Cardiokine Biopharma, LLC

Advisory Committee Briefing Document

FDA Cardio-Renal Drugs Advisory Committee Meeting
Scheduled for 13 September 2012

Lixivaptan for the Treatment of Symptomatic Euvolemic Hyponatremia Associated with Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and Symptomatic Hypervolemic Hyponatremia Associated with Heart Failure

Lixivaptan Capsules, 25 mg, 50 mg
NDA 203,009

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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LIST OF ABBREVIATIONS

Abbreviation	Term
ACE	angiotensin converting enzyme
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-168}	area under the curve from zero to 168 hours
AUC_{0-24}	area under the concentration-time curve from zero to 24 hours
AUC_{∞}	area under the curve from zero to infinity
AUC_{t}	area under the curve from zero to the last observable concentration at time t
AUC_{tau}	area under the concentration-time curve from zero to the end of the dosing interval
AVP	arginine vasopressin
BID	twice daily
CI	confidence interval
CL/F	clearance
CL_{H20}	free-water clearance
C_{max}	maximum plasma drug concentration
conc	concentration
CYP	cytochrome P450
DAOH	days alive and out of the hospital
DDI	drug-drug interaction
ECG	electrocardiogram
HCTZ	hydrochlorothiazide
HF	heart failure
ITT	intent to treat
INR	international normalized ratio
IV	intravenous(ly)
LOCF	last observation carried forward
LS	least squares
max	maximum
mEq	milliequivalents
mEq/L	milliequivalents per liter
min	minimum
MOS-6	Medical Outcomes Survey 6-item Cognitive Function Scale
nAUC	normalized area under the curve
$nAUC_{0-28}$	normalized area under the curve from baseline to Day 28
$nAUC_{0-30}$	normalized area under the curve from baseline to Day 30

Abbreviation	Term
$nAUC_{0-60}$	normalized area under the curve from baseline to Day 60
NDA	New Drug Application
NOCB	next observation carried back
ODS	osmotic demyelination syndrome
OV	observed values
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per protocol
QD	once daily
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SD	standard deviation
SE	standard error
SIADH	syndrome of inappropriate antidiuretic hormone (secretion)
SOC	system organ class
S_{osm}	serum osmolality
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration
TMT-B	Trail-Making Test, part B
U_{flow}	urine flow
ULN	upper limit of normal
U_{osm}	urine osmolality
USP	United States Pharmacopeia
U_{vol}	urine volume

1. EXECUTIVE SUMMARY

Lixivaptan is an important therapeutic option to address the medical need for patients with euvolemic and hypervolemic hyponatremia, providing the following:

- Controlled increase in serum sodium concentrations through dose titration
- Lower need for fluid restriction when compared to placebo
- Initiation or re-initiation of lixivaptan in broader controlled medical settings
- Low risk of overly rapid correction of serum sodium concentrations at rates comparable to placebo
- Absence of osmotic demyelination syndrome
- Low frequency of adverse events

This briefing document was prepared by Cardiokine Biopharma, LLC (Sponsor) for pending lixivaptan NDA 203,009. The document is intended to provide background information for Cardio-Renal Drugs Advisory Committee Meeting to be convened on 13 September 2012, during which the Sponsor will make presentations to discuss:

- The effect on serum sodium concentrations produced by lixivaptan
- The safety of lixivaptan

Burden of Hyponatremia

Hyponatremia is an electrolyte disturbance that results from an imbalance of total body water and total body sodium. The condition is diagnosed when serum sodium concentration falls below the lower limit of the normal range (<135 mEq/L). Hyponatremia is the most commonly observed laboratory abnormality, occurring in up to 30% of hospitalized patients and up to 21% of ambulatory patients (Schrier 2006, Hawkins 2003). The incidence of hyponatremia increases with age and is more frequently observed in elderly patients (Upadhyay et al, 2006). Incidences of 18% to 22% have been reported in chronic care facilities, with 53% of patients having one or more episodes of hyponatremia over a 12-month period (Miller et al, 1995, Chen et al, 2006). Clinical evidence highlights that the occurrence of symptoms associated with mild hyponatremia may have an impact on patient symptoms and outcomes (Bissram et al, 2007).

Hyponatremia may be either an acute or chronic medical condition. Acute hyponatremia is often a life-threatening emergency and is usually managed by infusion of hypertonic saline. Chronic hyponatremia is commonly associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH, a euvolemic state) and heart failure (a hypervolemic state). Euvolemic and hypervolemic hyponatremia are the targets for treatment with vasopressin V_2-receptor antagonists. Due to their mechanism of action, use of these agents would be contraindicated in patients with hypovolemic hyponatremia.

Current Therapy for Hyponatremia

Prior to the availability of specific drugs that block the action of arginine vasopressin, correction of mild-to-moderate hyponatremia by medical means most often included fluid restriction and/or non-FDA approved treatments such as demeclocycline or isotonic saline infusion. These treatment modalities have been associated with efficacy, safety or compliance limitations.

Beginning in 2005, with the FDA approval of intravenous conivaptan (Vaprisol®, Astellas®), arginine vasopressin receptor antagonists (vaptans) have been available as treatment options for hyponatremia that increase serum sodium concentration through sodium-sparing diuresis (aquaresis). In 2009, the FDA approved tolvaptan (SAMSCA®, Otsuka®) as the first oral vaptan for treatment of both euvolemic and hypervolemic hyponatremia.

Unmet Medical Need

Despite the current availability of two drugs in the vaptan class, unmet medical needs remain. Conivaptan and tolvaptan are only approved for initiation or re-initiation in a hospital, in part due to the potential risk for overly rapid correction of serum sodium concentration which may lead to osmotic demyelination syndrome (ODS). This has resulted in important access issues for patients diagnosed in outpatient settings whose conditions would not justify hospital admission solely for initiation of vaptan therapy. Patients in medical settings other than hospitals, e.g. long-term care facilities, where the prevalence of chronic hyponatremia is high, are unlikely to be admitted to a hospital for initiation of therapy. If an oral agent were approved based upon clinical support that hyponatremia could be safely and effectively corrected in both the inpatient and outpatient settings, a significant gap in current hyponatremia therapy would be addressed.

Development Program for Lixivaptan

Lixivaptan is an orally-active, selective vasopressin 2 receptor antagonist. The recommended indication is for the treatment of symptomatic hypervolemic and euvolemic hyponatremia associated with heart failure and SIADH, respectively.

Carefully conducted Phase 1 and 2 evaluations identified the doses of lixivaptan that would effectively increase serum sodium concentrations and minimize the risk of overly rapid correction. Lixivaptan should be initiated and re-initiated only in settings where sodium concentration can be monitored. The recommended dosing regimen for lixivaptan is:

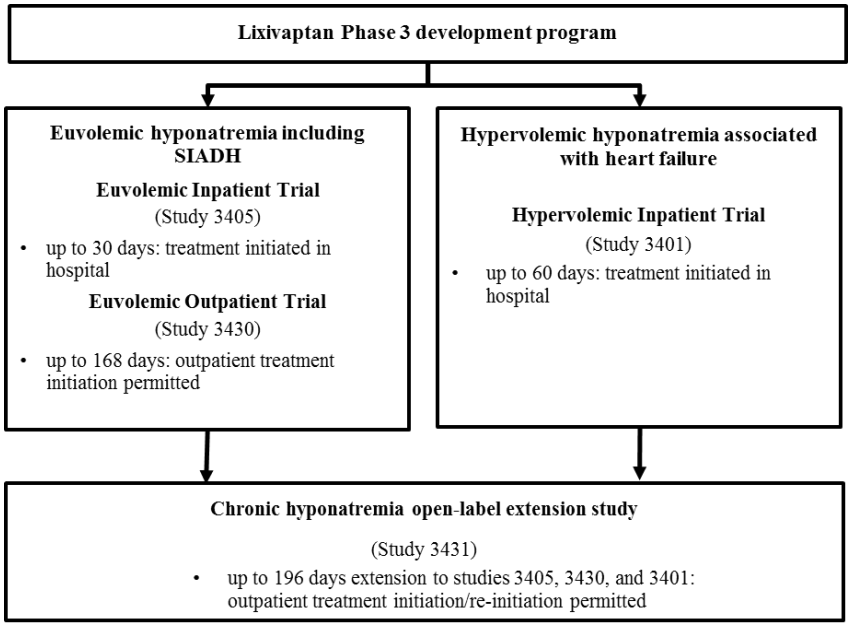
> Hospitalized patients: The starting dose for hospitalized patients with hyponatremia is 50 mg once daily without regard to meals. The dose may be doubled every 24 hours depending on individual patient response to a maximum of 100 mg once daily (total daily dose 100 mg) in SIADH patients and to a maximum of 100 mg BID (total daily dose 200 mg) in heart failure patients, as needed, to achieve the desired sodium concentration.

Outpatients: The starting dose for outpatients with hyponatremia is 25 mg once daily without regard to meals. The dose may be doubled every 24 hours depending on individual patient response to a maximum of 100 mg once daily (total daily dose 100 mg) in SIADH patients and to a maximum of 100 mg twice daily (total daily dose 200 mg) in heart failure patients, as needed, to achieve the desired sodium concentration.

In the Phase 3 studies, lixivaptan was initiated and re-initiated safely in both the hospital and outpatient settings with significant positive treatment effects on hyponatremia.

Consistent with a positive recommendation from the Cardiovascular and Renal Drugs Advisory Committee on June 25, 2008 following a review of the tolvaptan development program, the FDA accepted a significant increase in serum sodium concentration in patients with hyponatremia as the basis for approval of oral tolvaptan. Therefore, the precedent for approval was established for the vaptan class and the primary endpoint was confirmed at the August 2008 Type C meeting between the FDA and the Sponsor.

In consultation with the FDA, a comprehensive clinical program for lixivaptan has been conducted. This clinical development program included three Phase 3 randomized, double-blind, placebo-controlled studies and an open-label extension study that support approval based on statistically significant improvements in serum sodium concentrations.



The three Phase 3 studies were designed to support lixivaptan use in specific disease states including inpatients with hypervolemic hyponatremia associated with heart failure (Study 3401: Hypervolemic Inpatient Trial), inpatients with SIADH and other conditions of euvolemic hyponatremia (Study 3405: Euvolemic Inpatient Trial), and outpatients with SIADH and other conditions of euvolemic hyponatremia (Study 3430: Euvolemic Outpatient Trial). A lower dosing and specific titration regimen for lixivaptan was evaluated in the Euvolemic Outpatient Trial to reduce the potential risk of overly rapid

correction of serum sodium concentrations, and in the open label extension study to evaluate re-initiation of therapy in the outpatient setting for up to an additional 6 months of treatment.

In all three Phase 3 studies, lixivaptan met the primary endpoint of statistically significant improvements in change of serum sodium concentration from baseline to day 7 compared to placebo. Fluid restriction was utilized according to investigator discretion in both arms of each Phase 3 study. In each clinical setting, lixivaptan demonstrated controlled, significant and sustained increases in serum sodium concentration. These findings were supported by pre-specified sensitivity analyses. In all studies, lixivaptan was well tolerated. Importantly, overly rapid correction of serum sodium concentration in the lixivaptan treated population was comparable to placebo.

In addition to studying lixivaptan in SIADH, a population of patients with hyponatremia associated with acute worsening of heart failure was evaluated in the lixivaptan Phase 3 program. This study consisted of patients hospitalized with acute worsening of heart failure (HF) who were treated for up to 60 days. Lixivaptan treatment was associated with a significant increase in serum sodium concentrations compared to placebo. A numerical imbalance in early mortality from all causes compared with placebo treatment was observed. Thorough analysis of the data is complete. The reason for this difference remains unclear and no causal relationship of mortality with lixivaptan has been identified. An unusually low mortality rate for patients with acute worsening of heart failure was observed in the placebo group. There was no potential signal of increased mortality in any of the Phase 2 or 3 studies that enrolled subjects with hyponatremia secondary to SIADH, nor in a Phase 2 study in subjects with stable heart failure. Evidence from the overall clinical program for lixivaptan support the drug to be safe and well tolerated in patients with hyponatremia.

Conclusion

Lixivaptan has demonstrated through a comprehensive clinical development program to be an important treatment for hyponatremia. In the inpatient setting, lixivaptan demonstrated significant efficacy coupled with low rates of overly rapid correction of serum sodium concentrations which were similar to those observed with placebo. In the outpatient setting, a titration regimen employing a lower starting dose of lixivaptan was demonstrated to be safe and effective without the need to hospitalize the patient for initiation or re-initiation of treatment.

As such, the recommended indication is:

> *The treatment of symptomatic hypervolemic and euvolemic hyponatremia, associated with heart failure and syndrome of inappropriate antidiuretic hormone (SIADH), respectively.*
>
> *Important limitation: Patients requiring intervention to raise sodium concentration urgently to prevent or to treat serious neurological symptoms should not be treated with lixivaptan.*

2. INTRODUCTION

2.1. Pharmacologic Class and Mode of Action

Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is involved in the regulation of body fluid osmolality, blood volume, vascular tone, and blood pressure in mammals. AVP plays a crucial role in regulating the rate of CL_{H20} by the kidney and exerts its actions in the kidney through vasopressin V_2 receptors expressed primarily in the collecting duct of the renal medulla. Stimulation of the V_2 receptor by AVP activates adenylate cyclase and increases intracellular cyclic adenosine monophosphate (cAMP) levels, which triggers an increase in the water permeability of the collecting duct epithelia and thus promotes solute-free water reabsorption. In addition, activation of the V_2 receptor can contribute to water conservation through ancillary mechanisms that increase medullary osmolality. Reabsorption of water from the collecting duct back into the body produces a smaller volume of more concentrated urine (antidiuresis) (Oghlakian et al 2009, Ku et al 2009, and Jackson 2006).

Lixivaptan is an orally-active, non-peptide, competitive, and selective antagonist for the vasopressin V_2 receptor (Chan et al 1998). By antagonizing the effects of AVP that are mediated by the V_2 receptor, lixivaptan decreases U_{osm} and increases U_{flow}, CL_{H20}, and S_{osm}.

2.2. Recommended Indication and Dosing Regimen

The recommended indication for lixivaptan is:

> For the treatment of symptomatic hypervolemic and euvolemic hyponatremia, associated with heart failure and SIADH, respectively. An important limitation is that patients requiring intervention to raise sodium concentration urgently to prevent or to treat serious neurological symptoms should not be treated with lixivaptan.
>
> Important limitation: Patients requiring intervention to raise sodium concentration urgently to prevent or to treat serious neurological symptoms should not be treated with lixivaptan.

Lixivaptan would be available for oral administration as hard gelatin capsules in doses of 25 mg or 50 mg. The recommended storage is at a controlled room temperature, United States Pharmacopeia (USP), 25°C allowing for excursions between 15° and 30°C.

Lixivaptan should be initiated and re-initiated only in settings where sodium concentration can be monitored. The recommended dosing regimen for lixivaptan is:

> Hospitalized patients: The starting dose for hospitalized patients with hyponatremia is 50 mg once daily without regard to meals. The dose may be doubled every 24 hours depending on individual patient response to a maximum of 100 mg once daily (total daily dose 100 mg) in SIADH patients and to a maximum of 100 mg BID (total daily

dose 200 mg) in heart failure patients, as needed, to achieve the desired sodium concentration.

Outpatients: The recommended starting dose for outpatients with hyponatremia is 25 mg once daily without regard to meals. The dose may be doubled every 24 hours depending on individual patient response to a maximum of 100 mg once daily (total daily dose 100 mg) in SIADH patients and to a maximum of 100 mg twice daily (total daily dose 200 mg) in heart failure patients, as needed, to achieve the desired sodium concentration.

2.3. Regulatory Background

The development of lixivaptan was initiated by Wyeth Pharmaceuticals in 1995 and continued by Cardiokine Biopharma in 2004. Cardiokine submitted an NDA for lixivaptan in December 2011; Cornerstone Therapeutics Inc. subsequently acquired Cardiokine in December 2011. The regulatory history of lixivaptan was reflective of the communications between the Sponsor and FDA

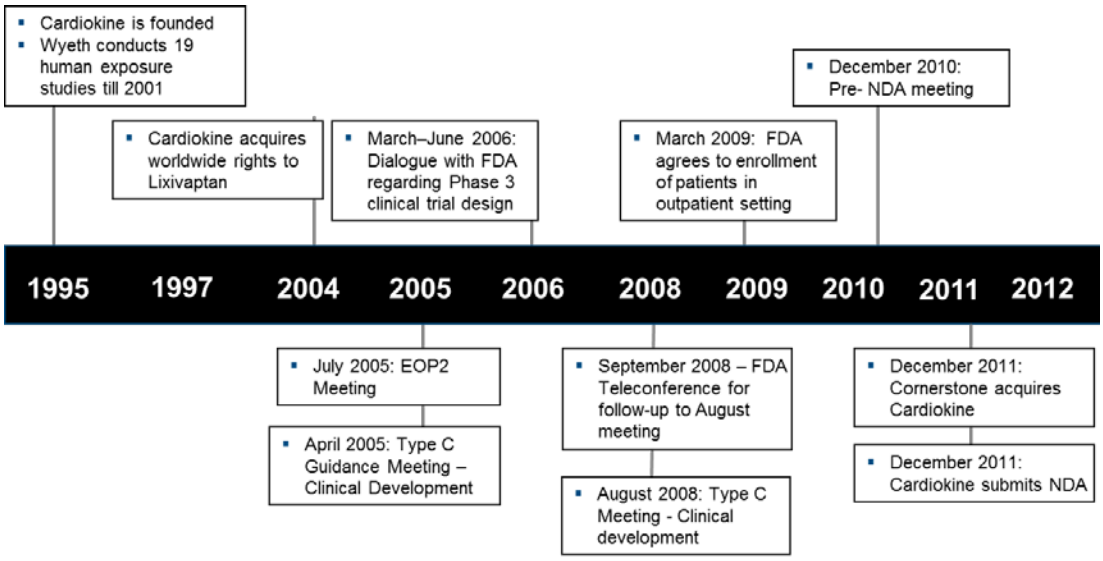


Figure 1 Regulatory and corporate background for lixivaptan development

Consistent with a positive recommendation from the Cardiovascular and Renal Drugs Advisory Committee on June 25, 2008 following a review of the tolvaptan development program, the FDA accepted a statistically significant increase in serum sodium concentration in patients with hyponatremia as the basis for approval of oral tolvaptan. Therefore, the precedent for approval was established for the vaptan class, and the primary endpoint was confirmed at the August 2008 Type C meeting between the FDA and the Sponsor.

In consultation with the FDA, a comprehensive clinical program for lixivaptan has been conducted. The development program includes three Phase 3 randomized, double-blind, placebo-controlled studies and an open-label extension study that support approval based

on statistically significant improvements in serum sodium concentrations in specific patient populations.

3. OVERVIEW OF HYPONATREMIA

Hyponatremia is an electrolyte disturbance that results from an imbalance of total body water and total body sodium. The condition is diagnosed when sodium concentration falls below the lower limit of the normal range (<135 mEq/L). Hyponatremia is the most commonly observed laboratory abnormality, occurring in up to 30% of hospitalized patients and up to 21% of ambulatory patients (Schrier 2006, Hawkins 2003). The incidence of hyponatremia increases with age and is more frequently observed in elderly patients (Upadhyay et al, 2006). Incidences of 18% to 22% have been reported in chronic care facilities, with 53% of patients having one or more episodes of hyponatremia over a 12-month period (Miller et al, 1995, Chen et al, 2006).

Hyponatremia may be either an acute or chronic medical condition. Acute hyponatremia is often a life-threatening emergency and is usually managed by infusion of hypertonic saline. Chronic hyponatremia is commonly associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH, a euvolemic state) and heart failure (a hypervolemic state).

Hyponatremia is associated with complications of co-morbid conditions, significantly greater lengths of hospital stay (Chin and Goldman 1996, Krumholz et al, 1999), and higher hospital re-admission rates than in patients with normal sodium concentrations. (Adrogue 2005) Further, hyponatremia is a strong predictor of both in-hospital and post-discharge mortality. Increased mortality rates have been reported in hyponatremic patients independently from the underlying disease. In-hospital mortality rates of 16% have also been reported for patients >65 years of age with hyponatremia on admission versus 8% for those with normal sodium concentrations on admission (Terzian et al, 1994).

The incidence and the severity of symptoms of hyponatremia are associated with the extent of decreased sodium concentration. Acute, severe hyponatremia may result in seizures, coma, and death, while chronic hyponatremia has manifestations that are more subtle and mostly neurological in nature, and often under-diagnosed and under-treated. Mounting evidence highlights that even mild hyponatremia is an important medical concern. Worsening hyponatremia has been associated with an elevated risk of altered mental status (Bissram et al, 2007). Recent data suggest that patients with mild chronic hyponatremia have subtle neurological manifestations undetected during standard physical examination, including concentration and attention deficits, impairment of balance and gait, and falls (Decaux 2006, Renneboog et al, 2006, Sterns et al, 2010). Importantly, these findings are reversible following sodium correction (Renneboog et al, 2006, Schrier et al, 2006). Furthermore, hyponatremia can lead to decreased bone mineral density with increasing bone fragility (Verbalis et al, 2010, Ayus and Moritz 2010) and has been shown to be a significant risk factor for bone fracture (Kengne et al, 2008), independent of osteoporosis (Kinsella et al, 2010). As a result of this combination

of neurologic impairment and decreased bone mineral density, elderly patients with hyponatremia are more susceptible to serious fractures.

Body water homeostasis is maintained throughout the day through unregulated fluid intake in concert with AVP-directed changes in U_{flow}. However, in the elderly population, regulation of total body water may often be disrupted due a decline in responsiveness to AVP. This, combined with further disruption of water excretory capacity due to declining renal function with aging (e.g., decreased glomerular filtration rate), puts the elderly at risk of developing hyponatremia, which may be fatal in severe cases.(Beck 2000, Epstein 1996, Bissram et al, 2007)

3.1. Euvolemic Hyponatremia Associated with SIADH

Euvolemic hyponatremia is dilutional and associated with the absence of evidence of volume depletion or volume overload. Euvolemic hyponatremia is commonly observed in the elderly and is often associated with SIADH.

3.2. Hypervolemic Hyponatremia Associated with Heart Failure

Hypervolemic hyponatremia is associated with an increase in total body water and is characterized by the presence of edema and increased extracellular fluid. Hypervolemic hyponatremia is associated with conditions that include heart failure.

3.3. Treatment of Hyponatremia

Prior to the availability of specific drugs that antagonize the action of arginine vasopressin, correction of mild-to-moderate hyponatremia by medical means most often included the use of fluid restriction and/or non-FDA approved treatments such as demeclocycline or isotonic saline infusion. These modalities have been associated with efficacy, safety or compliance limitations.

Beginning in 2005, with the FDA approval of intravenous conivaptan, arginine vasopressin receptor antagonists (vaptans) have been available as treatment options for hyponatremia that increase serum sodium concentration through sodium-sparing diuresis (aquaresis). In 2009, the FDA approved tolvaptan as the first oral vaptan for treatment of both euvolemic and hypervolemic hyponatremia.

3.4. Unmet Medical Need

Despite the current availability of two drugs in the vaptan class, an unmet medical need remains. Conivaptan and tolvaptan are only approved for initiation or re-initiation in a hospital, in part due to the potential risk of overly rapid correction of serum sodium concentration which may lead to osmotic demyelination syndrome (ODS). This has resulted in important access issues for patients diagnosed in outpatient settings whose conditions would not justify hospital admission solely for initiation of vaptan therapy. Patients in medical settings other than hospitals, e.g. chronic care facilities, where the prevalence of chronic hyponatremia may be high, are unlikely to be admitted to a hospital for initiation of therapy (Miller et al, 1995, Chen et al, 2006).

4. CLINICAL PHARMACOLOGY

4.1. Pharmacokinetic Characteristics

Upon oral administration, lixivaptan is rapidly absorbed and peak concentrations [t_{max}] are achieved in 0.5 to 1 hour).

Absolute bioavailability data for lixivaptan are not available. An estimate of 8% was determined using the ratio of plasma lixivaptan area under the curve (AUC) to the total plasma radioactivity AUC.

The average half-life ($t_{1/2}$) of lixivaptan following administration of doses ≥25 mg was 11.4 hours.

With once daily (QD) and twice daily (BID) dosing, lixivaptan steady-state was achieved after 2 to 6 days of chronic dosing.

In vitro studies demonstrated that lixivaptan is highly (>99.95%) protein bound in the human plasma and did not undergo significant erythrocyte uptake or binding.

Lixivaptan is extensively metabolized primarily by CYP3A4 pathway with CYP2C8 and CYP3A5 pathways also contributing. Most of the characterized metabolites are formed by single or multiple oxidations of the pyrrolobenzodiazepine headpiece of the lixivaptan molecule. The major circulating metabolites (WAY-138451, WAY-141624, and WAY-138758) were pharmacologically inactive or only weakly active.

After administration of ^{14}C-lixivaptan (100 mg) to healthy subjects, lixivaptan was extensively metabolized and no unchanged lixivaptan or lixivaptan-conjugates were detected in urine samples. Excretion in urine represented a minor route of elimination of radioactivity; the major route of excretion of radioactivity was via the feces.

4.2. Pharmacodynamic Characteristics

Lixivaptan is a selective, non-peptide, AVP V_2-receptor antagonist. Its site of action is the V_2 receptor located on the renal medullary collecting duct where it inhibits water reabsorption.

Lixivaptan produces dose-related increases in U_{flow}, S_{osm} and $CL_{H20,}$ and decreases in U_{osm}, resulting in corresponding increases in sodium concentrations.

Lixivaptan produces maximum effects occurring at approximately 2 to 4 hours after chronic dosing. Pharmacodynamic studies demonstrate that after delivery of 25 to 800 mg once daily (QD) doses to healthy subjects, sodium concentration increased between 0.2 and 8.75 mEq/L. After 100 to 400 mg twice daily (BID) doses, sodium concentration increased between 4.8 and 7.8 mEq/L. After 30 to 250 mg BID doses to heart failure subjects, Day 1 increases in serum sodium concentrations were significantly greater than those seen with placebo. On Day 6, serum sodium concentrations for all doses were greater than placebo. Pre-dose values on Day 6 were all significantly greater than

placebo. Serum sodium concentrations appeared to plateau between 75 and 150 mg BID, with only minor incremental increases at 250 mg BID. In hyponatremic patients with mixed etiologies (e.g., HF and SIADH), 25 and 125 mg BID doses provided similar increases in serum sodium concentration (5.3 and 5.7 mEq/L, respectively) after three days of dosing; the effect remained relatively constant until study exit for the 25 and 125 mg BID groups.

Despite differences in study designs and populations (e.g., healthy subjects, subjects with HF, subjects with SIADH), there is evidence for dose-related effects of lixivaptan on measures of renal water handling, sodium concentrations, and plasma AVP concentrations. There is no evidence of dose-related hypokalemia. These data support that lixivaptan doses of 25 mg may be considered as a starting dose since an effect was seen on maximal U_{flow}, 4-hour U_{vol}, urine CL_{H2O}, (free –water clearance) and resultant increases in serum sodium concentration.

5. CLINICAL DEVELOPMENT PROGRAM

5.1. Background of Lixivaptan Clinical Development

The clinical development program for lixivaptan was comprehensive. The Phase 3 studies were performed with the important goal to establish the safety and efficacy of initiation and re-initiation of lixivaptan in medical settings where change in serum sodium concentration could be monitored for the first hours after the initial dose, but without a requirement for hospitalization. The primary aim of clinical development was to assess the effect of lixivaptan on serum sodium concentrations. Therefore, a more gradual increase in dose than that utilized for hospitalized patients was undertaken. Additionally, the normalization serum sodium concentration was a key target of evaluation and analysis.

The clinical development program for lixivaptan for the treatment of symptomatic hypervolemic and euvolemic hyponatremia associated with HF and SIADH in adult subjects included:

- Three Phase 3, double-blind, placebo-controlled studies:
  - CK-LX3405 (Study 3405: Euvolemic Inpatient Trial with SIADH)
  - CK-LX3430 (Study 3430: Euvolemic Outpatient Trial with SIADH)
  - CK-LX3401 (Study 3401: Hypervolemic Inpatient Trial with HF)
- One open-label extension study conducted in subjects who had previously participated in one of the double-blind, placebo-controlled Phase 3 studies (CK-LX3401, CK-LX3405, or CK-LX3430)
- Nine Phase 2 studies conducted in subjects with euvolemic and hypervolemic hyponatremia
- One Phase 2 drug-drug interaction study with amiodarone in subjects with cardiac arrhythmias

- Twenty-two Phase 1 clinical pharmacology studies in either healthy or renally impaired subjects

5.2. Dose Selection

The lixivaptan dose range selected for the Phase 3 clinical development program had several objectives. It was important to demonstrate that therapy with lixivaptan would (1) produce controlled increases in serum sodium concentrations, (2) demonstrate dose dependent increases in serum sodium concentrations, (3) optimize patient tolerability, (4) minimize the risk of overly rapid correction of serum sodium concentrations, and (5) support the initiation and re-initiation of therapy in medical settings where serum sodium concentrations could be monitored. Based upon these objectives, and a thorough review of the Phase 1 and Phase 2 data, the dose range for the Phase 3 program was set at 25 mg once daily (QD) to 100 mg twice daily (BID). The maximal dose of lixivaptan varied within this range based upon the underlying etiology studied (SIADH and HF).

5.3. Phase 3 Clinical Program

The Phase 3 clinical program focused on the use of lixivaptan for the management of symptomatic euvolemic hyponatremia associated with syndrome of inappropriate antidiuretic hormone (SIADH) and symptomatic hypervolemic hyponatremia associated with heart failure. The Phase 3 program is depicted in Figure 2.

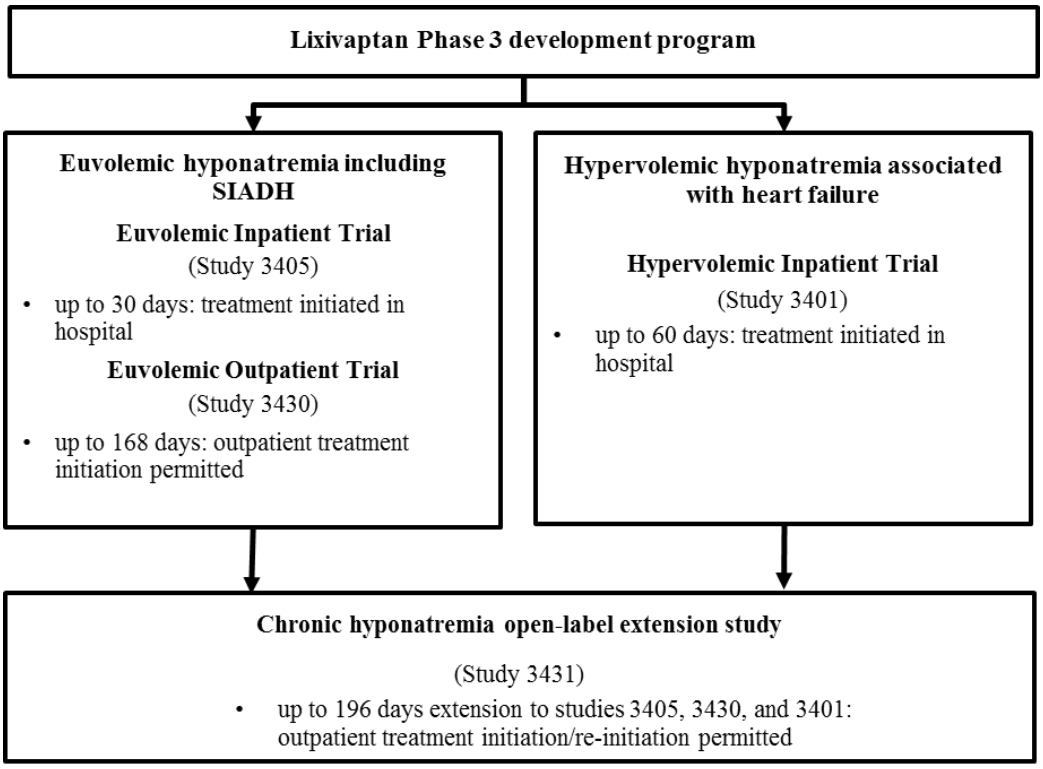


Figure 2 Lixivaptan phase 3 clinical development program

6. CLINICAL EFFICACY

6.1. Lixivaptan Studies in Euvolemic Hyponatremia

Two separate Phase 3 studies demonstrated the effectiveness of lixivaptan in achieving and maintaining increased serum sodium concentrations in subjects with euvolemic hyponatremia. Superiority of lixivaptan versus placebo was demonstrated by the results of the primary endpoint, a statistically significantly greater mean increase in central serum sodium concentration from baseline to Day 7 in the lixivaptan group when compared to the placebo group. The ability of lixivaptan to achieve the clinical goal of normalizing serum sodium concentrations was demonstrated in hospitalized patients (Study 3405) and outpatients (Study 3430).

The efficacy of lixivaptan was durable, as evidenced by statistically significant superiority to the placebo group for $nAUC_{0-30}$ in Study 3405 and $nAUC_{0-28}$ in Study 3430, a larger mean increase from baseline in central serum sodium concentrations versus placebo at end of treatment, a greater percentage of subjects with normal central serum sodium values versus placebo at end of treatment, a smaller percentage of subjects on fluid restriction versus placebo at end of treatment, and a greater percentage of subjects in the lixivaptan group than in the placebo group shifting at least one category of improvement from baseline at Day 7 and end of treatment.

These studies demonstrate the effective use of lixivaptan at a starting dose of 50 mg administered once daily and titratable to 100 mg once daily in hospitalized patients (Study 3405), and the effective use of lixivaptan at a starting dose of 25 mg once daily and titratable to 50 to 100 mg once daily in the outpatient setting (Study 3430).

6.2. Study 3405 (Euvolemic Inpatient Trial)

6.2.1. Study 3405: Design, Endpoints, Statistical Analysis

Design

Study 3405 was a Phase 3, international, multicenter, randomized, double-blind, placebo-controlled, two-arm, parallel study of oral lixivaptan in the management of hyponatremia in subjects with euvolemic hyponatremia.

Hospitalized subjects were randomized in a 1:1 ratio to 50 mg lixivaptan or matching placebo, once daily. Following initiation of therapy, subjects were carefully monitored over the initial eight (±1) hours for signs and symptoms of treatment response. The rate of serum sodium correction was also measured at eight hours following therapy initiation. Subjects were released from the medical setting with a stable dose of study drug when an optimal increase in serum sodium was achieved.

During the titration phase, subjects received blinded medication in an inpatient setting for the first 48 to 72 hours. After completing the titration phase, subjects were managed as outpatients and returned to the clinical site on Days 7, 14, and 30 (end of treatment), prior

to taking their doses of study drug, for efficacy and safety assessments. The follow-up period included assessments seven days and 30 days post-treatment.

If possible, fluid restriction was withheld for at least the first 72 hours to establish the rate and magnitude of serum sodium concentration change and to ensure subject safety by avoiding the potential accentuation of the rate of serum sodium correction with concurrent administration of a lixivaptan. Otherwise, investigators were allowed to institute fluid restriction concurrently with study drug, if needed, for treating hyponatremia.

Study drug could have been titrated up to 100 mg once daily, similar to the general titration guidelines (Table 1). Study drug could also have been down titrated to 25 mg once daily at any time during the treatment period. Acceptable dosages of lixivaptan were once daily administration of 25 mg, 50 mg, or 100 mg as a single dose.

Table 1: General Lixivaptan Dosing Titration Scheme

Change in Serum Sodium			**Dosing Guidelines Based on Serum Sodium Concentration**		
8 Hour Change (mEq/L)	24 Hour Change (mEq/L)	48 Hour Change (mEq/L)	<135 mEq/L	135 - 145 mEq/L	>145 mEq/L
<5	<5	<5	Increase dose to next dose level	No change in dose	Hold/decrease dose until serum sodium is ≤145
5-8	5-12	5-17	No change in dose	No change in dose	Hold/decrease dose until serum sodium is ≤145
>8	>12	>18	Hold the next dose, decrease study medication or diuretic dose, and contact the Medical Monitor for guidance regarding withdrawal of the subject from the study.		

Endpoints

The primary endpoint was the change from baseline to Day 7 in central serum sodium concentration. The secondary endpoints were: (1) time-normalized AUC of change from baseline to Day 30 ($nAUC_{0-30}$), (2) percentage of subjects with normalized serum sodium (≥135 mEq/L and ≤145 mEq/L) at Day 7, (3) percentage of subjects whose fluid restriction was initiated or tightened versus baseline, (4) percentage of subjects with worsening hyponatremia (a reduction of ≥3 mEq/L in serum sodium concentration from the preceding measurement with a value <135 mEq/L), and (5) change from baseline in the recorded time to complete the Trail-Making Test, part B (TMT-B) at Day 30.

An analysis of categorical change from baseline in local serum sodium was performed by hyponatremia category (i.e., mild [≥130 and <135 mEq/L], moderate [>125 and <130 mEq/L], severe [≤125 mEq/L], and normal [≥135 mEq/L]).

Statistical Methods

For the primary endpoint, a sample size of 50 subjects per group was determined to have 80% power to detect a difference in treatment means of 4.2 mEq/L, assuming a common standard deviation of 7.422 using a two-group *t*-test with a 0.05 two-sided significance level.

The ITT population (all randomized subjects) was the primary population for efficacy analyses. The MITT (all randomized subjects who received at least one dose of study drug and had both a baseline and at least one scheduled on-therapy assessment of serum sodium) and PP populations (subjects in the MITT population who met key inclusion/exclusion criteria, had average compliance of 80-120%, and did not experience any major protocol deviations during the study that may have impacted efficacy) were used in sensitivity analyses.

The primary efficacy analysis was based on an analysis of covariance model of change from baseline in serum sodium concentration at Day 7 with treatment and pooled country as factors and baseline serum sodium value as the covariate. Per the statistical analyses plan, missing data were handled by last observation carried forward/next observation carried back (LOCF/NOCB). If the two-sided p-value was ≤0.05 and the least squares mean difference of lixivaptan versus placebo was positive, then the primary efficacy objective was achieved.

Sensitivity analyses were conducted to assess the impact of missing data, analysis population, and type of serum sodium value (central, local, and central corrected for hyperglycemia). Subpopulations based on baseline serum sodium concentration (e.g., for subjects with baseline serum sodium ≤125 mEq/L) were also used for certain analyses. Analyses by race, sex, and age were also performed.

Provided that the null hypothesis for the primary variable was rejected using the primary efficacy analysis, the secondary efficacy analyses were performed as a fixed-sequence of hierarchical tests comparing the two treatment groups for the secondary endpoints. A test was to be performed only if all previous tests in the sequence had been rejected at the two-sided 0.05 level of significance.

6.2.2. Study 3405: Demographics and Baseline Characteristics

The majority of randomized subjects were Caucasian (83.0%). The elderly population was well represented (≥65 years of age = 54.7%). Mean baseline local serum sodium concentrations ranged from 105.0 to 129.2 mEq/L. Nearly 50% of subjects were female. At baseline, the percentages of subjects who were on fluid restriction were 37.0% in the lixivaptan group and 65.4% in the placebo group.

6.2.3. Study 3405: Efficacy Results

The mean increase in central serum sodium concentration from baseline to Day 7 was statistically significantly greater in the lixivaptan group than in the placebo group (6.7 mEq/L versus 4.5 mEq/L, p=0.034) in the ITT population. (Table 2). Superiority of the

lixivaptan group versus the placebo group was not affected by handling of missing data, analysis population, or type of serum sodium value (central, local, and central corrected for hyperglycemia). Further analysis of the mean increase in serum sodium concentration from baseline to Day 7 showed that lixivaptan group was superior to the placebo group regardless of gender and age.

Table 2 Mean Change in Central Serum Sodium Concentration from Baseline to Day 7 (Study 3405, ITT Population, LOCF/NOCB)

Parameter	Statistic	Lixivaptan (N=54)	Placebo (N=52)
	Number of subjects in analysis	54	52
Baseline, mEq/L	Mean (SD)	127.6 (5.7)	126.1 (5.9)
Change from Baseline, mEq/L	Mean (SD)	6.1 (6.5)	4.8 (6.1)
	Median	5.0	3.5
	Within-treatment p-value[a]	<0.001	<0.001
	Between-group p-value[b]	0.325	
ANCOVA[c]	LS mean (SE)	6.7 (0.7)	4.5 (0.8)
	Difference from placebo		
	LS mean (SE)	2.1 (1.0)	
	p-value	0.034	

LOCF=last observation carried forward; LS=least squares; NOCB=next observation carried back; SD=standard deviation; SE=standard error
[a] From one-sample t-test for change from Baseline
[b] From two-sample t-test for treatment difference in change from Baseline
[c] Model included treatment and pooled country as factors with Baseline central sodium value as covariate.

The mean increase from baseline in central serum sodium concentration was larger in the lixivaptan group than in the placebo group from Day 2 through the end of treatment. The percentage of subjects on fluid restriction was smaller in the lixivaptan group than in the placebo group from Day 2 until end of treatment. No statistically significant treatment group differences were observed for the percentages of subjects with liberalized/eliminated fluid restrictions or with worsening hyponatremia.

The mean $nAUC_{0-30}$ was statistically significantly greater in the lixivaptan group than in the placebo group (6.6 mEq/L versus 4.7 mEq/L, p=0.043) in the ITT population using LOCF/NOCB and in the majority of sensitivity analyses. The mean $nAUC_{0-3}$ (3.3 mEq/L versus 1.7 mEq/L, p=0.011) was also statistically significantly greater in the lixivaptan group than in the placebo group in the ITT population using LOCF/NOCB and in all sensitivity analyses.

The percentage of subjects with normalized central serum sodium (≥135 and ≤145mEq/L) on Day 7 was statistically significantly higher in the lixivaptan group than in the placebo group (44.4% versus 23.1%, p=0.022) in the ITT population using LOCF/NOCB. The percentage of subjects with normal central serum sodium (≥135 to ≤145 mEq/L) at the end of treatment remained higher in the lixivaptan group than in the placebo group (44.9% versus 26.5%, p=0.058).

A statistically significant treatment group difference was observed for the shifts between hyponatremia severity categories between baseline and Day 7 (p=0.001) and between baseline and Day 30 (p=0.023), with a greater percentage of subjects in the lixivaptan than in the placebo group having shifts of at least one category of improvement from Baseline at Day 7 (40/46 [87.0%] versus 31/45 [68.9%]) and at Day 30 (36/41 [87.8%] versus 25/37 [67.6%]), respectively. A similar pattern of results was observed at end of treatment (41/49 [83.7%] versus 35/50 [70.0%]).

No statistically significant differences between the lixivaptan and placebo groups were observed for mean change in TMT-B from baseline.

6.3. Study 3430 (Euvolemic Outpatient Trial)

6.3.1. Study 3430: Design, Endpoints, and Statistical Methods

Design

Study 3430 was a Phase 3, international, multicenter, randomized, double-blind, placebo controlled, two-arm, parallel-group study of orally administered lixivaptan in the management of hyponatremia in subjects with euvolemic hyponatremia (local laboratory sodium concentration <135 mEq/L) secondary to SIADH.

Subjects were enrolled to the study on an outpatient basis and randomized in a 3:1 ratio to 25 mg lixivaptan or matching placebo, once daily. The medical setting during study drug dose titration was either a clinic, long-term care facility/nursing home, or hospital. Subjects were released from the medical setting if the rate of change in serum sodium concentration did not exceed 8 mEq/L at eight hours, and scheduled to return for clinical visits at 24 and 48 hours post treatment initiation for study dose optimization based on serum sodium concentration response. After initiation of lixivaptan therapy, the dose was permitted similar to the general titration guidelines (Table 1). Fluid restrictions were also similar to Study 3405.

Subjects were to be evaluated on Days 2, 3, 4, 7, 14, 21, and 28, at Weeks 8, 12, 16, 20, and 24 (or early termination), and seven and 30 days (telephone contact) post-treatment.

Endpoints

Efficacy and safety assessments were the same as Study 3405. The primary and secondary endpoints and the statistical analysis were also similar to Study 3405 except the study endpoint was Day 28.

Statistical Methods

A two-group t-test with a 0.050 two-sided significance level has 80% power to detect the difference between a placebo mean change from baseline of 1.3 and a lixivaptan mean change from Baseline of 5.0, a difference in means of -3.7, assuming that the common standard deviation is 8.0, when the sample sizes in the two groups are 50 and 150, respectively (a total sample size of 200). Although power statements are not generally

given for secondary variables, it was appropriate for the daily average AUC of change from baseline to Day 28 because this shows the continued effect of treatment on serum sodium concentration. A sample size of 50 in each group has 90% power to detect a difference in means of 3.6 (the difference between a lixivaptan mean daily average AUC of change from baseline in serum sodium of 5.6 and a placebo daily average AUC of change from baseline of 2.0) assuming that the common standard deviation is 5.49 using a two-group t-test with a 0.050 two-sided significance level. These results also represent an extrapolation from Schrier (2006). The extrapolation included additional conservative estimates due to missing data.

Preliminary power calculations based on a poster presentation for satavaptan indicated that a sample size of approximately 80 per group provides 80% power to detect treatment group differences based on change from baseline to Day 28 in the time to complete the TMT-B, again based on a two-sample t-test with a 0.050 two-sided significance level. Mean changes and sample sizes were used to infer a standard deviation that would make the reported results significant at the 0.05 level. This led to an estimated effect size (difference of mean changes divided by the common standard deviation of change) of approximately 0.46, resulting in the estimate of 80 per group. Since this study was underpowered for this particular endpoint, pooling of data from Study 3405 and Study 3430 for the express purpose of attaining adequate power for this endpoint as well as other secondary and exploratory endpoints was pre-specified.

The statistical analyses were performed similarly to Study 3405.

6.3.2. Study 3430: Demographics and Baseline Characteristics

A total of 206 subjects were randomized and included in the ITT population: 154 subjects to lixivaptan and 52 subjects to placebo. The majority of randomized subjects were Caucasian (78.2%). Slightly more than half of the subjects were female (51.5%). Mean age was 65.6 years and approximately half of subjects (53.9%) were ≥65 years of age. Mean baseline local laboratory sodium concentrations were approximately 130 mEq/L (range: 111.8 to 134.5 mEq/L). Percentages of subjects who were on fluid restriction at baseline were 16.9% in the lixivaptan group and 11.5% in the placebo group. Treatment was initiated in medical clinics for 128 subjects (62.1%), in a long-term care facility for 44 subjects (21.4%), and in hospital for 34 subjects (16.5%).

6.3.3. Study 3430: Efficacy Results

The mean increase in central serum sodium concentration from baseline to Day 7 was statistically significantly greater in the lixivaptan group than in the placebo group (3.2 mEq/L versus 0.8 mEq/L, $p<0.001$) in the ITT population (Table 3). Superiority of the lixivaptan group versus the placebo group was not affected by handling of missing data, analysis population, or type of serum sodium value (central, local, and central corrected for hyperglycemia). Further analysis of the mean increase in serum sodium concentration from baseline to Day 7 showed that lixivaptan group was superior to the placebo group within females, males, subjects <65 years of age, subjects ≥65 years of age, and whites.

Table 3 Mean Change in Central Serum Sodium Concentration from Baseline to Day 7 (Study 3430, ITT Population, LOCF/NOCB)

Parameter	Statistic	Lixivaptan (N=154)	Placebo (N=52)
	Number of subjects in analysis	154	52
Baseline, mEq/L	Mean (SD)	131.5 (4.9)	131.6 (5.2)
Change from Baseline, mEq/L	Mean (SD)	3.0 (4.1)	0.6 (3.4)
	Median	3.0	1.0
	Within-treatment p-value[a]	<0.001	0.187
	Between-group p-value[b]	<0.001	
ANCOVA[c]	LS mean (SE)	3.2 (0.5)	0.8 (0.6)
	Difference from placebo		
	LS mean (SE)	2.4 (0.6)	
	p-value	<0.001	

LOCF=last observation carried forward; LS=least squares; NOCB=next observation carried back; SD=standard deviation; SE=standard error
[a] From one-sample t-test for change from Baseline
[b] From two-sample t-test for treatment difference in change from Baseline
[c] Model included treatment and pooled country as factors with Baseline central sodium value as covariate.

The percentages of subjects with liberalized/eliminated fluid restrictions (8.5% lixivaptan, 3.8% placebo at end of treatment) and worsening hyponatremia (57.1% lixivaptan, 71.2% placebo overall) were directionally consistent with the superiority of lixivaptan to placebo.

The mean increase from baseline in central serum sodium concentration was larger in the lixivaptan group than in the placebo group from Day 3 through end of treatment. At end of treatment, the treatment group difference was statistically significant in the ITT population using OV (4.0 mEq/L versus 1.4 mEq/L, p=0.002).

The mean $nAUC_{0-28}$ was statistically significantly greater in the lixivaptan group than in the placebo group (3.3 mEq/L versus 1.8 mEq/L, p=0.004) in the ITT population using LOCF/NOCB and in all sensitivity analyses. The means of $nAUC_{0-3}$ (2.0 mEq/L versus 1.3 mEq/L, p=0.042) and $nAUC_{0-8w}$ (3.5 mEq/L versus 1.9 mEq/L, p=0.004) were also statistically significantly greater in the lixivaptan group than in the placebo group in the ITT population using LOCF/NOCB and in all sensitivity analyses.

For the subgroup of subjects from the ITT population with baseline central serum sodium <130 mEq/L, statistically significant treatment group differences favoring lixivaptan were observed for $nAUC_{0-3}$, $nAUC_{0-28}$, and $nAUC_{0-8w}$.

The percentage of subjects with normalized central serum sodium (≥135 and ≤145mEq/L) on Day 7 was statistically significantly higher in the lixivaptan group than in the placebo group (39.4% versus 12.2%, p<0.001) in the ITT population using OV and in all sensitivity analyses. The percentage of subjects with normal central serum sodium (≥135 to ≤145 mEq/L) at end of treatment remained statistically significantly higher in the lixivaptan group than in the placebo group (66.7% versus 48.1%, p=0.017).

A statistically significant treatment group difference was observed for the shifts between hyponatremia severity categories between baseline and Day 7 (p=0.001) and between baseline and the end of treatment (p=0.014), with a greater percentage of subjects in the lixivaptan than in the placebo group having shifts of at least one category of improvement from baseline at Day 7 (97/146 [66.4%] versus 23/49 [46.9%]) and at end of treatment (114/153 [74.5%] versus 29/52 [55.8%]), respectively.

No statistically significant differences between the lixivaptan and placebo groups were observed for mean change in TMT-B from baseline.

6.4. Study 3431: Open-Label Extension Study

6.4.1. Study 3431: Design, Analyses and Statistical Methods

Design

Study 3431 was an international, multicenter study of open-label, orally administered lixivaptan in titrated doses for up to 28 weeks, plus a 7-day follow-up. Subjects were entered in the study after participation in a randomized, blinded, placebo-controlled Phase 3 lixivaptan study of hyponatremia (Study 3401, Study 3405, or Study 3430). Subjects completed a minimum 30-day washout from the preceding placebo-controlled study.

Subjects were treated for up to 28 weeks with open-label lixivaptan. Study drug was initiated at 25 mg once daily (QD) and could have been titrated up to optimize the subject dose, similar to the general dose titration guidelines (Table 1).

If possible, fluid restriction was to be withheld for at least the first 72 hours to determine the rate and magnitude of serum sodium change and to ensure subject safety by avoiding the potential accentuation of the rate of serum sodium correction with concurrent administration of fluid restriction and lixivaptan. Fluid restriction could have been instituted, maintained, or further adjusted at the investigator's discretion at any time during the study.

Analyses and Statistical Methods

There was no primary efficacy analysis. Serum sodium concentration measurements were obtained at designated intervals and were compared to each subject's open-label baseline sodium level using both the observed cases (OC) and last observation carried forward (LOCF) datasets. Summary statistics for the reported value and changes from open-label baseline were provided by visit and end of treatment. Summary statistics were also provided for subgroups of subjects by open-label study baseline serum sodium (<135 mEq/L and ≥135 mEq/L). A paired t-test was applied to the change from open-label baseline to all post-baseline study visits and end of treatment. The number and percentage of subjects with varying degrees of hyponatremia ("severe" <130 mEq/L, "moderate" 125 to <130 mEq/L, "mild" 130 to <135 mEq/L, "normal" ≥135 mEq/L) were presented at open-label study baseline, by study visit, and at end of treatment using both the OC and

LOCF datasets. Hyponatremia was also summarized by open-label study baseline serum sodium (i.e., <135 mEq/L and ≥135 mEq/L).

Subjects requiring prescription of fluid restriction, hypertonic saline, or other medicines for the express purpose of treating hyponatremia were summarized as follows: (1) number and percentage of subjects by study visit, and (2) number and percentage of subjects by study visit by open-label study baseline serum sodium subgroups.

Prescription of hypertonic saline or other medicines for treatment of hyponatremia was identified using data collected on the concomitant medication electronic case report form (eCRF). To identify the prescription by visit, start and stop dates in the concomitant medication data were mapped to study visit dates.

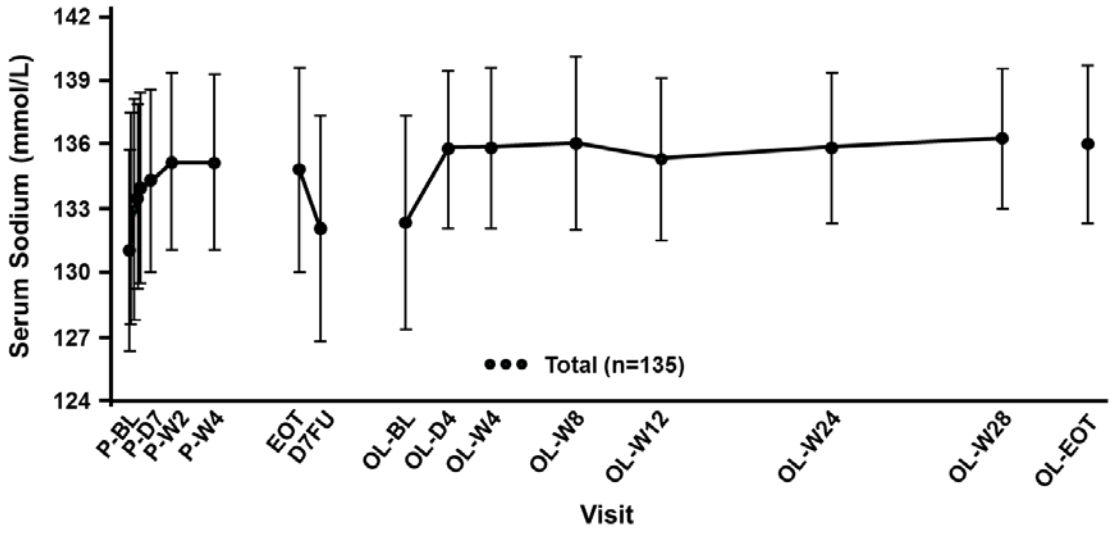
TMT-B and MOS-6 at each visit collected and the change from baseline (Day 1 pre-dose, 0 Hour) were summarized using descriptive statistics overall and by open-label trial Baseline serum severity subgroups (<130 mEq/L, 130 to <135 mEq/L, and ≥135 mEq/L). Additionally, a paired t-test was applied to the change from baseline (Day 1 pre-dose, 0 Hour) at all post-baseline study visits.

6.4.2. Study 3431: Demographics and Baseline

The majority of enrolled subjects were Caucasian (80.7%). Slightly more than half of the subjects were female (51.9%). Mean age was 67.5 years. Using local serum sodium concentrations, subjects enrolled in this study were mildly hyponatremic (130 to <135 mEq/L, 44.4%), moderately to severely hyponatremic (<130 mEq/L, 30.4%), or normonatremic (≥ 135mEq/L, 25.2%). The mean pre-treatment local serum sodium concentration was 132 mEq/L.

6.4.3. Study 3431: Results

Statistically significant increases in central serum sodium concentrations were observed in the intention-to-treat (ITT) population (defined as all subjects who received at least one dose of lixivaptan) at all measured time-points compared to baseline (Figure 3). Similar statistically significant increases in serum sodium concentrations were observed at all on-treatment visits in both the prior lixivaptan group (i.e., subjects who received lixivaptan in a prior study) and the prior placebo group (i.e., subjects who received placebo in a prior study). In the prior lixivaptan group, increases were sustained over time, indicating no apparent loss of effect.



P = prior study, BL = baseline, D = day, w = week, EOT = end of treatment, FU = follow-up, OL = open-label study

Figure 3 Secondary efficacy: Central laboratory: Serum sodium mean ± SD at all visits overall (Study 3431, ITT population, Observed Value)

Mean increases in central serum sodium concentration from baseline for subjects who entered the trial with a serum sodium <130 mEq/L were slightly greater than for the ITT population and for the ≥135 mEq/L subset. At Week 28, 72.9% of subjects were normonatremic (central serum sodium ≥135 mEq/L) compared with 25.2% at baseline.

The use of fluid restriction in the ITT population was similar at the baseline and Week 28 visits (25.5% versus 25.2%, respectively). Fluid restriction use increased in the subset of subjects with baseline serum sodium <130 mEq/L and decreased in the subset of subjects with serum sodium 130 to <135 mEq/L and in the normonatremic subjects (sodium ≥135 mEq/L).

A statistically significant improvement over baseline in mean time to complete the TMT-B was observed for Week 4, Week 28, and end of treatment in subjects in the ITT population and in the subset of subjects with baseline central serum sodium concentration <130 mEq/L.

A statistically significant improvement over baseline in mean MOS-6 score was observed for all ITT subjects at Week 4. This improvement was not observed at Week 28 or at the end of treatment.

6.5. Study 3401 (Hypervolemic Inpatient Trial): Lixivaptan for Symptomatic Hypervolemic Hyponatremia Associated with Acute Worsening of Heart Failure

6.5.1. Study 3401: Design, Endpoints, and Statistical Methods

Design

Study 3401 was a Phase 3, international, multicenter, randomized, double-blind, placebo controlled, two-arm, parallel-group study of orally administered lixivaptan in the management of hospitalized subjects with hyponatremia (local laboratory sodium concentration <135 mEq/L) secondary to acute worsening of heart failure.

Approximately 650 eligible subjects with hyponatremia (serum sodium <135 mEq/L) and hypervolemia were randomized in a 1:1 ratio to either placebo or lixivaptan after eligibility was confirmed, and the diagnosis of hyponatremia was established. Randomization was stratified by country and baseline serum sodium, providing for a minimum of 200 subjects with serum sodium <130 mEq/L and the remainder of subjects with serum sodium ≥130 to <135 mEq/L.

Upon randomization, all study subjects entered an inpatient dose-titration phase for up to 72 hours. Lixivaptan or placebo was administered at a starting dose of 50 mg and subsequently titrated up to a maximum dose of 100 mg twice daily similar to the dosage titration guidelines (Table 1). If once-daily dosing was prescribed, the maximum total daily dose was 100 mg. The treatment objective of the dose-titration phase was to optimize the dose to achieve a controlled correction of serum sodium concentration over the initial few days of therapy and to achieve normalization of serum sodium concentration (i.e., 135-145 mEq/L).

Subjects could have been released from the titration phase early if their condition stabilized. The treatment phase extended from Day 4 (or the day of hospital discharge, whichever was later) to Day 60 of treatment or early termination. The initial dosage in the treatment phase was the same dosage established as the subject's optimized dose at the end of the titration phase.

Subjects were evaluated on Days 7, 14, 28, 42, and 60. Subjects could have continued to receive conventional therapy, including diuretics, digoxin, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and the fixed combination of hydralazine and isosorbide dinitrate (ISDN), nitrates, beta blockers, and aldosterone antagonists at the discretion of the investigator. Fluid restriction could have been instituted, maintained, or further adjusted at the investigator’s discretion at any time during the study.

If possible, fluid restriction was to be withheld for at least the first 72 hours in order to determine the rate and magnitude of serum sodium change and to ensure subject safety by avoiding the potential accentuation of the rate of serum sodium correction with concurrent administration of fluid restriction and a vaptan.

At the end of the treatment period, all subjects were to enter a post-treatment follow-up period for concomitant medication dose adjustment, study drug withdrawal effects assessment, and subject safety monitoring. Post-treatment visits were to occur seven and 30 days post-treatment.

Endpoints

The primary endpoint was the change from baseline to Day 7 in central serum sodium. Secondary endpoints were: (1) the normalized AUC from Baseline to Day 60 ($nAUC_{0-60}$), (2) the change from baseline in the recorded time to complete the TMT-B at Day 28, (3) percentage of subjects with worsening hyponatremia (a reduction of ≥3 mEq/L in serum sodium concentration with a value <135 mEq/L) during the double-blind on-therapy period, (4) the percentage of subjects with normalized serum sodium (≥135 mEq/L and ≤145 mEq/L) at Days 7 and 60, and (5) days alive and out of the hospital (DAOH) during the double-blind on-therapy period (up to 60 days from randomization).

Statistical Methods

Based on extrapolation of previously published differences between baseline and Day 4 (Schrier et al, 2006), a sample size of 125 in each group will have 98% power to detect a difference in means of 4.2 (the difference between the lixivaptan mean change from baseline at Day 7 of 5.2 and placebo mean change from baseline at Day 7 of 1.0) assuming that the common SD of changes is 8.23 using a two group t-test with a 0.05 two-sided significance level.

The study was also powered to detect a significant treatment effect on DAOH for the MITT population. Based on the results from the ESCAPE Trial (Stevenson et al 2005) and Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) (Klein et al 2005), a sample size estimate for analysis of the endpoint “Number of days dead or in hospital through the 60-day follow-up period from the day of randomization” of 325 subjects per arm (total 650) would achieve 89% power to detect a difference of three days between the two treatment groups at a significance level (alpha) of 0.05 using a two-sided two sample t-test. This was based upon the assumption the mean number of days “dead or hospitalized” would improve from 12 to nine days in the lixivaptan group compared with the placebo group. The common SD was assumed to be 12 days. If the SD was 11 days, with 650 subjects, there would be a 93% power to detect a difference.

The ITT (all randomized subjects) was the primary population for efficacy analyses. The MITT (all randomized subjects who received at least one dose of study drug and had both a baseline and at least one scheduled on-therapy assessment of serum sodium) and PP efficacy (subjects who met criteria based on inclusion and exclusion criteria, compliance, and prohibited medications during the treatment period) populations were used in sensitivity analyses. The primary efficacy analysis was based on an analysis of covariance (ANCOVA) model of change from baseline in serum sodium concentration at Day 7 with treatment, pooled country, and baseline local sodium stratum (<130 mEq/L versus ≥130 mEq/L) as factors, and baseline central serum sodium value as the covariate.

If the two-sided p-value was ≤0.05 and the least squares mean difference of lixivaptan versus placebo was positive, then the primary efficacy objective was achieved.

Sensitivity analyses were conducted to assess the impact of missing data, analysis population, and type of serum sodium value (central, local, and central corrected for hyperglycemia). Subpopulations based on baseline serum sodium level (e.g., for subjects with baseline serum sodium <130 mEq/L, for subjects with baseline serum sodium ≤125 mEq/L) were also used for certain analyses.

Provided that the null hypothesis for the primary variable was rejected using the primary efficacy analysis, the secondary efficacy analyses were performed as a fixed-sequence of hierarchical tests comparing the two treatment groups for the five secondary endpoints listed above. A test was to be performed only if all previous tests in the sequence had been rejected at the two-sided 0.05 level of significance.

An analysis of categorical change from baseline in local serum sodium was performed by hyponatremia category (i.e., mild [≥130 and <135 mEq/L], moderate [>125 and <130 mEq/L], severe [≤125 mEq/L], and normal [≥135 mEq/L]).

6.5.2. Study 3401: Demographics and Baseline Characteristics

A total of 652 subjects were randomized and included in the ITT population: 323 subjects to lixivaptan and 329 subjects to placebo. The majority of randomized subjects were Caucasian (75.8%) and male (71.6%). Mean age was 64.8 years; approximately half of subjects were ≥65 years of age. Mean body mass index was 28.20 kg/m^2 and most subjects were NYHA class III or IV (59.5% and 36.8%, respectively). Baseline local serum sodium was <130 mEq/L for 31.4% of subjects. No clinically important treatment group differences for demographic and baseline characteristics were observed.

6.5.3. Study 3401: Efficacy Results

The mean increase in serum sodium concentration, as measured by the central laboratory (hereafter referred to as central serum sodium) from Baseline to Day 7 was statistically significantly greater in the lixivaptan group than in the placebo group (2.5 mEq/L versus 1.3 mEq/L, p=0.001) in the ITT population (Table 4). Superiority of the lixivaptan group versus the placebo group was not affected by handling of missing data, analysis population, or type of serum sodium value (central, local, and central corrected for hyperglycemia). The mean increase was greater for the lixivaptan group than the placebo group within females, males, subjects <65 years of age, subjects ≥65 years of age, Asians, Caucasians, and other races. The magnitude of the change from baseline in serum sodium concentrations increased with increasing severity of hyponatremia.

Table 4 Mean Change in Central Serum Sodium Concentration From Baseline to Day 7 (Study 3401, ITT Population, LOCF/NOCB)

Parameter	Statistic	Lixivaptan (N=323)	Placebo (N=329)
	Number of subjects in analysis	323	329
Baseline, mEq/L	Mean (SD)	132.9 (5.6)	132.6 (6.2)
Change from Baseline, mEq/L	Mean (SD)	2.6 (5.1)	1.6 (5.6)
	Median	2.0	1.0
	Within-treatment p-value[a]	<0.001	<0.001
	Between-group p-value[b]	0.017	
ANCOVA[c]	LS mean (SE)	2.5 (0.3)	1.3 (0.3)
	Difference from placebo		
	LS mean (SE)	1.2 (0.4)	
	p-value	0.001	

ANCOVA=analysis of covariance; LS=least squares; SD=standard deviation; SE=standard error
[a] From one-sample t-test for change from Baseline
[b] From two-sample t-test for treatment difference in change from Baseline
[c] Model included treatment, pooled country, and baseline local sodium stratum as factors and baseline central sodium value as covariate.

The mean increase from baseline in central serum sodium was larger in the lixivaptan group than in the placebo group from Day 2 through Day 60 in the ITT population. Statistically significant treatment group differences were observed at Day 2, Day 3, Day 4, and Day 7.

According to the hierarchical testing procedure for secondary endpoints, the mean $nAUC_{0-60}$ was statistically significantly greater in the lixivaptan group than in the placebo group in the ITT population using LOCF/NOCB (2.6 mEq/L versus 1.9 mEq/L, p=0.039). Although not part of the hierarchical testing procedure, the mean $nAUC_{0-3}$ was statistically significantly greater in the lixivaptan group than the placebo group in the ITT population using LOCF/NOCB (1.8 mEq/L versus 0.8 mEq/L, p<0.001). Sensitivity analyses indicated that these results were not affected by handling of missing data, analysis population, or type of serum sodium value.

The percentage of subjects with worsening of hyponatremia during the double-blind treatment period was lower in the lixivaptan group than in the placebo group in the ITT population using OV (51.6% versus 61.0%, p=0.010). Similar results were observed using LOCF/NOCB in the ITT population (51.7% versus 61.7%, p=0.008).

Per the hierarchical testing procedure, the treatment group difference is not considered statistically significant. However, a statistically significant treatment group difference was observed for the shift in hyponatremia categories between baseline and Day 7 (p<0.001) and between baseline and Day 60 (p=0.023), with a greater percentage of subjects in the lixivaptan group than in the placebo group shifting at least one category of improvement from baseline at Day 7 (202/279 [72.4%] versus 172/296 [58.1%]) and at Day 60 (174/235 [74.0%] versus 158/244 [64.8%]).

A greater percentage of subjects in the lixivaptan group than subjects in the placebo group showed a shift from severe hyponatremia (≤125 mEq/L) at baseline to normal serum sodium (≥135 mEq/L) at Day 7 (8/34 [23.5%] versus 2/31 [6.5%]), respectively. At Day 60, the percentage of subjects who shifted from severe hyponatremia at baseline to normal serum sodium was 50.0% (13/26) in the lixivaptan group and 45.8% (11/24) in the placebo group.

The percentage of subjects who achieved normalized central serum sodium (≥135 and ≤145 mEq/L) was higher in the lixivaptan group than in the placebo group in the ITT population using OV on Day 7 (30.1% versus 24.3%, p=0.091) and Day 60 (36.6% versus 25.0%, p=0.007), respectively. At end of treatment, the percentage of subjects with normal central serum sodium values (≥135 to ≤145 mEq/L) was statistically significantly higher in the lixivaptan group than in the placebo group (66.9% versus 53.0%, p<0.001) in the ITT population using OV.

No statistically significant treatment group differences were observed in mean number of DAOH. Based on adjudicated hospitalizations from first dose to Day 60, the overall incidence of hospitalization was 27.2% in the lixivaptan group versus 29.2% in the placebo group. No statistically significant treatment group differences were observed for mean change from Baseline in time to complete the TMT-B.

7. SAFETY RESULTS

7.1. Introduction to Lixivaptan Safety

This section presents the Sponsor's analyses of overall safety data available from the lixivaptan clinical development program for treatment of euvolemic and hypervolemic hyponatremia associated with heart failure, SIADH, and other conditions. Included are analyses of all available safety data and details of AEs, SAEs, and clinical laboratory data from placebo-controlled studies. This section also includes analyses describing evidence relating to effects of lixivaptan on the potential risk related to the lixivaptan mode of action, i.e. overly rapid correction or over correction of serum sodium concentrations during initiation and continuation of treatment.

7.2. Exposure, Disposition and Demographics

A total of 36 clinical studies provide information on safety and tolerability of lixivaptan. A total of 1673 unique subjects received at least one dose of orally administered lixivaptan across these studies.

The primary lixivaptan safety population consists of subjects with hyponatremia (baseline local laboratory serum sodium concentration < 135 mEq/L) who were enrolled in the three Phase 3 placebo-controlled studies. A total of 525 subjects received lixivaptan and 425 received placebo in the placebo-controlled Phase 3 studies. The mean duration of exposure to lixivaptan across these three studies was 63.5 days (SD 46.9).

Subjects in the primary safety population received total daily doses of lixivaptan ranging from 25 mg to 200 mg.

The majority of subjects in the primary safety population were male (approximately 63%) and Caucasian (approximately 77%). The mean age was approximately 65 years. Twenty-six to 29% of subjects were aged 75 years or more. Subjects were enrolled by investigators in North America, Latin America, Western Europe, Eastern Europe, and India (Table 6).

The distribution of baseline local laboratory serum sodium concentrations among all subjects in the Phase 3 studies was: ≤ 125 mEq/L – 147 subjects (16%); > 125 - < 130 mEq/L – 232 subjects (24%); and ≥ 130 - < 135 mEq/L – 571 (60%). The categorical serum sodium concentrations among subjects randomized to lixivaptan and placebo are shown in Table 5.

Table 5 Distribution of Baseline Local Laboratory Serum Sodium Concentrations in Placebo-Controlled Phase 3 Studies

Serum Sodium Concentration (mEq/L)	Lixivaptan (n=525)	Placebo (n=425)
≤ 125	85	62
> 125 - < 130	119	113
≥ 130 - ≤ 135	321	250

Among all subjects who received lixivaptan in placebo-controlled Phase 3 studies, 322 (61%) were enrolled in Study 3401 (hypervolemic hyponatremia associated with acute worsening heart failure). Subjects with euvolemic hyponatremia associated with SIADH and other conditions were enrolled in Studies 3405 and 3430 and subjects receiving lixivaptan numbered 203 (39% of the total exposed to lixivaptan).

Table 6 Demographic and Baseline Characteristics in Placebo-Controlled Phase 3 Studies in Subjects With Hypervolemic and Euvolemic Hyponatremia Associated With Heart Failure and SIADH (ITT Population)

	---------- Study 3430 ----------		---------- Study 3405 ----------		---------- Study 3401 ----------	
Characteristic	**Lixivaptan N=154**	**Placebo N=52**	**Lixivaptan N=54**	**Placebo N=52**	**Lixivaptan N=323**	**Placebo N=329**
Age (years)						
Mean (SD)	66.6 (14.1)	62.7 (13.6)	66.4 (14.1)	65.2 (13.3)	64.9 (14.1)	64.7 (12.9)
Median	67.0	64.0	68.5	64.5	66.0	65.0
n (%) <65	67 (43.5)	28 (53.8)	22 (40.7)	26 (50.0)	153 (47.4)	164 (49.8)
n (%) ≥65	87 (56.5)	24 (46.2)	32 (59.3)	26 (50.0)	170 (52.6)	165 (50.2)
Sex, n (%)						
Male	73 (47.4)	27 (51.9)	26 (48.1)	30 (57.7)	233 (72.1)	234 (71.1)
Female	81 (52.6)	25 (48.1)	28 (51.9)	22 (42.3)	90 (27.9)	95 (28.9)
Ethnicity, n (%)						
Hispanic or Latino	19 (12.3)	8 (15.4)	2 (3.7)	3 (5.8)	33 (10.2)	33 (10.0)
Not Hispanic or Latino	135 (87.7)	44 (84.6)	52 (96.3)	49 (94.2)	290 (89.8)	296 (90.0)
Race, n (%)						
American Indian or Alaska native	2 (1.3)	1 (1.9)	0	0	0	0
Asian	18 (11.7)	8 (15.4)	8 (14.8)	6 (11.5)	58 (18.0)	58 (17.6)
Black or African American	7 (4.5)	8 (15.4)	2 (3.7)	2 (3.8)	25 (7.7)	13 (4.0)
Hispanic or Latino	0	0	0	0	1 (0.3)	2 (0.6)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0	0	0	0	1 (0.3)
Caucasian	126 (81.8)	35 (67.3)	44 (81.5)	44 (84.6)	239 (74.0)	255 (77.5)
On fluid restriction, n (%)						
No	128 (83.1)	46 (88.5)	34 (63.0)	18 (34.6)	112 (34.7)	123 (37.4)
Yes	26 (16.9)	6 (11.5)	20 (37.0)	34 (65.4)	210 (65.0)	206 (62.6)
Region, n (%)						
Asia (India)	17 (11.0)	7 (13.5)	7 (13.0)	6 (11.5)	55 (17.0)	56 (17.0)
Eastern Europe	0	0	9 (16.7)	9 (17.3)	133 (41.2)	135 (41.0)
Western Europe	8 (5.2)	4 (7.7)	19 (35.2)	18 (34.6)	40 (12.4)	38 (11.6)
North America	122 (79.2)	37 (71.2)	19 (35.2)	19 (36.5)	72 (22.3)	76 (23.1)
South America	7 (4.5)	4 (7.7)	0	0	23 (7.1)	24 (7.3)

7.3. Overview of the Safety of Lixivaptan in Specific Hyponatremia Populations

This section presents an overview of the safety profile of lixivaptan as observed in each of the two placebo-controlled Phase 3 studies of euvolemic hyponatremia secondary to SIADH and other conditions (Studies 3405 and 3430) and in the open-label extension study (Study 3431). This is followed by a review of the safety experience in subjects with hypervolemic hyponatremia associated with acute worsening heart failure enrolled in Study 3401.

7.4. Study 3405 (Euvolemic Hyponatremia Inpatient Trial)

This study was a Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled parallel group study of oral lixivaptan in subjects with euvolemic hyponatremia (baseline serum sodium concentration < 130 mEq/L) associated with SIADH and other conditions. Hospitalized subjects were randomized in a 1:1 ratio to lixivaptan 50 mg or placebo once daily for a treatment period of up to 30 days. After a 48-72 hour in-hospital titration period, the subject could be discharged. Study drug could have been increased to 100 mg per day or decreased to 25 mg per day. Subjects randomized numbered 106 and demographics are shown in Table 6. In the safety population, 50 subjects received lixivaptan and 51 subjects received placebo. The average daily dose of lixivaptan was 77.6 mg and the mean duration of exposure was 26 days (SD 8.8). Seventy-two percent (36/50) of subjects treated with lixivaptan received a maximum daily dose of 100 mg. An overview of the occurrence of treatment-emergent adverse events is shown in Table 7.

Table 7 Overview of Treatment-Emergent Adverse Events in Subjects Enrolled in Study 3405 (Euvolemic Hyponatremia Inpatient Trial)

Subjects with:	Lixivaptan (n=50)	Placebo (n=51)
Any treatment-emergent AE (TEAE)	35 (70%)	37 (72.5%)
Any severe TEAE	3 (6.0%)	7 (13.7%)
Any TEAE leading to discontinuation of study drug	2 (4.0%)	6 (11.8%)
Any treatment-emergent serious adverse event (SAE)	8 (16.0%)	15 (29.4%)
Any TEAE leading to death	0	4 (7.8%)

TEAEs with at least a 5% greater incidence in the lixivaptan group compared to placebo were constipation, insomnia, dizziness, and asthenia. TEAEs with at least a 5% greater incidence in the placebo group compared to lixivaptan were urinary tract infection, hyponatremia, diarrhea, hypertension, and cough. Three subjects receiving placebo and one subject receiving lixivaptan discontinued from the study due to hyponatremia.

As shown in Table 8, eight subjects treated with lixivaptan and 15 subjects treated with placebo had at least one treatment-emergent SAE, including 4 events with outcome of death in subjects receiving placebo. The most common non-fatal SAE reported for subjects receiving lixivaptan was hyponatremia, and in 2 of the 3 cases this event occurred shortly after cessation of lixivaptan treatment. One SAE was reported as hypernatremia in a subject who experienced an overly rapid increase in serum sodium

after one day of lixivaptan treatment; the subject recovered after interruption of treatment. As shown in Table 8, no type of SAE by SOC (System Organ Class) and/or individual event (with the exception of an event of fungal meningitis) was more commonly reported in subjects treated with lixivaptan.

Table 8 Overview of Treatment-Emergent Serious Adverse Events Reported by Subjects in Either Treatment Group -- Study 3405 (Euvolemic Inpatient Trial)

System Organ Class and/or Preferred Term	Lixivaptan (n=50)	Placebo (n=51)
Any treatment-emergent SAE	8 (16.0%)	15 (29.4%)
Cardiac Disorders	1(2.0%)	2 (3.9%)
Acute cardiac failure	1 (2.0%)	1 (2.0%)
Cardiorespiratory arrest	0	2 (3.9%)
Hypotension	1 (2.0%)	1 (2.0%)
Metabolism and nutrition disorders		
Hyponatremia	3 (6.0%)	4 (7.8%)
Blood sodium increased	1 (2.0%)	0
Endocrine disorders	1 (2.0%)	1 (2.0%)
Gastrointestinal disorders	1 (2.0%)	1 (2.0%)
Hepatobiliary disorders / bile duct stenosis	0	1 (2.0%)
Infection and infestations	1 (2.0%)	5 (9.8%)
Urinary tract infection	0	3 (5.9%)
Herpes zoster	0	1 (2.0%)
Meningitis coccidiodes	1 (2.0%)	0
Osteomyelitis	0	1 (2.0%)
Neoplasms, benign and malignant	0	2 (3.9%)
Nervous system disorders	0	2 (3.9%)
Altered state of consciousness	0	1 (2.0%)
Cognitive disorder	0	1 (2.0%)
Injury / Humerus fracture	0	1 (2.0%)
Psychiatric disorders / depression`	0	1 (2.0%)
Renal and urinary disorders / dysuria	0	1 (2.0%)
Respiratory disorders / COPD	0	1 (2.0%)

No deaths were reported in subjects who received lixivaptan. Four subjects treated with placebo had SAEs with fatal outcomes. Causes of death were reported as cardio-respiratory arrest, acute cardiac failure, chronic obstructive pulmonary diseases, and progression of neoplasm. One additional death occurred > 30 days after the last dose of placebo in a subject in a nursing home.

7.4.1. Clinical Laboratory Parameters

For all hematology parameters, mean changes from baseline to end of treatment were small and not judged to be clinically significant. Changes were similar in subjects who received either lixivaptan or placebo.

Biochemistry parameters, not including serum sodium concentrations, did not show important differences from baseline to end of treatment with either lixivaptan or placebo. Treatment-emergent changes in hepatic enzymes (ALT, AST, alkaline phosphatase) or

bilirubin did not differ meaningfully between treatment groups. No subject in either treatment group had a treatment-emergent finding of ALT and/or AST > 3 x ULN with total bilirubin ≥2 x ULN and alkaline phosphatase < 2 x ULN.

The frequency of overly rapid correction of serum sodium concentrations, as defined in Table 9 , was low and occurred in only 2 subjects treated with lixivaptan (4.0%) and 3 subjects treated with placebo (5.9%).

Table 9 Percentage of Subjects with Overly Rapid Correction of Central Serum Sodium in Study 3405 (Euvolemic Hyponatremia Inpatient Trial)

Parameter	Lixivaptan (n=50)	Placebo (n=51)
Change from pre-dose of > 8 mEq/L at 8 hours	1 (2.0%)	2 (3.9%)
Change from pre-dose of > 12 mEq/L at 12 hours	0	0
Change from pre-dose of > 18 mEq/L at 48 hours	1 (2.0%)	1 (2.0%)

No subjects in either group experienced overly rapid correction of serum sodium at 12 hours. Two subjects receiving lixivaptan and one subject treated with placebo had one central serum sodium concentration > 145 mEq/L during treatment (the highest value was 151 mEq/L on day 3 in a subject treated with lixivaptan).

7.4.2. Vital Signs

No clinically meaningful changes from baseline were observed for standing or supine systolic or diastolic blood pressures, standing or supine heart rate, respiratory rate, or temperature. The proportion of subjects who had a decrease in weight of ≥ 3 kg from baseline at end of treatment was higher in the lixivaptan group (7/46; 15.2%) than in the placebo group (4/49; 8.2%), likely reflecting the mechanism of action of lixivaptan.

7.4.3. Safety Conclusions – Subjects with Euvolemic Hyponatremia in Study 3405 (Euvolemic Hyponatremia Inpatient Trial)

In Study 3405, lixivaptan treatment at an initial dose of 50 mg per day with titration, if appropriate, to a maximum of 100 mg per day was demonstrated to be safe and well-tolerated for up to 30 days in this population of subjects with euvolemic hyponatremia. Overall adverse event frequencies did not differ between the lixivaptan and placebo groups, but events likely to be result of the pharmacologic action of lixivaptan (e.g., constipation, dry mouth, dizziness, insomnia) were somewhat more common with lixivaptan treatment. Overly rapid correction or over correction of serum sodium concentration was observed infrequently and was not different between treatment groups.

7.5. Study 3430 (Euvolemic Hyponatremia Outpatient Trial)

This study was a Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled parallel group study of oral lixivaptan in subjects with euvolemic hyponatremia (baseline serum sodium concentration < 135 mEq/L) associated with SIADH and other conditions. Subjects were randomized in a 3:1 ratio to lixivaptan or placebo once daily for a treatment period of up to 24 weeks. The medical setting during

the dose titration phase was a clinic, a long-term care facility, or a hospital. Treatment was initiated in medical clinics for 128 subjects (62.1%), in a long-term care facility for 44 subjects (21.4%), and in hospital for 34 subjects (16.5%). Subjects were released from the clinic medical setting if the increase in serum sodium concentration did not exceed 8 mEq/L at 8 hours after the first dose. Subjects with an increase in serum sodium concentration of > 8 mEq/L at 8 hours after the first dose of study drug underwent further safety assessments in the medical setting. For subjects who met protocol criteria at 8 hours after the first dose, subsequent clinic visits were scheduled for 24 and 48 hours after treatment initiation. During the titration period, study drug was initiated at the 25 mg dose of lixivaptan and could have been increased to 50 mg or 100 mg per day. Study drug could have been decreased to as low as 25 mg per day at any time during the study. Subjects randomized numbered 206 and the study demographics are shown in Table 6. The lixivaptan treatment group contained slightly more subjects aged ≥ 65 years (56.5%) than the placebo group (46.2%).

In the safety population, 153 subjects received lixivaptan and 52 subjects received placebo due to the 3:1 randomization. The average daily dose of lixivaptan was 71.5 mg and the mean duration of exposure was 112.4 days (SD 55.7). Sixty-five percent (100/153) of subjects treated with lixivaptan received a maximum daily dose of 100 mg. The rates of non-serious adverse events and adverse events leading to discontinuation of study treatment were lower in the lixivaptan group. An overview of the occurrence of treatment-emergent adverse events is shown in Table 10 .

Table 10 Overview of Treatment-Emergent Adverse Events in Subjects Enrolled in Study 3430 (Euvolemic Hyponatremia Outpatient Trial)

Subjects with:	Lixivaptan (n=153)	Placebo (n=52)
Any treatment-emergent AE (TEAE)	123 (80.4%)	44 (84.6%)
Any severe TEAE	19 (12.4%)	13 (25.0%)
Any TEAE leading to discontinuation of study drug	17 (11.1%)	9 (17.3%)
Any treatment-emergent serious adverse event (SAE)	28 (18.3%)	14 (26.9%)
Any TEAE leading to death	6 (3.9%)	1 (1.9%)

TEAEs with at least a 5% greater incidence in the lixivaptan group compared to placebo were urinary tract infection, polyuria, and upper respiratory tract infection. TEAEs with at least a 5% greater incidence in the placebo group compared to lixivaptan were headache, nausea, hyponatremia, and dehydration. Two subjects receiving lixivaptan discontinued from the study due to septic shock, two discontinued due to increased GGT, and two discontinued due to flatulence.

As shown in Table 11, 28 subjects (18.3%) treated with lixivaptan and 14 subjects (26.9%) treated with placebo had at least one treatment-emergent SAE, including events with outcome of death. SAEs with outcome of death were reported for six subjects who received lixivaptan. The causes of death were myocardial ischemia, pneumonia, septic shock, metastatic small cell lung cancer, cerebrovascular accident, and completed suicide. The subject in the placebo group who died was reported as having acute cardiac failure.

Treatment-emergent SAEs occurred less frequently overall in the lixivaptan group than among subjects receiving placebo, as shown in Table 11. Among subjects receiving lixivaptan, SAEs of urinary tract infection, pneumonia, and septic shock were more common than for subjects receiving placebo; however, due to the unbalanced randomization, the rates of these events did not differ meaningfully between treatment groups.

Table 11 Overview of Treatment-Emergent Serious Adverse Events Reported by at Least Two Subjects in Either Treatment Group -- Study 3430 (Outpatient Euvolemic Hyponatremia Trial)

Subjects with:	Lixivaptan (n=153)	Placebo (n=52)
Any treatment-emergent SAE	28 (18.3%)	14 (26.9%)
Acute cardiac failure	2 (1.3%)	2 (3.8%)
Anemia	1 (0.7%)	2 (3.8%)
Urinary tract infection	4 (2.6%)	1 (1.9%)
Pneumonia	3 (2.0%)	1(1.9%)
Septic shock	2 (1.3%)	0
Hyponatremia	3 (2.0%)	2 (3.8%)
Grand mal convulsion	0	2 (3.8%)

7.5.1. Clinical Laboratory Parameters

For all hematology parameters, mean changes from baseline to end of treatment were small and not judged to be clinically significant. Changes were similar in subjects who received either lixivaptan or placebo.

Biochemistry parameters, not including serum sodium concentrations, did not show important differences from baseline to end of treatment with either lixivaptan or placebo. A slightly larger proportion of subjects receiving placebo had increases in serum creatinine (3/52; 5.8%) than with lixivaptan treatment (2/153; 1.3%). Overall, treatment-emergent changes in hepatic enzymes (ALT, AST, alkaline phosphatase) or bilirubin did not differ meaningfully between treatment groups. No subject in either treatment group had a treatment-emergent finding of ALT and/or AST > 3 x ULN with total bilirubin ≥2 x ULN and alkaline phosphatase < 2 x ULN.

The frequency of overly rapid correction of serum sodium concentration was low and was balanced between treatment groups with a total of 3 subjects treated with lixivaptan (2.0%) and 1 subject treated with placebo (1.9%) (Table 12).

Table 12 Percentage of Subjects with Overly Rapid Correction of Central Serum Sodium in Study 3430

Parameter:	Lixivaptan (n=153)	Placebo (n=52)
Change from pre-dose of > 8 mEq/L at 8 hours	3 (2.0%)	0
Change from pre-dose of > 12 mEq/L at 12 hours	0	1 (1.9%)
Change from pre-dose of > 18 mEq/L at 48 hours	0	0

Two subjects (1.3%) receiving lixivaptan and four subjects (7.7%) treated with placebo had at least one central serum sodium concentration > 145 mEq/L during treatment. The highest value in a lixivaptan recipient was 148 mEq/L and the highest value in a subject treated with placebo was 150 mEq/L on day 2.

7.5.2. Vital Signs

No clinically meaningful changes from baseline were observed for standing or supine systolic or diastolic blood pressures, standing or supine heart rate, respiratory rate, or temperature. The proportion of subjects who had a decrease in weight of ≥ 3 kg from baseline to end of treatment was lower in the lixivaptan group (19/153; 12.4%) than in the placebo group (10/50; 20.0%).

7.5.3. Safety Conclusions – Subjects with Euvolemic Hyponatremia in Study 3430 (Euvolemic Hyponatremia Outpatient Trial)

In this study, over 80% of subjects initiated lixivaptan treatment in a non-hospital medical setting – either in a clinic or in a long-term care facility. Treatment with lixivaptan was demonstrated to be safe and well-tolerated in this total population of subjects with euvolemic hyponatremia who had enrollment serum sodium concentrations < 135 mEq/L. Overall adverse event frequencies did not differ importantly between the lixivaptan and placebo groups. Overly rapid correction or over correction of serum sodium concentration was uncommon in both treatment groups. SAEs occurred less frequently in subjects treated with lixivaptan; however the SAEs with fatal outcomes were more common in the lixivaptan group. Review of the causes of death confirmed that they were due to underlying conditions or acute events with no plausible relationship to lixivaptan treatment.

7.6. Study 3431 (Outpatient Extension Trial)

This study was a Phase 3, multinational, multicenter, open-label extension study of oral lixivaptan in subjects with hyponatremia (serum sodium concentration < 135 mEq/L) who had previously participated in any one of three placebo-controlled Phase 3 studies. Only the investigators participating in a placebo-controlled Phase 3 study could enroll subjects in Study 3431. In this study, lixivaptan treatment was initiated utilizing a mandatory 8 hour observation period at the investigative site. During the titration period, lixivaptan was begun at 25 mg once daily and could be titrated to a maximum of 100 mg once daily. The duration of study treatment was up to 28 weeks.

A total of 135 subjects were enrolled; the majority of whom had received lixivaptan in a previous Phase 3 blinded study – for these subjects enrollment in Study 3431 constituted re-initiation of lixivaptan treatment. A total of 32 subjects had received placebo in a prior Phase 3 study and thus were naïve to lixivaptan treatment. The average daily dose of lixivaptan was 68.57 mg and the mean duration of exposure was 171.5 days (SD 58.2). Eighty percent of subjects were treated with lixivaptan for greater than 180 days. The rates of non-serious adverse events, adverse events leading to discontinuation of study treatment, SAEs and TEAE leading to death are shown in Table 13.

Table 13 Overview of Treatment-Emergent Adverse Events in Subjects Enrolled in Study 3431 (Outpatient Extension Trial)

Subjects with:	Lixivaptan (n=135)
Any treatment-emergent AE (TEAE)	109 (80.7%)
Any severe TEAE	14 (10.4%)
Any TEAE leading to discontinuation of study drug	10 (7.4%)
Any treatment-emergent serious adverse event (SAE)	28 (20.7%)
Any TEAE leading to death	4 (3.0%)

Treatment-emergent adverse events reported by ≥ 5% of subjects included urinary tract infection (8.9%), headache (5.2%), nausea (7.4%), bronchitis (6.7%), pneumonia (5.9%), hypertension (5.9%), diarrhea (5.2%), fatigue (5.2%), nasopharyngitis (5.2%), contusion (5.2%), hyperkalemia (5.2%), and cough (5.2%).

Four subjects (3.0%), each previously enrolled in a Phase 3 study of euvolemic hyponatremia had treatment emergent SAEs with an outcome of death. The reported causes of death were acute coronary syndrome, arrhythmia, failure to thrive, and acute respiratory failure. Non-fatal SAEs reported for two or more subjects were atrial fibrillation (2), hyponatremia (3), gastrointestinal hemorrhage (2), urinary tract infection (4), convulsion (2), acute renal failure (2), COPD (3), and pneumonia (6).

7.6.1. Clinical Laboratory Parameters

For all hematology parameters, mean changes from baseline were small and not judged to be clinically significant.

Biochemistry parameters, not including serum sodium concentrations, did not show important differences from baseline to end of treatment with lixivaptan treatment. It was noted that uric acid increases of approximately 10-15% over baseline were present at all on-treatment visits. Overall, treatment-emergent changes in hepatic enzymes (ALT, AST, alkaline phosphatase) or bilirubin were minor and not clinically meaningful. No subject had a treatment-emergent finding of ALT and/or AST > 3 x ULN with total bilirubin ≥2 x ULN and alkaline phosphatase < 2 x ULN.

The frequency of overly rapid correction of serum sodium concentration during the titration phase of lixivaptan treatment was low (Table 14). Increases in serum sodium concentration for six subjects met the protocol criteria; none of these subjects had a serum sodium concentration that exceeded 145 mEq/L.

Table 14 Percentage of Subjects with Overly Rapid Correction of Central Serum Sodium during Titration Phase - Study 3431 (Outpatient Extension Trial)

Parameter:	Lixivaptan (n=135)
Change from open-label trial baseline of > 8 mEq/L within 8 hours of first dose	5 (3.7%)
Change from open-label trial baseline of > 12 mEq/L within 12 hours of first dose	1 (0.7%)
Change from open-label trial baseline of > 18 mEq/L within 48 hours of first dose	0

7.6.2. Vital Signs

No clinically meaningful changes from baseline were observed for standing or supine systolic or diastolic blood pressures, standing or supine heart rate, respiratory rate, or temperature. The proportion of subjects who had a decrease in weight of ≥ 3 kg from baseline to end of treatment was 12.9% (16/135).

7.6.3. Safety Conclusions – Subjects with Euvolemic Hyponatremia in Study 3431(Outpatient Extension Trial)

Treatment with lixivaptan was well-tolerated in this population of outpatient subjects with euvolemic hyponatremia who had enrollment serum sodium concentrations < 135 mEq/L. The types and frequencies of adverse events observed were similar to that in the double-blind placebo controlled studies evaluating subjects with hyponatremia associated with SIADH or other conditions. Overly rapid correction or over correction of serum sodium was uncommon. In this study, lixivaptan treatment was successfully and safely initiated or re-initiated in a non-hospital medical setting.

7.7. Study 3401 (Hypervolemic Hyponatremia Inpatient Trial)

This study was a Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled parallel group study of oral lixivaptan in the management of hyponatremia (serum sodium concentration < 135 mEq/L) in hospitalized subjects who had acute worsening of chronic heart failure and volume overload.

Subjects were enrolled as hospital inpatients and randomized in a 1:1 ratio to lixivaptan 50 mg or placebo. Randomization was stratified by country/region and by baseline serum sodium concentration obtained at the local laboratory. An inpatient dose titration phase of 72 hours duration was required to allow the investigator to adjust the study drug dose up to a maximum of lixivaptan 100 mg twice daily (or placebo). The dose administered in the treatment phase from day 4 to end of treatment was to be the dose determined at the end of the titration phase. The maximum treatment duration was up to 60 days.

Subjects randomized numbered 652 and the demographics are shown in Table 6. The treatment groups were well-balanced across demographic variables. Females made up a minority of the subjects randomized (185/652; 28.4%). In the safety population, 322 subjects received lixivaptan and 322 subjects received placebo. The average daily dose of lixivaptan was 105.0 mg and the mean duration of exposure was 46.6 days (SD 21.8). The maximum daily doses of lixivaptan received (by dose) were: 50 mg (95/322; 29.5%), 100 mg (123/322 (38.2%), and 200 mg (102/322; 31.7%).

The rates of non-serious adverse events, adverse events leading to discontinuation of study treatment, and treatment-emergent SAEs were similar between the two treatment groups as shown in Table 15. TEAEs with fatal outcome were slightly more common among subjects treated with lixivaptan.

Table 15 Overview of Treatment-Emergent Adverse Events in Subjects Enrolled in Study 3401 (Inpatient Hypervolemic Hyponatremia Trial)

Subjects with:	Lixivaptan (n=322)	Placebo (n=322)
Any treatment-emergent AE (TEAE)	254 (78.9%)	250 (77.6%)
Any severe TEAE	101 (31.4%)	87 (27.0%)
Any TEAE leading to discontinuation of study drug	50 (15.5%)	50 (15.5%)
Any treatment-emergent serious adverse event (SAE)	138 (42.9%)	128 (39.8%)
Any TEAE leading to death	43 (13.4%)	34 (10.6%)

TEAEs with at least a 2% greater incidence in the lixivaptan group compared to placebo were constipation, GGT increased, and vertigo. TEAEs with at least a 2% greater incidence in the placebo group compared to lixivaptan were acute cardiac failure, hypotension, hyponatremia, pyrexia, and anorexia.

Treatment-emergent AEs that led to discontinuation of study drug in at least 1% of subjects in either treatment group included acute cardiac failure (6.2% lixivaptan; 8.4% placebo) and hyponatremia (0.6% lixivaptan; 2.2% placebo).

The percentages of subjects with treatment-emergent SAEs were similar among the two treatment groups as shown in Table 16. There was no apparent imbalance between treatment groups with respect to the types of events that met SAE criteria, with the possible exception of Infections and Infestations which were more common in the lixivaptan group. However, review of the types of the infections reported did not suggest that an identifiable risk accompanied lixivaptan treatment.

Table 16 Overview of Treatment-Emergent Serious Adverse Events Reported by at Least Two Subjects in Either Treatment Group -- Study 3401 (Hypervolemic Hyponatremia Inpatient Trial)

System Organ Class and Preferred Term	Lixivaptan (n=322)	Placebo (n=322)
Any treatment-emergent SAE	138 (42.9%)	128 (39.8%)
Blood and lymphatic disorders	2 (0.6%)	2 (0.6%)
Anemia	2 (0.6%)	1 (0.3%)
Cardiac Disorders	99 (30.7%)	98 (30.4%)
Acute cardiac failure	82 (25.5%)	86 (26.7)
Cardiac arrest	6 (1.9)	2 (0.6)
Atrial fibrillation	5 (1.6)	2 (0.6)
Cardiogenic shock	4 (1.2%)	3 (0.9%)
Ventricular tachycardia	5 (1.6%)	2 (0.6%)
Coronary artery disease	1 (0.3%)	3 (0.9%)
Acute myocardial infarction	2 (0.6%)	1 (0.3%)
Acute coronary syndrome	2 (0.6%)	0
Angina pectoris	0	2 (0.6%)
Bradycardia	0	2 (0.6%)
Gastrointestinal disorders	8 (2.5%)	10 (3.1%)
Constipation	2 (0.6%)	0
General disorders and administration site conditions	2 (0.6%)	3 (0.9%)
Non-cardiac chest pain	2 (0.6%)	0
Sudden death	0	2 (0.6%)
Infection and infestations	24 (7.5%)	14 (4.3%)
Pneumonia	4 (1.2%)	3 (0.9%)
Sepsis	3 (0.9%)	3 (0.9%)
Septic shock	4 (1.2%)	2 (0.6%)
Cellulitis	1 (0.3%)	2 (0.6%)
Osteomyelitis	2 (0.6%)	1 (0.3%)
Urinary tract infection	2 (0.6%)	0
Metabolism and Nutrition disorders	11 (3.4%)	14 (4.3%)
Hyponatremia	2 (0.6%)	12 (3.7%)
Dehydration	4 (1.2%)	0
Hyperkalemia	0	3 (0.9%)
Hyperglycemia	2 (0.6%)	0
Nervous system disorders	11 (3.4%)	7 (2.2%)
Syncope	2 (0.6%)	0
Renal and urinary disorders	8 (2.5%)	8 (2.5%)
Acute renal failure	4 (1.2%)	5 (1.6%)
Renal impairment	3 (0.9%)	2 (0.6%)
Respiratory disorders	13 (4.0%)	9 (2.8%)
Pulmonary embolism	3 (0.9%)	2 (0.6%)
Respiratory failure	4 (1.2%)	1 (0.3%)
COPD	1 (0.3%)	3 (0.9%)
Acute pulmonary edema	1 (0.3%)	2 (0.6%)
Pleural effusion	2 (0.6%)	0
Vascular disorders	9 (2.8%)	7 (2.2%)
Hypotension	3 (0.9%)	6 (1.9%)
Arterial hemorrhage	2 (0.6%)	0

A total of 103 subjects who received at least one dose of either lixivaptan or placebo had a fatal event either during the period of drug administration, within 1-30 days after the last dose, or > 30 days after the last dose. The numbers of deaths by period are shown in Table 17.

Table 17 Mortality at Any Time after Randomization in Study 3401 (Hypervolemic Hyponatremia Inpatient Trial)

Subjects with:	**Lixivaptan (n=322)**	**Placebo (n=322)**
Death while receiving study drug	13	5
Death 1-30 days after last dose of study drug	37	35
Death > 30 days after last dose of study drug	7	6
Totals	57	46

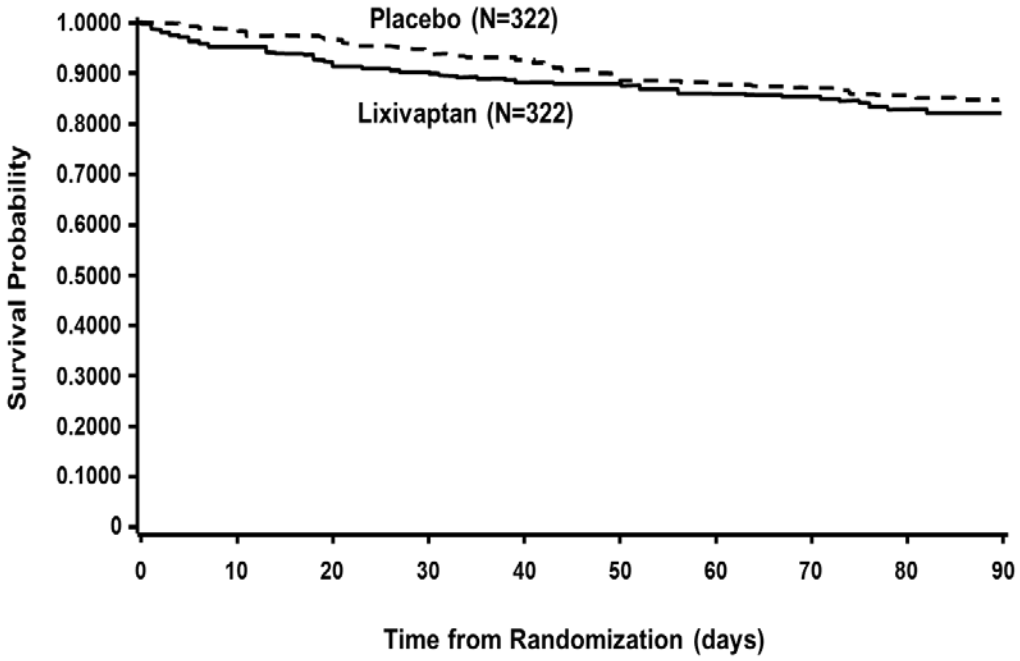
The total numbers of deaths, excluding the deaths occurring > 30 days after the last dose of study drug, are shown in Table 18. A numerical imbalance occurred in the percentage of deaths in the two treatment groups during the first 15 days after randomization when 19 deaths occurred among lixivaptan subjects and 8 deaths occurred among placebo subjects. The difference in the overall mortality rates between the two treatments may be accounted for by the difference during the first six days following randomization (Days 0-5) when 12 deaths (3.7%) occurred in the lixivaptan group and 2 deaths (0.6%) occurred in the placebo group.

Table 18 Mortality at Various Time Intervals after Randomization in Study 3401 (Hypervolemic Hyponatremia Inpatient Trial)

Study Day[a]	**Lixivaptan (n=322)**	**Placebo (n=322)**
Day 0 - 15	19 (5.9%)	8 (2.5%)
Day 0 - 5	12 (3.7%)	2 (0.6%)
Day 6 - 10	3 (0.9%)	3 (0.9%)
Day 11 – 15	4 (1.2%)	3 (0.9%)
Day 16 – 30	12 (3.6%)	11 (3.4%)
Day 31 – 60	9 (2.8%)	13 (4.0%)
Day 61 – 90	10 (3.1%)	8 (2.5%)
Total[b]	50 (15.5%)	40 (12.4%)

[a] Day 0 is the first day of randomization
[b] Deaths occurring >30 days after the last dose of study drug are excluded.

The hazard ratio for the overall excess of deaths in the lixivaptan treatment group was 1.3 (95% CI: 0.82-2.07) (p=0.1585). A Kaplan-Meier plot of survival for both treatment arms is shown in Figure 4.



Survival curves have been truncated at 90 days post randomization

Figure 4 Kaplan-Meier plot of survival in Study 3401

Analyses confirmed that the two treatment groups appeared to be well-balanced in terms of medical history, clinical presentation, and concomitant medications.

A blinded, independently performed and prospectively defined assessment of disease severity was conducted prior to database lock and led to the identification of subjects at increased risk of death at randomization. However, these subjects appeared to be evenly distributed between the two treatment groups, and this observation was confirmed by application of the OPTIMIZE-HF nomogram for risk of death (Abraham et al, 2008).

Available information for the 90 deaths that occurred during the study and up to 30 days after the last dose of study drug was reviewed. When more than one AE was reported with death as the outcome, the primary cause of death was identified based on medical judgment. The following categorical schema was employed.

- Deaths due to acute cardiac failure, cardiac arrest, sudden death, cardiogenic shock, arrhythmia, hypotension, ventricular failure, pulmonary edema, acute myocardial infarction, and ventricular rupture were classified as cardiac deaths.
- Deaths due to respiratory failure and pulmonary embolism were classified as respiratory deaths.
- Deaths due to sepsis, septic shock, and pneumonia were classified as due to infection.
- Deaths due to arterial hemorrhage, aortic aneurysm rupture, and cerebral hemorrhage were classified as due to hemorrhage.

Deaths occurring on Days 0-15 of the study were examined in particular detail. There were 27 deaths during this study interval in subjects enrolled across 22 study sites in 9 countries. Table 19 shows the primary causes of death that occurred during Day 0-15 based on review of the cases.

Table 19 Primary Causes of Death during the First 15 Days after Randomization: Study 3401 (Hypervolemic Hyponatremia Inpatient Trial)

	Cause of Death				
Day after Randomization	**Cardiac**	**Respiratory**	**Infection**	**Hemorrhage**	**Total**
Day 0 – 5					
Lixivaptan	8	1	2	1	12
Placebo	2	0	0	0	2
Day 6 - 10					
Lixivaptan	3	0	0	0	3
Placebo	2	0	1	0	3
Day 11 - 15					
Lixivaptan	2	0	1	1	4
Placebo	2	1	0	0	3

With respect to the imbalance in mortality observed during Day 0-5, a review of the eight cases described as cardiac deaths among subjects randomized to lixivaptan does not suggest any unifying hypothesis that might explain these events as being directly related to lixivaptan exposure. The pre-randomization clinical histories of the eight subjects describe severely ill individuals with multiple comorbidities and unstable medical conditions at time of enrollment.

In summary, the reason for the difference in early mortality observed between the two treatment groups in Study 3401 (Hypervolemic Hyponatremia Inpatient Trial) remains unclear. An unexpectedly low early mortality rate (0.6%) for the subjects in the placebo group with acute worsening of heart failure was noted. After the initial Day 0-5 period, there were no differences in mortality rates between the two treatments groups.

7.7.1. Clinical Laboratory Parameters

For all hematology parameters, mean changes from baseline were small and not judged to be clinically significant. Changes were similar in subjects who received either lixivaptan or placebo.

No clinically meaningful changes from baseline were observed in INR or prothrombin times among subjects who received coumarin derivatives.

Biochemistry parameters, not including serum sodium concentrations, did not show important differences from baseline to end of treatment in either the lixivaptan or placebo groups. Overall, treatment-emergent changes in hepatic enzymes (ALT, AST, alkaline phosphatase) or bilirubin did not differ meaningfully between treatment groups. There were 7 lixivaptan subjects (2.2%) and 8 placebo subjects (2.5%) who had the treatment-emergent finding of ALT and/or AST > 3 x ULN with total bilirubin ≥2 x ULN and

alkaline phosphatase < 2 x ULN. In each case, the laboratory findings appeared to result from hepatic congestion due to heart failure.

The frequency of overly rapid correction of serum sodium concentration during the titration phase differed by treatment and was lowest for the lixivaptan treatment group with a total of 7 subjects (2.2%) meeting the protocol-defined criteria for this event as compared with 16 subjects (5.0%) treated with placebo (Table 20).

Table 20 Percentage of Subjects with Overly Rapid Correction of Central Serum Sodium during the Titration Phase in Study 3401 (Hypervolemic Hyponatremia Inpatient Trial)

Parameter:	Lixivaptan (n=322)	Placebo (n=322)
Change from pre-dose of > 8 mEq/L at 8 hours	4 (1.2%)	11 (3.4%)
Change from pre-dose of > 12 mEq/L at 12 hours	4 (1.2%)	6 (1.9%)
Change from pre-dose of > 18 mEq/L at 48 hours	0	1 (0.3%)

Thirty-one subjects (9.6%) receiving lixivaptan and 37 subjects (11.5%) treated with placebo had at least one central serum sodium concentration > 145 mEq/L during treatment. Of these 68 subjects, 12 subjects in each treatment group had at least one central serum sodium concentration > 145 mEq/L during the titration phase.

7.7.2. Vital Signs

No clinically meaningful changes from baseline were observed for standing or supine systolic or diastolic blood pressures, standing or supine heart rate, respiratory rate, or temperature. The proportion of subjects who had a decrease in weight of ≥ 3 kg from baseline to end of treatment was slightly lower in the lixivaptan group (103/316; 32.6%) than in the placebo group (122/316; 38.6%).

7.7.3. Safety Conclusions – Subjects with Hypervolemic Hyponatremia in Study 3401 (Hypervolemic Hyponatremia Inpatient Trial)

In this study, treatment with lixivaptan was demonstrated to be safe and well-tolerated in this population of subjects with hypervolemic hyponatremia associated with acute worsening heart failure who had baseline local serum sodium concentrations < 135 mEq/L. Overall the frequencies of non-serious adverse events did not differ importantly between the lixivaptan and placebo groups. Overly rapid correction or over correction of serum sodium was less common in the lixivaptan treatment group. SAEs occurred slightly more frequently in subjects treated with lixivaptan and SAEs with fatal outcomes were slightly more common overall in the lixivaptan group. Acute cardiac failure was the most common cause of death in both treatment groups. A numerical imbalance in the number and percentage of deaths in the two treatment groups was present during the Day 0-5 period after randomization. Careful examination of the clinical details of these cases does not suggest any unifying hypothesis that might explain these events as being directly related to lixivaptan exposure.

7.8. Assessment of Mortality within the Lixivaptan Development Program

Table 21 provides an overview of the mortality experience in all Phase 2 and Phase 3 studies conducted.

Among subjects enrolled in studies evaluating lixivaptan for treatment of euvolemic hyponatremia associated with SIADH and other conditions, mortality rates were numerically higher with placebo treatment (5.0%) than with lixivaptan treatment (3.6%).

The heart failure population was comprised of subjects with stable heart failure in Phase 2 studies as well as subjects with acute worsening of heart failure in one Phase 3 study. In the overall population of subjects with heart failure, mortality rates were comparable between subjects who received lixivaptan treatment (10.0%) or placebo treatment (10.6%).

A higher mortality rate was observed among subjects randomized to lixivaptan treatment compared to placebo treatment in the Phase 2 studies that enrolled subjects with liver cirrhosis and ascites.

Table 21 Disposition of Deaths Occurring ≤ 30 Days after Last Dose in Phase 2 and Phase 3 Studies

Studies	Lixivaptan Subjects	Number of Deaths	Placebo Subjects	Number of Deaths
All subjects in Phase 2/3 Studies	867	70 (8.1%)	572	53 (9.3%)
Subjects in SIADH Studies*	251	9 (3.6%)	120	6 (5.0%)
Subjects in Heart Failure Studies	502	50 (10.0%)	414	45 (10.9%)
Subjects with Liver Cirrhosis and Ascites	114	11 (9.6%)	39	2 (5.1%)

*Three subjects in the SIADH group re-enrolled and received both lixivaptan and placebo. These subjects are represented in the 'Lixivaptan Subjects' column and the 'Placebo Subjects' column.

Table 22 presents the results from analyses of the confidence boundaries for potential absolute increased mortality risk with lixivaptan treatment compared to placebo based on observed all-cause mortality in the Phase 2 and Phase 3 studies. The mortality experience in the Phase 3 study of worsening heart failure (Study 3401) represents an outlier when overall mortality risk is considered (Figure 5). In summary, within the total lixivaptan clinical development program there is no confirmed and/or definite signal of increased mortality risk.

Table 22 Potential Absolute Mortality Risk (Lixivaptan versus Placebo)

Population	Number treated with lixivaptan	95% boundary for increased absolute mortality (%)	95% boundary for reduced absolute mortality (%)
All Phase 2 & 3 Studies	867	1.7	4.2
Phase 2 & 3 SIADH Studies*	251	3.3	6.8
Phase 2 & 3 Heart Failure Studies	502	2.7	5.0
Phase 3 SIADH Studies*	203	2.9	8.2
Phase 3 Worsening Heart Failure Study	322	7.4	2.6

*Three subjects in the SIADH group re-enrolled and received both lixivaptan and placebo. These subjects are represented in the 'Lixivaptan Subjects' column and the 'Placebo Subjects' column.

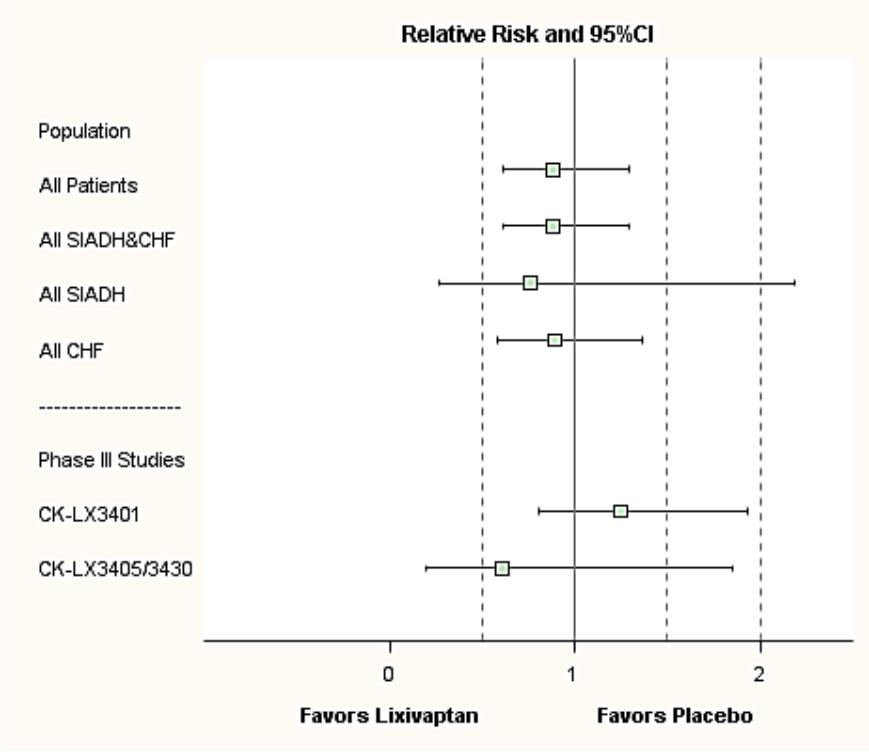


Figure 5 Forest plot of relative risks of mortality at 60 days after randomization in Phase 2 and Phase 3 studies (with 95% confidence intervals).

7.9. Pooled Evaluation of Overly Rapid Correction of Serum Sodium Concentration in Phase 3 Studies

Low numbers of subjects receiving lixivaptan had overly rapid correction of serum sodium concentration and the rates were lower than for placebo treatment (Table 23). The data are pooled by medical setting of the initiation of treatment as either outpatients or inpatients. There was no suggestion of a higher risk of overly rapid correction of serum sodium in Study 3430, in which the majority of subjects initiated therapy in an outpatient medical setting.

Table 23 Subjects with Overly Rapid Correction of Central Serum Sodium Concentration

Parameter	n/N (%) of Subjects	
	Lixivaptan N=525	Placebo N=425
Overly rapid correction at 8 hours (>8 mEq/L increase)		
Study 3430 (Outpatients*)	3/153 (2.0)	0/52
Studies 3401 and 3405 combined (Inpatients)	5/372 (1.3)	13/373 (3.5)
Overly rapid correction at 24 hours (>12 mEq/L increase)		
Study 3430 (Outpatients*)	0/153	1/52 (1.9)
Studies 3401 and 3405 combined (Inpatients)	4/372 (1.1)	6/373 (1.6)
Overly rapid correction at 48 hours (>18 mEq/L increase)		
Study 3430 (Outpatients*)	0/153	0/52
Studies 3401 and 3405 combined (Inpatients)	1/372 (0.3)	2/373 (0.5)

* > 80% of subjects had treatment initiated in non-hospital medical setting

7.10. Pooled Analysis of Adverse Events in Phase 3 Studies

Adverse event data reported in the placebo-controlled Phase 3 studies that evaluated subjects with hypervolemic and euvolemic hyponatremia were pooled to provide additional information to describe the safety profile of the lixivaptan. The pharmacologic action of lixivaptan explains the higher incidence of thirst and polyuria observed with lixivaptan treatment. The higher rate of constipation is also characteristic of the vaptan class. The higher incidence of upper respiratory tract infections is currently unexplained.

Table 24 Adverse Events Reported in Subjects Treated with Lixivaptan in Phase 3 Studies with Incidence ≥ 2% Greater than for Subjects Treated with Placebo

SOC and MedDRA Preferred Term	Lixivaptan (n=525)	Placebo (n=425)
Gastrointestinal disorders Constipation	44 (8.4%)	24 (5.6%)
General disorders and administrative site conditions Thirst	11 (2.1%)	0
Infections and infestations Upper respiratory tract infection	15 (2.9%)	3 (0.7)
Renal and urinary disorders Polyuria	15 (2.9%)	3 (0.7%)

7.11. Study 1430: Thorough QTc Study of Lixivaptan in Healthy Volunteers

A double-blind, randomized, repeat-dose, single-site, parallel group Phase 1 study was conducted to define the ECG effects of lixivaptan using a clinical and a supratherapeutic

dose compared to placebo and moxifloxacin (a positive control) in healthy adult men and women.

A total of 316 subjects were randomized into the study, 298 subjects received study treatment and 288 subjects completed the study. Subjects ranged in age from 18 to 45 years (mean age 28 years).

Study treatments were placebo BID x 7d, lixivaptan 100 mg PO BID x 7d, lixivaptan 400 mg BID x 7d, and placebo BID x 6d + moxifloxacin 400 mg on day 7.

There were no SAEs and no deaths in this study. All adverse events reported were of mild or moderate severity (Table 25).

Table 25 Overview of Treatment-Emergent Adverse Events in Subjects Enrolled in Study 1403

Subjects with:	Placebo (n=77)	Lixivaptan 100 mg BID x 7d (n=75)	Lixivaptan 400 mg BID x 7d (n=69)	Positive control (moxifloxacin) (n=77)
Any treatment-emergent AE (TEAE)	27 (35.1%)	33(44.0%)	42 (60.9%)	25 (32.5%)

Examination of the TEAEs that were judged related to treatment by the investigator showed statistically significant associations of the events of dry mouth, headache, and dizziness for subjects receiving the supratherapeutic dose of lixivaptan (400 mg BID x 7 days).

7.11.1. Clinical Laboratory Parameters

No changes in hematologic parameters were noteworthy. Analysis of the mean serum sodium concentration values showed changes increasing up to approximately two standard deviations within the supratherapeutic group from Day 2 to Day 6, with return to baseline values by time of the follow-up visit. For subjects in the therapeutic dose group, the increases in mean serum sodium concentrations were approximately one standard deviation by Day 6, and returned to baseline by time of the follow-up visit.

7.11.2. Vital Signs

There were no apparent treatment-related changes in vital signs within or between treatment groups.

7.11.3. Conclusions – Thorough QTc Study of Lixivaptan in Healthy Volunteers

The moxifloxacin positive control group showed the expected small change in QTc duration that averaged 7 msec. This study showed no effect of lixivaptan at a therapeutic dose of 100 mg BID or at a supratherapeutic dose of 400 mg BID on heart rate, AV conduction, or cardiac depolarization as measured by the PR and QRS interval durations.

All doses of lixivaptan and control study drugs were well tolerated. Certain non-serious and non-severe adverse events, as well as shifts in creatinine and blood electrolyte values, occurred more frequently in subjects receiving the supratherapeutic dose of lixivaptan and these findings were consistent with the known pharmacologic actions of lixivaptan.

7.12. Overview of Drug-Drug Interaction Studies

Clinical drug-drug interaction (DDI) studies have been conducted to determine the presence and extent of interactions via CYP3A4 (ketoconazole, grapefruit juice, simvastatin, atorvastatin, and amiodarone), CYP2C9 (warfarin), and CYP2C8 (carbamazepine) pathways. Clinical DDI studies were also conducted with drugs likely to be co-administered with lixivaptan in target patient populations (furosemide, digoxin, enalapril, hydrochlorothiazide, and spironolactone).

The key findings of the lixivaptan DDI studies are summarized in Table 26.

Table 26 Overview of Drug-Drug Interaction Studies with Lixivaptan

Interaction Studied	Results	Study Number
Amiodarone	After steady-state co-administration of lixivaptan and amiodarone; amiodarone C_{max} increased by only 12%; AUC_{tau} and AUC_{last} increased by 14% and 11%, respectively. DEA C_{max} increased by only 2%; AUC_{tau} decreased by 2% and AUC_{last} increased by 6%. All CIs met the pre-established bioequivalence limits. Therefore, co-administration of lixivaptan + amiodarone did not have a significant effect on amiodarone or DEA concentrations.	CK-LX2402
Atorvastatin	Lixivaptan's effect on atorvastatin was minimal and did not appear to be dose-dependent. Lixivaptan increased atorvastatin C_{max} by 8% to 58% and AUC_{∞} by 9% to 33%.	CK-LX1420
Carbamazepine	After co-administration of carbamazepine, lixivaptan mean C_{max} and AUC_{tau} values decreased approximately 67.5% and 71.5%, respectively, and mean CL/F values increased by approximately three-fold. Co-administration of carbamazepine with lixivaptan resulted in significantly lower urine output and fluid intake. No significant changes in the PK of carbamazepine or its metabolite, CBZ-E. These results demonstrate that lixivaptan did not statistically significantly inhibit the metabolism of carbamazepine, and that lixivaptan does not inhibit the metabolism of CYP2C8 substrates.	CK-LX1422
Digoxin	Both lixivaptan and digoxin C_{max} increased by approximately 25% when used in combination. No significant effect on digoxin AUC_{24} was observed; lixivaptan AUC_{∞} increased by 11% (marginally significant).	0892A1-106-US
Enalapril	No effect on lixivaptan AUC_{24} or on enalapril C_{max} was observed when used in combination. Lixivaptan C_{max} increased 14.5% and enalapril AUC_4 increased 16.2% when used in combination. These changes were not clinically relevant. C_{max} and AUC_{24} for the active metabolite of enalapril (enalaprilat) increased by 35.9% and 29.7%, respectively.	0892A1-107-US

Furosemide	There was no effect on lixivaptan exposure when used in combination with furosemide. Lixivaptan C_{max} and AUC_{∞} CIs were within 80%-125%. Furosemide AUC not affected when used in combination with lixivaptan; AUC_{∞} was within the 80%-125% CI, but C_{max} was 6% lower when co-administered with lixivaptan (CI=64%-136%). Furosemide urinary excretion was unchanged when co-administered with lixivaptan.	0892A1-105- US
Grapefruit juice	Grapefruit juice significantly increased the extent of lixivaptan absorption as compared to lixivaptan administered under fasted conditions but not under fed conditions.	CK-LX1411
Hydrochloro-thiazide (HCTZ)	No statistically significant ($p<0.05$) changes in lixivaptan or HCTZ C_{max} and AUC_{∞} after co-administration of HCTZ (25 or 50 mg) with either 50 mg or 100 mg of lixivaptan were observed. The highest strengths tested (100 mg lixivaptan + 50 mg HCTZ) met the 80%-125% CIs for lixivaptan C_{max} and AUC_{∞}. In addition, lixivaptan AUC_{∞} met the 80%-125% CI for 50 mg lixivaptan + 50 mg HCTZ. A 17% reduction in HCTZ AUC_{∞} occurred in the highest dose group (100 mg lixivaptan + 50 mg HCTZ).	0892A1-119-EU
Ketoconazole	Lixivaptan C_{max} and AUC_{∞} increased by 2.4-fold and 3.2-fold, respectively, when lixivaptan was administered with ketoconazole.	CK-LX1410
Simvastatin	Lixivaptan + simvastatin increased simvastatin and simvastatin acid exposure, resulting in a three-fold increase in C_{max}, AUC_t, and AUC_{∞}. A noticeable prolongation in simvastatin and simvastatin acid $t_{1/2}$ was associated with a 70% decrease in PO administered simvastatin plasma CL/F.	CK-LX1415
Simvastatin	Co-administration of the 50-mg QD dose of lixivaptan with either the AM or PM dose of simvastatin (40 mg) resulted in small differences in simvastatin and simvastatin acid PK parameters (-6% to 37%). However, simvastatin exposure increased by a factor of two- to three-fold when administered with lixivaptan doses of 100 to 200 mg per day.	CK-LX1419
Spironolactone	Lixivaptan C_{max} and AUC_{∞} increased 29% and 34%, respectively, when lixivaptan was dosed with spironolactone. Spironolactone C_{max} and AUC_t increased by 39% and 18%, respectively, when spironolactone was dosed with lixivaptan. Mean canrenone Cl_r values were 83.7 and 89.8 mL/hr for spironolactone dosed alone on Day 6 and lixivaptan dosed with spironolactone on Day 12, respectively. The percent excreted in urine was less than 0.2% on all days. Canrenone C_{max} values did not change when spironolactone was dosed with and without lixivaptan.	0892A1-121-US
Warfarin	Warfarin increased lixivaptan AUC_{∞} and C_{max} by 27% and 16%, respectively. No significant changes in R- or S-warfarin exposure or prothrombin time following co-administration of steady-state warfarin and lixivaptan compared to warfarin alone were observed.	0892A1-115- US

AM=Morning. AUC=Area under the concentration-time curve. AUC_4=Area under the concentration-time curve from zero to four hours. AUC_{24}=Area under the concentration-time curve from zero to 24 hours. AUC_{last}=Area under the concentration-time curve from zero to the last measurable concentration. AUC_{∞}=Area under the concentration-time curve from zero to infinity. AUC_t=Area under the concentration-time curve from zero to the last observable concentration at time t. AUC_{tau}=Area under the concentration-time curve from zero to the end of the dosing interval. BID=Twice daily. CBZ-E=Carbamazepine 10,11-epoxide. CI=Confidence interval. CL/F=Clearance. Cl_r=Apparent renal clearance. C_{max}=Maximum concentration. CYP=Cytochrome P450. DEA=N-desethylamiodarone. HCTZ=Hydrochlorothiazide. INR=International normalized ratio. OS=Oral suspension. PD=Pharmacodynamic. PK=Pharmacokinetic. PM=Evening. PO=Orally. Q12h=Every 12 hours. QD=Once daily. SD=Standard deviation. $t_{1/2}$=Half-life.

8. POST-MARKETING SAFETY SURVEILLANCE AND RISK MANAGEMENT

The Sponsor will institute a Risk Evaluation and Mitigation Strategy (REMS) upon approval of lixivaptan.

Goals of the REMS will be to:

- Ensure appropriate selection of patients
- Ensure appropriate dosing in patients
- Mitigate the potential risk of ODS through education of patients and healthcare professionals
- Educate healthcare professionals on the need for initiation and re-initiation of lixivaptan treatment in a medical setting where sodium concentration can be monitored
- Educate healthcare professionals on the requirement to distribute a Medication Guide with physician samples dispensed to outpatients

Elements of the REMS will include a medication guide, a communication plan, and a timetable for submission of assessments. The proposed timetable for submission of assessments is as follows:

- First REMS Assessment—18 months following approval
- Second REMS Assessment—3 years following approval
- Third REMS Assessment—7 years following approval

9. BENEFIT-RISK EVALUATION

Lixivaptan was studied separately in both euvolemic and hypervolemic hyponatremia. Dosing was carefully selected to produce controlled increases in serum sodium concentrations, optimize patient tolerability, minimize the risk of overly rapid correction of serum sodium concentrations, and to support the initiation and re-initiation of therapy in medical settings where serum sodium concentrations could be monitored.

In euvolemic hyponatremia, the comprehensive development program including two separate Phase 3 studies and an open-label extension study demonstrated the efficacy of lixivaptan. In these two studies, the primary endpoint was met and supported by secondary analyses. A significant, controlled, and sustained increase in serum sodium concentrations was observed. Lixivaptan was well tolerated and showed similar low rates of overly rapid correction of serum sodium concentrations compared to placebo. No adverse safety signals were observed in this population and mortality rates were numerically higher with placebo treatment than with lixivaptan treatment. Furthermore, the ability to safely initiate and re-initiate of therapy in the inpatient and outpatients settings was proven. The benefit:risk of lixivaptan in euvolemic hyponatremia is evident.

In hypervolemic hyponatremia, one large well-controlled clinical study demonstrated the efficacy of lixivaptan. In this study, the primary endpoint was met and supported by secondary analyses. A significant, controlled, and sustained increase in serum sodium concentrations was observed. Lixivaptan was well tolerated and showed similar low rates of overly rapid correction of serum sodium concentrations compared to placebo. A numerical imbalance in early mortality from all causes compared with placebo treatment was observed. An unusually low mortality rate for patients with acute worsening of heart failure was observed in the placebo group. The reason for this difference remains unclear and no causal relationship of mortality with lixivaptan has been identified. Heart failure patients may require ongoing treatment for chronic hyponatremia, including the need for re-initiation of therapy post-discharge. Therefore, the overall benefits of controlled and sustained increases in serum sodium concentrations provided by lixivaptan outweigh the potential risk in heart failure patients. The benefit:risk of lixivaptan in hypervolemic hyponatremia is evident.

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