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Oral lixivaptan effectively increases serum sodium concentrations in outpatients with euvolemic hyponatremia

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Hyponatremia is the most common electrolyte disorder in clinical practice. Its incidence increases with age and it is associated with increased morbidity and mortality. Recently, the vaptans, antagonists of the arginine vasopressin pathway, have shown promise for safe treatment of hyponatremia. Here we evaluated the efficacy, safety, and tolerability of oral lixivaptan, a selective vasopressin V2-receptor antagonist, for treatment of nonhospitalized individuals with euvolemic hyponatremia (sodium less than 135 mmol/l) in a multicenter, randomized, double-blind, placebo-controlled, phase III study. About half of the 206 patients were elderly in a chronic care setting. Of these patients, 52 were given a placebo and 154 were given 25–100 mg per day lixivaptan, titrated based on the daily serum sodium measurements. Compared with placebo (0.8 mmol/l), the serum sodium concentration significantly increased by 3.2 mmol/l from baseline to day 7 (primary efficacy endpoint) with lixivaptan treatment. A significantly greater proportion of patients that received lixivaptan achieved normal serum sodium (39.4%) by day 7 relative to placebo (12.2%). Overall, lixivaptan was considered safe and well-tolerated. Thus, oral lixivaptan can be safely initiated in the outpatient setting and effectively increases serum sodium concentrations in outpatients with euvolemic hyponatremia.

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[10]Please see Appendix 1 for the list of researchers.

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Hyponatremia is the most common laboratory abnormality, occurring in up to 30% of hospitalized patients and in up to 21% of ambulatory patients.[1] Hyponatremia also is more frequently observed in elderly patients—an incidence of 18–22% has been reported in chronic care facilities, with 53% of patients having one or more episodes of hyponatremia over a 12-month period.[2,3] As hyponatremia is associated with multiple etiologies and underlying disease states, diagnosis and treatment can be complex.[4] Mild hyponatremia is often characterized as 'asymptomatic'. However, this concept has been more recently challenged, and 'asymptomatic' hyponatremia appears to be a misnomer.[5] Patients with chronic hyponatremia have been shown to exhibit cognitive impairment, gait disturbances, and an increased incidence of falls and fractures.[6,7] In addition, hyponatremia is associated with increased risk of death, even when considered mild.[8–10] Researchers have often considered hyponatremia a marker of the severity of underlying conditions.[11] However, at least one study has demonstrated significantly lower rates of death when hyponatremia was managed compared with when it was uncontrolled, indicating that treatment may be beneficial.[12]

Hyponatremia can occur in the hypovolemic, euvolemic, and hypervolemic states. In the euvolemic state, hyponatremia often results from the syndrome of inappropriate antidiuretic hormone (SIADH).[10,13] SIADH occurs when arginine vasopressin is released despite serum hypo-osmolarity. This condition can be caused by the presence of tumors, central nervous system disease, pulmonary disease, or the use of certain drugs that act directly or indirectly on the arginine vasopressin pathway.[13]

Treatment of chronic hyponatremia is challenging. Fluid restriction and pharmacological agents, such as demeclocycline, lithium, and urea, have been used.

More recently, the vaptans, a class of drugs that antagonize the arginine vasopressin pathway, have shown promise for

safe treatment of hyponatremia.[14] Two vaptans, conivaptan, a mixed V_1/V_2-receptor antagonist, and tolvaptan, an oral, V_2-selective antagonist, are approved in the United States for the treatment of hyponatremia. Conivaptan is an intravenously administered agent that has demonstrated efficacy in hospitalized subjects with hyponatremia.[15–17] Tolvaptan is orally administered and has demonstrated efficacy in increasing serum sodium concentrations in phase III studies of subjects with euvolemic or hypervolemic hyponatremia.[18] All the studies conducted with these two agents excluded symptomatic subjects and those with serum sodium concentrations <120 mmol/l in association with neurological impairment, and they required initiation of therapy in hospitalized subjects.

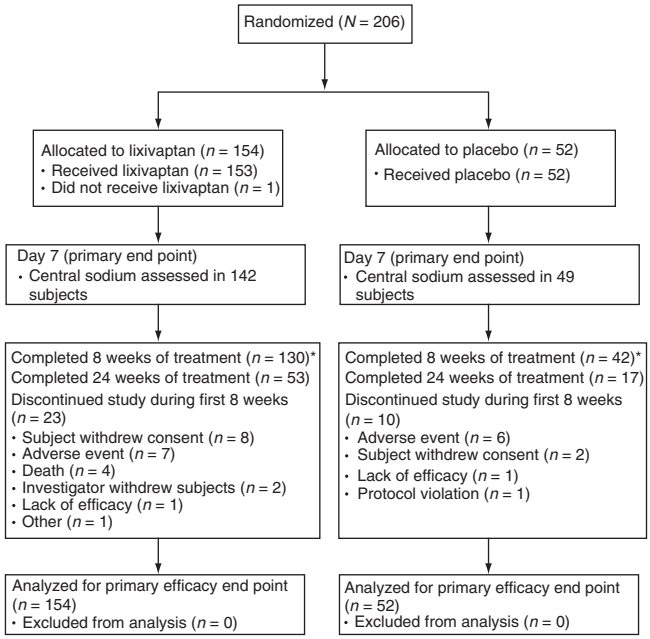
Lixivaptan is a selective vasopressin V_2-receptor antagonist that blocks arginine vasopressin-mediated aquaporin synthesis and membrane insertion.[19] In phase II trials, lixivaptan has increased water excretion, increased serum osmolarity, and increased serum sodium concentration in subjects with heart failure, cirrhosis, or SIADH.[20–22] In this multicenter, double-blind, placebo-controlled study (HARMONY study), the efficacy, safety, and tolerability of oral lixivaptan were evaluated for the treatment of chronic euvolemic hyponatremia in outpatient settings that included long-term care facilities and nursing homes. Subjects with symptoms attributable to hyponatremia were included in the study.

RESULTS

Subjects

A total of 206 randomized subjects (154 to lixivaptan and 52 to placebo) were included in the intent-to-treat (ITT) population. Subject disposition is shown in Figure 1. All subjects received at least one dose of medication except for one in the lixivaptan group. Twenty-one percent of the randomized population (44 subjects) was enrolled from long-term care facilities/nursing homes, with the remainder of the population being enrolled from a variety of settings, including outpatient clinics, doctors' offices, and hospitals. Overall, approximately 83% of the subjects were enrolled in a non-hospital setting. In all, 130 (84.4%) subjects receiving lixivaptan and 42 (80.8%) subjects receiving placebo completed 8 weeks of treatment. The most common reasons for discontinuation during the first 8 weeks were subject withdrawal of consent (5.2% of subjects receiving lixivaptan and 3.8% of subjects receiving placebo), adverse events (4.5 and 11.5%, respectively), and death (2.6 and 0%, respectively). As sufficient efficacy data had been gathered, the study was ended once the last subject had completed a minimum of 8 weeks of treatment. A total of 34.4% of subjects receiving lixivaptan and 32.7% of subjects receiving placebo completed the entire 24-week period of treatment.

Baseline characteristics of the treatment groups were generally well balanced (Table 1). A greater percentage of white subjects were enrolled in the lixivaptan group compared with the placebo group (81.8 vs. 67.3%). Approximately half of the subjects were aged 65 years or older. The most common concomitant prescription medications used by subjects were omeprazole (31.8% of subjects in the lixivaptan group and 30.8% of subjects in the placebo group), simvastatin (18.2 and 26.9%, respectively), and amlodipine (24.0 and 17.3%, respectively). Baseline symptoms associated with hyponatremia (reported in $\geqslant 10\%$ of subjects) included fatigue (40.7%), mental slowing (27.0%), headache (19.1%), confusion (16.7%), and irritability (16.2%). The underlying cause of SIADH was not collected prospectively in the study. At baseline, 4 patients (2.0%) had lung cancer, 1 (0.5%) had HIV infection, 3 (1.5%) had a history of subarachnoid hemorrhage, 1 (0.5%) had the Guillain–Barre syndrome, 1 (0.5%) had sarcoidosis, 48 (23.4%) had underlying hypothyroidism, and 95 (46.3%) were receiving drugs known to induce hyponatremia, including carbamazepine (7.8%), phenothiazines (2.0%), selective serotonin re-uptake inhibitors (21.5%), thiazides (7.5%), and monoamine oxidase inhibitors (10.5%).



*Blinded study treatment was discontinued by sponsor once the last randomized subject completed week 8. All subjects were to enter a 30-day follow-up period following cessation of treatment.

Figure 1 | Subject disposition.

Efficacy

Significantly greater serum sodium increases from baseline were observed at day 7 in subjects receiving lixivaptan compared with those receiving placebo (least-squared mean with s.e. of 3.2. (0.5) vs. 0.8 (0.6) mmol/l; $P<0.001$). Sensitivity analyses also showed significant differences between lixivaptan and placebo for the primary efficacy variable ($P<0.001$ for all). A sensitivity assessment using a mixed model repeated measures analysis also demonstrated a 2.6 ± 0.3 mmol/l difference (least-squared mean $\pm$ s.e.) between lixivaptan and placebo in changes in central sodium

Table 1 | Subject demographics and baseline characteristics

Demographic parameter	Lixivaptan (*n*=154)	Placebo (*n*=52)
Age, years		
Mean (s.d.)	66.6 (14.1)	62.7 (13.6)
Range	24–98	29–90
Subjects aged ⩾65 years, *n* (%)	87 (56.5)	24 (46.2)
Male subjects, *n* (%)	73 (47.4)	27 (51.9)
Race, n (%)		
White	126 (81.8)	35 (67.3)
Asian	18 (11.7)	8 (15.4)
Black	7 (4.5)	8 (15.4)
Other[a]	3 (1.9)	1 (1.9)
Hispanic ethnicity	19 (12.3)	8 (15.4)
Region, n (%)		
North America	122 (79.2)	37 (71.2)
India	17 (11.0)	7 (13.5)
Europe/Israel	8 (5.2)	4 (7.7)
South America	7 (4.5)	4 (7.7)
Body mass index, kg/m²	n=*149*	n=*49*
Mean (s.d.)	26.4 (5.7)	26.9 (6.3)
Range	16.0–41.7	17.1–41.9
Local serum sodium, mmol/l (s.d.)[b]		
Mean (s.d.)	129.7 (4.4)	129.9 (4.3)
Range	113.0–134.0	111.8–134.5
Central serum sodium, mmol/l (s.d.)[c]		
Mean (s.d.)	131.5 (4.9)	131.6 (5.2)
Range	113–144	115–142
N (%) of subjects with history of:[d]		
Hyponatremia	148 (96.1)	49 (94.2)
Hyperlipidemia	43 (27.9)	17 (32.7)
Hypertension	126 (81.8)	42 (80.8)
Gastroesophageal reflux disease	82 (53.2)	17 (32.7)
Constipation	63 (40.9)	16 (30.8)
Osteoarthritis	51 (33.1)	13 (25.0)
Depression	61 (39.6)	20 (38.5)
Anxiety	46 (29.9)	11 (21.2)
Insomnia	35 (22.7)	11 (21.2)
Chronic obstructive pulmonary disease	35 (22.7)	13 (25.0)
Drug hypersensitivity	43 (27.9)	14 (26.9)
Anemia	50 (32.5)	11 (21.2)
Hypothyroidism	41 (26.6)	7 (13.5)

[a]Including native American, Alaskan native, native Hawaiian, Pacific Islander.
[b]Measured at local laboratory.
[c]Measured at central laboratory.
[d]Condition reported by ⩾20% of subjects in any group.

from baseline to day 7 ($P<0.001$). Additional sensitivity analyses showed that the mean increase in serum sodium concentrations from baseline to day 7 was significantly greater ($P<0.05$) in the lixivaptan group compared with placebo regardless of sex or age (⩾65 years or <65 years). Numerically greater increases in serum sodium levels occurred in patients with more severe hyponatremia at baseline.

Within 8 h of lixivaptan administration, serum sodium concentrations were significantly higher in the lixivaptan group compared with the placebo group (Figure 2). Lixivaptan remained numerically superior to placebo at all

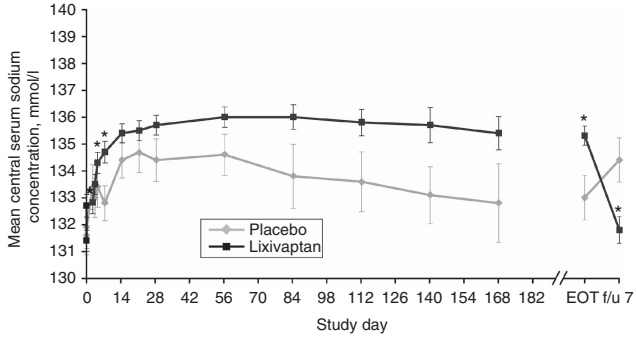


Figure 2 | Mean central serum sodium concentration over time (ITT population). *$P<0.05$ vs. placebo for mean change from baseline. Error bars represent s.e. EOT, end of treatment (overall summary value of all EOT values, regardless of when actual EOT occurred); f/u 7, follow-up at day 7; ITT, intent-to-treat.

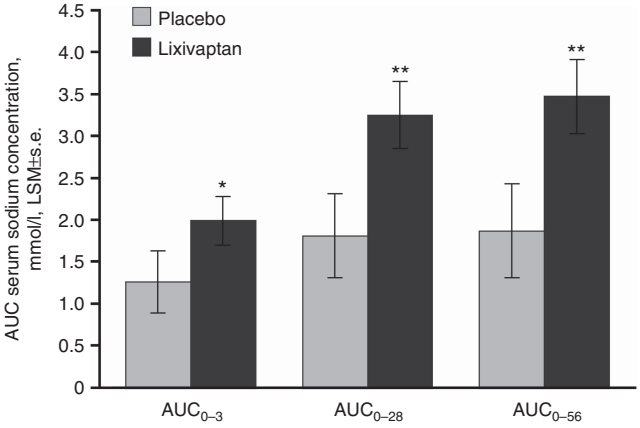


Figure 3 | Normalized daily average AUC for serum sodium concentration through days 3, 28, and 56 (ITT population). *$P<0.05$, **$P<0.01$ by ANCOVA. ANCOVA, analysis of covariance; AUC, area under the concentration curve; ITT, intent-to-treat; LSM, least-squared mean.

subsequent study visits. The mean increase in central serum sodium from baseline to the end of treatment (4.0 vs. 1.4 mmol/l) was significantly different between groups ($P=0.002$) for the ITT population using observed values (OV). Importantly, after discontinuation of the study drug, serum sodium concentrations in the lixivaptan group declined over the ensuing week to values similar to baseline.

The least-squared mean (s.e.) daily normalized change in area under the concentration curve (AUC) for central serum sodium levels from baseline to day 3 (AUC_{0-3}), baseline to day 28 (AUC_{0-28}), and baseline to day 56 (AUC_{0-56}) was significantly higher for subjects receiving lixivaptan than for subjects receiving placebo ($P=0.042$, $P=0.004$, and $P=0.004$, respectively; Figure 3). Sensitivity analyses also found significantly greater AUC_{0-28} for subjects receiving lixivaptan compared with those receiving placebo ($P\leqslant0.005$ for all).

By day 7, 39.4% of subjects receiving lixivaptan and 12.2% of subjects receiving placebo had achieved normalized serum sodium concentrations ($P<0.001$). At the end of treatment,

66.7% of subjects who received lixivaptan achieved normalized serum sodium compared with 48.1% of subjects who received placebo ($P=0.017$). The results of the local laboratory analysis demonstrated that lixivaptan subjects achieved normal serum sodium concentration more rapidly than placebo (logrank $P=0.019$). However, time to normalization was not significantly different between treatment groups based on central laboratory serum sodium results (logrank $P=0.051$; Figure 4). Significantly greater percentages of subjects in the lixivaptan group compared with the placebo group shifted from moderate (>125 and <130 mmol/l) or severe ($\leqslant 125$ mmol/l) hyponatremia at baseline to normal serum sodium ($\geqslant 135$ mmol/l) at day 7 (31.4 ($n/n=16/51$) vs. 15% (3/20) ; $P=0.001$) and at the end of treatment (40.0 (22/55) vs. 27.3% (6/22); $P=0.014$).

At baseline, 16.9% of subjects in the lixivaptan group and 11.5% in the placebo group were on fluid restriction (Figure 5). Numerically lower percentages of subjects on fluid restriction were reported in the lixivaptan-treated group compared with the placebo group from as early as day 3 until the end of treatment, with statistically significant differences observed at weeks 8, 12, 16, and 20.

No significant differences were observed between treatment groups in the percentage of subjects with worsening hyponatremia at any point in the study, although there was a trend favoring fewer subjects experiencing worsening hyponatremia in the lixivaptan group (57.1% in lixivaptan group vs. 71.2% in placebo group; $P=0.056$). The time required to complete the Trail Making Test, part B (TMT-B) was significantly improved from baseline to day 28 in subjects receiving lixivaptan ($P<0.001$ for baseline vs. day 28 value) but not in those receiving placebo ($P=0.051$); however, no statistically significant differences in TMT-B were observed between treatment groups. No significant differences were observed between treatment groups in Medical Outcomes Survey 6-Item Cognitive Function Scale (MOS-6) scores at day 28 and week 24; however, significantly greater mean (s.d.) increases from baseline for MOS-6 scores were observed in the lixivaptan group compared with the placebo group at week 8 (7.23 (17.7) vs. −0.62 (13.0); $P=0.021$) and week 12 (6.21 (18.4) vs. −1.66 (14.6); $P=0.047$).

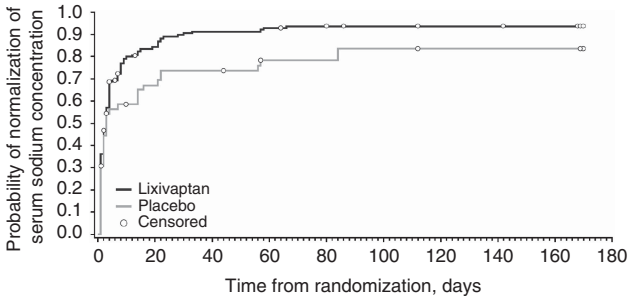


Figure 4 | Time to normalization of serum sodium concentration.

Safety

Adverse event profiles in the two treatment groups were similar for all intratrial comparisons. At least one treatment-emergent adverse event was experienced by 80.4% of subjects who received lixivaptan and 84.6% of subjects who received placebo (Table 2), and the majority of these were mild or moderate in severity. Adverse events reported by $\geqslant 5\%$ subjects in the lixivaptan group compared with the placebo group were urinary tract infection, polyuria, and upper respiratory tract infection (Table 2). A total of 11.1% subjects on lixivaptan and 17.3% on placebo had $\geqslant 1$ adverse events leading to study discontinuation. Adverse events that led to discontinuation in >1 subject in either study group included septic shock ($n=2$ (1.3%) with lixivaptan), increased γ-glutamyltransferase ($n=2$ (1.3%) with lixivaptan), and flatulence ($n=2$ (1.3%) with lixivaptan). Serious treatment-emergent adverse events were reported in 18.3% of subjects receiving lixivaptan and 26.9% of subjects receiving placebo (Table 2). Only one serious adverse event, a case of hyponatremia in the placebo group, was considered by the investigator to be possibly related to the study drug.

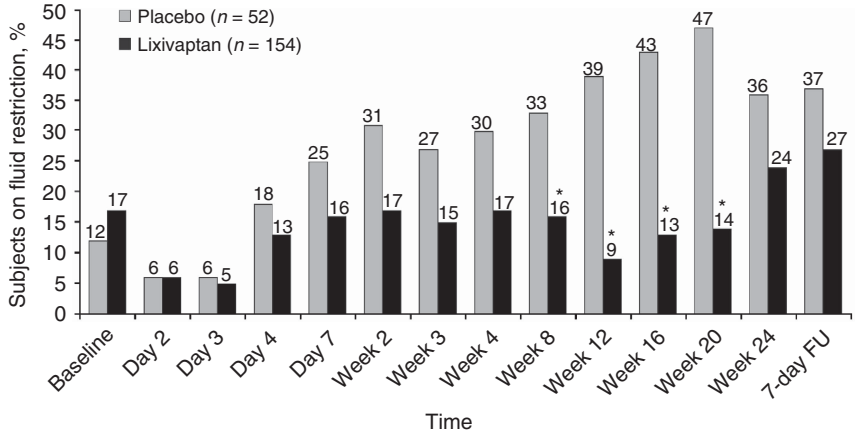


Figure 5 | Percent of subjects on fluid restriction by study day (ITT population, OV). *$P<0.05$ vs. placebo. FU, follow-up; ITT, intent-to-treat; OV, observed value.

Table 2 | Treatment-emergent adverse events in ⩾5% of subjects, serious adverse events in ⩾2 subjects in either treatment group, and serious adverse events leading to death

Treatment-emergent adverse event, *n* (%)	Lixivaptan (*n*=153)	Placebo (*n*=52)
Any adverse event	123 (80)	44 (85)
Urinary tract infection	19 (12)	2 (4)
Headache	12 (8)	7 (14)
Nausea	11 (7)	7 (14)
Diarrhea	10 (7)	4 (8)
Bronchitis	10 (7)	4 (8)
Peripheral edema	10 (7)	4 (8)
Dizziness	10 (7)	2 (4)
Cough	8 (5)	4 (8)
Polyuria	10 (7)	0
Hypertension	9 (6)	1 (2)
Fall	8 (5)	2 (4)
Upper respiratory tract infection	9 (6)	0
Anemia	6 (4)	4 (8)
Vomiting	5 (3)	3 (6)
Hyponatremia	4 (3)	4 (8)
Dehydration	0	3 (6)
Any serious adverse events	26 (17)	14 (27)
Urinary tract infection	4 (3)	2 (4)
Pneumonia	2 (1)	1 (2)
Hyponatremia	3 (2)	2 (4)
Acute cardiac failure	2 (1)	2 (4)
Septic shock	1 (0.7)	0
Grand mal convulsion	0	2 (4)
Serious adverse events leading to death	6 (4)	1 (2)
Acute cardiac failure	0	1 (2)
Myocardial ischemia	1 (0.7)	0
Pneumonia	1 (0.7)	0
Septic shock	1 (0.7)	0
Metastatic small cell lung cancer	1 (0.7)	0
Cerebrovascular accident	1 (0.7)	0
Suicide	1 (0.7)	0
Death from unknown cause[a]	1 (0.7)	0

[a]This subject died 8 days after the last recorded dose of study drug and is not counted in the overall sum of seven deaths but was still considered a treatment-related adverse event by the investigator.

Seven deaths occurred during the study (six in the lixivaptan group (3.9%) and one in the placebo group (1.9%)), and one additional subject in the lixivaptan group died 8 days after the last recorded dose of the study drug (Table 2). None of the serious adverse events that led to death were considered by investigators to be related to the study drug.

At the end of study treatment, more subjects in the placebo group than in the lixivaptan group had serum sodium concentrations <125 mmol/l (9.6 vs. 3.3%). On the basis of central sodium measurements, during the entire duration of exposure, two (1.3%) lixivaptan subjects and four (7.7%) placebo subjects had serum sodium concentrations >145 mmol/l, the predefined level for potential clinical importance. Only three subjects in the lixivaptan group and one subject in the placebo group exceeded desirable sodium correction rates in the first 24 h. No subject experienced an increase in sodium concentration of >18 mmol/l within a 48- or 72-h period. No subjects had osmotic demyelination syndrome (ODS) or had symptoms consistent with ODS. No subject experienced a sodium level of >155 mmol/l at any time during the study. No clinically significant changes were observed in either treatment group for vital signs, 12-lead electrocardiogram, weight, hematology, biochemistry, or urinalysis parameters during the study.

DISCUSSION

In this international, multicenter, double-blind, placebo-controlled, phase III study, once-daily oral lixivaptan safely and effectively corrected serum sodium concentrations in outpatients with euvolemic hyponatremia, with significantly greater effect relative to placebo. This effect was maintained over the treatment period, despite increased use of fluid restriction in the placebo group. A greater percentage of subjects who received lixivaptan (39.4%) achieved normal serum sodium concentrations after 7 days of treatment compared with placebo (12.2%). In addition, compared with placebo, a greater percentage of subjects receiving lixivaptan had shifted from moderate or severe hyponatremia at baseline to normal serum sodium after 7 days of treatment (31.4 vs. 15.0%, respectively) and at the end of treatment (40.0 vs. 27.3%, respectively). Discontinuation of lixivaptan at the conclusion of the treatment period resulted in a decrease in serum sodium concentrations back toward baseline values, confirming the chronic nature of the euvolemic hyponatremia and the therapeutic efficacy of lixivaptan. In analyses of subgroups, lixivaptan effectively corrected serum sodium concentrations regardless of sex, age, or baseline serum sodium concentration. The ability to safely treat elderly subjects is particularly important, as rates of this condition increase with age,[1] and hyponatremic sequelae such as gait disturbances are particularly harmful in the elderly.[6] The study, however, was not adequately powered to evaluate changes in mental state, falls, and other clinical end points. Given the importance of such assessments, this should be the target of future trials.

In our study, most adverse events observed with lixivaptan were mild or moderate and did not lead to disruption of study medication. As cellular adaptation to chronic hyponatremia may occur, patients are at risk for ODS if serum sodium levels rise too rapidly.[23] Current recommendations call for sodium increases of no more than 12 mmol/l in 24 h or 18 mmol/l in 48 h.[13] Because of the potential risk of ODS, it was felt important to assess the safety of initiating lixivaptan in the outpatient setting. In this study, no cases of ODS were observed, confirming the safety of chronic lixivaptan treatment in this patient population. Only three subjects (2.0%) in the lixivaptan group and one subject (1.9%) in the placebo group exceeded the predefined criteria for rapid rise in serum sodium during the titration phase, and these subjects did not experience any clinically significant adverse events. The initial lixivaptan dose (25 mg) allowed for a safe implementation of treatment in an outpatient setting. Higher doses were used for treatment initiation in lixivaptan trials requiring hospitalization (50 mg). The required assessment of rapidity of change in

serum sodium concentrations 8 h after initiation of therapy could have been conducted using point-of-care devices, which would facilitate implementation in settings such as outpatient clinics and chronic care facilities.

Although an overall favorable safety profile was observed, a numerically greater incidence of urinary and upper respiratory infections was reported in lixivaptan-treated patients in this study. The finding was unexpected and not easily explainable from a mechanistic point of view. Given the limited sample size and the number of events, its clinical relevance is uncertain. More definitive information should become available after pooling of all lixivaptan clinical trials.

Another randomized, double-blind, placebo-controlled, phase III study of lixivaptan in hospitalized patients with euvolemic hyponatremia (LIBRA) was recently completed.[24] Compared with subjects in the LIBRA study, the subjects in the current study had less severe hyponatremia (baseline serum sodium level of <135 mmol/l in HARMONY vs. <130 mmol/l in LIBRA). Subjects in the current study received a lower starting dose of lixivaptan compared with those in the LIBRA study to allow for steady increases in serum sodium concentrations in the outpatient setting. When taken together, the LIBRA and HARMONY trials support the safety, tolerability, and efficacy of lixivaptan for the treatment of mild, moderate, and severe hyponatremia when initiated in either the inpatient or outpatient settings. Limitations of our study include inability by design to assess the relationship between improvement of serum sodium and reduction in symptoms of hyponatremia. In addition, the study was not powered to assess outcomes such as mortality and neurological clinical end points.

Among the class of vasopressin V_2-receptor antagonists, tolvaptan was evaluated in two trials: Studies of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 (SALT1 and SALT2).[18] These studies enrolled hypervolemic (congestive heart failure and liver cirrhosis) and euvolemic (SIADH) hyponatremic subjects for a 30-day double-blind, placebo-controlled study period (SALT1: $n=108$; SALT2: $n=243$). The studies achieved their primary co-endpoints of significantly increased change over placebo in daily sodium AUC from baseline to day 4 and from baseline to day 30. Although direct comparison between HARMONY and SALT1/SALT2 cannot be made, three key differences in study design warrant discussion: SALT1 and SALT2 excluded subjects with symptoms of hyponatremia, whereas HARMONY allowed subjects with symptoms (other than severe symptoms such as seizures and coma); the SALT studies excluded enrollment of subjects with a baseline serum sodium <120 mmol/l accompanied with neurological manifestations, whereas HARMONY allowed subjects with more severe hyponatremia; and finally, SALT1/SALT2 required hospitalization of subjects for a minimum of 3 days after randomization, whereas HARMONY recruited and treated subjects in outpatient settings.

In conclusion, once-daily oral lixivaptan given in an outpatient setting increased serum sodium concentrations in subjects with euvolemic hyponatremia in a gradual, well-tolerated manner, separating significantly from placebo by day 3. An open-label extension of this study is ongoing to further define long-term efficacy and safety.

MATERIALS AND METHODS

Subjects

Subjects aged $\geqslant 18$ years with a diagnosis of chronic euvolemic hyponatremia (serum sodium <135 mmol/l within 24 h of study entry) were eligible to participate in the study. Patients with symptoms associated with hyponatremia were allowed to participate, provided that their symptoms did not require immediate intervention (e.g., seizures or coma). Patients with acute or transient hyponatremia, pseudohyponatremia, hypovolemic hyponatremia, drug-induced hyponatremia, hyponatremia due to hypothyroidism or adrenal insufficiency, hypertonic hyponatremia, or hypokalemia were excluded. Other key exclusion criteria were as follows: treatment for hyponatremia with demeclocycline, lithium carbonate, urea, or any other vasopressin antagonist within 7 days of participation, supine systolic arterial blood pressure $\leqslant 90$ mm Hg, serum creatinine >3.0 mg/dl, uncontrolled diabetes, liver disease, psychogenic polydipsia, urinary tract obstruction, or myocardial ischemia, myocardial infarction, or cerebrovascular accident within 30 days of enrollment, neurological impairments such as dementia, and conditions causing an inability to respond to thirst. Women who were pregnant, planning to become pregnant, or breastfeeding were also excluded. The HARMONY study protocol was approved by the Institutional Review Board or Independent Ethics Committee at the participating sites and was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All subjects provided written informed consent to participate.

Study design

The HARMONY study (ClinicalTrials.gov. identifier: NCT00876798) was a multicenter randomized, double-blind, placebo-controlled, phase III study conducted at 61 sites enrolling in eight countries (Belgium, Czech Republic, Israel, India, Italy, Mexico, Peru, and the United States). Eligible subjects were randomized 3:1 to 25 mg lixivaptan or matched placebo given in the morning as an oral capsule with or without food. Following administration of the first dose, serum sodium was retested at 8 h; subjects with changes of <8 mmol/l were scheduled to return for assessments at 24 and 48 h following treatment initiation for possible uptitration. Subjects with an initial change in serum sodium concentration $\geqslant 8$ mmol/l were expected to be kept under observation and follow-up measurements to be conducted at 12, 24, 48, and 72 h post dose or until sodium levels had stabilized.

The daily lixivaptan dose was 25, 50, or 100 mg, titrated based on serum sodium levels. Titration was based on the following criteria: subjects whose serum sodium changed by <5 mmol/l in a 24-h period were eligible to be titrated to the next highest dose level if their sodium levels were <135 mmol/l, and subjects with serum sodium changes $\geqslant 5$ mmol/l were maintained at the current dose or had their dose decreased to maintain serum sodium concentrations of 135–145 mmol/l; treatment was downtitrated or stopped in subjects whose serum sodium concentrations changed >12 mmol/l within 24 h or >18 mmol/l within 48 h, those whose serum sodium was >145 mmol/l, or who experienced symptoms of over-rapid sodium correction. Investigators were encouraged, when clinically appropriate, not to institute fluid restriction during the first 72 h of study drug administration to allow for assessment of treatment

effect on serum sodium concentrations; fluid restriction could be implemented, maintained, or adjusted at the investigator's discretion during the entire treatment period. A 24-week treatment period was planned. This was followed by a 7-day post-treatment visit and a telephone follow-up 30 days after subject discontinuation or at the end of the study.

Study assessments

The primary study end point was the change from baseline in serum sodium concentration at day 7. Secondary end points were as follows: the change in the normalized AUC of serum sodium from baseline to week 4, the percentage of subjects with normalized sodium at day 7 (135–145 mmol/l inclusive), the percentage of subjects who required fluid restriction after baseline, the number of subjects with worsening hyponatremia (reduction in serum sodium concentration of $\geqslant 3$ mmol/l from the preceding measurement and serum sodium < 135 mmol/l), and the change from baseline to week 4 in time required to complete the TMT-B. MOS-6 scores at week 4 and week 24 were an exploratory end point.

Serum sodium was assessed on site without delay by local laboratories or with a point-of-care device to direct the titration of study medication as noted above. However, a central laboratory was used to measure serum sodium concentrations for the assessment of efficacy variables, unless otherwise noted. In addition to serum sodium, standard hematology, biochemistry, and urinalysis were performed at each visit. Visits occurred at baseline, on days 1, 2, 3, and 4, within 2 days of day 7, and weeks 2, 3, 4, 8, 12, 16, 20, and 24. The TMT-B, a performance-based measure of motor speed and visual attention, was administered at baseline and weeks 4 and 24 (or early termination visit). The MOS-6, a six-item cognitive function survey, was administered at weeks 4, 8, 12, 16, 20, and 24 (or at early termination visit).

Physical examination, 12-lead electrocardiogram, weight, and vital signs were recorded during study visits at screening and at regular intervals. Adverse events were recorded at each visit and were treated in the inpatient setting where necessary until resolution. Subjects could report adverse events to their investigators throughout the study. Fluid restriction, use of diuretics, and daily fluid requirements were also recorded.

Statistical analyses

A sample size of 200 (150 in lixivaptan group and 50 in the placebo group) was determined to allow for 80% power to detect a mean difference of 3.7 mmol/l between treatment groups using a two-sided *t*-test at the 0.05 significance level. These values were based on those used in the SALT 1 and SALT 2 trials,[18] which reported data for day 4 and day 11. However, no information was available for day 7, the time point for the HARMONY trial primary end point. Hence, for sample size calculations for the HARMONY trial, day 4 values from the SALT studies were used in place of day 7. The value of 3.7 mmol/l for the differential change from baseline is also consistent with Schrier *et al.*,[18] allowing for inclusion of subjects with mild hyponatremia.

Efficacy analyses were performed for the ITT population, which included all randomized subjects. Secondary efficacy analyses were also performed for a modified ITT population, which consisted of all randomized subjects who had received at least one dose of the study drug, had a baseline serum sodium measurement, and had at least one recorded postbaseline serum sodium measurement while on the study drug.

The primary efficacy variable was analyzed using analysis of covariance, with treatment and pooled site as factors and baseline serum sodium as the covariate. The primary analysis was based on the change from baseline at day 7 in central sodium concentrations from the ITT population using last observation carried forward/next observation carried back (LOCF/NOCB) as the imputation method for missing observations. Subjects in the modified ITT and ITT subgroups, based on age, sex, race, and baseline local serum sodium levels, were analyzed for the primary efficacy variable. Sensitivity analyses were also performed using central laboratory or local sodium measurements, including baseline observation carried forward, OV, and mixed effects model repeated measures analyses of the ITT population and OV analysis of the modified ITT population.

The ITT population was analyzed using LOCF/NOCB for all secondary end points and central sodium values were used where applicable. The secondary end points of time-normalized AUC change from baseline and time to complete the TMT-B were analyzed using analysis of covariance as for the primary variable. As sensitivity analyses, AUC change from baseline was also analyzed for the ITT population using OV and LOCF/NOCB for central and local sodium, and for the modified ITT population using OV for central sodium and LOCF/NOCB for central and local sodium. The other secondary end points (subjects with normalized serum sodium concentration, subjects requiring fluid restriction, and subjects with worsening hyponatremia) were analyzed using the Cochran–Mantel–Haenszel test controlling for pooled site.

DISCLOSURE

WTA has received consulting fees from Cardiokine. GD has received consulting fees from Wyeth (Pfizer), Sanofi, Cardiokine, Otsuka Pharmaceuticals, and Yamanouchi. RCJ has served as a Principal Investigator on vaptan-related phase III clinical trials sponsored by Astellas, Otsuka, and Cardiokine. He has also served as a consultant for Otsuka and Cardiokine. NK has served on the speakers' bureau for Otsuka. DGB has received consulting fees from Cardiokine, receives grants from Otsuka, and is a paid consultant for Otsuka Canada. CO is an employee of Cardiokine. MM received consulting fees from Otsuka. HPT and YY have no relevant relationships to disclose.

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Appendix 1

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