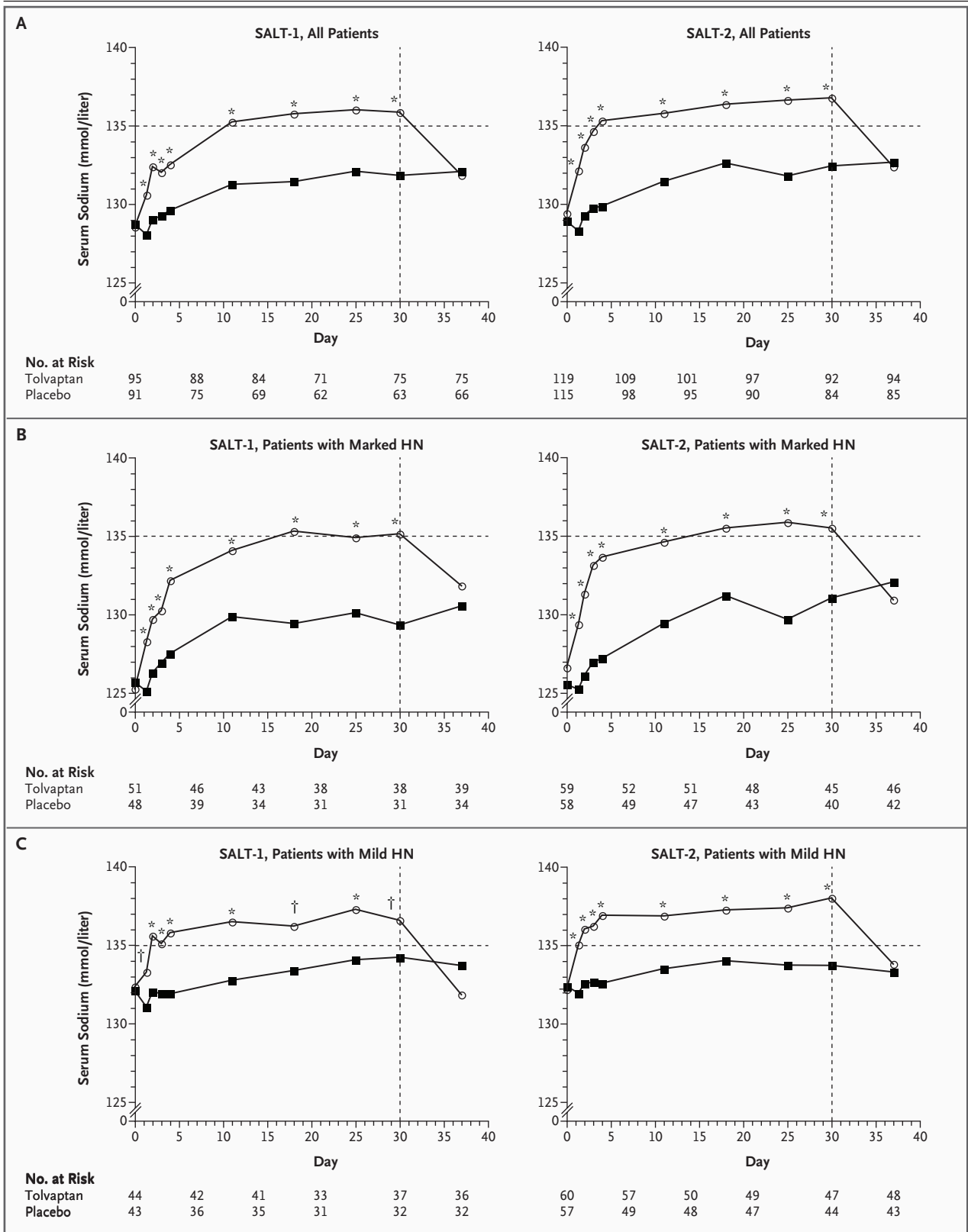


Table 3. Adverse Events.*				
Variable	SALT-1		SALT-2	
	Tolvaptan (N=100)	Placebo (N=101)	Tolvaptan (N=123)	Placebo (N=119)
<b>Total patient-days of drug exposure</b>	2669	2292	3228	3055
	<i>no. of patients (%)</i>			
<b>Adverse events occurring during study (all causes)</b>	88 (88)	83 (82)	91 (74)	85 (71)
Serious adverse events	31 (31)	35 (34)	33 (27)	30 (25)
Withdrawal because of adverse events	9 (9)	17 (17)	14 (11)	9 (8)
<b>Adverse events (potentially study-related)</b>	50 (50)	34 (34)	42 (34)	29 (24)
Serious adverse events	2 (2)†	6 (6)‡	6 (5)§	4 (3)¶
Withdrawal because of adverse events	4 (4)∥	7 (7)**	4 (3)††	1 (1)‡‡
	<b>Tolvaptan Group (N=223)</b>		<b>Placebo Group (N=220)</b>	
<b>Common adverse events — body system and MedDRA preferred term§§</b>				
Gastrointestinal disorders				
Ascites	14 (6)		13 (6)	
Constipation	16 (7)		4 (2)	
Diarrhea (not organ-specific)	12 (5)		12 (6)	
Dry mouth	28 (13)		9 (4)	
Nausea	18 (8)		13 (6)	
Vomiting (not organ-specific)	7 (3)		19 (9)	
General disorders				
Fatigue	12 (5)		11 (5)	
Peripheral edema	16 (7)		15 (7)	
Thirst	32 (14)		10 (5)	
Weakness	21 (9)		10 (5)	

patients assigned to tolvaptan had normal serum sodium concentrations on day 4 and on day 30 than did patients assigned to placebo (Table 2). Similarly, in both trials, significantly fewer patients in the tolvaptan group had marked hyponatremia on day 4 and on day 30 (Table 2).

The difference between urine production and fluid intake during the first day was significantly greater in the tolvaptan group than in the placebo group (Table 2). Among patients assigned to tolvaptan in the combined population of the two studies and in the subgroups with marked hyponatremia in both studies, the trend was toward requiring less fluid restriction ( $P=0.08$  for each study). Neither outpatient fluid intake nor urine osmolality was measured.

The effect of the study drugs on self-assessed health status was determined on day 30 in a pre-

specified combined analysis of scores for the Physical Component Summary and the Mental Component Summary of the SF-12 Health Survey (Fig. 1 of the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). Scores on the Physical Component Summary did not differ significantly between groups, but those for the Mental Component Summary improved in the tolvaptan group in the combined analysis ( $P=0.02$ ) and in SALT-1 ( $P=0.04$ ), although not in SALT-2 ( $P=0.14$ ). Scores for the Mental Component Summary improved significantly in the combined subgroup of patients with marked hyponatremia ( $P=0.04$ ).

#### ADVERSE EVENTS AND SAFETY

Adverse event profiles in the two study groups were similar for all intratrial and intertrial com-

Table 3. (Continued.)

Variable	Tolvaptan Group (N = 223)	Placebo Group (N = 220)
Infections and infestations		
Urinary tract infection (not organ-specific)	13 (6)	8 (4)
Metabolism and nutritional disorders		
Hyperglycemia (not organ-specific)	12 (5)	2 (1)
Hyperkalemia	12 (5)	11 (5)
Nervous system disorders		
Dizziness	15 (7)	11 (5)
Headache (not organ-specific)	15 (7)	15 (7)
Renal and urinary tract disorders		
Urinary frequency	15 (7)	6 (3)
Vascular disorders		
Hypotension (not organ-specific)	15 (7)	14 (6)

- \* Patients who received at least one dose of the study medication (tolvaptan or placebo) were included in the safety analysis. MedDRA denotes the *Medical Dictionary for Regulatory Activities*.
- † Serious adverse events in this group included dehydration with hypotension (1 patient) and increased serum creatinine concentrations.
- ‡ Serious adverse events in this group included acute renal failure (2 patients), rash (2 patients), cardiac failure (twice in 1 patient), and vomiting.
- § Serious adverse events in this group included dehydration with dizziness (1 patient), syncope, acute renal failure, ascites, increased serum sodium concentrations, *Escherichia coli* sepsis, and respiratory failure (1 patient).
- ¶ Serious adverse events in this group included hepatic encephalopathy, acute dyspnea and edema (1 patient), worsening anemia, increased serum creatinine concentrations with lower hemoglobin and hematocrit values, and dyspepsia (1 patient).
- || Serious adverse events in this group included rash (2 patients) and nocturia.
- \*\* Serious adverse events in this group included rash (2 patients), acute renal failure (2 patients), dysgeusia, decreased serum sodium concentrations, vomiting, and aggravated hyponatremia.
- †† Serious adverse events in this group included urinary frequency, exanthema, muscle weakness, and hypernatremia.
- ‡‡ The serious adverse event in this group was increased serum creatinine concentration.
- §§ Common adverse events are defined as events occurring in more than 5% of patients.

parisons (Table 3). The most common adverse events occurring during the study in the tolvaptan groups were thirst and dry mouth. Overall, there were 26 serious adverse events potentially related to the study treatment in SALT-1 and SALT-2. Eleven occurred in 8 patients assigned to tolvaptan (dehydration with hypotension, dehydration with dizziness, syncope, acute renal failure, ascites, increased serum sodium and creatinine concentrations and *Escherichia coli* sepsis with respiratory failure in 1 patient each), and 15 occurred in 10 patients assigned to placebo (acute renal failure in 2 patients, rash in 2 patients, aggravated cardiac failure [twice in 1 patient], and acute dyspnea with edema, worsened anemia with increased serum creatinine concentration and decreased hemoglobin and hematocrit, vomiting, hepatic encephalopathy, and dyspepsia in 1 patient each). Eight patients in the tolvaptan group withdrew because of adverse events that were potentially related to the study treatment (rash in two patients and dys-

geusia, nocturia, urinary frequency, exanthema, muscle weakness, and hypernatremia in one patient each), as well as eight patients in the placebo group (rash in two patients, acute renal failure in two patients, and increased serum creatinine concentration, decreased serum sodium concentration, aggravated hyponatremia, and vomiting in one patient each). The number of deaths in the two study groups was similar (14 deaths among 223 patients in the tolvaptan groups and 13 deaths among 220 patients in the placebo groups), and they occurred within the defined observation period.

In only 4 of the 223 patients in the tolvaptan group were desirable rates of sodium correction exceeded during the first 24 hours of the study (>0.5 mmol per liter per hour; maximum observed rate, 0.61 mmol per liter per hour). In only four patients (1.8%) was the predefined, potentially clinically important serum sodium concentration (>146 mmol per liter) exceeded.

## DISCUSSION

We examined the use of an orally active vasopressin  $V_2$ -receptor antagonist for 30 days to correct and maintain serum sodium concentrations in a population with hyponatremia from various causes (e.g., chronic heart failure, cirrhosis, and SIADH). Previous, short-term studies have shown that vasopressin  $V_2$ -antagonists correct hyponatremia in patients with chronic heart failure,<sup>11,19</sup> cirrhosis,<sup>20</sup> or SIADH.<sup>21</sup> A long-term study examined the effects of tolvaptan in patients with chronic heart failure,<sup>12</sup> but the primary end point was the change in body weight, not correction of hyponatremia.

The present study was conducted primarily in the outpatient setting, without mandated fluid restriction or a change in the patient's medication regimen, such as use of diuretics, to treat the patient's primary disease. Tolvaptan was superior to placebo with respect to several measures, including the change in the average daily AUC for serum sodium concentrations from baseline to day 4 and from baseline to day 30, the mean serum sodium concentration at each visit, the time to normalized serum sodium concentrations, the percentage of patients with serum sodium concentrations that were normal on day 4 and on day 30, and the categorical change in the serum sodium concentration from baseline to day 4 and from baseline to day 30. Tolvaptan was superior to placebo from the first observation point (8 hours) after administration of the first dose until the last treatment day (day 30) in patients with either mild or marked hyponatremia and among patients with hyponatremia from all major causes. During the 7-day follow-up period, serum sodium concentrations reverted to degrees of hyponatremia that were equivalent to those associated with the use of placebo, indicating that the aquaretic effect of tolvaptan (excretion of electrolyte-free water) was required to maintain normal sodium concentrations in patients with chronic hyponatremia.

Hyponatremia occurs in 15 to 20% of hospitalized patients and constitutes a common serum electrolyte abnormality.<sup>22</sup> Hyponatremia is reported to be an independent predictor of complications and death in patients with heart disease,<sup>23,24</sup> cirrhosis,<sup>6</sup> or neurologic disorders.<sup>8</sup> Recent clinical data suggest that hyponatremia not only is a marker of disease severity but also contributes to illness, even in patients with mild chronic hyponatremia, increasing the risk of falls

and cognitive dysfunction.<sup>9</sup> This factor is particularly relevant given the aging population in the United States and the high prevalence of hyponatremia reported among residents of nursing homes.<sup>25</sup> Current approaches to the treatment of hyponatremia are suboptimal, have variable efficacy, have slow responses, are poorly tolerated, and have important side effects.<sup>26,27</sup> Thus, recent limited regulatory approval of the vasopressin antagonists mozavaptan in Japan (oral OPC-31260, for paraneoplastic SIADH [Physuline, Otsuka Pharmaceutical]) and conivaptan in the United States (parenteral formulation, for hospitalized patients with euvolemic SIADH [Vaprisol, Astellas Pharma]) are promising for the management of hyponatremia.<sup>21,28</sup> Despite the approval of these drugs, it is not known whether treating hyponatremia alone will result in a long-term survival benefit.

In addition to assessing the efficacy of tolvaptan for increasing serum sodium concentrations, its effect on scores on the SF-12 Health Survey was examined. There was no significant effect on scores for the Physical Component Summary of the survey. However, there was a demonstrable effect on scores for the Mental Component Summary (for vitality, social functioning, emotionally limited accomplishment, calmness, and sadness). The size of the effect on scores for the Mental Component Summary would be considered clinically significant.<sup>18</sup>

These two month-long trials of efficacy and safety in the treatment of hyponatremia suggest that the vasopressin  $V_2$ -receptor antagonist tolvaptan, when added to standard therapy, was superior to placebo in raising and maintaining serum sodium concentrations in patients with euvolemic or hypervolemic hyponatremia of diverse origin. Tolvaptan had side effects that were consistent with its physiological activity. The dose could be increased gradually to achieve the desired rate and the desired degree of serum sodium correction in most patients.

Supported by the Otsuka Maryland Research Institute.

Dr. Schrier reports having served as a consultant to Otsuka, Astellas, Bayer, and Amgen. Dr. Gross reports having served as a consultant to Sanofi-Synthelabo, having received lecture fees from Astellas, and having received grant support from GlaxoSmithKline, Takeda, Amgen, Roche, and Fresenius. Dr. Gheorghide reports having served as a consultant to Otsuka, PDL, Sigma Tau, Medtronic, and GlaxoSmithKline and having received honoraria from Medtronic, Astra Zeneca, Scios, GlaxoSmithKline, Otsuka, PDL, Abbott, and Sigma Tau. Dr. Berl reports having served as a consultant to Bayer and Astellas and having received grant support from Otsuka. Dr. Verbalis reports having served as a consultant to Otsuka, Yamanouchi Pharma American, Astellas, Ferring Research, Bristol-Myers Squibb, and

Sanofi Aventis and having received grant support from Yamnouchi Pharma American and Astellas. Drs. Czerwiec and Orlandi are employees of Otsuka Maryland Research Institute. No other potential conflict of interest relevant to this article was reported.

We thank the patients involved in the SALT-1 and SALT-2 trials for their participation and contribution; the study investigators, subinvestigators, and nurses (including those at the National Center for Research Resources General Clinical Re-

search Center), the study monitors, and the data coordinators and their managers; C. Zimmer, J. Ouyang, S. Shoaf, A. Ozaki, and Y. Yamamura for their scientific advice; D. Norris and J. Darling for assistance in the preparation of the manuscript; and the members of the Safety Oversight Committee (SALT-1 and SALT-2): R. Schrier, chair; D.G. Bichet (Hôpital du Sacre-Coeur de Montreal, Montreal); M. Yarborough (University of Colorado, Denver); and J. Ouyang (Otsuka Maryland Research Institute, Rockville, MD).

#### APPENDIX

In addition to the authors, the following investigators participated in the SALT-1 and SALT-2 trials: **SALT-1:** Veterans Affairs Greater Los Angeles Health Care Center, Los Angeles — B. Levine; Heart Consultants, Omaha, NE — D. Chapman; Charlotte Heart Group Research Center, Port Charlotte, FL — R. Martinez; Arthur P. Noyes Research Foundation, Norristown, PA — R. Josiassen; Illinois Center for Clinical Research, Chicago — S. Castillo; Duke Medical Center, Durham, NC — M. Felker; University of Texas Medical Branch, Galveston — T. Ahuja; Aurora Denver Cardiology Association, Denver — N. Vijay; University of Iowa Hospital, Iowa City — R. Oren; University of Chicago, Chicago — A. Anderson; University of California, Los Angeles, Los Angeles — M. Nguyen; Tennessee Center for Clinical Trials, Tullahoma, TN — D. Gupta; University of Florida at Gainesville, Gainesville — L. Kennedy; Medical College of Georgia, Augusta — L. Mulloy; University of Pittsburgh Medical Center, Pittsburgh — M. Rabinovitz; Loma Linda University, Loma Linda, CA — T. Heywood; Bellevue Hospital Center, New York — N. Keller; Staten Island University Hospital, Staten Island, NY — M. Levy; University of California, San Francisco, Medical Center, San Francisco — N. Bass; University of Illinois Chicago, Chicago — M. Goldman; Virginia Commonwealth University, Richmond — A. Sanyal; Minneapolis Veterans Affairs Medical Center, Minneapolis — I. Anand; St. Vincent's Hospital, New York — M. Klapholz; Baptist Clinical Research Center, Memphis, TN — F. McGrew; Heart Group, Nashville — D. Pearce; University Hospital of Cleveland, Cleveland — B. Berger; Louisiana State University Health Sciences Center, Shreveport — L. Ghali; Diabetes Endocrinology Center of Western New York, Buffalo, NY — P. Dandona; Rhode Island Hospital, Providence, RI — L. Dworkin; University of Wisconsin, Madison — M. Hofmann; Washington Hospital Center, Washington, DC — J. Moore; Washington University, St. Louis — J. Crippin; University of North Carolina, Chapel Hill — K. Adams, Sr.; Ohio State University Medical Center, Columbus — W. Abraham; North Shore University Hospital, Great Neck, NY — A. Ashfaq; Los Angeles County—University of Southern California Medical Center, Los Angeles — V. Campese; Dialysis Clinic, Cincinnati — K. Kant; New England Medical Center, Boston — K. Fawaz; Mercury Street Medical, Butte, MT — J. Pullman; Jacksonville Center for Clinical Research, Jacksonville, FL — M. Koren; University of Maryland Medical Center, Baltimore — S. Gottlieb. **SALT-2:** Beth Israel Deaconess Medical Center, Boston — N. Afdhal; Fakultni Nemocnice Plzeň, Plzeň-Bory, Czech Republic — J. Filipovsky; Primary Care Cardiology Research, Ayer, MA — T. Hack; Research Center for Traumatology and Surgery, Brno, Czech Republic — P. Svoboda; University Camp, London Health Sciences Centre, London, ON, Canada — P. Marotta; University of Cincinnati, Cincinnati — L. Wagoner; Salus Clinical Research, Fallbrook, CA — F. Wood; Klinikum Hannover Nordstadt, Hanover, Germany — J. Hensen; Nzoz Polimedica, Lodz, Poland — R. Mordaka; Charles University Hospital, Prague, Czech Republic — L. Golan; Dorn Veterans Affairs Medical Center, Columbia, SC — S. Rosansky; Jacksonville Center for Clinical Research, Jacksonville, FL — M. Koren; Clinica Puerta de Hierro, Madrid — C. Barrios; University Hospital of Bulovka, Prague, Czech Republic — F. Padour; University of Miami, Miami — C. O'Brien; InterMountain Research Consultants, Thunder Bay, ON, Canada — S. Malik; Hôpital Erasme, Anderlecht, Belgium — G. Decaux; Hospital Liberec, Liberec, Czech Republic — M. Ryba; eStudy Site, San Diego, CA — W. O'Riordan; Veterans Affairs Medical Center, Dayton, OH — M. Saklayen; Hospital Clinic I Provincial, Barcelona — P. Gines; Lecznica Prosen, Warsaw, Poland — M. Zarebinski; Institut für Klinische Forschung, Dortmund, Germany — W. Sehnert; Pandy Kalman Hospital, Gyula, Hungary — M. Dudas; Niepubliczny Zakład Opieki Zdrowotnej-Grudziądzkie Centrum Pomocy, Grudzi-dz, Poland — P. Kubalski; Mt. Sinai Medical Center, New York — B. Sauter; Hospital Universitario de Bellvitge, Barcelona — M. Kozina; Oklahoma Heart Institute, Tulsa, OK — W. Leimbach; Diabetes and Glandular Disease Clinic, San Antonio, TX — M. Kipnes; Physician's Drug Research, Denver — R. Charles; Charles University Hospital, Prague, Czech Republic — V. Tesar; Hospital Virgen de la Victoria, Malaga, Spain — M. Jimenez; Regional Hospital Rzeszow No. 2, Rzeszow, Poland — M. Grzywa; University of Debrecen Medical and Health Science, Debrecen, Hungary — E. Nagy; Columbia Presbyterian Medical Center, New York — R. Brown; Veterans Affairs Medical Center, Washington, DC — S. Singh; Christiana Care Health Services, Newark, DE — M. Stillabower; Lakeridge Health Oshawa, Oshawa, ON, Canada — E. Dessouki; California Pacific Medical Center, San Francisco — N. Bzowej; Clinical Research Limited, Canton, OH — F. Whittier; Hospital Germans Trias I Pujol, Badalona, Spain — R. Planas; Elisabeth-Krankenhaus, Essen, Germany — B. Grosch; Klinikum Mannheim, Mannheim, Germany — M. Singer; Semmelweis University, Budapest, Hungary — K. Racz; Catholic University Sacro Cuore, Rome — M. Serio; Universita di Firenze, Florence, Italy — A. Pontecorvi; Universita degli studi di Perugia, Perugia, Italy — F. Santeusano; University Hospital, Ghent, Belgium — P. Peeters; Hospital Ramon y Cajal, Madrid — M. Garcia; University of Texas Health Science Center at San Antonio, San Antonio — J. Ayus; Santa Monica, CA — L. Glaser; East Bay Clinical Trial Center, Concord, CA — R. Kaplan; Southbay Pharma Research, Buena Park, CA — S. Lee; University of Massachusetts Memorial Medical Center, Worcester — L. Shick; John Buhler Research Centre, Winnipeg, MB, Canada — K. Kaita.

#### REFERENCES

1. Verbalis JG. The syndrome of inappropriate antidiuretic hormone secretion and other hypoosmolar disorders. In: Schrier RW, ed. *Diseases of the kidney and urinary tract*. 8th ed. Philadelphia: Lippincott Williams & Wilkins (in press).
2. Schrier RW. Body water homeostasis: clinical disorders of urinary dilution and concentration. *J Am Soc Nephrol* 2006; 17:1820-32.
3. Goldberg A, Hammerman H, Petcherski S, et al. Hyponatremia and long-term mortality in survivors of acute ST-elevation myocardial infarction. *Arch Intern Med* 2006;166:781-6.
4. De Luca L, Klein L, Udelson JE, et al. Hyponatremia in patients with heart failure. *Am J Cardiol* 2005;96:19L-23L.
5. Sica DA. Hyponatremia and heart failure — pathophysiology and implications. *Congest Heart Fail* 2005;11:274-7.
6. Wu CC, Yeung LK, Tsai WS, et al. Incidence and factors predictive of acute

- renal failure in patients with advanced liver cirrhosis. *Clin Nephrol* 2006;65:28-33.
7. Londono MC, Guevara M, Rimola A, et al. Hyponatremia impairs early post-transplantation outcome in patients with cirrhosis undergoing liver transplantation. *Gastroenterology* 2006;130:1135-43.
  8. Bhardwaj A. Neurological impact of vasopressin dysregulation and hyponatremia. *Ann Neurol* 2006;59:229-36.
  9. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 2006;119:71.e1-71.e8.
  10. Doggrel SA. Tolvaptan (Otsuka). *Curr Opin Investig Drugs* 2004;5:977-83.
  11. Gheorghide M, Niazi I, Ouyang J, et al. Vasopressin V<sub>2</sub> receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation* 2003;107:2690-6.
  12. Gheorghide M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA* 2004;291:1963-71.
  13. Costello-Boerrigter LC, Smith WB, Boerrigter G, et al. Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. *Am J Physiol Renal Physiol* 2006;290:F273-F278.
  14. Gheorghide M, Gottlieb SS, Udelson JE, et al. Vasopressin v(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. *Am J Cardiol* 2006;97:1064-7.
  15. Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. *Stat Med* 1990;9:811-8.
  16. Fleiss JL. Design and analysis of clinical experiments. New York: Wiley-Interscience, 1999:150-61.
  17. Ware JE, Kosinski M, Keller SD. SF-12: how to score the SF-12 physical and mental health summary scales. 2nd ed. Boston: Health Institute, New England Medical Center, 1995.
  18. Guyatt GH, Osoba D, Wu AW, Wywich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 2002;77:371-83.
  19. Abraham WT, Shamshirsaz AA, McFann K, Oren RM, Schrier RW. Aquaretic effect of lixivaptan, an oral non-peptide, selective V<sub>2</sub> receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic failure patients. *J Am Coll Cardiol* 2006;47:1615-21.
  20. Gerbes AL, Gulberg V, Gines P, et al. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. *Gastroenterology* 2003;124:933-9.
  21. Saito T, Ishikawa S, Abe K, et al. Acute aquaresis by the nonpeptide arginine vasopressin (AVP) antagonist OPC-31260 improves hyponatremia in patients with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *J Clin Endocrinol Metab* 1997;82:1054-7.
  22. Janicic N, Verbalis JG. Evaluation and management of hypo-osmolality in hospitalized patients. *Endocrinol Metab Clin North Am* 2003;32:459-81.
  23. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation* 1986;73:257-67.
  24. Klein L, O'Connor CM, Leimberger JD, et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation* 2005;111:2454-60.
  25. Miller M, Morley JE, Rubenstein LZ. Hyponatremia in a nursing home population. *J Am Geriatr Soc* 1995;43:1410-3.
  26. Hantman D, Rossier B, Zohlman R, Schrier RW. Rapid correction of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone: an alternative treatment to hypertonic saline. *Ann Intern Med* 1973;78:870-5.
  27. Miller PD, Linas SL, Schrier RW. Plasma demeclocycline concentrations and nephrotoxicity: correlation in hyponatremic cirrhotic patients. *JAMA* 1980;243:2513-5.
  28. Udelson JE, Smith WB, Hendrix GH, et al. Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation* 2001;104:2417-23.

Copyright © 2006 Massachusetts Medical Society.