Tolvaptan, a Selective Oral Vasopressin V2-Receptor Antagonist, for Hyponatremia

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*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.

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 V2-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 euvoletic 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 euvoletic or hypervolemic hyponatremia, tolvaptan, an oral vasopressin V2-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].)
HYponatREMIA, THE MOST COMMON electrolyte derangement occurring in hospitalized patients,\textsuperscript{1,2} is usually classified as hypovolemic, euvolemic, or hypervolemic. The secretion of arginine vasopressin appears to be of central importance in the decline of serum sodium concentrations in all these conditions.\textsuperscript{1,2} Hyponatremia is reported to be associated with increased morbidity and mortality among patients with heart, liver, or neurologic disease.\textsuperscript{9,8} 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.\textsuperscript{9} These deficits may be reversed with the correction of the hyponatremia.

Tolvaptan, a novel, orally active, selective, nonpeptide antagonist that blocks arginine vasopressin from binding to $V_2$ receptors of the distal nephron, induces the excretion of electrolyte-free water without changing the total level of electrolyte excretion.\textsuperscript{10} 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.\textsuperscript{11-14}

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 euvolemic hyponatremia of diverse causes. These trials assessed the outpatient use of a vasopressin $V_2$-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 euvolemic 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 $50\%$ of 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 $\mu$mol 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.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tolvaptan (N = 102)</th>
<th>Placebo (N = 103)</th>
<th>Tolvaptan (N = 123)</th>
<th>Placebo (N = 120)</th>
<th>SALT-1</th>
<th>SALT-2</th>
<th>SALT-1 and SALT-2</th>
</tr>
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<tbody>
<tr>
<td>Age — yr</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>60±14</td>
<td>60±13</td>
<td>62±15</td>
<td>63±14</td>
<td>0.94</td>
<td>0.66</td>
<td>0.72</td>
</tr>
<tr>
<td>Range</td>
<td>18–86</td>
<td>35–90</td>
<td>27–92</td>
<td>28–100</td>
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<tr>
<td>Female sex — no. (%)</td>
<td>50 (49)</td>
<td>41 (40)</td>
<td>48 (39)</td>
<td>47 (39)</td>
<td>0.21</td>
<td>1.00</td>
<td>0.39</td>
</tr>
<tr>
<td>Race — no. (%)</td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>71 (70)</td>
<td>76 (74)</td>
<td>118 (96)</td>
<td>109 (91)</td>
<td>0.26</td>
<td>0.47</td>
<td>0.56</td>
</tr>
<tr>
<td>Black</td>
<td>13 (13)</td>
<td>17 (17)</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hispanic</td>
<td>13 (13)</td>
<td>9 (9)</td>
<td>3 (2)</td>
<td>6 (5)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td>5 (5)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean body weight — kg</td>
<td>78±23</td>
<td>75±22</td>
<td>73±19</td>
<td>75±21</td>
<td>0.44</td>
<td>0.39</td>
<td>0.96</td>
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<tr>
<td>Mean height — cm</td>
<td>167±10</td>
<td>170±11</td>
<td>168±11</td>
<td>167±9</td>
<td>0.02</td>
<td>0.42</td>
<td>0.14</td>
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<tr>
<td>Fluid status — no. (%)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Euvolemic</td>
<td>61 (60)</td>
<td>67 (65)</td>
<td>63 (51)</td>
<td>60 (50)</td>
<td>0.38</td>
<td>0.80</td>
<td>0.70</td>
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<tr>
<td>Hypervolemic</td>
<td>41 (40)</td>
<td>34 (33)</td>
<td>58 (47)</td>
<td>60 (50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of hyponatremia — no. (%)</td>
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<td></td>
<td></td>
<td></td>
<td>0.63</td>
<td>0.96</td>
<td>0.70</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>35 (34)</td>
<td>33 (32)</td>
<td>36 (29)</td>
<td>34 (28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>25 (25)</td>
<td>21 (20)</td>
<td>38 (31)</td>
<td>36 (30)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SIADH and other</td>
<td>42 (41)</td>
<td>49 (48)</td>
<td>49 (40)</td>
<td>50 (42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean serum sodium — mmol/liter</td>
<td>128.7±4.5</td>
<td>128.8±4.1</td>
<td>129.5±3.5</td>
<td>129.1±4.5</td>
<td>0.85</td>
<td>0.37</td>
<td>0.60</td>
</tr>
<tr>
<td>Degree of hyponatremia — no. (%)</td>
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<td></td>
<td></td>
<td></td>
<td>0.89</td>
<td>1.00</td>
<td>0.93</td>
</tr>
<tr>
<td>Mild</td>
<td>49 (48)</td>
<td>51 (50)</td>
<td>64 (52)</td>
<td>62 (52)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean serum sodium — mmol/liter</td>
<td>132.4±1.5</td>
<td>132.1±1.3</td>
<td>132.3±1.6</td>
<td>132.4±1.3</td>
<td>0.37</td>
<td>0.56</td>
<td>0.88</td>
</tr>
<tr>
<td>Marked</td>
<td>53 (52)</td>
<td>52 (50)</td>
<td>59 (48)</td>
<td>58 (48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean serum sodium — mmol/liter</td>
<td>125.4±3.5</td>
<td>125.5±3.2</td>
<td>126.6±2.5</td>
<td>125.5±3.8</td>
<td>0.84</td>
<td>0.07</td>
<td>0.26</td>
</tr>
<tr>
<td>Mean score on SF-12 Health Survey†</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Physical Component Summary</td>
<td>33.4±10.7</td>
<td>33.9±10.5</td>
<td>33.0±10.6</td>
<td>33.1±10.8</td>
<td>0.78</td>
<td>0.95</td>
<td>0.81</td>
</tr>
<tr>
<td>Mental Component Summary</td>
<td>42.4±11.6</td>
<td>44.7±11.9</td>
<td>44.3±11.9</td>
<td>44.9±11.6</td>
<td>0.15</td>
<td>0.89</td>
<td>0.30</td>
</tr>
</tbody>
</table>

* 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 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
A SALT-1

244 Patients underwent screening
205 Met inclusion criteria

102 Assigned to tolvaptan
15 mg daily
Increased to 30 mg or 60 mg,
if necessary
100 Included in safety analysis
95 Included in efficacy analysis
79 Completed 30-day study period
and 7-day follow-up
23 Withdrew

103 Assigned to placebo
15 mg daily
Increased to 30 mg or 60 mg,
if necessary
101 Included in safety analysis
89 Included in efficacy analysis
65 Completed 30-day study period
and 7-day follow-up
38 Withdrew

B SALT-2

304 Patients underwent screening
243 Met inclusion criteria

123 Assigned to tolvaptan
15 mg daily
Increased to 30 mg or 60 mg,
if necessary
123 Included in safety analysis
118 Included in efficacy analysis
92 Completed 30-day study period
and 7-day follow-up
31 Withdrew

120 Assigned to placebo
15 mg daily
Increased to 30 mg or 60 mg,
if necessary
119 Included in safety analysis
114 Included in efficacy analysis
89 Completed 30-day study period
and 7-day follow-up
31 Withdrew
The significance level of 0.025) to detect a mean (±SD) between-group difference of 1.99±2.7 mmol of sodium per liter in the change from baseline to day 4 and of 3.00±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.15

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tolvaptan (N = 102)</th>
<th>Placebo (N = 103)</th>
<th>P Value</th>
<th>Tolvaptan (N = 123)</th>
<th>Placebo (N = 120)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point: change in average AUC for serum sodium — mmol/liter</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All patients</td>
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<td></td>
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</tr>
<tr>
<td>Day 4</td>
<td>3.62±2.68</td>
<td>0.25±2.08</td>
<td>&lt;0.001</td>
<td>4.33±2.87</td>
<td>0.42±2.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 30</td>
<td>6.22±4.10</td>
<td>1.66±3.59</td>
<td>&lt;0.001</td>
<td>6.20±3.92</td>
<td>1.84±3.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild hyponatremia</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>2.52±1.95</td>
<td>-0.32±2.27</td>
<td>&lt;0.001</td>
<td>3.59±2.34</td>
<td>0.18±2.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 30</td>
<td>3.87±3.01</td>
<td>0.68±2.78</td>
<td>&lt;0.001</td>
<td>4.68±2.91</td>
<td>0.94±2.89</td>
<td>&lt;0.001</td>
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<tr>
<td>Marked hyponatremia</td>
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<tr>
<td>Day 4</td>
<td>4.56±2.88</td>
<td>0.76±1.77</td>
<td>&lt;0.001</td>
<td>5.06±3.16</td>
<td>0.7±2.99</td>
<td>&lt;0.001</td>
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<td>Day 30</td>
<td>8.24±3.84</td>
<td>2.54±4.01</td>
<td>&lt;0.001</td>
<td>7.60±4.31</td>
<td>2.72±4.41</td>
<td>&lt;0.001</td>
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<tr>
<td>Absolute change in serum sodium — mmol/liter</td>
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<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>128.5±4.5</td>
<td>128.7±4.1</td>
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<td>129.3±3.5</td>
<td>128.9±4.5</td>
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</tr>
<tr>
<td>Day 4</td>
<td>133.9±4.8</td>
<td>129.7±4.9</td>
<td>&lt;0.001</td>
<td>135.3±3.6</td>
<td>129.6±5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of patients</td>
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<td>88</td>
<td></td>
<td>115</td>
<td>112</td>
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</tr>
<tr>
<td>Day 30</td>
<td>135.7±5.0</td>
<td>131.0±6.2</td>
<td>&lt;0.001</td>
<td>135.9±5.9</td>
<td>131.5±5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of patients</td>
<td>95</td>
<td>89</td>
<td></td>
<td>114</td>
<td>98</td>
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<tr>
<td>Categorical change in hyponatremia — no./total no. (%)</td>
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<td></td>
<td></td>
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<td>Baseline</td>
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</tr>
<tr>
<td>Mild hyponatremia</td>
<td>49/102 (48%)</td>
<td>51/103 (50%)</td>
<td></td>
<td>64/123 (52%)</td>
<td>62/120 (52%)</td>
<td></td>
</tr>
<tr>
<td>Marked hyponatremia</td>
<td>53/102 (52%)</td>
<td>52/103 (50%)</td>
<td></td>
<td>59/123 (48%)</td>
<td>58/120 (48%)</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>38/95 (40%)</td>
<td>12/89 (13%)</td>
<td>&lt;0.001</td>
<td>65/118 (55%)</td>
<td>12/114 (11%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marked hyponatremia</td>
<td>12/95 (13%)</td>
<td>44/89 (49%)</td>
<td>&lt;0.001</td>
<td>12/118 (10%)</td>
<td>46/114 (40%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 30</td>
<td>50/95 (53%)</td>
<td>22/89 (25%)</td>
<td>&lt;0.001</td>
<td>69/118 (58%)</td>
<td>28/114 (25%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marked hyponatremia</td>
<td>7/95 (7%)</td>
<td>31/89 (35%)</td>
<td>&lt;0.001</td>
<td>18/118 (15%)</td>
<td>37/114 (32%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fluid status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output on day 1 — ml</td>
<td>3218±1646</td>
<td>2076±1534</td>
<td>&lt;0.001</td>
<td>3185±2543</td>
<td>1914±1366</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluid intake on day 1 — ml</td>
<td>1825±1057</td>
<td>1492±945</td>
<td>0.04</td>
<td>2129±2110</td>
<td>1705±1396</td>
<td>0.09</td>
</tr>
<tr>
<td>Difference on day 1 — ml</td>
<td>-1533±1429</td>
<td>-636±1275</td>
<td>&lt;0.001</td>
<td>-1059±1877</td>
<td>-185±870</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients requiring fluid restriction — %</td>
<td>9.3</td>
<td>17.5</td>
<td>0.08</td>
<td>9.2</td>
<td>16.8</td>
<td>0.08</td>
</tr>
</tbody>
</table>

* 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.\textsuperscript{16}

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.\textsuperscript{17} 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.\textsuperscript{18} 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 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
A

SALT-1, All Patients

SALT-2, All Patients

No. at Risk

Tolvaptan | Placebo
---|---
95 | 91
88 | 75
84 | 69
71 | 62
75 | 63
75 | 66
119 | 115
115 | 110
109 | 95
98 | 90
101 | 84
97 | 85
94 | 84
92 | 94

B

SALT-1, Patients with Marked HN

SALT-2, Patients with Marked HN

No. at Risk

Tolvaptan | Placebo
---|---
51 | 48
46 | 39
43 | 34
38 | 31
38 | 31
39 | 32
59 | 58
52 | 49
51 | 47
48 | 43
45 | 40
46 | 42

C

SALT-1, Patients with Mild HN

SALT-2, Patients with Mild HN

No. at Risk

Tolvaptan | Placebo
---|---
44 | 43
42 | 36
41 | 35
33 | 31
37 | 32
36 | 32
60 | 57
57 | 49
50 | 48
49 | 47
47 | 44
48 | 43

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The New England Journal of Medicine

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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 prespecified 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). 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. Adverse Events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SALT-1</th>
<th>SALT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patient-days of drug exposure</td>
<td>2669</td>
<td>2292</td>
</tr>
<tr>
<td>Adverse events occurring during study (all causes)</td>
<td>88 (88)</td>
<td>83 (82)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>31 (31)</td>
<td>35 (34)</td>
</tr>
<tr>
<td>Withdrawal because of adverse events</td>
<td>9 (9)</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Adverse events (potentially study-related)</td>
<td>50 (50)</td>
<td>34 (34)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>2 (2)†</td>
<td>6 (6)‡</td>
</tr>
<tr>
<td>Withdrawal because of adverse events</td>
<td>4 (4)¶</td>
<td>7 (7)∥</td>
</tr>
</tbody>
</table>

**Common adverse events — body system and MedDRA preferred term**

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>14 (6)</td>
<td>13 (6)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>16 (7)</td>
<td>4 (2)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea (not organ-specific)</td>
<td>12 (5)</td>
<td>12 (6)</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>28 (13)</td>
<td>9 (4)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (8)</td>
<td>13 (6)</td>
<td></td>
</tr>
<tr>
<td>Vomiting (not organ-specific)</td>
<td>7 (3)</td>
<td>19 (9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>12 (5)</td>
<td>11 (5)</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>16 (7)</td>
<td>15 (7)</td>
<td></td>
</tr>
<tr>
<td>Thirst</td>
<td>32 (14)</td>
<td>10 (5)</td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>21 (9)</td>
<td>10 (5)</td>
<td></td>
</tr>
</tbody>
</table>
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 concentrations, *Escherichia coli* sepsis, and respiratory failure in 1 patient). Six occurred in 6 patients assigned to placebo (acute renal failure in 2 patients, rash in 2 patients, cardiac failure (twice in 1 patient), and vomiting. Four patients in the tolvaptan group withdrew because of adverse events that were potentially related to the study treatment (rash in two patients and dysgeusia, nocturia, urinary frequency, exanthema, muscle weakness, and hypernatremia). 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.

### Table 3. (Continued.)

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

* 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.
‡‡ 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.
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,\textsuperscript{11,19} cirrhosis,\textsuperscript{20} or SIADH.\textsuperscript{21} A long-term study examined the effects of tolvaptan in patients with chronic heart failure,\textsuperscript{12} 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.\textsuperscript{22} Hyponatremia is reported to be an independent predictor of complications and death in patients with heart disease,\textsuperscript{23,24} cirrhosis,\textsuperscript{6} or neurologic disorders.\textsuperscript{8} 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.\textsuperscript{9} 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.\textsuperscript{35} Current approaches to the treatment of hyponatremia are suboptimal, have variable efficacy, have slow responses, are poorly tolerated, and have important side effects.\textsuperscript{26,27} Thus, recent limited regulatory approval of the vasopressin antagonists mavacaptan 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.\textsuperscript{21,28}

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.\textsuperscript{18}

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. Gheorghiade reports having served as a consultant to Otsuka, PDL, Sigma Tau, Medtronic, and GlaxoSmithKline and having received honoraria from Medtronic, AstraZeneca, 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 Otsuka.
APPENDIX

In addition to the authors, the following investigators participated in the SALT-1 and SALT-2 trials: SALT-1: Veterans Affairs 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. Abuja; 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. Mullow; University of Pittsburgh Medical Center, Pittsburgh — M. Rabinovitz; Loma Linda University, Loma Linda, CA — T. Heywood; Bellevue Hospital Center, New York — N. Kello; 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. Hoffmann; Washington Hospital Center, Washington, DC — J. Moore; Washington University, St. Louis — J. Grippin; 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–UCLA Medical Center, Los Angeles — V. Campese; Dyalisys Clinic, Cincinnati — K. Kant; New England Medical Center, Boston — K. Fawaz; Mercy 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. Adhikali; Fakultki Nemocnici Pheki, Pheki-Bory, Czech Republic — J. Filipovsky; Primary Care Cardiology Research, Ayr, MA — T. Hack; Research Center for Traumatology and Surgery, Bero, Czech Republic — P. Svoboda; University Camp, London Health Sciences Centre, London, ON, Canada — P. Maretta; University of Cincinnati, Cincinnati — L. Wagoner; Salus Clinical Research, Fallbrook, CA — F. Wood; Klinikum Hannover Nordstadt, Hanover, Germany — J. Hensen; Nax Polimiedica, Lodz, Poland — R. Mordaka; Charles University Hospital, Prague — L. Golán; Dorn Veterans Affairs Medical Research Center, Columbia, SC — S. Kosansky; Jacksonville Center for Clinical Research, Jacksonville, FL — M. Koren; Clínica Puerta de Hierro, Madrid — C. Barrios; University Hospital of Bulevka, Prague, Czech Republic — P. Padour; University of Miami, Miami — C. O’Brien; InterMountain Research Consultants, Thunder Bay, ON, Canada — S. Mall; Hôpital Erasme, Anderlecht, Belgium — G. Decaux; Hospital Libre, Liberec, Czech Republic — M. Ryba;ести Pédio, San Antonio, TX — 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; Nipueczszy Zaklad Opieki Zdrowotnej Grudziadzkie Centrum Pomoc, Grudziadz, Poland — P. Kubański; 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. Khan; 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. Grywa; University of Debrecen Medical and Health Sciences, Debrecen, Hungary — E. Nagy; Columbia Presbyterian Medical Center, New York — R. Brown; Veterans Affairs Affairs Medical Center, Washington, DC — S. Singh; Christiana Care Health Sciences, Newark, DE — M. Stillabower; Lakerrige Health Oshawa, Oshawa, Canada — E. Dessouki; California Pacific Medical Center, San Francisco — N. Bzowje; Clinical Research Limited, Canton, OH — F. Whitlfer; Hospital Germans Trias I Pujol, Badalona, Spain — R. Planas; Elisabeth-Krankenhaus, Essen, Germany — B. Groesch; Klinikurn Mannheim, Mannheim, Germany — M. Singer; Semmelweis University, Budapest, Hungary — K. Race; Catholic University Sacro Cuore, Rome — M. Serio; Universita di Firenze, Florence, Italy — A. Poncevici; Università degli Studi di Perugia, Perugia, Italy — F. Santeusanio; 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.

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