FDA Briefing Document for the
Cardiovascular and Renal Drugs Advisory (CRDAC)

Meeting Date:	13 September 2012
NDA:	203009
Sponsor:	Cardiokine Biopharma, LLC
Drug:	Lixivaptan
Proposed Indication for Use:	The treatment of symptomatic hypervolemic and euvolemic hyponatremia associated with heart failure and syndrome of inappropriate antidiuretic hormone (SIADH), respectively. **Important Limitations** Patients requiring intervention to raise sodium concentration urgently to prevent or to treat serious neurological symptoms should not be treated with lixivaptan.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the Lixivaptan NDA to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

CLINICAL REVIEW

Application Type	NDA 203,009
Application Number(s)	000-000
Priority or Standard	Standard
Submit Date(s)	December 29, 2011
Received Date(s)	December 29, 2011
PDUFA Goal Date	October 29, 2012
Division / Office	Cardiovascular and Renal Products/ ODE1
Reviewer Name(s)	Nancy N. Xu, M.D.
Review Completion Date	August 16, 2012
Established Name	Lixivaptan
(Proposed) Trade Name	LIXAR®
Therapeutic Class	Vasopressin 2 receptor antagonist
Applicant	Cornerstone Therapeutics
Formulation(s)	Oral 25 mg and 50 mg capsules
Dosing Regimen	Start at 25 mg QD (outpatient) or 50 mg QD (inpatient), titrate to 100 mg QD (SIADH) or 100 mg BID (Heart Failure and Hyponatremia)
Indication(s)	Treatment of hyponatremia
Intended Population(s)	Adult subjects with hyponatremia associated with SIADH or heart failure

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on currently available information, I believe an argument can be made for lixivaptan approval for the treatment of hyponatremia associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH), with use restricted to inpatient initiation. I recommend a complete response for hyponatremia associated with congestive heart failure (CHF).

1.2 Risk Benefit Assessment

1.2.1 Assessment of Efficacy

Lixivaptan's clinical development program sought to establish the product's efficacy in raising serum sodium in SIADH (euvolemic hyponatremia) and hypervolemic hyponatremia associated with CHF. Three placebo-controlled phase 3 clinical trials were conducted to support an indication in these populations: BALANCE (hyponatremia associated with CHF, inpatient initiation), LIBRA (SIADH, inpatient initiation), and HARMONY (SIADH, outpatient initiation). Though these trials excluded subjects with overt symptoms of hyponatremia requiring immediate medical intervention (such as severe lethargy, coma, or seizure), the majority of enrolled subjects (51% to 62.9%, depending on the trial) had non-specific symptoms at baseline that have been associated with hyponatremia (i.e., fatigue, headache, irritability, mental slowing), but that could also be attributed to their underlying condition (e.g., heart failure, cancer, depression).

All phase 3 trials won on their primary efficacy endpoint, a change in serum sodium from Baseline to Day 7. The primary endpoint findings were shown to be robust in sensitivity analyses conducted to address the impact of missing values (SIADH population 9%; CHF and hyponatremia 21%) and/or the use of local versus central serum sodium measurements. Nonetheless, the effect sizes at Day 7 were modest (BALANCE 1.2 mEq/L, LIBRA 2.2 mEq/L, HARMONY 2.4 mEq/L).

In both treatment arms, the absolute level of serum sodium increase was largest in those with lower serum sodium levels at baseline (as would be expected since lixivaptan and background fluid restriction were to be titrated to correct to a desired sodium level/ceiling), however across the levels of serum sodium studied, lixivaptan had a relatively constant effect size over placebo. The treatment effect on serum sodium appeared to persistent over the duration of treatment (similar effect size on Day 7 to end of therapy on Day 30 or Day 60, depending on the trial). Upon discontinuation of lixivaptan, serum sodium largely returned to pre-dose baseline levels (as seen with discontinuation of orally administered tolvaptan). As noted in the Clinical Pharmacology

Review, a larger treatment effect (5-6 mEq/L) was seen in the applicant's phase 2 hyponatremia trials which studied a twice daily regimen against a backdrop of fluid restriction. An important question is whether a different dosing regimen and/or different instructions related to the use of fluid restriction would have resulted in a larger treatment effect in the phase 3 trials (see the Clinical Pharmacology Review for further discussion).

While an abundance of data on the pharmacologic effect (e.g. increasing free water excretion, raising serum sodium) in phase 2 trials, beyond pre-specified treatment effects on serum sodium, none of the anticipated clinical benefits (pre-specified secondary endpoints) was detected in the phase 3 program. The BALANCE trial (n=652), the largest of the three trials, did not detect a change in days alive and out of hospital. In addition, none of the three trials detected a favorable treatment effect on TRAIL Making Test-B, an instrument used to assess cognitive function (in BALANCE trial, the TRAIL Making Test score appeared to be even unfavorable in the lixivaptan arm). Nonetheless, the treatment effect on serum sodium was modest; as such the expected treatment effects on the symptomatic manifestations of hyponatremia would likely be modest as well. Arguably, the two SIADH trials (enrolling a total of 312 subjects, with only a fraction of these subjects with serum sodium levels <125 mEq/L and <130 mEq/L) were not powered to detect such modest effects on cognitive function as might result from such modest changes in serum sodium.

Historically, changes in serum sodium have been accepted as a surrogate endpoint by FDA for the approval of two vasopressin receptor antagonists: conivaptan (an intravenously administered V1a and V2 receptor antagonist) and tolvaptan (an orally administered V2 receptor antagonist). The issue of surrogacy--that is whether serum sodium, in and of itself, captured the benefit), was discussed with the Agency and the Advisory Committee. Based on the available evidence as a whole, the Agency, with input from Advisory Committee, believed it was reasonable to accept raising serum sodium concentration as a valid surrogate for clinical benefit, particularly in certain populations (e.g. subject with clinical significant hyponatremia in tolvaptan).

Nonetheless, the modest treatment effect size by lixivaptan raises concern about the size of the clinical benefit. On the other hand, the modest treatment effect by lixivaptan in raising serum sodium was seen across the levels of hyponatremia studied, including subjects with clinical significant hyponatremia. While the positive treatment effect on serum sodium is regarded as a valid surrogate expected to translate into a clinical benefit, the size of the clinical benefit, in my opinion, should be weighed against the potential risk of therapy.

1.2.2 Assessment of Safety

The key question on approval hinges upon whether lixivaptan's benefit (i.e., effect on serum sodium) outweighs the increased risks for the target populations.

The lixivaptan phase 3 program studied different classifications hyponatremia (i.e., euvolemic hyponatremia [SIADH] versus hypervolemic hyponatremia [congestive heart failure] in distinct clinical trials where dose up-titration was more rapid and the maximum daily dose was higher in CHF and hyponatremia subjects than SIADH subjects.

While no concerning safety findings was seen in the studied SIADH population, there was an imbalance in death, worse in lixivaptan (n=57, 17.7%) than placebo subjects (n=46, 14.3%) in the BALANCE trial's safety population (subjects who received at least one dose of study drug). The BALANCE trial enrolled subjects with New York Heart Association class III or IV CHF who were hospitalized for symptoms suggestive of acute CHF exacerbation, at times in the presence of inciting infection/sepsis (further decrease the effective circulatory volume). In this setting, the subjects were found with hyponatremia by one or more measurement. Thirty percent of the BALANCE study population was on inotropic support, and virtually all of them were on diuretics, consistent with a fluid hemodynamic status. This imbalance in death occurred early, (e.g. with 9 lixivaptan versus 1 placebo death within the first 5 days of initiation therapy). While overall the numeric imbalance in death was not statistically significant (p=0.26), post hoc analyses in subjects who died soon after randomization or first dose found p-values that were nominally significant.

The deaths in BALANCE appeared to be largely from cardiac causes where subjects died suddenly from an acute CHF exacerbation and appeared largely consistent with acute hemodynamic decompensation. There was no clear evidence of arrhythmia as a primary cause of death. In addition, no significant QT prolongation was seen in a thorough QT study. Analysis of the baseline demographics factors (age, sex, race, weight, country, NYHA class, degree of systolic dysfunction, presence and severity ischemic coronary artery disease), and concomitant medications of these who died early versus late, or were alive at the last follow-up were not revealing. Baseline and on-treatment vital signs, rate of rise in serum sodium, symptoms suggestive of osmotic demyelination syndrome, laboratory findings (degree of hyponatremia, new/worsening electrolyte abnormalities preceding death) were also unrevealing, with the exception of a baseline and on-treatment orthostatic increase in heart rate in those who died early.

In comparison, an excess in deaths was not seen (lixivaptan 0/24, 0% versus placebo [1/16, 6.3%] in the phase 2 CHF and hyponatremia population where higher doses up to

250 mg BID for up to 30 days were tested, in the phase 2-3 SIADH population (lixivaptan [9/250, 3.6%] versus placebo [6/120, 5.0%]), nor the overall program.

Currently, it is not clear whether lixivaptan played a causal role in the early deaths. While the early death in hyponatremia and CHF population could reflect the underlying disease, I can not exclude the possibility that some subjects with hyponatremia associated with acute worsening congestive failure were exquisitely sensitive to intravascular free water shifts and may not tolerate even a small change in intravascular volume status or osmolality, induced by lixivaptan and/or effects resulting from a compensatory neurohumoral activation (e.g. arginine vasopressin increase). Therefore, weighing the modest benefit, as established by a surrogate, our tolerance for the uncertainty in risk is arguably low. Hence, while the excessive in deaths could be due to "a play of chance", in this reviewer's opinion, there is currently insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling in the subjects with hyponatremia associated with CHF.

In weighing the benefit versus risk in SIADH population, one may reasonably argue against outright approval; with a modest benefit, the corresponding safety database in lixivaptan should be large to characterize rare and unexpected adverse events that are unique to lixivaptan.

On the other hand, the size of the lixivaptan's safety database in SIADH population was similar to the pre-approval tolvaptan database. The adverse events in the lixivaptan program, and in particular in the SIADH population were largely consistent with the known pharmacologic effects. As a class, the labeling for the two vaptans cautions against too rapid correction of serum sodium, with the potential for osmotic demyelination syndrome, hypotension or volume depletion. Specifically, the orally administered tolvaptan's labeling requires subjects to be hospitalization for initiation/re-initiation so that serum sodium can be monitored closely. Importantly, the two approved vaptans are contraindicated in hypovolemic hyponatremia. The years of safety experience with this class of drugs may also be informative.

Furthermore, the adverse event rates in lixivaptan program appear commensurate with the modest treatment effect size. Most of the rise of serum sodium occurred within the first 3 days of drug initiation, even with the lower (25 mg per day) initial dose in the outpatient SIADH. The rate of sodium response and the incidence of treatment-related adverse events that lead to the discontinuation of therapy suggest a benefit for closely monitoring volume status during dose titration.

Therefore, in my opinion, an argument can be made for approval with restricted use similar to the two approved vaptans. If approved in the SIADH population, lixivaptan's labeling should limit the initiation to the inpatient setting where volume status, fluid balance and serum sodium concentration can be closely monitored.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

If lixivaptan were approved for the SIADH population and restricted initiation to the inpatient setting, a medication guide to subjects and communication plan to physician can be engineered, in or outside of a Risk Evaluation and Mitigation Strategy (REMS).

A medication guide should education subjects how to mitigate the risk of lixivaptan treatment. Specifically, subjects should be advised that: 1) they should not be initiating treatment at home; 2) they should not use lixivaptan if they don't have free access to water; 3) they should not use lixivaptan if they are incapable of sensing thirst; 4) they should work with their physician if there are changes in fluid balances since titration; and 5) if they discontinue lixivaptan on their own, they should not restart treatment.

A communication plan to physician should educate physician on osmotic demyelination syndrome and the assessment of volume status with initiating therapy.

1.4 Recommendations for Postmarket Requirements and Commitments

Pediatric studi(es) will be needed. The inclusion/exclusion criteria should be congruent with the indicated adult subject population.

2 Introduction and Regulatory Background

2.1 Product Information

Lixivaptan (proposed trade name LIXAR®) is an orally available, vasopressin V2 receptor antagonist and new molecular entity (NME) with a proposed indication for the treatment of "symptomatic hypervolemic and euvolemic hyponatremia associated with

heart failure (HF) and SIADH, respectively". The chemical structure of lixivaptan and an overview of key product attributes are provided below.

Figure 1. Chemical structure of lixivaptan

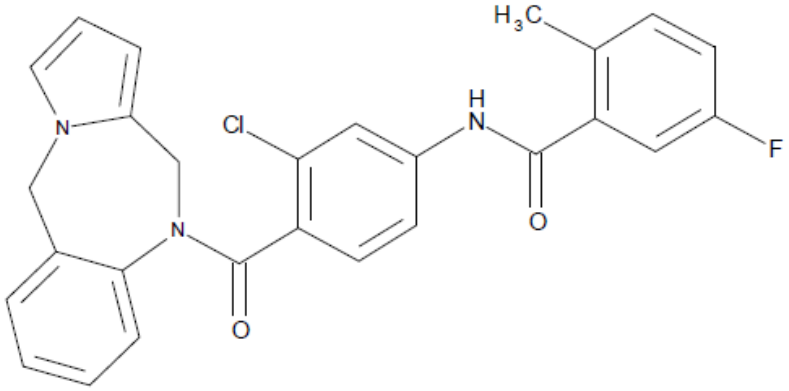


Table 1. Overview of key product attributes

Attribute	Description
Chemical Name	5-fluoro-2-methyl-N-[4-(5H-pyrrolo[2,1-C] [1,4]benzodiazepin-10(11H)-yl carbonyl)-3-chlorophenyl]benzamide.
Appearance	Lixivaptan is a white, off white or slightly pink solid.
Molecular Formula	$C_{27}H_{21}ClFN_3O_2$ Molecular Weight 473.93
Dosage form and strength	25mg and 50 mg hard gelatin capsules
Dosing Regimen	Start at 25 mg QD (initiation in a monitored setting) or 50 mg QD (initiation in an inpatient setting), titrate to 100 mg QD (SIADH) or 100 mg BID (Heart Failure associate with Hyponatremia)
Proposed Age Group	Adults

2.2 Tables of Currently Available Treatments for Proposed Indications

The cause of hyponatremia is thought to be a disorder of water balance. The key therapies to treat hyponatremia are listed below. The treatments tackle water intake, excretion and/or the amount of solutes administered. Of these, two vaptans have been approved for the treatment of hyponatremia. All approved therapies are thought to carry

a risk of overly rapidly correction of serum sodium, particularly if thirst mechanism is impaired. In addition, the effectiveness of fluid restriction is thought to be limited by thirst.

Table 2. Currently available alternatives to the treatment of hyponatremia

Treatment	Proposed Mechanism of Action	Population	Limitations
Fluid Restriction	Limits free water	SIADH, hypervolemic hyponatremia	Difficult to implement at stringent level* due to limited compliance.
Hypertonic saline (IV)	Direct addition of concentrated salt solution to intravascular space	Used for acute reversible of symptomatic hyponatremia	Volume overload.
Conivaptan (IV)	V1a/V2 receptor antagonism	euvolemic and hypervolemic hyponatremia	In-hospital use. Duration not to exceed 4-days.
Tolvaptan (PO)	V2 receptor antagonism	clinically significant hyponatremia associated with SIADH, cirrhosis & heart failure	Not for urgent rise of serum sodium. In-hospital initiation/re-initiation.

* Stringent fluid restriction is often required for those with high urine osmolality.

In addition, other therapies (e.g. the combination of diuretics and salt tablets, demeclocycline, lithium, urea) are used off-label to treat hyponatremia but do not appear to be widely used due to varied effectiveness and/or toxicity.

2.3 Availability of Proposed Active Ingredient in the United States

Lixivaptan is not currently approved in the United States. The applicant indicates that lixivaptan has not been approved in any other country.

2.4 Important Safety Issues With Consideration to Related Drugs

Lixivaptan is a vasopressin V2 receptor antagonist. Approved vasopressin V2 receptor antagonists in the US are Conivaptan (parenteral) and Tolvaptan (oral). These agents are approved for hyponatremia in euvolemic and hypervolemic conditions. The labeling for vaptans carries warning/precautions about osmotic demyelination syndrome which can happen with rapid correction of sodium. See section 7 for a discussion of treatment emergent adverse events associated with the use of lixivaptan.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Source (date of meeting or submission)	**Advice from Agency**
April 12, 2005 Advice Letter from DMEP on the design of phase 3 program	• Expressed reservation about serum sodium as a surrogate in certain populations: those with serum sodium that were not markedly low (e.g. ≥130 mEq/L), or heart failure
May 12, 2006 Special Protocol Assessment Response-No agreement	• Expressed significant concern about lixivaptan use in patients with liver cirrhosis with ascites (LCWA) in phase 2 studies (imbalance in death) • Indicated approval for a hyponatremia indication in LCWA will require full review of complete data from the LCWA study because there may be unique safety issues in this population
Review of the vaptan class was transferred from DMEDP to DCaRP on April 6, 2007. At that time, only one of the phase 3 lixivaptan trials (i.e. the BALANCE trial in CHF and hyponatremia population) had been initiated, and had just began enrollment.	
April 22, 2008 Type C Guidance meeting	• Need to define a clear schedule for lixivaptan dosing during the titration phase to provide adequate instruction for safe use
August 12, 2008 Advice letter following tolvaptan Advisory Committee meeting to address changes in serum sodium as the basis for approval of drugs developed to treat hyponatremia	• DCaRP agreed that the data similar to that collected in the tolvaptan development program are sufficient to support the use of serum sodium as a surrogate endpoint in (1) asymptomatic subjects with markedly low serum sodium (i.e. < 125 mEq/L) and (2) mildly or moderately symptomatic subjects with a serum sodium ≥125 mEq/L but < 130 mEq/L, who do not require urgent intervention to raise serum sodium acutely • For an indication in an asymptomatic heart failure population with less severe hyponatremia, need to establish a clinical benefit beyond a change in a laboratory value • For an indication in HF population with a mildly or moderately symptomatic hyponatremia with a serum sodium >125, a vulnerable population, need a sufficiently large safety database to provide reassurance of safety

Source (date of meeting or submission)	Advice from Agency
	• Encouraged secondary endpoints to establish additional clinical benefits, e.g. reversing clinically significant symptoms of hyponatremia
Sept 19, 2008 TC between DCaRP and Cardiokine	• Division agreed that the revised primary endpoint (now a change in serum sodium at a time point later than 72 hours, such as day 7) was acceptable • Recommended a randomized withdrawal over late assessment of serum sodium as a co-primary efficacy endpoint (to limit problem with interpretation with dropouts) to assess a long term effect on serum sodium. Have a follow-up period off drug (even if it did not represent a randomized withdrawal from treatment) to help establish persistence of effect. • Indicated the sponsor's plan to collect information on subjects' baseline symptoms but not to study the effect of treatment on these symptoms was acceptable • Suggested submitting complete validation package for the instrument to the FDA Subject Reported Outcomes Group for review as soon as possible
November 20, 2008 Advice Letter, DCaRP provided comments on submitted clinical protocol involving initiation of lixivaptan in the outpatient setting	• Expressed concern about outpatient initiation of therapy in SIADH subjects with serum sodium slightly lower than <135 mEq/L. • Expressed uncertainty on whether the response to therapy of subjects with mild hyponatremia can be extrapolated to those with more severe hyponatremia. In order to establish the safety and efficacy of the proposed outpatient regimen in subjects with more severe hyponatremia, you will need data demonstrating the safety and efficacy of this regimen in such subjects.
August 3rd, 2009 TC between DCaRP and Cardiokine	• Division expressed concerns over the excess death in lixivaptan arm in subjects with cirrhosis based on the preliminary data in the lixivaptan development program. • The sponsor indicated that they were not going to seek an indication in the cirrhosis population and that the phase 3 trials will exclude the cirrhosis population.
December 17, 2010 Pre-NDA meeting	• Division expressed concern about a numerical imbalance in deaths during the first 2 weeks of treatment in the BALANCE trial that did not favor lixivaptan and the implication of the deaths in BALANCE for the size of safety database needed for non-HF subjects with hyponatremia • Advised sponsor to include a calculus of the absolute risk ruled out in their NDA submission • Advised sponsor to define an outpatient population where the benefit obtained by a change in serum sodium of the magnitude effected by lixivaptan would be expected to predict a clinically meaningful benefit, and the proposed monitoring would be

Source (date of meeting or submission)	Advice from Agency
	adequate to ensure safety • Advised sponsor to address the potential for confusion with different dosing strategies used in the inpatient vs. outpatient setting in REMS • Advised sponsor to characterize the relationship between lixivaptan dose/plasma concentrations and change in serum sodium and symptoms

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission quality and integrity appears adequate. In their clinical overview (section 2.5), the applicant indicates that all clinical studies were compliant with Good Clinical Practices; conducted under the supervision of an IRB and with adequate informed consent procedures.

3.2 Compliance with Good Clinical Practices

According to the applicant, the clinical trials were conducted in accordance with Good Clinical Practices and clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures.

The DSMB for the BALANCE trial raised concern about protocol violations and their potential impact on subject safety. The review team communicated these concerns to the Office of Scientific Investigations, and specifically whether there was evidence of poor compliance with good clinical practices, and if the monitoring by the sponsor and the CROs was adequate.

Four clinical sites and the sponsor were inspected for this NDA. For inspections of two of the clinical sites, Sites 1669 and 1600 from the BALANCE trial, no violations were cited and the inspections are classified as no action indicated (NAI). For Site #3122 of the HARMONY trial, violations were cited concerning adherence to protocol that were considered minor in nature. For Site # 5312 from the LIBRA trial, violations cited included lack of adherence to study protocol. These violations were not considered of the significance to impact data integrity or subject safety. The review of Site # 5312 from the LIBRA trial has not been finalized.

The report of the sponsor inspection has not been received at the time of this review, however, communications with the FDA field inspection indicate that no violations were cited and the trials were adequately monitored.

3.3 Financial Disclosures

Forms certifying financial interests and arrangements with clinical investigators were submitted by the applicant. The applicant indicated, as of February 28, 2011, they have received forms from 1628 out of 1629 investigators. According to the applicant, one sub-investigator for site 1162 in the BALANCE trial, did not respond despite repeated requests were sent to the investigator.

No subject was enrolled from site 1162, and therefore would not impact the efficacy and safety findings of this clinical program.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemistry manufacturing and controls (CMC) review is pending.

4.2 Clinical Microbiology

The microbial testing of the drug product was adequate.

4.3 Preclinical Pharmacology/Toxicology

In vitro studies showed that lixivaptan was highly selective with approximately 90-fold higher potency for V2 receptor (*K*i of 0.60 nM) relative to V1a receptor (Ki 55 nM). In addition, lixivaptan was more than 400-fold more selective for the human V2 receptor than for the closely related human oxytocin OT receptor (275 nM).

A receptor screen assay of 39 established receptors did not detect any notable lixivaptan parent-drug off-target interaction at therapeutic concentrations. Specifically, lixivaptan demonstrated only weak antagonism of the Cav1.x and Cav3.x calcium channels (48% inhibition at 10 µM lixivaptan [$16x10^3$ -fold of the Ki for V2 receptor]), but no effects were observed at lower concentrations that reflect the therapeutic range. However, the metabolites of Lixivaptan were not assayed, and the potential for unexpected receptor interactions with these metabolites cannot be ruled out based on the available data.

Safety pharmacology

Cardiovascular safety studies in conscious Beagle dogs demonstrated that a 50-mg/kg dose of lixivaptan elicited only isolated effects in cardiac endpoints (mean arterial blood pressure, heart rate, cardiac output, and ECG) that were not considered to be physiologically significant. This study, however, was not conducted in a heart-failure animal model.

Acute Toxicology

Acute toxicity was studied in both rats and mice. The LD_{50} was approximately 1200mg/kg in both mice and rats in both species, which translate to 400x human therapeutic dose. The intraperitoneal route (LD_{50} of approximately 1200mg/kg) was more toxic than the oral route (LD_{50} > 1200mg/kg) of administration.

Please see Dr. William T. Link's review for more detail.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Lixivaptan blocks the binding of arginine vasopressin (AVP) to V2 receptors, thereby inhibiting AVP-induced water reabsorption at the renal collecting tubule and increasing free water excretion.

Pharmacodynamics

In general, in clinical pharmacology studies in healthy subjects, CHF, SIADH and LCWA subjects, there is evidence for dose-related effects of lixivaptan on measures of renal water handling (increase urine flow, increase urine output, increase serum and decrease urine osmolality), and increase plasma AVP concentrations, and corresponding increase serum sodium concentrations and serum osmolality.

Specifically, there is a dose- dependent increase in serum sodium in Phase II studies after administration of lixivaptan in doses similar to those used in the Phase III trials. In the phase 2 trials (203, 207) in subjects with hyponatremia associated with LCWA, SIADH, CHF subjects, dose-dependent increase in serum sodium was demonstrated in the daily dose range of 25 mg to 125 mg BID. With the BID regimen, the average effect size (5-6 mEq/L) was observed with daily dose studied, on top of fluid restriction. (See section 7.1 for the description of the phase 2 trials). In contrast, a shallow exposure-response relationship for change in serum sodium is observed in Phase I (healthy subjects) and Phase III studies (with individualized dose titration in subjects).

The onset of these pharmacodynamic effects, and the onset to the maximum observed effect, is generally within a few hours. Lixivaptan produced rapid dose-related aquaresis, the urinary flow peaked in two hours in all studied populations (healthy subjects, SIADH, LCWA and CHF subjects) with corresponding urine volume increased at the initial measurement, 4-hours after dosing. Furthermore, lixivaptan generally produced dose-related increases in sodium concentration with maximum effects on sodium concentration occurring at approximately two to four hours after chronic dosing. There are also dose-dependent increases in AVP (generally within four to six hours) of dosing.

Daily dose of lixivaptan in excess of 200 mg daily are associated with an increased rate of mechanism-based adverse events for this class of drug, including dry mouth, thirst, constipation, headache, and dizziness.

4.4.3 Pharmacokinetics

Lixivaptan is rapidly absorbed with peak concentration achieved generally achieved within 1 hour after oral administration, and the time to maximum concentration is within 8 hours of dosing. Absorption is followed by multi-exponential disposition with an apparent terminal phase t1/2z of 8-16 hours. The pharmacokinetics of lixivaptan is non-linear as evidenced by a more than dose proportional increase in exposure. In clinical dose range up to 100 mg BID, there was dose-proportional increase in exposure.

The parent drug undergoes extensive first-pass metabolism and is cleared almost exclusively via non-renal route. It is metabolized primarily by cytochrome P450 (CYP) 3A4, with CYP2C8 and CYP3A5 also contributing. Most of the characterized metabolites were formed by single or multiple oxidations of the pyrrolobenzodiazepine headpiece of the lixivaptan molecule, and were pharmacologically inactive or only weakly active.

Intrinsic Covariates
A population PK analysis showed that relative to healthy subjects, SIADH and LCWA subjects had an up to 2- to 3- fold increase in mean exposure at the100 mg BID level. In contrast, there appeared to be no significant impact on exposure in subjects with CHF. Liver cirrhosis increased the exposure to lixivaptan significantly. End-stage renal disease reduced exposure to lixivaptan marginally, as may be expected from its non-renal route of elimination.

Extrinsic Covariates
In vitro data indicated that lixivaptan is a substrate of CYP3A, CYP2C8 and has the potential to inhibit CYP3A, CYP2C8, CYP2C9 and BCRP. *In vivo* data confirmed that lixivaptan is substrate of CYP3A. Co-administration of CYP3A inducers decreased the exposure to lixivaptan to about 30%. Co-administration of strong CYP3A inhibitors increased the exposure to lixivaptan by 3- fold in healthy subjects. Weak and moderate CYP3A inhibitors increased exposure to lixivaptan up to 1.9 fold in subjects with SIADH, CHF or LCWA. *In vivo* data confirmed that lixivaptan, when co-administered with simvastatin, is an inhibitor of CYP3A and possibly BCRP (dose dependent 2-3 fold increase in exposure). However, exposure to and response of the CYP2C9 substrate warfarin in the presence of lixivaptan were unchanged.

Unidentified Circulating Moieties in Plasma in Mass Balance Study
After administration of ^{14}C-lixivaptan, only 40-50% of the total radioactivity in plasma was structurally identified in humans, and with only 7% representing the parent drug. Thus, 50-60% of the circulating radioactivity was made up of uncharacterized and potentially human-specific metabolites. The uncharacterized human metabolites leave

uncertainty about the applicability of the animal pharmacology toxicology findings to humans.

Please see the clinical pharmacology review by Drs. Hinderling, Lai, Sahre and Fang for more detail.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

According to the applicant, lixivaptan has been studied in 22 phase I studies, three phase 2 studies, three completed phase 3 trials, and a long term extension trial. An overview of phase 2 studies conducted in healthy or renally impaired subjects and subjects with SIADH, CHF, or LCWA is provided in section 6.1.8. The three international, randomized, double-blind placebo-controlled phase 3 trials are discussed in section 5.3. The open-label lixivaptan long term extension trial in subjects with hyponatremia who completed the three phase 3 trials is discussed in Section 7. Notable aspects of the phase 3 trials and lixivaptan's long term extension study are highlighted below.

Table 3. Phase 3 placebo controlled clinical trials and long-term open-label study

Study Name and ID	Study Population	Treatment Arm(s) (ITT)	Primary & Secondary Endpoints	Treatment Regimen, Dose	Duration of Rx Planned

BALANCE 3401	Hospitalized adult subjects with CHF, volume overload, and hyponatremia (<135 mEq/L)	1:1 Lixi: 323, Pla: 329	Serum sodium, TMT-B, DAOH	50 mg titrated to a maximum of 100 mg BID or 100 mg QD	60 Days
LIBRA 3405	Adult subjects with euvolemic hyponatremia (<130 mEq/L); hospitalized for initiation of study drug	1:1 Lixi: 54, Pla: 52	Serum sodium, TMT-B	50 mg titrated to a maximum of 100 mg QD or a minimum of 25 mg QD	30 Days
HARMONY 3430	Adult subjects with euvolemic hyponatremia (<135 mEq/L); could be initiated in a "monitored" setting outside the hospital	3:1 Lixi: 154, Pla: 52	Serum sodium, TMT-B	25 mg titrated to a maximum of 100 mg QD	24 weeks*
Long-term open-labeled 3431	Open-label extension of 3401,3405, 3405	Lixi: 167		25 mg titrated to a maximum of 100 mg QD	up to 28 weeks

TMT-B: TRAIL Making Test, Part B. DAOH: Days Alive Out of Hospital
Lixi=lixivaptan; Pla=placebo
*The applicant instructed the investigators to stop blinded therapy in all subjects after the last subject enrolled in the study had completed 8 weeks of treatment. Therefore, the trial did not have 24 weeks of treatment data for most subjects

As shown above, the BALANCE trial studied subjects with hyponatremia in the setting of CHF (NYHA class III or IV heart failure); the two SIADH (euvolemic hyponatremia) trials, LIBRA and HARMONY, specifically excluded subject with established diagnosis of NYHA class III or IV heart failure. In addition, the upper level of baseline sodium cut-off differed (<130 mEq/L or <135 mEq/L). Lastly, while the BALANCE and LIBRA trials required hospitalization for initiation of therapy, the HARMONY trial allowed subjects to be initiated on therapy in a “monitored” setting as an out-patient

The trials also differed in the number of subjects exposed to lixivaptan (BALANCE was the largest in size) and the randomization scheme (1:1 vs. 3:1). In addition, the length of exposure or Treatment Period differed (30 days to 24 weeks).

In terms of endpoints, all three phase 3 trials had the same serum sodium based primary endpoint: change from baseline in serum sodium at Day 7.

In addition, all 3 trials have largely similar secondary endpoints that assess 1) other effects on serum sodium, 2) effects on cognitive function tests, e.g. Trail Making Test part B (TMT-B) (see below).

1. The average daily AUC of change from baseline in serum sodium concentrations up to end of treatment phase (specifically, at Day 60 in BALANCE, Day 30 in LIBRA, and Day 28 in HARMONY).
2. The change from baseline in the recorded time to complete the TMT – B at Day 28 (BALANCE), at Day 30 (LIBRA), and at Day 28 (HARMONY).
3. Percentage of subjects with worsening of hyponatremia during the double-blind on-therapy period. Worsening of hyponatremia is defined as a reduction ≥3 mEq/L in serum sodium concentrations (BALANCE), not defined in the LIBRA and HARMONY trials.
4. Percentage of subjects with normalized serum sodium concentration (>135 mEq/L) at day 60 (BALANCE), defined as >135 mEq/L and </= 145 mEq/L (LIBRA & HARMONY).

There were two notable differences in secondary endpoints, as listed below.

1. BALANCE was the only trial that had a clinical outcome based endpoint, namely, days alive and out of the hospital (DAOH) (for cardiovascular causes) during the double-blind on-therapy period (up to 60 days from randomization).
2. LIBRA and HARMONY, but not the BALANCE trial assessed the percentage of subjects requiring fluid restriction at any time during the treatment period of study.

As shown in the

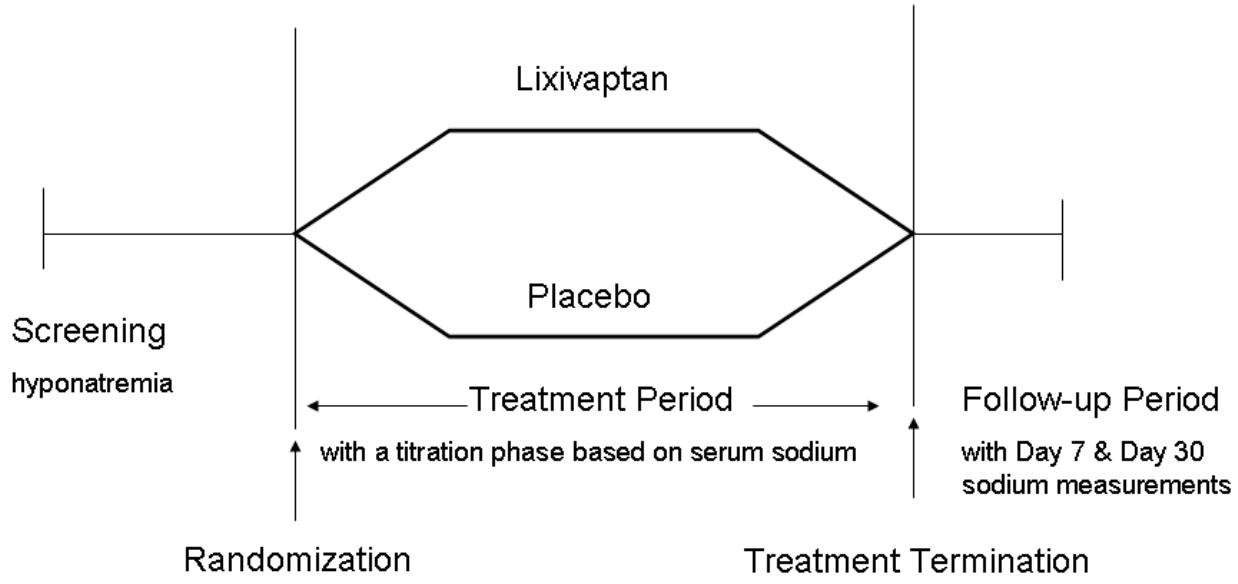
Table 3 above, in term of the dosing strategies, the phase 3 trials differed in the initial dose (25 mg to 50 mg), maximum dose (100 mg QD vs. 100 mg BID), and the interval between dosing in dose escalation (can be adjusted twice on the first day of dosing in

BALANCE vs. once in LIBRA and HARMONY). However, all trials employed similar general guidelines for adjusting treatment dosage, fluid, and concomitant diuretics. If the rate of rise in serum sodium exceeded the target rate (either ≥12 mEq/L/24 hours or >8 mEq/L/8 hours) or if it exceeded the normal range (i.e. >145 mEq/L), the investigators were instructed to:

- Adjust fluid intake
- Adjust diuretic dosage
- Hold the next dose
- Decrease the dose of study medication.

Lastly, these 3 phase 3 trials had largely similar design (see Figure 2 below).

Figure 2. Commonalities in phase 3 trial design



Primary Endpoint: Change from baseline in serum sodium at Day 7

As shown above, subjects with laboratory evidence of hyponatremia were enrolled in the phase 3 trials. For all studies, repeated measures of serum sodium levels were allowed to determine eligibility. However, to meet hyponatremia eligibility criterion, a single serum sodium < 135 mEq/L, based on local laboratory measurement (central laboratories values took additional time to become available to the investigator), within 24 hours prior to randomization was suffice. A second confirmatory local serum sodium value was generally not required. For HARMONY, but not in BALANCE and LIBRA,

prior to administering the first dose, if greater than 24 hours had elapsed since the last screening/qualifying serum sodium measurement, the Baseline serum sodium was to be repeated. Specifically, the Baseline ("pre-dose") serum sodium was required within 1 hours preceding the first dose to 8 hours after the first dose.

All phase 3 trials excluded subjects with overt symptoms (e.g., severe lethargy, coma, seizures) of hyponatremia that required immediate medical intervention, severe hyponatremia (<120 mEq/L), advanced liver disease/cirrhosis, or other causes of hyponatremia for which therapies other than a vaptan are indicated (e.g., adrenal insufficiency, or uncorrected thyroid disease). In addition, subjects with inability to continue fluid intake in response to thirst were also excluded.

Furthermore, as shown above, all three phase 3 trials had an initial dose titration phase based on sodium during the Treatment Period. Following Treatment Period (of varying lengths), all trials had a Follow-up period where serum sodium were to be measured on post-treatment Day 7 & Day 30.

During dose titration, all phase 3 trials allowed fluid restriction to be initiated at Investigator discretion, and discouraged, but did not prohibited, fluid restriction (in general) for at least the first 72 hours of study drug dosing (i.e., the dose titration phase). Subjects, in general, were to assume the target dose achieved in the dose titration phase through the rest of the Treatment Period; dose can still be modified at investigators' discretion. Subjects who stopped study treatment early were to complete the end-of treatment procedures and the post-treatment follow-up visits.

The trial specific features are discussed in more detail in Section 5.3.

5.2 Review Strategy

The Clinical Review focused on the design and conduct of the three phase 3 trials and the resulting data.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 An Overview of the BALANCE Trial:

Study Title
"Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Subject Evaluation". The following description of the trial reflects the August 5, 2009 final protocol.

Date of trial conduct
February 12, 2008 to June 17th, 2010.

Geographic Distribution
173 sites in the United States (46 sites), Poland (30 sites), India (19 sites), Russia (16 sites), Argentina (11 sites), Germany (11 sites), Canada (six sites), Israel (six sites), Italy (six sites), Czech Republic (five sites), Romania (five sites), Chile (four sites), Spain (four sites), and Slovakia (four sites)

Study Population
In BALANCE trial, subjects with hyponatremia (sodium concentration <135 mEq/L) hospitalized for acute worsening of chronic heart failure with clinical or laboratory evidence for volume overload. The implemented protocol in BALANCE did not require a second laboratory confirmation of hyponatremia. For full entry criteria, please see appendix.

Reviewer's comment: Acuity of hyponatremia was not assessed as part of the eligibility criteria.

Study Procedure (based on the final amendment August 5, 2009)
In the BALANCE trial, subjects were randomized by an Interactive Voice Response System (IVRS) 1:1 to lixivaptan and placebo treatment arms. The randomization was stratified country and by serum sodium (<130 mEq/L, or ≥130 to <135 mEq/L).

Baseline serum sodium was used for determining eligibility and for the imputation of the primary endpoint. To meet the eligibility requirement, repeat measures of serum sodium were allowed and the last serum sodium result (e.g. a single value) within 24 hours prior to randomization could be used. The baseline serum sodium values were determined from both local and central laboratory measurements from different blood draws, rather than a split specimen. The central sodium values were used for primary endpoint analysis; the local sodium values were used for dose titration.

The BALANCE trial had a 60-Day treatment phase, which included a 3-day, inpatient Dose Titration Phase followed by an outpatient treatment phase (see study procedure below).

Dosology
The maximum dose was highest (100 mg BID) in the BALANCE trial. In BALANCE, both QD and BID dosing were allowed, per investigator discretion, for the Dose Titration Phase and the Out-patient Treatment Period.

During the Dose Titration Phase, study medication dose titration was to occur with each dose (BID or QD schedule), until the serum sodium treatment targets were met, based on sample drawn 1 hour prior to dosing. The serum sodium cut-offs to guide dosing are summarized below.

Table 4. General dosing guideline based on serum sodium (the Balance trial)

Change in Serum Sodium		Dosing Guidelines Based on Serum Sodium		
8 Hour Change (mEq/L)	24 Hour Change (mEq/L)	<135 mEq/L	135 – 145 mEq/L	>145 mEq/L
<5	<5	Increase dose to next dose level	No change in dose	Hold/decrease dose until serum sodium is ≤ 145
5-7	5 – 11	No change in dose	No change in dose	Hold/decrease dose until serum sodium is ≤ 145
≥8	≥12	Hold the next dose, decrease study medication or diuretic dose, and contact the Medical Monitor for guidance.		

Applicant's table 1, in the August 2009 protocol amendment for 3401

The Steps for Up-titration is specified below.

- Step 1: All subjects are given a 50 mg dose on Day 1.
- Step 2: Based on the subject's response at the **8 hour** serum sodium assessment a second dose of 50 mg may be administered (e.g., dosing may be increased to 50 BID).
- Step 3: Based on the subject's serum sodium concentration, dosing may be increased to 100 mg QD.

- Step 4: Based on the subject's serum sodium concentration, dosing may be increased to 100 mg BID.

Reviewer's comment: step 2 (doubling the dose based on a post-dose 8-hour serum sodium value on Day 1) was only in the phase 3 BALANCE trial.

According to the protocol, for qualification, the subjects were to have documented hyponatremia on baseline fluid restriction (<1.5 liter). Of note, in the initial implemented protocol dated January 14, 2008, during the dose titration phase, the option of initiating fluid restriction (as low as 1 liter/day) for subjects with serum sodium < 130 mEq/L was available at the Investigator's discretion. If possible, fluid restriction was advised to be withheld for at least the first 24 hours in order to determine the rate and magnitude of serum sodium change. Subsequently, on October 6, 2008, the applicant revised the fluid restriction guideline, to advise investigator to avoid fluid restriction for at least the first 72 hours "if possible" (see Section 9.4.2 for key protocol amendments; see Section for baseline fluid balance).

Reviewer's comment:
Concomitant implementation of more stringent fluid restriction during the dose titration phase may lead to rapid onset of negative free water balance.

In addition, "fluid restriction may be instituted, maintained, or further adjusted at the Investigator's discretion at any time during the study". "At any time during the 60-Day treatment period, the option of increasing or decreasing the dosage treatment period was always available at the discretion of the Investigator. However, if the subject was taking diuretics or was on fluid restriction, an adjustment in diuretic dose or fluid restriction should be considered first."

Key Stopping Criteria for Study Treatment for Individual

1. Severe hyponatremia (defined as serum sodium <120 mEq/L), with or without severe signs or symptoms (e.g., lethargy, coma, seizures, changes in mental status attributable to hyponatremia)
2. serum sodium continues to exceed 145 mEq/L following down titration or other adjustments outlined in dose titration table
3. missing doses on more than seven consecutive days
4. requiring IV infusion of hypertonic saline (defined as 1-3% saline solution) for hyponatremia (treatment failure)
5. becoming lost to follow-up.

Reviewer's comment:
The serum sodium entry criterion was not based on central laboratory values. Some subjects had central serum sodium greater than 145 mEq/L at "Baseline", a stopping criterion. (see Figure 3*).*

Statistical Analysis Plan
The primary endpoint was pre-specified as the change from Baseline to Day 7 where Last Observation Carried Forward (LOCF) from expected visits was to be used for the subjects missing Day 7 data for Central laboratory sodium data and similarly for analyses with Local sodium values. The next available serum sodium value (Next Observation Carried Back, NOCB) was to be used to impute the missing Baseline serum sodium values. Sensitivity analyses of the primary endpoint were to be based on an observed value analysis using only subjects with non-missing values at Baseline and Day 7, and an analysis using the imputation based on the Baseline Observation Carried Forward (BOCF) approach for subjects with missing Day 7 data. A mixed-effect model repeated measures analysis (MMRM) was specified. The secondary endpoints were to be performed and presented as a fixed-sequence of hierarchical tests. The null hypothesis of superiority of the effect lixivaptan versus placebo on the change from Baseline to Day 7 serum sodium was to be tested at a significance level of two-sided p-value, less than or equal to 0.05. The statistical analysis plan (SAP) was finalized on August 30, 2010, which was after when the last subject completed the trial (5/14/2010). However, there was no significant difference between the original and final statistical plan.

Trial Administrative Structure
The trial administrative structure originally consisted of an Independent Data Monitoring Committee (IDMC), Lixivaptan Steering Committee, and Clinical Endpoints Committee (CEC).

IDMC's responsibilities included reviewing unblinded safety (and not efficacy) data at predefined intervals during the study. The IDMC could advise the Steering Committee regarding possible changes to the protocol or study procedures required to protect the subjects enrolled in the study.

The Clinical Endpoints Committee (CEC) was to perform a review (blinded to treatment group and serial serum sodium levels) and adjudicate all events assessed by the Investigators as clinical endpoints using pre-determined criteria for each endpoint as detailed in the CEC charter. The adjudicated clinical endpoints was be used for the final analysis of study results, unless otherwise stated.

Adjudication Process

The Clinical Endpoint Committee (CEC) was responsible for adjudicating:

- Cause of death - due to HF or another cause.
- Date of death
- Cause of hospitalizations - due to HF, other cardiac disease or other (non-cardiac) causes.
- Start and Stop date of hospitalization.
- Assessment of Hospitalization equivalent.
- Worsening Heart Failure

Reviewer's comment: There was not a systematic approach to attribution of death.

Because of an early imbalance in deaths (Section 7), the applicant also enlisted additional groups: statistical group (Applied Clinical Intelligence [ACI]) a blinded a Protocol Eligibility Adjudication Committee [PEAC]) of expert physicians in heart failure (consultants) to re-evaluate the eligibility of all 652 subjects enrolled into the BALANCE study.

There were a number of protocol amendments to the original protocol. The amendments were enacted, for the most part, prior to trial initiation or significant enrollment. One notable amendment was to delete the assessment of weight as part of the criteria for dose titration. For rest of protocol amendment, please see appendix.

The collection of blood for the purpose of AVP concentration determination was discontinued by the Sponsor on 05 April 2010 for CK-LX3401 (BALANCE) and on 04 May 2010 for studies CK-LX3405 (LIBRA) and CK-LX3430 (HARMONY).

5.3.2 An Overview of the LIBRA Trial, 3405:

Title of the study: "Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Oral Lixivaptan Capsules in Subjects With Euvolemic Hyponatremia".

Date of trial conduct

Date first subject enrolled: July 30, 2008
Date last subject completed: May 14, 2010

Geographic Distribution
37 sites in Belgium (one site), Canada (one site), Germany (seven sites), India (four sites), Poland (seven sites), and the United States (17 sites)

Study Procedure (per the final December 23rd, 2009 protocol)
As mentioned earlier, the study procedures in LIBRA and BALANCE were similar in many aspects (e.g. both have an inpatient dose titration phase). Additional differences in study population and titration schedule, length of treatment phase are highlighted below.

1) LIBRA's entry criteria excluded subjects with recent cerebral vascular accident (who would need to be differentiated from the SIADH subjects).
2) Exclusion of "acute or transient hyponatremia (e.g., associated with head trauma or postoperative state)" as an exclusion criterion. Though the study did not specify how it was to be done operationally.
3) Excluded subjects with any significant neurological impairment such that the subjects were not able to complete study procedures, (e.g. TMT-B). (Examples of neurological conditions which could exclude subject from participating, included but were not limited to Alzheimer's disease, normal pressure hydrocephalus, Parkinsonian dementia complex, multi-infarct dementia, mixed dementia,or Huntington's disease).

Dose Titration
As shown in the table below, the dose titration scheme was similar to that in the BALANCE study, except LIBRA did not allow up-titration based on a less than 24 hour evaluation of serum sodium, and had a lower maximum dose of 100 mg QD.

Table 5. General dosing guideline based on serum sodium (the LIBRA trial)

Change in Serum Sodium **24 Hour Change** (mEq/L)		Absolute Value (mEq/L)	Dosing Guidelines Based on Serum Sodium
<5	AND	<135	Increase dose to next dose level
>5	OR	>135 and <145	No change in dose
>8 mEq/ 8 hours on Day 1	OR	>145 mEq/L	Adjust fluid intake, decreasing dose, withhold study medication, and/or contract medical monitor for guidance on withdrawal subjects from the study

[source: reviewer's summary of the titration scheme]

Withdrawal Criteria
In addition to the similar withdraw criteria as seen in the BALANCE trial, in the LIBRA trial, subjects could also be withdrawn if serum sodium increased by more than 8 mEq/L in any eight hour period following dosing on Day 1, and the rate of rise was confirmed with a repeat STAT lab.

Statistical Analysis Plan
The SAP was similar to that in the BALANCE trial. The SAP was finalized on August 30, 2010, after last subject completed the treatment (May 14, 2010); however, no significant difference was made in the final SAP.

5.3.3 An Overview of the HARMONY Trial, 3430:

Title of the study: Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Tolerability of Oral Lixivaptan Capsules in Subjects with Euvolemic Hyponatremia

Studied period (years):
Date first subject enrolled: July 30, 2008
Date last subject completed: May 14, 2010

Geographic Distribution
61 sites in Belgium (two sites), Czech Republic (one site), Israel (three sites), India (nine sites), Italy (two sites), Mexico (one site), Peru (three sites), and the United States (40 sites)

Study Procedure:
The procedures were similar in the HARMONY and LIBRA (SIADH) trials, with the exception of the earlier mentioned differences in section 5.1.

Dose and Titration:
As mentioned earlier, in the HARMONY trial the initial dose was the lowest (25-mg once daily) among the 3 phase 3 trials. Following initiation of therapy, subjects were monitored over the initial 8 hours (± 1 hour) for signs and symptoms of treatment response. Subjects were to be released from the monitored setting if the rate of change in serum sodium concentration did not exceed 8 mEq/L at 8 hours. Subjects who had an increase in serum sodium concentration of > 8 mEq/L at 8 hours were not to be released from the monitored setting until further safety assessments had been conducted. Therefore, in the HARMONY trial, a minimal of 8-hour dose titration in the inpatient setting was required. The dosing guideline is provided below.

Table 6. General dosing guideline based on serum sodium (the HARMONY trial)

Change in Serum Sodium			**Dosing Guidelines Based on Serum Sodium**		
8 Hour Change Day 1 (mEq/L)	**24 Hour Chang**	**48 Hour Chang**	**< 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	At 8 hours following treatment initiation: Monitor subject symptoms; retest serum sodium at 12, 24, and 48 hours. Consider: adjusting fluid intake, holding the next dose, decreasing study medication, and contacting		

Source: table 4, the applicant's dosing guidelines

The Steps for Up-titration are specified below:
Step 1 (Hour 0): All subjects are given a 25-mg dose on Day 1.
Step 2 (24 hours): Based on the subject's serum sodium concentration at **24** hours, dosing may be increased to 50 mg QD.
At the Investigator's discretion, the serum sodium assessment may be repeated 8 hours following administration of the 50 mg QD dose.
Step 3 (48 hours): Based on the subject's serum sodium assessment at **48** hours, dosing may be increased to 100 mg QD.
At the Investigator's discretion, the serum sodium assessment may be repeated 8 hours following administration of the 100 mg QD dose.

Reviewer's comment:
Note the rate of change in 48 hour change can also be used to determine dosing.

The Harmony protocol specified that the screening local serum sodium findings were used to establish subject eligibility. All subjects were to have a STAT baseline serum sodium assessment performed by the local laboratory on the day of randomization, prior to administration of the first dose. The baseline local laboratory sodium values were used to evaluate changes in serum sodium following initial dosing.

Reviewer's comment:
Despite an initially planned Treatment Period of 24 weeks, the serum sodium secondary endpoints are based a difference between baseline and Day 28.

STATISTICAL ANALYSIS
The SAP was similar to that in the BALANCE trial. The SAP was finalized on August 30, 2010, before the last subject completed the treatment (December 2010); however, no material difference in the final SAP.

6 Review of Efficacy

Efficacy Summary

In support of the proposed indications, the applicant conducted 3 phase 3 trials in different study populations. These trials showed a consistent but modest treatment effect on serum sodium, larger in the SIADH population (2.2 to 2.4 mEq/L) than in the CHF and hyponatremia (1.2 mEq/L) population. Effects beyond serum sodium (e.g.,

days alive and out of hospital, use of fluid restriction, and cognitive function) were not detected.

6.1 Indication

The applicant proposes the use lixivaptan to treat hyponatremia in two populations: 1) symptomatic hypervolemic hyponatremia, associated with heart failure and, 2) and symptomatic euvolemic hyponatremia (SIADH).

6.1.1 Methods

Three phase 3 trials, BALANCE [hypervolemic hyponatremia, associated with heart failure], LIBRA [SIADH], and HARMONY [SIADH]) were reviewed for lixivaptan's efficacy. The primary efficacy endpoint for all 3 trials was a change in serum sodium on Day 7. The FDA statistical reviewer conducted a number of sensitivity analyses to assess the impact of missing values, different analysis populations (ITT, MITT, PP), and the discrepancies between local and central serum sodium measurements on the primary endpoint result. The definition of the populations is as follows.

- The MITT population consisted of all randomized subjects who receive at least 1 dose of study medication and have both a Baseline and one scheduled on-therapy assessment of serum sodium.
- The per-protocol (PP) population excluded subjects with entry criteria violations that were felt to not impact the interpretability of the study's safety finding (see Section 5).

All these analyses produced consistent results on serum sodium.

These efficacy results for different study populations were not pooled. In the following sections, the trial findings are discussed separately and in more detail.

6.2 The BALANCE trial in the congestive heart failure and hyponatremia population

6.2.1 Demographics in the BALANCE trial

The baseline demographics, including age, sex, race, co-morbid conditions, concomitant medications, were similar across treatment arms (see Table 61 in appendix).

As shown in Table 61, approximately 76% of the randomized subjects were white, and 28% percent were female, and approximately half of subjects were ≥65 years of age. Furthermore, the majority (96.3%) subjects had NYHA class III or IV. The percentages of subjects with history of coronary artery disease, and decreased systolic function were similar between two arms, and reflected the target population with CHF. Lastly, 23% of subjects were enrolled from the North America, of whom 18% from the United States (see Table 61 in appendix).

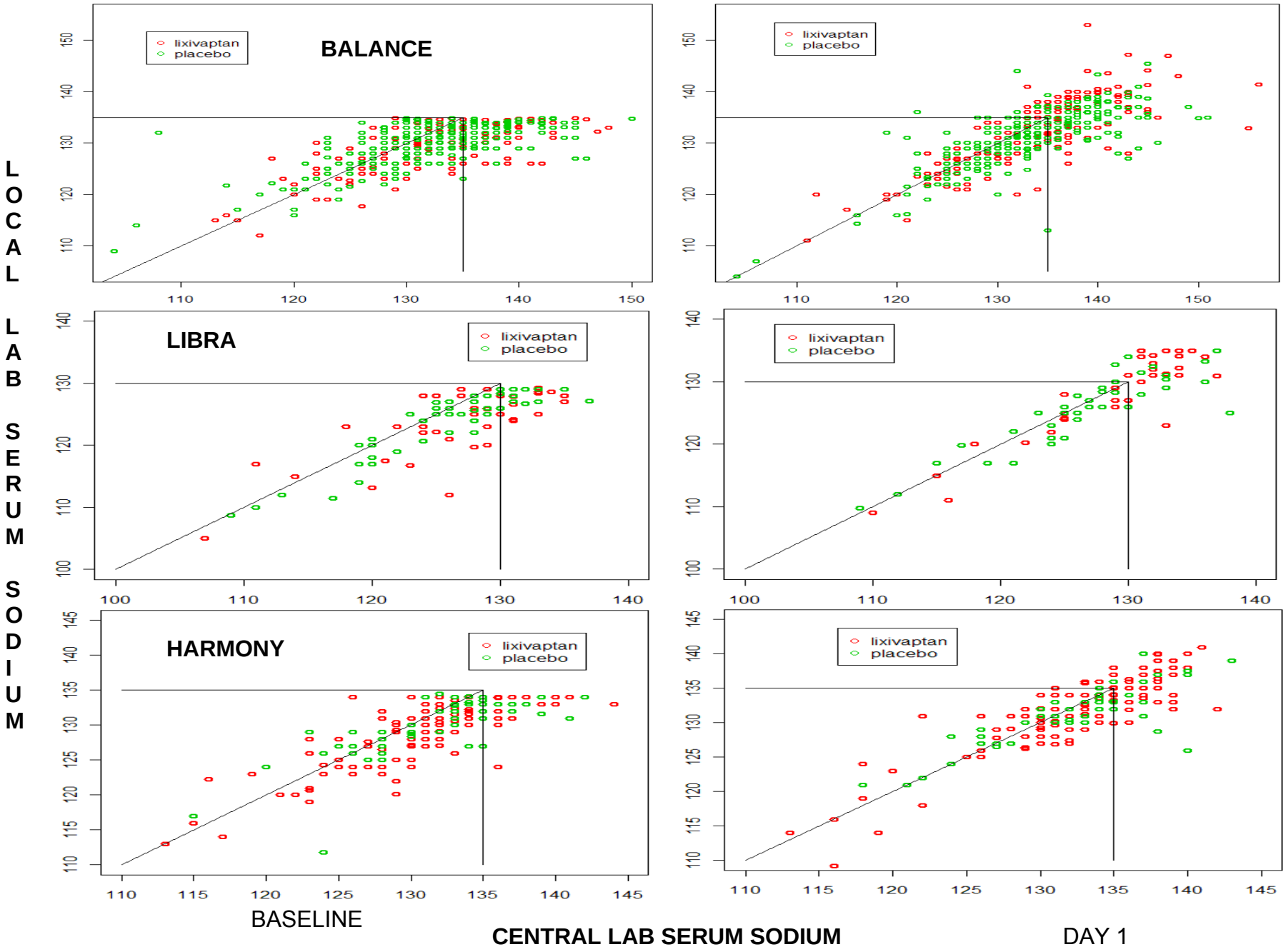
The Baseline serum sodium values in the BALANCE trial were not very low (the median sodium values by local and central laboratories were 131 mEq/L and 132 mEq/L, respectively). Only a fraction of the subjects had moderate (<130 mEq/L, 20-29%) to severe (<125 mEq/L, 7-8%) hyponatremia at (see Table 61 in appendix).

In addition, as shown in the table appendix, in terms of baseline serum sodium values, despite a modest difference (<2 mEq/L) between the mean or median values by local versus central laboratories in the BALANCE trial, the maximum serum sodium values were much higher by central (>148 mEq) than local (<135 mEq) laboratories. Furthermore, while all randomized subjects had baseline serum sodium values <135 mEq/L by local laboratories, about 40% of the central baseline serum sodium values were ≥ 135 mEq/L. This sizable difference between the local and central laboratory serum sodium values was seen in the BALANCE trial, but was not seen in the SIADH phase 3 trials (Figure 3).

As shown in Figure 3, this difference between baseline local versus central sodium values for the same subjects in the BALANCE trial appeared to be an issues only at Baseline. The BALANCE trial required only a single local serum sodium less than <135 mEq/L to fulfill the hyponatremia requirement for enrollment. A separate blood draw for the central sodium and were available in 621 (95.2%) subjects. The vast majority (≥ 90%) of the Baseline central sodium samples were drawn 12 to 13 hours after that of the local Baseline sodium values, in the respective treatment arms, which may have contributed to the difference between the two Baseline laboratory values for the same

subject. This could result in the phenomenon called “regression to the mean”, where the later value reflects the true mean value. In addition, the higher central than local laboratory Baseline serum sodium may be due to additional treatment effects from lixivaptan or fluid restriction. Moreover, as shown in the figure below of central and local serum sodium values at baseline and at Study Day 1, 8-hour after study drug dose, the correspondence between central and local serum sodium values at Day 1 was much better than at Baseline, suggesting the issue of discordance was unique to the definition of “Baseline” measurement. Lastly, based on available information, I can not rule out, whether there was more intra-subject variability in serum sodium in the BALANCE (hyponatremia in the setting of acute CHF exacerbation) as compared to the SIADH population.

Figure 3. Local versus central serum sodium in the BALANCE trial (Baseline and Day 1)



Source: FDA statistical reviewer

The effect of the discrepant local and central serum sodium baseline values was assessed in a sensitivity analysis (see FDA statistical reviewer's figure 2). For the efficacy endpoints, the serum sodium values were analyzed separately for local and central laboratory results with the corresponding baseline observations from local versus central laboratories.

Lastly, while all countries in the BALANCE trial enrolled subjects with central serum sodium ≥135 mEq/L (e.g. not hyponatremia) at baseline, United States was among the countries with the lowest (25%) percentage of enrollment of these subjects (see Table below). The US showed better than average consistency between central and local serum sodium measurements. Also, of note, the distributions of central serum sodium values were also largely similar between the two treatment arms.

Table 7. Baseline central serum sodium by country in the BALANCE trial

Country	Frequency	Total N	Percent (%)
Russia	79	116	68.1
Poland	49	104	47.1
Argentina	18	39	46.2
Chile	3	8	37.5
Romania	3	8	37.5
Czech Republic	9	28	32.1
Spain	4	13	30.8
Israel	10	34	29.4
India	31	111	27.9
Germany	5	18	27.8
Canada	7	26	26.9
United States of America	30	122	24.6
Italy	2	13	15.4
Slovakia	1	12	8.3
Total	251	652	40.0

[source: table 10 of the FDA statistical review]

Concomitant medications were also similar across the two treatment arms at baseline (see table below).

Table 8. Baseline medication use in the BALANCE trial

Concomitant medications (ITT population)	**Lixivaptan (n=323)**	**Placebo (n=329)**
	Number (%) of Subjects	

ACE inhibitors	219 (67.8)	238 (72.8)
Angiotensin II antagonists	66 (20.4)	61 (18.5)
Acetylsalicylic acid (Aspirin)	211 (65.5)	209 (64.9)
Beta-Blockers	255 (78.9)	275 (83.6)
Sulfonamides diuretics	317 (98.1)	325 (99.0)
Aldosterone antagonist diuretics	234 (72.4)	260 (79.0)
Digitalis glycosides	169 (52.3)	170 (52.0)
Clopidogrel	59 (18.3)	56 (17.0)
Organic nitrates	121 (37.5)	121 (36.8)
Statins	163 (50.5)	151 (45.9)
Adrenergic and dopaminergic agents	96 (29.7)	101 (30.7)

[source: largely from applicant table 18 of CSR for BALANCE study, verified by the reviewer using the concomitant medication dataset]

As shown above, the use of concomitant medications was similar between two treatment arms. Virtually all subjects were on diuretics, consistent with the treatment for hypervolemic CHF. The concomitant medication consumption pattern (ARB, ACEI, statins) largely reflects that of the standard of care for CHF in the United States. Of note, about 30% of the subjects were on inotrophic agents, reflecting a sick population with acute decompensated heart failure. In the acute decompensated heart failure population, the increase in ADH release is thought to be compensatory baroreceptor-mediated in response to the effective circulating volume depletion (due to low cardiac output, low systemic blood pressure).

As mentioned earlier, the medications that are thought to enhance AVP release or increase receptor sensitivity to AVP were permitted in the trial as long as they were for chronic use, and there was no plan to discontinue them during the treatment period. Some medications taken by subjects with CHF were thought to be associated with SIADH and/or hyponatremia in the drug labeling and/or medical literature. The concomitant medications that may be associated with enhanced ADH release are summarized in the table below. Aside from amiodarone and ciprofloxacin, few subjects were on any medications that also may be associated with inappropriate elevation in ADH.

Table 9. Concomitant medications associated with hyponatremia (BALANCE)

	Lixivaptan N=323 n (%)	Placebo N=329 n (%)
Amiodarone	66 (20.4)	75 (22.8)
Amitriptyline	3 (0.9)	2 (0.6)
Carbamazepine	3 (0.9)	2 (0.6)
Ciprofloxacin	31 (9.6)	23 (7.0)
Escitalopram	4 (1.2)	4 (1.2)
Fluoxetine	2 (0.6)	3 (0.9)
Haloperidol	7 (2.2)	4 (1.2)
Sertraline	8 (2.5)	2 (0.6)
valproate sodium/ valproic acid	1 (0.3)	1 (0.3)

Source: reviewer's analysis of concomitant medication dataset.
According to the amiodarone labeling, there were postmarketing reports of SIADH associated with amiodarone, but causality is not established. Ciprofloxacin does not carry a SIADH association in the labeling, but has been implicated in published literature.

The majority (greater than 60%) of the subjects were also on fluid restriction (defined as intake of fluid less than 2 liter per day) at baseline. A fluid restriction of <2 L/day is recommended by the current Heart Failure Society of America guidelines on treating acute decompensated heart failure in subjects with serum sodium <130 mEq/L and volume overload. As shown in the table below, the percentage of subjects on baseline fluid restriction was balanced across the level of fluid restriction.

Table 10. Baseline fluid restriction (BALANCE)

	<1 L	>1 L, <1.5 L	1.5 L -2 L	Total n, % with any fluid restriction
Lixivaptan N=323 n, %	76 (23.5)	110 (34.1)	24 (7.4)	210 (65.0)
Placebo N=329 n, %	72 (21.9)	113 (34.3)	21 (6.4)	206 (62.6)

[source: reviewer's analysis of the fluid dataset for the balance trial]
Lastly, the percentage of subjects with symptoms potential attributable to hyponatremia at screening are shown below. These symptoms were non-specific and could be attributed to underlying disease.

Table 11. Baseline symptoms that may be attributable to hyponatremia (BALANCE)

BALANCE trial, ITT population	Lixivaptan N=323 n (%)	Placebo N=329 n (%)
Any inquired symptom	198 (61.3)	207 (62.9)
confusion	15 (4.6)	20 (6.1)
delirium	1 (0.3)	2 (0.6)
disorientation	3 (0.9)	7 (2.1)
fatigue	189 (58.5)	196 (59.6)
headache	47 (14.6)	55 (16.7)
irritability	31 (9.6)	44 (13.4)
mental slowing	49 (15.2)	48 (14.6)
nausea	47 (14.6)	41 (12.5)
vomiting	13 (4.0)	14 (4.3)

[source: reviewer's analysis of the clinical findings' dataset for the balance trial]

6.2.2 Subject Disposition in the BALANCE Trial

In the BALANCE trial, 756 subjects were screened, and a total of 652 were randomized. Of the 104 subjects who were not randomized, the more common (> 2 subjects) reasons for screen failure were baseline serum sodium ≥ 135 mEq/L (n=44), baseline serum sodium <120 mEq/L (n=7), CHF due to uncorrected thyroid disease (n=5), supine systolic arterial blood pressure <90 mmHg (n=3), and uncontrolled diabetic mellitus (n=3).

Of the 652 subjects randomized, a number of subjects (n=210, 32.2%) did not complete either the treatment period and/or follow-up period (Table below). Common reasons for not completing included death, subject withdrew of consent, or investigator withdrew consent, and occurrence of adverse event(s). With the exception of discontinuation due to death, and perhaps "reason not given", which both occurred at a greater incidence in the lixivaptan treatment arm, the numbers of subjects discontinuation for other reasons were similar between the two groups. Please see Sections 6 and 7 for explorations of the major reasons discontinuation (due to death, investigator and subject withdrew consent) and the impact of missing values on efficacy and safety analysis.

Also, as shown in the table below, any subject who did not completed the treatment and/or the follow-up period was considered not completed the trial. The subjects who were withdrawn by investigators from the treatment phase all subsequently completed the 30 Day Follow-Up Visit (therefore were considered to have completed the follow-up phase, despite not completing the trial). Majority (75%) of the subjects who did not complete the treatment phase because of withdrawing consent (n=55) completed the 30-Day follow-up phase (n=41). Similarly, about half of the subjects who did not complete treatment phase because of the adverse events completed the 30-Day Follow-up Visit. The applicant reported vital status for all subjects and provided case report forms for all subjects discontinued for adverse events.

Table 12. Subject disposition (BALANCE)

	Number (%) of Subjects		
	Lixivaptan n (%)	**Placebo n (%)**	**Total**
Subjects randomized (ITT)	323	329	652
Subjects treated (Safety Population)	322 (97.9)	322 (97.9)	644 (98.8)
Subjects Completed the Trial (n, % of the safety population)[1]	191 (59.1)	213 (64.7)	404 (62.0)
Subjects completed treatment period	207 (64.1)	227(69.0)	434 (66.6)
Subjects not completed treatment period[2]	115 (35.6)	95 (28.9)	210 (32.2)
Adverse event	15	16	31
Death	35	25	60
Investigator withdrew subject	19	18	37
Lack of efficacy	1	0	1
Lost to follow-up	0	3	3
Other	8	6	14
Protocol violation	2	0	2
Subject withdrew consent	29	26	55
Reason not given[3]	6	1	7
Subjects completed follow-up period	233 (64.1)	239 (70.5)	472 (67.4)
Subjects not completed follow-up period[4]	89 (27.6)	83 (25.8)	172 (26.7)
Adverse event	6	10	16
Death	43	33	76
Investigator withdrew subject	10	11	21
Lost to follow-up	4	4	8
Other	5	3	8
Subject withdrew consent	20	21	41

[Applicant's Table 11 in the CK-LX3401 Clinical Study Report, verified by the reviewer]

[1] Completed trial requires completion of both the treatment and follow-up period. Treatment phase non-completers can be counted as completers for the follow-up period (thus the sum of treatment and follow-up phase completers/non-completers exceeds the total number of subjects enrolled).
[2] Reasons for early termination of treatment are derived from the investigator assessment of the primary reason for early termination.
[3] The 7 subjects who did not have any reason not given for not completing the treatment phase, all completed the follow-up phase. None of these subjects died. Four of these 6 lixivaptan treated subjects had an episode of SAE.
[4] According to the applicant, for subjects who did not attend the 30-Day Follow-Up Visit were considered to have not completed the follow-up phase with the reason for non-completion assigned as the reason for not completing the treatment phase.

6.2.3 Analysis of Primary Endpoint(s) in the BALANCE trial

The primary endpoint analysis was conducted in the ITT population, using the ANCOVA model with treatment, pooled country and baseline local sodium stratum (<130 mEq/L vs. ≥130 mEq/L) as factors, and with baseline central serum sodium value as the covariate. The applicant imputed the missing serum sodium data by last observation carried forward (LOCF). If the baseline value was missing, the next available observation was carried backward as baseline (NOCB). The mean increase in central serum sodium from Baseline to Day 7 was modest (1.2 mEq/L), but statistically significantly higher in the lixivaptan as compared to the placebo group (p=0.001, as shown in the table below).

Table 13 Mean change in central serum sodium from Baseline to Day 7 (BALANCE)

Parameter	Statistic	Lixivaptan (N=323)	Placebo (N=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 Change	2.0	1.0
ANCOVA	LS mean change from baseline (SE)	2.5 (0.3)	1.3 (0.3)
	p-value	0.001	

[Source: Applicant's clinical study report CK-LX3401 Table 20, verified by the FDA statistical reviewer]
* In this analysis, 7 subjects in lixivaptan group and 21 subjects in placebo group did not have pre-dose measurements in central serum sodium and had to impute the missing value by carrying the next available post-dose observation backward.

The FDA statistical reviewer, Dr. Jialu Zhang, also performed a number of sensitivity analyses to assess the impact of missing values, the discrepancies between local and central serum sodium measurements, country, and level of serum sodium on the primary result. All these sensitivity analyses showed consistent results: a statistically significant treatment effect on serum sodium with a modest effect size in the range 1.2 to 1.4 mEq/L (see FDA statistical reviewer's Table 5).

While the absolute level of serum sodium increase was largest in those with lower serum sodium levels (expected as lixivaptan and background fluid restriction were titrated to correct to a desired level of serum sodium), across the levels of serum sodium studied, lixivaptan had a relatively constant effect size over placebo.

6.2.4 Analysis of Secondary Endpoints(s) in the BALANCE trial

The secondary efficacy endpoints were tested for treatment group differences in the hierarchical sequence at significance level of 0.05 (two-sided), in accordance with the final version of the SAP. In the BALANCE trial, ANCOVA models were used for area under the serum sodium concentration and time curve (AUC) and TMT-B test between two treatment groups. CMH test was used to compare the percentage of subjects with worsening of hyponatremia and the percentage of subjects who achieve normalized serum sodium between two treatment groups. The FDA statistical reviewer performed the specified analyses (the results are summarized in Dr. Jialu Zhang's Table 6 below). In addition, a number of sensitivity analyses, including those conducted by the applicant (ITT population with OV) also showed similar results (see statistical review for details).

Table 14 Secondary Efficacy Endpoints (BALANCE)

Secondary Efficacy Endpoint (BALANCE), as specified in the SAP	**Lixivaptan**	**Placebo**	**Nominal p-value**
1. Normalized Average Daily nAUC0-60 for central serum sodium concentration from Day 0 to Day 60	2.6 (0.27)	1.9 (0.27)	0.042
2. Change from Baseline to Day 28 for the recorded time to complete the TMT-B	-7.3 (5.1)	-20.9 (5.1)	0.021
3. Percentage of subjects with worsening of hyponatremia during the double- blind on-therapy period*	166/323 (51.4%)	195/329 (59.3%)	0.04
4. Percentage of subjects who achieved normalized serum sodium (135 to 145 mEq/L) at:			
Day 7	89/323 (27.6%)	74/329 (22.5%)	0.14
Day 60	108/323 (33.4%)	83/329 (25.2%)	0.02
5. Days Alive and Out of Hospital (DAOH)	41.3 (19.3)	42.6 (17.6)	0.652

[source: FDA statistical reviewer's analysis, table 6]

1. LS mean change on normalized average daily AUC for central serum sodium with standard error (ITT LOCF)
2. LS mean change from baseline on time to complete TMT-B Trail Test with standard deviation (ITT OV)
3. Total number of subjects with worsening of hyponatremia over total number of subjects and percentage (ITT LOCF), p-value was computed by CMH test controlling for pooled country
4. Total number of subjects achieving normalized serum sodium at Day 7 or Day 60 versus total number of subjects (ITT LOCF)
5. Total number of days out of hospital with standard deviation (ITT, p-value was from Wilcoxon rank-sum test)

* Worsening hyponatremia was defined as a reduction of ≥3 mEq/L in serum sodium concentration from the preceding measurement with a value <135 mEq/L. These results are somewhat different from the applicant reported that 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). The FDA statistical reviewer's OV (162/242 in lixivaptan group versus 185/249 in placebo group, nominal p-value=0.055 by CMH test).

Unlike the applicant's results on the TMT-B test (an instrument for measuring cognitive function) which showed a non-significant difference between lixivaptan and placebo groups, the ANCOVA model in the FDA statistical reviewer's analysis (specified in the SAP) showed a nominal p-value of 0.02, suggesting that the placebo group had a greater reduction in TMT-B score than the lixivaptan group, contrary to what was anticipated. By either analysis, in the CHF and hyponatremia population, there was no evidence that lixivaptan treatment improved cognitive function, as assessed by TMT-B, nor any effect beyond that on serum sodium. In addition, there was no effect on days alive and out of the hospital.

6.3 The SIADH population (the LIBRA trial, in-patient dose titration)

6.3.1 Demographics of the LIBRA trial

Of the 136 subjects screened for the LIBRA trial, 106 were randomized. Baseline demographics, including age, sex, race, co-morbid conditions, concomitant medications, were similar across treatment arms and reflected the target population in the United States (see Table 15). Approximately, 83% of the randomized subjects were white, and 47% were female. Slightly more than half of subjects were ≥65 years of age. Approximately 38 % of study subjects were enrolled from U.S. and Canadian sites (see Table 63 in appendix).

Among the three phase 3 trials, the baseline serum sodium values were lowest in the LIBRA trial (mean and median about 124 -127 mEq/L, respectively, see table below), consistent with the trial's the lowest serum sodium entry criteria requirement. About 34% of subjects had hyponatremia <125 mEq/L. The central and local baseline serum sodium values generally agreed and were largely (96% to 100%) met the definition for hyponatremia (<135 mEq/L). There were a few subjects with slightly higher central than local values.

Table 15 Baseline serum sodium (LIBRA)

Characteristics (ITT population)	Lixivaptan (n=54)	Placebo (n=52)
Baseline local serum sodium	**n= 54**	**n= 52**
Mean (SD)	124.7 (5.2)	124.1 (5.4)
Median	127	126
minimum, maximum	105.0, 129.2	108.7,129.0
Number (%) < 135 mEq/L	54 (100)	52 (100)
Number (%) <125 mEq/L	19 (35.2)	17 (32.7)
Baseline central serum sodium	**n= 51**	**n= 51**
Mean (SD)	127.5	126.1
Median	129	128
minimum, maximum	107.0, 135.0	109,137
Number (%) < 135 mEq/L	49 (96.1)	49 (96.1)
Number (%) <125 mEq/L	12 (23.5)	16 (31.4)

Source: adapted from the applicant table 13, CK-LX3405 Clinical Study Report. Confirmed with the keyvars dataset for 3405 study.

Because conditions such as infection, trauma, psychosis, pain are thought to enhance ADH release, I reviewed the indications for using concomitant medications. The most

common indications for the use concomitant medication were pain, infection, various mood disorders and psychosis (Table 64 appendix), consistent with the conditions that are associated with SIADH. Concomitant medications were largely similar across the three treatment arms at baseline. Reviewing the recognized causes of acute and more easily reversible SIADH syndrome, according to the medical history, one subject had a history of head trauma, but no recent hemorrhagic stroke, nor major surgery.

Because some medications are thought to be associated with SIADH and/or hyponatremia in the drug labeling and/or medical literature, I reviewed the concomitants drugs taken by the LIBRA subjects. These drugs included selective serotonin reuptake inhibitors, oncologic agents, anti-seizure medications. The medications that may be associated with SIADH syndrome are summarized in Table 16.

Table 16 Concomitant Medications that were associated with SIADH use (LIBRA)

ITT Population	Lixivaptan n (%)	Placebo n (%)
amitriptyline	1 (1.9)	1 (1.9)
carbamazepine	2 (3.7)	5 (9.6)
ciprofloxacin	7 (13.0)	7 (13.5)
cyclophosphamide	1 (1.9)	0 (0.0)
fluoxetine	1 (1.9)	1 (1.9)
haloperidol	2 (3.7)	2 (3.8)
oxcarbazepine	1 (1.9)	2 (3.8)
sertraline	2 (3.7)	0 (0.0)
valproate sodium/ valproic acid	2 (3.7)	2 (3.8)

[source: reviewer's analysis of the concomitant medications dataset. Search conducted with the following terms: amiodarone, amitriptyline, carbamazepine, cisplatin, cyclophosphamide, ciprofloxacin [add or not?], desmopressin, escitalopram, fluoxetine, ifosfamide, imatinib, melphalan, haloperidol, oxcarbazepine, oxytocin, sertraline, valproate sodium/ valproic acid, vincristine, vinorelbine, vinblastine]

Reviewer's comment:
The medications above can be important to the treatment of a subject's underlying condition (e.g. cancer, psychosis, depression, seizure), and therefore may not feasibly be discontinued/dose reduced.

Lastly, fluid restriction is often part of the treatment for SIADH, though subjects may find fluid restriction, particularly if stringent, difficult to comply with. The following table summarizes the baseline fluid restrictions in the LIBRA trial.

Table 17 Fluid restriction at Baseline screening visit (LIBRA)

	Fluid Restriction per Day			
n,%	<1 L	>1 L, <1.5 L	≥1.5 L &<2 L	Total Fluid Restriction
Lixivaptan N=54	5 (9.3)	8 (14.8)	7 (13.0)	20 (37.0)
Placebo N=52	5 (9.3)	12 (23.1)	17 (31.5)	34 (65.4)

Source: reviewer's analysis of the fluid dataset in the LIBRA trial

As shown above, the baseline fluid restriction was not balanced between the treatment arms except when the level of fluid restriction was < 1 liter per day. In SIADH, where there is a primary elevation in ADH release not driven by decreased intravascular volume, stringent fluid restriction may be required, particularly in those with high urine osmolality. Some believed that stringent fluid (e.g. < 1 liter) restriction is needed to induce negative free water balance to raise serum sodium in SIADH, therefore may be more than that in the CHF population (<2 liter).

The number of subjects on any type of fluid restriction at screening is higher in placebo than lixivaptan arm. It is not clear however, whether this imbalance at higher levels of fluid restriction (>1 liter but < 2 liters) can affect the treatment effect. However, the number of subjects with <1 liter of baseline fluid restriction is the same and small (n=5, <10%) as shown in the table above.

Lastly, at baseline most subjects had some non-specific symptoms that could be attributable to hyponatremia. A fraction had symptoms (confusion, disorientation, mental slowing) that may be addressed by TMT-B test.

Table 18 Baseline symptoms that could be attributed to hyponatremia (LIBRA)

ITT population	Lixivaptan N=54 n (%)	Placebo N=52 n (%)	Total N=106 n (%)
Any inquired symptoms	35 (64.8)	31 (59.6)	66 (62.3)
confusion	10 (18.5)	8 (15.4)	18 (17.0)
delirium	0 (0.0)	0 (0.0)	0 (0.0)
disorientation	1 (1.9)	3 (5.8)	4 (3.8)
fatigue	27 (50.0)	24 (46.2)	51 (48.1)
headache	11 (20.4)	9 (17.3)	20 (18.9)
irritability	12 (22.2)	15 (28.8)	27 (25.5)
mental slowing	22 (40.7)	21 (40.4)	43 (40.6)
nausea	11 (20.4)	8 (15.4)	19 (17.9)
vomiting	2 (3.7)	4 (7.7)	6 (5.7)

[source: reviewer's analysis of the clinical findings' dataset for the LIBRA trial]

6.3.2 Subject Disposition-the LIBRA Trial

Of 136 subjects screened, a total of 104 were randomized. Of the 32 subjects excluded from randomization, the more common (>2 subjects) reasons for screen failure included 1) serum sodium <130 mEq/L, 2) not hospitalized or not willing to be admitted to a monitored setting for approximately the first 48-72 hours of treatment. The disposition of the subjects is shown in the table below.

Table 19 Subject disposition (LIBRA)

	Number (%) of Subjects		
	Lixivaptan	**Placebo**	**Total**
Subjects randomized (ITT population)	54	52	106
Subjects treated (Safety Population)	50 (92.6)	51 (98.1)	101 (95.3)
Subjects completed the trial[1]	39 (72.2)	34 (65.4)	73 (68.9)
Subjects not completed the trial	11 (20.4)	17 (32.7)	28 (26.4)
Subjects completed the 30-day treatment period	41	37	78
Subjects not completed the treatment period	9	14	23
Adverse event	2	4	6
Death	0	2	2
Investigator withdrew of subject	1	0	1
Lost to follow-up	1	2	3
Other	2	1	3
Subject withdrew consent	3	5	8
Subjects completed the 30-day follow-up period	42	38	80
Subjects not completed follow-up period	8	13	21
Adverse event	1	1	2
Death	0	4	4
Investigator withdrew of subject	1	0	1
Lost to follow-up	1	2	3
Other	2	2	4
Subject withdrew consent	3	4	7

[source: reviewers' analysis]
[1] Completed trial requires completion of both the treatment and follow-up period. Treatment phase non-completers can be counted as completers for the follow-up period (thus the sum of treatment and follow-up phase completers/non-completers exceeds the total number of subjects enrolled).
For the 4 subjects not treated in the lixivaptan arm: 2 withdrew consent, 2 were grouped into others (left AMA, or transferred to another hospital for surgery).
One of the lixivaptan pts who was grouped into others had back pain and withdrew consent.

6.3.3 Analysis of Primary Endpoint(s) for the LIBRA trial

The same analytic methods were used for the LIBRA and the BALANCE trials.
The treatment effect, the mean increase in central serum sodium from baseline to Day 7 was statistically significant in the lixivaptan group compared to the placebo group (2.2

mEq/L, p=0.039), effect size was numerically larger than that seen in the BALANCE trial population.

Table 20 Mean change in central serum sodium concentration from Baseline to Day 7 (LIBRA)

Parameter	**Statistic**	**Lixivaptan**	**Placebo (N=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
ANCOVA*	LS mean (SE)	6.7 (0.7)	4.5 (0.8)
	p-value	0.03	

[Source: FDA statistical reviewer]* ANCOVA model use central serum sodium as covariate and include pooled country and treatment group as factors

6.3.4 Analysis of Secondary Endpoints(s) for the LIBRA trial

As shown in Table 21, the first two secondary efficacy endpoints (mean nAUC0-30, % of subjects with normalized serum sodium) showed treatment effect sizes on serum sodium that were still modest, but that were larger than the treatment effects seen in the BALANCE trial.

All subsequent secondary endpoints showed non-statistically significant difference between the two treatment arms. But of note, the percentage of subjects whose fluid restriction was initiated or tightened at Day 30 was numerically higher in the lixivaptan than placebo arm, raising the hypothesis that the efficacy may reflect, in part, the increased use of fluid restriction. Nonetheless, taking into consideration the numerically lower level of fluid restriction in lixivaptan than placebo arm at baseline (pre-treatment), the level of fluid restriction on-treatment appears similar in the two treatment arms. In addition, the number of sensitivity analyses all showed no treatment difference on fluid restriction between the two arms. Similarly, there was no improvement in cognitive functional on lixivaptan demonstrated. In sum, there was no treatment effect observed beyond the effects on serum sodium, as specified in the first two sequentially tested secondary efficacy endpoints.

Table 21 Summary of Secondary Efficacy Endpoints (LIBRA)

Secondary Efficacy Endpoint	Lixivaptan	Placebo	Nominal p-value
nAUC0-30 for central serum sodium concentration	6.8 (0.7)[1]	4.8 (0.7)[1]	0.03
Percentage of subjects who achieved normalized serum sodium (≥135 to ≤145 mEq/L) at Day 7	24/54 (44%)[2]	12/52(23%)[2]	0.021
Percentage of subjects whose fluid restriction was initiated or tightened at Day 30	17/54 (32%)[3]	12/52 (23%)[3]	0.064
Percentage of subjects with worsening of hyponatremia at any time during the treatment period	25/54 (46.3%)[4]	30/52 (57.7%)[4]	0.25
Change from Baseline to Day 30 for the recorded time to complete the TMT-B	-16.1 (8.2)[5]	-7.8 (8.5)[5]	0.48

[Source: FDA statistical reviewer]*

1. LS mean change on normalized average daily AUC for central serum sodium with standard error (ITT LOCF)
2. Total number of subjects achieving normalized serum sodium at Day 7 versus total number of subjects (ITT LOCF)
3. Number of subjects who initiated or increased fluid restriction at Day 30 (ITT LOCF)
4. Total number of subjects with worsening of hyponatremia versus total number of subjects (ITT LOCF)
5. Mean change from baseline on time to complete TMT-B Trail Test with standard deviation

6.4 The SIADH population (the HARMONY trial, monitored out-patient dose titration)

6.4.1 Demographics: the HARMONY trial, SIADH population

Of the 333 subjects screened, 206 subjects were randomized. Of the 127 subjects excluded, the most common reason for screen failure was serum sodium greater than the cut-off values (n=96).

Of the subjects randomized (3:1) to lixivaptan and placebo arms, the baseline demographics, were largely similar across treatment arms (see Table 67 in appendix). In the HARMONY trial, most (77%) subjects were from the United States.

As shown in the Table 22 and Figure 3, below, in HARMONY, the central and local baseline serum sodium values generally agreed and met the hyponatremia definition (< 135 mEq/L). There were a few subjects with slightly higher central than local values, but this difference was consistent across treatment groups.

Table 22. Baseline central and local serum sodium (HARMONY)

	Lixivaptan (n=154)	**Placebo (n=52)**
Baseline local serum sodium		
Mean (SD)	130 (4.4)	130 (4.3)
Median	131	131
minimum, maximum	113, 134	112.0, 134.5
Number (%) < 130 mEq/L	55 (35.7)	22 (42.3)
Number (%) <125 mEq/L	27 17.5)	9.6 (32.0)
Baseline central serum sodium		
Mean (SD)	131.5 (4.9)	131.6 (5.2)
Median	132	133
minimum, maximum	113, 144	115, 142
Number (%) < 130 mEq/L	38 (24.7)	15 (28.9)
Number (%) <125 mEq/L	14 (9.1)	5 (9.6)

[source: reviewer' analysis]

At baseline, a slightly greater number of subjects were on fluid restriction in the lixivaptan than placebo arm (see Table below).

Table 23. Baseline fluid restriction (HARMONY)

	Fluid Restriction per Day n (%)			
ITT population	<1 L	>1 L & <1.5 L	≥1.5 L & <2 L	Total
Lixivaptan, N=154	4 (2.6)	14 (9.1)	8 (5.2)	26 (16.9)
Placebo, N=52	1 (1.9)	3 (5.8)	2 (3.8)	6 (11.5)

[source: reviewer' analysis]

Similar to the LIBRA trial, the most common conditions for which the subjects were receiving medications were pain, mood disorders, infection, and psychosis, which were also the conditions that have been associated with inappropriately increased release of ADH. There were a number of subjects who were receiving medications for dementia, seizure, or cancer. My review of the medical history for other recognized causes of acute or easily reversible causes of SIADH, I found no case of acute stroke hemorrhage and only one case recent trauma.

Similarly, a number of subjects were on medications that can cause or associated SIADH (see Table below).

Table 24. Concomitant medications that can cause or associated SIADH (HARMONY trial)

ITT population	Lixivaptan N=154 n (%)	Placebo N=52 n (%)	Total N=206 n (%)
amiodarone	2 (1.3)	1 (1.9)	3 (1.5)
amitriptyline	4 (2.6)	2 (3.8)	6 (2.9)
carbamazepine	11 (7.1)	1 (1.9)	12 (5.8)
ciprofloxacine	13 (8.4)	3 (5.8)	16 (7.8)
desmopressin	1 (0.6)	0 (0.0)	1 (0.5)
escitalopram	1 (0.6)	0 (0.0)	1 (0.5)
fluoxetine	3 (1.9)	4 (7.7)	7 (3.4)
haloperidol	4 (2.6)	1 (1.9)	5 (2.4)
oxcarbazepine	4 (2.6)	0 (0.0)	4 (1.9)
sertraline	2 (1.3)	2 (3.8)	4 (1.9)
valprote sodium/valproic acid	5 (3.2)	0 (0.0)	5 (2.4)

[source: reviewer's analysis]

Lastly, at baseline, approximately half of the subjects had some non-specific symptoms that could be attributable to hyponatremia. A fraction had symptoms (confusion, disorientation, mental slowing) that may be addressed by TMT-B test.

Table 25. Baseline symptoms that may be attributable to hyponatremia (HARMONY)

	Lixivaptan N=154 n (%)	Placebo N=52 n (%)	Total N=206 n (%)
Any inquired symptoms	84 (54.5)	31 (59.6)	105 (51.0)
confusion	27 (17.5)	7 (13.5)	34 (16.5)
delirium	2 (1.3)	1 (1.9)	3 (1.5)
disorientation	12 (7.8)	4 (7.7)	16 (7.8)
fatigue	61 (39.6)	22 (42.3)	83 (40.3)
headache	28 (18.2)	11 (21.2)	39 (18.9)
irritability	24 (15.6)	9 (17.3)	33 (16.0)
mental slowing	40 (26.0)	15 (28.8)	55 (26.7)
nausea	11 (7.1)	4 (7.7)	15 (7.3)
vomiting	3 (1.9)	0 (0.0)	3 (1.5)

[source: reviewer's analysis of the clinical findings' dataset for the Harmony trial]

6.4.2 Subject Disposition (HARMONY)

The disposition of the subjects is shown in table 26 below.

Table 26. Disposition according to the original design in the HARMONY trial

	Lixivaptan	Placebo
Subjects randomized	**154**	**52**
Subjects treated	153 (99.4)	52 (100.0)
Subjects completed study	53 (34.4)	17 (32.7)
Subjects not completed study	100 (64.9)	35 (67.3)
Subjects completed the 24-week treatment period	53 (34.4)	17 (32.7)
Subjects not completed the 24-week treatment period	101 (65.6)	35 (67.3)
Adverse event	8	7
Death	6	1
Investigator withdrew of subject	3	0
Lack of efficacy	1	1
Other	4	0
Protocol violation	1	1
Study terminated by applicant	65	19
Subject withdrew consent	13	5
Subjects completed the follow-up period	131 (85.1)	44 (84.6)
Subjects not completed the follow-up period	22 (14.3)	8 (15.4)
Adverse event	1	2
Death	6	1
Investigator withdrew of subject	1	0
Other	1	0
Protocol violation	1	1
Study terminated by applicant	1	1
Subject withdrew consent	11	4

Source: FDA reviewers' analysis on the applicant's disposition dataset.

According to the applicant, because the primary and secondary efficacy endpoints targeted time points within the initial eight weeks from randomization, therefore, when the last subject enrolled in the study had completed eight weeks of treatment, the applicant instructed the investigators to stop blinded therapy in all subjects in the study.

These subjects entered the protocol-specified, 30-day safety follow-up period. Majority (about 80%) of the subjects finished the 8-week treatment phase (see Table 27 below). The completion in terms of the 8-weeks of treatment period as follows.

Table 27. Disposition according to truncated treatment phase (HARMONY)

	Lixivaptan	Placebo
Subjects randomized	154	52
Subjects treated	153 (99.4)	52 (100.0)
Subjects completing first 8 weeks of treatment period*	127 (82.5)	40 (76.9)
Subjects not completing first 8 weeks of treatment period	24 (15.6)	11 (21.2)
Adverse event	7	6
Death	4	0
Investigator withdrew subject from	2	0
Lack of efficacy	1	1
Study terminated by the applicant	0	1
Protocol violation	0	1
Subject withdrew consent	8	2
Other	2	0

[Source: The FDA statistical reviewer's table 24]
* 3 subjects had last dose date missing and were not counted in either completers or non-completers

Reviewer's comment:
It is not clear whether the death finding in the BALANCE trial had any influence on the applicant's decision to stop the HARMONY treatment phase earlier.
The last dose dates in HARMONY were after when the BALANCE death findings were made available.

6.4.3 Analysis of Primary Endpoint(s)

There was a modest (2.4 mEq/L), but a statistically significant mean increase in central serum sodium from Baseline to Day 7 in the lixivaptan compared to the placebo group (Table 28).

Table 28. Mean change in central serum sodium from Baseline to Day 7 (HARMONY)

Parameter	**Statistic**	**Lixivaptan**	**Placebo N=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
ANCOVA	LS mean (SE)	3.2 (0.5)	0.8 (0.6)
	p-value	<0.00	

[Source: Applicant's Clinical Study Report CK-LX3430 Table 17, verified by the FDA statistical reviewer]

6.4.4 Analysis of Secondary Endpoints(s)

Similar to the LIBRA trial, there was statistical significant treatment effect on the first two secondary efficacy endpoints (AUC serum sodium [area under the concentration time curve average over the time span] and percent of subjects achieving normalized serum sodium), but no effect beyond effects on serum sodium was demonstrated (see table 29 below).

Table 29. Summary of secondary efficacy endpoints (HARMONY)

Secondary Efficacy Endpoint (HARMONY)	Lixivaptan	Placebo	Nominal p-value
nAUC0-28 for central serum sodium concentration	3.3 (0.4)[1]	1.8 (0.5)[1]	0.004
Percentage of subjects who achieved normalized serum sodium (≥135 to ≤145 mEq/L) at Day 7	60/154 (39%)[2]	6/52 (12%)[2]	<0.001
Percentage of subjects whose fluid restriction was initiated or tightened at the end of treatment versus Baseline	17/153 (11%)[3]	11/52 (21%)[3]	0.2
Percentage of subjects with worsening of hyponatremia during the double-blind on-therapy period	86/154 (56%)[4]	35/52 (67%)[4]	0.11
Change from Baseline to Day 28 for the recorded time to complete the TMT-B	-11.4 (7.8)[5]	-11.5 (6.4)[5]	0.99

[Source: FDA statistical reviewer, table 27]

1. LS mean change on normalized average daily AUC for central serum sodium with standard error (ITT LOCF)
2. Total number of subjects achieving normalized serum sodium at Day 7 versus total number of subjects (ITT LOCF)
3. Number of subjects who initiated or increased fluid restriction at the end of treatment (ITT LOCF)
4. Total number of subjects with worsening of hyponatremia versus total number of subjects (ITT LOCF)
5. Mean change from baseline on time to complete TMT-B Trail Test with standard deviation

Similar to the findings in the LIBRA trial, the percentage of subjects whose fluid restriction was initiated or tightened at end of treatment was numerically higher in the lixivaptan than placebo arm, raising the hypothesis that the efficacy may reflect, in part, the increased use of fluid restriction. Nonetheless, taking into consideration the numerically lower level of fluid restriction in lixivaptan than placebo arm at baseline (pre-treatment), the level of fluid restriction on-treatment appears similar in the two treatment arms.

6.5 Other Endpoints

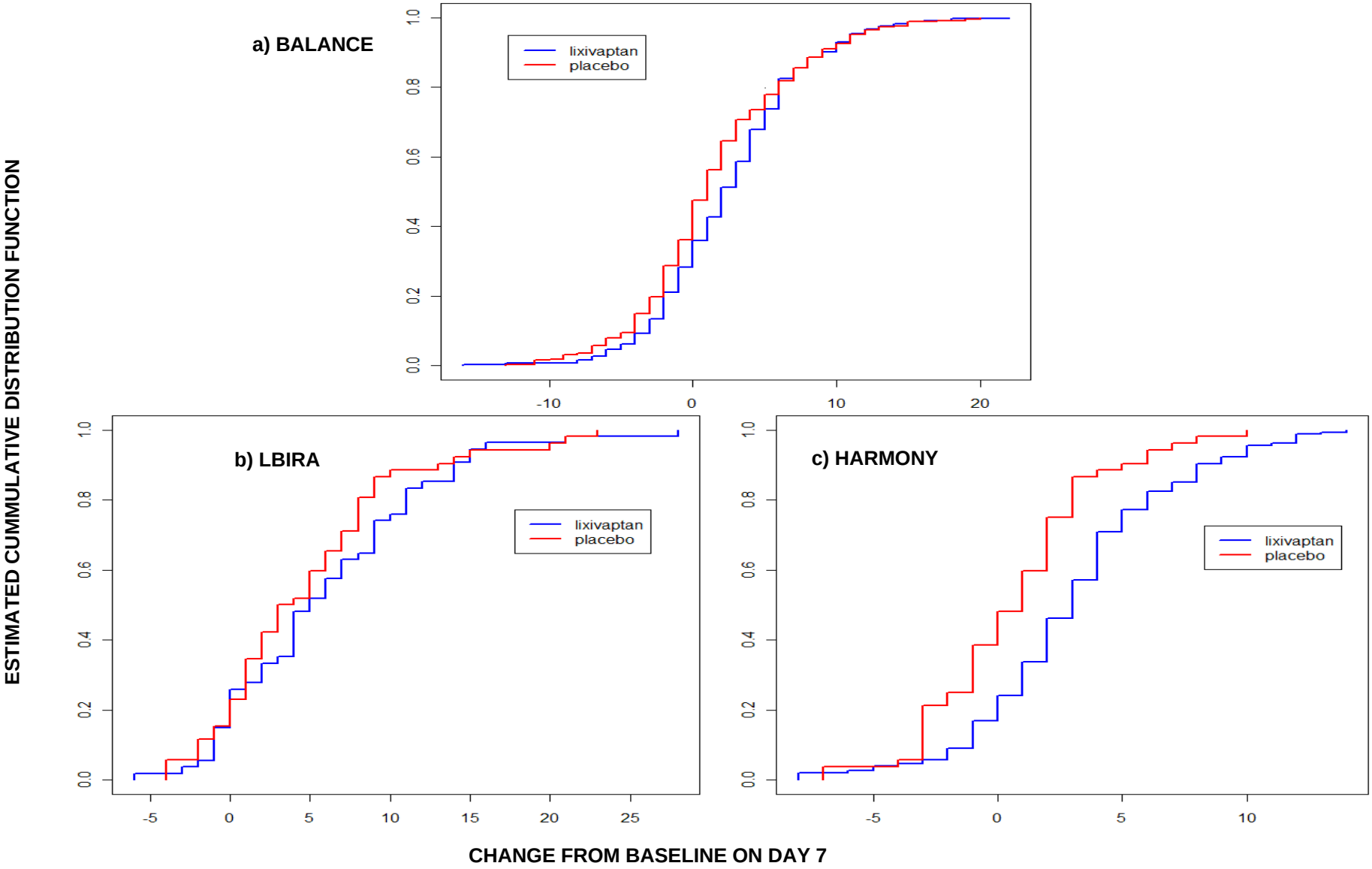
AVP concentrations were included as a tertiary endpoint for the BALANCE trial and as exploratory endpoints for the SIADH trials. However, the applicant reports that "improper sample collection and unreliable data" for AVP led the applicant to discontinue collection of these samples.

As a result, AVP levels were collected in a faction of subjects (24% in CK-LX3430; 65% in CK-LX3405; 74% in CK-LX3401) in the 3 trials. Furthermore, most values were collected at baseline/screening, and therefore, effects on treatment could not be determined.

6.6 Subpopulations

The cumulative distribution of the change in serum sodium values from Baseline showed that the lixivaptan treated subjects tend to have greater increase in serum sodium as compared to the placebo treated subjects across a large range of change in serum sodium. There distribution of change in serum change did not suggest a lixivaptan treatment effect driven by a small subgroup of subjects with marked effect.

Figure 4. Cumulative distribution of the change in serum sodium values from Baseline (BALANCE, LIBRA & HARMONY)



6.7 Analysis of Clinical Information Relevant to Dosing Recommendations

See section 4.4.

6.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

As shown in the table below, the serum sodium for lixivaptan-treated subjects return largely back down to their pre-treatment baseline level after discontinuing therapy (as measured on Day 7 post treatment follow-up).

Table 30. Serum sodium on and off-therapy

Evaluation	HARMONY		LIBRA		BALANCE	
	Lixivaptan N=154	Placebo N=52	Lixivaptan N=54	Placebo N=52	Lixivaptan N=323	Placebo N=329
Baseline	**n=125**	**n=39**	**n=41**	**n=38**	**n=212**	**N=213**
Mean (SD)	131.6 (4.5)	132.1 (4.4)	127.2 (5.5)	125.3 (6.2)	133.4 (5.4)	133.1 (6.0)
End of treatment	**n=125**	**n=39**	**n=41**	**n=38**	**n=212**	**n=213**
Mean (SD)	135.2 (4.9)	134.3 (5.4)	134.4 (5.7)	131.9 (6.8)	137.0 (4.8)	136.0 (5.8)
Follow-up Day 7	**n=125**	**n=39**	**n=41**	**n=38**	**n=212**	**n=213**
Mean (SD)	131.8 (5.6)	134.4 (5.1)	129.7 (6.8)	133.4 (5.6)	136.3 (4.8)	136.2 (6.2)

[source: FDA statistical reviewer's analysis]

7 Review of Safety

Safety Summary

The concerning safety finding was the imbalance in death in the BALANCE trial (hyponatremia associated with CHF). Adverse events were largely consistent with the pharmacology class. See section 1 for summary.

7.1 Methods

Studies/Clinical Trials Used to Evaluate Safety

The safety database included phase 3 trials in two populations: 1) hyponatremia associated with CHF, 2) SIADH), and an open-label long term extension study that enrolled the subjects who completed the phase 3 trials. In addition, phase 2 dose-ranging, placebo-controlled trials studied subjects with CHF, with or without hyponatremia, LCWA, but limited numbers (30) of subjects with SIADH. Trials 203 (LCWA subjects n=25, 78%; CHF subjects n=3) and 207 (LCWA subjects n=40, 53%; CHF subjects, n=7) studied predominately LCWA subjects. Of note, trial 203 was stopped early (see discussion on the numeric balance in death). An indication for LCWA was not further pursued (see discussion under regulatory history).

Table 31 provides an overview of the trials that were analyzed to evaluate safety.

Table 31. An overiew of the trials used to evaluate safety

Trials used for the primary safety analyses Number of lixivaptan treated subjects (n)		
Single or Multiple-Dose Placebo-controlled Phase 2 Trials	**Phase 3 trials**	**Open-label long term extension study**
phase 2 CHF with serum sodium </=145 mEq/L (n=170) 0892A1-103-US [1, 2] (n=30) 0892A1-114-US[1, 3] (n=29) 2401[4] (n=111) **phase 2 Liver Cirrhosis with Ascites (n=49)** 0892A1-104[5] (n=22) 0892A1-118[6] (n=27) **Hyponatremia due to a mix of etiologies (n=105)** 0892A1-203-US/CA*[7] (N=32) 0892A1-207-EU**[8] (n=73)	**Hyponatremia associated with CHF & (n=322)** 3401 **SIADH (n=203)** 3405 (n=50) 3030 (n=153)	3431 (n=135)

Source: Reviewer's analysis ADAL dataset, verification the applicant's Figure 1a, Summary of Clinical Safety.
* CHF, SIADH, and Liver Cirrhosis with Ascites subjects.
[1]These trials included subjects with HF, and only a small fraction also had hyponatremia at Baseline (i.e., 6 subjects (20%) from 0892A1-103-US, 3 subjects (10%) from 0892A1-114- US).
[2] Single ascending dose study with doses: 10, 30, 75, 150, 250, 400 mg X1.
[3] Multiple dose ascending study with maximum lixivaptan doses of: 30 mg QD, 30 mg BID, 75 mg BID, 150 mg QD, 150 mg BID, 250 mg QD, 250 mg BID for up to 6 days.
[4] 100 mg QD of lixivaptan or placebo for 8 weeks
[5] lixivaptan doses of 25, 50, 100, 200 and 300 mg x1.
[6] lixivaptan doses of 25, 50, 100, or 150 mg BID, or 300 mg QD for 6 days
[7] lixivaptan doses of 25, 125 and 250 mg BID for up to 30 days.
[8] lixivaptan doses of 50 and 100 mg BID for up to 7 days; oral suspension.

7.1.2 Categorization of Adverse Events

Adverse events (AE) were coded to MedDRA versions 8, 10, 11.1 and 12. For the pivotal studies, the applicant used MedDRA version 11.1.

I reviewed the verbatim and dictionary-derived terms and confirmed the appropriateness of the mapping from verbatim to dictionary-derived terms. To explore safety issues, terms that are part of a clinical syndrome were grouped in addition to being evaluated separately.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For the most part, data from different studies were not pooled, due to different study populations and/or indications.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

According to the applicant, a total of 1673 subjects received at least one dose of lixivaptan across the 36 Phase 1, 2, and 3 clinical studies.

By indication, according to the applicant, a total of 250 subjects with euvolemic hyponatremia associated with SIADH received at least one dose of lixivaptan in the placebo-controlled Phase 2/3 trials. The average mean daily dose of lixivaptan during these studies was 81 mg. Mean duration of exposure was 74 days. In the phase 3 LIBRA trial, 62% (n=31) of the lixivaptan treated subjects required up-titration from the starting dose of 50 mg QD, and 58% (n=29) were titrated to the maximum dose of 100 mg QD on Day 7. In the phase 3 HARMONY trial, 94% (n=144) of subjects required up-titration from the starting dose of 25 mg QD, and 76% (n=70) were titrated to the maximum dose of 100 mg QD on Day 7.

In terms of heart failure (HF), a total of 502 subjects (from trials 0892A1 -103-US, 0892A1-114- US, and CK-LX2401, and 3401) received at least one dose of lixivaptan in the placebo-controlled Phase 2/3 studies in subjects with HF (with or without hyponatremia). Of these 502 subjects exposed to lixivaptan, 346 had CHF and laboratory evidence of hyponatremia (<135 mEq/L) at Baseline. Compared to the SIADH population, the average mean daily dose of lixivaptan during these studies was higher (117 mg) and mean duration of exposure was shorter (41 days) in the CHF

population (with or without hyponatremia). At the end of the inpatient titration phase in the BALANCE study, 73 subjects (25%) titrated to the maximum dose of 100 mg BID of lixivaptan.

A summary of the extent of exposure in the phase 3 trial population is presented in Table 31.

Table 32. Doses used in the phase 2 and 3 trial population

Phase 2/3 trials	Subjects with SIADH	Subjects with HF*
Duration of exposure	Lixivaptan (n=250)	Lixivaptan (n=502)
mean (SD)	74 (65)	41 (24)
min, max	1, 172	1, 71
Mean Daily Dose (mg)		
mean (SD)	81 (47)	117 (77)
min, max	10, 452	10, 500
Maximum Daily Dose (mg)		
mean (SD)	88 (49)	128 (82)
min, max	10, 500	10, 500

Adapted from the applicant's tables 8.3.3.1 and 8.4.3.1, Summary of Clinical Safety.
* heart failure with or without hyponatremia

A total of 518 subjects received at least one dose of lixivaptan in the placebo-controlled Phase 3 trials (see Table 33 below). Mean duration of exposure was 63.5 days.

Table 33. Size and duration of lixivaptan exposure in the phase 3 trial population

Lixivaptan Exposure	**Hyponatremia with CHF (BALANCE)**	**SIADH (LIBRA)**	**SIADH (HARMONY)**
Total number of subjects (number of subjects with exposure duration in formation)	**322 (318)**	**50 (49)**	**153 (151)**
Interval (days)*			
Days 1-30	77	38	20
Days 31-60	142	11	16
Days 61-90	99		23
Days 91-180			92

Source: reviewer's analysis.
*The number of subjects with lixivaptan exposure duration information (in parentheses) is fewer than the total number of subjects exposed. The reason for this difference was because a few subjects did not have date and time for the last dose recorded.
Note despite, the actual length of exposure can be slightly longer than the Treatment Day, given the window for Treatment Visits.

In the subjects with evidence of more moderate hyponatremia (<130 mEq/L) by local lab, a total of 151 subjects with serum sodium <130 mEq/L (and 84 subjects with serum sodium <125 mEq/L) were exposed to lixivaptan in the phase 3 controlled trials (see table below).

Table 34. Size and duration of lixivaptan exposure by Baseline local serum sodium levels (phase 3 trials)

Lixivaptan Exposure by local serum sodium	**"Hyponatremia" with CHF (BALANCE)**	**SIADH (LIBRA)**	**SIADH (HARMONY)**
<130 mEq/L	**98**	**49**	**54**
Interval (days)			
Days 1-30	28	38	11
Days 31-60	43	11	5
Days 61-90	27		6
Days 91-180			32
<125 mEq/L	**38**	**20**	**26**
Interval (days)			
Days 1-30	11	16	10
Days 31-60	15	4	1
Days 61-90	12		1
Days 91-180			14

[source: reviewer' analysis]

Reviewer's comment:
The size of exposure data is modest in the lixivaptan phase 3 controlled trials. In comparison to tolvaptan's controlled phase 3 trials (607 hyponatremic subjects [sodium <135 mEq/L] *by local lab, and of whom, 52 subjects had serum sodium <125* mEq/L*), the number of subjects exposed is similar.*

The number of subjects, exposed to lixivaptan, with low serum sodium (<130 mEq/L, <125 mEq/L) was smaller by central serum sodium than local sodium levels (Table 33). Tolvaptan clinical program did not obtain central serum sodium, therefore, one can not compare safety database for these with low serum sodium levels by central sodium measurements.

Table 35. Size and duration of lixivaptan exposure by central serum sodium values (phase 3 trials)

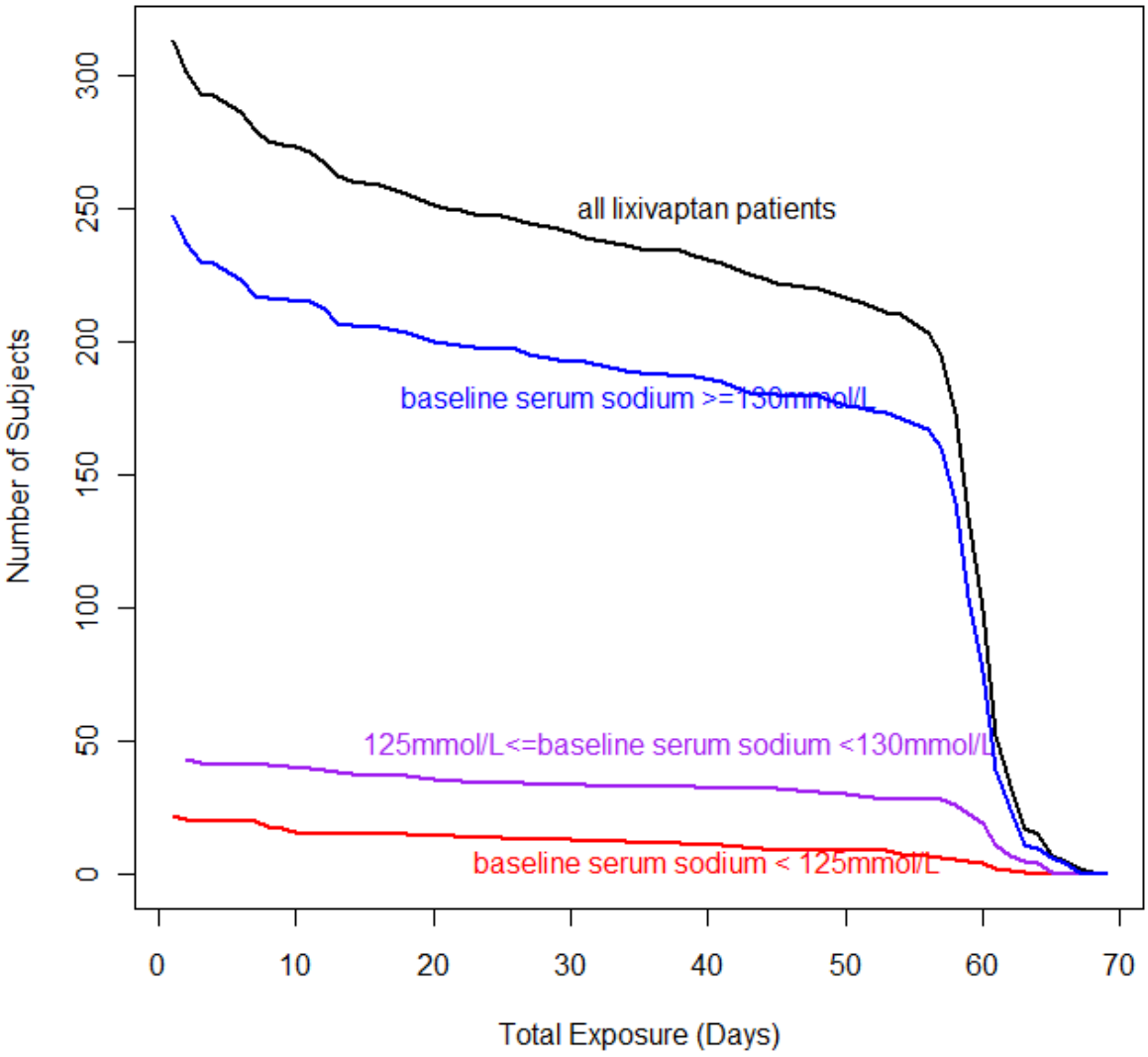
Lixivaptan Exposure by central serum sodium	**"Hyponatremia" with CHF**	**SIADH (LIBRA)**	**SIADH (HARMONY)**
<130 mEq/L	**67**	**31**	**37**
Interval (days)			
Days 1-30	19	22	11
Days 31-60	25	9	2
Days 61-90	23		5
Days 91-180			19
<125 mEq/L	**23**	**12**	**13**
Interval (days)			
Days 1-30	10	10	5
Days 31-60	9	2	1
Days 61-90	4		1
Days 91-180			6

[source: reviewer' analysis]

In comparison, the size and duration of the lixivaptan exposure in the subjects with hyponatremia and congestive heart failure (BALANCE) was the largest.

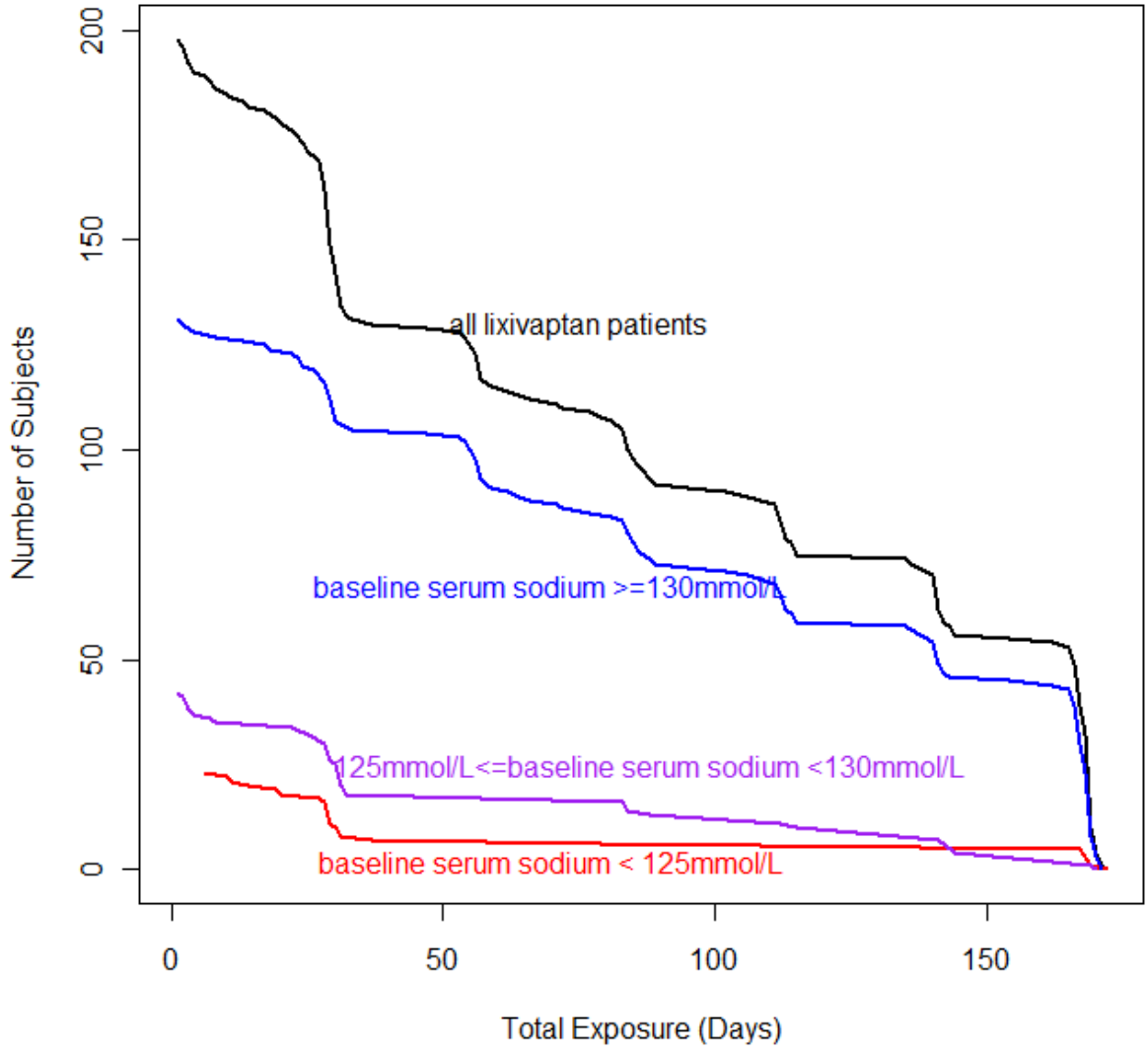
The size of exposure data is modest in the lixivaptan phase 3 controlled trials (Figure 5 & Figure 6). Central sodium values were used in these graphs. The extent exposure by central laboratory serum sodium values had smaller number of subjects with very low serum sodium (e.g. <125 mEq/L).

Figure 5. The size and duration of the lixivaptan exposure in the subjects with hyponatremia and congestive heart failure (BALANCE)



Source: FDA statistical reviewer

Figure 6: The size and duration of exposure in the SIADH population (the LIBRA and HARMONY trial)



Source: FDA statistical reviewer

Reviewer's comment: The extent of exposure by central lab can not be compared to the tolvaptan experience because only local serum sodium was evaluated in tolvaptan.

7.2.2 Explorations for Dose Response

Explorations for Dose Response are discussed under Clinical Pharmacology Section 4.4.

The phase 3 individualized dose titration design limits the analysis of dose response relationship. Therefore phase 2 program in subjects (LCWA, SIADH, CHF) exposed to high daily doses were used. As discussed in Pharmacodynamics section, a daily dose of > 200 mg significantly increases the incidence (rate > 5%) of mechanism-related adverse events including thirst, dry mouth, constipation, headache, and dizziness.

7.2.3 Special Animal and/or In Vitro Testing

No sign of anaphylaxis was seen.
No sign of immunotoxicity was seen in the animal repeat dose studies. As such, no specific immunotoxicity study was performed.

7.2.4 Routine Clinical Testing

Routine clinical testing of study subjects was adequate, including periodic monitoring (at least weekly during the treatment phase) of biochemistry and hematology panels. There were also original plans to check vasopressin, urine and serum osmolality on treatment, but later amendments eliminated these procedures (See appendix for protocol amendments).

Arginine vasopressin levels (also referred to as ADH) were collected in a faction of subjects in the 3 trials (24% in CK-LX3430; 65% in CK-LX3405; 74% in CK-LX3401). According to the applicant, the investigators were not instructed to keep the ADH samples refrigerated during centrifugation, which the applicant felt could lead to false elevated ADH values.

Because the applicant questioned the reliability of the vasopressin results, therefore, the stopped collection of ADH samples during the trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

Drug metabolism and excretion are discussed in Section 4.4. Drug-drug interactions are discussed in Section 4.4 and Section 7.5.5.

Briefly, lixivaptan is mainly eliminated via the cytochrome P450 pathway (a substrate of CYP3A, CYP2C8), and has potential to inhibit CYP3A, CYP2C8, CYP2C9. Effects on BCRP is not clearly established.

In addition, there is evidence for unidentified metabolites, which may or may not have pharmacologic activity. If these unknown metabolites were pharmacologically active, it is not clear whether these metabolites may have differential effects in the distinct hyponatremia populations.

Please see the clinical pharmacology review for a more in depth review of pharmacology data.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events for the two approved vaptans largely reflect the known pharmacologic effects. Both members of the class can induce a rapid rate of correction of serum sodium with the potential to lead to osmotic demyelination syndrome (ODS). In addition, hypotension and/or hypovolemia have also been seen. Lastly, tolvaptan carries a warning/precaution about the potential increased risk of gastrointestinal bleeding in subjects with cirrhosis.

7.3 Major Safety Results

7.3.1 Deaths

In the Phase 2/3 trials, the mortality rate (i.e. deaths within 30 days of the last dose) was numerically lower in the lixivaptan than placebo arm (see table below). However, in the BALANCE trial that enrolled subjects with congestive heart failure and hyponatremia hospitalized for acute worsening of CHF, there was a numeric imbalance in deaths (see table below).

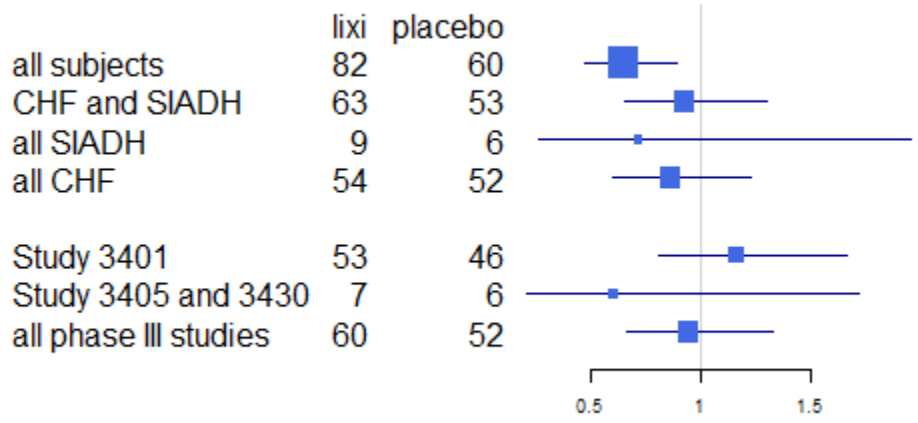
Table 36. Deaths within 30 days of last dose (lixivaptan safety population)

Death within 30 day of last dose	Lixivaptan Death/ exposed (%)		Placebo death / exposed (%)	
Phase 3 CHF and hyponatremia (BALANCE)	50/322	(15.5)	40/322	(12.4)
phase 3 SIADH (LIBRA)	0/50	(0.0)	4/51	(7.8)
phase 3 SIADH (HARMONY)	7/153	(4.6)	1/52	(1.9)
phase 2 CHF	0/180	(0.0)	5/92	(5.4)
phase 2 CHF with hyponatremia	0/24	(0.0)	1/16	(6.3)
phase 2 Liver Cirrhosis with Ascites	11/114	(9.6)	2/39	(5.1)
phase 2 SIADH	2/48	(4.2)	1/17	(5.9)

Adapted from the applicant's Table 9 and Figure 2a, ISS

The relative risk of death for the populations in which the applicant is seeking an indication is shown below. In all phase 3 trial combined (hyponatremia associated with CHF and SIADH), there is no increased relative risk for death. In the hyponatremia associated with CHF population (3401/BALANCE), the confidence interval also included null, with point estimate favoring placebo. This result is consistent with the applicant's analysis finding.

Figure 7. Forest plot of relative risks of death at 30 Days and 95% confidence interval

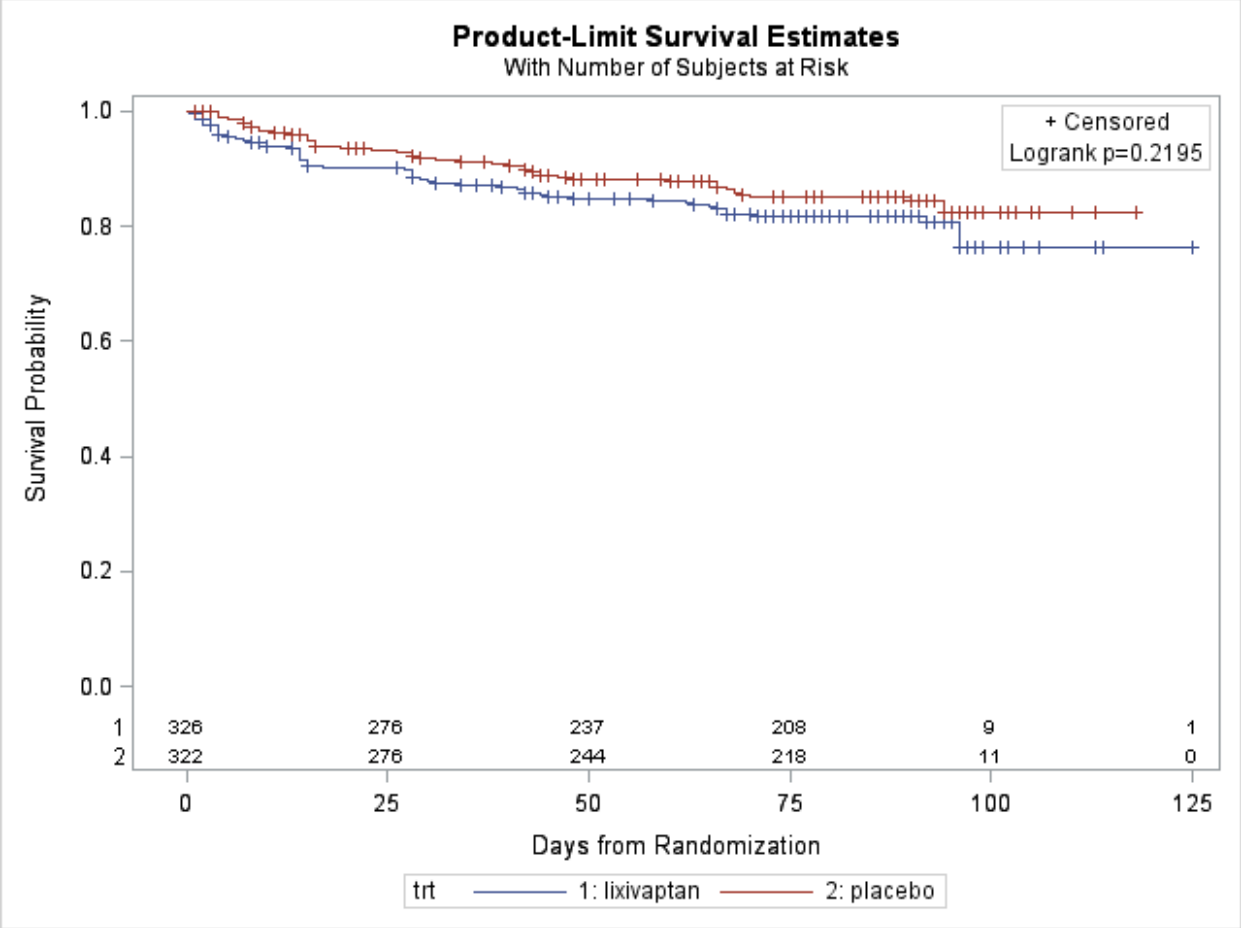


*source: FDA reviewers' analysis. Only subjects who died after 30 days post-treatment were counted in the above analysis.

7.3.1.1 Deaths in the BALANCE Trial

In the safety population for the BALANCE trial, there were 57 (17.7%) deaths in the lixivaptan arm vs. 46 (14.3%) in the placebo arm (no statistically significant difference 0.2195; counts include deaths that occurred more than 30 days after last dose in the population exposed at least one dose of study drug [safety population]). See the Figure below. Similarly, in the ITT population, the p-value from log-rank test on time to all deaths was also not statistically significant (0.2631).

Figure 8. Kaplan-Meir survival analysis (the Balance trial, safety population)



[source: FDA statistical reviewer' analysis]

By both analyses, there was a numeric imbalance in death, against lixivaptan as compared to placebo arm that occurred early with respect to the time of randomization

or first dose. There was a numeric imbalance in death that occurred early with treatment, for example, death within Day 5 of randomization (lixivaptan 12 vs. placebo 2, nominal p-value= 0.036, ITT population). (see Table 37 below).

In the subgroup who died early death (by Day 15 of randomization), the log-rank test on time to all deaths up to Day 15 had a nominally significant p-value of (ITT population).

Table 37. Deaths by days after randomization (BALANCE)

Days after randomization	Lixivaptan (N=322) n (%)	Placebo (N=322) n (%)
Day 0-5	**12 (3.7)**	**2 (0.6)**
Day 0	1 (0.3)	0 (0)
Day 1	3 (0.9)	0 (0)
Day 2	2 (0.6)	0 (0)
Day 3	2 (0.6)	0 (0)
Day 4	1 (0.3)	1 (0.3)
Day 5	3 (0.9)	1 (0.3)
Day 6-10	3 (0.9)	3 (0.9)
Day 11-30	16 (5.0)	14 (4.3)
Day 31-60	11 (3.4)	17 (5.3)
Day 61-90	10 (3.1)	8 (2.5)
Day >90	2* (0.6)	2 (0.6)
Total	57 (17.7)	46 (14.3)

[source: reviewer' analysis]*According to the applicant, one subject in the lixivaptan arm died after 30 days Follow-up phase, but the date of death and reason for death unknown. Therefore, this reviewer assigned this subject to the Day > 90 group.

Because the date of first exposure may differ somewhat from the day of randomization, I also tabulated deaths by days after initiating study drug (see table below). By this analysis, there was also an early (within 10 days after initiating study drug) numeric imbalance in death between treatment arms (see the Table below). For a graphic representation of the death within the first 10 days, see Figure 10 in appendix).

Table 38. Deaths by days after initiating study drug (BALANCE)

Days after Initiating Study Drug	Lixivaptan (N=322) n (%)	Placebo (N=322) n (%)
Day 1-5	**9 (2.8)**	**1 (0.3)**
Day 1	1 (0.3)	0 (0)
Day 2	4 (1.2)	0 (0)
Day 3	2 (0.6)	0 (0)
Day 4	1 (0.3)	0 (0)
Day 5	1 (0.3)	1 (0.3)
Day 6-10	6 (1.9)	3 (0.9)
Day 11-30	15 (4.7)	13 (4.0)
Day 31-60	12 (3.7)	19 (5.9)
Day 61-90	11 (3.4)	8 (2.5)
Day >90*	3 (0.9)	2 (0.6)
Total	57 (17.7)	44 (13.7)

[source: reviewer' analysis] *One subject in the lixivaptan arm died after 30 days Follow-up phase, but the date of death and reason for death unknown. Therefore, this reviewer assigned this subject to the Day > 90 group.

The imbalance in the early death rate between the treatment groups prompted the data safety monitoring committee to issue a letter on June 9, 2010 urging the applicant to terminate the trial. The letter stated that "the board voted unanimously that due to safety concerns that the study should be terminated as soon as possible" after the board reviewed data on "469 subjects with observations at 15 days and 463 subjects with observations at 30 days

7.3.1.2 Cause of Deaths in the BALANCE Trial

According to the applicant, deaths that occurred "through 60 days of treatment/follow-up" in the BALANCE trial were adjudicated. The deaths were adjudicated was caused by heart-failure versus non-heart failure. In both treatment arms, most (lixivaptan 33/44 [75%], placebo 28/36 [78%]) of the adjudicated deaths in subjects whom were exposed to at least one dose of study medication (safety population), were thought to be caused by heart-failure (seeTable 39 below).

Table 39. Adjudicated causes of death (BALANCE trial, safety population)

Overall Deaths (Safety Population)	Lixivaptan N=322 n (%)	Placebo N=322 n (%)
All Deaths with Cause Reported	**53* (16.5)**	**46 (14.3)**
All Adjudicated Cause of Death	**44**	**36**
Heart Failure	33	28
Non Heart Failure	9	7
Unknown	2	1

Source: reviewer's analysis of the HO dataset.
* No investigator reported cause of death was reported for the four lixivaptan treated subjects who died "outside the 30-day of post-treatment follow-up". Four lixivaptan treated subjects who died "outside the 30-day of post-treatment follow-up" did not have the investigator reported cause of death.

The reviewer also requested for a dataset with all investigator-reported cause of death. The applicant provided the investigator reported causes of death for 53 out of the 57 deaths in the lixivaptan arm, extracted from the case report forms. Of note, three out of the four subjects missing investigator reported cause of death in the CRFs, dates of death were available for three of these four subjects (allowing their count in the reviewers' Kaplan-Meir sensitivity analyses).

Based the review of dataset, case reported forms and narratives, the reviewer summarized the investigator reported causes of death (see Table 40 below). For some subjects, more than one term were given as causes of deaths, the number of terms exceeds the number of deaths. The reviewer assigned the verbatim terms together (i.e. mapped sudden cardiac death, sudden cardiac arrest, asystole, electromechanic dissociation to mean a sudden cardiac death; mapped terms of worsening heart failure, exacerbation of heart failure, end stage heart failure, decompensated heart failure, cardiogenic shock in the absence of myocardial infarction, or arrhythmia to worsening heart failure).

Similarly, deaths from cardiac causes were the major cause of death and were balanced between the 2 treatment groups. Death from sudden cardiac death was more than twice that of the placebo arm.

Table 40. Investigator reported causes of death (BALANCE trial, safety population)

Investigator Reported Cause of Deaths	Lixivaptan (N=322)	Placebo (N=322)
All Deaths with Cause Reported	**53 (17.7)**	**46 (14.3)**
Terms Suggestive of Cardiac causes of Death	**44**	**41**
Arrhythmia	1	1
Sudden Cardiac Death[a]	11	5
Sudden Death	2	2
Ventricular fibrillation	0	1
Worsening Heart Failure[b]	30	32[d]
Other terms reported	**11**	**5**
Bleed*	2	0
Cerebrovascular Accident	0	1
Kidney Failure	1[c]	0
Mesenteric ischemia	1[d]	0
Respiratory Failure	3[f]	2
Sepsis	3[d]	1[e]
Severe Symptomatic Hyponatremia	0	1
Subdural hematoma	1	0
Unknown	**2**	**0**

Source: reviewer's analysis of the HO, keyvars, and the investigator reported cause of death datasets.
[a] The reviewer defined sudden cardiac death when investigator reported verbatim terms of sudden cardiac death, sudden cardiac arrest, asystole, electromechanic dissociation.
[b] The reviewer defined worsening heart failure when investigator reported verbatim terms of worsening heart failure, exacerbation of heart failure, end stage heart failure, decompensated heart failure, cardiogenic shock in the absence of myocardial infarction, or arrhythmia.
[c] Kidney failure was in the setting of worsening heart failure.
[d] Cause of death was both sepsis and mesenteric ischemia in one lixivaptan treated subject.
[e] One subject in the placebo grouped died from septic shock following heart transplant surgery according to narrative was counted only as sepsis in my assignment.
[f] Two respiratory failures represented pulmonary edema/heart failure.
* A subject with cirrhosis died from "epigastric artery bleed into rectus muscle".

Similar to the overall safety population, deaths within 5 days of the first dose were largely attributed to cardiac causes, likely reflecting underlying diseases. A numerically greater number of subjects in the lixivaptan than the placebo arm died from cardiac causes (including worsening of heart failure and sudden cardiac death).

Table 41. Investigator reported causes of death (early deaths in BALANCE trial)

Investigator Reported Cause of Deaths	Lixivaptan (N=322)	Placebo (N=322)
Deaths within 5 days of first dose	**n=9 (2.8%)**	**n=1 (0.3%)**
Terms Suggestive of Cardiac causes of Death	7	1
Arrhythmia*	1	0
Ventricular fibrillation	0	1
Sudden Cardiac Death	2	1
Heart Failure, Worsening	4	0
Other terms	1	0
Bleed	1	0
Respiratory Failure	0	1
Unknown	1	0

Source: reviewer's analysis of the death dataset.
*arrhythmia was found in a 72 white man with NYHA IV, severe LV dysfxn (EF <15%), also had coronary artery disease, right ventricular failure, liver congestion, pace maker for vfib/vtach/afib.

As shown in Section 6, the baseline characteristics of the lixivaptan and placebo treated subjects were balanced. Exploration of the differences between those who died early (death within 5 days of initiating drug) versus those who did not, revealed that subjects who died early had orthostatic increase in heart rate at baseline (average heart rate went up from 87 to 97 beats per minute) and on-treatment. This finding suggests that those who died early were hemodynamically more fragile individuals at baseline.

Other explorations were not revealing. Comparing the characteristics of the subjects who died early with respect to Day of randomization or Day of first dose versus the overall population (e.g. within 5 or 10 days of randomization, 5 or 10 days from first dose), there was no significant difference in co-morbidities (e.g. CHF severity or degree of hyponatremia). No clear differences in demographic (age, sex, race, weight, country, NYHA class, degree of hyponatremia, degree of baseline liver function test (values as continuous variables) or adjudicated cause of death in those who died early as compared to the overall trial population.

In the overall deaths or early deaths, I found no imbalance between treatment arms in rapid rise in serum sodium, new/worsening electrolyte abnormalities that preceded the death (including hypokalemia, hypomagnesium, hypocalcemia), nor adverse event

terms that suggest overly rapid diuresis. There were also no cases of osmotic demyelination syndrome. The response in serum sodium in these subjects who died early was not notably different from the rest of the group.

In terms of the daily dose of lixivaptan received by these 10 subjects who died within 10 days of the study drug treatment, the mean daily dose were 68 mg, 70 mg, 25mg, 5 mg on treatment days 1 to 4, respectively. Only one subject had a more rapid dose titration (Day 1: first dose 50 mg, second dose 100 mg) than the general dosing guideline (up to 50 mg bid on Day 1). The rate of escalation in dose was not more rapid in those who died in the overall population, died early with respect to dosing, as compared to those who did not die.

Furthermore, there was no clear evidence of primary arrhythmia as a cause of death. In the overall development program, there was no imbalance in arrhythmia between treatment arms as a whole. The through QT study was negative.

7.3.1.3 Role of Protocol Violation in the Deaths Seen in the BALANCE Trial

Following the May 25, 2010's IDMC meeting for the BALANCE trial (last subject completed on May 13, 2010), the IDMC concluded that "significant protocol deviations took place during the recruitment phase of BALANCE that could have important impact on the safety outcome provided to IDMC" and recommended that the BALANCE trial "be concluded as expeditiously as possible". According to the applicant, the applicant contracted additional experts who were tasked with a) defining a "per-protocol" (PP) safety population by identifying entry criteria violations that could impact the observed death finding, b) reviewing the individual cases for violation.

Four entry criteria were identified for defining the per protocol safety population (see below). The numbers of subjects with violations in these criteria are shown in the parentheses.

- Inclusion: Hospitalized for worsening CHF (n=34)
- Inclusion: Supine SBP ≥ 90 mmHg (n=31)
- Exclusion: On cardiac mechanical support (n=2)
- Exclusion: Expected survival less than 6 months (n=30).

Reviewer's comment:
These criteria seemed to be aimed at excluding subjects who had very advanced heart failure and/or were hemodynamically marginal.

After excluding the subjects with the aforementioned violations (some with more than one violations), the PP safety population were left with 580 subjects. After excluding the potentially sicker subjects from the ITT population, the numeric imbalance in death is lessened in the overall population (lixivaptan 44 vs. placebo

37), though still higher in the lixivaptan arm. The numeric imbalance in early deaths was also lessened, but not eliminated (see tables below for counts of early death with respect to the Day randomization [Table 42] or Day of first dose [Table 43]).

Table 42. Deaths by day after randomization (BALANCE, per protocol safety population)

Days after randomization	Lixivaptan (N=291) n (%)	Placebo (N=289) n (%)
Day 0-5	**5 (1.7)**	**1 (0.3)**
Day 0	1 (0.3)	0 (0)
Day 1	1 (0.3)	0 (0)
Day 2	0 (0)	0 (0)
Day 3	1 (0.3)	0 (0)
Day 4	0 (0)	1 (0.3)
Day 5	2 (0.69)	1 (0.3)
Day 6-10	2 (0.69)	3 (1.0)
Day 11-30	15 (5.2)	11 (3.8)
Day 31-60	10 (3.4)	13 (4.5)
Day 61-90	10 (3.4)	7 (2.4)
Day >90	2 (0.7)	1 (0.3)
Total	44 (15.1)	37 (12.8)

[source: reviewer' analysis]

Table 43. Deaths by days after initiating study drug (BALANCE, per protocol safety population)

Days after Initiating Study Drug	Lixivaptan (N=291) n (%)	Placebo (N=289) n (%)
Day 1-5	**3 (1.0)**	**1 (0.3)**
Day 1	1 (0.3)	0 (0)
Day 2	1 (0.3)	0 (0)
Day 3	1 (0.3)	0 (0)
Day 4	0 (0)	0 (0)
Day 5	0 (0)	1 (0.3)
Day 6-10	4 (1.4)	3 (1.0)
Day 11-30	14 (4.8)	11 (3.8)
Day 31-60	11 (3.8)	14 (4.8)
Day 61-90	10 (3.4)	7 (2.4)
Day >90	2 (0.7)	1 (0.3)
Total	44 (15.1)	37 (12.8)

[source: reviewer' analysis]

Based on ACI and PEAC's assessment, the applicant attributed the numeric early imbalance in death in the BALANCE trial to "a play of chance."

Reviewer's comment:
I reviewed these cases and found the determination of which subjects met the entry criteria violation, and therefore excluded from the analysis, to be subjective. See appendix for the list of all entry criteria. That' being said, it is not surprising that some subjects who died early were "sicker" at baseline (significant protocol violations) than the rest of the group. Even if this were true, the BALANCE trial suggests that the investigators did not know enough to differentiate those who were at-risk versus not at-risk among the subjects with hyponatremia associated with CHF and hyponatremia, in setting of acute CHF decompensation.

7.3.1.4 Deaths in the SIADH Trials: LIBRA and HARMONY

Death in LIBRA
In LIBRA, there was no death in the lixivaptan arm but were 4 deaths (7.7%) in the placebo arm.

Death in Harmony
In HARMONY, there were 7/153 (4.6%) deaths in the lixivaptan arm but 1/52 (1.9 %) in the placebo arm. The size of the SIADH/outpatient initiation trial was modest, and therefore is limited in the detection of safety signal. The causes of death in the lixivaptan arm were: infection/ acute cardiac failure (n=1), sepsis (n=1), myocardial infarction (n=1), suicide (n=1), CVA (n=1), cancer (n=1), and sudden death of unclear etiology (n=1). The cause(s) of death in the placebo arm was infection/acute cardiac failure (n=1).

In the SIADH program, subjects with NYHA class III or IV CHF were excluded. However, subjects with CHF risk factors were allowed. There were small numbers of death in both arms attributed to cardiac causes in both arms (lixivaptan n=3 [2%] vs. placebo 1 [2%]). These deaths generally did not occur early with respect to treatment (see table below).

Table 44. Investigator reported cause of death in the HARMONY trial

Investigator reported cause of death	Day of death	Days of exposure
Lixivaptan (3, 2.0%)		
Acute cardiac failure	168	166
Myocardial infarction	26	25
* Sudden death	15	7
Placebo (1, 2.0%)		
Acute cardiac failure	75	75

* Sudden death attributed to "natural cause" in the narrative

7.3.1.5 Deaths in phase 2 trials

In terms of the phase 2 programs, deaths in hyponatremia associated with CHF or SIADH was not higher in the lixivaptan arm. Nonetheless, there was a numeric imbalance in deaths in subjects with hyponatremia and LCWA.

As shown in Table 45 and Table 47, two phase 2 trials, 0892A1-203-US/CA (referred to hereon as trial 203) and 0892A1-207-EU (referred to hereon as trial 207) with longer exposure (up to 30 days), enrolled subjects with hyponatremia due to a mix of etiologies.

In trial 207, all subjects was placed on stringent fluid restriction of <1 liter per day. The rate of deaths was numerically higher in the lixivaptan than the placebo arm (see table below). The numbers were small to determine if there was a relationship to dose in trial 207. The treatment phase was 7 days in duration.

Table 45. Deaths within 30 days of follow-up across hyponatremia classifications and doses (trial 207)

Number died/number exposed	Placebo	Lixivaptan	
		50 mg BID	100 mg BID
	N=39	N=37	N=36
LCWA & hyponatremia	1/ 20	4*/ 22	4 / 18
CHF & hyponatremia	0 / 8	0 / 3	0 / 4
SIADH	0 /10	1 / 12	1 / 14

*one subject who died at Day 32 after treatment is not counted in the deaths here.
source: reviewer's analysis based on the 207 clinical study report, subject-level analysis datasets for integrated summary of safety, and ISS figure 2a (revised figure.)

The applicant is not seeking a claim in LCWA population. Nonetheless, the implication of the numeric excess in death in the LCWA population studied to the population with lesser degree of hepatic impairment remains. According to the Clinical Pharmacology Review (table 13), the exposure is higher in LCWA subjects (Cmax 2 x that of healthy subjects, and AUC 3.5x that of healthy subjects) due to decreased hepatic clearance. Currently no dedicated hepatic impairment study has been conducted. (Please see their review for details).

The cause of death in LCWA could reflect the underlying disease (these deaths occurred late, of therapy). Among other things, LCWA subjects are also sensitive to volume shift and have higher bleeding risks (see my draft Labeling recommendation based on currently available information).

The causes of death in the trial 207 for the LCWA subjects are summarized below.

Table 46. The causes of death in the LCWA subjects in trial 207

Treatment Arm	Cause of death (days post-treatment)
Placebo **1/ 20**	Terminal liver cirrhosis (+20 days)
Lixivaptan **4*/22**	Esophageal variceal hemorrhage (+13 days) Aggravation of liver function/decompensation secondary to ascites infection (+32 days) Cirrhosis, gastrointestinal bleeding, pancreatic carcinoma (+3 days) Hepatic failure (+3 days)
Lixivaptan **4/18**	Bronchopneumonia and cirrhosis (+6 days) Sepsis and acute renal failure (+2 days) Hematemesis (+16 days) Capillary leak syndrome (+22 days)

[source: reviewer' analysis]

In trial 203, lixivaptan doses of 25 mg to 250 mg BID were studied on top of 1.5 L fluid restriction (less stringent than in trial 207). According to the sponsor, 200 subjects were planned, 44 enrolled, 25 withdrew, 19 completed, 44 analyzed for safety for the trial 203. As mentioned earlier, trial 203 was terminated prematurely for "administrative reasons" on January 1999.

There were 4 deaths reported within 30 days of follow-up, all of whom with subjects with LCWA. According to the applicant, all death occurred in the post-therapy period. The counts were balanced across the treatment and dosage arms (specifically, 1 death in placebo and each of the three lixivaptan arms, respectively). Furthermore, all reported deaths regardless of onset within 30 days of follow-up appeared balanced (see

Table 47). According to the applicant, the investigators reported the cause of death as not associated with the use of the drug.

Table 47. All reported deaths at follow-up across hyponatremia classifications and doses (trial 203)

	Placebo	**Lixivaptan**		
		25 mg BID	**125 mg BID**	**250 mg BID**
	N = 11	**N= 12**	**N= 11**	**N = 10**
LCWA & hyponatremia	2 / 9	1 / 8	3 / 10	2 / 7
CHF & hyponatremia	1/ 2	0/ 1	0/ 1	1/ 2
SIADH	0 / 1	0 / 3	0 / 0	0 / 1

source: reviewer's analysis based on the 203 clinical study report, subject-level analysis datasets for integrated summary of safety, and ISS figure 2a

Reviewer's comments: The high drop-out rate may limit our ability to detect a safety signal in the LCWA population. The treatment phase is 30 days in trial 203.

According to the applicant, "adverse events observed during this study were mainly due to the subject's underlying diseases or to volume depletion due to the pharmacological action of the drug in conjunction with fluid restriction." The adverse events profile in trial 203 was consistent with largely known pharmacologic effects of vaptan (massive urine output [necessitated IV fluid replacement and omission of study medication], renal impairment, constipation, dehydration, postural dizziness, postural orthostatic and tachycardiac syndrome, hypotension, upper gastrointestinal hemorrhage/varices esophageal), with some evidence of dose relationship. AEs that led to discontinuation of dose were only in the lixivaptan arm.

7.3.2 Nonfatal Serious Adverse Events

The percentage of subjects who had serious AEs (SAE) was similar between two treatment arms in phase 3 trials (see Table 48 below). The number of SAEs was higher in lixivaptan than placebo arm in subjects with hyponatremia associated with CHF, but lower in SIADH population. Furthermore, aside from what is expected from pharmacology, there was no serious adverse event (by preferred term or organ system) that occurred more frequently in lixivaptan than placebo treated subjects.

Table 48. Serious adverse events in the phase 3 trials

Subjects with Serious Adverse Events	Lixivaptan n (%)		Placebo n (%)	
BALANCE (Hyponatremia associated with CHF)	158	(49.1)	141	(43.8)
LIBRA (SIADH, inpatient dose titration)	11	(22.0)	16	(31.3)
HARMONY (SIADH, outpatient dose titration)	31	(20.3)	14	(26.9)

[source: reviewer' analysis]

7.3.3 Dropouts and/or Discontinuations

The reasons for dropouts and/or discontinuations are discussion in Section 6. As shown in Section 6, a number of subjects discontinued treatments due to adverse events. Subjects who withdrew due to AE (as a percentage of subjects exposed to at-least one dose of study medication) in lixivaptan versus placebo arms were as follows: BALANCE (4.7% vs. 4.9%), LIBRA (4% vs. 7.8%), HARMONY (5.2% vs. 11.5%).

The percentage of subjects not completing the lixivaptan treatment phase and discontinuation due to adverse events were numerically lowest in the SIAHD/inpatient dose titration population (LIBRA trial).

Across the 3 trials, the adverse events of interest that lead to discontinuation of treatment in lixivaptan as compared to placebo were: hyponatremia (BALANCE: 1 vs. 4; LIBRA: 1 vs. 3; HARMONY: 1 vs. 1), hypovolemia/hypotension (BALANCE: 1 vs. 0; LIBRA: 0 vs. 1; HARMONY: 1 vs. 1). Dizziness (3 vs. 0), dry mouth (2 vs. 0), lethargy (2 vs. 0), polyuria (1 vs. 0) lead to discontinuation only in the HARMONY trial. In addition, electrolyte abnormalities, classified as adverse events, that are consistent with a rapid diuresis and/or compensatory increased reasbsorption were also only seen in HARMONY: "blood creatinine increase" (1 vs. 0), "blood potassium decrease" (1 vs. 0), "hypercalcaemia" (1 vs. 0). Lastly, "gamma-glutamyltransferase increased" (2 vs. 0), "hepatic enzyme increased" (1 vs. 0).

7.3.4 Significant Adverse Events

Aside from deaths and serious adverse events discussed earlier, no other significant adverse events of interest were noted. See following section for submission specific effects.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Rate of Correction in Serum Sodium

Because too rapid of correction of hyponatremia can potentially lead to ODS, I further explored the rate of rise in serum sodium, using both the applicant's definitions and other common definitions: actual rate of rise >8 mEq/L/8 hours or >12 meq/L/24hours. The incidence of rapid rise in serum sodium during the dose titration phase was similar between treatment arms in the BALANCE trial; however, depending upon the analysis, (see table below).

Table 49. Incidence of rapid rise in serum sodium during the dose titration phase in the CHF and hyponatremia population, the BALANCE trial

Subjects with a Rapid Rise in Serum Sodium During Dose Titration Phase	Lixivaptan N=322 n(%)	Placebo N=322 n(%)
Rapid increase in serum sodium* (by central or local laboratory values)	54 (16.8)	61 (18.9)
Rapid increase in serum sodium*, central lab	37 (11.5)	49 (15.2)
Rapid increase in serum sodium*, local lab	35 (10.9)	27 (8.4)

Source: reviewer's analysis of the labs and keyvars datasets, using the applicant's definition of rapid increases in serum sodium

.

The applicant's calculation of the rate of change in serum sodium between two visits (e.g. Pre-Dose Visit and the 8-hour Post-Dose Visit) did not take into account the actual amount of time that elapsed between the two visits or laboratory measurements, and instead assumed the measurements were done exact at the supposed time. In essence, the applicant assessed whether an absolute increase in serum sodium level was seen in an approximate time interval. Rapid increase in serum sodium was defined as observed increases above 8, 12, 18 mEq/Lin approximately 8, 24, or 48 hour intervals, respectively.

In addition, this reviewer calculated the average rate of rise in serum sodium for a time interval based on actual time elapsed between two serum sodium values and on the assumption of a linear/constant rate of rise. I used the serum sodium values collected in Days 1 to 4. I evaluated the number of subjects with absolute rise greater than 12 mEq increase at or over 24 hours intervals, greater than 8 mEq/L at or over 8 hours interval, and the average rate of increases greater than 0.5 mEq/L per hour or greater 1 mEq/L per hour for time span over 8 hours. As a whole, the results were consistent with the applicant's findings.

The fraction of subjects with rapid rate of rise in serum sodium was higher in hyponatremia associated with CHF than SIADH. However, comparing between the two treatment arms, in the CHF and hyponatremia population, the rate of rise in serum sodium was similar or slightly higher in lixivaptan than placebo arm. Given the modest effect on serum sodium (primary endpoint) observed, this finding is perhaps not surprising.

Reviewer's comment:
Note, in general, the rate of change based on central serum sodium was lower than that by local values, because the "pre-dose Baseline" central serum sodium was more likely to be from a post-dose measurement than the "pre-dose Baseline" local serum sodium values.

In the SIADH population (inpatient titration), the rate of rise in serum sodium was in general higher in lixivaptan than placebo arm, consistent with a larger treatment effect in SIADH than CHF subjects.

Table 50. Incidence of rapid rise in serum sodium during the dose titration phase in the SIADH, the LIBRA trial

Subjects with a Rapid Rise in Serum Sodium During Dose Titration Phase	Lixivaptan N=50 n (%)	Placebo N=51 n (%)
Rapid increase in serum sodium*	7 (14.0)	4 (7.8)
Rapid increase in serum sodium*, central lab	2 (4.0)	3 (5.9)
Rapid increase in serum sodium*, local lab	5 (10.0)	3 (5.9)

Source: reviewer's analysis of the adverse events dataset, using the applicant's flag of rapid increases in serum sodium.

In the HARMONY trial (SIADH, outpatient titration), subjects were started on a lower dose (25 mg once daily) of lixivaptan. Using the applicant's flag of the rate of increase in serum sodium suggest that the incidence of rapid increases in serum sodium was low (1.3% to 2.6%), and at times even lower than the placebo arm (see Table 50 below).

Table 51. Incidence of rapid rise in serum sodium during the dose titration phase in the SIADH, the HARMONY trial

Subjects with a Rapid Rise in Serum Sodium During Dose Titration Phase	Lixivaptan N=153 n (%)	Placebo N=52 n(%)
Rapid increase in serum sodium*	4 (2.6)	3 (5.7)
Rapid increase in serum sodium*, central lab	4 (2.6)	3 (5.8)
Rapid increase in serum sodium*, local lab	2 (1.3)	0 (0.0)

Source: reviewer's analysis of the adverse events dataset, using the applicant's flag of rapid increases in serum sodium.

My analyses suggest that rapid increases in serum sodium, though lower than in the HARMONY trials, were still higher in lixivaptan as compared to placebo arm (see table below for average rate of change in central serum sodium values). Note that most of the increase in serum sodium (by central laboratory measurements) was reached within the first day of therapy.

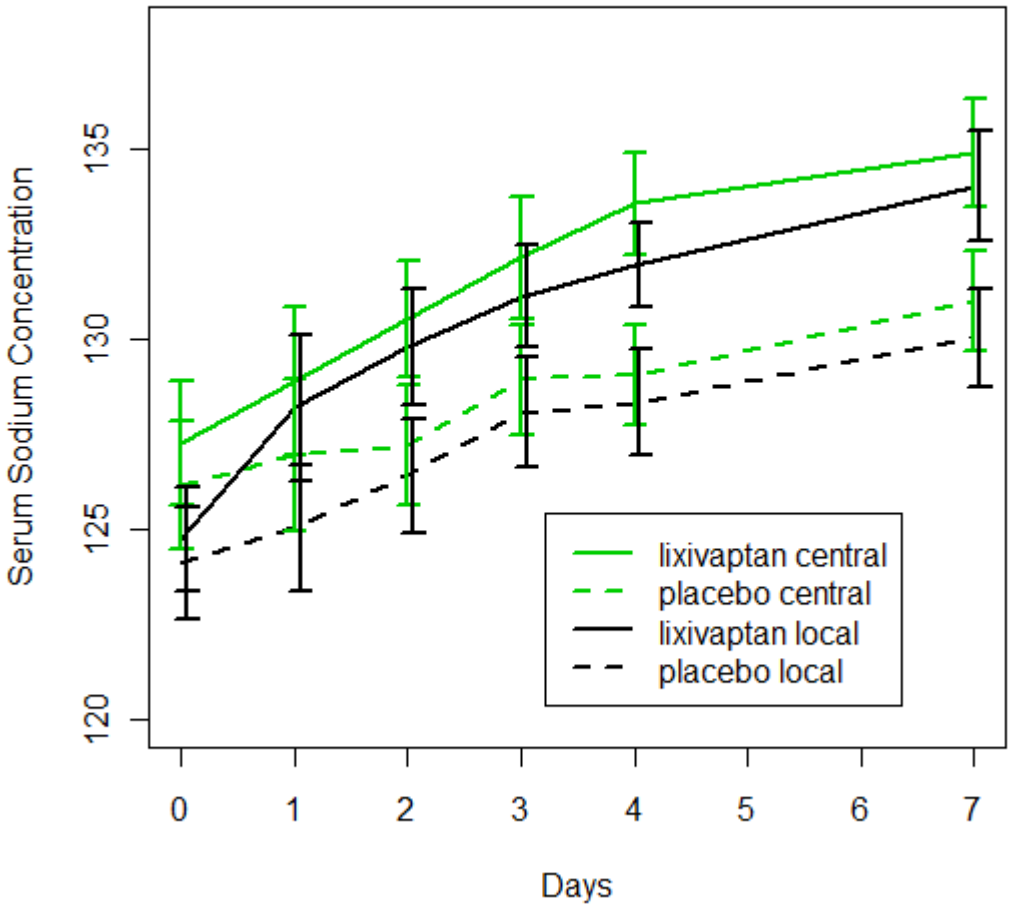
Table 52 Average Rate of Change in Central Serum Sodium in the SIADH Population (the HARMONY trial)

Actual Rate of Change in Serum Sodium (mEq/L/hour)	Lixivaptan					Placebo				
	N	Mean (SD)	Median	Min	Max	N	Mean (SD)	Median	Min	Max
Treatment Day 1	147	0.14 (0.37)	0.12	-1.33	1.38	50	0.04 (0.25)	0.05	-0.44	0.78
Treatment Day 2	149	0.01 (0.21)	0.00	-0.48	0.90	50	0.06 (0.22)	0.00	-0.38	1.20
Treatment Day 3	149	0.03 (0.15)	0.00	-0.50	0.70	51	-0.01 (0.29)	0.00	-0.67	0.29
Treatment Day 4	147	0.03 (0.11)	0.00	-0.25	0.26	50	0.01 (0.14)	0.00	-0.35	0.42

[source: reviewer' analysis]

In addition, the graphs of the mean serum sodium values by Treatment Day also showed that the lixivaptan's effect on serum sodium (and therefore free water clearance) starts within the Day 1 of treatment (see Figure below).

Figure 9. Early change in serum sodium levels by Treatment Day (HARMONY)



Source: FDA statistical reviewers' graph of the serum sodium values in the HARMONY trial.

Reviewer's comment: Local serum sodium values were used for dose-titration. As shown earlier, for some subjects, the Baseline central sodium measurements obtained at separate blood draws returned higher values than the local Baseline serum sodium measurement for the same subjects. The difference between the central versus local Baseline serum sodium on the apparent effect size on the Day 1 will be explored further. The inter-subject variability in serum sodium level and vitals signs in response to treatment will also be explored, as permitted by available information.

7.3.5.2 Exploration of osmotic demyelination syndrome

No case of osmotic demyelination syndrome (ODS) was reported in the phase 3 development program. Because osmotic demyelination syndrome (ODS), a serious AE of interest, given the mechanism of action of the drug, was not a dictionary-derived term in MedDRA version until 12.1, I pulled cases with the following adverse events that could suggest ODS: aphasia, behavioral disturbances, disorientation, coma, confusion, convulsion, dysarthria, dysphagia, epilepsy, lethargy, obtundation, paraparesis or quadriparesis, and seizure.

The number of cases with neurologic symptoms is summarized in the appendix. I reviewed serum sodium laboratory values and available case report forms and narratives to determine the cases could represent symptoms due to rapid rise in serum sodium.

My exploration of emergent neurologic symptoms with or without documentation of rapid rise in serum sodium resulted in no potential case of ODS in the CHF and hyponatremia population (see appendix for tabulation of the cases with neurologic symptoms). In the SIADH population (LIBRA), there was a 41 year female who developed mild lethargy that onset with the rapid rise in sodium (20 mEq/L over 20 hours), and lasted 44 days, prolonging her hospitalization. She had brisk urine output (3L/24hour) after 1st dose (50 mg) of lixivaptan. According to the narrative, to address the polyuria, she self-initiated fluid restriction. Day 2 dose held, restarted at reduced 25 mg per day on Day 3. She received free water on Day 2 which successfully keeping her serum sodium from rising further. The following table summarizes her sodium changes with treatment.

Table 53. A case with rapid rise in serum sodium with fluid restriction

Day	**Day 1**		**Day 2**	
Hour(s) after 1st Lixivaptan dose	**Hour 0**	**Hour 7**	**Hour 20**	**Hour 25**
Local sodium	122	134	142	
Central sodium	128	none	none	136

[source: reviewer' analysis]

Reviewer's comments: This case illustrates the importance of a subject's understanding fluid restriction and the effect of therapy.

7.3.5.3 Exploration of clinically significant rapid diuresis

To detect increased diuresis, I pooled the dictionary derived terms that could suggest this event: dehydration, polyuria, presyncope, syncope, hypovolaemia, dizziness postural. Polyuria was only counted toward the combined syndrome of over-diuresis if it was accompanied by/led to other terms, e.g. potential clinically manifestations of over-diuresis (hypotension, hypovolaemia). No rapid diuresis was detected in the CHF and hyponatremia group (see table below).

Table 54. Treatment emergent adverse events that potentially reflect clinically manifestations of over-diuresis in hyponatremia with CHF population (the BALANCE trial)

Total Incidence (Safety Population)	**Lixivaptan 32 (9.9)**		**Placebo 34 (10.6)**	
Dehydration	4	(1.2)	1	(0.3)
Dizziness, Postural	0	(0.0)	1	(0.3)
Hypotension	18	(5.6)	32	(9.9)
Hypovolaemia	2	(0.6)	0	(0.0)
Presyncope	2	(0.6)	0	(0.0)
Syncope	6	(1.9)	0	(0.0)

Source: reviewer's analysis of AE dataset for the BALANCE trial.
*The sum of the adverse events exceeds the total of subjects with the adverse events because subjects have multiple adverse events.

In contrast, in the SIADH population, adverse event terms compatible with rapid diuresis were more frequent in the lixivaptan than placebo arm, consistent with the larger effect size on serum sodium seen in this population as compared to the CHF and hyponatremia population (see Table 55 & Table 56 below).

Table 55. Treatment emergent adverse events that potentially reflect clinically significant over-diuresis in the SIADH population (the LIBRA trial)

Terms Suggestive of Excessive Diuresis	Lixivaptan n (%) N=50		Placebo n (%) N=51	
N (%) subjects	5	10.0	4	7.8
Dehydration	0	0.0	1	2.0
Hypotension	3	6.0	2	3.9
Hypovolaemia	0	0.0	1	2.0
Syncope	2	4.0	0	0.0

Source: reviewer's analysis of AE dataset for the LIBRA trial.
Patients with polyuria: 2 in lixivaptan arm, 1 in placebo arm. None of these subjects had the other clinical symptoms of over-diuresis as shown above.
* The syncope episodes were not characterized as serious; therefore, narrative was not provided.

Table 56. Treatment emergent adverse events that potentially reflect clinically significant over-diuresis in the SIADH population (the HARMONY trial)

Terms Suggestive of Excessive Diuresis	Lixivaptan n (%) N=153		Placebo n (%) N=52	
N (%) subjects	6	3.9	7	13.5
Dehydration	0	0.0	3	5.8
Hypotension	3	2.0	1	1.9
Hypovolaemia	0	0.0	1	1.9
Syncope	0	0.0	2	3.8
Postural Dizziness	3	2.0	0	0.0

Source: reviewer's analysis of AE dataset for the HARMONY trial.
* 10 subjects in the lixivaptan arm versus 0 in placebo arm had treatment emergent polyuria. However, the polyuria was not associated with any other adverse events that suggest clinical manifestation of over diuresis.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the CHF and hyponatremia phase 3 trial population (BALANCE trial), the adverse events were what would be expected from the pharmacology of the lixivaptan (e.g. thirst, dry mouth, constipation).

The adverse events that occurs in >2% of the lixivaptan population and occur at numerically greater frequency than placebo arm are listed below. For cardiac events, only two events was numerically higher in lixivaptan arm; other events, myocardial

infarct, sinus tachycardia, tachyarrhythmia, tachycardia, ventricular arrhythmia, ventricular fibrillation were numerically higher in the placebo arm. For renal and urinary disorders, acute renal failure was numerically higher in placebo than lixivaptan arm, despite a higher blood creatinine increase noted in lixivaptan arm. While AST and bilirubin levels were increased in lixivaptan than placebo arm, according to the applicant, no imbalance in number of cases that met Hy's law criteria between the 2 arms (lixivaptan 8, placebo 7). The reviewer's analysis of concomitant elevations of transaminase (e.g. > 3x upper limit of normal), total bilirubin (e.g. >2x upper limit of normal) did not gave a different impression from the applicant's finding.

Table 57. Common adverse events in the BALANCE trial

Safety Population/Dictionary Derived AE term	Lixivaptan n (%) N=322		Placebo n (%) N=322	
Cardiac disorders	183	56.8	191	59.3
Atrial Fibrillation	16	5.0	12	3.7
Cardiac arrest	7	2.2	4	1.2
Gastrointestinal disorders	147	45.7	139	43.2
Constipation	35	10.9	22	6.8
Nausea	25	7.8	21	6.5
Vomiting	15	4.7	12	3.7
Renal and Urinary Disorders	43	13.4	56	17.4
Blood creatinine increased	16	5.0	12	3.7
Hepatobiliary Disorders	15	4.7	14	4.3
AST increase	10	3.1	4	1.2
Blood bilirubin increased	8	2.5	2	0.6
GGT increased	16	5.0	9	2.8
Hyperuricaemia	13	4.0	8	2.5

Source: reviewer's analysis of the AE dataset for the BALANCE trial.

On the whole, the adverse events profile in SIADH subjects did not raise much concern. In general, the common adverse events were consistent with the pharmacologic effects of a vaptan (see Table 58 below).

Table 58. Common adverse events in the LIBRA trial

Subjects with AEs >2%	Lixivaptan n (%) N=50		Placebo n (%) N=51	
Organ System				
Gastrointestinal disorders				
Anorexia	2	4.0	0	0.0
Constipation	7	14.0	6	11.8
Dry mouth	4	8.0	2	3.9
Renal and urinary disorders				
Polyuria	2	4.0	1	2.0

Source: reviewer's analysis of the AE dataset for the LIBRA trial.
*only adverse events where the rates were higher in lixivaptan as compared to placebo were shown.

There was one exception-pain (see Table 59 below). The reason for the increased pain on lixivaptan is not clear. There were also more falls in lixivaptan as compared to the placebo group. However, falls did not appear to explain the numeric excess of pain in the lixivaptan arm (one of the three falls was in subjects with musculoskeletal and connective tissue pain, but the fall was after the onset of arthralgia). Lixivaptan is not known to affect pain receptors. Although creatinine kinase was not measured during the trial, the AST elevations with lixivaptan as compared to the placebo arm was not very high, making lixivaptan induced rhabdomyolysis less likely, but does not rule out drug-related myopathy. Please see clinical pharmacology review for whether potential drug-drug interaction could have contributed to this finding.

Table 59. Common treatment emergent adverse events in the LIBRA trial

Patients with AEs	Lixivaptan n (%) N=50		Placebo n (%) N=51	
Percentage of subjects with pooled events	12	(24.0)	2	(3.9)
Organ System				
Musculoskeletal and Connective Tissue Disorders	8*	(16.0)	2	3.9
Arthralgia	4	8.0	0	0.0
Back pain	3	6.0	2	3.9
Pain in extremity	2	4.0	0	0.0
Injury, poisoning and procedural complications	3	6.0	0	0.0
Fall	3	6.0	0	0.0
General disorders and administration site conditions	6	12.0	0	0.0
Gait disturbance	2	4.0	0	0.0
Asthenia	4	8.0	0	0.0

Source: reviewer's analysis of the AE dataset for the LIBRA trial. Note for the determining of treatment emergent adverse events, I used the definition, any adverse events that happened after starting drug therapy, or an event that occurred prior to randomization that worsened during study treatment.
* The total number of events exceeds the total number of subjects with any of these events.

Similarly, the common adverse events were consistent with the pharmacologic effects of a vaptan in the HARMONY trial (see table below). The uric acid increase is consistent lower of intravascular volume.

Table 60. Common adverse events in the HARMONY trial

Safety Population/Dictionary Derived AE term	**Lixivaptan n (%) N=153**		**Placebo n (%) N=52**	
Gastrointestinal disorders	79	52.0	30	57.7
Constipation	6	3.9	2	3.8
Diarrhea	13	4.0	4	1.2
Dry mouth	7	2.2	1	0.3
Vomiting	6	3.9	3	5.8
Thirst	5	3.3	1	1.9
Renal and Urinary Disorders	27	17.8	6	11.5
Blood creatinine increased	4	2.6	0	0.0
Polyuria	10	6.6	0	0.0
Hepatobiliary Disorders	3	2.0	2	3.8
Conjugated bilirubin increased	5	3.3	0	0.0
Blood bilirubin increased	8	5.3	2	3.8
GGT increased	5	3.3	1	1.9
Blood uric acid increased	4	2.6	0	0.0
Hyperuricaemia	1	0.7	1	1.9

[source: reviewer' analysis]

According to the applicant's analysis in the overall trial population, the mean, median ALT, total bilirubin over time did not suggest a trend of severe hepatic injury. Additional exploration will be conducted of the LFT will be conducted by this reviewer, and if results differ, will be added to this review.

7.4.2 Laboratory Findings

See earlier sections on rapid rate of rise in serum sodium and common adverse events. There were no other notable laboratory findings.

7.4.3 Vital Signs

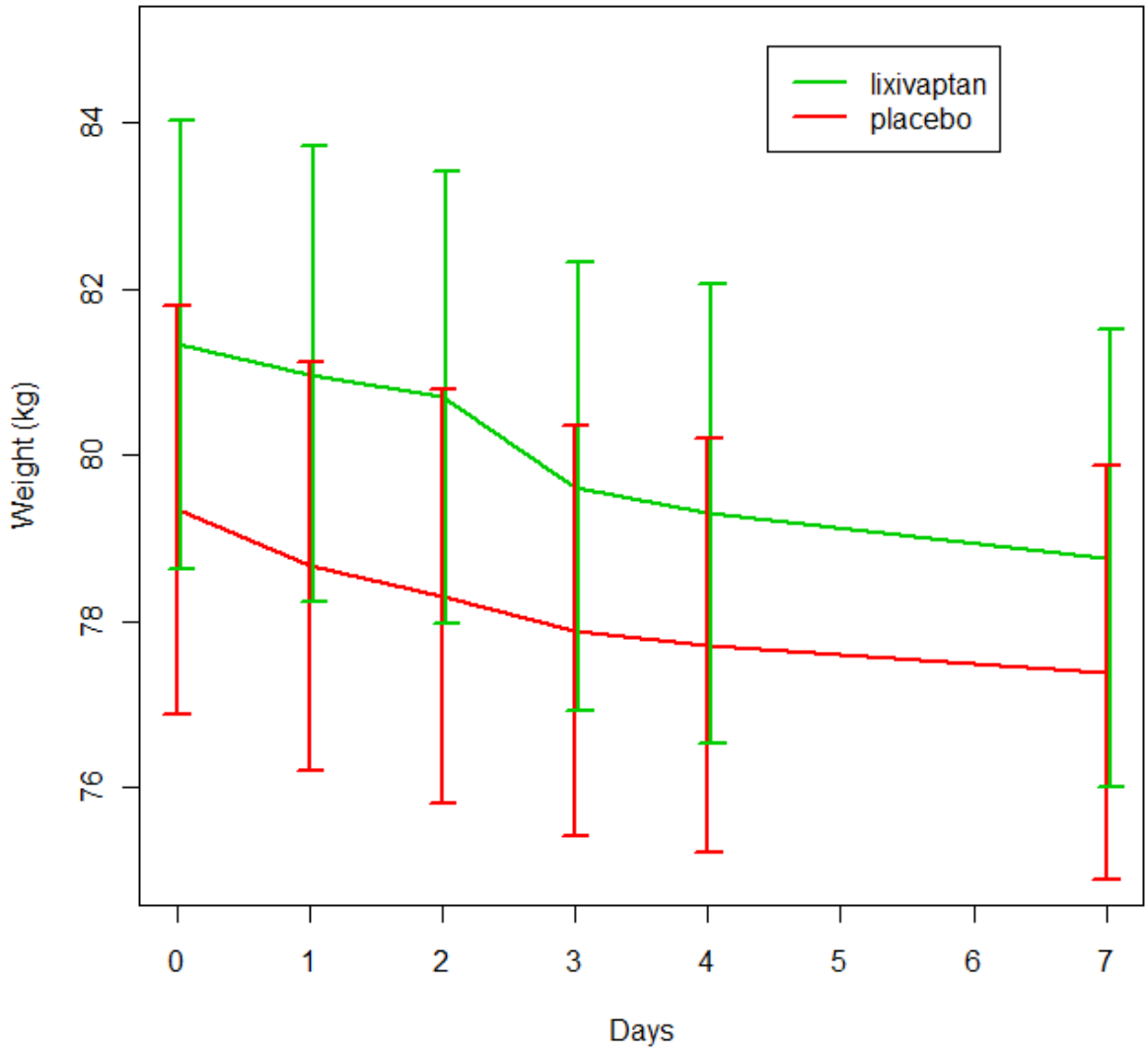
See earlier discussions on orthostatic heart rate increase at baseline and on-treatment in subjects who died earlier in the BALANCE trial.

In the FDA analysis of the blood pressure, heart rate, weight in the respective trial populations as **a whole**, no notable difference was found between treatment arms. In BALANCE trial, the focus was on the dose titration phase. Baseline mean and median

supine and standing SBP, supine and standing DBP, supine and standing HR, and weight were similar in the lixivaptan and placebo groups.

There was a drop in mean weight about one kilogram more in the lixivaptan than placebo arm from Day 2 to 3 (from randomization), likely reflecting the free water clearance effect of lixivaptan (see figure below).

Figure 10. The change in weight within the first 7 study days for the BALANCE trial



[

source: FDA statistical reviewers' analysis]

7.4.4 Electrocardiograms (ECGs)

The applicant reports that ECG showed no evidence of untoward effects associated with lixivaptan treatment in the Phase 3 studies. Results were similar in the other study groups.

7.4.5 Special Safety Studies/Clinical Trials

A thorough QT study did not show a clinically significant QTc prolongation over the lixivaptan dose range studied (25 to 100 mg BID).

According to the applicant, of the total number of hyponatremic subjects treated with lixivaptan in clinical studies, 54% were 65 and over, while 29% were 75 and over. Increasing age has no effect on lixivaptan plasma concentrations or adverse event profile. Hepatic impairment does not affect exposure to lixivaptan to a clinically relevant extent. No dose adjustment of lixivaptan is necessary.

7.4.6 Immunogenicity

Immunogenicity was not evaluated in animal studies for this small molecule.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As discussed in section 4, the FDA pharmacometric reviewer's analysis of the adverse events expected from pharmacology (headache, dizziness, constipation, drug mouth and thirst) showed a dose-related relationship to the occurrence of these adverse events.

7.5.2 Time Dependency for Adverse Events

As noted a greater number of deaths were seen in the lixivaptan compared to placebo arm following the initiation of therapy in the BALANCE trial. Rapid rates of rise in serum sodium that occurred during the titration phase are discussed in Section 7.3.5 for submission specific safety concern.

7.5.3 Drug-Demographic Interactions

The applicant did not report adverse event rates in subjects by age (e.g. subjects with more advanced age, e.g. >75 years), gender, race. If the reviewer's finding were to differ from that of the applicant, an addendum will be added to this review.

Reviewer's comment:
Compared to those with less advanced age, assessing volume status in subjects with very advanced age may be more difficult clinically.

7.5.4 Drug-Disease Interactions

The phase 3 trials studied lixivaptan in different study populations. The review addressed benefit and risk of lixivaptan in different populations in earlier sections.

7.5.5 Drug-Drug Interactions

According the clinical pharmacology review, the maximum safe increase in the exposure to lixivaptan in SIADH subjects was estimated to be 3 in SIADH subjects. Please see their review for recommendations on dose adjustment.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new case of cancer was reported in the trial. SIADH can be associated with existing cancer.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of lixivaptan in pregnant women. There was no reported pregnancy in the clinical development program. Also see discussion on reproductive findings in animal studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

Lixivaptan has not been studied in pediatric subjects, therefore, the safety and effectiveness of lixivaptan in these subjects have not been established.
The effects of growth in children are not currently known. Also see discussion on effects on growth from animal studies.

Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant does not report any overdose in the clinical program.
Single oral doses up to 500 mg and multiple doses up to 800 mg and twice daily doses up to 400 mg for 14 days had been studied in phase 1 (healthy subjects). According to the applicant, the above mentioned doses were well-tolerated in healthy subjects, and the signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect, i.e., an increase in sodium concentration, polyuria, thirst, and dehydration/hypovolemia.

Based on in vitro testing, there is no reason to suspect abuse potential.

The concepts of “withdrawal” and “rebound” are discussed with respect to changes in serum sodium following drug discontinuation (see section 6.8).

7.7 Additional Submissions / Safety Issues

The 120-Day Safety Update was submitted. Because all trials have been completed, no additional information has been received. The AE profile for lixivaptan during the long-term extension study (3431) was similar to that observed in the placebo-controlled Phase 3 trials. With the exception of 7 subjects who had hyponatremia associated with CHF (from BALANCE), the rest of the subjects enrolled in this study had SIADH (previously enrolled in LIBRA and HARMONY).

8 Postmarket Experience

Lixivaptan is not currently marketed in any country.

9 Appendices

9.1 Literature Review/References

Conivaptan Package Insert, March 2007.
Tolvaptan Package Insert, May 2009.
Hyponatremia Treatment Guidelines 2007: Expert Panel Recommendations. Verbalis J.G., Goldsmith SR, Greenberg A, Schrier R.W. R.H. Sterns. Am J Med. 2007;120(11A):S1-S21
Rose, BD, Post, TW, Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed, McGraw-Hill, New York, 2001, pp. 720-723.
Clinical assessment of extracellular fluid volume in hyponatremia. Chung HM, Kluge R, Schrier RW, Anderson RJ. Am J Med. 1987;83(5):905. [limitation in correct clinical assessment of volume status]
The electrolytes in hyponatremia. Graber M, Corish D Am J Kidney Dis. 1991;18(5):527.
Adrogue HJ, Madias NE. Hyponatremia, N Engl J Med. 2000; 342 (21):1581.

9.2 Labeling Recommendations

The following recommendations are based on the review of available information and may subject to change after reviewing additional information and/or feedback from the advisory committee meeting.

- Currently, this reviewer has reservation about approval of lixivaptan in population with hyponatremia associated with CHF, the approvability of lixivaptan in this population will be discussed at the Advisory Committee.
- Initiation/re-initiation should be only in settings where sodium concentration can be carefully monitored in hospitalized subjects (unless more data is there to provide assurance).
- Contraindicate lixivaptan use in cirrhosis subjects with hyponatremia, due to the excess number of death against lixivaptan arm in phase 2 trial and exclusion of the these subjects in the phase 3 trial. It is not clear how to dose lixivaptan in the cirrhotic population in order for the net expected benefit to outweigh the risk.

9.3 Advisory Committee Meeting

An advisory committee meeting is scheduled for September 13, 2012. The purpose of this meeting is to obtain guidance from the Cardiovascular and Renal Drugs Advisory Committee on approval in SIADH and hyponatremia associated with CHF, and the restriction of use. The results of this meeting will be provided in a separate addendum to this review.

9.4 The BALANCE Trial, Additional Summaries

9.4.1 BALANCE Trial Entry Criteria

The BALANCE trial entry criteria as finalized in protocol dated August 5, 2009.

Inclusion Criteria

A subject meeting the following criteria will be considered eligible for the study.
1. Men and Women with age greater than or equal to 18 years.
2. Baseline Serum sodium concentration < 135 mEq/L. Repeat measures of serum sodium are allowed; the last serum sodium result within 24 hours prior to randomization will serve as the qualifying measurement.
3. Current hospitalization for worsening of chronic congestive heart failure.
a) Chronic heart failure is defined as requiring treatment for a minimum of 30-Days prior to hospitalization. Study subjects are expected to be on standard background therapy for Congestive Heart Failure.
4. The subject has clinical evidence of volume overload with at least two of the following:
a) dyspnea,
b) pulmonary congestion (rales),
c) peripheral edema,
d) increased jugular venous pressure and/or hepatic congestion with ascites,
e) chest x-ray consistent with CHF, or
f) plasma BNP ≥150 pg/mL or NT pro-BNP ≥ 450 pg/mL.
5. The subject has a documented Left Ventricular Ejection Fraction (LVEF) within the past year.
6. Supine systolic arterial blood pressure ≥90 mmHg.

Reviewer's comment: Inotrophic agents were allowed in the protocol. The supine systolic arterial blood pressure ≥ 90 mmHg was later clarified by PEAC as in the absence of any pressor use. Case report forms did not document 30 days of treatment to allow verification of the chronicity of CHF by PEAC/ACI.

Exclusion Criteria
1. Previous participation in this or any other lixivaptan clinical trial.

2. Participation in any other investigational study of drugs or devices within 30-Days prior to Screening.
3. Women who will not adhere to the reproductive precautions as outlined in section 4.3 of this protocol and in the informed consent form.
4. Positive urine pregnancy test.
5. Inability to provide informed consent.
6. Inability to respond to thirst.
7. Inability to take oral medications.
8. Acute severe hyponatremia
9. Overt symptoms of hyponatremia requiring immediate medical intervention (e.g., severe lethargy, coma, seizures).
10. Hemodynamically significant uncorrected primary cardiac valvular disease.
11. Hypertrophic cardiomyopathy (obstructive or non-obstructive).
12. CHF due to uncorrected thyroid disease, (i.e. T4 above or below the limits of the reference range), active myocarditis or known amyloid cardiomyopathy.
13. History of sustained ventricular tachycardia or ventricular fibrillation within 30-Days, unless in the presence of an automatic implantable cardioverter defibrillator.
14. ST-segment elevation myocardial infarction (STEMI) within 30-Days or active myocardial ischemia at the time of enrollment.
15. History of stroke within 30-Days prior to screening.
16. History of a cardiac revascularization procedure within 30-Days prior to screening.
17. Subjects who are on cardiac mechanical support.
18. History of bi-ventricular pacer placement within the last 30-Days.
19. Planned revascularization procedures, electrophysiologic (EP) device implantation, cardiac mechanical support implantation, ultrafiltration or dialysis, or other cardiac surgery within 30-Days following study enrollment.
20. Serum creatinine > 3.0 mg/dL/265.2 mol/L
21. Uncontrolled diabetes mellitus as defined by the Investigator (e.g. HbA1c > 9%).
22. Adrenal insufficiency, whether treated or not. If serum cortisol is less than the lower limit of the reference range, the subject is excluded and should be referred for follow-up evaluation.
23. History of primary significant liver disease or acute hepatic failure, as defined by the Investigator.
24. History of chronic drug/medication abuse within 6 months; or current alcohol abuse.
25. Co-morbid condition with an expected survival of less than six months.

9.4.2 The BALANCE trial key protocol amendments

BALANCE protocol amendments

Date	Key changes enacted
1/14/08	The original implemented protocol, amendment 3 a. Deleted the requirement for measuring urine output in the dose titration phase b. Deleted weight assessment for determining dose titration scheme. c. Deleted measurements of urine osmolality and the tertiary endpoint related to change from baseline in urine osmolality.
10/6/08	a.Revised entry criteria by deleting: i. requirement for entry criteria to be met within 48 hours of hospitalization ii. lower boundary for qualify serum sodium levels (≥120 mEq/L) iii. requirements for EF of < 40% within one year iv. requirement of NYHA class III/IV at entry v. requirement for systolic arterial blood pressure of ≥90 mmHg b. Revised entry criteria by adding: i. BNP level criteria and chest x-ray consistent with CHF to establish volume overload ii. exclusion of subjects with an inability to continue fluid intake in response to thirst iii. Exclusion of acute severe hyponatremia (acuity was not specified) iv. Criterion number 7 modified to read as follows: Overt symptoms of hyponatremia requiring immediate medical intervention (e.g., severe lethargy, coma, seizures). v. revised to exclude subjects with ST-segment elevation myocardial infarction (STEMI) within 30 days or active myocardial ischemia at the time of enrollment. c. Added Trail Making Test, part B (TMT-B) and the Medical Outcomes Study 6 item Cognitive Function Scale (MOS-6) to study assessments and appendices d. Added appendix delineating Dyspnea Assessment e. Deleted the requirement for fluid restriction (“if possible, fluid restriction should not be instituted for at least the first 72 hours in order to determine the rate and magnitude of serum sodium change.”)
8/5/09	Changed Contract Research Organization for serious adverse event reporting from PAREXEL to PPD. Delete allowance for the resumption of dosing at half of the last dose

	level taken can occur after serum sodium concentrations returned to less than 135 mEq/L or when clinical worsening of volume overload is observed.
6/17/10	Last subject completed

[source: reviewer' summary]

9.4.3 The BALANCE Trial Baseline Demographics

Table 61 . Key Baseline Subject Characteristics in the BALANCE Trial

Characteristics (ITT population)	**Lixivaptan N=323 n (%)**	**Placebo N=329 n (%)**	**Total N=652 n (%)**
Age (years)			
Mean (SD)	64.9 (14.1)	64.7 (12.9)	64.8 (13.5)
Number (%) ≥65	170 (52.6)	165 (50.2)	335 (51.4)
Sex, n (%)			
Male	233 (72.1)	234 (71.1)	467 (71.6)
Female	90 (27.9)	95 (28.9)	185 (28.4)
Weight (kg)	(n=320)	(n=326)	(n=646)
Mean (SD)	81.3 (24.4)	80.0 (23.0)	80.1 (23.5)
NYHA class, n (%)			
II	8 (2.5)	16 (4.8)	24 (3.7)
III	210 (65.0)	178 (54.1)	388 (59.5)
IV	105 (32.5)	135 (41.0)	240 (36.8)
Percent left ventricular ejection fraction			
Mean	31 (14)	31 (14)	31 (14)
minimum, maximum	9, 75	6, 78	6, 78
Number (%) ≥ 40%	69 (21)	69 (21)	138 (21)
Number (%) <40%	253 (78)	257 (78)	510 (78)
Number (%) of subjects with history of:			
Unstable Angina within 1 month	3 (0.9)	3 (0.9)	6 (0.9)
Coronary artery disease	102 (32)	100 (30)	203 (31)
Coronary artery bypass graft	59 (18)	49 (15)	108 (17)
Geographic Regions			
Asia	55 (17.0)	56 (17.0)	111 (17.0)
Eastern Europe	133 (41.2)	135 (41.0)	268 (41.1)
North America	72 (22.3)	76 (23.1)	148 (22.7)
South America	23 (7.1)	24 (7.3)	47 (7.2)

[source: applicant table 13, 15 of CSR for BALANCE study, verified by reviewer]

Figure 11. Deaths with Within First Ten Days after Initiating Study Drug in the BALANCE Trial (CHF and Hyponatremia Population).

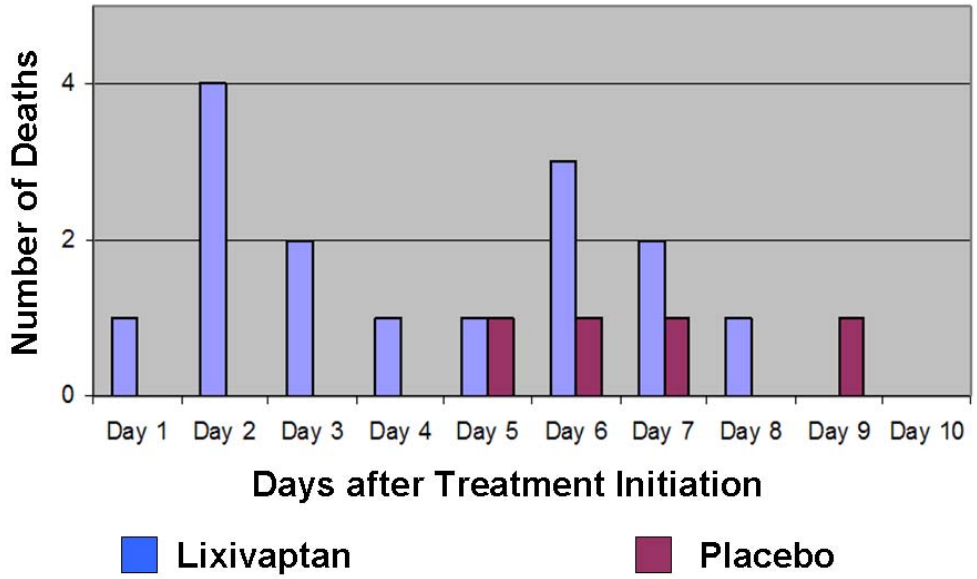


Table 62. Hyponatremia with CHF (BALANCE): No osmotic demyelination syndrome

Safety population	**Lixivaptan n (%) N=322**		**Placebo n (%) N=322**	
Neurologic symptoms*	5	(1.6)	4	(1.2)
convulsion	1	(0.3)	1	(3.7)
aphasia and epilepsy	1	(0.3)	1	(1.2)
lethargy	2	(0.6)	2	(0.3)
dysphagia	1	(0.3)	0	(0)

[source: reviewer' analysis]

Around AE onset no rapidly increasing (<8/ 8hour and <12/24 h) in sodium; clinical picture **not** consistent with ODS (e.g. neurologic findings after stroke)**.**

*Terms searched: aphasia, dysarthria, dysphagia, lethargy, confusion, epilepsy, seizure, convulsion, paraparesis, quadriparesis and obtundation.

9.5 The LIBRA Trial, Additional Summaries

Key Protocol Amendments for LIBRA Trial

Date	Key changes enacted
2/29/08	Amendment 2, the original implemented version of the protocol After starting dose of 50 mg on Day 1, randomized subjects will have an option to titrate upwards to 100 mg of lixivaptan, if needed, and/or titrate downward to 25 mg
10/20/08 Protocol Amendment 3	Changed the original two co-primary endpoints (sodium change as a area under the concentration time curve at Day 3 and Day 30) to change from baseline in serum sodium concentration at Day 7. Remove one secondary endpoint: time to first normalization of serum sodium. Add one secondary endpoint: percentage of subjects with worsening of hyponatremia. Add back the biochemistry profile that included serum sodium by central lab in addition to local lab at 8 hours after first study drug dose. This blood draw was to be sent to both central and local labs.
8/4/09	Added more sites for enrollment. 9/21/09: “Transition to new EU Medical Monitor”
11/19/09:	Clarified that subject with a history of a diagnosis of a neurologic disorder (e.g. permanent neurological deficits, probable Alzheimer’s disease, normal pressure hydrocephalus, Parkinsonian dementia complex, multi-infarct dementia, mixed dementia, or Huntington’s disease) was not in itself exclusionary. Exclude subjects with significant neurological impairment such that the subject is unable to perform the required subject assessments (e.g. TRAIL Making Test).
5/14/10	Last subject completed. Discontinue blood collection for vasopressin concentration determination.
5/13/10	Statistical Analysis Plan version 1 finalized
8/30/10	Statistical Analysis Plan version 3, finalized

Table 63. Baseline Subject Characteristics in the LIBRA Trial, ITT population

Characteristics	Lixivaptan (N=54)	Placebo (N=52)	Total (N=106)
Male n (%)	26 (48.1)	30 (57.7)	56 (52.8)
Age (years)			
Mean (SD)	66.4 (14.1)	65.2 (13.3)	65.8 (13.7)
Number (%) ≥65	32 (59.3)	26 (50.0)	58 (54.7)
Race/Ethnicity			
Asian	8 (14.8)	6 (11.5)	14 (13.2)
Black or African American	2 (3.7)	2 (3.9)	4 (3.8)
White	44 (81.5)	44 (84.6)	88 (83.0)
Weight (kg)	n=51	n=48	n=99
Mean (SD)	72.0 (15.3)	70.0 (16.0)	71.0 (15.4)
Region, n (%)			
Asia (India)	7 (13.0)	6 (11.5)	13 (12.3)
Eastern Europe (Poland)	9 (16.7)	9 (17.3)	18 (17.0)
North America (United states and Canada)	19 (35.2)	19 (36.5)	38 (35.8)
United States	19 (35.2)	17 (32.6)	36 (34.0)
Western Europe	19 (35.2)	18 (34.6)	37 (34.9)

[Source: Applicant's CK-LX3405 Clinical Study Report Table 13, verified by the reviewer]

Table 64 Indications for concomitant medications (LIBRA)

Concomitant medications for Treating (ITT population)	Lixivaptan (N=54)	Placebo (N=52)	Total (N=106)
	Number (%) of Subjects		
Anxiety*	4 (7.4)	2 (3.8)	6 (5.7)
Depression	10 (18.5)	7 (13.5)	17 (16.0)
Cancer	1 (1.9)	3 (5.8)	4 (3.8)
Infection	15 (27.8)	21 (40.4)	36 (34.0)
Pain	22 (40.7)	22 (42.3)	44 (41.5)
Schizoprenia, Schizoaffective Disorder, or Psychosis	2 (3.7)	2 (3.8)	4 (3.8)
Seizure	2 (3.7)	8 (15.4)	10 (9.4)

[source: reviewer's analysis of the concomitant medications dataset]
Anxiety disorder included keywords of anxiety, nervousness, agitation [lixivaptan 6 (%11.1) vs. placebo 3 (5.8%)].
One subject in the lixivaptan group was on tiotropium bromide for an indication of "CHF". This reviewer is not clear if the subject truly had CHF.

One subject on the placebo arm also was on sodium potassium tablets along with furosemide for the treatment of SIADH.

Table 65. Terms explored for osmotic demyelination syndrome (LIBRA)

Safety population	**Lixivaptan n (%) N=40**		**Placebo n (%) N=39**	
Terms searched for Osmotic demyelination syndrome	1	(2.5)	2	(5.1)
Dysarthria	0	(0.0)	1	(2.6)
Epilepsy*	0	(0.0)	1	(2.6)
Lethargy	1	(2.5)	0	(0.0)

[source: reviewer' analysis]

9.6 The HARMONY Trial, Additional Summaries

Table 66. Key Protocol Amendments for HARMONY trial are as follows.

Date	**Key changes enacted**
3/13/09	Original protocol Clarify that supplemental oral sodium and normal saline infusion was strongly discouraged.
6/30/09 Amendment 1	Clarified that subjects with significant neurologic impairment can be entered the trial if able to complete subject assessments.
8/18/09	Clarified that subjects screened and randomized on the same day, vital signs, physical exam and pre-dose central laboratory assessments need not be repeated. All assessments outlined for Study Day 1 (Pre-dose) must be performed.
12/7/09	Memo to all Cardiokine Clinical Investigators on steps to prevent introduction of sodium concentration variability into local and central samples
1/7/10 Clarification	Discontinue monitoring of vasopressin levels.
1/19/10 Amendment 2	Added exclusion criteria: • Pseudohyponatremia (i.e., hyponatremia resulting from a laboratory artifact). • Hypertonic hyponatremia (e.g., hyponatremia in the setting of hyperglycemia). • Significant neurological disorders (e.g., permanent neurological deficits, probable Alzheimer's disease, normal pressure hydrocephalus, Parkinsonian dementia complex, multi-infarct dementia, mixed dementia, or Huntington's disease). • Conditions limiting access to water or an inability to respond to thirst (e.g., hydrophobia, or noncommunicative).
3/8/10 clarification	Remove the blind to central sodium levels to investigators as of February 2010.
5/14/10	Last subject completed.

Table 67. Key Baseline Demographics for HARMONY population (ITT)

Characteristics	Lixivaptan (n=154)	Placebo (n=52)
Age (years)		
Mean (SD)	66.6 (14.1)	62.7 (13.6)
Number (%) ≥65	87(56.5)	111 (53.9)
Sex		
Male	73 (47.4)	27 (51.9)
Female	81 (52.6)	73 (47.4)
Race/Ethnicity		
Asian	18 (11.7)	8 (15.4)
Black or African American	7 (4.5)	8 (15.4)
White	126 (81.8)	35 (67.3)
Regions, n %		
Europe/Israel	8 (5.2)	4 (7.7)
Asia (India)	17 (11.0)	7 (13.5)
South America	7 (4.5)	4 (7.7)
North American (United States)	122 (79.2)	37 (71.2)

Source: adapted from the applicant table 14.4.1, CK-LX3430 Clinical Study Report. Verified by the reviewers.

Table 68: Baseline medical condition for which the subjects were receiving medical therapy (HARMONY)

Concomitant medications for Treating	Lixivaptan (N=154)	Placebo (N=52)	Total (N=206)
ITT Population	Number (%) of Subjects		
Anxiety*	43 (27.9)	14 (26.9)	57 (27.7)
Cancer	2 (1.3)	0 (0.0)	2 (1.0)
Dementia	8 (5.2)	2 (3.8)	10 (4.9)
Depression	52 (33.8)	15 (28.9)	67 (32.5)
Infection	36 (23.4)	14 (26.9)	50 (24.7)
Pain	68 (44.1)	24 (46.2)	92 (44.7)
Schizoprenia, Schizoaffective Disorder, or Psychosis	14 (9.1)	2 (3.8)	16 (7.8)
Seizure	14 (9.1)	6 (11.5)	20 (9.7)
Stroke	4 (2.6)	2 (3.8)	6 (2.9)

[source: reviewer's analysis]

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	203-009
Drug Name:	lixivaptan
Indication(s):	symptomatic hypervolemic and euvolemic hyponatremia associated with heart failure (HF) and syndrome of inappropriate anti-diuretic hormone (SIADH)
Applicant:	Cardiokine
Date(s):	12/30/2011
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	James Hung, Ph. D.
Medical Division:	Division of Cardiovascular and Renal Products, HFD-110
Clinical Team:	Nancy Xu, M.D.
Project Manager:	Russell Fortney

Keywords:
Missing Data, ANCOVA, CMH test, DSMB, early death

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1. EXECUTIVE SUMMARY

This NDA application included three phase III trials in subjects with hyponatremia associated with heart failure (HF) and associated with syndrome of inappropriate anti-diuretic hormone (SIADH). BALANCE (Study 3401) was conducted in subjects with hyponatremia associated with HF. LIBRA (Study 3405) and HARMONY (Study 3430) were conducted in subjects with hyponatremia associated with SIADH.

About 23%, 21% and 17% of subjects (excluding deaths) did not complete the treatment in BALANCE, LIBRA and HARMONY, respectively. No further serum sodium measurements can be obtained in some of these subjects. The percentage of such subjects can be from 6% to 17% across the studies. A number of sensitivity analyses were performed on primary and secondary endpoints in all three trials to assess the impact of missing data. As a whole, these analyses produced consistent results. Although the percentage of missing data is relatively high, the consistent findings in sensitivity analyses seemed reassuring.

The discrepancy between central and local serum sodium measurements and the fact that the applicant used one (central lab values) for analyses and the other (local lab values) for study entry criteria prompted sensitivity analyses of the primary endpoint using local serum sodium measurements. The results remained mostly unchanged although 40% subjects in BALANCE, 35% subjects in LIBRA and 25% subjects in HARMONY would not have been eligible to enter the study, had central serum sodium values been used instead of local serum sodium measurements.

Although all three trials showed highly statistical significant results, treatment effects on serum sodium appeared small (1.2 mmol/L in BALANCE, 2.2 mmol/L in LIBRA and 2.4 mmol/L in HARMONY). Furthermore, there was an imbalance in early deaths against lixivaptan in BALANCE with a greater number occurring in subjects randomized to lixivaptan. The safety concern prompted the data safety monitoring committee to issue a letter on June 9, 2010 urging the applicant to terminate the trial as soon as possible. No specific factor was reported or found to be associated with imbalance of early death in BALANCE. The benefit gained from lixivaptan and the potential mortality risk, especially in the heart failure population, need to be carefully weighed.

2. INTRODUCTION

2.1 Overview

Lixivaptan was developed for the treatment of symptomatic hypervolemic and euvolemic hyponatremia associated with heart failure (HF) and syndrome of inappropriate anti-diuretic hormone (SIADH), respectively. The clinical development of lixivaptan was initiated by Wyeth Pharmaceuticals in 1995 under IND 47,850 and has been continued by Cardiokine since 2004.

This NDA includes efficacy and safety data from three Phase 3, double blind, placebo-controlled studies in subjects with hypervolemic and euvolemic hyponatremia: CK-LX3401 (BALANCE), CK-LX3405 (LIBRA), and CK-LX3430 (HARMONY).

Table 1. List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
Study 3401 (BALANCE)	Phase 3, double-blind, two-arm, parallel-group	60-day double-blind treatment period	30 days	323 lixivaptan and 329 placebo	inpatients with hypervolemic hyponatremia associated with CHF
Study 3405 (LIBRA)	Phase 3, double-blind, two-arm, parallel-group	30-day double-blind treatment period	30 days	54 lixivaptan and 52 placebo	inpatients with euvolemic hyponatremia associated with SIADH
Study 3430 (HARMONY)	Phase 3, double-blind, two-arm, parallel-group	6-month double-blind treatment period	30 days	154 lixivaptan and 52 placebo	outpatients with euvolemic hyponatremia associated with SIADH

2.2 Data Sources

The applicant's electronic data are stored under \\Cdsesub5\evsprod\NDA203009\0000\m5\datasets

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer was able to reproduce the results of the primary analysis and many of the secondary analyses. The applicant submitted the raw datasets used to derive the primary analysis dataset and the reviewer is able to trace how the primary endpoint was derived in all three trials.

3.2 Evaluation of Efficacy

3.2.1 Study 3401 (BALANCE)

3.2.1.1 Study Design and Endpoints

This was a Phase 3, randomized, prospective, double-blind, placebo-controlled, parallel-group study of oral lixivaptan in treating hyponatremia in subjects hospitalized with acute worsening of chronic HF and volume overload.

Subjects with hyponatremia (local serum sodium <135 mmol/L) and hypervolemia were randomized in a 1:1 ratio to either placebo or lixivaptan. Randomization was stratified by both country and baseline serum sodium concentration. The trial required the enrollment of a minimum of 200 subjects with a serum sodium concentration <130 mmol/L.

The applicant estimated that a sample size of 125 subjects in each group had 98% power to detect a difference in means of 4.2, assuming a common standard deviation of 8.23. The study was also powered to detect a significant treatment effect on days alive and out of hospital (DAOH). 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 of 0.05

All study subjects entered a dose-titration phase for up to 72 hours to optimize the dose. The objective of the titration phase was to slowly increase serum sodium to the treatment target. 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. Subjects were treated for up to 60 days.

At the end of the treatment period, two post-treatment visits occurred, one at seven days post-treatment and the final study visit 30 days post-treatment. The post-treatment follow-up visits for discontinued subjects were completed seven and 30 days after the last dose of study drug. In

addition, prematurely discontinued subjects were contacted by telephone for assessment of secondary endpoints 60 days after randomization (eg, DAOH and worsening HF).

The primary efficacy endpoint was the change from baseline in serum sodium concentration on Day 7.

Secondary endpoints included:

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. The percentage of subjects with worsening hyponatremia (a reduction of ≥3 mmol/L in serum sodium concentration from the preceding measurement with a value<135 mmol/L) during the double-blind on-therapy period

4. The percentage of subjects with normalized serum sodium (≥135 mmol/L and ≤145 mmol/L) at Days 7 and 60

5. Days alive and out of hospital

3.2.1.2 Patient Disposition, Demographic 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 (**Table 2**). The ITT population (all randomized subjects) was used for the primary analysis of efficacy.

Subjects who completed the treatment period were defined as subjects who had been on treatment for no less than 54 days by the applicant. It is not clear why the sponsor defined treatment period this way. Excluding deaths, 24.8% of subjects randomized to lixivaptan and 21.7% of subjects randomized to placebo did not complete the 8-week treatment. The main reasons included an adverse event, subject withdrew consent and investigator withdrew subject from study.

Table 2 Subject Disposition (BALANCE Study)

	Number (%) of subjects		
	Lixivaptan	Placebo	Total
Subject randomized	323	329	652
Subjects treated	322 (99.7)	322 (97.9)	644 (98.8)
Subjects not treated	1	7	8
Subjects completing treatment period	207 (64.1)	227 (69.0)	434 (66.6)
Subjects not completing treatment period	115 (35.6)	95 (28.9)	210 (32.2)
Adverse event	15	16	31
Death	35	25	60
Investigator withdrew subject from study	19	18	37
Lack of efficacy	1	0	1
Lost to follow up	0	3	3
Other	8	6	14
Protocol violation	2	0	2
Subject withdrew consent	29	26	55
Reason missing	6	1	7

[Source: Applicant's CK-LX3401 Clinical Study Report Table 11, verified by the reviewer]

The majority of randomized subjects were white (75.8%) and male (71.6%). The majority of subjects were from Eastern Europe (41.1%) and North America (22.7%). Mean age was 64.8 years and approximately half of subjects were 65 or older.

Table 3 Demographic and Baseline Characteristics (BALANCE Study)

Characteristic	**Lixivaptan (N=323)**	**Placebo (N=329)**	**Total (N=652)**
Age (years)			
Mean (SD)	64.9 (14.1)	64.7 (12.9)	64.8 (13.5)
Number (%) <65	153 (47.4)	164 (49.8)	317 (48.6)
Number (%) ≥65	170 (52.6)	165 (50.2)	335 (51.4)
Sex, n (%)			
Male	233 (72.1)	234 (71.1)	467 (71.6)
Female	90 (27.9)	95 (28.9)	185 (28.4)
Race, n (%)			
Asian	58 (18.0)	58 (17.6)	116 (17.8)
Black or African American	25 (7.7)	13 (4.0)	38 (5.8)
Hispanic or Latino	1 (0.3)	2 (0.6)	3 (0.5)
Native Hawaiian or Other Pacific Islander	0	1 (0.3)	1 (0.2)
White	239 (74.0)	255 (77.5)	494 (75.8)
Region, n (%)			
Asia	55 (17.0)	56 (17.0)	111 (17.0)
Eastern Europe	133 (41.2)	135 (41.0)	268 (41.1)
North America	72 (22.3)	76 (23.1)	148 (22.7)
South America	23 (7.1)	24 (7.3)	47 (7.2)
Western Europe	40 (12.4)	38 (11.6)	78 (12.0)
Weight (kg)	(n=320)	(n=326)	(n=646)
Mean (SD)	81.36 (24.42)	79.68 (22.58)	80.51 (23.51)

[Source: applicant's CK-LX3401 clinical study report Table 13, verified by the reviewer]

3.2.1.3 Statistical Methodologies

The primary efficacy endpoint was the change from baseline in serum sodium concentration on Day 7. The primary analysis used the ANCOVA model with treatment, pooled country and baseline local sodium stratum (<130 mmol/L vs. >=130 mmol/L) as factors, and with baseline central serum sodium value as the covariate. The primary analysis was performed in the ITT

population. The applicant imputed the missing data by last observation carried forward. If the baseline value was missing, the next available observation was carried backward as baseline. This approach was also used for the secondary analyses and was referred as LOCF/NOCB.

Sensitivity analyses were conducted to assess the impact of missing data (mixed effect model repeated measures analysis [MMRM], and observed value [OV]), analysis population (ITT, MITT, and PP efficacy), and type of serum sodium value (central and local serum sodium) on the primary efficacy endpoint.

Due to multiple versions of SAP submitted and multiple analyses proposed on secondary endpoints in three studies (different population, different imputation, et al), the applicant submitted a summary on secondary analyses on August 17, 2010 at a request from the Division to address questions on analysis populations, imputation methodology, analyses of laboratory sodium values and multiplicity among secondary endpoints. In the document, it was stated that all secondary endpoints were to be analyzed with the ITT population using LOCF/NOCB imputation as the primary analysis (using Central sodium values where applicable). The secondary efficacy endpoints were tested for treatment group differences in the hierarchical sequence at a significance level of 0.05 (two-sided). The applicant incorporated these into the final version SAPs.

In this study, ANCOVA models were used to for AUC and TMT-B test between two treatment groups. CMH test was used to compare the percentage of subjects with worsening of hyponatremia and the percentage of subjects who achieve normalized serum sodium between two treatment groups.

3.2.1.4 Results and Conclusions

The mean increase in central serum sodium from Baseline to Day 7 was statistically significantly greater in the lixivaptan group than in the placebo group in the ITT population (p=0.001, as shown in Table 4). In the primary analysis, the applicant imputed the missing data by LOCF/NOCB. The reviewer also performed a number of sensitivity analyses to assess the impact of missing values as well as the discrepancies between local and central serum sodium measurements on the primary endpoint analysis. The sensitivity analyses showed consistent results (**Table 5**).

It was also noted that this study was overpowered for the primary endpoint. In fact, according to the applicant, a sample size of 125 in each group would have 98% power to detect a difference in means of 4.2 in the primary endpoint assuming that the common SD of changes is 8.23. The common SD of changes in this trial was 5.34. So the primary endpoint was well overpowered. This is because that the study was also powered to detect significant difference in a clinically important secondary endpoint, Days Alive and Out of Hospital (DAOH). According to the

applicant in the SAP, 325 per arm (total 650) would achieve 89% power to detect a difference of 3 days in DAOH. As a result, despite the relatively small treatment difference (2.5 mmol/L in lixivaptan versus 1.3 mmol/L in placebo), the results remained highly significant in the primary analysis and all sensitivity analyses.

Table 4 Mean Change in Central Serum Sodium from Baseline to Day 7 (BALANCE Study)

Parameter	**Statistic**	**Lixivaptan (N=323)**	**Placebo (N=329)**
	Number of subjects in analysis	323	329
Baseline, mmol/L	Mean (SD)	132.9 (5.6)	132.6 (6.2)
Change from Baseline, mmol/L	Mean (SD)	2.6 (5.1)	1.6 (5.6)
	Median	2.0	1.0
ANCOVA	LS mean (SE)	2.5 (0.3)	1.3 (0.3)
	p-value	0.001	

[Source: Applicant's clinical study report CK-LX3401 Table 20, verified by the reviewer]

Table 5 Sensitivity Analyses on Change from Baseline to Day 7 in Serum Sodium (BALANCE Study)

Population	Sensitivity analysis	Sodium measurement	LS means (SE)* Lixivaptan	Placebo	p-value
ITT	LOCF	Local	4.2 (0.3)	2.8 (0.3)	<0.001
ITT	Observed value	Central	2.8 (0.3)	1.5 (0.3)	<0.001
ITT	Observed value	Local	4.4 (0.3)	3.0 (0.3)	<0.001
PP	Observed value	Central	2.8 (0.3)	1.4 (0.3)	<0.001
PP	Observed value	Local	4.5 (0.3)	3.1 (0.3)	<0.001
ITT	MMRM	Central	2.6 (0.3)	1.4 (0.3)	<0.001
ITT	MMRM	Local	4.3 (0.3)	2.8 (0.3)	<0.001

* Analyses for central serum sodium used the ANCOVA model that included treatment, pooled country, and Baseline local sodium stratum (<130 mmol/L vs. >=130 mmol/L) as factors and Baseline central sodium value as covariate. The ANCOVA model for change in local serum sodium included treatment and pooled country as factors and Baseline local sodium value as covariate.

The secondary efficacy endpoints were tested for treatment group differences in the hierarchical sequence shown in Table 6. Additional information on some individual secondary endpoints is provided in **Table 7** and **Table 8**.

Table 6 Secondary Efficacy Endpoints (BALANCE Study)

Secondary Efficacy Endpoints (BALANCE)	Lixivaptan	Placebo	Nominal p-value
Normalized Average Daily nAUC0-60 for central serum sodium concentration from Day 0 to Day 60	2.6 (0.27)[1]	1.9 (0.27) [1]	0.042
Change from Baseline to Day 28 for the recorded time to complete the TMT-B	-7.3 (5.1) [2]	-20.9 (5.1) [2]	0.021
Percentage of subjects with worsening of hyponatremia during the double- blind on-therapy period*	166/323 (51.4%)[3]	195/329 (59.3%)[3]	0.04
Percentage of subjects who achieved normalized serum sodium (135 to 145 mmol/L) at:			
Day 7	89/323 (27.6%)[4]	74/329 (22.5%)[4]	0.14
Day 60	108/323 (33.4%)	83/329 (25.2%)	0.02
DAOH	41.3 (19.3) [5]	42.6 (17.6) [5]	0.652

1. LS mean change on normalized average daily AUC for central serum sodium with standard error (ITT LOCF)
2. LS mean change from baseline on time to complete TMT-B Trail Test with standard deviation (ITT OV)
3. Total number of subjects with worsening of hyponatremia over total number of subjects and percentage (ITT LOCF), p-value was computed by CMH test controlling for pooled country
4. Total number of subjects achieving normalized serum sodium at Day 7 or Day 60 versus total number of subjects (ITT LOCF)
5. Total number of days out of hospital with standard deviation (ITT, p-value was from Wilcoxon rank-sum test)

* Worsening hyponatremia was defined as a reduction of ≥3 mmol/L in serum sodium concentration from the preceding measurement with a value <135 mmol/L

The mean nAUC0-60 was statistically significantly greater in the lixivaptan group than in the placebo group in the ITT population using LOCF/NOCB. The ANCOVA model used for the analysis included treatment, pooled country, and Baseline local sodium stratum as factors and Baseline central sodium value as covariate.

The TMT-B test endpoint only had measurements at baseline, Day 28 and Day 60 (or early termination visit). Most subjects had baseline measurements but only 362 subjects had measurement on Day 28. Although the sponsor mentioned in their SAP that LOCF would be used for missing data imputation, the reviewer did not think LOCF in this case would yield meaningful results. If all the subjects that did not have Day 28 measurements ended up carrying over the baseline value, over 200 zeroes would be included in the analysis. The results reported by the sponsor also were based on OV analysis. Unlike the sponsor's results on TMT-B test showing non-significant difference between lixivaptan and placebo groups, the ANCOVA model

in reviewer's analysis showed nominal p-value of 0.02. Contrary to what was anticipated, the results favored the placebo group (**Table 7**).

Table 7 Mean Change in Time to Complete the TMT-B from Baseline to Day 28 (BALANCE Study)

Parameter	**Statistic**	**Lixivaptan**	**Placebo**
	Number of subjects in analysis	167	173
Baseline, seconds	Mean (SD)	218.4 (77.2)	219.7 (73.0)
Change from Baseline, seconds	Mean (SD)	-10.1 (53.0)	-24.2 (58.7)
	Median	0.0	-16.0
ANCOVA*	LS mean (SE)	-7.3 (5.1)	-20.9 (5.1)
	Nominal p-value	0.021	

* ANCOVA model included treatment, pooled country, and Baseline local sodium stratum as factors and baseline score as covariate, OV analysis included subjects with both baseline and Day 28 measurements

The applicant reported that 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). The reviewer had somewhat different results using LOCF (**Table 6**) and OV (162/242 in lixivaptan group versus 185/249 in placebo group, nominal p-value=0.055 by CMH test).

The worsening of hyponatremia endpoint was defined as a reduction of ≥3 mmol/L at any time point in serum sodium concentration from the preceding measurement with a value <135 mmol/L. As long as a subject had one visit with big decrease in serum sodium of ≥3 mmol/L and a preceding measurement <135 mmol/L, the subject would be counted as having worsening of hyponatremia. It is questionable whether this endpoint captured a "real" worsening of hyponatremia. The reviewer found that a considerable number of subjects had a much higher reading (>= 3 mmol/L increase) in serum sodium concentration in the subsequent visits. Clinical significance does not seem clear.

The applicant reported that the percentage of subjects who achieved normalized central serum sodium (≥135 and ≤145 mmol/L) on Day 7 was nominally higher in the lixivaptan group than in the placebo group in the ITT population using OV (30.1% versus 24.3%, p=0.091). The percentage of subjects who achieved normalized central serum sodium was also higher in the lixivaptan group than in the placebo group on Day 60 (36.6% versus 25.0%, p=0.007). The reviewer had slightly different results. Nevertheless, the conclusion was not affected. Subjects in lixivaptan group had a nominally higher percentage in achieving normalized central serum sodium on Day 60 but did not appear to show much advantage on Day 7 (**Table 6** and **Table 8**).

Table 8 Percentage of Subjects with Normalized Serum Sodium on Day 7 and Day 60 (ITT OV)

	Lixivaptan	Placebo	Nominal p-value
Day 7 normalized (including subjects with normalized central baseline serum sodium)	164 (60.3%)	158 (53.9%)	
Day 7 not normalized	108 (39.7%)	135 (46.1%)	0.13
Normalized at Day 7 but not at baseline	79 (29%)	71 (24%)	
Not normalized at Day 7	193 (70.1%)	222 (75.8%)	0.196
Day 60 normalized (including subjects with normalized central baseline serum sodium)	178 (72.4%)	148 (56.9%)	
Day 60 not normalized	68 (27.6%)	112 (43.1%)	<0.001
Normalized at Day 60 not at baseline	88 (35.8%)	71 (27.3%)	
Not normalized at Day 60	158 (64.2%)	189 (72.7%)	0.04

The applicant used local serum sodium values as entry criteria (local baseline serum sodium < 135mmol/L) but used central serum sodium values in their primary and secondary endpoint analyses. Approximately 40% of subjects who were enrolled had a central serum sodium measurement >=135 mmol/L. Thus, had central values been used for inclusion criteria, a significant number of subjects would not have been eligible for enrollment. **Table 9** shows summary statistics on central and local baseline serum sodium by treatment group. Certain countries were found to have a greater discrepancy between the central and local serum sodium measurements (**Table 10**). 79 out of 116 subjects (68%) from Russia in this trial had central baseline serum sodium >= 135 mmol/L. The US showed better than average consistency between central and local serum sodium measurements. 25% subjects in the US had central baseline serum sodium measurements that were higher than or equal to 135 mmol/L.

Table 9 Summary Statistics on Central and Local Baseline Serum Sodium

	Central Serum Sodium		Local Serum Sodium	
	Lixivaptan (n=323)	Placebo (n=329)	Lixivaptan (n=323)	Placebo (n=329)
Mean	132.9	132.6	130.3	130.5
Median	133	133	131	132
minimum, maximum	113, 148	104,150	112,134.9	109,134.9
Number (%) ≥135 mmol/L	128	123	0	0
Number (%) ≥130 mmol/L <135 mmol/L	126	124	223	224
Number (%) < 130 mmol/L ≥ 120 mmol/L	62	68	92	99
Number (%) <120 mmol/L	7	14	8	6

Table 10 Percentage of Subjects with Central Serum Sodium Measurement>=135 by country

Country	Frequency	Total N	Percent (%)
Russia	79	116	68.1
Poland	49	104	47.1
Argentina	18	39	46.2
Chile	3	8	37.5
Romania	3	8	37.5
Czech Republic	9	28	32.1
Spain	4	13	30.8
Israel	10	34	29.4
India	31	111	27.9
Germany	5	18	27.8
Canada	7	26	26.9
United States of America	30	122	24.6
Italy	2	13	15.4
Slovakia	1	12	8.3
Total	251	652	40.0

The left panel in **Figure 1** is the plot of central serum sodium versus local serum sodium at baseline. The red circles represent lixivaptan subjects; the green circles represent placebo subjects. The right panel is a plot of central serum sodium values versus local serum sodium values obtained at the 8-hour post-dose visit (Day 1). The distribution of the circles appears to be similar between the two groups. The circles seem balanced along the diagonal line. There was considerable measurement variability between central and local serum sodium measurements but the direction of difference was both ways, i.e., central serum sodium can be higher than local serum sodium or vice versa. By comparing the baseline plot and Day 1 plot, we can see that quite some subjects had a much higher local serum sodium measurements at 8 hours post-dose. Some subjects could probably enter the study by some random low observations at baseline.

Figure 2 shows the simple mean of local and central serum sodium (OV) by visit and treatment group. It is interesting to see that the mean local serum sodium was consistently lower than the mean central serum sodium. The treatment difference between lixivaptan and placebo remained similar in local and central serum sodium measurements. This was also confirmed by the sensitivity analysis using local serum sodium. Therefore, although 40% subjects enrolled in the trial would be excluded if central serum sodium was used as entry criteria, the discrepancy between central and local serum sodium did not seem to affect the main conclusions of this study.

Figure 3 shows the funnel plots by individual country and site. A few sites with small sample sizes are outside of the funnel plot boundary. The overall conclusion of the study was not affected by excluding these sites.

Figure 1 Local Serum Sodium versus Central Serum Sodium in BALANCE (Study 3401, Baseline and Day 1)

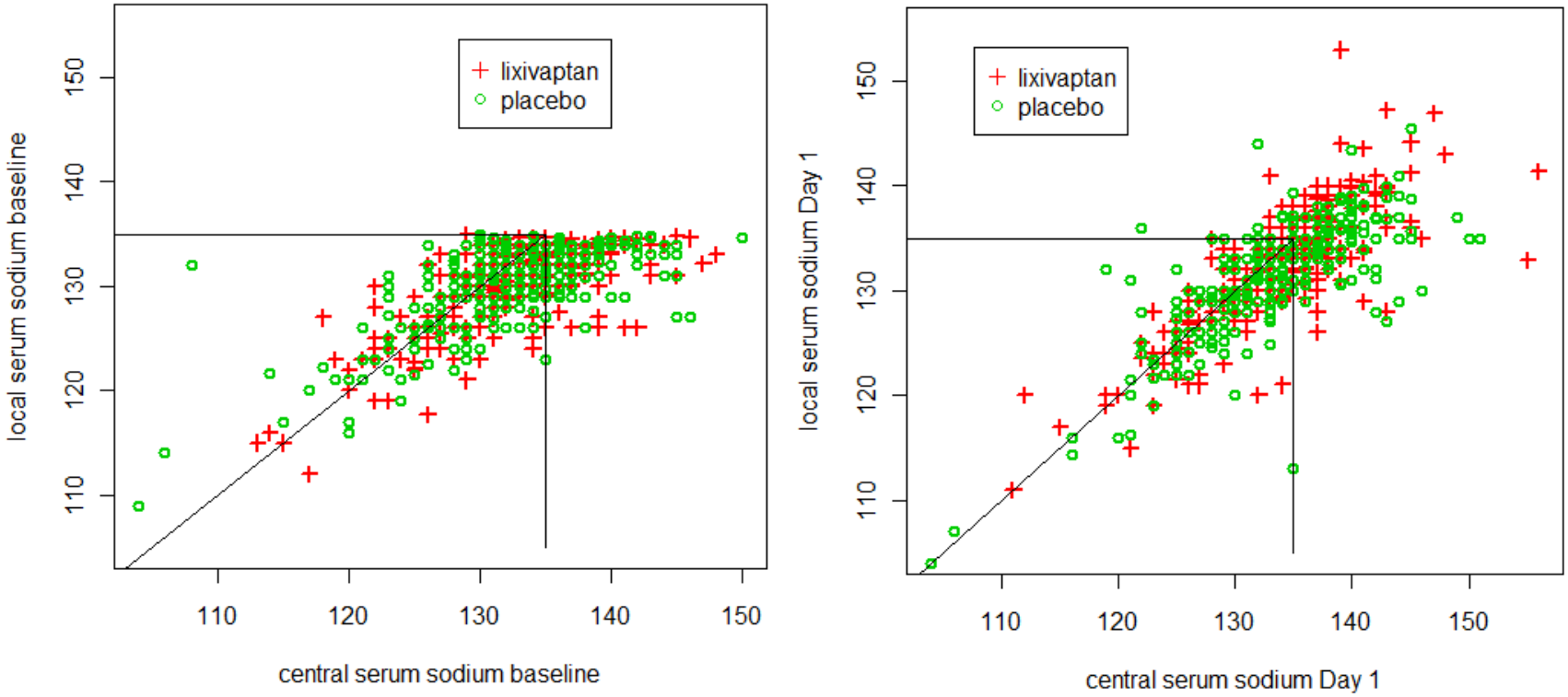


Figure 2 Central and Local Serum Sodium Measurements by Day

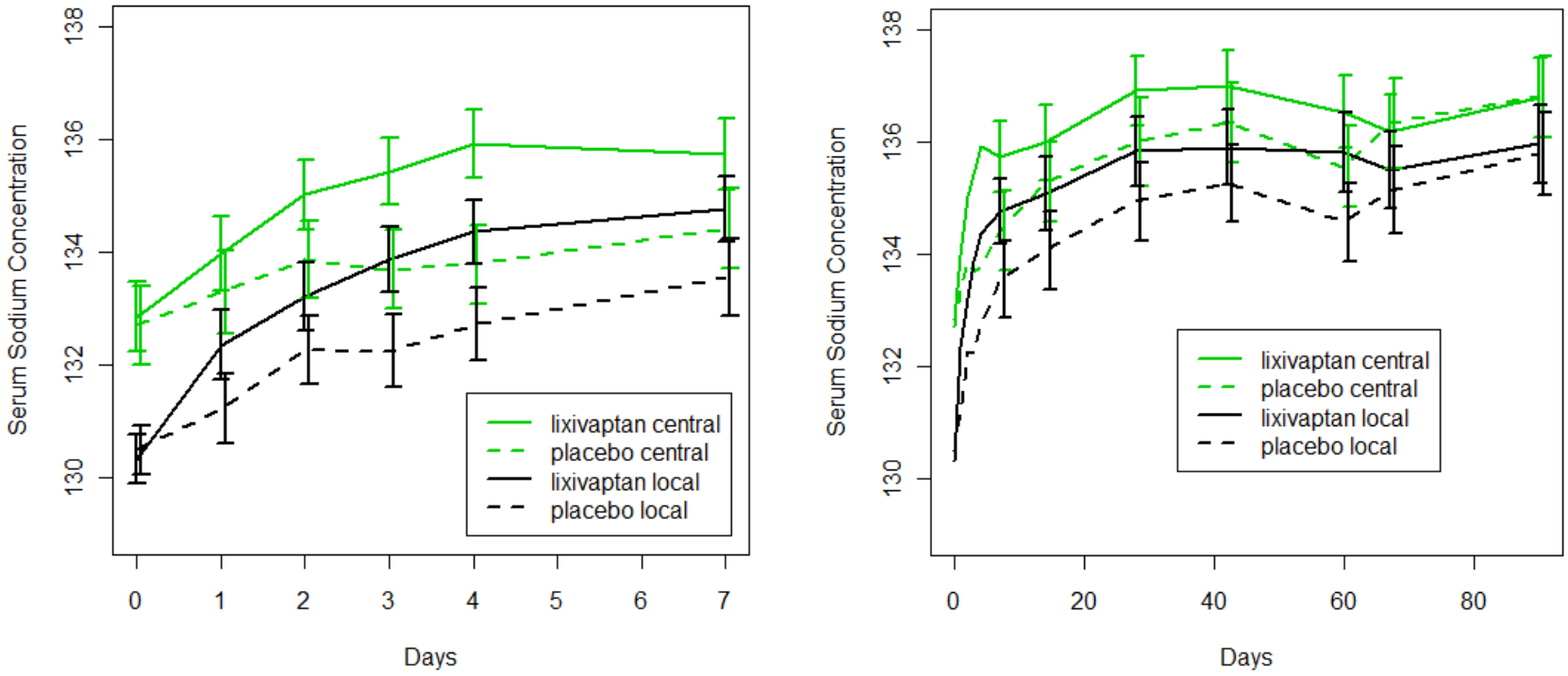


Figure 3 Funnel Plots by Country and Site (BALANCE)

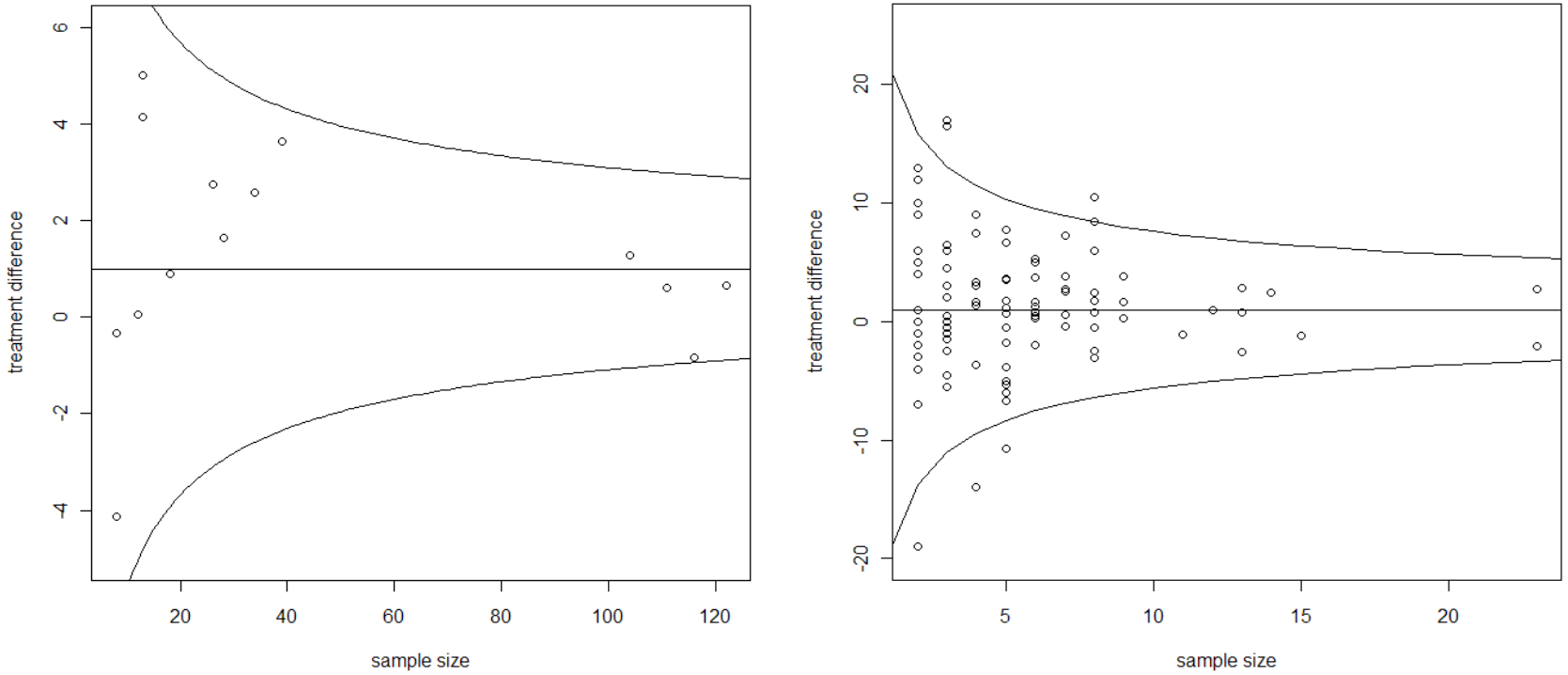


Table 11 shows the total number of observed values for each treatment group. 7 subjects in the lixivaptan group and 21 subjects in the placebo group had no pre-dose measurement for central serum sodium and the missing value had to be imputed by carrying the next available post-dose observation backward.

Table 11 Total Number of Observed Values and Deaths in Each Visit (BALANCE Study)

		pre-dose	Day 1 post-dose	Day2	Day3	Day4	Day7	Day14	Day28	Day42	Day60
Observed number of subjects	lixivaptan	316	299	301	297	291	272	264	238	218	246
	placebo	308	289	308	299	303	293	266	257	236	260
	Total	624	588	609	596	594	565	530	495	454	506
Total number of death up to the date	lixivaptan		5	7	9	10	16	20	31	37	43
	placebo		0	0	1	2	4	9	18	27	38
	Total		5	7	10	12	20	29	49	64	81

There was a considerable amount of missing data in all three studies. Over 20% of subjects (excluding deaths) discontinued treatment early. Some subjects were followed through to the end of the study but some were not. **Table 12** showed the number and percentage of subjects who no longer had serum sodium observations after Day 7 and Day 60.

Table 12 Summary on Missing Data for All Three Trials

		lixivaptan			placebo		
		N	dropout	death	N	dropout	death
BALANCE	Day 7	323	13 (4%)	16 (5%)	329	14 (4%)	4 (1%)
	Day 60	323	25 (8%)	43 (13%)	329	29 (9%)	38 (12%)
LIBRA	Day 7	54	7 (13%)	0	52	2 (4%)	1 (2%)
	Day 30	54	9 (17%)	0	52	6 (12%)	2 (4%)
HARMONY	Day 7	154	4 (3%)	0	52	2 (4%)	0
	Day 60	154	9 (6%)	6 (4%)	52	4 (8%)	0

The impact of missing data was evaluated through various sensitivity analyses for primary and secondary endpoints (**Table 13**). The results of sensitivity analyses were consistent with the primary and secondary analyses. The missing observations did not seem to have significant impact on the conclusion of the study.

Table 13 Sensitivity Analyses on Primary and Secondary Endpoints

Endpoints	Sensitivity analysis	Sodium measurement	Lixivaptan	Placebo	p-value
Serum sodium at Day 7	LOCF	Local	4.2 (0.3)[1]	2.8 (0.3)[1]	<0.001
	OV	Central	2.8 (0.3)[1]	1.5 (0.3)[1]	<0.001
	OV	Local	4.4 (0.3)[1]	3.0 (0.3)[1]	<0.001
	MMRM	Central	2.6 (0.25)[1]	1.4 (0.24)[1]	<0.001
Normalized Daily $nAUC_{0-60}$	OV	Central	2.6 (0.25)[2]	1.9 (0.25)[2]	0.017
Worsening of hyponatremia	OV	Central	162/242 (66.9%)[3]	185/249 (74.3%)[3]	0.055[2]
Normalized serum sodium at Day 7	OV	Central	79/272 (29%)[4]	71/293 (24%)[4]	0.196[3]

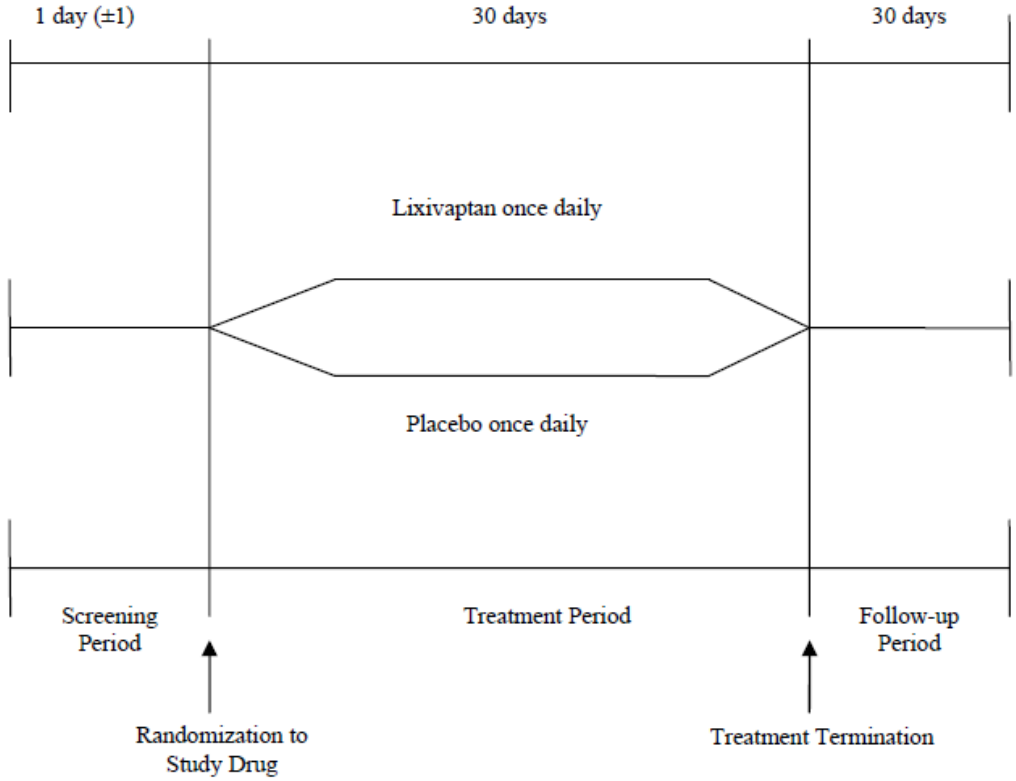
1 LS means from ANCOVA models
2 LS means from ANCOVA model with standard error
3 Total number of subjects with worsening of hyponatremia at Day 7 over total number of subjects included in the analysis, p-value was computed by CMH test controlling for pooled country
4 Total number of subjects with normalized serum sodium at Day 7 over total number of subjects included in the analysis, p-value was computed by CMH test controlling for pooled country

3.2.2 Study 3405 (LIBRA)

3.2.2.1 Study Design and Endpoints

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel study of oral lixivaptan in the management of hyponatremia in subjects with euvolemic hyponatremia. The study consisted of three periods: a screening period, a treatment period (titration phase + treatment phase), and a follow-up period (**Figure 4**). The total study duration for a subject participating in all three periods was a maximum of approximately 60 days. All randomized subjects entered the follow-up period.

Figure 4 LIBRA Study Design (Study 3405)



[Source: Applicant's CK-LX3405 Clinical Study Report Figure 1]

Subjects were randomized in a 1:1 ratio to 50 mg lixivaptan or matching placebo, once daily. During the titration phase, subjects received blinded medication in an inpatient setting for the first 48 to 72 hours. If subjects were eligible for discharge prior to completion of the titration phase, titration was discontinued and subjects remained on the dose at the time of discharge. After completing the titration phase, subjects were managed as outpatients. Study drug could have been titrated up to a maximum of 100 mg or down to 25 mg, once daily, based on the subject's change in serum sodium. The dose titration scheme was designed to achieve a slow correction of serum sodium over the initial few days of therapy.

The primary efficacy variable was the change from Baseline to Day 7 in serum sodium as reported by the central laboratory. The last central serum sodium result within 24 hours prior to first dose served as the baseline for central laboratory measurements. The intention-to-treat (ITT) population consisted of all randomized subjects and was the primary analysis population for efficacy.

The secondary efficacy endpoints included

1. The time-normalized AUC of change from Baseline to Day 30 ($nAUC_{0-30}$)

2. The percentage of subjects with normalized serum sodium (≥135 mmol/L and ≤145 mmol/L) at Day 7

3. The percentage of subjects whose fluid restriction was initiated or tightened

4. The percentage of subjects with worsening hyponatremia (a reduction of ≥3 mmol/L in serum sodium concentration from the preceding measurement with a value <135 mmol/L)

5. The change from Baseline in the recorded time to complete the TMT-B at Day 30

3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 106 subjects from 37 sites were randomized and included in the ITT population: 54 subjects to lixivaptan and 52 subjects to placebo. The main reasons for not completingthe 4 week treatment period (28 days) included adverse event and withdrawal consent.

Table 14 Subject Disposition (LIBRA Study 3405)

	Lixivaptan	Placebo	Total
Subject randomized	54	52	106
Subjects treated	50	51	101
Subjects not treated	4	1	5
Subjects completing treatment period	41	37	78
Subjects not completing treatment period	9	14	23
Adverse event	2	4	6
Death	0	2	2
Investigator withdrew subject from study	1	0	1
Lost to follow up	1	2	3
Other	2	1	3
Subject withdrew consent	3	5	8

[Source: Applicant's Clinical Study Report CK-LK3405 Table 11, verified by the reviewer]

The majority of randomized subjects were white (83.0%). 53% subjects were male (52.8%). Mean age was 65.8 years and 55% subjects were 65 years or older. Mean pre-treatment local serum sodium was 124.4 mmol/L. The placebo group had more male subjects (58%) than female subjects (42%).

Table 15 Demographics and Baseline Characteristics (LIBRA Study 3405)

Characteristic	**Lixivaptan (N=54)**	**Placebo (N=52)**	**Total (N=106)**
Age (years)	66.4 (14.1)	65.2 (13.3)	65.8 (13.7)
Mean (SD)	22 (40.7)	26 (50.0)	48 (45.3)
Number (%) <65	32 (59.3)	26 (50.0)	58 (54.7)
Number (%) ≥65			
Sex, n (%)	26 (48.1)	30 (57.7)	56 (52.8)
Male	28 (51.9)	22 (42.3)	50 (47.2)
Female			
Race, n (%)	8 (14.8)	6 (11.5)	14 (13.2)
Asian	2 (3.7)	2 (3.8)	4 (3.8)
Black or African American	44 (81.5)	44 (84.6)	88 (83.0)
White			
Region, n (%)	7 (13.0)	6 (11.5)	13 (12.3)
Asia (India)	9 (16.7)	9 (17.3)	18 (17.0)
Eastern Europe (Poland)	19 (35.2)	19 (36.5)	38 (35.8)
North America[a]	19 (35.2)	18 (34.6)	37 (34.9)
Western Europe[b]			
Weight (kg)	n=51	n=48	n=99
Mean (SD)	71.09 (15.25)	69.93 (15.74)	70.53 (15.42)

[Source: Applicant's CK-LX3405 Clinical Study Report Table 13, verified by the reviewer]

3.2.2.3 Statistical Methodologies

The primary efficacy variable was the change from Baseline to Day 7 in central serum sodium. The primary analysis was based on the ITT population using the ANCOVA model with treatment and pooled country as factors and central baseline serum sodium value as the covariate. Missing data were imputed using LOCF/NOCB.

The secondary efficacy analyses were performed as a fixed-sequence of hierarchical tests comparing the two treatment groups. Time-normalized AUC and TMT-B were analyzed by ANCOVA models. The CMH test controlling for pooled country was used to compare the percentage of subjects with normalized serum sodium, the percentage of subjects whose fluid restriction was initiated or tightened, and the percentage of subjects with worsening

hyponatremia between two treatment groups. All secondary endpoints were analyzed with the ITT population using LOCF/NOCB imputation.

The applicant also performed a number of sensitivity analyses using the MITT and PP populations, different data imputation methods (MMRM, OV), and different serum sodium measurements (central versus local).

3.2.2.4 Results and Conclusions

The treatment effect on mean increase in central serum sodium from baseline to Day 7 was statistically significant in the lixivaptan group compared to the placebo group (6.7 mmol/L in lixivaptan versus 4.5 mmol/L in placebo, p=0.039).

Table 16 Mean Change in Central Serum Sodium Concentration from Baseline to Day 7

Parameter	**Statistic**	**Lixivaptan (N=54)**	**Placebo (N=52)**
	Number of subjects in analysis	54	52
Baseline, mmol/L	Mean (SD)	127.6 (5.7)	126.1 (5.9)
Change from Baseline, mmol/L	Mean (SD)	6.1 (6.5)	4.8 (6.1)
	Median	5.0	3.5
ANCOVA*	LS mean (SE)	6.7 (0.7)	4.5 (0.8)
	p-value	0.039	

* ANCOVA model use central serum sodium as covariate and include pooled country and treatment group as factors

The secondary efficacy endpoints were tested for treatment group differences in the hierarchical sequence summarized in **Table 17**. More details on individual secondary endpoint were also shown in **Table 18** (AUC), **Table 19** (fluid restriction) and **Table 20** (TMT-B).

Table 17 Summary of Secondary Efficacy Endpoints (LIBRA Study 3405)

Secondary Efficacy Endpoint	**Lixivaptan**	**Placebo**	Nominal **p-value**
nAUC0-30 for central serum sodium concentration	6.8 (0.7)[1]	4.8 (0.7)[1]	0.03
Percentage of subjects who achieved normalized serum sodium (≥135 to ≤145 mmol/L) at Day 7	24/54 (44%)[2]	12/52(23%)[2]	0.021
Percentage of subjects whose fluid restriction was initiated or tightened at Day 30	17/54 (32%)[3]	12/52 (23%)[3]	0.064
Percentage of subjects with worsening of hyponatremia at any time during the treatment period	25/54 (46.3%)[4]	30/52 (57.7%)[4]	0.25
Change from Baseline to Day 30 for the recorded time to complete the TMT-B	-16.1 (8.2)[5]	-7.8 (8.5)[5]	0.48

1. LS mean change on normalized average daily AUC for central serum sodium with standard error (ITT LOCF)
2. Total number of subjects achieving normalized serum sodium at Day 7 versus total number of subjects (ITT LOCF)
3. Number of subjects who initiated or increased fluid restriction at Day 30 (ITT LOCF)
4. Total number of subjects with worsening of hyponatremia versus total number of subjects (ITT LOCF)
5. Mean change from baseline on time to complete TMT-B Trail Test with standard deviation (OV)

The mean $nAUC_{0\text{-}30}$ was statistically significantly greater in the lixivaptan group than in the placebo group in the ITT population using LOCF/NOCB (**Table 18**).

Table 18 Normalized Average Daily AUC for Central Serum Sodium for Days 0 to 30 (ITT LOCF)

Parameter	**Statistic**	**Lixivaptan (N=54)**	**Placebo (N=52)**
$nAUC_{0\text{-}30}$, mmol/L	Number of subjects in analysis	54	52
	Mean (SD)	5.88 (5.84)	4.94 (5.98)
	Median	5.71	3.75
ANCOVA*	LS mean (SE)	6.82 (0.68)	4.77 (0.69)
	p-value	0.03	

* ANCOVA model included treatment and pooled country as factors and baseline central sodium as covariate

24 subjects in lixivaptan and 12 subjects in placebo achieved normalized central serum sodium (≥135 and ≤145 mmol/L) at Day 7. The percentage of subjects with normalized central serum sodium on Day 7 was statistically significantly higher in the lixivaptan group than in the placebo group (44.4% versus 23.1%, p=0.021) in the ITT population using LOCF/NOCB.

17 subjects in the lixivaptan group and 12 subjects in the placebo group initiated or increased fluid restriction by Day 30. The p-value of the CMH test controlling for pooled country is 0.064 (**Table 19**). This may raise concern that efficacy findings may reflect in part increased use of fluid restriction. No further secondary endpoints should be considered statistically significant after this endpoint due to the sequential testing procedure.

Table 19 Change From Baseline to Day 30 in Fluid Restriction Requirements (ITT LOCF)

Evaluation	Change[a] in Fluid Restriction	n/N (%) of Subjects		p-value[b]
		Lixivaptan (N=54)	Placebo (N=52)	
Day 30	Initiated or increased	17/54 (31.5)	12/52 (23.1)	
	Liberalized or eliminated	1/54 (1.9)	7/52 (13.5)	
	No change	36/54 (66.7)	33/52 (63.5)	0.064

* p-value was calculated by CMH test for association between treatment group controlling for pooled country
[Source: Applicant's Clinical Study Report CK-LX3405 Table 24, verified by the reviewer]

Worsening hyponatremia was defined as a reduction of ≥3 mmol/L in serum sodium concentration from the preceding measurement with a value <135 mmol/L. Based on the reviewer's analysis, 25 out of 54 lixivaptan subjects and 30 out of 52 placebo subjects had worsening hyponatremia at any time point during the double-blind treatment period (from Day 1 to Day 30). The nominal p-value is 0.25 based on CMH test controlling for pooled country. Like the BALANCE Study, this endpoint seemed to capture quite a few transient decreases in central serum sodium. Many subjects had a considerable increase (>= 3 mmol/L) in serum sodium measurement at subsequent visits immediately following the visit with "worsening hyponatremia".

No difference was found between lixivaptan and placebo groups for mean change in time to complete the TMT-B from Baseline to Day 30 (**Table 20**).

Table 20 Mean Change in Time to Complete the TMT-B from Baseline to Day 30

Parameter	**Statistic**	**Lixivaptan (N=54)**	**Placebo (N=52)**
	Number of subjects in analysis	40	38
Baseline, seconds	Mean (SD)	252.8 (63.5)	226.0 (76.3)
Change from Baseline, seconds	Mean (SD)	-17.6 (42.6)	-6.9 (55.6)
	Median	0.0	0.0
ANCOVA*	LS mean (SE)	-16.1 (8.2)	-7.8 (8.5)
	p-value	0.48	

* ANCOVA model included treatment and pooled country as factors and baseline score as covariate.

Like the BALANCE Study, LIBRA enrolled subjects who would not have meet entry criteria if central serum sodium values had been used. The left panel in Figure 5 is a plot of central serum sodium versus local serum sodium at baseline. The red circles represent lixivaptan subjects and green circles represent placebo subjects. The right panel is the plot of central serum sodium versus local serum sodium at 8-hour post-dose visit (Day 1). As in BALANCE, the variability between central and local serum sodium measurements was visible but the difference between central and local serum sodium did not appear to affect the conclusions of this study.

Figure 5 Local Serum Sodium versus Central Serum Sodium in LIBRA (Study 3405, Baseline and Day 1)

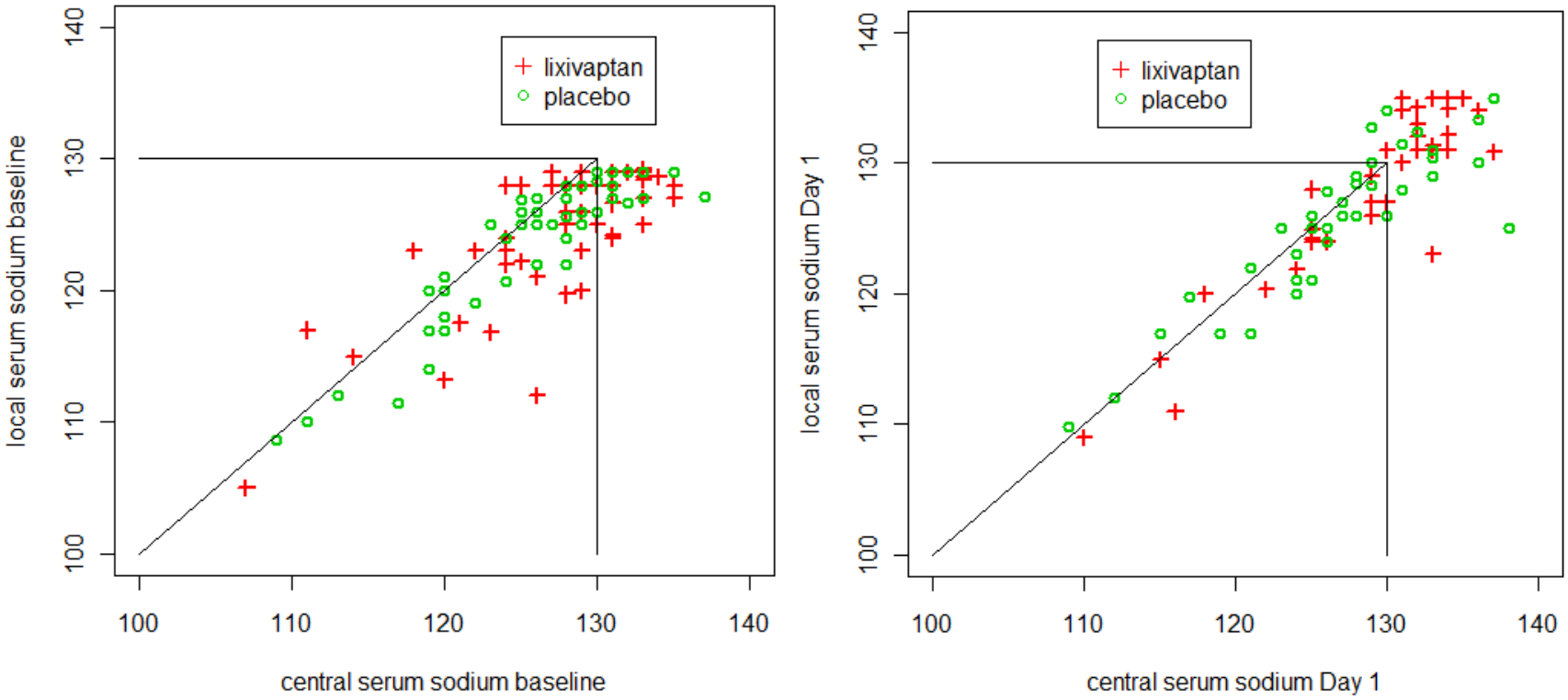


Table 21 shows summary statistics for central and local baseline serum sodium by treatment group in each country.

Table 21 Percentage of Subjects with Central Serum Sodium measurement>=130 by country

Country	Total N	Frequency	Percent (%)
Canada	2	1	50.0
Germany	36	17	47.2
Poland	18	8	44.4
United States of America	36	9	25.0
India	13	2	15.4
Belgium	1	0	0
Total	106	37	34.9

Figure 6 shows the funnel plot for individual sites in LIBRA and no site is outside of the funnel plot boundary. The site with the largest sample (N=20) was selected for inspection.

Figure 6 Funnel plot by site (LIBRA Study 3405)

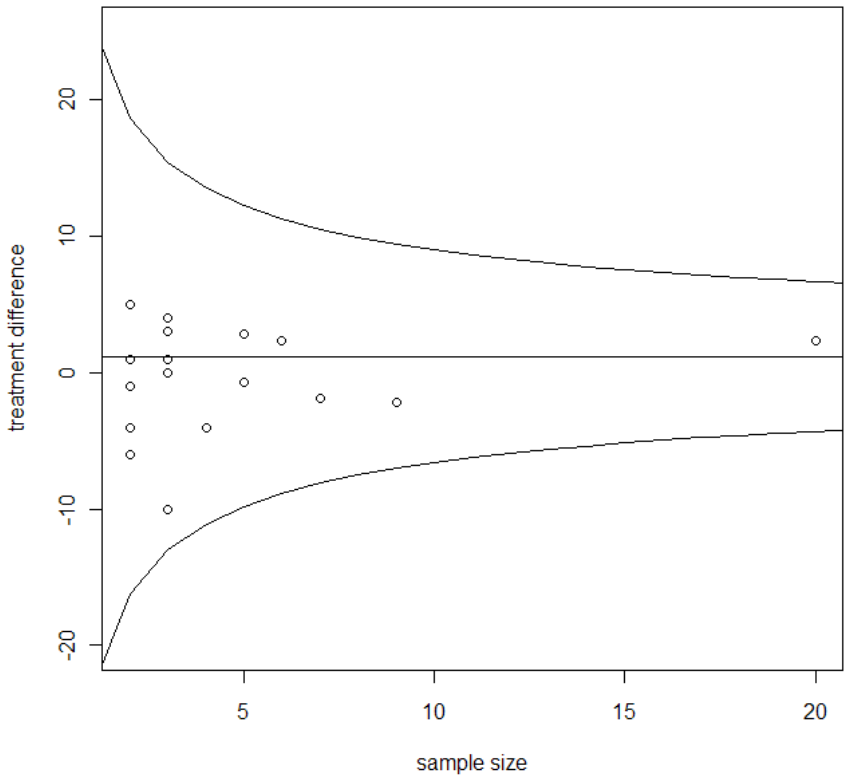


Table 22 shows the total number of observed values for each treatment group. The impact of missing data on the primary and secondary endpoint findings was evaluated through various sensitivity analyses (**Table 23**). Other than fluid restriction at Day 30, in which the observed

value analysis had a much larger p-value compared with the analysis using LOCF, the sensitivity analyses on other endpoints had similar conclusions. The missing observations did not seem to have significant impact on the conclusion of the study.

Table 22 Observed Subjects in Each Visit (LIBRA Study 3405)

	screening or pre-dose	Day 1 post-dose	Day2	Day3	Day4	Day7	Day14	Day28
lixivaptan	50	39	46	47	45	47	42	42
placebo	49	40	47	45	45	45	42	37
Total	99	79	93	92	90	92	84	79

Table 23 Sensitivity Analysis on Primary and Secondary Endpoints (LIBRA)

Endpoints	Sensitivity analysis	Sodium measurement	Lixivaptan	Placebo	p-value
Serum sodium at Day 7	LOCF	Local	8.3 (0.7)[1]	5.4 (0.7)[1]	0.004
	OV	Central	7.9 (0.7)[1]	4.6 (0.7)[1]	0.001
	OV	Local	9.5 (0.7)[1]	5.6 (0.7)[1]	<0.001
	MMRM	Central	7.7 (0.6)[1]	4.9 (0.7)[1]	0.002
Normalized daily $nAUC_{0-30}$	OV	Central	7.4 (0.6) [2]	4.5 (0.6) [2]	0.001
Normalized serum sodium at Day 7	OV	Central	24/47 (51%)[3]	11/45 (24%)[3]	0.009
Fluid restriction at Day 30	OV	Central	12/42 (29%)[4]	9/40 (23%)[4]	0.56
Worsening of hyponatremia	OV	Central	29/37 (78%)[5]	25/40 (63%)[5]	0.13

1 LS means from ANCOVA models

2 LS means from ANCOVA model with standard error

2 Total number of subjects with normalized serum sodium at Day 7 over total number of subjects included in the analysis, p-value was computed by CMH test controlling for pooled country

3 Total number of subjects who initiated or increased fluid restriction over total number of subjects included in the analysis, p-value was computed by CMH test

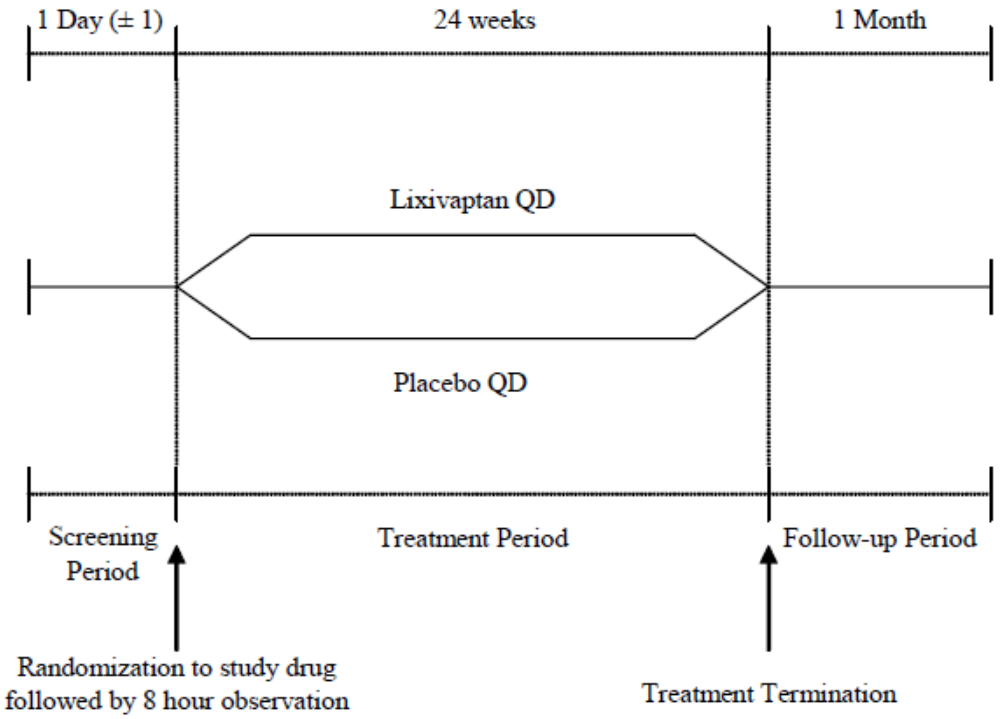
4 Total number of subjects with worsening of hyponatremia over total number of subjects included in the analysis, p-value was computed by CMH test controlling for pooled country

3.2.3 Study 3430 (HARMONY)

3.2.3.1 Study Design and Endpoints

This was a Phase 3, randomized, double-blind, placebo-controlled, parallel study of oral lixivaptan in the management of hyponatremia in subjects with euvolemic hyponatremia. Subjects were admitted to the study on an outpatient basis. The study consisted of a screening period, a treatment period, and a follow-up period (**Figure 7**). The total study duration for a subject participating in all three periods was a maximum of seven months.

Figure 7 Study Design (HARMONY Study 3405)



Subjects were randomized in a 3:1 ratio on an outpatient basis to 25 mg lixivaptan or matching placebo, once daily. The medical setting during the dose titration phase 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 mmol/L at eight hours.

After initiating therapy at 25 mg on Day 1, study drug could be titrated up to 50 mg or 100 mg, once daily on Days 2 and 3, respectively. Down titration was allowed at any time during the treatment period. The treatment period was expected to be six months in duration.

According to the applicant, investigators were instructed to stop blinded therapy in all subjects after the last subject enrolled in the study had completed eight weeks of treatment. All subjects entered the protocol-specified, 30-day safety follow-up period whether they completed the trial or discontinued early for any reason.

The primary efficacy variable was the change from Baseline to Day 7 in central serum sodium. The baseline value is defined as the last observation prior to the first dose of study medication administration. Secondary efficacy endpoints included

1. The time-normalized AUC of change from Baseline to Day 28

2. The percentage of subjects with normalized serum sodium (≥135 mmol/L and ≤145 mmol/L) at Day 7

3. The percentage of subjects whose fluid restriction was initiated or tightened

4. The percentage of subjects with worsening hyponatremia (a reduction of ≥3 mmol/L in serum sodium concentration from the preceding measurement with a value <135 mmol/L)

5. The change from Baseline in the recorded time to complete the TMT-B at Day 28

3.2.3.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 206 subjects from 61 sites were randomized and included in the ITT population: 154 subjects to lixivaptan and 52 subjects to placebo.

Table 24 Patient Disposition in HARMONY

Characteristic	Lixivaptan	Placebo	Total
Subjects randomized	154	52	206
Subjects treated	153 (99.4)	52 (100.0)	205 (99.5)
Subjects not treated	1 (0.6)	0	1 (0.5)
Subjects completing first 8 weeks of treatment	127 (82.5)	40 (76.9)	167 (81.1)
Subjects not completing first 8 weeks of treatment	24 (15.6)	11 (21.2)	33 (16.0)
Adverse event	7	6	13 (6.3)
Death	4	0	4 (1.9)
Investigator withdrew subject from study	2	0	2 (1.0)
Lack of efficacy	1	1	2 (1.0)
Study terminated by the applicant	0	1	1 (0.5)
Protocol violation	0	1	1 (0.5)
Subject withdrew consent	8	2	10 (4.9)
Other	2	0	1 (0.5)
Subjects completing 24-week treatment period	53 (34.4)	17 (32.7)	70 (34.0)
Subjects not completing 24-week treatment period	100 (64.9)	35 (67.3)	135 (65.5)

* 3 subjects had last dose date missing and were not counted in either completers or non-completers

The majority of randomized subjects were white (78.2%). 52% of subjects were female. Mean age was 65.6 years and 54% of subjects were 65 years or older.

Table 25 Demographic and Baseline Characteristics (HARMONY)

Characteristic	**Lixivaptan (N=154)**	**Placebo (N=52)**	**Total (N=206)**
Age (years)			
Mean (SD)	66.6 (14.1)	62.7 (13.6)	65.6 (14.0)
Number (%) <65	67 (43.5)	28 (53.8)	95 (46.1)
Number (%) ≥65	87 (56.5)	24 (46.2)	111 (53.9)
Sex, n (%)			
Male	73 (47.4)	27 (51.9)	100 (48.5)
Female	81 (52.6)	25 (48.1)	106 (51.5)
Race, n (%)			
American Indian or Alaska native	2 (1.3)	1 (1.9)	3 (1.5)
Asian	18 (11.7)	8 (15.4)	26 (12.6)
Black or African American	7 (4.5)	8 (15.4)	15 (7.3)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0	1 (0.5)
White	126 (81.8)	35 (67.3)	161 (78.2)
Region, n (%)			
Europe/Israel[a]	8 (5.2)	4 (7.7)	12 (5.8)
Asia (India)	17 (11.0)	7 (13.5)	24 (11.7)
South America[b]	7 (4.5)	4 (7.7)	11 (5.3)
North America (United States)	122 (79.2)	37 (71.2)	159 (77.2)
Weight (kg) Mean (SD)	73.2 (18.7)	73.8 (18.8)	73.3 (18.7)

[Source: Applicant's CK-LX3430 Clinical Study Report Table 13, verified by the reviewer]

3.2.3.3 Statistical Methodologies

The primary analysis was ANCOVA model on change from baseline in central serum sodium at Day 7 with treatment as factor and baseline central serum sodium as covariate.

The secondary efficacy endpoints were analyzed in a fixed-sequence hierarchical manner at significance level of 0.05. All secondary endpoints were supposed to be analyzed with ITT population using LOCF/NOCB imputation method. However, LOCF/NOCB was presented as a sensitivity analysis for some endpoints in the clinical study report.

Time-normalized AUC and TMT-B were analyzed by ANCOVA models. CMH test controlling for pooled country was used to compare the percentage of subjects with normalized serum sodium, the percentage of subjects whose fluid restriction was initiated or tightened, and the percentage of subjects with worsening hyponatremia between two treatment groups.

3.2.3.4 Results and Conclusions

The mean increase in central serum sodium from Baseline to Day 7 between lixivaptan group and placebo group was statistically significant (**Table 26**).

Table 26 Mean Change in Central Serum Sodium from Baseline to Day 7 (HARMONY)

Parameter	**Statistic**	**Lixivaptan (N=154)**	**Placebo (N=52)**
	Number of subjects in analysis	154	52
Baseline, mmol/L	Mean (SD)	131.5 (4.9)	131.6 (5.2)
Change from Baseline, mmol/L	Mean (SD)	3.0 (4.1)	0.6 (3.4)
	Median	3.0	1.0
ANCOVA	LS mean (SE)	3.2 (0.5)	0.8 (0.6)
	p-value	<0.001	

[Source: Applicant's Clinical Study Report CK-LX3430 Table 17, verified by the reviewer]

The secondary efficacy endpoints were tested for treatment group differences in the hierarchical sequence shown in **Table 27**. More details on individual secondary endpoint were also shown in **Table 28** and **Table 29**.

Table 27 Summary of Secondary Efficacy Endpoints (HARMONY Study 3430)

Secondary Efficacy Endpoint (HARMONY)	lixivaptan	placebo	Nominal p-value
nAUC0-28 for central serum sodium concentration	3.3 (0.4)[1]	1.8 (0.5)[1]	0.004
Percentage of subjects who achieved normalized serum sodium (≥135 to ≤145 mmol/L) at Day 7	60/154 (39%)[2]	6/52 (12%)[2]	<0.001
Percentage of subjects whose fluid restriction was initiated or tightened at the end of treatment versus Baseline	17/153 (11%)[3]	11/52 (21%)[3]	0.2
Percentage of subjects with worsening of hyponatremia during the double-blind on-therapy period	86/154 (56%)[4]	35/52 (67%)[4]	0.11
Change from Baseline to Day 28 for the recorded time to complete the TMT-B	-11.4 (7.8)[5]	-11.5 (6.4)[5]	0.99

1. LS mean change on normalized average daily AUC for central serum sodium with standard error (ITT LOCF)
2. Total number of subjects achieving normalized serum sodium at Day 7 versus total number of subjects (ITT LOCF)
3. Number of subjects who initiated or increased fluid restriction at the end of treatment (ITT LOCF)
4. Total number of subjects with worsening of hyponatremia versus total number of subjects (ITT LOCF)
5. Mean change from baseline on time to complete TMT-B Trail Test with standard deviation

The mean $nAUC_{0-28}$ was statistically significantly greater in the lixivaptan group than in the placebo group (**Table 28**) in the ITT population using LOCF/NOCB.

Table 28 Normalized Average Daily AUC for Central Serum Sodium for Days 0 to 28 (ITT LOCF)

Parameter	**Statistic**	**Lixivaptan (N=154)**	**Placebo (N=52)**
$nAUC_{0-28}$, mmol/L	Number of subjects in analysis	154	52
	Mean (SD)	3.11 (3.6)	1.64 (3.3)
	Median	3.10	1.11
ANCOVA	LS mean (SE)	3.25 (0.4)	1.81 (0.5)
	LS mean difference (SE)	1.44 (0.5)	
	p-value	0.004	

[Source: Applicant's Clinical Study Report CK-LX3430 Table 20, verified by the reviewer]

The percentage of subjects with normalized central serum sodium (≥135 and ≤145mmol/L) on Day 7 was statistically higher in the lixivaptan group than in the placebo group. Lixivaptan had 60 out of 154 subjects (39.0%) who achieved normal serum sodium level based on central measurement on Day 7 while placebo only had 6 out of 52 subjects (11.5%). The p-value for the CMH test was less than 0.001.

No statistical significant treatment difference was observed in fluid restriction at the end of treatment (**Table 29**), percentage of subjects with worsening hyponatremia, or TMT-B test.

Table 29 Change From Baseline in Fluid Restriction Requirements (HARMONY)

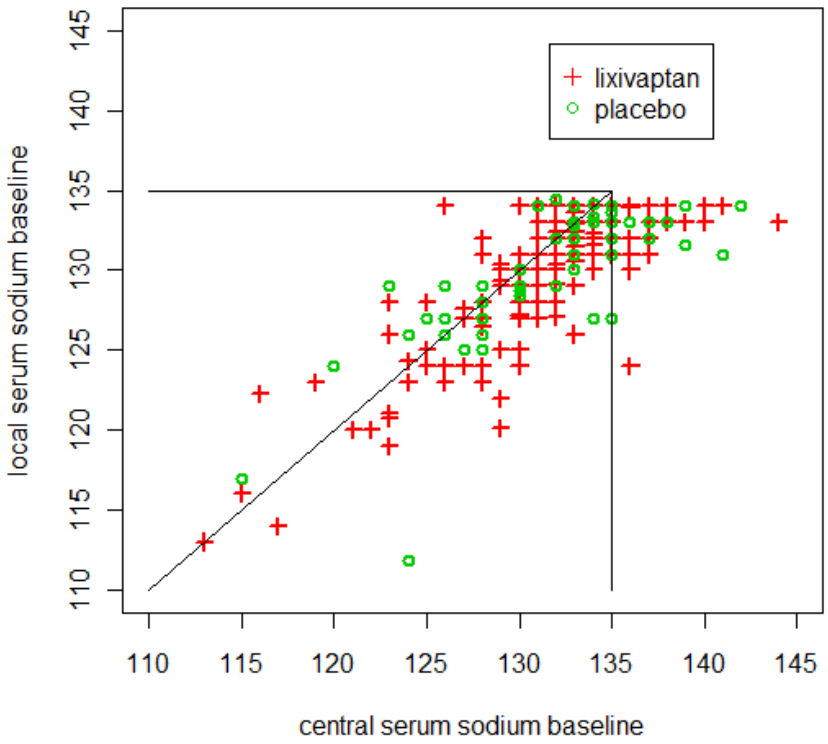
Evaluation	Change in Fluid Restriction	Lixivaptan	Placebo	Nominal p-value*
End of treatment (LOCF)	Initiated or increased	17/151 (11.0)	11/52 (21.2)	0.232
	Liberalized or eliminated	11/151 (7.1)	2/52 (3.8)	
	No change	123/151 (80.0)	39/52 (75.0)	
Week 24 (OV)	Initiated or increased	15/137 (10.9)	11/47 (23.4)	0.174
	Liberalized or eliminated	11/137 (8.0)	2/47 (4.3)	
	No change	111/137 (81.0)	34/47 (72.3)	

* p-value was calculated by CMH test for association between treatment group controlling for pooled country

The left panel in **Figure 8** is the plot of central serum sodium versus local serum sodium at baseline. The right panel is the plot of central serum sodium versus local serum sodium at 8-hour post-dose visit (Day 1). Distribution of the circles did not show any obvious direction. Like BALANCE and LIBRA, the difference between central and local serum sodium did not appear to affect the conclusions of this study.

Figure 9 shows the funnel plot by individual site. There were two sites outside of the funnel plot boundary. One site had enrolled two subjects and the other site had enrolled 10 subjects. The site with 10 subjects had a large treatment effect and was the third largest center in this trial so it was selected for inspection. Excluding these sites did not affect the overall conclusion of the study.

Figure 8 Local Serum Sodium versus Central Serum Sodium in HARMONY (Study 3430, Baseline and Day 1)



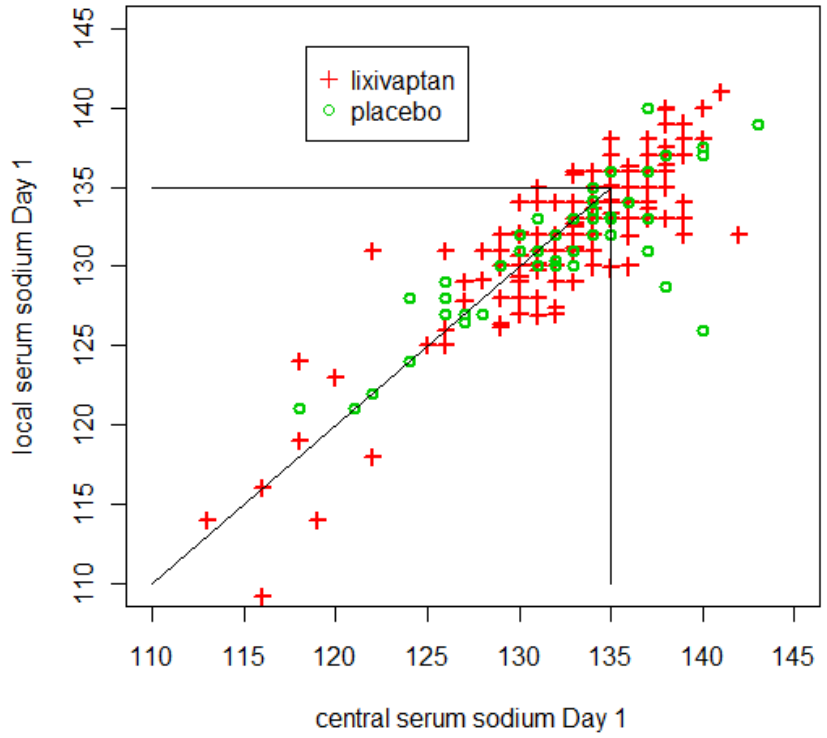


Figure 9 Funnel plot by site (HARMONY Study 3430)

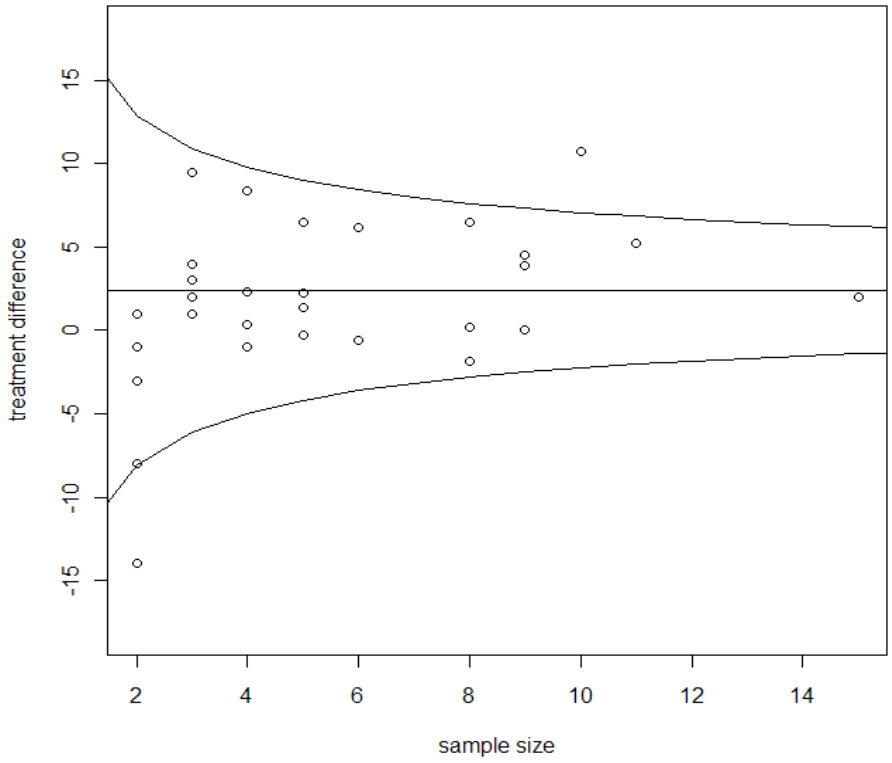


Table 30 shows summary statistics for central and local baseline serum sodium by treatment group. The percentage of subjects with a central serum sodium over 135 mmol/L at baseline in the US was consistent with BALANCE and LIBRA.

Table 30 Percentage of Subjects with Central Serum Sodium measurement>=135 by country

Country	Total N	Frequency	Percent (%)
United States of America	159	47	29.6
Peru	10	2	20.0
India	24	2	8.3
Belgium	3	0	0
Czech Republic	1	0	0
Israel	6	0	0
Italy	2	0	0
Mexico	1	0	0
Total	206	51	24.8

Table 31 shows the total number of observed values for each treatment group. The impact of missing data was evaluated through various sensitivity analyses for primary and secondary

endpoints (**Table 32**). The results remained consistent. The missing observations did not seem to have significant impact on the conclusion of the study.

Table 31 Observed Subjects in Each Visit (HARMONY Study 3430)

	pre-dose	Day 1 post-dose	Day2	Day3	Day4	Day7	Day14	Day21	Day28
lixivaptan	151	149	152	150	148	142	140	135	131
placebo	52	50	51	50	49	49	45	42	43
Total	203	199	203	200	197	191	185	177	174

Table 32 Sensitivity Analyses on Primary and Secondary Endpoints (HARMONY)

Endpoints	Sensitivity analysis	Sodium measurement	Lixivaptan	Placebo	p-value
Serum sodium at Day 7	LOCF	Local	3.9 (0.7)[1]	1.3 (0.5)[1]	<0.001
	OV	Central	3.3 (0.5)[1]	1.0 (0.6)[1]	<0.001
	OV	Local	4.0 (0.5)[1]	1.4 (0.7)[1]	<0.001
	MMRM	Central	3.4 (0.4)[1]	1.0 (0.5)[1]	<0.001
Normalized daily $nAUC_{0-28}$	OV	Central	3.3 (0.4)[1]	1.9 (0.5)[1]	0.003
Normalized serum sodium at Day 7	OV	Central	56/142 (39%)[2]	6/49 (12%)[2]	<0.001
Fluid restriction at Week 24	OV	Central	15/137 (10.9)[3]	11/47 (23.4)[3]	0.087
Worsening of hyponatremia	OV	Central	85/154 (55%)[4]	35/52 (67%)[4]	0.096

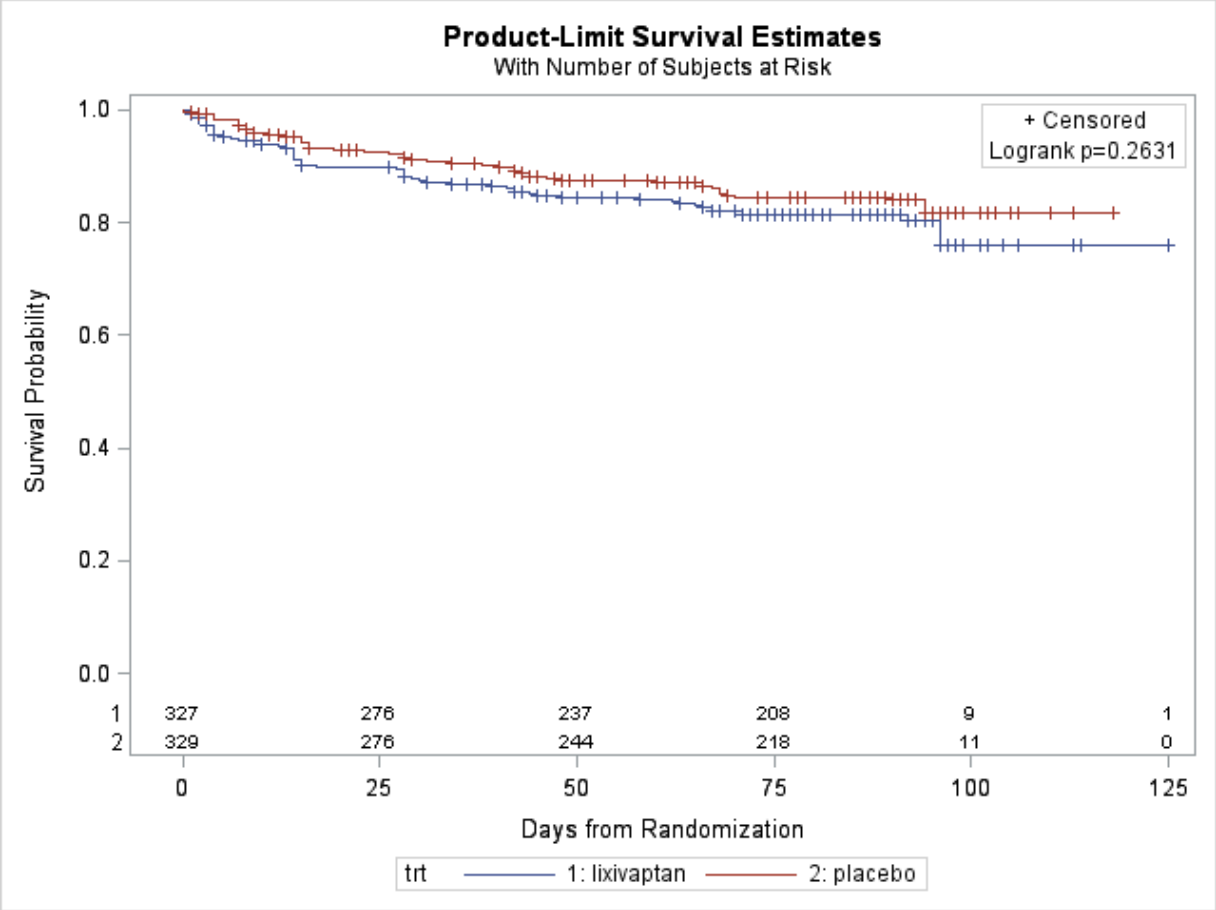
1 LS means from ANCOVA model with standard error
2 Total number of subjects with normalized serum sodium at Day 7 over total number of subjects included in the analysis, p-value was computed by CMH test controlling for pooled country
3 Total number of subjects who initiated or increased fluid restriction over total number of subjects included in the analysis, p-value was computed by CMH test
4 Total number of subjects with worsening of hyponatremia over total number of subjects included in the analysis, p-value was computed by CMH test controlling for pooled country

3.3 Evaluation of Safety

An important issue found in BALANCE is the imbalance of early death. 20 subjects died before or on Day 7 and 16 of them were from the lixivaptan group (ITT population). The number of deaths became more balanced as time went on. Table 11 summaries the number of deaths by

treatment group for each visit. By Day 60, 43 subjects in the lixivaptan group and 38 subjects in the placebo group in the ITT population died. The p-value from the log-rank test on time to all deaths was 0.26. If we only look at early deaths (deaths by Day 15), the log-rank test for time to all deaths up to Day 15 gives a nominal p-value of 0.036. This p-value needs to be interpreted with caution since the cut-off date was artificially chosen. Figure 10 shows the Kaplan-Meier curve for lixivaptan and placebo group.

Figure 10 Kaplan-Meier Curves on All Deaths by Treatment



The safety concern prompted the data safety monitoring committee to issue a letter on June 9, 2010 urging the applicant to terminate the trial. The letter stated that “the board voted unanimously that due to safety concerns that the study should be terminated as soon as possible” after the board reviewed data on “469 subjects with observations at 15 days and 463 subjects with observations at 30 days”. No specific factor was reported or found to be associated with imbalance of early death in BALANCE.

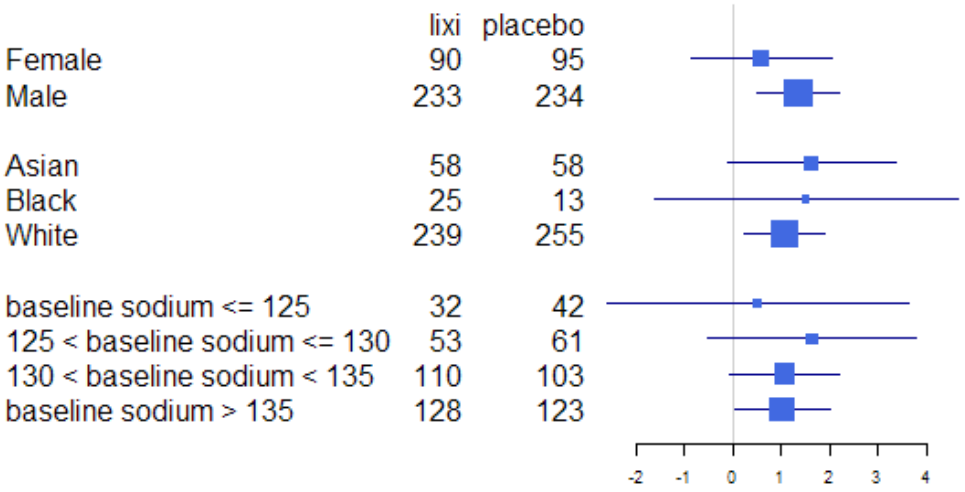
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Figure 11, **Figure 12** and **Figure 13** are forest plots showing the treatment difference between lixivaptan and placebo in various subgroups. The treatment effect appeared to be relatively constant across different subgroups. Mean change on central serum sodium on Day 7 from baseline was also summarized by baseline central serum sodium strata and shown in **Table 33**. HARMONY seemed to show a treatment effect on serum sodium that tended to decrease with increasing baseline serum sodium. However, caution needs to be taken in interpreting this find since the sample size for each baseline subgroup in HARMONY was small and this finding was not consistently seen in BALANCE Study and LIBRA Study.

Caucasians seemed to experience a greater increase in sodium level relative to Asian and Black in LIBRA and HARMONY. But the extremely small sample size in Asian and Black limits interpretation.

Figure 11 Forest Plot on Subgroups in Study 3401 (BALANCE)



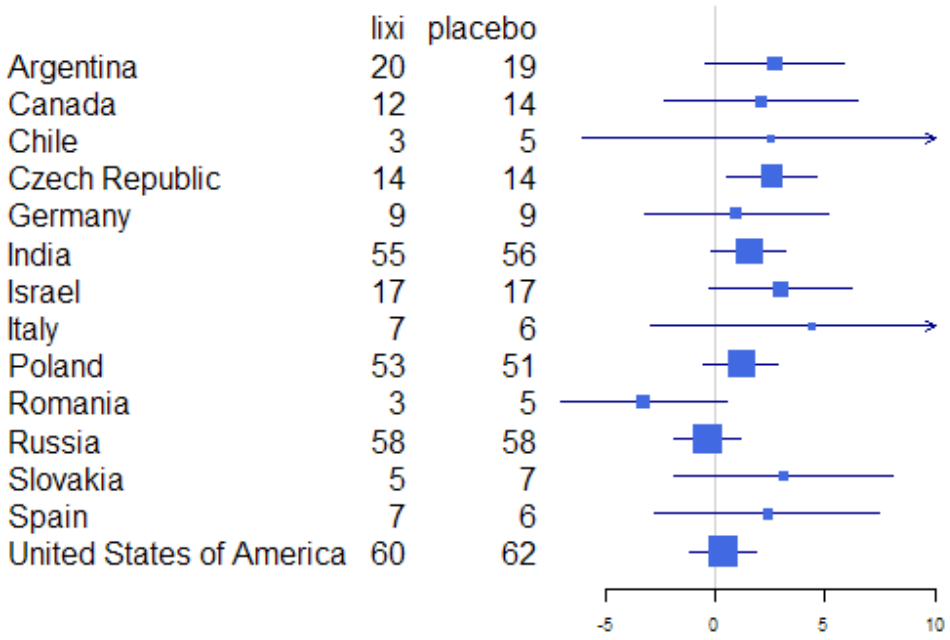


Figure 12 Forest Plot on Subgroups in Study 3405 (LIBRA)

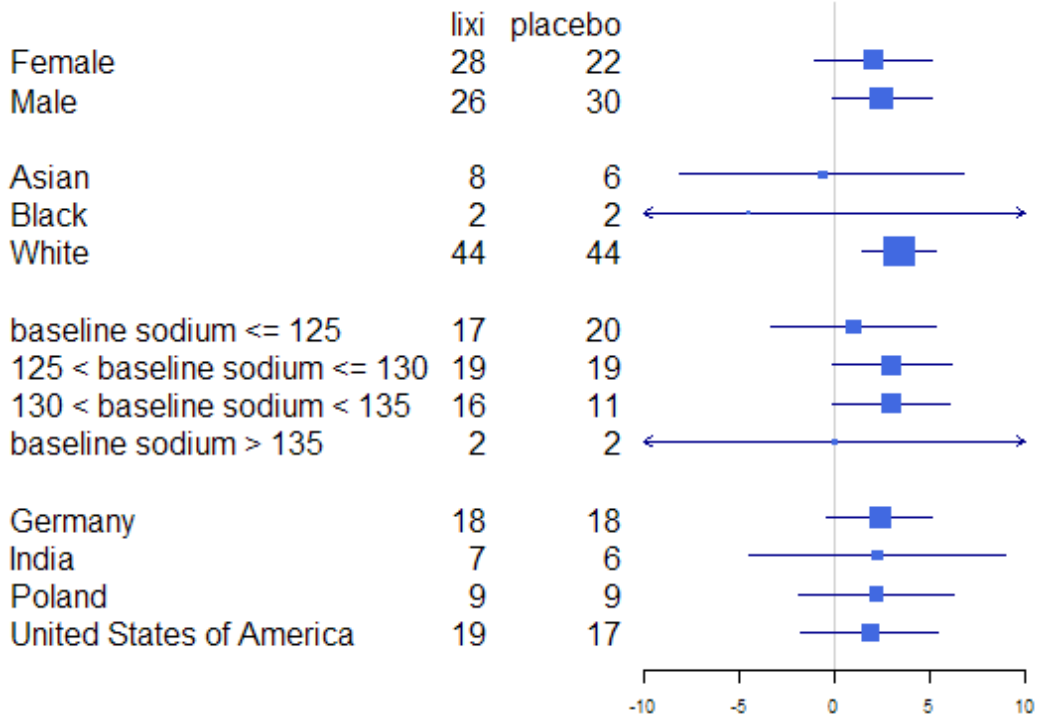


Figure 13 Forest Plot on Subgroups in Study 3430 (HARMONY)

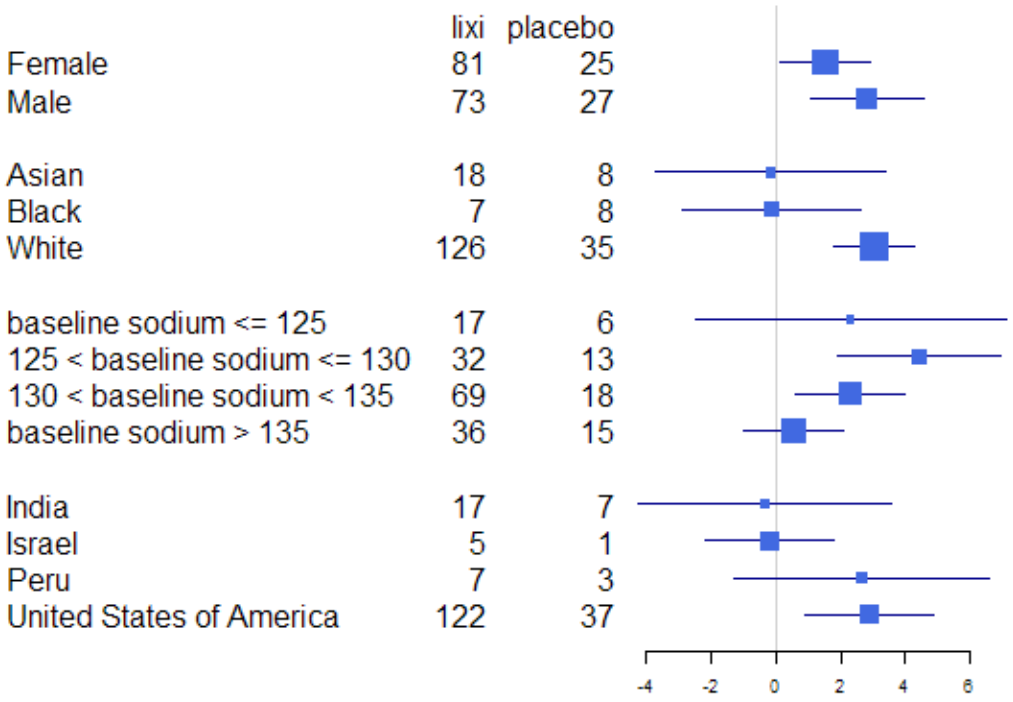


Table 33 Subgroup Analyses by Baseline Serum Sodium

Study	Baseline Serum Sodium	Lixivaptan		Placebo	
		N	Mean Chg (Std)	N	Mean Chg (Std)
BALANCE	<=125	32	6.4 (6.5)	42	5.5 (6.5)
	125-130	53	4.9 (5.3)	61	3.2 (6.7)
	130-135	110	3.2 (4.0)	103	2.0 (4.6)
	>=135	128	0.1 (4.3)	123	-1.0 (3.9)
LIBRA	<=125	17	8.4 (8.3)	20	8.9 (7.0)
	125-130	19	5.9 (6.2)	19	2.7 (3.9)
	130-135	16	4.1 (3.8)	11	1.7 (3.8)
HARMONY	<=125	17	5.6 (5.6)	6	3.5 (2.6)
	125-130	32	4.8 (3.5)	13	0.7 (4.6)
	130-135	69	3.2 (3.4)	18	0.8 (2.5)
	>=135	36	-0.1 (2.9)	15	-0.8 (3.1)

4.2 Other Special/Subgroup Populations

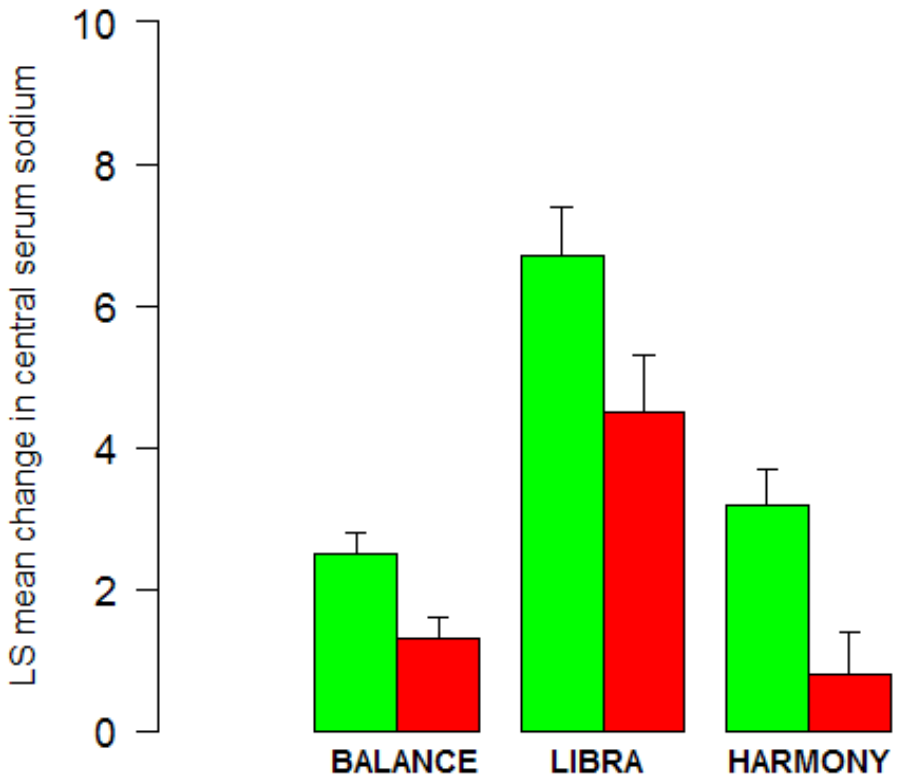
No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This NDA application included three phase III trials in two patient populations (HF and SIADH). **Figure 14** showed the LS mean change from baseline in central serum sodium for each treatment group in all three trials. The lixivaptan group was in green and placebo group in red. Overall, the treatment effects were 1.2 mmol/L, 2.2 mmol/L and 2.4 mmol/L in BALANCE, LIBRA and HARMONY, respectively. The treatment effect appeared to be small.

Figure 14 Treatment Effect in Three Phase III Trials



About 23%, 21% and 17% subjects (excluding death) did not complete the treatment in BALANCE, LIBRA and HARMONY. No further serum sodium measurements can be obtained in some of these subjects. The percentage of such subjects can be from 6% to 17%. With such a high percentage of missing data, a number of sensitivity analyses were performed on primary and secondary endpoints in all three trials. Most results remained consistent. Although the percentage of missing is relatively high, the impact of the missing data did not seem affect the study conclusions in this case.

The discrepancy between central and local serum sodium and the fact that the applicant used one for entry criteria and the other for analyses prompted sensitivity analyses using local serum sodium. The results remained mostly unchanged although 40% subjects in BALANCE, 35% subjects in LIBRA and 25% subjects in HARMONY would not be eligible to enter the study, had central serum sodium been used instead of local serum sodium.

There were a few inconsistencies between the clinical study reports and statistical analysis plans for the three trials. For example, although SAP stated that all secondary endpoints would be analyzed using LOCF, observed value analyses were reported in the overview of secondary endpoints. Also the ANCOVA model reported in the clinical study report did not include exact the factors proposed in the SAP. The dataset definition files had a few different variable names from the real datasets (for example, variable CMPSDY became variable CMPSTDY). Some variables in the definition file did not even exist. The reviewer followed SAP and the results of most analyses did not differ much even by different imputation method or an extra factor in ANCOVA model.

5.2 Conclusions and Recommendations

Although all three trials showed highly statistical significant results, the treatment effects on serum sodium appeared small (1.2 mmol/L in BALANCE, 2.2 mmol/L in LIBRA and 2.4 mmol/L in HARMONY). Furthermore, there was an imbalance on early death between lixivaptan and placebo in BALANCE. The safety concern prompted the data safety monitoring committee to issue a letter on June 9, 2010 urging applicant to terminate the trial as soon as possible. No specific factor was reported or found to be associated with imbalance of early death in BALANCE. The benefit gained from lixivaptan and the potential risk, especially in the heart failure population, need to be carefully weighed.

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/s/

JIALU ZHANG
08/10/2012

HSIEN MING J HUNG
08/10/2012

CLINICAL PHARMACOLOGY REVIEW

NDA:	**203009**	**N000**
IND:	**47850**	
Submission Dates:	**12-29-2012**	
Brand Name:	**NA**	
Generic Name:	**Lixivaptan, VPA-985**	
Dosage & Strength:	**Capsules of 25 and 50 mg strength**	
Indication:	**Treatment of euvolemic and hypervolemic hyponatremia**	
Applicant:	**Cardiokine, Biopharma, LLC**	
Submission:	**Original NDA**	
Division:	**DCRP, HFD-110**	
Primary Clinical Pharmacology Reviewer:	**Peter H. Hinderling, MD** **Ju-Ping Lai, PhD** **Martina Sahre, PhD**	
Pharmacometrics Reviewer:	**Fang Li, PhD**	
Clinical Pharmacology Team Leader:	**Raj Madabushi, PhD**	
Pharmacometrics Team Leader:	**Yaning Wang, PhD**	

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1. EXECUTIVE SUMMARY

Cardiokine submitted NDA 203009 for lixivaptan capsules (LIXAR®) seeking approval of the indication "treatment of symptomatic hypervolemic and euvolemic hyponatremia, associated with heart failure (CHF) and syndrome of inappropriate antidiuretic hormone (SIADH), respectively. Important limitations: patients requiring interventions to raise sodium concentration urgently to prevent or to treat serious neurological symptoms should not be treated with lixivaptan". Lixivaptan is an oral, non-peptide, competitive, selective antagonist of the antidiuretic hormone, adiuretin or vasopressin, at the V_2-receptor in the collecting ducts of the kidney. By displacing vasopressin from the V_2-receptor lixivaptan increases the free water clearance, CL_{H20}, with subsequent reduction of extracellular water and increase in serum sodium. Tolvaptan, another oral, non-peptide drug with the same mechanism of action, was approved in 2009 for the indication treatment of clinically significant hypervolemic and euvolemic hyponatremia [serum sodium <125 mEq/L or less marked hyponatremic that is symptomatic and has resisted correction with fluid restriction], including patients with CHF, cirrhosis and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).
A capsule formulation of strengths 25 and 50 mg is available for commercial distribution of lixivaptan (LIXAR®).
Three randomized, placebo controlled, double-blind Phase III efficacy and safety trials, 1 in hypervolemic hyponatremic patients with CHF and 2 euvolemic hyponatremic patients with SIADH present the evidential basis for seeking the above indication. Supportive evidence for safety is provided by a randomized, placebo controlled, double-blind Phase II study in CHF patients. Clinical Pharmacology information is available from 50 reports 15 studies with human biomaterials, 31 Phase I studies, 1 Phase II study and 3 Phase III studies.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the Clinical Pharmacology and Biopharmaceutic information submitted in NDA 203009 and finds the submitted information acceptable, provided an agreement on the label and post-marketing comittments can be obtained from the sponsor.

The Office has the following comments/recommendations:

- Given the safety concerns raised by the greater number of deaths with lixivaptan compared to placebo in the Phase III studies with CHF patients with hyponatremia OCP is not in a position to provide recommendations for any dose adjustment of lixivaptan with co-administered CYP3A inhibitors in this population at this point in time. Any dosing recommendations in CHF patients will depend on the benefit-risk assessment which is the subject of discussion at the upcoming Advisory Committee Meeting on September 13, 2012
- Co-administration of lixivaptan with CYP3A inducers should be avoided

- No dose adjustment is necessary for lixivaptan in SIADH patients when co-administering lixivaptan with weak and moderate CYP3A inhibitors

- Initiate lixivaptan at 25 mg in patients on strong CYP3A inhibitors
- Co-administration of CYP2C8 inhibitors and lixivaptan should be avoided
- Co-administration of lixivaptan and CYP2C8 substrates should be avoided
- When co-administering lixivaptan with simvastatin the dose of simvastatin should be reduced
- When co-administering lixivaptan with substrates of BCRP such as e.g. methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan, patients should be closely monitored for signs and symptoms of excessive exposure, and the dose of the BCRP substrates, if appropriate, reduced.
- Administration of lixivaptan in liver impairment caused by cirrhosis should be avoided
- No dose adjustment of lixivaptan in patients with renal impairment is necessary

1.2 POSTMARKETING REQUIREMENTS (PMR)/COMMITMENTS (PMC)

The following are the specific requests

- A drug interaction study to determine the impact of lixivaptan co-administration on the exposure to sensitive substrates of CYP2C8 in healthy subjects should be performed (PMC)
- An *in vitro* study determining whether lixivaptan is a substrate of OATP1B1/B3 should be performed (PMC)
- An *in vitro* study determining whether lixivaptan is a substrate of BCRP should be performed (PMC)

The Clinical Pharmacology Briefing was held on August 13, 2012

Attendees included: Mehta, Mehul U; Hariharan, Sudharshan; Yang, Xinning; Kim, Myong-Jin; Abernethy, Darrell; Huang, Shiew Mei; Bhattaram, Atul; Wu, Ta-Chen; Menon-Andersen, Divya; Yu, Jingyu (Jerry); Shukla, Chinmay; Stockbridge, Norman L; Unger, Ellis; Reynolds, Kellie S; Burckart, Gilbert; Xu, Nancy; Thompson, Aliza; Jain, Lokesh; Rahman, Nam Atiqur; Marathe, Dhananjay; Florian, Jeffry; Khurana, Manoj; Zineh, Issam; Pacanowski, Michael A; Zhao, Ping; Bewernitz, Michael; Lu, An-Chi; Sarntivijai, Sirarat *; Momper, Jeremiah; Lon, Hoi Kei *; Liu, Dongyang *; Sabarinath, Sreedharan; Li, Fang; Lai, Ju-Ping; Sahre, Martina; Hinderling, Peter

2. SUMMARY OF OCP FINDINGS

2.1 Background

Cardiokine is seeking approval of Lixivaptan (Lixar®) for the indication for the treatment of symptomatic hypervolemic and euvolemic hyponatremia associated with heart failure and SIADH, respectively.

2.2 Current Submission

The efficacy and safety claims for lixivaptan in NDA 203009 are based on the findings of 3 adequate and well controlled studies in the target populations in subjects with SIADH (2 studies) or CHF (1 study). The submission contains 46 Clinical Pharmacology studies providing information relating to human biomaterials and the PK and/or PD of lixivaptan in healthy subjects and patients with SIADH, CHF or liver cirrhosis with ascites (LCWA). Of these 39 were reviewed. Eleven (11) of the reviewed studies investigated the interaction of lixivaptan with human biomaterial including the plasma protein binding of lixivaptan (1 study), lixivaptan as substrate, inhibitor or inducer of CYP enzymes (7 studies) and lixivaptan as substrate or inhibitor of transporters (3 studies). Among the 28 reviewed clinical studies, 11 single and multiple ascending dose studies evaluated the pharmacokinetics, pharmacological activity and tolerability of lixivaptan in healthy subjects and in patients with SIADH, CHF or LCWA, 13 studies assessed the interaction liability of lixivaptan including the impact of food and the bioavailability of the 25 mg relative to the 50 mg to be marketed capsule formulations, and 1 study each examined dose proportionality, mass balance, the effect of lixivaptan on the QTc interval and the impact of end-stage renal disease on the exposure to lixivaptan. The results from a population PK analysis using the pooled dense sampling information from Phase I and II studies and sparse sampling data from Phase III studies were also available. The salient Clinical Pharmacology findings and issues of the submission are summarized in sections 2.1.3 and 2.1.4, respectively:

2.3 Salient Clinical Pharmacology Findings

Exposure-Response Relationship

Target Population

In general, higher exposure leads to a greater increase in serum sodium. There is a dose-dependent increase in serum sodium in Phase II studies after administration of lixivaptan in doses similar to those used in the Phase III trials. A shallow exposure-response relationship for change in serum sodium is observed in Phase I and Phase III studies. The effect size in the Phase III trials is small 1-2 mEq/L and the clinical relevance of these changes in serum sodium is uncertain.

Daily dose of lixivaptan in excess of 200 mg daily are associated with an increased rate of mechanism-based adverse events for this class of drug, including dry mouth, thirst, constipation, headache, and dizziness.

Healthy Subjects and Patients with SIADH, CHF target LCWA

Among the circulating moieties identified in plasma, lixivaptan appears to be the only compound to exhibit significant pharmacological activity. The onset of lixivaptan's effect on free water clearance (CL_{H_2O}) and serum sodium occurs about 2 h post-dose. The peak effect on CL_{H_2O} follows swiftly thereafter, whereas the peak effect on serum sodium occurs with a delay between 4 and 8 h after administration. The peak effect of lixivaptan on CL_{H_2O} and time to offset increase with dose. The exposure-effect relationship for CL_{H_2O} follows an Emax model. No clear dose-effect relationship for the serum sodium increasing effect of lixivaptan is seen. The effects on CL_{H_2O} and serum sodium do not show overt tolerance or tachyphylaxis after multiple dose administration of lixivaptan.

Pharmacokinetics

The pharmacokinetics of lixivaptan is characterized by rapid absorption (tmax of 0.8 h) followed by multi-exponential disposition with an apparent terminal phase t1/2z of 8-16 h. The pharmacokinetics of lixivaptan is non-linear as evidenced by a more than dose proportional increase in exposure. Lixivaptan is extensively plasma protein bound (percent unbound << 1.0%) and partitions widely into tissues. The drug is eliminated from the body by non-renal pathways, mainly by metabolism. Among the structurally identified 5 metabolites in plasma pharmacokinetic information is available for 3 metabolites, 1 of the 2 active metabolites, WAY138451, and 2 inactive metabolites, WAY141624 and WAY138758.

Intrinsic Covariates

Based on a population PK analysis, patients with LCWA and SIADH show an increase in mean exposure to lixivaptan relative to healthy subjects of 2.3 and 1.6 fold, respectively, at the 100 mg QD level and 3.5 and 2.0 fold, respectively, at the 100 mg BID level. In contrast, there appears to be no relevant impact on exposure to lixivaptan in patients with CHF. Liver cirrhosis, as evidenced by the findings in the LCWA patients, increases the exposure to lixivaptan significantly. End-stage renal disease reduces exposure to lixivaptan marginally.

Extrinsic Covariates

In vitro data indicate that lixivaptan is a substrate of CYP3A and CYP2C8 and has the potential to inhibit CYP3A, CYP2C8, CYP2C9 and BCRP. *In vivo* data confirm that lixivaptan is substrate of CYP3A. Co-administration of CYP3A inducers decreases the exposure to lixivaptan to about 30%. Co-administration of strong CYP3A inhibitors increases the exposure to lixivaptan significantly 3 fold in healthy subjects. Weak and moderate CYP3A inhibitors increase exposure to lixivaptan up to 1.9 fold in patients with SIADH, CHF or LCWA. *In vivo* data confirm that lixivaptan when co-administered with simvastatin is an inhibitor of CYP3A and possibly BCRP (dose dependent 2-3 fold

increase in exposure). However, exposure to and response of the CYP2C9 substrate warfarin in the presence of lixivaptan are unchanged.

Biopharmaceutics
The drug substance lixivaptan is lipophilic and sparingly soluble in water over the pH range of 1.2-7.5 of the gastrointestinal tract. The amounts of active and inactive ingredients of the-to-be marketed 25 and 50 mg capsules of lixivaptan are dose proportional. The sponsor compared in dose-strength proportionality study AUC and Cmax after administration of single 25 mg and 50 mg capsules and dose normalized the bioavailability measures. The point estimate and 90% CI for AUC with the 25 mg capsule are within the bioequivalence limits. In contrast, the corresponding estimates of 1.34 and 1.54 for the lower strength capsule exceed the upper limit. Food of high fat and caloric content does not impact the exposure to lixivaptan.

2.4 Issues

Safety
Unexplained cases of death occurred in the Phase III trial in patients with CHF and hyponatremia. The discrepancy in death rate between lixivaptan and placebo treatments occurred pre-dominantly during the first 5 days after initiation of the regimens during the up-titration phase. Most of these deaths had a cardiac cause. In the SIADH patients death due to cardiac causes was balanced between the two treatment arms. Please see the review of the Clinical Reviewer, Dr. Nancy Xu, for details.

Small Effect Size of Serum Sodium Increasing Effect of Lixivaptan

The increase in serum sodium is 1 mEq/L in CHF patients and 2 mEq/L in SIADH patients. The clinical significance of this small effect size is uncertain.

Unexplored Interaction Liability of Lixivaptan
The *in vitro* studies show that CYP3A is the major enzyme involved in the metabolism of lixivaptan. There is also evidence that CY2C8 plays a role. However, the information available does not allow an assessment of the quantitative contribution of CYP2C8 to the disposition of lixivaptan. Moreover, the pharmacokinetics of lixivaptan *in vivo* is nonlinear, most likely due to saturation of the CYP3A pathway. Information on absolute bioavailability and relative contribution of first pass and systemic metabolism to the disposition of lixivaptan is unknown. Hence the review team is recommending that the co-administration of CYP2C8 inhibitors with lixivaptan should be avoided.

In vitro data indicate that lixivaptan has the potential *in vivo* to inhibit the metabolism of CYP2C8 substrates. A study with co-administration of lixivaptan and CYP28 substrates in healthy subjects should be performed (PMC).

Lixivaptan as a possible substrate of OATP1B1/B3 or BCRP *in vitro* was not studied. This information should be provided by performing *in vitro* studies (PMCs)**.**

Unidentified Circulating Moieties in Plasma in Mass Balance Study
After administration of ^{14}C-lixivaptan only 40-50% of the total radioactivity in plasma is structurally identified in humans with only 7% representing lixivaptan. Thus, 50-60% of the circulating radioactivity is made up of metabolites with unknown exposure and activities pointing to the possibility that the unidentified metabolites in man and in the animal species of the toxicology studies are different. This finding increases the uncertainty about the safety of lixivaptan.

3. QUESTION BASED REVIEW

3.1. GENERAL ATTRIBUTES

3.1.1 History of Regulatory Development

Tolvaptan (Samsca ®) was the first orally administered specific V_2 receptor antagonist approved by the FDA in 2009 for the treatment of clinically significant hypervolemic and euvolemic hyponatremia [(serum sodium < 125 mEq/L) or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction], including patients with SIADH, CHF or cirrhosis.

The IND for lixivaptan was filed in 1995. The drug was originally developed by Wyeth-Ayerst and then by Cardiokine, Inc., the current holder of the IND. At present lixivaptan is not marketed outside of the US. Lixivaptan is formulated as capsules with 2 strengths of 25 and 50 mg.

3.1.2 Highlights of Chemistry and Physical-Chemical Properties of the Drug Substance

Lixivaptan is chemically described as 5-fluoro-2-methyl-N-[4-(5H-pyrrolo[2, 1-C] [1,4]benzodiazepin-10(11)-yl carbonyl)-3-chlorophenyl]benzamide. The structure of lixivaptan is shown in Figure 1 below:

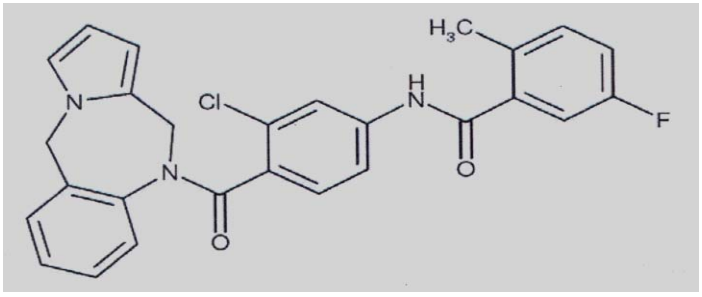


Figure 1: Structure of lixivaptan

The MW of lixivaptan is 478 dalton. Lixivaptan is achiral, non-peptidic and lipophilic. Lixivaptan is sparingly soluble (20 ng/mL) in aqueous solutions over the range of pH 1.2-7.5 of the gastrointestinal tract. The log n-octanol/water partition coefficient of lixivaptan is 1.02.

3.1.3 What are the Proposed Mechanisms of Action and Therapeutic Indications?

Vasopressin regulates the osmotic pressure of plasma via V_2 receptors located on the basolateral membrane of tubular and collecting duct cells. In healthy subjects vasopressin is secreted by the pituitary when the osmotic pressure in plasma exceeds 280 mosmol/kg fluid. In patients with SIADH, CHF and cirrhosis vasopressin is secreted at values lower than 280 mosmol/kg fluid. The V_2 receptors are coupled to the adenyl cyclase signal pathway. Activation of the V_2 receptors results in the insertion of channels in distal tubule and collecting duct of the nephrons through which free water is reabsorbed from urine into blood as shown in the below scheme:

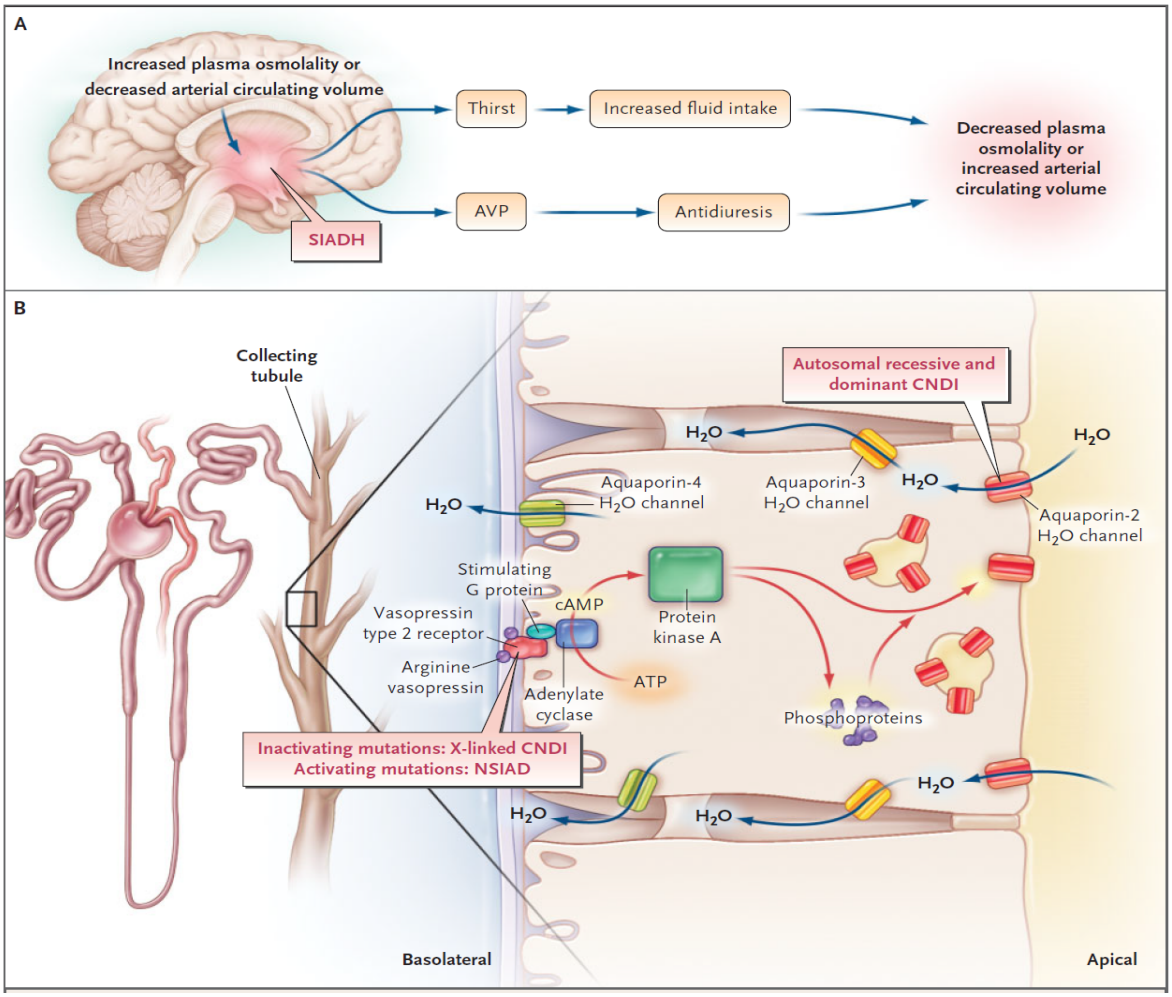


Figure 2: Water balance and regulation of osmotic pressure

Vasopressin not only interacts with V_2 receptors but also with V_{1a} - and V_{1b}-receptors as shown in the below table:

Table 1: Vasopressin receptor subtypes and function

Receptor	Location	Effects of Vasopressin
V_{1a}	Platelets	Aggregation
	Vascular smooth muscle cells	Vasoconstriction
	Hepatocytes	Glycogenolysis
	Myometrium	Uterus contraction
V_{1b}	Anterior pituitary	ACTH-release*
V_2	Basal membrane collecting duct cells	AQP channel synthesis and insertion
	Vascular endothelium	vWF- and Factor 8 release
	Vascular smooth muscle	Vasodilation

* Suspected additional functions

The V_{1a} and V_{1b} receptors use the phopholipase C signal pathway. In contrast, the V_2 receptor uses the adenylate cyclase pathway.

The respective affinity of lixivaptan to the different receptors of interest is summarized in the below table:

Table 2: Affinity and selectivity of lixivaptan to target receptors and other receptors

Human IC_{50}, nM				
V_{1a}	**V_2***	**Oxytocin**	**V_{1a}/V_2**	**Oxytocin/V_2**
124	1.2	519	103	433

* 0.95 pg/mL

Lixivaptan is a weak V_{1a} receptor antagonist exhibiting negligible antagonism at V_{1b}- , oxytocin-, 5HT-recptors, and dihydropyridine-type Ca++ channels.

The relative *in vitro* and *in vivo* pharmacological activities of the identified metabolites of lixivaptan are shown in the below table:

Table 3: Pharmacological activity *in vitro (human) and in vivo* (rat) of the identified metabolites:

Citation term	WAY #	Human V_2 binding[1]	Human V_{1a} binding[1]	Human OT binding[1]	Rat urine[1,2]	
		IC_{50} (nM)	IC_{50} (nM)	IC_{50} (nM)	Volume (%)[3]	Osmolality (%)[3]
2	Lixivaptan	1.2	124	519	+158**	-53**
5b	WAY-137930	11	1000	1000	+35	-31**
6b	WAY-138451	34	1000	1000	+42	-26**
12b	WAY-138758	1000	1000	1000	-17	-7
15b	WAY-141624	1000	1000	1000	+3	-13

[1] *In vitro* binding data is taken from Molinari et al 2007 in Table 2.6.3.3. *In vivo* data is taken from Study GTR-28438 in Table 2.6.3.3.
[2] Rats were dosed intravenously with 10 mg/kg metabolite (a 10-fold higher dose) compared to 1 mg/kg lixivaptan.
[3] Urine volumes and osmolality are expressed as mean % change from vehicle-treated controls and were collected over a 4-hr postdose period (n=4 to 6 rats). Urine volume and osmolality values were extracted from Figure 1 and Figure 2 of Study GTR-28438.
**p≤0.001 compared to vehicle control.

The V_2 receptor blocking activity of WAY137930 and WAY138451 compared to lixivaptan is < 10%. Their *in vivo* potency after an intravenous dose 10 fold greater than that for the parent drug is about 50% of lixivaptan in the rat. The results of Table 3 indicate that the metabolites WAY137930 and WAY138451 retain minor aquaretic activity compared to that of lixivaptan.

In both hypervolemic and euvolemic hyponatremia conditions an increase in the extracellular water occurs that decreases the osmotic pressure and the serum sodium concentration to values < 135 mEq/L. Euvolemic hyponatremia is caused by SIADH. In patients with SIADH vasopressin is secreted in the blood stream at a normal osmotic pressure in plasma. Hypervolemic hyponatremia occurs in patients with CHF or cirrhosis. In patients with CHF or cirrhosis the baroreceptor in the carotid sinus and the kidney perceive the intravascular volume as too low triggering the release not only of vasopressin, but also of aldosterone. The end-result is a hyponatremia with a surplus of free water relative to sodium. However, total body sodium is increased. The below schemes depict the major actors involved in the regulation of osmotic pressure in healthy subjects and patients with SIADH, CHF or cirrhosis:

Euvolemic Hyponatremia

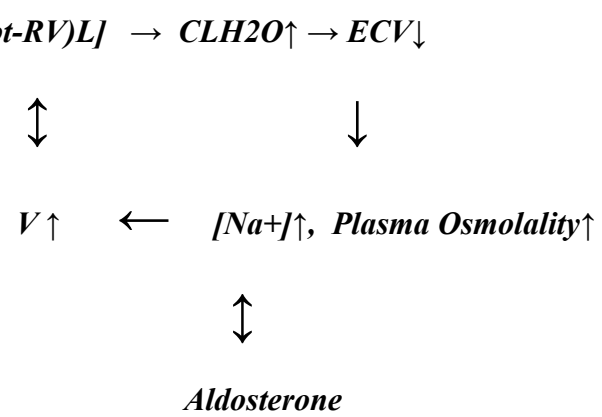
$$L + (Rtot - RV) \longleftrightarrow [(Rtot-RV)L] \longrightarrow CLH2O\uparrow \rightarrow ECV\downarrow$$

$$\updownarrow \qquad\qquad \downarrow$$

$$V\uparrow \longleftarrow [Na+]\uparrow,\ Plasma\ Osmolality\uparrow$$

where L is lixivaptan, Rtot and RV are the total number of receptors and the receptors bound by vasopressin, respectively, CL_{H20} is the free water clearance, ECV is the extracellular volume and V is vasopressin.

Hypervolemic Hyponatremia



3.1.4 What are the Proposed Dosages and Routes of Administration?

Lixivaptan is administered orally. A titration regimen is proposed for patients with euvolemic or hypervolemic hyponatremia. However, the proposed dose interval and the maximum administered daily doses vary between euvolemic and hypervolemic hyponatremic patients. The initial dose also varies dependent on whether treatment is started in an inpatient- or outpatient setting. The recommended dose regimens for outpatients are: an initial dose of 25 mg QD without regards to meals. The dose may be doubled every 24 h dependent on individual patient response up to maximally 100 mg QD in euvolemic hyponatremia patients or 100 mg BID (Q12h) in hypervolemic hyponatremia patients. The recommended dose regimens for hospitalized patients are: an initial dose of 50 mg QD without regards to meals. The dose can be doubled every 24 h dependent on individual patient response up to 100 mg QD in euvolemic hyponatremia patients or 100 mg BID (Q12h) in hypervolemic hyponatremia patients.

3.2 GENERAL CLINICAL PHARMACOLOGY

3.2.1 What are the Design Features of the Clinical Pharmacology and Clinical Studies Used to Support Dosing or Claims?

Clinical Pharmacology Studies

Phase I Studies in Healthy Subjects

Parallel group, single and multiple ascending dose studies were conducted in healthy subjects covering a dose range of between 1 and 800 mg after single dose administration and between 25 and 800 mg QD or 100 and 400 mg BID after multiple dose administration. Other studies investigated the dose proportionality of lixivaptan after administration of 100, 200 and 400 mg BID, the mass balance of lixivaptan, the impact of lixivaptan in doses of 100 mg and 400 mg given BID on the QT/QTc interval with moxifloxacin as control using a double-blind, placebo controlled, parallel group design,

the relative bioavailability of a suspension relative to the to be marketed 50 mg capsule. Thirteen (13) studies investigated the interaction liability of lixivaptan. Of these the impact of other possibly co-administered drugs on lixivaptan exposure including the CYP3A inhibitors ketoconazole (strong), single strength orange juice (moderate), amiodarone (weak), the CYP3A/2C inducer carbamazepine, warfarin, digoxin, enalapril, furosemide, hydrochlorothiazide and spironolactone was investigated in 9 studies. Eight (8) studies investigated the impact of lixivaptan on the exposure to possibly co-administered drugs including simvastatin (CYP3A and BCRP substrate), atorvastatin (CYP3A substrate), amiodarone (CYP3A substrate), digoxin, enalapril, furosemide, hydrochlorothiazide and spironolactone. The studies with warfarin, enalapril, furosemide, hydrochlorothiazide, evaluated also PD parameters. The dose strength proportionality of the to-be-marketed 25 and 50 mg capsules and the impact of food on the exposure to lixivaptan were investigated as part of two of the drug-drug interaction studies.

Phase I/II Studies in Patients

Parallel group, placebo controlled, double-blind, single ascending dose studies were conducted in patients with SIADH covering a dose range of lixivaptan between 10 mg and 150 mg or between 10 and 300 mg, and in patients with CHF covering a dose range of lixivaptan between 10 and 400 mg. Single and multiple dose studies with the same design were performed in CHF patients covering a dose range between 10 and 400 mg and 30 and 250 mg BID (Q8h/16h), respectively. Parallel group, multiple dose ascending, placebo controlled, double-blind studies with doses ranging between 25 and 300 mg and between 25 and 150 mg BID or 300 mg QD were conducted in patients with LCWA. Parallel group, double-blind, placebo controlled studies were performed in patients with CHF receiving a fixed dose of 100 mg lixivaptan QD for 8 weeks, in patients with CHF or cirrhosis receiving fixed multiple doses of lixivaptan 25, 125 or 250 mg BID (Q8h/Q16h) and in patients with either SIADH, CHF or LCWA receiving fixed doses of lixivaptan of 50 mg or 100 mg. A single dose study in patients with end-stage renal disease and matched healthy subjects receiving a single dose of 100 mg investigated the impact of severe renal impairment on the exposure to lixivaptan.

Phase III Studies in Patients with SIADH or CHF

Three Phase III studies, two in SIADH patients (3405 and 3430) and one in CHF patients (3401) were randomized, placebo controlled studies. All three studies used the to-be-marketed capsule formulations. Study 3401 enrolled 652 hypervolemic hyponatremic patients hospitalized with acute worsening of CHF. Upon randomization the patients entered an in-patient dose-titration phase for up to 72 h. The treatment phase extended from Day 4 to Day 60 or early termination. The initial dose of lixivaptan or placebo was 50 mg QD which could be up-titrated to maximally 100 mg BID. If QD dosing was prescribed the maximum daily dose was 100 mg. Serum sodium guided the titration. The primary endpoint was the change from baseline to Day 7 in serum sodium.

Study 3430 in euvolemic hyponatremia SIADH patients enrolled 206 subjects in outpatient settings (clinic, hospital, long term care facility/nursing home). The

hospitalized patients were randomized to either 25 mg lixivaptan or placebo, QD. The dose could be up-titrated to 50 or maximally 100 mg QD on Days 2 and 3, respectively. Changes in dose were guided by serum sodium. Study drug could also be down-titrated to 25 mg QD. Acceptable were also 25, 50 or 100 mg QD. After completion of the titration phase the patients were managed as outpatients. The study duration was 6 months. The primary endpoint was the change from baseline to Day 7 in serum sodium.

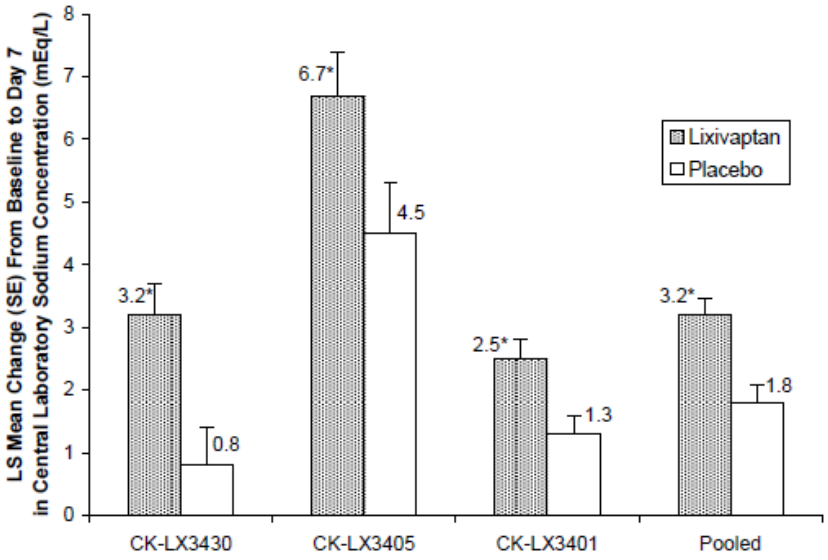
Study 3405 in euvolemic hyponatremia associated with SIADH enrolled 106 subjects. The patients were randomized to receive either lixivaptan 50 mg or placebo, QD, in the hospital. Guided by serum sodium the initial dose of 25 mg QD could be up-titrated to maximally 100 mg QD during the titration phase of 48 to 72 h. Study drug could also be down-titrated to 25 mg QD at any time during the 30 day treatment period. After discontinuation of the titration the subjects remained on the same dose as at the time of discharge. They were then managed as outpatients and returned to the clinic on Days 7, 14 and 30. The primary endpoint was the change from baseline on Day 7 of serum sodium.

3.2.2 Were the Correct Moieties Identified and Properly Measured to Assess Clinical Pharmacology?

The parent drug, lixivaptan, the major active circulating moiety identified in plasma, was determined in all, but 2 conducted clinical studies. Of the 2 metabolites WAY137930 and WAY138451 exhibiting minor pharmacological activity in rats, only WAY137930 was quantified in the mass balance study in humans. The sponsor identified structurally and quantified only 40-50% of the circulating total radioactivity in the mass balance study. Therefore, it is possible that among the 50-60% unidentified circulating radioactivity other metabolites with unknown pharmacological activity exist. Another possibility is that the unidentified metabolites in man and in the animal species used in the toxicology studies are different. This possibility increases the uncertainty about the safety of lixivaptan.
Pharmacokinetic information exists for 3 of the 5 structurally identified metabolites, namely for the active WAY138451 and the inactive WAY141624 and WAY138758 after multiple dose administration of lixivaptan.

3.2.3 What are the Characteristics of the Exposure-Response Relationships for Efficacy?

Phase II and III Studies in Patients
With the proposed dosing regimen, lixivaptan is effective in raising serum sodium in patients with hyponatremia associated with either CHF or SIADH. The drug effect is statistically different from the placebo effect in all three Phase III studies (CK-LX3401, CK-LX3405, and CK-LX3430).



LS=least squares; SE=standard error
Note: Sample sizes for lixivaptan and placebo groups, respectively, were as follows: CK-LX3430 (154 and 52), CK-LX3405 (54 and 52), CK-LX3401 (323 and 329), and pooled (531 and 433)

Figure 3: LS Mean (SE) change from baseline to Day 7 in central laboratory sodium concentration in placebo-controlled Phase III studies in subjects with hypervolemic and euvolemic hyponatremia associated with HF and SIADH (CK-LX3430, CK-LX3405, and CK-LX3401; ITT Population, LOCF/NOCB)

The baseline- and placebo-adjusted change in serum sodium on Day 7 is 1.2 mEq/L (P-value = 0.001) in CHF patients, 2.1 mEq/L (P-value=0.0345) and 2.4 mEq/L (P-value <0.0011) in SIADH inpatients and outpatients, respectively. Lixivaptan's effect on serum sodium is slightly greater in SIADH patients than in CHF patients.

The Phase II studies (207-EU, 203-US/CA) with BID regimens indicate that the effect size on serum sodium increases with higher doses, as shown in Figure 4. The doses between 25 mg to 125 mg BID achieved an effect size of about 5-6 mEq/L in both studies. However, this average effect size of 5 to 6 mEq/L was not achieved in the Phase III trials.

There were differences between Phase II and Phase III trials: 1) Phase II trials enrolled patients predominantly with liver cirrhosis while Phase III trials included either CHF or SIADH patients; 2) All patients in Phase II trials required aggressive fluid restriction (<1500 ml per day) while only a small portion of patients in Phase III trials were subject to similar fluid restriction; 3) BID regimens without titration were studied in Phase II trials while titrated QD regimen for SIADH patients or titrated QD/BID regimen with initial QD regimen for CHF patients were studied in Phase III trials. Due to these differences, the dose-efficacy relationship obtained in Phase II may not apply to Phase III studies.

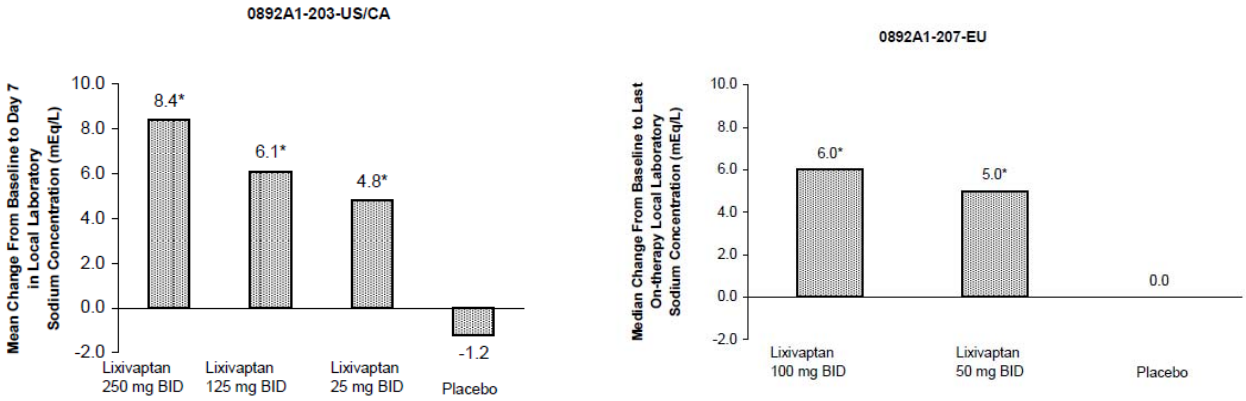


Figure 4: Dose-dependent increase in serum sodium from baseline in Study 0892A1-203-US/CA and 08921A-207-EU

As shown in the Figure 5, the change in serum sodium from baseline is baseline-dependent, with a larger increase observed in patients with lower baseline values for both placebo and lixivaptan arms. However, there is no obvious relationship between the baseline sodium level and the placebo-corrected change in serum sodium.

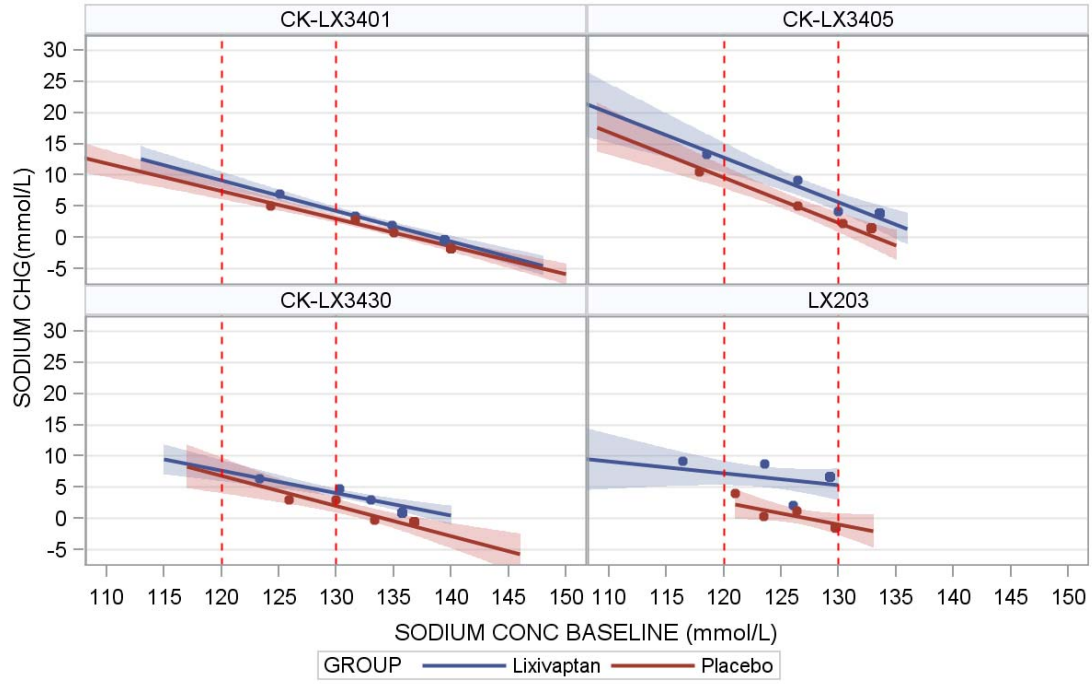


Figure 5: Baseline-dependent change in serum sodium from baseline to Day 7 in Phase II (LX203: 0892A1-203-US/CA) and Phase III studies of lixivaptan (CK-LX3401, CK-LX3405, CK-LX3430). Lines and shaded areas represent the model predicted change in serum sodium and the point-wise 95% confidence interval based on a linear model. Dots represent the observed means of quartile groups.

One of the reasons that may explain the placebo effect is the effect of fluid restriction. The consequence of imbalanced fluid restriction between drug (less fluid restriction) and placebo (more fluid restriction) treatments might decrease the difference between drug and placebo arms, and lead to an underestimation of the drug effect.

However, the data from the Phase III trials indicate that the impact of fluid restriction is not consistent and is unlikely to contribute by itself as the reason for small treatment effect observed in the Phase III studies. In the Phase III study CK-LX3401, the percentage of subjects under fluid restriction in the lixivaptan arm and placebo arm was balanced (63% vs. 64%, P-value = 0.791). Lixivaptan treatment effect in this study is small (ΔΔNa = 1.2 mEq/L). In contrast, the Phase III Study CK-LX3405 showed an imbalance in the percentage of patients under fluid restriction (37% for lixivaptan vs. 71% for placebo, P-value < 0.001). Despite a higher percentage of fluid restriction in the placebo arm, lixivaptan demonstrated a larger effect size (ΔΔNa = 2.1 mEq/L) than in study CK-LX3401. Therefore, fluid restriction by itself may not significantly interfere with the assessment of the true aquaretic effect size of lixivaptan. If the regimen is effective, it is possible to demonstrate the drug effect even when aggressive fluid restriction is applied in the placebo arm.

Phase I Studies
The clinical pharmacological activity endpoints of primary interest are CL_{H2O}, including plasma- and urine osmolality, and the concentrations of sodium in serum, and vasopressin and aldosterone in plasma as shown in the above schemes for euvolemic and hypovolemic hypernatremia (see pp. 16, 17).

Dose/Concentration-Effect Relationships for CL_{H2O}, Serum Sodium and Vasopressin

The below figures summarize the major findings on the dose/concentration–effect relationship of lixivaptan for CL_{H2O}, serum sodium and vasopressin:

CL_{H2O}

The below 2 figures show the time course of the mean effect on CL_{H2O} after placebo or single dose administration of lixivaptan doses ranging between 1 and 500 mg in healthy subjects:

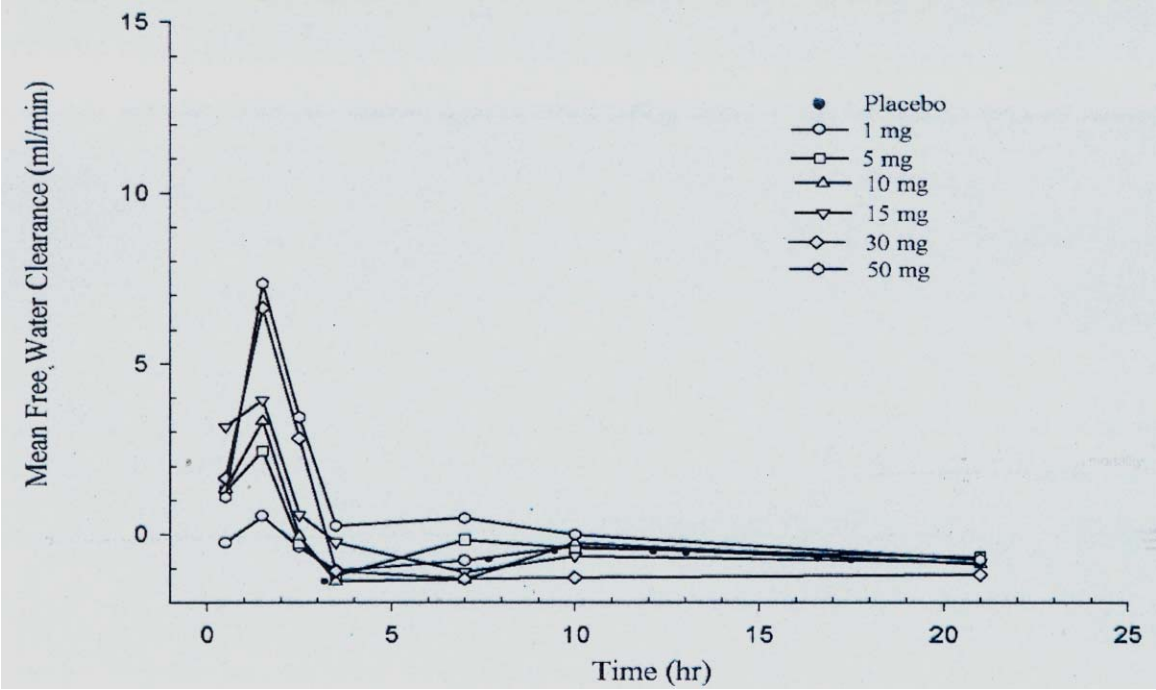


Figure 6: Mean free water clearance after placebo and single doses of lixivaptan ranging between 1 and 50 mg in healthy subjects

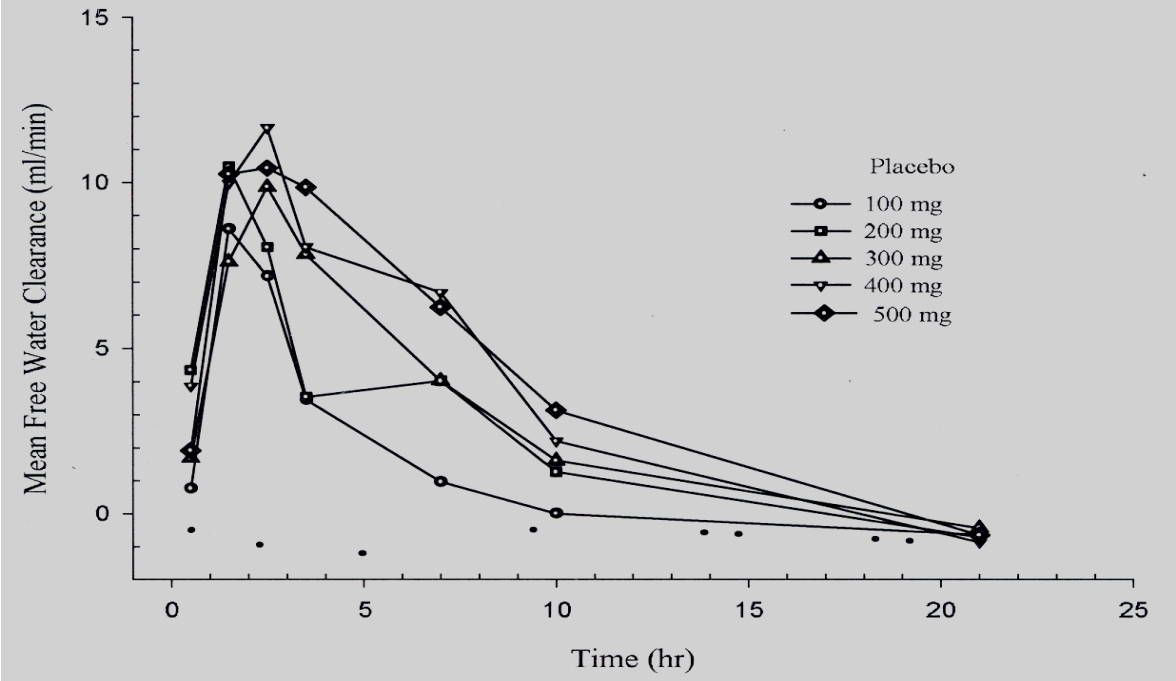


Figure 7: Mean free water clearance after placebo and single doses of lixivaptan ranging between 100 and 500 mg in healthy subjects

The CL_{H_2O} after doses of lixivaptan ≥ 5 mg shows a distinct time profile characterized by a rapid onset occurring within 2 h after administration and peak values between 2 and 4 h post-dose which are followed by a slower and dose dependent decline of the aquaretic effect. The offset of the aquaretic effect of lixivaptan occurs at about 3 h post-dose and more delayed after the highest doses tested, i.e. 200-500 mg.

The dose-response curve of the peak aquaretic effect of lixivaptan in healthy subjects and patients with SIADH, LCWA or CHF appears to follow an Emax function as shown by the below figure:

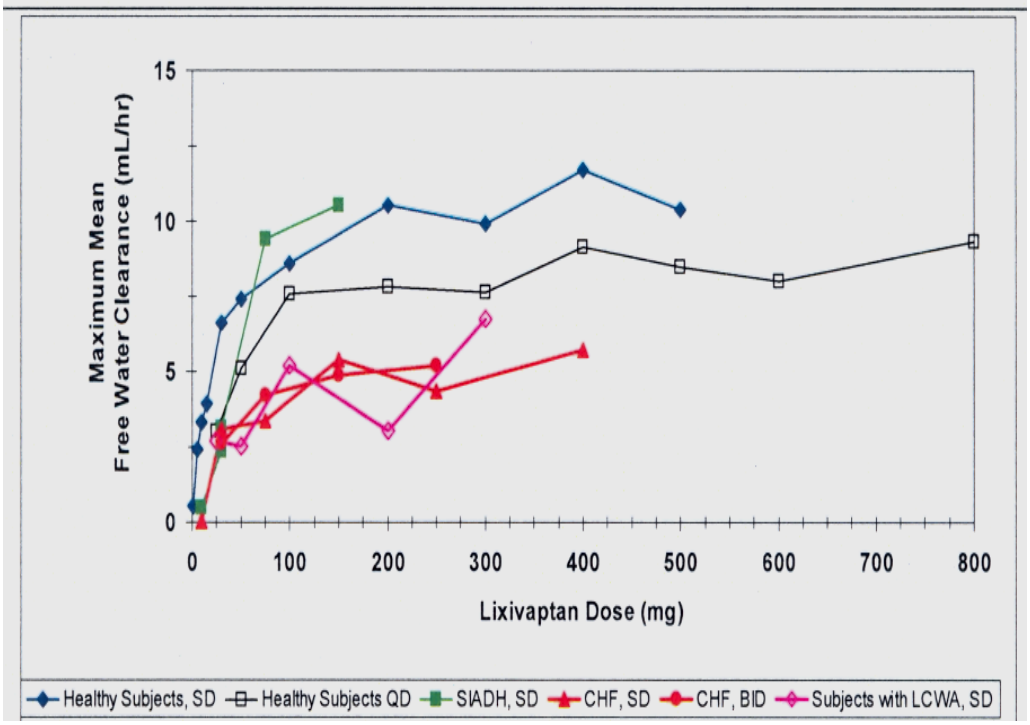
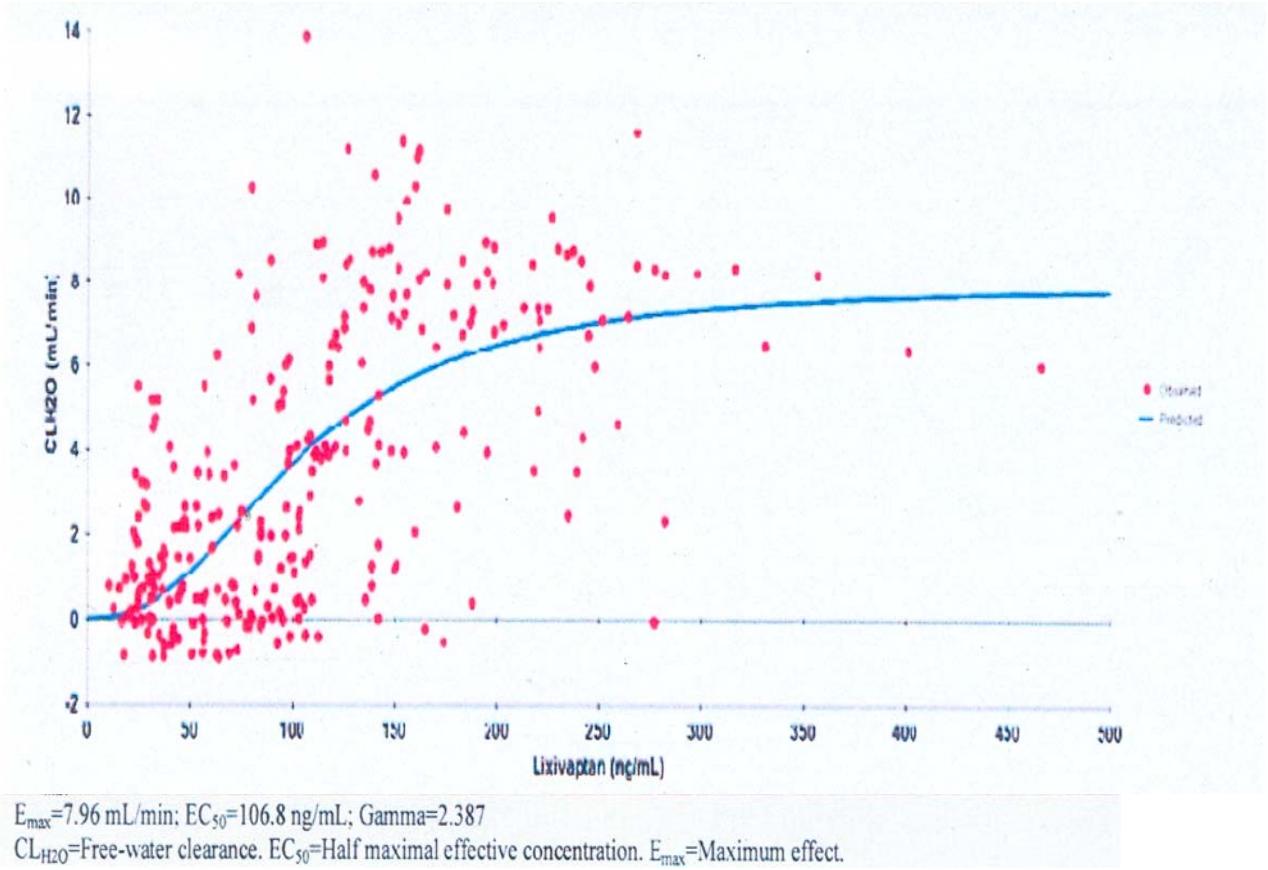


Figure 8: Dose-response curve of the mean maximum free water clearance for lixivaptan in healthy subjects and patients with CHF after single and multiple doses, and patients with SIADH or LCWA after single doses

The saturable characteristics of the aquaretic effect of lixivaptan is also confirmed by Figure 9 showing a fit of the CL_{H_2O} to Cmax relationship in healthy subjects after a single dose of lixivaptan of 100 mg using a sigmoid Emax model:



E_{max}=7.96 mL/min; EC_{50}=106.8 ng/mL; Gamma=2.387

CL_{H2O}=Free-water clearance. EC_{50}=Half maximal effective concentration. E_{max}=Maximum effect.

Figure 9: Fit of the free water clearance vs. the plasma concentration of lixivaptan in healthy subjects using a sigmoid Emax model

There is significant inter-subjects variability. The CL_{H2O} values were measured over a sufficiently large concentrations range so that the estimated parameters obtained by the fit, EC_{50} (107 ng/mL), Emax (8.0 mL/min) and γ (2.4) are plausible.

Serum Sodium

The dose response relationship for serum sodium after single and multiple doses of placebo and lixivaptan 25 to 800 mg, administered QD for 14 days to healthy subjects, is depicted in the next figure:

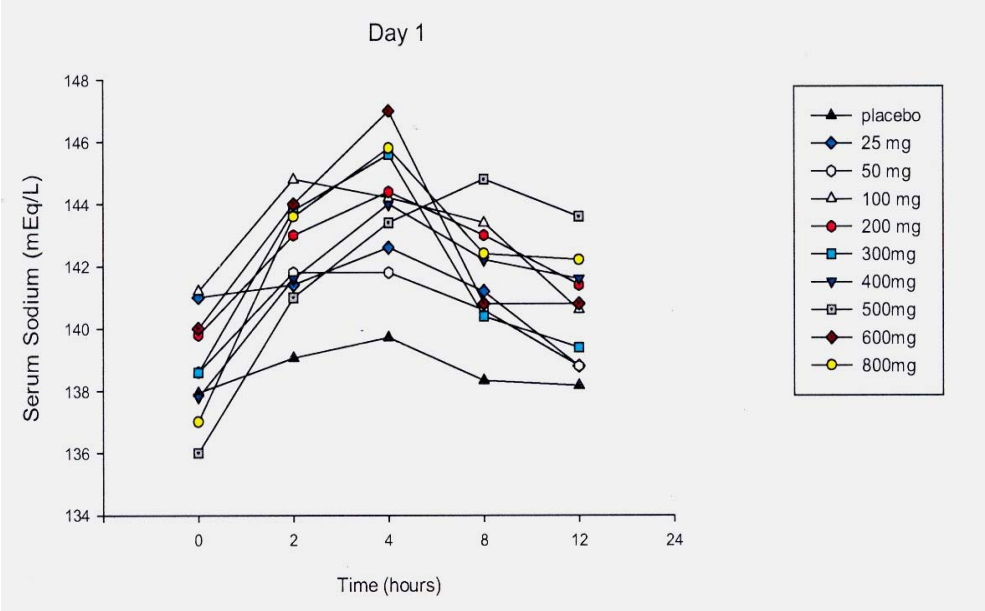


Figure 10: Mean serum sodium time profiles in healthy subjects on Day 1 after placebo or a single dose of lixivaptan ranging between 25 mg and 800 mg

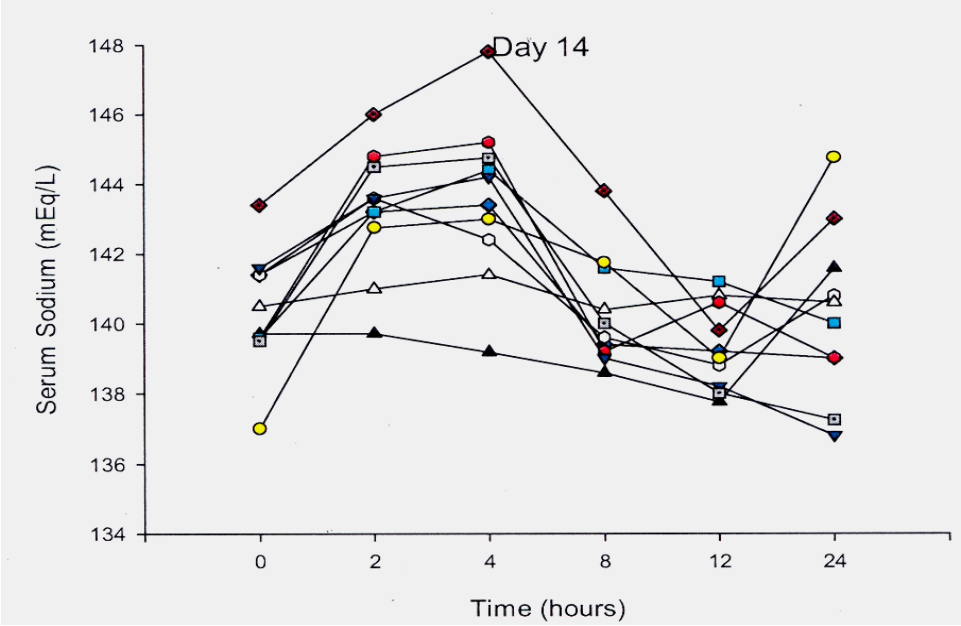


Figure 11: Mean serum sodium time profiles in healthy subjects on Day 14 after a QD regimen of placebo or lixivaptan with doses ranging between 25 and 800 mg QD

After a single dose administration of placebo the mean serum sodium concentrations relative to baseline remain constant whereas after lixivaptan 50-800 mg a more distinct time profile is visible characterized by an onset of the hypernatremic effect in the first 2 h after administration, peak serum sodium concentrations occurring between 2 and 8 h post-dose followed by a decline of the hypernatremic effect which is not clearly dose dependent. The time to offset of the hypernatremic effect cannot be reliably estimated.

After a multiple dose BID treatment for 14 days with placebo the serum sodium concentrations relative to baseline remain constant, whereas after multiple doses of lixivaptan 50-800 mg the onset of the hypernatremic effect is observed 2 h after administration with peak values occurring between 2 and 4 h followed by a decline of the effect. A comparison of the Day 1 baseline values with the morning trough values on Day 14 and the values 12 h post dose does not indicate presence of significant hypernatremic activity of lixivaptan 24 or 12 h after a QD treatment with lixivaptan.

The below figure shows that in contrast to the fluctuating plasma concentrations of lixivaptan relative to placebo significantly increased serum sodium concentrations are maintained during the morning 8 h dosing interval in CHF patients receiving lixivaptan 30, 75 , 150 or 250 mg BID (Q8/16h):

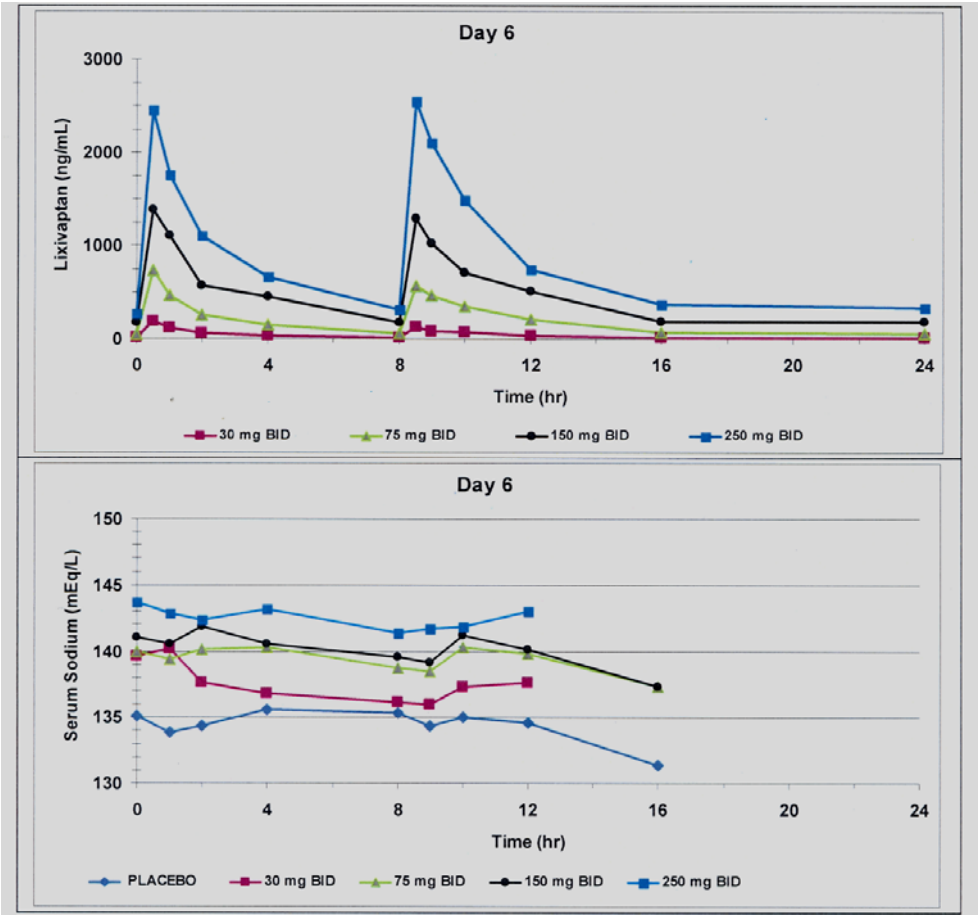


Figure 12: Mean concentration time profiles of lixivaptan (upper panel) and sodium (lower panel) on Day 6 in CHF patients receiving a BID (Q8/Q16h) regimen of placebo (blue rhombi in lower panel) or 30, 75, 150 or 250 mg lixivaptan

There is not enough information available on serum sodium during the afternoon interval to determine the time to offset of the effect.

Vasopressin

A significant and apparently dose dependent increase of the pooled mean peak plasma levels of vasopressin in healthy volunteers after multiple dose QD and BID treatments and in subjects with CHF after multiple dose BID treatments of lixivaptan are shown in the next figure:

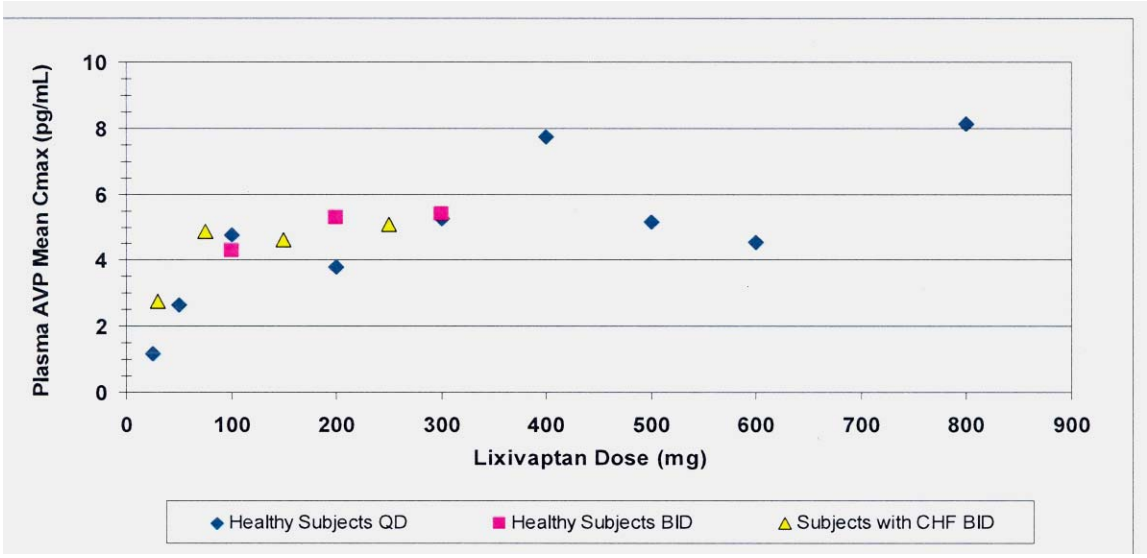


Figure 13: Pooled mean plasma concentrations of vasopressin against lixivaptan dose in healthy subjects after multiple dose QD and BID(Q12h) treatments and in subjects with CHF after a multiple dose BID(Q8/16h) regimen

The results show that administration of lixivaptan triggers a counter-regulatory release of vasopressin which appears to follow a shallow Emax model reflecting likely the limited efficacy of lixivaptan as V_2-antagonist.

Aldosterone

Aldosterone was not routinely measured in the Phase I studies. The available information is too small to draw conclusions.

3.2.4 What are the Characteristics of the Dose-Response Relationships for Safety?

A daily dose of > 200 mg significantly increases the incidence (rate > 5%) of mechanism-related adverse events including thirst, dry mouth, constipation, headache, and dizziness as shown in the below figures. It should be noted that the effects observed > 200 mg could be entirely driven by the findings observed in patients (such as LCWA) who were exposed to very high doses.

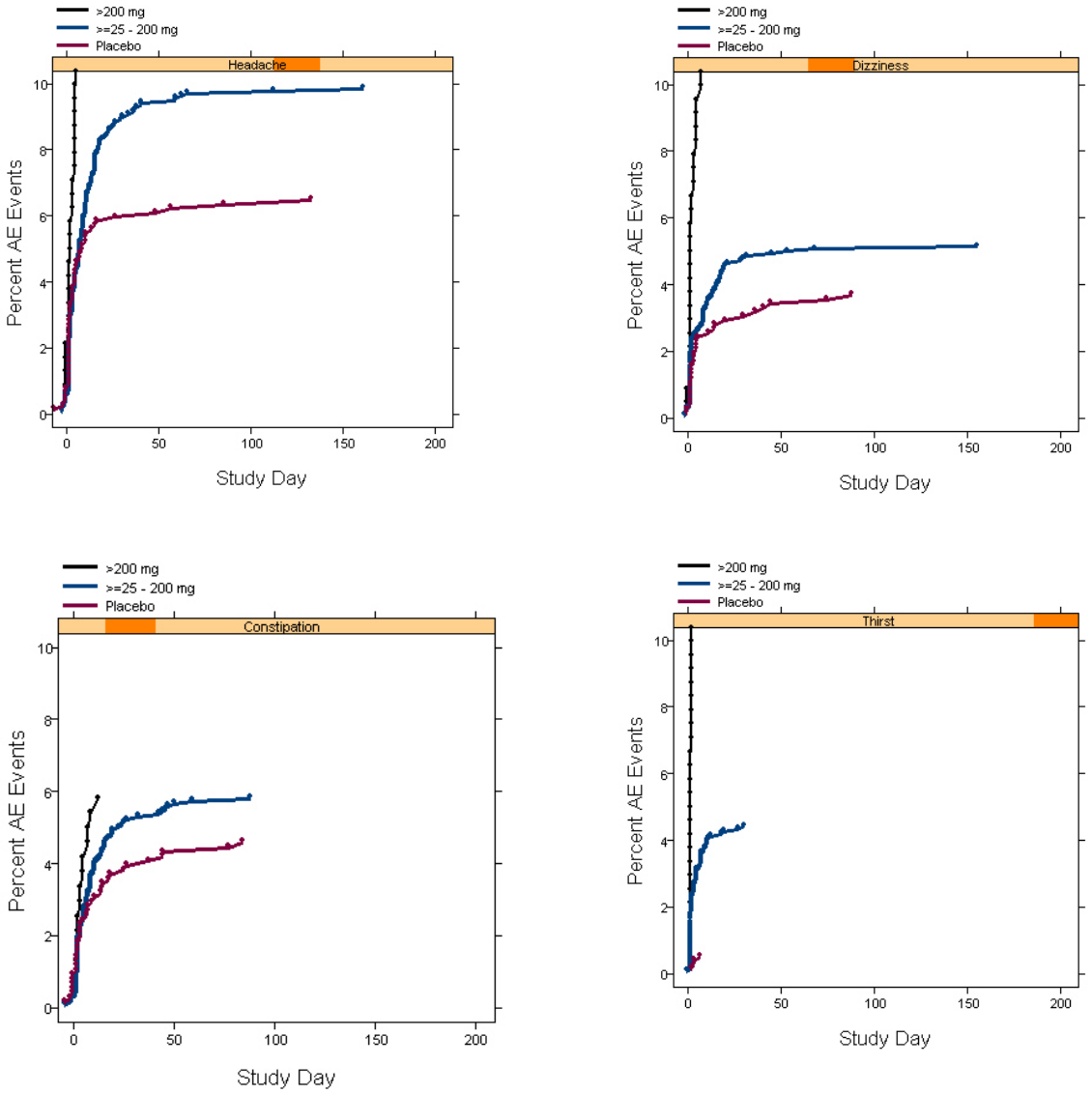


Figure 14: Dose-response relationship for most frequently occurring adverse events observed in Phase I to Phase III trials

3.2.5 Is the proposed dose regimen selected by the sponsor consistent with the known relationship between exposure-response? Are there any unresolved dosing or administration issues?

No. The selected dose regimens may not provide an effect size that is clinically relevant even though they demonstrate a statistically significant increase in serum sodium in the Phase III trials in SIADH and CHF patients.

The dose regimens used in the Phase III trials may have used too low doses and/or too large dose intervals. In Phase II, larger doses and shorter dose intervals were studied, which showed relatively larger effect size in LCWA patients. A prudent approach would

have been to conduct another phase II study in SIADH population spanning the dose range studied in LCWA patients. The uncertain clinical relevance of the small effect size of lixivaptan in SIADH and CHF patients is an unresolved issue.

3.2.6 Was pharmacodynamics of the drug measured in clinical studies? What endpoints were used for exposure-response analysis for either efficacy or safety?

Yes for efficacy. The pharmacodynamic endpoints measured include free water clearance and serum sodium concentration. The change from baseline for serum sodium was used for the exploration of the exposure-effect relationship and the rate of adverse events was used for the evaluation of the exposure-safety-relationship.

3.2.7 Does Lixivaptan or its Metabolites Prolong the QT or QTc Interval?

Lixivaptan in doses of 100 mg or 400 mg BID (Q12h) does not prolong the ΔΔQTcI interval significantly, i.e. the maximum value of the one sided upper 95% CI bound of ΔΔQTcI of 4.85 ms is smaller than 10 ms. It is expected that the 7 day BID treatment used with lixivaptan leads to a significant accumulation not only of the parent drug, but also of the metabolites, so that an inherent significant QTc prolonging activity of the metabolites would have become apparent (see also IRT-QT review)

3.2.8 What are the Single and Multiple Dose PK Parameters of Lixivaptan and Metabolites in Healthy Subjects?

PK parameters for lixivaptan after single and multiple dose administration are available in healthy subjects. Pharmacokinetic information after multiple dose administration of lixivaptan amenable to deriving PK parameters is available for 3 of the 5 structurally identified metabolites, the pharmacologically active WAY137930 and the 2 inactive WAY 141624 and WAY138758.

Non-Compartment Model Approach Using Data from Healthy Subjects

Lixivaptan

The below figure shows the mean plasma concentrations time profile of lixivaptan after single dose administration of 100 mg as three different formulations:

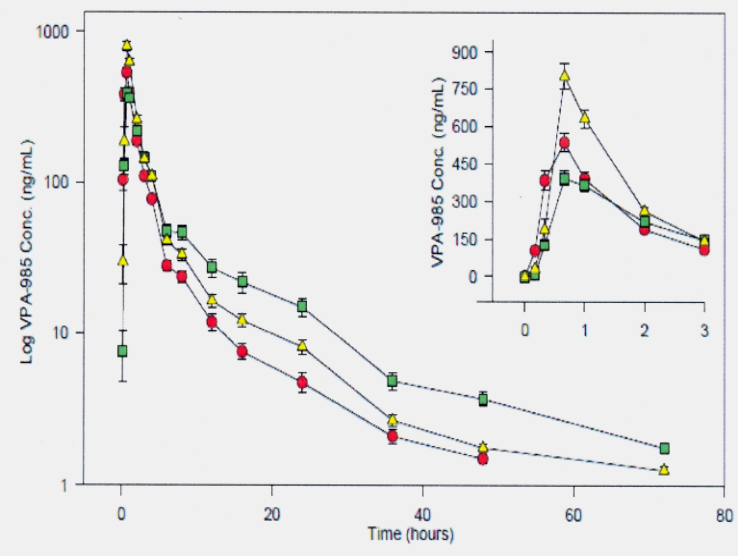


Figure 15: Mean plasma concentrations of lixivaptan after single dose administration of 100 mg lixivaptan as 2 x 50 mg of the-to-be marketed capsule (green squares), 2 x 50 mg of an experimental capsule (red circles) and 100 mg of a suspension (yellow triangles)

With all three formulations peak plasma concentrations are attained in less than 1 h after administration. Thereafter the concentrations of lixivaptan fall off rapidly in an apparent poly-exponential fashion.

PK Parameters after Single Dose Treatments with Lixivaptan in Healthy Subjects (Study 101)

The below tables lists the relevant PK parameters of lixivaptan after single doses ranging between 1 and 500 mg administered as a suspension and between 100 and 400 mg administered as a capsule:

Table 4: Mean (SD)[CV] PK parameters of lixivaptan after single ascending doses ranging from 1 to 500[a] mg administered as a suspension to 7 healthy subjects (Study 101)

Dose	AUC0-inf	Cmax	tmax	t1/2z	CL/F [b]	V_D/F^b
mg	ng•h/L	ng/L	h	h	mL/min	L
15	139 (50.1)[36]	63.8 (23.6)[37]	0.50 (0.10)[20]	5.7 (2.1)[37]	2153(887)[42]	950 (236)[25]
50	767 (219)[28]	287 (36.6)[13]	0.50 (0.20)[42]	12.1 (12)[96]	1267(253)[25]	1079 (661)[61]
100	1609 (283)[18]	670 (121)[18]	0.50 (0.0)[0.0]	6..9 (1.4)[20]	1013(253)[20]	623 (160)[26]
200[c]	3253 (933)[29]	1099 (330)[30]	0.70 (0.30)[36]	8.3 (2.4)[28]	1013(253)[23]	752 (205)[27]
500	10944 (3951)[36]	2875(1028)[36]	0.90 (0.20)[20]	8.9 (1.1)[12]	887(380)[45]	699 (304[43]

[a] PK parameters at selected dose levels are shown [b] normalized to a mean body weight of 76 kg by the Reviewer [c] n=14

After single dose administration of a suspension the absorption of lixivaptan is fast with peak concentrations occurring between 0.50 and 0.70 h. Mean AUC0-inf and Cmax

increases more dose proportionally. The percent coefficient of variation (CV%) for AUC0-inf and Cmax ranges between 18 and 38% and 20 and 38%, respectively. The CL/F decreases with increasing doses indicating nonlinear PK of lixivaptan. The V_D/F appears to decrease with dose as well. The terminal t1/2z of lixivaptan ranges between 5.7 and 16.4 h in different studies with no trend for dose dependency.

PK Parameters after Multiple Dose Treatments with Lixivaptan Administered to Healthy Subjects (Study 102)

The below tables list the relevant PK parameters of lixivaptan after 14 day QD(Q24h) regimens with doses ranging from 25 to 800 mg and BID (12h) regimens with doses of 100, 200 and 400 mg administered as a suspension to healthy subjects:

Table 5: Mean (SD)[CV] PK parameters[a] of lixivaptan on Day 14 after 14 day QD(Q24h) treatments with multiple ascending doses from 25-800 mg lixivaptan as suspension in 5 healthy subjects (Study 102)

Dose	AUC0-24	Cmax	Tmax[b]	CL/F	t1/2z	FI[c]	R_A[d]
mg	ng•h/L	ng/mL	h	mL/min	h		
25	322(100) [31]	153(47)[31]	0.33	1463(698)[48]	11.8(6.0)[51]	128	1.2
50	799(187)[23]	396(94)[24]	0.67	1110(365)[33]	11.2 (1.1)[10]	107	1.3
100	2068(473)[23]	844(158)[19]	0.67	852(250[29]	16.8 (9.2)[55]	106	1.4
200	4779(1474)[31]	1458(348)[24]	0.67	738(170)[23]	12.3 (7.9)[64]	72	1.6
300	398971065)[11]	3042(647)[21]	0.67	510(92)[22]	9.4(2.1)[22]	68	1.6
800	31980(4577)[14]	7874 (1320)[17]	0.83	423(69)[16]	9.7(1.8)[19]	28	1.5

[a] PK parameters at selected dose levels are shown [b]median tmax [c]FI= $Cmax_{Day14post\text{-}morning\ dose}/Cmin_{Day14pre\text{-}morning\ dose}$ [d] $R_A=AUC0\text{-}24_{Day14}/AUC0\text{-}24_{Day1}$

Table 6: Mean (SD)[CV] parameters of lixivaptan on Day 14 after a 14 day BID(Q12h) treatment with doses of 100-400 mg BID as suspension in 5 healthy subjects (Study 102)

Dose	AUC0-12	Cmax	tmax[a]	CL/F	t1/2z	FI[b]	R_A[c]
mg	ng•h/L	ng/mL	h	mL/min	h		
100	2189(513)[23]	859(1340[16]	0.67	795(183)[23]	9.2(3.6)[30]	21	2.1
200	3719(994)[27]	1567(478)[21]	0.67	945 (230)[24]	8.7(3.1)[36]	21	1.3
400	22459(4437)[20]	6471(627)[10]	0.67	307(58)[19]	10.4(3.9)[38]	11	2.7

[a]median tmax [b]$FI=Cmax_{Day14post\text{-}morning\ dose}/Cmin_{Day14pre\text{-}morning\ dose}$ [c] $R_A=AUC0\text{-}12_{Day14}/AUC0\text{-}12_{Day1}$

Under steady-state conditions median tmax varies between 0.33 and 0.83 h with the multiple dose QD regimens indicating rapid absorption of lixivaptan after administration of a suspension or a capsule. The CL/F decreases from 1463 mL/min at the 25 mg dose level to 423 mL/min at the 800 mg dose level indicating non-linear PK with the QD regimen. The apparent t1/2z ranges between 7.9 and 16.8 h. The fluctuation index, FI, decreases from 128 at the lowest dose to 28 at the highest dose as expected for a drug with nonlinear PK. There is little accumulation with the QD regimen over the tested dose range. The CV for AUC0-24 ranges between 10 and 31% and Cmax between 8 and 31%.

With the BID regimen tmax remains small confirming rapid absorption of lixivaptan.

The t1/2 value with the BID regimen is about 9 h. As expected, FI is smaller and R_A is greater with the BID regimen than after the QD treatment at comparable dose levels. The CV(%) for AUC0-12 ranges between 20 and 27% and Cmax between 10 and 21%.

The below table lists the PK parameters of lixivapan on Day 8 of a 7 day BID treatment (Q12h) with doses of 50, 100 and 200 mg administered to healthy subjects:

Table 7: Mean (SD)[CV] PK parameters[a] of lixivaptan on Day 8 after a 7 day BID (Q12h) treatment with multiple doses of 50, 100 or 200 mg lixivaptan administered as the 50 mg to be marketed capsule to 19 healthy subjects (Study CK0407)

Dose	**AUC0-12[a]**	**Cmax[a]**	**tmax[a,b]**	**CL/F**	**t1/2z**	**FI[a,c]**	**R[a,d]**
mg	**ng●h/mL**	**ng/mL**	**h**	**mLl/min**	**h**		
50	1113(501) [45]	390(205) [53]	0.80	1001(716)[72]	8.9	11	2.1
100	2964(1056) [36]	968(199) [20]	0.80	634 (221)[35]	10.3	7.4	2.7
200	6940(2703) [39]	2209(1129)[51]	0.80	550 (201)[37]	10.5	7.0	3.6

[a] after morning dose [b]median tmax [c]$FI=Cmax_{Day8,\ post\text{-}morning\ dose}/Cmin_{Day8,pre\text{-}morning\ dose}$ [d]$R_A= AUC0\text{-}12_{Day\ 8}/AUC0\text{-}inf_{Day\ 1}$

The comparison of the mean PK parameters of studies CK0407 and 102 with identical 100 and 200 mg BID regimens shows a similar tmax with the capsule and suspension formulations. However, the other parameters show significant across study differences for Cmax and AUC0-12 and the derived parameters. Both studies show a trend for a dose dependent decrease in CL/F. The CV for AUC0-12 ranges between 36 and 45% and Cmax between 20 and 53%.

Metabolites

Among the five structurally identified metabolites the pharmacokinetic parameters are known for three, WAY141624, WAY138758 and WAY138451. The below table lists the exposure measures of the metabolites and lixivaptan in healthy subjects receiving a 100 mg BID regimen:

Table 8: Mean (SD)[CV] AUC0-τ and Cmax of WAY141624, WAY138758,WAY138451 and lixivaptan after a 7 day BID regimen with 100 mg lixivaptan as the 50 mg capsule in 36 healthy subjects

Analyte	AUC0-11.5	Cmax	% of Lixivaptan	
	ng● h/mL	ng/mL	AUC0-τ	Cmax
WAY141624	3076(994)[32]	456(138)[30]	110	42
WAY138758	6918(2202)[32]	678(211)[31]	248	63
WAY138451	411(169)[41]	110(44)[40]	15	10
Lixivaptan	2789(972)[35]	1080(461)[43]	100	100

Among the compounds measured the inactive WAY138758 displays the greatest mean exposure followed by the active WAY141624 and lixivaptan and the inactive WAY138451. Lixivaptan shows the greatest peak exposure followed by WAY138758.

Population PK Approach Using Data from Healthy Subjects and Patients

The population PK analysis performed by the sponsor provides a mechanistic explanation for the nonlinearity observed with the two-stage approach. The nonlinearity of the PK of lixivaptan is explained by the existence of parallel linear and nonlinear, nonrenal elimination pathways resulting in a concentration dependent oral clearance as shown in the below figure:

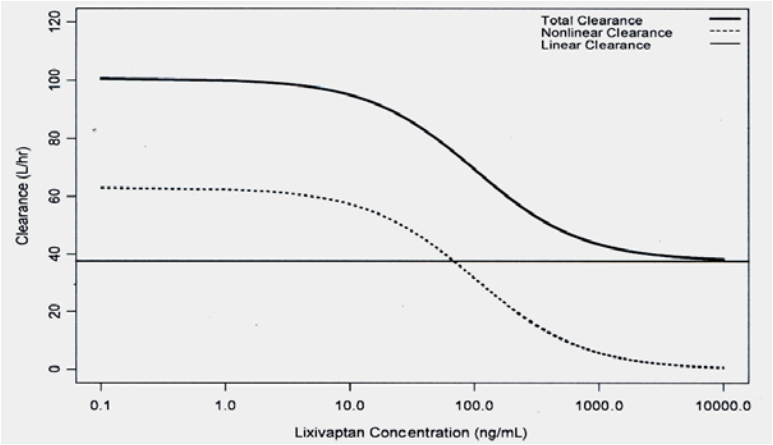


Figure 16: Relationship between total clearance and its linear and nonlinear components and the plasma concentrations of lixivaptan predicted by the population PK model

At concentrations ≤ 1 ng/mL the total, saturable and linear oral clearances of lixivaptan are about 1600, 1000 and 600 mL/min, respectively. At a concentration of 60 ng/mL total, the non-linear and linear clearances are 1200, 600 and 600 mL/min, respectively. At a concentrations of 1000 ng/mL lixivaptan total, saturable and linear clearances are 650, 600 and 50 mL/min, respectively, indicating minimal contribution of the saturable component to the elimination of lixivaptan. The concentrations of lixivaptan at the dose levels tested range up to about to about 1500 ng/mL. The nonlinearity of lixivaptan's PK appears to be largely du to saturability of the first pass. The systemic disposition of lixivaptan appears to be largely dose proportionate.

The mean Vss/F by the population PK approach is about 500 L and dose independent. The volume term with the two stage approach is obtained from $V_D/F= (CL/F)/\lambda z$. With the population PK approach and the two stage approach CL/F is dose dependent, whereas λz as determined by the compartment model independent approach, in contrast to the population approach, is not. This is because λz derived from the terminal low log linear plasma concentrations of lixivaptan. Therefore, the apparent observed dose dependent

decrease of V_D/F by the two stage approach is likely an artifact, and only Vss/F estimated by the population PK analysis should be considered.

3.2.9 How does the PK of either Drug and its Major Metabolites in Healthy Volunteers Compare to that in Patients?

Plasma levels are available only for lixivaptan, but not for the identified metabolites in patients with LCWA, SIADH and CHF.

Non-compartment Model Approach Data in Healthy Subjects

For patients with SIADH the pharmacokinetic information is at hand is insufficent. Data after single and multiple dose administration are available for lixivaptan in CHF and LCWA patients. Only the data after multiple dose BID regimens with unequal Q8 and Q16 h intervals are listed in the below tables:

Table 9: Mean (SD)[CW] PK parameters of lixivaptan in subjects with CHF (NYHA Class II-IV) on Day 6 of a 6 day BID (Q8/Q16h) treatment with multiple doses of lixivaptan administered as suspension All groups contain 5 subjects (Study 114)

Dose	Cmax	tmax	AUC(0-16)	Ctrough[a]	FI[b]
mg	ng/mL	h	ng•h/mL	ng/mL	
30	182(80)[44]	3.5(4.5)[128]	872(87)[10]	12.8	14
75	776(286)[37]	2.6(3.7)[143]	3956(969)[24]	50.5	15
150	1509(463)[31]	2.9(3.9)[135]	10006(4946)[49]	177	8.5
250	2855(803)[28]	5.8(4.1)[71]	17120(31722)[20]	264	3.8

[a] Day 6 pre-morning dose [b]FI=Cmax,Day 6 post-dose/Ctrough, Day 6 pre- morning dose

Table 10: Mean (SD)[CW] PK parameters of lixivaptan in patients with LCWA and mild, moderate or severe Child-Pugh Scores on Day 6 of a 6 day BID (Q8/Q16h) treatment with doses ranging between 25 and 150 mg or a QD(24h) treatment with a dose of 300 mg administered as suspension. All groups contain 5 subjects (Study 118)

Dose	Cmax	tmax[a]	AUC(0-16)	Ctrough[b]	CL/F	FI[c]
mg	ng/mL	h	ng•h/mL	ng/mL	mL/min	
25[d]	287(77)[27]	1.0	2339(467)[20]	45(13[30]	291(56)[19]	6.4
50[d]	438(185)[42]	2.0	5575(2944)[53]	109(36)[33]	321(127)[40]	4.0
100[d]	1952(1218)[62]	1.0	25559(14276)[56]	563(313)[56]	202(152)[76]	3.5
150[d]	2133(1398)[66]	1.0	31323(30335)[97]	635(564)[89]	246(122)[50]	3.4
300[e]	7304(2644)[36]	0.5	39613(21768)[58]	458(211)[46]	157(80)[51]	16

[a] median [b] Day 6 pre-morning dose [c] FI=Cmax,Day 6 post-morning dose/Ctrough,Day 6 pre-morning dose [d]BID [e] QD

The tmax appears to increase in the order healthy subjects, patients with LCWA and patients with CHF. The results on the exposure measures suggest that patients with LCWA (with mild to severe hepatic impairment) exhibit a greater exposure than patients with CHF (NYHA Class II-IV). The smaller FI of LCWA patients relative to CHF patients points to a slower elimination of lixivaptan in the cirrhotic patients. Because of the difference in the dose intervals between the BID regimens in healthy subjects and patients a comparison of the respective parameters is more difficult. The mean CL/F in LCWA patients appears to be smaller than in healthy subjects suggesting that the average exposure in LCWA patients is greater than in healthy subjects. The greater FI seen in healthy subjects than in patients with LCWA patients when both collects receive a 300 mg QD treatment supports this interpretation.
The CV for AUC0-12 ranges between 20 and 97% and for Cmax between 27 and 46% for LCWA patients. The corresponding figures for the CHF patients range between 10 and 46% and 28% and 44%. The inter-subject variability of lixivaptan appears not to be significantly greater in patients compared to healthy subjects after multiple dose administration.

Population PK Approach

The population PK analysis allows a comparison of the PK data in healthy subjects with the three patient populations studied by the sponsor, i.e. patients with LCWA, SIADH and CHF:

Table 11: Fold increase in geometric mean AUC and Cmax of Lixivaptan in LCWA, SIADH and CHF patients referenced to healthy subject, treatments of 100 mg QD or BID, capsules, population PK approach

Covariate	Treatment			
	100 mg QD		100 mg BID	
	Cmax	AUC	Cmax	AUC
LCWA	1.26	2.26	2.01	3.47
SIADH	0.88	1.61	1.22	2.01
CHF	1.08	1.34	1.19	1.46

Compared to the reference subject, a non-African, male healthy volunteer with a lean body weight of 55 kg, the exposure in the patients is increased in the order CHF, SIADH and LCWA. Disease factors impact the exposure in the 3 patient populations differently. The results of the population approach indicate an increased exposure to lixivaptan in patients with SIADH, CHF or LCWA relative to healthy subjects.

3.2.10 What are the Characteristics of Drug Absorption (Possible Transporters and pH Impact)?

Lixivaptan is absorbed rapidly after single dose administration of a suspension in healthy subjects and patients with SIADH, CHF or LCWA with a tmax ranging between 0.3 and

2.5 h post-dose. After multiple dose administration of a suspension of lixivaptan tmax tends to increase in healthy subjects and patients with LCWA and SIADH with no clear dose dependency. The absolute bioavailability of lixivaptan is unknown. However the absorption efficiency determined in the mass balance study indicates that ≥ 26% of a dose of lixivaptan is absorbed systemically. Lixivaptan is highly lipophilic exhibiting low and pH independent water solubility. In vitro data indicate that lixivaptan is not a sensitive substrate of P-gp. Thus, a possibly low absolute bioavailability of lixivaptan is not due to active extrusion via this transporter. However, lixivaptan as a potential substrate of BCRP, an intestinal and hepatic efflux transporter, was not tested.

3.2.11 What are the Characteristics of Drug Distribution (Including Plasma Protein Binding)?

The plasma protein binding of lixivaptan in healthy subjects is extensive with mean percent of free drug ranging between 0.02 and 0.04% in one study and between 0.0081 and 0.0162% in the second study.The proteins involved in the binding of lixivaptan are not known. The fu in patients with ESRD is increased by about 11% compared to healthy subjects. The plasma protein binding of lixivaptan in the other patient group of special interest, subjects with liver impairment, has not been determined by the sponsor. Due to the extensive plasma protein binding of lixivaptan the red cell partitioning is minimal. The estimated mean Vss/F referenced to the unbound drug concentration is about $2 \bullet 10^6$ L in healthy subjects and exceeds total body water by a factor of 40000. This result suggests extensive tissue partitioning of the lipohilic lixivaptan even if the absolute bioavailability of lixivaptan is small.

3.2.12 Does the Mass Balance Study Suggest Renal or Hepatic as the Major Route of Elimination?

The mass balance study indicates that lixivaptan is eliminated exclusively by non-renal pathways. About 26% of the administered radioactivity is recovered in urine and about 74% in the feces. Metabolism contributes significantly to the elimination of lixivaptan. Biliary excretion is possibly an additional route of elimination for lixivaptan and metabolites cannot be excluded. Significant amounts of metabolites were identified in the feces in the mass balance study. Whether they were generated systemically or in the lower intestinal tract by bacteria is unknown.

3.2.13 What are the Characteristics of Drug Metabolism?

The mass balance structurally identified the structure of 5 compounds, lixivaptan and 4 metabolites in plasma. However, only lixivaptan and 3 metabolites were also quantified, namely the aquaretically active metabolite WAY137930 and the inactive WAY141624 and WAY138758. The percent of total radioactivity assignable to lixivaptan, WAY137930, WAY141624 and the end-product WAY138758 is 7.3, 1.1 and 22%, respectively. When expressing the exposure of these metabolites in % of lixivaptan the following values result for WAY137930, 141624 and WAY138758 15.1%, 141%, and 305%, respectively. The other pharmacological active metabolite, WAY138451, was not

quantified in the mass balance study. Thus, a possible contribution of WAY138451 to aquaresis after administration of lixivaptan cannot be excluded.

After multiple doses of 100 mg lixivaptan BID in healthy subjects the average exposure to the active metabolite WAY138451 and the inactive metabolites WAY138758 and WAY141624 relative to lixivaptan is 15%, 248% and 110%, respectively. The value for the exposure to WAY 138758, the metabolite exhibiting the greatest exposure relative to lixivaptan obtained in the single dose mass balance study and the multiple dose study LX-CK0407 are not incompatible.

Lixivaptan contributes 26% and unknown polar metabolites 67% to the total radioactivity excreted in the feces. Polar metabolites are also the major contributors to total radioactivity excreted in urine. Only a small amount of unchanged lixivaptan is excreted in urine. Considering that up to 74% of the administered radioactivity is recovered in the feces, excretion of lixivaptan and/or metabolites in the bile cannot be excluded. The relative contributions of metabolism and bile excretion to the elimination of lixivaptan from the body is unknown.

Based on *in vitro and in vivo* information in animals and man the following metabolic scheme is proposed by the sponsor:

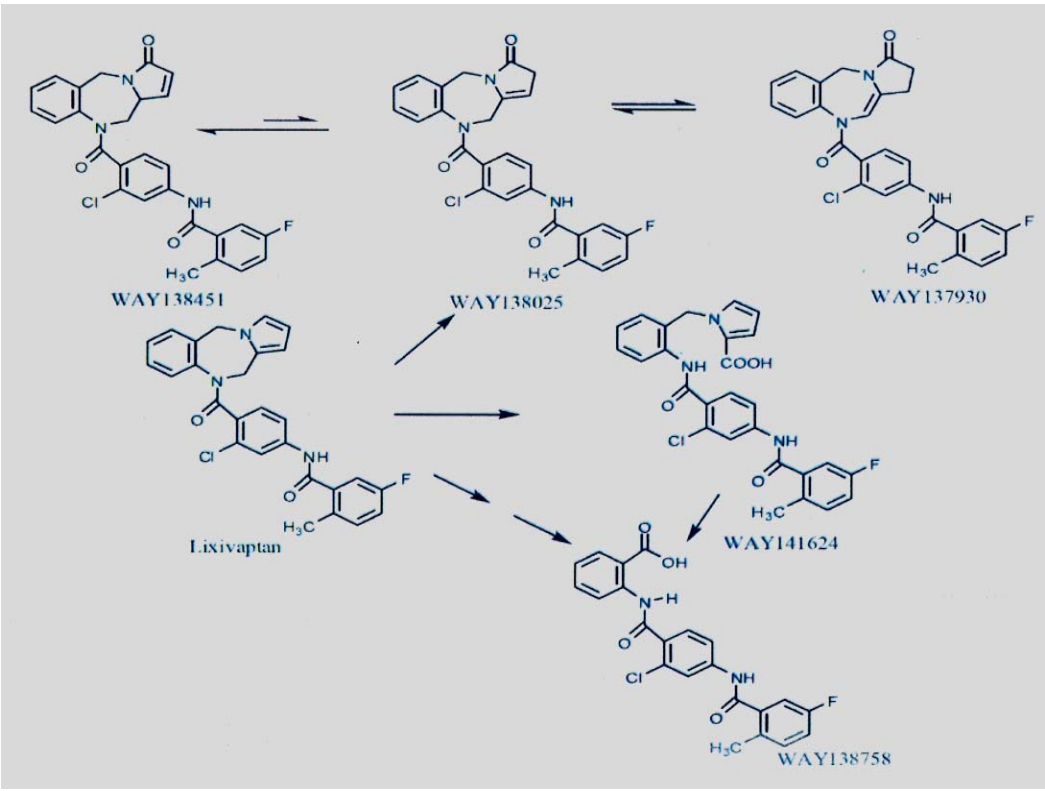


Figure 17: Proposed scheme of the metabolism of lixivaptan in humans

The major metabolites formed by lixivaptan in man include the first generation metabolites WAY138025, WAY141624 and WAY138758. WAY138025 produces non-enzymatically and reversibly the pharmacologically active WAY138451 and WAY137930. WAY138758 is not only produced by lixivaptan, but also by WAY141624. All of these metabolites except WAY141624 are metabolic end-products. In addition to WAY 138758 the other proposed metabolic end products include WAY138451, WAY138025 and WAY137930, but evidence for these claims is not provided. All proposed metabolites appear to retain the fluoride. WAY141624 (pyrrolocarboxylic acid) and WAY138758 (anthranilic acid) contain COOH groups and are expected to be more hydrophilic. The metabolite WAY138025 is not among the metabolites structurally identified in the mass balance study.

3.2.14 Based on the PK Parameters, what is the Degree of Linearity or Non-Linearity in the Dose-Concentration Relationship?

The population PK analysis and the statistical analyses on AUC and AUC0-τ obtained by the non-compartment model PK approach showed that lixivaptan exhibits more than dose proportional PK over the dose range of interest, namely 25 mg to 100 mg QD or BID proposed by the sponsor for the treatment of euvolemic and hypervolemic hyponatremia. The nonlinearity of the PK of the parent drugs is further supported by the less than dose proportional PK of the metabolite WAY141624. The deviation from linearity of the PK of lixivaptan is best illustrated by Figure 16 of Section 3.2.8 depicting the concentration dependency of CL/F established by the population PK analysis approach.

3.2.15. What is the Inter-and Intra-Subject Variability of the PK Parameter, and What are the Major Causes of Variability?

The range of the inter-subject variability of the exposure measures of lixivaptan expressed as coefficient of variation about the respective mean values are shown in the below table for the multiple dose regimens of lixivaptan with doses ranging between 25 and 100 mg lixivaptan QD and BID:

Table 12: CV(%) about mean Cmax and AUC0-τ of lixivaptan after multiple dose QD and BID regimens in healthy subjects and patients with LCWA or CHF

Regimen	**Healthy Subjects[a]**		**LCWA[b]**		**CHF[c]**	
	Cmax	**AUC**	**Cmax**	**AUC0-τ**	**Cmax**	**AUC0-τ**
25 mg QD	31	31	ND	ND	ND	ND
50 mg QD	23	24	ND	ND	ND	ND
100 mg QD	23	19	ND	ND	ND	ND
200 mg QD	31	24	ND	ND	ND	ND
25 mg BID	ND	ND	27	20	44[e]	10[e]
50 mg BID	ND	ND	42	53	37[f]	24[f]
100 mg BID	19	23	62	56	31[g]	49[g]
200 mg BID	24	27	66[d]	97[d]	28[h]	20[h]

ND= not determined [a] Study 102 [b]Study 118 [c]Study 114 [d]150 mg [e]30 mg [f]75 mg [g]150 mg

[h]250 mg

The exposure measures of lixivaptan show intermediate intersubject variability in patients with CHF and LCWA. The small numbers of between 5 and 7 subjects per dose group used in the studies should be noted. Contributing factors to inter-subject variability may be the limited aqueous solubility of the drug substance, the nonlinearity of the kinetics and disease factors in the patients. The inter-subject variability of CL/F estimated by the population PK approach is 55%.

3.3 INTRINSIC FACTORS

3.3.1 What Intrinsic Factors (Age, Gender, Race, Weight, Height, Disease, Genetic Polymorphism, Pregnancy, and Organ Dysfunction) influence Exposure and/or Response, and what is the Impact of any Differences in Exposure on Efficacy or Safety Responses?

Impact of Hepatic Impairment, Congestive Heart Failure (NYHA Class II-IV), Bodyweight, Sex, or Race:
The relative importance of the individual intrinsic factors for the exposure of lixivaptan assessed by the sponsor's population PK analysis is shown in the below table:

Table 13: Impact of intrinsic covariates[a] on exposure to lixivaptan in subjects on lixivaptan 100 mg QD or BID estimated by the population approach

Covariate	**Treatment**			
	100 mg QD		**100 mg BID**	
	Cmax	**AUC0-τ**	**Cmax**	**AUC0-τ**
LCWA[b]	1.3	2.3	2.0	3.5
SIADH[b]	0.88	1.6	1.2	2.0
CHF[b]	1.1	1.3	1.2	1.5
Female	1.2	1.0	1.2	1.0
African American	1.0	0.95	0.94	0.98
LBWT =35 kg	1.1	1.3	1.1	1.3
LBWT = 85 kg	0.93	0.79	0.89	0.75

[a] impact of a particular covariate is estimated from the ratio of the geometric means of Cmax or AUC in presence and absence of that covariate [b] relative to healthy reference subject (non-African, male)

The results indicate that BW, age, race, or sex do not exhibit a significant impact on the exposure to lixivaptan. However, disease factors in SIADH- or LCWA- patients, but not in CHF patients alter the exposure to lixivaptan. The below table compares the exposure measures obtained in LCWA patients to those in patients with SIADH and CHF to better quantify the impact of liver impairment in the LCWA patients:

Table 14: Impact of cirrhosis on the exposure to lixivaptan in LCWA patients on 100 mg QD or BID estimated by comparison with SIADH and CHF patients, population PK approach

Comparison	100 mg QD		100 mg BID	
	AUC	Cmax	AUC	Cmax
LCWA/SIADH	1.4	1.4	1.7	1.7
LCWA/ CHF	1.7	1.2	2.4	1.7

The results indicate that LCWA patients experience a greater increase in exposure to lixivaptan than patients with CHF or SIADH, which is attributable to liver cirrhosis. The increase in exposure in the LCWA patients relative to the CHF patients is greater than relative to the SIADH patients. The reason for the difference between SIADH and CHF patients is not overt. A dedicated study in patients with hepatic impairment of different etiologies was not conducted by the sponsor.

Renal Impairment: The geometric mean ratios of AUC and Cmax of lixivaptan referenced to the total (bound+unbound) plasma concentration in patients with end-stage renal disease relative to healthy subjects matched for age, weight and sex are 68 and 69%, respectively. When referenced to the unbound plasma concentration of lixivaptan the geometric mean ratios for AUC and Cmax are 87 and 90%, respectively. The latter values indicate a marginal decrease in exposure to lixivaptan in ESRD.

Genetic Polymorphism: No PD or PK related genetic polymorphisms are known for lixivaptan.

3.3.2 Based on what is Known about Exposure-Response Relationships, what Dosage Regimen Adjustment, if any, are Recommended Based Upon the Exposure-Response Relationship?

None of the intrinsic factors age, BW, race, sex or CLcr impacts the exposure such that an adjustment of the dose of lixivaptan is warranted in patients with SIADH, CHF or LCWA. Disease factors in SIADH and LCWA affect exposure to lixivaptan significantly, but not in patients with CHF.

The significantly greater exposure observed in LCWA patients when compared to CHF or SIADH patients indicates that liver cirrhosis impairs the disposition of lixivaptan. The unbalanced deaths and higher dropout rates in LCWA patients occurring in the Phase II trials suggested a reduced tolerability for lixivaptan. Therefore, administration of lixivaptan to patients with SIADH or CHF with liver impairment caused by cirrhosis should be avoided.

3.4 EXTRINSIC FACTORS

3.4.1 Is there an in vitro Basis to Suspect in Vivo Drug-Drug Interactions?

Yes. Reaction phenotyping with human liver and intestinal microsomes shows that CYP3A is involved in the metabolism of lixivaptan. *In vitro* evidence suggests that CYP2C8 plays also a role in the hepatic metabolism of lixivaptan. However, the relative quantitative contribution of CYP2C8 to the overall metabolism of lixivaptan is unclear.

In vitro studies with hepatic microsomes exposed to lixivaptan and 3 of the 5 structurally identified metabolites provide the results summarized in the below 2 tables:

Table 15: *In vitro* potential (I/Ki) of lixivaptan and metabolites WAY141624, WAY138451, and WAY138758 to inhibit CYPs3A, 2C8 and 2C9 using human liver microsomes

		Inhibition of CYP2C8			Inhibition of CYP2C9 [a]			Inhibition of CYP3A4 (Midazolam)			Inhibition of CYP3A4 (Testosterone)		
Compound	Units	K_i [b]	C_{max} [c]	I/K_i	K_i	C_{max} [c]	I/K_i	K_i	C_{max} [c]	I/K_i	K_i	C_{max} [c]	I/K_i
Lixivaptan	µM	0.43	2.04	4.74	0.35	2.04	5.8	0.3	2.04	6.8	0.2	2.04	10.2
	ng/mL	203	968		166	968		142	968		95	968	
WAY-138451	µM	2.2	0.23	0.10	4.0	0.23	0.06	1.7	0.23	0.14	4.9	0.23	0.05
	ng/mL	1043	112		1896	112		806	112		2322	112	
WAY-141624	µM	4.4	0.89	0.20	>30	0.89	<0.03	>30	0.89	<0.03	>30	0.89	<0.03
	ng/mL	2085	454		>14218	454		>14218	454		>14218	454	
WAY-138758	µM	1.5	1.54	1.03	0.54	1.54	2.9	>30	1.54	<0.05	>30	1.54	<0.05
	ng/mL	711	658		256	658		>14218	658		>14218	658	

[a] From the FDA Guidance, Drug Interaction Studies—Study Design, Data Analysis, and Implications for Dosing and Labeling, September 2006, which defines clinical relevance of $[I]/K_i$ ratios (µM metabolite concentrations calculated using molecular weights of 490, 506, and 427 for WAY-138451, WAY-141624, and WAY-138758, respectively). The prediction of clinical relevance of competitive CYP inhibition is as follows: $I/K_i>1$=Likely; $1>I/K_i>0.1$=Possible; $0.1>I/K_i$=Remote.

[b] Study 2110-0520-2300 contains the K_i values.

[c] C_{max} values of lixivaptan and metabolites observed in Study CK0407 and Study CK-LX1403, respectively, after dosing 100 mg lixivaptan capsules BID for seven days.

BID=Twice daily. C_{max}=Maximum plasma concentration. CYP=Cytochrome P450. FDA=Food and Drug Administration. I=Concentration of inhibitor. K_i=Dissociation constant of inhibitor.

Table 16: In vitro potential (IC_{50} µM) of lixivaptan, WAY141624, WAY138451 and WAY138758 to inhibit the major CYP enzymes using human liver and intestinal microsomes

	Estimated IC_{50} (µM)			
	VPA-985	WAY-138451	WAY-141624	WAY-138758
CYP1A2	>100	>30	>30	>30
CYP2A6	>100	>30	>30	>30
CYP2B6	12	>30	>30	>30
CYP2C8	0.57	4.2	8.5	3.3
CYP2C9	0.79	6.3	>30	1.0
CYP2C19	54	>30	>30	>30
CYP2D6	>100	24	>30	>30
CYP2E1	>100	>30	>30	>30
CYP3A4 (M) HLM*	10	3.4	>30	>30
CYP3A4 (M) HIM**	4.4	3.5	>30	>30
CYP3A4 (M) 3A5-***	4.3	2.9	>30	>30
CYP3A4 (T) HLM	28	17	>30	>30
CYP3A4 (T) HIM	22	20	>30	>30
CYP3A4 (T) 3A5-	28	>30	>30	>30

M = Midazolam
T = Testosterone
*HLM = Human Liver Microsomes
**HIM = Human Intestinal Microsomes
***3A5- = Human Liver Microsomes known to be deficient in CYP3A5

The combined results from Tables 15 and 16 indicate:

- Both lixivaptan and WAY138451 are time dependent inhibitors of CYP3A
- Lixivaptan, WAY141624, WAY138451, and WAY138758 reversibly inhibit CYP2C8
- Lixivaptan, WAY138451 and WAY138758 inhibit reversibly CYP2C9
- Lixivaptan exhibits a weak inhibitory potential for CYPs2B6 and 2C19
- WAY138451 shows a weak inhibitory potential for CYP2D6

The calculated I/Ki ratios predict the following probabilities for a CYP mediated drug interaction *in vivo*:

- Lixivaptan is likely to inhibit CYPs2C8, 2C9 and 3A
- WAY138758 is likely to inhibit CYPs2C8 and 2C9
- WAY138451 possibly inhibits CYPs2C8 and 3A
- WAY141624 possibly inhibits CYP2C8

Additional *in vitro* results show that:

- Lixivaptan is a substrate of CYP3A and CYP2C8 in that order
- Lixivaptan is an inhibitor of the efflux transporter BCRP
- Lixivaptan appears not to be a significant inducer of CYP3A in vitro
- Lixivaptan is not a sensitive substrate of P-gp
- Lixivaptan is not an inhibitor of the efflux transporter P-gp or the hepatic uptake transporters OATP or OCT1 or the renal uptake transporters OCT2, OAT1 or OAT3

In conclusion, lixivaptan shows a significant drug interaction potential *in vitro*: as a substrate of CYP3A and possibly CYP2C8 co-administered drugs inducing or inhibiting these enzymes may impact *in vivo* the exposure to lixivaptan. On the other hand lixivaptan can significantly inhibit the activity of CYPs3A, 2C8 and 2C9 and the efflux transporter BCRP, thus impacting the exposure to other drugs which are substrates of these functional proteins. Of note the possibility that lixivaptan is a substrate of OATP or BCRP was not investigated.

3.4.2 Is Lixivaptan a Substrate of CYP enzymes?

Yes, see Section 3.4.1

3.4.3 Is Lixivaptan an Inhibitor and/or an Inducer of Enzymes?

See 3.4.1 for lixivaptan and metabolites as inhibitors. Lixivaptan does not exhibit a significant potential for enzyme induction.

3.4.4 Is the Drug a Substrate, an Inhibitor and/or an Inducer of Transporters?

See 3.4.1 The induction of transporters by lixivaptan was not studied.

3.4.5 Are there other Metabolic/Transporter Pathways that may be Important?

The identified radioactivity in percent of total radioactivity is 40-50%, indicating formation of additional metabolites with unknown pharmacological activity and elimination pathways. Exposure to some of these metabolites may be significant.

3.4.6 Are there any in-vivo Drug-Drug Interaction Studies that indicate the Exposure alone and/or Exposure-Response Relationships are Different when Drugs are co-administered? If yes, is there a Need for Dosage Adjustment?

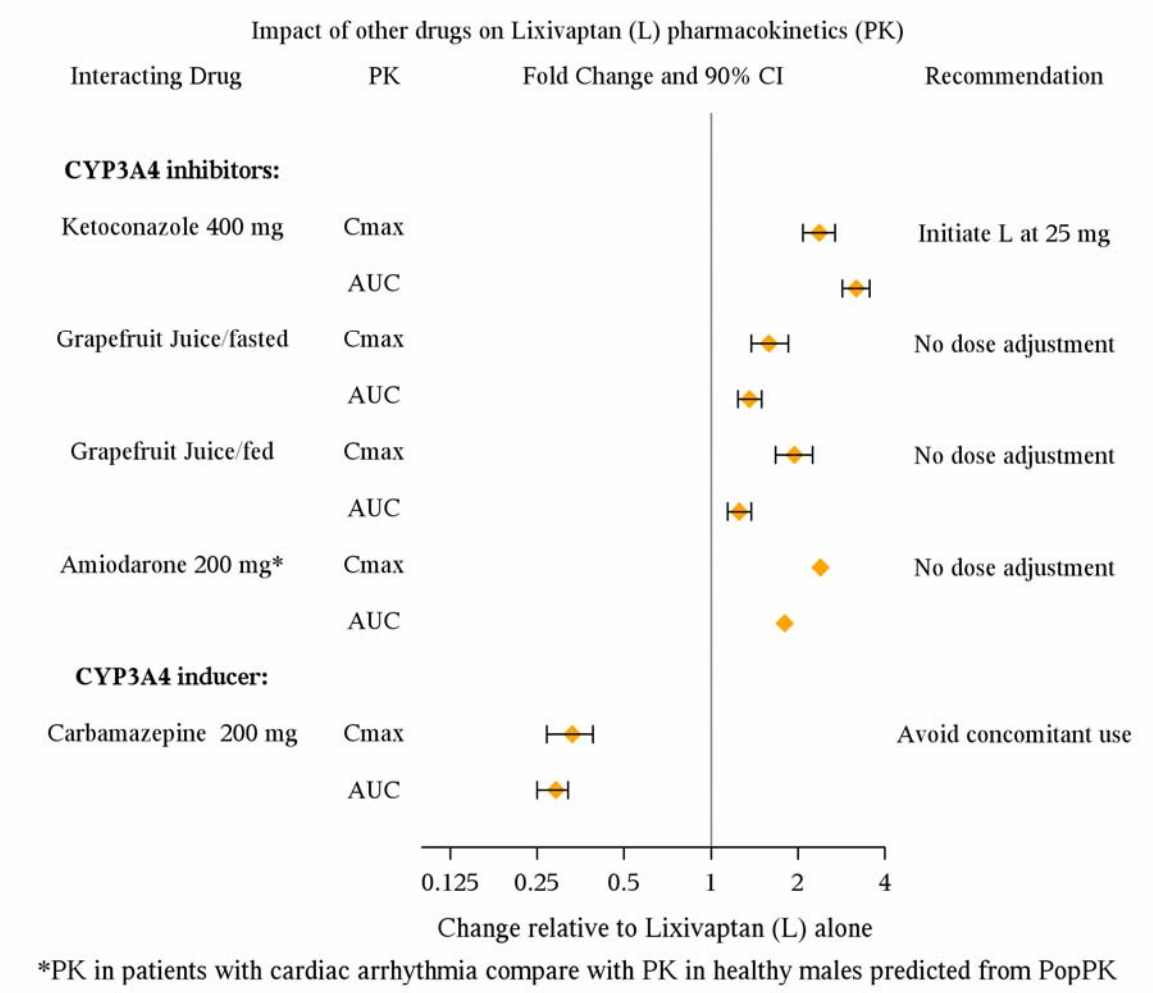
Based on nonclinical data, the potential for other drugs to affect lixivaptan exposure appears to be primarily related to the inhibition or induction of CYP3A and CYP2C8 and the inhibition of BCRP. In addition, the potential of lixivaptan to affect exposure of other drugs is primarily related to the inhibition of CYPs3A, 2C8 and 2C9 and BCRP by lixivaptan. Therefore, the primary focus of clinical interaction studies was to evaluate the effect of CYP3A modulators on lixivaptan's PK and the effect of lixivaptan on substrates of CYPs3A, 2C8 and 2C9 and BCRP. Thirteen (13) clinical drug interaction studies with lixivaptan and CYP3A modulators, CYP3A- and CYP2C9 substrates and commonly co-administered drugs investigated the impact on exposure alone or on exposure and response. These dedicated drug interaction studies were, except for one, conducted in healthy subjects and analyzed by the non-compartment model approach. In the Phase III trials co-administration of weak and moderate CYP3A inhibitors and CYP3A inducers was permitted and these data were analyzed by the population PK approach. *In vivo* studies determining the impact of CYP2C8 inhibitors on lixivaptan and of lixivaptan on CYP2C8 substrates were not conducted. In addition, there is a need for *in vitro* studies determining whether lixivaptan is a substrate of OATP or BCRP.

The PK and PD results of the dedicated drug-drug interaction studies in healthy subjects analyzed by the non-compartment model approach as well as the PK results obtained in the Phase III trials in patients with SIADH or CHF using the population PK approach are shown below:

3.4.6.1 Pharmacokinetic results

3.4.6.1.1 Impact of other drugs on lixivaptan in healthy subjects, non-compartment model approach

The impact of CYP3A modulators on lixivaptan PK including recommendations for dose adjustment is summarized in the below Forest plot:



3.4.6.1.2 Impact of other drugs on lixivaptan in healthy subjects and patients with SIADH, CHF or LCWA analyzed by the population PK approach

The impact of CYP3A inducers and weak or moderate CYP3A inhibitors is summarized in the below table:

Table 17: Fold change in exposure to lixivaptan by weak or moderate CYP3A inhibitors in patients or CYP3A inducers in healthy subjects or patients, geometric means ratios are shown

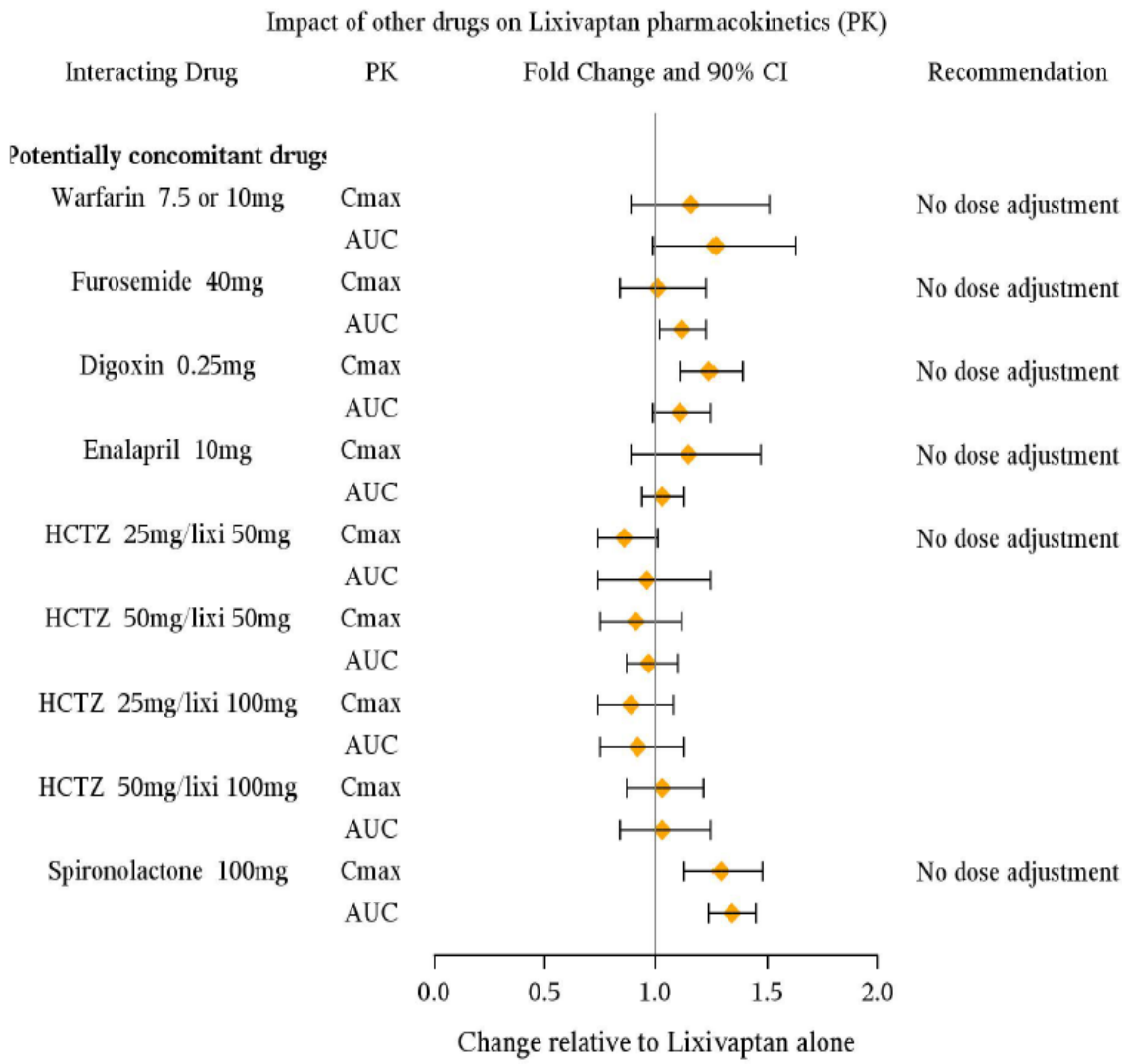
	Treatment			
	100 mg QD		**100 mg BID**	
	AUC0-τ	**Cmax**	**AUC0-τ**	**Cmax**

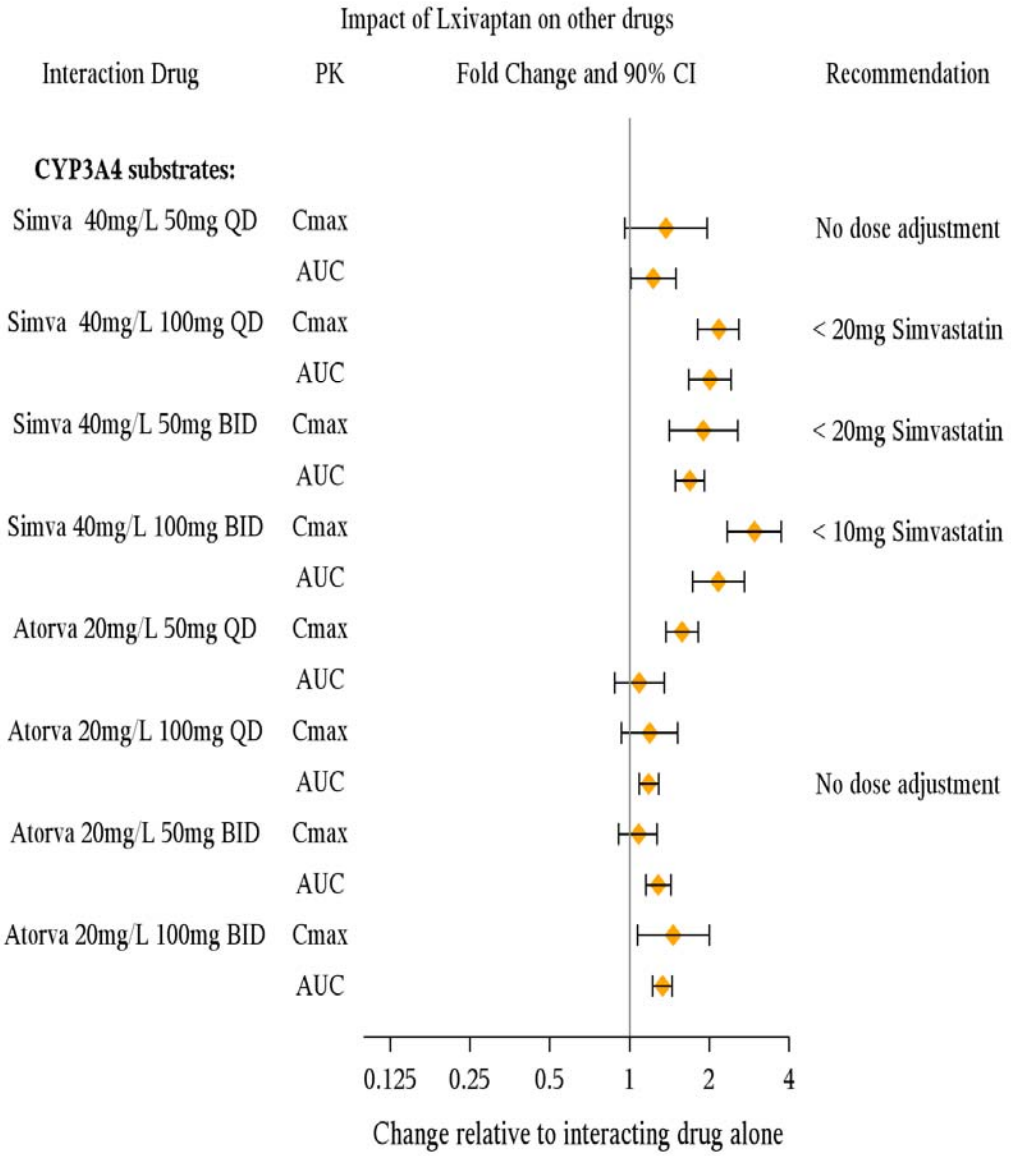
Healthy subjects, CYP3A inducers	0.14	0.27	0.13	0.24
SIADH, CYP3A inducer	0.16	0.32	0.12	0.22
SIADH, weak or moderate CP3A inhibitor	1.4	1.1	1.9	1.6
CHF, weak or moderate CYPA inhibitor	1.5	1.1	1.8	1.4
LCWA, weak or moderate CYP inhibitor	1.3	1.1	1.8	1.6

The results indicate a large reduction of the exposure to lixivaptan by co-administered CYP3A inducers in healthy subjects and SIADH patients. The increase in exposure of lixivaptan when co-administered with moderate or weak inhibitors in patients with SIADH, CHF or LCWA is comparable.

3.4.6.1.3 Impact of other drugs on lixivaptan, healthy subjects, noncompartment model approach

The effect of other often co-administered drugs on the PK of lixivaptan including recommendations is shown in the next 2 Forest plots:





3.4.6.2 Pharmacodynamic Results:

3.4.6.2.1 Dedicated studies, healthy volunteers, non-compartment model dependent approach

Warfarin
The results show a trend for marginally lower INR values after concomitant administration of warfarin and lixivaptan. The INR values before concomitant treatment average 1.8, with relatively low variability. On Day 2 of concomitant administration mean INR values reach their nadir at 1.6 and then remain steady at 1.7. The 90% confidence intervals of the geometric means ratios for each treatment day are within 81 to 102%.

Digoxin, furosemide, enalapril, hydrochlorothiazide and spironolactone
The studies with co-administration of lixivaptan and digoxin, enalapril, furosemide, hydrochlorothiazide and spironolactone showed no impact on mutual exposure. Pharmacodynamic measures including urinary output, urine osmolality and serum sodium were assessed in the interaction studies with enalapril, furosemide, and hydrochlorothiazide. When lixivaptan and furosemide were co-administered urinary output and flow at 2 and 3 h post-dose increased significantly, whereas the serum sodium concentration did not change compared to alone treatment with lixivaptan or furosemide. No significant difference in urine output or osmolality was observed when enalapril is added to lixivaptan. Co-administration of 25 or 50 mg hydrochlorothiazide with lixivaptan produced an increase in 4 h urine volume compared to lixivaptan or hydrochlorothiazide alone. The additive aquaretic effect after co-administration of the two diuretics is expected. However, no statistically significant increase in the 24 h urine volume was observed when 50 mg HCTZ is co-administered with 100 mg lixivaptan

Recommendations based on the Results of the Drug-Drug Interactions Studies

Given the safety concerns caused by the unexplained deaths in the CHF patients in the Phase 3 trials OCP is not in a position to recommend labeling of lixivaptan in the CHF population.

With the SIADH population no overt safety issues became apparent in the Phase III trials. The maximum safe increase in the exposure to lixivaptan was estimated from the inter-subject variability about the mean exposure observed in the Phase III trials in the patients receiving 100 mg QD or BID treatments. The so estimated value is about 3. The below recommendations are for patients with SIADH:

Initiate lixivaptan at 25 mg in hospitalized patients on strong CYP3A inhibitors.
In the Phase III trials co-administration of strong CYP3A inhibitors with lixivaptan was not permitted. Therefore, the Phase 3 trial population was not exposed to a 3 fold higher exposure to lixivaptan when lixivaptan is initiated at the 25 mg or 50 mg dose level, in the presence of strong CYP3A inhibitors. However, the 3 fold increase in lixivaptan exposure could results in a too rapid increase in serum sodium. The reduction of the dose from 50 to 25 mg minimizes the risk of this occurring.

No dose adjustment is warranted in patients when weak and moderate CYP3A inhibitors are co-administered with lixivaptan

The exposure increase to lixivaptan by the moderate and weak CYP3A inhibitors, single strength orange juice and amiodarone, respectively, in the range between 1.9 to 2.4 fold, is well within the safe range. Co-administration of weak to moderate CYP3A inhibitors was permitted in the Phase III trials and the results confirmed the about 2 fold increase of the exposure to lixivaptan seen in the dedicated interaction studies in healthy subjects when lixivaptan was co-administered with grapefruit juice or amiodarone.

Co-administration of CYP3A inducers and lixivaptan should be avoided

Co-administration of the CYP3A/2C inducer carbamazepine reduces the exposure to livipatan to at least 30%. As a result of the induction peak exposure and possibly average exposure to the lixivaptan metabolites could be increased substantially and beyond levels expected for the Phase III trials.

Dose adjustments of simvastatin are required when co-administering lixivaptan with simvastatin

Co-administration of lixivaptan and simvastatin increases dose- and dose interval dependently the exposure to simvastatin requiring a dose reduction from 40 mg to 20 mg when lixivaptan 100 mg, QD or 50 mg BID or 10 mg when lixivaptan 100 mg BID is co-administered. The proposed dose adjustment is consistent with that proposed for simvastatin when co-administered with other CYP 3A inhibitors.

3.5 GENERAL BIOPHARMACEUTICS

3.5.1 What is the Bioavailability of the-to-be-Marketed 25 mg Capsule to the to-be-Marketed 50 mg Capsule and the Bioavailability of the Suspension relative to the-to-be Marketed Capsule?

Bioavailability of the 25 mg Capsule Relative to the 50 mg Capsule

The below table lists the exposure measures for lixivaptan for the 25 mg capsule relative to the 50 mg capsule:

Table 18: Geometric means ratios (90% CI) of Cmax and AUC of lixivaptan for the-to-be marketed 25 mg capsule relative to the to-be-marketd 50 mg capsule, healthy subjects, non-compartment model dependent approach

25 mg vs 50 mg Capsule (n=27)	
AUC[a]	**Cmax[a]**
1.12 (1.01, 1.24)	1.34 (1.16, 1.54)

[a] AUC and Cmax of the 25 mg capsule are dose normalized to 50 mg
Red colored numbers are outside of the bioequivalence range

A single 50 mg capsule and a single 25 mg capsule instead of two 25 mg capsules were administered to the subjects in the study. The Cmax and AUC values after administration of the 25 mg capsule were normalized to a dose of 50 mg. After administration of two capsules of 25 mg the point estimate for AUC is expected be greater than 1.2 using dose normalization, given that the kinetics of lixivaptan is nonlinear. The point estimates and 90% CI of the 25 mg capsule are meeting the bioequivalence criteria, whereas the corresponding estimates for Cmax do not. The increase in Cmax of the lower strength capsule relative to the higher strength capsule is small. Both formulations were tested in the pivotal Phase 3 trials. Therefore, the noted shortcomings are unlikely to affect efficacy or safety of lixivaptan significantly.

Bioavailability of the Suspension Relative to the to-be-marketed 50 mg Capsule
The single dose comparison of the formulations using the two stage approach shows that peak exposure to lixivaptan with the suspension is greater, whereas the average exposure to lixivaptan is smaller compared to the 50 mg capsule.

The population PK analysis using information from multiple dose studies in healthy subjects and patients provides estimates for the bioavailability of the suspension relative to the 50 mg capsule. The results are shown below:

Table 19: Point estimates (90% CI) for Cmax and AUC of a suspension relative to the-to-be marketed 50 mg capsule in healthy subjects and patients

Single Dose Administration, Non-compartment Model Approach			
100 mg Suspension vs. 2 x 50 mg Capsule (n=24)			
AUC		**Cmax**	
0.76 (0.70, 0.81)		1.32 (1.18, 1.49)	
Multiple Dose Administration, Population PK Approach			
100 mg Suspension QD vs. 2x 50 Capsule BID			
AUC	**Cmax**	**AUC**	**Cmax**
0.85 (0.82, 0.88)	1.51 (1.45, 1.57)	0.80 (0.77, 0.82)	1.35 (1.30, 1.40)

The single dose data evaluated by the non-compartment model approach and the multiple dose data analyzed by a population PK approach show similar results. The suspension is absorbed faster than the capsule, but that the suspension exhibits a 15-20% smaller extent of absorption than the capsule after a multiple dose treatments of 100 mg QD or Q12 in healthy subjects.

3.5.2 What is the impact of food on the bioavailability of lixivaptan from the-to-be marketed 50 mg capsule?

The AUC and Cmax measures of lixivaptan in the fasted state and after ingestion of a fat and calorie rich breakfast are listed in the below table:

Table 20: Point estimates and 90% confidence intervals for AUC and Cmax of lixivaptan administered as 4 x 50 mg capsules to young healthy subjects in the fasted state or after intake of a fat and calorie rich breakfast (FDA breakfast), two stage approach

Treatment	Point Estimate (90% CI)	
	AUC	Cmax
FDA Breakfast	1.09 (0.99, 1.19)	0.88 (0.76, 1.01)

The results indicate that a high fat and caloric breakfast has not impact on the exposure to lixivaptan. Lixivaptan is likely a BCS Class IV compound and the absence of a food effect is not a given.

3.5.3 Is there a Dose–Dumping for Lixivaptan when the- to-be marketed Capsules are administered together with Food?

No.

3.5.4 What Dosing Recommendations should be made, if any, regarding Administrationof the Product in Relation to Meals or Meal Types?

Lixivaptan can be administered in the fasted or fed state.

3.6 ANALYTICAL SECTION

3.6.1 How are the Active Moieties Identified and Measured in Plasma in the Clinical Pharmacology and Biopharmaceutics Studies?

Lixivaptan, WAY141624, WAY138451 and WAY138758 are measured by validated LC-MS/MS methods.

3.6.2 What is the Range of the Standard Curve? How does it relate to the Requirements for Clinical Studies? What Curve Fitting Techniques are used?

The plasma samples for lixivaptan were assayed by Wyeth-Ayerst, Taylor Technology, Inc. (formerly SFBC Taylor Technology, Inc., and currently Pharmanet) and Covance Bioanalytical Services using validated procedures including liquid/liquid extraction of the plasma samples using methyl-tert- butyl ether, separation, evaporation, and reconstitution with 50% acetonitrile of the supernatant extract, followed by HPLC-ESI/MS/MS chromatography and quantitation with an internal standard using the peak response ratios of the samples and lixivaptan QC- and calibration standard samples against a deuterated lixivaptan internal standard spiked into each standard and sample.

The plasma concentrations for WAY141624, WAY138451 and WAY138758 are also measured by a LC-MS/MS assay with an internal standard. The assay was performed by Pharmanet USA, Inc. (formerly known as Taylor Technology, Inc.)

The assay methods and respective linear range of the calibration curves are listed in the below Table 21:

Table 21: Linear range of calibration curves of assay methods used to measure lixivaptan in plasma

Laboratory	Linear Range ng/mL
Lixivaptan	
Taylor	1-200
Covance	1-200
Wyeth-Ayerst	5-5000
WAY141624	
Taylor	5-2000
WAY138451	5-2000
Taylor	
WAY138758	5-2000
Taylor	

The selected ranges of the standard curves of the assays for lixivaptan (after appropriate dilution) cover the plasma concentrations of interest.

The identification and quantification methods for lixivaptan and metabolites in plasma, urine and feces in the mass balance study determined by used two HPLC systems and 5 different chromatographic gradients.

3.6.3 What Analytical Methodologies were used to Assess Pharmacodynamic Action?

Serum Sodium Concentration Measurements

The method for measuring serum sodium in the clinical pharmacology studies is not indicated in the study reports.

Free Water Clearance

Serum and urine osmolality are quantified by a freezing point depression osmometer. Urine flow is measured by dividing the urine volume excreted by the time of the collection interval.

Vasopressin

Vasopressin (AVP) is measured by a RIA method using Durr antibody after extraction. A validation report for the RIA method does not exist. QC samples are measured along the samples with unknown concentrations. The inter-assay precision is ≤17% estimated from 5 studies. Results on the vasopressin levels are available from 7 studies in healthy subjects, patients with SIADH, CHF or LCWA. The protocols of 9 studies prescribed measurement of vasopressin levels. However, no assay reports are available for 2 studies. For one of these studies the vasopressin levels are reported in the main report.

3.6.4 Were the Validation Characteristics of the Assays Acceptable?

LC-MS/MS Assay for Lixivaptan

The validation characteristics of the LC-MS/MS assays for lixivaptan and WAY141624, WAY178451 and WAY 138758 are acceptable. Short term matrix stability with exposure of the samples to room temperature for 24 h or at -70 °C for 7 days and long term matrix stability with exposure of the samples to up to 1124 days at -70 °C and 4 freeze/thaw cycles are demonstrated. Process sample viability is demonstrated for 72 h at ambient temperature. Non-interference of lixivaptan with the assays of co-administered drugs and vice versa is also demonstrated.

Assays for Amiodarone, Atorvastatin, Carbamazepine, Digoxin, Furosemide, Enalapril, Ketoconazole, Simvastatin, Spironolactone, Warfarin and Measured Metabolites
The validation characteristics of the different assays are acceptable. There is no evidence for interference of lixivaptan with the assays measuring the above compounds or vice versa.

3.7 WHAT IS THE OVERALL CONCLUSION REGARDING NDA 203009?

From a Clinical Pharmacology point of view the submission is acceptable if agreement on the label can be attained with the sponsor.

4 LABELING RECOMMENDATIONS (DRAFT)