CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-697

MEDICAL REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Date:	Friday, December 23, 2005
NDA:	21-697
Sponsor:	Astellas Pharma US (formerly Yamanouchi)
Proprietary Name:	Vaprisol (conivaptan HCL) injection
Author:	Robert J. Meyer, MD, Director, ODE II

Summary: This is a second cycle review for this drug, conivaptan, which works via antagonism of the vasopressin V2 (renal) receptor. The original sign-off memo for the approvable action taken on November 23, 2004, was written by Dr. Orloff with my concurrence and the reader is referred to that document for details on the first cycle action.

[redacted]

4 days), IV administration in the hospital setting for the treatment of hypervolemic and euvolemic hyponatremia. The former group as studied was mainly comprised of CHF patients, but clinically would include hepatic and nephritic patients as well. The latter is tantamount to the syndrome of inappropriate antidiuretic hormone (SIADH). The major issue that prevented approval last cycle was inadequate clinical safety data to cover the exposure resulting from IV administration of the drug. The sponsor's PK modeling which led them to believe the safety data from the oral administration would cover the IV doses proposed, as they felt the oral bioavailability would be very high. It turned out that actual PK data proved this assumption/modeling to be false and exposure in oral patients was about 1/3 of that in IV. Therefore, the sponsor was requested to provide a more robust relevant safety database. Additionally, some signals of potential concern with regard to renal, cardiac and hepatic safety were raised, as were issues related to the lowest effective dose and the need for a loading dose. Some CMC issues were also included as needing to be addressed in the resubmission.

The resubmission was received June 30, 2005 and was considered a complete response. The action goal date is December 30th, 2005.

Note that Dr. Parks has done an excellent team leader memorandum that goes into detail on many of the salient issues for this resubmission and therefore this memorandum will more briefly summarize the FDA findings and conclusions. Readers are referred to Dr. Parks' memo.

CMC: Vaprisol is supplied as a glass, single use ampule containing 4 mL of solution with a total amount of conivaptan of 20 mg (concentration is 5 mg/mL). It is administered by adding an ampule to a 100 mL bag of 5% dextrose, with the bag then administered over a 30 minute time period for the loading dose. For the continuous infusion portion of dosing, 2 ampules (40 mg) are added to a 250 mL bag of 5% dextrose and administered over 24 hours. The CMC issue cited in the first action letter included new specifications, additional stability data and investigations of [redacted] These issues have been satisfactorily addressed by the sponsor and the CMC team is now recommending approval with a [redacted] expiry.

Pharm-Tox: There were no P-T issues in the previous action letter and the P-T team is recommending approval.

Clinical Pharmacology: The clinical pharmacology reviewers for both cycles were Sang Chung, PhD and Hae-Young Ahn, PhD. The relevant issues for this cycle were the sponsor's data to support their dosing regimen as being acceptable (as opposed to lower doses) and to clarify the exposure response relationship in renally impaired patients. The further exploration of dosing in 404 patient administered the drug IV suggests that a 20 mg/day infusion will be as effective as the 40 mg infusion in most patients and therefore will be recommended as the preferred starting dose. As for the PK-PD relationship in the renally impaired patient, the sponsor presented evidence that as creatinine clearance falls, so does the responsiveness to conivaptan. This is not surprising given the renal mechanism of the drug. However, there is also evidence that exposure rises as CrCl falls, so the net effect is hard to predict and therefore the labeling will urge cautious use in renally impaired patients, but not make specific recommendations on dosing adjustments.

The clinical pharmacology team is also recommending approval this cycle.

Clinical/Statistical:

Besides the issue of dosing, touched on above, the main issues to be addressed by the sponsor was to provide more IV dosing experience to allow for an evaluation of safety at these higher levels of exposure (more than 3 fold higher than that from the same nominal dose provided orally). From the FDA standpoint, these data were needed to further evaluate various safety concerns. The data from the same 404 patients mentioned above significantly expands the safety database at relevant exposures in the proposed use settings and clarifies some of the issues raised by Dr. Mahoney in her first cycle review.

With regard to renal issues, much of the events appear related to pre-renal effects predictable for a diuretic drug. There does not appear to be an intrinsic renal toxicity of the drug but rather those effects related to its pharmacologic effect. Proper cautions can be placed in labeling to instruct on consideration of potential renal consequences of over brisk diuresis.

This drug leads to significant infusion site reactions that are not significantly modified by the lower infusion rate. Due to this concern, the sponsor has placed wording into the PI that recommends use of large veins for infusing the drug and rotating sites. I believe this may be an

acceptable route, but I think a precautionary statement in the labeling is needed, beyond the statement in the Dosage and Administration section.

The main issue that was identified and perhaps further clarified and supported as a concern with these additional data is the potential negative consequences of conivaptan in patients with CHF (i.e., hypervolemic hyponatremia on the basis of congestive heart failure). There is a weak signal of a mortality disadvantage for patients given drug vs. placebo, with the mortality rate in controlled IV trials (all doses combined) of 3.9% vs. 2.8%. If one looks at all controlled phase 2 and 3 studies combined (oral and IV), the mortality rate is 2.5% on drug vs. 3.2% in placebo. However, this group includes effective lower doses that those proposed for marketing, especially when one considers the 2/3 lower exposure in patients given orally. Much of this signal seems to emanate from the use in CHF/hypervolemic patients. There is less than perfect dose relatedness to the apparent mortality disadvantage in this population when provided conivaptan IV, even when adjusted for duration of exposure (i.e., when given as a rate). The mortality rate per 100 patient-months is 4.1% in placebo, 6.9% at 40 mg/day, 6.4% at 80 mg/day, 15.6% at any other dose (generally higher). The overall rate for any conivaptan vs. placebo in this same population is 4.1% vs. 9.2%.

This excess of events related to drug appears to be present for non-fatal serious AEs as well, particularly related to the cardiovascular system in patients with CHF. In these patients, the rate of atrial arrhythmias (0.3% in placebo, vs. 6.2% at 40 mg/day) and CHF aggravated (2.8% and 6.2%) were elevated. The latter finding is surprising, yet concerning, for a drug that is a diuretic. The sponsor sent some late data suggesting that if one uses broader terms (a sponsor-modified standard MedDRA query for CHF events plus dyspnea-related terms) much of this signal goes away. This suggests some differential in patients being assigned terms related to dyspnea vs. CHF aggrevation between the two treatment groups. It is impossible to understand the basis of this differential between dyspnea vs. CHF terms (whether it is some sort of biased assignment due to incomplete blinding, whether it is a chance occurrence or whether it represents a true clinical difference).

In any case, the concern over the potential implications of these imbalances remains on the part of the primary reviewer, the secondary reviewer and for me - that the use of conivaptan in the setting of CHF may potentially be detrimental. Until we have more data to sort this out, given the differential in AEs and deaths, we believe the drug should not be used in that setting. It is possible that other causes of hypervolemic hyponatremia may be appropriate patients for conivaptan, the data are insufficient to reach any conclusions, as the IV data we have on hypervolemic patients comes substantially from patients with CHF and the data otherwise do not allow any conclusions. Therefore, the labeling will be silent on this issue, but will specifically state that the drug is NOT indicated for the treatment of congestive heart failure. Should data become available in the future to change this determination, we will appropriately modify the Indications section.

Data Integrity/Financial Disclosure: Dr. Mahoney has reviewed all the financial disclosure information and has found this not to change the clinical determinations on this application. Clinical audits were likewise acceptable.

Labeling/Nomenclature: DMETS does not object to the name of the product and previous carton and container comments from DMETS and the ONDQA reviewers were included in the first action cycle letter and have been satisfactorily addressed by the sponsor.

Planned Action: C

3 euvolemic hyponatremia can be approved and the hypervolemic patients can be declared approvable. The latter population will need more safety data to clarify the signals or outcomes data to show the drug has, if not a positive effect on outcomes, at least not a deleterious effect. While improving serum sodium can be taken to be a clinically important function of a drug, it cannot be considered so in the face of potentially worsening CHF and even death. The euvolemic patients in essence are those with SIADH, a syndrome for which this drug seems quite appropriate given its blockade of the V2 receptor.

For the approved indication, we would like the sponsor to further explore dosing in the post-marketing setting, specifically whether the loading dose as currently recommended is necessary and, if so, under what clinical circumstances.

NDA 21-697: Approval

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/s/

Robert Meyer
12/23/2005 02:59:04 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER MEMO

NDA#:	21-697
Sponsor:	Astellas Pharma US, Inc.
Drug:	Vaprisol® (conivaptan hydrochloride)
Indication:	Treatment of euvolemic and hypervolemic hyponatremia
Date of Submission:	June 30, 2005
Subject:	Resubmission to NDA approvable action letter issued November 30, 2004

I. Introduction and Background

This is a resubmission to an approvable action letter issued for NDA 21-697 on November 30, 2004 for Vaprisol® (conivaptan hydrochloride), hereafter referred to as conivaptan. Conivaptan is a non-peptide, vasopressin (AVP) antagonist that is under clinical development for the treatment of hyponatremia in euvolemic and hypervolemic patients.

Vasopressin is a hypothalamic neuropeptide that is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and stored in the posterior pituitary where it is released in response to osmotic and non-osmotic stimuli. Vasopressin functions as an antidiuretic hormone (ADH) at physiologic plasma concentrations; vasoconstrictive activity occurs only at higher plasma levels. Release of vasopressin in response to increasing plasma osmolality occurs via stimulation of neurons located in the anterior hypothalamus. Release of AVP secondary to osmolar changes is an extremely sensitive response with only a 1-2% increase in plasma osmolality required to stimulate AVP secretion. In contrast, the release of AVP secondary to changes in blood pressure/volume is mediated via the baroreceptors located in the major blood vessels. A 5-10% reduction in blood volume or blood pressure is required to stimulate AVP secretion.

Three types of AVP receptors are known: V1a (vascular and hepatic); V1b (anterior pituitary); and V2 (kidney). Of these, the most significant function of vasopressin is at the V2 receptor located on the renal collecting tubules. Stimulation of these receptors results in the renal water conservation to maintain plasma osmolality within a narrow range of 280 to 285 mEq/L. This is accomplished through AVP-mediated insertion of water channels (aquaporins) along the luminal surface of the collecting tubules with subsequent passive reabsorption of solute-free water down the inner medullary concentration gradient. In the absence of AVP, the distal collecting tubules remain impermeable to water and larger volumes of solute-free water are excreted.

Derangements of AVP regulation, synthesis/release, or action result in hypernatremia (deficiency or non-response to hormone activity) or hyponatremia (excessive or inappropriate release of AVP relative to plasma osmolality).

Hyponatremia remains the most common laboratory abnormality in clinical practice. Multiple disease processes can result in hyponatremia and the approach to identifying the cause first focuses on the patient's volume status. Hypovolemic (or extracellular fluid contraction)

hyponatremia is due to loss of salt in excess of water. Diarrhea, vomiting, or diuretic use often accompanied by hypotonic fluid replacement are common causes of hypovolemic hyponatremia. In these states, treatment with isotonic fluid replacement typically corrects the hyponatremia.

Hyponatremia in euvolemic and hypervolemic states may also be due to many different disease processes. In both states though, the total body water is in excess of total body salt. The syndrome of inappropriate antidiuretic hormone release (SIADH) is the most common cause of euvolemic hyponatremia. AVP release can occur in the setting of malignancies that secrete AVP in an unregulated fashion or due to diseases of the pulmonary or central nervous system. Certain drugs have also been associated with hyponatremia due to stimulation of AVP release (e.g., narcotics, serotonin-reuptake inhibtors) or potentiation of AVP action at the kidneys (e.g., chlorpropamide). Although it is the leading cause of euvolemic hyponatremia, SIADH remains a diagnosis of exclusion after certain conditions have been ruled out (hypothyroidism, hypocortisolism, renal disorders, and diuretic use).

Hypervolemic hyponatremia is found in edematous states such as congestive heart failure (CHF), advanced liver disease, and nephrotic syndrome. In these disease states, AVP may be inappropriately elevated for the degree of plasma osmolality; however, the release of AVP is partly due to the reduced effective circulating volume in these patients (i.e., stimulation of AVP release via the baroreceptors). It important to recognize that in hypervolemic hyponatremia other processes may contribute, if not cause, the hyponatremia. For example, use of angiotensin converting enzyme inhibitors (ACE-inhibitors) or diuretics may cause hyponatremia due to effects on the renin-angiotensin system or renal sodium loss.

The clinical manifestations of hyponatremia are primarily neurological and reflect the brain cell adaptive process to ECF hypoosmolality. Variable presentations of hyponatremia reflect the magnitude and duration of hyponatremia. With reductions in ECF osmolality, brain cells adapt via losses of electrolytes and organic solutes to reduce the risk of brain edema (fluids shifting from extracellular to intracellular space). Acute hyponatremia is generally symptomatic as the brain volume has not sufficiently adjusted to the extracellular hypoosmolar state. Chronic hyponatremia is less symptomatic although severe hyponatremia (e.g., < 120-125 mEq/L) may be associated with nausea, headaches, and seizure activity. Consequently, the correction of hyponatremia is often undertaken to reduce the risk of serious neurologic complications.

The management of hyponatremia must take into consideration the duration of hyponatremia and the presence or absence of symptoms. In general, acute symptomatic hyponatremia can be rapidly corrected without complications. Correction of chronic hyponatremia, particularly asymptomatic states, requires a limited and controlled approach to avoid the complications of increasing the ECF osmolality in patients whose brain cells have undergone a protective adaptive process. Rapid correction of serum sodium in this setting increases the risk of rapid fluid shift from the intracellular to extracellular space. Patients may present with tremor, incontinence, hyperreflexia, quadriparesis, quadriplegia, dysarthria, cranial nerve palsies, and mutism. The most severe complication is central pontine myelinolysis, a massive demyelination of descending axons in the pons.

Hyponatremia in both euvolemic and hypervolemic states requires the treatment of the underlying disease process and fluid restriction. Severe or recalcitrant hyponatremia may require other measures including the administration of hypertonic saline. Regardless of the treatment(s) applied, correction is slow and challenging to clinicians and patients as extreme fluid restrictions may be difficult to adhere to and interfere with the medical management of other conditions. As already discussed, choice of treatment must be made with consideration of the degree and duration of hyponatremia to avoid the complications of overly rapid serum sodium correction.

Non-peptide vasopressin antagonists block the effect of AVP at the V2 receptors (selective) and V1A (non-selective). Inhibition of AVP action induces a solute-free diuresis as renal distal collecting tubules remain impermeable to the reabsorption of water resulting in volume depletion, and increases in plasma osmolality and serum sodium. It is this pharmacologic action of conivaptan that is the basis for proposing its use for the treatment of euvolemic and hypervolemic hyponatremia.

II. Clinical Basis for Non-Approval

Conivaptan is a CYP3A4 inhibitor and substrate. During the Phase 2 clinical program, two patients experienced rhabdomyolysis secondary to the co-administration of the CYP3A4 substrate. As a consequence of these adverse events, the review division informed the applicant [redacted] for hyponatremia may result in an unacceptably high risk of serious drug-drug interactions post-approval. The applicant addressed this safety concern by proposing to market only an intravenous (iv) formulation intended for the short-term treatment (4 days) of hyponatremia in hospitalized patients. However, as the clinical development program had already included studies using the oral formulation, the applicant proposed submission of three Phase 3 clinical studies, one using the intravenous formulation and two using the oral formulation, in support of its NDA. The two oral studies were considered supportive and were initially thought to include doses that would provide equivalent drug levels as obtained with iv dosing. However, results of a formal bioequivalence study made available during the review of the original NDA demonstrated that the oral doses studied provided approximately one-third the drug exposure of equivalent iv doses. Consequently, the safety exposure for the proposed iv dosing regimen was limited to only one single iv study comprising data in only 63 patients.

Furthermore, data from the oral studies suggested that the proposed dosing regimen of 20 mg IV loading dose followed by a daily infusion of 40 mg conivaptan for 4 days did not represent the lowest effective dose. Given several dose-related safety concerns identified in the review of the original application, the applicant was required to explore a more optimal dosing regimen that would mitigate risk while achieving acceptable efficacy results.

In conclusion, the Clinical Deficiencies discussed in the November 30, 2004 approvable letter were:

1. The number of subjects receiving conivaptan at the systemic exposures associated with the dose and dosing regimen proposed for marketing is inadequate for the evaluation of the safety of conivaptan. Additional clinical trial data addressing risk versus benefit are therefore needed.

2. The lowest effective dose of intravenous conivaptan in the treatment of [redacted] has not been established nor has the optimal dosing regimen. Given the now established lower absolute bioavailability of conivaptan when given orally, data from your oral conivaptan studies provide strong evidence that intravenous doses of

conivaptan lower than those studied and proposed for marketing would be effective for raising serum sodium concentration in the target population. Additionally, serious adverse events plausibly related to hypovolemia suggest that moderation of the aquaretic effect of vasopressin antagonism may render a better safety profile of conivaptan. A study or studies to identify the most appropriate intravenous dose (one that best balances efficacy and safety) are needed.

III. Response to AE Letter

With this re-submission, the applicant has adequately addressed the two clinical deficiencies outlined in the approvable letter. As summarized in Dr. Mahoney's review, data are now available for 404 patients who received ≥ 40 mg/day for 2 to 4 days. The majority of these patients came from an on-going, open-label study in euvolemic and hypervolemic hyponatremic patients (Study 080), a double-blind, placebo-controlled study in patients with decompensated congestive heart failure with or without hyponatremia (Study 071), and a QTc study in healthy volunteers (Study 079). The remainder of the data was derived from smaller pK studies in healthy volunteers (Study 083 and Study 074) and the original pivotal IV study in the initial NDA submission (Study 027). The overall patient safety population provided safety exposure data in 1,148 conivaptan-treated patients.

This larger clinical database has allowed for a more thorough review of conivaptan in the treatment of hyponatremia that will support its safe and effective use in euvolemic hyponatremic patients with some modification to the proposed dosing regimen. In section IIIa, this memo will discuss the range of effective doses recommended for approval. The review of this resubmission has raised some safety concerns in the CHF patient population precluding the approval of conivaptan for treating hypervolemic hyponatremia as this population was comprised primarily of patients with CHF. Section IIIb will discuss the safety findings based on Dr. Mahoney's interpretation of this larger database and her team leader's conclusion of these results.

IIIa. Efficacy at Doses Lower than 40 mg

As summarized under Section II, the applicant was required to establish a lowest effective dose for conivaptan as data from oral studies suggested effectiveness at doses lower than 40 mg/day iv of conivaptan. In Study 080, the efficacy of 20 mg/day iv conivaptan was evaluated in 21 hyponatremic patients. The 20 mg/day dose had comparable efficacy to the 40 mg/day dose as determined by a baseline adjusted serum sodium AUC over the duration of treatment. The median duration for patients to achieve a ≥ 4 mEq/L increase in serum sodium was 24 hrs compared to 24.6 hrs in the 40 mg/day group. Although there were more patients who achieved this goal in the 40 mg dose group, the overall percentage of patients achieving normal serum sodium levels (defined as ≥ 135 mEq/L) or having a ≥6 mEq/L increase from baseline at any point in time during treatment was comparable between the two doses (71.4% vs. 73.0%). The following table was taken from Dr. Mahoney's review to summarize the efficacy findings of the 20 and 40 mg doses.

Table 6.1 Interim Efficacy Results, Study 080, 20 mg/day and 40 mg/day Dosing Regimens

Efficacy Variable	Conivaptan 20 mg/day n=21	Conivaptan 40 mg/day n=115
Primary Efficacy Endpoint		
Baseline Adjusted Serum Sodium AUC over Duration of Treatment (mEq·hr/L)		
Mean (SD)	770.5 (446.85)	651.4 (403.39)
Secondary Efficacy Endpoints		
Number of Patients and Time to confirmed ≥4 mEq/L increase from Baseline Serum Sodium		
n (%)	15 (71.4%)	96 (83.5%)
Median time (h)	24.0	24.6
[95% CI]	[6.8, 60.0]	[24.0, 36.0]
Total time (h) to ≥4 mEq/L increase in Serum Sodium		
Mean (SD)	61.3 (37.77)	59.6 (33.10)
Serum Sodium (mEq/L)		
Baseline mean (SD)	122.1 (4.81)	124.1 (4.49)
Mean (SD) at end of treatment	132.3 (3.91)	132.4 (4.25)
Mean Change (SD) from Baseline to End of Treatment	10.2 (5.46)	8.3 (5.29)
Mean (SD) at Follow-up Day 11	130.5 (7.34)	132.0 (5.71)
Mean Change (SD) from Baseline to Follow-up Day 11	7.9 (9.60)	8.0 (6.55)
Mean (SD) at Follow-up Day 34	135.5 (4.29)	134.2 (4.94)
Mean Change (SD) from Baseline to Follow-up Day 34	13.1 (6.98)	10.3 (6.47)
Number (%) of patients with ≥6 mEq/L increase from Baseline in Serum Sodium or a Normal Serum Sodium Concentration ≥135 mEq/L During Treatment	15 (71.4%)	84 (73.0%)

Source: Applicant's Table 2, Response to Deficiencies in Original NDA

Dr. Mahoney commented that no data are available from a concurrent placebo group in Study 080. However, Study 080 had similar inclusion/exclusion criteria and treatment algorithm as in the pivotal placebo-controlled study submitted to the original NDA. In that study, (Study 027) efficacy for the 40 mg and 80 mg daily doses of conivaptan was compared to placebo. These results are summarized in the following table in Dr. Mahoney's review of the original NDA.

Table 6.1.4.1.3:Efficacy Results for Primary and Secondary Efficacy Parameters, Study -027

	Placebo n = 29	Coni[1] 40 mg/day n = 29	Coni 80 mg/day n = 26	P-value
Primary Efficacy Parameter				
Change from baseline in baseline-adjusted serum sodium AUC (mean ± SD, in mEq-hr/L)	61.4 ± 242.3	500.8 ± 365.46	661.7 ± 331.14	Overall: <0.0001 C40[2] vs pbo: <0.0001 C80[3] vs pbo: <0.0001
Secondary Efficacy Parameters				
Median Event Time to when at least 50% of patients had sodium increase ≥ 4 mEq/L over baseline [mean in hours (95% CI)]	NE[4]	23.7 (10, 24.0)	23.4 (6.0, 24.0)	Overall: <0.0001 C40: <0.0001 C80: <0.0001

Table 6.1.4.1.3:Efficacy Results for Primary and Secondary Efficacy Parameters, Study -027

	Placebo n = 29	Coni[1] 40 mg/day n = 29	Coni 80 mg/day n = 26	P-value
Mean Total Time from first dose to end of treatment during which serum sodium ≥4 mEq/L over baseline (LS mean in hours ± SE)	14.2 ± 5.25	53.2 ± 5.17	72.7 ± 5.43	Overall: <0.0001 C40: <0.0001 C80: <0.0001
Mean change in serum sodium from baseline to end of day 4 [LS mean in mEq ± SE (# of evaluable patients)]	2.0 ± 0.82 [25 pts]	6.8 ± 0.81 [24 pts]	9.0 ± 0.80 [24 pts]	Overall: <0.0001 C40: <0.0001 C80: <0.0001
Number of patients with ≥ 6 mEq/L increase in serum sodium, or increase to normal serum sodium (>135 mEq/L). Shown as # patients (% of arm)	6 (20.7%)	20 (69%)	23 (88.5%)	Overall: <0.0001 C40: <0.0002 C80: <0.0001

1 Conivaptan
2 Conivaptan 40 mg/day
3 Conivaptan 80 mg/day
4 Not estimable

Although efficacy in Study 080 appears better than Study 027, it is reasonable to conclude that conivaptan 20 mg/day will be more effective at correcting serum sodium than placebo which in Study 027 increased serum sodium by only 61.4 mEq-hr/L over the 4 day treatment period and only corrected serum sodium or increased serum sodium by ≥ 6 mEq/L in approximately 21% of patients.

Based on these efficacy findings, I concur with Dr. Mahoney that sufficient evidence of efficacy exists for the 20 mg dose of conivaptan. As correction of chronic hyponatremia in asymptomatic patients should employ a carefully monitored approach to avoid rapid increases in serum sodium, the dosing regimen for conivaptan should recommend initiation of treatment with the lowest, effective dose of conivaptan with frequent determinations of serum sodium, and dose titration as dictated by patient response and tolerability. The recommended starting dose for conivaptan should be 20 mg/day with titration to 40 mg after periodic monitoring of serum sodium and patient tolerability supports an upward titration.

The applicant also evaluated whether recommendations on dosing duration can encompass a 2 to 4 day period versus its original proposal to treat for a minimum of 4 days. In Study 027, by Day 2 a statistically significant increase in serum sodium from baseline relative to placebo was observed at the 40 mg/day dose for all efficacy parameters assessed. While some patients may require longer treatment to achieve adequate correction of serum sodium, the proposal to recommend dosing from 2 to 4 days is supported by these data.

Information on durability of response was requested in the AE letter to determine whether correction of serum sodium over a 4 day treatment period would be sustained over longer periods of time. Follow-up serum sodium levels at visits days 11 and 34 in Study 080 were evaluated and mean and median values were similar to end-of-treatment values (Day 4) suggesting that

improvement in serum sodium levels can be sustained beyond treatment with conivaptan. Dr. Mahoney commented that maintenance of normal serum sodium levels may reflect other interventions for the underlying medical conditions. Given that the half-life of conivaptan is approximately 5 hours, it is likely the case that sustained correction of serum sodium will depend on treatment of underlying disease or continued fluid restriction. This is certainly expected as conivaptan is not intended to treat the underlying medical condition that has contributed to the hyponatremia. The applicant has reasonably demonstrated that the correction of hyponatremia during treatment of conivaptan can be sustained post-treatment. A Phase 4 commitment is not required to further characterize whether durability of response is an effect of conivaptan or other therapeutic measures, although other post-marketing studies may incorporate serum sodium measurements in the period immediately following last dose of drug.

IIIb. Safety

The overarching safety deficiency in the original NDA was the inadequate number of patients exposed to the dosing regimen proposed for marketing. As stated earlier, only 63 patients received a loading dose of 20 mg iv followed by an infusion of 40 mg daily for 4 days. This small number of patients could not allow for an adequate assessment of drug safety. Specific safety concerns raised in the action letter included effects on renal function and infusion site reactions.

Renal Adverse Events

From section 7.1.3.3.1 of her review, Dr. Mahoney has evaluated the renal adverse events in this NDA and has found "no clear evidence of primary nephrotoxic effect of conivaptan". The brisk diuretic effect of this drug may likely explain the higher incidence of increased serum creatinine from baseline. Labeling should discuss these findings with recommendations for careful monitoring of vital status, daily intake and output, and renal function with discontinuation of therapy or repletion of fluids if over-diuresis occurs.

Infusion Site Reactions

Infusion site reactions were identified early in the clinical development program by the applicant and changes in the administration of drug were made during Phase 2/3 studies to reduce the risk of these adverse reactions. Despite these changes, the placebo-controlled studies still revealed a higher rate of infusion site reactions that were markedly higher than placebo and were dose-related. The incidence of such events was 7.3% in placebo-treated patients compared to 36.4%, 52.8%, and 57.1% in the 40 mg, 80 mg, and 120 mg dose groups, respectively. In Study 080, this incidence was 76.2% in the 20 mg dose group and 77.4% in the 40 mg dose; however, the higher rates in this study may have reflected a more directed worksheet that collected specific adverse events related to the infusion. While these adverse reactions were not considered approvability issues, it was recommended that the applicant explore methods for decreasing the incidence of infusion site reactions. No specific change to the dosing regimen was made to specifically address this safety concern; however, the applicant proposes labeling that recommends administration of conivaptan through large veins and to change the infusion site every 24 hours. Dr. Mahoney has recommended that a Phase 4 study be conducted to determine whether a loading dose is necessary for efficacy and whether the elimination of a loading dose will reduce the incidence of infusion site reactions. As the reaction appears dose-related and often occurs on Day 1, she has suggested that it may be related to higher drug concentration levels.

While the proposed labeling is appropriate and may be effective in reducing the risk of serious infusion-site reactions, the target population for conivaptan will likely include elderly or seriously-ill patients who have poor venous access and for whom, insertion of central venous access lines will be the only option for safe administration of conivaptan. Such procedures are

not without risks and the applicant should therefore explore whether different dosing regimens will reduce the risk of infusion site reactions. I concur with Dr. Mahoney that this type of investigation may provide important information for the safe use of this product such that it merits a Phase 4 commitment from the applicant.

Mortality

The overall incidence of deaths occurring during treatment, within 30 days following treatment, or due to an adverse event that had its onset during treatment was 5.5% (63/1148) in the conivaptan group and 3.2% (12/372) in placebo group. Dr. Mahoney further explored this finding by evaluating the rate of mortality in different safety databases and by dose of conivaptan. She noted that the rate of mortality appears dose-related as summarized in her Table 7.1.1.3.2 which presents rate of death by dose group and approximate IV equivalent dosing. As explained in Section 7.1 of her review she describes 6 different safety populations evaluated and Table 7.1.1.3.1 (below) enumerates the rates of death in the conivaptan and placebo treatment groups within each safety population.

Table 7.1.1.3.1 Rates of Death in IV and Total Populations

Population	Coni # deaths/# pts in pop (%)	Pbo # deaths/# pts in pop (%)
"Full Dose" IV Studies Conducted in Patients[1]	28/292 (9.6%)	3/69 (4.3%)
Controlled "Full Dose" IV Patient Studies[2]	10/177 (5.6%)	3/69 (4.3%)
All "Full Dose" IV Studies (Patients and Healthy Volunteers)[3]	28/404 (6.9%)	3/109 (2.8%)
All "Full Dose" Controlled IV Studies (Patients and Healthy Volunteers)[4]	10/258 (3.9%)	3/109 (2.8%)
All Phase 2/3 Studies (oral and IV)[5]	64/1148 (5.6%)	12/372 (3.2%)
All Placebo-Controlled Phase 2/3 Studies (oral and IV)[6]	24/942 (2.5%)	12/372 (3.2%)
"Full Dose" IV hyponatremia studies[7]	22/170 (12.9%)	3/29 (10.3%)
"Full Dose" Controlled IV CHF study[8]	6/122 (4.9)	0
All IV[9]	36/445 (8.1)	7/132 (5.3)

1 Studies 027, 071, 080
2 Studies 027, 071
3 Studies 027, 071, 080 (patients); 079, 083, 074 (healthy volunteers)
4 Studies 027, 071 (pts); 079 (healthy vols)
5 Studies 016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 031, 032, 033, 034, 038, 043, 047, 071, 080
6 Studies 017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071
7 Studies 027, 080
8 Study 071
9 Studies 016, 017, 023, 025, 027, 032, 038, 044, 071, 080
The above table includes deaths that occurred during study drug administration or within 30 days of study drug administration. Deaths that occurred >30 days after study drug administration could be included if the event that led to death had its onset during or within 30 days of study drug administration

With the exception of the "all placebo-controlled Phase 2/3 studies (oral and IV)", the incidence of death is higher in the conivaptan group than in the placebo group. However, Dr. Mahoney noted that this group included patients treated with lower doses than proposed for marketing. It should also be noted that any safety population which include open-label studies will not only increase the patient exposure in the conivaptan group but it will enrich this population with patients who have serious illnesses that will affect the rate of mortality. This is exemplified by comparing rates in the "Full Dose" IV Studies Conducted in Patients to the Controlled "Full Dose" IV Patient Studies. The latter group excludes data from an open-label study in patients with decompensated CHF. The incidence of death in the placebo group remains the same as no placebo patients are studied in the open-label CHF study while the rate of death increases from 5.6% to 9.6% in the conivaptan group.

From Table 7.1.1.3.1, this reviewer has highlighted in yellow only the controlled safety populations which excluded open-label, uncontrolled studies. Except for the All Placebo-controlled Phase 2/3 group, the rate of death remains higher in the conivaptan patient population. However, it should be noted that these data include patients exposed to higher doses of conivaptan than proposed for marketing. More conivaptan deaths in these controlled safety populations occurred at doses higher than 40 mg/day. For the Controlled Full Dose IV Patient Studies and All Full Dose Controlled IV Studies, 7/10 deaths occurred at the 80 mg (n=3) or 120 mg (n=4) doses. For the Full Dose Controlled IV CHF Study 4/6 deaths were at the 120 mg dose.

The following table (Table 7.1.1.4) explores the relationship between rate of death and dose. It is evident that the mortality rate is higher in the the conivaptan group than placebo, at any dose evaluated. Dr. Mahoney performed a similar analysis in the euvolemic hyponatremic patient population and no apparent dose-related increase in death was observed (see Table 7.1.1.4.2 from her review) and the incidence was similar between conivaptan (any dose 9.9% and 40 mg 11.7%) and placebo (10%).

Table 7.1.1.4 Mortality by Treatment Group for Patients with an Initial Diagnosis of CHF, Full-Dose IV Studies Conducted in Patients (Studies 027, 071, 080)

Treatment Group	Total Number of Subjects	Total Number of Deaths	Crude Mortality [1]	Patient-Months (PM)	Mortality per 100 PM [2]
Placebo	49	2	4.1%	48.6	4.1
YM087 40 mg/day	81	5	6.2%	72.3	6.9
YM087 80 mg/day	48	3	6.3%	46.6	6.4
YM087 Other Dose	42	7	16.7%	44.8	15.6
YM087 Any Dose	171	15	8.8%	163.7	9.2

*Note: YM087 Other Dose refers to 120 mg/day dose

I concur that the incidence of death appears to be dose-related (see Table 7.1.1.3.2 and Figures 7.1.1.3.1 and 7.1.1.3.2 in Dr. Mahoney's review) and that across different analyses in the CHF population, the rate is higher in the conivaptan group than placebo group. Given the limitations of these analyses, discussed above, particularly the imbalance in exposure between treatment groups and possible bias due to exposure of patients at higher risk of death to conivaptan as opposed to placebo in the overall database, the data are insufficient to implicate conivaptan treatment as a primary cause of death in CHF patients treated with the drug. It must be conceded, however, that there is certainly pharmacologic and pathophysiologic plausibility to potential hazards of conivaptan in CHF, as there is for potent conventional diuretics. That is, brisk diuresis with intravascular volume depletion in a patient population with severe cardiac and vascular functional compromise, may, in some instances contribute to severe circulatory decompensation with ultimately irreversible sequelae..

Other Serious Adverse Events

Section 7.1.2 of Dr. Mahoney provides an in-depth review of other serious AEs. This memo will highlight her findings in patients with underlying CHF (section 7.1.3.3.5 of her review) and other significant adverse events that will be discussed in labeling.

Atrial Arrhythmias and Cardiac Failure Events

Higher incidences of atrial arrhythmias and cardiac failure events were noted in the conivaptan group compared to placebo. In Table 7.1.3.3.5.3, the rate of atrial arrhythmias in Study 071 (a CHF population) was 7.4% in the conivaptan group compared to none in placebo. In this same study, the incidence of cardiac failure was 3.3% in conivaptan vs. none in placebo. The applicant

was asked to evaluate the incidence of these two events within the CHF population by dose groups. A similar finding of greater risk in the conivaptan group than placebo was also noted in their analyses summarized in Table A below which excerpts data submitted by the applicant in an e-mail correspondence from Dr. Donald Raineri of Astellas to the FDA sent December 1, 2005 at 4:11 pm.

Table A. Incidence of Atrial Arrythmias and Selected Cardiac AE Events in CHF Patients in all Phase 2/3 Trials

	Placebo (IV and oral) N=321	Coni 20 mg IV/day N=32	Coni 40 mg IV/day N=130
Any Atrial Arrhythmia	1 (0.3%)	1 (3.1%)	8 (6.2%)
Afib	1 (0.3%)	0	8 (6.2%)
Aflutter	0	1 (3.1%)	0
Cardiac Failure Events			
Any AE	15 (4.7%)	1 (3.1%)	16 (12.3%)
CHF aggravated	9 (2.8%)	1 (3.1%)	8 (6.2%)

Dr. Mahoney has noted that 28.6% of the atrial arrhythmias events in the overall safety population occurred in patients with hypokalemia suggesting that electrolyte depletion may play a role in some of these events. This is an unexpected finding related to the pharmacologic action of the drug as conivaptan induces a predominantly solute-free diuresis. Nonetheless, the higher rate of atrial arrhythmias and cardiac failure events in the CHF population treated with conivaptan adds additional concern to the overall safety of this drug to treat hypervolemic hyponatremia which in this NDA was comprised primarily of CHF patients.

Rapid Serum Sodium Correction

As discussed under the Introduction/Background section of this memo, rapid correction of serum sodium in the management of hyponatremia may result in serious, irreversible neurologic damage or death. The clinical studies in this program defined a rapid correction of serum sodium as:

- Serum sodium increased by more than 12 mEq/L in 1 day.
- Serum sodium increased by more than 24 mEq/L total.
- Serum sodium exceeded 145 mEq/L.
- The investigator believed serum sodium was correcting too quickly.

None of these events occurred in a placebo-treated patient. The incidence in the overall conivaptan-treated population was 5% (59/1148), and 9.1% of the 20 to 40 mg IV dose group experienced rapid correction of serum sodium. Dr. Mahoney noted only one patient who had a clinical adverse event that was considered related to a rapid rate of correction. This was a patient who had a seizure two days after rapid correction of her serum sodium. Her initial dose was 40 mg/day IV which was reduced to 20 mg/day IV. The patient recovered without any serious sequelae.

Rapid correction of serum sodium can occur with any measure used to correct hyponatremia. Consequently, the management of this condition should employ careful monitoring of urinary output, frequently measured serum sodium levels, and routine patient evaluation. The availability of conivaptan will provide an effective drug for treating hyponatremia but its judicious use should be recommended to avoid rapid correction of serum sodium.

As the 20 mg/day IV dose has clinically significant effects on raising serum sodium, this dose should be recommended as the start dose with titration only after careful monitoring of patient

response and tolerability support the use of 40 mg/day IV. The label should also include a section under WARNINGS and PRECAUTIONS regarding the risk of raising serum sodium too rapidly in patients with chronic hyponatremia.

Hypotension
In the overall safety population (Table 7.1.5.3.3), treatment-emergent AEs due to hypovolemia-related events occurred at a rate of 9.8% in the conivaptan group versus 8.3% in the placebo group. This is not an unexpected finding for a drug whose pharmacologic action is marked diuresis. Recommendations for initiation at the lowest dose of 20 mg/day IV and careful monitoring of blood pressure during infusion will be necessary to reduce the risk of serious adverse events from hypotension/hypovolemia.

Transaminase Elevations
Higher rates of transaminase elevations (> 3x ULN and > 10x ULN) were observed in the conivaptan-treated patients compared to placebo-treated patients. The rate of hepatobiliary AEs was, however, < 1% in the overall safety population and in both treatment groups (0.8% in conivaptan and 0.3% in placebo). In one CHF study population, the mean increase in transaminases was much greater in the conivaptan group than placebo; however, these data were skewed by 14 patients in the drug group who had markedly higher transaminase elevations that resolved without any serious clinical consequence. Dr. Mahoney has summarized 6 cases of hepatic failure and/or jaundice in her review (see section 7.1.3.3.7). These cases involved patients with serious underlying medical/surgical conditions that may have more likely contributed to the liver disease (e.g., multiorgan failure s/p cardiac transplant, gallbladder cancer, infectious hepatitis and endstage heart failure w/ multiorgan failure).

A pK study was conducted in patients with hepatic impairment with an oral dose of 10 mg/day conivaptan which revealed a mean 2.8-fold increase in systemic exposure. [redacted]. The label should summarize the difference in rates of transaminase elevations between conivaptan and placebo, the pK study results, and recommend that caution be used when administering conivaptan in patients with hepatic impairment.

CYP3A4 Drug Interactions
As noted in the Introduction/Background section, the applicant modified its hyponatremia clinical development program for conivaptan to restrict its use to short-term, intravenous use in hospitalized patients as a result of serious drug-drug interactions during early clinical studies with the CYP3A4 substrate, simvastatin. Dr. Mahoney noted that the approvable letter requested information on risk management plans to prevent serious drug interactions with CYP3A4 substrates. She noted that despite restrictions on use of certain drugs in the clinical trials, there were multiple protocol violations in which patients received restricted medications. The applicant provided a response to a request regarding these protocol violations. While unfortunate that such violations occurred during a clinical investigation, they noted that no serious AEs resulted as a direct result of co-administration of conivaptan and some restricted drugs (email correspondence from Dr. Donald Raineri on 12/5/2005 sent at 3:56 pm).

The availability of this drug as only an intravenous formulation for continuous infusion out to a maximum of 4 days substantially restricts its use. Furthermore, it can only be dispensed by a hospital pharmacist who can also access all drugs that the hospitalized patients is currently receiving. Such restricted use and distribution will likely reduce the potential for serious drug-drug interaction compared to other potent CYP3A4 inhibitors marketed (e.g., anti-retroviral therapies, ketoconazole, clarithromycin). This conclusion may also be supported by Dr.

Mahoney's finding of a lower rate of protocol violations for restricted drug use in the iv studies compared to the po studies. The division will request that the company distribute information to hospital formularies regarding potential for drug-drug interactions to ensure that hospital pharmacists are aware of the metabolism of this drug and to alert prescribing physicians when a patient is concurrently taking a CYP3A4 substrate or inhibitor.

As conivaptan is also a CYP3A4 substrate, the applicant is proposing to contraindicate concomitant use with known potent CYP3A4 inhibitors.

IIIc. Biopharmaceutics Clinical Pharmacology

The applicant stated that a loading dose is necessary as a pharmacodynamic response is evident within 6 hrs on Day 1 of dosing, suggesting that the absence of a loading dose would result in a longer duration until steady-state pharmacokinetics are established and might thereby delay time to correction of serum sodium. The applicant did not conduct a study to confirm that efficacy would be affected by the absence of a loading dose. This application can be approved based on the data from the current dosing regimen; however, the applicant will be required to conduct a study without a loading dose as a Phase 4 commitment to evaluate efficacy and safety, particularly, the rate of infusion-related adverse events.

The clinical pharmacology reviewer requested that the applicant explore the relationship between pharmacodynamic response and creatinine clearance in the 2004 action letter. With this resubmission, the applicant noted a modest proportional correlation between creatinine clearance and PD endpoints suggesting that efficacy is reduced in patients with reduced renal function.

While there are data suggesting reduced efficacy with reduced renal function, clinical pharmacology is proposing dose adjustment for patients with renal impairment as studies conducted with the 10 mg oral dose of conivaptan demonstrated higher systemic exposure (up to 80%) in patients with renal impairment compared to patients with normal renal function. Labeling should be modified to state that caution be exercised when administering conivaptan to patients with renal impairment. Like all patients receiving treatment for hyponatremia, use of conivaptan in patients with renal impairment will require routine monitoring of serum sodium to determine if response to therapy is appropriate. If upward titration is necessary in patients with renal impairment, the prescriber must consider that the higher systemic exposure to conivaptan levels may increase the risk for serious drug-drug interactions.

IIId. CMC

CMC information was deemed adequate to support approval of the NDA by Dr. William Adams of Office of New Drug Chemistry.

IV. Other Regulatory Requirements

IVa. Financial Disclosure

Dr. Mahoney has reviewed financial disclosure statements submitted by the applicant and all concerns have been adequately addressed by the applicant.

IVb. Pediatrics

Euvolemic and hypervolemic hyponatremia are relatively uncommon in the pediatric patient population. However, childhood malignancies, particularly brain tumors or cranial insults/pathologic processes may result in inappropriate secretion of vasopressin causing hyponatremia. Given the similar pathophysiology of pediatric and adult hyponatremic states and the lack of concern over differences in metabolism of conivaptan in children versus adults (the CYP3A4 system is mature early in life), it is reasonable to assume that a safe and effective drug exposure in adults may be extrapolated to children. For this intravenously administered drug, adjustment of dose relative to adults according to body weight or body surface area is an obvious approach to the treatment of children with hyponatremia requiring correction. The requirement for pediatric studies should be deferred and a phase 4 commitment to undertake an open-label treatment protocol in a limited number of children with euvolemic hyponatremia should be required.

IVc. Clinical Audits/Inspections

Reviewed by Dr. Mahoney and found to be adequate.

V. Phase 4 Commitments

The applicant will be asked to conduct a clinical study evaluating the efficacy of conivaptan administration without a loading dose and assess whether the absence of a loading dose will mitigate the risk of infusion-related adverse events. In addition, an interaction study between warfarin and the 40 mg iv dose of conivaptan will be required as a Phase 4 study.

VI. Labeling

The main recommendation for labeling is to grant an indication for use in only patients with euvolemic hyponatremia. As outlined in Dr. Mahoney's review, the overall safety database raised several concerns regarding AEs that appear more prevalent in the CHF population which comprised the entire database for hypervolemic hyponatremia. Labeling negotiations are underway with the applicant and final, agreed-upon language will be reflected in subsequent minutes/memoranda, and the action letter.

VI. Conclusions/Recommendations

The second cycle review of NDA 21-697 for Vaprisol® (conivaptan hydrochloride) has found sufficient evidence to approve this drug for the treatment of euvolemic hyponatremia. Conivaptan raises serum sodium effectively compared to placebo and data support use of a lower dose than proposed by the applicant.

Conivaptan [redacted] patients with hypervolemic hyponatremia; however, several safety findings presently preclude the approval of conivaptan for use in this population. In this database, hypervolemic hyponatremic patients were comprised primarily of CHF patients. An increase rate of cardiac-related adverse events and dose-related effect on mortality in this patient population suggest a counterbalancing effect of the drug on any benefit that may arise from correcting serum sodium in this patient population. Additional safety data in CHF patients are required to adequately characterize the risks of conivaptan use before extending the indication to treat hyponatremia in the hypervolemic patient population.

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/s/

Mary Parks
12/14/2005 02:22:08 PM
MEDICAL OFFICER

David Orloff
12/20/2005 05:20:09 PM
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Concur.

CLINICAL REVIEW

Application Type	NDA
Submission Number	21697
Submission Code	N-000-AZ
Letter Date	30 Jun 05
Stamp Date	30 Jun 05
PDUFA Goal Date	26 Dec 05
Reviewer Name	Karen Murry Mahoney, MD
Review Completion Date	2 Dec 05
Established Name	Conivaptan hydrochloride
(Proposed) Trade Name	Vaprisol®
Therapeutic Class	Vasopressin receptor antagonist, aquaretic
Applicant	Astellas Pharma US, Inc.
Priority Designation	S
Formulation	Intravenous injection
Dosing Regimen	20 mg IV loading dose followed by 40 mg/24 hrs by continuous IV infusion for 2-4 days
Indication	Treatment of euvolemic and hypervolemic hyponatremia in hospitalized adults
Intended Population	[ ]

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends an "approval" action, but recommends that the indication be restricted to the use of conivaptan for the treatment of euvolemic hyponatremia. Approval for the treatment of hypervolemic hyponatremia is not recommended at this time; the study population for hypervolemic hyponatremia consisted essentially entirely of patients with congestive heart failure, and in the clinical reviewer's opinion, the safety of conivaptan in congestive heart failure patients has not been established.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No specific recommendations are made at this time other than routine postmarketing surveillance of adverse events as required by FDA for newly approved drugs. Additional recommendations may be made after discussions with the Office of Drug Safety and other review disciplines.

1.2.2 Required Phase 4 Commitments

The clinical reviewer recommends a required Phase IV commitment of a controlled trial to answer the question of whether a loading dose is needed for conivaptan, and whether a regimen which does not include a loading dose could have a lower risk of adverse events, particularly infusion site reactions. Such a study was also requested in the first cycle "approvable" action, because the pharmacokinetics of conivaptan do not suggest that a loading dose is needed, but the applicant's dosing regimen includes a loading dose.

A Phase IV commitment for a warfarin interaction study using the full labeled dose of conivaptan is also recommended.

1.2.3 Other Phase 4 Requests

[redacted]

Other Phase 4 requests which were included in the first cycle "approvable" letter, and which continue to apply, include the need for a study to fully establish the lowest effective dose of

conivaptan, the need for a study to establish the durability of the sodium effect of conivaptan after discontinuation of conivaptan, and the need for full-dose special population studies in patients with underlying hepatic and renal impairment. If the applicant desires, studies of the lowest effective dose and the duration of effect could be included within the Phase 4 commitment loading dose study.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Conivaptan hydrochloride (Vaprisol®) is a nonpeptide vasopressin receptor antagonist with V2 and V1a receptor activity. It is a member of a potential new class of drugs known as "aquaretics", i.e. drugs that cause a substantial increase in the urinary elimination of free water without a substantial increase in urinary elimination of sodium or other solutes. The applicant proposes intravenous use of conivaptan in patients with euvolemic and hypervolemic hyponatremia, to increase the elimination of free water and thereby raise serum sodium concentration.

Conivaptan acts through antagonism of vasopressin V2 receptors located in the distal collecting tubules of the kidney. Vasopressin is a neurohypophyseal hormone; its primary function is to permit conservation of free water by the kidney. Activation of vasopressin V2 receptors results in the insertion of water channels, or aquaporins, in the collecting tubule, allowing for passive reabsorption of water.

Hyponatremia is the most common electrolyte abnormality in hospitalized patients. Hyponatremia is generally divided into classes according to the patient's intravascular volume status; this affects treatment decisions. Hypovolemic hyponatremia requires volume repletion for treatment, and a vasopressin receptor antagonist would not be an appropriate treatment for this type of hyponatremia. However, euvolemic and hypervolemic patients with hyponatremia have dilutional forms of hyponatremia, and are the applicant's target populations for conivaptan. Euvolemic hyponatremia is exemplified by the Syndrome of Inappropriate Antidiuretic Hormone (SIADH); hypervolemic hyponatremia occurs in the edematous states of congestive heart failure and hepatic failure. Blockade of vasopressin's action could allow patients with dilutional hyponatremia (euvolemic or hypervolemic) to eliminate their excess free water, and thereby increase their serum sodium concentration. There are no currently approved therapies for hyponatremia.

This is a second cycle review for conivaptan; the original New Drug Application (NDA) submission received an "approvable" action, primarily because of inadequate numbers of patients exposed to the relevant intravenous (IV) dose. The applicant now submits data regarding a larger population of patients exposed to the full proposed IV regimen.

The following is a summary of the clinical issues identified in the first cycle "approvable" letter:

Clinical issues affecting approvability:

- The number of subjects who received conivaptan at the systemic exposures associated with the dose and dosing regimen proposed for marketing was inadequate for evaluation of safety.
- The lowest potentially effective dose of conivaptan did not appear to have been established. Evidence from oral studies with lower conivaptan exposure suggested that lower intravenous doses might be effective in a substantial percentage of patients with hyponatremia.

Additional clinical issues for which a response was requested:

- The incidence of infusion site reactions was high, and exploration of methods for decreasing the incidence of infusion site reactions was requested.
- In the original NDA, there was a higher incidence of serious renal adverse events for conivaptan patients than for placebo patients. Information provided did not permit complete characterization of these events. Updated and more complete information on renal adverse events was requested.
- Information on the durability of effect of conivaptan was requested.
- Analysis of the efficacy of conivaptan when infused for less than four days was requested.
- The Agency recommended that the applicant develop a risk management plan for reduction of the likelihood that patients would receive concomitant CYP3A4-metabolized drugs. Conivaptan is a potent inhibitor of CYP3A4, and two cases of rhabdomyolysis occurred in clinical trials in patients who had received oral conivaptan along with a CYP3A4-metabolized statin.

Review by other disciplines is ongoing, and may affect regulatory decisions by signatory authorities regarding this application.

1.3.2 Efficacy

The applicant proposes the following indication for conivaptan:

"Vaprisol® is indicated for the treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients."

[redacted]

In a reanalysis of data from the pivotal IV hyponatremia trial, a duration of treatment of two days appeared to be effective for many patients. By two days of treatment, baseline adjusted serum sodium AUC, serum sodium, and the percentage of patients achieving serum sodium goals were already statistically significantly greater in the conivaptan group than in the placebo group. The majority of the effect of conivaptan on these parameters had occurred by two days of treatment, although serum sodium parameters and the percentage of patients achieving serum sodium goals continued to increase up to four days of treatment. The clinical reviewer concurs with the applicant that a proposed duration of treatment of 2-4 days (rather than the originally proposed 4 days) is reasonable.

The applicant did not provide new information regarding the duration of effect of conivaptan. There are no data regarding serum sodium from cessation of treatment to approximately one week after treatment. At that point, sparse data indicated that significant hyponatremia had not recurred in conivaptan-treated patients. However, at that point, placebo patients and conivaptan patients had similar serum sodiums. The sodium "effect" of conivaptan one week after cessation of treatment may actually be due to treatment of underlying causes of hyponatremia. The applicant proposes Phase IV study of the duration of effect of conivaptan.

1.3.3 Safety

In the original NDA submission, a total of only 63 subjects appeared to have received conivaptan at the full dose and dosing regimen proposed for labeling. The applicant now submits data for a total of 404 patients and healthy volunteers who received conivaptan at a dose of at least 40 mg/day IV, and for a duration of 2-4 days.

In the review, multiple breakdowns of patient populations were considered. In an ideal setting, a large amount of placebo-controlled data would have been presented for patients being treated for hyponatremia with intravenous conivaptan used in the full dose and dosing regimen proposed for labeling. However, this resubmission did not provide a large body of information for this specific patient population. Although the applicant did submit additional intravenous conivaptan safety data for review, none of these were placebo-controlled data from IV studies in hyponatremia. In the entire development program, there was only one Phase 3 controlled IV hyponatremia study, which included 55 patients exposed to conivaptan, and this study was presented in the original NDA. Therefore, the clinical reviewer had to rely on a variety of other types of data to augment the safety evaluation. All of the additional IV safety data were either from uncontrolled studies in hyponatremia, studies in congestive heart failure (CHF), or studies

in healthy volunteers. The vast majority of safety data from the original NDA submission were from oral studies with lower conivaptan exposure. Because little controlled IV hyponatremia study information was available, and the full Phase 2/3 population was heavily weighted with oral conivaptan patients with lower exposure, the clinical reviewer often had to separate out populations, e.g. all IV, all controlled, all hyponatremia, CHF, etc. When an apparent safety signal was identified, consideration of separate populations allowed the clinical reviewer to evaluate the overall finding, to assess whether the event was occurring with equal frequency in hyponatremia and CHF patients, and to assess whether the event was related to route of administration The following groups of studies were often used:

- Overall Safety Population (1148 conivaptan-treated subjects): included all Phase 2/3 studies, IV and oral, controlled and uncontrolled, hyponatremia and CHF, subjects who received the full proposed dose and subjects who had lower exposure
- Overall Placebo-Controlled Phase 2/3 Population (942 conivaptan-treated subjects): the placebo-controlled subset of the overall safety population
- Controlled "full dose" IV (258 conivaptan-treated subjects- patients and healthy volunteers): Study 027 (hyponatremia, 55 conivaptan-treated patients), Study 071 (CHF, 122 conivaptan-treated patients), Study 079 (QT study, 81 conivaptan-treated healthy volunteers); included studies in which subjects received at least 40 mg/day of intravenous conivaptan for at least 2 days
- "Full dose" IV in patients (292 conivaptan-treated patients): Study 027, Study 071, and Study 080 (open-label hyponatremia, 115 conivaptan-treated patients); included studies in which patients received at least 40 mg/day of intravenous conivaptan for at least 2 days
- All "full dose" IV (404 conivaptan-treated subjects): controlled "full dose" IV studies plus Study 080, Study 083 (healthy volunteer, oral vs IV PK, 21 conivaptan subjects), and 074 (healthy volunteer PK, 10 conivaptan subjects); included studies in which subjects received at least 40 mg/day of intravenous conivaptan for at least 2 days
- All Phase 2/3 IV (445 conivaptan-treated subjects): included Studies 027, 071, and 080, plus all other Phase 2/3 IV studies (153 additional conivaptan patients), controlled and uncontrolled, in CHF and hyponatremia; most additional patients had lower dose and/or shorter duration

The reader may find it useful to refer back to this list when multiple populations are mentioned. When conclusions regarding adverse events have been based on an evaluation of multiple populations, the clinical reviewer has attempted to explain which populations were most useful in providing clarity and in reaching the overall conclusion.

A total of 64 deaths occurred during conivaptan treatment, within 30 days of conivaptan treatment, or later but due to an adverse event which had its onset during treatment. The incidence of death appeared to be numerically higher among conivaptan-treated patients for the controlled "full dose" IV population and the controlled "full dose" IV congestive heart failure (CHF) study. The incidence of death did not appear to be higher for conivaptan patients than for placebo patients in the overall controlled Phase 2/3 population, which included oral patients with lower exposure. There appeared to be a correlation between IV-equivalent dose and incidence of death. Among congestive heart failure patients treated with full-dose IV conivaptan, there appeared to be a relationship between dose and both crude mortality and mortality per unit of

patient-time. Numerous analyses were done to evaluate the question of mortality risk with conivaptan. Overall, there does not appear to be an increased risk of mortality with conivaptan for the treatment of hyponatremia in the absence of congestive heart failure. However, there is a signal of a dose-related increase in the incidence of death for congestive heart failure patients. Use of conivaptan in CHF patients outside the clinical trial setting is not recommended at this time.

The following serious adverse events occurred more frequently numerically among intravenous-conivaptan-treated patients than among placebo-treated patients:

- serious "congestive cardiac failure aggravated"
- total serious cardiac failure events
- total serious infection events (no single infection predominated)
- total serious nervous system events (no single event predominated)
- total serious hypovolemia-related events
- serious infusion-site related events (occurred exclusively in conivaptan-treated patients; included severe infections and thrombophlebitides)

Withdrawal from study was more common among conivaptan-treated patients than among placebo-treated patients; most withdrawals were due to adverse events. The most common category of adverse events leading to discontinuation were was that of infusion-site-related events; twelve conivaptan patients discontinued study due to infusion-site-related events, compared to zero placebo patients.

Several adverse events of special interest were considered because of signals seen preclinically or in the original NDA submission. Findings regarding these events include:

- Total renal adverse events, and "nonserious" events of renal failure occurred more commonly numerically among conivaptan-treated patients than among placebo-treated patients in the "full dose" IV study population. In the controlled "full-dose" IV population, renal failure events occurred slightly more frequently in conivaptan-treated patients than in placebo patients; this was not seen in the overall controlled (IV + oral) safety population, which included oral patients with lower exposure. Special search criteria were developed for renal adverse events, and all serious events and cases of renal failure were examined. There was no evidence of a primary nephrotoxic effect of conivaptan, although data to assess this were limited. Most patients who developed renal failure had an underlying diagnosis of congestive heart failure, which carries a high baseline risk of acute renal failure with best current treatment. Overall, it appears that conivaptan may be associated with a slightly greater risk of nonserious, reversible renal adverse events. Most events were reversible moderate increases in creatinine, which may have been associated with volume depletion due to conivaptan, or with the patients' underlying diseases. As with patients treated with currently available diuretics in the acute hospitalized setting, renal function must be monitored, and patients may require volume repletion if an overly brisk aquaresis occurs with conivaptan.
- Overly rapid correction of serum sodium, which carries a risk of permanent neurologic sequelae, occurred only in conivaptan-treated patients. About 6% of IV conivaptan

patients overall, and about 9% of patients who received doses in the range under consideration for labeling, met laboratory criteria for overly rapid correction of serum sodium. One patient who met laboratory criteria for overly rapid correction of serum sodium suffered a delayed seizure without sequelae. Otherwise, there were no clinically apparent consequences of overly rapid correction of serum sodium.

- Infusion site reactions were very common among conivaptan-treated patients. The incidence of these events appears to correlate with dose and concentration. This underscores the need for consideration of a lower starting dose of conivaptan, and the need for study of a regimen without a loading dose.
- Hypovolemia-related events (e.g. hypotensive, hypovolemic, syncopal, fall and shock events) occurred more commonly among intravenous-conivaptan-treated patients than among placebo-treated patients. One hypovolemia-related death may have occurred due to hypovolemic shock after marked aquaresis.

Among patients with underlying congestive heart failure, cardiac failure events, atrial arrhythmia events, and bleeding events occurred more frequently among conivaptan-treated patients than among placebo-treated patients. The incidence of these events within the 20-40 mg/day IV dosage range was also specifically considered (i.e. excluding lower and higher exposures). As with the overall population, within this dose range, cardiac failure events occurred more frequently in conivaptan-treated patients than in placebo-treated patients, and there appeared to be a relationship between dose and incidence of cardiac failure events.

In addition to the above events of interest, the following adverse events occurred more frequently numerically among conivaptan-treated patients than among placebo-treated patients in controlled IV studies (including both CHF and non-CHF patients):

- Atrial arrhythmia events
- Cardiac failure events
- Hypernatremia (reported as adverse event)
- Hyperglycemia (reported as adverse event)
- Pneumonia
- "Dyspnea exacerbated"
- Aesthenia
- Thirst
- Pollakiuria

Atrial arrhythmia events may have been related to electrolyte depletion; hypokalemia was more common among patients experiencing these events than among the overall controlled IV study population.

Clinical laboratory findings of note include:

- Conivaptan-treated patients were more likely to develop transaminase elevations of >3x the upper limit of normal (ULN) and >10x ULN than were placebo-treated patients. Hepatobiliary adverse events did not occur more commonly among conivaptan-treated patients. In Study 071, a congestive heart failure study, fourteen conivaptan-treated patients had relatively large increases in transaminases. However, conivaptan-treated

patients were also more likely to have baseline elevations in transaminases, making this finding difficult to interpret.

- Mean fasting plasma glucose declined for placebo patients, but increased for conivaptan patients. Plasma glucose values of >250 mg/dL were also more common among conivaptan-treated patients. The difference between treatment groups was less marked for nonfasting plasma glucose. The reason for this difference between groups is unclear, but may be related to the fact that conivaptan is infused in 5% dextrose in water (D5W).
- Increases in serum creatinine to >1.6 mg/dL were more common among conivaptan-treated patients than among placebo-treated patients; in the IV studies, there appeared to be a relationship between conivaptan dose and the incidence of serum creatinine >2 mg/dL.
- In the IV studies, significant hypernatremia (>150 mEq/L) occurred exclusively in conivaptan-treated patients, although the incidence was low (1.2%-1.4%).
- Low hematocrit (<30%) occurred more frequently among IV-conivaptan-treated patients than among placebo-treated patients.
- In IV studies, women treated with conivaptan were more likely to develop hyperuricemia than were women treated with placebo.

1.3.4 Dosing Regimen and Administration

The applicant's recommended dosing regimen is a 20 mg IV loading dose administered over 30 minutes, followed by a continuous IV infusion of 40 mg/day for 2-4 days.

Biopharmaceutics had requested that the applicant justify the use of a loading dose, with provision of efficacy data both with and without an initial loading dose. The applicant did not provide such data. In their response to the "approvable" letter, the applicant cites the high plasma concentrations achieved after the initial loading dose, and the rapid initial pharmacodynamic effect of conivaptan. The applicant argues that increases in effective water clearance were seen at 6 hours after initial loading dose of conivaptan, that achievement of steady state without a loading dose would require approximately 50 hours, and that onset of the desired pharmacodynamic effect would likely be delayed. In the clinical reviewer's opinion, the applicant has not addressed this issue, and direct study of the pharmacodynamic effect of conivaptan with and without an initial loading dose is needed. The applicant proposes postmarketing study of this question, and the clinical reviewer recommends that this study be a postmarketing commitment. This question has safety implications, because the incidence of infusion site reactions appears concentration-dependent, as discussed in the initial NDA review. If equal efficacy could be achieved without a loading dose, and the incidence of infusion site reactions could be decreased with a non-loading-dose regimen, administration without a loading dose would be the desired regimen.

1.3.5 Drug-Drug Interactions

Conivaptan is a potent inhibitor of CYP3A4, and should not be coadministered with drugs metabolized by CYP3A4. The applicant seeks to minimize the risk of severe adverse drug-drug

interactions by limiting conivaptan to intravenous use in hospitalized patients. However, this might not prevent concomitant administration of CYP3A4 drugs. In the controlled hyponatremia trials, multiple protocol violations involving administration of prohibited CYP3A4 drugs occurred, despite a highly controlled clinical setting. In the "approvable" letter, explorations for reducing the likelihood that patients would receive concomitant CYP3A4-metabolized drugs were recommended. New data regarding specific adverse events occurring in patients who received prohibited CYP3A4-metabolized drugs showed that most protocol violations were related to benzodiazepines or calcium channel blockers, and that the adverse events which occurred in these patients did not appear to be related to the prohibited CYP3A4 drugs. The incidence of adverse events among hospitalized patients who received prohibited CYP3A4 drugs was lower than the incidence of adverse events among outpatients who received prohibited CYP3A4 drugs, indicating that restriction of use to the hospital setting may indeed reduce the risks associated with concomitant administration of CYP3A4-metabolized drugs.

In the approvable letter, a warfarin interaction study was recommended, using the full dose proposed for labeling. The applicant did not provide the results of a study, but states that a protocol is being developed. A Phase IV commitment for completion of a full-dose warfarin interaction study is recommended.

1.3.6 Special Populations

Information in this review related to special populations was obtained from summary information submitted by the applicant. Expert review by FDA Biopharmaceutics is ongoing, and should be considered to be the more definitive review if conclusions differ from the clinical review.

In the original NDA, the applicant conducted special population studies in the elderly, in patients with mild to moderate renal dysfunction (creatinine clearance $\geq$10 to <60 mL/min), and in patients with hepatic dysfunction, and concluded that dosage adjustment was not needed in these populations. However, the oral conivaptan dose used would have had lower exposure than the proposed IV dose, and the Agency recommended that the applicant repeat these studies using the proposed IV dosing regimen.

Use of adequate conivaptan doses for drug:drug interaction and special population studies is of particular importance because conivaptan exhibits nonlinear pharmacokinetics, with plasma levels increasing in a higher-than-dose-proportionate fashion. This nonlinearity occurs at multiple levels, including with increasing dose, with repeated dose, and with time. Patients in the target patient population have significantly higher exposures than healthy subjects, and significant intersubject variability occurs.

With this submission, the applicant examined the pharmacokinetics of patients age 65 years or older in an open-label study. As was noted in healthy volunteers, the pharmacokinetics of conivaptan were nonlinear, with a more than proportionate increase in exposure with increasing dose. Comparison of the PK of conivaptan in the elderly to the PK of conivaptan in younger patients was not possible with the data provided.

2 INTRODUCTION AND BACKGROUND

Conivaptan hydrochloride (Vaprisol®) is a nonpeptide vasopressin receptor antagonist with V2 and V1a receptor activity. It is a member of a potential new class of drugs known as "aquaretics", i.e. drugs that cause a substantial increase in the urinary elimination of free water without a substantial increase in urinary elimination of sodium or other solutes. The applicant proposes intravenous use of conivaptan in patients with euvolemic and hypervolemic hyponatremia, to increase the elimination of free water and thereby raise serum sodium concentration.

Conivaptan's acts through antagonism of vasopressin V2 receptors located in the distal collecting tubules of the kidney. Vasopressin is a neurohypophyseal hormone; its primary function is to permit conservation of free water by the kidney. Activation of vasopressin V2 receptors results in the insertion of water channels, or aquaporins, in the collecting tubule, allowing for passive reabsorption of water.

This is a second cycle review for conivaptan; the original NDA submission received an "approvable" action, primarily because of inadequate numbers of patients exposed to the relevant intravenous (IV) dose. The applicant now submits data regarding a larger population of patients exposed to the full proposed IV regimen.

Please see the original clinical review of conivaptan for detailed background information. Please see the "approvable" letter for the original NDA for details of the deficiencies noted in review of the original NDA. The following is a summary of the clinical issues identified in the "approvable" letter:

Clinical issues affecting approvability:

- The number of subjects who received conivaptan at the systemic exposures associated with the dose and dosing regimen proposed for marketing was inadequate for evaluation of safety.
- The lowest potentially effective dose of conivaptan did not appear to have been established. Evidence from oral studies with lower conivaptan exposure suggested that lower intravenous doses might be effective in a substantial percentage of patients with hyponatremia.

Additional clinical issues for which a response was requested:

- The incidence of infusion site reactions was high, and exploration of methods for decreasing the incidence of infusion site reactions was requested.
- In the original NDA, there was a higher incidence of serious renal adverse events for conivaptan (coni) patients than for placebo (pbo) patients. Information provided did not

permit complete characterization of these events. Updated and more complete information on renal adverse events was requested.

- Information on the durability of effect of conivaptan was requested.
- Analysis of the efficacy of conivaptan when infused for less than four days was requested.
- The Agency recommended that the applicant develop a risk management plan for reduction of the likelihood that patients would receive concomitant CYP3A4-metabolized drugs. Conivaptan is a potent inhibitor of CYP3A4, and two cases of rhabdomyolysis occurred in clinical trials in patients who had received conivaptan along with a CYP3A4-metabolized statin.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

In the original NDA, a total of 63 patients received conivaptan at a dose and duration consistent with the full exposure proposed for labeling. The applicant now submits additional data for a new total of 404 patients who received IV conivaptan at doses of 40 mg/day IV or higher. The following table lists the studies from which these patients are derived.

Table 4.1 Intravenous Studies with Full Proposed Dose

			Number of Subjects[a]	
Study Number	**Indication/Patient Population**	**Treatment Duration†**	**≥40 mg/day**	**Placebo**
087-CL-027	hyponatremia	4 days	55	29
087-CL-080‡	hyponatremia	4 days	115	--
087-CL-079	healthy volunteer (QT_c study)	4 days	81	40
087-CL-083	healthy volunteer (oral vs IV PK)	4 days	21	--
TOTAL with 4 days of treatment			**272**	**69**
087-CL-074	Healthy Volunteer (PK)	3 days	10	--
087-CL-071	CHF	2 days	122	40
TOTAL with <4 days of treatment			**132**	**40**
TOTAL with ≥2 days of treatment			**404**	**109**

Subject base: Safety analysis set (all subjects who received any IV study drug)

† based on study design

‡ ongoing study; number of patients represents number who completed the treatment phase as of 1 Sept. 2004

Source: Applicant's Table 1, pg 13, Summary of Intravenous Safety

Please refer to the original clinical NDA review for tables of all clinical studies included in the original NDA. Of the above studies in Table 4.1, new safety information was derived primarily from interim safety reports for Studies 071 and 080. It should be noted that no new placebo-controlled data were submitted regarding the use of conivaptan for the treatment of hyponatremia; all additional data are either from an open-label hyponatremia study, a CHF study, or healthy volunteer studies.

Study 071 was a randomized, double-blind, placebo-controlled, dose-ranging pilot study to evaluate the efficacy and safety of conivaptan in patients with decompensated chronic heart failure. [redacted]

Study 071 included both hyponatremic and nonhyponatremic patients, [redacted] The study included 122 patients exposed to conivaptan (40 at 40 mg/day, 40 at 80 mg/day and 42 at 120 mg/day), and 40 patients exposed to placebo. A full study report was not submitted; only safety data were included.

Study 080 is an ongoing, 4-day, open-label Phase 3 safety study in patients with euvolemic and hypervolemic hyponatremia. Interim safety information was included for 115 patients exposed to 40 mg/day conivaptan for up to 4 days.

This NDA resubmission may be accessed via the path
\\CDESUB1\N21697\N_000\2005-06-30
The original New Drug Application may be accessed via the path
\\CDSESUB1\N21697\N_000\2004-01-30.
An intensive QT study was submitted during the original review cycle and may be accessed via the paths
\\CDSESUB1\N21697\N_000\2004-03-31 and
\\CDSESUB1\N21697\N_000\2004-05-14.
A safety update was submitted four months into the original review cycle and may be accessed via the path
\\CDSESUB1\N21697\N_000\2004-05-28.

4.6 Financial Disclosures

Please see the initial clinical NDA review for discussion of financial disclosure. The applicant provided updated form 3454s stating that the applicant had exhibited due diligence in attempting to obtain financial disclosure forms from all investigators. On 1 Nov 05, the clinical reviewer requested information from Dr. Donald Raineri regarding their method for due diligence. On 11 Nov 05, Dr Raineri stated that he was still attempting to obtain this information from the former sponsor (Yamanouchi Pharmaceuticals). As of 25 Nov 05, the information regarding method of due diligence has not yet been received by the clinical reviewer.

5 CLINICAL PHARMACOLOGY

Please see the Biopharmaceutics review for an indepth discussion of the applicant's response to deficiencies identified in the original NDA; Biopharmaceutics review is ongoing, and should be considered to be more definitive than the summary information presented below.

5.2 Pharmacodynamics

Biopharmaceutics had requested that the applicant justify the use of a loading dose, with provision of efficacy data both with and without an initial loading dose. The applicant did not provide such data. The applicant provides a discussion in their Section 9.1 of their response, in which they cite the high plasma concentrations achieved after the initial loading dose, and the rapid initial pharmacodynamic effect of conivaptan. The applicant argues that increases in effective water clearance were seen at 6 hours after initial loading dose of conivaptan, that achievement of steady state without a loading dose would require approximately 50 hours, and that onset of the desired pharmacodynamic effect would likely be delayed.

In the clinical reviewer's opinion, the applicant has not addressed this issue, and direct study of the pharmacodynamic effect of conivaptan with and without an initial loading dose is needed. The applicant proposes postmarketing study of this question, and the clinical reviewer proposes this as a postmarketing commitment. This question has safety implications, also, because the incidence of infusion site reactions appears concentration-dependent, as discussed in the initial NDA review. If equal efficacy could be achieved without a loading dose, and the incidence of infusion site reactions could be decreased with a non-loading-dose regimen, administration without a loading dose would be the desired regimen. The clinical reviewer will defer to the Biopharmaceutics reviewer's opinion, however.

5.3 Exposure-response Relationships

Biopharmaceutics had requested that the applicant systematically analyze the relationship between pharmacodynamic response and creatinine clearance. In analyses from Study 027, the applicant's major Phase 3 efficacy trial for IV conivaptan in hyponatremia, there appeared to be a positive correlation between baseline creatinine clearance, and change in free water clearance and effective water clearance. This correlation was seen in the 40 mg/day IV group, but was not seen in the 80 mg/day IV group. No correlation was seen between baseline creatinine clearance and serum sodium.

6 INTEGRATED REVIEW OF EFFICACY

Please see the original clinical NDA review of conivaptan for a discussion of the efficacy findings from that review. A brief summary of those findings follows.

The applicant conducted a single Phase 3 intravenous efficacy trial for the hyponatremia indication. The applicant's [redacted] intravenous formulation for short term administration was prompted by concerns regarding conivaptan's marked inhibitory effect on the activity of cytochrome P450 3A4 (CYP3A4), which is important in the metabolism of many drugs. A severe drug-drug interaction with simvastatin had resulted in a case of rhabdomyolysis in Phase 2. The applicant proposed a single IV efficacy trial and two supportive oral efficacy trials. The IV efficacy trial (Study 027) was a randomized, placebo-controlled trial of the efficacy of two different doses of conivaptan for the treatment of hyponatremia in euvolemic and hypervolemic patients. Hyponatremia was defined as a serum sodium <130 mEq/L (normal range 135-145 mEq/L). The placebo group included 29 patients. Conivaptan was administered as an initial 20 mg intravenous loading dose, followed by continuous intravenous infusion of either 40 mg/day (29 patients) or 80 mg/day (26 patients) of conivaptan. Conivaptan was continuously infused for four days, or until normonatremia occurred. Two oral Phase 3 hyponatremia trials were of nearly identical design to the intravenous Phase 3 hyponatremia trial. In the oral trials, conivaptan was administered as 20 mg BID or 40 mg BID (40 or 80 mg/day) for a total of five days or until normonatremia occurred.

All three trials used the same primary endpoint, change from baseline in baseline-adjusted area under the serum sodium effect curve (AUC). Both doses of intravenous conivaptan were highly

effective, resulting in 8- and 11- fold increases in serum sodium AUC for the 40 mg/day and 80 mg/day groups respectively. This effect was highly statistically significant, regardless of age, gender, race, baseline volume status, or presence or absence of congestive heart failure. Eighty mg/day of oral conivaptan was also highly effective in both oral trials; 40 mg/day oral conivaptan was also effective, although with less significance in one trial.

Both doses of intravenous conivaptan were also strongly statistically significantly effective for all secondary efficacy parameters, which included:

- mean change in serum sodium from baseline to end of Study Day 4
- median event time to when at least 50% of patients had an increase in serum sodium of at least 4 mEq/L over baseline
- mean total time from first dose to end of treatment during which serum sodium was at least 4 mEq/L over baseline
- percentage of patients with a ≥6 mEq/L increase in serum sodium, or an increase to a normal serum sodium.

Oral conivaptan 80 mg/day was also highly effective for the secondary parameters. Oral conivaptan 40 mg/day was also effective, but in one of the two studies, these effects were less statistically significant. Important tertiary efficacy parameters for which intravenous conivaptan was strongly superior to placebo included increase in effective water clearance, increase in free water clearance, increase in serum osmolality, and decrease in urine sodium.

Thus, intravenous conivaptan in doses of 40 mg/day or 80 mg/day was highly effective in the treatment of hyponatremia. The applicant proposes the 40 mg/day dose regimen for labeling. However, the fact that oral conivaptan, which achieves lower conivaptan exposure (approximately 1/3 that of intravenous), was also highly effective, called into question whether the minimum effective dose of intravenous conivaptan had been established. Establishment of lowest potentially effective dose of drugs is an important clinical issue, and was cited as a deficiency that must be corrected prior to approval of conivaptan. The applicant did not perform a randomized placebo-controlled trial to examine this question, but rather presented some additional data and analyses to explore this question. This information is presented in Section 6.1.

[redacted] the applicant proposes a 2-4 day regimen, and provides supporting data for this proposal. This information is presented in Section 6.2.

In the approvable letter, information regarding the durability of the effect of conivaptan was requested. This information is discussed in Section 6.3.

6.1 Indication: Treatment of Hyponatremia (with Doses <40 mg/day IV)

To address the Agency's request for evaluation of the efficacy of a lower dose of intravenous conivaptan, the applicant used two approaches. In their IV study 080, an open-label study of patients with hyponatremia, the applicant added an arm of 21 patients treated with 20 mg/day, in addition to the ongoing main body of the study in which patients received 40 mg/day for up to 4

days. The applicant also examined the exposure-response relationship to assess whether efficacy was related to exposure to conivaptan.

The following table compares efficacy variables for the 20 mg/day and 40 mg/day regimens for Study 080.

Table 6.1 Interim Efficacy Results, Study 080, 20 mg/day and 40 mg/day Dosing Regimens

Efficacy Variable	Conivaptan 20 mg/day n=21	Conivaptan 40 mg/day n=115
Primary Efficacy Endpoint		
Baseline Adjusted Serum Sodium AUC over Duration of Treatment (mEq·hr/L)		
Mean (SD)	770.5 (446.85)	651.4 (403.39)
Secondary Efficacy Endpoints		
Number of Patients and Time to confirmed ≥4 mEq/L increase from Baseline Serum Sodium		
n (%)	15 (71.4%)	96 (83.5%)
Median time (h)	24.0	24.6
[95% CI]	[6.8, 60.0]	[24.0, 36.0]
Total time (h) to ≥4 mEq/L increase in Serum Sodium		
Mean (SD)	61.3 (37.77)	59.6 (33.10)
Serum Sodium (mEq/L)		
Baseline mean (SD)	122.1 (4.81)	124.1 (4.49)
Mean (SD) at end of treatment	132.3 (3.91)	132.4 (4.25)
Mean Change (SD) from Baseline to End of Treatment	10.2 (5.46)	8.3 (5.29)
Mean (SD) at Follow-up Day 11	130.5 (7.34)	132.0 (5.71)
Mean Change (SD) from Baseline to Follow-up Day 11	7.9 (9.60)	8.0 (6.55)
Mean (SD) at Follow-up Day 34	135.5 (4.29)	134.2 (4.94)
Mean Change (SD) from Baseline to Follow-up Day 34	13.1 (6.98)	10.3 (6.47)
Number (%) of patients with ≥6 mEq/L increase from Baseline in Serum Sodium or a Normal Serum Sodium Concentration ≥135 mEq/L During Treatment	15 (71.4%)	84 (73.0%)

Source: Applicant's Table 2, Response to Deficiencies in Original NDA

No placebo control was included in Study 080. However, data from the placebo arm of Study 027, the applicant's major hyponatremia study, are useful for illustrating the very low expected rates of response for placebo-treated patients. These data are presented below in Table 6.2.

In the above Table (6.1), conivaptan at 20 mg/day resulted in a numerically greater baseline-adjusted serum sodium AUC over treatment than did 40 mg/day (771 +/- 447 mEq-hr/L vs 651 +/- 403 mEq-hr/L). In Study 027, the placebo group had achieved a baseline-adjusted serum sodium AUC at 4 days of 61 +/- 242 mEq-hr/L.

In Study 080, 15/21 (71%) of patients in the 20 mg/day group had achieved a serum sodium increase of ≥4 mEq/L by 4 days. In the 40 mg/day group, 96/115 (83.5%) had done so. In Study

027, 9/29 (31%) of placebo patients had achieved a serum sodium increase of ≥4 mEq/L by 4 days.

In Study 080, mean serum sodium at end of treatment was equal in the 20 mg/day and 40 mg/day groups, and mean change from baseline in serum sodium was numerically greater in the 20 mg/day group than in the 40 mg/day group (10.2 +/- 5.5 mEq/L vs 8.3 +/- 5.3 mEq/L). In Study 027, mean increase in serum sodium in the placebo group at 4 days was 1.5 +/- 4.6 mEq/L.

In Study 080, 15/21 (71%) of patients in the 20 mg/day group had an increase in serum sodium of ≥6 mEq/L or had a serum sodium of ≥135 mEq/L at end of treatment. In the 40 mg/day group, 84/115 (73%) had met one of these goals. In study 027, 6/29 (21%) of placebo patients met one of these goals at 4 days.

The applicant's examination of exposure-response relationships did not demonstrate a relationship between plasma conivaptan concentration and serum sodium or effective free water clearance. However, data were included for only 4 patients (from Study 025) who received 20 mg/day.

The data from Study 080 regarding the efficacy of the 20 mg/day dose are highly suggestive of efficacy of this lower dose. The applicant proposes the 40 mg/day dose for approval and initial labeling, and states that they are designing a pilot study to explore the effect of IV conivaptan at various dosing regimens as part of a Phase IV commitment. However, the clinical reviewer finds the data for efficacy of the 20 mg/day dose compelling, and recommends that the initial label include information regarding the probable efficacy of this dose, and the possibility of a 20 mg/day initial dose.

6.2 Indication: Treatment of Hyponatremia (with Duration of Treatment of 2-4 Days)

To support the [redacted] duration of 2-4 days, the applicant reanalyzed the efficacy measures for Study 027, their intravenous hyponatremia efficacy study. The following table presents the data for the primary and secondary efficacy endpoints, for the timepoints at both 2 and 4 days.

Table 6.2 Study 027 Summary of Efficacy Results at 2 and 4 Days of Treatment

Efficacy variable	Placebo N=29		IV YM087 40 mg/d N=29		IV YM087 80 mg/d N=26	
Primary efficacy endpoint	2d	4d	2d	4d	2d	4d
Baseline adjusted serum Na^+ AUC over duration of treatment (mEq·hr/L) Mean (SD)	6.2 (61.77)	61.4 (242.30)	205.9 (171.63)	530.8 (385.46)	269.9 (155.71)	861.7 (331.14)
LS Mean ± SE	3.6 ± 26.84	12.9 ± 61.16	205.6 ± 28.66***	490.9 ± 56.79***	274.4 ± 27.87***	716.8 ± 80.45***
Secondary efficacy endpoints						
Number of patients (%) and median event time (h) from first dose of study medication to a confirmed ≥4 mEq/L increase from Baseline in serum Na^+, [95% CI]	2 (6.9%) NE NE	9 (31.0%) NE NE	22 (75.9%) 23.7*** [10, 24]	23 (79.3%) 23.7*** [10, 24]	23 (88.5%) 23.4*** [6, 24]	24 (92.3%) 23.4*** [6, 24]
Total time (h) from first dose of study medication to Day 2 or Day 4 end of treatment during which patients had a confirmed ≥4 mEq/L increase in serum Na^+ from Baseline Mean (SD)	2.2 (5.91)	13.7 (20.45)	22.3 (15.95)	53.4 (34.30)	28.8 (12.12)	71.2 (24.95)
LS Mean ± SE	2.1 ± 2.29	14.2 ± 5.25	22.3 ± 2.26***	53.2 ± 5.17***	30.6 ± 2.37***	72.7 ± 5.43***
Serum Na^+ (mEq/L)						
Baseline mean (SD)	124.3 (4.05)	124.3 (4.05)	123.3 (4.66)	123.3 (4.66)	124.8 (3.41)	124.8 (3.41)
Mean (SD) at end of treatment	124.5 (4.65)	125.8 (4.94)	128.6 (5.85)	129.8 (4.78)	131.5 (4.67)	133.4 (3.50)
Change from Baseline to end of treatment						
Mean change (SD)	0.2 (2.48)	1.5 (4.84)	5.3 (4.38)	6.5 (4.43)	6.7 (4.16)	8.6 (4.00)
LS Mean change ± SE	0.1 ± 0.71	0.8 ± 0.80	5.2 ± 0.70***	6.3 ± 0.74***	6.8 ± 0.73***	9.4 (0.79)***
Number (%) of patients who obtained a confirmed ≥6 mEq/L increase from Baseline in serum Na^+ or a normal serum Na^+ concentration ≥135 mEq/L during treatment	0 (0)	6 (20.7%)	12 (41.4%)***	20 (69.0%)***	18 (69.2%)***	23 (88.5%)***

* P value <0.05 vs placebo ** P value <0.01 vs placebo *** P value ≤0.001 vs placebo NE = not estimable

Source: Applicant's Table 8.1, pg 548, Response to Deficiencies in Original NDA

At 2 days of treatment, baseline-adjusted serum sodium AUC was already highly statistically significantly greater in the conivaptan-treated group than in the placebo-treated group. This difference further widened by 4 days of treatment.

At 2 days of treatment, all but one of the patients who would achieve a ≥4 mEq/L increase in serum sodium by 4 days had already done so at 2 days.

At 2 days of treatment with 40 mg/day IV, serum sodium had increased by 5.2 mEq/L (+/- 0.7) more in the conivaptan-treated group than in the placebo-treated group. By four days, this treatment difference was 6.5 mEq/L (+/- 0.7). The majority of the increase in serum sodium attributable to conivaptan effect had occurred by 2 days of treatment.

At 2 days of treatment, 12/20 (60%) of patients in the 40 mg/day conivaptan group had achieved a ≥6 mEq/L increase in serum sodium or an increase to >135 mEq/L, compared to zero in the placebo group. At 4 days, 20/29 (69%) of conivaptan patients had reached one of these goals, compared to 6/29 (21%) of placebo patients.

Overall, it appears that a substantial percentage of patients could have a clinically significant improvement in serum sodium after two days of treatment, although the number of patients who reach serum sodium goals may further increase through 4 days of treatment. It is reasonable to label conivaptan for a duration of treatment of 2-4 days.

6.3 Durability of Effect of Conivaptan

In the approvable letter, the Agency had requested information regarding the durability of effect of conivaptan. The applicant provided information from hyponatremia Study 080 for the 40 mg/day dose, which was administered for up to 4 days.

Table 6.3 Interim Data Regarding Durability of Effect of Conivaptan, Study 080

Serum Sodium (mEq/L)	IV Conivaptan 40 mg/day	
	Visit	Change from Baseline
Baseline		
n	115	
Mean	124.9	NA
Median	124.9	
Range	106.0 – 135.0	
End of Treatment		
n	113	113
Mean	132.4	7.5
Median	132.7	7.3
Range	118.3 – 142.1	-6.7 – 28.0
Follow-up: Day 11		
n	104	104
Mean	132.0	7.1
Median	132.0	6.0
Range	114.0 – 150.2	-10.0 – 21.2
Follow-up: Day 34		
n	90	90
Mean	134.2	9.4
Median	134.2	9.0
Range	118.0 – 150.0	-10.0 – 28.0

Source: Applicant's Table 7, Section 4.1.6, pg 23, Response to Deficiencies in Original NDA

At followup visits at day 11 (at least 7 days after last dose of conivaptan) and day 34 (at least 30 days after last dose of conivaptan), mean and median serum sodium remained near values seen at end of treatment, and well above baseline values. This information is of value in that it does not appear that low mean serum sodium recurred quickly. However, this may be due to treatment of underlying causes of hyponatremia, rather than to an effect of conivaptan. Of more use would have been daily values from the end of treatment for serum sodium and other endpoints, in order to assess if the effect of short-term administration of conivaptan wanes before correction (by other treatments) of underlying causes of hyponatremia can come into effect.

The clinical reviewer also examined data from Study 027 in the original NDA. In that study, serum sodium was only measured up to the end of treatment (Study Day 4), and then one more time at Study Day 10-13. At this final measurement, mean serum sodium was 131 mg/dL in the placebo group, 129 mg/dL in the 40 mg/day IV conivaptan group, and 134 mg/dL in the 80 mg/day IV group (original NDA submission, 027 study report, pg 60, Figure 9-2; and pg 419, Table 13.3). The most that can be said from this information is that by 6-9 days after cessation of conivaptan infusion, the serum sodium effect was no longer seen for the proposed 40 mg/day conivaptan regimen vs placebo, but significant hyponatremia had not recurred in any treatment group, including placebo.

Overall, it appears that significant hyponatremia does not recur quickly after cessation of conivaptan. However, this might not be due to continued activity of conivaptan, but rather to treatment of underlying causes of hyponatremia. No data are available from cessation of

treatment to 7 days after last dose of conivaptan. The applicant proposes Phase IV study of the duration of effect of conivaptan.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In the original NDA submission, a total of only 63 subjects appeared to have received conivaptan at the exposure expected in the proposed dosing regimen for labeling, [redacted] Therefore, the additional data in this resubmission are from studies of intravenous conivaptan used at dosage levels at least as high and durations at least as long as those proposed for labeling. With this resubmission, there are now a total of 404 subjects who have received IV conivaptan at doses and durations at least as large as those proposed for labeling.

The following table enumerates patients from the "full dose" IV studies which contribute the 404 conivaptan patients who received the full dose and duration proposed for labeling.

Table 7.0 Number of Subjects who Received "Full Dose" Intravenous Conivaptan, by Study
(Source: Applicant's Table 1, Response to Deficiencies in Original NDA)

Study Number	Population/Indication	Treatment Duration (days)	Conivaptan 40 mg per day§	Conivaptan > 40 mg per day§	Placebo
087-CL-027	Patients/Hyponatremia	4	29	26	29
087-CL-080†	Patients/Hyponatremia	4	115	--	--
087-CL-079	Healthy volunteer/ QTc Study	4	41	40	40
087-CL-083	Healthy volunteer/ PK oral vs iv	4	21	--	--
087-CL-074	Healthy volunteer/PK	3	10	--	--
087-CL-071	Patients/CHF	2	40	82	40
Total			**256**	**148**	**109**
Total Intravenous Conivaptan			**404**		--

§ Dosing regimen included a 20 mg loading dose.

† Number represents an interim cut and includes patients who completed the treatment phase by September 1, 2004.

The applicant submitted a small amount of controlled data for the use of intravenous conivaptan in the treatment of hyponatremia, essentially limited to Study 027, in which 55 patients were exposed to conivaptan. These data were not new and were included in the original NDA. All new IV safety data come from an open-label IV hyponatremia study, a controlled IV CHF study,

and 3 studies in healthy volunteers. Because the amount of safety data from the single controlled full-dose IV hyponatremia study was small, the clinical reviewer had to consider various sources of pooled data. Depending on the safety issue in question, one or more of several safety pooled populations may have been considered, e.g.:

- Controlled "full dose" IV (258 coni subjects): Included Study 027 (hyponatremia- 55 coni pts), Study 071 (CHF- 122 coni pts), Study 079 (QT study, 81 coni healthy volunteers)
- "Full dose" IV in patients (292 coni pts): Included Study 027, Study 071, and Study 080 (open-label hyponatremia, 115 coni pts); included studies in which patients received at least 40 mg/day of intravenous conivaptan for at least 2 days; did not include healthy volunteers
- All "full dose" IV (404 coni subjects): controlled "full dose" IV studies plus Study 080, 083 (healthy volunteer, oral vs IV PK, 21 coni subjects), and 074 (healthy volunteer PK, 10 coni subjects); included studies in which subjects received at least 40 mg/day of intravenous conivaptan for at least 2 days; included patients and healthy volunteers
- All Phase 2/3 IV (445 coni subjects): included Studies 027, 071, and 080, plus all other Phase 2/3 IV studies (153 additional coni patients), controlled and uncontrolled, in CHF and hyponatremia; most patients had lower dose and/or shorter duration
- Placebo-controlled Phase 2/3 (942 coni subjects): included IV and oral; included studies for hyponatremia and CHF indications; included patients with lower than "full dose" exposure
- Overall safety population (1148 coni subjects): included IV and oral; included controlled and uncontrolled studies; included studies for hyponatremia and CHF indications; included patients with "full-dose" exposure and lower than "full dose" exposure

In order to increase the interpretability of the data, the clinical reviewer has often presented information separately for two or more of these populations, particularly when it appeared that a potential safety signal was occurring more frequently in one population compared to others.

7.1.1 Deaths

A total of 70 deaths occurred among conivaptan-treated patients in the development program; among these, 63 deaths occurred during treatment, within 30 days following treatment, or due to an adverse event that had its onset during treatment. An additional 6 deaths occurred >30 days after end of conivaptan treatment. One death occurred in a patient in a Japanese study that was not included in the safety population. A total of 12 deaths occurred among placebo-treated patients during treatment, within 30 days following treatment, or due to an adverse event that had its onset during treatment. An additional 6 deaths occurred >30 days after placebo treatment. Overall, death occurred in 5.5% (63/1148) of conivaptan patients and 3.2% (12/372) of placebo patients (during treatment, within 30 days following treatment, or due to an adverse event that had its onset during treatment).

7.1.1.1 Tabular Listing of Deaths

The following tables list deaths occurring in the conivaptan development program. Tables 7.1.1.1.1 and 7.1.1.1.2 list deaths occurring in the "full dose" studies conducted in patients, in the conivaptan and placebo groups; and Tables 7.1.1.1.3 and 7.1.1.1.4 list deaths occurring in all other studies in the conivaptan program.

Table 7.1.1.1.1
Deaths Listing[1], Studies 027, 071 and 080
Treatment = Conivaptan
Cutoff Date 1 Sep 04

Trial	Ctr	Pt	Age (yrs)	Gender	Dose[2] (mg/day IV)	Time[3] (days)	Source[4]	Patient-Time (days)	Description
027	58	075806	81	f	40	2 (1)	N	2	metastatic gallbladder (GB) cancer, sepsis, hypotension, liver failure
027	16	071602	91	m	80	2 (19)	N	2	pneumonia, congestive heart failure (CHF)
027	24	072412	59	f	80	5 (15)	N	5	out of hospital death, cause unknown
027	58	075801	90	f	80	4 (2)	N	4	CHF, pneumonia, renal failure
071	7	0043	69	m	40	2 (3)	N	2	dilated cardiomyopathy
071	7	0063	78	m	40	2 (25)	N	2	worsening cardiomyopathy
071	4	0041	47	m	120	2 (16)	N	2	human immunodeficiency virus infection (HIV), *Pneumocystis carinii* pneumonia, CHF, cardiac arrest
071	24	0089	25	f	120	2 (2)	N	2	sudden cardiac death, postpartum cardiomyopathy, anomalous left coronary artery
071	26	0017	62	f	120	1 (1)	N	1	ventricular fibrillation (V fib)
071	32	0088	49	m	120	2 (23)	N	2	cardiopulmonary arrest
080	100	10003	42	f	40	4 (23)	N	4	sepsis, hepatic failure, renal failure
080	101	10110	80	f	20	4 (17)	N	4	metastatic gastric carcinoma
080	102	10203	76	m	40	2 (2)	N	2	found dead in hospital bed 2 days after conivaptan (coni) stopped for hypotension; suspected cerebrovascular accident (CVA)
080	103	10307	63	m	40	2 (16)	N	2	*Morganella morganii* sepsis after pacemaker insertion
080	105	10501	76	m	40	4 (9)	N	4	mesenteric artery occlusion, sepsis, multiorgan failure
080	112	11238	61	f	40	4 (1)	N	1	myocardial infarction (MI), hemorrhage after anticoagulation, V fib
080	113	11303	85	m	40	4 (15)	N	4	acute resp failure due to food aspiration; had hypernatremia after coni
080	203	20303	67	f	40	4 (19)	N	4	found dead in hospital bed; presumed arrhythmia due to digitalis toxicity
080	204	20401	67	f	40	4 (21)	N	4	found dead at home, cause unknown
080	204	20402	70	m	40	4	N	4	sudden death, possible myocardial infarction
080	206	20602	27	f	40	4 (18)	N	4	multiorgan failure, abdominal tuberculosis (TB), *Pseudomonas aeruginosa* pneumonia
080	206	20603	76	f	40	4 (26)	N	4	bronchial carcinoma
080	206	20616	71	f	40	4 (37)	N	4	CVA; hx overly rapid correction

Table 7.1.1.1.1
Deaths Listing[1], Studies 027, 071 and 080
Treatment = Conivaptan
Cutoff Date 1 Sep 04

Trial	Ctr	Pt	Age (yrs)	Gender	Dose[2] (mg/day IV)	Time[3] (days)	Source[4]	Patient-Time (days)	Description
									of serum sodium (Na)
080	207	20703	64	m	40	4 (18)	N	4	tuberculous pneumonia
080	209	20902	64	f	40	4 (2)	N	4	worsening right heart failure
080	211	21103	40	m	40	2 (6)	N	2	resp failure
080	211	21104	34	f	40	4 (19)	N	4	suspected meningitis, acquired immune deficiency syndrome (AIDS), probable pulmonary TB
080	211	21106	25	f	40	4 (22)	N	4	sudden death, no autopsy, also had AIDS

1 All deaths occurring during drug exposure, or within 30 days following drug exposure, or due to an adverse event that occurred within 30 days of drug exposure. Studies 027, 071, 080
2 Last dose prior to death
3 Days on drug prior to death. If patient was off drug at time of death, time off drug prior to death follows in parentheses.
4 Source of death report: N = NDA
Source: Table 2.7.4-4.6a

Table 7.1.1.1.2
Deaths Listing[1], Studies 027, 071 and 080
Treatment = Placebo
Cutoff Date 1 Sep 04

Trial	Ctr	Pt	Age (yrs)	Gender	Dose[2] (mg/day)	Time[3] (days)	Source	Patient-Time	Description
027	24	072413	42	m	n/a	4 (4)	N	n/a	severe hyponatremia with coma and resp arrest
027	72	077208	71	m	n/a	3 (5)	N	n/a	worsening CHF, hypotension, renal failure and hyperkalemia
027	79	077901	87	f	n/a	2 (3)	N	n/a	sick sinus syndrome, arrest after hip fracture

1 All deaths occurring during drug exposure, or within 30 days following drug exposure, or due to an adverse event that occurred within 30 days of drug exposure. Studies 027, 071, 080
2 Last dose prior to death
3 Days on drug prior to death. If patient was off drug at time of death, time off drug prior to death follows in parentheses.
Source: Table 2.7.4-4.6a

Table 7.1.1.1.3
Deaths Listing[1], all Studies in Original NDA (other than Study 027)
Treatment = Conivaptan
Cutoff Date: 1 Sep 03

Trial	Ctr	Pt	Age (yrs)	Gender	Dose[2] (mg)/ Route	Time[3] (Days)	Source[4]	Patient-Time (Days)	Description
016	001	016-0000110	81	M	20/ oral	1 (4)	N	1	CHF, MI, cardiogenic shock
017	001	017-0001001	47	F	10/ oral	7 (8)	N	7	Dilated cardiomyopathy, cardiac arrest, suspected pulmonary embolism
019	JPN	019-0001101	56	M	15/ iv	1 (1)	N	1	CHF; respiratory arrest followed by cardiac arrest
020	021	020-0021002	58	M	40/ oral	72 (3)	N	72	Pulmonary embolus; autopsy performed
	032	020-0032008	64	M	40/ oral	68	N	68	Sudden death at home

Table 7.1.1.1.3
Deaths Listing[1], all Studies in Original NDA (other than Study 027)
Treatment = Conivaptan
Cutoff Date: 1 Sep 03

Trial	Ctr	Pt	Age (yrs)	Gender	Dose[2] (mg)/ Route	Time[3] (Days)	Source[4]	Patient-Time (Days)	Description
023	001	023-0001004	64	M	80/ iv	3 (3)	N	3	Pulmonary embolism
	004	023-0004001	63	M	80/ iv	3 (15)	N	3	Aspiration pneumonia
025	001	025-0001002	56	M	40/ iv	4 (15)	N	4	Pneumonia, ventricular tachycardia (V tach) and renal failure after heart transplant
026	001	026-0060103	45	F	40/ oral	4 (17)	N	4	End-stage CHF, renal failure
	007	026-0060708	54	F	40/ oral	3 (6)	N	3	Cardiorespiratory arrest, CHF; had been hypotensive on coni
031	060	031-0060702	95	F	40/ oral	68 (2)	N	68	Decompensated CHF
	060	031-0060607	68	F	80/ oral	113	N	113	Cerebral hemorrhage
	061	031-0061407	67	M	80/ oral	10 (1)	N	10	Lung cancer
	061	031-0061411	94	M	40/ oral	7 (13)	N	7	Pneumonia
	061	031-0061414	76	F	40/ oral	63 (1)	N	63	Metastatic pancreatic cancer
	062	031-0062501	80	F	40/ oral	13	N	13	CHF; died at home
	062	031-0062503	63	M	40/ oral	61 (1)	N	61	Hyperkalemia, myocardial infarction, cardiac arrest
	062	031-0062505	83	M	40/ oral	151 (1)	N	151	Endstage CHF; died at home
	071	031-0071304	79	F	80/ oral	302 (1)	N	302	Endstage cirrhosis
	071	031-0071313	92	M	40/ oral	159	N	159	Bilateral pleural effusions; respiratory arrest then cardiac arrest
	075	031-0075804	59	F	20/ oral	9	N	9	Endstage CHF
	075	031-0075807	78	F	40/ oral	66	N	66	CHF; acute renal failure after high-dose vitamin C therapy
	076	031-0076503	70	M	40/ oral	230 (9)	N	230	Lung cancer (died in hospice)
032	010	032-0010009	54	M	40/ iv	1 (2)	N	1	Arrest with pulseless electrical activity. Had CHF and multiple medical problems (MMP)
	010	032-0010011	51	M	20/ iv	1 (19)	N	1	Cardiac arrest at home; autopsy stated ischemic cardiomyopathy cause of death
	027	032-0027002	62	M	40/ iv	1 (33)	N	1	CHF cause of death at autopsy
033	013	033-0013010	67	M	40/ oral	175 (25)	N	175	Family refused to release medical record of death
034	024	034-0024005	69	M	80/ oral	27 (30)	N	27	Thrombotic middle cerebral stroke
	032	034-0032018	74	M	80/ oral	61	N	61	Died at home, reported as cardiac arrest
	049	034-0049020	60	M	20/ oral	48	N	48	Found dead at home; history CHF
043	04	043-0230409	78	F	40/ oral	4	N	4	Refractory heart failure

Table 7.1.1.1.3
Deaths Listing[1], all Studies in Original NDA (other than Study 027)
Treatment = Conivaptan
Cutoff Date: 1 Sep 03

Trial	Ctr	Pt	Age (yrs)	Gender	Dose[2] (mg)/ Route	Time[3] (Days)	Source[4]	Patient-Time (Days)	Description
	13	043-0231339	67	M	40/ oral	2	N	2	Hypovolemic shock after marked aquaresis
047	023	047-0230106	58	M	40/ oral	32	N	32	Found dead at home
	023	047-0230113	53	M	80/ oral	175	N	175	Found dead at home
	023	047-0231326	65	M	40/ oral	14	N	14	Ventricular tachycardia, hypotension, congestive heart failure
	023	047-0231334	80	F	40/ oral	15 (>1)	N	15	Perforated esophageal cancer

[1]All deaths occurring during conivaptan exposure or within 30 days following discontinuation of conivaptan, and all those occurring later but resulting from adverse events that had an onset during drug exposure or during the 30 days following drug exposure
[2]Dose at time of death. If death occurred after discontinuation, last dose before discontinuation
[3]Days on drug at time of death. If death occurred after discontinuation, includes number of days on drug before discontinuation and number of subsequent days off drug before death (in parentheses)
[4]N = NDA

Table 7.1.1.1.4
Deaths Listing[1], all Studies in Original NDA (other than Study 027)
Treatment = Placebo
Cutoff Date: 1 Sep 03

Trial	Ctr	Pt	Age (yrs)	Gender	Dose[2] (mg)/ Route	Time[3] (Days)	Source[4]	Patient-Time (Days)	Description
026	014	026-0061401	83	F	Pbo/ oral	4 (4)	N	4	Lung cancer, cardiopulmonary arrest
	029	026-0062903	83	M	Pbo/ oral	2	N	2	Colon cancer
032	021	032-0021004	82	M	Pbo/ iv	1 (5)	N	1	Ventricular fibrillation
	027	032-0027003	73	M	Pbo/ iv	1 (21)	N	1	Bacterial sepsis
038	002	038-0002007	44	M	Pbo/ iv	1 (23)	N	1	History CHF; found unresponsive at home; asystole on Emergency Medical Technician (EMT) electrocardiogram (EKG)
	002	038-0002011	83	F	Pbo/ iv	1 (18)	N	1	Endstage CHF
043	04	043-0230405	92	F	Pbo/ oral	5 (22)	N	5	Died at home of unknown cause
	13	043-0231343	65	M	Pbo/ oral	2 (1)	N	2	Acute MI
	30	043-0233005	62	F	Pbo/ oral	2 (10)	N	2	Bleeding after hip surgery for renal cancer metastases

[1]All deaths occurring during conivaptan exposure or within 30 days following discontinuation of conivaptan, and all those occurring later but resulting from adverse events that had an onset during drug exposure or during the 30 days following drug exposure
[2]Dose at time of death. If death occurred after discontinuation, last dose before discontinuation
[3]Days on drug at time of death. If death occurred after discontinuation, includes number of days on drug before discontinuation and number of subsequent days off drug before death (in parentheses)
[4]N = NDA

7.1.1.2 Brief Summaries of Death Narratives for Conivaptan Patients

Subject 016-0000110: 82 year old (yo) man (M) with prior New York Heart Association Functional Class (NYHA FC) III/IV CHF. Received single 20 mg dose conivaptan. Inotropic treatment started on Study Day 2 for dyspnea and CHF. On Study Day 4, MI with cardiogenic shock and death.

Subject 017-0001001: 47 yo female (F) with NYHA FC III dilated cardiomyopathy, gangrenous lesions both feet. Received conivaptan 10 mg/day for 7 days. Eight days after last dose of conivaptan, developed tonic clonic seizures, ventricular tachycardia and hypotension, and died. Suspected pulmonary embolism.

Subject 019-0001101: 56 year old man with CHF, ischemic heart disease and history of multiple strokes. Received single dose of 15 mg IV conivaptan. One day after the dose, the patient had a respiratory arrest, followed by a cardiac arrest and death. Study 019 was conducted in Japan, and was not included in the Phase 2/3 study group.

Subject 020-0021002: 58 year old man with ischemic CHF. On day 75 of conivaptan treatment, and two days after sinus surgery, patient collapsed. Resuscitation unsuccessful. Autopsy revealed massive pulmonary embolus.

Subject 020-0032008: 64 year old man with congestive heart failure. On day 67, developed abdominal discomfort at home. On day 68 of conivaptan treatment, died at home.

Subject 023-0001004: 64 yo M with hyponatremia and CHF, automatic implantable defibrillator, chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM). Admitted with pulmonary embolism (PE); two days later, began conivaptan. Received 50 mg IV/day for 2 days, then 80 mg for 1 day. At some point between admission and Study Day 3, developed tachyarrhythmias. On Study Day 3, deep peroneal vein thrombus noted on Doppler. Systolic blood pressure (BP) in 80s-90s Study Days 3-5. Study Day 6, died due to cardiorespiratory arrest refractory to defibrillation and medical therapy. Suspected recurrent pulmonary embolism.

Subject 023-0004001: 63 year old man with euvolemic hyponatremia and a history of squamous cell carcinoma of the right pyriform sinus. Received 50 mg IV conivaptan on Study Day 1, then 80 mg/day for two days. On Study Day 3, dyspnea, decreased oxygen saturation and chest X-ray (CXR) consistent with aspiration pneumonia. Intubated. Died on Study Day 19 from respiratory failure.

Subject 025-0001002: 56 yo M with hyponatremia; history of MI, biventricular heart failure, pulmonary embolism (PE), atrial fibrillation (A fib). Received IV conivaptan 60 mg for one day followed by 40 mg/day for 4 days. Serum sodium went from 129 mEq/L to 139 over the four days. Four days after last dose of conivaptan, received heart transplant. Developed acute renal failure and pneumonia. Sixteen days after last dose of conivaptan, syncopal symptoms followed by cardiorespiratory arrest, ventricular tachycardia (V tach) and death.

Subject 026-0060103: 45 yo F with history of CHF, pulmonary hypertension, rheumatic heart disease, atrial fibrillation, bacterial endocarditis, aortic and mitral valve replacements. Admitted with end-stage CHF and hyponatremia. Started conivaptan 40 mg by mouth (po) q day; took for 4 days. On Study Day 4, worsening renal function, decreased oncotic pressure, treated with venovenous hemofiltration. Renal scan 15 days after last dose of drug showed severe bilateral renal cortical disease, delayed renal blood flow to both kidneys, small right kidney. Developed bradycardia and died 17 days after last dose of conivaptan.

Subject 026-0060708: 54 yo F with history severe cardiomyopathy, COPD, MI, chronic renal impairment. Admitted with decompensated CHF; hyponatremic. Started on oral conivaptan 40 mg/day. On Study Day 2, became hypotensive, hyperkalemic and developed ventricular tachycardia (V tach). Treated with lidocaine, but lidocaine stopped due to lidocaine toxicity with mental status changes. Study Day 3, lidocaine restarted due to recurrent V tach. Study Day 4, lidocaine replaced with amiodarone. Conivaptan stopped due to hypovolemia. Study Day 5, blood urea nitrogen (BUN) increased to 69 mg/dL from baseline 16; creatinine (Cr) increased to 1.9 mg/dL from baseline 0.8. Study Day 10, had cardiorespiratory arrest and died.

Subject 027-0071602: 91 yo M with CHF. Received IV conivaptan for 2 days; stopped due to phlebitis at multiple sites. Study Day 5, CHF worsened. Study Day 14, bilateral pneumonia diagnosed. Died on Study Day 22 from pneumonia and CHF (19 days after last dose of conivaptan).

Subject 027-0072412: 59 yo F with history of breast cancer 15 yrs prior, treated with mastectomy. Received 5 days of 80 mg IV conivaptan; 1 day later, developed "decline in her general condition". Died out-of-hospital, one day after her final (day 15) study visit.

Subject 027-0075801: 90 year old woman hospitalized with CHF and pneumonia. Received conivaptan 80 mg/day for four days. Throughout treatment phase, had worsening CHF with hypotension; worsening pneumonia with decreasing oxygen saturation and cyanosis of extremities; and decreasing urine output. Died on Study Day 6 after family requested comfort measures only.

Subject 027-0075806: 81 yo F with metastatic gallbladder cancer. Received 40 mg IV conivaptan for 2 days; stopped after patient developed gram-negative sepsis. Developed hypotension and jaundice and died one day later (Study Day 3). Baseline Cr 0.6; increased to 1.5 on Study Day 3.

Subject 031-0060702: 95 year old F with hyponatremia and CHF. Received oral conivaptan 40 mg/day. On day 45 of treatment, admitted with worsening CHF. Conivaptan discontinued on day 68; patient died two days later of decompensated CHF.

Subject 031-0060607: 68 year old woman with idiopathic hyponatremia. History of hypertension, stroke and epilepsy. Received 40 mg conivaptan for 6 days, followed by 80 mg for 107 days, for a total of 113 days of treatment. On Study Day 112, had sudden loss of

consciousness; computerized tomography (CT) revealed cerebral hemorrhage. Intubated, ventilated and transferred to tertiary care hospital. Died on Study Day 113.

Subject 031-0061407: 67 year old M with hyponatremia secondary to lung cancer. Received 40 mg oral conivaptan for 7 days, and 80 mg for 3 days. One day after his last dose of conivaptan, he died of "terminal lung cancer".

Subject 031-0061411: 94 year old man with hyponatremia secondary to malignancy. Received oral conivaptan 40 mg for 7 days. Discharged to nursing home and readmitted on Study Day 10 with pneumonia. Placed in hospice and died of pneumonia on Study Day 20.

Subject 031-0061414: 76 year old woman with hyponatremia and metastatic pancreatic cancer. Received 63 days of oral conivaptan 40 mg/day. On Day 63, conivaptan stopped due to decision to go into hospice. Died one day later of metastatic pancreatic cancer.

Subject 031-0062501: 80 year old woman with hyponatremia secondary to congestive heart failure. Hospitalized for CHF; conivaptan initiated while in hospital. Discharged on Study Day 14. Died at home on Study Day 16.

Subject 031-0062503: 63 yo M in extension study. NYHA FC IV CHF, pacemaker for history of asystole, aortic valve replacement (AoVR), pulmonary hypertension, chronic renal insufficiency. Received 40 mg/day conivaptan for 62 days total. Placed on Zaroxolyn in second month of conivaptan therapy. Potassium decreased to 2.9; Zaroxolyn held on day 52 of conivaptan treatment. Potassium increased over several days until 6.6 on day 62. Suffered cardiac arrest on day 62 and died; autopsy revealed extensive myocardial infarction.

Subject 031-0062505: 83 year old man with hyponatremia and CHF. Received 40 mg oral conivaptan for 151 days. On Study Day 82, admitted to hospital with worsening CHF and acute on chronic renal failure. Discharged on Study Day 88. Died at home on Study Day 152; cause of death cited as endstage CHF.

Subject 031-0071304: 79 year old woman with hyponatremia secondary to cirrhosis. Received 80 mg conivaptan/day for 75 days, then 40 mg/day for 14 days, then 80 mg/day for 213 days, for a total treatment duration of 302 days. In a longterm care facility for most of the study, but went home for terminal care. On Treatment Day 289, she developed decreased level of consciousness at home. Received supportive treatment only. Conivaptan discontinued on Study Day 302; patient died one day later due to endstage hepatic failure.

Subject 031-0071313: 92 year old man with hyponatremia secondary to SIADH. History of myocardial infarction and chronic renal failure. Received 40 mg conivaptan for 159 days. On Study Day 147, admitted with chest pain, bilateral pleural effusions and pulmonary interstitial infiltrate on CT. Thoracentesis done twice, on Study Days 147 and 156. On Study Day 159, had a respiratory arrest and was intubated. A few hours later had a cardiac arrest and died.

Subject 031-0075804: 59 year old woman with hyponatremia secondary to CHF. Received oral conivaptan 20 mg/day for 9 days. On Study Day 7, admitted with worsening CHF. Was in "Do Not Resuscitate" (DNR) status and died two days later of endstage CHF.

Subject 031-0075807: 78 year old woman with hyponatremia secondary to CHF. Received 40 mg conivaptan for 68 days. Did not take from Study Day 53-55. Seen on Study Day 54 for worsening CHF with increasing pleural effusions. Refused admission; one day later, checked into a "natural healing" center. Received "high dose" Vitamin C (1-10 gm IV) on Study Days 61-65. Developed wrist cellulitis, white blood cell count (wbc) 25,000/mm^3, and acute renal failure. Died on Study Day 71.

Subject 031-0076503: 79 yo man with hyponatremia secondary to metastatic lung cancer. Received 40 mg oral conivaptan for 230 days. On treatment day 230, admitted to hospice for increasing pain. Died 9 Days later; cause of death listed as metastatic lung cancer.

Subject 032-0010009: 54 yo M with history of CHF, CVA, aortofemoral bypass (AoFB), mitral insufficiency. Admitted for heart transplant evaluation. Received single dose of 40 mg IV conivaptan. Study Day 2 (1 day after conivaptan dose), developed chest pain, wide-complex bradycardia and then pulseless electrical activity. Resuscitation ineffective; pericardiocentesis performed without effect. Died early on Study Day 3.

Subject 032-0010011: 51 yo M with history of CHF, mitral and tricuspid regurgitation and MI. Received single IV dose of conivaptan 20 mg. 19 days later, cardiac arrest at home. Autopsy stated ischemic cardiomyopathy was cause of death.

Subject 032-0027002: 62 yo M with history of CHF, DM, supraventricular tachycardia (SVT), chronic renal insufficiency (CRI), coronary artery disease (CAD). Received single dose IV conivaptan 40 mg. One day after conivaptan dose, developed worsening CHF and became hypotensive. Study Day 22, developed V tach. Study Day 25 acute renal failure (ARF); placed on hemofiltration, developed heparin-induced thrombocytopenia. Made DNR and died on Study Day 34. Autopsy listed CHF as primary cause of death.

Subject 033-0013010: 68 yo M with idiopathic cardiomyopathy and congestive heart failure. Received 40 mg oral conivaptan/day for 175 days; hospitalized on day 175 with dyspnea, conivaptan discontinued. Treated with IV diuretics, recovered and was discharged on Study Day 185. Died on Study Day 200; family refused to release medical records, and cause of death unknown.

Subject 034-024005: 69 yo M with CHF. Received 80 mg oral conivaptan/day for 27 days. Presented with CVA on Study Day 26; conivaptan discontinued next day. Did not recover from stroke and died on Study Day 57, 30 days after discontinuation of conivaptan.

Subject 034-0032018: 74 yo M with history of ischemic cardiomyopathy, diabetes. Received 80 mg oral conivaptan/day for 60 days. Died at home on day 61; reported as cardiac arrest.

Subject 034-0043003: 52 yo M with CHF [ejection fraction (EF) 10% prior to study], history multiple myocardial infarctions (MIs). Received 80 mg conivaptan/day for 101 days. Thirty-two days after last dose conivaptan, found dead in bed at home. No autopsy.

Subject 034-0049020: 60 year old man with CHF. Received conivaptan 20 mg/day for 48 days. Sudden death at home on Study Day 48.

Subject 043-0230409: 78 yo F with history of heart failure, atrial fibrillation. Prior to hospitalization for study, had been hospitalized for three months with arrhythmia, cardiac decompensation and respiratory insufficiency. Two days after discharge, returned with pulmonary edema and congestive heart failure. Began study and received 4 days of conivaptan 20 mg po bid. Condition declined steadily from the time of admission, and she died 3 days after her last dose of study drug of "uncontrollable cardiovascular insufficiency".

Subject 043-0231339: 67 yo M with chronic heart failure and interstitial pulmonary fibrosis. Admitted for respiratory insufficiency, serum sodium 126 mEq/L. Received conivaptan 20 mg po bid; on second day of administration, serum sodium 134, weight down 1 kg, urine output increased from baseline of 1850 mL/day to 3550 mL/day, systolic BP fell to 90 mm Hg. Conivaptan dose halved, but progressively deteriorated with worsening hyponatremia and hypotension. Found dead that night. Cause of death reported as hypovolemic shock.

Subject 047-0230106: 58 yo M with right heart failure due to interauricular communication, mitral insufficiency, pulmonary hypertension, shunt inversion and history of supraventricular tachycardia (SVT). Received conivaptan 40 mg/day for 32 days. Seen on Study Day 29; Cr increased to 1.4 mg/dL from baseline 0.8; BUN 35; sodium 136 mEq/L; digoxin level 3.6 ng/mL (therapeutic range 1-2). Digoxin stopped; was to resume on Study Day 31. Found dead at home on Study Day 33.

Subject 047-0230113: 53 yo M undergoing chemotherapy for cancer, type unknown. History aortic stenosis (AoS) and atrial flutter. On 80 mg conivaptan/day. On day 174 of conivaptan, presented with atrial flutter and severe leg edema. Refused hospitalization; found dead in bed two days later.

Subject 047-231326: 65 yo M with ischemic cardiomyopathy, chronic renal insufficiency, COPD and history of SVT. Admitted on Study Day 12 (conivaptan 40 mg/day) with BP 70/50, decompensated CHF. Conivaptan stopped, but family member brought it in and patient received for two more days. Study Day 13, developed V tach which lasted 7 hrs. On Study Day 15, developed ventricular tachycardia and died.

Subject 047-0231334: 80 yo F with history of surgery and stent for esophageal perforation due to esophageal cancer. Received conivaptan 40 mg/day. On Study Day 17, developed another esophageal perforation. Study drug was stopped, and parenteral nutrition begun. Died from esophageal cancer; exact date of death unknown.

Subject 071-0017: 62 yo F with decompensated CHF, ischemic cardiomyopathy, mitral regurgitation (regurg), tricuspid regurgitation, automatic implantable cardiac defibrillator (AICD). She was in the 120 mg/day group, but received only 5.75 hrs of conivaptan infusion (approximately 29 mg). 5.5 hrs after infusion began, AICD fired for v tach, with conversion to normal sinus rhythm (NSR). Potassium (K), magnesium (Mg) normal (nl). Calcium (Ca) 8.3 mg/dL (no albumin value given). Coni discontinued. The next morning, she developed V fib; resuscitation attempts failed and she progressed to asystole and death.

Subject 071-0041: 47 yo M with decompensated CHF, AIDS. Received coni 120 mg/day IV x 2 days. 6 days after last dose of coni, admitted to hospital with increased dyspnea. He was initially treated with IV diuretics, but deteriorated rapidly with suspected sepsis. He developed respiratory failure due to *Pneumocystis carinii* infection. He did not respond to vasopressors and antibiotics. 16 days after last dose of coni, had cardiac arrest and died.

Subject 071-0043: 69 yo M with decompensated CHF, DM, ischemic cardiomyopathy, A fib. Received coni 40 mg/day IV x 2 days. On Day 2 of coni, ultrafiltration performed after study drug completed. Condition deteriorated, with A fib and increasing creatinine. 1 day after coni, renal failure continued to worsen, and family made pt DNR. Died 3 days after last dose of coni, due to "congestive heart failure secondary to dilated cardiomyopathy and secondary to coronary artery disease".

Subject 071-0063: 78 yo M with CHF, COPD, chronic renal failure (CRF), A fib, history of (hx) V tach, valvular disease, CAD. In study for decompensated CHF. Received coni 40 mg IV/day x 2 days. 6 days after last dose of coni, presented to ER with increasing dyspnea, high international normalized ratio (INR) on coumadin, digoxin toxicity, thrombocytopenia, generalized weakness, confusion, and worsening renal failure. Coumadin and digoxin withheld and pt treated with fluids. Hypernatremia noted. INR decreased and digoxin level declined. Hypernatremia resolved by 23 days after last dose of coni. However, his mental status declined, he refused nutrition, and family made the patient DNR. His thrombocytopenia and renal failure continued to worsen. 25 days after last dose of coni, patient expired; cause of death given as worsening of severe cardiomyopathy.

Subject 071-0088: 50 yo M with decompensated CHF, CAD. Received coni 120 mg/day IV x 2 days. 23 days after last dose of coni, was found unconscious and pulseless at home. Cardiopulmonary resuscitation (CPR) initiated and paramedics called. Patient was felt by paramedics to have pulseless electrical activity. Patient was intubated and received multiple doses of epinephrine and atropine and one dose of lidocaine, with treatment both en route and in the emergency room (ER), but did not respond and was pronounced dead in the ER.

Subject 071-0089: 25 yo F with decompensated CHF, postpartum cardiomyopathy; 4 months postpartum at time of study. Received 120 mg coni IV/day x 2 days. On the last day of coni administration, developed a fever and was found to have pneumonia. She was treated with antibiotics. 2 days after last dose of coni, found dead on the floor of her hospital room with pulseless electrical activity. Did not respond to advanced cardiac life support (ACLS). Autopsy revealed bicuspid aortic valve (AoV), anomalous angulated left coronary artery, 80% left

anterior descending coronary artery (LAD) stenosis, subaortic endocardial fibrosis, probable glomerulonephritis (immunoflourescence positive). Cause of death listed as sudden cardiac death from myocardial ischemia due to an anomalous left coronary artery with a bicuspid AoV.

Subject 080-10003: 42 yo F with hepatic cirrhosis, hypoadrenalism, hypothyroidism, hypogonadism. Received conivaptan 40 mg/day IV for 4 days. 10 days after last coni dose, developed cellulitis right (rt) leg. 15 days after last coni dose, developed sepsis, liver failure, renal failure, hemodynamic instability. Died 23 days after last dose of coni, of multiorgan failure.

Subject 080-10110: 80 yo F with metastatic gastric carcinoma with lung metastases (mets). Received conivaptan 20 mg/day IV for 4 days. 4 days after last dose of conivaptan, hospitalized with dyspnea related to lung mets. Died 17 days after last dose of coni with progressive dyspnea and gastric carcinoma.

Subject 080-10203: 76 yo M with CHF and hyponatremia (Na 115 mEq/L). Received conivaptan 20 mg/day IV for 2 days. Became confused and apathetic with deteriorating level of consciousness (LOC). Conivaptan discontinued on day 2 of administration due to hypotension. No focal neurologic signs. Two days after last dose of conivaptan, pt found deal in his hospital bed. Cause of death listed as CVA, but no autopsy done.

Subject 080-10307: 63 yo M with CHF, CRF, CAD, chronic A fib, hyponatremia. Admitted with symptomatic bradycardia and serum Na 123 mEq/L. Received coni 40 mg/day x 2 days; stopped because Na fell from 128 to 122 mEq/L. Three days later underwent pacemaker insertion and drainage of large pleural effusion. Developed *Morganella morganii* sepsis and worsening renal failure. Died of sepsis 16 days after last dose of coni.

Subject 080-10501: 76 yo M with CHF received coni 40 mg/day IV x 4 days. Four days after last dose of coni, developed severe abdominal pain and found to have intraabdominal air. Exploratory laparotomy (X-lap) revealed fecal peritonitis without evidence of perforation, and gangrenous colon due to mesenteric artery occlusion. Right hemicolectomy performed. Postoperatively developed sepsis with respiratory failure and multiorgan failure. Died of multiorgan failure 9 days after last dose of coni.

Subject 080-11238: 81 yo F with hyponatremia, hx A fib, hypokalemia, hypomagnesemia. Baseline Na 115 mEq/L. Received coni 40 mg/day x 14 hrs; temporarily stopped due to overly rapid correction to 122 mEq/L. Resumed 8 hrs later and continued at 40 mg/day IV x 3 more days. On last day of coni infusion, had MI with A fib. Treated with anticoagulation; hemoglobin (Hb) dropped to 5.6 mg/dL. One day after last coni dose, V fib and death.

Subject 080-11303: 85 yo M with non-Hodgkin's lymphoma, CRF, pacemaker. Received coni 40 mg/day x 4 days. 5 days after last coni dose, had serum sodium 153 mEq/L with persistent hypernatremia. 12 days after last dose of coni, became lethargic and renal function deteriorated further. Treated for dehydration with IV and oral fluids; urinary retention and postobstructive uropathy occurred. That day, one hour after a meal, severe dyspnea, cyanosis, decreased oxygen

saturation. Improved with oxygen, but then developed "unstable" blood pressure and "signs of severe respiratory failure" Intubated; deep suction of trachea and bronchial tree revealed food masses. Mechanically ventilated; next day, serum Na 137 mEq/L. Next day (14 days after last coni dose), aspirated again, was intubated again, but died 3 hours later.

Subject 080-20303: 67 yo F with CHF. Received coni 40 mg/day x 4 days. 4 days after last dose of coni, started digoxin. 17 days after last dose of coni, hospitalized with nausea and vomiting (N&V), dyspnea, bigeminy, elevated digoxin level of 5.1 ng/mL. 19 days after last dose of coni, found dead in hospital bed. Presumed arrhythmia due to digitalis toxicity.

Subject 080-20401: 67 yo F with hypertension (htn), hyperlipoproteinemia (HLP), hypothyroidism, asthma, COPD, chronic back pain. Received coni 40 mg/day IV for 4 days. 19 days after last dose of coni, presented to general practitioner (GP) with severe back pain; antiinflammatory med prescribed. 21 days after last dose of coni, pt died in her sleep. Death presumed to be due to stroke or overdose of benzodiazepine to antidepressant.

Subject 080-20402: 70 yo M with ischemic cardiomyopathy and CAD; hospitalized with pneumonia. Received coni 40 mg/day IV x 4 days. On last day of coni, creatinine and creatine phosphokinase (CPK) "elevated". Troponin not measured. Later on the last day of coni administration, patient found dead sitting in a chair. Presumed MI and sudden death.

Subject 080-20602: 27 yo F with hx small bowel resection for abdominal tuberculosis, with requirement for reintubation postoperatively (postop). 16 days postop, coni started; pt received 40 mg/day IV x 4 days. 8 days after last coni dose, developed jaundice, nausea and fever. Cholecystitis diagnosed; cholecystectomy (ccty) attempted, but unsuccessful because stone fused to duodenum; pencil drain placed. 11 days after last coni dose, diagnosed with *Pseudomonas aeruginosa* pneumonia. 16 days after last coni dose, pt intubated. Became hypotensive, developed metabolic acidosis, liver failure and multiorgan failure. Died due to multiorgan failure 18 days after last dose of coni.

Subject 080-20603: 76 yo F with chronic myelogenous leukemia (CML). Admitted with dyspnea and acute left thoracic chest pain; found to have bronchial carcinoma. Received coni 40 mg/day IV for 4 days. Received chemotherapy for lung carcinoma. 26 days after last dose of coni, died of bronchial carcinoma.

Subject 080-20616: 71 yo F with CAD, A fib, hx hepatitis. Hospitalized for pneumonia. Received coni 40 mg/day IV x 1 day: Na rose rapidly in one day from 117-134 mmol/L. Dose decreased to 20 mg/day x 3 more days. On 3rd day of coni infusion, decreased oxygen saturation and increased heart rate (HR); received positive pressure ventilation, and antibiotics changed. Discharged from hospital 10 days after last coni administration. 18 days after last coni admin, readmitted to hospital with N&V, diarrhea and hyponatremia. Dyspnea progressed. 20 days after last coni admin, pt became confused and aphasic. CT revealed CVA. Died in hospital 37 days after last dose of coni.

Subject 080-20703: 64 yo M with hx hepatitis B, hepatitis C. Hospitalized with pneumonia. HIV noted in hospital. Sputum + for *Mycobacterium tuberculosis* complex. Received coni 40 mg IV/day x 4 days. Discharged to home 8 days after last dose of coni. Died out of hospital 19 days after last dose of coni, reportedly due to tuberculous pneumonia.

Subject 080-20902: 64 yo F with ischemic heart disease, DM2, COPD, A fib, rt ventricular failure. Received coni 40 mg IV x 4 days. 1 day after last coni dose, developed sudden onset dyspnea. Treated with beta agonist inhaler, but had respiratory arrest. Died 2 days after last dose of coni.

Subject 080-21103: 40 yo M with pulmonary tuberculosis (TB). Received coni 40 mg IV x 2 days. Coni stopped due to positive sputum test for acid fast bacilli (AFB). Patient died 6 days after last dose of coni due to worsening pulmonary TB and pneumonia.

Subject 080-21104: 34 yo F with AIDS and "probable" TB. Received coni 40 mg IV for 4 days. 17 days after last dose of coni, presented with dehydration, confusion, neck stiffness, + Kernig's sign, thrombocytopenia, bilateral pulmonary reticulonodular infiltrate. Died 1 day later due to suspected meningitis.

Subject 080-21106: 25 yo F with AIDS, Kaposi sarcoma face and neck. Received coni 40 mg/day x 4 days. 12 days after last dose of coni, presented to hospital with cough, fever, back pain, night sweats, patchy infiltrates on CXR. Treated for presumed TB, but treatment (tx) discontinued after 7 days due to negative sputum for AFB. Discharged to home 19 days after last dose of coni. Found dead at home 22 days after last dose of coni. No autopsy. Presumed cause of death advanced AIDS.

7.1.1.3 Rates of Death in IV and Total Populations

The following table displays the rates of death in the IV and total study populations:

Table 7.1.1.3.1 Rates of Death in IV and Total Populations

Population	Coni # deaths/# pts in pop (%)	Pbo # deaths/# pts in pop (%)
"Full Dose" IV Studies Conducted in Patients[1]	28/292 (9.6%)	3/69 (4.3%)
Controlled "Full Dose" IV Patient Studies[2]	10/177 (5.6%)	3/69 (4.3%)
All "Full Dose" IV Studies (Patients and Healthy Volunteers)[3]	28/404 (6.9%)	3/109 (2.8%)
All "Full Dose" Controlled IV Studies (Patients and Healthy Volunteers)[4]	10/258 (3.9%)	3/109 (2.8%)
All Phase 2/3 Studies (oral and IV)[5]	64/1148 (5.6%)	12/372 (3.2%)
All Placebo-Controlled Phase 2/3 Studies (oral and IV)[6]	24/942 (2.5%)	12/372 (3.2%)
"Full Dose" IV hyponatremia studies[7]	22/170 (12.9%)	3/29 (10.3%)
"Full Dose" Controlled IV CHF study[8]	6/122 (4.9)	0
All IV[9]	36/445 (8.1)	7/132 (5.3)

1 Studies 027, 071, 080
2 Studies 027, 071
3 Studies 027, 071, 080 (patients); 079, 083, 074 (healthy volunteers)
4 Studies 027, 071 (pts); 079 (healthy vols)
5 Studies 016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 031, 032, 033, 034, 038, 043, 047, 071, 080
6 Studies 017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071
7 Studies 027, 080
8 Study 071
9 Studies 016, 017, 023, 025, 027, 032, 038, 044, 071, 080
The above table includes deaths that occurred during study drug administration or within 30 days of study drug administration. Deaths that occurred >30 days after study drug administration could be included if the event that led to death had its onset during or within 30 days of study drug administration

For most comparisons in the above table, the rate of death in the conivaptan group is higher than that in the placebo group. For controlled studies, the incidence of death was numerically greater for conivaptan-treated patients than for placebo-treated patients in the "full dose" IV controlled and "full dose" IV controlled CHF populations, but not in the overall controlled Phase 2/3 (IV + oral) population, which included oral conivaptan patients with lower exposure.

Several of the deaths in patients receiving intravenous conivaptan occurred in patients who were receiving doses higher than the proposed dose for labeling of 40 mg IV/day. Deaths occurring at doses higher than 40 mg/day IV may be less relevant, but cannot be entirely discounted. One reason that these deaths must also be considered is because conivaptan exhibits marked intersubject variability in pharmacokinetic parameters, and thus some patients receiving a dose of 40 mg IV/day may achieve serum concentrations much higher than the mean. Intersubject variability appears to be attributable to several factors, including volume status, underlying disease state, nonlinear kinetics due to saturation of clearance mechanisms, age, et al. Congestive heart failure patients exhibited an 8-fold higher conivaptan exposure than did healthy volunteers, probably due to a smaller central compartment in CHF. Additionally, if one excludes consideration of safety information from patients treated with higher doses, one again encounters the problem that led to inability to approve conivaptan in the first cycle, i.e. an inadequately small safety population at the relevant IV dose. Exclusion of subjects receiving doses of >40 mg/day IV decreases the "full-dose" IV safety population from 404 subjects to 256 subjects. Of these 256 subjects who received IV conivaptan 40 mg/day, 72 were healthy volunteers, and thus probably at less risk for adverse events. Of the remaining 184 patients, only 144 were in hyponatremia studies, and only 29 were in a controlled hyponatremia study. The applicant chose to augment their safety information to adequate levels by including these subjects who were

treated with doses higher than 40 mg/day IV; inclusion of these patients brought the "full-dose" intravenous conivaptan safety database up to a minimally acceptable number. One cannot then discount events in these higher-dose subjects without bringing the safety population under consideration down to an inadequately small number for the detection of serious events.

The following table examines the incidence of death in relation to dose. "IV-equivalent" doses are included for oral dose groups, because oral conivaptan results in approximately 1/3 the exposure observed with IV conivaptan.

Table 7.1.1.3.2 Incidence of Death by Conivaptan Dose[2] (mg/day IV dose equivalent), Overall Phase 2/3 Population

Dose Group	Appr IV Equivalent[1]	Total N	# Deaths	% Deaths
10 mg/day oral	**3 mg/day**	82	1	**1.2**
20 mg/day oral	**7 mg/day**	213	3	**1.4**
40 mg/day oral	**13 mg/day**	274	19	**6.9**
20 mg/day IV	**20 mg/day**	35	2	**5.7**
80 mg/day oral	**27 mg/day**	167	6	**3.6**
40 mg/day IV	**40 mg/day**	241	23	**9.5**
80 mg/day IV	**80 mg/day**	86	5	**6.3**
120 mg/day IV	**120 mg/day**	43	4	**9.3**

1 Oral conivaptan results in appr 1/3 the exposure of IV conivaptan
2 Dose at time of death (may not be the same as original treatment assignment)
Source of exposure data: Email from D. Raineri, Astellas Reg Affairs, 26 Oct 05

From this table, there appears to be a relationship between the IV equivalent dose of conivaptan and the incidence of death. In a statistical analysis by Dr. Choudhury, a correlation was noted, with a p value of 0.0566 for the significance of the correlation.

On 27 Oct 05, the applicant was asked to perform analyses using IV equivalent dose to look for a correlation between dose and incidence of death by baseline CHF status. The applicant was also asked to examine the relationship between pharmacodynamic response and incidence of death. On 14 Nov 05, the applicant submitted some analyses of the relationship between dose and death. Important considerations regarding these analyses include:

- Presence or absence at baseline of hyponatremia and/or CHF was considered, including the group of patients who had hyponatremia without CHF (euvolemic hyponatremic patients), the group of patients who had CHF without hyponatremia (CHF only patients), the group of patients who had CHF + hyponatremia (representative of the hypervolemia hyponatremic population), and the group of all patients
- In addition to the deaths reported in Tables 7.1.1.1.1-7.1.1.1.4 above, the applicant included patients who died more than 30 days after discontinuation of study drug, and who did not die of an event that had its onset during study drug administration or during the 30 day period after study drug administration. These deaths are less likely to be related to study medication, and more likely to be related to the natural history of the underlying condition.
- The applicant used the dose at treatment assignment, while the clinical reviewer's table 7.1.1.3.2 used the dose at time of death. Some patients had a reduction in dose prior to death.

The following Cox regression analysis on the time from first dose to death for the overall Phase 2/3 study population is from the applicant's "Model 1", which took into consideration daily dose (continuous), route (oral or IV), daily dose by route interaction, and baseline presence of CHF and/or hyponatremia (called "Indication" in the applicant's table below). It does not take into account the fact that exposure was lower for oral than for IV; patients who took 40 mg IV were considered to have the same dose as patients who took 40 mg oral, even though the exposure for oral conivaptan was approximately 1/3 that of IV.

Table 7.1.1.3.3 Cox Regression Analysis of Time from First Dose to Death, Overall Phase 2/3 Population (Without Exposure Conversion for Oral Conivaptan; Includes Late Deaths)

Variable	Hazard ratio (95% C.I.)	P value
Dose	1.01 (0.99-1.02)	0.332
Route		
Oral		
IV	4.04 (1.79-9.13)	0.001
Dose by Route interaction		
Oral		
IV	1.00 (0.98-1.01)	0.688
Indication		
CHF		
Hyponatremia	6.34 (3.91-10.29)	<0.0001
CHF+Hyponatremia	5.37 (2.45-11.76)	<0.0001

Model 1: daily dose (continuous), route (Oral/IV), daily dose by route interaction, indication (CHF/Hyponatremia/CHF+Hyponatremia)

Source: Applicant's Text Table 3.1, email from Dr. Donald Raineri, 14 Nov 05

In this model, no relationship was noted between death and dose. The IV route of administration was associated with greater mortality risk than oral dosing, and hyponatremia without CHF was associated with greater mortality risk than hyponatremia with CHF, or CHF alone. The difference in mortality risk for these populations by this analysis compared to the apparent rates of death in Table 7.1.1.3.1 above may be due to the fact that the applicant included deaths in CHF placebo patients that occurred more than 30 days after study drug discontinuation. This increased the percentage of placebo deaths among total and CHF populations, and actually increased the IV placebo rate of death above the IV conivaptan rate of death; the converse is true when deaths beyond 30 days are not included.

The following Cox regression analysis on the time from first dose to death for the overall Phase 2/3 study population is from the applicant's "Model 2", which took into consideration "converted dose", and baseline presence of CHF and/or hyponatremia (called "Indication" in the applicant's table below). The applicant multiplied oral doses by 1/3; e.g. a patient taking 40 mg/day orally would have a converted dose of 13 mg/day, while a patient taking 40 mg/day IV would not have a dose conversion, and would be counted as a 40 mg/day patient.

Table 7.1.1.3.4 Cox Regression Analysis of Time from First Dose to Death, Overall Phase 2/3 Population (Includes Exposure Conversion for Oral Conivaptan; Includes Late Deaths)

Variable	Hazard ratio (95% C.I.)	P value
Converted Dose	1.02 (1.01-1.02)	<0.0001
Indication		
CHF		
Hyponatremia	7.42 (4.65-11.84)	<0.0001
CHF+Hyponatremia	7.53 (3.49-16.25)	<0.0001

Model 2: "converted" daily dose (continuous: oral doses were multiplied by 1/3), indication

Source: Applicant's Text Table 3.2, email from Dr. Donald Raineri, Astellas Regulatory Affairs, 14 Nov 05

In this model, a very strong dose-response relationship was detected. The difference between groups by baseline presence or absence of CHF and/or hyponatremia was the same as that noted for "Model 1" above, with the same limitations due to inclusion of late deaths.

The following Cox regression analysis on the time from first dose to death for the overall Phase 2/3 population is from the applicant's "Model 3", which took into consideration daily dose (categorical, with separation of IV and oral); and presence of baseline hyponatremia, CHF or both. Hazard ratios were calculated by comparing rates of death in all conivaptan groups to the applicant's IV placebo group, which was enriched with late deaths.

Table 7.1.1.3.5 Cox Regression Analysis of Time from First Dose to Death, Overall Phase 2/3 Population, with Hazard Ratios Using only IV Placebo (Includes Late Deaths)

Variable	Hazard ratio (95% C.I.)	P value
Dose		
IV Placebo		
IV 20mg	0.56 (0.07-4.33)	0.578
IV 40mg	0.42 (0.21-0.87)	0.019
IV 80mg	0.68 (0.27-1.71)	0.408
IV >80mg	1.59 (0.62-4.12)	0.338
Oral Placebo	0.17 (0.06-0.48)	0.001
Oral 10mg	0.09 (0.01-0.69)	0.021
Oral 20mg	0.07 (0.02-0.22)	<.0001
Oral 40mg	0.29 (0.14-0.61)	0.001
Oral 80mg	0.15 (0.06-0.41)	0.0002
Indication		
CHF		
Hyponatremia	8.27 (4.81-14.22)	<0.0001
CHF+Hyponatremia	6.88 (3.06-15.46)	<0.0001

Model 3: daily dose (categorical: oral and IV are separated), indication

Source: Applicant's Text Table 3.3, email from Dr. Donald Raineri, Astellas Regulatory Affairs, 14 Nov 05

In this model, the applicant asserts that the hazard ratio for risk of death for all conivaptan dose groups (except for the >80 mg/day IV group) was <1 compared to the risk of death for the IV pbo group. As mentioned earlier, the applicant's IV pbo group used for these analyses is enriched with late deaths. For comparison, the clinical reviewer has calculated hazard ratios using all deaths that occurred during treatment, within 30 days following treatment, or later but due to an adverse event that had its onset during treatment or within 30 days following treatment. IV and oral groups were considered separately, and combined oral + IV placebo is used for hazard ratios (HRs) for the "converted" dose group. As mentioned earlier, the applicant's analyses used the dose at the time of treatment assignment, and the clinical reviewer used the dose at time of death.

Table 7.1.1.3.6 Hazard Ratios for Death for Separate Dose Groups Compared to Placebo (Excludes Late Deaths), Phase 2/3 Population

Dose Group	Death Rate in Dose Group n/N (%)	"IV Equivalent"[1]	HR vs IV Pbo Death Rate (7/132, 5.3%)	HR vs Oral Pbo Death Rate (5/240, 2.1%)	HR vs all Pbo Death Rate (12/372, 3.2%)
10 mg/day oral	1/82 (1.2%)	3 mg/day	n/a	0.57	0.38
20 mg/day oral	3/213 (1.4%)	7 mg/day	n/a	0.67	0.44
40 mg/day oral	19/274 (6.9%)	13 mg/day	n/a	3.29	2.16
20 mg/day IV	2/35 (5.7%)	20 mg/day	1.08	n/a	1.78
80 mg/day oral	6/167 (3.6%)	27 mg/day	n/a	1.71	1.13
40 mg/day IV	23/241 (9.5%)	40 mg/day	1.79	n/a	2.97
80 mg/day IV	5/86 (5.8%)	80 mg/day	1.09	n/a	1.81
120 mg/day IV	4/43 (9.3%)	120 mg/day	1.75	n/a	2.91

1 Oral conivaptan exposure is about 1/3 that of IV conivaptan, therefore oral doses were divided by 3
Includes all deaths that occurred during treatment, within 30 days following treatment, or later but due to an adverse event that had its onset during treatment or within 30 days following treatment.
Doses used are dose at time of death; applicant's analyses used dose at time of treatment assignment
Source of Exposure Data: Email from D Raineri, Astellas Reg Affairs, 26 Oct 05

When potentially confounding late deaths are not included, hazard ratios for 6/8 (all but the lowest two) conivaptan dose groups exceed 1 for comparisons of rates of death to relevant placebo groups.

Because the inclusion of late deaths clouded the issue of the relationship between conivaptan and risk of death, and the possibility of a dose-related increase in risk of death, the applicant was asked on 16 Nov 05 to provide further analyses excluding deaths occurring more than 30 days after discontinuation of study drug. On 22 Nov 05, the applicant provided several new analyses which excluded these late deaths. The following figures and tables are from those analyses by the applicant. Please note that the numbers of deaths in each dose group may differ from those in the clinical reviewer's tables above, because the clinical reviewer's tables used the dose at the

time of death (some patients had dose reductions prior to death), and the applicant's tables used the dose at the time of treatment assignment.

The following table depicts mortality by dose group (crude mortality and mortality by patient-time) for all Phase 2/3 Studies:

Table 7.1.1.3.7 Mortality by Dose Group, All Phase 2/3 Studies, Excludes Deaths Beyond 30 Days After Treatment Cessation

(016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 031, 032, 033, 034, 038, 043, 044, 047, 071, 080)

TREATMENT GROUP (1)	TOTAL NUMBER OF SUBJECTS	TOTAL NUMBER OF DEATHS	CRUDE MORTALITY (2)	PATIENT-MONTHS (PM)	MORTALITY PER 100 PM (3)
ORAL PLACEBO	240	5	2.1%	590.6	0.9
IV PLACEBO	132	7	5.3%	118.7	5.9
ORAL 10MG	82	1	1.2%	235.1	0.4
ORAL 20MG	213	4	1.9%	700.6	0.6
ORAL 40MG	274	16	5.8%	737.5	2.2
IV 20MG	35	1	2.9%	33.4	3.0
ORAL 80MG	167	5	3.0%	409.7	1.2
IV 40MG	241	18	7.5%	228.1	7.9
IV 80MG	86	3	3.5%	71.4	4.2
IV >80MG	43	4	9.3%	42.3	9.5
ORAL TOTAL	976	31	3.2%	2663.5	1.2
IV TOTAL	537	33	6.1%	493.9	6.7
TOTAL	1513	64	4.2%	3157.3	2.0

Source: Applicant's Table 1.1, email from Dr. Donald Raineri, Astellas Reg Affairs, 22 Nov 05
Dose = dose at treatment assignment, not dose at time of death

In this table, the applicant divided placebo patients into IV and oral placebo; the overall rate for placebo deaths was 12 deaths/372 placebo patients (3.2%) for crude mortality, and 1.7 deaths/100 placebo patient-months. In this table, the percentage of deaths in the IV conivaptan 40 mg/day group slightly numerically exceeded that in the IV placebo group (7.5% vs 5.3%), and deaths in the >80 mg/day IV group (all but one patient received 120 mg/day) numerically exceeded deaths in the IV placebo group (9.3% vs 5.3%).

The following table depicts mortality by dose group when considering only placebo-controlled Phase 2/3 studies.

Table 7.1.1.3.8 Mortality by Dose Group, Placebo-controlled Phase 2/3 Studies, Excludes Deaths Beyond 30 Days After Treatment Cessation

(017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071)

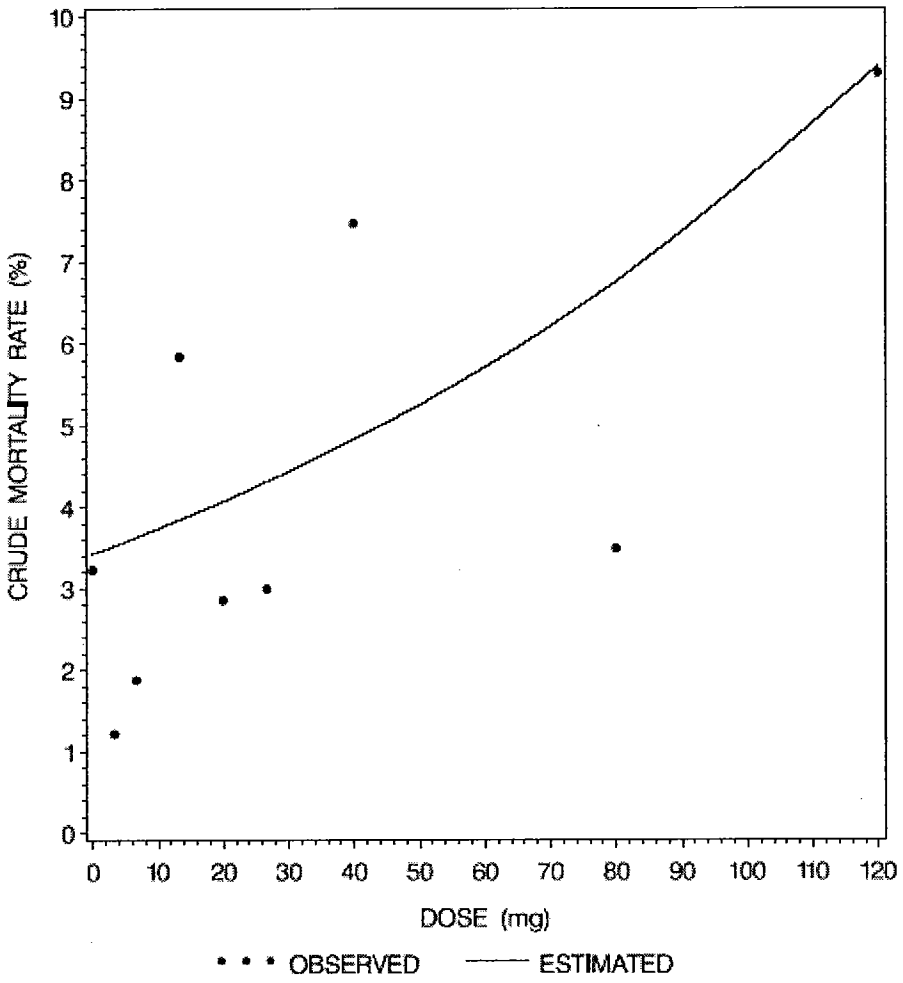
TREATMENT GROUP(1)	TOTAL NUMBER OF SUBJECTS	TOTAL NUMBER OF DEATHS	CRUDE MORTALITY (2)	PATIENT-MONTHS (PM)	MORTALITY PER 100 PM (3)
ORAL PLACEBO	240	5	2.1%	580.6	0.9
IV PLACEBO	132	7	5.3%	118.7	5.9
ORAL 10MG	76	1	1.3%	227.1	0.4
ORAL 20MG	171	1	0.6%	539.9	0.2
ORAL 40MG	223	6	2.7%	569.0	1.1
IV 20MG	32	1	3.1%	31.6	3.2
ORAL 80MG	147	2	1.4%	328.7	0.6
IV 40MG	118	4	3.4%	102.1	3.9
IV 80MG	79	2	2.5%	68.7	2.9
IV >80MG	42	4	9.5%	41.8	9.6
ORAL TOTAL	857	15	1.8%	2245.3	0.7
IV TOTAL	403	18	4.5%	362.9	5.0
TOTAL	1260	33	2.6%	2608.2	1.3

Source: Applicant's Table 2.1, email from Dr. Donald Raineri, Astellas Reg Affairs, 22 Nov 05
Dose = dose at treatment assignment, not at time of death

When considering only placebo-controlled Phase 2/3 Studies, the rate of death in the 40 mg/day IV group (3.4%) does not exceed that seen in the IV placebo group (5.3%), and does not numerically exceed that seen in the overall placebo group (3.2%).

The following figure presents a logistic regression of crude mortality by dose for the full Phase 2/3 population.

Figure 7.1.1.3.1 Logistic Regression Analysis on Crude Mortality Rate by Dose, All Phase 2/3 Studies, Excludes Deaths Beyond 30 Days after Cessation of Treatment



Source: Applicant's Figure 2.1, email from Dr. Donald Raineri, Astellas Reg Affairs, 22 Nov 05
Dose = dose at time of treatment assignment, not dose at time of death; oral doses were multiplied by 1/3 to account for lower exposure

This logistic regression analysis detected a small positive trend in the dose-death relationship, with odds ratios vs placebo for the 20, 40 and 80 mg IV conivaptan groups of 1.20, 1.43 and 2.04 respectively. The applicant notes that this relationship was mostly driven by studies conducted for the congestive heart failure indication, with a greater contribution from doses >80 mg/day in the CHF population. The applicant provides the following breakdown of the logistic regression analysis by presence or absence of CHF and hyponatremia.

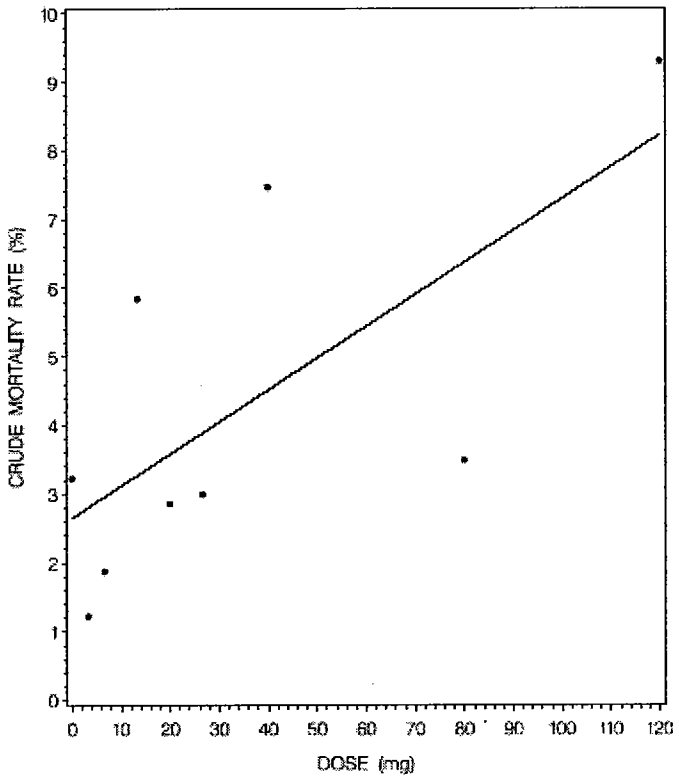
Table 7.1.1.3.9 Estimated Odds Ratios by Population (CHF vs Hyponatremia) for Death Using Converted Dose[1] by Logistic Regression Analysis, All Phase 2/3 Studies, Excludes Deaths Beyond 30 Days after Last Treatment Dose

Populations	Odds Ratio (95% C.I.)	P value
All patients	1.01 (1.00-1.02)	0.024
CHF population	1.02 (1.01-1.03)	0.005
Hyponatremia without CHF population	0.99 (0.97-1.01)	0.158
Hyponatremia with CHF population	1.02 (0.99-1.05)	0.159

Source: Applicant's Text Table 3, email from Dr. Donald Raineri, Astellas Reg Affairs, 22 Nov 05
1 Oral doses were multiplied by 1/3 to account for lower exposure

The following figure presents a linear regression analysis on crude mortality by dose.

Figure 7.1.1.3.2 Linear Regression Analysis on Crude Mortality by Dose, All Phase 2/3 Studies, Excludes Deaths Beyond 30 Days after Last Treatment Dose



This analysis again detects a positive trend in the dose-death relationship. The relative contribution of the CHF population remains somewhat greater in this analysis, also, as depicted in the following table:

Table 7.1.1.3.10 Estimated Odds Ratios by Population (CHF vs Hyponatremia) for Death Using Converted Dose[1] by Linear Regression Analysis, All Phase 2/3 Studies, Deaths up to 30 Days after Last Treatment Dose

Populations	Slope (95% C.I.)	P value	Adjusted R-square
All patients	0.05 (0.00-0.09)	0.038	0.41
CHF population	0.05 (0.00-0.09)	0.038	0.41
Hyponatremia without CHF population	-0.07 (-0.20-0.06)	0.267	0.05
Hyponatremia with CHF population	0.24 (-0.17-0.64)	0.164	0.37

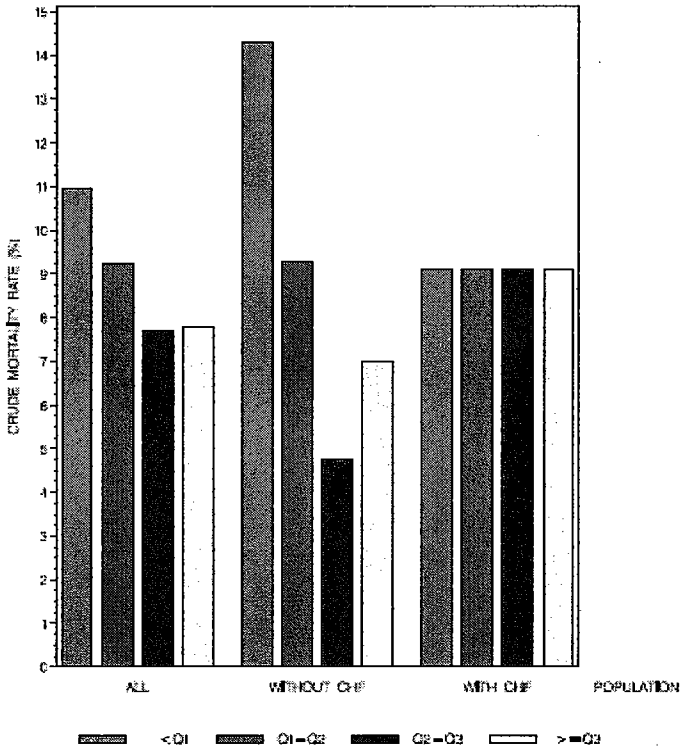
Source: Applicant's Text Table 4, email from Dr. Donald Raineri, Astellas Reg Affairs, 22 Nov 05
1 Oral doses were multiplied by 1/3 to account for lower exposure

In this analysis, there again appears to be a greater contribution from the CHF population to the dose-death relationship than from the hyponatremia population.

In addition to the request for examination of the relationship between dose and death, the Division requested that the applicant examine the relationship between sodium efficacy outcomes and rates of death. The Division wished to know whether death was more likely among those patients who had the most robust pharmacodynamic response to conivaptan.

For the hyponatremia studies (026, 027, 043, and 080), the applicant provided summaries of mortality by change from baseline in serum sodium AUC, which was the primary endpoint for these studies. Serum sodium AUC was not an endpoint in CHF studies, and therefore these studies are not included. The following figure depicts crude mortality by AUC quartile in populations, separated out by presence or absence of CHF among these patients (all had hyponatremia). The applicant used AUC quartiles to allow the number of patients in each AUC response group to be approximately the same. The applicant also included the placebo patients in the lowest quartile, which may make the rate in this quartile more difficult to interpret. This figure was provided by the applicant in color, but without differing patterns for quartiles; for each patient group, the quartiles are presented left to right in ascending order of AUC response.

Figure 7.1.1.3.3 Crude Mortality Rate by Serum Sodium AUC Response Quartile in Hyponatremia Studies, with Rates in Hyponatremia Populations with and without CHF



Source: Applicant's Figure 4.7, email from Dr. Donald Raineri, Astellas Reg Affairs, 22 Nov 05
Excludes patients with deaths beyond 30 days after treatment cessation

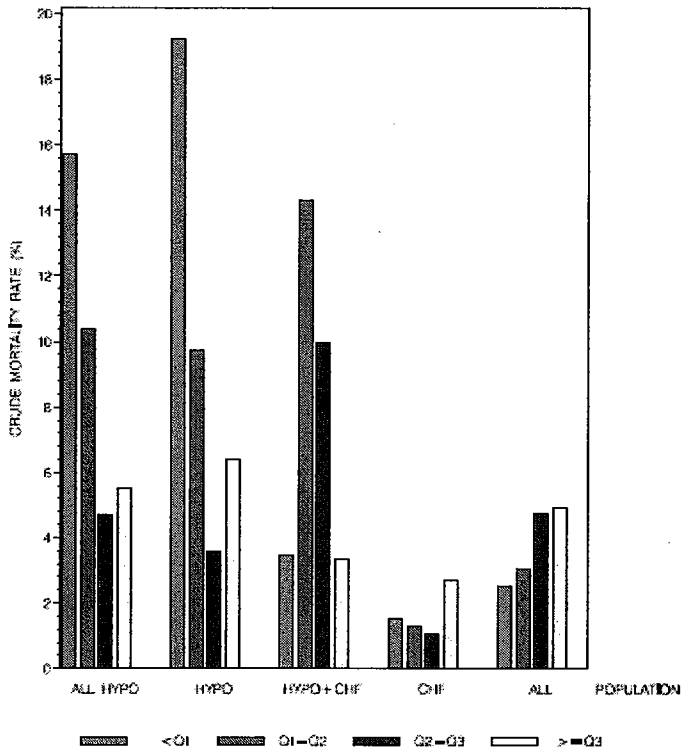
Although the inclusion of placebo patients in the lowest serum sodium response quartile makes interpretation of this quartile somewhat difficult, there is no evidence of a relationship between change from baseline in serum sodium AUC and rate of death for the other quartiles.

In order to examine the relationship between pharmacodynamic response and rate of death for the entire Phase 2/3 population, the applicant provided an analysis of the relationship between change from baseline in absolute serum sodium and rate of death. The following figure depicts rates of death by serum sodium response quartile. Five different populations were considered, including:

- all patients with hyponatremia, regardless of CHF status
- all patients with hyponatremia but without a baseline diagnosis of CHF
- all patients with both hyponatremia and CHF at baseline
- all patients with CHF, but without hyponatremia at baseline
- all Phase 2/3 patients, regardless of hyponatremia or CHF status

The applicant again included placebo patients in the lowest response quartile, making this quartile somewhat difficult to interpret.

Figure 7.1.1.3.4 Crude Mortality Rate by Change from Baseline in Serum Sodium (by Quartile), All Phase 2/3 Studies, With Consideration of Presence or Absence of CHF and/or Hyponatremia



Source: Applicant's Figure 5.1, email from Dr. Donald Raineri, Astellas Reg Affairs, 22 Nov 05

For the overall Phase 2/3 population, there appears to be a relationship between serum sodium response and rate of death. However, for each of the subpopulations considered, there is not a clear response relationship. This may be related in part to the fact that patients who are not hyponatremic at baseline have less of a response in serum sodium with conivaptan than do patients who are hyponatremic at baseline, and the "CHF only" population (4th set of bars in Figure 7.1.1.3.4) had little change in serum sodium in its lower quartiles. This population was the largest population of patients, and results for the "All Phase 2/3" population are heavily weighted by the "CHF only" population. The following table details the serum sodium changes seen in each quartile for the populations in Figure 7.1.1.3.4.

Table 7.1.1.3.11 Summary of Quartiles of Change from Baseline in Serum Sodium (mEq/L), All Phase 2/3 Studies, With Consideration of Presence or Absence of CHF and/or Hyponatremia

(016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 031, 032, 033, 034, 038, 043, 044, 047, 071, 080)

		POPULATION				
PARAMETER	CLASS	ALL HYPONATREMIA	HYPONATREMIA WITHOUT CHF	HYPONATREMIA WITH CHF	CHF POPULATION	ALL PATIENTS
CHANGE FROM BASELINE	N	429	312	117	1028	1457
	MEAN	6.313	6.390	6.107	0.008	1.865
	MIN	-12.00	-12.00	-8.00	-22.00	-22.00
	Q1	2.475	2.671	2.000	-2.000	-1.000
	Q2	6.25	6.00	6.25	0.00	1.00
	Q3	9.833	10.208	9.333	1.850	4.000
	MAX	24.67	24.67	18.20	14.00	24.67

Source: Applicant's Table 4.2, email from Dr. Donald Raineri, Astellas Reg Affairs, 22 Nov 05
Lowest quartile includes placebo patients

In the "CHF only" population, the median value for the second quartile was zero, while in the hyponatremia populations (with or without CHF), the median values for the second quartiles ranged from 6.00-6.25 mEq/L. When examining the hyponatremia subpopulations, with or without CHF, there is no clear relationship between change from baseline in serum sodium (by quartile) and rate of death. When examining the overall Phase 2/3 population, 70% of whom had CHF without hyponatremia, there does appear to be a relationship between change from baseline in serum sodium and incidence of death.

Overall, there does not appear to be a relationship between pharmacodynamic response and incidence of death when one considers only hyponatremia patients. However, when one adds patients from the congestive heart failure studies to the analyses of serum sodium response, there does appear to be a trend of an increased incidence of death by serum sodium response quartile.

7.1.1.4 Mortality among Patients with an Initial Diagnosis of Congestive Heart Failure

Congestive heart failure patients are of special interest, because the medical literature indicates great interest in the use of conivaptan for treatment of CHF per se (with or without hyponatremia), and potential exists for widespread off-label use. Therefore, mortality among all patients with an initial diagnosis of CHF was examined.

Table 7.1.1.4.1 Mortality by Treatment Group for Patients with an Initial Diagnosis of CHF, Full-Dose IV Studies Conducted in Patients (Studies 027, 071, 080)

Treatment Group	Total Number of Subjects	Total Number of Deaths	Crude Mortality [1]	Patient-Months (PM)	Mortality per 100 PM [2]
Placebo	45	2	4.4%	48.6	4.1
YM087 40 mg/day	81	5	6.2%	72.3	6.9
YM087 80 mg/day	48	3	6.3%	46.6	6.4
YM087 Other Dose	42	7	16.7%	44.8	15.6
YM087 Any Dose	171	15	8.8%	163.7	9.2

Source: Applicant's Table 2.7.4-12.6B, Summary of IV Safety, pg 277

Among CHF patients, there was an apparent dose-related trend in crude mortality, and in mortality by patient-time. In the above table, YM087 "Other Dose" refers to 120 mg IV/day. YM087 was the developmental name for conivaptan. This dose-related trend was not evident when considering all patients in these IV studies, and when considering IV euvolemic hyponatremia patients alone. The following table illustrates mortality among patients in these full dose IV studies in patients, considering only non-CHF patients, which represents the euvolemic hyponatremia population.

Table 7.1.1.4.2 Mortality by Treatment Group for Patients Who did Not Have an Initial Diagnosis of CHF, Full-Dose IV Studies Conducted in Patients (Studies 027, 071, 080)

Treatment Group	Total Number of Patients	Total Number of Deaths	Crude Mortality	Patient-Months (PM)	Mortality per 100 PM
Placebo	20	2	10.0%	10.0	20.0
Conivaptan 40 mg/day IV	103	12	11.7%)	87.6	13.7
Conivaptan 80 mg/day IV	18	0	0 (none detected)	10.0	0 (none detected)
Conivaptan 120 mg/day IV	0	0	n/a	n/a	n/a
Conivaptan any dose	121	12	9.9%	97.6	12.3

Source: Applicant's Tables 2.7.4-11.6B and 2.7.4-12.6B, Summary of IV Safety, pgs 271 and 277

Thus, in full-dose IV studies, patients who did not have an initial diagnosis of congestive heart failure did not exhibit the apparent dose-related trend in mortality that was seen in patients with an initial diagnosis of CHF. Because the vast majority of hypervolemic hyponatremia patients in these studies had CHF, the data summarized in Table 7.1.1.4.2 represent the euvolemic hyponatremia patient population.

7.1.1.5 Deaths in Tuberculosis Patients

Of the 18 deaths reported for Study 080, 5 occurred in patients with tuberculosis or suspected tuberculosis (Pt IDs 80-20602, 80-21104, 80-21103, 80-21106, 80-20703). Three of these patients were at Study Center 211, [redacted] one at Study Center 206 [redacted], and one at Study Center 207, [redacted]. Three of the five patients who died with TB or suspected TB also had reported HIV disease. One other conivaptan patient who died also had HIV disease (Pt ID 071-040041). No placebo patients who died were reported

to have either TB or HIV disease. Study 080 had no placebo group; if there had been placebo patients from South Africa, it is very likely that some of them would have had TB and/or HIV, as both of these infections are highly prevalent in South Africa. There does not appear to be a signal for increased risk of death from TB or HIV with conivaptan.

7.1.1.6 Conclusions Regarding Mortality

The incidence of death appears to be numerically higher among conivaptan-treated patients for the "full dose" controlled IV population, "full-dose" controlled IV CHF population, overall safety population, "full dose" IV (patients) population, "full dose" IV "patients plus healthy volunteers" population, and "full dose" IV hyponatremia population. The incidence of death did not appear higher for conivaptan patients than for placebo patients in the overall controlled Phase 2/3 population, which included oral patients with lower exposure. There appears to be a correlation between IV-equivalent dose of conivaptan and incidence of death for the overall safety population, both in analyses by the Agency and in repeat analyses by the applicant. When examining hyponatremia and CHF populations separately, the death-dose relationship was strongest for CHF patients, and was not significant when considering only hyponatremia patients. Among all full-dose IV conivaptan patients with a diagnosis of congestive heart failure at study entry, there appeared to be a dose-related increase in the rates of crude mortality and mortality per unit of patient-time. When examining the relationship between pharmacodynamic response and incidence of death for the overall Phase 2/3 population, there appeared to be an increase in incidence of death by increasing quartile of change from baseline in serum sodium. However, when one examined only patients in hyponatremia studies, there was no apparent relationship between incidence of death and pharmacodynamic response quartile for either the primary endpoint of these studies (change from baseline in serum sodium AUC), or change from baseline in absolute serum sodium. With the addition of patients from CHF studies to the patients from hyponatremia studies, to make up the entire Phase 2/3 population, the aforementioned apparent relationship between serum sodium response and incidence of death emerged.

In the clinical reviewer's opinion, there does not appear to be an increased risk of death for conivaptan used in the treatment of hyponatremia in the absence of congestive heart failure. However, there appears to be a signal for a dose-related increase in risk of death among patients with underlying congestive heart failure. While the clinical reviewer cannot definitively conclude that conivaptan increases the risk of death for congestive heart failure patients, this signal is such that the clinical reviewer recommends that congestive heart failure patients not receive conivaptan outside the clinical trial setting at this time.

7.1.2 Other Serious Adverse Events

A series of tables follows, which lists all serious treatment-emergent adverse events for the overall safety population (broken down into IV, oral, and IV + oral), the overall controlled Phase 2/3 population (IV + oral), and the population of "full dose" IV studies in patients.

Table 7.1.2.1: Serious Treatment-emergent Adverse Events, Overall Safety Population[1], Number and Percentage of Subjects with each Type of Event

		All IV		Oral		IV + Oral	
		Pbo n (%) n = 132	Coni n (%) n = 445	Pbo n (%) n = 240	Coni n (%) n = 715	Pbo n (%) n = 372	Coni n (%) n = 1160
System	**Event**						
Cardiac		13 (9.8)	37 (8.3)	8 (3.3)	48 (6.7)	21 (5.6)	85 (7.3)
	Acute Coronary Syndrome			1 (0.4)		1 (0.3)	
	Acute MI			1 (0.4)		1 (0.3)	
	MI	1 (0.8)	1 (0.2)	1 (0.4)	1 (0.1)	2 (0.5)	2 (0.2)
	Angina pectoris			1 (0.4)	4 (0.6)	1 (0.3)	4 (0.3)
	Angina unstable	2 (1.5)			3 (0.4)	2 (0.5)	3 (0.3)
	Arrhythmia NOS				2 (0.3)		2 (0.2)
	A fib		1 (0.2)				1 (0.1)
	Atrial flutter (A flutter)		2 (0.4)				2 (0.2)
	Atrioventricular (AV) block not otherwise specified (NOS)		1 (0.2)				1 (0.1)
	AV block complete		1 (0.2)		1 (0.1)		2 (0.2)
	Bradyarrhythmia		1 (0.2)				1 (0.1)
	Bradycardia NOS	1 (0.8)		1 (0.4)	1 (0.1)	2 (0.5)	1 (0.1)
	Cardiac arrest		3 (0.7)		4 (0.6)		7 (0.6)
	Cardiac failure NOS	1 (0.8)	2 (0.4)	2 (0.8)	8 (1.1)	3 (0.8)	10 (1.2)
	Cardiac failure acute		1 (0.2)				1 (0.1)
	Cardiac failure chronic	1 (0.8)	1 (0.2)		1 (0.1)	1 (0.3)	2 (0.2)
	Cardiac failure congestive		2 (0.4)		2 (0.3)		4 (0.3)
	Cardiomyopathy NOS		3 (0.7)				3 (0.3)
	Cardiopulmonary failure	1 (0.8)			1 (0.1)	1 (0.3)	1 (0.1)
	Congestive cardiac failure aggravated	1 (0.8)	6 (1.3)	2 (0.8)	17 (2.4)	3 (0.8)	23 (2.0)
	Congestive cardiomyopathy		1 (0.2)				1 (0.1)
	Ischaemic cardiomyopathy		2 (0.4)				2 (0.2)
	Cardiorespiratory arrest	1 (0.8)	1 (0.2)		1 (0.1)	1 (0.3)	2 (0.2)
	Cardiogenic shock				1 (0.1)		1 (0.1)
	Coronary artery disease aggravated		1 (0.2)				1 (0.1)
	Coronary artery disease NOS				1 (0.1)		1 (0.1)
	Mitral valve incompetence		1 (0.2)				1 (0.1)
	Right ventricular failure		1 (0.2)				1 (0.1)
	Sick sinus syndrome	1 (0.8)	1 (0.2)			1 (0.3)	1 (0.1)
	Sinus arrhythmia				1 (0.1)		1 (0.1)
	Sudden cardiac death		1 (0.2)				1 (0.1)
	Sudden death		2 (0.4)		2 (0.3)		4 (0.3)
	Supraventricular (SV) arrhythmia NOS	1 (0.8)				1 (0.3)	
	Supraventricular tachycardia (SVT)				1 (0.1)		1 (0.1)
	V fib	1 (0.8)	2 (0.4)			1 (0.3)	2 (0.2)
	V tach	3 (2.3)	5 (1.1)		2 (0.3)	3 (0.8)	7 (0.6)
Cardiac Procedures				1 (0.4)	1 (0.1)	1 (0.3)	1 (0.1)
	Cardioversion			1 (0.4)		1 (0.3)	
	Heart transplant				1 (0.1)		1 (0.1)
Vascular disorders		3 (2.3)	7 (1.6)	3 (1.3)	7 (1.0)	6 (1.6)	14 (1.2)
	Arterial occlusion	1 (0.8)				1 (0.3)	
	Deep vein thrombosis	1 (0.8)	2 (0.4)			1 (0.3)	2 (0.2)
	Hypertension NOS				1 (0.1)		1 (0.1)
	Hypotension NOS	2 (1.5)	3 (0.7)	1 (0.4)	5 (0.7)	3 (0.8)	8 (0.7)
	Intermittent claudication			1 (0.4)		1 (0.3)	
	Jugular vein thrombosis		1 (0.2)				1 (0.1)
	Malignant hypertension NOS			1 (0.4)		1 (0.3)	

Table 7.1.2.1: Serious Treatment-emergent Adverse Events, Overall Safety Population[1], Number and Percentage of Subjects with each Type of Event

		All IV		Oral		IV + Oral	
		Pbo n (%) n = 132	Coni n (%) n = 445	Pbo n (%) n = 240	Coni n (%) n = 715	Pbo n (%) n = 372	Coni n (%) n = 1160
System	**Event**						
	Peripheral vascular disorder NOS				1 (0.1)		1 (0.1)
	Shock hemorrhagic		1 (0.2)				1 (0.1)
Blood and Lymphatic		1 (0.8)	3 (0.7)		3 (0.4)	1 (0.3)	6 (0.5)
	Anemia		1 (0.2)		1 (0.1)		2 (0.2)
	Febrile neutropenia		1 (0.2)				1 (0.1)
	Coagulopathy				1 (0.1)		1 (0.1)
	Thrombocytopenia	1 (0.8)	1 (0.2)		1 (0.1)	1 (0.3)	2 (0.2)
Congenital					1 (0.1)		1 (0.1)
	Arteriovenous (AV) malformation				1 (0.1)		1 (0.1)
Endocrine					1 (0.1)		1 (0.1)
	Hypothyroidism				1 (0.1)		1 (0.1)
Eye			1 (0.2)				1 (0.1)
	Glaucoma NOS		1 (0.2)				1 (0.1)
Gastrointestinal (GI)		3 (2.3)	4 (0.9)		11 (1.5)	3 (0.8)	15 (1.3)
	Abdominal (Abd) pain NOS		1 (0.2)		3 (0.4)		4 (0.3)
	Abd pain upper				1 (0.1)		1 (0.1)
	Ascites				1 (0.1)		1 (0.1)
	Colitis ischaemic	1 (0.8)	1 (0.2)		1 (0.1)	1 (0.3)	1 (0.1)
	Colon gangrene	1 (0.8)				1 (0.3)	
	Constipation				1 (0.1)		1 (0.1)
	Dyspepsia		1 (0.2)		1 (0.1)		2 (0.2)
	Gastric ulcer	1 (0.8)			1 (0.1)	1 (0.3)	1 (0.1)
	GI hemorrhage NOS	1 (0.8)				1 (0.3)	
	Inguinal hernia NOS				1 (0.1)		1 (0.1)
	Intestinal obstruction NOS				1 (0.1)		1 (0.1)
	Mesenteric occlusion		1 (0.2)				1 (0.1)
	Peritonitis		1 (0.2)				1 (0.1)
	Small bowel obstruction				2 (0.3)		2 (0.2)
	Upper GI hemorrhage	1 (0.8)				1 (0.3)	
	Vomiting NOS				1 (0.1)		1 (0.1)
Hepatobiliary			3 (0.7)		4 (0.6)		7 (0.6)
	Cholecystitis NOS		1 (0.2)				1 (0.1)
	Cholelithiasis				2 (0.3)		2 (0.2)
	Cholestasis				1 (0.1)		1 (0.1)
	Hepatic cyst NOS		1 (0.2)				1 (0.1)
	Hepatic failure	1 (0.8)	1 (0.2)			1 (0.3)	1 (0.1)
	Hepatitis NOS				1 (0.1)		1 (0.1)
General Disorders and Administration Site Conditions		4 (3.0)	12 (2.7)	2 (0.8)	18 (2.5)	6 (1.6)	30 (2.6)
	Anasarca		1 (0.2)				1 (0.1)
	Asthenia		2 (0.4)				2 (0.2)
	Edema NOS		1 (0.2)				1 (0.1)
	Edema peripheral				1 (0.1)		1 (0.1)
	Chest pain	1 (0.8)			9 (1.3)	1 (0.3)	9 (0.8)
	Drug interaction NOS				1 (0.1)		1 (0.1)
	Fatigue	1 (0.8)				1 (0.3)	
	Impaired healing		1 (0.2)				1 (0.1)
	Influenza-like illness		2 (0.4)		1 (0.1)		3 (0.3)
	Infusion site phlebitis		2 (0.4)				2 (0.2)
	Injection site cellulitis		2 (0.4)				2 (0.2)
	Injection site reaction NOS		1 (0.2)				1 (0.1)

Table 7.1.2.1: Serious Treatment-emergent Adverse Events, Overall Safety Population[1], Number and Percentage of Subjects with each Type of Event

		All IV		Oral		IV + Oral	
		Pbo n (%) n = 132	Coni n (%) n = 445	Pbo n (%) n = 240	Coni n (%) n = 715	Pbo n (%) n = 372	Coni n (%) n = 1160
System	**Event**						
	Mechanical complication of implant	1 (0.8)				1 (0.3)	
	Mass NOS				1 (0.1)		1 (0.1)
	Multiorgan failure	1 (0.8)	3 (0.7)			1 (0.3)	3 (0.3)
	Pain NOS			1 (0.4)		1 (0.3)	
	Pyrexia	1 (0.8)	1 (0.2)		1 (0.1)	1 (0.3)	2 (0.2)
	Systemic inflammatory response syndrome	1 (0.8)				1 (0.3)	
Immune			1 (0.2)				1 (0.1)
	Urticaria NOS		1 (0.2)				1 (0.1)
Infections		6 (4.5)	31 (7.0)	1 (0.4)	13 (1.8)	7 (1.9)	44 (3.8)
	Abdominal abscess		1 (0.2)				1 (0.1)
	Appendicitis				1 (0.1)		1 (0.1)
	Bronchial infection				1 (0.1)		1 (0.1)
	Bronchitis acute NOS		1 (0.2)		1 (0.1)		2 (0.2)
	Cellulitis		2 (0.4)	1 (0.4)	1 (0.1)	1 (0.3)	3 (0.3)
	Clostridium colitis	1 (0.8)			1 (0.1)	1 (0.3)	1 (0.1)
	Herpes zoster		1 (0.2)				1 (0.1)
	HIV infection		1 (0.2)				1 (0.1)
	Implant site infection	1 (0.8)				1 (0.3)	
	Incision site abscess		1 (0.2)				1 (0.1)
	Infection NOS		1 (0.2)				1 (0.1)
	Meningitis		1 (0.2)				1 (0.1)
	Pneumonia NOS	2 (1.5)	9 (2.0)		4 (0.6)	2 (0.5)	13 (1.1)
	Purulent pericarditis		1 (0.2)				1 (0.1)
	Pyothorax				1 (0.1)		1 (0.1)
	Sepsis NOS	2 (1.5)	5 (1.1)		1 (0.1)	2 (0.5)	6 (0.5)
	Sinusitis NOS				1 (0.1)		1 (0.1)
	Staphylococcal sepsis		1 (0.2)				1 (0.1)
	Upper respiratory tract infection NOS				1 (0.1)		1 (0.1)
	Urinary tract infection NOS		6 (1.3)		1 (0.1)		7 (0.6)
	Urosepsis		1 (0.2)		1 (0.1)		2 (0.2)
Injury, Poisoning and Procedural Complications			3 (0.7)	2 (0.8)	4 (0.6)	2 (0.5)	7 (0.6)
	Accident NOS				1 (0.1)		1 (0.1)
	Anastomotic leak				1 (0.1)		1 (0.1)
	Ankle fracture		1 (0.2)				1 (0.1)
	Drug toxicity NOS		1 (0.2)				1 (0.1)
	Fall				2 (0.3)		2 (0.2)
	Postprocedural hemorrhage			1 (0.4)		1 (0.3)	
	Therapeutic agent poisoning		2 (0.4)	1 (0.4)		1 (0.3)	2 (0.2)
Investigations			2 (0.4)	1 (0.4)	7 (1.0)	1 (0.3)	9 (0.8)
	Alanine aminotransferase (ALT) increased (incr)				2 (0.3)		2 (0.2)
	Aspartate aminotransferase (AST) incr				2 (0.3)		2 (0.2)
	Creatine phosphokinase (CPK) incr				2 (0.3)		2 (0.2)
	Lactate dehydrogenase (LDH) incr				1 (0.1)		1 (0.1)
	BP decreased (decr)			1 (0.4)	1 (0.1)	1 (0.3)	1 (0.1)
	Blood urea nitrogen (BUN):Cr ratio incr				1 (0.1)		1 (0.1)
	Body temperature (temp) incr				1 (0.1)		1 (0.1)

Table 7.1.2.1: Serious Treatment-emergent Adverse Events, Overall Safety Population[1], Number and Percentage of Subjects with each Type of Event

		All IV		Oral		IV + Oral	
		Pbo n (%) n = 132	Coni n (%) n = 445	Pbo n (%) n = 240	Coni n (%) n = 715	Pbo n (%) n = 372	Coni n (%) n = 1160
System	Event						
	Hemoglobin (Hb) decr				1 (0.1)		1 (0.1)
	International normalized ratio (INR) incr		1 (0.2)				1 (0.1)
	Liver function test (LFT) abnormal (abnl)		1 (0.2)		1 (0.1)		2 (0.2)
Metabolism (Metab) and Nutrition (Nutr)		3 (2.3)	12 (2.7)	1 (0.4)	16 (2.2)	4 (1.1)	28 (2.4)
	Dehydration		3 (0.7)		5 (0.7)		8 (0.7)
	Diabetes mellitus insulin dependent		1 (0.2)				1 (0.1)
	Diabetes mellitus NOS			1 (0.4)	1 (0.1)	1 (0.3)	1 (0.1)
	Failure to thrive				1 (0.1)		1 (0.1)
	Hyperglycemia NOS				2 (0.3)		2 (0.2)
	Hyperkalemia	1 (0.8)			1 (0.1)	1 (0.3)	1 (0.1)
	Hypernatremia		1 (0.2)				1 (0.1)
	Hypoglycemia NOS		1 (0.2)		2 (0.3)		3 (0.3)
	Hypokalemia		1 (0.2)				1 (0.1)
	Hyponatremia	2 (1.5)	6 (1.3)		5 (0.7)	2 (0.5)	11 (0.9)
	Hypovolemia		1 (0.2)		1 (0.1)		2 (0.2)
Musculoskeletal			1 (0.2)		3 (0.4)		4 (0.3)
	Musculoskeletal chest pain		1 (0.2)		1 (0.1)		2 (0.2)
	Myalgia				1 (0.1)		1 (0.1)
	Rhabdomyolysis				1 (0.1)		1 (0.1)
Neoplasm			3 (0.7)	1 (0.4)	5 (0.7)	1 (0.3)	8 (0.7)
	Bladder neoplasm NOS				1 (0.1)		1 (0.1)
	Bronchial carcinoma		1 (0.2)				1 (0.1)
	Metastatic carcinoma			1 (0.4)		1 (0.3)	
	Esophageal carcinoma NOS				2 (0.3)		2 (0.2)
	Lung carcinoma				1 (0.1)		1 (0.1)
	Pancreatic carcinoma				1 (0.1)		1 (0.1)
	Ovarian cancer metastatic		1 (0.2)				1 (0.1)
	Renal cell carcinoma		1 (0.2)				1 (0.1)
Nervous System		1 (0.8)	7 (1.6)		16 (2.2)	1 (0.3)	23 (2.0)
	Ataxia				1 (0.1)		1 (0.1)
	CVA		4 (0.9)		1 (0.1)		5 (0.4)
	Dizziness				2 (0.3)		2 (0.2)
	Epilepsy NOS		1 (0.2)				1 (0.1)
	Grand mal convulsion				1 (0.1)		1 (0.1)
	Headache				1 (0.1)		1 (0.1)
	Paresthesia				1 (0.1)		1 (0.1)
	Stroke hemorrhagic				1 (0.1)		1 (0.1)
	Syncope	1 (0.8)	2 (0.4)		6 (0.8)	1 (0.3)	8 (0.7)
	Syncope vasovagal	1 (0.8)			1 (0.1)	1 (0.3)	1 (0.1)
	Tardive dyskinesia				1 (0.1)		1 (0.1)
Psychiatric			2 (0.4)		4 (0.6)		6 (0.5)
	Anxiety				1 (0.1)		1 (0.1)
	Confusional State		2 (0.4)		1 (0.1)		3 (0.3)
	Depression				1 (0.1)		1 (0.1)
	Mental Status Changes				1 (0.1)		1 (0.1)
	Psychotic disorder				1 (0.1)		1 (0.1)
Renal and Urinary		4 (3.0)	10 (2.2)		11 (1.5)	4 (1.1)	21 (1.8)
	Anuria		1 (0.2)				1 (0.1)

Table 7.1.2.1: Serious Treatment-emergent Adverse Events, Overall Safety Population[1], Number and Percentage of Subjects with each Type of Event

		All IV		Oral		IV + Oral	
		Pbo n (%) n = 132	Coni n (%) n = 445	Pbo n (%) n = 240	Coni n (%) n = 715	Pbo n (%) n = 372	Coni n (%) n = 1160
System	**Event**						
	Hematuria		1 (0.2)				1 (0.1)
	Obstructive uropathy		1 (0.2)				1 (0.1)
	Renal disorder NOS				2 (0.3)		2 (0.2)
	Renal failure acute	2 (1.5)	2 (0.4)		3 (0.4)	2 (0.5)	5 (0.4)
	Renal failure acute on chronic		1 (0.2)				1 (0.1)
	Renal failure chronic		1 (0.2)				1 (0.1)
	Renal failure NOS	2 (1.5)	3 (0.7)		3 (0.4)	2 (0.5)	6 (0.5)
	Urinary retention				1 (0.1)		1 (0.1)
Reproductive system and breast disorders			1 (0.2)				1 (0.1)
	Ovarian mass		1 (0.2)				1 (0.1)
Respiratory and thoracic		7 (5.3)	24 (5.4)	2 (0.8)	13 (1.8)	9 (2.4)	37 (3.2)
	Acute pulmonary edema			1 (0.4)		1 (0.3)	
	Bronchitis NOS				1 (0.1)		1 (0.1)
	COPD		1 (0.2)				1 (0.1)
	COPD exacerbated		1 (0.2)		2 (0.3)		3 (0.3)
	Cough		1 (0.2)				1 (0.1)
	Dyspnea		2 (0.4)		1 (0.1)		3 (0.3)
	Dyspnea exacerbated	5 (3.8)	6 (1.3)		2 (0.3)	5 (1.3)	8 (0.7)
	Hypercapnia				1 (0.1)		1 (0.1)
	Esophagobronchial fistula				1 (0.1)		1 (0.1)
	Pleural effusion				2 (0.3)		2 (0.2)
	Pulmonary congestion	1 (0.8)	3 (0.7)		1 (0.1)	1 (0.3)	4 (0.3)
	Pulmonary embolism		1 (0.2)	1 (0.4)	3 (0.4)	1 (0.3)	4 (0.3)
	Pulmonary edema NOS		2 (0.4)		1 (0.1)		3 (0.3)
	Respiratory arrest	1 (0.8)	1 (0.2)			1 (0.3)	1 (0.1)
	Respiratory distress		1 (0.2)				1 (0.1)
	Respiratory failure		4 (0.9)				4 (0.3)
	Respiratory failure acute		1 (0.2)				1 (0.1)
Social Circumstances					1 (0.1)		1 (0.1)
	Drug abuser				1 (0.1)		1 (0.1)

[1] Studies 016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 031, 032, 033, 034, 038, 043, 044, 047. 071, 080
2 The applicant included the terms "sudden cardiac death" and "sudden death" under "General Disorders". The clinical reviewer moved these terms to "Cardiac Disorders", and adjusted the total numbers of events accordingly
Source: Original NDA, Applicant's Table 2.7.4-129, Module 5, Section 5.3.3.5,; NDA resubmission, Safety Update, Table 8

In the overall safety population, the following individual events and event term groupings occurred at a rate of at least 1%, and with an excess rate of at least 1%, for conivaptan vs placebo in one or more of the above populations (all IV, all oral, or all IV + all oral).

Table 7.1.2.2 Serious Adverse Events, and Serious Adverse Event Groupings; Incidence at Least 1% and Conivaptan Rate ≥1% Higher than Placebo Rate (Overall Safety Population)

	All IV		All Oral		All IV + All Oral	
Event or Event Grouping	**Pbo n (%) N = 132**	**Coni n (%) N = 445**	**Pbo n (%) N = 240**	**Coni n (%) N = 715**	**Pbo n (%) N = 372**	**Coni n (%) N = 1160**
Total cardiac events	13 (9.8)	37 (8.3)	8 (3.3)	48 (6.7)	21 (5.6)	85 (7.3)
Congestive cardiac failure aggravated (individual term)	1 (0.8)	6 (1.3)	2 (0.8)	17 (2.4)	3 (0.8)	23 (2.0)
Total cardiac failure events[1]	4 (3.0)	19 (4.7)	4 (1.7)	29 (4.1)	8 (2.2)	48 (4.1)
Total infusion site reactions and infusion site infections[2]		6 (1.3)				6 (0.5)
Total infection events	6 (4.5)	31 (7.0)	1 (0.4)	13 (1.8)	7 (1.9)	44 (3.8)
Total metabolic and nutrition events	3 (2.3)	12 (2.7)	1 (0.4)	16 (2.2)	4 (1.1)	28 (2.4)
Total nervous system events	1 (0.8)	7 (1.6)		16 (2.2)	1 (0.3)	23 (2.0)

1 Includes event terms cardiac failure NOS, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiomyopathy NOS, congestive cardiac failure aggravated, congestive cardiomyopathy, ischemic cardiomyopathy, right ventricular failure
2 Includes event terms jugular vein thrombosis, infusion site phlebitis, injection site cellulitis, injection site reaction NOS
3 Includes syncope and syncope vasovagal

Total serious cardiac events occurred at a higher rate in the oral conivaptan groups than in the oral placebo groups, and at a higher frequency in the overall coni population than in the overall placebo population. Serious cardiac failure event terms occurred more frequently in conivaptan groups than in placebo groups for the IV, oral, and total populations. This was also true for the individual serious adverse event term "congestive cardiac failure aggravated". Serious infusion site events occurred exclusively in IV conivaptan-treated patients, with no placebo patients experiencing such events. For total serious infection events, total serious metabolic events, and total serious nervous system events, a higher numerical event rate was observed for the conivaptan groups than for the placebo groups for all treatment populations (IV, oral, and overall safety), but no single type of event appeared to occur in clear excess in any of these categories.

Please see Appendix 10.3 for a complete table of serious adverse events occurring in the overall controlled Phase 2/3 population (Studies 017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071). The following table lists serious adverse event groupings of interest. No single adverse event occurred at a rate of at least 1% in the conivaptan groups and at a rate at least 1% higher for conivaptan than for placebo, for the overall controlled Phase 2/3 population. The only MedDRA System Organ Class to meet this criterion was Nervous System Disorders, where 1.5% of conivaptan patients experienced serious nervous system events, compared to 0.3% of placebo patients.

Table 7.1.2.3 Serious Adverse Event Groupings of Interest, Overall Controlled Phase 2/3 Population (IV + Oral)

System Organ Class	Pbo N=372 n (%)[8]	Coni N=942 n (%)[8]
Total bleeding terms[2]	3 (0.8)	3 (0.3)
Total cardiac failure terms[1]	7 (1.9)	24 (2.5)
Total arrhythmia terms[3]	8 (2.2)	17 (1.8)
Total atrial arrhythmia terms[4]	0	3 (0.3)
Nervous system disorders	1 (0.3)	14 (1.5)
Total infusion site-related terms[5]	0	5 (0.5)
Total hypovolemia-related terms[6]	4 (1.1)	24 (2.5)
Total renal failure terms[7]	4 (1.1)	12 (1.3)

1 Includes event terms cardiac failure NOS, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiomyopathy NOS, congestive cardiac failure aggravated, congestive cardiomyopathy, ischemic cardiomyopathy
2 Includes event terms coagulopathy, hemorrhagic disorder, conjunctival hemorrhage, eye hemorrhage NOS, retinal hemorrhage, duodenitis hemorrhagic, gastric hemorrhage, GI hemorrhage NOS, gingival bleeding, hemorrhoidal hemorrhage, melena, rectal hemorrhage, upper GI hemorrhage, catheter site hemorrhage, implant site hemorrhage, injection site hemorrhage, hematuria traumatic, postprocedural hemorrhage, CVA, hemorrhagic stroke, hematuria, epistaxis, shock hemorrhagic
3 Includes event terms arrhythmia NOS, A fib, A flutter, atrial tachycardia, bradyarrhythmia, bradycardia, nodal rhythm, sick sinus syndrome, sinus arrhythmia, sinus bradycardia, sinus tachycardia, SV arrhythmia NOS, SVT, tachycardia NOS, ventricular arrhythmia NOS, ventricular bigeminy, V fib, V tach, ventricular trigeminy
4 Includes event terms A fib, A flutter, atrial tachycardia
5 Includes event terms cannula site reaction, infusion related reaction, infusion site erythema, infusion site induration, infusion site inflammation, infusion site edema, infusion site pain, infusion site phlebitis, infusion site reaction, infusion site swelling, infusion site tenderness, infusion site warmth, injection site bruising, injection site cellulitis, injection site discomfort, injection site erythema, injection site hemorrhage, injection site inflammation, injection site pain, injection site phlebitis, injection site pruritus, injection site reaction NOS, injection site swelling, injection site tenderness, injection site thrombosis, infusion site infection, injection site infection, jugular vein thrombosis, phlebitis NOS, phlebitis superficial, thrombophlebitis, thrombophlebitis superficial
6 Includes event terms cardiogenic shock, fall, blood pressure decreased, dehydration, hypovolemia, syncope, hypotension NOS, orthostatic hypotension
7 Includes acute prerenal failure, anuria, azotemia, renal failure NOS, renal failure acute, renal failure acute on chronic, renal failure chronic
8 n = # events; % = # events per 100 pts. Within a combined event category, a patient may have had more than one event within that category, e.g. injection site infection and injection site pain. Therefore, the percentage presented may not correspond with the actual percentage of patients who experienced any event.
Source: Applicant's Table 2.7.4-9P23_ALL, email from Dr. Raineri, Astellas Reg Affairs, 7 Nov 05

In the overall controlled Phase 2/3 population (IV + oral), serious hypovolemia-related events occurred more frequently per 100 patients in the conivaptan group than in the placebo group. All serious infusion site reactions occurred in conivaptan patients. System Organ Class Serious Nervous System adverse events occurred more frequently numerically in conivaptan-treated patients than in placebo patients, but no one type of nervous system event predominated. For the System Organ Class Nervous System events, the rate represents the percentage of patients who had any nervous system event. However, for the hypovolemia-related term grouping, the rate reflects the number of events per 100 patients, and not the percentage of patients who experienced any hypovolemia-related event, because a single patient could have had more than one event.

Table 7.1.2.4 Serious Treatment-emergent Adverse Events, "Full Dose" IV Studies in Patients

		Controlled[1] "Full Dose" IV in Pts		All "Full Dose"[2] IV in Pts	
		Pbo Total N = 69 n (%)	Coni Total N = 177 n (%)	Pbo Total N = 69 n (%)	Coni Total N = 292 n (%)
System	**Event[3]**				
Cardiac		8 (11.6)	24 (13.6)	8 (11.6)	44 (15.1)
	Angina unstable	1 (1.4)		1 (1.4)	2 (0.7)
	Atrial arrhythmia	1 (1.4)		1 (1.4)	
	A fib with rapid ventric response		1 (0.6)		1 (0.3)
	A flutter exacerbated		1 (0.6)		1 (0.3)
	A flutter with rapid ventric response		1 (0.6)		1 (0.3)
	AV block complete		1 (0.6)		1 (0.3)
	Bradyarrhythmia				1 (0.3)
	Cardiac arrest bradycardic		1 (0.6)		1 (0.3)
	Cardiac failure congestive				1 (0.3)
	Cardiac failure decompensated				1 (0.3)
	Cardiac failure worsening				1 (0.3)
	Cardiomyopathy decompensated		1 (0.6)		1 (0.3)
	Cardiomyopathy worsening		2 (1.1)		2 (0.7)
	Cardiomyopathy dilated worsening		1 (0.6)		1 (0.3)
	Cardiomyopathy ischemic worsening		1 (0.6)		1 (0.3)
	Cardiopulmonary arrest		1 (0.6)		1 (0.3)
	Cardiopulmonary decompensation acute	1 (1.4)		1 (1.4)	
	Complete heart block		1 (0.6)		1 (0.3)
	CHF		1 (0.6)		1 (0.3)
	CHF exacerbation		1 (0.6)		7 (2.4)
	CHF worsening	1 (1.4)	2 (1.1)	1 (1.4)	2 (0.7)
	CAD exacerbated		1 (0.6)		1 (0.3)
	Mitral regurg severe worsening		1 (0.6)		1 (0.3)
	MI	1 (1.4)		1 (1.4)	3 (1.0)
	MI suspected				1 (0.3)
	Prosthetic aortic valve occlusion		1 (0.6)		1 (0.3)
	Right heart failure, worsening				1 (0.3)
	Sick sinus syndrome	1 (1.4)	1 (0.6)	1 (1.4)	1 (0.3)
	Sudden cardiac death		1 (0.6)		1 (0.3)
	Sudden death				1 (0.3)
	V fib		1 (0.6)		2 (0.7)
	V tach	2 (2.9)	2 (1.1)	2 (2.9)	3 (1.0)
Eye					1 (0.3)
	Glaucoma aggravation				1 (0.3)
GI		4 (5.8)	2 (1.1)	4 (5.8)	11 (3.8)
	Abdominal pain		1 (0.6)		1 (0.3)
	Ascites worsening				1 (0.3)
	Cholecystitis				1 (0.3)
	Colitis pseudomembranous	1 (1.4)		1 (1.4)	
	Colon gangrene				1 (0.3)
	Constipation worsening	1 (1.4)		1 (1.4)	
	Epigastric pain				1 (0.3)
	Gastroenteritis				1 (0.3)
	GI bleed upper	1 (1.4)		1 (1.4)	
	GI bleeding	1 (1.4)		1 (1.4)	1 (0.3)
	Liver cyst				1 (0.3)
	Liver failure		1 (0.6)		2 (0.7)
	Melena				1 (0.3)
General disorders and administration site conditions		2 (2.9)	7 (4.0)	2 (2.9)	16 (5.5)

Table 7.1.2.4 Serious Treatment-emergent Adverse Events, "Full Dose" IV Studies in Patients

		Controlled[1] "Full Dose" IV in Pts		All "Full Dose"[2] IV in Pts	
		Pbo Total N = 69 n (%)	Coni Total N = 177 n (%)	Pbo Total N = 69 n (%)	Coni Total N = 292 n (%)
System	Event[3]				
	Anasarca		1 (0.6)		1 (0.3)
	Cellulitis infusion site		2 (1.1)		2 (0.7)
	Cellulitis injection site				1 (0.3)
	Chest pain				1 (0.3)
	Edema generalized				1 (0.3)
	Fatigue worsening	1 (1.4)		1 (1.4)	
	Fever neutropenic				1 (0.3)
	Hemorrhagic shock				1 (0.3)
	Injection site reaction		2 (1.1)		2 (0.7)
	Multiorgan failure	1 (1.4)		1 (1.4)	3 (1.0)
	Phlebitis infusion site		2 (1.1)		2 (0.7)
	Weakness				1 (0.3)
Hematologic (Heme)		1 (1.4)	1 (0.6)	1 (1.4)	3 (1.0)
	Anemia				1 (0.3)
	Anemia worsening				1 (0.3)
	Thrombocytopenia worsening	1 (1.4)	1 (0.6)	1 (1.4)	1 (0.3)
Infection		3 (4.3)	10 (6.0)	3 (4.3)	26 (8.9)
	Abscess at malignant esophagocutaneous fistula				1 (0.3)
	Cellulitis				1 (0.3)
	Cornea abscess				1 (0.3)
	HIV infection end-stage		1 (0.6)		1 (0.3)
	Infection implantable cardiac defibrillator (ICD) pocket	1 (1.4)		1 (1.4)	
	Meningitis, suspected				1 (0.3)
	Peritonitis, fecal				1 (0.3)
	Pneumonia	1 (1.4)	4 (2.3)	1 (1.4)	6 (2.1)
	Pneumonia worsening		1 (0.6)		2 (0.7)
	Sepsis		1 (0.6)		4 (1.4)
	Sepsis, gram negative		1 (0.6)		1 (0.3)
	Sepsis syndrome	1 (1.4)		1 (1.4)	
	Septic shock				1 (0.3)
	Septicemia Staphylococcal		1 (0.6)		1 (0.3)
	Tuberculosis pulmonary				1 (0.3)
	UTI				2 (0.7)
	Urosepsis				1 (0.3)
	Zoster infection sacral		1 (0.6)		1 (0.3)
Immune			1 (0.6)		1 (0.3)
	Urticaria allergic, worsening		1 (0.6)		1 (0.3)
Injury, poisoning and procedural complications			3 (1.7)		4 (1.4)
	Coumadin toxicity		1 (0.6)		1 (0.3)
	Digoxin toxicity		1 (0.6)		2 (0.7)
	Sternotomy poorly healed		1 (0.6)		1 (0.3)
Investigations			1 (0.6)		2 (0.7)
	Liver function tests (LFTs) elevated		1 (0.6)		1 (0.3)
	INR prolonged				1 (0.3)
Metab and Nutr		3 (4.3)	6 (3.4)	3 (4.3)	22 (7.5)
	Dehydration		1 (0.6)		2 (0.7)
	DM, brittle, exacerbation				1 (0.3)
	Hyperkalemia	1 (1.4)		1 (1.4)	1 (0.3)
	Hypernatremia				1 (0.3)
	Hypervolemia		1 (0.6)		1 (0.3)

Table 7.1.2.4 Serious Treatment-emergent Adverse Events, "Full Dose" IV Studies in Patients

		Controlled[1] "Full Dose" IV in Pts		All "Full Dose"[2] IV in Pts	
		Pbo Total N = 69 n (%)	Coni Total N = 177 n (%)	Pbo Total N = 69 n (%)	Coni Total N = 292 n (%)
System	Event[3]				
	Hypoglycemia				1 (0.3)
	Hypokalemia		1 (0.6)		1 (0.3)
	Hyponatremia	1 (1.4)	1 (0.6)	1 (1.4)	2 (0.7)
	Hyponatremia exacerbation				9 (3.1)
	Hyponatremia recurrent				1 (0.3)
	Hyponatremia worsening	1 (1.4)	1 (0.6)	1 (1.4)	1 (0.3)
	Hypovolemia		1 (0.6)		1 (0.3)
Musculoskeletal					1 (0.3)
	Chest pain musculoskeletal				1 (0.3)
Neoplasm			2 (1.1)		6 (2.1)
	Bronchial carcinoma				1 (0.3)
	Gastric cancer				1 (0.3)
	Gastric carcinoma progression				1 (0.3)
	Laryngeal carcinoma squamous cell				1 (0.3)
	Ovarian mass		1 (0.6)		1 (0.3)
	Renal cancer progression				1 (0.3)
Neurologic			1 (0.6)		5 (1.7)
	Confusion		1 (0.6)		1 (0.3)
	Encephalopathy hepatic				1 (0.3)
	Presyncope				1 (0.3)
	Seizure epileptic				2 (0.7)
Renal		4 (5.8)	6 (3.4)	4 (5.8)	12 (4.1)
	Hematuria				1 (0.3)
	Hematuria persistent				1 (0.3)
	Renal failure acute	1 (1.4)	1 (0.6)	1 (1.4)	3 (1.0)
	Renal failure acute oliguric		1 (0.6)		1 (0.3)
	Renal failure acute onset chronic		1 (0.6)		1 (0.3)
	Renal failure acute worsening	1 (1.4)		1 (1.4)	1 (0.3)
	Renal failure worsening	1 (1.4)	2 (1.1)	1 (1.4)	2 (0.7)
	Renal failure chronic worsening		1 (0.6)		1 (0.3)
	Renal insufficiency	1 (1.4)		1 (1.4)	
	Uropathy postobstructive				1 (0.3)
Respiratory		9 (13.0)	16 (9.0)	9 (13.0)	26 (8.9)
	COPD worsening		1 (0.6)		1 (0.3)
	Cough due to angiotensin converting enzyme inhibitor (ACEI)		1 (0.6)		1 (0.3)
	Dyspnea				3 (1.0)
	Dyspnea exacerbation				1 (0.3)
	Dyspnea worsening	6 (8.7)	6 (3.4)	6 (8.7)	7 (2.4)
	Pleural effusion				1 (0.3)
	Pulmonary congestion				1 (0.3)
	Pulmonary congestion worsening	2 (2.9)	3 (1.7)	2 (2.9)	3 (1.0)
	Pulmonary edema worsened		2 (1.1)		2 (0.7)
	Respiratory arrest	1 (1.4)	1 (0.6)	1 (1.4)	1 (0.3)
	Respiratory distress		1 (0.6)		1 (0.3)
	Respiratory failure		1 (0.6)		2 (0.7)
	Respiratory failure, acute, due to food aspiration				1 (0.3)
	Respiratory failure, suspected				1 (0.3)
Vascular		3 (4.3)	5 (2.8)	3 (4.3)	13 (4.5)
	Arterial occlusion	1 (1.4)		1 (1.4)	
	CVA				1 (0.3)
	Deep venous thrombosis (DVT)		1 (0.6)		2 (0.7)

Table 7.1.2.4 Serious Treatment-emergent Adverse Events, "Full Dose" IV Studies in Patients

		Controlled[1] "Full Dose" IV in Pts		All "Full Dose"[2] IV in Pts	
		Pbo Total N = 69 n (%)	Coni Total N = 177 n (%)	Pbo Total N = 69 n (%)	Coni Total N = 292 n (%)
System	Event[3]				
	Hemorrhage				1 (0.3)
	Hypertension				1 (0.3)
	Hypertension uncontrolled				1 (0.3)
	Hypotension	2 (2.9)	1 (0.6)	2 (2.9)	2 (0.7)
	Mesenteric artery occlusion acute				1 (0.3)
	Stroke		1 (0.6)		1 (0.3)
	Stroke, unconfirmed				1 (0.3)
	Thrombus external iliac vein		1 (0.6)		1 (0.3)
	Thrombus common femoral vein		1 (0.6)		1 (0.3)

1 Studies 027, 071
2 Studies 027, 071, 080
3 Serious adverse events (SAEs) were provided in a different format from the source used for the overall SAE table above (7.1.2.1). Event terms may differ slightly.
Source: Applicant's response document, Table 14

Table 7.1.2.5 Serious Adverse Events, and Serious Adverse Event Groupings; Incidence at Least 1% and Conivaptan Rate >1% Higher than Placebo Rate ("Full Dose" IV Studies in Patients)

	Controlled "Full Dose" IV[1] in Patients		All "Full Dose" IV[2] in Patients
Event or Event Term Grouping	Pbo N = 69 n (%)	Coni N = 177 n (%)	Coni N = 292 n (%)
Total serious cardiac events	8 (11.6)	24 (13.6)	44 (15.1)
CHF exacerbation (individual SAE term)	0	1 (0.6)	7 (2.4)
Total serious cardiac failure events[3]	1 (1.4)	9 (5.1)	19 (6.5)
Total serious infusion site reactions and infections[4]	0	6 (3.4)	7 (2.4)
Total serious infection events	3 (4.3)	10 (6.0)	26 (8.9)
Total serious metabolic and nutritional events	3 (4.3)	6 (3.4)	22 (7.5)
Total serious hyponatremia events[5]	2 (2.9)	2 (1.1)	13 (4.5)
Total serious neoplastic events	0	2 (1.1)	6 (2.1)

1 Studies 027, 071
2 Studies 027, 071, 080
3 Includes event terms cardiac failure congestive, cardiac failure decompensated, cardiac failure worsening, cardiomyopathy decompensated, cardiomyopathy worsening, cardiomyopathy dilate worsening, cardiomyopathy ischemic worsening, CHF, CHF exacerbation, CHF worsening, right heart failure worsening
4 Includes event terms cellulitis infusion site, cellulitis injection site, injection site reaction, phlebitis infusion site
5 Includes event terms hyponatremia, hyponatremia exacerbation, hyponatremia recurrent, hyponatremia worsening

For the "full dose" IV studies conducted in patients, serious cardiac events occurred more frequently numerically among conivaptan-treated patients than among placebo-treated patients, both for the controlled studies and the group of all three studies. In particular, serious cardiac failure events occurred with greater frequency (1.4% pbo, 5.1% controlled coni, 6.5% total coni). Serious infusion site events occurred exclusively in conivaptan-treated patients. Serious infection events occurred more frequently in conivaptan-treated patients, but no single type of infection drove the excess. Serious metabolic and nutritional events also occurred more frequently in

conivaptan-treated patients than in placebo-treated patients; this was driven in part by an excess of serious hyponatremia events.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The following table outlines the reasons for discontinuation in the full IV and overall safety populations.

Table 7.1.3.1.1 Reasons for Discontinuation, "Full Dose" IV and Overall Safety Populations

	Full IV[1]		Overall Safety (IV + Oral)[2]	
Reason for Discontinuation	**Pbo N = 132 n (%)**	**Coni N = 445 n (%)**	**Pbo N = 372 n (%)**	**Coni N = 1148 n (%)**
AE	5 (3.8)	22 (4.9)	16 (4.3)	68 (5.9)
Lack of Efficacy	2 (1.5)	6 (1.3)	3 (0.8)	13 (1.1)
Withdrawal of Consent		7 (1.6)	1 (0.3)	9 (0.8)
Lost to Followup				
Protocol Violation			2 (0.5)	4 (0.3)
Patient Died				3 (0.3)
Lack of Compliance		3 (0.7)		14 (1.2)
Other/Admin	2 (1.5)	18 (4.0)	9 (2.4)	35 (3.0)
Satisfactory Response				1 (0.1)
Total Discontinuations	9 (6.8)	56 (12.6)	31 (8.3)	147 (12.8)

1 Studies 027, 071, 080, 016, 017, 023, 025, 032, 038, 044
2 Studies 027, 071, 080, 079, 083, 074, 016, 017, 020, 021, 022, 023, 024, 025, 026, 031, 032, 033, 034, 043, 044, 047

Dropouts were more common among conivaptan-treated patients than among placebo-treated patients; most dropouts were due to adverse events.

On 25 Oct 05, the clinical reviewer requested information on the actual reasons given for discontinuation for those patients listed as having withdrawn for "Other/Admin". On 27 Oct 05, Astellas provided these reasons in an email from Dr. Donald Raineri. Most of these reasons were for withdrawal of consent or for relocation of the patient. However, some may actually have been due to adverse events. The following table lists those patients whose withdrawal may actually have been due to an adverse event rather than to "Other/Admin".

Table 7.1.3.1.2 Discontinuations Listed as Due to "Admin/Other" that May Actually Have Been Due to Adverse Events

Study	Pt ID	Tx Grp	Reason for Discontinuation
027	27-72901	Pbo	worsening of hyponatremia
027	27-75602	Coni	respiratory arrest
080	80-10601	Coni	serum sodium increase exceeded 12 mEq/L/day
080	80-11404	Coni	rapid correction of serum sodium from 127 mEq/L to 138 mEq/L in 20 hours
080	80-20701	Coni	sodium increased 16 mEq/L over 6 hours

Source: Applicant's Listing 1, email from applicant 27 Oct 05

Studies 027 and 080 were both IV studies. It appears that a few more patients may actually have discontinued due to adverse events than indicated by the applicant. These events would change the percentages of intravenous-conivaptan-treated patients who discontinued due to adverse events to 5.8% for the IV conivaptan groups and 4.5% for the placebo group, but would not substantially change the difference between groups.

7.1.3.2 Adverse events associated with dropouts

Table 7.1.3.2 Adverse Events Leading to Discontinuation, IV and Full Safety Populations

		All IV[1]		Overall Safety (IV + Oral)[2]	
		Pbo N = 132 n (%)	Coni N = 445 n (%)	Pbo N = 372 n (%)	Coni N = 1148 n (%)
System Organ Class	MedDRA Term				
Blood and lymphatic system disorders					1 (0.1)
	Thrombocytopenia				1 (0.1)
Cardiac disorders		1 (0.8)	3 (0.7)	3 (0.8)	12 (1.0)
	Angina pectoris				1 (0.1)
	Arrhythmia NOS				1 (0.1)
	Cardiac arrest				1 (0.1)
	Cardiac failure NOS			1 (0.3)	3 (0.3)
	Congestive cardiac failure aggravated	1 (0.8)	1 (0.2)	1 (0.3)	3 (0.3)
	Right ventricular failure		1 (0.2)		1 (0.1)
	V tach		1 (0.2)	1 (0.3)	2 (0.2)
Ear and labyrinth disorders				1 (0.3)	
	Vertigo			1 (0.3)	
Endocrine disorders			1 (0.2)		1 (0.1)
	Hypopituitarism		1 (0.2)		1 (0.1)
GI disorders		1 (0.8)		2 (0.5)	4 (0.3)
	Abdominal pain NOS				2 (0.2)
	Abdominal pain upper				1 (0.1)
	Dyspepsia				1 (0.1)
	Fecal abnormality NOS				1 (0.1)
	Flatulence				1 (0.1)
	Small intestinal obstruction NOS				1 (0.1)
	Upper GI hemorrhage	1 (0.8)		1 (0.3)	
	Vomiting NOS			1 (0.3)	
General disorders and administration site conditions			8 (1.8)		14 (1.2)

Table 7.1.3.2 Adverse Events Leading to Discontinuation, IV and Full Safety Populations

		All IV[1]		Overall Safety (IV + Oral)[2]	
		Pbo N = 132 n (%)	Coni N = 445 n (%)	Pbo N = 372 n (%)	Coni N = 1148 n (%)
System Organ Class	**MedDRA Term**				
	Chest pain				1 (0.1)
	Feeling abnormal				1 (0.1)
	Infusion related reaction		1 (0.2)		1 (0.1)
	Infusion site phlebitis		7 (1.6)		7 (0.6)
	Injection site reaction NOS		1 (0.2)		1 (0.1)
	Malaise				1 (0.1)
	Mass NOS				1 (0.1)
	Sudden death				1 (0.1)
	Thirst				1 (0.1)
Immune system disorders				1 (0.3)	1 (0.1)
	Drug hypersensitivity				1 (0.1)
	Hypersensitivity NOS			1 (0.3)	
Infections and infestations			3 (0.8)		4 (0.3)
	Injection site infection		1 (0.2)		1 (0.1)
	Pneumonia NOS		1 (0.2)		2 (0.2)
	Sepsis NOS		1 (0.2)		1 (0.1)
Injury, poisoning and procedural complications				1 (0.3)	1 (0.1)
	Head injury				1 (0.1)
	Postprocedural hemorrhage			1 (0.3)	
Investigations			4 (0.9)	1 (0.3)	4 (0.3)
	Blood creatinine increased		1 (0.2)		1 (0.1)
	Blood sodium increased		1 (0.2)		1 (0.1)
	Blood urea increased		1 (0.2)		1 (0.1)
	Heart rate increased		1 (0.2)		1 (0.1)
	Liver function test abnormal	1 (0.8)	3 (0.8)	1 (0.3)	
Metabolism and nutrition disorders				1 (0.3)	5 (0.4)
	Appetite decreased NOS				1 (0.1)
	Hyperkalemia				1 (0.1)
	Hypernatremia		3 (0.8)		3 (0.3)
	Hyponatremia	1 (0.8)		1 (0.3)	
Neoplasms					1 (0.1)
	Esophageal carcinoma NOS				1 (0.1)
Nervous system disorders		1 (0.8)	1 (0.2)	1 (0.3)	5 (0.4)
	CVA				1 (0.1)
	Dizziness				1 (0.1)
	Epilepsy NOS		1 (0.2)		1 (0.1)
	Grand mal convulsion				1 (0.1)
	Headache				1 (0.1)
	Syncope				1 (0.1)
	Syncope vasovagal	1 (0.8)		1 (0.3)	
Psychiatric disorders		1 (0.8)	2 (0.4)	2 (0.5)	2 (0.2)
	Agitation		1 (0.2)		1 (0.1)
	Confusional state	1 (0.8)	2 (0.4)	1 (0.3)	2 (0.2)
	Insomnia			1 (0.3)	
Renal and urinary disorders		1 (0.8)	2 (0.4)	1 (0.3)	5 (0.4)
	Renal failure NOS	1 (0.8)		1 (0.3)	2 (0.2)
	Renal failure acute		1 (0.2)		1 (0.1)
	Renal failure acute on chronic		1 (0.2)		1 (0.1)
	Renal impairment NOS				1 (0.1)
Reproductive system and breast disorders					1 (0.1)
	Erectile dysfunction NOS				1 (0.1)

Table 7.1.3.2 Adverse Events Leading to Discontinuation, IV and Full Safety Populations

		All IV[1]		Overall Safety (IV + Oral)[2]	
		Pbo N = 132 n (%)	Coni N = 445 n (%)	Pbo N = 372 n (%)	Coni N = 1148 n (%)
System Organ Class	**MedDRA Term**				
Respiratory, thoracic and mediastinal disorders			2 (0.4)		6 (0.5)
	Dyspnea exacerbated				1 (0.1)
	Nocturnal dyspnea				1 (0.1)
	Esophagobronchial fistula				1 (0.1)
	Pulmonary embolism				1 (0.1)
	Respiratory arrest		1 (0.2)		1 (0.1)
	Respiratory failure		1 (0.2)		1 (0.1)
Skin and subcutaneous tissue disorders			1 (0.2)		2 (0.2)
	Cyanosis peripheral		1 (0.2)		1 (0.1)
	Rash NOS				1 (0.1)
Vascular disorders		2 (1.5)	3 (0.8)	2 (0.5)	4 (0.3)
	Hypotension NOS	2 (1.5)	1 (0.2)	2 (0.5)	2 (0.2)
	Phlebitis NOS		1 (0.2)		1 (0.1)
	Phlebitis superficial		1 (0.2)		1 (0.1)

1 Studies 027, 071, 080, 016, 017, 023, 025, 032, 038, 044
2 Studies 027, 071, 080, 079, 083, 074, 016, 017, 020, 021, 022, 023, 024, 025, 026, 031, 032, 033, 034, 043, 044, 047
Source: Applicant's ISS, Table 3

Discontinuations due to infusion site related events occurred exclusively in intravenous conivaptan-treated patients; 12 infusion site-related events led to discontinuation among these patients (2.7 such events per 100 IV conivaptan patients). As noted above in Table 7.1.3.1.2, three additional conivaptan patients appear to have discontinued study due to overly rapid correction of serum sodium. There is no MedDRA term for this particular event, and these events and other cases of overly rapid correction of serum sodium may not have been captured as adverse events.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Renal Adverse Events

In the original clinical NDA review, the incidence of total renal adverse events and serious renal adverse events appeared to be higher in the conivaptan groups than in the placebo groups. Few data were available to permit further characterization of this observation, and the clinical reviewer requested additional information with the resubmission. The applicant provided a systematic search of its databases for all studies for several requested search criteria. The incidence of these findings is presented in the following table.

Table 7.1.3.3.1.1 Number and Percentage of Patients Meeting Renal Adverse Event Search Criteria

Renal Search Criteria	Number of Subjects	
	Conivaptan n=1256	Placebo n=372
Any Renal Search Criterion	40 (3.2%)	7 (1.9%)
Doubling of serum creatinine over baseline	15 (1.2%)	2 (0.5%)
Tripling of serum creatinine over baseline	4 (0.3%)	1 (0.3%)
Serum creatinine > 4 mg/dL at any time during the study§	4 (0.3%)	1 (0.3%)
Any serious renal adverse event, regardless of causality	18 (1.4%)	4 (1.1%)
Renal adverse event requiring hospitalization	18 (1.4%)	4 (1.1%)
Oliguria as an adverse event	3 (0.2%)	1 (0.3%)
Adverse event requiring dialysis	0†	0†

A subject may have met more than 1 criterion with the exception of subjects who had a tripling of serum creatinine; these subjects were only counted as having a tripling of serum creatinine and were not included as having a doubling of serum creatinine.

† No subjects were identified based on the search method described.

Source: Applicant's Table 1, Section 7.3, pg 351, Response to Deficiencies in Original NDA

The majority of these adverse events were moderate increases in serum creatinine values, and most occurred well after day 4 of study participation. Serious renal adverse events did not occur with significantly higher frequency in conivaptan-treated patients than in placebo patients in this table by the applicant. In the IV populations presented in Section 7.1.2, serious renal adverse events did not occur with greater frequency in conivaptan-treated patients than in placebo-treated patients. Overall renal adverse events (serious and nonserious) did occur with slightly greater frequency in "full dose" IV-treated conivaptan patients and in the overall safety population than such events occurred in placebo-treated patients. In the overall controlled Phase 2/3 population (IV + oral), serious renal adverse events, and serious adverse events of renal failure, did not occur more frequently among conivaptan patients than among placebo patients.

In further examining serious renal adverse events, the clinical reviewer focused on those events occurring after five or fewer days of conivaptan administration, and occurring during conivaptan administration or within 30 days of cessation of conivaptan administration. These events were deemed to provide the most relevant information regarding the possible profile of events that could occur with the proposed dosing regimen. The following table summarizes information from those events.

Table 7.1.3.3.1.2 Serious Renal Adverse Events Occurring After 5 or Fewer Days of Conivaptan Administration, and Occurring During Administration or Within 30 Days after Last Dose of Conivaptan

ID	Age	Sex	BL CHF?	Date 1st Dose	Date Last Dose	BL Cr[1]	1st Cr ≥2x BL	Date 1st Cr ≥2x BL	Dose (mg) at 1st Cr ≥2x BL	1st Cr >4 mg/dL	Date 1st Cr >4 mg/dL	Dose at 1st Cr >4 mg/dL	Coni Conc >1000 ng/mL?	Date of Death	Comment
26-60103	45	f	y	15 Jul 00	19 Jul 00	2.1		ARF reported 19 Jul 05	40 mg/day oral				no	5 Aug 00	Reported AE renal failure NOS, dialysis day 5, death day 17 due to endstage CHF, Sp Gr on tx 1.0
27-77208	71	m	n	22 Jul 01	24 Jul 01	2.4		[redacted] SAE of renal failure NOS reported	Pbo				n/a	30 Jul 01	Dialysis, U.O. Day 1 = 2300 cc
71-40006	73	f	y	15 Jun 03	16 Jun 03	1.5		[redacted] SAE of acute on chronic renal failure reported	80 mg/day IV				no	n/a	U.O. Day 1 = 3375 cc, Day 2 = 1670, Day 3 = 980.
71-70003	51	m	y	1 May 03	2 May 03	1.1	5.1	[redacted]	Pbo	5.1	31 May 03		n/a	3 Jun 03	
71-90011	49	m	y	13 Mar 03	14 Mar 03	1.4		[redacted] SAE of ARF reported	Pbo				n/a	n/a	
71-220003	66	f	y	12 Feb 03	14 Feb 03	1.1		[redacted] SAE of ARF reported	40 mg/day IV last dose prior to ARF				no	n/a	
71-240002	52	f	y	10 Mar 03	10 Mar 03	2.2		[redacted] SAE of renal failure NOS reported	20 mg/day IV last dose prior to renal failure				not done	11 Apr 03	
80-20402	70	m	n	23 Jul 04	27 Jul 04	0.8	2.0	[redacted]	60 mg/day IV	5.1	26 Jul 04	40 mg/day IV	y	27 Jul 04	

1 creatinine measured in mg/dL

From these cases, no clear pattern emerges to describe a typical occurrence of a serious renal adverse event associated with conivaptan. Most cases were included because an event of renal failure was reported, but no clearly elevated creatinine was recorded. No events had laboratory evidence of acute tubular necrosis, although data were sparse. Most patients had congestive heart failure, which has a high incidence of renal failure even with best available care. In the group of all "full dose" IV studies, serious renal adverse events did not occur more frequently among conivaptan-treated patients than among placebo-treated patients. When considering common adverse events (serious and nonserious), total renal adverse events and nonserious adverse events of "renal failure" occurred slightly more frequently in conivaptan-treated patients than in placebo-treated patients. Renal failure adverse events (serious and nonserious combined) did not occur more frequently among conivaptan-treated patients than among placebo-treated

patients in the overall controlled Phase 2/3 (IV + oral) population. In the controlled "full dose" IV population, renal failure adverse events (serious and nonserious combined) occurred in 14/258 (5.4%) of conivaptan-treated patients and 5/109 (4.6%) of placebo-treated patients.

Overall, the clinical reviewer concludes that, although the original NDA raised a question of an increased incidence of serious renal adverse events among conivaptan-treated patients compared to placebo-treated patients, the full body of information now presented does not show evidence of a significant difference between conivaptan and placebo for the risk of serious adverse renal events. This conclusion is based on the absence of a significant difference in incidence of serious renal events (by multiple criteria) in any of the controlled populations examined. The evidence suggests that conivaptan is associated with an increased risk for moderate increases in serum creatinine, which may be the result of volume depletion or of exacerbation (due to volume depletion) of a tendency toward renal dysfunction due to an underlying disease state, such as congestive heart failure. There is no clear evidence of a primary nephrotoxic effect of conivaptan. As with patients treated with diuretics in the acute hospitalized setting, patients treated with this aquaretic in the acute hospitalized setting must have careful monitoring of renal function, and may require volume repletion if an overly brisk aquaresis results in volume depletion and prerenal renal failure.

7.1.3.3.2 Overly Rapid Correction of Serum Sodium

Overly rapid correction of low serum sodium has been well-described to be associated with increased risk of permanent neurologic sequelae, classically central pontine myelinolysis. The applicant, based on the medical literature, identified an increase in serum sodium of ≥12 mEq/L over any 24 hour period, or an increase over baseline at any time of ≥24 mEq/L, or an increase to ≥145 mEq/L at any time, as a laboratory definition of an undesirably rapid correction in serum sodium. This did not occur in placebo-treated patients, but did occur in a total of 59/1148 (5%) of conivaptan-treated patients across the development program. Of these 59 patients, 21 had discontinuation of conivaptan or reduction in dose. Among all patients in the Phase 2/3 study population (excluding healthy subjects) treated with conivaptan 40 mg/day IV or higher, 6% of patients met the above definition of overly rapid response. When considering all patients in the controlled Phase 2/3 population who received conivaptan in doses within the range under consideration for labeling (20-40 mg/day IV equivalent), 9.1% of patients met a criterion for overly rapid correction of serum sodium; there was not an apparent dose-response for the dose groups in this range, as illustrated in the following table.

Table 7.1.3.3.2

Number and Percentage of Patients who Met Criteria for Overly Rapid Rise in Serum Sodium
20 mg/Day IV, 80 mg/day Oral, and 40 mg/day IV Groups
All Placebo-Controlled Phase 2/3 Studies

TREATMENT GROUP	TOTAL N in Group	n (%) (1)
IV PLACEBO	132	7 (5.3%)
ORAL PLACEBO	240	8 (3.3%)
ALL PLACEBO	372	15 (4.0%)
20 mg/day IV	32	3 (9.4%)
80 mg/day Oral	147	14 (9.5%)
40 mg/day IV	118	10 (8.5%)
All Subjects in 20 mg/day IV, 80 mg/day Oral, and 40 mg/day IV Groups	297	27 (9.1%)

Source: Applicant's Table A1.RAPIDNA.2, email from Dr. Donald Raineri, Astellas Reg Affairs, 1 Dec 05

The applicant approached the evaluation of this adverse event by searching the medical literature for adverse events (AEs) potentially associated with rapid correction of serum sodium. These included:

- renal failure
- encephalopathy
- central pontine myelinolysis
- extrapontine demyelination
- spastic quadriparesis
- pseudobulbar palsy
- mutism dysarthria
- cerebral edema
- aseptic meningitis
- seizures
- transtentorial herniation
- ventricular tachycardia
- ventricular fibrillation
- rhabdomyolysis
- obtundation
- severe headache
- confusion
- agitation
- lethargy
- brain death
- coma.

Only one patient who met the criterion for overly rapid correction of serum sodium had any of these events. Patient 80-21404 had a seizure two days after a reduction in conivaptan dose due

to overly rapid rise in serum sodium. On Day 1 of conivaptan, 40 mg/day IV, the patient's sodium rose from 127 mEq/L to 140 mEq/L from 0505 to 2045 hours. Conivaptan was reduced to 20 mg/day IV. Two days later, the patient experienced a seizure lasting three minutes, which resolved spontaneously. There were no focal neurologic deficits, but the patient had postictal confusion "of short duration". Serum sodium at the time of the seizure was 132 mEq, and reportedly had been stable in the range of 131-132 mEq/L. The patient had evidence of a prior parieto-occipital cerebral infarct on CT, but no other cause of seizure was noted. The investigator considered the event as probably related to conivaptan, and conivaptan was permanently discontinued immediately after the seizure.

Among other patients who met the criteria for overly rapid correction of sodium, there was one reported event of severe weakness in a 40 mg/day group patient, and one event each of shakiness, hallucination and insomnia in 80 mg/day group patients. These events are neuropsychiatric in nature, but not classically associated with overly rapid correction of serum sodium.

Data are lacking in the medical literature regarding the expected incidence of neurologic sequelae of overly rapid correction of serum sodium in patients with moderate hyponatremia. However, among patients with severe hyponatremia (≤105 mEq/L) in one case series (Sterns 1994), 14/56 patients whose serum sodium was corrected by >12 mEq/L/24 hours developed neurologic complications. Ten of these complications were permanent, and three were central pontine myelinolysis.

Overall, it appears that about 9% of patients treated with IV conivaptan can be expected to meet laboratory criteria for overly rapid correction of serum sodium, a clinically concerning event which must be immediately addressed by a reduction in dose or discontinuation of conivaptan. Patients must then be carefully monitored for neurologic consequences of that overly rapid correction. However, only 1/59 patients who met a criterion for an overly rapid correction of serum sodium suffered a neurologic event likely to be related to that rapid correction, and this event (seizure) resolved without apparent sequelae. Although strictly comparable data are not available from the medical literature, it does not appear that patients treated with conivaptan are more likely to develop neurologic consequences of overly rapid serum sodium correction than are patients who are treated with hypertonic saline.

7.1.3.3.3 Infusion Site Reactions

In the approvable letter from the original NDA, the Division recommended that the applicant explore methods for decreasing the incidence of infusion site reactions. Please see the original NDA clinical review (Section 7.1.3.3.2) for a discussion of infusion site reactions. Updated safety data for this NDA resubmission continue to show a high incidence of infusion site reactions, as illustrated in the following table.

Table 7.1.3.3.3.1 Incidence of Infusion Site Reactions in IV Studies

Study	Placebo	IV Conivaptan§			
		20 mg/day	40 mg/day	80 mg/day	120 mg/day
Open-Label Study (087-CL-080)	--	16/21 (76.2%)	89/115 (77.4%)	--	--
Placebo-Controlled Studies (087-CL-027, -071 and -079)	8/109 (7.3%)	--	40/110 (36.4%)	56/106 (52.8%)	24/42 (57.1%)

Source: Applicant's Table 5, pg 18, Response to Deficiencies in Original NDA

Study 080, an open-label hyponatremia safety study, had a specific worksheet for infusion site reactions, and this may explain the greater percentage of reported cases of infusion site reactions in this study compared to the controlled IV population. In controlled IV studies, the incidence of infusion site reactions appears dose-related. The majority of these infusion site reactions occurred on the first day of conivaptan administration; most were nonserious.

The following patients had serious adverse events related to conivaptan infusion sites:

Table 7.1.3.3.3.2 Serious Infusion Site Related Adverse Events Among Intravenous Conivaptan Patients

Study	Pt ID	Coni Dose (mg/day)	SAE	D/C?[1]
071	520007	120	left arm veins phlebitis at infusion site	no
071	550001	120	right hand phlebitis at infusion site	no
071	510003	120	cellulitis left arm at infusion site, Staphylococcal septicemia	no
071	110008	120	bilateral injection site reaction	yes
071	150004	40	cellulitis left arm at infusion site	no
080	011411	40	cellulitis at injection site	yes

1 Discontinued due to event

The applicant did not provide information regarding any new efforts to reduce the incidence of infusion site reactions. In Phase 1 Study 074, a midazolam interaction study discussed in the original NDA review, infusion site reactions occurred at all infusion concentrations (0.05, 0.08, and 0.16 mg/mL), but were more marked and more frequent at higher concentrations. The clinical reviewer had considered the possibility of a relationship between the use of an initial loading dose (with attendant high conivaptan concentrations) and the incidence of infusion site reactions, and had requested that the applicant study the pharmacodynamics of conivaptan with and without a loading dose, but the applicant has not done this at the time of this resubmission. The applicant proposes to included directions in the package insert to administer conivaptan via large veins, and to change the infusion site every 24 hours.

In summary, infusion site reactions are very common with intravenous conivaptan, and sometimes result in serious adverse events. The incidence of these reactions appears to correlate with concentration of the conivaptan infusion. At a minimum, the clinical reviewer recommends the study of the incidence of infusion site reactions in regimens with and without loading doses.

7.1.3.3.4 Hypotension and Hypovolemia

The marked polyuria associated with conivaptan use may lead to intravascular volume depletion and hypotension. The following table details the incidence of the event terms "hypotension NOS" and "orthostatic hypotension" in the IV and Ph 2/3 controlled populations.

Table 7.1.3.3.4 Incidence of "Hypotension NOS" and "Orthostatic Hypotension"

	All IV[1]		All Contr "Full Dose" IV[2]		All Contr Ph 2/3[3]	
	Coni N = 445 n (%)	Pbo N = 132 n (%)	Coni N = 258 n (%)	Pbo N = 109 n (%)	Coni N = 942 n (%)	Pbo N = 372 n (%)
Hypotension NOS	14 (3.1)	0	4 (1.6)	0	44 (4.7)	21 (5.6)
Orthostatic hypotension NOS	15 (3.8)	0	5 (1.9)	0	10 (1.1)	4 (1.1)

1 Includes studies 027, 080, 071, 016, 017, 023, 025, 032, 038, 044
2 Includes studies 027, 071, 079
3 Includes studies 017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071

In this table, the incidence of these terms is numerically higher for IV conivaptan groups than for IV placebo groups, but this is not true for the overall controlled Phase 2/3 population, which included patients with lower conivaptan exposure.

In the overall controlled Phase 2/3 population (IV + oral), combined serious hypovolemia-related adverse event terms occurred more frequently among conivaptan-treated patients (24 events/942 patients, 2.5%) than among placebo-treated patients (4/372, 1.1%). Please see Table 7.1.2.3 for details of the included adverse event terms.

When considering combined serious and nonserious adverse events, hypovolemia-related events occurred more frequently numerically among conivaptan-treated patients than among placebo-treated patients for the overall safety (IV + oral), "full dose" controlled IV, and "full dose" IV hyponatremia populations. Please see the footnote to Table 7.1.5.4.1 for the list of events included in this grouping. In general, it included hypotensive, hypovolemic, syncopal, fall and shock events. In the "full dose" controlled IV population, hypovolemia-related events occurred in 29/258 (11.2%) of conivaptan-treated patients and 11/109 (10.1%) of placebo-treated patients. In the "full dose" IV hyponatremia studies, hypovolemia-related events occurred in 31/170 (18.2%) of conivaptan-treated patients and 4/29 (13.8%) of placebo-treated patients.

One patient (ID 43-231339) treated with oral conivaptan, 40 mg/day for 2 days, died of hypovolemic shock after marked aquaresis. Four other deaths occurred in which hypotension occurred in the peritreatment perimortem period in conivaptan-treated patients (Pt IDs 27-75806, 80-10203, 26-60708, 47-231326).

Intravenous conivaptan appears to be associated with an increased risk for hypovolemia- and hypotension- related events, both serious and nonserious. This conclusion is based on the finding of an increased incidence of these events in the overall controlled and controlled intravenous populations. One death may have occurred due to hypovolemic shock after marked aquaresis. Limitation of use of the drug to the acute hospitalized patient may reduce this risk; physicians must be aware that frequent monitoring of vital signs and volume status is necessary.

7.1.3.3.5 Adverse Events in Patients with Underlying Congestive Heart Failure

There is considerable interest in the medical literature in the use of vasopressin antagonists for the treatment of congestive heart failure per se (with or without hyponatremia), and conivaptan is also under development for the treatment of congestive heart failure, although an NDA has not yet been submitted for that indication. If conivaptan is approved for treatment of hyponatremia, the potential exists for widespread off-label use for the treatment of congestive heart failure. Therefore, the safety of conivaptan in congestive heart failure patients is of special interest. Congestive heart failure patients have a smaller central compartment than do patients with normal ventricular function; Dr. Chung of Biopharmaceutics calculated that congestive heart failure patients would be expected to have an approximately 8-fold higher conivaptan exposure than would healthy subjects. The original NDA review raised the question of a higher rate of mortality and serious cardiac failure adverse events among congestive heart failure patients treated with conivaptan than among CHF patients treated with placebo. A single controlled "full dose" intravenous study of conivaptan for the treatment of congestive heart failure was conducted; this study included 122 patients who received a total of 40 mg/day or more of intravenous conivaptan for a total of 2 days. The full study report has not been submitted, but safety data were included with this NDA.

The following table summarizes adverse events in Study 071.

Table 7.1.3.3.5.1 Summary of Adverse Events, Study 071 (Controlled "Full Dose" IV Study for CHF Indication)

	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Number of Patients	40	40	40	42	122
Number of TEAEs Reported	190	200	181	206	587
Number of Patients with TEAEs	35 (87.5%)	33 (82.5%)	38 (95.0%)	35 (83.3%)	110 (90.2%)
Number of Serious TEAEs	26	15	15	20	60
Number of Patients with Serious TEAEs	16 (40.0%)	9 (22.5%)	11 (27.5%)	18 (42.9%)	38 (31.1%)
Number of Patients with TEAEs by Severity					
Mild	13 (32.5%)	13 (32.5%)	18 (45.0%)	11 (26.2%) *	42 (34.4%)
Moderate	15 (37.5%)	13 (32.5%)	13 (32.5%)	17 (40.5%)	43 (35.2%)
Severe	7 (17.5%)	7 (17.5%)	7 (17.5%)	11 (26.2%)	25 (20.5%)
Severity Unknown	0	0	0	0	0
Number of Patients Discontinued Study Medication due to TEAE	2 (5.0%)	2 (5.0%)	3 (7.5%)	6 (14.3%)	11 (9.0%)
Patients with Treatment - Related TEAEs	10 (25.0%)	16 (40.0%)	21 (52.5%)	36 (85.7%)	63 (51.6%)
Number of Deaths due to TEAEs	1 (2.5%)	2 (5.0%)	1 (2.5%)	7 (16.7%)	10 (8.2%)
Number of Deaths	1 (2.5%)	2 (5.0%)	1 (2.5%)	7 (16.7%)	10 (8.2%)

* All indicated doses are in milligrams/day.
Note: 'Deaths due to TEAE' includes all TEAEs within 30-days post-treatment where the outcome was 'Died, due to AE'. 'Deaths' includes all deaths occurring during treatment, within 30-days post-treatment, or beyond 30-days post-treatment but resulted from an AE that had its onset during treatment or within 30-days post-treatment. Only Serious AEs occurring within 30-days of post-treatment will be included in this table.
Note: Patients are assigned to a treatment group based on the nominal dose.
Data Source: ae.sas7bdat, demog.sas7bdat, disp.sas7bdat, hrtvisit.sas7bdat, Program Source: t_anaum.sas

YM087 Other = 120 mg/day
Source: Applicant's Table 2.7.4-8.6E, pg 157, Summary of Intravenous Safety

Overall, CHF patients in this study who were treated with conivaptan did not experience adverse events at a higher rate than did placebo patients. Among conivaptan-treated patients, there appeared to be a dose-related trend for the incidence of serious adverse events, but conivaptan patients overall experienced serious adverse events at a lower numerical rate than did placebo patients [Pbo 16/40 (40%), Coni 40 mg 9/40 (23%), all Coni 38/122 (31%)].

The following table identifies those treatment-emergent adverse events which occurred in at least 3 conivaptan patients in any dose group, and at a rate at least 1% higher for the conivaptan group than for the placebo group.

Table 7.1.3.3.5.2 Number and Percentage of Patients with Treatment-emergent Adverse Events Occurring in at Least 3 Conivaptan Patients in any Dose Group, and at a Rate at Least 1% Higher for the Conivaptan Group than for the Placebo Group, Study 071 (Controlled IV CHF Study)

System Organ Class	MedDRA Term	Pbo N=40 n (%)	Coni 40 mg/day N=40 n (%)	Coni 80 mg/day N=40 n (%)	Coni 120 mg/day N=42 n (%)	All Coni N=122 n (%)
Blood and lymphatic system disorders						
	Anemia NOS	1 (2.5)	0	3 (7.5)	3 (7.1)	6 (4.9)
Cardiac disorders						
	A fib	0	3 (7.5)	2 (5.0)	1 (2.4)	6 (4.9)
	A flutter	0	0	1 (2.5)	3 (7.1)	4 (3.3)
	Cardiomyopathy NOS	0	2 (5.0)	0	1 (2.4)	3 (2.5)
Eye disorders		0	2 (5.0)	0	1 (2.4)	3 (2.5)
Gastrointestinal disorders						
	Vomiting NOS	2 (5.0)	3 (7.5)	1 (2.5)	0	4 (3.3)
General disorders and administration site conditions		13 (32.5)	19 (47.5)	24 (60.0)	29 (69.0)	72 (59.0)
	Asthenia	0	2 (5.0)	2 (5.0)	3 (7.1)	7 (5.7)
	Infusion site erythema	0	0	3 (7.5)	1 (2.4)	4 (3.3)
	Infusion site edema	0	2 (5.0)	1 (2.5)	0	3 (2.5)
	Infusion site pain	0	2 (5.0)	2 (5.0)	1 (2.4)	5 (4.1)
	Infusion site phlebitis	2 (5.0)	7 (17.5)	13 (32.5)	14 (33.3)	34 (27.9)
	Infusion site reaction	0	0	2 (5.0)	3 (7.1)	5 (4.1)
	Infusion site tenderness	0	0	3 (7.5)	0	3 (2.5)
	Injection site cellulitis	0	4 (10.0)	2 (5.0)	3 (7.1)	9 (7.4)
	Injection site reaction NOS	2 (5.0)	2 (5.0)	1 (2.5)	3 (7.1)	6 (4.9)
	Injection site thrombosis	0	0	2 (5.0)	1 (2.4)	3 (2.5)
	Thirst	0	0	2 (5.0)	3 (7.1)	5 (4.1)
Immune system disorders		0	1 (2.5)	0	2 (4.8)	3 (2.5)
Infections and infestations		7 (17.5)	6 (15.0)	7 (17.5)	10 (23.8)	23 (18.9)
	Pneumonia NOS	1 (2.5)	1 (2.5)	2 (5.0)	5 (11.9)	8 (6.6)
Investigations		5 (12.5)	10 (25.0)	14 (35.0)	9 (21.4)	33 (27.0)
	Blood creatinine increased	1 (2.5)	0	2 (5.0)	1 (2.4)	3 (2.5)
	Blood magnesium decreased	0	1 (2.5)	3 (7.5)	0	4 (3.3)
	Body temperature increased	1 (2.5)	0	2 (5.0)	1 (2.4)	3 (2.5)
	Heart sounds abnormal	0	2 (5.0)	0	1 (2.4)	3 (2.5)
	White blood cell count increased	0	0	2 (5.0)	1 (2.4)	3 (2.5)
Metabolism and nutrition disorders		11 (27.5)	17 (42.5)	14 (35.0)	14 (33.3)	45 (36.9)
	Hyperglycemia NOS	0	2 (5.0)	1 (2.5)	3 (7.1)	6 (4.9)
	Hyperkalemia	2 (5.0)	5 (12.5)	2 (5.0)	1 (2.4)	8 (6.6)
	Hypernatremia	0	2 (5.0)	3 (7.5)	2 (4.8)	7 (5.7)
	Hypoglycemia NOS	0	2 (5.0)	0	2 (4.8)	4 (3.3)
	Hyponatremia	1 (2.5)	1 (2.5)	2 (5.0)	1 (2.4)	4 (3.3)
Musculoskeletal and connective tissue disorders		3 (7.5)	5 (12.5)	7 (17.5)	8 (19.0)	20 (16.4)
	Back pain	0	2 (5.0)	2 (5.0)	1 (2.4)	5 (4.1)
	Muscle cramp	0	1 (2.5)	2 (5.0)	0	3 (2.5)
	Pain in extremity	0	3 (7.5)	2 (5.0)	4 (9.5)	9 (7.4)
Nervous system disorders						
	Dizziness	2 (5.0)	3 (7.5)	0	1 (2.4)	4 (3.3)
	Headache	3 (7.5)	2 (5.0)	1 (2.5)	4 (9.5)	7 (5.7)
Psychiatric disorders						
	Agitation	0	2 (5.0)	0	2 (4.8)	4 (3.3)

Table 7.1.3.3.5.2 Number and Percentage of Patients with Treatment-emergent Adverse Events Occurring in at Least 3 Conivaptan Patients in any Dose Group, and at a Rate at Least 1% Higher for the Conivaptan Group than for the Placebo Group, Study 071 (Controlled IV CHF Study)

System Organ Class	MedDRA Term	Pbo N=40 n (%)	Coni 40 mg/day N=40 n (%)	Coni 80 mg/day N=40 n (%)	Coni 120 mg/day N=42 n (%)	All Coni N=122 n (%)
Renal and urinary disorders		6 (15.0)	8 (20.0)	7 (17.0)	5 (11.9)	20 (16.4)
	Hematuria	1 (2.5)	1 (2.5)	3 (7.5)	0	4 (3.3)
	Leukocyturia	0	1 (2.5)	2 (5.0)	0	3 (2.5)
	Renal failure NOS	1 (2.5)	3 (7.5)	1 (2.5)	2 (4.8)	6 (4.9)
Respiratory, thoracic and mediastinal disorders		17 (42.5)	11 (27.5)	19 (47.5)	14 (33.3)	44 (36.1)
	Dyspnea exacerbated	8 (20.0)	7 (17.5)	10 (25.0)	8 (19.0)	25 (20.5)
	Pulmonary edema NOS	0	0	1 (2.5)	2 (4.8)	3 (2.5)
Skin and subcutaneous disorders		3 (7.5)	2 (5.0)	5 (12.5)	4 (9.5)	11 (9.0)
	Erythema	0	0	2 (5.0)	1 (2.4)	3 (2.5)
Vascular disorders						
	Htn NOS	0	2 (5.0)	2 (5.0)	0	4 (3.3)

Source: Applicant's Table 2.7.4-10.6E, Summary of IV Safety, pg 250

The following table includes event term groupings of interest; the table presents the number and percentage of patients who had one or more events within each event grouping.

Table 7.1.3.3.5.3 Treatment-Emergent Adverse Events by Event Grouping, IV CHF Study 071

Event Grouping[1]	Coni N = 122 n[2] (%)	Pbo N = 40 n[2] (%)
Atrial arrhythmia events	9 (7.4)	0
Bleeding events	9 (7.4)	2 (5.0)
Cardiac failure events	4 (3.3)	0
Electrolyte depletion events	24 (19.7)	9 (22.5)
Infusion site events	65 (53.3)	5 (12.5)
Injury events	1 (<1)	0
Potential hypovolemia-related events	14 (11.5)	7 (17.5)
Renal failure events	9 (7.4)	4 (10.0)

1 For event terms included in event term groupings, see footnote to Table 7.1.5.4.1
2 n = number of patients who experienced any event within event grouping
Source: Applicant's Table 2.7.4-25.6E, email from applicant 9 Nov 05

Atrial arrhythmia events, bleeding events, cardiac failure events, and infusion site events occurred with greater numerical frequency among conivaptan-treated patients than among placebo-treated patients in this single "full dose" IV CHF trial. Please see discussions of these events in Sections 7.1.3.3.1, 7.1.3.3.3, 7.1.3.3.4 and 7.1.3.3.6.

When examining the overall Phase 2/3 population, cardiac failure events also occurred at a higher rate for conivaptan patients than for placebo patients (6.5% vs 4.0% respectively). This was also true for the group of all patients who received conivaptan in at least the full dose proposed for labeling (≥40 mg/day IV), with rates of 4.5% and 0.9% for the conivaptan and placebo populations respectively. These populations include both subjects who did and did not

have an initial diagnosis of congestive heart failure. The overall Phase 2/3 population includes subjects who received doses lower and higher than the doses being considered for labeling by the Division (i.e. includes doses > and < 20-40 mg/day IV equivalent). The "full-dose IV" population includes subjects who received doses from 40-120 mg/day IV, and who therefore received higher doses than the Division is considering for labeling. As was previously discussed in the deaths section, it may not be prudent to discount adverse events occurring at higher doses, because of marked intersubject variability in conivaptan PK, and the risks of narrowing down an already small "full-dose" population. However, for the CHF population, further clarity may be provided by presenting information for events with an apparent signal when considering the group of all Phase 2/3 patients who had an initial diagnosis of congestive heart failure, and examining the events of interest that occurred at the doses under consideration for labeling. The following tables present this information for the overall Phase 2/3 and controlled Phase 2/3 populations, and present information both by number of events per 100 patients, and by percentage of patients who experienced any one event. Events considered included cardiac failure events, death and atrial arrhythmias.

Table 7.1.3.3.5.4

Atrial Arrhythmia Events, Cardiac Failure Events, and Death among CHF Patients Receiving Conivaptan 20 mg IV/Day, 80 mg Oral/Day, or 40 mg IV/Day
All Patients with an Initial Diagnosis of Heart Failure in all Phase 2/3 Trials
Number of Events Per 100 Patients in Each Group

		TREATMENT GROUP (1)											
		IV PLACEBO (N=112)		ORAL PLACEBO (N=209)		ALL PLACEBO (N=321)		20mg/DAY IV (N=32)		80mg/DAY ORAL (N=118)		40mg/DAY IV (N=130)		ALL YM087* (N=280)	
CLASS	PREFERRED TERM														
Atrial Arrhythmia Events	ANY AE	0	0.0%	1	0.5%	1	0.3%	1	3.1%	0	0.0%	8	6.2%	9	3.2%
	Atrial fibrillation	0	0.0%	1	0.5%	1	0.3%	0	0.0%	0	0.0%	8	6.2%	8	2.9%
	Atrial flutter	0	0.0%	0	0.0%	0	0.0%	1	3.1%	0	0.0%	0	0.0%	1	0.4%
Cardiac Failure Events	ANY AE	2	1.8%	13	6.2%	15	4.7%	1	3.1%	5	4.2%	16	12.3%	22	7.9%
	Cardiac failure NOS	1	0.9%	3	1.4%	4	1.2%	0	0.0%	0	0.0%	1	0.8%	1	0.4%
	Cardiac failure chronic	1	0.9%	0	0.0%	1	0.3%	0	0.0%	0	0.0%	1	0.8%	1	0.4%
	Cardiac failure congestive	0	0.0%	1	0.5%	1	0.3%	0	0.0%	1	0.8%	1	0.8%	2	0.7%
	Cardiomyopathy NOS	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	3	2.3%	3	1.1%
	Congestive cardiac failure aggravated	0	0.0%	9	4.3%	9	2.8%	1	3.1%	4	3.4%	8	6.2%	13	4.6%
	Congestive cardiomyopathy	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.8%	1	0.4%
	Right ventricular failure	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.8%	1	0.4%
Deaths (2)		5	4.5%	0	0.0%	5	1.6%	1	3.1%	2	1.7%	6	4.6%	9	3.2%

Source: Applicant's Table A1.1, email from Dr. Donald Raineri, Astellas Reg Affairs, 1 Dec 05
Death = death while receiving study drug or within 30 days after cessation of study drug
Dose = dose at treatment assignment
80 mg/day oral roughly equivalent to 27 mg/day IV
Percentage is number of events per 100 patients in each group

Table 7.1.3.3.5.5

Atrial Arrhythmia Events, Cardiac Failure Events, and Death among CHF Patients
Receiving Conivaptan 20 mg IV/Day, 80 mg Oral/Day, or 40 mg IV/Day
All Patients with an Initial Diagnosis of Heart Failure in all Phase 2/3 Trials
Number of Patients with any Event Per 100 Patients in Each Group

		TREATMENT GROUP (1)							
		IV PLACEBO (N=112)	ORAL PLACEBO (N=209)	ALL PLACEBO (N=321)	20mg/DAY IV (N=32)	80mg/DAY ORAL (N=118)	40mg/DAY IV (N=130)	ALL YM087* (N=280)
CLASS	PREFERRED TERM							
Atrial Arrhythmia Events	ANY AE	0 (0.0%)	1 (0.5%)	1 (0.3%)	1 (3.1%)	0 (0.0%)	6 (4.6%)	7 (2.5%)
	Atrial fibrillation	0 (0.0%)	1 (0.5%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	6 (4.6%)	6 (2.1%)
	Atrial flutter	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Cardiac Failure Events	ANY AE	2 (1.8%)	12 (5.7%)	14 (4.4%)	1 (3.1%)	5 (4.2%)	15 (11.5%)	21 (7.5%)
	Cardiac failure NOS	1 (0.9%)	3 (1.4%)	4 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Cardiac failure chronic	1 (0.9%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Cardiac failure congestive	0 (0.0%)	1 (0.5%)	1 (0.3%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	2 (0.7%)
	Cardiomyopathy NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.3%)	3 (1.1%)
	Congestive cardiac failure aggravated	0 (0.0%)	8 (3.8%)	8 (2.5%)	1 (3.1%)	4 (3.4%)	7 (5.4%)	12 (4.3%)
	Congestive cardiomyopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
	Right ventricular failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
Deaths (2)		5 (4.5%)	0 (0.0%)	5 (1.6%)	1 (3.1%)	2 (1.7%)	6 (4.6%)	9 (3.2%)

Source: Applicant's Table A1.2, email from Dr. Donald Raineri, Astellas Reg Affairs, 1 Dec 05
Death = death while receiving study drug or within 30 days after cessation of study drug
Dose = dose at treatment assignment
80 mg/day oral roughly equivalent to 27 mg/day IV
Percentage is number of patients with any event per 100 patients in each group

Table 7.1.3.3.5.6

Atrial Arrhythmia Events, Cardiac Failure Events, and Death among CHF Patients
Receiving Conivaptan 20 mg IV/Day, 80 mg Oral/Day, or 40 mg IV/Day
All Patients with an Initial Diagnosis of Heart Failure in all Placebo-Controlled Phase 2/3 Trials
Number of Events Per 100 Patients in Each Group

		TREATMENT GROUP (1)											
		IV PLACEBO (N=112)		ORAL PLACEBO (N=209)		ALL PLACEBO (N=321)		20mg/DAY IV (N=32)		80mg/DAY ORAL (N=118)		40mg/DAY IV (N=99)		ALL YM087* (N=249)	
CLASS	PREFERRED TERM														
Atrial Arrhythmia Events	ANY AE	0	0.0%	1	0.5%	1	0.3%	1	3.1%	0	0.0%	3	3.0%	4	1.6%
	Atrial fibrillation	0	0.0%	1	0.5%	1	0.3%	0	0.0%	0	0.0%	3	3.0%	3	1.2%
	Atrial flutter	0	0.0%	0	0.0%	0	0.0%	1	3.1%	0	0.0%	0	0.0%	1	0.4%
Cardiac Failure Events	ANY AE	2	1.8%	13	6.2%	15	4.7%	1	3.1%	5	4.2%	7	7.1%	13	5.2%
	Cardiac failure NOS	1	0.9%	3	1.4%	4	1.2%	0	0.0%	0	0.0%	1	1.0%	1	0.4%
	Cardiac failure chronic	1	0.9%	0	0.0%	1	0.3%	0	0.0%	0	0.0%	1	1.0%	1	0.4%
	Cardiac failure congestive	0	0.0%	1	0.5%	1	0.3%	0	0.0%	1	0.8%	1	1.0%	2	0.8%
	Cardiomyopathy NOS	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	2.0%	2	0.8%
	Congestive cardiac failure aggravated	0	0.0%	9	4.3%	9	2.8%	1	3.1%	4	3.4%	1	1.0%	6	2.4%
	Congestive cardiomyopathy	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.0%	1	0.4%
Deaths (2)		5	4.5%	0	0.0%	5	1.6%	1	3.1%	2	1.7%	3	3.0%	6	2.4%

Source: Applicant's Table A1.3, email from Dr. Donald Raineri, Astellas Reg Affairs, 1 Dec 05
Death = death while receiving study drug or within 30 days after cessation of study drug
Dose = dose at treatment assignment
80 mg/day oral roughly equivalent to 27 mg/day IV
Percentage is number of events per 100 patients in each group

Table 7.1.3.3.5.7

Atrial Arrhythmia Events, Cardiac Failure Events, and Death among CHF Patients
Receiving Conivaptan 20 mg IV/Day, 80 mg Oral/Day, or 40 mg IV/Day
All Patients with an Initial Diagnosis of Heart Failure in all Placebo-Controlled Phase 2/3 Trials
Number of Patients with any Event Per 100 Patients in Each Group

		TREATMENT GROUP (1)											
		IV PLACEBO (N=112)		ORAL PLACEBO (N=209)		ALL PLACEBO (N=321)		20mg/DAY IV (N=32)		80mg/DAY ORAL (N=118)		40mg/DAY IV (N=99)		ALL YM087* (N=249)	
CLASS	PREFERRED TERM														
Atrial Arrhythmia Events	ANY AE	0	0.0%	1	0.5%	1	0.3%	1	3.1%	0	0.0%	3	3.0%	4	1.6%
	Atrial fibrillation	0	0.0%	1	0.5%	1	0.3%	0	0.0%	0	0.0%	3	3.0%	3	1.2%
	Atrial flutter	0	0.0%	0	0.0%	0	0.0%	1	3.1%	0	0.0%	0	0.0%	1	0.4%
Cardiac Failure Events	ANY AE	2	1.8%	12	5.7%	14	4.4%	1	3.1%	5	4.2%	7	7.1%	13	5.2%
	Cardiac failure NOS	1	0.9%	3	1.4%	4	1.2%	0	0.0%	0	0.0%	1	1.0%	1	0.4%
	Cardiac failure chronic	1	0.9%	0	0.0%	1	0.3%	0	0.0%	0	0.0%	1	1.0%	1	0.4%
	Cardiac failure congestive	0	0.0%	1	0.5%	1	0.3%	0	0.0%	1	0.8%	1	1.0%	2	0.8%
	Cardiomyopathy NOS	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	2.0%	2	0.8%
	Congestive cardiac failure aggravated	0	0.0%	8	3.8%	8	2.5%	1	3.1%	4	3.4%	1	1.0%	6	2.4%
	Congestive cardiomyopathy	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.0%	1	0.4%
Deaths (2)		5	4.5%	0	0.0%	5	1.6%	1	3.1%	2	1.7%	3	3.0%	6	2.4%

Source: Applicant's Table A1.4, email from Dr. Donald Raineri, Astellas Reg Affairs, 1 Dec 05
Death = death while receiving study drug or within 30 days after cessation of study drug
Dose = dose at treatment assignment
80 mg/day oral roughly equivalent to 27 mg/day IV
Percentage is number of patients with any event per 100 patients in each group

In each of the above tables (7.1.3.3.5.4-7.1.3.3.5.7), cardiac failure events occurred at a higher rate for conivaptan patients than for IV placebo, for all three conivaptan dose groups that fall within the range under consideration for approval (20-40 mg/day IV equivalent). For the three dose groups presented, there is an apparent dose-related trend in the incidence of cardiac failure events. In the placebo-controlled Phase 2/3 population, the incidence of cardiac failure events in the 40 mg/day IV group is 7.1% vs 1.8% in the IV placebo group, and the percentage of patients experiencing any cardiac failure event in the 40 mg/day IV group is also 7.1% for the conivaptan group and 1.8% for the IV placebo group. At the 20 mg/day IV dose, only 1/32 patients experienced a cardiac failure event. The higher incidence of cardiac failure events at the dose proposed by the applicant for labeling (40 mg/day IV) represents a safety concern for congestive heart failure patients. Exploration of lower doses of conivaptan for the treatment of hyponatremia in congestive heart failure could be of use; CHF patients have an approximately 8-fold higher exposure by AUC than do healthy volunteers. It is possible that efficacy could be achieved at a lower dose in CHF patients, with a lower risk of adverse events such as cardiac failure.

Among patients with an underlying diagnosis of congestive heart failure in the overall Phase 2/3 population, atrial arrhythmia events were reported only in conivaptan-treated patients, and not in placebo-treated patients. No events were reported in the 80 mg/day oral group. Atrial

arrhythmia events occurred with approximately equal frequency in the 20 mg/day IV and 40 mg/day IV groups in the controlled Phase 2/3 CHF population, but the number of events was low in these dose groups in the controlled population.

For CHF patients, when considering only the dose groups in the range under consideration for labeling (20-40 mg IV/day), the incidence of death in these dose groups was not higher for conivaptan than for placebo. However, the clinical reviewer again feels that it would be unwise to discount mortality information from other dose groups. As discussed in Section 7.1.1.4, for patients with an initial diagnosis of CHF in the full-dose IV population when considering all dose groups, both crude mortality, and mortality by patient-month, were higher among conivaptan-treated patients than among placebo-treated patients. There was also a dose-related trend for both crude mortality and mortality per 100 patient-months.

In summary, questions remain about the safety of conivaptan in patients with an underlying diagnosis of congestive heart failure. Atrial arrhythmia events, bleeding events and cardiac failure events appear to have occurred more frequently in conivaptan-treated patients than in placebo-treated patients. There was an increased incidence of cardiac failure events among conivaptan patients compared to placebo patients in the controlled full-dose IV CHF study. For the doses under consideration for approval, there was also an increased incidence of cardiac failure events among all conivaptan patients with underlying CHF in the controlled Phase 2/3 population. Also of concern is an apparent increase in mortality among IV-conivaptan-treated CHF patients compared to placebo patients (deaths occurring on treatment, within 30 days of treatment, or from an event that had its onset during treatment). There appears to be an increase both in crude mortality (# deaths/# patients) and mortality by patient-time (# deaths/# patient-months). This increased mortality appears to be dose-related, and was evident at the dose proposed for labeling.

The clinical reviewer recommends that conivaptan not be used outside the clinical trial setting in patients with an underlying diagnosis of congestive heart failure, and that the use of conivaptan be limited to patients with euvolemic hyponatremia. While one cannot definitively state that conivaptan causes worsening of CHF and increased death among congestive heart failure patients, the totality of information on death and adverse events in congestive heart failure patients is such that the clinical reviewer cannot establish the safety of conivaptan in these patients. A stepwise approach to approval of conivaptan for hyponatremia seems prudent, with approval for euvolemic hyponatremia now, and reconsideration of hypervolemic hyponatremia in the future when further CHF safety data are available to address these safety concerns. The

[redacted]

7.1.3.3.6 Bone marrow function

In preclinical studies in dogs, reversible bone marrow changes were noted at higher exposures than those used in the human clinical trials. Please see the initial clinical NDA review of this topic.

In the updated information in this submission, the incidences of adverse events of anemia, leukopenia and thrombocytopenia were not higher for conivaptan groups for any of the populations examined, except for the incidence of anemia in Study 071, the controlled "full dose" IV study in congestive heart failure patients. In this study, 6/122 (4.9%) of conivaptan patients had treatment-emergent adverse events of anemia, compared to 1/40 (2.5%) of placebo patients. When examining treatment-emergent laboratory abnormalities, low (value <30%) hematocrit emerged during treatment more often numerically for conivaptan-treated patients than for placebo-treated patients in the "full dose" IV, but only slightly more frequently in the "full dose" controlled IV populations (5.7% of placebo patients for both populations; 10.2% of coni patients in all "full dose" IV studies; 6.5% of coni patients in "full dose" controlled IV). A finding of decreased hematocrit would be unexpected from the standpoint of the physiologic effect of the drug; one would expect the free water loss associated with the drug to result in hemoconcentration rather than decreased hematocrit.

All bleeding terms were examined, both because of the preclinical information, and because of the fact that DDAVP, a synthetic polypeptide which is structurally related to vasopressin, has a *procoagulant* effect on platelet function, and is used to treat bleeding in von Willebrand's disease and Hemophilia A. In the "full dose" IV population, and in the overall safety population (IV + oral), combined bleeding terms occurred at a higher rate among conivaptan-treated patients than among placebo-treated patients ("full-dose" IV: coni 4.9 events per 100 pts vs pbo 3.8 events per 100 pts; "overall safety population" coni 4.1 events per 100 pts vs pbo 2.9 events per 100 pts). However, in the "full dose" controlled IV and the overall controlled Phase 2/3 populations (IV + oral), the incidence of these events was not higher for conivaptan patients compared to placebo patients. Please see Table 7.1.5.4.1 for further details of these incidences. Because it was possible that more than one related bleeding event term could have occurred in a given patient, the clinical reviewer requested that the applicant provide data reflecting the percentage of patients who had any bleeding events. Please see Tables 7.1.5.4.3-7.1.5.4.9 for details of these event groupings. These tables present the percentage of patients who had one or more bleeding events. As when examining events/100 patients, the percentage of patients with any bleeding event was not higher for conivaptan compared to placebo in the overall controlled Phase 2/3 (IV + oral) population or in the "full dose" IV controlled population. In Study 071, the single controlled "full dose" IV CHF study, bleeding events occurred in 9/122 (7.4%) of conivaptan-treated patients and 2/40 (5.0%) of placebo-treated patients.

Overall, conivaptan does not appear to be associated with an increased risk of adverse events of bleeding, or of laboratory abnormalities of cytopenias. This conclusion is based on the lack of excess events among conivaptan patients in the overall controlled and controlled IV populations. In the single controlled "full dose" IV CHF study, bleeding events and anemia events occurred at a somewhat higher numerical frequency for conivaptan patients than for placebo patients, but relatively small event numbers prevent firm conclusions regarding the risk of these events in CHF patients.

7.1.3.3.7 Hepatic function

Preclinical studies of conivaptan revealed hepatic changes in dogs (jaundice, increased hepatic enzymes) and rats (hepatocyte necrosis, increased hepatic enzymes).

In the original NDA review, elevations of transaminases to >3x ULN were more common among conivaptan group patients, and elevations of >10x ULN occurred only in conivaptan patients. Please see Tables 7.1.7.3.2.1 and 7.1.7.3.2.2 for treatment-emergent hepatic laboratory abnormalities for the updated IV and overall safety populations. In the IV pbo populations for "full dose" IV studies, no cases of elevations of ALT >3x ULN or >10x ULN occurred. One case of AST>3x ULN occurred in the overall IV pbo population, and no cases of >10x ULN occurred. Among "full dose" IV conivaptan-treated groups, 5/246 (2.0%) of patients in controlled IV studies developed ALT >3x ULN, and 4/246 (1.6%) developed AST >3x ULN. For elevations of >10x ULN among conivaptan-treated patients, 3/246 (1.2%) occurred for AST and 3/246 (1.2%) occurred for ALT. In the overall safety population, percentages included 2.2% and 2.3% of patients developing treatment-emergent ALT and AST values >3x ULN compared to 0.9% of pbo patients for each of these tests. No placebo patients developed AST or ALT >10x ULN, but 5 conivaptan patients (0.5%) developed ALT >10x ULN and 6 conivaptan patients (0.5%) developed AST >10x ULN. Elevated bilirubin was not more common among conivaptan-treated patients than among placebo-treated patients. In Study 071, the "full dose" IV CHF study, mean increases in transaminases were higher in the conivaptan groups than in the placebo group. This finding was driven by 14 patients who had relatively large increases in transaminases; differences in baseline transaminases between the conivaptan and placebo groups made interpretation difficult. Please see Section 7.1.7.3.2 for further discussion.

Hepatobiliary adverse events occurred in <1% of patients in both the conivaptan (9 events in 1148 patients) and placebo groups (1 event in 372 patients) for the overall safety population. In the conivaptan groups, this included two events of cholelithiasis, and one event each of cholecystitis, cholestasis, hepatic cyst, hepatic failure, hepatitis NOS, hepatomegaly, and jaundice cholestatic.

The clinical reviewer examined the cases of hepatic failure and jaundice, and the cases of liver function tests >10x the upper limit of normal (uln) (a total of 6 subjects). The hepatic failure case occurred in a subject who developed multiorgan failure and died in the postoperative period after a failed cardiac transplant. The case of jaundice occurred in a patient with obstructive cholelithiasis. Among the other cases, causes of elevated liver function tests included metastatic gallbladder cancer, infectious hepatitis and endstage decompensated heart failure with multiorgan failure. One patient in Study 071 (ID 71-70002) had baseline AST of 17 IU/mL and ALT of 33 IU/mL, which had increased by 48 hours to 1380 IU/mL and 812 IU/mL respectively; the patient had no reported hepatobiliary adverse events, and followup liver function tests were not reported.

For the overall IV population, conivaptan does not appear to be associated with an increased risk of significant hepatobiliary adverse events. Conivaptan-treated patients overall appear slightly more likely to develop elevations in transaminases of >3x ULN and >10x ULN than do placebo-treated patients. Some conivaptan-treated CHF patients had large increases in transaminases in

Study 071. Baseline transaminase differences between the placebo and conivaptan groups in the CHF study make interpretation of this finding difficult.

7.1.5 Common Adverse Events

Please see the original clinical review of conivaptan for information regarding how adverse events were elicited and categorized.

7.1.5.3 Incidence of common adverse events

The following tables summarize the overall incidence of adverse events in the full IV, "full-dose" IV studies in patients, controlled IV and full controlled Phase 2/3 (IV + oral) populations.

Table 7.1.5.3.1: Summary of Treatment-Emergent Adverse Events, All "Full Dose" IV Studies (Studies 027, 071, 080, 079, 074, 083)

	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 other n(%)	YM087 Any Dose n(%)
Number of Patients	109	256	106	42	404
Number of TEAEs Reported	256	1091	349	206	1646
Number of Patients with TEAEs	61 (56.0%)	210 (82.0%)	91 (85.8%)	39 (92.9%)	340 (84.2%)
Number of Serious TEAEs	38	89	22	30	141
Number of Patients with Serious TEAEs	22 (20.2%)	51 (19.9%)	15 (14.2%)	18 (42.9%)	84 (20.8%)
Number of Patients with TEAEs by Severity					
Mild	29 (26.6%)	80 (31.3%)	55 (51.9%)	11 (26.2%)	146 (36.1%)
Moderate	20 (18.3%	88 (34.4%)	26 (24.5%)	17 (40.5%)	132 (32.7%)
Severe	12 (11.0%)	41 (16.0%)	10 (9.4%)	11 (26.2%)	62 (15.3%)
Severity Unknown	0	0	0	0	0
Number of Patients Discontinued Study Medication due to TEAE	5 (4.6%)	15 (5.9%)	9 (8.5%)	6 (14.3%)	30 (7.4%)
Patients with Treatment - Related TEAEs	21 (19.2%)	169 (66.0%)	68 (64.2%)	26 (61.9%)	263 (65.1%)
Number of Deaths due to TEAEs	4 (3.7%)	16 (6.3%)	3 (2.8%)	7 (16.7%)	26 (6.4%)
Number of Deaths	4 (3.7%)	17 (6.6%)	3 (2.8%)	7 (16.7%)	27 (6.7%)

* All indicated doses are in milligrams/day.
Note: 'Deaths due to TEAE' includes all TEAEs within 30-days post-treatment where the outcome was 'Died, due to AE'. 'Deaths' includes all deaths occurring during treatment, within 30-days post-treatment, or beyond 30-days post-treatment but resulted from an AE that had its onset during treatment or within 30-days post-treatment. Only Serious AEs occurring within 30-days of post-treatment will be included in this table.
Note: Patients are assigned to a treatment group based on the dose.
Data Source: aa.sas7bdat, demog.sas7bdat, disp.sas7bdat, ttrtdis.sas7bdat, Program Source: t_seaae.sas

Source: Applicant's Table 2.7.4-8.6A, Summary of Intravenous Safety

Table 7.1.5.3.2 Summary of Treatment-Emergent Adverse Events, "Full-Dose" IV Studies in Patients (027, 071, 080)

	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any dose n(%)
Number of Patients	69	184	66	42	292
Number of TEAEs Reported	247	981	270	206	1456
Number of Patients with TEAEs	58 (81.2%)	166 (90.2%)	61 (92.4%)	39 (92.9%)	266 (91.1%)
Number of Serious TEAEs	38	88	22	30	141
Number of Patients with Serious TEAEs	22 (31.9%)	51 (27.7%)	15 (22.7%)	18 (42.9%)	84 (28.8%)
Number of Patients with TEAEs by Severity					
Mild	24 (34.8%)	44 (23.9%)	30 (45.5%)	11 (26.2%)	85 (29.1%)
Moderate	20 (29.0%)	81 (44.0%)	21 (31.8%)	17 (40.5%)	119 (40.8%)
Severe	12 (17.4%)	41 (22.3%)	10 (15.2%)	11 (26.2%)	62 (21.2%)
Severity Unknown	0	0	0	0	0
Number of Patients Discontinued Study Medication due to TEAE	5 (7.2%)	13 (7.1%)	9 (13.6%)	6 (14.3%)	28 (9.6%)
Patients with Treatment - Related TEAEs	17 (24.6%)	127 (69.0%)	38 (57.6%)	26 (61.9%)	191 (65.4%)
Number of Deaths due to TEAEs	4 (5.8%)	16 (8.7%)	3 (4.5%)	7 (16.7%)	26 (8.9%
Number of Deaths	4 (5.8%)	17 (9.2%)	3 (4.5%)	7 (16.7%)	27 (9.2%)

* All indicated doses are in milligrams/day.
Note: 'Deaths due to TEAE' includes all TEAEs within 30-days post-treatment where the outcome was 'Died, due to AE'. 'Deaths' includes all deaths occurring during treatment, within 30-days post-treatment, or beyond 30-days post-treatment but resulting from an AE that had its onset during treatment or within 30-days post-treatment. Only Serious AEs occurring within 30-days of post-treatment will be included in this table.
Note: Patients are assigned to a treatment group based on the nominal dose.
Data Source: ae.sas7bdat, dsmog.sas7bdat, disp.sas7bdat, irtvisit.sas7bdat, Program Source: t_aesum.sas

Source: Applicant's Table 2.7.4-8.6B. Summary of Intravenous Safety

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Table 7.1.5.3.3 Summary of Treatment-Emergent Adverse Events, "Full Dose" Controlled IV Studies (027, 071, 079)

	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Number of Patients	109	110	106	42	358
Number of TEAEs Reported	256	348	349	206	903
Number of Patients with TEAEs	81 (56.0%)	77 (70.0%)	91 (62.8%)	39 (92.9%)	207 (80.2%)
Number of Serious TEAEs	36	29	32	30	91
Number of Patients with Serious TEAEs	22 (20.2%)	17 (15.5%)	15 (14.2%)	18 (42.9%)	50 (13.4%)
Number of Patients with TEAEs by Severity					
Mild	29 (26.6%)	34 (30.9%)	55 (51.9%)	11 (26.2%)	100 (38.8%)
Moderate	20 (18.3%)	30 (27.3%)	26 (24.5%)	17 (40.5%)	73 (28.3%)
Severe	12 (11.0%)	13 (11.8%)	10 (9.4%)	11 (26.2%)	34 (13.2%)
Severity Unknown	0	0	0	0	0
Number of Patients Discontinued Study Medication due to TEAE	5 (4.6%)	6 (5.5%)	9 (8.5%)	6 (14.3%)	21 (8.1%)
Patients with Treatment - Related TEAEs	21 (19.3%)	52 (47.3%)	68 (64.2%)	36 (85.7%)	146 (56.6%)
Number of Deaths due to TEAEs	4 (3.7%)	3 (2.7%)	3 (2.8%)	7 (16.7%)	13 (5.0%)
Number of Deaths	4 (3.7%)	3 (2.7%)	3 (2.8%)	7 (16.7%)	13 (5.0%)

* All indicated doses are in milligrams/day.
Note: 'Deaths due to TEAE' includes all TEAEs within 30-days post-treatment where the outcome was 'Died, due to AE'. 'Deaths' includes all deaths occurring during treatment, within 30-days post-treatment, or beyond 30-days post-treatment but resulted from an AE that had its onset during treatment or within 30-days post-treatment. Only Serious AEs occurring within 30-days of post-treatment will be included in this table.
Note: Patients are assigned to a treatment group based on the nominal dose.
Data Source: ae.sas7bdat, demog.sas7bdat, disp.sas7bdat, trtvisit.sas7bdat, Program Source: t_pssum.sas

Source: Applicant's Table 2.7.4-8.6F, Summary of Intravenous Safety

Table 7.1.5.3.4 Summary of Adverse Events, all Controlled Phase 2 and Phase 3 Studies, IV and Oral (017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071)

	Pbo N = 372 n (%)	Coni N = 942 n (%)
Number of TEAEs reported	858	2663
Number of patients with TEAEs	243 (65.3)	646 (68.6)
Number of serious TEAEs	72	225
Number of patients with serious TEAEs	45 (12.1)	145 (15.4)
Number of patients with TEAEs by severity		
Mild	100 (26.9)	273 (29.0)
Moderate	112 (30.1)	261 (27.7)
Severe	31 (8.3)	111 (11.8)
Number of patients who discontinued study medication due to TEAE	14 (3.8)	48 (5.1)
Number of deaths[1]	12 (3.2)	24 (2.5)

1 deaths occurring during study drug administration, within 30 days after study drug administration, or due to an adverse event that had its onset during study drug administration
Source: Applicant's Table 2.7.4-8.P23_ALL, email from Dr. Donald Raineri, Astellas Regulatory Affairs, 2 Nov 05

In all populations in the above tables, treatment-emergent adverse events occurred more frequently among conivaptan-treated patients than among placebo-treated patients. Most of this excess can be attributed to infusion site events. In the controlled IV studies, serious treatment-emergent adverse events did not occur more frequently among conivaptan-treated patients than

among placebo-treated patients, but in the full controlled Phase 2/3 (IV + oral) population, 15.4% of conivaptan-treated patients experienced treatment-emergent serious adverse events compared to 12.1% of placebo-treated patients.

7.1.5.4 Common adverse event tables

Please see Appendix 10.1 for tables of adverse events occurring in ≥1% of conivaptan patients. Separate tables are included for the total "full dose" IV population, "full-dose" IV patient population, "full dose" IV hyponatremia population, "full dose" IV CHF population, and overall safety (IV + oral) population. The summary information in this section is extracted from those tables.

Table 7.1.5.4.1 Adverse Events and Event Term Groupings Occurring in at Least 1% of Conivaptan Patients, and at a Frequency at Least 1% Higher for Conivaptan Patients than for Placebo Patients

		All IV[1]		"Full Dose" IV[2] in Pts		"Full Dose" Controlled IV[6]		All Controlled Phase 2/3[7]		Overall Safety[3]	
System Organ Class	MedDRA Term (or Combined MedDRA Terms)	Coni N=445 n[17](%)	Pbo N=132 n[17](%)	Coni N=292 n[17](%)	Pbo N=69 n[17](%)	Coni N=258 n[17](%)	Pbo N=109 n[17](%)	Coni N=942 n[17](%)	Pbo N=372 n[17](%)	Coni N=1148 n[17](%)	Pbo N=372 n[17](%)
Blood and lymphatic system disorders											
	Leukocytosis	3 (<1)	0	3 (1.0)	0	2 (<1)	0	2 (<1)	0	3 (<1)	0
	Combined bleeding terms[4]	22 (4.9)	5 (3.8)	21 (7.2)	5 (7.2)	11 (4.3)	5 (4.6)	32 (3.4)	12 (3.2)	47 (4.1)	11 (2.9)
Cardiac disorders											
	A fib	13 (2.9)	0	13 (4.5)	0	6 (2.3)	0	13 (1.4)	2 (<1)	21 (1.8)	2 (<1)
	A flutter	4 (<1)	0	4 (1.4)	0	4 (1.6)	0	9 (1.0)	0	9 (<1)	0
	Cardiomyopathy NOS	4 (<1)	0	4 (1.4)	0	3 (1.2)	0	3 (<1)	0	4 (<1)	0
	Congestive cardiac failure aggravated	9 (2.0)	1 (<1)	9 (3.1)	1 (1.4)	3 (1.2)	1 (<1)	26 (2.8)	9 (2.4)	49 (4.3)	9 (2.4)
	Combined cardiac failure terms[5]	17 (3.8)	2 (1.5)	17 (5.8)	2 (2.9)	8 (3.1)	1 (<1)	43 (4.6)	15 (4.0)	77 (6.7)	15 (4.0)
	Combined arrhythmia terms[8]	37 (8.3)	13 (9.8)	37 (12.7)	13 (18.8)	24 (9.3)	13 (11.9)	65 (6.9)	33 (8.9)	91 (7.9)	33 (8.9)
	Combined atrial arrhythmia terms[9]	17 (3.8)	0	17 (5.8)	0	10 (3.9)	0	24 (2.5)	3 (0.8)	30 (2.6)	3 (<1)
	Sinus tachycardia	3 (<1)	0	3 (1.0)	0	1 (<1)	0	1 (<1)	1 (<1)	4 (<1)	1 (<1)
	Ventricular extrasystoles	3 (<1)	0	3 (1.0)	0	3 (1.2)	0	3 (<1)	1 (<1)	5 (<1)	1 (<1)
Eye disorders		11 (2.5)	0	10 (3.4)	0	4 (1.6)	0	15 (1.6)	7 (1.9)	22 (1.9)	7 (1.9)
	Eye pruritus	3 (<1)	0	3 (1.0)	0			2 (<1)	0	3 (<1)	0
GI disorders		88 (19.8)	25 (18.9)	81 (27.8)	22 (31.9)	49 (19.0)	25 (22.9)	142 (15.1)	60 (16.1)	212 (18.5)	60 (16.1)
	Diarrhea NOS	19 (4.3)	3 (2.3)	19 (6.5)	3 (4.3)	9 (3.5)	3 (2.8)	24 (2.5)	8 (2.2)	39 (3.4)	8 (2.2)
	Dry mouth	12 (2.7)	2 (1.5)	6 (2.0)	0	9 (3.5)	2 (1.8)	16 (1.7)	1 (<1)	21 (1.8)	1 (<1)
	Loose stools	3 (<1)	0	3 (1.0)	0	1 (<1)	0	1 (<1)	1 (<1)	3 (<1)	1 (<1)
	Vomiting NOS	21 (4.7)	2 (1.5)	21 (7.2)	2 (2.9)	7 (2.7)	2 (1.8)	12 (1.3)	8 (2.2)	30 (2.6)	8 (2.2)
General disorders and administration site conditions		252 (56.6)	19 (14.4)	186 (63.7)	16 (23.2)	140 (54.3)	19 (17.4)	250 (26.5)	65 (17.5)	380 (33.1)	65 (17.4)
	Application site erythema	3 (<1)	0	3 (1.0)	0	3 (1.2)	0	3 (<1)	0	3 (<1)	0
	Asthenia	13 (2.9)	0	13 (4.5)	0	7 (2.7)	0	21 (2.2)	4 (1.1)	35 (3.0)	4 (1.1)
	Cannula site reaction	10 (2.2)	0	0	0	0	0	0	0	0[3]	0[3]
	Chest pain	4 (<1)	0	4 (1.4)	0	0	0	33 (3.5)	12 (3.2)	43 (3.7)	12 (3.2)

Table 7.1.5.4.1 Adverse Events and Event Term Groupings Occurring in at Least 1% of Conivaptan Patients, and at a Frequency at Least 1% Higher for Conivaptan Patients than for Placebo Patients

		All IV[1]		"Full Dose" IV[2] in Pts		"Full Dose" Controlled IV[6]		All Controlled Phase 2/3[7]		Overall Safety[3]	
System Organ Class	MedDRA Term (or Combined MedDRA Terms)	Coni N=445 n[17](%)	Pbo N=132 n[17](%)	Coni N=292 n[17](%)	Pbo N=69 n[17](%)	Coni N=258 n[17](%)	Pbo N=109 n[17](%)	Coni N=942 n[17](%)	Pbo N=372 n[17](%)	Coni N=1148 n[17](%)	Pbo N=372 n[17](%)
	Infusion site edema	3 (<1)	0	3 (1.0)	0	3 (1.2)	0	3 (<1)	0	3 (<1)	0
	Infusion site erythema	23 (5.2)	0	16 (5.5)	0	10 (3.9)	0	4 (<1)	0	16 (1.4)	0
	Infusion site pain	36 (8.1)	1 (<1)	8 (2.7)	0	28 (10.9)	1 (<1)	6 (<1)	1 (<1)	8[16,37] (<1)	1 (<1)
	Infusion site phlebitis	79 (17.8)	3 (2.3)	75 (25.7)	3 (4.3)	41 (15.9)	3 (2.8)	37 (3.9)	3 (<1)	75[3] (6.5)	3 (<1)
	Infusion site reaction	48 (10.8)	0	47 (16.1)	0	9 (3.5)	0	9 (1.0)	0	47[3] (4.1)	0
	Infusion site swelling	23 (5.2)	2 (1.5)	5 (1.7)	1 (1.4)	21 (8.1)	2 (1.8)	3 (<1)	1 (<1)	5[3] (<1)	1[3] (<1)
	Infusion site tenderness	4 (<1)	0	4 (1.4)	0	3 (1.2)	0	0	3 (<1)	4 (<1)	0
	Injection site cellulitis	9 (2.0)	0	9 (3.1)	0	9 (3.5)	0	9 (1.0)	0	9 (<1)	0
	Injection site phlebitis	5 (1.1)	0	5 (1.7)	0	5 (1.9)	0	5 (0.5)	0	5 (<1)	0
	Injection site reaction NOS	6 (1.3)	2 (1.5)	6 (2.0)	2 (2.9)	6 (2.3)	2 (1.8)	12 (1.3)	2 (<1)	18 (1.6)	2 (<1)
	Injection site thrombosis	3 (<1)	0	3 (1.0)	0	3 (1.2)	0	3 (<1)	0	3 (<1)	0
	Combined injection and infusion site terms[10]	287 (64.5)	9 (6.8)	215 (73.6)	7 (10.1)	169 (65.5)	9 (8.3)	119 (12.6)	10 (2.7)	239 (20.8)	10 (2.7)
	Edema NOS	3 (<1)	0	3 (1.0)	0	2 (<1)	0	10 (1.1)	1 (<1)	14 (1.2)	1 (<1)
	Edema peripheral	14 (3.1)	1 (<1)	12 (4.1)	1 (1.4)	2 (<1)	0	16 (1.7)	4 (1.1)	30 (2.6)	4 (1.1)
	Pain NOS	7 (1.6)	0	7 (2.4)	0	2 (<1)	0	3 (<1)	2 (<1)	9 (<1)	2 (<1)
	Pyrexia	20 (4.5)	4 (3.0)	18 (6.2)	4 (5.8)	12 (4.7)	4 (3.7)	19 (2.0)	6 (1.6)	31 (2.7)	6 (1.6)
	Thirst	39 (8.8)	1 (<1)	9 (3.1)	0	31 (12.0)	1 (<1)	40 (4.2)	8 (2.2)	53 (4.6)	8 (2.2)
Hepatobiliary disorders		4 (<1)	0	4 (1.4)	0	1 (<1)	0	5 (<1)	1 (<1)	9 (<1)	1 (<1)
Immune system disorders		3 (<1)	0	3 (1.0)	0	3 (1.2)	0	7 (<1)	3 (<1)	7 (<1)	3 (<1)
Infections and infestations		55 (12.4)	11 (8.3)	55 (18.8)	11 (16.0)	29 (11.2)	11 (10.1)	141 (15.0)	52 (14.0)	185 (16.1)	52 (14.0)
	Oral candidiasis	5 (1.1)	0	5 (1.7)	0	0	0	1 (<1)	0	6 (<1)	0
	Pneumonia NOS	15 (3.4)	1 (<1)	15 (5.1)	1 (1.4)	10 (3.9)	1 (<1)	16 (1.7)	6 (1.6)	26 (2.3)	6 (1.6)
	Sepsis NOS	5 (1.1)	0	5 (1.7)	0	3 (1.2)	0	5 (<1)	3 (<1)	8 (<1)	3 (<1)
	URI NOS	1 (<1)	1 (<1)	1 (<1)	1 (1.4)	1 (<1)	1 (<1)	19 (2.0)	4 (1.1)	20 (1.7)	4 (1.1)
Injury, poisoning and procedural complications		14 (3.1)	3 (2.3)	13 (4.5)	3 (4.3)	7 (2.7)	3 (2.8)	29 (3.1)	10 (2.7)	44 (3.8)	10 (2.7)
	Combined injury terms[13]	4 (<1)	0	3 (1.0)	0	2 (<1)	0	19 (2.0)	4 (1.1)	28 (2.4)	4 (1.1)
Investigations		50 (11.2)	5 (3.8)	50 (17.1)	5 (7.2)	38 (14.7)	5 (4.6)	131 (13.9)	32 (8.6)	150 (13.1)	32 (8.6)
	Blood alkaline phosphatase increased	3 (<1)	0	3 (1.0)	0	2 (<1)	0	3 (<1)	1 (<1)	4 (<1)	1 (<1)
	Blood CPK increased	3 (<1)	0	3 (1.0)	0	1 (<1)	0	6 (<1)	0	8 (<1)	4 (1.1)
	Blood magnesium decreased	4 (<1)	0	4 (1.4)	0	4 (1.6)	0	4 (<1)	0	4 (<1)	0
	Heart sounds abnormal	3 (<1)	0	3 (1.0)	0	3 (1.2)	0	5 (<1)	0	5 (<1)	0
	Hemoglobin decreased	3 (<1)	0	3 (1.0)	0	2 (<1)	0	6 (<1)	0	8 (<1)	0
	Liver function test abnormal	3 (<1)	0	3 (1.0)	0	2 (<1)	0	9 (1.0)	2 (<1)	11 (<1)	2 (<1)
	Weight decreased	3 (<1)	0	3 (1.0)	0	2 (<1)	0	4 (<1)	1 (<1)	6 (<1)	1 (<1)

Table 7.1.5.4.1 Adverse Events and Event Term Groupings Occurring in at Least 1% of Conivaptan Patients, and at a Frequency at Least 1% Higher for Conivaptan Patients than for Placebo Patients

		All IV[1]		"Full Dose" IV[2] in Pts		"Full Dose" Controlled IV[6]		All Controlled Phase 2/3[7]		Overall Safety[3]	
System Organ Class	MedDRA Term (or Combined MedDRA Terms)	Coni N=445 n[17](%)	Pbo N=132 n[17](%)	Coni N=292 n[17](%)	Pbo N=69 n[17](%)	Coni N=258 n[17](%)	Pbo N=109 n[17](%)	Coni N=942 n[17](%)	Pbo N=372 n[17](%)	Coni N=1148 n[17](%)	Pbo N=372 n[17](%)
	White blood cell count increased	3 (<1)	0	3 (1.0)	0	3 (1.2)	0	4 (<1)	0	5 (<1)	0
Metabolism and nutrition disorders		97 (21.8)	17 (12.9)	97 (33.2)	17 (24.6)	57 (22.1)	17 (15.6)	131 (13.9)	46 (12.4)	192 (16.8)	46 (12.4)
	Dehydration	7 (1.6)	1 (<1)	7 (2.4)	1 (1.4)	3 (1.2)	1 (<1)	9 (1.0)	1 (<1)	15 (1.3)	1 (<1)
	Hyperglycemia	13 (2.9)	0	13 (4.5)	0	7 (2.7)	0	20 (2.1)	6 (1.6)	27 (2.4)	6 (1.6)
	Hyperkalemia	15 (3.4)	3 (2.3)	15 (5.1)	3 (4.3)	11 (4.3)	3 (2.8)	22 (2.3)	5 (1.3)	33 (2.9)	5 (1.3)
	Hypernatremia	8 (1.8)	0	8 (2.7)	0	7 (2.7)	0	7 (<1)	0	8 (<1)	0
	Hypoglycemia NOS	11 (2.5)	0	11 (3.8)	0	4 (1.6)	0	9 (1.0)	3 (<1)	17 (1.5)	3 (<1)
	Hypokalemia	43 (9.7)	10 (7.6)	43 (14.7)	10 (14.5)	19 (7.4)	10 (9.2)	29 (3.1)	14 (3.8)	54 (4.7)	14 (3.8)
	Hyponatremia	13 (2.9)	2 (1.5)	13 (4.5)	2 (2.9)	6 (2.3)	2 (1.8)	8 (<1)	2 (<1)	20 (1.7)	2 (<1)
	Combined electrolyte depletion terms[11]	62 (13.9)	14 (10.6)	62 (21.2)	14 (20.3)	31 (12.0)	14 (12.8)	46 (4.9)	19 (5.1)	81 (7.1)	19 (5.1)
	Combined hypovolemia-related terms[12]	55 (12.4)	20 (15.2)	55 (18.8)	11 (20.3)	33 (12.8)	10 (9.2)	87 (9.2)	31 (8.3)	137 (11.9)	31 (8.3)
Musculoskeletal and connective tissue disorders		32 (7.2)	4 (3.0)	30 (10.3)	4 (5.8)	23 (8.9)	4 (3.7)	89 (9.4)	24 (6.5)	114 (9.9)	24 (6.5)
	Arthralgia	8 (1.8)	1 (<1)	8 (2.7)	1 (1.4)	5 (1.9)	1 (<1)	16 (1.7)	9 (2.4)	20 (1.7)	9 (2.4)
	Back pain	5 (1.1)	1 (<1)	5 (1.7)	1 (1.4)	5 (1.9)	1 (<1)	17 (1.8)	4 (1.1)	20 (1.7)	4 (1.1)
	Muscle cramp	3 (<1)	0	3 (1.0)	0	3 (1.2)	0	13 (1.4)	4 (1.1)	15 (1.3)	4 (1.1)
	Pain in extremity	12 (2.7)	0	10 (3.4)	0	9 (3.5)	0	22 (2.3)	4 (1.1)	26 (2.3)	4 (1.1)
Neoplasms, benign, malignant and unspecified		4 (<1)	0	4 (1.4)	0	1 (<1)	0	8 (<1)	1 (<1)	15 (1.3)	1 (<1)
Nervous system disorders		56 (12.6)	11 (8.3)	40 (13.7)	11 (16.0)	29 (11.2)	11 (10.1)	108 (11.5)	37 (9.9)	147 (12.8)	37 (9.9)
	Dizziness	10 (2.2)	3 (2.3)	10 (3.4)	3 (4.3)	5 (1.9)	3 (2.8)	41 (4.4)	11 (3.0)	55 (4.8)	11 (2.9)
	Epilepsy NOS	3 (<1)	0	3 (1.0)	0	0	0	0	0	3 (<1)	0
	Headache	32 (7.2)	5 (3.8)	16 (5.5)	5 (7.2)	16 (6.2)	5 (4.6)	36 (3.8)	19 (5.1)	56 (4.9)	19 (5.1)
Psychiatric disorders		37 (8.3)	10 (7.6)	37 (12.7)	10 (14.5)	19 (7.4)	10 (9.2)	54 (5.7)	23 (6.2)	90 (7.8)	23 (6.2)
	Agitation	5 (1.1)	0	5 (1.7)	0	4 (1.6)	0	4 (<1)	0	7 (<1)	0
	Confusional state	12 (2.7)	2 (1.5)	12 (4.1)	2 (2.9)	3 (1.2)	2 (1.8)	7 (<1)	3 (<1)	19 (1.7)	3 (<1)
	Restlessness	4 (<1)	0	4 (1.4)	0	3 (1.2)	0	6 (<1)	0	7 (<1)	0
Renal and urinary disorders		77 (17.3)	10 (7.6)	58 (19.9)	10 (14.5)	40 (15.5)	10 (9.2)	81 (8.6)	25 (6.7)	123 (10.7)	25 (6.7)
	Dysuria	4 (<1)	0	4 (1.4)	0	2 (<1)	0	5 (<1)	1 (<1)	8 (<1)	1 (<1)
	Leukocyturia	4 (<1)	0	4 (1.4)	0	3 (1.2)	0	3 (<1)	0	4 (<1)	0
	Pollakiuria	19 (4.3)	0	0	0	12 (4.7)	0	6 (<1)	2 (<1)	17[3] (1.5)	0
	Polyuria	10 (2.2)	0	10 (3.4)	0	1 (<1)	0	8 (<1)	0	17 (1.5)	0
	Renal failure NOS	12 (2.7)	2 (1.5)	12 (4.1)	2 (2.9)	9 (3.5)	2 (1.8)	25 (2.7)	5 (1.3)	35 (3.0)	5 (1.3)
	Renal failure acute on chronic	3 (<1)	0	3 (1.0)	0	1 (<1)	0	1 (<1)	0	3 (<1)	0
	Renal impairment NOS	3 (<1)	0	3 (1.0)	0	2 (<1)	0	4 (<1)	0	5 (<1)	0
	Combined renal failure terms[14]	24 (5.4)	5 (3.8)	24 (8.2)	5 (7.2)	14 (5.4)	5 (4.6)	14 (3.1)	5 (3.8)	52 (4.5)	10 (2.7)
	Urinary retention	5 (1.1)	0	5 (1.7)	0	2 (<1)	0	4 (<1)	0	8 (<1)	0
Reproductive system and breast disorders		3 (<1)	0	3 (1.0)	0	1 (<1)	0	15 (1.6)	3 (<1)	17 (1.5)	3 (<1)
Respiratory, thoracic and											

Table 7.1.5.4.1 Adverse Events and Event Term Groupings Occurring in at Least 1% of Conivaptan Patients, and at a Frequency at Least 1% Higher for Conivaptan Patients than for Placebo Patients

		All IV[1]		"Full Dose" IV[2] in Pts		"Full Dose" Controlled IV[6]		All Controlled Phase 2/3[7]		Overall Safety[3]	
System Organ Class	MedDRA Term (or Combined MedDRA Terms)	Coni N=445 n[17](%)	Pbo N=132 n[17](%)	Coni N=292 n[17](%)	Pbo N=69 n[17](%)	Coni N=258 n[17](%)	Pbo N=109 n[17](%)	Coni N=942 n[17](%)	Pbo N=372 n[17](%)	Coni N=1148 n[17](%)	Pbo N=372 n[17](%)
mediastinal disorders											
	Bronchitis NOS	3 (<1)	0	3 (1.0)	0	1 (<1)	0	11 (1.2)	1 (<1)	14 (1.2)	1 (<1)
	Cough	9 (2.0)	4 (3.0)	9 (3.1)	4 (5.8)	6 (2.3)	4 (3.7)	21 (2.2)	8 (2.2)	29 (2.5)	8 (2.2)
	Dyspnea exacerbated	25 (5.6)	8 (6.0)	25 (8.6)	8 (11.6)	25 (9.7)	8 (7.3)	50 (5.3)	14 (3.8)	51 (4.4)	14 (3.8)
	Pulmonary edema NOS	3 (<1)	0	3 (1.0)	0	3 (1.2)	0	4 (<1)	0	4 (<1)	0
	Pulmonary embolism	0	0	0	0	0	0	1 (<1)	1 (<1)	13 (1.1)	3 (<1)
	Respiratory failure	4 (<1)	0	4 (1.4)	0	2 (<1)	0	2 (<1)	1 (<1)	5 (<1)	1 (<1)
Skin and subcutaneous disorders		27 (6.1)	4 (3.0)	24 (8.2)	4 (5.8)	16 (6.2)	4 (3.7)	45 (4.8)	14 (3.8)	61 (5.3)	14 (3.8)
	Contusion	3 (<1)	0	3 (1.0)	0	2 (<1)	0	4 (<1)	0	5 (<1)	0
	Erythema	9 (2.0)	0	6 (2.0)	0	4 (1.6)	0	4 (<1)	0	6[3] (<1)	0
Vascular disorders		76 (17.1)	12 (9.1)	75 (25.7)	11 (16.0)	41 (15.9)	12 (11.0)	76 (8.1)	32 (8.6)	130 (11.3)	32 (8.6)
	Htn NOS	14 (3.1)	0	14 (4.8)	0	4 (1.6)	0	44 (4.7)	21 (5.6)	18 (1.6)	1 (<1)
	Orthostatic hypotension	15 (3.8)	0	15 (5.1)	0	5 (1.9)	0	10 (1.1)	4 (1.1)	21 (1.8)	4 (1.1)
	Phlebitis NOS	16 (3.6)	1 (<1)	16 (5.5)	1 (1.4)	8 (3.1)	1 (<1)	8 (<1)	2 (<1)	17 (1.5)	2 (<1)
	Thrombophlebitis	3 (<1)	0	3 (1.0)	0	3 (1.2)	0	3 (<1)	0	3 (<1)	0

1 Includes Studies 027, 071, 080, 016, 017, 023, 025, 032, 038, 044
2 Includes Studies 027, 071, 080
3 Includes Studies 016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 031, 032, 033, 034, 038, 043, 044, 047, 071, 080. NB: because the full safety population does not include Studies 074, 079, and 083 (IV studies in healthy volunteers), the total number of events in the "full safety" population may in some cases be less than that seen in the "full IV" population, e.g. for infusion site reactions et al.
4 Includes event terms coagulopathy, hemorrhagic disorder, conjunctival hemorrhage, eye hemorrhage NOS, retinal hemorrhage, duodenitis hemorrhagic, gastric hemorrhage, GI hemorrhage NOS, gingival bleeding, hemorrhoidal hemorrhage, melena, rectal hemorrhage, upper GI hemorrhage, catheter site hemorrhage, implant site hemorrhage, injection site hemorrhage, hematuria traumatic, postprocedural hemorrhage, CVA, hemorrhagic stroke, hematuria, epistaxis, shock hemorrhagic
5 Includes event terms cardiac failure NOS, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiomyopathy NOS, congestive cardiac failure aggravated, congestive cardiomyopathy, right ventricular failure, ventricular dysfunction
6 Includes Studies 027, 071, 079
7 Includes Studies 017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071
8 Includes event terms arrhythmia NOS, A fib, A flutter, atrial tachycardia, bradyarrhythmia, bradycardia, nodal rhythm, sick sinus syndrome, sinus arrhythmia, sinus bradycardia, sinus tachycardia, SV arrhythmia NOS, SVT, tachycardia NOS, ventricular arrhythmia NOS, ventricular bigeminy, V fib, V tach, ventricular trigeminy
9 Includes event terms A fib, A flutter, atrial tachycardia
10 Includes event terms cannula site reaction, infusion related reaction, infusion site erythema, infusion site induration, infusion site inflammation, infusion site edema, infusion site pain, infusion site phlebitis, infusion site reaction, infusion site swelling, infusion site tenderness, infusion site warmth, injection site bruising, injection site cellulitis, injection site discomfort, injection site erythema, injection site hemorrhage, injection site inflammation, injection site pain, injection site phlebitis, injection site pruritus, injection site reaction NOS, injection site swelling, injection site tenderness, injection site thrombosis, infusion site infection, injection site infection, jugular vein thrombosis, phlebitis NOS, phlebitis superficial, thrombophlebitis, thrombophlebitis superficial
11 Includes event terms blood magnesium decreased, blood potassium decreased, electrolyte depletion, hypokalemia, hypomagnesemia, hypophosphatemia
12 Includes event terms cardiogenic shock, fall, blood pressure decreased, dehydration, hypovolemia, syncope, hypotension NOS, orthostatic hypotension
13 Includes event terms accident NOS, ankle fracture, caustic injury, compression fracture, eye injury NOS, fall, foot fracture, hand fracture, head injury, joint sprain, limb injury NOS, rib fracture, pneumothorax traumatic, traumatic hematoma, wound NOS
14 Includes acute prerenal failure, anuria, azotemia, renal failure NOS, renal failure acute, renal failure acute on chronic, renal failure chronic
15 Not reported
16 Although 2 events are reported for the full IV population in Table 2.7.4-10.6A, only 1 event is reported for the full safety population in Table 1, Safety Update
17 n = # events; % = # events per 100 pts. Within a combined event category, a patient may have had more than one event within that category, e.g. injection site infection and injection site pain. Therefore, the percentage presented may not correspond with the actual percentage of patients who experienced any event.
Source: Applicant's Tables 2.7.4-9.6F, 2.7.4-9.6B, 2.7.4-9.6A, Summary of Intravenous Safety; Table 1, Safety Update; Table 2.7.4-9.P23_ALL, email from Dr. Raineri, Astellas Reg Affairs, 2 Nov 05

For the "full dose" controlled IV and overall controlled Phase 2/3 (IV + oral) populations, the following events occurred at a rate ≥2% higher in the conivaptan group than in the placebo group for one or both of these populations.

Table 7.1.5.4.2 Adverse Events and Event Term Groupings Occurring at a Frequency at Least 2% Higher for Conivaptan Groups than Placebo Groups, "Full Dose" Controlled IV and Overall Controlled Phase 2/3 (Oral + IV) Populations

		"Full Dose" Controlled IV		Controlled Phase 2/3 (Oral + IV)	
System Organ Class	**MedDRA Term (or Combined MedDRA Terms)[1]**	**Coni N = 258 n[2] (%)**	**Pbo N = 109 n[2] (%)**	**Coni N = 942 n[2] (%)**	**Pbo N = 372 n[2] (%)**
Cardiac disorders					
	Atrial fibrillation	6 (2.3)	0	13 (1.4)	2 (0.5)
	Combined cardiac failure terms	8 (3.1)	1 (0.9)	43 (4.6)	15 (4.0)
	Combined atrial arrhythmia terms	10 (3.9)	0	24 (2.5)	3 (0.8)
GI disorders					
	Dry mouth	9 (3.5)	2 (1.8)	16 (1.7)	1 (0.3)
General disorders and administration site conditions		140 (54.3)	19 (17.4)	250 (26.5)	65 (17.5)
	Aesthenia	7 (2.7)	0	21 (2.2)	4 (1.1)
	Infusion site erythema	10 (3.9)	0	4 (0.4)	0
	Infusion site pain	28 (10.9)	1 (0.9)	6 (0.6)	1 (0.3)
	Infusion site phlebitis	41 (15.9)	3 (2.8)	37 (3.9)	3 (0.8)
	Infusion site reaction	9 (3.5)	0	9 (1.0)	0
	Infusion site swelling	21 (8.1)	2 (1.8)	3 (0.3)	1 (0.3)
	Injection site cellulitis	9 (3.5)	0	9 (1.0)	0
	Combined injection and infusion site terms	169 (65.5)	9 (8.3)	119 (12.6)	10 (2.7)
	Thirst	31 (12.0)	1 (0.9)	40 (4.2)	8 (2.2)
Infections and infestations					
	Pneumonia NOS	10 (3.9)	1 (0.9)	16 (1.7)	6 (1.6)
Investigations		38 (14.7)	5 (4.6)	131 (13.9)	32 (8.6)
Metabolism and nutrition disorders		57 (22.1)	17 (15.6)	131 (13.9)	46 (12.4)
	Hyperglycemia	7 (2.7)	0	20 (2.1)	6 (1.6)
	Hypernatremia	7 (2.7)	0	7 (0.7)	0
	Combined hypovolemia-related terms	33 (12.8)	10 (9.2)	87 (9.2)	31 (8.3)
Musculoskeletal and connective tissue disorders		23 (8.9)	4 (3.7)	89 (9.4)	24 (6.5)
	Pain in extremity	9 (3.5)	0	22 (2.3)	4 (1.1)
Renal and urinary disorders		40 (15.5)	10 (9.2)	81 (8.6)	25 (6.7)
	Pollakiuria	12 (4.7)	0	6 (0.6)	2 (0.5)
Respiratory and mediastinal disorders					
	Dyspnea exacerbated	25 (9.7)	8 (7.3)	50 (5.3)	14 (3.8)
Skin and subcutaneous disorders		16 (6.2)	4 (3.7)	45 (4.8)	14 (3.8)
Vascular disorders		41 (15.9)	12 (11.0)	76 (8.1)	32 (8.6)
	Phlebitis NOS	8 (3.1)	1 (0.9)	8 (0.8)	2 (0.5)

1 See footnote to Table 7.1.5.4.1 for details of terms included in event term groupings
2 For individual events and Total System Organ Class events, % = # patients with events/100 pts. For event term groupings, % = summed events/100 pts
Source: Table 7.1.5.4.1 above

The populations in Table 7.1.5.4.1 raised concerns for event term groupings of atrial arrhythmias, bleeding events, cardiac failure events, electrolyte depletion events, infusion site events, injury events, hypovolemia-related events and renal failure events. These events will be further clarified in Tables 7.1.5.4.3-9.

In the "full dose" controlled IV and overall controlled Phase 2/3 (oral + IV) populations, the frequency of events in the conivaptan group was ≥2% higher than in the placebo group for the following additional individual terms and System Organ Classes:

- System Organ Class General Disorders and Administration Site Conditions (contr IV, and contr IV + oral; largely accounted for by excess infusion site reactions)
- Thirst ("full dose" contr IV, and contr IV + oral)
- Infusion site phlebitis ("full dose" contr IV, and contr IV + oral)
- System Organ Class Musculoskeletal and Connective Tissue Disorders ("full dose" contr IV, and contr IV + oral; no one term predominates)
- Infusion site erythema ("full dose" contr IV)
- Infusion site pain ("full dose" contr IV)
- Infusion site reaction ("full dose" contr IV)
- Infusion site swelling ("full dose" contr IV)
- Injection site cellulitis ("full dose" contr IV)
- Aesthenia ("full dose" contr IV)
- Atrial fibrillation ("full dose" contr IV)
- Pneumonia NOS ("full dose" contr IV)
- System Organ Class Investigations ("full dose" contr IV; no one term predominates)
- System Organ Class Metabolism and Nutrition Disorders ("full dose" contr IV)
- Hyperglycemia ("full dose" contr IV)
- Hypernatremia ("full dose" contr IV)
- System Organ Class Renal and Urinary Disorders ("full dose" contr IV)
- Pollakiuria ("full dose" contr IV)
- Dyspnea exacerbated ("full dose" contr IV)
- System Organ Class Skin and Subcutaneous Tissue Disorders ("full dose" contr IV; infusion-site-related events contribute)
- System Organ Class Vascular Disorders ("full dose" contr IV; infusion-related phlebitides contribute)
- Phlebitis NOS ("full dose" contr IV)

Many of these events are infusion-site-related, and are discussed in Section 7.1.3.3.3. Thirst and pollakiuria are expected physiologic effects of the drug. The occurrence of hypernatremia is included in the definition of "overly rapid correction of serum sodium", and is discussed in Section 7.1.3.3.2. Hyperglycemia may be related to the D5W in which conivaptan is diluted and is discussed further in Section 7.1.7. Atrial fibrillation and other atrial arrhythmias are further discussed following Table 7.1.5.4.9.

Pneumonia is an event of interest because there was a preclinical signal of aspiration of food in laboratory animals. In clinical studies, one death occurred following aspiration of food material. Drying of mucous membranes and/or inspissation of secretions, with swallowing difficulty or decreased barrier to infection, are plausible mechanisms, but were not specifically noted in the clinical program.

"Dyspnea exacerbated" may be related to worsening of congestive heart failure; the majority of patients who experienced "dyspnea exacerbated" had underlying congestive heart failure.

In order to avoid overcounting of events, the clinical reviewer requested (3 Nov 05) that the applicant provide the number and percentage of patients who had any event in each of the above combined event term groupings, for the major IV and combined IV + oral, overall and controlled populations. On 9 Nov 05, the applicant provided these adverse event term grouping tables in an email. The following tables show the number and percentage of patients who experienced any event within an event term grouping.

Table 7.1.5.4.3 Treatment-Emergent Adverse Events by Event Grouping, Overall Safety Population (IV + Oral)[1]

Event Grouping[2]	Coni N = 1148 n[3] (%)	Pbo N = 372 n[3] (%)
Atrial arrhythmia events	28 (2.4)	2 (<1)
Bleeding events	46 (4.0)	11 (3.0)
Cardiac failure events	75 (6.5)	15 (4.0)
Electrolyte depletion events	70 (6.1)	16 (4.3)
Infusion site events	198 (17.2)	10 (2.7)
Injury events	27 (2.4)	4 (1.1)
Potential hypovolemia-related events	113 (9.8)	31 (8.3)
Renal failure events	52 (4.5)	9 (2.4)

1 Includes studies 016, 017, 020, 022, 023, 024, 026, 027, 031, 032, 033, 034, 038, 043, 044, 047, 071, 080
2 For event terms included in event term groupings, see footnote to Table 7.1.5.4.1 above
3 n = number of patients who experienced any event within event grouping
Source: Applicant's Table 25.1, email from applicant 9 Nov 05

Table 7.1.5.4.4 Treatment-Emergent Adverse Events by Event Grouping, All Placebo-Controlled Phase 2/3 Studies (IV + Oral)[1]

Event Grouping[2]	Coni N = 445 n[3] (%)	Pbo N = 132 n[3] (%)
Atrial arrhythmia events	10 (2.2)	0
Bleeding events	13 (2.9)	5 (3.8)
Cardiac failure events	13 (2.9)	3 (2.3)
Electrolyte depletion events	31 (7.0)	12 (9.1)
Infusion site events	100 (22.5)	8 (6.1)
Injury events	1 (<1)	0
Potential hypovolemia-related events	34 (7.6)	13 (9.8)
Renal failure events	14 (3.1)	5 (3.8)

1 Includes studies 017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 047, 071
2 For event terms included in event term groupings, see footnote to Table 7.1.5.4.1 above
3 n = number of patients who experienced any event within event grouping
Source: Applicant's Table 25.2, email from applicant 9 Nov 05

Table 7.1.5.4.5 Treatment-Emergent Adverse Events by Event Grouping, "Full Dose" IV Safety Population[1]

Event Grouping[2]	Coni N = 404 n[3] (%)	Pbo N = 109 n[3] (%)
Atrial arrhythmia events	16 (4.0)	0
Bleeding events	19 (4.7)	4 (3.7)
Cardiac failure events	18 (4.5)	1 (0.9)
Electrolyte depletion events	53 (13.1)	11 (10.1)
Infusion site events	190 (47.0)	7 (6.4)
Injury events	3 (<1)	0
Potential hypovolemia-related events	45 (11.1)	11 (10.1)
Renal failure events	24 (5.9)	5 (4.6)

1 Includes studies 027, 071, 074, 079, 080, 083
2 For event terms included in event term groupings, see footnote to Table 7.1.5.4.1 above
3 n = number of patients who experienced any event within event grouping
Source: Applicant's Table 2.7.4-25.6A, email from applicant 9 Nov 05

Table 7.1.5.4.6 Treatment-Emergent Adverse Events by Event Grouping, "Full-Dose" IV Studies[1] in Patients

Event Grouping[2]	Coni N = 292 n[3] (%)	Pbo N = 69 n[3] (%)
Atrial arrhythmia events	16 (5.5)	0
Bleeding events	19 (6.5)	4 (5.8)
Cardiac failure events	18 (6.2)	1 (1.4)
Electrolyte depletion events	53 (18.2)	11 (15.9)
Infusion site events	180 (61.6)	7 (10.1)
Injury events	3 (1.0)	0
Potential hypovolemia-related events	45 (15.4)	11 (15.9)
Renal failure events	24 (8.2)	5 (7.2)

1 Includes studies 027, 071, 080
2 For event terms included in event term groupings, see footnote to Table 7.1.5.4.1 above
3 n = number of patients who experienced any event within event grouping
Source: Applicant's Table 2.7.4-25.6B, email from applicant 9 Nov 05

Table 7.1.5.4.7 Treatment-Emergent Adverse Events by Event Grouping, "Full Dose" Controlled IV Studies[1]

Event Grouping[2]	Coni N = 258 n[3] (%)	Pbo N = 109 n[3] (%)
Atrial arrhythmia events	9 (3.5)	0
Bleeding events	9 (3.5)	4 (3.7)
Cardiac failure events	9 (3.5)	1 (<1)
Electrolyte depletion events	27 (10.5)	11 (10.1)
Infusion site events	91 (35.3)	7 (6.4)
Injury events	1 (<1)	0
Potential hypovolemia-related events	29 (11.2)	11 (10.1)
Renal failure events	14 (5.4)	5 (4.6)

1 Includes studies 027, 071, 079
2 For event terms included in event term groupings, see footnote to Table 7.1.5.4.1 above
3 n = number of patients who experienced any event within event grouping
Source: Applicant's Table 2.7.4-25.6B, email from applicant 9 Nov 05

Table 7.1.5.4.8 Treatment-Emergent Adverse Events by Event Grouping, "Full Dose" IV Hyponatremia Studies[1]

Event Grouping[2]	Coni N = 170 n[3] (%)	Pbo N = 29 n[3] (%)
Atrial arrhythmia events	7 (4.1)	0
Bleeding events	10 (5.9)	2 (6.9)
Cardiac failure events	14 (8.2)	1 (3.4)
Electrolyte depletion events	29 (17.1)	2 (6.9)
Infusion site events	115 (67.6)	2 (6.9)
Injury events	2 (1.2)	0
Potential hypovolemia-related events	31 (18.2)	4 (13.8)
Renal failure events	15 (8.8)	1 (3.4)

1 Includes studies 027, 080
2 For event terms included in event term groupings, see footnote to Table 7.1.5.4.1 above
3 n = number of patients who experienced any event within event grouping
Source: Applicant's Table 2.7.4-25.6D, email from applicant 9 Nov 05

Table 7.1.5.4.9 Treatment-Emergent Adverse Events by Event Grouping, "Full Dose" IV CHF Study 071

Event Grouping[1]	Coni N = 122 n[2] (%)	Pbo N = 40 n[2] (%)
Atrial arrhythmia events	9 (7.4)	0
Bleeding events	9 (7.4)	2 (5.0)
Cardiac failure events	4 (3.3)	0
Electrolyte depletion events	24 (19.7)	9 (22.5)
Infusion site events	65 (53.3)	5 (12.5)
Injury events	1 (<1)	0
Potential hypovolemia-related events	14 (11.5)	7 (17.5)
Renal failure events	9 (7.4)	4 (10.0)

1 For event terms included in event term groupings, see footnote to Table 7.1.5.4.1 above
2 n = number of patients who experienced any event within event grouping
Source: Applicant's Table 2.7.4-25.6E, email from applicant 9 Nov 05

In the overall safety (IV + oral) population, all these event term groupings occurred at a higher numerical rate among conivaptan-treated patients than among placebo-treated patients (see Table 7.1.5.4.3). However, this was not true in all the above populations (Tables 7.1.5.4.4-7.1.5.4.9). Each event grouping is discussed in the following paragraphs.

Atrial Arrhythmia Events

Atrial arrhythmia events occurred at a higher numerical rate among conivaptan-treated patients than among placebo-treated patients for all the populations examined; there were a total of 28 events among conivaptan treated patients (2.4%) compared to 2 events among placebo-treated patients (0.5%) in the overall safety population (IV + oral, CHF + hyponatremia, full dose + lower exposure). In the group of "full dose" IV studies in patients, 16/292 (5.5%) of conivaptan-treated patients developed atrial arrhythmias, and no placebo-treated patients did. Nine of these events occurred in Study 080, an open-label IV hyponatremia safety study; and seven occurred in Study 071, a placebo-controlled IV CHF efficacy and safety study. It is unclear why 7.4% of patients in controlled Study 071 had atrial arrhythmias, and no placebo patients did. Congestive heart failure itself is a strong predisposing factor to atrial fibrillation, due at least in part to

activation of atrial stretch receptors. Of the 28 conivaptan patients who developed atrial arrhythmias in the overall safety population, 5 also had events potentially related to exacerbation of congestive heart failure (one event each of CHF aggravated, congestive cardiomyopathy, cardiomyopathy NOS, pulmonary edema and increased central venous pressure). A common precipitating factor for atrial fibrillation is electrolyte depletion, and this may well have played a role here; 8/28 conivaptan patients who had atrial arrhythmias also had reported adverse events of hypokalemia, and 1/28 had hypomagnesemia (total 9/28 conivaptan patients with atrial arrhythmias who also had electrolyte depletion). Four of these patients with atrial arrhythmias and electrolyte depletion were in Study 071 (3 decr K, 1 decr Mg), and 3 were in Study 080 (3 decr K). In the overall safety population, the total number of conivaptan patients who developed hypokalemia was 54/1148 (4.7%); among the 28 conivaptan patients who developed atrial arrhythmias, the percentage of patients with hypokalemia was 28.6% (8/28). It appears likely that electrolyte depletion, particularly hypokalemia, played a role in the increased numerical rate of atrial arrhythmias in conivaptan-treated patients compared to placebo-treated patients.

Overall, conivaptan appears to be associated with a slightly increased risk for atrial arrhythmia events. This conclusion is based on a higher incidence of these events in all populations examined, including the overall controlled Phase 2/3 population and the controlled IV population. Hypokalemia may have played a role in these atrial arrhythmias.

Bleeding Events

As mentioned earlier, bone marrow toxicity was a finding in preclinical studies; in clinical trials, conivaptan patients did not develop cytopenias more often than did placebo patients. However, for some populations, bleeding events appeared to occur more frequently for conivaptan patients than for placebo patients, when examining events per 100 patients. Tables 7.1.5.4.3-7.1.5.4.9 look at event groupings by patients, and identify the number and percentage of patients who had any bleeding event. Bleeding events are also of interest because the vasopressin DDAVP, a synthetic polypeptide that is structurally similar to vasopressin, has *procoagulant* activity, and is used in the treatment of von Willebrand's disease and Hemophilia A.

While bleeding events occurred at a somewhat higher numerical rate among conivaptan patients in the overall safety (IV + oral) and "full dose" IV populations, these events did not occur more commonly among conivaptan patients in the controlled Phase 2/3 (oral + IV), or the "full dose" controlled IV populations. In Study 071, the "full dose" controlled IV CHF study, bleeding events occurred in 9/122 (7.4%) of conivaptan-treated patients and 2/40 (5.0%) of placebo-treated patients.

Overall, it appears that conivaptan is not associated with an increased risk of adverse bleeding events. This conclusion is based on a lack of excess of these events in the overall controlled population and the IV controlled population. However, there was a somewhat higher numerical rate of bleeding events for conivaptan patients than for placebo patients in the "full dose" IV CHF study.

Cardiac Failure Events

Adverse events of cardiac failure occurred more frequently numerically among conivaptan-treated patients than among placebo-treated patients in the overall safety (IV + oral), "full dose" IV, "full-dose" IV in patients, "full dose" IV hyponatremia, "full dose" IV CHF, and "full dose" controlled IV populations. However, in the overall controlled Phase 2/3 (IV + oral) studies (which included patients with lower exposure), this excess frequency did not occur. The clinical reviewer finds the increased numerical frequency of cardiac failure events in the "full dose" controlled IV population concerning [coni 9/258 (3.5%), pbo 1/109 (0.9%)]. In Study 071, the "full dose" controlled IV CHF study, 4/122 (3.3%) of conivaptan patients had cardiac failure adverse events, and no placebo patients did. Please see Section 7.1.3.3.5 for further discussion of adverse events occurring with greater frequency in patients with underlying congestive heart failure; when considering all patients with an underlying diagnosis of congestive heart failure, adverse cardiac failure events occurred with significantly greater frequency among patients treated with conivaptan in the dose proposed for labeling (40 mg/day IV; 7.1% of conivaptan patients vs 1.8% of IV placebo patients). There is a signal of increased risk for cardiac failure events with conivaptan when used in patients with underlying congestive heart failure.

Electrolyte Depletion Events

Electrolyte depletion events (decreased potassium, magnesium or phosphate) occurred more often among conivaptan-treated patients than among placebo-treated patients in the overall safety (IV + oral), "full dose" IV safety, IV "full-dose" patient and "full dose" IV hyponatremia populations. However, these events did not occur more commonly among conivaptan-treated patients than among placebo-treated patients in the controlled Phase 2/3 (IV + oral), "full dose" controlled IV, and "full dose" IV CHF (controlled study 071) populations. These events refer to reported adverse events of electrolyte depletion. As discussed in the laboratory section (7.1.7), laboratory findings of decreased mean or excess low outliers for electrolytes were also not seen. Based on the lack of excess of these events and laboratory findings in the overall controlled Phase 2/3 and controlled IV populations, conivaptan does not appear to be associated with an increased risk of adverse events (or laboratory events) of electrolyte depletion, As discussed above, there may be an association between hypokalemia and atrial arrhythmias for conivaptan patients, but overall, adverse events of electrolyte depletion do not appear to occur more often among conivaptan-treated patients than among placebo-treated patients in controlled trials.

Infusion Site Events

In all populations examined, infusion site events occurred with higher frequency among conivaptan patients than among placebo patients. In the "full dose" controlled IV population, this finding exhibited dose dependency, with 27.3% of 40 mg/day patients, 34.9% of 80 mg/day patients, and 57.1% of 120 mg/day patients experiencing one or more infusion site reactions. The concentration dependence of infusion site reactions was described in the original NDA; the clinical reviewer is concerned that the high concentrations achieved after the initial 20 mg IV loading dose may contribute to an unnecessarily high incidence of these reactions. The applicant proposes post-marketing study of non-loading-dose regimens, and as mentioned earlier, the clinical reviewer recommends that this be a postmarketing commitment study.

Injury Events

Injury events were of interest as a possible consequence of orthostatic hypotension from volume depletion associated with conivaptan. Injury events occurred more commonly among conivaptan-treated patients than among placebo-treated patients in the overall safety (IV + oral) population, but did not occur at a higher rate among conivaptan patients for the controlled Phase 2/3 (IV + oral), "full dose" IV, "full dose" controlled IV, or any of the other populations considered. Because of the lack of excess of these events in most populations, and especially in the controlled populations, there does not appear to be a clear signal for increased risk of injury with conivaptan.

Potential Hypovolemia-related Events

Please see the footnote to Table 7.1.5.4.1 for the list of events included in this grouping. In general, it included hypotensive, hypovolemic, syncopal, fall and shock events. These events occurred more frequently numerically among conivaptan-treated patients than among placebo-treated patients for the overall safety (IV + oral), "full dose" controlled IV, and "full dose" IV hyponatremia populations. Intravenous conivaptan appears to be associated with an increased risk for hypovolemia- and hypotension- related events. This conclusion is based on a higher incidence of these events in controlled IV populations and the overall IV population.

Renal Failure Events

These events, which included acute prerenal failure, anuria, azotemia, renal failure NOS, renal failure acute, and renal failure acute on chronic, occurred more commonly among conivaptan-treated patients than among placebo-treated patients for the overall safety (IV + oral), "full dose" IV (pts + healthy vols), IV "full-dose" patients, and "full dose" IV hyponatremia populations. Renal failure events did not occur more commonly among conivaptan-treated patients in the overall controlled Phase 2/3 (IV + oral) population. In the controlled "full dose" IV population, renal failure events occurred in 14/258 (5.4%) of conivaptan-treated patients and 5/109 (4.6%) of placebo-treated patients. In the original NDA, concern existed for renal failure events with IV conivaptan, but with the additional resubmission data, these events do not appear to occur in marked excess for conivaptan patients compared to placebo patients. This conclusion is based on the lack of excess of these renal events in the overall controlled population; the slight excess of these events in the controlled full-dose IV population (5.4% coni vs 4.6% pbo) does not represent a strong signal.

7.1.7 Laboratory Findings

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Please see Appendix 10.2 for tables summarizing mean change from baseline for laboratory values for intravenous populations. The following table summarizes findings from those data, and from the data for the full safety population.

There were no clinically notable findings for mean change in hematology or urinalysis parameters. There were some differences between treatment groups for mean change in certain liver function tests, and for plasma glucose.

Table 7.1.7.3.1.1 Mean Change from Baseline for Liver Function and Plasma Glucose Laboratory Tests, Using Last On-Treatment Measurement

	"Full Dose" IV[1]				"Full Dose" IV[2] in Pts				"Full Dose" Contr IV[3]				Overall Safety[4]	
Test (units)	Pbo	Coni 40/day	Coni 80/day	Any Coni Dose	Pbo	Coni 40/day	Coni 80/day	Any Coni Dose	Pbo	Coni 40/day	Coni 80/day	Any Coni Dose	Pbo	All Coni
ALT (g/dL)	-5.2	5.8	6.6	5.6	-5.2	6.0	6.7	5.8	-5.2	27.5	6.6	14.9	-1.3	2.2
Alk Phos (U/L)	0.1	1.8	5.7	2.9	0.1	2.2	5.5	3.3	0.1	2.2	5.6	4.3	-2.1	-1.9
AST (U/L)	-3.8	8.1	-7.8	4.4	-3.4	10.0	-8.0	5.4	-3.8	44.9	47.8	15.3	-1.1	1.9
GGT (U/L)	2.3	5.5	-0.1	2.6	2.3	5.9	-0.2	2.8	2.3	5.5	-0.1	2.6	4.9	1.2
LDH (U/L)	-23.8	-8.8	3.0	-6.7	-23.8	-8.8	3.0	-6.7	-23.8	29.8	ND[5]	17.2	-6.5	-4.1
Total Bili (mg/dL)	0.0	0.0	-0.1	0.0	0.0	0.0	-0.1	0.0	0.0	0.1	-0.1	0.0	0.0	0.0
Glucose (mg/dL)	-0.5	4.2	1.9	3.3	-0.5	5.1	1.8	4.4	-0.5	2.4	1.9	2.6	-6.8	1.0
Glucose fasting (mg/dL)	-22.4	-2.4	10.0	0.1	-22.4	-2.4	10.0	0.1	-22.4	10.3	10.0	10.2	-2.5	3.8

Doses in mg
Sources: Applicant's Tables 2.7.4-14. 6F, 2.7.4-14.6B, 2.7.4-14.6A, Summary of Intravenous Safety; Table 14, Safety Update
1 Studies 027, 071, 074, 079, 080, 083
2 Studies 027, 071, 080
3 Studies 027, 071, 079
4 Studies 016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 031, 032, 033, 034, 038, 043, 044, 047, 071, 080
5 No data provided in applicant's table

In each of the populations presented above, small dose-related mean increases were noted for conivaptan patients for AST, ALT and alkaline phosphatase, while placebo patients had little mean change or a slight decline in these values. These changes were most marked in the 40 mg/day IV group in the set of "full dose" controlled intravenous studies. In this population, mean AST and ALT more than doubled in the conivaptan group (ALT BL 24.0, LOTM incr 27.5; AST BL 30.4, LOTM incr 44.9). The clinical reviewer requested further information regarding this finding and received details in an email from Dr. Donald Raineri on 3 Nov 05. The mean increase in transaminases for the "full dose" controlled IV population was largely driven by 14 patients from Study 071, which was done in patients with congestive heart failure. In this study, apparently by chance, a larger percentage of patients from the conivaptan groups had elevated transaminases at baseline than did patients in the placebo group. These differences

included any baseline transaminase elevation above ULN (18% coni, 15% pbo), any baseline transaminase >3x ULN (13% vs 10%) and any baseline transaminase >10x ULN (4% coni, 0% pbo). Among these patients with elevated baseline values, conivaptan patients were not more likely to have an increase from baseline than were placebo patients [7/18 coni with increase (39%); 4/6 pbo with increase (67%)]. Most patients in the conivaptan groups who had an elevated ALT or AST at baseline had a decline in their values by 48 hours, rather than an increase. Among those conivaptan group patients who had an elevated baseline and a further increase from baseline to end of treatment, 4/7 had declines in transaminases to below their baseline by the 30-day followup, and two remained above baseline at 30-day followup (one had no followup value). Among those placebo patients who had an elevated baseline and a further increase from baseline to end of treatment, 2/4 had declines in transaminases to below their baseline by the 30 day followup, and two remained above baseline at the 30-day followup. The effect of Study 071 on the mean increase in transaminases is shown in the following table, which includes separate columns for combined Studies 027, 080 and 071; 027 + 080; and 071 alone.

Table 7.1.7.3.1.2 Mean Change in Transaminases, Full Dose IV Studies in Patients, Shown With and Without Study 071

Lab	027 + 080 + 071		027 + 080 (Without 071)		071 Alone	
	Coni	Pbo	Coni	Pbo	Coni	Pbo
ALT (IU/L)	5.78	-5.16	1.95	-4.88	20.26	-5.56
AST (IU/L)	5.39	-3.75	-1.23	-1.88	30.26	-6.44

Source: Applicant's Tables 2.7.4-14.6B, 2.7.4-14.6D, 2.7.4-14.6E, Summary of Intravenous Safety

Thus, it appears that, for the "full dose" IV studies, the differences between conivaptan and placebo groups for mean change in transaminases are largely attributable to the conivaptan patients within Study 071. Within that study, a larger percentage of patients in the conivaptan group had baseline transaminase elevations than did patients in the placebo group. These conivaptan patients with baseline elevations were not more likely to increase their values by end of treatment than were placebo patients, and most of the conivaptan patients with baseline elevations in transaminases had declines at end of study. However, one cannot rule out the possibility that CHF patients, with or without baseline hepatic dysfunction, are more vulnerable to hepatic dysfunction when exposed to conivaptan than to placebo. One can only state that baseline differences between the groups make interpretation difficult, and caution is warranted. For the full dose IV population excluding the CHF study 071, there does not appear to be a signal of increased mean transaminases.

Fasting plasma glucose declined significantly in all placebo groups, but increased in all conivaptan groups, for each of the populations in the above table. For intravenous populations, the difference in mean change between groups was 32 mg/dL. This difference between treatment groups was less marked for nonfasting glucose measurements. The reason for this difference between treatment groups is not clear. Conivaptan is diluted in D5W, and it is possible that the continuous infusion of dextrose-containing fluid contributes to this difference. There was no difference between conivaptan and placebo groups for adverse events related to diabetes mellitus.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The following tables summarize those laboratory parameters for which conivaptan groups had more shifts from normal to abnormal than did placebo groups. All liver function tests are also included, because of the higher mean increases noted above in Section 7.1.7.3.1. Low electrolyte values are also presented, because of the question raised in Section 7.1.5 (Common Adverse Events) regarding adverse events of electrolyte depletion.

Table 7.1.7.3.2.1 Number and Percentage of Patients with Treatment-emergent Clinical Chemistry and Hematology Laboratory Values, "Full Dose" IV Populations

	"Full Dose" IV[1]				"Full Dose" Contr IV[3]				All "Full Dose" IV[2]			
Abnl Test (units)	**Pbo n/N (%)**	**Coni 40/day n/N (%)**	**Coni 80/day n/N (%)**	**Any Coni Dose n/N (%)**	**Pbo n/N (%)**	**Coni 40/day n/N (%)**	**Coni 80/day n/N (%)**	**Any Coni Dose n/N (%)**	**Pbo n/N (%)**	**Coni 40/day n/N (%)**	**Coni 80/day n/N (%)**	**Any Coni Dose n/N (%)**
ALT (g/dL) >3x ULN	0	3/241 (1.2)	2/102 (2.0)	5/382 (1.3)	0	3/105 (2.9)	2/102 (2.0)	5/246 (2.0)	0	3/179 (1.6)	1/62 (1.6)	4/280 (1.4)
ALT (g/dL) >10x ULN	0	1/241 (0.4)	2/102 (2.0)	3/382 (0.8)	0	1/105 (1.0)	2/102 (2.0)	3/246 (1.2)	0	1/179 (0.6)	2/62 (3.2)	3/280 (1.1)
Albumin (g/dL) <2.5 g/dL	4/104 (3.8)	9/220 (4.1)	7/102 (6.9)	18/361 (5.0)	4/104 (3.8)	3/105 (2.9)	7/102 (6.9)	12/246 (4.9)	4/64 (6.3)	9/179 (11.3)	7/62 (11.3)	18/280 (6.4)
Alk Phos (U/L) >400 U/L	0	3/251 (1.2)	1/102 (1.0)	5/392 (1.3)	0	1/105 (1.0)	1/102 (1.0)	3/246 (1.2)	0	3/179 (1.7)	1/62 (1.6)	5/280 (1.8)
AST (U/L) >3x ULN	1/105 (1.0)	5/251 (2.0)	1/103 (1.0)	6/392 (1.5)	1/105 (1.0)	3/105 (2.9)	1/103 (1.0)	4/246 (1.6)	1/65 (1.5)	5/179 (2.8)	1/63 (1.6)	6/280 (2.1)
AST (U/L) >10x ULN	0	2/251 (0.8)	1/103 (1.0)	3/392 (0.8)	0	2/105 (1.9)	1/103 (1.0)	3/246 (1.2)	0	2/179 (1.1)	1/63 (1.6)	3/280 (1.1)
BUN:Cr Ratio >20	15/109 (13.8)	53/254 (20.9)	6/105 (5.7)	65/399 (16.3)	15/109 (13.8)	11/108 (10.2)	6/105 (5.7)	23/253 (9.1)	15/69 (21.7)	52/182 (28.6)	6/65 (9.2)	64/287 (22.3)
CPK (IU/L) >3x ULN	0	7/218 (3.2)	1/102 (1.0)	8/357 (2.2)	0	1/104 (1.0)	1/102 (1.0)	2/243 (0.8)	0	7/177 (4.0)	1/62 (1.6)	8/276 (2.9)
Cr (mg/dL) >2 mg/dL	5/109 (4.6)	14/254 (5.5)	11/105 (10.5)	32/399 (8.0)	5/109 (4.6)	9/108 (8.3)	11/105 (10.5)	27/253 (10.7)	5/69 (7.2)	14/182 (7.7)	11/65 (16.9)	32/287 (11.1)
GGT (U/L) >3x ULN	1/74 (1.4)	1/70 (1.4)	1/69 (1.4)	3/168 (1.8)	1/74 (1.4)	1/70 (1.4)	1/69 (1.4)	3/168 (1.8)	1/34 (2.9)	1/29 (3.4)	1/29 (3.4)	3/87 (3.4)
GGT (U/L) >10x ULN	1/74 (1.4)	0	0	1/168 (0.6)	1/74 (1.4)	0	0	1/168 (0.6)	1/34 (2.9)	0	0	1/87 (1.1)
LDH (U/L) >3x ULN	0	0	0	0	0	0	0	0	0	0	0	0
LDH (U/L) >10x ULN	0	0	0	0	0	0	0	0	0	0	0	0
Phosphorus (mg/dL) <2 mg/dL	0	0	1/74 (1.4)	1/189 (0.5)	0	0	1/74 (1.4)	1/189 (0.5)	0	0	0	1/108 (0.9)
Potassium (mEq/L) <3 mg/dL	0	0	0	3/396 (0.8)	0	0	0	0	0	3/180 (1.7)	0	3/284 (1.1)
Sodium (mEq/L) >150 mEq/L	0	3/252 (1.2)	0	5/396 (1.3)	0	0	0	3/250 (1.2)	0	2/180 (1.1)	0	4/284 (1.4)
Total Bili (mg/dL) >2 mg/dL	2/104 (1.9)	8/248 (3.2)	3/102 (2.9)	11/389 (2.8)	2/104 (1.9)	7/104 (6.7)	3/102 (2.9)	10/245 (4.1)	2/64 (3.1)	8/176 (4.5)	3/62 (4.8)	11/277 (4.0)
Glucose (mg/dL)	5/103 (4.9)	13/247 (5.3)	6/101 (5.9)	27/386 (7.0)	5/103 (4.9)	5/103 (4.9)	6/101 (5.9)	19/242 (7.9)	5/63 (7.9)	13/175 (7.4)	6/61 (9.8)	27/274 (9.9)

Table 7.1.7.3.2.1 Number and Percentage of Patients with Treatment-emergent Clinical Chemistry and Hematology Laboratory Values, "Full Dose" IV Populations

	"Full Dose" IV[1]				"Full Dose" Contr IV[3]				All "Full Dose" IV[2]			
Abnl Test (units)	**Pbo n/N (%)**	**Coni 40/day n/N (%)**	**Coni 80/day n/N (%)**	**Any Coni Dose n/N (%)**	**Pbo n/N (%)**	**Coni 40/day n/N (%)**	**Coni 80/day n/N (%)**	**Any Coni Dose n/N (%)**	**Pbo n/N (%)**	**Coni 40/day n/N (%)**	**Coni 80/day n/N (%)**	**Any Coni Dose n/N (%)**
>250 mg/dL												
Uric acid, female (umol/L) >475 umol/L	4/50 (8.0)	10/125 (8.0)	7/45 (15.6)	20/178 (11.2)	4/50 (8.0)	5/50 (10.0)	7/45 (15.6)	15 (103 (14.6)	4/28 (14.3)	10/106 (9.4)	7/26 (26.9)	20/140 (14.3)
Uric acid, male (umol/L) >600 umol/L	1/53 (1.9)	6/90 (6.7)	9/52 (17.3)	20/170 (11.8)	1/53 (1.9)	3/51 (5.9)	9/52 (17.3)	17/131 (13.0)	1/35 (2.9)	6/68 (8.8)	9/31 (29.0)	20/127 (15.7)
Hct (%) <30%	6/106 (5.7)	29/249 (11.6)	9/104 (8.7)	40/392 (10.2)	6/106 (5.7)	5/104 (4.8)	9/104 (8.7)	16/247 (6.5)	6/66 (9.1)	29/177 (16.4)	9/64 (14.1)	40/280 (14.3)

Doses in mg
Sources: Applicant's Tables 2.7.4-16. 6F, 2.7.4-16.6B, 2.7.4-16.6A, 2.7.4-19.6A, 2.7.4-19.6B, 2.7.4-19.6F; Summary of Intravenous Safety; Tables 13 and 14, Safety Update
1 Studies 027, 071, 074, 079, 080, 083
2 Studies 027, 071, 080
3 Studies 027, 071, 079

Table 7.1.7.3.2.2 Number and Percentage of Patients with Treatment-emergent Clinical Chemistry and Hematology Laboratory Values, Overall Safety Population[1]

Test	Range of Clin Concern[2]	Pbo[3] n (%)	All Coni[3] n (%)
ALT	>3x ULN	3 (0.9)	24 (2.2)
ALT	>10x ULN	0	5 (0.5)
Alk Phos	>220 IU/L	31 (9.0)	126 (11.5)
AST	>3x ULN	3 (0.9)	25 (2.3)
AST	>10x ULN	0	6 (0.5)
CPK	>1450 IU/L	0	5 (0.5)
Creatinine	>1.6 mg/dL	80 (22.1)	312 (27.7)
GGT	>3x ULN	13 (11.4)	37 (10.9)
GGT	>10x ULN	2 (1.8)	3 (0.9)
Total bilirubin	>3x ULN	3 (0.8)	12 (1.1)
Total bilirubin	>10x ULN	1 (0.3)	0
Hematocrit	<33% (women); <37% (men)	121 (33.8)	363 (32.5)

1 Includes Studies 016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 031, 032, 033, 034, 038, 043, 044, 047, 071, 080
2 Applicant's identified range of concern; NB- differs from applicant's range of clin concern identified for IV populations
3 Total number of patients who underwent each test not provided; applicant's tables state "percentages are based on the total number of patients with a valid lab result for the given analyte"
Source: Applicant's Tables 16, 17 and 18, Safety Update; ranges from Appdx 1, Safety Update

In each of the IV populations, and in the full safety population, a slightly larger percentage of patients developed treatment-emergent transaminase elevations >3x ULN in the conivaptan groups than did patients in the placebo groups. In Study 071 (CHF), which had a disproportionate effect on mean transaminase levels for the total IV conivaptan population, 1/39 (2.6%) of placebo patients developed an AST of >3x ULN and none developed an ALT >3x

ULN. No placebo patients in Study 071 developed any transaminase >10x ULN. Among conivaptan patients in Study 071, a total of 3 patients developed an ALT and/or an AST >3x ULN. Two conivaptan patients in Study 071 developed an ALT >10x ULN, and one conivaptan patient developed an AST >10x ULN. The conivaptan patients in Study 071 with transaminases >3x ULN and >10x ULN were distributed among the 40 mg/day and 80 mg/day IV groups, with no patients with these changes in the 120 mg/day group. Overall, intravenous conivaptan appears to be associated with a slightly increased risk of development of transaminases >3x ULN and >10x ULN.

Increases in serum creatinine were more common among conivaptan-treated patients than among placebo-treated patients; in the IV studies, there appeared to be a relationship between conivaptan dose and incidence of serum Cr >2 mg/dL.

In the IV studies, significant hypernatremia (serum sodium >150 mEq/L) occurred exclusively in conivaptan-treated patients, although the incidence was low (1.2-1.4% for conivaptan-treated subjects).

In the IV studies, the incidence of plasma glucose values >250 mg/dL was somewhat higher among conivaptan-treated subjects than among placebo-treated subjects, with a possible relationship between the incidence of significant hyperglycemia and conivaptan dose.

In the IV studies, hyperuricemia occurred more frequently among conivaptan-treated subjects than among placebo-treated subjects. For female subjects, there appeared to be a relationship between incidence of hyperuricemia and conivaptan dose.

In the IV studies, low hematocrit (<30%) occurred more frequently among conivaptan-treated subjects than among placebo-treated subjects, without an apparent relationship to dose.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

In the "full dose" IV population, only one placebo subject was reported to have withdrawn due to a laboratory abnormality (hyponatremia). Among conivaptan-treated subjects, four patients withdrew due to increased blood creatinine, three withdrew due to hypernatremia, and one withdrew due to "blood urea increased".

7.1.8 Vital Signs

No new information was provided by the applicant regarding vital signs. Please see original clinical NDA review.

7.1.9 Electrocardiograms (ECGs)

No new information was provided by the applicant regarding electrocardiographic findings. Please see original clinical NDA review.

7.1.12 Special Safety Studies

Please see the original clinical NDA review regarding applicant's intensive QT study, which did not reveal evidence of a QT-prolonging effect of conivaptan.

7.1.14 Human Reproduction and Pregnancy Data

No new information regarding human reproduction was reported. FDA Toxicology recommends Pregnancy Category C, and the clinical reviewer concurs.

7.1.16 Overdose Experience

No cases of conivaptan overdose have been reported

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.2 Demographics

Please see the original clinical review for demographic characteristics of the overall safety population which included all oral + IV studies. In the original NDA, there was no evidence of imbalances in demographic characteristics to suggest problems with randomization. The following table illustrates demographic characteristics of the "full dose" IV population.

Table 7.2.1.2 Demographic Characteristics of "Full Dose" IV Population (Studies 027, 071, 080, 074, 079, 083)

	Placebo n(%)	Conivaptan 40/d n(%)	Conivaptan 80/d n(%)	Conivaptan Other n(%)	Conivaptan Any Dose n(%)
Number of Patients	109	256	106	42	404
Age (yrs)					
Mean	55.6	60.0	58.3	62.3	59.0
SD	22.22	20.46	21.21	11.61	20.03	
Minimum, Maximum	18, 97	20, 92	18, 95	35, 84	18, 95
<65	63 (57.8%)	123 (48.0%)	61 (57.5%)	26 (61.9%)	210 (52.0%)
>=65	46 (42.2%)	133 (52.0%)	45 (42.5%)	16 (38.1%)	194 (48.0%)
>=75	26 (23.9%)	86 (33.6%)	26 (24.5%)	9 (21.4%)	121 (30.0%)
Sex					
Male	57 (52.3%)	116 (45.3%)	59 (55.7%)	32 (76.2%)	207 (51.2%)
Female	52 (47.7%)	140 (54.7%)	47 (44.3%)	10 (23.8%)	197 (48.8%)
Race					
Caucasian	63 (57.8%)	176 (68.8%)	57 (53.8%)	31 (73.8%)	264 (65.3%)
Black	17 (15.6%)	29 (11.3%)	15 (14.2%)	8 (19.0%)	52 (12.9%)
Hispanic	26 (23.9%)	48 (18.8%)	32 (30.2%)	2 (4.8%)	82 (20.3%)
Asian	1 (0.9%)	0	0	1 (2.4%)	1 (0.2%)
Other	2 (1.8%)	3 (1.2%)	2 (1.9%)	0	5 (1.2%)

Source: Applicant's Table 3, pg 17, Summary of IV Safety

There are no imbalances in demographic characteristics between the conivaptan and placebo groups to suggest problems with randomization. Genders are equally represented, and a substantial proportion of the study population was non-Caucasian (black or Hispanic). Almost half of the study population was age 65 years or older; when one considers only patients (and not healthy volunteers), 67% of placebo patients and 66% of conivaptan patients were age 65 years or older. Overall results of these studies could reasonably be extrapolated to the elderly population. Patients in the "full dose" controlled IV congestive heart failure Study 071 were younger than those in the hyponatremia studies (027 and 080), with conivaptan group mean ages of 63 years for CHF patients and 72 years for hyponatremia patients. CHF patients were also more likely than hyponatremia patients to be male (64% male CHF conivaptan vs 38% male hyponatremia conivaptan); this is reflective of the gender distribution of CHF patients in the general population.

7.2.1.3 Extent of exposure (dose/duration)

Please see the original NDA review for information regarding the exposure by dose and duration of the original full NDA safety population (IV + oral).

The following table enumerates subjects in the full development program, as of 1 Sep 04.

Table 7.2.1.3.1

Enumeration of Subjects in the Conivaptan Development Program Cutoff Date: September 1, 2004		
Study Groups	Treatment Groups	
	Conivaptan	Placebo
Completed Phase 1		
Single Dose	251	33
Multiple Dose	308	58
Phase 1 Subtotal	**559**	**91**
Completed Phase 2 and Phase 3		
Placebo-controlled	942	374
Short Term (< 4 days)	*308*	*134*
Long Term (≥ 4 days)	*634*	*240*
Uncontrolled†	91	0
Short Term (< 4 days)	*57*	*0*
Long Term (≥ 4 days)	*34*	*0*
Completed Phase 2 and Phase 3 Subtotal	**1033**	**374**
Ongoing Phase 2 and Phase 3 Trials		
Placebo-controlled	0	0
Uncontrolled	115	0
Ongoing Phase 2 and Phase 3 Trials Subtotal	**115**	**0**
Single Dose Subtotal	**394**	**96**
Multiple Dose Subtotal	**1313**	**369**
Grand Total	**1707**	**465**

† Patients from Study 087-CL-026 or 087-CL-027 could roll over into the open-label extension study 087-CL-031. Only patients who received placebo in 087-CL-026 or -027 were counted as "new patients" for Study -031. Patients from Study 087-CL-043 could roll over into Study 087-CL-047. Only patients who received placebo in 087-CL-043 were counted as "new patients" for Study -047.

Source: Applicant's Appendix 2, Safety Update, pg 441

The following tables provide updated disposition and exposure by duration for the overall safety population of all Phase 2 and Phase 3 studies.

Table 7.2.1.3.2 Disposition, Overall Safety Population

	All IV + Oral Studies			
	YM087 Any Dose		Placebo	
	NDA n(%)	Updated n(%)	NDA n(%)	Updated n(%)
Patients treated	896	1148	332	372
Completed treatment	834 (93.1)	1040 (90.6)	302 (91.0)	341 (91.7)
Premature discontinuations:	84 (9.4)	147 (12.8)	30 (9.0)	31 (8.3)
Adverse Event	42 (4.7)	68 (5.9)	15 (4.5)	16 (4.3)
Lack of Efficacy	8 (0.8)	13 (1.1)	3 (0.9)	3 (0.8)
Withdrawal of Consent	2 (0.2)	9 (0.8)	1 (0.3)	1 (0.3)
Lost to Follow-up	0	0	0	0
Protocol Violation	4 (0.4)	4 (0.3)	2 (0.6)	2 (0.5)
Patient Died	3 (0.3)	3 (0.3)	0	0
Lack of Compliance	10 (1.1)	14 (1.2)	0	0
Other/Admin. Reasons	14 (1.6)	35 (3.0)	9 (2.7)	9 (2.4)
Satisfactory Response	1 (0.1)	1 (0.1)	0	0

Source: Applicant's Table 10, Safety Update, pg 259

Table 7.2.1.3.3 Exposure by Duration, Overall Safety Population

	All IV + Oral Studies			
	YM087 Any Dose		Placebo	
	NDA n(%)	Updated n(%)	NDA n(%)	Updated n(%)
# of Patients in Safety Population	896	1148	332	372
Length of Exposure (Days)				
N	896	1148	332	372
Mean	53.8	51.4	48.3	43.3
SD	48.93	72.53	47.75	47.34
Median	77.0	22.0	67.5	7.0
Minimum,Maximum	1, 267	1, 771	1, 229	1, 229
Number of Patients				
>= 1 Day	896 (100)	1148 (100)	332 (100)	372 (100)
>= 2 Days	739 (82.4)	971 (84.6)	264 (79.5)	303 (81.5)
>= 3 Days	718 (80.1)	833 (72.6)	256 (77.1)	256 (68.8)
>= 4 Days	689 (76.9)	800 (69.7)	251 (75.6)	251 (67.5)
>= 5 Days	640 (71.4)	667 (58.1)	228 (68.7)	228 (61.3)
>= 6 Days	556 (62.1)	606 (52.8)	183 (55.1)	183 (49.2)
>= 7 Days	555 (61.9)	604 (52.6)	183 (55.1)	183 (49.2)
>= 14 Days	536 (59.8)	582 (50.7)	174 (52.4)	174 (46.8)
>= 28 Days	525 (58.6)	568 (49.5)	172 (51.8)	172 (46.2)
>= 84 Days	285 (31.8)	319 (27.8)	96 (28.9)	96 (25.8)
>= 182 Days	25 (2.8)	42 (3.7)	10 (3.0)	10 (2.7)

Source: Applicant's Table 11, Safety Update, pg 264

A total of 971 patients received conivaptan for a duration of at least 2 days, and 800 patients received conivaptan for at least 4 days. However, the majority of these patients received a dose that resulted in a lower exposure than would occur with the full proposed dose of 40 mg/day IV. Therefore, the intravenous exposure data are very important for assessment of safety.

The following tables detail exposure by dose and duration for the "full dose" IV population.

Table 7.2.1.3.4 Disposition of Subjects, All "Full Dose" IV Studies

	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Patients treated	109	256	106	42	404
Completed treatment	102 (93.6%)	218 (85.2%)	97 (91.5%)	33 (78.6%)	348 (86.1%)
Primary reason for premature discontinuation:	7 (6.4%)	38 (14.8%)	9 (8.5%)	9 (21.4%)	56 (13.9%)
Adverse Event	4 (3.7%)	11 (4.3%)	8 (7.5%)	5 (11.9%)	24 (5.9%)
Lack of Efficacy	1 (0.9%)	2 (0.8%)	1 (0.9%)	1 (2.4%)	4 (1.0%)
Lost to Follow-up	0	0	0	0	0
Other/Admin. Reasons	2 (1.8%)	25 (9.8%)	0	3 (7.1%)	28 (6.9%)

Source: Applicant's Table 4, pg 19, Summary of IV Safety

Most patients (86% of conivaptan patients) completed treatment; adverse events leading to discontinuation from study are discussed in Section 7.1.3.

Table 7.2.1.3.5 Duration of Exposure, All "Full Dose" IV Studies

	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
# of Patients in Safety Population	109	256	106	42	404
Length of Exposure (Days)					
N	109	256	106	42	404
Mean	3.2	3.4	3.2	1.9	3.2
SD	1.00	1.01	1.00	0.33	1.06
Median	4	4	4	2	4
Minimum, Maximum	1, 4	1, 4	1, 4	1, 2	1, 4
Number of Patients					
>= 1 Day	109 (100%)	256 (100%)	106 (100%)	42 (100%)	404 (100%)
>= 2 Days	107 (98.2%)	238 (93.0%)	105 (99.1%)	37 (88.1%)	380 (94.1%)
>= 3 Days	66 (60.6%)	192 (75.0%)	63 (59.4%)	0	255 (63.1%)
>= 4 Days	62 (56.9%)	177 (69.1%)	63 (59.4%)	0	240 (59.4%)

Source: Applicant's Table 5, pg 21, Summary of IV Safety

A total of 380 patients completed at least two days of IV conivaptan treatment in doses of at least 40 mg/day IV, and 240 completed at least 4 days; the applicant proposes a duration of treatment of 2-4 days.

7.2.3 Adequacy of Overall Clinical Experience

The additional data submitted for intravenous use of conivaptan in the full dosing regimen proposed for labeling permit characterization of the safety of intravenous conivaptan with regard to commonly-occurring adverse events. Very rare events may not have been captured with this number of patients.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The following adverse events appear likely to be related to use of intravenous conivaptan:

- Serious and nonserious infusion-site-related events, including pain, thrombophlebitis and infection
- Serious and nonserious cardiac failure events
- Serious and nonserious hypovolemia-related events
- Overly rapid correction of serum sodium (without apparent neurologic sequelae)
- Atrial arrhythmias, with a possible relationship to hypokalemia
- Pneumonia
- Dyspnea
- Pollakiuria
- Thirst
- Transaminase elevations of >3x ULN and >10x ULN
- Reversible increases in serum creatinine
- Increases in fasting plasma glucose

The incidence of death appears to be numerically higher among conivaptan-treated patients for the "full dose" controlled IV population, "full-dose" controlled IV CHF population, overall safety population, "full dose" IV (patients) population, "full dose" IV "patients plus healthy volunteers" population, and "full dose" IV hyponatremia population. The incidence of death did not appear higher for conivaptan patients than for placebo patients in the overall controlled Phase 2/3 population, which included oral patients with lower exposure. There appears to be a correlation between IV-equivalent dose of conivaptan and incidence of death for the overall safety population, both in analyses by the Agency and in repeat analyses by the applicant. When examining hyponatremia and CHF populations separately, the death-dose relationship was strongest for CHF patients, and was not significant when considering only hyponatremia patients. Among all patients with a diagnosis of congestive heart failure at study entry who were treated with full-dose IV conivaptan, there appeared to be a dose-related increase in the rates of crude mortality and mortality per unit of patient-time. When examining the relationship between pharmacodynamic response and incidence of death for the overall Phase 2/3 population, there appeared to be an increase in incidence of death by increasing quartile of change from baseline in serum sodium. However, when one examined only patients in hyponatremia studies, there was no apparent relationship between incidence of death and pharmacodynamic response quartile for either the primary endpoint of these studies (change from baseline in serum sodium AUC), or change from baseline in absolute serum sodium. With the addition of patients from CHF studies to the patients from hyponatremia studies, to make up the entire Phase 2/3 population, the aforementioned apparent relationship between serum sodium response and incidence of death emerged.

In the clinical reviewer's opinion, there does not appear to be an increased risk of death for conivaptan used in the treatment of hyponatremia in the absence of congestive heart failure. However, there appears to be a signal for a dose-related increase in risk of death among patients

with underlying congestive heart failure. While the clinical reviewer cannot definitively conclude that conivaptan increases the risk of death for congestive heart failure patients, this signal is such that the clinical reviewer recommends that congestive heart failure patients not receive conivaptan outside the clinical trial setting at this time.

A potentially significant limitation of interpretation of the safety of conivaptan is related to blinding. Investigators were blinded to treatment assignment, but not to serum sodium levels, and might have been able to surmise which subjects were receiving conivaptan. It is also quite likely that investigators and other caregivers could tell by signs and symptoms which patients were receiving conivaptan and which were receiving placebo; urine output and thirst were markedly higher in conivaptan-treated patients. This could have resulted in differences in investigator behavior in choice of other treatments and fluids. It could also have influenced handling of adverse event risk and categorization. For example, a very high urine output could have prompted nursing concern for volume depletion risk, and extra nursing vigilance for orthostatic hypotension and fall prevention. An investigator who could be fairly certain that a patient was receiving conivaptan might be unconsciously less likely to record an adverse event or assign causality for an adverse event to conivaptan. Thus, underrepresentation of adverse event risk of conivaptan could have occurred.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The applicant submitted a small amount of controlled data for the use of intravenous conivaptan in the treatment of hyponatremia, essentially limited to Study 027, in which 55 patients were exposed to conivaptan. Therefore, the clinical reviewer considered pooled data for the following populations:

- "Full Dose" Controlled IV (258 coni subjects): Study 027 (hyponatremia- 55 coni pts), Study 071 (CHF- 122 coni pts), Study 079 (QT study, 81 coni healthy volunteers); included patients who received at least 40 mg/day intravenous conivaptan for at least 2 days
- "Full-dose" IV in patients (292 coni pts): Study 027, Study 071, and Study 080 (open-label hyponatremia, 115 coni pts); included patients who received at least 40 mg/day intravenous conivaptan for at least 2 days
- "Full Dose" IV (404 coni subjects): "Full dose" controlled IV studies plus Study 080 (open-label hyponatremia, 115 coni pts), 083 (healthy volunteer, oral vs IV PK, 21 coni subjects), and 074 (healthy volunteer PK, 10 coni subjects); included patients and healthy volunteers who received at least 40 mg/day intravenous conivaptan for at least 2 days
- Placebo-controlled Phase 2/3 (942 coni subjects): included IV and oral; included studies for hyponatremia and CHF indications; included "full dose" and lower exposures

- Overall safety population (1148 coni subjects): included IV and oral; included controlled and uncontrolled studies; included studies for hyponatremia and CHF indications; included "full dose" and lower exposures

In order to increase the interpretability of the data, the clinical reviewer often presented information separately for two or more of these populations, particularly when it appeared that a potential safety signal was occurring more frequently in one population compared to others.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Please see Sections 5.2 and 6.1-6.3 for issues related to dosing regimen and administration.

8.2 Drug-Drug Interactions

In the approvable letter, a warfarin interaction study was recommended, using the full dose proposed for labeling. The applicant did not provide the results of a study, but states that a protocol is being developed. A Phase IV commitment for completion of a full-dose warfarin interaction study is recommended.

Conivaptan is a potent inhibitor of CYP3A4, and two cases of rhabdomyolysis occurred in early clinical trials in patients who were taking CYP3A4-metabolized statins. This led to the applicant's proposed restriction of use of the drug to short-term intravenous use in hospitalized patients only, in order to reduce the likelihood that the drug would be coadministered with certain statins or other CYP3A4 metabolized drugs. However, in the original NDA, multiple protocol violations occurred in which patients received prohibited CYP3A4-metabolized drugs. This led to doubt regarding whether the proposed restriction to the setting of use would be adequate to minimize the risk that patients would received these drugs. In the approvable letter, the Agency recommended that the applicant develop a risk management plan to minimize this risk. The applicant did not include a risk management plan with this submission, but states that they intend to develop one. The applicant states that they are "committed to providing information to physicians and pharmacists to optimize patient care and ensure the safe use of the product".

On 29 Nov 05, the clinical reviewer requested from Astellas a listing of all adverse events that occurred in hospitalized patients who received prohibited CYP3A4 drugs, and on 5 Dec 05, the applicant responded via an email from Dr. Donald Raineri. New data regarding specific adverse events occurring in patients who received prohibited CYP3A4-metabolized drugs showed that most protocol violations were related to benzodiazepines or calcium channel blockers. Adverse events which occurred in these patients did not appear to be related to the prohibited CYP3A4 drugs. Specifically, patients who received prohibited benzodiazepines did not experience coma or altered level of consciousness. Patients who received prohibited CYP3A4 drugs also did not develop events plausibly related to excess action of conivaptan, such as events of hypotension, at

a rate higher than that seen in the overall Phase 2/3 study population. Specific events plausibly related to CYP3A4 interactions, such as ventricular dysrhythmias, did not occur at a higher rate among patients who received prohibited CYP3A4 drugs than among those who did not receive CYP3A4 drugs in the same group of studies. The incidence of adverse events among hospitalized patients who received prohibited CYP3A4 drugs was lower than the incidence of adverse events among outpatients who received prohibited CYP3A4 drugs, indicating that restriction of use to the hospital setting may indeed reduce the risks associated with concomitant administration of CYP3A4-metabolized drugs.

8.3 Special Populations

In the approvable letter, Biopharmaceutics requested special population studies, using the full planned dose for labeling, in the elderly and in patients with hepatic impairment.

8.3.1 Hepatic Impairment

The applicant provided no new information regarding use of conivaptan in patients with hepatic impairment.

8.3.2 Elderly

The applicant did not provide a separate study in the elderly at the full planned dose for labeling, but provided analysis of data from elderly patients in Study 080. Please see the Biopharmaceutics review for complete discussion of these data. In Study 080, the majority of patients for whom rich PK data were available were ≥65 years of age (11/12 patients in the 20 mg/day group; 12/14 in the 40 mg/day group). The applicant provided the following PK data for the patients who were ≥65 years of age.

Table 8.3.2 Conivaptan PK Parameters for Patients ≥65 Years of Age, Study 080

Parameter	IV Conivaptan 20 mg/day§	IV Conivaptan 40 mg/day§
Conivaptan concentration at 0.5 hours† (ng/mL)		
n	11	12
Mean ± SD	530.30 ± 174.689	787.24 ± 328.963
Median	566.72	746.00
Range	[redacted]	[redacted]
Conivaptan concentration at 96 hours (ng/mL)		
n	8	10
Mean ± SD	166.71 ± 185.517	447.04 ± 505.347
Median	117.03	258.00
Range	[redacted]	[redacted]
$AUC_{0\text{-}inf}$ (ng·hr/mL)		
n	11	12
Mean ± SD	13327.41 ± 12961.593	33879.63 ± 35680.561
Median	9777.64	19119.07
Range	[redacted]	[redacted]
Elimination Half-life (hr)		
n	11	12
Mean ± SD	8.01 ± 3.373	9.60 ± 3.772
Median	7.15	8.60
Range	[redacted]	[redacted]
Clearance (L/hr)		
n	11	12
Mean ± SD	13.07 ± 9.965	13.82 ± 13.771
Median	10.23	9.51
Range	[redacted]	[redacted]

Source: Applicant's Table 3, Section 6.2.2, Pg 342, Response to Deficiencies in NDA

As was noted in healthy volunteers, the pharmacokinetics of conivaptan are nonlinear in the elderly, with a more than proportionate increase in exposure with increasing dose. In the initial NDA, the applicant calculated a 2-fold increase in exposure for healthy elderly subjects compared to healthy young subjects. In healthy volunteers after a single dose, the half-life of conivaptan was approximately 5 hours, but declined to 3 hours with repeated dosing.

The data presented by the applicant above do not permit comparison of the PK in elderly patients to the PK in younger patients. The clinical reviewer defers to Biopharmaceutics regarding whether the data provided adequately characterize the PK of conivaptan in the elderly, and whether further study is needed.

8.4 Pediatrics

The use of conivaptan in pediatric patients has not been studied, and use in children under age 18 years is not recommended. [redacted]

8.7 Postmarketing Risk Management Plan

The applicant did not submit a risk management plan with this NDA resubmission. The applicant states that they intend to develop a risk management plan to reduce the risk that conivaptan will be administered to patients who are receiving other CYP3A4-metabolized drugs.

9 OVERALL ASSESSMENT

9.1 Conclusions

For conclusions below, the relevant section of the review is included in parentheses at the ends of sentences bearing conclusion points.

9.1.1 Efficacy Conclusions

The applicant proposes the following indication for conivaptan:

"Vaprisol® is indicated for the treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients."

[redacted]

For the question regarding effectiveness of a lower dose of conivaptan, the applicant did not perform a randomized placebo-controlled trial. Instead, a 20 mg/day arm was added to an ongoing open-label study which was using the full planned dose of 40 mg/day (Section 6.1). The 20 mg/day regimen appeared to be at least as effective as the 40 mg/day regimen with respect to change in serum sodium AUC from baseline, change in serum sodium, and the percentage of patients who met serum sodium goals at end of treatment. The changes in sodium parameters seen in the 20 mg/day IV group in this open-label study were substantially greater than those seen in the placebo group of the controlled IV hyponatremia study. Although the data for the 20 mg/day regimen were from an open-label study, the clinical reviewer finds them compelling, and recommends inclusion in the product label of information regarding the possibility of a lower starting dose.

In a reanalysis of data from the pivotal IV hyponatremia trial, a duration of treatment of two days appeared to be effective for many patients (Section 6.2). By two days of treatment, baseline adjusted serum sodium AUC, serum sodium, and the percentage of patients achieving serum sodium goals were already statistically significantly greater in the conivaptan group than in the placebo group. The majority of the effect of conivaptan on these parameters had occurred by two days of treatment, although serum sodium parameters and the percentage of patients

achieving serum sodium goals continued to increase up to four days of treatment. The clinical reviewer concurs with the applicant that a proposed duration of treatment of 2-4 days [redacted] is reasonable.

The applicant did not provide new information regarding the duration of effect of conivaptan. There are no data regarding serum sodium from cessation of treatment to approximately one week after treatment. At that point, sparse data indicated that significant hyponatremia had not recurred in conivaptan-treated patients (Section 6.3). However, at that point, placebo patients and conivaptan had similar serum sodiums. The sodium "effect" of conivaptan one week after cessation of treatment may actually be due to treatment of underlying causes of hyponatremia. The applicant proposes Phase IV study of the duration of effect of conivaptan.

9.1.2 Safety Conclusions

In the original NDA submission, a total of only 63 subjects appeared to have received conivaptan at the full dose and dosing regimen proposed for labeling. The applicant now submits data for a total of 404 patients and healthy volunteers who received conivaptan at a dose of at least 40 mg/day IV, and for a duration of 2-4 days.

In the review, multiple breakdowns of patient populations were considered. In an ideal setting, a large amount of placebo-controlled data would have been presented for patients being treated for hyponatremia with intravenous conivaptan used in the full dose and dosing regimen proposed for labeling. However, this resubmission did not provide a large body of information for this specific patient population. Although the applicant did submit additional intravenous conivaptan safety data for review, none of this was placebo-controlled data from IV studies in hyponatremia. In the entire development program, there was only one Phase 3 controlled IV hyponatremia study, which included 55 patients exposed to conivaptan, and this study was presented in the original NDA. Therefore, the clinical reviewer had to rely on a variety of other types of data to augment the safety evaluation. All of the additional IV safety data were either from uncontrolled studies in hyponatremia, studies in congestive heart failure, or studies in healthy volunteers. The vast majority of safety data from the original NDA submission were from oral studies with lower conivaptan exposure. Because little controlled IV hyponatremia study information was available, and the full Phase 2/3 population was heavily weighted with oral conivaptan patients with lower exposure, the clinical reviewer often had to separate out populations, e.g. all IV, all controlled, all hyponatremia, CHF, etc. When an apparent safety signal was identified, consideration of separate populations allowed the clinical reviewer to evaluate the overall finding, to assess whether the event was occurring with equal frequency in hyponatremia and CHF patients, and to assess whether the event was related to route of administration The following groups of studies were often used:

- Overall Safety Population (1148 conivaptan-treated subjects): included all Phase 2/3 studies, IV and oral, controlled and uncontrolled, hyponatremia and CHF, subjects who received the full proposed dose and subjects who had lower exposure
- Overall Placebo-Controlled Phase 2/3 Population (942 conivaptan-treated subjects): the placebo-controlled subset of the overall safety population

- Controlled "full dose" IV (258 conivaptan-treated subjects- patients and healthy volunteers): Study 027 (hyponatremia, 55 conivaptan-treated patients), Study 071 (CHF, 122 conivaptan-treated patients), Study 079 (QT study, 81 conivaptan-treated healthy volunteers); included studies in which subjects received at least 40 mg/day of intravenous conivaptan for at least 2 days
- "Full dose" IV in patients (292 conivaptan-treated patients): Study 027, Study 071, and Study 080 (open-label hyponatremia, 115 conivaptan-treated patients); included studies in which patients received at least 40 mg/day of intravenous conivaptan for at least 2 days
- All "full dose" IV (404 conivaptan-treated subjects): controlled "full dose" IV studies plus Study 080 (open-label hyponatremia, 115 coni pts), 083 (healthy volunteer, oral vs IV PK, 21 coni subjects), and 074 (healthy volunteer PK, 10 coni subjects); included studies in which subjects received at least 40 mg/day of intravenous conivaptan for at least 2 days
- All Phase 2/3 IV (445 conivaptan-treated subjects): included Studies 027, 071, and 080, plus all other Phase 2/3 IV studies (153 additional coni patients), controlled and uncontrolled, in CHF and hyponatremia; most additional patients had lower dose and/or shorter duration

A total of 64 deaths (63 in the Phase 2/3 population and one in a Japanese study that was not included in the Phase 2/3 population) occurred during conivaptan treatment, within 30 days of conivaptan treatment, or later but due to an adverse event which had its onset during treatment (Section 7.1.1.3). The incidence of death appeared to be numerically higher among conivaptan-treated patients for the "full dose" controlled IV population, "full dose" controlled IV CHF population, overall safety population, "full dose" IV population, "full-dose" IV patient population, and "full dose" IV hyponatremia population. The incidence of death did not appear higher for conivaptan patients than for placebo patients in the overall controlled Phase 2/3 population, which included oral patients with lower exposure. There appeared to be a correlation between IV-equivalent dose and incidence of death. Among congestive heart failure patients, there appeared to be a relationship between dose and both crude mortality and mortality per unit of patient-time for the full-dose controlled IV studies (Section 7.1.1.4). Numerous analyses were performed regarding the relationship between conivaptan and risk of death (Section 7.1.1.3). Overall, it appears that there is not an increased risk of death associated with conivaptan for treatment of hyponatremia in the absence of CHF. However, there does appear to be a signal for a dose-related increase in incidence of death among congestive heart failure patients, and the use of conivaptan in CHF patients outside the clinical trial setting is not recommended at this time.

The following serious adverse events occurred more frequently numerically among intravenous-conivaptan-treated patients than among placebo-treated patients (Section 7.1.2):

- serious "congestive cardiac failure aggravated"
- total serious cardiac failure events
- total serious infection events (no single infection predominated)
- total serious nervous system events (no single event predominated)
- total serious hypovolemia-related events

- serious infusion-site related events (occurred exclusively in conivaptan-treated patients; included severe infections and thrombophlebitides)

Withdrawal from study was more common among conivaptan-treated patients than among placebo-treated patients; most withdrawals were due to adverse events (Section 7.1.3.1). The most common types of adverse events leading to discontinuation were infusion-site-related events; twelve conivaptan patients discontinued study due to infusion-site-related events, compared to zero placebo patients (Section 7.1.3.2).

Several adverse events of special interest were considered because of signals seen preclinically or in the original NDA submission. Findings regarding these events include:

- Total renal adverse events, and "nonserious" events of renal failure occurred more commonly numerically among conivaptan-treated patients than among placebo-treated patients in the "full dose" IV study population (Section 7.1.3.3.1). In the "full dose" controlled IV population, renal failure events occurred slightly more frequently in conivaptan-treated patients than in placebo patients; this was not seen in the overall controlled (IV + oral) population. Special search criteria were developed for renal adverse events, and all serious events and cases of renal failure were examined. There was no evidence of a primary nephrotoxic effect of conivaptan, although data to assess this were limited. Most patients who developed renal failure had an underlying diagnosis of congestive heart failure, which carries a high baseline risk of acute renal failure with best current treatment. Overall, it appears that conivaptan may be associated with a slightly, but likely insignificantly greater risk of nonserious, reversible renal adverse events. Most events were reversible moderate increases in creatinine, which may have been associated with volume depletion due to conivaptan, or to the patients' underlying disease. As with patients treated with currently available diuretics in the acute hospitalized setting, renal function must be monitored, and patients may require volume repletion if an overly brisk aquaresis occurs with conivaptan.
- Overly rapid correction of serum sodium, which carries a risk of permanent neurologic sequelae, occurred only in conivaptan-treated patients (Section 7.1.3.3.2). About 6% of IV conivaptan patients overall, and about 9% of patients treated with doses in the range under consideration for labeling, met laboratory criteria for overly rapid correction of serum sodium. One patient who met laboratory criteria for overly rapid correction of serum sodium suffered a delayed seizure without sequelae. Otherwise, there were no clinically apparent consequences of overly rapid correction of serum sodium.
- Infusion site reactions were very common among conivaptan-treated patients (Section 7.1.3.3.3). The incidence of these events appears to correlate with dose and concentration. This underscores the need for consideration of a lower starting dose of conivaptan, and the need for study of a regimen without a loading dose.
- Hypovolemia-related events (e.g. hypotensive, hypovolemic, syncopal, fall and shock events) occurred more commonly among intravenous-conivaptan-treated patients than among placebo-treated patients (Section 7.1.3.3.4). One hypovolemia-related death may have occurred due to hypovolemic shock after marked aquaresis.

- Among CHF patients, atrial arrhythmia events, bleeding events, cardiac failure events and infusion-site-related events occurred more frequently among "full dose" conivaptan-treated patients than among placebo-treated patients in Study 071 (Section 7.1.3.3.5). Mean increases in transaminases were also greater for conivaptan patients than for placebo patients in Study 071, and several conivaptan-treated patients had marked increases in transaminases; however, baseline differences in transaminase levels between conivaptan and placebo groups made interpretation of this finding difficult. When considering all patients in controlled Phase 2/3 trials who had an initial diagnosis of congestive heart failure, events of cardiac failure and atrial arrhythmias were more common among patients treated with conivaptan in the range of doses under consideration for labeling (Section 7.1.3.3.5).

In addition to the above events of interest, the following adverse events occurred more frequently numerically among conivaptan-treated patients than among placebo-treated patients in "full dose" controlled IV studies (Section 7.1.5.4):

- Atrial arrhythmia events
- Cardiac failure events
- Hypernatremia (reported as adverse event)
- Hyperglycemia (reported as adverse event)
- Pneumonia
- "Dyspnea exacerbated"
- Aesthenia
- Thirst
- Pollakiuria

Atrial arrhythmia events may have been related to electrolyte depletion; hypokalemia was more common among patients experiencing these events than among the "full dose" controlled IV study population. Thirst and pollakiuria are expected events given the physiology of the drug.

Clinical laboratory findings of note include:

- Conivaptan-treated patients were more likely to develop transaminase elevations of >3x ULN and >10x ULN than were placebo-treated patients (Sections 7.1.7.3.1 and 7.1.7.3.2). Hepatobiliary adverse events did not occur more commonly among conivaptan-treated patients. In Study 071, a congestive heart failure study, fourteen conivaptan-treated patients had relatively large increases in transaminases. However, conivaptan-treated patients were also more likely than were placebo patients to have baseline elevations in transaminases making this finding difficult to interpret.
- Mean fasting plasma glucose declined for placebo patients, but increased for conivaptan patients (Sections 7.1.7.3.1 and 7.1.7.3.2). Plasma glucose values of >250 mg/dL were also more common among conivaptan-treated patients. The difference between treatment groups was less marked for nonfasting plasma glucose. The reason for this difference between groups is unclear, but may be related to the fact that conivaptan is infused in D5W.
- Increases in serum creatinine to >1.6 mg/dL were more common among conivaptan-treated patients than among placebo-treated patients; in the IV studies, there appeared to

be a relationship between conivaptan dose and the incidence of serum creatinine >2 mg/dL (Section 7.1.7.3.2).

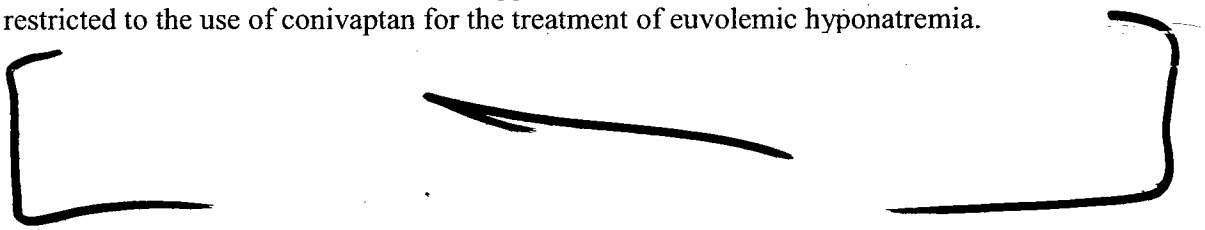
- In the IV studies, significant hypernatremia (>150 mEq/L) occurred exclusively in conivaptan-treated patients, although the incidence was low (1.2%-1.4%) (Section 7.1.7.3.2).
- Low hematocrit (<30%) occurred more frequently among IV-conivaptan-treated patients than among placebo-treated patients (Section 7.1.7.3.2).
- In IV studies, women treated with conivaptan were more likely to develop hyperuricemia than were women treated with placebo (Section 7.1.7.3.2).

The following adverse events appear likely to be related to use of intravenous conivaptan:

- Serious and nonserious infusion-site-related events, including pain, thrombophlebitis and infection
- Serious and nonserious cardiac failure events
- Serious and nonserious hypovolemia-related events
- Overly rapid correction of serum sodium (without apparent neurologic sequelae)
- Atrial arrhythmias, with a possible relationship to hypokalemia
- Pneumonia
- Dyspnea
- Pollakiuria
- Thirst
- Transaminase elevations of >3x ULN and >10x ULN
- Reversible increases in serum creatinine
- Increases in fasting plasma glucose

9.2 Recommendation on Regulatory Action

The clinical reviewer recommends an "approval" action, but recommends that the indication be restricted to the use of conivaptan for the treatment of euvolemic hyponatremia.



9.3.1 Risk Management Activity

No specific recommendations are made at this time other than routine postmarketing surveillance of adverse events as required by FDA for newly approved drugs. Additional recommendations may be made after discussions with the Office of Drug Safety and other review disciplines.

9.3.2 Required Phase 4 Commitments

The clinical reviewer recommends a Phase IV commitment of a controlled trial to answer the question of whether a loading dose is needed for conivaptan, and whether a regimen which does not include a loading dose could have a lower risk of adverse events, particularly infusion site reactions.

A warfarin interaction study using the full intravenous labeled dose is also recommended as a Phase IV commitment.

9.3.3 Other Phase 4 Requests

Other Phase 4 requests which were included in the first cycle "approvable" letter, and which continue to apply, include the need to fully establish the lowest effective dose of conivaptan, the need to establish the durability of the sodium effect of conivaptan after discontinuation of conivaptan, and the need for full-dose special population studies in patients with underlying hepatic and renal impairment. If the applicant desires, study of the lowest effective dose and the duration of effect could be included within the Phase 4 commitment loading dose study.

9.4 Labeling Review

The clinical reviewer has the following recommendations at this time regarding the applicant's proposed label. Labeling discussions with other review disciplines and signatory authorities are pending, and may alter labeling recommendations.

CLINICAL PHARMACOLOGY SECTION:

CLINICAL STUDIES SECTION

Add a paragraph at the end with the data from Study 080 regarding the likely efficacy of the 20 mg/day IV dose.

INDICATIONS AND USAGE SECTION:

Change the indication to:

"VAPRISOL is indicated for the treatment of euvolemic hyponatremia in hospitalized patients."

After the CONTRAINDICATIONS section, add a WARNINGS section:

"The safety of conivaptan in patients with underlying congestive heart failure has not been established. In clinical trials of conivaptan, patients with underlying congestive heart failure who received conivaptan had a higher incidence of cardiac failure events and other adverse events, when compared to congestive heart failure patients who received placebo. The effect of conivaptan on mortality in congestive heart failure and other clinical congestive heart failure outcomes has not been established. Conivaptan is not recommended for use in patients with underlying congestive heart failure."

PRECAUTIONS:

In the first paragraph, regarding overly rapid correction of serum sodium, change the subsection heading from "General" to "Overly Rapid Correction of Serum Sodium", and add this sentence after the first sentence:

"In clinical trials of conivaptan, about 9% of patients who received conivaptan in doses of 20-40 mg/day IV met laboratory criteria for overly rapid correction of serum sodium, but none of these patients had permanent neurologic sequelae."

In the Drug Interactions subsection of the PRECAUTIONS section, in the second paragraph, add this sentence after the second sentence:

"In clinical trials of oral conivaptan, two cases of rhabdomyolysis occurred in patients who were also receiving a CYP3A4-metabolized statin."

DOSAGE AND ADMINISTRATION:

Delete the first paragraph and add the following paragraphs:

"The recommended loading dose for VAPRISOL is 20 mg IV administered as a 30-minute infusion.

For patients who do not require emergent correction of serum sodium, the loading dose should be followed by 20 mg of conivaptan administered as a continuous intravenous infusion over 24 hours. Following the initial day of treatment, VAPRISOL is to be administered for an additional

1 to 3 days as a continuous infusion of 20 mg/day. If serum sodium is not rising at the desired rate, VAPRISOL may be titrated upward to a dose of 40 mg IV/day, again administered as a continuous intravenous infusion.

For patients who require emergent correction of serum sodium, the loading dose may be followed by 40 mg of IV conivaptan, administered as a continuous IV infusion over 24 hours. Following the initial day of treatment, VAPRISOL is to be administered for an additional 1 to 3 days as a continuous infusion of 40 mg/day.

The total duration of infusion of VAPRISOL (after the loading dose) should not exceed four days."

At the end of the first paragraph, change "(see PRECAUTIONS: General)" to "(see PRECAUTIONS: Overly Rapid Correction of Serum Sodium)"

After the first paragraph, add these paragraphs:

"Patients receiving VAPRISOL must have frequent monitoring of serum sodium and volume status. An overly rapid rise in serum sodium (>12 mEq/24 hours) may result in serious sequelae. For patients who develop an undesirably rapid rate of rise of serum sodium, VAPRISOL should be discontinued, and serum sodium and neurologic status should be carefully monitored. If the serum sodium continues to rise, VAPRISOL should not be resumed. If hyponatremia persists or recurs, and the patient has had no evidence of neurologic sequelae of rapid rise in serum sodium, VAPRISOL may be resumed at a reduced dose.

For patients who develop hypovolemia or hypotension while receiving VAPRISOL, VAPRISOL should be discontinued, and volume status and vital signs should be frequently monitored. Once the patient is again euvolemic and is no longer hypotensive, VAPRISOL may be resumed at a reduced dose if the patient remains hyponatremic."

9.5 Comments to Applicant

The indication for intravenous conivaptan will be limited to the treatment of euvolemic hyponatremia in hospitalized patients. [redacted]

The Agency requests a Phase IV commitment to complete and report a controlled trial to study the necessity of a loading dose with regard to efficacy and to study the effect of a regimen without a loading dose on the incidence and severity of infusion site reactions. Additionally, the Agency requests a Phase IV commitment to complete and report a warfarin interaction study using the full intravenous clinical dose.

[redacted]

Further study of the lowest effective dose of conivaptan for the treatment of hyponatremia is needed. This is particularly important for hyponatremic patients with underlying congestive heart failure, as heart failure patients exhibit higher conivaptan exposure than subjects without congestive heart failure, and there are safety questions regarding use of conivaptan in congestive heart failure patients.

Study is needed to establish the durability of sodium effect of conivaptan. You have provided information regarding serum sodium approximately one week after discontinuation of conivaptan, but you have not provided information on durability of sodium effect during the period from discontinuation of conivaptan to one week following discontinuation of conivaptan. Information on daily measures of persistence of serum sodium effect is needed from discontinuation to one week after discontinuation.

The studies regarding lowest effective dose and durability of effect could be incorporated into the Phase IV commitment loading dose study.

Special population studies in patients with underlying hepatic and renal impairment are needed, using the full clinical dose.

10 APPENDICES

10.1 Common Adverse Event Tables

Table 10.1.1 Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, All "Full Dose" IV Studies (027, 071, 074, 079, 080, 083)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Blood and lymphatic system disorders	7 (6.4%)	13 (5.1%)	5 (4.7%)	2 (7.1%)	21 (5.2%)
Anaemia NOS	3 (2.8%)	7 (2.7%)	3 (2.8%)	2 (7.1%)	12 (3.2%)
Leukocytosis	0	1 (0.4%)	2 (1.9%)	0	3 (0.7%)
Thrombocytopenia	2 (1.8%)	3 (1.2%)	0	0	3 (0.7%)
Cardiac disorders	18 (16.5%)	33 (12.9%)	11 (10.4%)	13 (31.0%)	57 (14.1%)
Angina pectoris	2 (1.8%)	2 (0.8%)	1 (0.9%)	1 (2.4%)	4 (1.0%)
Atrial fibrillation	0	10 (3.9%)	2 (1.9%)	1 (2.4%)	13 (3.2%)
Atrial flutter	0	0	1 (0.9%)	3 (7.1%)	4 (1.0%)
Atrioventricular block complete	1 (0.9%)	0	0	1 (2.4%)	1 (0.2%)
Atrioventricular block first degree	2 (1.8%)	0	0	0	0
Atrioventricular block second degree	2 (1.8%)	0	1 (0.9%)	0	1 (0.2%)
Bradycardia NOS	4 (3.7%)	2 (0.8%)	0	1 (2.4%)	3 (0.7%)
Cardio-respiratory arrest	0	0	0	1 (2.4%)	1 (0.2%)
Cardiomyopathy NOS	0	3 (1.2%)	0	1 (2.4%)	4 (1.0%)
Congestive cardiac failure aggravated	1 (0.9%)	7 (2.7%)	2 (1.9%)	0	9 (2.2%)
Coronary artery disease aggravated	0	0	0	1 (2.4%)	1 (0.2%)
Ischaemic cardiomyopathy	0	0	0	1 (2.4%)	1 (0.2%)
Mitral valve incompetence	0	1 (0.4%)	0	1 (2.4%)	2 (0.5%)
Sinus tachycardia	0	2 (0.8%)	0	1 (2.4%)	3 (0.7%)
Ventricular fibrillation	0	0	0	1 (2.4%)	1 (0.2%)
Ventricular tachycardia	7 (6.4%)	1 (0.4%)	5 (4.7%)	4 (9.5%)	10 (2.5%)
Endocrine disorders	1 (0.9%)	3 (1.2%)	0	0	3 (0.7%)
Eye disorders	0	9 (3.5%)	1 (0.9%)	1 (2.4%)	11 (2.7%)
Conjunctivitis	0	0	0	1 (2.4%)	1 (0.2%)
Gastrointestinal disorders	25 (22.9%)	62 (24.2%)	18 (17.0%)	8 (19.0%)	88 (21.8%)
Abdominal distension	2 (1.8%)	1 (0.4%)	0	0	1 (0.2%)
Abdominal haematoma	0	0	0	1 (2.4%)	1 (0.2%)
Abdominal pain NOS	3 (2.8%)	7 (2.7%)	3 (2.8%)	1 (2.4%)	11 (2.7%)
Colonic polyp	0	0	0	1 (2.4%)	1 (0.2%)

(cont below)

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Table 10.1.1 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, All "Full Dose" IV Studies (027, 071, 074, 079, 080, 083)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Constipation	8 (7.8%)	15 (5.9%)	6 (5.7%)	5 (11.9%)	26 (6.4%)
Diarrhoea NOS	3 (2.8%)	13 (5.1%)	4 (3.8%)	2 (4.8%)	19 (4.7%)
Dry mouth	2 (1.8%)	10 (3.9%)	2 (1.9%)	0	12 (3.0%)
Dyspepsia	1 (0.9%)	3 (1.2%)	0	1 (2.4%)	4 (1.0%)
Gastrointestinal haemorrhage NOS	2 (1.8%)	0	0	1 (2.4%)	1 (0.2%)
Gastrointestinal upset	0	0	0	1 (2.4%)	1 (0.2%)
Haemorrhoids	0	0	0	1 (2.4%)	1 (0.2%)
Nausea	9 (8.3%)	13 (5.1%)	4 (3.8%)	1 (2.4%)	18 (4.5%)
Vomiting NOS	2 (1.8%)	19 (7.4%)	2 (1.9%)	0	21 (5.2%)
General disorders and administration site conditions	19 (17.4%)	155 (61.7%)	65 (61.3%)	29 (69.0%)	252 (62.4%)
Anasarca	0	1 (0.4%)	0	1 (2.4%)	2 (0.5%)
Asthenia	0	6 (2.1%)	2 (1.9%)	3 (7.1%)	13 (3.2%)
Cannula site reaction	0	10 (3.9%)	0	0	10 (2.5%)
Chest pain	0	4 (1.6%)	0	0	4 (1.0%)
Fatigue	1 (0.9%)	2 (0.8%)	0	2 (4.8%)	4 (1.0%)
Infusion related reaction	0	0	0	1 (2.4%)	1 (0.2%)
Infusion site erythema	0	15 (5.9%)	7 (6.6%)	1 (2.4%)	23 (5.7%)
Infusion site induration	0	0	0	1 (2.4%)	1 (0.2%)
Infusion site pain	1 (0.9%)	17 (6.6%)	18 (17.0%)	1 (2.4%)	36 (8.9%)
Infusion site phlebitis	3 (2.8%)	45 (17.6%)	20 (18.9%)	14 (33.3%)	79 (19.6%)
Infusion site reaction	0	41 (16.0%)	4 (3.8%)	3 (7.1%)	48 (11.9%)
Infusion site swelling	2 (1.8%)	7 (2.7%)	16 (15.1%)	0	23 (5.7%)
Infusion site tenderness	0	1 (0.4%)	3 (2.8%)	0	4 (1.0%)
Infusion site warmth	0	0	0	1 (2.4%)	1 (0.2%)
Injection site cellulitis	0	4 (1.6%)	2 (1.9%)	3 (7.1%)	9 (2.2%)
Injection site erythema	0	0	2 (1.9%)	0	2 (0.5%)
Injection site inflammation	0	0	2 (1.9%)	0	2 (0.5%)
Injection site pain	0	0	0	2 (4.8%)	2 (0.5%)
Injection site phlebitis	0	3 (1.2%)	1 (0.9%)	1 (2.4%)	5 (1.2%)
Injection site reaction NOS	2 (1.8%)	2 (0.8%)	1 (0.9%)	3 (7.1%)	6 (1.5%)
Injection site thrombosis	0	0	2 (1.9%)	1 (2.4%)	3 (0.7%)
Multi-organ failure	1 (0.9%)	3 (1.2%)	0	0	3 (0.7%)
Oedema NOS	0	3 (1.2%)	0	0	3 (0.7%)

(cont below)

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Table 10.1.1 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, All "Full Dose" IV Studies (027, 071, 074, 079, 080, 083)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Oedema peripheral	1 (0.9%)	14 (5.5%)	0	0	14 (3.5%)
Pain NOS	0	5 (2.0%)	2 (1.9%)	0	7 (1.7%)
Pyrexia	4 (3.7%)	13 (5.1%)	3 (2.8%)	4 (9.5%)	20 (5.0%)
Sudden cardiac death	0	0	0	1 (2.4%)	1 (0.2%)
Thirst	1 (0.9%)	18 (7.0%)	18 (17.0%)	3 (7.1%)	39 (9.7%)
Hepatobiliary disorders	0	4 (1.6%)	0	0	4 (1.0%)
Immune system disorders	0	1 (0.4%)	0	2 (4.8%)	3 (0.7%)
Heart transplant rejection	0	0	0	1 (2.4%)	1 (0.2%)
Urticaria NOS	0	1 (0.4%)	0	1 (2.4%)	2 (0.5%)
Infections and infestations	11 (10.1%)	34 (13.2%)	11 (10.4%)	10 (23.8%)	55 (13.6%)
Asymptomatic bacteriuria	1 (0.9%)	0	2 (1.9%)	0	2 (0.5%)
Cellulitis	1 (0.9%)	4 (1.6%)	0	0	4 (1.0%)
Cytomegalovirus infection	0	0	0	1 (2.4%)	1 (0.2%)
Hiv infection	0	0	0	1 (2.4%)	1 (0.2%)
Oral candidiasis	0	5 (2.0%)	0	0	5 (1.2%)
Pneumonia NOS	1 (0.9%)	6 (2.3%)	4 (3.8%)	5 (11.9%)	15 (3.7%)
Sepsis NOS	0	3 (1.2%)	1 (0.9%)	1 (2.4%)	5 (1.2%)
Staphylococcal sepsis	0	0	0	1 (2.4%)	1 (0.2%)
Upper respiratory tract infection NOS	1 (0.9%)	0	0	1 (2.4%)	1 (0.2%)
Urinary tract infection NOS	6 (5.6%)	10 (3.9%)	2 (1.9%)	1 (2.4%)	13 (3.2%)
Injury, poisoning and procedural complications	3 (2.8%)	10 (3.9%)	2 (1.9%)	2 (4.8%)	14 (3.5%)
Confusion postoperative	0	0	0	1 (2.4%)	1 (0.2%)
Fall	0	2	0	1 (2.4%)	1 (0.2%)
Incision site complication	2 (1.8%)	0	0	0	0
Nausea postoperative	0	0	0	1 (2.4%)	1 (0.2%)
Post procedural pain	1 (0.9%)	2 (0.8%)	0	1 (2.4%)	3 (0.7%)
Post procedural vomiting	0	0	0	1 (2.4%)	1 (0.2%)
Investigations	5 (4.6%)	22 (8.6%)	19 (17.9%)	9 (21.4%)	50 (12.4%)
Blood alkaline phosphatase increased	0	1 (0.4%)	0	2 (4.8%)	3 (0.7%)

Table 10.1.1 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, All "Full Dose" IV Studies (027, 071, 074, 079, 080, 083)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Blood creatine phosphokinase increased	0	3 (1.2%)	0	0	3 (0.7%)
Blood creatinine increased	1 (0.9%)	0	3 (2.8%)	1 (2.4%)	4 (1.0%)
Blood magnesium decreased	0	1 (0.4%)	3 (2.8%)	0	4 (1.0%)
Body temperature increased	1 (0.9%)	0	3 (2.8%)	1 (2.4%)	4 (1.0%)
Cardiac murmur NOS	0	1 (0.4%)	0	1 (2.4%)	2 (0.5%)
Gamma-glutamyltransferase increased	1 (0.9%)	0	0	2 (4.8%)	2 (0.5%)
Heart sounds abnormal	0	2 (0.8%)	0	1 (2.4%)	3 (0.7%)
Pulmonary arterial pressure increased	0	0	0	1 (2.4%)	1 (0.2%)
Red blood cells urine	0	0	0	1 (2.4%)	1 (0.2%)
Urine output decreased	1 (0.9%)	1 (0.4%)	1 (0.9%)	1 (2.4%)	3 (0.7%)
Urine sodium decreased	0	1 (0.4%)	3 (2.8%)	0	4 (1.0%)
Weight decreased	0	1 (0.4%)	2 (1.9%)	0	3 (0.7%)
White blood cell count increased	0	0	2 (1.9%)	1 (2.4%)	3 (0.7%)
Metabolism and nutrition disorders	17 (16.0%)	63 (24.6%)	20 (18.9%)	14 (33.3%)	97 (24.0%)
Appetite decreased NOS	0	0	2 (1.9%)	0	2 (0.5%)
Dehydration	1 (0.9%)	6 (2.3%)	0	1 (2.4%)	7 (1.7%)
Fluid overload	1 (0.9%)	1 (0.4%)	1 (0.9%)	1 (2.4%)	3 (0.7%)
Hyperglycaemia NOS	0	9 (3.5%)	1 (0.9%)	3 (7.1%)	13 (3.2%)
Hyperkalaemia	3 (2.8%)	9 (3.5%)	5 (4.7%)	1 (2.4%)	15 (3.7%)
Hypernatraemia	0	3 (1.2%)	3 (2.8%)	2 (4.8%)	8 (2.0%)
Hyperphosphataemia	1 (0.9%)	0	0	1 (2.4%)	1 (0.2%)
Hypoglycaemia NOS	0	9 (3.5%)	0	2 (4.8%)	11 (2.7%)
Hypokalaemia	10 (9.2%)	31 (12.1%)	5 (7.5%)	4 (9.5%)	43 (10.6%)
Hypomagnesaemia	4 (3.7%)	7 (2.7%)	1 (0.9%)	2 (4.8%)	10 (2.5%)
Hyponatraemia	2 (1.8%)	9 (3.5%)	3 (2.8%)	1 (2.4%)	13 (3.2%)
Hypophosphataemia	0	2 (0.8%)	0	1 (2.4%)	3 (0.7%)
Musculoskeletal and connective tissue disorders	4 (3.7%)	15 (5.9%)	9 (8.5%)	8 (19.0%)	32 (7.9%)
Arthralgia	1 (0.9%)	4 (1.6%)	3 (2.8%)	1 (2.4%)	8 (2.0%)
Arthritis NOS	0	0	0	1 (2.4%)	1 (0.2%)
Back pain	1 (0.9%)	2 (0.8%)	2 (1.9%)	1 (2.4%)	5 (1.2%)
Chest wall pain	0	0	0	1 (2.4%)	1 (0.2%)
Groin pain	0	1 (0.4%)	0	1 (2.4%)	2 (0.5%)

Table 10.1.1 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, All "Full Dose" IV Studies (027, 071, 074, 079, 080, 083)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Muscle cramp	0	1 (0.4%)	2 (1.5%)	0	3 (0.7%)
Muscle spasms	0	0	0	1 (2.4%)	1 (0.2%)
Pain in extremity	0	6 (2.3%)	2 (1.5%)	4 (9.5%)	12 (3.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (1.6%)	0	0	4 (1.0%)
Nervous system disorders	11 (10.1%)	42 (16.4%)	9 (7.5%)	6 (14.3%)	56 (13.9%)
Cerebrovascular accident	0	2 (0.8%)	0	1 (2.4%)	3 (0.7%)
Dizziness	3 (2.8%)	6 (2.1%)	1 (0.5%)	1 (2.4%)	10 (2.5%)
Epilepsy NOS	0	3 (1.2%)	0	0	3 (0.7%)
Headache	5 (4.6%)	24 (9.4%)	4 (3.0%)	4 (9.5%)	32 (7.9%)
Syncope	1 (0.9%)	2 (0.8%)	0	1 (2.4%)	3 (0.7%)
Psychiatric disorders	10 (9.2%)	27 (10.5%)	6 (5.7%)	4 (9.5%)	37 (9.2%)
Agitation	0	3 (1.2%)	0	2 (4.8%)	5 (1.2%)
Anxiety	1 (0.9%)	3 (1.2%)	1 (0.9%)	0	4 (1.0%)
Confusional state	2 (1.8%)	11 (4.2%)	1 (0.9%)	0	12 (3.0%)
Depression	0	1 (0.4%)	0	1 (2.4%)	2 (0.5%)
Insomnia	6 (5.5%)	9 (3.5%)	2 (1.8%)	3 (7.1%)	15 (3.7%)
Restlessness	0	3 (1.2%)	1 (0.9%)	0	4 (1.0%)
Renal and urinary disorders	10 (9.2%)	52 (20.7%)	19 (17.9%)	5 (11.9%)	77 (19.1%)
Dysuria	0	3 (1.2%)	1 (0.9%)	0	4 (1.0%)
Haematuria	2 (1.8%)	6 (2.3%)	3 (2.8%)	0	9 (2.2%)
Leukocyturia	0	2 (0.8%)	2 (1.9%)	0	4 (1.0%)
Nocturia	0	0	0	1 (2.4%)	1 (0.2%)
Pollakiuria	0	11 (4.3%)	8 (7.5%)	0	19 (4.7%)
Polyuria	0	10 (3.9%)	0	0	10 (2.5%)
Renal failure NOS	2 (1.8%)	7 (2.7%)	3 (2.8%)	2 (4.8%)	12 (3.0%)
Renal failure acute	2 (1.8%)	5 (2.0%)	1 (0.9%)	0	6 (1.5%)
Renal failure chronic	0	0	0	1 (2.4%)	1 (0.2%)
Renal impairment NOS	0	3 (1.2%)	0	0	3 (0.7%)
Urinary retention	0	2 (1.2%)	1 (0.9%)	1 (2.4%)	5 (1.2%)

(cont below)

Table 10.1.1 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, All "Full Dose" IV Studies (027, 071, 074, 079, 080, 083)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Respiratory, thoracic and mediastinal disorders	24 (22.0%)	34 (16.2%)	21 (19.8%)	14 (82.3%)	69 (17.1%)
Bronchospasm NOS	0	1 (0.4%)	0	1 (2.4%)	2 (0.5%)
Chronic obstructive airways disease	1 (0.9%)	0	1 (0.9%)	1 (2.4%)	2 (0.5%)
Chronic obstructive airways disease exacerbated	0	0	0	1 (2.4%)	1 (0.2%)
Cough	4 (3.7%)	6 (2.9%)	2 (1.9%)	1 (2.4%)	9 (2.2%)
Crackles lung	2 (1.8%)	0	0	0	0
Dyspnoea	6 (5.5%)	5 (2.0%)	2 (1.9%)	0	7 (1.7%)
Dyspnoea exacerbated	8 (7.3%)	7 (1.7%)	10 (9.4%)	8 (19.0%)	25 (6.2%)
Hypercapnia	0	0	1 (0.9%)	1 (2.4%)	2 (0.5%)
Hypoventilation	0	0	0	1 (2.4%)	1 (0.2%)
Pharyngolaryngeal pain	4 (3.7%)	2 (0.8%)	2 (1.9%)	0	4 (1.0%)
Pulmonary congestion	2 (1.8%)	5 (2.0%)	2 (1.9%)	2 (4.8%)	9 (2.2%)
Pulmonary oedema NOS	0	0	1 (0.9%)	2 (4.8%)	3 (0.7%)
Respiratory failure	0	2 (0.8%)	1 (0.9%)	1 (2.4%)	4 (1.0%)
Rhinorrhoea	1 (0.9%)	0	0	1 (2.4%)	1 (0.2%)
Skin and subcutaneous tissue disorders	4 (3.7%)	15 (5.9%)	8 (7.5%)	4 (9.5%)	27 (6.7%)
Contusion	0	1 (0.4%)	2 (1.9%)	0	3 (0.7%)
Dry skin	0	0	0	1 (2.4%)	1 (0.2%)
Erythema	0	5 (2.0%)	3 (2.8%)	1 (2.4%)	9 (2.2%)
Pruritus	2 (1.8%)	3 (1.2%)	0	2 (4.8%)	5 (1.2%)
Rash NOS	2 (1.8%)	2 (0.8%)	0	0	2 (0.5%)
Skin hyperpigmentation	0	0	0	1 (2.4%)	1 (0.2%)
Vascular disorders	12 (11.0%)	56 (21.9%)	14 (13.2%)	6 (14.3%)	76 (15.8%)
Flushing	4 (3.7%)	2 (0.8%)	0	0	2 (0.5%)
Hypertension NOS	0	12 (4.7%)	2 (1.9%)	0	14 (3.5%)
Hypotension NOS	8 (7.3%)	14 (5.5%)	7 (6.6%)	5 (11.9%)	26 (6.4%)
Orthostatic hypotension	0	13 (5.1%)	2 (1.9%)	0	15 (3.7%)
Phlebitis NOS	1 (0.9%)	12 (4.7%)	4 (3.8%)	0	16 (4.0%)
Postoperative hypertension	0	0	0	1 (2.4%)	1 (0.2%)
Thrombophlebitis	0	3 (1.2%)	0	0	3 (0.7%)

Source: Applicant's Table 2.7.4-10.6A., Summary of Intravenous Safety

Table 10.1.2: Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full-Dose" IV Studies in Patients (027, 071, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Blood and lymphatic system disorders	7 (10.1%)	13 (7.1%)	5 (7.6%)	3 (7.1%)	21 (7.2%)
Anaemia NOS	3 (4.3%)	7 (3.8%)	3 (4.5%)	3 (7.1%)	13 (4.5%)
Leukocytosis	0	1 (0.5%)	2 (3.0%)	0	3 (1.0%)
Normochromic normocytic anaemia	1 (1.4%)	1 (0.5%)	0	0	1 (0.3%)
Secondary anaemia	1 (1.4%)	0	0	0	0
Thrombocytopenia	2 (2.9%)	3 (1.6%)	0	0	3 (1.0%)
Cardiac disorders	18 (26.1%)	33 (17.9%)	11 (16.7%)	13 (31.0%)	57 (19.6%)
Angina pectoris	2 (2.9%)	2 (1.1%)	1 (1.5%)	1 (2.4%)	4 (1.4%)
Angina unstable	1 (1.4%)	0	0	0	0
Atrial fibrillation	0	10 (5.4%)	2 (3.0%)	1 (2.4%)	13 (4.5%)
Atrial flutter	0	0	1 (1.5%)	3 (7.1%)	4 (1.4%)
Atrial thrombosis	0	2 (1.1%)	0	0	2 (0.7%)
Atrioventricular block complete	1 (1.4%)	0	0	1 (2.4%)	1 (0.3%)
Atrioventricular block first degree	2 (2.9%)	0	0	0	0
Atrioventricular block second degree	2 (2.9%)	0	1 (1.5%)	0	1 (0.3%)
Bradycardia NOS	4 (5.8%)	2 (1.1%)	0	1 (2.4%)	3 (1.0%)
Cardio-respiratory arrest	0	0	0	1 (2.4%)	1 (0.3%)
Cardiomyopathy NOS	0	3 (1.6%)	0	1 (2.4%)	4 (1.4%)
Cardiopulmonary failure	1 (1.4%)	0	0	0	0
Congestive cardiac failure aggravated	1 (1.4%)	7 (3.9%)	2 (3.0%)	0	9 (3.1%)
Coronary artery disease aggravated	0	0	0	1 (2.4%)	1 (0.3%)
Coronary artery occlusion	0	0	1 (1.5%)	0	1 (0.3%)
Ischaemic cardiomyopathy	0	0	0	1 (2.4%)	1 (0.3%)
Mitral valve incompetence	0	1 (0.5%)	0	1 (2.4%)	2 (0.7%)
Myocardial infarction	1 (1.4%)	0	0	0	0
Palpitations	1 (1.4%)	0	0	0	0
Sick sinus syndrome	1 (1.4%)	0	1 (1.5%)	0	1 (0.3%)
Sinus tachycardia	0	2 (1.1%)	0	1 (2.4%)	3 (1.0%)
Supraventricular arrhythmia NOS	1 (1.4%)	0	0	0	0
Ventricular bigeminy	1 (1.4%)	0	0	0	0
Ventricular extrasystoles	0	2 (1.1%)	1 (1.5%)	0	3 (1.0%)
Ventricular fibrillation	0	0	0	1 (2.4%)	1 (0.3%)

(cont below)

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Table 10.1.2 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full-Dose" IV Studies in Patients (027, 071, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Ventricular tachycardia	7 (10.1%)	1 (0.5%)	5 (7.6%)	4 (9.5%)	10 (3.4%)
Endocrine disorders	1 (1.4%)	3 (1.6%)	0	0	3 (1.0%)
Hypothyroidism	1 (1.4%)	1 (0.5%)	0	0	1 (0.3%)
Eye disorders	0	8 (4.3%)	1 (1.5%)	1 (2.4%)	10 (3.4%)
Conjunctivitis	0	0	0	1 (2.4%)	1 (0.3%)
Eye pain	0	2 (1.1%)	0	0	2 (0.7%)
Eye pruritus	0	2 (1.1%)	1 (1.5%)	0	3 (1.0%)
Gastrointestinal disorders	22 (31.9%)	57 (31.0%)	16 (24.2%)	8 (19.0%)	81 (27.7%)
Abdominal discomfort	0	0	1 (1.5%)	0	1 (0.3%)
Abdominal distension	2 (2.9%)	1 (0.5%)	0	0	1 (0.3%)
Abdominal haematoma	0	0	0	1 (2.4%)	1 (0.3%)
Abdominal pain NOS	3 (4.3%)	7 (3.8%)	3 (4.5%)	1 (2.4%)	11 (3.8%)
Abdominal pain lower	1 (1.4%)	0	0	0	0
Abdominal pain upper	1 (1.4%)	1 (0.5%)	0	0	1 (0.3%)
Anal fissure	1 (1.4%)	0	0	0	0
Colonic polyp	0	0	0	1 (2.4%)	1 (0.3%)
Constipation	8 (11.6%)	15 (8.2%)	6 (9.1%)	5 (11.9%)	26 (8.9%)
Diarrhoea NOS	3 (4.3%)	13 (7.1%)	4 (6.1%)	2 (4.8%)	19 (6.5%)
Dry mouth	0	6 (3.3%)	0	0	6 (2.1%)
Dyspepsia	1 (1.4%)	3 (1.6%)	0	1 (2.4%)	4 (1.4%)
Flatulence	1 (1.4%)	0	0	0	0
Gastric ulcer	1 (1.4%)	0	0	0	0
Gastritis NOS	0	1 (0.5%)	1 (1.5%)	0	2 (0.7%)
Gastrointestinal haemorrhage NOS	2 (2.9%)	0	0	1 (2.4%)	1 (0.3%)
Gastrointestinal upset	0	0	0	1 (2.4%)	1 (0.3%)
Gastrocesophageal reflux disease	1 (1.4%)	0	0	0	0
Haemorrhoids	0	0	0	1 (2.4%)	1 (0.3%)
Hiatus hernia	1 (1.4%)	0	1 (1.5%)	0	1 (0.3%)
Loose stools	0	2 (1.1%)	1 (1.5%)	0	3 (1.0%)
Nausea	8 (11.6%)	13 (7.1%)	4 (6.1%)	1 (2.4%)	18 (6.2%)
Toothache	1 (1.4%)	0	0	0	0

(cont below)

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Table 10.1.2 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full-Dose" IV Studies in Patients (027, 071, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Injection site thrombosis	0	0	2 (3.0%)	1 (2.4%)	3 (1.0%)
Intermittent pyrexia	1 (1.4%)	0	0	0	0
Mechanical complication of implant	1 (1.4%)	0	0	0	0
Multi-organ failure	1 (1.4%)	3 (1.6%)	0	0	3 (1.0%)
Oedema NOS	0	3 (1.6%)	0	0	3 (1.0%)
Oedema peripheral	1 (1.4%)	12 (6.5%)	0	0	12 (4.1%)
Pain NOS	0	5 (2.7%)	2 (3.0%)	0	7 (2.4%)
Pyrexia	4 (5.8%)	12 (6.5%)	2 (3.0%)	4 (9.8%)	18 (6.2%)
Rigors	0	1 (0.5%)	1 (1.5%)	0	2 (0.7%)
Sudden cardiac death	0	0	0	1 (2.4%)	1 (0.3%)
Sudden death	0	2 (1.1%)	0	0	2 (0.7%)
Systemic inflammatory response syndrome	1 (1.4%)	0	0	0	0
Thirst	0	4 (2.2%)	2 (3.0%)	3 (7.1%)	9 (3.1%)
Venipuncture site bruise	0	0	1 (1.5%)	0	1 (0.3%)
Hepatobiliary disorders	0	4 (2.2%)	0	0	4 (1.4%)
Immune system disorders	0	1 (0.5%)	0	2 (4.8%)	3 (1.0%)
Heart transplant rejection	0	0	0	1 (2.4%)	1 (0.3%)
Urticaria NOS	0	1 (0.5%)	0	1 (2.4%)	2 (0.7%)
Infections and infestations	11 (15.9%)	34 (18.5%)	11 (16.7%)	10 (23.8%)	55 (18.8%)
Asymptomatic bacteriuria	1 (1.4%)	0	2 (3.0%)	0	2 (0.7%)
Bronchitis acute NOS	1 (1.4%)	0	0	0	0
Candidal infection NOS	1 (1.4%)	1 (0.5%)	0	0	1 (0.3%)
Cellulitis	1 (1.4%)	4 (2.2%)	0	0	4 (1.4%)
Clostridium colitis	1 (1.4%)	0	0	0	0
Cytomegalovirus infection	0	0	0	1 (2.4%)	1 (0.3%)
Herpes zoster	0	0	1 (1.5%)	0	1 (0.3%)
Hiv infection	0	0	0	1 (2.4%)	1 (0.3%)
Implant site infection	1 (1.4%)	0	0	0	0
Injection site infection	0	0	1 (1.5%)	0	1 (0.3%)
Oral candidiasis	0	5 (2.7%)	0	0	5 (1.7%)
Pneumonia NOS	1 (1.4%)	6 (3.3%)	4 (6.1%)	5 (11.9%)	15 (5.1%)

Table 10.1.2 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full-Dose" IV Studies in Patients (027, 071, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Sepsis NOS	0	3 (1.6%)	1 (1.5%)	1 (2.4%)	5 (1.7%)
Staphylococcal sepsis	0	0	0	1 (2.4%)	1 (0.3%)
Upper respiratory tract infection NOS	1 (1.4%)	0	0	1 (2.4%)	1 (0.3%)
Urinary tract infection NOS	6 (8.7%)	10 (5.4%)	2 (3.0%)	1 (2.4%)	13 (4.5%)
Injury, poisoning and procedural complications	3 (4.3%)	9 (4.9%)	2 (3.0%)	2 (4.8%)	13 (4.5%)
Confusion postoperative	0	0	0	1 (2.4%)	1 (0.3%)
Drug toxicity NOS	0	2 (1.1%)	0	0	2 (0.7%)
Fall	0	0	0	1 (2.4%)	1 (0.3%)
Haematuria traumatic	0	0	1 (1.5%)	0	1 (0.3%)
Incision site complication	2 (2.9%)	0	0	0	0
Nausea postoperative	0	0	0	1 (2.4%)	1 (0.3%)
Post procedural complication	0	0	1 (1.5%)	0	1 (0.3%)
Post procedural pain	1 (1.4%)	2 (1.1%)	0	1 (2.4%)	3 (1.0%)
Post procedural vomiting	0	0	0	1 (2.4%)	1 (0.3%)
Therapeutic agent poisoning	0	2 (1.1%)	0	0	2 (0.7%)
Urethral injury	1 (1.4%)	0	0	0	0
Investigations	5 (7.2%)	22 (12.0%)	19 (28.8%)	9 (21.4%)	50 (17.1%)
Alanine aminotransferase increased	1 (1.4%)	0	0	0	0
Aspartate aminotransferase increased	1 (1.4%)	0	0	0	0
Blood alkaline phosphatase increased	0	1 (0.5%)	0	2 (4.8%)	3 (1.0%)
Blood creatine phosphokinase increased	0	3 (1.6%)	0	0	3 (1.0%)
Blood creatinine increased	1 (1.4%)	0	3 (4.5%)	1 (2.4%)	4 (1.4%)
Blood glucose increased	1 (1.4%)	2 (1.1%)	1 (1.5%)	0	3 (1.0%)
Blood magnesium decreased	0	1 (0.5%)	3 (4.5%)	0	4 (1.4%)
Blood potassium decreased	0	1 (0.5%)	1 (1.5%)	0	2 (0.7%)
Blood sodium increased	0	2 (1.1%)	0	0	2 (0.7%)
Blood urea increased	1 (1.4%)	0	1 (1.5%)	0	1 (0.3%)
Blood uric acid increased	0	0	1 (1.5%)	0	1 (0.3%)
Body temperature increased	1 (1.4%)	0	3 (4.5%)	1 (2.4%)	4 (1.4%)
Cardiac murmur NOS	0	1 (0.5%)	0	1 (2.4%)	2 (0.7%)
Gamma-glutamyltransferase increased	1 (1.4%)	0	0	2 (4.8%)	2 (0.7%)
Haematocrit decreased	0	0	1 (1.5%)	0	1 (0.3%)

Table 10.1.2 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full-Dose" IV Studies in Patients (027, 071, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Haemoglobin decreased	0	2 (1.1%)	1 (1.5%)	0	3 (1.0%)
Heart sounds abnormal	0	2 (1.1%)	0	1 (2.4%)	3 (1.0%)
Liver function test abnormal	0	2 (1.1%)	1 (1.5%)	0	3 (1.0%)
Pulmonary arterial pressure increased	0	0	0	1 (2.4%)	1 (0.3%)
Red blood cell sedimentation rate increased	1 (1.4%)	0	0	0	0
Red blood cells urine	0	0	0	1 (2.4%)	1 (0.3%)
Urine output decreased	1 (1.4%)	1 (0.5%)	1 (1.5%)	1 (2.4%)	3 (1.0%)
Urine sodium decreased	0	1 (0.5%)	3 (4.5%)	0	4 (1.4%)
Weight decreased	0	1 (0.5%)	2 (3.0%)	0	3 (1.0%)
White blood cell count increased	0	0	2 (3.0%)	1 (2.4%)	3 (1.0%)
ph urine increased	0	0	1 (1.5%)	0	1 (0.3%)
Metabolism and nutrition disorders	17 (24.6%)	63 (34.2%)	20 (30.3%)	14 (33.3%)	97 (33.2%)
Anorexia	1 (1.4%)	0	0	0	0
Appetite decreased NOS	0	0	2 (3.0%)	0	2 (0.7%)
Dehydration	1 (1.4%)	6 (3.3%)	0	1 (2.4%)	7 (2.4%)
Diabetes mellitus non-insulin-dependent	0	0	1 (1.5%)	0	1 (0.3%)
Electrolyte depletion	0	0	1 (1.5%)	0	1 (0.3%)
Fluid overload	1 (1.4%)	1 (0.5%)	1 (1.5%)	1 (2.4%)	3 (1.0%)
Gout	1 (1.4%)	0	0	0	0
Hyperglycaemia NOS	0	9 (4.9%)	1 (1.5%)	3 (7.1%)	13 (4.5%)
Hyperkalaemia	3 (4.3%)	9 (4.9%)	5 (7.6%)	1 (2.4%)	15 (5.1%)
Hyperlipidaemia NOS	0	0	1 (1.5%)	0	1 (0.3%)
Hypermagnesaemia	1 (1.4%)	1 (0.5%)	0	0	1 (0.3%)
Hypernatraemia	0	3 (1.6%)	3 (4.5%)	2 (4.8%)	8 (2.7%)
Hyperphosphataemia	1 (1.4%)	0	0	1 (2.4%)	1 (0.3%)
Hypocalcaemia	1 (1.4%)	0	0	0	0
Hypoglycaemia NOS	0	9 (4.9%)	0	2 (4.8%)	11 (3.8%)
Hypokalaemia	10 (14.5%)	31 (16.8%)	8 (12.1%)	4 (9.5%)	43 (14.7%)
Hypomagnesaemia	4 (5.8%)	7 (3.8%)	1 (1.5%)	2 (4.8%)	10 (3.4%)
Hyponatraemia	2 (2.9%)	9 (4.9%)	3 (4.5%)	1 (2.4%)	13 (4.5%)
Hypophosphataemia	0	2 (1.1%)	0	1 (2.4%)	3 (1.0%)
Hypovolaemia	1 (1.4%)	1 (0.5%)	1 (1.5%)	0	2 (0.7%)
Metabolic acidosis NOS	1 (1.4%)	1 (0.5%)	0	0	1 (0.3%)

(cont below)

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Table 10.1.2 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full-Dose" IV Studies in Patients (027, 071, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Musculoskeletal and connective tissue disorders	4 (5.8%)	13 (7.1%)	9 (13.6%)	8 (15.0%)	30 (10.3%)
Arthralgia	1 (1.4%)	4 (2.2%)	3 (4.5%)	1 (2.4%)	8 (2.7%)
Arthritis NOS	0	0	0	1 (2.4%)	1 (0.3%)
Back pain	1 (1.4%)	2 (1.1%)	2 (3.0%)	1 (2.4%)	5 (1.7%)
Chest wall pain	0	0	0	1 (2.4%)	1 (0.3%)
Groin pain	0	1 (0.5%)	0	1 (2.4%)	2 (0.7%)
Joint stiffness	1 (1.4%)	0	0	0	0
Limb discomfort NOS	0	0	1 (1.5%)	0	1 (0.3%)
Muscle cramp	0	1 (0.5%)	2 (3.0%)	0	3 (1.0%)
Muscle spasms	0	0	0	1 (2.4%)	1 (0.3%)
Musculoskeletal chest pain	0	2 (1.1%)	0	0	2 (0.7%)
Musculoskeletal discomfort	1 (1.4%)	0	0	0	0
Pain in extremity	0	4 (2.2%)	2 (3.0%)	4 (9.5%)	10 (3.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (2.2%)	0	0	4 (1.4%)
Nervous system disorders	11 (15.9%)	29 (15.8%)	5 (7.6%)	6 (14.3%)	40 (13.7%)
Carotid artery stenosis	1 (1.4%)	0	0	0	0
Cerebrovascular accident	0	2 (1.1%)	0	1 (2.4%)	3 (1.0%)
Convulsions NOS	0	0	1 (1.5%)	0	1 (0.3%)
Depressed level of consciousness	1 (1.4%)	0	0	0	0
Dizziness	3 (4.3%)	8 (4.3%)	1 (1.5%)	1 (2.4%)	10 (3.4%)
Dizziness postural	0	1 (0.5%)	1 (1.5%)	0	2 (0.7%)
Epilepsy NOS	0	3 (1.6%)	0	0	3 (1.0%)
Headache	5 (7.2%)	11 (6.0%)	1 (1.5%)	4 (9.5%)	16 (5.5%)
Loss of consciousness	1 (1.4%)	0	0	0	0
Syncope	1 (1.4%)	2 (1.1%)	0	1 (2.4%)	3 (1.0%)
Tremor	0	0	1 (1.5%)	0	1 (0.3%)
Psychiatric disorders	10 (14.5%)	27 (14.7%)	6 (9.1%)	4 (9.5%)	37 (12.7%)
Agitation	0	3 (1.6%)	0	2 (4.8%)	5 (1.7%)
Anxiety	1 (1.4%)	3 (1.6%)	1 (1.5%)	0	4 (1.4%)

(cont below)

Table 10.1.2 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full-Dose" IV Studies in Patients (027, 071, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Confusional state	2 (2.9%)	11 (6.6%)	1 (1.5%)	0	12 (4.1%)
Depression	0	1 (0.6%)	0	1 (2.4%)	2 (0.7%)
Disorientation	1 (1.4%)	0	0	0	0
Hallucination NOS	0	1 (0.6%)	1 (1.5%)	0	2 (0.7%)
Insomnia	6 (8.7%)	9 (4.8%)	3 (4.5%)	3 (7.1%)	15 (5.1%)
Restlessness	0	3 (1.6%)	1 (1.5%)	0	4 (1.4%)
Renal and urinary disorders	10 (14.5%)	42 (22.8%)	11 (16.7%)	5 (11.9%)	58 (19.9%)
Dysuria	0	3 (1.6%)	1 (1.5%)	0	4 (1.4%)
Haematuria	2 (2.9%)	6 (3.3%)	3 (4.5%)	0	9 (3.1%)
Leukocyturia	0	2 (1.1%)	2 (3.0%)	0	4 (1.4%)
Nocturia	0	0	0	1 (2.4%)	1 (0.3%)
Oliguria	1 (1.4%)	2 (1.1%)	0	0	2 (0.7%)
Polyuria	0	10 (5.4%)	0	0	10 (3.4%)
Renal disorder NOS	1 (1.4%)	0	0	0	0
Renal failure NOS	2 (2.9%)	7 (3.8%)	3 (4.5%)	2 (4.8%)	12 (4.1%)
Renal failure acute	3 (4.3%)	5 (2.7%)	1 (1.5%)	0	6 (2.1%)
Renal failure acute on chronic	0	2 (1.1%)	1 (1.5%)	0	3 (1.0%)
Renal failure chronic	0	0	0	1 (2.4%)	1 (0.3%)
Renal impairment NOS	0	3 (1.6%)	0	0	3 (1.0%)
Urinary incontinence	1 (1.4%)	2 (1.1%)	0	0	2 (0.7%)
Urinary retention	0	3 (1.6%)	1 (1.5%)	1 (2.4%)	5 (1.7%)
Reproductive system and breast disorders	0	2 (1.1%)	1 (1.5%)	0	3 (1.0%)
Ovarian mass	0	0	1 (1.5%)	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	23 (33.3%)	33 (17.5%)	20 (30.3%)	14 (33.3%)	67 (22.9%)
Bronchitis NOS	0	2 (1.1%)	1 (1.5%)	0	3 (1.0%)
Bronchospasm NOS	0	1 (0.5%)	0	1 (2.4%)	2 (0.7%)
Chronic obstructive airways disease	1 (1.4%)	0	1 (1.5%)	1 (2.4%)	2 (0.7%)
Chronic obstructive airways disease exacerbated	0	0	0	1 (2.4%)	1 (0.3%)
Cough	4 (5.8%)	6 (3.3%)	2 (3.0%)	1 (2.4%)	9 (3.1%)
Crackles lung	2 (2.9%)	0	0	0	0
Dyspnoea	6 (8.7%)	5 (2.7%)	2 (3.0%)	0	7 (2.4%)

Table 10.1.2 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full-Dose" IV Studies in Patients (027, 071, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Dyspnoea exacerbated	8 (11.6%)	7 (3.8%)	10 (15.2%)	8 (19.0%)	25 (8.6%)
Dyspnoea exertional	1 (1.4%)	1 (0.5%)	0	0	1 (0.3%)
Epistaxis	0	1 (0.6%)	1 (1.5%)	0	2 (0.7%)
Hypercapnia	0	0	1 (1.5%)	1 (2.4%)	2 (0.7%)
Hypoventilation	0	0	0	1 (2.4%)	1 (0.3%)
Lung infiltration NOS	1 (1.4%)	0	0	0	0
Pharyngolaryngeal pain	3 (4.3%)	2 (1.1%)	1 (1.5%)	0	3 (1.0%)
Pleural effusion	1 (1.4%)	1 (0.5%)	1 (1.5%)	0	2 (0.7%)
Pulmonary congestion	2 (2.9%)	5 (2.7%)	2 (3.0%)	2 (4.8%)	9 (3.1%)
Pulmonary oedema NOS	0	0	1 (1.5%)	2 (4.8%)	3 (1.0%)
Rales	1 (1.4%)	1 (0.5%)	0	0	1 (0.3%)
Respiratory acidosis	1 (1.4%)	0	0	0	0
Respiratory arrest	1 (1.4%)	1 (0.5%)	0	0	1 (0.3%)
Respiratory distress	1 (1.4%)	1 (0.5%)	1 (1.5%)	0	2 (0.7%)
Respiratory failure	0	2 (1.1%)	2 (3.0%)	1 (2.4%)	4 (1.4%)
Rhinorrhoea	1 (1.4%)	0	0	1 (2.4%)	1 (0.3%)
Wheezing	1 (1.4%)	0	1 (1.5%)	0	1 (0.3%)
Skin and subcutaneous tissue disorders	4 (5.8%)	12 (6.5%)	8 (12.1%)	4 (9.5%)	24 (8.2%)
Contusion	0	1 (0.5%)	2 (3.0%)	0	3 (1.0%)
Cyanosis peripheral	0	1 (0.5%)	1 (1.5%)	0	2 (0.7%)
Decubitus ulcer	0	2 (1.1%)	0	0	2 (0.7%)
Dry skin	0	0	0	1 (2.4%)	1 (0.3%)
Erythema	0	2 (1.1%)	3 (4.5%)	1 (2.4%)	6 (2.1%)
Pruritus	2 (2.9%)	3 (1.6%)	0	2 (4.8%)	5 (1.7%)
Purpura NOS	0	0	1 (1.5%)	0	1 (0.3%)
Rash NOS	2 (2.9%)	2 (1.1%)	0	0	2 (0.7%)
Skin hyperpigmentation	0	0	0	1 (2.4%)	1 (0.3%)
Skin irritation	0	0	1 (1.5%)	0	1 (0.3%)
Skin ulcer	0	0	1 (1.5%)	0	1 (0.3%)
Surgical and medical procedures	1 (1.4%)	0	0	0	0
Implantable defibrillator replacement	1 (1.4%)	0	0	0	0

Table 10.1.2 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full-Dose" IV Studies in Patients (027, 071, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Vascular disorders	11 (15.9%)	58 (29.9%)	14 (21.2%)	6 (14.3%)	78 (25.7%)
Arterial occlusion	1 (1.4%)	0	0	0	0
Deep vein thrombosis	0	2 (1.1%)	0	0	2 (0.7%)
Flushing	3 (4.3%)	2 (1.1%)	0	0	2 (0.7%)
Hypertension NOS	0	12 (6.8%)	2 (3.0%)	0	14 (4.8%)
Hypotension NOS	8 (11.6%)	14 (7.6%)	7 (10.6%)	5 (11.9%)	26 (8.9%)
Orthostatic hypotension	0	13 (7.1%)	2 (3.0%)	0	15 (5.1%)
Phlebitis NOS	1 (1.4%)	12 (6.5%)	4 (6.1%)	0	16 (5.5%)
Phlebitis superficial	0	0	1 (1.5%)	0	1 (0.3%)
Postoperative hypertension	0	0	0	1 (2.4%)	1 (0.3%)
Subclavian steal syndrome	0	0	1 (1.5%)	0	1 (0.3%)
Thrombophlebitis	0	3 (1.6%)	0	0	3 (1.0%)
Thrombophlebitis superficial	0	2 (1.1%)	0	0	2 (0.7%)

Source: Applicant's Table 2.7.4-10.6B., Summary of Intravenous Safety

Table 10.1.3: Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Hyponatremia Studies (027, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Any Dose n(%)
Blood and lymphatic system disorders	2 (6.9%)	12 (8.3%)	0	12 (7.1%)
Anaemia NOS	2 (6.9%)	7 (4.9%)	0	7 (4.1%)
Thrombocytopenia	0	2 (1.4%)	0	2 (1.2%)
Cardiac disorders	5 (17.2%)	24 (16.7%)	2 (7.7%)	26 (15.3%)
Atrial fibrillation	0	7 (4.9%)	0	7 (4.1%)
Atrioventricular block first degree	2 (6.9%)	0	0	0
Bradycardia NOS	0	2 (1.4%)	0	2 (1.2%)
Congestive cardiac failure aggravated	1 (3.4%)	7 (4.9%)	2 (7.7%)	9 (5.3%)
Sick sinus syndrome	1 (3.4%)	0	0	0
Sinus tachycardia	0	2 (1.4%)	0	2 (1.2%)
Supraventricular arrhythmia NOS	1 (3.4%)	0	0	0
Endocrine disorders	0	3 (2.1%)	0	3 (1.8%)
Eye disorders	0	6 (4.2%)	1 (3.8%)	7 (4.1%)
Eye pain	0	2 (1.4%)	0	2 (1.2%)
Eye pruritus	0	1 (0.7%)	1 (3.8%)	2 (1.2%)
Gastrointestinal disorders	7 (24.1%)	45 (31.3%)	5 (19.2%)	50 (29.4%)
Abdominal pain NOS	2 (6.9%)	6 (4.2%)	2 (7.7%)	8 (4.7%)
Abdominal pain upper	1 (3.4%)	1 (0.7%)	0	1 (0.6%)
Constipation	2 (6.9%)	10 (6.9%)	0	10 (5.9%)
Diarrhoea NOS	0	12 (8.3%)	2 (7.7%)	14 (8.2%)
Dry mouth	0	5 (3.5%)	0	5 (2.9%)
Dyspepsia	0	2 (1.4%)	0	2 (1.2%)
Gastric ulcer	1 (3.4%)	0	0	0
Gastritis NOS	0	1 (0.7%)	1 (3.8%)	2 (1.2%)
Gastrointestinal haemorrhage NOS	1 (3.4%)	0	0	0
Hiatus hernia	0	0	1 (3.8%)	1 (0.6%)
Loose stools	0	2 (1.4%)	1 (3.8%)	3 (1.8%)
Nausea	2 (6.9%)	9 (6.3%)	0	9 (5.3%)
Vomiting NOS	0	16 (11.1%)	1 (3.8%)	17 (10.0%)

(cont below)

Table 10.1.3 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Hyponatremia Studies (027, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Any Dose n(%)
General disorders and administration site conditions	3 (10.3%)	102 (70.8%)	12 (46.2%)	114 (67.1%)
Application site erythema	0	2 (1.4%)	1 (3.8%)	3 (1.8%)
Application site reaction NOS	0	0	1 (3.8%)	1 (0.6%)
Asthenia	0	6 (4.2%)	0	6 (3.5%)
Chest pain	0	4 (2.8%)	0	4 (2.4%)
Discomfort NOS	1 (3.4%)	0	0	0
Fatigue	0	2 (1.4%)	0	2 (1.2%)
General physical health deterioration	0	2 (1.4%)	0	2 (1.2%)
Infusion site erythema	0	12 (8.3%)	0	12 (7.1%)
Infusion site inflammation	0	0	1 (3.8%)	1 (0.6%)
Infusion site pain	0	2 (1.4%)	1 (3.8%)	3 (1.8%)
Infusion site phlebitis	1 (3.4%)	38 (26.4%)	3 (11.5%)	41 (24.1%)
Infusion site reaction	0	40 (27.8%)	2 (7.7%)	42 (24.7%)
Infusion site swelling	0	2 (1.4%)	1 (3.8%)	3 (1.8%)
Injection site bruising	0	0	1 (3.8%)	1 (0.6%)
Injection site erythema	0	0	1 (3.8%)	1 (0.6%)
Injection site inflammation	0	0	1 (3.8%)	1 (0.6%)
Injection site phlebitis	0	3 (2.1%)	1 (3.8%)	4 (2.4%)
Injection site swelling	0	2 (1.4%)	0	2 (1.2%)
Multi-organ failure	0	3 (2.1%)	0	3 (1.8%)
Oedema NOS	0	2 (1.4%)	0	2 (1.2%)
Oedema peripheral	1 (3.4%)	11 (7.6%)	0	11 (6.5%)
Pain NOS	0	5 (3.5%)	1 (3.8%)	6 (3.5%)
Pyrexia	0	10 (6.9%)	2 (7.7%)	12 (7.1%)
Rigors	0	0	1 (3.8%)	1 (0.6%)
Sudden death	0	2 (1.4%)	0	2 (1.2%)
Thirst	0	4 (2.8%)	0	4 (2.4%)
Hepatobiliary disorders	0	4 (2.8%)	0	4 (2.4%)
Infections and infestations	4 (13.8%)	28 (19.4%)	4 (15.4%)	32 (18.8%)
Bronchitis acute NOS	1 (3.4%)	0	0	0
Candidal infection NOS	1 (3.4%)	1 (0.7%)	0	1 (0.6%)

(cont below)

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Table 10.1.3 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Hyponatremia Studies (027, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Any Dose n(%)
Cellulitis	0	3 (2.1%)	0	3 (1.8%)
Injection site infection	0	0	1 (3.8%)	1 (0.6%)
Oral candidiasis	0	5 (3.5%)	0	5 (2.9%)
Pneumonia NOS	0	5 (3.5%)	2 (7.7%)	7 (4.1%)
Sepsis NOS	0	3 (2.1%)	0	3 (1.8%)
Upper respiratory tract infection NOS	1 (3.4%)	0	0	0
Urinary tract infection NOS	2 (6.9%)	8 (5.6%)	1 (3.8%)	9 (5.3%)
Injury, poisoning and procedural complications	0	6 (4.2%)	0	6 (3.5%)
Investigations	0	12 (8.3%)	5 (19.2%)	17 (10.0%)
Blood creatine phosphokinase increased	0	2 (1.4%)	0	2 (1.2%)
Blood creatinine increased	0	0	1 (3.8%)	1 (0.6%)
Blood glucose increased	0	0	1 (3.8%)	1 (0.6%)
Blood sodium increased	0	2 (1.4%)	0	2 (1.2%)
Blood urea increased	0	0	1 (3.8%)	1 (0.6%)
Body temperature increased	0	0	1 (3.8%)	1 (0.6%)
Liver function test abnormal	0	1 (0.7%)	1 (3.8%)	2 (1.2%)
Weight decreased	0	1 (0.7%)	2 (7.7%)	3 (1.8%)
Metabolism and nutrition disorders	6 (20.7%)	46 (31.9%)	6 (23.1%)	52 (30.6%)
Appetite decreased NOS	0	0	1 (3.8%)	1 (0.6%)
Dehydration	0	6 (4.2%)	0	6 (3.5%)
Diabetes mellitus non-insulin-dependent	0	0	1 (3.8%)	1 (0.6%)
Electrolyte depletion	0	0	1 (3.8%)	1 (0.6%)
Gout	1 (3.4%)	0	0	0
Hyperglycaemia NOS	0	7 (4.9%)	0	7 (4.1%)
Hyperkalaemia	1 (3.4%)	4 (2.8%)	3 (11.5%)	7 (4.1%)
Hypoglycaemia NOS	0	7 (4.9%)	0	7 (4.1%)
Hypokalaemia	2 (6.9%)	26 (18.1%)	0	26 (15.3%)
Hypomagnesaemia	0	6 (4.2%)	0	6 (3.5%)
Hyponatraemia	1 (3.4%)	8 (5.6%)	1 (3.8%)	9 (5.3%)
Hypovolaemia	1 (3.4%)	1 (0.7%)	1 (3.8%)	2 (1.2%)

(cont below)

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Table 10.1.3 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Hyponatremia Studies (027, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Any Dose n(%)
Musculoskeletal and connective tissue disorders	1 (3.4%)	8 (5.6%)	2 (7.7%)	10 (5.9%)
Arthralgia	0	3 (2.1%)	2 (7.7%)	5 (2.9%)
Back pain	1 (3.4%)	0	0	0
Musculoskeletal chest pain	0	2 (1.4%)	0	2 (1.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (2.8%)	0	4 (2.4%)
Nervous system disorders	5 (17.2%)	23 (16.0%)	2 (7.7%)	25 (14.7%)
Cerebrovascular accident	0	2 (1.4%)	0	2 (1.2%)
Dizziness	1 (3.4%)	5 (3.5%)	1 (3.8%)	6 (3.5%)
Epilepsy NOS	0	3 (2.1%)	0	3 (1.8%)
Headache	2 (6.9%)	9 (6.3%)	0	9 (5.3%)
Loss of consciousness	1 (3.4%)	0	0	0
Syncope	1 (3.4%)	1 (0.7%)	0	1 (0.6%)
Tremor	0	0	1 (3.8%)	1 (0.6%)
Psychiatric disorders	3 (10.3%)	20 (13.9%)	3 (11.5%)	23 (13.5%)
Anxiety	0	3 (2.1%)	0	3 (1.8%)
Confusional state	2 (6.9%)	10 (6.9%)	1 (3.8%)	11 (6.5%)
Disorientation	1 (3.4%)	0	0	0
Hallucination NOS	0	1 (0.7%)	1 (3.8%)	2 (1.2%)
Insomnia	0	6 (4.2%)	1 (3.8%)	7 (4.1%)
Restlessness	0	1 (0.7%)	1 (3.8%)	2 (1.2%)
Renal and urinary disorders	4 (13.8%)	34 (23.6%)	4 (15.4%)	38 (22.4%)
Dysuria	0	3 (2.1%)	1 (3.8%)	4 (2.4%)
Haematuria	1 (3.4%)	5 (3.5%)	0	5 (2.9%)
Oliguria	1 (3.4%)	2 (1.4%)	0	2 (1.2%)
Polyuria	0	10 (6.9%)	0	10 (5.9%)
Renal failure NOS	1 (3.4%)	4 (2.8%)	2 (7.7%)	6 (3.5%)
Renal failure acute	0	4 (2.8%)	1 (3.8%)	5 (2.9%)
Renal failure acute on chronic	0	2 (1.4%)	0	2 (1.2%)
Urinary incontinence	1 (3.4%)	2 (1.4%)	0	2 (1.2%)

(cont below)

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Table 10.1.3 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Hyponatremia Studies (027, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Any Dose n(%)
Urinary retention	0	3 (2.1%)	0	3 (1.8%)
Reproductive system and breast disorders	0	2 (1.4%)	1 (3.8%)	3 (1.8%)
Ovarian mass	0	0	1 (3.8%)	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	6 (20.7%)	22 (15.3%)	1 (3.8%)	23 (13.5%)
Bronchitis NOS	0	2 (1.4%)	0	2 (1.2%)
Chronic obstructive airways disease	0	0	1 (3.8%)	1 (0.6%)
Cough	1 (3.4%)	3 (2.1%)	0	3 (1.8%)
Dyspnoea	1 (3.4%)	4 (2.8%)	0	4 (2.4%)
Dyspnoea exertional	1 (3.4%)	0	0	0
Pharyngolaryngeal pain	2 (6.9%)	2 (1.4%)	0	2 (1.2%)
Pleural effusion	1 (3.4%)	1 (0.7%)	0	1 (0.6%)
Pulmonary congestion	0	4 (2.8%)	0	4 (2.4%)
Respiratory arrest	1 (3.4%)	1 (0.7%)	0	1 (0.6%)
Respiratory distress	1 (3.4%)	1 (0.7%)	0	1 (0.6%)
Respiratory failure	0	2 (1.4%)	0	2 (1.2%)
Skin and subcutaneous tissue disorders	1 (3.4%)	10 (6.9%)	3 (11.5%)	13 (7.6%)
Cyanosis peripheral	0	1 (0.7%)	1 (3.8%)	2 (1.2%)
Decubitus ulcer	0	2 (1.4%)	0	2 (1.2%)
Erythema	0	2 (1.4%)	1 (3.8%)	3 (1.8%)
Pruritus	0	2 (1.4%)	0	2 (1.2%)
Purpura NOS	0	0	1 (3.8%)	1 (0.6%)
Rash NOS	1 (3.4%)	1 (0.7%)	0	1 (0.6%)
Vascular disorders	4 (13.8%)	48 (33.3%)	9 (34.6%)	57 (33.5%)
Arterial occlusion	1 (3.4%)	0	0	0
Deep vein thrombosis	0	2 (1.4%)	0	2 (1.2%)
Flushing	1 (3.4%)	2 (1.4%)	0	2 (1.2%)
Hypertension NOS	0	10 (6.9%)	0	10 (5.9%)
Hypotension NOS	2 (6.9%)	9 (6.3%)	5 (19.2%)	14 (8.2%)
Orthostatic hypotension	0	13 (9.0%)	1 (3.8%)	14 (8.2%)
Phlebitis NOS	1 (3.4%)	12 (8.3%)	4 (15.4%)	16 (9.4%)

Table 10.1.3 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Hyponatremia Studies (027, 080)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Any Dose n(%)
Phlebitis superficial	0	0	1 (3.8%)	1 (0.6%)
Thrombophlebitis	0	3 (2.1%)	0	3 (1.8%)
Thrombophlebitis superficial	0	2 (1.4%)	0	2 (1.2%)

Source: Applicant's Table 2.7.4-10.6D, Summary of Intravenous Safety

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Table 10.1.4: Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Congestive Heart Failure Study (071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Blood and lymphatic system disorders	5 (12.5%)	1 (2.5%)	5 (12.5%)	3 (7.1%)	9 (7.4%)
Anaemia NOS	1 (2.5%)	0	3 (7.5%)	3 (7.1%)	6 (4.9%)
Leukocytosis	0	0	2 (5.0%)	0	2 (1.6%)
Normochromic normocytic anaemia	1 (2.5%)	0	0	0	0
Secondary anaemia	1 (2.5%)	0	0	0	0
Thrombocytopenia	2 (5.0%)	1 (2.5%)	0	0	1 (0.8%)
Cardiac disorders	13 (32.5%)	9 (22.5%)	9 (22.5%)	13 (31.0%)	31 (25.4%)
Angina pectoris	2 (5.0%)	2 (5.0%)	1 (2.5%)	1 (2.4%)	4 (3.3%)
Angina unstable	1 (2.5%)	0	0	0	0
Atrial fibrillation	0	3 (7.5%)	2 (5.0%)	1 (2.4%)	6 (4.9%)
Atrial flutter	0	0	1 (2.5%)	3 (7.1%)	4 (3.3%)
Atrial thrombosis	0	2 (5.0%)	0	0	2 (1.6%)
Atrioventricular block complete	1 (2.5%)	0	0	1 (2.4%)	1 (0.8%)
Atrioventricular block second degree	2 (5.0%)	0	1 (2.5%)	0	1 (0.8%)
Bradycardia NOS	4 (10.0%)	0	0	1 (2.4%)	1 (0.8%)
Cardiac arrest	0	1 (2.5%)	0	0	1 (0.8%)
Cardio-respiratory arrest	0	0	0	1 (2.4%)	1 (0.8%)
Cardiomyopathy NOS	0	2 (5.0%)	0	1 (2.4%)	3 (2.5%)
Cardiopulmonary failure	1 (2.5%)	0	0	0	0
Congestive cardiomyopathy	0	1 (2.5%)	0	0	1 (0.8%)
Coronary artery disease aggravated	0	0	0	1 (2.4%)	1 (0.8%)
Coronary artery occlusion	0	0	1 (2.5%)	0	1 (0.8%)
Ischaemic cardiomyopathy	0	0	0	1 (2.4%)	1 (0.8%)
Mitral valve incompetence	0	0	0	1 (2.4%)	1 (0.8%)
Myocardial infarction	1 (2.5%)	0	0	0	0
Palpitations	1 (2.5%)	0	0	0	0
Sick sinus syndrome	0	0	1 (2.5%)	0	1 (0.8%)
Sinus bradycardia	0	1 (2.5%)	0	0	1 (0.8%)
Sinus tachycardia	0	0	0	1 (2.4%)	1 (0.8%)
Ventricular bigeminy	1 (2.5%)	0	0	0	0
Ventricular extrasystoles	0	1 (2.5%)	1 (2.5%)	0	2 (1.6%)
Ventricular fibrillation	0	0	0	1 (2.4%)	1 (0.8%)

(cont below)

Table 10.1.4 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Congestive Heart Failure Study (071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Ventricular tachycardia	7 (17.5%)	0	5 (12.5%)	4 (9.5%)	9 (7.4%)
Endocrine disorders	1 (2.5%)	0	0	0	0
Hypothyroidism	1 (2.5%)	0	0	0	0
Eye disorders	0	2 (5.0%)	0	1 (2.4%)	3 (2.5%)
Conjunctivitis	0	0	0	1 (2.4%)	1 (0.8%)
Eye irritation	0	1 (2.5%)	0	0	1 (0.8%)
Eye pruritus	0	1 (2.5%)	0	0	1 (0.8%)
Gastrointestinal disorders	15 (37.5%)	12 (30.0%)	11 (27.5%)	8 (19.0%)	31 (25.4%)
Abdominal discomfort	0	0	1 (2.5%)	0	1 (0.8%)
Abdominal distension	2 (5.0%)	0	0	0	0
Abdominal haematoma	0	0	0	1 (2.4%)	1 (0.8%)
Abdominal pain NOS	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.4%)	3 (2.5%)
Abdominal pain lower	1 (2.5%)	0	0	0	0
Anal fissure	1 (2.5%)	0	0	0	0
Colonic polyp	0	0	0	1 (2.4%)	1 (0.8%)
Constipation	6 (15.0%)	5 (12.5%)	6 (15.0%)	5 (11.9%)	16 (13.1%)
Diarrhoea NOS	3 (7.5%)	1 (2.5%)	2 (5.0%)	2 (4.8%)	5 (4.1%)
Dry mouth	0	1 (2.5%)	0	0	1 (0.8%)
Dyspepsia	1 (2.5%)	1 (2.5%)	0	1 (2.4%)	2 (1.6%)
Flatulence	1 (2.5%)	0	0	0	0
Gastrointestinal haemorrhage NOS	1 (2.5%)	0	0	1 (2.4%)	1 (0.8%)
Gastrointestinal upset	0	0	0	1 (2.4%)	1 (0.8%)
Gastrooesophageal reflux disease	1 (2.5%)	0	0	0	0
Haemorrhoids	0	0	0	1 (2.4%)	1 (0.8%)
Hiatus hernia	1 (2.5%)	0	0	0	0
Nausea	6 (15.0%)	4 (10.0%)	4 (10.0%)	1 (2.4%)	9 (7.4%)
Toothache	1 (2.5%)	0	0	0	0
Upper gastrointestinal haemorrhage	1 (2.5%)	0	0	0	0
Vomiting NOS	2 (5.0%)	3 (7.5%)	1 (2.5%)	0	4 (3.3%)
General disorders and administration site conditions	13 (32.5%)	19 (47.5%)	24 (60.0%)	29 (69.0%)	72 (59.0%)

Table 10.1.4 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Congestive Heart Failure Study (071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Anasarca	0	0	0	1 (2.4%)	1 (0.8%)
Asthenia	0	2 (5.0%)	2 (5.0%)	3 (7.1%)	7 (5.7%)
Chest tightness	1 (2.5%)	0	0	0	0
Fatigue	1 (2.5%)	0	0	2 (4.8%)	2 (1.6%)
Impaired healing	0	1 (2.5%)	0	0	1 (0.8%)
Implant site haemorrhage	0	1 (2.5%)	0	0	1 (0.8%)
Infusion related reaction	0	0	0	1 (2.4%)	1 (0.8%)
Infusion site erythema	0	0	3 (7.5%)	1 (2.4%)	4 (3.3%)
Infusion site induration	0	0	0	1 (2.4%)	1 (0.8%)
Infusion site oedema	0	2 (5.0%)	1 (2.5%)	0	3 (2.5%)
Infusion site pain	0	2 (5.0%)	2 (5.0%)	1 (2.4%)	5 (4.1%)
Infusion site phlebitis	2 (5.0%)	7 (17.5%)	13 (32.5%)	14 (33.3%)	34 (27.9%)
Infusion site reaction	0	0	2 (5.0%)	3 (7.1%)	5 (4.1%)
Infusion site swelling	1 (2.5%)	0	2 (5.0%)	0	2 (1.6%)
Infusion site tenderness	0	0	3 (7.5%)	0	3 (2.5%)
Infusion site warmth	0	0	0	1 (2.4%)	1 (0.8%)
Injection site cellulitis	0	4 (10.0%)	2 (5.0%)	3 (7.1%)	9 (7.4%)
Injection site discomfort	0	1 (2.5%)	0	0	1 (0.8%)
Injection site erythema	0	0	1 (2.5%)	0	1 (0.8%)
Injection site haemorrhage	0	1 (2.5%)	0	0	1 (0.8%)
Injection site inflammation	0	0	1 (2.5%)	0	1 (0.8%)
Injection site pain	0	0	0	2 (4.8%)	2 (1.6%)
Injection site phlebitis	0	0	0	1 (2.4%)	1 (0.8%)
Injection site pruritus	0	1 (2.5%)	0	0	1 (0.8%)
Injection site reaction NOS	2 (5.0%)	2 (5.0%)	1 (2.5%)	3 (7.1%)	6 (4.9%)
Injection site tenderness	0	0	1 (2.5%)	0	1 (0.8%)
Injection site thrombosis	0	0	2 (5.0%)	1 (2.4%)	3 (2.5%)
Intermittent pyrexia	1 (2.5%)	0	0	0	0
Mechanical complication of implant	1 (2.5%)	0	0	0	0
Multi-organ failure	1 (2.5%)	0	0	0	0
Oedema NOS	0	1 (2.5%)	0	0	1 (0.8%)
Oedema peripheral	0	1 (2.5%)	0	0	1 (0.8%)
Pain NOS	0	0	1 (2.5%)	0	1 (0.8%)
Pyrexia	4 (10.0%)	2 (5.0%)	0	4 (9.5%)	6 (4.9%)

Table 10.1.4 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Congestive Heart Failure Study (071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Rigors	0	1 (2.5%)	0	0	1 (0.8%)
Sudden cardiac death	0	0	0	1 (2.4%)	1 (0.8%)
Systemic inflammatory response syndrome	1 (2.5%)	0	0	0	0
Thirst	0	0	2 (5.0%)	3 (7.1%)	5 (4.1%)
Venipuncture site bruise	0	0	1 (2.5%)	0	1 (0.8%)
Immune system disorders	0	1 (2.5%)	0	2 (4.8%)	3 (2.5%)
Heart transplant rejection	0	0	0	1 (2.4%)	1 (0.8%)
Urticaria NOS	0	1 (2.5%)	0	1 (2.4%)	2 (1.6%)
Infections and infestations	7 (17.5%)	6 (15.0%)	7 (17.5%)	10 (23.8%)	23 (18.9%)
Asymptomatic bacteriuria	1 (2.5%)	0	2 (5.0%)	0	2 (1.6%)
Bacteriuria	0	1 (2.5%)	0	0	1 (0.8%)
Cellulitis	1 (2.5%)	1 (2.5%)	0	0	1 (0.8%)
Clostridium colitis	1 (2.5%)	0	0	0	0
Cytomegalovirus infection	0	0	0	1 (2.4%)	1 (0.8%)
Herpes zoster	0	0	1 (2.5%)	0	1 (0.8%)
Hiv infection	0	0	0	1 (2.4%)	1 (0.8%)
Implant site infection	1 (2.5%)	0	0	0	0
Infusion site infection	0	1 (2.5%)	0	0	1 (0.8%)
Pneumonia NOS	1 (2.5%)	1 (2.5%)	2 (5.0%)	5 (11.9%)	8 (6.6%)
Sepsis NOS	0	0	1 (2.5%)	1 (2.4%)	2 (1.6%)
Staphylococcal sepsis	0	0	0	1 (2.4%)	1 (0.8%)
Upper respiratory tract infection NOS	0	0	0	1 (2.4%)	1 (0.8%)
Urinary tract infection NOS	4 (10.0%)	2 (5.0%)	1 (2.5%)	1 (2.4%)	4 (3.3%)
Injury, poisoning and procedural complications	3 (7.5%)	3 (7.5%)	2 (5.0%)	2 (4.8%)	7 (5.7%)
Confusion postoperative	0	0	0	1 (2.4%)	1 (0.8%)
Drug toxicity NOS	0	1 (2.5%)	0	0	1 (0.8%)
Fall	0	0	0	1 (2.4%)	1 (0.8%)
Haematuria traumatic	0	0	1 (2.5%)	0	1 (0.8%)
Incision site complication	2 (5.0%)	0	0	0	0
Medical device complication	0	1 (2.5%)	0	0	1 (0.8%)
Nausea postoperative	0	0	0	1 (2.4%)	1 (0.8%)

(cont below)

Table 10.1.4 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Congestive Heart Failure Study (071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Post procedural complication	0	0	1 (2.5%)	0	1 (0.8%)
Post procedural pain	1 (2.5%)	1 (2.5%)	0	1 (2.4%)	2 (1.6%)
Post procedural vomiting	0	0	0	1 (2.4%)	1 (0.8%)
Therapeutic agent poisoning	0	1 (2.5%)	0	0	1 (0.8%)
Urethral injury	1 (2.5%)	0	0	0	0
Investigations	5 (12.5%)	10 (25.0%)	14 (35.0%)	9 (21.4%)	33 (27.0%)
Alanine aminotransferase increased	1 (2.5%)	0	0	0	0
Aspartate aminotransferase increased	1 (2.5%)	0	0	0	0
Blood alkaline phosphatase increased	0	0	0	2 (4.8%)	2 (1.6%)
Blood bilirubin increased	0	1 (2.5%)	0	0	1 (0.8%)
Blood creatine phosphokinase increased	0	1 (2.5%)	0	0	1 (0.8%)
Blood creatinine increased	1 (2.5%)	0	2 (5.0%)	1 (2.4%)	3 (2.5%)
Blood glucose increased	1 (2.5%)	2 (5.0%)	0	0	2 (1.6%)
Blood magnesium decreased	0	1 (2.5%)	3 (7.5%)	0	4 (3.3%)
Blood potassium decreased	0	1 (2.5%)	1 (2.5%)	0	2 (1.6%)
Blood potassium increased	0	1 (2.5%)	0	0	1 (0.8%)
Blood pressure increased	0	1 (2.5%)	0	0	1 (0.8%)
Blood urea increased	1 (2.5%)	0	0	0	0
Blood uric acid increased	0	0	1 (2.5%)	0	1 (0.8%)
Body temperature increased	1 (2.5%)	0	2 (5.0%)	1 (2.4%)	3 (2.5%)
Cardiac murmur NOS	0	0	0	1 (2.4%)	1 (0.8%)
Catheterisation cardiac	0	1 (2.5%)	0	0	1 (0.8%)
Gamma-glutamyltransferase increased	1 (2.5%)	0	0	2 (4.8%)	2 (1.6%)
Haematocrit decreased	0	0	1 (2.5%)	0	1 (0.8%)
Haemoglobin decreased	0	1 (2.5%)	1 (2.5%)	0	2 (1.6%)
Heart sounds abnormal	0	2 (5.0%)	0	1 (2.4%)	3 (2.5%)
Liver function test abnormal	0	1 (2.5%)	0	0	1 (0.8%)
Nitrite urine present	0	1 (2.5%)	0	0	1 (0.8%)
Prothrombin time prolonged	0	1 (2.5%)	0	0	1 (0.8%)
Pulmonary arterial pressure increased	0	0	0	1 (2.4%)	1 (0.8%)
Red blood cell sedimentation rate increased	1 (2.5%)	0	0	0	0
Red blood cells urine	0	0	0	1 (2.4%)	1 (0.8%)
Urine output decreased	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.4%)	3 (2.5%)

Table 10.1.4 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Congestive Heart Failure Study (071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Urine sodium decreased	0	1 (2.5%)	3 (7.5%)	0	4 (3.3%)
Urobilin urine present	0	1 (2.5%)	0	0	1 (0.8%)
White blood cell count increased	0	0	2 (5.0%)	1 (2.4%)	3 (2.5%)
ph urine increased	0	0	1 (2.5%)	0	1 (0.8%)
Metabolism and nutrition disorders	11 (27.5%)	17 (42.5%)	14 (35.0%)	14 (33.3%)	45 (36.9%)
Alkalosis NOS	0	1 (2.5%)	0	0	1 (0.8%)
Anorexia	1 (2.5%)	0	0	0	0
Appetite decreased NOS	0	0	1 (2.5%)	0	1 (0.8%)
Dehydration	1 (2.5%)	0	0	1 (2.4%)	1 (0.8%)
Fluid overload	1 (2.5%)	0	1 (2.5%)	1 (2.4%)	2 (1.6%)
Hyperglycaemia NOS	0	2 (5.0%)	1 (2.5%)	3 (7.1%)	6 (4.9%)
Hyperkalaemia	2 (5.0%)	5 (12.5%)	2 (5.0%)	1 (2.4%)	8 (6.6%)
Hyperlipidaemia NOS	0	0	1 (2.5%)	0	1 (0.8%)
Hypermagnesaemia	1 (2.5%)	1 (2.5%)	0	0	1 (0.8%)
Hypernatraemia	0	2 (5.0%)	3 (7.5%)	2 (4.8%)	7 (5.7%)
Hyperphosphataemia	1 (2.5%)	0	0	1 (2.4%)	1 (0.8%)
Hypervolaemia	0	1 (2.5%)	0	0	1 (0.8%)
Hypocalcaemia	1 (2.5%)	0	0	0	0
Hypoglycaemia NOS	0	2 (5.0%)	0	2 (4.8%)	4 (3.3%)
Hypokalaemia	8 (20.0%)	5 (12.5%)	8 (20.0%)	4 (9.5%)	17 (13.9%)
Hypomagnesaemia	4 (10.0%)	1 (2.5%)	1 (2.5%)	2 (4.8%)	4 (3.3%)
Hyponatraemia	1 (2.5%)	1 (2.5%)	2 (5.0%)	1 (2.4%)	4 (3.3%)
Hypophosphataemia	0	1 (2.5%)	0	1 (2.4%)	2 (1.6%)
Metabolic acidosis NOS	1 (2.5%)	0	0	0	0
Musculoskeletal and connective tissue disorders	3 (7.5%)	5 (12.5%)	7 (17.5%)	8 (19.0%)	20 (16.4%)
Arthralgia	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.4%)	3 (2.5%)
Arthritis NOS	0	0	0	1 (2.4%)	1 (0.8%)
Back pain	0	2 (5.0%)	2 (5.0%)	1 (2.4%)	5 (4.1%)
Chest wall pain	0	0	0	1 (2.4%)	1 (0.8%)
Groin pain	0	0	0	1 (2.4%)	1 (0.8%)
Joint stiffness	1 (2.5%)	0	0	0	0
Joint swelling	0	1 (2.5%)	0	0	1 (0.8%)

Table 10.1.4 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Congestive Heart Failure Study (071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Limb discomfort NOS	0	0	1 (2.5%)	0	1 (0.8%)
Muscle cramp	0	1 (2.5%)	2 (5.0%)	0	3 (2.5%)
Muscle spasms	0	0	0	1 (2.4%)	1 (0.8%)
Musculoskeletal discomfort	1 (2.5%)	0	0	0	0
Pain in extremity	0	3 (7.5%)	2 (5.0%)	4 (9.5%)	9 (7.4%)
Pain in jaw	0	1 (2.5%)	0	0	1 (0.8%)
Shoulder blade pain	0	1 (2.5%)	0	0	1 (0.8%)
Nervous system disorders	6 (15.0%)	6 (15.0%)	3 (7.5%)	6 (14.3%)	15 (12.3%)
Carotid artery stenosis	1 (2.5%)	0	0	0	0
Cerebrovascular accident	0	0	0	1 (2.4%)	1 (0.8%)
Convulsions NOS	0	0	1 (2.5%)	0	1 (0.8%)
Depressed level of consciousness	1 (2.5%)	0	0	0	0
Dizziness	2 (5.0%)	3 (7.5%)	0	1 (2.4%)	4 (3.3%)
Dizziness postural	0	0	1 (2.5%)	0	1 (0.8%)
Headache	3 (7.5%)	2 (5.0%)	1 (2.5%)	4 (9.5%)	7 (5.7%)
Syncope	0	1 (2.5%)	0	1 (2.4%)	2 (1.6%)
Psychiatric disorders	7 (17.5%)	7 (17.5%)	3 (7.5%)	4 (9.5%)	14 (11.5%)
Agitation	0	2 (5.0%)	0	2 (4.8%)	4 (3.3%)
Anxiety	1 (2.5%)	0	1 (2.5%)	0	1 (0.8%)
Confusional state	0	1 (2.5%)	0	0	1 (0.8%)
Depression	0	0	0	1 (2.4%)	1 (0.8%)
Insomnia	6 (15.0%)	3 (7.5%)	2 (5.0%)	3 (7.1%)	8 (6.6%)
Restlessness	0	2 (5.0%)	0	0	2 (1.6%)
Renal and urinary disorders	6 (15.0%)	8 (20.0%)	7 (17.5%)	5 (11.9%)	20 (16.4%)
Haematuria	1 (2.5%)	1 (2.5%)	3 (7.5%)	0	4 (3.3%)
Leukocyturia	0	1 (2.5%)	2 (5.0%)	0	3 (2.5%)
Nocturia	0	0	0	1 (2.4%)	1 (0.8%)
Renal disorder NOS	1 (2.5%)	0	0	0	0
Renal failure NOS	1 (2.5%)	3 (7.5%)	1 (2.5%)	2 (4.8%)	6 (4.9%)
Renal failure acute	3 (7.5%)	1 (2.5%)	0	0	1 (0.8%)
Renal failure acute on chronic	0	0	1 (2.5%)	0	1 (0.8%)

Table 10.1.4 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Congestive Heart Failure Study (071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Renal failure chronic	0	0	0	1 (2.4%)	1 (0.8%)
Renal impairment NOS	0	2 (5.0%)	0	0	2 (1.6%)
Renal pain	0	1 (2.5%)	0	0	1 (0.8%)
Urinary retention	0	0	1 (2.5%)	1 (2.4%)	2 (1.6%)
Respiratory, thoracic and mediastinal disorders	17 (42.5%)	11 (27.5%)	19 (47.5%)	14 (33.3%)	44 (36.1%)
Bronchitis NOS	0	0	1 (2.5%)	0	1 (0.8%)
Bronchospasm NOS	0	0	0	1 (2.4%)	1 (0.8%)
Chronic obstructive airways disease	1 (2.5%)	0	0	1 (2.4%)	1 (0.8%)
Chronic obstructive airways disease exacerbated	0	0	0	1 (2.4%)	1 (0.8%)
Cough	3 (7.5%)	3 (7.5%)	2 (5.0%)	1 (2.4%)	6 (4.9%)
Crackles lung	2 (5.0%)	0	0	0	0
Dyspnoea	5 (12.5%)	1 (2.5%)	2 (5.0%)	0	3 (2.5%)
Dyspnoea exacerbated	8 (20.0%)	7 (17.5%)	10 (25.0%)	8 (19.0%)	25 (20.5%)
Dyspnoea exertional	0	1 (2.5%)	0	0	1 (0.8%)
Epistaxis	0	0	1 (2.5%)	0	1 (0.8%)
Hypercapnia	0	0	1 (2.5%)	1 (2.4%)	2 (1.6%)
Hypoventilation	0	0	0	1 (2.4%)	1 (0.8%)
Lung infiltration NOS	1 (2.5%)	0	0	0	0
Pharyngolaryngeal pain	1 (2.5%)	0	1 (2.5%)	0	1 (0.8%)
Pleural effusion	0	0	1 (2.5%)	0	1 (0.8%)
Pulmonary congestion	2 (5.0%)	1 (2.5%)	2 (5.0%)	2 (4.8%)	5 (4.1%)
Pulmonary oedema NOS	0	0	1 (2.5%)	2 (4.8%)	3 (2.5%)
Rales	1 (2.5%)	0	0	0	0
Respiratory acidosis	1 (2.5%)	0	0	0	0
Respiratory distress	0	0	1 (2.5%)	0	1 (0.8%)
Respiratory failure	0	0	1 (2.5%)	1 (2.4%)	2 (1.6%)
Rhinorrhoea	1 (2.5%)	0	0	1 (2.4%)	1 (0.8%)
Wheezing	1 (2.5%)	0	1 (2.5%)	0	1 (0.8%)
Skin and subcutaneous tissue disorders	3 (7.5%)	2 (5.0%)	5 (12.5%)	4 (9.5%)	11 (9.0%)
Contusion	0	0	2 (5.0%)	0	2 (1.6%)
Dry skin	0	0	0	1 (2.4%)	1 (0.8%)
Erythema	0	0	2 (5.0%)	1 (2.4%)	3 (2.5%)

Table 10.1.4 (cont): Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Any Dose (by mg) Group, "Full Dose" IV Congestive Heart Failure Study (071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 Other n(%)	YM087 Any Dose n(%)
Pruritus	2 (5.0%)	1 (2.5%)	0	2 (4.8%)	3 (2.5%)
Rash NOS	1 (2.5%)	1 (2.5%)	0	0	1 (0.8%)
Skin hyperpigmentation	0	0	0	1 (2.4%)	1 (0.8%)
Skin irritation	0	0	1 (2.5%)	0	1 (0.8%)
Skin ulcer	0	0	1 (2.5%)	0	1 (0.8%)
Surgical and medical procedures	1 (2.5%)	0	0	0	0
Implantable defibrillator replacement	1 (2.5%)	0	0	0	0
Vascular disorders	7 (17.5%)	7 (17.5%)	5 (12.5%)	6 (14.3%)	18 (14.8%)
Flushing	2 (5.0%)	0	0	0	0
Hypertension NOS	0	2 (5.0%)	2 (5.0%)	0	4 (3.3%)
Hypotension NOS	6 (15.0%)	5 (12.5%)	2 (5.0%)	5 (11.9%)	12 (9.8%)
Orthostatic hypotension	0	0	1 (2.5%)	0	1 (0.8%)
Postoperative hypertension	0	0	0	1 (2.4%)	1 (0.8%)
Subclavian steal syndrome	0	0	1 (2.5%)	0	1 (0.8%)

Source: Applicant's Table 2.7.4-10.6E, Summary of Intravenous Safety

Table 10.1.5 Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Conivaptan Patients, Overall Safety Population (all IV + all Oral)[1]

		Coni N = 1148 n (%)	Pbo N = 372 n (%)
System Organ Class	**MedDRA Term**		
Blood and lymphatic system disorders		59 (5)	17 (5)
	Anemia NOS	36 (3)	8 (2)
Cardiac disorders		182 (16)	58 (16)
	Angina pectoris	16 (1)	4 (1)
	A fib	21 (2)	2 (<1)
	Bradycardia NOS	12 (1)	8 (2)
	Cardiac failure NOS	13 (1)	4 (1)
	Congestive cardiac failure aggravated	49 (4)	9 (2)
	V tach	26 (2)	13 (3)
Eye disorders		22 (2)	7 (2)
GI disorders		212 (18)	60 (16)
	Abdominal pain NOS	19 (2)	7 (2)
	Constipation	47 (4)	15 (4)
	Diarrhea NOS	39 (3)	8 (2)
	Dry mouth	21 (2)	1 (<1)
	Dyspepsia	16 (1)	6 (2)
	Nausea	52 (4)	15 (4)
	Vomiting NOS	30 (3)	8 (2)
General disorders and administration site conditions		380 (33)	65 (17)
	Asthenia	35 (3)	4 (1)
	Chest pain	43 (4)	12 (3)
	Fatigue	44 (4)	15 (4)
	Infusion site erythema	16 (1)	0
	Infusion site phlebitis	75 (6)	3 (<1)
	Infusion site reaction	47 (4)	0
	Injection site reaction NOS	18 (2)	2 (<1)
	Edema NOS	14 (1)	1 (<1)
	Edema peripheral	30 (3)	4 (1)
	Pyrexia	31 (3)	6 (2)
	Thirst	53 (5)	8 (2)

Table 10.1.5 Number and Percentage of Patients with Treatment-Emergent Adverse Events Occurring in at Least 1% of Conivaptan Patients, Overall Safety Population (all IV + all Oral)[1]

System Organ Class	MedDRA Term	Coni N = 1148 n (%)	Pbo N = 372 n (%)
Infections and infestations		185 (16)	52 (14)
	Influenza	12 (1)	2 (<1)
	Nasopharyngitis	21 (2)	7 (2)
	Pneumonia NOS	26 (2)	6 (2)
	URI NOS	20 (2)	4 (1)
	UTI NOS	43 (4)	16 (4)
Injury, poisoning and procedural complications		44 (4)	10 (3)
Investigations		150 (13)	32 (9)
	Blood glucose increased	15 (1)	5 (1)
	Wt increased	14 (1)	2 (<1)
Metabolism and nutrition disorders		192 (17)	46 (12)
	Dehydration	15 (1)	1 (<1)
	Hyperglycemia NOS	27 (2)	6 (2)
	Hyperkalemia	33 (3)	5 (1)
	Hypoglycemia NOS	17 (1)	3 (<1)
	Hypokalemia	54 (5)	14 (4)
	Hypomagnesemia	15 (1)	4 (1)
	Hyponatremia	20 (2)	2 (<1)
	Hypophosphatemia	3 (<1)	0
Musculoskeletal and connective tissue disorders		114 (10)	24 (6)
	Arthralgia	20 (2)	9 (2)
	Back pain	20 (2)	4 (1)
	Muscle cramp	15 (1)	4 (1)
	Pain in extremity	26 (2)	4 (1)
Neoplasms benign, malignant and unspecified		15 (1)	1 (<1)
Nervous system disorders		147 (13)	37 (10)
	Dizziness	55 (5)	11 (3)
	Headache	56 (5)	19 (5)
	Syncope	15 (1)	2 (<1)
Psychiatric disorders		90 (8)	23 (6)
	Anxiety	13 (1)	1 (<1)
	Confusional state	19 (2)	3 (<1)
	Insomnia	33 (3)	13 (3)
Renal and urinary disorders		123 (11)	25 (7)
	Hematuria	16 (1)	5 (1)
	Polyuria	17 (1)	0
	Renal failure NOS	35 (3)	5 (1)
Reproductive system and breast disorders		17 (1)	3 (<1)
Respiratory, thoracic and mediastinal disorders		174 (15)	57 (15)
	Bronchitis NOS	14 (1)	1 (<1)
	Cough	29 (3)	8 (2)
	Dyspnea	27 (2)	10 (3)
	Dyspnea exacerbated	51 (4)	14 (4)
	Pulmonary embolism	13 (1)	3 (<1)
Skin and subcutaneous disorders		61 (5)	14 (4)
	Rash NOS	14 (1)	3 (<1)
Vascular disorders		130 (11)	32 (9)
	Htn NOS	18 (2)	1 (<1)
	Hypotension NOS	61 (5)	21 (6)
	Orthostatic hypotension	21 (2)	4 (1)
	Phlebitis NOS	17 (1)	2 (<1)

1 Includes studies 016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 031, 032, 033, 034, 038, 043, 044, 071, 080
Source: Applicant's Table 1, Safety Update

Appendix 10.2 Laboratory Tables

Table 10.2.1 Mean Change from Baseline, Clinical Chemistry Laboratory, Using Last On-treatment Measurement, All "Full Dose" IV Studies (027, 071, 074, 079, 080, 083)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
BUN:Cr Ratio	64	20.42	0.62	162	18.20	-0.96	63	21.17	-2.61	36	23.89	-2.80	261	19.70	-1.63
Albumin (g/dL)	43	3.83	-0.07	151	3.35	-0.07	41	3.42	-0.14	11	3.97	0.05	203	3.40	-0.06
ALT (U/L)	44	28.64	-5.16	161	26.56	5.76	41	36.24	8.59	12	34.75	0.17	214	28.86	5.61
Alkaline Phosphatase (U/L)	43	123.02	0.05	139	103.99	1.77	41	93.80	5.61	12	98.50	7.08	192	104.72	2.92
AST (U/L)	44	27.86	-3.75	169	22.97	5.06	42	42.96	-7.74	12	43.00	-4.83	223	85.37	4.89
Direct Bilirubin (mg/dL)				20	0.14	0.00							20	0.14	0.00
BUN (mg/dL)	65	26.30	-0.63	167	20.84	0.66	64	26.02	1.35	36	32.64	0.97	267	23.70	0.87
Calcium (mg/dL)	20	9.00	0.00	19	8.68	0.26	13	9.05	0.22	12	8.67	0.42	49	8.90	0.25
CPK (U/L)	41	90.02	-25.20	119	123.42	-45.18	37	169.05	-58.61	12	157.92	-48.75	162	136.40	-54.27
Chloride (mEq/L)	45	94.03	0.37	138	93.47	5.97	41	93.65	7.00	11	99.45	1.73	190	93.86	5.95
Carbon Dioxide (mEq/L)	26	24.76	0.76	37	26.19	-0.01	25	24.87	0.32				62	25.65	0.18
CPK-MB (U/L)				2	24.00	-24.00							2	24.00	-24.00
Creatinine (mg/dL)	65	1.26	-0.07	196	1.06	0.11	64	1.18	0.21	36	1.32	0.21	296	1.12	0.14
GGT (U/L)	11	61.64	3.27	11	70.82	5.45	14	73.21	-0.14	9	77.00	3.44	34	73.44	2.62
Glucose (mg/dL)	42	152.60	-0.45	148	139.96	4.17	37	131.27	1.68	11	151.92	5.56	196	139.99	3.81

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
[1] Change from baseline is calculated as the change from last pre-treatment measure to last on-treatment measure.
Data Source: demog.sas7bdat, lab.sas7bdat Program Source: t_chem.sas

(cont below)

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Table 10.2.1 (cont) Mean Change from Baseline, Clinical Chemistry Laboratory, Using Last On-treatment Measurement, All "Full Dose" IV Studies (027, 071, 074, 079, 080, 083)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
Glucose, Fasting (mg/dL)	4	132.20	-22.36	16	116.81	-2.44	4	114.50	10.00				20	117.96	0.08
Potassium (mEq/L)	62	4.24	-0.01	163	4.20	0.11	68	4.32	0.04	96	4.21	0.27	262	4.28	0.12
LDH (U/L)	25	324.40	-28.84	104	368.72	-8.58	28	389.96	8.00				127	371.49	-6.69
Sodium (mEq/L)	45	134.76	-0.12	169	129.13	5.56	47	134.69	4.13	96	136.96	2.60	268	131.96	4.92
Total Bilirubin (mg/dL)	42	0.74	-0.01	137	0.68	0.00	41	0.73	-0.05	12	0.90	-0.01	190	0.81	-0.02
Total Cholesterol (mg/dL)	15	176.53	-0.60	16	127.38	0.19	16	160.38	11.31	8	162.06	9.06	40	151.51	6.41
Total Protein (g/dL)	44	6.60	-0.06	118	6.45	-0.02	60	6.98	0.04	12	7.31	0.16	170	6.62	0.01
Triglycerides (mmol/L)				1	2.70	1.05	1	1.42	0.18				2	2.06	0.62
Uric Acid (umol/L)	40	393.75	-22.40	109	351.10	-45.11	35	354.94	42.35	11	411.86	46.61	155	353.28	-20.74
Digoxin (ng/mL)	1	2.43	-0.28												
INR	19	1.25	0.06	100	1.19	-0.04	28	1.20	0.04				128	1.19	-0.03
Phosphorus (mg/dL)	16	4.01	-0.35	15	3.75	0.12	15	3.69	0.12	12	3.21	0.55	42	3.57	0.25
Prothrombin Time (s)	18	14.53	0.41	89	13.58	-0.13	16	13.71	0.45				107	13.60	-0.02
Prothrombin Time (%)				9	82.46	1.78							9	82.46	1.78

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
[1] Change from baseline is calculated as the change from last pre-treatment measure to last on-treatment measure.
Data Source: demog.sas7bdat, lab.sas7bdat Program Source: c_chem.sas

Source: Applicant's Table 2.7.4-14.6A, Summary of Intravenous Safety

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Table 10.2.2 Mean Change from Baseline, Hematology Laboratory, Using Last On-treatment Measurement, All "Full Dose" IV Studies (027, 071, 074, 079, 080, 083)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
Basophils (/uL)				23	59.13	-5.70	2	0.00	0.00				25	56.00	-5.00
Basophils (%)	29	0.42	0.07	111	0.55	0.00	29	0.86	0.02	5	0.34	-0.05	145	0.60	0.06
Hematocrit (%)	44	35.59	-1.16	140	36.30	-0.84	43	35.52	-0.77	12	36.93	1.73	195	36.17	-0.66
Eosinophils (/uL)				23	169.57	-13.04	2	150.00	0.00				25	168.00	-12.00
Eosinophils (%)	31	2.42	0.65	113	1.76	0.32	29	1.86	0.12	8	3.25	-0.05	150	1.81	0.26
Hemoglobin (g/dL)	44	11.91	-0.38	140	12.32	-0.35	43	11.86	-0.26	12	12.13	0.55	195	12.21	-0.29
Lymphocytes (/uL)				23	1878.91	-121.74	2	1450.00	200.00				25	1932.00	-96.00
Lymphocytes (%)	32	17.63	-0.96	113	17.97	-1.10	29	18.14	-2.28	9	19.59	-0.17	151	18.10	-1.09
MCV (fL)	25	91.26	0.31	26	88.42	1.20	26	87.43	2.81				52	87.93	2.01
Monocytes (/uL)				23	434.78	52.17	2	400.00	-50.00				25	432.00	44.00
Monocytes (%)	31	7.38	0.72	113	8.00	-0.45	29	8.99	-1.16	8	9.84	0.86	150	8.24	-0.52
Neutrophils-Bands (%)	5	0.00	0.00	5	2.02	0.06	2	0.00	0.00	2	0.00	0.00	10	1.01	0.03
Neutrophils (/uL)				23	4708.70	218.04	2	3900.00	250.00				25	4596.00	216.00
Neutrophils (%)	15	75.78	-1.02	95	69.50	2.38	14	69.85	2.67	5	73.70	-1.24	114	69.72	2.26
Neutrophils-Segs (%)	14	67.65	0.51	13	68.19	-0.62	13	69.51	1.65	4	62.78	-0.20	30	68.03	0.42
Platelets (/uL)	44	264890.9	22.73	136	276601.5	6115.84	41	262697.7	20976.74	12	250583.3	14250.00	193	271596.0	9932.64

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
[1] Change from baseline is calculated as the change from last pre-treatment measure to last on-treatment measure.
Data Source: demog.sas7bdat, lab.sas7bdat Program Source: t_hema.sas

Table 10.2.2 (cont) Mean Change from Baseline, Hematology Laboratory, Using Last On-treatment Measurement, All "Full Dose" IV Studies (027, 071, 074, 079, 080, 083)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
RBC (million/uL)	44	3.98	-0.14	100	4.22	-0.11	43	3.99	-0.04	12	4.24	0.17	155	4.16	-0.07
Reticulocytes (%)				1	2.00	0.40	1	2.20	0.00				2	2.10	0.20
Reticulocytes (/uL)				1	110000.0	0.00	1	110600.0	-600.00				2	110300.0	-300.00
WBC (/uL)	44	5428.91	-548.64	169	9240.41	629.59	43	7661.86	1627.91	12	8342.50	950.00	224	8589.29	840.00

Source: Applicant's Table 2.7.4-17.6A, Summary of Intravenous Safety

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Table 10.2.3 Mean Change from Baseline, Clinical Chemistry Laboratory, Using Last On-treatment Measurement, "Full-Dose" IV Studies in Patients (027, 071, 080)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
BUN:Cr Ratio	64	20.42	0.62	141	18.92	-0.85	68	21.36	-2.61	36	23.89	-2.90	239	20.30	-1.60
Albumin (g/dL)	43	3.53	-0.07	159	3.34	-0.07	40	3.41	-0.16	11	3.97	0.05	201	3.39	-0.05
ALT (U/L)	44	28.64	-5.16	149	27.12	5.99	40	36.88	6.68	12	84.75	0.17	201	29.52	5.75
Alkaline Phosphatase (U/L)	42	122.02	0.05	117	105.56	2.16	40	95.05	5.46	12	92.50	7.08	169	102.15	3.30
AST (U/L)	44	37.86	-3.75	147	34.25	9.95	41	49.56	-7.98	12	48.00	-4.82	200	36.78	5.89
BUN (mg/dL)	65	26.80	-0.63	148	21.91	1.02	68	26.29	1.43	36	32.64	0.97	244	24.66	1.12
Calcium (mg/dL)	20	9.00	0.00	15	8.87	0.26	17	9.09	0.21	12	8.67	0.42	47	8.90	0.29
CPK (U/L)	41	90.02	-25.20	112	123.21	-45.30	36	171.36	-35.33	12	157.92	-48.75	160	136.65	-54.57
Chloride (mEq/L)	45	94.03	0.97	117	91.45	6.61	40	98.43	7.10	11	99.45	1.73	168	92.45	6.40
Carbon Dioxide (mEq/L)	26	24.76	0.76	26	25.50	-0.40	25	24.87	0.92				51	25.19	-0.04
CPK-MB (U/L)				2	34.00	-24.00							2	34.00	-24.00
Creatinine (mg/dL)	65	1.26	-0.07	175	1.06	0.12	68	1.19	0.21	36	1.82	0.21	274	1.12	0.15
GGT (U/L)	11	61.64	2.27	10	75.40	5.90	12	76.21	-0.23	9	77.00	2.44	32	77.03	2.72
Glucose (mg/dL)	42	152.60	-0.45	127	147.92	5.05	36	132.61	1.77	11	151.92	5.56	174	145.00	4.40
Glucose, Fasting (mg/dL)	4	132.20	-22.36	16	118.51	-2.44	4	114.50	10.00				20	117.95	0.05

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
[1] Change from baseline is calculated as the change from last pre-treatment measure to last on-treatment measure.
Data Source: demog.sas7bdat, lab.sas7bdat Program Source: t_chem.sas

Table 10.2.3 (cont) Mean Change from Baseline, Clinical Chemistry Laboratory, Using Last On-treatment Measurement, "Full-Dose" IV Studies in Patients (027, 071, 080)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
Potassium (mEq/L)	62	4.24	-0.01	141	4.18	0.14	62	4.32	0.05	36	4.21	0.17	239	4.22	0.13
LDH (U/L)	25	334.40	-28.54	104	366.71	-8.53	23	383.96	8.00				127	371.49	-6.69
Sodium (mEq/L)	45	134.76	-0.12	161	137.54	6.24	46	134.60	4.16	36	138.36	2.80	243	130.48	5.23
Total Bilirubin (mg/dL)	43	0.74	-0.01	115	0.87	-0.01	40	0.74	-0.09	12	0.90	-0.01	167	0.84	-0.01
Total Cholesterol (mg/dL)	15	176.53	-0.60	15	138.27	-0.67	15	159.73	9.53	8	162.06	9.02	38	150.57	5.40
Total Protein (g/dL)	44	6.60	-0.06	117	6.44	-0.02	39	6.54	0.01	12	7.31	0.16	168	6.62	0.00
Uric Acid (umol/L)	40	368.73	-28.40	108	380.66	-48.45	34	356.20	48.22	11	411.98	46.61	152	355.74	-21.24
Digoxin (ng/mL)	1	2.48	-0.35												
INR	19	1.15	0.06	58	1.23	-0.06	17	1.22	0.04				108	1.23	-0.04
Phosphorus (mg/dL)	16	4.01	-0.35	14	3.75	0.13	14	3.70	0.06	12	3.21	0.55	40	3.58	0.24
Prothrombin Time (s)	18	14.52	0.41	77	14.08	-0.19	17	13.66	0.45				94	14.00	-0.05
Prothrombin Time (%)				9	82.46	1.78							9	81.46	1.78

Source: Applicant's Table 2.7.4-14.6B, Summary of Intravenous Safety

Table 10.2.4 Mean Change from Baseline, Hematology Laboratory, Using Last On-treatment Measurement, "Full-Dose" IV Studies in Patients (027, 071, 080)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
Basophils (/uL)				1	0.00	0.00	1	0.00	0.00				2	0.00	0.00
Basophils (%)	29	0.42	0.07	100	0.54	-0.01	29	0.86	0.32	8	0.94	-0.06	137	0.49	0.06
Hematocrit (%)	44	35.58	-1.15	119	35.18	-0.77	42	35.55	-0.87	12	36.98	1.73	172	35.39	-0.62
Eosinophils (/uL)				1	100.00	0.00	1	100.00	100.00				2	100.00	50.00
Eosinophils (%)	31	2.42	0.65	102	1.69	0.84	29	1.88	0.12	8	2.25	-0.06	139	1.75	0.27
Hemoglobin (g/dL)	44	11.91	-0.38	119	11.86	-0.36	42	11.85	-0.29	12	12.13	0.58	172	11.88	-0.28
Lymphocytes (/uL)				1	2400.00	900.00	1	700.00	100.00				2	1550.00	500.00
Lymphocytes (%)	32	17.63	-0.56	101	16.99	-1.30	25	18.14	-1.25	9	19.59	-0.17	140	17.39	-1.22
MCV (fL)	25	91.96	0.21	25	88.60	1.25	25	87.59	2.92				50	88.10	2.10
Monocytes (/uL)				1	800.00	100.00	1	500.00	-100.00				2	650.00	0.00
Monocytes (%)	31	7.38	0.72	102	8.83	-0.56	29	8.99	-1.16	8	9.84	0.86	139	9.50	-0.58
Neutrophils-Bands (%)	5	0.00	0.00	5	2.02	0.06	9	0.00	0.00	2	0.00	0.00	10	1.01	0.03
Neutrophils (/uL)				1	2600.00	-100.00	1	5400.00	-1200.00				2	4000.00	-650.00
Neutrophils (%)	15	78.73	-1.02	84	70.95	2.86	14	69.55	2.67	5	73.70	-1.24	103	70.47	2.63
Neutrophils-Segs (%)	14	67.55	0.51	13	68.18	-0.62	13	69.51	1.65	4	62.78	-0.20	30	68.03	0.41
Platelets (/uL)	44	264590.9	22.73	116	281524.5	3336.21	42	261681.0	20404.76	12	250583.3	14250.00	170	274494.1	8323.53

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
[1] Change from baseline is calculated as the change from last pre-treatment measure to last on-treatment measure.
Data Source: demog.sas7bdat, lab.sas7bdat Program Source: p_hema.sas

Table 10.2.4 (cont) Mean Change from Baseline, Hematology Laboratory, Using Last On-treatment Measurement, "Full-Dose" IV Studies in Patients (027, 071, 080)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
RBC (million/uL)	44	3.98	-0.14	79	4.04	-0.11	42	3.98	-0.06	12	4.24	0.17	132	4.04	-0.07
WBC (/uL)	44	8425.91	-548.64	147	9502.24	710.88	42	7701.43	1619.05	12	8342.50	980.00	201	9056.72	916.72

Source: Applicant's Table 2.7.4-17.6B, Summary of Intravenous Safety

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Table 10.2.5 Mean Change from Baseline, Clinical Chemistry Laboratory, Using Last On-treatment Measurement, Controlled "Full Dose" IV Studies (027, 071, 079)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
BUN:Cr Ratio	64	20.42	0.62	54	20.46	0.56	62	21.17	-2.61	36	23.69	-2.90	169	21.49	-1.81
Albumin (g/dL)	43	3.53	-0.07	42	3.36	-0.06	41	3.42	-0.14	11	3.57	0.08	94	3.47	-0.08
ALT (U/L)	44	25.64	-5.16	41	24.00	27.46	41	36.24	6.59	12	34.75	0.17	94	30.71	14.57
Alkaline Phosphatase (U/L)	43	123.02	0.05	41	114.80	2.24	41	93.80	5.61	12	92.50	7.08	94	102.80	4.83
AST (U/L)	44	27.86	-3.75	41	30.44	44.85	42	42.86	-7.74	12	43.00	-4.83	95	37.52	15.23
BUN (mg/dL)	65	26.30	-0.62	55	25.21	2.62	64	26.02	1.35	36	32.34	0.97	165	28.37	1.79
Calcium (mg/dL)	20	9.00	0.00	19	8.88	0.26	18	9.08	0.22	12	8.67	0.42	49	8.90	0.29
CPK (U/L)	41	90.02	-25.20	41	97.12	-14.49	37	169.05	-82.81	12	157.92	-48.75	90	130.24	-47.56
Chloride (mEq/L)	45	94.04	0.27	43	93.21	4.24	41	93.68	7.00	11	98.45	1.73	95	94.14	5.14
Carbon Dioxide (mEq/L)	26	24.76	0.76	26	25.50	-0.40	25	24.87	0.32				51	25.19	-0.04
Creatinine (mg/dL)	65	1.26	-0.07	55	1.26	0.17	64	1.18	0.21	36	1.32	0.21	165	1.24	0.19
GGT (U/L)	11	61.64	2.27	11	70.82	5.45	14	79.21	-0.14	9	77.00	3.44	34	78.44	2.62
Glucose (mg/dL)	42	132.60	-0.45	29	142.90	2.41	37	131.27	1.59	11	151.92	5.56	87	139.10	2.55
Glucose, Fasting (mg/dL)	4	152.20	-21.86	6	128.06	10.27	4	114.60	10.00				10	123.32	10.16
Potassium (mEq/L)	62	4.24	-0.01	52	4.23	0.13	62	4.32	0.04	36	4.21	0.27	161	4.26	0.13

[*] All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
[1] Change from baseline is calculated as the change from last pre-treatment measure to last on-treatment measure.
Data Source: demog.sas7bdat, lab.sas7bdat Program Source: t_chem.sas

Table 10.2.5 (cont) Mean Change from Baseline, Clinical Chemistry Laboratory, Using Last On-treatment Measurement, Controlled "Full Dose" IV Studies (027, 071, 079)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
LDH (U/L)	25	334.40	-23.64	26	296.58	29.73	28	383.96	3.00				49	337.69	17.18
Sodium (mEq/L)	45	134.76	-0.11	48	135.04	2.51	47	134.69	4.13	36	138.86	2.80	131	135.83	3.17
Total Bilirubin (mg/dL)	43	0.74	-0.01	42	0.87	0.13	41	0.78	-0.08	12	0.90	-0.01	94	0.81	0.02
Total Cholesterol (mg/dL)	15	176.53	-3.60	16	137.38	0.19	16	160.38	11.91	8	162.06	9.03	40	151.51	6.91
Total Protein (g/dL)	44	6.60	-0.06	42	6.62	0.06	40	6.68	0.08	12	7.31	0.16	94	6.84	0.05
Triglycerides (mmol/L)				1	2.70	1.08	1	1.42	0.18				2	2.06	0.62
Uric Acid (umol/L)	40	393.75	-22.40	39	349.67	24.98	38	384.94	43.28	11	411.58	46.61	88	369.89	36.32
Digoxin (ng/mL)	1	0.46	-0.03												
INR	19	1.15	0.06	16	1.18	0.02	15	1.20	0.04				34	1.19	0.03
Phosphorus (mg/dL)	16	4.01	-0.25	16	3.75	0.12	15	3.69	0.18	12	3.21	0.58	42	3.57	0.28
Prothrombin Time (s)	18	14.52	0.41	16	13.57	0.55	13	13.71	0.45				34	13.64	0.40

Source: Applicant's Table 2.7.4-14.6F, Summary of Intravenous Safety

Table 10.2.6 Mean Change from Baseline, Hematology Laboratory, Using Last On-treatment Measurement, Controlled "Full Dose" IV Studies (027, 071, 079)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
Basophils (/uL)				2	0.00	0.00	2	0.00	0.00				4	0.00	0.00
Basophils (%)	29	0.42	0.07	27	0.52	0.05	29	0.36	0.02	8	0.34	-0.05	64	0.42	0.12
Hematocrit (%)	44	25.68	-1.15	42	36.36	-0.69	43	25.53	-0.77	12	36.96	1.73	97	26.05	-0.40
Eosinophils (/uL)				2	150.00	-50.00	2	150.00	0.00				4	150.00	-25.00
Eosinophils (%)	21	2.42	0.65	27	1.55	0.04	29	1.55	0.12	8	2.26	-0.05	64	1.79	0.06
Hemoglobin (g/dL)	44	11.91	-0.35	42	12.05	-0.36	43	11.86	-0.26	12	12.12	0.55	97	11.99	-0.30
Lymphocytes (/uL)				2	2000.00	350.00	2	1450.00	200.00				4	1725.00	275.00
Lymphocytes (%)	32	17.69	-0.95	27	16.72	-0.84	29	15.14	-1.28	9	19.59	-0.17	65	17.75	-0.82
MCV (fL)	25	91.36	0.31	26	88.48	1.00	26	87.48	2.31				52	87.98	2.01
Monocytes (/uL)				2	350.00	100.00	2	400.00	-50.00				4	375.00	25.00
Monocytes (%)	31	7.38	0.72	27	8.27	0.14	29	8.99	-0.16	8	9.34	0.56	64	8.76	-0.36
Neutrophils-Bands (%)	5	0.00	0.00	5	2.02	0.06	3	0.00	0.00	2	0.00	0.00	10	1.01	0.02
Neutrophils (/uL)				2	3000.00	550.00	2	3300.00	250.00				4	3150.00	600.00
Neutrophils (%)	18	75.78	-1.01	9	65.81	-0.10	14	69.85	2.67	5	73.70	-1.24	28	69.24	1.08
Neutrophils-Segs (%)	14	67.85	0.51	13	66.18	-0.62	13	69.51	1.65	4	62.78	-0.20	30	68.08	0.42
Platelets (/uL)	44	264590.9	22.73	42	256452.4	-4166.67	43	262697.7	20976.74	12	280583.3	14250.00	97	265494.9	9257.73

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
[1] Change from baseline is calculated as the change from last pre-treatment measure to last on-treatment measure.
Data Source: demog.sas7bdat, lab.sas7bdat Program Source: t_hema.sas

Table 10.2.6 (cont) Mean Change from Baseline, Hematology Laboratory, Using Last On-treatment Measurement, Controlled "Full Dose" IV Studies (027, 071, 079)

	Placebo			YM087 40/d			YM087 80/d			YM087 Other			YM087 Any Dose		
Lab Parameter	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change
RBC (million/uL)	44	3.98	-0.14	42	4.06	-0.12	43	3.99	-0.04	12	4.24	0.17	97	4.05	-0.05
Reticulocytes (%)				1	2.00	0.40	1	2.20	0.00				2	2.10	0.20
Reticulocytes (/uL)				1	110000.0	0.00	1	110600.0	-600.00				2	110300.0	-300.00
WBC (/uL)	44	8428.91	-348.64	42	7747.14	1959.10	43	7661.86	1627.91	12	8342.50	900.00	97	7781.99	1638.56

Source: Applicant's Table 2.7.4-17.6F. Summary of Intravenous Safety

Appendix 10.3 Serious Adverse Events in all Controlled Phase 2/3 Studies (IV + Oral) (Source: email from Dr. Donald Raineri, Astellas Reg Aff, 7 Nov 05)

Table 2.7.4-9.P23_ALL: Number and Percentage of Patients with Serious Treatment-Emergent Adverse Events by System Organ Class
Pool P23_ALL: All Phase 2 and 3 Placebo Controlled Studies (Population: SAF)*
(017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 10/d n(%)	YM087 20/d n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 >80/d n(%)	YM087 Any Dose n(%)
Blood and lymphatic system disorders	1 (0.3%)	1 (0.9%)	0	1 (0.3%)	0	0	2 (0.2%)
Anaemia NOS	0	1 (0.9%)	0	0	0	0	1 (0.1%)
Thrombocytopenia	1 (0.3%)	0	0	1 (0.3%)	0	0	1 (0.1%)
Cardiac disorders	21 (5.6%)	5 (4.4%)	12 (5.9%)	20 (5.7%)	9 (3.8%)	9 (21.4%)	55 (5.8%)
Acute coronary syndrome	1 (0.3%)	0	0	0	0	0	0
Acute myocardial infarction	1 (0.3%)	0	0	0	0	0	0
Angina pectoris	1 (0.3%)	1 (0.9%)	3 (1.5%)	0	0	0	4 (0.4%)
Angina unstable	2 (0.5%)	1 (0.9%)	1 (0.5%)	0	0	0	2 (0.2%)
Arrhythmia NOS	0	0	1 (0.5%)	0	0	0	1 (0.1%)
Atrial fibrillation	0	0	0	0	0	1 (2.4%)	1 (0.1%)
Atrial flutter	0	0	0	0	0	2 (4.8%)	2 (0.2%)
Atrioventricular block NOS	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Atrioventricular block complete	0	0	0	1 (0.3%)	0	1 (2.4%)	2 (0.2%)
Bradycardia NOS	2 (0.5%)	1 (0.9%)	0	0	0	0	1 (0.1%)
Cardiac arrest	0	1 (0.9%)	0	4 (1.1%)	1 (0.4%)	0	6 (0.6%)
Cardiac failure NOS	3 (0.8%)	0	1 (0.5%)	4 (1.1%)	0	0	5 (0.5%)
Cardiac failure acute	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Cardiac failure chronic	1 (0.3%)	0	0	2 (0.6%)	0	0	2 (0.2%)
Cardiac failure congestive	0	1 (0.9%)	0	1 (0.3%)	1 (0.4%)	0	3 (0.3%)
Cardio-respiratory arrest	1 (0.3%)	0	0	0	0	1 (2.4%)	1 (0.1%)
Cardiomyopathy NOS	0	0	0	2 (0.6%)	0	1 (2.4%)	3 (0.3%)
Cardiopulmonary failure	1 (0.3%)	0	0	0	0	0	0
Congestive cardiac failure aggravated	3 (0.8%)	1 (0.9%)	3 (1.5%)	1 (0.3%)	3 (1.3%)	0	8 (0.8%)
Congestive cardiomyopathy	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Coronary artery disease NOS	0	0	1 (0.5%)	0	0	0	1 (0.1%)
Coronary artery disease aggravated	0	0	0	0	0	1 (2.4%)	1 (0.1%)
Ischaemic cardiomyopathy	0	0	1 (0.5%)	0	0	1 (2.4%)	2 (0.2%)
Mitral valve incompetence	0	0	0	0	0	1 (2.4%)	1 (0.1%)
Myocardial infarction	2 (0.5%)	0	0	0	1 (0.4%)	0	1 (0.1%)
Sick sinus syndrome	1 (0.3%)	0	0	0	1 (0.4%)	0	1 (0.1%)
Sinus arrhythmia	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Supraventricular arrhythmia NOS	1 (0.3%)	0	0	0	0	0	0
Supraventricular tachycardia	0	0	0	1 (0.3%)	0	0	1 (0.1%)

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
Data Source: ae.sas7bdat, demog.sas7bdat Program Source: t_aetab.sas

Table 2.7.4-9.P23_ALL: Number and Percentage of Patients with Serious Treatment-Emergent Adverse Events by System Organ Class
Pool P23_ALL: All Phase 2 and 3 Placebo Controlled Studies (Population: SAP)*
(017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 10/d n(%)	YM087 20/d n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 >80/d n(%)	YM087 Any Dose n(%)
Ventricular fibrillation	1 (0.3%)	0	0	1 (0.3%)	0	1 (2.4%)	2 (0.2%)
Ventricular tachycardia	3 (0.8%)	0	1 (0.5%)	3 (0.9%)	1 (0.4%)	2 (4.8%)	7 (0.7%)
Congenital, familial and genetic disorders	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Arteriovenous malformation	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Endocrine disorders	0	0	1 (0.5%)	0	0	0	1 (0.1%)
Hypothyroidism	0	0	1 (0.5%)	0	0	0	1 (0.1%)
Gastrointestinal disorders	3 (0.8%)	0	4 (2.0%)	2 (0.6%)	1 (0.4%)	0	7 (0.7%)
Abdominal pain NOS	0	0	1 (0.5%)	0	1 (0.4%)	0	2 (0.2%)
Abdominal pain upper	0	0	1 (0.5%)	0	0	0	1 (0.1%)
Colitis ischaemic	0	0	1 (0.5%)	0	0	0	1 (0.1%)
Constipation	1 (0.3%)	0	0	0	0	0	0
Dyspepsia	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Gastric ulcer	0	0	1 (0.5%)	0	0	0	1 (0.1%)
Gastrointestinal haemorrhage NOS	1 (0.3%)	0	0	0	0	0	0
Inguinal hernia NOS	0	0	1 (0.5%)	0	0	0	1 (0.1%)
Small intestinal obstruction NOS	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Upper gastrointestinal haemorrhage	1 (0.3%)	0	0	0	0	0	0
General disorders and administration site conditions	6 (1.6%)	3 (2.7%)	5 (2.5%)	5 (1.4%)	5 (2.1%)	5 (11.9%)	23 (2.4%)
Anasarca	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Chest pain	1 (0.3%)	2 (1.8%)	4 (2.0%)	1 (0.3%)	1 (0.4%)	0	8 (0.8%)
Death NOS	1 (0.3%)	0	0	0	0	0	0
Drug interaction NOS	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Fatigue	1 (0.3%)	0	0	0	0	0	0
Impaired healing	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Influenza like illness	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Infusion site phlebitis	0	0	0	0	0	2 (4.8%)	2 (0.2%)
Injection site cellulitis	0	0	0	1 (0.3%)	0	1 (2.4%)	2 (0.2%)
Injection site reaction NOS	0	0	0	0	0	1 (2.4%)	1 (0.1%)
Mass NOS	0	1 (0.9%)	0	0	0	0	1 (0.1%)
Mechanical complication of implant	1 (0.3%)	0	0	0	0	0	0

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
Data Source: ae.sas7bdat, demog.sas7bdat Program Source: t_aetab.sas

Table 2.7.4-9.P23_ALL: Number and Percentage of Patients with Serious Treatment-Emergent Adverse Events by System Organ Class
Pool P23_ALL: All Phase 2 and 3 Placebo Controlled Studies (Population: SAF)*
(017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 10/d n(%)	YM087 20/d n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 >80/d n(%)	YM087 Any Dose n(%)
Multi-organ failure	1 (0.3%)	0	0	0	0	0	0
Oedema NOS	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Oedema peripheral	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Pain NOS	1 (0.3%)	0	0	0	0	0	0
Pyrexia	1 (0.3%)	0	0	1 (0.3%)	0	0	1 (0.1%)
Sudden cardiac death	0	0	0	0	0	1 (2.4%)	1 (0.1%)
Sudden death	0	0	1 (0.5%)	0	1 (0.4%)	0	2 (0.2%)
Systemic inflammatory response syndrome	1 (0.3%)	0	0	0	0	0	0
Hepatobiliary disorders	0	0	0	2 (0.6%)	2 (0.9%)	0	4 (0.4%)
Cholelithiasis	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Cholestasis	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Hepatic failure	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Hepatitis NOS	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Immune system disorders	0	0	0	0	0	1 (2.4%)	1 (0.1%)
Urticaria NOS	0	0	0	0	0	1 (2.4%)	1 (0.1%)
Infections and infestations	7 (1.9%)	4 (3.5%)	2 (1.0%)	6 (1.7%)	9 (3.8%)	5 (11.9%)	26 (2.8%)
Abdominal abscess NOS	0	1 (0.9%)	0	0	0	0	1 (0.1%)
Appendicitis	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Bronchial infection	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Bronchitis acute NOS	0	1 (0.9%)	0	0	1 (0.4%)	0	2 (0.2%)
Cellulitis	1 (0.3%)	0	0	1 (0.3%)	0	0	1 (0.1%)
Clostridium colitis	1 (0.3%)	0	0	0	0	0	0
Herpes zoster	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Hiv infection	0	0	0	0	0	1 (2.4%)	1 (0.1%)
Implant site infection	1 (0.3%)	0	0	0	0	0	0
Pneumonia NOS	2 (0.5%)	0	0	1 (0.3%)	3 (1.3%)	2 (4.8%)	6 (0.6%)
Purulent pericarditis	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Pyothorax	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Sepsis NOS	2 (0.5%)	1 (0.9%)	0	2 (0.6%)	0	1 (2.4%)	4 (0.4%)
Sinusitis NOS	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Staphylococcal sepsis	0	0	0	0	0	1 (2.4%)	1 (0.1%)
Upper respiratory tract infection NOS	0	0	1 (0.5%)	0	0	0	1 (0.1%)

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
Data Source: ae.sas7bdat, demog.sas7bdat Program Source: t_aetab.sas

Table 2.7.4-9.P23_ALL: Number and Percentage of Patients with Serious Treatment-Emergent Adverse Events by System Organ Class
Pool P23_ALL: All Phase 2 and 3 Placebo Controlled Studies (Population: SAF)*
(017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 10/d n(%)	YM087 20/d n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 >80/d n(%)	YM087 Any Dose n(%)
Urinary tract infection NOS	0	1 (0.9%)	1 (0.5%)	1 (0.3%)	1 (0.4%)	0	4 (0.4%)
Injury, poisoning and procedural complications	2 (0.5%)	0	0	3 (0.9%)	0	0	3 (0.3%)
Anastomotic leak	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Drug toxicity NOS	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Fall	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Post procedural haemorrhage	1 (0.3%)	0	0	0	0	0	0
Therapeutic agent poisoning	1 (0.3%)	0	0	1 (0.3%)	0	0	1 (0.1%)
Investigations	1 (0.3%)	0	0	4 (1.1%)	2 (0.9%)	0	6 (0.6%)
Alanine aminotransferase increased	0	0	0	1 (0.3%)	1 (0.4%)	0	2 (0.2%)
Aspartate aminotransferase increased	0	0	0	1 (0.3%)	1 (0.4%)	0	2 (0.2%)
Blood creatine phosphokinase increased	0	0	0	1 (0.3%)	1 (0.4%)	0	2 (0.2%)
Blood lactate dehydrogenase increased	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Blood pressure decreased	1 (0.3%)	0	0	1 (0.3%)	0	0	1 (0.1%)
Blood urea nitrogen/creatinine ratio increased	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Liver function test abnormal	0	0	0	1 (0.3%)	1 (0.4%)	0	2 (0.2%)
Metabolism and nutrition disorders	4 (1.1%)	1 (0.9%)	3 (1.5%)	6 (1.7%)	4 (1.7%)	0	14 (1.5%)
Dehydration	0	0	1 (0.5%)	1 (0.3%)	3 (1.3%)	0	5 (0.5%)
Diabetes mellitus NOS	1 (0.3%)	0	1 (0.5%)	0	0	0	1 (0.1%)
Hyperglycaemia NOS	0	0	1 (0.5%)	0	1 (0.4%)	0	2 (0.2%)
Hyperkalaemia	1 (0.3%)	0	0	1 (0.3%)	0	0	1 (0.1%)
Hypervolaemia	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Hypoglycaemia NOS	0	1 (0.9%)	0	0	0	0	1 (0.1%)
Hypokalaemia	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Hyponatraemia	2 (0.5%)	0	0	2 (0.6%)	1 (0.4%)	0	3 (0.3%)
Hypovolaemia	0	0	0	2 (0.6%)	0	0	2 (0.2%)
Musculoskeletal and connective tissue disorders	0	0	0	1 (0.3%)	1 (0.4%)	0	2 (0.2%)
Myalgia	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Rhabdomyolysis	0	0	0	0	1 (0.4%)	0	1 (0.1%)

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
Data Source: ae.sas7bdat, demog.sas7bdat Program Source: t_aetab.sas

Table 2.7.4-9.P23_ALL: Number and Percentage of Patients with Serious Treatment-Emergent Adverse Events by System Organ Class
Pool P23_ALL: All Phase 2 and 3 Placebo Controlled Studies (Population: SAF)*
(017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 10/d n(%)	YM087 20/d n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 >80/d n(%)	YM087 Any Dose n(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3%)	0	0	1 (0.3%)	1 (0.4%)	0	2 (0.2%)
Bladder neoplasm NOS	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Metastatic carcinoma	1 (0.3%)	0	0	0	0	0	0
Oesophageal carcinoma NOS	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Nervous system disorders	1 (0.3%)	1 (0.9%)	1 (0.5%)	7 (2.0%)	4 (1.7%)	1 (2.4%)	14 (1.5%)
Cerebrovascular accident	0	1 (0.9%)	0	0	1 (0.4%)	1 (2.4%)	3 (0.3%)
Dizziness	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Grand mal convulsion	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Paraesthesia	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Syncope	0	0	1 (0.5%)	5 (1.4%)	1 (0.4%)	0	7 (0.7%)
Syncope vasovagal	1 (0.3%)	0	0	1 (0.3%)	0	0	1 (0.1%)
Psychiatric disorders	0	0	1 (0.5%)	2 (0.6%)	0	0	3 (0.3%)
Anxiety	0	0	1 (0.5%)	0	0	0	1 (0.1%)
Confusional state	0	0	0	2 (0.6%)	0	0	2 (0.2%)
Psychotic disorder NOS	0	0	1 (0.5%)	0	0	0	1 (0.1%)
Renal and urinary disorders	4 (1.1%)	1 (0.9%)	1 (0.5%)	7 (2.0%)	2 (0.9%)	2 (4.8%)	13 (1.4%)
Renal disorder NOS	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Renal failure NOS	2 (0.5%)	1 (0.9%)	1 (0.5%)	4 (1.1%)	0	1 (2.4%)	7 (0.7%)
Renal failure acute	2 (0.5%)	0	0	2 (0.6%)	1 (0.4%)	0	3 (0.3%)
Renal failure acute on chronic	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Renal failure chronic	0	0	0	0	0	1 (2.4%)	1 (0.1%)
Reproductive system and breast disorders	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Ovarian mass	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	9 (2.4%)	1 (0.9%)	1 (0.5%)	8 (2.3%)	9 (3.8%)	5 (11.9%)	24 (2.5%)
Acute pulmonary oedema	1 (0.3%)	0	0	0	0	0	0
Bronchitis NOS	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Chronic obstructive airways disease	0	1 (0.9%)	0	0	0	0	1 (0.1%)
Chronic obstructive airways disease exacerbated	0	0	1 (0.5%)	1 (0.3%)	0	1 (2.4%)	3 (0.3%)

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
Data Source: ae.sas7bdat, demog.sas7bdat Program Source: t_aetab.sas
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Summary of Clinical Safety 07NOV2005 17:35
Astellas Pharma US, Inc.

Table 2.7.4-9.P23_ALL: Number and Percentage of Patients with Serious Treatment-Emergent Adverse Events by System Organ Class
Pool P23_ALL: All Phase 2 and 3 Placebo Controlled Studies (Population: SAF)*
(017, 020, 026, 027, 032, 033, 034, 038, 043, 044, 071)

System Organ Class MedDRA Term	Placebo n(%)	YM087 10/d n(%)	YM087 20/d n(%)	YM087 40/d n(%)	YM087 80/d n(%)	YM087 >80/d n(%)	YM087 Any Dose n(%)
Cough	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Dyspnoea	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Dyspnoea exacerbated	5 (1.3%)	0	0	2 (0.6%)	3 (1.3%)	3 (7.1%)	8 (0.8%)
Hypercapnia	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Pleural effusion	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Pulmonary congestion	1 (0.3%)	0	0	1 (0.3%)	1 (0.4%)	0	2 (0.2%)
Pulmonary embolism	1 (0.3%)	0	0	0	1 (0.4%)	0	1 (0.1%)
Pulmonary oedema NOS	0	0	0	1 (0.3%)	1 (0.4%)	1 (2.4%)	3 (0.3%)
Respiratory arrest	1 (0.3%)	0	0	1 (0.3%)	0	0	1 (0.1%)
Respiratory distress	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Respiratory failure	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Surgical and medical procedures	1 (0.3%)	0	0	1 (0.3%)	0	0	1 (0.1%)
Cardioversion	1 (0.3%)	0	0	0	0	0	0
Heart transplant	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Vascular disorders	6 (1.6%)	1 (0.9%)	0	7 (2.0%)	2 (0.9%)	0	10 (1.1%)
Arterial occlusion	1 (0.3%)	0	0	0	0	0	0
Deep vein thrombosis	0	0	0	2 (0.6%)	0	0	2 (0.2%)
Hypertension NOS	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Hypotension NOS	3 (0.8%)	1 (0.9%)	0	5 (1.4%)	1 (0.4%)	0	7 (0.7%)
Intermittent claudication	1 (0.3%)	0	0	0	0	0	0
Malignant hypertension NOS	1 (0.3%)	0	0	0	0	0	0

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
Data Source: ae.sas7bdat, demog.sas7bdat Program Source: t_aetab.sas

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/s/

Karen Mahoney
12/6/2005 06:39:14 PM
MEDICAL OFFICER

Mary Parks
12/6/2005 07:52:59 PM
MEDICAL OFFICER

David Orloff
12/7/2005 03:19:58 PM
MEDICAL OFFICER
Concur with recommendations.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: November 23, 2004

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-697
Vaprisol (conivaptan HCl) Injection
Yamanouchi Pharma America, Inc.
Treatment of euvolemic and hypervolemic hyponatremia

SUBJECT: NDA review issues and recommended action

Background

This is a first-in-class aquaretic agent, a non-peptide antagonist of vasopressin at the V2 receptor. Activation of this receptor by vasopressin and active analogues (e.g., DDAVP) results in reabsorption of water in the collecting duct of the nephron. This interaction is central to the regulation of the balance of salt and water in the body. Dilutional hyponatremia is proposed as the target condition for this drug. This is an extremely common derangement in salt and water homeostasis, most commonly associated with the syndrome of inappropriate ADH secretion (SIADH) and edematous states such as cirrhosis and congestive heart failure. Serum sodium concentration in these conditions is to some extent indicative of disease severity and prognostic in some cases, at least indirectly, of clinical outcomes related to the underlying disease. Hyponatremia *per se*, however, is also potentially life-threatening if it is severe and progressive. When hyponatremia is profound, there can be severe complications if it is corrected too rapidly. Additionally, because of the threat posed by hyponatremia itself, it very much complicates the management of patients with total body salt and water overload, as in patients with CHF and cirrhosis who are treated with diuretics.

The current management of dilutional hyponatremia involves fluid/water restriction, judicious use of diuretics (in edematous states), and democlocyline (non-ADH-antagonist promoter of free water excretion). The application of an agent that selectively blocks vasopressin action in the kidney, thereby addressing a central mechanistic step in the generation and maintenance of dilutional hyponatremia, is a rational approach to therapy of this condition. Vaprisol (conivaptan) is being developed as a clinical management tool for use in the manner that water restriction (which is extremely difficult to impose and accomplish) and other adjuncts (like democlocyline) are applied currently to permit, potentially, safer and more effective management of the primary conditions responsible for the metabolic derangement.

The division has provided guidance in the past to this sponsor [redacted] that approval for use in euvolemic and hypervolemic hyponatremia to raise serum

sodium levels could result from studies in representative populations showing that a vasopressin antagonist was safe and effective for correcting the laboratory abnormality compared to fluid restriction. Specifically, while a large safety experience has been requested, no requirement has been imposed for provision of information from clinical trials on disease outcomes. As above, given the dearth of options for the management of dilutional hyponatremia, the detailed understanding of the role of ADH in its genesis and maintenance, and the pharmacology of these drugs, the division believes that restoration of serum sodium toward normal via vasopressin-antagonism-mediated promotion of renal free water clearance is a clinically meaningful effect. Furthermore, if this correction of hyponatremia can be accomplished safely (i.e., from the standpoint of risks associated with osmotic shifts, depletion of intravascular volume, extra-renal vasopressin-antagonism-related side effects, and intrinsic toxicities of the drug), then this could support approval for the proposed use.

Summary of issues

Clinical efficacy and safety

Dr. Mahoney has completed a comprehensive review, and this has been summarized with additional comment by Dr. Parks.

Patient exposures

Because of inadequate patient experience at the dose, and systemic exposure proposed for marketing, additional clinical data are needed. Briefly, the sponsor's original application contained efficacy and safety information on ~1400 patients and normal volunteers. The majority of these had received conivaptan via oral administration. Because the drug is a potent inhibitor of CYP 3A4, the sponsor revised the clinical program and marketing proposal to restrict the drug to in-hospital, intravenous use only, in order to mitigate potentially hazardous drug-drug interactions (e.g., with lovastatin/simvastatin, eventuating in myopathy/rhabdomyolysis). Data emerged late in the review cycle showing that the systemic exposure to oral drug was approximately 33% of that to drug administered intravenously therefore, the safety database relevant to the product proposed for marketing is limited to 63 patients, clearly insufficient to inform adequately a judgment of the balance of risk and benefit across the large and heterogeneous target population. Additional clinical trial data addressing risk versus benefit are therefore needed.

Lowest effective dose; duration of therapy

With regard to efficacy, in the trials of oral conivaptan as well as in the single trial of the IV formulation, the drug was clearly superior to placebo plus water restriction in correcting serum sodium toward normal when given over a four-day period. The fact that the oral dose of 40 mg daily was effective raises the possibility that a dose of conivaptan IV below 40 mg daily may also be effective, in at least some patients, given the lower systemic exposure to orally administered drug. The concept of titrating the dose of conivaptan to a pharmacodynamic target (e.g., free water clearance or excretion) should be addressed by the sponsor. In addition, the peak pharmacodynamic effect of conivaptan occurs within 24 hours of initiation of therapy, as discussed by Drs. Mahoney and Parks, and the effect on serum sodium may be maintained in some patients for over a week after the end of treatment. A shorter duration of treatment [redacted] may therefore be possible and should be explored. Therefore studies of lower doses of IV conivaptan and of treatment durations shorter than 4 days

(as well as consideration of developing a method of use whereby dose is titrated to a direct pharmacodynamic measure) should be undertaken, either before approval or as a phase 4 commitment.

Questions about efficacy in patients with very low serum sodium
There were very few patients with baseline serum sodium < 120 mEq/L, and Dr. Mahoney notes that among these patients, the effect of conivaptan to raise serum sodium was not statistically significantly superior to placebo. The scant data that are available and summarized in her review, however, show that for the primary endpoint of baseline-adjusted AUC for serum sodium over the course of treatment, the mean change in serum sodium in patients receiving both placebo and conivaptan was much greater in this subgroup than in the group with baseline serum sodium levels > 120 mEq/L. The augmented effect in both treatment groups may reflect a greater sensitivity in this group of patients to fluid restriction (i.e., a greater contribution to dilution of oral intake), as this was imposed on those getting both placebo and drug. Needless to say, while the difference in efficacy between placebo and drug in the subgroup with marked hyponatremia perhaps bears further investigation in analyses of anticipated trial data, it does not appear that conivaptan is at all ineffective in patients with very low serum sodium. Rather, it seems that fluid restriction is relatively more effective in these patients than in those with lesser degrees of dilutional hyponatremia, thus impacting the contribution, both absolute and relative, of conivaptan to increasing serum sodium concentrations. Finally, Dr. Mahoney points out that fluid intake among patients receiving conivaptan was generally higher than among placebo patients. This demonstrates another potential "benefit" to patients of this therapy (presumably across the spectrum of severity of hyponatremia—though this may be explored further): that is, to promote normalization of serum sodium while relaxing the cumbersome, uncomfortable, and difficult-to-comply-with requirement for fluid restriction.

Safety
Renal adverse events
With regard to safety, there were excess overall serious adverse events among conivaptan-treated patients. These included, most notably, renal, hypovolemia, and hypotensive events, not surprising given the brisk diuresis induced by the drug.

Most of the renal adverse events appear from the medical review to involve deterioration in renal function as measured by serum creatinine (e.g., as opposed to proteinuria, hematuria), and occurred predominantly among patients with CHF. Whether these represent renal toxicity *per se* or are due to volume depletion is unresolved. Dr. Mahoney notes that the mean increase in urine output among conivaptan-treated patients with serious renal adverse events was actually less than the mean of the pooled phase 3 conivaptan and placebo patients combined. Still, even a small effect of conivaptan to induce water diuresis may precipitate renal insufficiency and failure in the subgroup of patients with greater degrees of baseline renal functional compromise (as is found commonly in patients with significant CHF). Glomerular filtration rate in such patients may be extremely sensitive to even relatively small pre-renal effects. Indeed, since maximum free water diuresis is limited by GFR, the apparent inferior response to drug (in terms of diuresis) in these patients may actually reflect a maximum drug effect in the setting of renal impairment due to glomerular dropout. While it is also notable that the systemic exposures to conivaptan were highest among patients with CHF (which is consistent with an expectation of a higher risk for

"toxicity" if it exists, the animal toxicology data are hardly consistent with a direct toxic effect of conivaptan on the kidney, even at multiples of human therapeutic exposures. The finding of "tubular degeneration" in animals treated with conivaptan at 4X the therapeutic exposure is not clearly a "toxic" effect. The induction of diabetes insipidus in animals, specifically if they are not provided adequate water (and I doubt seriously if the study monitored whether water bottles ever were allowed to run dry), may, if it results in dehydration, be associated with renal histologic findings. This perhaps bears further study. In the end, while there is not a strong "signal" of renal toxicity of conivaptan, the issue of whether the drug has such an effect requires further investigation, and additional safety data from trials to be submitted will, it is hoped, provide us with additional insight.

Cardiovascular safety
There is a small absolute increased incidence of cardiovascular deaths in patients treated with conivaptan in the CHF trials submitted to date. This is based on very small numbers of events. Specifically, for "all cardiac arrest related terms" there was one (0.4%) event in the placebo group, and there were six (0.9%) events in the conivaptan group. For "all CHF causes of death" there was 1 (0.4%) event in the placebo group, and there were 4 (0.6%) events in the conivaptan group. While these numbers are hardly alarming, given the potency of conivaptan as a diuretic, the fact that in the clinical trials CHF patients were permitted otherwise to be treated with approved diuretics, and given the known volume sensitivity of patients with CHF, if nothing else, these data further emphasize the need for exploration of the efficacy and safety of lower doses of conivaptan, of methods of use involving shorter durations of therapy, titration to direct pharmacodynamic effect (free water clearance, free water excretion, incremental urinary volume), and of inter-treatment interval in this patient population.

Infusion site reactions
Conivaptan IV is clearly associated with infusion site reactions, as a function of concentration and dose of drug, in up to ~20% of patients, some coded as phlebitis and DVT. This is obviously monitorable, and is not construed by the division as an unacceptable risk of this therapy.

Hepatic effects
A small number of patients treated with conivaptan had increases in hepatic transaminases and alkaline phosphatase. Three cases of hepatic failure occurred in patients with serious, complicated medical illnesses. There were eight cases in which elevations of hepatic transaminases > 3 X ULN occurred in conjunction with bilirubin elevation > 2 X ULN. These have been reviewed and discussed by Dr. Mahoney in an addendum to her review. Briefly, of the eight cases, one patient died before randomization and another occurred in a patient treated with placebo. All of the remaining six cases occurred in patients with evidence of pre-existing liver disease manifest as laboratory abnormalities indicative of impaired hepatobiliary function at baseline. In two of these cases, transaminase and bilirubin levels were highest at baseline and declined during therapy with conivaptan. Among the 4 other cases, all were medically complex. One involved an elderly woman with metastatic carcinoma of the gallbladder who died of sepsis and metabolic compromise on study day 3. The other three occurred in patients with severe congestive heart failure and multiple medical complications. In short, no case was at all strongly suggestive of a role of conivaptan in hepatic injury. This issue will be examined further in the review of the anticipated additional safety information to be submitted.

Drug interactions
Conivaptan increased prothrombin time in some patients treated with warfarin, though no pharmacokinetic interaction was documented between warfarin and oral conivaptan.

There were 4 cases of marked CK elevation/myopathy/rhabdomyolysis in clinical trials of conivaptan. All occurred in patients treated with oral drug. One was a patient treated with cerivastatin/gemfibrozil, a combination known to cause rhabdomyolysis. The three other cases were in patients taking lovastatin (1) and simvastatin (2), the two marketed statins whose bioavailability and metabolic inactivation are most dependent on CYP 3A4. The extent to which intravenous conivaptan impacts systemic exposures to 3A4-metabolized statins was assessed in a formal study. Conivaptan IV, 15 mg BID increased simvastatin AUC 3-fold. By way of reference, oral itraconazole increases simvastatin AUC 20-fold (published). Oral conivaptan 40 mg daily increased simvastatin ~6-fold. Risk management for conivaptan will still have to include addressing risks associated with its CYP 3A4 inhibitory effects.

As above, conivaptan is an inhibitor of CYP 3A4, but it is also a substrate for this isozyme. Ketoconazole increased conivaptan AUC 11-fold after oral administration.

Biopharmaceutics
PK/PD
With regard to effects of age, renal, and hepatic impairment on conivaptan pharmacokinetics, no studies have been conducted with IV administration. There were 3 to 4-fold increases in AUC relative to healthy young subjects in the elderly and in those with mild and moderate renal impairment and hepatic impairment dosed orally with conivaptan.

OCPB recommends additional investigations of the effect of renal function on efficacy. This bears comment. As maximum free water clearance is determined by GFR, if the doses of conivaptan IV that are effective in increasing serum sodium are saturating for aquaresis, then reductions in free water clearance will be in direct relationship to reductions in GFR. If, on the other hand, clinically effective doses of conivaptan are subsaturating for aquaresis, then there will be a threshold GFR above which reductions from "normal" in GFR will have no impact on efficacy. Formal investigations of this phenomenon go beyond the usual exposure-response experimental models. It seems that clinical investigations of lowest effective dose, shortest effective duration of treatment, consideration of method of use in which drug dose and duration are titrated to a direct pharmacodynamic response (e.g., free water clearance or excretion), which may well vary as a result of underlying renal impairment as well as cardiac function, will best inform the safe and effective use of this drug across the heterogeneous population to which it is targeted. Finally, ideally, therapeutic doses of conivaptan will permit "fine tuning" of the aquaretic effect of vasopressin antagonism along a dose-response curve. The possibility of such dosing has not been adequately investigated.

OCPB also requests additional justification for the IV dosing regimen, specifically the need for a loading dose. Additionally, OCPB requests further analysis to determine the optimum infusion time. Finally, OCPB recommends further sampling of patients treated with IV conivaptan to

better characterize drug exposures in patients treated with this regimen. These requests are acceptable.

Pharmacology-Toxicology
Most toxicities observed in animals occurred at extremely high exposures relative to human clinical exposures. One week of IV dosing in rats exposed to 4 X the clinical exposure was associated with renal tubular degeneration. The drug does induce significant aquaresis in animals and dehydration may well explain the renal findings associated with high doses and prolonged administration. Renal effects will need to be examined in additional patient safety databases to be submitted.

CMC/Microbiology
The ONDC primary review from 9-29-04 recommends approvable pending submission of additional CMC information and satisfactory GMP inspections. Outstanding items are delineated in the action letter.

The microbiology reviewer recommends approval based on sterility assurance.

ODS/DMETS
No objections to the proprietary name.

DSI/data integrity
Clinical site audits identified no critical deficiencies that would support non-acceptance of data for review.

Financial disclosure
Dr. Mahoney has reviewed the financial disclosure information, and after obtaining additional information from the sponsor, she concludes that there is no concern that financial conflicts of interest might have impacted the conduct of the trials.

Recommendation
This application is approvable pending submission and review of additional clinical trial data addressing the safety and efficacy of the IV dosing regimen. OCPB has requested additional information (see above) as has ONDC.

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/s/

David Orloff
11/23/04 10:26:07 AM
MEDICAL OFFICER

Robert Meyer
11/23/04 03:42:48 PM
MEDICAL OFFICER
I am in essential agreement with this memo and this will be the memo of record for this review cycle1

NDA 21697 (conivaptan, Vaprisol™) Addendum to Original Clinical Review

Topic of Addendum: Search for Cases of Serum Transaminases >3x the Upper Limit of Normal Accompanied by Serum Bilirubin >2x the Upper Limit of Normal

Applicable Section of Original NDA: 7.1.7.5

Clinical Reviewer: Karen Murry Mahoney, MD

Date of Addendum: 18 Nov 04

The clinical reviewer searched the entire original New Drug Application for NDA 21697 for cases of serum transaminases >3x the upper limit of normal (uln) accompanied by serum bilirubin >2x uln. This association has been identified as a marker for the potential for severe hepatotoxicity associated with other drugs. The upper limit of normal for transaminases was defined as >35 U/L, with >3x uln defined as >105 U/L. Bilirubin uln was defined as 1.0 mg/dL, with >2x uln defined as >2.0 mg/dL. Eight cases were identified by this method. One patient (027-0072403) died before randomization. One case (020-0031016) occurred in a patient taking placebo. Of the remaining six cases, all had abnormal hepatobiliary function at baseline. Two cases (032-0026002 and 043-0230401) had their highest transaminase and bilirubin values at baseline, and these values declined during conivaptan therapy.

The remaining four cases are discussed below.

Patient 027-0075806 was an 81 year old woman with metastatic gallbladder cancer and the Syndrome of Inappropriate Antidiuretic Hormone action (SIADH). She was admitted to the hospital with suspected biliary tract obstruction. Baseline laboratory included serum sodium 123 mEq/L, ALT 19 U/L, AST 31 IU/L, alkaline phosphatase 111 IU/L, LDH 338 IU/L, and serum bilirubin 1.9 mg/dL. She received IV conivaptan 40 mg/day by continuous infusion for 1.5 days. On Study Day 2, she developed gram-negative sepsis (biliary vs urinary), metabolic acidosis, respiratory distress, and hypotension. Liver function test values increased, including ALT 418 U/L, AST 146 U/L, alkaline phosphatase 231 IU/L, LDH 1,263 U/L, and serum bilirubin 4.8 mg/dL. Despite antibiotics, pressors, and bicarbonate, she died on Study Day 3. Due to the patient's underlying metastatic gallbladder cancer with its obvious hepatobiliary risk, the clinical reviewer cannot attribute this case to conivaptan toxicity.

Patient 026-0060708 was a 54 year old woman with cardiomyopathy, congestive heart failure, chronic obstructive pulmonary disease, prior myocardial infarction, cholelithiasis and chronic renal insufficiency. She had baseline liver function test elevations, with ALT 36 U/L, AST 52 U/L, serum bilirubin 1.2 mg/dL, and alkaline phosphatase 194 U/L. She received oral conivaptan 40 mg/day for 3 days. On Study Day 2, she developed ventricular tachycardia, hypotension, hypovolemia, hyperkalemia, hypoglycemia, and decreased urine output. She was treated with lidocaine, intravenous normal saline, Kayexalate, and glucose. At the end of Study Day 2, liver function tests had increased,

with ALT 188 U/L, AST 99 U/L, bilirubin 2.3 mg/dL and alkaline phosphatase 217 U/L. On Study Day 3, lidocaine was discontinued due to lidocaine toxicity, but was resumed when she developed recurrent ventricular tachycardia. Lidocaine toxicity recurred, and amiodarone was substituted for lidocaine. Hypotension persisted and conivaptan was discontinued. Her renal function worsened, with BUN and creatinine of 69 mg/dL and 1.7 mg/dL on Study Day 5. She temporarily stabilized, but on Study Day 10, she suffered a cardiorespiratory arrest and was placed on mechanical ventilation. She was subsequently made "DNR", extubated and died on Study Day 10. Due to the multiplicity of this patient's chronic and acute medical problems, the clinical reviewer cannot attribute this case to conivaptan toxicity.

Patient 038-0003001 had no case report form. Patient was a 24 year old man with congestive heart failure of unknown etiology. The patient entered the study with elevated baseline liver function tests, including a bilirubin of 4.5 mg/dL and AST of 54 U/L. The cause of the patient's baseline abnormal liver function tests was not mentioned in the study report. The patient received intravenous conivaptan, given as two 20 mg infusion over 30 minutes each. The infusions were separated by 8 hours. Serum bilirubin did not increase. On Posttreatment Day 1, AST increased to 146 U/L; on Posttreatment Day 7, AST was 61 U/L. It is possible that the patient's temporary increase in AST was related to conivaptan, but there was no concomitant rise in bilirubin.

Patient 034-0025002 was a 46 year old man with congestive heart failure, diabetes, and gout, who received oral conivaptan 80 mg/day for 16 days. Concomitant medications were reported to include allopurinol, amiodarone, bumetanide, colchicine, digoxin, enalapril, glipizide, lansoprazole, losartan, midazolam (sic), pethidine, potassium, warfarin and zoldipem. Baseline LFTs included an ALT of 51 U/L, AST 32 U/L and bilirubin 0.5 mg/dL. On Study Day 20, he presented with abdominal pain, light colored stools, dark urine, and a rash. ALT was 286 U/L, AST was 109 U/L, and bilirubin was 4.3 mg/dL. Abdominal CT was normal. Hepatic biopsy was compatible with hepatitis, possibly drug-induced. By Study Day 37, liver function tests had reportedly returned to normal. No rechallenge was reported. This case is confounded by the concomitant administration of medications known to be associated with adverse effects on hepatic function (allopurinol, amiodarone, enalapril) and by the patient's mild baseline ALT elevation. However, there is a possibility that this could represent a case of conivaptan-induced hepatitis with elevations of both transaminases and bilirubin.

For the cases which were associated with hepatic failure or transaminases >10 x uln, the following table summarizes information on dose, time to event, and therapeutic response in terms of serum sodium and urine output (when available).

Features of Cases of Hepatic Failure or Transaminases >10x uln					
Case	**Dose**	**Days on Coni Prior to Liver Event**	**Study Day on Which Event Occurred**	**Sodium Response**	**Urine Response**

27-75806	IV 40 mg/day	1.5 days	2	no value after baseline	4700 cc Day 1
26-60708	oral 40 mg/day	2	2	sodium 128-139 over Day 1	2100 cc Day 1
34-25002	oral 80 mg/day	16	20	always normal	not recorded

No clear connections can be made between the features of these cases, except perhaps that cases 27-75806 and 26-60708 had brisk efficacy responses as measured by urine output (27-75806) and rise in serum sodium (26-60708).

In summary, it is possible that one case of significant drug-induced hepatic dysfunction related to conivaptan occurred, although the case has confounding factors. If the sponsor submits additional safety information for their NDA, the clinical reviewer will pay careful attention for signals of hepatic adverse events and laboratory abnormalities.

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/s/

Karen Mahoney
11/18/04 01:29:38 PM
MEDICAL OFFICER

Mary Parks
11/19/04 09:30:09 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21697
Submission Code	IS
Letter Date	30 Jan 04
Stamp Date	30 Jan 04
PDUFA Goal Date	30 Nov 04
Reviewer Name	Karen Murry Mahoney, MD
Review Completion Date	24 Sep 04
Established Name	Conivaptan hydrochloride
(Proposed) Trade Name	Vaprisol™
Therapeutic Class	Aquaretic; Vasopressin Receptor Antagonist
Applicant	Yamanouchi Pharma America, Inc.
Priority Designation	S
Formulation	Intravenous Injection
Dosing Regimen	40 mg/day by continuous intravenous infusion for up to 4 days
Indication	Euvolemic and Hypervolemic Hyponatremia
Intended Population	Adults

Table of Contents

Yamanouchi Pharma America, the sponsor of this New Drug Application (NDA), proposes an indication for conivaptan for the treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients. Their NDA includes the results of a single intravenous hyponatremia efficacy study which included 55 patients treated with conivaptan and 29 patients treated with placebo. The NDA also includes data from two Phase 3 hyponatremia trials (104 conivaptan-treated patients and 53 placebo patients) with use of an oral form of conivaptan, intended as supportive efficacy and safety information. Data from a total of 1,421 subjects and patients exposed to conivaptan (intravenous and oral) were submitted to support safety. This included 456 subjects in Phase 1 trials, and 896 patients from a total of 19 Phase 2 and Phase 3 studies. The majority of these patients actually received the oral form of conivaptan, rather than the intravenous form. The safety population included trials for two different indications; treatment of hyponatremia and treatment of congestive heart failure. The sponsor considered the oral data and the congestive heart failure program data supportive of the safety of conivaptan.

At the time of submission of the NDA, Yamanouchi believed, based on a pharmacokinetic model, that oral conivaptan was bioequivalent to intravenous conivaptan, i.e. that 40 mg of oral conivaptan resulted in the same plasma concentrations of conivaptan as 40 mg of intravenous conivaptan. However, several months into the review cycle, the sponsor submitted data from an actual bioequivalence study which showed that oral conivaptan achieves plasma levels only one third that of intravenous conivaptan. Upon review, a total of only 63 subjects in the entire development program received conivaptan in the proposed dosage regimen, or an equivalent regimen. No patients in the oral development program had equivalent exposure to that seen with the proposed intravenous dosing regimen. Sixty-three subjects is an inadequate number for safety evaluation.

1.3.2 Efficacy

The sponsor conducted a single Phase 3 intravenous efficacy trial for the hyponatremia indication. The sponsor's decision to pursue only an intravenous formulation for short term administration was prompted by concerns regarding conivaptan's marked inhibitory effect on the activity of cytochrome P450 3A4, which is important in the metabolism of many drugs. A severe drug-drug interaction with simvastatin had resulted in a case of rhabdomyolysis in Phase 2. The sponsor proposed a single IV efficacy trial and two supportive oral efficacy trials. The IV efficacy trial was a randomized, placebo-controlled trial of the efficacy of two different doses of conivaptan for the treatment of hyponatremia in euvolemic and hypervolemic patients. Hypovolemia was defined as a serum sodium <130 mEq/L (normal range 135-145 mEq/L). The placebo group included 29 patients. Conivaptan was administered as an initial 20 mg intravenous bolus, followed by continuous intravenous infusion of either 40 mg/day (29 patients) or 80 mg/day (26 patients) of conivaptan. Conivaptan was continuously infused for four days, or until normonatremia occurred. The two oral Phase 3 hyponatremia trials were of nearly identical design to the intravenous Phase 3 hyponatremia trial. In the oral trials,

conivaptan was administered as 20 mg BID or 40 mg BID (40 or 80 mg/day) for a total of five days or until normonatremia occurred.

All three trials used the same primary endpoint, change from baseline in baseline-adjusted area under the serum sodium effect curve (AUC). Both doses of intravenous conivaptan were highly effective, resulting in 8- and 11- fold increases in serum sodium AUC for the 40 mg/day and 80 mg/day groups respectively. This effect was highly statistically significant, regardless of age, gender, race, baseline volume status, or presence or absence of congestive heart failure.

Both doses of intravenous conivaptan were also strongly statistically significantly effective for all secondary efficacy parameters, which included:

- mean change in serum sodium from baseline to end of Study Day 4
- median event time to when at least 50% of patients had an increase in serum sodium of at least 4 mEq/L over baseline
- mean total time from first dose to end of treatment during which serum sodium was at least 4 mEq/L over baseline
- percentage of patients with a $\geq$ 6 mEq/L increase in serum sodium, or an increase to a normal serum sodium.

Important tertiary efficacy parameters for which intravenous conivaptan was strongly superior to placebo included increase in effective water clearance, increase in free water clearance, increase in serum osmolality, and decrease in urine sodium.

Thus, intravenous conivaptan in doses of 40 mg/day or 80 mg/day was highly effective in the treatment of hyponatremia. The sponsor proposes the 40 mg/day dose regimen for labeling. However, the fact that oral conivaptan, which achieves lower conivaptan exposure, calls into question whether the minimum effective dose of intravenous conivaptan has been established.

1.3.3 Safety

The overall safety database was inadequate, due to the finding during the review cycle that oral conivaptan results in 1/3 the exposure of intravenous conivaptan. Although a total of 1,421 subjects were exposed to conivaptan, a total of only 63 of these subjects were exposed to the equivalent of 40 mg/day of intravenous conivaptan for four days. No oral conivaptan patient received equivalent exposure. However, all safety data were carefully examined for evidence of safety concerns for conivaptan.

A total of 456 subjects were exposed in Phase 1 studies; 89 received IV conivaptan for durations of 1-7 days. Thirty-eight of these subjects received at least one dose of conivaptan $\geq$ 40 mg. A total of 356 subjects received oral conivaptan for 1-8 days, and

an additional 11 subjects received oral or IV conivaptan as a single dose. For all Phase 2 and Phase 3 trials in both hyponatremia and CHF, 896 patients were exposed to conivaptan. Of these, 208 received IV conivaptan. A total of 525 patients (all in oral studies) had at least 28 days of treatment. Of these, 285 had at least 84 days of treatment and 25 had at least 182 days of treatment. A total of 208 patients received IV conivaptan, 77 in hyponatremia trials and 131 in CHF trials.

The mortality rate was similar between conivaptan-treated subjects and placebo subjects in the overall safety population. However, in the congestive heart failure trials, death occurred slightly more frequently among conivaptan patients than among placebo patients. Almost all deaths in congestive heart failure trials were attributed to cardiac causes; no single type of cardiac death occurred significantly more frequently in conivaptan-treated patients than in placebo patients.

Adverse events which occurred with statistically significantly greater frequency among subjects treated with conivaptan than among placebo subjects included:

- serious renal adverse events
- serious and nonserious hypovolemia-related events
- serious and nonserious hypotensive events
- infusion site reactions and infusion site reactions leading to withdrawal from study
- increases in mean serum creatinine, treatment-emergent elevated serum creatinine, and elevated creatinine values of clinical significance
- increases in mean serum alkaline phosphatase
- decreased supine and standing diastolic blood pressure (in pivotal efficacy trial)

Other adverse events of note which occurred more frequently among conivaptan subjects than among placebo subjects included:

- overly rapid correction of serum sodium (in pivotal efficacy trial)
- cardiac failure events, and angina/chest pain events, among patients with underlying congestive heart failure
- anemia events
- diarrhea
- pyrexia
- increases in mean liver transaminases and transaminase elevations of clinical significance
- increases in mean serum alkaline phosphatase
- increases in mean fasting plasma glucose, and treatment-emergent abnormalities of fasting plasma glucose
- treatment-emergent prolongations of prothrombin time (PT) in patients who had PT measured (primarily patients taking concomitant warfarin)

Thirst and polyuria were common expected physiologic events.

Based on adverse findings in animal studies, the toxicologic and clinical reviewers recommend Pregnancy Category C for conivaptan.

The above safety findings, which occurred at average exposures lower than that expected with the proposed dosing regimen, are concerning. In order to determine if conivaptan has an acceptable risk:benefit ratio, safety data from a substantially larger number of patients exposed to the proposed intravenous dose regimen, or a bioequivalent oral regimen, is required.

1.3.4 Dosing Regimen and Administration

The sponsor proposes a 20 mg intravenous bolus followed by a dose of [redacted] administered as a continuous infusion for up to [redacted].

1.3.5 Drug-Drug Interactions

Conivaptan is a potent inhibitor of CYP3A4, and should not be coadministered with drugs metabolized by CYP3A4. The sponsor seeks to minimize the risk of severe adverse drug-drug interactions by limiting conivaptan to intravenous use in hospitalized patients. However, this might not prevent concomitant administration of CYP3A4 drugs. In the controlled hyponatremia trials, multiple protocol violations involving administration of prohibited CYP3A4 drugs occurred, despite a highly controlled clinical setting.

Of note among other drug:drug interaction studies is the warfarin interaction study. No adverse interaction was seen, but the dose of conivaptan used would have had lower exposure than the proposed dose for labeling. In light of the laboratory signal of PT prolongation, the clinical reviewer recommends a repeat warfarin drug interaction study using the full proposed dosing regimen.

1.3.6 Special Populations

The sponsor conducted special population studies in the elderly, in patients with renal dysfunction, and in patients with hepatic dysfunction, and concluded that dosage adjustment was not needed in these populations. However, the oral conivaptan dose used would have had lower exposure than the proposed IV dose, and the clinical reviewer recommends that the sponsor repeat these studies using the proposed IV dosing regimen.

Use of adequate conivaptan doses for drug:drug interaction and special population studies is of particular importance because conivaptan exhibits nonlinear pharmacokinetics, with plasma levels increasing in a higher-than-dose-proportionate fashion. This nonlinearity occurs at multiple levels, including with increasing dose, with repeated dose, and with time. Patients in the target patient population have significantly higher exposures than healthy subjects, and significant intersubject variability occurs.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.1.1 Product Description

Conivaptan hydrochloride ([1,1'-biphenyl]-2-carboxamide,N-[4-[4,5-dihydro-2-methylimidazo [4,5-d][1]benzazepin-6(1H)-yl)carbonyl]phenyl]-, monohydrochloride) is an aquaretic which acts through inhibition of arginine vasopressin (AVP) V1a and V2 receptors.

2.1.2 Established Name

Conivaptan hydrochloride has been the primary internal development name used by the product's sponsor. The drug has also been previously referred to as YM087, CI-1025, PD185719, AVA 300 and YM-35087.

2.1.3 Proposed Trade Name

Vaprisol™ is the sponsor's proposed trade name.

The Division of Medication Errors and Technical Support (DMETS) evaluated the name Vaprisol™ for the potential for medication errors. Their full consultation is in the Division File system (DFS) archive. Potential sound-alike and look-alike names were identified, and phonetic and orthographic computer analyses were conducted. Three studies were conducted, employing a total of 123 health care professionals, to simulate the prescription ordering process. In general, although a few drugs have names that look or sound somewhat similar to Vaprisol™, DMETS' evaluation did not reveal limiting safety concerns for potential medication errors. DMETS made some recommendations regarding labeling and packaging; those that are pertinent are included in the recommended comments to the applicant in Section 9.5.2 of this review.

The Division of Drug Marketing and Advertising found the name Vaprisol™ acceptable from a promotional perspective.

2.1.4 Pharmacologic Class

"Aquaretic". Conivaptan's New Drug Application (NDA) is the first submitted for this new class of pharmacologic agents. Aquaretics may be defined as "agents that selectively increase free water excretion without inducing a significant solute diuresis, in contradistinction to 'saluretic' agents, such as furosemide, which increase urinary sodium chloride excretion to a much greater extent." (Verbalis 2002).

2.1.5 Applicant's Proposed Indication

"TRADENAME is indicated for the treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients."

2.1.6 Applicant's Proposed Dosing Regimen

20 mg intravenous bolus followed by a [redacted] dose administered as a continuous infusion [redacted] equaling a total daily dose of [redacted] for the first 24 hours. On Days 2-4, a total daily dose of [redacted] is administered as a continuous infusion of [redacted]

2.1.7 Applicant's Proposed Age Groups

Adults, ages 18 years and older

2.2 Currently Available Treatment for Indications

At this time, no other "aquaretics" or vasopressin receptor antagonists are marketed. There are no FDA-approved therapies for euvolemic or hypervolemic hyponatremia. Please see Section 2.6 for a brief background discussion of hyponatremia and vasopressin. Hypovolemic hyponatremia is usually treated initially with isotonic fluid. The mainstay of treatment of euvolemic and hypervolemic hyponatremia is restriction of intake of water and total fluids. A few other agents are sometimes used "off-label" for the treatment of hyponatremia. The following table summarizes agents that have been used to treat euvolemic and hypovolemic hyponatremia.

Table 2.2: Agents/Treatments Used Off-Label for Treatment of Euvolemic or Hypervolemic Hyponatremia

Agent/Treatment	Rationale for Use	Advantages	Disadvantages
Restriction of Intake of Water and Total Fluids	Reduction of volume of intravascular free water, resulting in increased sodium	Low toxicity; very low risk of overly rapid correction and its attendant neurologic consequences, such as central pontine myelinolysis	Slow (several days before significant increase in plasma osmolality), uncomfortable for patient
Demeclocycline	Induction of nephrogenic diabetes insipidus	Relatively predictable effect	Slow (several days to maximal effect); potential for nephrotoxicity
Hypertonic Intravenous Saline (for acute or severely symptomatic hyponatremia only)	Direct increase in intravascular sodium	Allows rapid correction in symptomatic acute hyponatremia	Potential for overly rapid rise in serum sodium, especially in chronically hyponatremic patients; carries risk of neurologic sequelae such as central pontine myelinolysis
Furosemide	Diuresis, with the		Inconsistent result; risk for

Table 2.2: Agents/Treatments Used Off-Label for Treatment of Euvolemic or Hypervolemic Hyponatremia			
Agent/Treatment	**Rationale for Use**	**Advantages**	**Disadvantages**
	goal of loss of water in excess of isotonic fluid, or replacement of diuresed volume with isotonic fluid		volume depletion
Lithium	Induction of nephrogenic diabetes insipidus		Inconsistent result; nausea; diarrhea; dermatologic reactions
Urea	Osmotic diuresis with urinary loss of water in excess of solute	Otherwise relatively pharmacologically inert	Poor commercial availability; risk of pulmonary edema; risk of further hemorrhage in patients with intracranial bleeding; poor oral palatability; intravenous infusion site irritation and risk of thrombosis

2.3 Availability of Proposed Active Ingredient in the United States

This agent is not yet marketed in any country.

2.4 Important Issues With Pharmacologically Related Products

This agent is the first in its class to be considered for marketing approval.

2.5 Presubmission Regulatory Activity

2.5.1 FDA Divisions Holding Investigational New Drug Applications for Conivaptan

Two Divisions within the FDA hold Investigational New Drug Applications (INDs) for conivaptan:

Table 2.5.1: FDA INDs for Conivaptan				
IND #	**Division**	**Indication**	**Route of Administration**	**Date IND Submitted**
[redacted]	DMEDP[1]	Hyponatremia	Oral	3 Apr 98
56813	DMEDP	Hyponatremia	IV	19 Aug 98
[redacted]				

[1]Division of Metabolic and Endocrine Drug Products

Table 2.5.1: FDA INDs for Conivaptan				
IND #	**Division**	**Indication**	**Route of Administration**	**Date IND Submitted**
[2]Division of Cardiorenal Drug Products [3]congestive heart failure				

2.5.2 Major Regulatory Interactions

The FDA has met with the sponsor, or formally responded to regulatory and scientific questions, more than thirty times during the development of conivaptan to date. Only major interactions are described below.

20 May 99: First End-of-Phase II meeting held between DMEDP and original sponsor (Parke-Davis) regarding IV hyponatremia IND. DMEDP agreed that hyponatremia could be recognized as an indication, and that a serum sodium of <130 mEq/L could be used to define hyponatremia. DMEDP stated that the indication would not include treatment of CHF *per se*, and that the sponsor would need to provide a rationale for the treatment of hyponatremia in CHF. DMEDP stated that the major adequate and well-controlled trials for demonstration of safety and efficacy could include one controlled IV study, two controlled oral studies, and one uncontrolled oral extension study. Only the IV trial would be considered "pivotal"; the oral studies would be considered supportive.

29 Dec 00: INDs transferred to Yamanouchi

30 Jan 01: Second End-of Phase II meeting held with DMEDP regarding both formulations for the hyponatremia IND, this time with Yamanouchi. Serious concerns raised regarding major effects of conivaptan on cytochrome P450 3A4 (CYP3A4) metabolism. DMEDP questioned whether it would be possible to manage this risk through labeling. Area under the curve (AUC) for serum sodium accepted as primary endpoint. Secondary efficacy measurement of change in serum sodium from baseline to last outcome accepted.

23 Aug 02: Yamanouchi informed DMEDP that Yamanouchi planned to continue development of only the IV formulation for the hyponatremia indication

18 Oct 02: Phase III development plan teleconference held with DMEDP. Agreed to limitation of the indication to short-term intravenous inpatient use, because of CYP3A4 concerns. DMEDP advised increase in sample size in major IV hyponatremia study. DMEDP agreed that proposed sample size of 500 subjects exposed to conivaptan in the hyponatremia program, and 500 exposed in the congestive heart failure program, appeared adequate to support the safety review.

6 Aug 03: Pre-NDA meeting between DMEDP and Yamanouchi regarding IV hyponatremia indication. DMEDP stated that the full report of an IV conivaptan and midazolam QT interaction study would be needed with the NDA. DMEDP agreed that restricted labeling, limiting the use of conivaptan to four days in hospitalized patients,

could be used to manage the risk of CYP3A4 interactions. DMEDP did not agree to the sponsor's request to include only information from the "pivotal" IV study as the source of safety data for the package insert; all adverse event data from both the IV and oral studies would likely be included in the label. Biopharmacology stated that review of the sponsor's pharmacokinetic model would be needed to determine if oral exposure was equivalent to IV exposure; the inclusion of data from the oral development program as support for the safety of the IV formulation was based on the sponsor's assertion that oral and IV exposure were equivalent.

30 Jan 04: NDA submitted

Important Postsubmission Regulatory Interaction:

19 Jul 04: Meeting held with sponsor regarding results of their Study -083, a bioequivalence study in healthy subjects, which compared the pharmacokinetics of the oral and intravenous formulations of conivaptan. The study showed that short-term oral exposure to conivaptan is approximately one third that of short-term intravenous exposure. No subjects who received oral conivaptan in the development programs had received equivalent exposure to the proposed dosing regimen for labeling for IV conivaptan. Although the sponsor's oral program could provide some types of safety information, it could not support the safety of the full planned IV dosing regimen.

2.6 Other Relevant Background Information

Brief Overview of Vasopressin and Hyponatremia

Vasopressin (AVP), also known as anti-diuretic hormone (ADH), is a neurohypophyseal peptide hormone which is stored in and released from the posterior pituitary. Vasopressin's basic function is to conserve body water by reducing urine output, but AVP has a number of other effects. AVP is released in response to increases in serum osmolality, decreases in blood pressure, and a number of other stimuli. In most persons, osmotic regulation of release of AVP is highly sensitive, and plasma osmolality is maintained within a very tight range.

AVP at the following receptors has different functions:

- Osmoregulatory V2 receptors, located predominantly in the distal collecting tubules of the kidney, regulate excretion of water. Activation of these receptors results in the insertion of water channels, or aquaporins, in the collecting tubule, allowing for the passive reabsorption of water. AVP action results in increased free water retention.
- Baroregulatory V1a receptors are located in certain vascular locations, and activation results in vasoconstriction. In healthy humans, little or no pressor effect occurs, but a pressor effect may be significant in certain disease states.
- V1b receptors are involved in adrenocorticotrophic hormone (ACTH) release.

Conivaptan has both V2 and V1a activity; the latter is evidenced by inhibition of the pressor response to vasopressin. Vasopressin receptors [V1a and perhaps V2 (Bernat 1997)] also mediate *ex vivo* platelet aggregation.

Some diseases or conditions associated with undesirably increased AVP levels or action include:

- SIADH (associated with euvolemic hyponatremia)
- CHF (associated with hypervolemic hyponatremia)
- Cirrhosis (associated with hypervolemic hyponatremia)

Increased AVP action in these conditions likely results in increased and undesirable free water retention, which can be reflected clinically by a dilutional hyponatremia.

Hyponatremia is the most common electrolyte abnormality in hospitalized patients (Anderson 1985). Clinical consequences of hypoosmolar hyponatremia are primarily neurologic, and range from mild symptoms such as headache and nausea, to more severe disorders such as disorientation, confusion, obtundation and seizures. In severe cases, death can result from respiratory arrest after cerebral herniation and brainstem compression. Significant symptoms usually do not occur until the serum sodium falls below 125 mEq/L (normal range 135-145). Symptoms are much more likely when the fall in serum sodium is rapid; patients with chronic, slowly developing hyponatremia can remain asymptomatic even at considerably lower serum sodium levels.

Vasopressin receptor antagonists target the hyponatremia associated with euvolemic and hypervolemic hypoosmolar hyponatremia. The Syndrome of Inappropriate Antidiuretic Hormone (SIADH) represents euvolemic hyponatremia. SIADH is classically defined by the presence of all the following:

- Hyponatremia with plasma hypoosmolality
- Urine osmolality higher than appropriate for plasma osmolality
- Excessive renal wasting of sodium
- Absence of clinical evidence of edema-forming states or volume depletion, and
- Normal kidney and adrenal function

SIADH occurs in a variety of diseases, especially in the setting of severe central nervous system infections and injuries, significant pulmonary disease, a number of malignancies (classically bronchogenic lung carcinoma), and the use of certain drugs. A wide variety of drugs have been associated with SIADH, but typical culprit drugs include chlorpropamide, vincristine, phenothiazines, tricyclic antidepressants, and selective serotonin reuptake inhibitors.

Initial management of hypoosmolar hyponatremia requires a careful history and physical examination of the patient, with special attention paid to the presence or absence of neurologic symptoms or signs, the extracellular fluid volume (ECF) status, the chronicity of the hyponatremia, and exclusion of certain disorders such as hypothyroidism and hypoadrenalism.

- Hypoosmolar hyponatremia associated with decreased ECF is initially treated with solute repletion (usually normal saline), followed by detection and treatment of the underlying causal condition.
- Hypoosmolar hyponatremia of mild to moderate degree associated with hypervolemic states (e.g., in CHF and cirrhosis) is usually managed by treating the underlying condition first. If serum sodium remains abnormal, fluid restriction and/or measures such as those in Table 2.2 are sometimes used.
- Euvolemic hypoosmolar hyponatremia (e.g. SIADH) of mild to moderate degree is managed primarily by fluid intake restriction; if ineffective, other agents as described in Table 2.2 may be used.

Acute symptomatic hyponatremia of less than 48 hours duration requires rapid (but controlled) correction of serum sodium; hypertonic saline infusion is usually used. Chronic but symptomatic hyponatremia also requires relatively rapid correction, but at a careful rate of serum sodium rise. A desirable rate of correction is 1-2 mEq/L/hr with an absolute correction over 24 hours no greater than 12 mEq/L. Overly rapid correction of serum sodium has been associated with permanent neurologic sequelae, classically pontine and extrapontine myelinolysis.

Correction of chronic asymptomatic hyponatremia should occur particularly carefully, as this group is particularly at risk for permanent neurologic sequelae of overly rapid correction. Fluid restriction is the mainstay of therapy.

There are currently no approved therapies for hyponatremia; treatments which are sometimes used off-label for its treatment are outlined in Table 2.2.

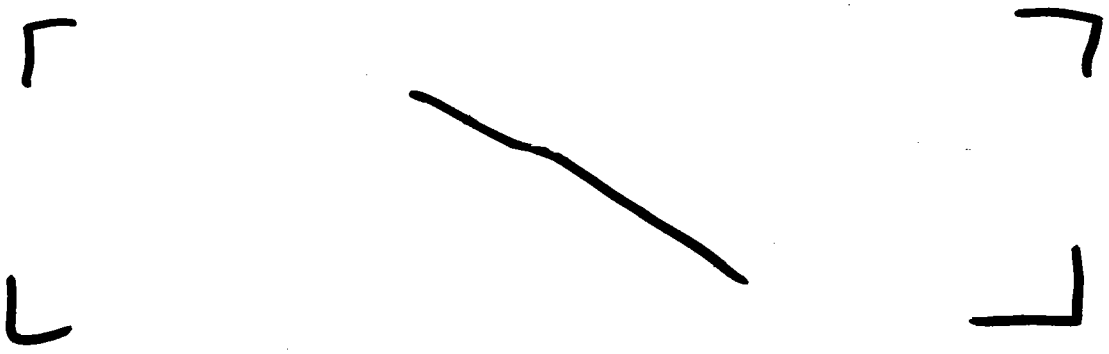
The medical literature has documented interest for years in the development of AVP receptor antagonists as potential treatments for hyponatremia. For causes of hyponatremia that are associated with undesirably elevated AVP action, such antagonists could specifically target the physiologic mechanism leading to hyponatremia. These states include SIADH, congestive heart failure and cirrhotic ascites.

Brief discussion of the potential for use of vasopressin antagonists in congestive heart failure is warranted. Conivaptan

[redacted]

functional classes III or IV (Leier 1994). Hyponatremia is associated with decreased median survival among patients with chronic severe CHF and with acutely decompensated CHF; the more severe the hyponatremia, the lower the survival (Lee 1986). However, this correlation might not hold up as an independent prognostic factor (Dargie 1987, Rockman 1989, Anguita 1993). Survival correlation data have not been shown in hepatic failure patients. In both these disease states, there is decreased effective extracellular fluid volume, which may trigger AVP secretion, and thus may lead to a

dilutional hyponatremia due to excess free water retention. There is evidence that AVP plays a role in the dilutional hyponatremia associated with these states, but other factors may also have a causal relationship (Oster 1992). As mentioned above, AVP not only acts on V2 renal receptors to affect free water reabsorption, but also acts on V1a receptors located in vascular beds, causing vasoconstriction. Such action is undesirable in CHF, as it might require the already ineffective heart to pump against higher pressures. Hyponatremia in CHF patients is a possible marker of V2 receptor activity, and perhaps an indirect marker of V1a receptor activity.



Because of the potential for off-label use of conivaptan in congestive heart failure, and because of the uncertainties about the significance of hyponatremia and the value of its correction in CHF, special attention will be paid to the safety of conivaptan in hyponatremic CHF patients in this review.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

3.1.1 Chemistry

Please see Dr. Adams' review for details of the chemistry of conivaptan. Conivaptan is an odorless white crystalline powder.

Dr. Adams recommends an "Approvable" action based on additional information needed regarding the manufacturing process. His requests for additional information are included below in section 9.5.2.11.

3.1.2 Microbiology

A complete microbiology review was performed by Dr. Paul Stinavage. The product is [redacted] into ampules and then undergoes [redacted] sterilization. The product met acceptance criteria for total microbiological count and maximum endotoxin concentration. Dr. Stinivage concludes that the product is acceptable on the basis of sterility assurance.

3.2 Animal Pharmacology/Toxicology

Please see Dr. Alavi's animal pharmacology and toxicology review for full details of the results of the applicant's preclinical program.

Conivaptan is not genotoxic, carcinogenic or teratogenic in animals. Target organ toxicity included bone marrow toxicity in dogs; hepatic and renal toxicity in rat and dog; effects on estrus cycle and reproduction in rats; vascular irritation in rats, rabbits and dogs; and adrenal gland toxicity in rats.

Human PK data in the target patient population were sparse, and exposure multiples were calculated using data from healthy subjects receiving the proposed regimen for labeling. Because conivaptan levels are higher in the target disease states, these exposure multiples could be less in the target patient population, thus narrowing the margin of safety between therapeutic and toxic levels of conivaptan.

Bone marrow toxicity consisted of focal/multifocal necrosis and degeneration, decreased erythroblastic islands, myeloid hyperplasia, hypocellularity and fibrosis. These effects occurred only at high systemic exposures (>40x the therapeutic exposure for durations of exposure beyond one week of dosing). These findings were reversible in a 13 week dog study that included a 6 week recovery phase.

Hepatotoxicity also occurred at high exposures given for more than one week. Findings included elevated enzymes, bile duct hyperplasia, sinusoidal dilatation, hepatocyte hypertrophy, inflammation, jaundice, cholestasis and hepatocyte necrosis at 40x therapeutic exposure. In a one week IV rat study, slight increases in liver enzymes, hepatocellular hypertrophy and hepatocyte necrosis were observed at 15x therapeutic exposure.

Renal tubular degeneration was observed in rats at exposures 4x human therapeutic exposure after one week of IV dosing. BUN elevations were also observed. These findings suggest some clinical relevance.

The degree of infusion site vascular inflammation was significant enough to result in termination of a 4 week rat IV infusion study and a dog IV bolus study. Both the PG/EtOH vehicle and conivaptan itself contribute to vascular irritation. In bolus studies in animals, more concentrated formulations caused more severe changes. Rats were more susceptible to this than dogs and rabbits; the sponsor felt this might be due to smaller vessel diameter, and recommends that conivaptan be administered via large veins.

Conivaptan caused significant aquaresis leading to dehydration in normal animals; this finding is expected based on the drug's physiologic effect.

Effects on estrus cycles and reproduction in rats occurred at doses comparable to human clinical exposure. Conivaptan caused delayed parturition, and physical and functional developmental deterioration in offspring. Placental and milk transfer of conivaptan to the fetus occurs. With placental transfer, fetal levels of conivaptan were 2-3x higher than maternal levels. Clearance in the fetus was much slower than in the mother, and fetal accumulation of conivaptan is possible. Conivaptan is contraindicated in pregnancy and lactation based on these findings.

Changes to the proposed label were recommended by the toxicology review team, and are included in Sections 9.4 and 9.5.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This New Drug Application was submitted electronically in the electronic Common Technical Document format. The original NDA submission path is
\\CDSESUB1\N21697\N_000\2004-01-30.
An intensive QT study was later submitted electronically with the paths
\\CDSESUB1\N21697\N_000\2004-03-31 and
\\CDSESUB1\N21697\N_000\2004-05-14.
A safety update was submitted four months into the review cycle and is located via the path
\\CDSESUB1\N21697\N_000\2004-05-28.

Together, these submissions totaled about 5.3 gigabytes of submitted information. Data submitted for review were primarily from trials conducted by the sponsor. The clinical

[redacted]

4.2 Tables of Clinical Studies

Table 4.2.1: Major Controlled Clinical Efficacy and Safety Studies in Nonhypovolemic Hyponatremia

Study Number	Objective(s)	Design and Control	Test Product and Route of Administration	Number and Type of Subjects	Duration of Conivaptan Exposure
087-CL-	Efficacy,	DB[1], PC[2],	Pbo[4]	84 (29 pbo, 29	4 days

Table 4.2.1: Major Controlled Clinical Efficacy and Safety Studies in Nonhypovolemic Hyponatremia

Study Number	Objective(s)	Design and Control	Test Product and Route of Administration	Number and Type of Subjects	Duration of Conivaptan Exposure
027	safety	MC[3]	CIVI[5] coni[6]: 40 or 80 mg/day	coni 40, 26 coni 80), Nonhypovolemic hyponatremia	
087-CL-026	Efficacy, safety	DB, PC, MC	Pbo Oral coni: 20 or 40 mg bid	74 (23 pbo, 24 coni 20 mg bid, 27 coni 40 mg bid), Nonhypovolemic hyponatremia	5 days
087-CL-043	Efficacy, safety	DB, PC, MC	Pbo Oral coni: 20 or 40 mg bid	83 (30 pbo, 27 coni 20 mg bid, 26 coni 40 mg bid)	5 days

[1] **Double-blind**
[2] **Placebo-controlled**
[3] **Multicenter**
[4] **Placebo**
[5] **Continuous intravenous infusion**
[6] **Conivaptan**

Table 4.2.2: Uncontrolled Clinical Study in Nonhypovolemic Hyponatremia

Study Number	Objectives	Design	Test Product and Route of Administration	Number and Type of Subjects	Duration of Conivaptan Exposure
087-CL-047	Safety, tolerability, efficacy	Open-label extension	Oral conivaptan: 10 and 40 mg q day; 10, 20, 30 and 40 mg bid	30, Nonhypovolemic hyponatremia	12 weeks (plus optional 12-week cycles)

Table 4.2.3: Controlled Clinical Studies in Congestive Heart Failure

Study Number	Objectives	Design and Control	Test Product and Route of Administration	Number and Type of Subjects	Duration of Conivaptan Exposure
087-CL-038	Efficacy, safety, PK[1]	R[2], DB[3], PC[4], PG[5]	Pbo IV coni[6], 20 mg bid	26 (12 pbo, 14 coni), [redacted]	1 day
087-CL-044	Efficacy, safety, PK	R, DB, PC, PG	Pbo IV coni, 40 mg bid	26 (13 pbo, 13 coni), [redacted]	1 day

Table 4.2.3: Controlled Clinical Studies in Congestive Heart Failure

Study Number	Objectives	Design and Control	Test Product and Route of Administration	Number and Type of Subjects	Duration of Conivaptan Exposure
				[redacted]	
087-CL-033	Longterm safety, efficacy	R, DB, PC, PG	Pbo Oral coni: 10, 20 or 40 mg bid	47 (12 pbo, 14 coni 10 mg bid, 11 coni 20 mg bid, 10 coni 40 mg bid), [redacted]	26 weeks
087-CL-027	Cardiopulmonary exercise testing	R, DB, PC, PG	Pbo Oral coni: 5, 10, or 20 mg bid	304 (74 pbo, 72 coni 5 mg, 77 coni 10 mg, 81 coni 20 mg), [redacted]	12 weeks
087-CL-034	DR[8], safety, PK	R, DB, PC, PG	Pbo Oral coni: 10, 20 or 40 mg bid	343 (93 pbo, 76 coni 10 mg, 85 coni 20 mg, 89 coni 40 mg)	12 weeks

1 Pharmacokinetics
2 Randomized
3 Double-blind
4 Placebo-controlled
5 Parallel group
6 Conivaptan
7 Congestive heart failure
8 Dose response

Table 4.2.4: Pharmacokinetic and Pharmacodynamic Studies in Target Disease States

Study Number	Objective(s)	Design and Control	Test Product and Route of Administration	Number and Type of Subjects	Duration of Conivaptan Exposure
087-CL-023	Efficacy, safety, PK[1], PD[2]	OL[3], NR[4], DT[5] and mnt[6]	IV coni[7]: 20 mg q day to 30 mg q day; then to 40 mg q day or bid (max 80 mg)	11 (5 SIADH[8], 6 CHF[9])	2-3 days
087-CL-025	DD[10] pilot safety and efficacy	OL	IV coni, 20 mg bolus, then CIVI[11] 40-100 mg	11 (nonhypovolemic hyponatremia)	2-4 days
087-CL-032	DR[12], efficacy, safety	R[13], DB[14], PC[15], PG[16]	Pbo[17] IV coni: 10, 20 or 40 mg	142 (CHF)	1 day
087-CL-021	Efficacy, safety, PK	OL, DT, mnt	Oral coni: 20, 40, 80 mg x 1 day ea, then 120 mg q day x 2	5 (euvolemic hyponatremia)	5-8 days

Table 4.2.4: Pharmacokinetic and Pharmacodynamic Studies in Target Disease States

Study Number	Objective(s)	Design and Control	Test Product and Route of Administration	Number and Type of Subjects	Duration of Conivaptan Exposure
			days, then 120 mg bid x 2 days		
087-CL-022	Tol[18], efficacy, safety	OL, DT, mnt	Oral coni: 10, 20, 40 and 60 mg	6 (CHF with hypervolemic hyponatremia)	5-8 days
087-CL-018	Aquaretic effect, safety	OL, DE[19]	Oral coni: 1,5,10,20 and 30 mg	30 (all with edema; 10 cardiac, 10 renal, 10 hepatic)	4-8 days

1 Pharmacokinetic
2 Pharmacodynamic
3 Open label
4 Nonrandomized
5 Dose titration
6 Maintenance
7 Conivaptan
8 Syndrome of Inappropriate Antidiuretic Hormone
9 Congestive heart failure
10 Dose-dependent
11 Continuous intravenous infusion
12 Dose response
13 Randomized
14 Double blind
15 Placebo-controlled
16 Parallel group
17 Placebo
18 Tolerability
19 Dose escalation

Table 4.2.5: Special Population, Food Effect, and Drug Interaction Pharmacokinetic Studies

Study Number	Objectives	Design and Control	Test Product and Route of Administration	Number and Type of Subjects	Duration of Conivaptan Exposure
087-CL-014	Safety, tol[1], PK[2]/PD[3] in elderly	R[4], DB[5], PC[6], SD[7], DE[8]	Pbo Oral coni[15]: 15, 30 and 60 mg q day	24 healthy elderly (6 pbo, 18 coni)	1 day
087-CL-059	PK, safety in renal impairment	OL[9], MD[10], PG[11]	Oral coni: 10 mg q day on days 1 and 8; 10 mg bid on days 2-7	24, mild-mod[12] renal impairment	8 days
087-CL-060	PK, safety in hepatic impairment	OL, MD, PG	Oral coni: 10 mg q day on days 1 and 8; 10 mg bid on days 2-7	21 (8 healthy, 13 with hepatic impairment)	8 days

Table 4.2.5: Special Population, Food Effect, and Drug Interaction Pharmacokinetic Studies

Study Number	Objectives	Design and Control	Test Product and Route of Administration	Number and Type of Subjects	Duration of Conivaptan Exposure
087-CL-010	Food effect	R, DB, XO[13]	Oral coni. 15, 30, 60 or 90 mg q day	84, healthy	2 days
087-CL-001	Food effect	R, SB, XO	Oral coni, 15 mg q day	8, healthy	2 days
087-CL-052	Midazolam interaction	NB[14], R	Oral midazolam 2 mg Oral coni, 20 or 40 mg	16, healthy	5 days
087-CL-074	Midazolam interaction	OL, R	Oral midazolam 2 mg days 1 and 5 IV midazolam 1 mg days 1 and 5 IV coni, 40 mg/day, days 3-5 IV coni, 80 mg/day, days 3-5	37, healthy	4 days
087-CL-057	Amlodipine interaction	OL	Oral amlodipine 5 mg q day Oral coni, 40 mg bid	12, healthy	12 days
087-CL-049	Warfarin interaction, PK/PD	OL, MD	Oral coni, 40 mg bid	12, on stable warfarin	10 days
087-CL-054	Simvastatin interaction	OL, R, MD	Oral simvastatin, 60 mg days 1 and 6 Oral coni, 20 or 40 mg bid days 2-6	16, healthy	5 days
087-CL-064	Simvastatin interaction	OL, NR	Oral simvastatin 60 mg days 1 and 5 IV coni, 15 mg bid days 3-5	4, healthy	3 days
087-CL-058	Ketoconazole interaction	OL	Oral ketoconazole 200 mg po bid days 4-6 Oral coni, 10 mg po days 1 and 5	12, healthy	2 days
087-CL-058	Digoxin interaction	DB, R, PC, XO	IV digoxin 0.5 mg q day Oral coni, 40 mg po q day	14, healthy	2 days
087-CL-011	Digoxin interaction	NB, MD	Oral digoxin 0.25 mg Oral coni, 40 mg bid	12, healthy	2 days
087-CL-012	Captopril interaction	DB, R, PC, XO	Oral captopril 25 mg q day Oral coni, 30 mg q day	15, healthy	2 days
087-CL-012	Furosemide interaction	OL, R, 4 arms	Oral furosemide, 40 or 80 mg q day Oral coni, 20 or 40 mg q day	24, CHF[16]	3 days

1 Tolerability
2 Pharmacokinetics
3 Pharmacodynamics
4 Randomized
5 Double-blind
6 Placebo-controlled
7 Single dose
8 Dose escalation
9 Open label
10 Multiple dose
11 Parallel group
12 Moderate
13 Crossover
14 Nonblinded
15 Conivaptan
16 Congestive heart failure

Table 4.2.6: Healthy Subject Initial Tolerability and Pharmacokinetics Studies

Study Number	Objectives	Design and Control	Test Product and Route of Administration	Number of Subjects	Duration of Conivaptan Exposure
087-CL-013	IV safety, tol[1], V1 and V2 blocking effects	OL[2], single dose	IV coni[7]: 0.1, 0.3, 1, 2.5, 5, 7.5, 10, 15, 25, and 50 mg	8	2 or 3 days
087-CL-006	IV tol and PK of single IV doses; aquaretic effect	R[3], PC[4], SB[5]	Pbo[6] IV coni: 0.2, 2, 10, 50, 125 or 250 µg/kg	27 (9 pbo, 18 coni)	2 days
087-CL-008	IV inhib[8] effect on plt[9] aggregation	R, PC, DB[10]	Pbo IV coni: 135, 270 or 540 µg/kg (over 3 hrs)	24 (9 pbo, 15 coni)	2 days
087-CL-007	IV tol and PK, aquaretic effect	R, PC, SB	Pbo IV coni, 250 µg/kg	11 (4 pbo, 7 coni)	7 days
087-CL-009	Oral safety, tol, PK of capsules	OL, DE[12]	Oral coni: Grp A = 0.2→3→10→40 mg Grp B = 1→5→20→60 mg	4	4 days
087-CL-002	Oral tol, PK, aquaretic effect	R, PC, SB, XO[11]	Pbo Oral coni: 0.2, 1, 5, 15, 30 or 60 mg	27 (9 pbo, 18 coni)	2 days
087-CL-003	Oral tol, PK, aquaretic effect	R, PC, SB	Pbo Oral coni 60 mg po bid	9 (3 pbo, 6 coni)	3.5 days
087-CL-004	Oral dose finding	R, PC, SB, XO	Pbo Oral coni, 15 mg q day or bid Oral coni, 30 mg q day or bid	9 (3 pbo, 6 coni)	2 days
087-CL-005	Oral tol, PK, bid vs q day dosing	R, PC, SB	Oral coni 15 mg bid or 30 mg q day	12	7 days
087-CL-063	Oral tol, safety, PK/PD	R, PC, SB	Pbo Oral coni; 20, 30 or 40 mg, all bid	24 (6 pbo, 18 coni)	7 days

1 Tolerability
2 Open label
3 Randomized
4 Placebo-controlled
5 Single blind
6 Placebo
7 Conivaptan
8 Inhibitory
9 Platelet
10 Double blind
11 Crossover
12 Dose escalation

Table 4.2.7: Oral Congestive Heart Failure Initial Safety, Tolerability and Pharmacokinetics Studies

Study Number	Design and Control	Test Product and Route of Administration	Number and Type of Patients	Duration of Conivaptan Exposure
087-CL-016	OL[1], DE[2]	Oral coni[3]; 5, 10 and 20 mg	12, severe CHF	1 day
087-CL-017	R[4], DB[5], PC[6], DE	Pbo[7] Oral coni bid: 5, 10, 20 and 40 mg	24 (8 pbo, 16 coni) Chronic CHF[8]	7 days

1 Open label
2 Dose escalation
3 Conivaptan
4 Randomized
5 Double blind
6 Placebo controlled
7 Placebo
8 Congestive heart failure

Table 4.2.8: Population Pharmacokinetic Studies

Study Number	Objectives	Design	Test Product and Route of Administration	Number and type of Subjects	Duration of Conivaptan Exposure
087-CL-075	Pop[1] PK[2]	Data taken from 4 OL[3] DR[4] Phase 2 studies	Oral coni[5], multiple doses ranging from 20-120 mg/day IV coni, multiple doses ranging from 10-90 mg/day	33 (from prior studies), SIADH[6] or CHF[7]	Oral coni up to 8 days IV coni up to 4 days (but all from prior studies)
087-CL-082	Pop PK	Data taken from 16 studies (Phases 1-3)	Oral coni, doses ranging from 5-80 mg/day IV coni, doses ranging from 0.13-100 mg	333 (from prior studies); healthy, or with hyponatremia and/or CHF	Oral coni up to 7 days IV coni up to 4 days (but all from prior studies)
087-CL-019	Hemodynamics	OL[8], SD[9]	IV coni: 2, 10, 25, 50, 125, or 250 µg/kg	42, acute heart failure	1 day

1 Population
2 Pharmacokinetics
3 Open label
4 Dose ranging
5 Conivaptan
6 Syndrome of Inappropriate Antidiuretic Hormone
7 Congestive heart failure
8 Open label
9 Single dose

4.3 Review Strategy

For the efficacy review, the clinical reviewer placed emphasis on the three trials which the sponsor considers to be "adequate and well-controlled" trials of the drug in nonhypovolemic hyponatremia. These included trial -027 conducted with the intravenous formulation, and trials -026 and -043 conducted with the oral formulation. The clinical reviewer obtained safety information from these trials, as well as from the extension trial -047. The clinical reviewer also evaluated pooled safety data from all clinical trials, and specific safety information regarding special populations and drug-drug interactions.

Separate reviews were conducted by other disciplines, including biopharmacology, toxicology, biostatistics, chemistry and microbiology. Brief synopses of the findings of these reviewers are included in this clinical review; complete reviews for each of these disciplines may be found in the electronic archival Division File System.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) conducted a routine audit from 21-25 Jun 04 at the WJB Dorn Veteran's Administration (VA) Hospital in Columbia, South Carolina. For the "pivotal" intravenous study, only two sites contributed patients in double digit numbers; this site and one in Israel. The Columbia VA site, under the supervision of investigator Dr. Steven Rosansky, contributed fifteen patients. The Division of Metabolic and Endocrine Drug Products recommended audit of the Columbia VA simply because it contributed a substantial proportion (18%) of the total population of the only "adequate and well-controlled" study of the intravenous formulation. No "for cause" issues were identified prior to the DSI site visit. For details of the audit findings, please refer to the letter (in DFS archive) sent to Dr. Rosansky by DSI. The audit revealed that a few laboratory values of serum sodium and osmolality were not drawn on time, and one urinalysis source document was missing. At one point, the study coordinator became unblinded to the treatment assignment of four patients. DSI concluded that overall there were no serious concerns regarding the integrity of data from that site.

The efficacy results for Study -027 were recalculated with exclusion of Dr. Rosansky's site. Exclusion of these patients did not change efficacy conclusions (see Section 6.1.4.1.3).

DSI also conducted an audit from 21-22 Jun 04 at the [redacted] which served as clinical monitor for Study -027. The audit found that [redacted] adhered to the applicable statutory requirements and FDA regulations governing the monitoring of clinical studies of human investigational new drugs and the protection of human subjects.

DSI also conducted an inspection of Yamanouchi Pharma America's management procedures for Study -027. The inspection found that Yamanouchi did not describe the transfer of responsibility for clinical trial material when Yamanouchi transferred sponsor

obligations to [redacted]. Yamanouchi committed to changing its procedures to assure that this would not occur in ongoing or future studies. Overall, the inspection did not reveal serious concerns regarding clinical trial management.

Details of the latter two inspections are also in DSI letters in the DFS archive.

4.5 Compliance with Good Clinical Practices

4.5.1 Institutional Review and Informed Consent

For each of the studies designated by the sponsor as "adequate and well-controlled", each investigator's institutional review board or ethics committee reviewed the protocol, informed consent form and investigator's brochure. The sponsor certifies that these studies were conducted in accordance with Good Clinical Practice, the International Committee on Harmonisation (ICH) document E6, and with Title 21, U.S. Code of Federal Regulations Parts §§ 50, 56 and 312. Informed consent was obtained from each subject or a legal representative of the subject. Clinical review of the patient informed consent forms found them to adequately describe the conduct of the studies, and potential risks of participation in the studies.

4.5.2 Protocol Violations

The sponsor described their populations of analysis according to recommendations described in ICH guidelines E3 and E9. For the major efficacy and safety trials, these populations were defined as follows:

Safety Population included all patients who met the following criteria:
- were randomized
- received any study medication.

Full Analysis Set included all patients who met the following criteria:
- were randomized
- received any study medication
- had at least one baseline serum sodium measurement available
- had at least one on-treatment serum sodium measurement available.

Per Protocol Set included all patients who met the following criteria:
- were randomized
- received at least 50% of study medication (for Study -027); or at least one dose of study medication (for Studies -026 and -043)
- had at least 1 baseline serum sodium measurement available.
- had at least 70% of the planned serum sodium measurements during the treatment phase; or 2 or more serum sodium measurements from Study Day 1 through Study Day 4 in the treatment phase
- had average baseline serum sodium measurement of < 132 mEq/L.

For all three "adequate and well-controlled" trials, the Safety Population and the Full Analysis Set were identical; all patients correctly received the treatment associated with their group assignment. Except where otherwise noted, all analyses were performed on the Safety Population/Full Analysis Set for each protocol.

The Per Protocol Sets for all three major efficacy studies did not include all patients from the Safety Populations. The following tables summarize the protocol violations leading to exclusion from the per protocol sets for Studies -027 and -043.

Table 4.5.2.1: Summary of Protocol Violations Leading to Exclusion from Per Protocol Analysis Set for Study -027

Protocol Violation	Placebo (n = 29)	Conivaptan 40 mg/day (n = 29)	Conivaptan 80 mg/day (n = 26)
< 70% of planned treatment phase serum sodium measurements	1 (3.4%)	2 (6.9%)	1 (3.8%)
Received < 50% of prescribed clinical trial material			1 (3.8%)
< 70% of planned treatment phase serum sodium measurements and received < 50% of prescribed clinical trial material	3 (10.3%)	4 (13.7%)	1 (3.8%)
Total n excluded from treatment arm	4 (13.7%)	6 (20.7%)	3 (11.5%)

Table 4.5.2.2: Summary of Protocol Violations Leading to Exclusion from Per Protocol Analysis Set for Study -043

Protocol Violation	Placebo (n = 30)	Conivaptan 40 mg/day (n = 27)	Conivaptan 80 mg/day (n = 26)
< 70% of planned treatment phase serum sodium measurements	5 (16.7%)	2 (7.4%)	1 (3.8%)
High Serum Creatinine at Screening		1 (3.7%)	
Average (Avg) Baseline Serum Sodium > 132			1 (3.8%)
Total n excluded from treatment arm	5 (16.7%)	3 (11.1%)	2 (7.7%)

For Study -026, 3/74 total treated patients, 1/23 placebo patients and 2/27 patients in the conivaptan 80 mg/day group were excluded from the Per Protocol Set. All exclusions were due to one or more missed doses of study drug.

For the three major clinical trials, protocol deviations which did not result in exclusion from the Per Protocol Set are summarized in the following table:

Table 4.5.2.3: Summary of Protocol Deviations Which did not Result in Exclusion from the Per Protocol Sets for Studies -027, -026 and -043

Protocol Deviation	Treatment Group	IV Study - 027 (total n = 84) n with deviation/ n in treatment group (% of treatment group)	Oral Study - 026 (total n = 74) n with deviation/ n in treatment group (% of treatment group)	Oral Study - 043 (total n = 83) n with deviation/ n in treatment group (% of treatment group)
Inclusion Criteria	Placebo	1/29 (3.4%)	4/23 (17.4%)	1/30 (3.3%)
	Coni[1] 40 mg/day	3/29 (10.3%)	6/24 (25.0%)	4/27 (14.8%)
	Coni 80 mg/day	0/26 (0.0%)	2/27 (7.4%)	5/26 (19.2%)
Exclusion Criteria	Placebo	4/29 (13.8%)	5/23 (21.7%)	1/30 (3.3%)
	Coni 40 mg/day	2/29 (6.9%)	4/24 (16.7%)	3/27 (11.1%)
	Coni 80 mg/day	0	1/27 (3.7%)	3/26 (11.5%)
Received CYP3A4 Medications	Placebo	3/29 (10.3%)	4/23 (17.4%)	15/30 (50.0%)
	Coni 40 mg/day	1/29 (3.4%)	2/24 (8.3%)	13/27 (48%)
	Coni 80 mg/day	5/26 (19.2%)	4/27 (14.8%)	19/26 (73%)
Management of Other[2] Restricted Medications	Placebo	2/29 (6.9%)	1/23 (4.3%)	1/30 (3.3%)
	Coni 40 mg/day	0	1/24 (4.2%)	0
	Coni 80 mg/day	1/26 (3.8%)	2/27 (7.4%)	0
Fluid intake > 2 L/day	Placebo	6/29 (20.7%)	14/23 (60.9%)	[redacted]
	Coni 40 mg/day	11/29 (37.9%)	18/24 (75.0%)	12/27 (44.4%)
	Coni 80 mg/day	14/26 (53.4%)	18/27 (66.7%)	11/26 (42.3%)

1 Conivaptan
2 Digoxin or amiodarone
3 For Study -043, derived data were not presented by the sponsor for protocol violations of restricted medications and fluid intake; clinical reviewer extracted this information from raw data.

It is worrisome that, even in a highly controlled clinical trial setting, a significant percentage of patients received additional CYP3A4 inhibitors. This fact calls into question the likelihood of management of the risk of CYP3A4 interactions via restricted use conditions described in product labeling. Although DMEDP had discussed the possibility of restricted use conditions as a means of risk management, this protocol deviation information was unavailable to reviewers at the time of that discussion.

Of interest is the fact that violations of the two liter per day fluid restriction occurred very frequently, especially among patients receiving conivaptan. As will be presented in the efficacy section, despite the higher fluid intake in the conivaptan groups, these patients were more likely than placebo patients to have amelioration of their hyponatremia.

4.6 Financial Disclosures

The sponsor submitted a list of clinical investigators who conducted studies for conivaptan; the sponsor certified that they made no financial arrangements with investigators that could affect study outcome. However, many investigators did not submit their financial disclosure forms, and the sponsor did not document due diligence regarding the sponsor's efforts to contact investigators who had not submitted their forms. That is, the sponsor did not include an explanation of how they attempted to obtain the forms and why they were not obtainable; the sponsor simply put the letters "N/R" beside nonresponding investigators' names in the listing of investigators in the financial disclosure section. In particular, very few financial disclosure forms were received by the sponsor for their major Study -043, conducted in Europe. Demographic tables for this study did not permit the clinical reviewer to determine how many patients were contributed by investigators who did not submit their forms. The sponsor was notified of this concern on 13 Feb 04 and on 18 Feb 04, the sponsor sent a facsimile with this information. A total of seven out of 82 total patients in Study -043 were contributed by investigators who did not submit financial disclosure forms; it is unlikely that any payments these investigators received affected study outcome.

Among those investigators who did submit financial disclosure forms, only one subinvestigator, [redacted] had a significant financial interest. [redacted] owned $50,000 in [redacted] stock; [redacted] was the sponsor of Study [redacted] at the time [redacted] was a subinvestigator for that study. However, [redacted] contributed only two patients to the study, and thus his financial interest was unlikely to have significant impact on that study outcome.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Please see Dr. Chung's biopharmacology review for in-depth pharmacokinetic (PK) information.

Pharmacokinetic exposure information for intravenous (IV) conivaptan in the target population was limited, and did not permit extrapolation of preclinical data to humans. Dr. Chung recommends further characterization of conivaptan exposure in target patients (i.e. patients with nonhypovolemic hyponatremia).

Conivaptan's clearance is affected by a number of factors. It is both a substrate for and a potent inhibitor of CYP3A4 (IC50 = 0.47μM). Subject age and health status also affect its clearance. The sponsor calculated a 2-fold difference in systemic exposure for healthy elderly subjects >60 years old compared to young healthy subjects. The sponsor calculated that systemic exposure with the recommended regimen (40 mg/day IV for four days) is 2.4-fold higher in patients with nonhypovolemic hyponatremia than in healthy subjects. For 80 mg/day given for four days, the sponsor calculated the exposure as five-

fold higher in patients than in healthy subjects. For congestive heart failure patients, who have a smaller central compartment than healthy subjects, exposure with the recommended regimen was calculated by Dr. Chung to be 8-fold higher in CHF patients than in healthy subjects.

Maximum plasma concentration (C_{max}) occurs at the end of infusion of an IV bolus. Intravenous conivaptan is distributed rapidly (within 5 minutes) and widely to body tissues in animal studies. The sponsor estimated the volume of distribution to be 50 L in a mass balance study (-061) in healthy young volunteers. Conivaptan is extensively >99%) bound to human plasma proteins in healthy subjects (Study ME-023), patients with hepatic impairment (Study -060) and patients with renal (Study -059) impairment. The half-life of conivaptan after a single intravenous dose is approximately five hours. However, after repeated dosing, the half-life declines to approximately three hours. Plasma concentration nadir occurs at approximately 12 hours after a bolus IV dose. Elimination is primarily in feces (83%), with 12% in urine.

Three minor metabolites of conivaptan were identified; the most abundant of these (M2) comprises only about 3% of circulating conivaptan.

Dose-proportionality of the pharmacokinetics of conivaptan is nonlinear at multiple levels. Plasma concentrations increase by dose, with repeated dosing and over time. PK also varies by route of administration and by input rate. Large intersubject variability occurs.

Gender and race were not found to affect conivaptan pharmacokinetics.

5.2 Pharmacodynamics

Conivaptan is a functional antagonist of vasopressin V1a and V2 receptors with nanomolar affinity for both receptors. V1a receptors are widespread throughout the body, especially in the vasculature and on platelets. V2 receptors are located primarily in the renal collecting duct where they mediate conservation of water. The primary pharmacologic effect of conivaptan occurs in the renal collecting duct, where antagonism of the V2 receptor decreases water conservation and results in an aquaresis.

Hypovolemia in the target states of the euvolemic Syndrome of Inappropriate Antidiuretic Hormone action (SIADH), and the hypervolemic state of congestive heart failure, is caused by an undesirably low excretion of electrolyte-free water for the patient's plasma osmolality. Antagonism of the vasopressin receptor could increase electrolyte-free water clearance. Conivaptan's effects in clinical pharmacology studies are consistent with V2 receptor antagonism. These effects include increased electrolyte-free water clearance (effective water clearance, EWC), increased free water clearance (FWC), increased net fluid loss, increased urine output and decreased urine osmolality. In Study -027, the major Phase 3 intravenous efficacy study for conivaptan, increases in EWC, FWC and net fluid loss were dose-related.

5.3 Exposure-Response Relationships

Intravenous PK data in the target population were sparse, and were not adequate for complete assessment of exposure-response relationships. More extensive PK data are needed for IV treatment of hyponatremic patients. This is particularly important since conivaptan exhibits nonlinearity of dose-proportionality at multiple levels, including nonlinearity by time and dose. Drug levels at steady state were 8-fold higher in CHF patients than in healthy subjects. From the efficacy results of the oral Phase 3 studies, it appears that a lower dose of IV conivaptan could be used with preservation of efficacy. Conivaptan 40 mg/day po was effective, even though oral conivaptan results in blood levels only 1/3 that of IV conivaptan on a mg per mg basis. During earlier clinical development, oral conivaptan 20 mg/day was effective in raising serum sodium in some subjects. Thus, conivaptan doses as low as 7 mg/day IV could be effective in some patients, and a dose of 13 mg/day could reasonably be expected to result in predictable efficacy. However, because of the marked multilayer nonlinearity of conivaptan's PK, these IV doses need to be studied rather than extrapolated from oral.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Treatment of Euvolemic and Hypervolemic Hyponatremia

6.1.1 Methods

The primary clinical data used in the review of efficacy for conivaptan came from three controlled studies of the treatment of nonhypovolemic hyponatremia. Study -027 included 84 patients and used the intravenous form of conivaptan in the regimen proposed for labeling. Studies -026 (74 patients) and -043 (82 patients) used the oral formulation, and were very similar in design to Study -027.

6.1.2 General Discussion of Endpoints

During the development of conivaptan, the drug's sponsors and DMEDP put considerable thought into selection of endpoints. There are no approved treatments for hyponatremia, and thus no precedent existed. Considerable discussion occurred regarding the validity of serum sodium as an endpoint. The sponsors and DMEDP considered the possibility of endpoints specific to the underlying disease states associated with hyponatremia. However, serum sodium was ultimately selected as a legitimate endpoint for a number of reasons:

- Hyponatremia has characteristic neurologic signs and symptoms that are independent of the underlying disease state.
- The severity of neurologic manifestations is inversely correlated with serum sodium; this progression of severity of manifestations can be independent of the severity of the underlying disease state.

- Correction of serum sodium will often reverse the neurologic signs of hyponatremia, even when the underlying disease state remains untreated or unchanged in severity.

Although hyponatremia usually has an identifiable underlying cause, its characteristic manifestations are noteworthy. One can debate whether hyponatremia is merely a sign, and not a disease or syndrome. Stedman's Medical Dictionary defines a disease as "a morbid entity characterized usually by at least two of these criteria: recognized etiologic agent(s), identifiable group of signs and symptoms, or consistent anatomic alterations". In Stedman's, a syndrome is defined as "the aggregate of symptoms and signs associated with any morbid process, and constituting together the picture of the disease". In the clinical reviewer's opinion, hyponatremia is more than a sign, and approaches the definition of a disease or syndrome. Serum sodium is the direct measure of hyponatremia, and thus constitutes the appropriate endpoint.

6.1.3 Study Design

Please see Section 10.1 for a more comprehensive description of the design of Study -027, the single intravenous Phase 3 hyponatremia trial.

The three major efficacy studies (-027, -026 -043) were very similar to one another in design. The design of Study -027, the intravenous efficacy study, is described in this section in moderate detail. The few differences in study design for the oral studies are discussed in Section 10.1.

6.1.3.1 Study Designs

6.1.3.1.1 Description of Design of Study -027

Study -027 was the major intravenous efficacy trial for conivaptan. Its objective was to evaluate the efficacy and safety of two different doses of conivaptan on the rate and magnitude of serum sodium change in patients with euvolemic or hypervolemic hyponatremia.

A total of 84 adult patients with nonhypovolemic hyponatremia were randomized (ratio 1:1:1) to receive either a placebo, conivaptan 40 mg/day, or conivaptan 80 mg/day. Hyponatremia was defined as a serum sodium $\geq$ 115 mEq/L and < 130 mEq/L. Patients were classified as either euvolemic or hypervolemic, and were stratified by volume status. Euvolemic patients were defined as having no pitting edema or ascites, and no evidence of extracellular volume depletion either clinically or by defined supine and orthostatic blood pressure criteria. Hypervolemic patients were defined as having edema, and also no evidence of extracellular volume depletion by the same criteria. All patients were hospitalized during the treatment phase of the study.

Inclusion criteria are described in the preceding paragraph. They are appropriate in that they target a population with significant hyponatremia, in the range for which physicians

would currently consider attempts at correction. They also seek to ensure that patients actually have nonhypovolemic hyponatremia.

Full exclusion criteria are described in Section 10.1. Notable among the exclusion criteria are:

- Evidence of volume depletion (specific vital sign and clinical criteria were described to prevent entry of hypovolemic patients into the study)
- Fasting blood sugar (FBS) $\geq$ 275 mg/dL
- Uncontrolled hypertension
- Untreated hypothyroidism, hyperthyroidism or adrenal insufficiency
- Creatinine clearance (CrCl) < 20 mL/min
- Urinary outflow obstruction
- Serum glutamic-pyruvic transaminase (SGPT) or serum glutamic-oxaloacetic transaminase (SGOT) > 5 times the upper limit of normal (uln)
- Serum albumin $\leq$ 1.5 g/dL
- Prothrombin time (PT) > 22 sec or increased International Normalized Ratio (INR) (> 2 if not on anticoagulant; > 3 if on anticoagulant)
- White blood cell count (WBC) < 3,000/μL

In general, these exclusion criteria sought to ensure that study patients did indeed have nonhypovolemic hyponatremia, that they did not have an underlying readily remediable cause of hyponatremia or pseudohyponatremia, and that their renal/urinary function was adequate. Exclusion of hypovolemic hyponatremic patients is important; one would not want to induce brisk fluid loss in such patients. These types of exclusion criteria do not affect the generalizability of conclusions about the efficacy of conivaptan; eventual labeling should include similar exclusions to assist physicians in correct identification of suitable patients. The exclusion criteria for low serum albumin and white blood cell count (wbc) could have excluded a small segment of the possible target population, i.e. very ill cancer patients with SIADH. There is no reason to assume that conivaptan would not be effective for treatment of hyponatremia in such patients, but safety information will not be available.

The list of prohibited medications was large and is detailed in Section 10.1.. Almost all prohibited drugs were either CYP3A4-metabolized drugs or agents currently used off-label to treat hyponatremia. Because careful labeling regarding CYP3A4 use is planned, exclusion of use of these drugs does not affect generalizability of study results.

Prior to the sponsor's Protocol Amendment 2 (14 Jun 2001), patients in the conivaptan groups received a 20 mg bolus of conivaptan (in D5W) by intravenous infusion over 30 minutes, on Study Days 1 and 3. Each bolus was followed by either 40 mg/day or 80 mg/day, as a continuous intravenous infusion, for 2 days. After Protocol Amendment 2, the Study Day 3 bolus was eliminated. Placebo patients received an equal volume of D5W administered in the same fashion as for the conivaptan infusion protocol in effect. An unblinded pharmacist prepared the infusions, but the investigators and study patients were blinded to treatment assignment. Investigators were not blinded to serum sodium

measurements, however. Infusions were given into central lines or intravenous catheters inserted into an arm vein. Hand veins were not used.

The primary efficacy endpoint was the change in serum sodium from baseline over the duration of treatment, as measured by the area under the serum sodium effect curve (from beginning through end of treatment), corrected for baseline serum sodium.

Secondary efficacy parameters included the following:

- time from first dose of study medication to confirmed ≥ 4 mEq/L increase from baseline in serum sodium
- total time from first dose of study medication to end of treatment during which patients had a serum sodium ≥ 4 mEq/L higher than that observed at baseline
- change in serum sodium from baseline to end of treatment
- number of patients who obtained a confirmed ≥ 6 mEq/L increase from baseline in serum sodium or a confirmed normal serum sodium (≥ 135 mEq/L)

Tertiary efficacy parameters included change from baseline in:

- free water clearance
- effective water clearance
- net fluid loss
- serum osmolality
- urine osmolality
- urine sodium
- arginine vasopressin
- plasma renin activity
- plasma aldosterone
- plasma epinephrine
- plasma norepinephrine

Although investigators were blinded to treatment assignment, they were not blinded to serum sodium levels; the sponsor cites safety concerns for this decision.

Safety measures included the usual monitoring for adverse events and changes in vital signs and laboratory blood chemistry and hematology. Patients were also monitored for overly rapid changes in serum sodium and orthostasis. A thirst index was used.

A statistical analysis plan was finalized prior to unblinding of the study, and is described in detail in Dr. Choudhury's statistical review.

6.1.3.1.2 Differences From Study -027 in Design of Studies -026 and -043

Design of Study -026

Study -026 studied the efficacy and safety of the oral formulation of conivaptan, and was otherwise identical in design to Study -027, with the following exceptions:

- The double blind treatment phase of the study lasted five days instead of four.
- A total of 74 study patients received treatment.
- Study patients in the 40 mg/day conivaptan group received oral 10 mg conivaptan tablets, two BID, plus two placebo tablets BID. Study patients in the 80 mg/day group received four 10 mg conivaptan tablets BID. Patients in the placebo group received four placebo tablets BID.

Design of Study -043

Study -043 was an oral efficacy and safety study, also very similar in design to the IV Study -027, with the following exceptions:

- Eighty-three patients were randomized.
- No lower limit for serum sodium level was specified
- Fasting blood glucose (FBG) at entry was to be < 126 mg/dL; in Studies -026 and -027, FBG needed only to be < 275 mg/dL.
- Oral conivaptan and placebo were administered identically to the method for the other oral Study -026.

6.1.3.2 Adequacy of Study Designs and Compliance with Regulatory Requirements for Adequate and Well-controlled Studies

The characteristics of "adequate and well-controlled" studies are described in 21 CFR 314.126; an abbreviated description includes the following:

- There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results.
- The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. A placebo concurrent control is the first acceptable type of control recognized in the regulation; other types of controls are possible in certain circumstances.
- The method of selection of subjects provides adequate assurance that they have the disease or condition being studied.
- The method of assigning patients to treatment and control groups minimizes bias and is intended to assure the comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease and use of drugs or therapy other than the test drug.
- Adequate measures are taken to minimize bias on the part of the subjects, observers and analysts of the data.
- The methods of assessment of subjects' response are well-defined and reliable.
- There is an analysis of the results of the study adequate to assess the effects of the drug.

The design of these three major efficacy and safety studies met these criteria in all areas, although the areas of blinding and duration of therapy warrant some discussion.

Although investigators were blinded to treatment assignment, the sponsor decided for safety reasons that investigators would not be blinded to serum sodium. Because the treatments were not titrated, this did not result in differing administration of study medication for patients with higher or lower serum sodiums. The effect of this unblinded status on investigator behavior regarding other interventions, such as fluid restriction or choice of other medications, is unknown. With regard to choice of other medications, the clinical reviewer examined concomitant medications for drug classes that were given at a different frequency to conivaptan patients compared to placebo patients in Study -027. Drug classes which were given somewhat more frequently to conivaptan patients than to placebo patients included benzodiazepines, beta blockers, aldosterone antagonists, cephalosporins, platelet aggregation inhibitors, proton pump inhibitors, digoxin and propulsives. None of these classes of drugs is likely to have favorable effects in the treatment of hyponatremia. Aldosterone antagonists actually increase urinary sodium excretion, and the propulsive agent metoclopramide actually raises plasma vasopressin levels (Chiodera 1993, Phillips 1994). Proton pump inhibitors decrease the clearance of CYP3A4 metabolized drugs, and may have increased conivaptan levels, but this would not create a sodium-raising effect if conivaptan did not already exhibit such an effect.

It is also quite likely that investigators and other caregivers could tell by signs and symptoms which patients were receiving conivaptan and which were receiving placebo; urine output and thirst were markedly higher in conivaptan-treated patients. This could have resulted in differences in investigator behavior in choice of other treatments and fluids. It could also have influenced handling of adverse event risk and categorization, as discussed further in the safety section.

These studies are of short duration (4-5 days), and provide no information regarding chronic or chronic intermittent use. However, this short duration aspect was specifically discussed between the sponsor and the Division of Metabolic and Endocrine Drug Products in light of the conivaptan's marked CYP3A4 inhibitory activity. Both parties agreed that the risk for adverse drug interactions with conivaptan was high, and that the drug should be administered in a highly controlled setting. Short-term intravenous use in hospitalized patients was considered a reasonable approach.

Please see Section 8.1 for a discussion of dose selection.

6.1.4 Efficacy Findings

6.1.4.1 Study -027

6.1.4.1.1 Demography and Baseline Characteristics

The following table summarizes demographic characteristics of the full analysis set for Study -027.

Table 6.1.4.1.1.1: Demographic Characteristics by Treatment Group, Full Analysis Set, Study -027					
Parameter	**Categories**	**Placebo n = 29**	**Coni[1] 40 n = 29**	**Coni 80 n = 26**	**Total n = 84**
Gender					
	Male	15 (51.7%	12 (41.4%)	14 (53.8%)	41 (48.8%)
	Female	14 (48.3%)	17 (58.6%)	12 (46.2%)	43 (51.2%)
Race					
	White, non-Hispanic	26 (89.7%)	27 (93.1%)	19 (73.1%)	72 (85.7%)
	Black, non-Hispanic	2 (6.9%)	1 (3.4%)	6 (23.1%)	9 (10.7%)
	Hispanic	0	0	1 (3.8%)	1 (1.2%)
	Other	1 (3.4%)	1 (3.4%)	0	2 (2.4%)
Age (Years)					
	≤ 65 years	3 (10.3%)	8 (27.6%)	7 (26.9%)	18 (21.4%)
	> 65 years	26 (89.7%)	21 (72.4%)	19 (73.1%)	66 (78.6%)
	Mean	75.7	73.8	72.5	74
	SD	11.61	11.51	13.82	12.22
	Min	42	46	32	32
	Median	75.0	76.0	75.0	75.5
	Max	97	91	95	97

In general, numbers of males and females were evenly distributed, both for the total group and among treatment groups. The vast majority of patients were white; there were a few more blacks in the conivaptan 80 mg/day group than in the placebo or 40 mg/day groups. The study population was quite elderly, with mean and median ages near 75 years for all groups.

For other baseline characteristics, study groups were acceptably balanced for such parameters as smoking status, alcohol consumption history, and use of most concomitant medications. Patients were stratified for volume (euvolemic or hypervolemic) status at baseline, and were evenly distributed among treatment groups. The following abbreviated table describes other characteristics of special interest and some for which the numbers of patients with certain characteristics differed somewhat between treatment groups. However, by Dr. Choudhury's statistical review, there were no statistically significant baseline imbalances.

Table 6.1.4.1.1.2: Abbreviated Table of Baseline Characteristics, Safety Analysis Set (from Sponsor's Listing 4.1.3), Study -027					
Parameter	**Category**	**Placebo n = 29**	**Coni 40 n = 29**	**Coni 80 n = 26**	**Total n = 84**
Inclusion/ Exclusion Criteria					
	Met	24 (82.8%)	27 (93.1%)	26 (100.0%)	77 (91.7%)

Table 6.1.4.1.1.2: Abbreviated Table of Baseline Characteristics, Safety Analysis Set (from Sponsor's Listing 4.1.3), Study -027					
Parameter	**Category**	**Placebo n = 29**	**Coni 40 n = 29**	**Coni 80 n = 26**	**Total n = 84**
	Not Met	5 (17.2%)	2 (6.9%)	0	7 (8.3%)
Cause of Hyponatremia					
	COPD	2 (6.9%)	0	0	2 (2.4%)
	Malignancy	2 (6.9%)	3 (10.3%)	2 (7.7%)	7 (8.3%)
	Idiopathic	4 (13.8%)	5 (17.2%)	6 (23.1%)	15 (17.9%)
	CHF	7 (24.1%)	10 (34.5%)	8 (30.8%)	25 (29.8%)
	Postsurgery	1 (3.4%)	1 (3.4%)	1 (3.8%)	1 (3.6%)
	Other	13 (44.8%)	10 (34.5%)	9 (34.6%)	32 (38.1%)
Days Since Earliest Known Hyponatremia					
	Mean	485	360	313	387
	SD	911	1023	715	895
	Min	1	2	1	1
	Median	86	60	5	27
	Max	3903	5296	3075	5296
Days Since Current Hyponatremia Began					
	Mean	43	15	28	28
	SD	124	25	89	87
	Min	1	1	1	1
	Median	5	4	3	4
	Max	607	95	423	607
Prior and Concomitant Medications[1]					
	Proton Pump Inhibitors	13 (45%)	12 (41%)	4 (15%)	29 (35%)
	Benzodiazepines	4 (14%)	10 (34%)	9 (35%)	23 (27%)
	Digitalis Glycosides	9 (31%)	2 (7%)	6(23%)	17 (20%)
	Cephalasporins	3 (10%)	5 (17%)	8 (31%)	16 (19%)
	Beta-2 Agonists	8 (28%)	2 (7%)	6 (23%)	16 (19%)
	Propulsives	1 (3%)	6 (21%)	0	7 (8%)

[1]Medications for which little difference existed between placebo patients and either of the conivaptan groups included angiotensin converting enzyme inhibitors (ACEIs), sulfonamides, salicylates, potassium, anilides, beta blockers, thyroid hormone, aldosterone antagonists, H2-receptor antagonists, nitrates, laxatives, magnesium, anticholinergics, urea, enemas, heparin, antihistamines, non-heparin antiplatelet agents, calcium, pyrazolones, selective serotonin reuptake inhibitors (SSRIs), and thiazides.

The differences between the placebo group and the conivaptan groups in the numbers of patients who met or did not meet inclusion/exclusion criteria could have a small effect on interpretability of efficacy outcomes. However, as will be discussed below, conivaptan was so strongly superior to placebo for most efficacy endpoints that any effect from differences in inclusion/exclusion criteria violations between conivaptan and placebo is far overshadowed. Thus, these differences are likely insignificant.

Distribution of etiologies of hyponatremia between groups was acceptably even. Patients in the placebo group tended to have had their hyponatremia for a longer average duration than those in the conivaptan groups. However, median durations were similar, except for the difference in days since earliest known hyponatremia between the placebo and conivaptan 80 mg/day groups. In that area, the median duration for conivaptan 80 mg/day patients was much shorter than that for placebo. Theoretically, this could give an advantage for apparent efficacy to the 80 mg/day group if the placebo group included more refractory patients. However, the 40 mg/day group should be quite comparable to placebo, and 40 mg/day is the proposed dose; thus adequate comparability is likely.

For the majority of classes of prior and concomitant medications, little difference existed between groups. The few differences are specified in the above table, and those differences would not be expected to have an effect on efficacy.

6.1.4.1.2 Study Subject Disposition

The sponsor states that the total number of screened patients was "not captured accurately". Reasons given for incomplete data on numbers of screened patients included a change in study management firm, initial lack of a study procedures manual, lack of a protocol definition for a screened patient, and inconsistent completion of case report forms (CRFs) for screened patients. Many sites claimed to have screened hundreds of patients by review of hospital clinical laboratory databases.

A total of 104 patients met screening criteria and were entered into the baseline placebo phase of the study. Of these, 88 met study entry criteria and were randomized into the study. Reasons for study patients not moving from the baseline phase to randomization included:

- Average baseline serum sodium did not remain 115-<130 mEq/L (n = 8)
- "Other/administrative" reasons (n = 6)
- Adverse events (n = 2)

The disposition of the 88 randomized patients is summarized in the following table.

Table 6.1.4.1.2 Disposition of Randomized Study Patients, Study -027

Disposition Category	Reason for Patient Withdrawal at Each Stage	Total	Placebo	Coni 40	Coni 80
# Randomized		88	30	30	28
# Entered Study		86	30	29	27
# did not Enter Study		2	0	1	1
	Administrative/Other[1]	2	0	1	1
# Treated		84	29	29	26
# not Treated		2	1	0	1
	Administrative/Other[1]	2	1	0	1
# Completed		66	23	22	21

Table 6.1.4.1.2 Disposition of Randomized Study Patients, Study -027					
Disposition Category	**Reason for Patient Withdrawal at Each Stage**	**Total**	**Placebo**	**Coni 40**	**Coni 80**
Treatment					
# did not Complete Treatment after Entering Study		20	7	7	6
	Adverse Event	13	3	5[2]	5
	Lack of Efficacy	4	3	1	0
	Withdrawal of Consent	1	1	0	0
	Diagnosis of Hypopituitarism after Initial Study Treatment	1	0	1	0
	Administrative	1	0	0	1
# in Safety Analysis Set[3]		84	29	29	26
# in Full Analysis Set[3]		84	29	29	26
# in Per Protocol Set[3]		69	24	22	23
# Treated but not in Per Protocol Set[4]		15	5	7	3

[1]Reasons for not receiving study drug after randomization included withdrawal of consent (n = 2), "no longer met inclusion/exclusion criteria" (n = 1) and poor venous access (n = 1)
[2]Sponsor's Text Table 10-1 (p 104 of study report) states that 2 patients in the conivaptan 40 mg/day group withdrew due to adverse events. However, medical officer review of the CRFs revealed that 3 of the cases classified as "administrative/other" were actually withdrawals due to adverse events
[3]See Section 4.5.2 for definitions of analysis sets
[4]See Table 4.5.2.1 for details of reasons for exclusion from Per Protocol Set.

6.1.4.1.3 Efficacy Results

Please see Dr. Choudhury's statistical review for detailed statistical analysis of efficacy for Study -027.

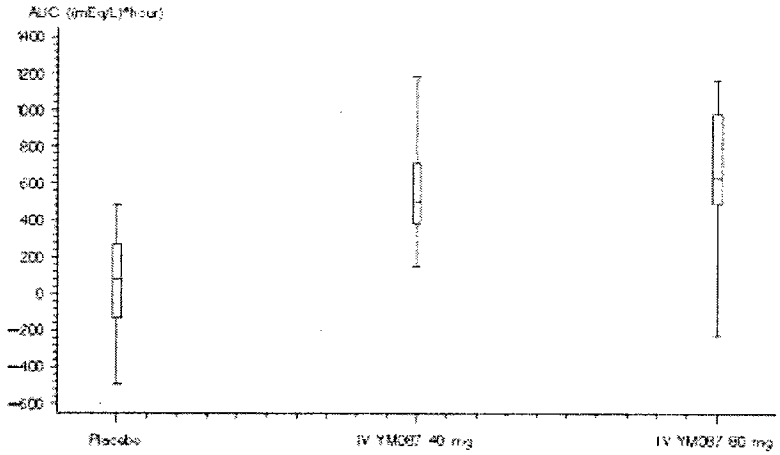
Findings for the primary and secondary efficacy parameters are summarized in the following table. For all chosen parameters, both dosage regimens of conivaptan were associated with highly significant differences from placebo. Exclusion of Dr. Steven Rosansky's site (subject of DSI audit with minor violations) did not alter the statistical significance of the difference between placebo and conivaptan for any of these endpoints.

Table 6.1.4.1.3: Efficacy Results for Primary and Secondary Efficacy Parameters, Study -027				
	Placebo n = 29	**Coni[1] 40 mg/day n = 29**	**Coni 80 mg/day n = 26**	**P-value**
Primary Efficacy Parameter				
Change from baseline in baseline-adjusted serum sodium AUC (mean ± SD, in mEq-hr/L)	61.4 ± 242.3	500.8 ± 365.46	661.7 ± 331.14	Overall: <0.0001 C40[2] vs pbo: <0.0001 C80[3] vs pbo: <0.0001
Secondary Efficacy Parameters				
Median Event Time to when at least 50% of patients had sodium increase ≥ 4 mEq/L over baseline [mean in hours (95% CI)]	NE[4]	23.7 (10, 24.0)	23.4 (6.0, 24.0)	Overall: <0.0001 C40: <0.0001 C80: <0.0001
Mean Total Time from first dose to end of treatment during which serum sodium ≥4 mEq/L over baseline (LS mean in hours ± SE)	14.2 ± 5.25	53.2 ± 5.17	72.7 ± 5.43	Overall: <0.0001 C40: <0.0001 C80: <0.0001
Mean change in serum sodium from baseline to end of day 4 [LS mean in mEq ± SE (# of evaluable patients)]	2.0 ± 0.82 [25 pts]	6.8 ± 0.81 [24 pts]	9.0 ± 0.80 [24 pts]	Overall: <0.0001 C40: <0.0001 C80: <0.0001
Number of patients with ≥ 6 mEq/L increase in serum sodium, or increase to normal serum sodium (>135 mEq/L). Shown as # patients (% of arm)	6 (20.7%)	20 (69%)	23 (88.5%)	Overall: <0.0001 C40: <0.0002 C80: <0.0001
1 Conivaptan 2 Conivaptan 40 mg/day 3 Conivaptan 80 mg/day 4 Not estimable				

6.1.4.1.3.1 Primary Efficacy Parameter

For the primary efficacy parameter (change from baseline in baseline-adjusted serum sodium AUC), placebo treatment was associated with a modest increase in serum sodium AUC (61.4 mEq-hr/L ± SD 242.3), possibly attributable to modest fluid restriction or treatment of underlying disease. Treatment with 40 mg/day of IV conivaptan resulted in an 8-fold increase in serum sodium AUC (500.8 mEq-hr/L ± SD 365.5) compared to placebo. Treatment with 80 mg/day of IV conivaptan resulted in an almost 11-fold increase in serum sodium AUC (661.7 mEq-hr/L ± SD 331.1). P values were <0.0001 for comparisons of each conivaptan dose to placebo, and for comparison of the combined conivaptan groups to placebo. The effect of conivaptan vs pbo for the primary efficacy analysis is illustrated in the following box and whisker plots:

Figure 6.1.4.1.3.1.1: Box and Whisker Plots for Baseline-adjusted Area Under the Serum Sodium Effect Curve over the Duration of Treatment, by Treatment Group, Full Analysis Set, Study -027



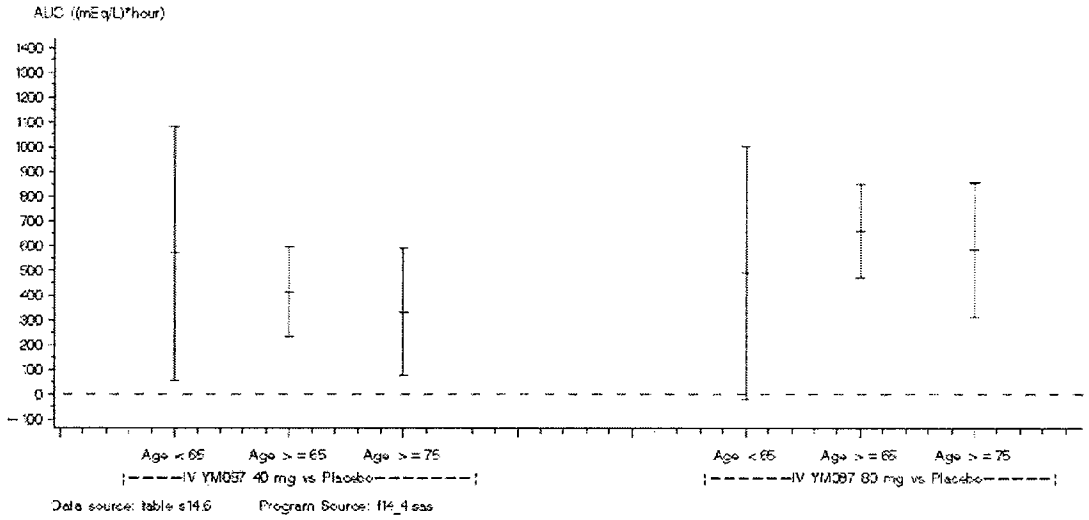
For this figure, the bottom and top edges of the boxes represent the sample 25th and 75th percentiles. The center horizontal line of each box represents the 50th percentile (median). The upper and lower ends of the long vertical lines represent the highest and lowest actual observed values.
Source: Sponsor's figure 6.1.2, page 359, -027 study report

Although the study was not powered to look at subgroups, almost all subgroup analyses for the primary efficacy endpoint provided highly significant evidence in favor of efficacy of conivaptan. Subgroups included:

- age (≤ 65 years, > 65 years - ≤ 75 years, > 75 yrs)
- gender (white nonhispanic, black nonhispanic, other)
- baseline serum sodium (1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 99th percentiles)
- gender
- study center
- baseline volume status (hypervolemic or euvolemic)
- cause of hyponatremia (CHF or non-CHF; SIADH or non-SIADH)

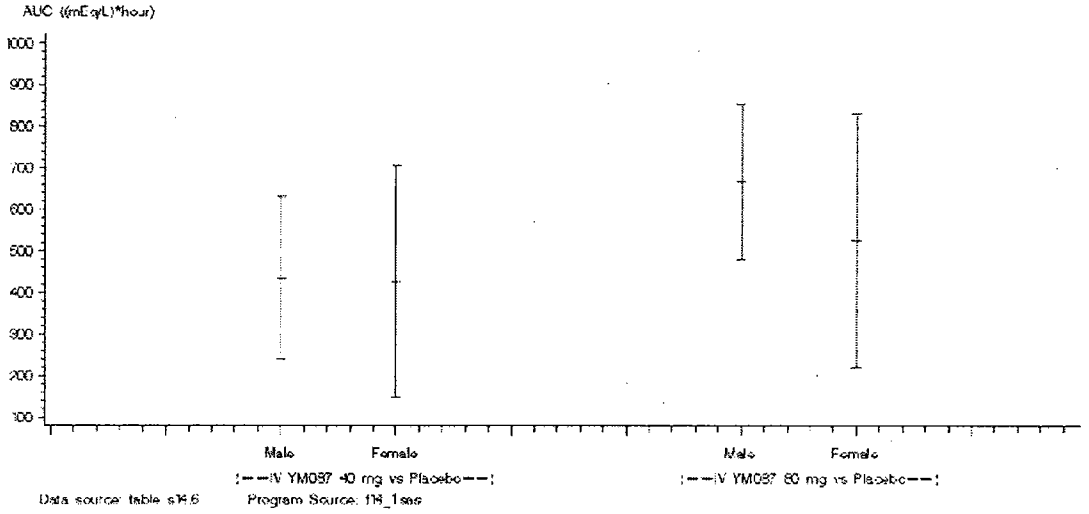
In general, conivaptan's effect on serum sodium (primary endpoint Study -027) remained significant when breaking down results by age group (≤ 65 years, > 65 - ≤ 75 years, > 75 years). There was no difference when comparing study patients < 65 years of age with those ≥ 65 years (p 0.71 for the 40 mg dose) or when comparing those < 65 years to those ≥ 75 years (p 0.61 for the 40 mg dose). However, Dr. Choudhury found that for the age < 65 years group, the p value for the effect of conivaptan in the 80 mg group was not statistically significant when compared to the placebo group. He also found that there was a statistically significant difference in effect for the 80 mg dose group when comparing those patients < age 65 to those ≥ age 65 years. This group may not have had sufficient power. Because only the 40 mg dose is proposed by the sponsor, this age effect is not applicable to the recommended use. Age subgroup analyses are illustrated in the following figure.

Figure 6.1.4.1.3.1.2: Change in Serum Sodium from Baseline (AUC, LS Mean with 95% CI) over Duration of Treatment by Age Group, Study -027



Conivaptan's effect on serum sodium (primary endpoint Study -027) was highly significant for both men and women, and there was no difference when comparing the effect between men and women (p 0.54 for 40 mg dose). Gender effects are illustrated in the following figure.

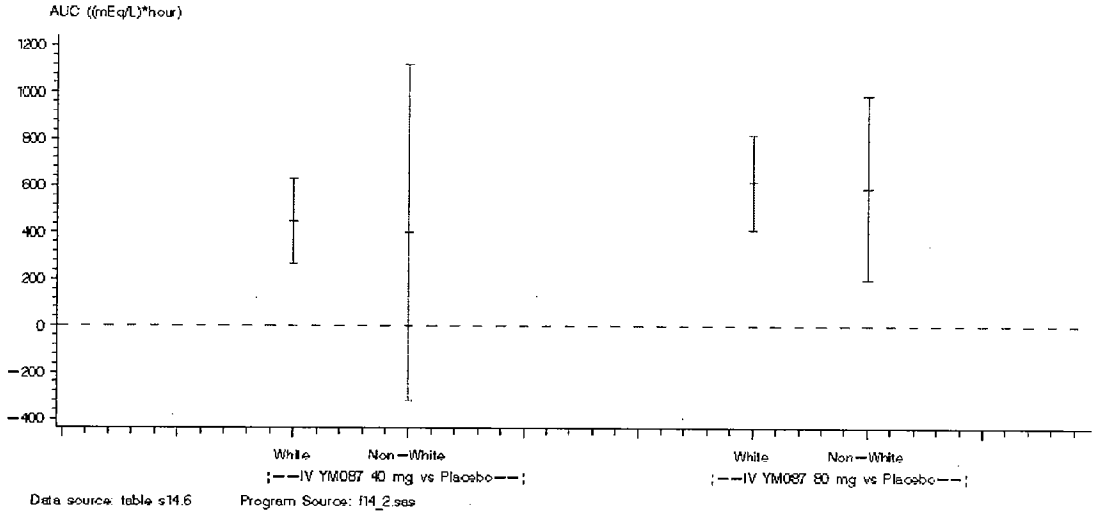
Figure 6.1.4.1.3.1.3: Change in Serum Sodium from Baseline (AUC, LS Mean with 95% CI) Over Duration of Treatment by Gender, Full Analysis Set, Study -027



Source: Sponsor's Figure f14.1, p 454, -027 study report

Conivaptan's effect on serum sodium (primary endpoint Study -027) was highly significant among both white and non-white patients, and there was no difference when comparing the effect between racial groups (p 0.67 for 40 mg dose). The following figure illustrates the primary efficacy results by race.

Figure 6.1.4.1.3.1.4: Change in Serum Sodium from Baseline (AUC, LS Mean with 95% CI) over Duration of Treatment by Race, Full Analysis Set, Study -027

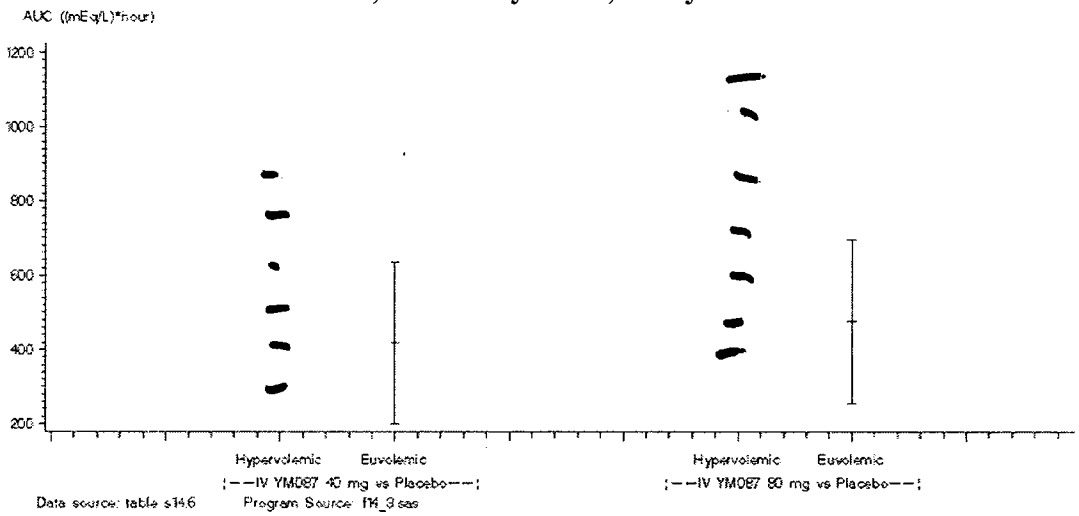


Source: Sponsor's Figure f14.2, p 455, -027 study report

The analyses by volume status and underlying cause of hyponatremia are of interest to the clinical reviewer because of the potential for off-label use for the treatment of congestive heart failure, a hypervolemic state. A lack of efficacy for correction of hyponatremia, if found in hypervolemic or CHF patients, would be important information for clinicians who might consider administration of conivaptan off-label for treatment of CHF.

However, conivaptan was significantly effective, regardless of baseline volume status, and [redacted] By Dr. Choudhury's review, there was a statistically significant interaction (p 0.0851 with interaction significance at 0.1) when considering subgroups by baseline volume status. [redacted] However, because conivaptan was also significantly effective in patients who were euvolemic at baseline, the statistical interaction is unlikely to be of clinical significance, as long as clinicians are vigilant for evidence of overly rapid correction of hyponatremia. The statistical interaction by baseline volume status is illustrated in the following figure:

Figure 6.1.4.1.3.1.5: Change in Serum Sodium from Baseline (AUC, LS Mean with 95% CI) over Duration of Treatment by Volume Status at Baseline, Full Analysis Set, Study -027



Source: sponsor's figure f14.5, p 458, -027 study report

When considering cause of hyponatremia [redacted] there was not a statistically significant interaction (p 0.3587), and the [redacted]

There was no statistically significant interaction by study center. The effect on the primary endpoint of placebo was least in Study Center Group 1 and greatest in Study Center Group 5. Dr. Choudhury therefore did an analysis excluding these centers, and found that the results remained highly statistically significant favoring conivaptan. When excluding Dr. Steven Rosansky's site, which had minor violations on a DSI audit, efficacy results for the primary efficacy variable remained highly significantly in favor of conivaptan (p 0.0001 for either conivaptan dose group vs placebo).

When considering patients by baseline serum sodium, there was no statistically significant baseline serum sodium by treatment interaction. However, when examining study patients with serum sodium $\leq$ 120 mEq/L (n = 15), statistically significant efficacy was not demonstrated for 40 mg conivaptan/day vs placebo, although serum sodium AUCs were higher in those patients who were treated with conivaptan. Because of the small number of patients with serum sodium in this range, one cannot definitively conclude that conivaptan would not be effective in patients with serum sodiums $\leq$ 120 mEq/L. The following table breaks down serum sodium effect by baseline serum sodium percentile.

Table 6.1.4.1.3.1: Mean Baseline-adjusted Area Under the Serum Sodium Effect Curve over the Duration of Treatment, at Percentiles of Baseline Serum Sodium Value

Quartile/Percentile [2]	LSMEAN [3]			LSMEAN [4]		
	Placebo	IV YM087 40 mg	IV YM087 80 mg	Placebo	IV YM087 40 mg	IV YM087 80 mg
First Percentile (112.5)	315.9	734.8	927.4	235.9	697.4	1148.1
Fifth Percentile (116.75)	224.0	643.0	835.5	122.9	620.2	929.8
Tenth Percentile (117.5)	207.8	628.7	819.2	161.8	606.8	950.1
Twenty-fifth Percentile (122.125)	107.7	526.7	719.3	93.2	522.6	767.6
Fiftieth Percentile (124.75)	51.0	470.8	662.5	54.3	474.9	663.1
Seventy-fifth Percentile (127.41)	-6.6	412.4	604.9	14.8	426.6	557.7
Ninety Percentile (128.75)	-35.5	383.5	576.0	-5.1	402.2	504.7
Ninety-fifth Percentile (129.75)	-46.3	372.6	565.2	-12.5	393.1	484.9
Ninety-ninth Percentile (130.5)	-73.4	345.6	538.1	-31.0	370.4	435.4

[1] Baseline serum sodium value is the average of serum sodium measurements at hour 4, 6, 10, 12 and at end of the Baseline Phase (Hours 20-28).
[2] Quartile/Percentile is the quartile/percentile of baseline serum sodium value.
[3] LSMEAN was computed from the model baseline-adjusted AUC = treatment + (baseline serum sodium value) at each quartile/percentile.
[4] LSMEAN was computed from the model baseline-adjusted AUC = treatment + baseline serum sodium value + treatment x (baseline serum sodium value) at each quartile/percentile.

Source: Sponsor's Table s8.2, -027 Study Report pg 401

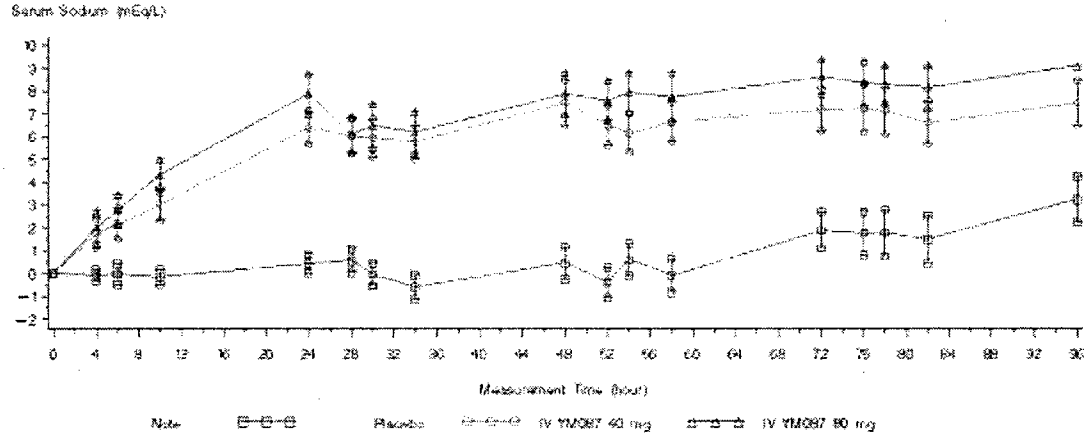
Of interest is the fact that violations of the two liter per day fluid restriction occurred very frequently, especially among patients receiving conivaptan. Despite the higher fluid intake in the conivaptan groups, these patients were more likely to have amelioration of their hyponatremia than patients in the placebo group. This presents a possible benefit to patients; the traditional mainstay of treatment of hyponatremia is fluid restriction. This is uncomfortable for patients, and compliance is problematic. If the safety of conivaptan is established, its use might increase patient comfort as well as serum sodium.

6.1.4.1.3.2: Secondary Efficacy Parameters

Examination of the secondary efficacy parameters provides further information on the comparative action of conivaptan over time, and allows the clinician to compare conivaptan's action in familiar measures of serum sodium.

Mean serum sodium, measured from baseline to the end of Study Day 4, increased more for the conivaptan groups than for placebo. These changes, expressed as least squares means in mEq/L, were +2.0 for placebo, +6.8 for IV conivaptan 40 mg/day, and +9.0 for IV conivaptan 80 mg/day. All groups had standard errors (SEs) near 0.8. P values were <0.0001 for comparisons of each conivaptan dose to placebo, and for comparison of the combined conivaptan groups to placebo. The degree of additional change in serum sodium associated with conivaptan treatment was highly statistically significant, and likely clinically significant, also. Increases in serum sodium of several mEq/L are often sufficient for reversal of acute neurologic symptoms associated with hyponatremia. The effect of conivaptan on this secondary efficacy parameter is illustrated in the following figure:

Figure 6.1.4.1.3.2: Mean Change (with SE) in Serum Sodium from Baseline over Time, by Treatment Group, Full Analysis Set, Study -027



Exclusion of Dr. Steven Rosansky's site (subject of DSI audit with minor violations) did not alter the statistical significance of the difference between placebo and conivaptan for this endpoint ($p < 0.0001$).

Two of the secondary efficacy parameters provide information about the potential for timely correction of serum sodium with use of conivaptan. Correction of serum sodium is often frustratingly slow by currently available off-label means; several days are often required before any effect occurs. During that time period, the persistent hyponatremia often complicates management of fluids and medical therapy, and can delay the institution of treatments for other disorders. The ability to safely correct serum sodium more quickly is likely not only to ameliorate any clinical consequences of the hyponatremia itself, but also to simplify the management of other medical conditions. Secondary efficacy parameters providing information about timeliness of serum sodium correction included measures of the median event time to when at least 50% of patients had an increase in serum sodium of at least 4 mEq/L over baseline, and of the mean total time from first dose to end of treatment during which serum sodium was at least 4 mEq/L over baseline.

In the placebo group, throughout study, less than 50% of patients achieved a serum sodium $\geq$ 4mEq over their baseline. In the 40 mg/day conivaptan group, 50% of patients had an increase in serum sodium of at least 4 mEq/L by 23.7 hours (95% CI 10-24) after the first conivaptan dose. In the 80 mg/day conivaptan group, this goal was achieved by 23.4 hours (95% CI 6-24). In the placebo group, patients maintained a serum sodium of at least 4 mEq/L over their baseline for a mean of only 14.2 hours (SE $\pm$ 5.25 hrs) out of the 4-day study. Conivaptan study patients maintained this degree of sodium increase for 53.2 hrs $\pm$ 5.17 (40 mg/day group) and 72.7 hrs $\pm$ 5.43 (80 mg/day group). For all comparisons of conivaptan effect to placebo described in this paragraph, p values were <0.0001. Exclusion of Dr. Steven Rosansky's site (subject of DSI audit with minor violations) did not alter the statistical significance of the difference between placebo and conivaptan for these endpoints ($p < 0.0001$).

These results support a likelihood that nonhypovolemic hyponatremic patients treated with conivaptan will achieve clinically significant increases in their serum sodium more quickly than patients managed by currently available off-label treatments, and that these serum sodium increases are sustainable over the recommended duration of treatment.

A larger percentage of study patients in the conivaptan groups (compared to placebo) achieved serum sodiums of $\geq$ 6 mEq/L over baseline, again with strong statistical significance, as presented in table 6.1.4.1.3 above.

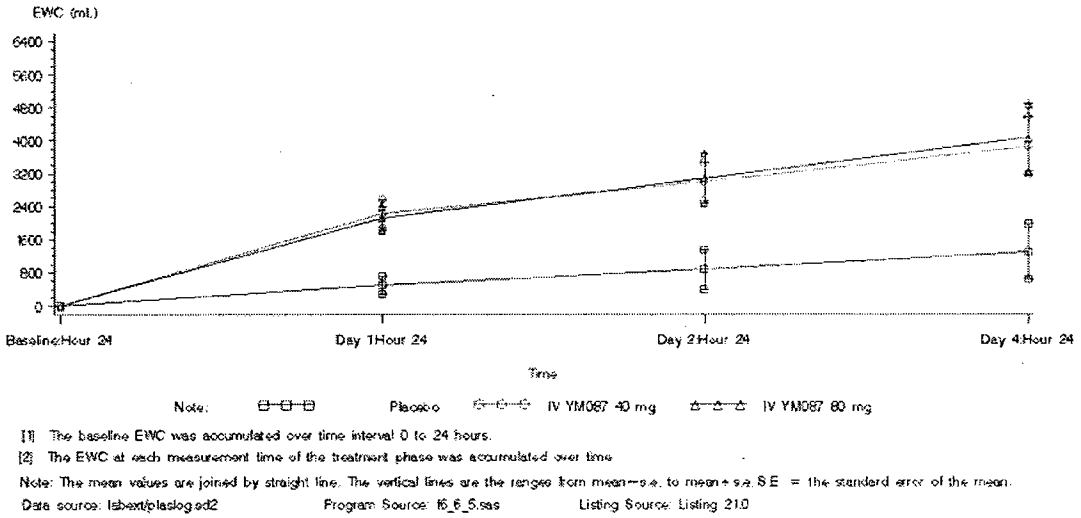
6.1.4.1.3.3 Tertiary Efficacy Measures

Tertiary efficacy measures were presented descriptively. Among the tertiary measures, effective water clearance (EWC) and free water clearance (FWC) are the clinical measures of most interest to the clinical reviewer, and are presented in more detail.

Effective Water Clearance (EWC):

EWC is electrolyte-free water clearance, and is calculated from serum and urine sodium and potassium concentrations. Free water clearance, the more familiar measure, is osmolar-free water clearance, and can be affected by solutes such as urea and creatinine, and therefore by daily diet and renal function. The mean change (increase) in electrolyte-free water clearance was significantly greater in the conivaptan groups when compared to placebo. On Treatment Day 1, this difference was most marked, with a mean change of 564 cc/day in the placebo group compared to 2415 and 2527 in the conivaptan 40 and 80 mg/day groups, respectively. This effect declined on subsequent treatment days; on Day 4, the mean change in the placebo group was 486, compared with 743 and 1078 in the conivaptan 40 and 80 mg/day groups, respectively. These differences are illustrated in the following figure:

Figure 6.1.4.1.3.3.1: Mean (with SE) Change in Effective Water Clearance from Baseline to each Measurement Time by Treatment Group, Full Analysis Set, Study -027

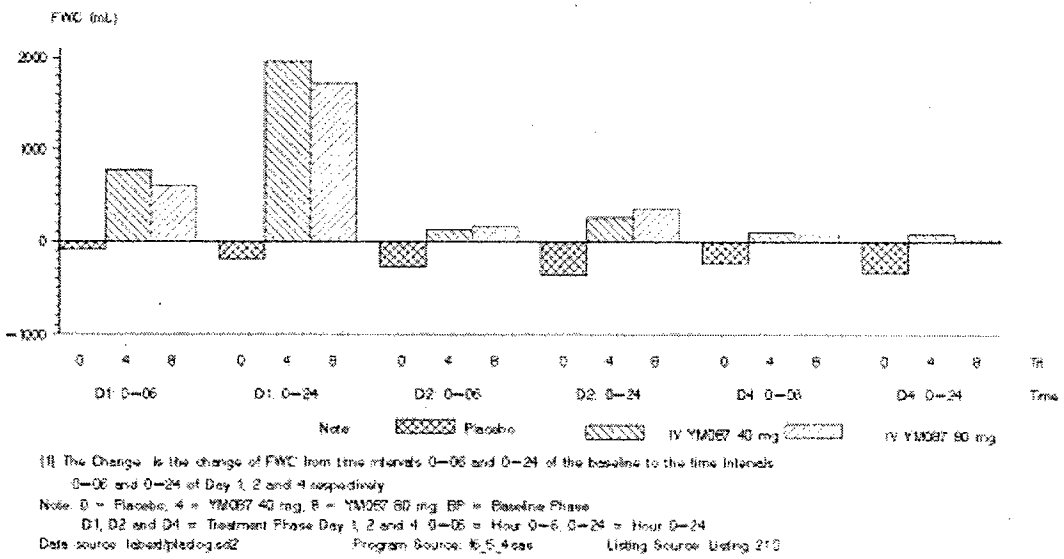


Source: sponsor's figure 11-6, -027 study report

Free Water Clearance:

During the baseline phase, FWC was negative for all groups. On Treatment Day 1, FWC remained negative in the placebo group (mean change -450 mL), but increased significantly in the conivaptan groups (mean changes 1953 for 40 mg/day and 1670 for 80 mg/day). Over Treatment Days 2-4, FWC remained negative in the placebo group, and returned to near zero in both conivaptan groups. The following figure illustrates these changes:

Figure 6.1.4.1.3.3.2: Mean Change in FWC by Time Interval and Treatment Group, Full Analysis Set, Study -027



[1] The Change is the change of FWC from time intervals 0-06 and 0-24 of the baseline to the time intervals 0-06 and 0-24 of Day 1, 2 and 4 respectively

Note: 0 = Placebo, 4 = YM087 40 mg, 8 = YM087 80 mg, BP = Baseline Phase

D1, D2 and D4 = Treatment Phase Day 1, 2 and 4, 0-06 = Hour 0-6, 0-24 = Hour 0-24

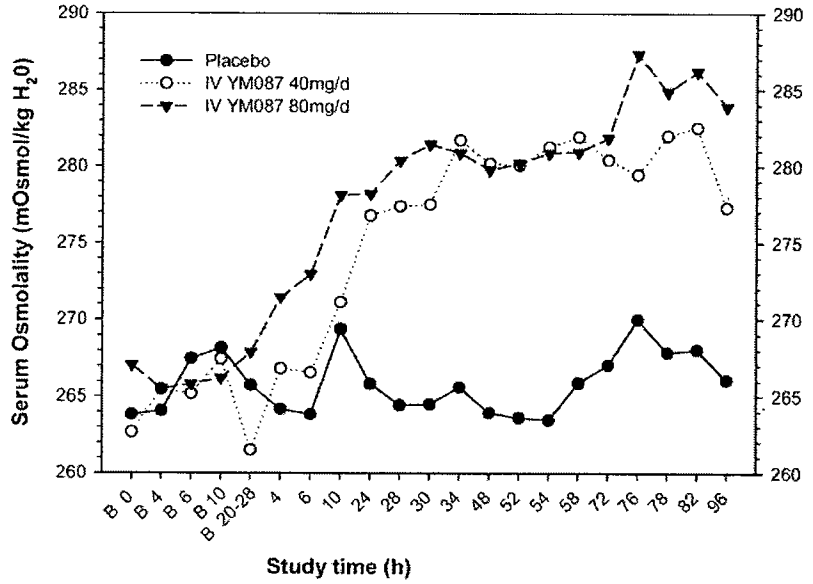
Data source: labed/pledog.sd2 Program Source: fc_5_4.sas Listing Source: Listing 2.1.3

Source: sponsor's figure 11-8, -027 study report

Serum Osmolality

Serum osmolality was higher in the conivaptan groups compared to placebo throughout the treatment phase. The mean change in serum osmolality from Treatment Day 1 to Treatment Day 2 was -0.9 mOsm/kg for the placebo group compared to +11.3 for the 40 mg/day conivaptan group and +15.2 for the 80 mg/day conivaptan group. This effect did not begin to wane until the end of the treatment period, and is illustrated in the following figure:

Figure 6.1.4.13.3.3: Mean Serum Osmolality by Treatment Group, Full Analysis Set, Study -027



Source: Statistical Table 13.5, Section 14.2

Source: sponsor's figure 11-9, -027 study report

Net fluid loss was greater in the conivaptan groups than in the placebo group on Treatment Days 1 and 2. On Treatment Day 1, the mean change in net fluid loss for that day was -92 mL for the placebo group, +753 mL/day for the conivaptan 40 mg/day group and +392 mL/day for the conivaptan 80 mg/day group. On Treatment Day 4, the mean change for that day in net fluid loss was actually less favorable in the conivaptan 80 mg/day group than in the placebo group (-573 mL for 80 mg/day conivaptan, -139 mL for placebo). The clinical significance, if any, of the latter is uncertain.

Mean urine osmolality was modestly lower in the conivaptan treatment groups compared with placebo throughout the treatment phase. For Treatment Day 2, mean urine osmolality in the placebo group was 713 mOsm/kg in the placebo group compared to 608 mOsm/kg and 516 mOsm/kg in the conivaptan 40 and 80 mg/day groups respectively.

Mean urine sodium was lower in the conivaptan groups compared with placebo throughout the treatment phase. This effect was most marked on Treatment Day 1 (placebo mean = 54 mEq/L; conivaptan 40 mg/day = 23 mEq/L ; conivaptan 80 mg/day = 28 mEq/L). By Treatment Day 4, mean urine sodium in the placebo group remained essentially unchanged at 55 mEq/L, while in the conivaptan groups, mean urine sodium had gradually increased from the Treatment Day 1 nadir to means of 47 and 38 mEq/L for the 40 and 80 mg/day groups, respectively.

Plasma AVP levels increased with both doses of conivaptan compared to placebo. An increase in AVP levels might be undesirable, but the clinical significance of these

particular degrees of increase is uncertain. Mean levels are presented in the following abbreviated table.

Table 6.1.4.1.3.3: Mean (with SD) AVP Levels by Treatment Group over Time, Full Analysis Set, Study -027*

	Placebo mean (SD)	Coni 40 mean (SD)	Coni 80 mean (SD)
Baseline	0.8 (0.73)	0.5 (0.08)	0.6 (0.33)
Treatment Day 2	0.5 (0.13)	0.7 (0.32)	2.0 (1.22)
Treatment Day 4	0.5 (0)	1.1 (0.84)	1.8 (1.55)

*Low specimen collection rate, ranging from 12-27% in any given treatment group. This low collection rate might be due to the special handling required for AVP samples.
Source: Sponsor's Table 6.12, -027 study report

There was no difference in the change in mean plasma renin activity from Baseline to Treatment Day 4 for the placebo and conivaptan 40 mg/day groups. For the 80 mg/day group, there was an increase from a baseline of 7.7 ng/mL/hr to 16.8 on Day 4. However, the standard deviation for the change was large (22.74), and no significance can be assigned to this change.

Mean plasma aldosterone levels decreased slightly and to the same degree (baseline 20 and 21; change -1.7 and -1.6 pg/dL) in the placebo and conivaptan 40 mg/day groups respectively from Baseline to Treatment Day 4. For the 80 mg/day group, there was a larger mean decrease (baseline 17 pg/dL; change -5.7), but the standard deviation was large (25.75).

Mean plasma norepinephrine levels increased moderately in the placebo and conivaptan 80 mg/day groups over treatment, and declined moderately in the conivaptan 40 mg/day group. All mean changes had large standard deviations.

Mean plasma epinephrine levels increased slightly in the placebo and conivaptan 80 mg/day groups over treatment, and declined slightly in the conivaptan 40 mg/day group. All mean changes had large standard deviations.

6.1.4.1.3.4 Duration of Sodium Effect After Cessation of Conivaptan

The duration of conivaptan's effect on serum sodium after cessation of infusion was not precisely determined in Study -027, or in any other study in the application. Study -027 was the only study that gave continuous IV conivaptan for four days, but serum sodium was only measured up to the end of treatment (Study Day 4), and then one more time at Study Day 10-13. At this final measurement, mean serum sodium was 131 mg/dL in the placebo group, 129 mg/dL in the 40 mg/day conivaptan group, and 134 mg/dL in the 60 mg/day group (-027 study report, pg 60, Figure 9-2; and pg 419, Table 13.3). The most that can be said from this information is that by 6-9 days after cessation of conivaptan infusion, the serum sodium effect is no longer seen for the proposed 40 mg/day

conivaptan regimen vs placebo. It is possible that the effect wanes earlier than 6 days after cessation of infusion.

6.1.4.1.3.5 Summary of Efficacy in Study -027

Both the 40 mg/day and 80 mg/day IV regimens for conivaptan were strongly statistically significantly superior to placebo for the following measures:

- The primary efficacy endpoint of change in serum sodium AUC from baseline over duration of treatment. This effect was consistent regardless of age, gender, race, baseline volume status, and presence or absence of CHF. For patients with serum sodiums <120 mEq/L at baseline, the 40 mg/day IV regimen was associated with increased sodium, although not statistically significantly so. Both doses were statistically significantly effective in patients with baseline serum sodiums >120 mEq/L, and the 80 mg/day regimen was also statistically significantly effective for patients whose serum sodium was <120 mEq/L at baseline.
- Mean change in serum sodium from baseline to end of Study Day 4
- Median event time to when at least 50% of patients had an increase in serum sodium of at least 4 mEq/L over baseline
- Mean total time from first dose to end of treatment during which serum sodium was at least 4 mEq/L over baseline
- Percentage of patients with a $\geq$ 6 mEq/L increase in serum sodium, or an increase to a normal serum sodium

The following tertiary measures were also favorably affected by conivaptan:

- Increased effective water clearance throughout treatment
- Increased free water clearance on Treatment Day 1, with a waning of effect thereafter
- Increased mean serum osmolality throughout treatment
- Decreased mean urine sodium, with a nadir on Treatment Day 1

Mean neurohormone levels trended upward, but not significantly, for conivaptan-treated patients. Increases in neurohormone levels could be undesirable in certain patients populations, such as those with congestive heart failure.

Conivaptan, given in the IV regimen proposed for labeling, appears highly effective in the treatment of hyponatremia. However, as will be discussed in the following section, it is possible that a lower dose could also be effective.

6.1.4.2 Combined Efficacy Effects of the Three Major Efficacy Studies

The combined evidence of all three major trials of conivaptan supports efficacy of both the 40 and 80 mg/day dosage regimens when administered over four days (IV) or five days (oral).

For both Study -026 and -043, for the primary and secondary efficacy endpoints, 80 mg/day oral conivaptan was significantly more effective than placebo. The 40 mg/day oral regimen of conivaptan was significantly more effective than placebo for the primary

and secondary efficacy endpoints in Study -043, but not for all in Study -026. The [redacted] Since oral conivaptan results in plasma concentrations 1/3 those of IV conivaptan, an 80 mg/day oral conivaptan dose is roughly equivalent to a 27 mg/day IV dose, considerably less than the proposed 40 mg/day IV dose. Because 40 mg/day oral conivaptan was effective on some efficacy parameters, doses as low as 13 mg IV conivaptan could also be effective. The sponsor also states that oral conivaptan doses as low as 20 mg/day were effective in some studies, indicating possible efficacy of IV conivaptan for some patients at doses as low as 7 mg/day.

The effect of oral conivaptan 40 mg/day vs placebo on the primary endpoint was less significant (p 0.0299 uncorrected) in Study -026 than the effect of 80 mg/day of conivaptan in Study -026, and of either dose in Studies -027 and -043. The results of all three trials for the primary efficacy variable are presented in the following table and figure.

Table 6.1.4.2.1: Summary of Change in Serum Sodium from Baseline (AUC) over duration of Treatment, "Pivotal" IV and Supportive Oral Phase 3 Hyponatremia Studies

	Pivotal IV Hyponatremia				Supportive Oral Hyponatremia							
	027				026				043			
Statistics	Placebo	YM087 40 mg/d	YM087 80 mg/d	P-value (b)	Placebo	YM087 40 mg/d	YM087 80 mg/d	P-Value (b)	Placebo	YM087 40 mg/d	YM087 80 mg/d	P-Value (b)
Number of Patients	29	29	26		[redacted]							
Baseline Adjusted AUC												
Mean (SD)	61.4 (242.30)	590.8 (365.46)	661.7 (331.14)									
LS Mean (SE)	32.9 (61.16)	590.9 (56.79)	716.6 (60.45)									
Treatment Differences												
Across All Treatment Group				0.0000								
40 mg/d YM087 vs Placebo				0.0001								
80 mg/d YM087 vs Placebo				0.0001								

[a] For study 027, baseline value is the average of serum [illegible] measurements at hour 4, 6, 10 and at end of the Baseline Phase (Hours 20-28). AUC is calculated by the baseline value multiplied by 96 (hours). For studies 026 and 043, baseline value is the average of serum sodium measurements at hour 4, 6, [illegible] end of the Baseline Phase (Hours 20 28). AUC is calculated by the baseline value multiplied by 120 (hours).
[b] Two-sided p-values across all treatment groups was from an ANCOVA model including baseline value as a covariate, treatment, volume status, and center as factors and the [illegible] level 0.1) interaction term(s) between treatment and baseline value, volume status, and center. P-values for treatment differences were from a two-sided Dunnett's test on the difference of LS means.
Data Source: plasioa (026), plasioa027, [illegible].sdf   Program Source: t27311.sas

Source: Sponsor's Table 2.7.3-13, p 79, summary of clinical efficacy

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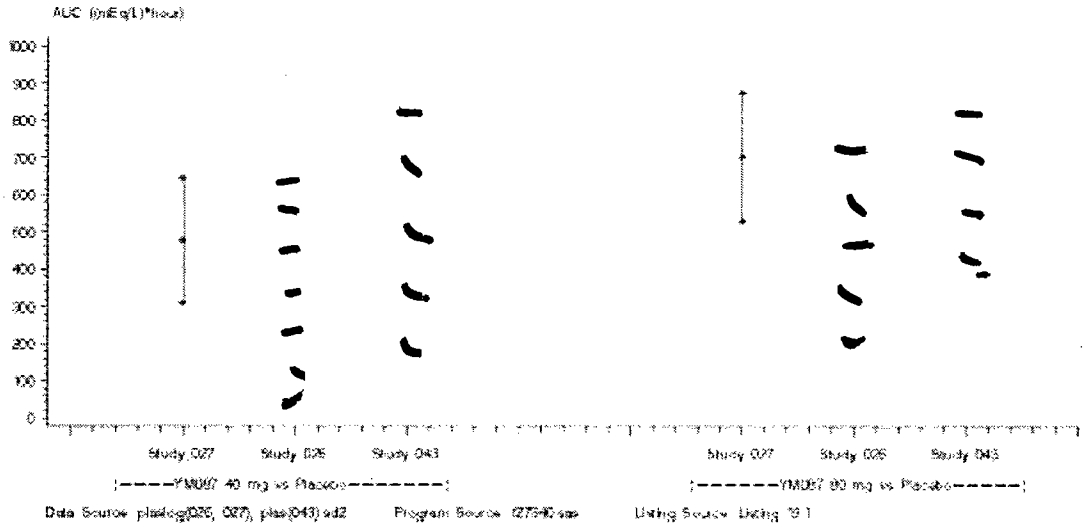
Figure 6.1.4.2.1: **Treatment Effect Size Compared with Placebo for Baseline-adjusted Area under the Serum Sodium Effect Curve (LS Mean with 95% CI) over Duration of Treatment, Studies -027 (IV), -026 (Oral) and -043 (Oral), Full Analysis Set**



Source: Sponsor's Figure 2.7.3-16, p 78, summary of clinical efficacy

For secondary endpoints, oral doses of conivaptan were also effective for most of these endpoints, as illustrated in the following tables:

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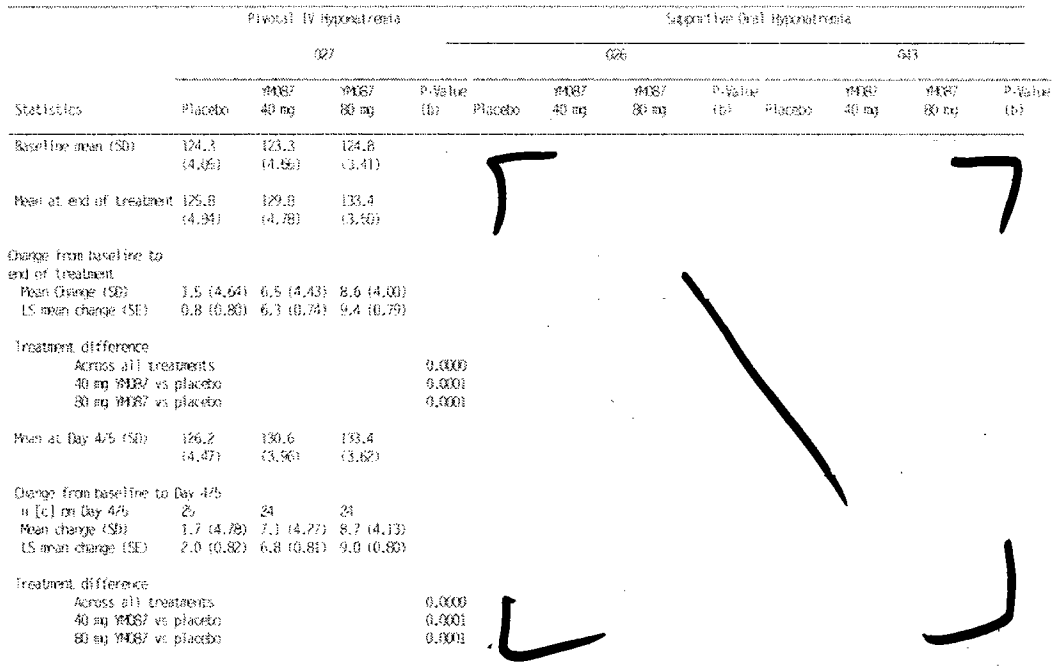
Table 6.1.4.2.2: Summary of Mean and Mean Change in Serum Sodium (mEq/L) from Baseline to End of Treatment, and at Day 4/5, Phase 3 Controlled Hyponatremia Trials



	Pivotal IV Hyponatremia				Supportive Oral Hyponatremia							
	027				026				043			
Statistics	Placebo	YM087 40 mg	YM087 80 mg	P-Value (b)	Placebo	YM087 40 mg	YM087 80 mg	P-Value (b)	Placebo	YM087 40 mg	YM087 80 mg	P-Value (b)
Baseline mean (SD)	124.3 (4.05)	123.3 (4.85)	124.8 (3.41)									
Mean at end of treatment	125.8 (4.94)	129.8 (4.78)	133.4 (3.60)									
Change from baseline to end of treatment												
Mean Change (SD)	1.5 (4.64)	6.5 (4.43)	8.6 (4.00)									
LS mean change (SE)	0.8 (0.80)	6.3 (0.74)	9.4 (0.79)									
Treatment difference												
Across all treatments				0.0000								
40 mg YM087 vs placebo				0.0001								
80 mg YM087 vs placebo				0.0001								
Mean at Day 4/5 (SD)	126.2 (4.47)	130.6 (3.96)	133.4 (3.62)									
Change from baseline to Day 4/5												
n [c] on Day 4/5	24	24	24									
Mean change (SD)	1.7 (4.78)	7.1 (4.27)	8.7 (4.13)									
LS mean change (SE)	2.0 (0.82)	6.8 (0.81)	9.0 (0.80)									
Treatment difference												
Across all treatments				0.0000								
40 mg YM087 vs placebo				0.0001								
80 mg YM087 vs placebo				0.0001								

Source: Sponsor's Table 2.7.3-17

For mean change in serum sodium from baseline to end of treatment,

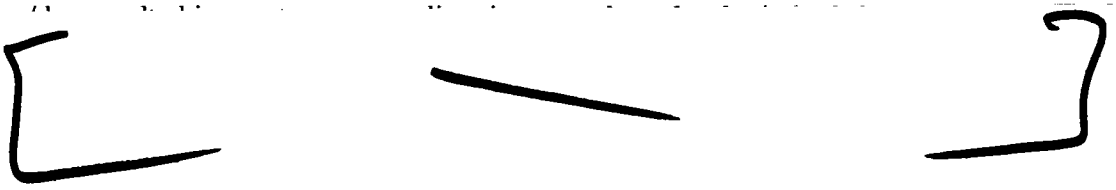


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Table 6.1.4.2.3: Summary of Hours from First Dose to Confirmed ≥ 4 mEq/L Increase in Serum Sodium from Baseline, Phase 3 Controlled Hyponatremia Studies (from Sponsor's Table 2.7.3-15)

	Pivotal IV Hyponatremia				Supportive Oral Hyponatremia							
	022				026				043			
Statistics	Placebo	YM087 40 mg/d	YM087 80 mg/d	P-Value [b]	Placebo	YM087 40 mg/d	YM087 80 mg/d	P-Value [b]	Placebo	YM087 40 mg/d	YM087 80 mg/d	P-Value [b]
Number of patients	9	23	24									
Median event time (hours) [a]	NE	23.7	23.4									
95% confidence interval for median event time	NE	(10.0,24.0)	(6.0 ,24.0)									
Treatment Differences												
All Treatment Group				0.0001								
40 mg YM087 vs Placebo				0.0001								
80 mg YM087 vs Placebo				0.0001								

NE = not estimable.
[a] Event time is the time from the first dose of study medication to a confirmed >= 4 mEq/L increase in serum sodium from baseline.
[b] P values were from a two-sided long-rank test, stratified by volume status, for comparing distribution of event time among all treatment groups and then between each of the YM087 dosage group and placebo.
Data Source: plaslog(026), plaslog(022), plas (043).sd2 Program Source: t2732.sas

For this endpoint, 80 mg/day [redacted] for the difference between placebo and the 40 mg/day conivaptan group was just below [redacted]

For the secondary endpoint of total time from first dose of study drug to end of treatment during which patients had a ≥ 4 mEq/L increase in serum sodium from baseline, oral 80 mg/day conivaptan was significantly more effective than placebo in both Study -043 and Study -026 ([redacted] . Oral conivaptan 40 mg/day was significantly more effective than placebo in Study -043 ([redacted]), but not in Study -026 ([redacted] .

Thus, oral conivaptan, given as 80 mg/day for 5 days, [redacted] (Study -026). Oral conivaptan results in blood levels 1/5 that of IV conivaptan. Given these efficacy findings with oral doses with likely lower exposure, lower doses of IV conivaptan than proposed for labeling might be effective, and should be explored.

6.1.4.3 Lack of Effect of Violations of Fluid Restriction on Efficacy of Conivaptan

Of interest is the fact that violations of the two liter per day fluid restriction occurred very frequently; excess fluid intake was especially marked among patients receiving conivaptan. Despite higher fluid intakes in the conivaptan groups, these patients were more likely to have amelioration of their hyponatremia. Thus, the potential exists for a relaxation of the fluid restriction required for treatment of hyponatremia in regimens used to date. This could result in greater patient comfort, and could help in the management of

those very ill patients who require more than two liters of intravenous fluids per day to meet their needs for parenteral nutrition or administration of intravenous medications.

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

In Study -027, the single well-controlled Phase 3 IV efficacy study, both the 40 mg/day and 80 mg/day conivaptan continuous IV infusion regimens (with an initial 20 mg IV bolus) were strongly statistically significantly superior to placebo for the following measures:

- The primary efficacy endpoint of change in serum sodium AUC from baseline over duration of treatment. This effect was consistent regardless of age, gender, race, baseline volume status, and presence or absence of CHF. The effect was highly significant despite the fact that violations of the protocol-specified fluid restriction were common. For patients with serum sodiums <120 mEq/L at baseline, the 40 mg/day IV regimen was associated with increased sodium compared to placebo, but the effect was not statistically significant. The 80 mg/day regimen was statistically significantly effective for patients with serum sodiums <120 mEq/L at baseline, and both doses were effective in patients with baseline serum sodiums >120 mEq/L.
- Mean change in serum sodium from baseline to end of Study Day 4
- Median event time to when at least 50% of patients had an increase in serum sodium of at least 4 mEq/L over baseline
- Mean total time from first dose to end of treatment during which serum sodium was at least 4 mEq/L over baseline
- Percentage of patients with a $\geq$ 6 mEq/L increase in serum sodium, or an increase to a normal serum sodium

The following tertiary measures were also favorably affected by conivaptan:

- Increased effective water clearance throughout treatment
- Increased free water clearance on Treatment Day 1, with a waning of effect thereafter
- Increased mean serum osmolality throughout treatment
- Decreased mean urine sodium, with a nadir on Treatment Day 1

Mean neurohormone levels trended upward, but not significantly, for conivaptan-treated patients. Increases in neurohormone levels could be undesirable in certain patients populations, such as those with congestive heart failure.

Conivaptan, given in the IV regimen proposed for labeling, appears highly effective in the treatment of hyponatremia. However, results of the two Phase 3 controlled oral hyponatremia trials indicate that the lowest effective dose for IV conivaptan might not be established. Oral conivaptan reaches blood levels 1/3 that of IV conivaptan. Oral conivaptan, 80 mg/day, was highly effective in treatment of hyponatremia by the primary and secondary efficacy measures also used in Study -027. Oral conivaptan, 40 mg/day,

was very effective in one study and came close to statistically significant superiority over placebo in the other. Roughly equivalent IV doses of 27 mg/day (compared to 80 mg oral) and perhaps 13 mg/day (compared to 40 mg oral) warrant exploration for efficacy.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Of great significance in evaluating the safety of conivaptan is the fact that a maximum of only 63 subjects in the entire development program received the dosing regimen (or equivalent exposure) that the sponsor is proposing for labeling. Please see Section 7.2.1 for a full explanation of this low exposure. At the time of submission of the NDA, the sponsor believed, based on a pharmacokinetic model, that their large oral program could support the safety of their IV program. However, an actual oral vs IV bioequivalence study (-083) revealed that the oral form is only 1/3 as bioavailable as the IV form. No subject in any oral study received conivaptan in a dose and regimen equivalent to the proposed IV dosing regimen. A total of 63 subjects from three IV studies received an equivalent regimen (Study -027 = 43 subjects; Study -025 = 4 subjects; Study -074 = 16 subjects). Although the clinical reviewer has reviewed and presented information on the full oral and IV population presented in the application, only a small fraction of these subjects received the relevant exposure. Separate information is presented, when possible, for the subjects who actually did receive the full exposure.

Safety information is presented for three primary groups of patients:

- Study -027, which contains the majority of patients who received the full proposed dose for labeling (29 placebo and 55 conivaptan patients total; 43 conivaptan patients who received full planned labeling dose)
- The pool of the three Phase 3 controlled hyponatremia trials, -027, -026 and -043 (82 placebo and 159 conivaptan patients)
- The pool of all 17 Phase 2 and Phase 3 studies, IV and oral, in both the congestive heart failure and hyponatremia development programs. This pool contains 332 placebo and 896 conivaptan subjects, and is referred to as the "Full Safety" population.

In a few instances, the reviewer extracted adverse event data from the few additional subjects from Studies -025 and -074, who received the proposed labeling dosing regimen, and added their information to that of Study -027. This is referred to as the "Full Dose" population.

7.1.1 Deaths

There were a total of 45 deaths reported among 1421 patients and healthy subjects treated with conivaptan in the 48 completed studies included in the application. There were no deaths in Phase 1 studies or healthy subjects. An additional 13 patients who received conivaptan had died in ongoing studies at the time of data cutoff (1 Sep 03).

In the 17 completed Phase 2/3 studies included in the application, a total of 40 deaths occurred, 27 (3%) among conivaptan subjects and 13 (4%) among placebo subjects. Table 7.1.1.1 lists all individual reports of deaths for which treatment assignment was unblinded, and which were received up to the sponsor's original NDA cutoff date of 1 Sep 03. This table includes only deaths which occurred during conivaptan exposure or within 30 days after the last dose of conivaptan (or later if death was due to an adverse event that occurred during conivaptan treatment or within 30 days after last dose).

Additional deaths from the safety update of 28 May 04 are listed in Section 7.2.9.

Table 7.1.1.1.1
Deaths Listing[1]
Cutoff Date: 1 Sep 03

Trial	Center	Patient	Age (yrs)	Gender	Dose[2] (mg)/ Route	Time[3] (Days)	Source[4]	Person Days	Description
-016	001	016-0000110	81	M	20/ oral	1 (4)	I°	1	CHF, MI, cardiogenic shock
-017	001	017-0001001	47	F	10/ oral	7 (8)	I°	7	Dilated cardiomyopathy, cardiac arrest, suspected pulm embolism
-019	JPN	019-0001101	56	M	15/ iv	1 (1)	I°	1	CHF; respiratory arrest followed by cardiac arrest
-020	021	020-0021002	58	M	40/ oral	72 (3)	I°	72	Pulmonary embolus; autopsy performed
	032	020-0032008	64	M	40/ oral	68	I°	68	Sudden death at home
-023	001	023-0001004	64	M	80/ iv	3 (3)	I°	3	Pulmonary embolism
	004	023-0004001	63	M	80/ iv	3 (15)	I°	3	Aspiration pneumonia
-025	001	025-0001002	56	M	40/ iv	4 (15)	I°	4	Pneumonia, V tach and renal failure after heart transplant
-026	001	026-0060103	45	F	40/ oral	4 (17)	I°	4	End-stage CHF, renal failure
	007	026-0060708	54	F	40/ oral	3 (6)	I°	3	Cardiorespiratory arrest. CHF; had been hypotensive on coni
	014	026-0061401	83	F	Pbo/ oral	4 (4)	I°	4	Lung cancer, cardiopulmonary arrest
	029	026-0062903	83	M	Pbo/ oral	2	I°	2	Colon cancer
-027	071	027-0071602	91	M	80/ iv	2 (19)	I°	2	Pneumonia, CHF
	072	027-0072412	59	F	80/ iv	5 (11)	I°	5	Out-of-hospital death, cause unknown
	072	027-0072413	42	M	Pbo/ iv	3 (5)	I°	3	Severe hyponatremia with coma and respiratory arrest
	072	027-0072906	91	F	Pbo/ iv	4 (53)	I°	4	Femoral artery occlusion and multiorgan failure
	075	027-0075801	90	F	80/ iv	4 (2)	I°	4	Pneumonia, CHF, hypotension, renal failure
	075	027-0075806	81	F	40/ iv	2 (1)	I°	2	Metastatic GB cancer, sepsis, hypotension, hepatic failure
	077	027-0077208	71	M	Pbo/ iv	2 (6)	I°	2	Worsening CHF, hypotension, renal failure, hyperkalemia
	077	027-0077901	87	F	Pbo/ iv	3 (3)	I°	3	Sick sinus syndrome, arrest after hip fracture
-031	060	031-0060702	95	F	40/ oral	68 (2)	I°	68	Decompensated CHF
	060	031-0060607	68	F	80/ oral	113	I°	113	Cerebral hemorrhage
	061	031-0061407	67	M	80/ oral	10 (1)	I°	10	Lung cancer
	061	031-0061411	94	M	40/ oral	7 (13)	I°	7	Pneumonia
	061	031-0061414	76	F	40/ oral	63 (1)	I°	63	Metastatic pancreatic cancer
	062	031-0062501	80	F	40/ oral	13	I°	13	CHF; died at home
	062	031-0062503	63	M	40/ oral	61 (1)	I°	61	Hyperkalemia, myocardial infarction, cardiac arrest
	062	031-0062505	83	M	40/ oral	151 (1)	I°	151	Endstage CHF; died at home
	071	031-0071304	79	F	80/ oral	302 (1)	I°	302	Endstage cirrhosis
	071	031-0071313	92	M	40/ oral	159	I°	159	Bilateral pleural effusions; respiratory arrest then cardiac arrest
	075	031-0075804	59	F	20/ oral	9	I°	9	Endstage CHF
	075	031-0075807	78	F	40/ oral	66	I°	66	CHF; acute renal failure after high-dose vitamin C therapy
	076	031-0076503	70	M	40/ oral	230 (9)	I°	230	Lung cancer (died in hospice)

Table 7.1.1.1.1
Deaths Listing[1]
Cutoff Date: 1 Sep 03

Trial	Center	Patient	Age (yrs)	Gender	Dose[2] (mg)/ Route	Time[3] (Days)	Source[4]	Person Days	Description
-032	010	032-0010009	54	M	40/ iv	1 (2)	I°	1	Arrest with pulseless electrical activity. Had CHF and MMP
	010	032-0010011	51	M	20/ iv	1 (19)	I°	1	Cardiac arrest at home; autopsy stated ischemic cardiomyopathy cause of death
	021	032-0021004	82	M	Pbo/ iv	1 (5)	I°	1	Ventricular fibrillation
	027	032-0027002	62	M	40/ iv	1 (33)	I°	1	CHF cause of death at autopsy
	027	032-0027003	73	M	Pbo/ iv	1 (21)	I°	1	Bacterial sepsis
-033	013	033-0013010	67	M	40/ oral	175 (25)	I°	175	Family refused to release medical record of death
-034	024	034-0024005	69	M	80/ oral	27 (30)	I°	27	Thrombotic middle cerebral stroke
	032	034-0032018	74	M	80/ oral	61	I°	61	Died at home, reported as cardiac arrest
	043	034-0043003	52	M	80/ oral	101(32)	I°	101	Found dead in bed at home. History CHF. No autopsy.
	049	034-0049020	60	M	20/ oral	48	I°	48	Found dead at home; history CHF
-038	002	038-0002007	44	M	Pbo/ iv	1 (23)	I°	1	History CHF; found unresponsive at home; asystole on EMT EKG
	002	038-0002011	83	F	Pbo/ iv	1 (18)	I°	1	Endstage CHF
-043	04	043-0230405	92	F	Pbo/ oral	5 (22)	I°	5	Died at home of unknown cause
	04	043-0230409	78	F	40/ oral	4	I°	4	Refractory heart failure
	13	043-0231339	67	M	40/ oral	2	I°	2	Hypovolemic shock after massive aquaresis
	13	043-0231343	65	M	Pbo/ oral	2 (1)	I°	2	Acute MI
	30	043-0233005	62	F	Pbo/ oral	2 (10)	I°	2	Bleeding after hip surgery for renal cancer metastases
-044	003	044-0003010	62	M	80/ oral	1 (59)	I°	1	Purulent necrotic pericarditis following heart transplant: autopsy
-047	023	047-0230106	58	M	40/ oral	32	I°	32	Found dead at home
	023	047-0230113	53	M	80/ oral	175	I°	175	Found dead at home
	023	047-0231326	65	M	40/ oral	14	I°	14	Ventricular tachycardia, hypotension, congestive heart failure
	023	047-0231334	80	F	40/ oral	15 (>1)	I°	15	Perforated esophageal cancer

[1]All deaths occurring during conivaptan exposure or within 30 days following discontinuation of conivaptan, and all those occurring later but resulting from adverse events that had an onset during drug exposure or during the 30 days following drug exposure

[2]Dose at time of death. If death occurred after discontinuation, last dose before discontinuation

[3]Days on drug at time of death. If death occurred after discontinuation, includes number of days on drug before discontinuation and number of subsequent days off drug before death (in parentheses)

[4]I° = primary source clinical trial, II° = secondary source

The most common cause of death was congestive heart failure, in a development program that had a large percentage of congestive heart failure patients.

The following table looks at the incidence of death in several study populations of interest.

Table 7.1.1.1.2: Numbers of Deaths in Conivaptan Trials, Grouped by Control and Indication

Studies in Group		Placebo Deaths (n,%)	IV Coni Deaths (n, %)	Oral Coni Deaths (n, %)	All Coni Deaths (n, %)	Total Deaths (n, %)
All[1] Controlled Studies, IV and Oral, Hyponatremia and CHF		13/332 (3.9%)			27/896 (3.0%)	40/1228 (3.3%)
All Controlled IV Studies		8/112 (7.1%)	8/228 (3.5%)			16/340 (4.7%)
All Controlled Oral Studies		5/301 (1.7%)		12/738 (1.6%)		17/1039 (1.6%)
All Controlled Hyponatremia Studies[2]		9/82 (11.0%)			8/159 (5.0%)	17/241 (7.1%)
All Controlled CHF Studies[3]		4/250 (1.6%)			13/661 (2.0%)	17/911 (1.9%)
All Controlled Studies in Healthy Subjects[4]		0/86 (0.0%)			0/143 (0.0%)	0/229 (0.0%)
Major Controlled Efficacy Studies for Hyponatremia (-026, -027 and -043)		9/82 (11.0%)	4/55 (7.3%)	4/104 (3.8%)	8/159 (5.0%)	17/241 (7.1%)
Study -027 Alone (Major IV Hyponatremia Efficacy Study)		4/29 (13.7%)	4/55 (7.3%)			8/84 (9.5%)
Studies -026 and -043 Alone (Major Oral Hyponatremia Efficacy Studies)		5/53 (9.4%)		4/104 (3.8%)		9/104 (8.6%)
Population with Full Planned Labeling Dose Regimen[5]		4/29 (13.7%)	3/63 (4.8%)			7/92 (7.6%)

[1] IV: -006, -007, -008, -027, -032, -038, -044
Oral: -002, -003, -004, -005, -011, -012, -014, -017, -020, -026, -033, -034, -043, -063
[2] -026, -027, -043
[3] -017, -020, -032, -033, -034, -038, -044
[4] -002, -003, -004, -005, -006, -007, -008, -011, -012, -014, -063
[5]-Includes only those subjects who received the full dose proposed for labeling (43 patients from -027, 4 subjects from -025, and 16 subjects from -074)
Sources: Sponsor's Tables 2.7.4 -21, -22, -60, Module 2, Section 2.7.4, pages 103, 104 and 279, original NDA. Review of all death narratives, accessible via NDA TOC Section 12, to links in CRF TOC, pages 1-14.

Of note from the above table are the following observations:

- When considering the population which received the full planned labeling dose, the incidence of death was somewhat lower among conivaptan-treated subjects (4.8%)

than among IV placebo-treated subjects (13.7%). IV placebo subjects were used as a comparator because no subject in an oral conivaptan group received an equivalent of the full planned labeling dose.

- When considering the major IV hyponatremia trial (-027) alone, the incidence of death was lower among IV conivaptan-treated patients (7.3%) than among IV placebo-treated patients (13.7%). The overall incidence of death in this trial (9.5%) was somewhat higher than in the overall controlled population (2.4%) and overall IV controlled population (4.7%). This difference may be due in part to the inclusion of healthy subjects in the other populations, and to the severity of underlying disease in the hyponatremia study populations.
- When considering all IV and oral controlled studies, the incidence of death was somewhat lower among all conivaptan-treated subjects (3.0%) than among all placebo subjects (3.9%).
- When considering only controlled IV studies, the incidence of death was again somewhat lower among all IV conivaptan-treated subjects (3.5%) than among all IV placebo-treated subjects (7.1%).
- When considering only controlled oral studies, the incidence of death was slightly lower among oral conivaptan-treated subjects (1.6%) than among oral placebo-treated subjects (1.7%).
- When considering all controlled studies in hyponatremia, including both oral and IV conivaptan, the incidence of death was lower among conivaptan-treated patients (5.0%) than among placebo-treated patients (11.0%). This population includes only the three major efficacy trials in hyponatremia (-026, -027, -043).
- When considering the major oral hyponatremia trials (-026 and -043), the incidence of death was lower among oral conivaptan-treated patients (3.8%) than among oral placebo-treated patients (9.4 %).
- In the controlled CHF trials, a slightly higher percentage of deaths occurred in the conivaptan group (2.0%) vs the placebo group (1.6%). This difference was not statistically significant.
- There were no deaths among healthy subjects.

Of possible concern is the fact that, when one considers all controlled CHF studies, the incidence of death for conivaptan-treated patients is actually somewhat higher (2.0%) than that for placebo-treated patients (1.6%), although this difference is not statistically significant. There is significant interest in the medical literature in using vasopressin receptor antagonists for the treatment of CHF *per se*, and not just for treatment of hyponatremia in CHF. Because of the potential for off-label use in CHF if the FDA grants an indication for hyponatremia, information regarding the safety of conivaptan in CHF patients is of interest to DMEDP.

The clinical reviewer examined cause-specific mortality in the sponsor's congestive heart failure trials. Almost all deaths for both the placebo and conivaptan groups were attributed to cardiac causes. No single cause of cardiac death emerged with significantly greater frequency than other cardiac causes. When cardiac arrest-related cause of death terms were grouped, they occurred slightly more frequently in conivaptan patients than

in placebo patients. Death attributed to congestive heart failure terms also occurred slightly more frequently in conivaptan patients than in placebo patients.

Table 7.1.1.1.3: Cause-specific Mortality Among Patients in Conivaptan CHF Trials, Phase 2 and 3, IV and Oral (Sponsor's Pool 5D, compiled from Sponsor's Tables 2.7.4-111-17 and 2.7.4-66-9, IAS)

Cause	Pbo n = 250	Coni n = 661
Any Cause of Death	4 (1.6%)	13 (2.0%)
V Fib	1 (0.4%)	
Sepsis	1 (0.4%)	
Cardiorespiratory Arrest	1 (0.4%)	1 (0.2%)
Decompensated CHF	1 (0.4%)	
Ischemic Cardiomyopathy		1 (0.2%)
Cardiac Arrest		4 (0.6%)
"Other Cause" and no Death CRF		2 (0.3%)
Endstage CHF		1 (0.2%)
Acute Cardiac Failure		1 (0.2%)
Sudden Death		2 (0.3%)
Cardiac Failure		1 (0.2%)
CVA		1 (0.2%)
All Cardiac Arrest-related Terms[1]	1 (0.4%)	6 (0.9%)
All CHF Causes of Death[2]	1 (0.4%)	4 (0.6%)

1 includes cardiorespiratory arrest, cardiac arrest, and sudden death
2 (includes decompensated CHF, ischemic cardiomyopathy, endstage CHF, acute cardiac failure, and cardiac failure

7.1.1.2 Brief Summaries of Death Narratives for Conivaptan Patients

Subject 016-0000110: 82 year old (yo) M with prior NYHA FC III/IV CHF. Received single 20 mg dose conivaptan. Inotropic treatment started on Study Day 2 for dyspnea and CHF. On Study Day 4, MI with cardiogenic shock and death.

Subject 017-0001001: 47 yo F with NYHA FC III dilated cardiomyopathy, gangrenous lesions both feet. Received conivaptan 10 mg/day for 7 days. Eight days after last dose of conivaptan, developed tonic clonic seizures, ventricular tachycardia and hypotension, and died. Suspected pulmonary embolism.

Subject 019-0001101: 56 year old man with CHF, ischemic heart disease and history of multiple strokes. Received single dose of 15 mg IV conivaptan. One day after the dose, the patient had a respiratory arrest, followed by a cardiac arrest and death.

Subject 020-0021002: 58 year old man with ischemic CHF. On day 75 of conivaptan treatment, and two days after sinus surgery, patient collapsed. Resuscitation unsuccessful. Autopsy revealed massive pulmonary embolus.

Subject 020-0032008: 64 year old man with congestive heart failure. On day 67, developed abdominal discomfort at home. On day 68 of conivaptan treatment, died at home.

Subject 023-0001004: 64 yo M with hyponatremia and CHF, automatic implantable defibrillator, COPD, DM. Admitted with pulmonary embolism (PE); two days later, began conivaptan. Received 50 mg IV/day for 2 days, then 80 mg for 1 day. At some point between admission and Study Day 3, developed tachyarrhythmias. On Study Day 3, deep peroneal vein thrombus noted on Doppler. Systolic BP in 80s-90s Study Days 3-5. Study Day 6, died due to cardiorespiratory arrest refractory to defibrillation and medical therapy. Suspected recurrent pulmonary embolism.

Subject 023-0004001: 63 year old man with euvolemic hyponatremia and a history of squamous cell carcinoma of the right pyriform sinus. Received 50 mg IV conivaptan on Study Day 1, then 80 mg/day for two days. On Study Day 3, dyspnea, decreased oxygen saturation and CXR consistent with aspiration pneumonia. Intubated. Died on Study Day 19 from respiratory failure.

Subject 025-0001002: 56 yo M with hyponatremia; history of MI, biventricular heart failure, PE, atrial fibrillation (A fib). Received IV conivaptan 60 mg for one day followed by 40 mg/day for 4 days. Serum sodium went from 129 mEq/L to 139 over the four days. Four days after last dose of conivaptan, received heart transplant. Developed acute renal failure and pneumonia. Sixteen days after last dose of conivaptan, syncopal symptoms followed by cardiorespiratory arrest, V tach and death.

Subject 026-0060103: 45 yo F with history of CHF, pulmonary hypertension, rheumatic heart disease, atrial fibrillation, bacterial endocarditis, aortic and mitral valve replacements. Admitted with end-stage CHF and hyponatremia. Started conivaptan 40 mg po q day; took for 4 days. On Study Day 4, worsening renal function, decreased oncotic pressure, treated with venovenous hemofiltration. Renal scan 15 days after last dose of drug showed severe bilateral renal cortical disease, delayed renal blood flow to both kidneys, small right kidney. Developed bradycardia and died 17 days after last dose of conivaptan.

Subject 026-0060708: 54 yo F with history severe cardiomyopathy, COPD, MI, chronic renal impairment. Admitted with decompensated CHF; hyponatremic. Started on oral conivaptan 40 mg/day. On Study Day 2, became hypotensive, hyperkalemic and developed ventricular tachycardia (V tach). Treated with lidocaine, but lidocaine stopped due to lidocaine toxicity with mental status changes. Study Day 3, lidocaine restarted due to recurrent V tach. Study Day 4, lidocaine replaced with amiodarone. Conivaptan stopped due to hypovolemia. Study Day 5, blood urea nitrogen (BUN) increased to 69 mg/dL from baseline 16; creatinine (Cr) increased to 1.9 mg/dL from baseline 0.8. Study Day 10, had cardiorespiratory arrest and died.

Subject 027-0071602: 91 yo M with CHF. Received IV conivaptan for 2 days; stopped due to phlebitis at multiple sites. Study Day 5, CHF worsened. Study Day 14, bilateral pneumonia diagnosed. Died on Study Day 22 from pneumonia and CHF (19 days after last dose of conivaptan).

Subject 027-0072412: 59 yo F with history of breast cancer 15 yrs prior, treated with mastectomy. Received 5 days of 80 mg IV conivaptan; 1 day later, developed "decline in her general condition". Died out-of-hospital, one day after her final (day 15) study visit.

Subject 027-0075801: 90 year old woman hospitalized with CHF and pneumonia. Received conivaptan 80 mg/day for four days. Throughout treatment phase, had worsening CHF with hypotension; worsening pneumonia with decreasing oxygen saturation and cyanosis of extremities; and decreasing urine output. Died on Study Day 6 after family requested comfort measures only.

Subject 027-0075806: 81 yo F with metastatic gallbladder cancer. Received 40 mg IV conivaptan for 2 days; stopped after patient developed gram-negative sepsis. Developed hypotension and jaundice and died one day later (Study Day 3). Baseline Cr 0.6; increased to 1.5 on Study Day 3.

Subject 031-0060702: 95 year old F with hyponatremia and CHF. Received oral conivaptan 40 mg/day. On day 45 of treatment, admitted with worsening CHF. Conivaptan discontinued on day 68; patient died two days later of decompensated CHF.

Subject 031-0060607: 68 year old woman with idiopathic hyponatremia. History of hypertension, stroke and epilepsy. Received 40 mg conivaptan for 6 days, followed by 80 mg for 107 days, for a total of 113 days of treatment. On Study Day 112, had sudden loss of consciousness; CT revealed cerebral hemorrhage. Intubated, ventilated and transferred to tertiary care hospital. Died on Study Day 113.

Subject 031-0061407: 67 year old M with hyponatremia secondary to lung cancer. Received 40 mg oral conivaptan for 7 days, and 80 mg for 3 days. One day after his last dose of conivaptan, he died of "terminal lung cancer".

Subject 031-0061411: 94 year old man with hyponatremia secondary to malignancy. Received oral conivaptan 40 mg for 7 days. Discharged to nursing home and readmitted on Study Day 10 with pneumonia. Placed in hospice and died of pneumonia on Study Day 20.

Subject 031-0061414: 76 year old woman with hyponatremia and metastatic pancreatic cancer. Received 63 days of oral conivaptan 40 mg/day. On Day 63, conivaptan stopped due to decision to go into hospice. Died one day later of metastatic pancreatic cancer.

Subject 031-0062501: 80 year old woman with hyponatremia secondary to congestive heart failure. Hospitalized for CHF; conivaptan initiated while in hospital. Discharged on Study Day 14. Died at home on Study Day 16.

Subject 031-0062503: 63 yo M in extension study. NYHA FC IV CHF, pacemaker for history of asystole, aortic valve replacement (AoVR), pulmonary hypertension, chronic renal insufficiency. Received 40 mg/day conivaptan for 62 days total. Placed on Zaroxolyn in second month of conivaptan therapy. Potassium decreased to 2.9; Zaroxolyn held on day 52 of conivaptan treatment. Potassium increased over several days until 6.6 on day 62. Suffered cardiac arrest on day 62 and died; autopsy revealed extensive myocardial infarction.

Subject 031-0062505: 83 year old man with hyponatremia and CHF. Received 40 mg oral conivaptan for 151 days. On Study Day 82, admitted to hospital with worsening CHF and acute on chronic renal failure. Discharged on Study Day 88. Died at home on Study Day 152; cause of death cited as endstage CHF.

Subject 031-0071304: 79 year old woman with hyponatremia secondary to cirrhosis. Received 80 mg conivaptan/day for 75 days, then 40 mg/day for 14 days, then 80 mg/day for 213 days, for a total treatment duration of 302 days. In a longterm care facility for most of the study, but went home for terminal care. On Treatment Day 289, she developed decreased level of consciousness at home. Received supportive treatment only. Conivaptan discontinued on Study Day 302; patient died one day later due to endstage hepatic failure.

Subject 031-0071313: 92 year old man with hyponatremia secondary to SIADH. History of myocardial infarction and chronic renal failure. Received 40 mg conivaptan for 159 days. On Study Day 147, admitted with chest pain, bilateral pleural effusions and pulmonary interstitial infiltrate on CT. Thoracentesis done twice, on Study Days 147 and 156. On Study Day 159, had a respiratory arrest and was intubated. A few hours later had a cardiac arrest and died.

Subject 031-0075804: 59 year old woman with hyponatremia secondary to CHF. Received oral conivaptan 20 mg/day for 9 days. On Study Day 7, admitted with worsening CHF. Was in "Do Not Resuscitate" (DNR) status and died two days later of endstage CHF.

Subject 031-0075807: 78 year old woman with hyponatremia secondary to CHF. Received 40 mg conivaptan for 68 days. Did not take from Study Day 53-55. Seen on Study Day 54 for worsening CHF with increasing pleural effusions. Refused admission; one day later, checked into a "natural healing" center. Received "high dose" Vitamin C (1-10 gm IV) on Study Days 61-65. Developed wrist cellulitis, wbc 25,000/mm^3, and acute renal failure. Died on Study Day 71.

Subject 031-0076503: 79 year old man with hyponatremia secondary to metastatic lung cancer. Received 40 mg oral conivaptan for 230 days. On Treatment Day 230, admitted to hospice for increasing pain. Died 9 days later; cause of death listed as metastatic lung cancer.

Subject 032-0010009: 54 yo M with history of CHF, CVA, aortofemoral bypass (AoFB), mitral insufficiency. Admitted for heart transplant evaluation. Received single dose of 40 mg IV conivaptan. Study Day 2 (1 day after conivaptan dose), developed chest pain, wide-complex bradycardia and then pulseless electrical activity. Resuscitation ineffective; pericardiocentesis performed without effect. Died early on Study Day 3.

Subject 032-0010011: 51 yo M with history of CHF, mitral and tricuspid regurgitation and MI. Received single IV dose of conivaptan 20 mg. 19 days later, cardiac arrest at home. Autopsy stated ischemic cardiomyopathy was cause of death.

Subject 032-0027002: 62 yo M with history of CHF, DM, SVT, CRI, CAD. Received single dose IV conivaptan 40 mg. One day after conivaptan dose, developed worsening CHF and became hypotensive. Study Day 22, developed V tach. Study Day 25 ARF; placed on hemofiltration, developed heparin-induced thrombocytopenia. Made DNR and died on Study Day 34. Autopsy listed CHF as primary cause of death.

Subject 033-0013010: 68 yo M with idiopathic cardiomyopathy and congestive heart failure. Received 40 mg oral conivaptan/day for 175 days; hospitalized on day 175 with dyspnea, conivaptan discontinued. Treated with IV diuretics, recovered and was discharged on Study Day 185. Died on Study Day 200; family refused to release medical records, and cause of death unknown.

Subject 034-024005: 69 yo M with CHF. Received 80 mg oral conivaptan/day for 27 days. Presented with CVA on Study Day 26; conivaptan discontinued next day. Did not recover from stroke and died on Study Day 57, 30 days after discontinuation of conivaptan.

Subject 034-0032018: 74 yo M with history of ischemic cardiomyopathy, diabetes. Received 80 mg oral conivaptan/day for 60 days. Died at home on day 61; reported as cardiac arrest.

Subject 034-0043003: 52 yo M with CHF (EF 10% prior to study), history multiple myocardial infarctions (MIs). Received 80 mg conivaptan/day for 101 days. Thirty-two days after last dose conivaptan, found dead in bed at home. No autopsy.

Subject 034-0049020: 60 year old man with CHF. Received conivaptan 20 mg/day for 48 days. Sudden death at home on Study Day 48.

Subject 043-0230409: 78 yo F with history of heart failure, atrial fibrillation. Prior to hospitalization for study, had been hospitalized for three months with arrhythmia, cardiac decompensation and respiratory insufficiency. Two days after discharge, returned with pulmonary edema and congestive heart failure. Began study and received 4 days of conivaptan 20 mg po bid. Condition declined steadily from the time of admission, and she died 3 days after her last dose of study drug of "uncontrollable cardiovascular insufficiency".

Subject 043-0231339: 67 yo M with chronic heart failure and interstitial pulmonary fibrosis. Admitted for respiratory insufficiency, serum sodium 126 mEq/L. Received conivaptan 20 mg po bid; on second day of administration, serum sodium 134, weight down 1 kg, urine output increased from baseline of 1850 mL/day to 3550 mL/day, systolic BP fell to 90 mm Hg. Conivaptan dose halved, but progressively deteriorated with worsening hyponatremia and hypotension. Found dead that night. Cause of death reported as hypovolemic shock.

Subject 044-0003010: 62 yo M with endstage cardiomyopathy. Received 80 mg IV conivaptan for one day. On Study Day 28, had heart transplant. On Study Day 62, died of purulent necrotic pericarditis. Autopsy performed.

Subject 047-0230106: 58 yo M with right heart failure due to interauricular communication, mitral insufficiency, pulmonary hypertension, shunt inversion and history of supraventricular tachycardia (SVT). Received conivaptan 40 mg/day for 32 days. Seen on Study Day 29; Cr increased to 1.4 mg/dL from baseline 0.8; BUN 35; sodium 136 mEq/L; digoxin level 3.6 ng/mL (therapeutic range 1-2). Digoxin stopped; was to resume on Study Day 31. Found dead at home on Study Day 33.

Subject 047-0230113: 53 yo M undergoing chemotherapy for cancer, type unknown. History aortic stenosis (AoS) and atrial flutter. On 80 mg conivaptan/day. On day 174 of conivaptan, presented with atrial flutter and severe leg edema. Refused hospitalization; found dead in bed two days later.

Subject 047-231326: 65 yo M with ischemic cardiomyopathy, chronic renal insufficiency, COPD and history of SVT. Admitted on Study Day 12 (conivaptan 40 mg/day) with BP 70/50, decompensated CHF. Conivaptan stopped, but family member brought it in and patient received for two more days. Study Day 13, developed V tach which lasted 7 hrs. On Study Day 15, developed ventricular tachycardia and died.

Subject 047-0231334: 80 yo F with history of surgery and stent for esophageal perforation due to esophageal cancer. Received conivaptan 40 mg/day. On Study Day 17, developed another esophageal perforation. Study drug was stopped, and parenteral nutrition begun. Died from esophageal cancer; exact date of death unknown.

7.1.2 Other Serious Adverse Events

In the three Phase 3 controlled hyponatremia trials, serious treatment-emergent events (TEAEs) were reported in 28 (18%) of the conivaptan-treated patients and 12 (15%) of the placebo patients. This difference was more marked for the 80 mg/day groups (15% vs 6% pbo) than for the 40 mg/day groups (28% vs 25% pbo), but most TEAEs occurred in the 40 mg/day groups. In the full safety population of all Phase 2 and Phase 3 studies, IV and oral, in hyponatremia and CHF, serious TEAEs were also reported more frequently in conivaptan treated subjects (15%) than in placebo-treated patients (11%).

Table 7.1.2.1 summarizes serious adverse events occurring in all Phase 2 and Phase 3 studies, for both hyponatremia and CHF.

Table 7.1.2.1: Serious Treatment-emergent Adverse Events, Full Safety Population[1], Number and Percentage of Subjects with each Type of Event

		IV		Oral		IV + Oral	
		Pbo n (%) n = 92	Coni n (%) n = 208	Pbo n (%) n = 240	Coni n (%) n = 688	Pbo n (%) n = 332	Coni n (%) n = 896
System	Event						
Cardiac		9 (9.8)	17 (8.2)	8 (3.3)	34 (4.9)	17 (5.1)	51 (5.7)
	Acute Coronary Syndrome			1 (0.4)		1 (0.3)	
	Acute MI			1 (0.4)		1 (0.3)	
	MI		1 (0.5)	1 (0.4)		1 (0.3)	1 (0.1)
	Angina pectoris			1 (0.4)	4 (0.6)	1 (0.3)	4 (0.4)
	Angina unstable	1 (1.1)			3 (0.4)	1 (0.3)	3 (0.3)
	Arrhythmia NOS				1 (0.1)		1 (0.1)
	AV block NOS		1 (0.5)				1 0.1)
	AV block complete				1 (0.1)		1 (0.1)
	Bradycardia NOS	1 (1.1)		1 (0.4)	1 (0.1)	2 (0.6)	1 (0.1)
	Cardiac arrest		2 (1.0)		4 (0.6)		6 (0.7)
	Cardiac failure NOS	1 (1.1)	2 (1.0)	2 (0.8)	8 (1.2)	3 (0.9)	10 (1.1)
	Cardiac failure acute		1 (0.5)				1 (0.1)
	Cardiac failure chronic	1 (1.1)	1 (0.5)		1 (0.1)	1 (0.3)	2 (0.2)
	Cardiac failure congestive		2 (1.0)		1 (0.1)		3 (0.3)
	Cardiopulmonary failure				1 (0.1)		1 (0.1)
	Congestive cardiac failure aggravated	1 (1.1)	3 (1.4)	2 (0.8)	6 (0.9)	3 (0.9)	9 (1.0)
	Ischaemic cardiomyopathy		1 (0.5)				1 (0.1)
	Cardiorespiratory arrest	1 (1.1)				1 (0.3)	
	Cardiogenic shock				1 (0.1)		1 (0.1)
	Coronary artery disease NOS				1 (0.1)		1 (0.1)
	Sick sinus syndrome	1 (1.1)				1 (0.3)	
	Sinus arrhythmia				1 (0.1)		1 (0.1)
	SV arrhythmia NOS	1 (1.1)				1 (0.3)	

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		IV		Oral		IV + Oral	
		Pbo n (%) n = 92	Coni n (%) n = 208	Pbo n (%) n = 240	Coni n (%) n = 688	Pbo n (%) n = 332	Coni n (%) n = 896
System	Event						
	SVT				1 (0.1)		1 (0.1)
	V fib	1 (1.1)	1 (0.5)			1 (0.3)	1 (0.1)
	V tach	1 (1.1)	3 (1.4)		2 (0.3)	1 (0.3)	5 (0.6)
Cardiac Procedures				1 (0.4)	1 (0.1)	1 (0.3)	1 (0.1)
	Cardioversion			1 (0.4)		1 (0.3)	
	Heart transplant				1 (0.1)		1 (0.1)
Vascular disorders		2 (2.2)	4 (1.9)	3 (1.3)	6 (0.9)	5 (1.5)	10 (1.1)
	Arterial occlusion	1 (1.1)				1 (0.3)	
	Deep vein thrombosis		2 (1.0)				2 (0.2)
	Hypertension NOS				1 (0.1)		1 (0.1)
	Hypotension NOS	1 (1.1)	1 (0.5)	1 (0.4)	5 (0.7)	2 (0.6)	6 (0.7)
	Intermittent claudication			1 (0.4)		1 (0.3)	
	Jugular vein thrombosis		1 (0.5)				1 (0.1)
	Malignant hypertension NOS			1 (0.4)		1 (0.3)	
Blood and Lymphatic					2 (0.3)		2 (0.2)
	Anemia				1 (0.1)		1 (0.1)
	Coagulopathy				1 (0.1)		1 (0.1)
Congenital					1 (0.1)		1 (0.1)
	AV malformation				1 (0.1)		1 (0.1)
Endocrine					1 (0.1)		1 (0.1)
	Hypothyroidism				1 (0.1)		1 (0.1)
GI		1 (1.1)			6 (0.9)	1 (0.3)	6 (0.7)
	Abd pain NOS				1 (0.1)		1 (0.1)
	Abd pain upper				1 (0.1)		1 (0.1)
	Colitis ischaemic				1 (0.1)		1 (0.1)

Table 7.1.2.1: Serious Treatment-emergent Adverse Events, Full Safety Population[1], Number and Percentage of Subjects with each Type of Event

		IV		Oral		IV + Oral	
		Pbo n (%) n = 92	Coni n (%) n = 208	Pbo n (%) n = 240	Coni n (%) n = 688	Pbo n (%) n = 332	Coni n (%) n = 896
System	Event						
	Dyspepsia				1 (0.1)		1 (0.1)
	Gastric ulcer				1 (0.1)		1 (0.1)
	GI hemorrhage NOS	1 (1.1)				1 (0.3)	
	Inguinal hernia NOS				1 (0.1)		1 (0.1)
	Small bowel obstruction				1 (0.1)		1 (0.1)
Hepatobiliary			1 (0.5)		3 (0.4)		4 (0.4)
	Cholelithiasis				1 (0.1)		1 (0.1
	Cholestasis				1 (0.1)		1 (0.1)
	Hepatic failure		1 (0.5)				1 (0.1)
	Hepatitis NOS				1 (0.1)		1 (0.1)
General Disorders		1 (1.1)	1 (0.5)	2 (0.8)	14 (2.0)	3 (0.9)	15 (1.7)
	Anasarca		1 (0.5)				1 (0.1)
	Edema NOS		1 (0.5)				1 (0.1)
	Edema peripheral				1 (0.1)		1 (0.1)
	Chest pain	1 (1.1)			9 (1.3)	1 (0.3)	9 (1.0)
	Drug interaction NOS				1 (0.1)		1 (0.1)
	Influenza-like illness				1 (0.1)		1 (0.1)
	Mass NOS				1 (0.1)		1 (0.1)
	Pain NOS			1 (0.4)		1 (0.3)	
	Pyrexia	1 (1.1)	1 (0.5)			1 (0.3)	1 (0.1)
Infections		3 (3.3)	14 (6.7)	1 (0.4)	8 (1.2)	4 (1.2)	22 (2.5)
	Abdominal abscess		1 (0.5)				1 (0.1)
	Appendicitis				1 (0.1)		1 (0.1)
	Bronchial infection				1 (0.1)		1 (0.1)
	Bronchitis acute NOS		1 (0.5)		1 (0.1)		2 (0.2)

Table 7.1.2.1: Serious Treatment-emergent Adverse Events, Full Safety Population[1], Number and Percentage of Subjects with each Type of Event							
		IV		Oral		IV + Oral	
		Pbo n (%) n = 92	Coni n (%) n = 208	Pbo n (%) n = 240	Coni n (%) n = 688	Pbo n (%) n = 332	Coni n (%) n = 896
System	Event						
	Cellulitis		1 (0.5)	1 (0.4)		1 (0.3)	1 (0.1)
	Infection NOS		1 (0.5)				1 (0.1)
	Pneumonia NOS	1 (1.1)	3 (1.4)		2 (0.3)	1 (0.3)	5 (0.6)
	Purulent pericarditis		1 (0.5)				1 (0.1)
	Pyothorax				1 (0.1)		1 (0.1)
	Sepsis NOS	2 (2.2)	2 (1.0)		1 (0.1)	2 (0.6)	3 (0.3)
	Sinusitis NOS				1 (0.1)		1 (0.1)
	Upper respiratory tract infection NOS				1 (0.1)		1 (0.1)
	Urinary tract infection NOS		4 (1.9)				4 (0.4)
Injury, Poisoning and Procedural Complications			1 (0.5)	2 (0.8)	2 (0.3)	2 (0.6)	3 (0.3)
	Anastomotic leak				1 (0.1)		1 (0.1)
	Ankle fracture		1 (0.5)				1 (0.1)
	Fall				1 (0.1)		1 (0.1)
	Postprocedural hemorrhage			1 (0.4)		1 (0.3)	
	Therapeutic agent poisoning			1 (0.4)		1 (0.3)	
Lab and VS			1 (0.5)	1 (0.4)	7 (1.0)	1 (0.3)	8 (0.9)
	ALT incr				2 (0.3)		2 (0.2)
	AST incr				2 (0.3)		2 (0.2)
	CPK incr				2 (0.3)		2 (0.2)
	LDH incr				1 (0.1)		1 (0.1)
	BP decr			1 (0.4)	1 (0.1)	1 (0.3)	1 (0.1)
	BUN:Cr ratio incr				1 (0.1)		1 (0.1)

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		IV		Oral		IV + Oral	
		Pbo n (%) n = 92	Coni n (%) n = 208	Pbo n (%) n = 240	Coni n (%) n = 688	Pbo n (%) n = 332	Coni n (%) n = 896
System	Event						
	Body temp incr				1 (0.1)		1 (0.1)
	Hb decr				1 (0.1)		1 (0.1)
	LFT Abnl		1 (0.5)		1 (0.1)		2 (0.2)
Metab and Nutr		2 (2.2)	3 (1.4)	1 (0.4)	10 (1.5)	3 (0.9)	13 (1.5)
	Dehydration		2 (1.0)		4 (0.6)		6 (0.7)
	Diabetes mellitus NOS			1 (0.4)	1 (0.1)	1 (0.3)	1 (0.1)
	Hyperglycemia NOS				2 (0.3)		2 (0.2)
	Hyperkalemia	1 (1.1)			1 (0.1)	1 (0.3)	1 (0.1)
	Hypoglycemia NOS				1 (0.1)		1 (0.1)
	Hyponatremia	1 (1.1)	1 (1.0)		1 (0.1)	1 (0.3)	2 (0.2)
	Hypovolemia		1 (1.0)		1 (0.1)		2 (0.2)
Muscle					3 (0.4)		3 (0.3)
	Myalgia				1 (0.1)		1 (0.1)
	Rhabdomyolysis				1 (0.1)		1 (0.1)
Neoplasm				1 (0.4)	3 (0.4)	1 (0.3)	3 (0.3)
	Bladder neoplasm NOS				1 (0.1)		1 (0.1)
	Metastatic carcinoma			1 (0.4)		1 (0.3)	
	Esophageal carcinoma NOS				2 (0.3)		(0.2)
Nervous System		1 (1.1)	3 (1.4)		10 (1.5)	1 (0.3)	13 (1.5)
	CVA		1 (0.5)		1 (0.1)		2 (0.2)
	Dizziness				1 (0.1)		1 (0.1)
	Grand mal convulsion				1 (0.1)		1 (0.1)
	Paresthesia				1 (0.1)		1 (0.1)
	Syncope		2 (1.0)		5 (0.7)		7 (0.8)
	Syncope vasovagal	1 (1.1)			1 (0.1)	1 (0.3)	1 (0.1

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		IV		Oral		IV + Oral	
		Pbo n (%) n = 92	Coni n (%) n = 208	Pbo n (%) n = 240	Coni n (%) n = 688	Pbo n (%) n = 332	Coni n (%) n = 896
System	Event						
Psychiatric			1 (0.5)		4 (0.6)		5 (0.6)
	Anxiety				1 (0.1)		1 (0.1)
	Confusional State		1 (0.5)		1 (0.1)		2 (0.2)
	Depression				1 (0.1)		1 (0.1)
	Mental Status Changes				1 (0.1)		1 (0.1)
	Psychotic disorder				1 (0.1)		1 (0.1)
Renal and Urinary		1 (1.1)	9 (4.3)		18 (2.6)	1 (0.3)	27 (3.0)
	Renal disorder NOS		1 (0.5)		2 (0.3)		1 (0.1)
	Renal failure NOS	1 (1.1)			3 (0.4)	1 (0.3)	12 (1.3)
	Renal failure acute		3 (1.4)		5 (0.7)		2 (0.2)
	"Acute renal injury" [2]		5 (2.4)		8 (1.2)		
Reproductive system and breast disorders			1 (0.5)				1 (0.1)
	Ovarian mass		1 (0.5)				1 (0.1)
Respiratory and thoracic		1 (1.1)	4 (1.9)	2 (0.8)	11 (1.6)	3 (0.9)	15 (1.7)
	Acute pulmonary edema			1 (0.4)		1 (0.3)	
	Bronchitis NOS				1 (0.1)		1 (0.1)
	COPD		1 (0.5)				1 (0.1)
	COPD exacerbated				2 (0.3)		2 (0.2)
	Dyspnea				1 (0.1)		1 (0.1)
	Dyspnea exacerbated				2 (0.3)		2 (0.2)
	Hypercapnia				1 (0.1)		1 (0.1)
	Esophagobronchial fistula				1 (0.1)		1 (0.1)
	Pleural effusion				1 (0.1)		1 (0.1)
	Pulmonary embolism		1 (0.5)	1 (0.4)	3 (0.4)	1 (0.3)	4 (0.4)
	Pulmonary edema NOS				1 (0.1)		1 (0.1)

Table 7.1.2.1: Serious Treatment-emergent Adverse Events, Full Safety Population[1], Number and Percentage of Subjects with each Type of Event

		IV		Oral		IV + Oral	
		Pbo n (%) n = 92	Coni n (%) n = 208	Pbo n (%) n = 240	Coni n (%) n = 688	Pbo n (%) n = 332	Coni n (%) n = 896
System	Event						
	Respiratory arrest	1 (1.1)	1 (0.5)			1 (0.3)	1 (0.1)
	Respiratory failure		1 (0.5)				1 (0.1)
Social Circumstances					1 (0.1)		1 (0.1)
	Drug abuser				1 (0.1)		1 (0.1)

[1] Studies 016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 032, 033, 034, 038, 043, 044, 047
2 See Section 7.1.2.4.3 for definitions of acute renal failure and "acute renal injury"
Source: Sponsor's Table 2.7.4-129, Module 5, Section 5.3.3.5, beginning p 1386

The following table looks at serious adverse events occurring among subjects who received the full IV dose regimen proposed for labeling. It does not include any subjects who discontinued study or died before receiving the full planned dose.

Table 7.1.2.2: Serious Treatment-emergent Adverse Events among all Study Subjects Receiving Full Planned Labeling Dose Regimen, Number and Percentage of Subjects with each Type of Event

		Pbo n (%) n = 29	Coni n (%) n = 63
System	**Event**		
Cardiac		3 (10.3%)	5 (7.9%)
	AV block NOS		1 (1.6%)
	Cardiac arrest		1 (1.6%)
	Cardiac failure NOS		1 (1.6%)
	Cardiac failure congestive		1 (1.6%)
	Congestive cardiac failure aggravated	1 (3.4%)	1 (1.6%)
	Sick sinus syndrome	1 (3.4%)	
	SV arrhythmia NOS	1 (3.4%)	
Vascular disorders		2 (6.9%)	3 (4.8%)
	Arterial occlusion	1 (3.4%)	
	Deep vein thrombosis		2 (3.2%)
	Hypotension NOS	1 (3.4%)	
	Jugular vein thrombosis		1 (1.6%)
GI		1 (3.4%)	0
	GI hemorrhage NOS	1 (3.4%)	
General Disorders		0	2 (3.2%)
	Anasarca		1 (1.6%)
	Edema NOS		1 (1.6%)
Infections			
	Infection Jugular Vein		1 (1.6%)
	Pneumonia NOS		1 (1.6%)
Lab and VS		0	1 (1.6%)
	LFT Abnl		1 (1.6%)
Metab and Nutr		2 (6.9%)	3 (1.8%)
	Dehydration		1 (1.6%)
	Hyperkalemia	1 (3.4%)	
	Hyponatremia	1 (3.4%)	1 (1.6%)
	Hypovolemia		1 (1.6%)
Psychiatric		0	1 (1.6%)
	Confusional State		1 (1.6%)
Renal and Urinary		1 (3.4%)	8 (12.7%)
	Renal disorder NOS		1 (1.6%)
	Renal failure NOS	1 (3.4%)	3 (4.8%)
	"Acute renal injury" [1]		4 (6.3%)
Reproductive system and breast disorders		0	1 (1.6%)
	Ovarian mass		1 (1.6%)
Respiratory and thoracic		1 (3.4%)	0
	Respiratory arrest	1 (3.4%)	

1 See section 7.1.2.4.3 for definition of "acute renal injury"
Source: Sponsor's Table 2.7.4-61, case report forms, adverse event narratives

This table does not include subjects who discontinued treatment prior to receiving four days of conivaptan. Those study subjects are captured in the Table 7.1.2.1 above for the Full Safety Population, in the IV conivaptan column. The adverse events in the three "Full Exposure" studies which resulted in discontinuation of conivaptan prior to the study

subject having received four full days included one case each of respiratory arrest, hepatic failure and sepsis.

Serious renal adverse events occurred with significantly higher frequency among subjects receiving the full planned labeling dose of conivaptan than among placebo subjects; this is discussed further in section 7.1.2.4.3.

Table 7.1.2.3 examines serious adverse events in the sponsor's major controlled IV and oral efficacy trials.

Table 7.1.2.3: Serious Treatment-Emergent Adverse Events, Phase 3 Controlled IV and Oral Hyponatremia Trials, with Number and Percentage of Patients Experiencing Each Type of Event													
		Controlled IV Hyponatremia (-027)				Controlled Oral Hyponatremia (-026 and -043)				Combined Oral and IV Hyponatremia			
		Pbo n (%) (n=29)	Coni 40[1] n (%) (n=29)	Coni 80[2] n (%) (n=26)	All IV Coni n (%) (n=55)	Pbo n (%) (n=53)	Coni 40 n (%) (n=51)	Coni 80 n (%) (n=53)	All Oral Coni n (%) (n=103)	All Pbo n (%) (n=82)	All Coni 40 n (%) (n=80)	All Coni 80 n (%) (n=79)	All Coni n (%) (n=159)
Organ System	Event Term												
Cardiac		3 (10.3)	3 (10.3)	2 (7.7)	5 (9.1)	1 (1.9)	5 (9.8)	1 (1.9)	6 (5.8)	4 (4.9)	8 (10.0)	3 (3.8)	11 (6.9)
	Acute MI					1 (1.9)				1 (1.2)			
	AV Block		1 (3.5)		1 (1.8)						1 (1.3)		1 (0.6)
	Cardiac Failure NOS						3 (5.9)		3 (2.9)		3 (3.8)		3 (1.9)
	Cardiac Failure Chronic						1 (2.0)		1 (1.0)		1 (1.3)		1 (0.6)
	Cardiac Failure Congestive	1 (3.5)	1 (3.5)	2 (7.7)	3 (5.5)			1 (1.9)	1 (1.0)	1 (1.2)	1 (1.3)	3 (3.8)	4 (2.5)
	Congestive Cardiac Failure Aggravated	1 (3.5)	1 (3.5)	2 (7.7)	3 (5.5)			1 (1.9)	1 (1.0)	1 (1.2)	1 (1.3)	3 (3.8)	4 (2.5)
	Sick Sinus Syndrome	1 (3.5)								1 (1.2)			
	SV Arrhythmia NOS	1 (3.5)								1 (1.2)			
	SVT						1 (1.8)				1 (1.3)		1 (0.6)
	V Tach						1 (1.8)				1 (1.3)		1 (0.6)
Cardiac Procedures						1 (1.9)	1 (2.0)		1 (1.0)	1 (1.2)	1 (1.3)		1 (0.6)
	Cardioversion					1 (1.9)				1 (1.2)			
	Heart Transplant						1 (2.0)		1 (1.0)		1 (1.3)		1 (0.6)
Vascular Disorders		2 (6.9)	2 (6.9)		2 (3.6)		2 (3.9)	1 (1.9)	2 (1.9)	2 (2.4)	4 (5.0)	1 (1.3)	5 (3.1)
	Arterial Occlusion	1 (3.4)								1 (1.2)			
	Deep Vein Thrombosis		2 (6.9)		2 (3.6)						2 (2.5)		2 (1.3)
	Hypertension							1 (1.9)	1 (1.0)			1 (1.3)	1 (0.6)

Table 7.1.2.3: Serious Treatment-Emergent Adverse Events, Phase 3 Controlled IV and Oral Hyponatremia Trials, with Number and Percentage of Patients Experiencing Each Type of Event													
		Controlled IV Hyponatremia (-027)				Controlled Oral Hyponatremia (-026 and -043)				Combined Oral and IV Hyponatremia			
		Pbo n (%) (n=29)	Coni 40[1] n (%) (n=29)	Coni 80[2] n (%) (n=26)	All IV Coni n (%) (n=55)	Pbo n (%) (n=53)	Coni 40 n (%) (n=51)	Coni 80 n (%) (n=53)	All Oral Coni n (%) (n=103)	All Pbo n (%) (n=82)	All Coni 40 n (%) (n=80)	All Coni 80 n (%) (n=79)	All Coni n (%) (n=159)
Organ System	Event Term												
	NOS												
	Hypotension NOS	1 (3.4)					2 (3.9)		2 (1.9)	1 (1.2)	2 (2.5)		2 (1.3)
GI		1 (3.5)								1 (1.2)			
	GI Hemorrhage NOS	1 (3.5)								1 (1.2)			
General Disorders			1 (3.4)		1 (1.8)	2 (3.8)		1 (1.9)	1 (1.0)	2 (2.4)	1 (1.3)	1 (1.3)	2 (1.3)
	Anasarca		1 (3.4)		1 (1.8)						1 (1.3)		1 (0.6)
	Edema NOS		1 (3.4)		1 (1.8)						1 (1.3)		1 (0.6)
	Edema Peripheral							1 (1.9)	1 (1.0)			1 (1.3)	1 (0.6)
	Pain NOS					1 (1.9)				1 (1.2)			
Hepatobiliary			1 (3.4)		1 (1.8)		1 (2.0)		1 (0.9)		2 (2.5)		2 (1.3)
	Cholestasis						1 (2.0)		1 (0.9)		1 (1.3)		1 (0.6)
	Hepatic Failure		1 (3.4)		1 (1.8)						1 (1.3)		1 (0.6)
	See Lab and VS below for LFTs												
Infection			1 (3.4)	2 (7.7)	3 (5.5)						1 (1.3)	2 (2.5)	3 (1.9)
	Pneumonia			2 (7.7)	2 (3.6)							2 (2.5)	2 (1.3)
	Sepsis NOS		1 (3.4)		1 (1.8)						1 (1.3)		1 (0.6)
Procedural Complication						1 (1.9)				1 (1.2)			
	Postprocedural hemorrhage					1 (1.9)				1 (1.2)			
Lab and VS				1 (3.8)	1 (1.8)	1 (1.9)	2 (3.9)		2 (1.9)	1 (1.2)	2 (2.5)	1 (1.3)	3 (1.9)
	ALT incr						1 (2.0)		1 (0.9)		1 (1.3)		1 (0.6)
	AST incr					1 (1.9)	1 (2.0)		1 (0.9)	1 (1.2)	1 (1.3)		1 (0.6)
	Liver Function			1 (3.8)	1 (1.8)							1 (1.3)	1 (0.6)

Table 7.1.2.3: Serious Treatment-Emergent Adverse Events, Phase 3 Controlled IV and Oral Hyponatremia Trials, with Number and Percentage of Patients Experiencing Each Type of Event													
		Controlled IV Hyponatremia (-027)				Controlled Oral Hyponatremia (-026 and -043)				Combined Oral and IV Hyponatremia			
		Pbo n (%) (n=29)	Coni 40[1] n (%) (n=29)	Coni 80[2] n (%) (n=26)	All IV Coni n (%) (n=55)	Pbo n (%) (n=53)	Coni 40 n (%) (n=51)	Coni 80 n (%) (n=53)	All Oral Coni n (%) (n=103)	All Pbo n (%) (n=82)	All Coni 40 n (%) (n=80)	All Coni 80 n (%) (n=79)	All Coni n (%) (n=159)
Organ System	Event Term												
	Test Abnl												
	BP decr					1 (1.9)	1 (2.0)		1 (0.9)	1 (1.2)	1 (1.3)		1 (0.6)
Metab and Nutr		2 (6.8)	2 (6.8)		2 (3.6)		2 (3.9)		2 (1.9)	2 (2.4)	4 (5.0)		4 (2.5)
	Dehydration		1 (3.4)		1 (1.8)						1 (1.3)		1 (0.6)
	Hypovolemia		1 (3.4)		1 (1.8)		1 (2.0)		1 (1.0)		2 (2.5)		2 (1.3)
	Hyperkalemia	1 (3.4)								1 (1.2)			
	Hyponatremia	1 (3.4)	1 (3.4)		1 (1.8)		1 (2.0)		1 (1.0)	1 (1.2)	2 (2.5)		2 (1.3)
Neoplasms						1 (1.9)				1 (1.2)			
	Metastatic Carcinoma					1 (1.9)				1 (1.2)			
Neurologic			1 (3.4)		1 (1.8)						1 (2.5)		1 (0.6)
	Confusional State		1 (3.4)		1 (1.8)						1 (2.5)		1 (0.6)
Renal		1 (3.4)	4 (13.8)	3 (11.5)	7 (12.7)		3 (5.9)	1 (1.9)	4 (3.9)	1 (1.2)	7 (8.8)	4 (5.1)	11 (6.9)
	Renal disorder NOS		2 (6.9)		2 (3.6)		1 (2.0)		1 (1.0)		3 (3.8)		3 (1.9)
	Renal Failure NOS	1 (3.4)					1 (2.0)		1 (1.0)	1 (1.2)	1 (2.5)		1 (0.6)
	Renal Failure Acute			1 (3.8)	1 (1.8)							1 (1.3)	1 (0.6)
	"Acute renal injury"[5]		2 (6.9)	2 (7.7)	4 (7.3)		1 (2.0)	1 (1.9)	2 (1.9)		3 (3.8)	3 (3.8)	6 (3.8)
Reproductive				1 (3.8)	1 (1.8)							1 (1.3)	1 (0.6)
	Ovarian Mass			1 (3.8)	1 (1.8)							1 (1.3)	1 (0.6)
Respiratory		1 (3.4)	1 (3.4)		1 (1.8)		2 (3.9)		2 (1.9)	1 (1.2)	1 (2.5)	2 (2.5)	3 (1.9)
	COPD Exacerbation						1 (3.9)		1 (1.0)		1 (2.5)		1 (0.6)
	Dyspnea							1 (1.9)	1 (1.0)			1 (1.3)	1 (0.6)

Table 7.1.2.3: Serious Treatment-Emergent Adverse Events, Phase 3 Controlled IV and Oral Hyponatremia Trials, with Number and Percentage of Patients Experiencing Each Type of Event

		Controlled IV Hyponatremia (-027)				Controlled Oral Hyponatremia (-026 and -043)				Combined Oral and IV Hyponatremia			
		Pbo n (%) (n=29)	Coni 40[1] n (%) (n=29)	Coni 80[2] n (%) (n=26)	All IV Coni n (%) (n=55)	Pbo n (%) (n=53)	Coni 40 n (%) (n=51)	Coni 80 n (%) (n=53)	All Oral Coni n (%) (n=103)	All Pbo n (%) (n=82)	All Coni 40 n (%) (n=80)	All Coni 80 n (%) (n=79)	All Coni n (%) (n=159)
Organ System	**Event Term**												
	Hypercapnia						1 (3.9)		1 (1.0)		1 (2.5)		1 (0.6)
	Pulmonary Embolism							1 (1.9)	1 (1.0)			1 (1.3)	1 (0.6)
	Respiratory Arrest	1 (3.4)	1 (3.4)		1 (1.8)					1 (1.2)	1 (2.5)		1 (0.6)

1 Conivaptan 40 mg/day
2 Conivaptan 80 mg/day
3 Blood pressure decreased, hypotension, dehydration, hypovolemia
4 Acute MI, AV block, all cardiac failure terms, all arrhythmia terms, blood pressure decreased, hypotension, dehydration, hypovolemia, pulmonary embolism, deep vein thrombosis, cardioversion, heart transplant
5 See Section 7.1.2.4.3 for definition of "acute renal injury"

Prior to evaluation of the sponsor's serious adverse event data, the reviewer planned to examine groups of event terms possibly related to hypovolemia, cardiac failure, arrhythmia, total cardiovascular events, renal adverse events, muscle adverse events, neuropsychiatric events, and bleeding events. The reviewer found these terms of interest in advance of review for the following reasons:

- Brisk aquaresis with conivaptan might lead to hypovolemic events.
- The potential for volume depletion also prompted interest in renal terms to look for an excess of prerenal renal dysfunction. Renal tubular necrosis seen in short-term IV animal studies at four times the proposed human therapeutic exposure (from healthy subject PK data) was also of concern, especially since CHF patients have higher exposure than healthy subjects and nonCHF patients.
- The medical literature indicates interest in the use of conivaptan for the treatment of CHF; adverse cardiac failure events are therefore of interest. This concern also led to examination of the grouping of all cardiovascular event and procedure terms
- Mild HERG channel study findings prompted examination of arrhythmia terms.
- The finding of CYP3A4 inhibition by conivaptan prompted concern regarding the potential for interaction with statins, and thus examination of the data for possible myopathic events.
- The potential for neurologic consequences of overly rapid sodium correction led to grouping of potentially related neuropsychiatric events.
- Bleeding events were examined because DDAVP, an AVP *agonist*, is used in the treatment of von Willebrand's disease. Since this AVP *agonist* has procoagulant effects, the reviewer wanted to look for potential *anticoagulant* effects of the vasopressin receptor *antagonist*, conivaptan.

After serious adverse event data review, the reviewer noted differences in rates of infection and respiratory adverse events.

These selected groups of adverse event terms are summarized in the following table:

Table 7.1.2.4: Serious Adverse Event Groupings of Special Interest, Full Safety Population

Event Term Group	IV		Oral		IV + Oral	
	Pbo n (%) n = 92	Coni n (%) n = 208	Pbo n (%) n = 240	Coni n (%) n = 688	Pbo n (%) n = 332	Coni n (%) n = 896
All SAE Terms Possibly Related to Hypovolemia[1]	2 (2.2)	6 (2.9)	2 (0.8)	19 (2.8)	4 (1.2)	25 (2.8)
All Cardiac Failure SAE Terms[2]	3 (3.3)	9 (4.3)	5 (2.1)	18 (2.6)	8 (2.4)	27 (3.0)
All Arrhythmia SAE Terms[3]	5 (5.4)	5 (2.4)	1 (0.4)	7 (1.0)	6 (1.8)	12 (1.3)
All Serious Cardiovascular Event and Procedure Terms[4]	12 (13.0)	22 (10.6)	12 (5.0)	52 (7.5)	24 (7.2)	74 (8.3)
All Renal SAE Terms[5]	1 (1.1)	9 (4.3)	0	18 (2.6)	1 (0.3)	27 (3.0)
All Muscle SAE Terms[6]	0	0	0	5 (0.7)	0	5 (0.6)
All Neuropsychiatric AE Terms[7]	0	2 (1.0)	0	5 (0.7)	0	7 (0.8)
All Bleeding SAEs[8]	1 (1.1)	0	1 (0.4)	2 (0.3)	2 (0.6)	2 (0.2)
All Infection SAEs[9]	3 (3.3)	14 (6.7)	1 (0.4)	9 (1.3)	4 (1.2)	23 (2.6)

Table 7.1.2.4: Serious Adverse Event Groupings of Special Interest, Full Safety Population

Event Term Group	IV		Oral		IV + Oral	
	Pbo n (%) n = 92	Coni n (%) n = 208	Pbo n (%) n = 240	Coni n (%) n = 688	Pbo n (%) n = 332	Coni n (%) n = 896
All Respiratory SAEs[10]	2 (2.2)	7 (3.4)	1 (0.4)	13 (1.9)	3 (0.9)	20 (2.2)

[1] Includes hypotension, BP decr, BUN:Cr ratio incr, dehydration, hypovolemia, syncope, vasovagal syncope, fall
[2] Includes cardiac failure NOS, cardiac failure acute, cardiac failure congestive, cardiopulmonary failure, pulmonary edema NOS, acute pulmonary edema and congestive cardiac failure aggravated
[3] Includes arrhythmia NOS, AV block NOS, AV block complete, bradycardia NOS, sick sinus syndrome, sinus arrhythmia, SV arrhythmia NOS, SVT, V fib and V tach
[4] Includes acute coronary syndrome, acute MI, MI, angina pectoris, angina unstable, cardiac arrest, ischaemic cardiomyopathy, cardiorespiratory arrest, cardiogenic shock, coronary artery disease NOS, cardioversion, heart transplant, arterial occlusion, deep vein thrombosis, chest pain, hypotension, BP decr, CVA, jugular vein thrombosis and all terms in [2] and [3] above
[5] Includes renal disorder NOS, renal failure NOS, renal failure acute, BUN:Cr ratio incr, and "acute renal injury". See Section 7.1.2.4.3 for definition of "acute renal injury"
[6] Includes myalgia, rhabdomyolysis and CPK incr
[7] Includes CVA, grand mal convulsion, confusional state, mental status changes and psychotic disorder
[8] Includes coagulopathy, GI hemorrhage NOS, anastomotic leak and postprocedural hemorrhage
[9] Includes influenza-like illness, abdominal abscess, appendicitis, bronchial infection, bronchitis acute NOS, cellulitis, infection NOS, pneumonia NOS, purulent pericarditis, pyothorax, sepsis NOS, sinusitis NOS, upper respiratory tract infection NOS and urinary tract infection NOS
[10] Includes acute pulmonary edema, COPD, COPD exacerbated, dyspnea, dyspnea exacerbated, hypercapnia, pleural effusion, pulmonary edema NOS, respiratory arrest, respiratory failure, bronchitis NOS, bronchial infection, bronchitis acute NOS, upper respiratory tract infection NOS and pneumonia

Source: Extracted from Sponsor's Table 2.7.4-129, Module 5, Section 5.3.3.5, beginning p 1386

Among the groups of event terms of special interest, arrhythmia and bleeding SAEs actually occurred slightly numerically more frequently in placebo-treated subjects than in conivaptan-treated subjects. Total serious cardiovascular event and procedure terms occurred with similar frequency between conivaptan and placebo subjects. Muscle-related events are further discussed in Section 7.1.3.3.6.

The remaining terms are discussed in the following sections.

7.1.2.4.1 Serious Hypovolemia-related Event Terms, Full Safety Population

The clinical reviewer looked at all conivaptan group narratives for SAE terms which she had identified prior to review as possibly related to hypovolemia (see Table 7.1.2.4, footnote 1 for terms). Serious hypovolemia-related SAEs occurred more frequently in conivaptan group subjects than in placebo group subjects in Study -027, the pool of all Phase 3 hyponatremia trials, and the full safety population. In the full safety population, this difference was statistically significant. Brief summaries follow of those cases which are, in the reviewer's opinion, possibly related to conivaptan.

Also see death narratives above for Subjects 026-0060708 and 043-0231339.

Subject 020-0015003: 70 year old woman with underlying idiopathic dilated cardiomyopathy, NYHA class III. Patient's screening visit form (page 17 of 97) states

that her screening blood pressure was 90/60, but there is a handwritten note stating that "under normal conditions patient is normotensive". Systolic BP <100 mm Hg was an exclusion criterion. She also had a baseline creatinine of 207.7 μmol/L (2.3 mg/dL); a serum creatinine of >2.5 mg/dL was an exclusion criterion at the time of her screening. The patient was randomized and received 5 mg oral conivaptan po BID. However, page 52 of 97 of the CRF states "pt was randomized before monitor realized protocol violations". Was also taking lisinopril, digitoxin, allopurinol, xipamid, furosemide and cardevilol. On Study Day 4, patient was hospitalized with worsening renal function, diarrhea and vomiting. On Study Day 8, serum Cr had increased to 4.8 mEq/L and BP was 84/30. Conivaptan was discontinued. Underwent hemofiltration. Study medication not restarted; discharged on Study Day 15 with blood pressure and Cr at baseline.

Subject 020-0027012: 48 year old man with congestive heart failure, received conivaptan 20 mg po BID. Progressive renal deterioration was noted from Study Day 29 (while still on conivaptan). Hospitalized with BUN 53, Cr 6.4 mg/dL. Supine blood pressure 102/62; standing blood pressure not in the portion of the CRF provided. Conivaptan and diuretics discontinued. Received IV fluids for three days. Diuretics restarted at a reduced dose; patient discharged from hospital on Study Day 62, still not on conivaptan. Conivaptan was resumed on Study Day 68. "To date the patient recovered without sequelae." It appears that this was as of Study Day 143, although it is difficult to tell from the case report form. It should be noted that only 153/193 pages of the case report form were included in the NDA.

Subject 020-0039003: 72 year old man with congestive heart failure received conivaptan 40 mg/day. Hospitalized due to several fainting episodes. First faint occurred on Treatment Day four; withdrew from the trial due to recurrent fainting on Treatment Day 27; hospitalized for orthostatic hypotension on Study Day 31. Fainted again Study Day 32. Narrative states that patient's physician felt the patient's fainting episodes were due to his history of ventricular tachycardia, and his amiodarone dose was adjusted. Narrative states "Amiodarone was increased from 200 mg daily to 2400 (sic) mg daily until day 34, and further stabilised at 400 mg daily."

Subject 026-0061301: 38 year old man with schizophrenia and hyponatremia related to psychogenic polydipsia. Screening supine and standing blood pressures 105/65 and 105/60. At end of baseline, supine and standing blood pressures 144/94 and 126/104. Baseline urine output 10,000 mL/day. Screening serum sodium 131 mEq/L (maximum for inclusion criterion = 130). At end of baseline, serum sodium 139 mEq/L (page 9 of 52, case report form). Under protocol, patient should not have entered the treatment phase, because serum sodium was not <130. However, received oral conivaptan 40 mg/day. After first dose, supine blood pressure was 94/60 and standing blood pressure was 80/50; asymptomatic. Treatment Day 1 urine output 10,500 mL. Next dose of conivaptan held; additional fluids permitted. Narrative states patient drank as much as 12-13 liters/day after that. However, CRF states that fluid intake on baseline day was 1300 mL; day 1 = 1890 mL, day 2 = 2890 mL, day 3 = 2760 mL, day 4 = 8260 mL and day 5 = 6160 mL. On Study Day 2, serum sodium 142 mEq/L, 24 hour urine output 13,000 mL. On Study Day 2 (case report form) or Study Day 5 (narrative), conivaptan

reportedly resumed at 20 mg/day and continued until 5 days total dosing. On Study Day 5, serum sodium was 141, and 24 hour urine output was 13,500. No further hypotension. On Study Day 10, serum sodium was 123 mEq/L.

Subject 026-0062601: 53 year old man with SIADH. Baseline urine output 2900 mL/day. Received oral conivaptan 40 mg/day for 5 days. Day 5 urine output 3800 mL/day. Discharged to home. One day after last dose of conivaptan, lost consciousness at home and was hospitalized for "severe hypotension". Antihypertensive medication doses reduced and patient recovered.

Subject 027-0071701: 74 year old woman with underlying congestive heart failure, hospitalized with acute bronchitis. During hospitalization, developed hyponatremia and randomized to IV conivaptan 40 mg/day. On day two of conivaptan treatment, complained of thirst and developed elevated BUN and creatinine. Peripheral leg edema and jugular venous congestion present on admission resolved. Given 0.3% sodium chloride; spironolactone, furosemide and captopril tapered and discontinued. Conivaptan was not discontinued; protocol called for four days of treatment. Recovered and discharged on Study Day seven. Ten days after last dose of conivaptan, readmitted with dehydration, BUN 67 mg/dL, Cr 2.4 mg/dL. Recovered with fluid therapy and discharged with Cr 1.75 after four days. The clinical reviewer added this case to the renal AEs.

Subject 027-0075601: 69 yo woman. No case report form. Received 80 mg/day IV. On Study Day 1, developed hypotension, which lasted for 1.5 days, and oliguria. Blood pressures as low as 60/40 were documented on Study Day 2. Patient had high conivaptan levels (see Table 7.1.2.4.3.1).

Subject 034-0011005: 54 year old woman with congestive heart failure and osteoporosis. Received conivaptan 80 mg/day. On Study Day 2, started alendronate, estrogen and progesterone. On conivaptan day 29, patient discontinued alendronate, estrogen and progesterone due to persistent nausea and fatigue. On that day, found to have serum potassium 4.4 mEq/L, BUN 40 and Cr 1.5. Patient hospitalized for "dehydration". Received IV fluids; diuretics held. Conivaptan not held. Discharged after one day in hospital. On Study Day 31, serum creatinine 2.4. On Study Day 49, serum Cr 2.7; conivaptan permanently discontinued.

Subject 034-0015002: 55 year old man with congestive heart failure. Screening creatinine 1.7, BUN 31. Received conivaptan 40 mg po BID. Treatment Day 29, BUN 44, Cr 2.3. On approximately Treatment Day 30, patient had sudden loss of consciousness lasting "a few minutes"; no nausea, vomiting, incontinence, or postictal state. After office visit on Treatment Day 41, hospitalized for evaluation of cause of syncope; also noted to have "decreasing renal function". On ECG, sinus bradycardia with first degree AV block and LBBB. Pulmonary capillary wedge pressure low at 8; EF 17%. Diuretics discontinued; renal function improved. Permanent pacemaker placed on Treatment Day 52 and discharged on Treatment Day 53. Study medication not interrupted. The clinical reviewer added this case to the renal AEs.

Subject 034-030006: 46 year old man with congestive heart failure who was receiving conivaptan 20 mg po BID. On day 84 of conivaptan treatment, had a syncopal episode, without injury, which the investigator believed was related to hypovolemia. Patient recovered, and study medication was not discontinued.

Subject 034-0068016: 48 year old man with congestive heart failure, on oral conivaptan 40 mg po BID. On Study Day 47, conivaptan discontinued due to hypotension and dehydration. Hospitalized on Study Day 50 with systolic blood pressure 84 mm Hg. Received IV fluids; discharge on Study Day 53. Conivaptan resumed.

The one reported case of "fall" (subject 034-0002008) did not appear to be related to hypovolemia on review.

Among the other hypovolemia-related events which the clinical reviewer did not feel were likely to be related to conivaptan, the most common reason for the reviewer's conclusion was that the event occurred many days after discontinuation of conivaptan, well after any expected residual pharmacologic effect. Even when taking these cases out of consideration, hypovolemia-related events occurred more frequently in the conivaptan-treated subjects than in placebo-treated subjects.

In the clinical reviewer's opinion, conivaptan may cause significant hypovolemia with attendant serious adverse events such as decline in renal function. This appeared to occur more frequently in patients with congestive heart failure who were also taking diuretics. The consequences of these hypovolemia events were usually, but not always, reversible, and one patient died. Careful monitoring of volume status appears warranted, and caution is needed when administering conivaptan to congestive heart failure patients.

Serious Hypovolemia-related Event Terms, "Full Dose" Population

In the subset of subjects (n = 63) who received the full dose regimen proposed for labeling, one hypovolemia-related event occurred in the placebo group (3.4%) and two such events occurred in the conivaptan group (3.2%). The total number of study subjects in this group is insufficient for safety analysis.

7.1.2.4.2 Serious Cardiac Failure-related Event Terms, Full Safety Population

The clinical reviewer looked at all conivaptan group narratives for SAE terms which she had identified prior to review as possibly related to cardiac failure (see Table 7.1.2.4, footnote 2, for terms). As shown above in Table 7.1.2.4, cardiac failure SAE terms occurred more frequently among conivaptan patients than among placebo patients for Study -027, the pool of all Phase 3 hyponatremia trials, and the full safety population. Brief summaries follow for all cardiac failure SAEs which the reviewer considered possibly related to conivaptan.

Also see death narratives for Subjects 016-0000110, 026-0060103, 026-0060708, 027-0075801 and 047-0231326.

Subject 020-0005007: 42 year old man with ischemic cardiomyopathy and history of multiple myocardial infarctions. Treated with conivaptan 5 mg po BID. Narrative states that on Treatment Day 90, hospitalized with angina, worsening heart failure, ascites, and edema. Doses of furosemide and enalapril reduced; given IV solinitrine, morphine and dopamine. Study drug temporarily discontinued. Discharged on Treatment Day 98. Although the SAE narrative states that the event began on Treatment Day 90, the case report form documents increasing leg edema from at least as early as Treatment Day 45. Although the SAE listing and narrative did not mention a decline in renal function, the fact that the patient was treated for an exacerbation of CHF with *reduction* in doses of furosemide and enalapril led the clinical reviewer to wonder whether a decline in renal function had occurred. Examination of the individual case report tabulation laboratory data revealed the following serum creatinine values:

[redacted] 1.24 mg/dL
1.31
1.4
): 1.46
1.82
[redacted]. 2.67 (last recorded value)

Therefore, the clinical reviewer added this case to the events of worsening renal function.

Subject 020-0030002: 47 year old man with underlying NYHC III CHF, hypertrophic cardiomyopathy. Received 10 mg oral conivaptan BID. On Treatment Day 32, hospitalized with progression of CHF to NYHC IV, dyspnea, hepatomegaly and pleural effusion. Treated with IV furosemide and spironolactone. On Day 37, dobutamine added. On Day 39, study med permanently discontinued. Back to NYHC III after Study Day 43.

Subject 020-0031009: 70 year old man with history CHF. Received oral conivaptan 10 mg BID. On Treatment Day 29, hospitalized for progression of heart failure, with nocturnal dyspnea, and dyspnea after minimal exertion. Treated with IV furosemide; discharged on Study Day 36. Study med not discontinued.

Subject 020-0038001: 79 year old man with underlying ischemic CHF. Received conivaptan 10 mg po bid. On Treatment Day 28, developed aggravated combined right and left heart failure. Hospitalized Study Day 34 and treated with IV furosemide and fluid restriction. Discharged at his CHF baseline on Day 38. Study drug not interrupted.

Subject 020-0051005: 80 year old man with history of CHF. Received oral conivaptan 10 mg bid. Hospitalized Treatment Day 24 with worsening heart failure. Treated with intravenous bumetanide; discharged on Study Day 37.

Subject 025-0001004: 57 year old man with CHF NYHC IV, idiopathic cardiomyopathy. Received IV conivaptan 100 mg IV on Treatment Day 1, followed by 80 mg/day on

Treatment Days 2-5. On Study Day 10, developed decompensated CHF. Study Day 12, placed on left ventricular assist device. Conivaptan not stopped; final outcome unknown.

Subject 026-0064602: 73 year old man with NYHC III CHF. Received oral conivaptan 80 mg/day for five days. Rehospitalized five days after last dose of conivaptan for worsening CHF and worsening renal function, with Cr 2.52 mg/dL. Outcome not reported.

Subject 027-0075807: 78 year old woman with known aortic stenosis and AoVR. Receiving 40 mg/day IV conivaptan for four days. Three days after last dose of conivaptan, readmitted with congestive heart failure and pleural effusion. Discharged home three days later. Readmitted on Study Day 13 (8 days after last dose of conivaptan) with confusion and serum sodium 121 mEq/L, which decreased further to 119. Treated with hypertonic saline and mental status normalized.

Subject 047-0233101: 52 year old man with dilated cardiomyopathy and history of v tach. Received 80 mg/day oral conivaptan. On Treatment Day 220, hospitalized with worsening congestive heart failure and increase in serum creatinine from baseline of 1.48 mg/dL to 2.15. Treated with IV dobutamine. Study medication discontinued on Treatment Day 255 in anticipation of heart transplant. Successful heart transplant Study Day 256. Study Day 262 creatinine 1.37. Clinical reviewer added this case to the events of decline in renal function.

Upon review of all cardiac failure-related events for study subjects in conivaptan groups, 14 appear possibly related to conivaptan. The most common reason that the clinical reviewer did not feel an event was likely related to conivaptan was a long interval from last administration of conivaptan to onset of event. Serious cardiac failure event terms occurred more frequently in conivaptan subjects than in placebo subjects in Study -027 (4.3% vs 3.3%), the pool of Phase 3 hyponatremia trials (2.6% vs 2.1%), and the full safety population (3.0% vs 2.4%). In addition to the safety implications of this signal, it also underscores the need for establishment of the lowest effective dose of conivaptan, because conivaptan exposure is 8-fold higher in congestive heart failure patients than in healthy subjects,

Serious Cardiac Failure-related Adverse Event Terms, "Full Dose" Population

In the subset of subjects (n = 63) who received the full dosing regimen proposed for marketing, one cardiac failure-related serious adverse event occurred in the placebo group (3.4%), and three events occurred in the conivaptan group (4.5%). The total number of subjects in the subsets is insufficient for safety evaluation.

7.1.2.4.3 Serious Renal Adverse Event Terms, Full Safety Population

Serious renal adverse event terms occurred more frequently among subjects treated with conivaptan than subjects treated with placebo in the pool of controlled Phase 3 hyponatremia trials [11/159 (6.9%) vs 1/82 (1.2%)] and in the full safety population

[27/896 (3.0%) vs 1/332 (0.3%)]. For the full safety population, this difference was statistically significant.

In the medical literature, consensus does not exist for the definition of a serious renal adverse event. As discussed in the laboratory section 7.1.7.3.1, Cox defines a significant rise in serum Cr as an increase of 0.5 mg/dL, or an increase of 25% from baseline (Cox 2002). The clinical reviewer used this sensitive definition in the review of serum creatinine laboratory changes. However, for review of renal adverse events, the clinical reviewer desired a fairly specific (rather than sensitive) definition of a renal SAE, in order to determine if there was a difference in renal adverse events that were likely to be of clinical significance. The clinical reviewer chose Bellomo's recent definitions for acute renal injury and acute renal failure (Bellomo 2004). Bellomo uses serum Cr to define "acute renal risk" as Cr >1.5x baseline; "acute renal injury" as a doubling of baseline Cr; and "acute renal failure" as a tripling of baseline Cr, or any Cr > 4 mg/dL that is also 0.5 mg/dL over the patient's baseline. The clinical reviewer searched all laboratory in the safety case report tabulations, and found all patients who met criteria for acute renal failure or acute renal injury. The clinical reviewer did not include those with "acute renal risk" in the following discussion. During the laboratory search, the clinical reviewer was blinded to treatment assignment.

The following table includes all patients who, in the clinical reviewer's opinion, had a serious renal adverse event by one or more of the following criteria:
1 Acute renal failure by Bellomo criteria
2 Acute renal injury by Bellomo criteria
3 Renal adverse event designated as a serious adverse event by the sponsor
4 Additional cases noted by the clinical reviewer during review of other events, where the patient was admitted because of worsening renal function or had reported sustained oliguria

By these criteria, 27/896 (3.0%) of conivaptan-treated patients, and 1/332 (0.3%) of placebo patients developed serious renal adverse events in the full safety population of Phase 2 and Phase 3 studies.

Table 7.1.2.4.3.1: All Serious Renal Adverse Events, Full Safety Population

ID	Why SAE?[5]	Tx	Tx Start Date	Tx Stop Date	BL[6] Cr	BL Date	1st Cr ≥2x BL[7]	Date of 1st Cr ≥2x BL[8]	1st Cr >4 mg/dL[9]	Date of 1st Cr > 4 mg/dL[10]	Max Cr	Max Cr Date	?CHF	Outcome
17-3015	2	40 mg/day oral			0.7						1.9		yes	no case report form: Cr 1.3
20-5007	2,4	10 mg/day oral			1.2						2.7		yes	2.7 = last recorded Cr
***20-15003**	1,3	10 mg/day oral			2.3						4.8		yes	dialysis, hosp admission; permanent discontinuation of study drug
***20-27012**	1,2,3	40 mg/day oral			1.6						6.4		yes	hosp admission Study Day 57; temporary discontinuation; states renal fxn recovered
***25-1002**	3	40 mg/day IV			2.3						CRF states ARF; Cr not recorded		yes	heart transplant Study Day 8; arrested and died on Study Day 20
***26-60103**	3	40 mg/day oral			2.1						CRF states ARF; Cr not recorded		yes	hosp admission; renal failure worsened; dialysis; died on Study Day 22 of CHF
26-60708	2,4	40 mg/day oral			0.8						1.9		yes	decreased UO, incr K Study Day 2; arrested and died on Study Day 10 due to CHF
26-62902	2	80 mg/day oral			1.1		2.4				3.0		no	unknown
27-71603	2,4	40 mg/day IV			0.7						1.9		no	no case report form: oliguria noted Study Days 2-3; conivaptan plasma concentration 2010 ng/mL (>1000 = high); sp gr 1.015 Day 4, neg bld
27-71701	4	40 mg/day IV			1.5						?2.4		yes	Cr increased Study Day 2; resolved with hydration; readmitted Study Day 14 with dehydration and incr Cr; Cr decreased to 1.8 by Study Day 18
27-	4	80 mg/day			0.8						states		yes	CRF states patient had

Table 7.1.2.4.3.1: All Serious Renal Adverse Events, Full Safety Population

ID	Why SAE?[5]	Tx	Tx Start Date	Tx Stop Date	BL[6] Cr	BL Date	1st Cr ≥2x BL[7]	Date of 1st Cr ≥2x BL[8]	1st Cr >4 mg/dL[9]	Date of 1st Cr > 4 mg/dL[10]	Max Cr	Max Cr Date	?CHF	Outcome
75601		IV x 1 day; then 40 mg/day									sustained oliguria: Cr not recorded			sustained oliguria; hypotension; plasma concentration conivaptan = 2092 ng/mL (high = >1000; [redacted] sp gr 1.020, sm bld
***27-75801**	3	80 mg/day IV			1.4						CRF states ARF; Cr not recorded		yes	died on Study Day 6 of pneumonia and CHF; conivaptan plasma concentration 8850 ng/mL (>1000 = high)
27-75806	2	40 mg/day IV			0.6						1.5		no	metastatic GB cancer; developed jaundice and hypotension on Study Day 3 and died
27-76201	2	80 mg/day IV			0.7						1.4		no	case report form does not mention renal dysfunction; had conivaptan plasma concentration 3019 ng/mL (>1000 = high)
27-76202	2	80 mg/day IV			0.6		1.4				1.7		no	no case report form; had conivaptan plasma concentration 4249 ng/mL (>1000 = high); urine SG 13 Dec = 1.010 with Cr 1.5
***27-77208**	3	Pbo			2.4						CRF states decr renal function and dialysis; Cr not recorded		yes	dialysis without recovery; death from heart failure Study Day 9
***33-7004**	1,2,4	40 mg/day oral			2.0				4.2		5.3		yes	CRF does not mention renal function; [redacted] = last recorded Cr. UA sp gr [redacted] = 1.010; neg bld
***34-7021**	3	20 mg/day oral			1.5						states ARF; Cr not reported		yes	hosp admission; temporary discontinuation; Cr 1.4 o[redacted]

Table 7.1.2.4.3.1: All Serious Renal Adverse Events, Full Safety Population

ID	Why SAE?[5]	Tx	Tx Start Date	Tx Stop Date	BL[6] Cr	BL Date	1st Cr ≥2x BL[7]	Date of 1st Cr ≥2x BL[8]	1st Cr >4 mg/dL[9]	Date of 1st Cr > 4 mg/dL[10]	Max Cr	Max Cr Date	?CHF	Outcome
34-11005	2,4	80 mg/day oral	[redacted]		1.0	[redacted]	2.5	[redacted]			2.7	[redacted]	yes	admitted to hospital; permanent discontinuation
***34-13004**	3	40 mg/day oral			1.2						?2.7		yes	hosp admission Study Day 49; permanent discontinuation; K incr to 6.6 mol/L from baseline of 3.8; [redacted] Cr 1.5
***34-14003**	1,2	20 mg/day oral			0.5			[redacted]			1.8		yes	no case report form: last recorded Cr 1.6 on [redacted]
34-34012	2	40 mg/day oral	[redacted]		1.2	[redacted]					3.0		yes	no case report form; 3.0 is last recorded Cr
34-49028	3	40 mg/day oral			1.3						?2.5	[redacted]	yes	hosp admission Study Day 49; K 6.2; Cr 1.6 by Study Day 57
38-10001	2	20 mg/day IV			1.1		2.4				2.7		yes	case report form does not mention renal function; 2.7 is last recorded Cr
43-230401	2	40 mg/day oral			0.5			[redacted]			1.4		no	no case report form; hypotension [redacted] Cr 0.6
***47-230901**	3	40 mg/day oral			1.4						?2.7; states ARF		yes	hosp admission; Cr 1.5 [redacted]
47-233101	4	80 mg/day oral			1.5						?2.1		yes	admitted on Study Day 220 due to worsening renal function and CHF; heart transplant Study Day 256; Cr 1.4 Study Day 262
***47-233601**	1,2	80 mg/day oral	[redacted]		5.4	[redacted]			6.0	[redacted]	6.7	[redacted]	yes	no case report form; dialysis [redacted] study report states withdrew [redacted] due to lack of efficacy

* indicates case of acute renal failure, either by criteria (Bellomo 2004), or termed acute renal failure by sponsor

Table 7.1.2.4.3.1: All Serious Renal Adverse Events, Full Safety Population

ID	Why SAE?[5]	Tx	Tx Start Date	Tx Stop Date	BL[6] Cr	BL Date	1st Cr ≥2x BL[7]	Date of 1st Cr ≥2x BL[8]	1st Cr >4 mg/dL[9]	Date of 1st Cr > 4 mg/dL[10]	Max Cr	Max Cr Date	?CHF	Outcome

1 Meets criteria for acute renal failure (Bellomo 2004)
2 Meets criteria for acute renal injury (Bellomo 2004)
3 Sponsor designated as serious adverse event
4 Reviewer noted during review of a narrative for another event; patient admitted for worsening renal function or had sustained oliguria
5 Reason reviewer identified event as a serious renal adverse event
6 Baseline
7 If different from max Cr
8 If different from date of max Cr
9 If different from max Cr: shows first Cr > 4 mg/dL if BL < 4 mg/dL; if BL >4 mg/dL, shows first Cr >0.5 mg/dL over BL
10 If different from date of max Cr

In Study -027, 18/55 conivaptan-treated patients had conivaptan plasma levels >1000 ng/mL (4 in the 40 mg/day group and 14 in the 80 mg/day group). The highest reported plasma level in the 40 mg/day group was 2010 ng/mL (Patient 20-71603). Five of these 18 patients (27.8%) who had conivaptan plasma concentrations >1000 ng/mL developed a serious renal adverse event. One of the four patients in the 40 mg/day group who had a conivaptan plasma concentration >1000 ng/mL developed a serious renal adverse event.

After identifying the cases of serious renal adverse events in Table 7.1.2.4.3.1, the clinical reviewer summarized the categories and outcomes of these renal SAEs, by study population and when possible, by conivaptan dose. This summary is presented in the following table:

Table 7.1.2.4.3.2: Categories and Outcomes of Serious Renal Adverse Events, by Study Population and Dose

	Any Renal SAE	Acute Renal Failure	Acute Renal Injury	Other Renal SAE	New Hospitalization for Worsening Renal Function	CRF States DC of Coni	Dialysis	No Documented Reversal	Death Within 30 Days of Renal SAE
Study -027 (Pbo)	1/29 (3.4%)	1/29 (3.4%)	1/29 (3.4%)	0	0	1/29 (3.4%)	1/29 (3.4%)	1/29 (3.4%)	1/29 (3.4%)
Study -027 (40 mg/day)	4/29 (13.8%)	0	2/29 (6.9%)	2/29 (6.9%)	1/29 (3.4%)	1/29 (3.4%)	0	3/29 (10.3%)	1/29 (3.4%)
Study -027 (80 mg/day)	3/26 (11.5%)	1/26 (3.8%)	3/26 (11.5%)	0	0	0	0	3/26 (11.5%)	1/26 (3.8%)
Study -027 (all Coni)	7/55 (12.7%)	1/55 (1.8%)	5/55 (9.1%)	2/55 (3.6%)	1/55 (1.8%)	1/55 (1.8%)	0	6/55 (10.9%)	3/55 (5.5%)
Phase 3 Controlled HypoNa Trials (Pbo)	1/82 (1.2%)	1/82 (1.2%)	1/82 (1.2%)	0	0	1/82 (1.2%)	1/82 (1.2%)	1/82 (1.2%)	1/82 (1.2%)
Phase 3 Controlled HypoNa Trials (oral 40 mg/day)	3/51 (5.9%)	1/51 (2.0%)	2/51 (3.9%)	1/51 (2.0%)	1/51 (2.0%)	1/51 (2.0%)	1/51 (2.0%)	2/51 (3.9%)	2/51 (3.9%)
Phase 3 Controlled HypoNa Trials (oral 80 mg/day)	1/53 (1.9%)	0	1/53 (1.9%)	0	0	0	0	1/53 (1.9%)	0
(Phase 3 Controlled IV = Study -027 only- see above)									
Phase 3 Controlled HypoNa Trials (all coni)	11/159 (6.9%)	2/159 (1.3%)	8/159 (5.0%)	3/159 (1.9%)	2/159 (1.3%)	2/159 (1.3%)	1/159 (0.6%)	9/159 (5.7%)	2/159 (1.3%)
Full Safety Population (all Pbo)	1/332 (0.3%)	1/332 (0.3%)	1/332 (0.3%)	0	0	1/332 (0.3%)	1/332 (0.3%)	1/332 (0.3%)	1/332 (0.3%)
Full Safety Population (all oral Pbo)	0	0	0	0	0	0	0	0	0
Full Safety Population (all IV Pbo)	1/92 (1.1%)	1/92 (1.1%)	1/92 (1.1%)	0	0	1/92 (1.1%)	1/92 (1.1%)	1/92 (1.1%)	1/92 (1.1%)
Full Safety Population (10 mg/day oral)	2/82 (2.4%)	1/82 (1.2%)	2/82 (2.4%)	0	1/82 (1.2%)	1/82 (1.2%)	1/82 (1.2%)	2/82 (2.4%)	0
Full Safety Population (20 mg/day oral)	2/206 (1.0%)	2/206 (1.0%)	1/206 (0.5%)	0	1/206 (0.5%)	1/206 (0.5%)	0	1/206 (0.5%)	0
Full Safety Population (40 mg/day oral)	10/255 (3.9%)	5/255 (2.0%)	7/255 (2.7%)	1/255 (0.4%)	5/255 (2.0%)	2/255 (0.8%)	1/255 (0.4%)	6/255 (2.4%)	2/255 (0.8%)
Full Safety Population (80 mg/day oral)	4/159 (2.5%)	1/159 (0.6%)	3/159 (1.9%)	1/159 (0.6%)	2/159 (1.3%)	2/159 (1.3%)	1/159 (0.6%)	3/159 (1.9%)	0
Full Safety Population	18/688	8/688 (1.2%)	13/688	2/688	9/688 (1.3%)	6/688 (0.9%)	3/688	12/688 (1.7%)	2/688 (0.3%)

Table 7.1.2.4.3.2: Categories and Outcomes of Serious Renal Adverse Events, by Study Population and Dose									
	Any Renal SAE	Acute Renal Failure	Acute Renal Injury	Other Renal SAE	New Hospitalization for Worsening Renal Function	CRF States DC of Coni	Dialysis	No Documented Reversal	Death Within 30 Days of Renal SAE
(any oral Coni dose)	(2.6%)		(1.9%)	(0.3%)			(0.4%)		
Full Safety Population (20 mg/day IV)	1/35 (2.9%)	0	1/35 (2.9%)	0	0	0	0	1/35 (2.9%)	0
Full Safety Population (40 mg/day IV)	5/86 (5.8%)	1/86 (1.2%)	2/86 (2.3%)	3/86 (3.5%)	1/86 (1.2%)	1/86 (1.2%)	1/86 (1.2%)	3/86 (3.5%)	2/86 (2.3%)
Full Safety Population (80 mg/day IV)	3/46 (6.5%)	1/46 (2.2%)	2/46 (4.3%)	0	0	0	0	3/46 (6.5%)	1/46 (2.2%)
Full Safety Population (any IV Coni dose)	9/208 (4.3%)	3/208 (1.4%)	5/208 (2.4%)	3/208 (1.4%)	1/208 (0.5%)	1/208 (0.5%)	1/208 (0.5%)	7/208 (3.4%)	3/208 (1.4%)
Full Safety Population (all Coni)	27/896 (3.0%)	11/896 (1.2%)	18/896 (2.0%)	6/896 (0.7%)	10/896 (1.1%)	7/896 (0.8%)	4/896 (0.4%)	19/896 (2.1%)	5/896 (0.6%)

The following summary findings from this table are of note:

- Serious renal adverse events occurred in 27/896 (3.0%) of conivaptan-treated patients and 1/332 (0.3%) of all placebo patients in the population of all Phase 2 and Phase 3 trials in hyponatremia and CHF.
- Serious renal adverse events occurred in 7/55 (12.7%) of conivaptan-treated patients and 1/29 (3.4%) of placebo patients in Study -027, the single controlled Phase 3 intravenous hyponatremia trial.
- Serious renal adverse events occurred in 11/159 (6.9%) of conivaptan-treated patients and 1/82 (1.2%) of placebo patients in the pool of all Phase 3 controlled hyponatremia trials.
- Acute renal failure occurred in 11/896 (1.2%) of conivaptan-treated patients and 1/332 (0.3%) of placebo patients in the population of all Phase 2 and Phase 3 trials in hyponatremia and CHF.
- New hospitalization for worsening renal function was reported in 10/896 (1.1%) of conivaptan-treated patients and 0/332 (0%) of placebo patients in the population of all Phase 2 and Phase 3 trials in hyponatremia and CHF.
- Discontinuation of study medication at the time of occurrence of a serious renal adverse event was reported in 7/896 (0.8%) of conivaptan-treated patients and 1/332 (0.3%) of placebo patients in the population of all Phase 2 and Phase 3 trials in hyponatremia and CHF.
- Serious renal adverse events without documented reversal occurred in 6/55 (10.9%) of conivaptan-treated patients and 1/29 (3.4%) of placebo patients in Study -027, the single controlled Phase 3 hyponatremia trial.
- Serious renal adverse events without documented reversal occurred in 9/159 (5.7%) of conivaptan-treated patients and 1/82 (1.2%) of placebo patients in the pool of Phase 3 controlled hyponatremia trials.
- Serious renal adverse events without documented reversal occurred in 19/896 (2.1%) of conivaptan-treated patients and 1/332 (0.3%) of placebo patients in the population of all Phase 2 and Phase 3 trials in hyponatremia and CHF.
- Death occurred within 30 days of a serious renal adverse event in 3/55 (5.5%) of conivaptan-treated patients and 1/29 (3.4%) of placebo patients in Study -027, the single controlled Phase 3 hyponatremia trial.
- Death occurred within 30 days of a serious renal adverse event in 5/896 (0.6%) of conivaptan-treated patients and 1/332 (0.3%) of placebo patients in the population of all Phase 2 and Phase 3 trials in hyponatremia and CHF.
- Five out of eighteen patients (27.8%) in Study -027 who had plasma conivaptan levels >1000 ng/mL developed serious renal adverse events.
- In general, dose-dependency for serious renal adverse events was not demonstrated. However, in the population of all intravenous Phase 2 and Phase 3 trials in hyponatremia and CHF, 1/35 (2.9%) of patients taking conivaptan 20 mg/day, 5/86 (5.8%) taking 40 mg/day, and 3/46 (6.5%) taking 80 mg/day developed serious renal adverse events in these intravenous trials.
- All cases of acute renal failure occurred in congestive heart failure patients.
- In the pool of all Phase 2 and Phase 3 studies in congestive heart failure and hyponatremia, patients with an underlying diagnosis of CHF were not more likely to

experience serious renal adverse events overall than those patients without CHF. Congestive heart failure was present in 774/896 (86.4%) of all patients in the Phase 2 and Phase 3 trials in hyponatremia and CHF. A total of 21 serious renal adverse events occurred among congestive heart failure patients, while 6 occurred in patients without CHF; 77.8% of all serious renal adverse events occurred in CHF patients.

The clinical reviewer examined all narratives for serious renal adverse events; in addition to the information in the summary tables above, synopses of these events follow. As reported above, a few cases of decline in renal function that were not coded as such were noted by the clinical reviewer among SAE narratives for subjects with hypovolemia SAEs and CHF SAEs.

Also see death narratives above for Subjects 025-0001002, 026-0060103, 026-0060708, 027-0075801 and 027-0075806. Also see Subjects 020-0005007 and 047-0233101 in the CHF SAE narratives above. Also see Subjects 034-0015002, 027-0071701, 020-0027012, 027-75601, 020-0015003 and 034-0011005 in the hypovolemia SAE narratives above.

Subject 017-0003015: No case report form found; case noted on review of laboratory data. See Table 7.1.2.4.3.1.

Subject 026-0062902: 67 year old man with euvolemic hyponatremia and chronic obstructive pulmonary disease. Received 80 mg oral conivaptan for 5 days. Baseline Cr 1.4; increased to 3.0 by Study Day 5. Narrative states patient had vancomycin toxicity, but gives no details; no followup laboratory.

Subject 027-0071603: No case report form. See Table 7.1.2.4.3.1. In -027 study report, Text Table 11-17, a summary of patients with high conivaptan plasma concentrations states that patient had oliguria.

Subject 027-0076201: 87 year old woman with idiopathic hyponatremia. Received 4 days of intravenous conivaptan, 80 mg/day. Had high conivaptan levels. Case report form discusses increased SGOT and SGPT of 63 and 52 mg/dL respectively, but does not mention renal function. Creatinine increased from baseline of 0.7 mg/dL to 1.4 mg/dL on Study Day 4. See Table 7.1.2.4.3.1.

Subject 027-0076202: 78 year old man. No case report form found. Patient had high conivaptan blood levels. See Table 7.1.2.4.3.1.

Subject 033-0007004: 79 year old man with CHF. Case report form does not mention renal function. Creatinine increased from baseline 2.0 mg/dL to 4.3 on Study Day 92, and to 5.3 on Study Day 193.

Subject 034-0007021: 76 year old woman with CHF and Type 2 DM. Case report form mentions acute renal failure during hospitalization for hyperglycemia which began on Study Day 23. Creatinine values not in narrative.

Subject 034-0013004: 56 year old man with CHF, on oral conivaptan 40 mg/day. On Treatment Day 49, hospitalized with BUN 55 mg/dL, Cr 2.7 mg/dL (baseline 1.4) and serum potassium 6.6 mmol/L (baseline 3.8). Treated with "hydration", recovered by Treatment Day 53. Conivaptan permanently discontinued.

Subject 034-0014003: No case report form found. See Table 7.1.2.4.3.1. Creatinine increased from baseline of 0.5 to 1.8 on Study Day 18.

Subject 034-0034012: No case report form found. See Table 7.1.2.4.3.1. Creatinine increased from baseline of 1.2 mg/dL to 3.0 on Study Day 98.

Subject 034-0049028: 63 year old man with CHF. Received oral conivaptan 20 mg bid. On Treatment Day 34, presented with increasing episodes of near-syncope. Found to have 3.2 second sinus pause on monitor; carvedilol dose reduced and digoxin discontinued and pt discharged.. On Treatment Day 49, readmitted with dyspnea; serum Cr had gone up from baseline of 1.3 mg/dL to 2.5. Given fluids; furosemide, lisinopril and spironolactone stopped temporarily. Cr returned to baseline. Found to have 80% left main coronary artery occlusion; pacemaker placed and treated medically. Conivaptan not interrupted.

Subject 038-0010001: Case report form does not mention renal function. See Table 7.1.2.4.3.1. Creatinine increased from baseline of 1.1 mg/dL to 2.7 mg/dL on Study Day 7; this is last recorded creatinine.

Subject 043-0230401: Case report form not found. See Table 7.1.2.4.3.1. Creatinine increased from baseline of 0.4 mg/dL to 1.5 mg/dL on Study Day 2.

Subject 047-0230901: 54 year old man with history of myocardial infarction. On oral conivaptan 20 mg/day. On Treatment Day 52, admitted with nausea and vomiting and acute renal failure. Peak serum creatinine unknown; highest documented creatinine 2.7. Bumetanide discontinued; recovered without interruption of conivaptan.

Subject 047-00233601: Case report form not found. See Table 7.1.2.4.3.1. Baseline creatinine 5.4 mg/dL; unclear why patient was included in study. Creatinine on Study Day 7 increased to 6.0. By Study Day 64, had increased to 6.7 mg/dL. In the study report, there is one mention of a dialysis procedure. Study report states patient withdrew due to "lack of efficacy" on Study Day 64 (same day as max Cr).

When examining serious renal adverse events possibly related to conivaptan, serious renal adverse events occurred more frequently in study subjects taking conivaptan (27/896; 3.0%) than in those taking placebo (1/332; 0.3%) in the full safety population. The mean duration of conivaptan therapy prior to first recorded onset of a serious renal adverse event was 31 days. The median time to event, however, was six days, and twelve events (44%) occurred in subjects who had taken conivaptan for 4 or fewer days.

As noted above, all cases meeting criteria for acute renal failure occurred in patients with congestive heart failure. Acute renal failure in congestive heart failure in general is a common event, even when controlling for other risk factors for renal failure (Shusterman 1987). In S, a trial examining the effect of carvedilol treatment on CHF outcomes in 2168 patients, the incidence of abnormal renal function in the placebo group was 3.1% over an average treatment duration of 10.4 months (Packer 2002). However, the fact that renal dysfunction is common in CHF does not explain why, in this application, a significant decline in renal function occurred more frequently in subjects taking conivaptan than in those taking placebo.

For those subjects who developed renal dysfunction within the first five days of administration of conivaptan, a prerenal etiology related to fluid loss would seem likely. In order to examine this, the reviewer looked at the efficacy datasets, which included only Studies -026, -027 and -043, to see if the patients with renal dysfunction had indeed had high urine output. These patients actually did not have brisk urinary output responses to conivaptan. Mean urine output for these patients over Treatment Day 1 was 1526 mL/24 hours compared to 2435 mL/day for the overall Phase 3 study population (including placebo). Only four of the twelve patients in these studies who had a serious renal adverse event and had urine output recorded had urine output over Treatment Day 1 that was higher than the mean for the overall Phase 3 study population (including placebo). Thus, with what data are available, the clinical reviewer cannot definitively say that the serious declines in renal function were all due to overly brisk urine output with prerenal volume depletion.

The clinical reviewer also attempted to look for evidence of acute tubular necrosis by review of the urine dipstick values for specific gravity and urine blood for patients with renal dysfunction. If acute tubular necrosis had occurred, the specific gravity would likely be 1.010 due to an inability of the kidney to either concentrate or dilute urine. The urine dipstick might also be positive for blood. However, the datasets included very few of these parameters at the time of renal dysfunction, and review of the full case report forms revealed few documented urinalyses overall, and fewer still with documented collection at the time of occurrence of increased serum creatinine.

The sponsor asserts that "virtually all cases of potentially significant creatinine elevations have good alternate explanations or resolved or improved while therapy was continued" (NDA Section 2.5.5, p 18). For examples of cases that are not in line with this assertion, please see the death narratives in Section 7.1.1.2 for subjects 025-0001002, 026-0060103, 026-0060708 and 027-0075801; and the serious hypovolemia event narratives in Section 7.1.2.4.1 for patients 020-0015003, 020-0027012 and 020-0005007. Resolution did not always occur without discontinuation of conivaptan, and while most of these patients had underlying risk factors for renal failure, one cannot exclude the possibility that conivaptan contributed to these adverse renal events.

Please also see the serious renal adverse event summary information following Table 7.1.2.4.3.2.

Serious Renal Adverse Events, "Full Dose" Population

In the subset of subjects (n = 63) who received the full dosing regimen proposed for labeling of conivaptan, one placebo subject (3.4%) and three conivaptan subjects (4.8%) developed renal failure. The size of this subset is inadequate for safety evaluation.

7.1.2.4.4 Neuropsychiatric SAE Terms, Full Safety Population

The incidence of serious neuropsychiatric adverse events was low in the conivaptan group (0.8%), but no events of this kind occurred in the placebo group. The clinical reviewer was interested in these terms because of the potential for overly rapid correction of serum sodium with attendant serious neurologic consequences. However, a review of all these cases revealed that no study subject who experienced a serious neuropsychiatric event also had an overly rapid correction of serum sodium, and none had protocol violations related to rate of correction of serum sodium. Only one event (a CVA) had permanent sequelae. One case of confusion (Subject 027-0075807), described in the cardiac failure cases above, occurred due to rapid (within days) recurrence of severe hyponatremia after cessation of conivaptan. Overall, conivaptan does not appear to be associated with increased risk for neuropsychiatric adverse events.

Neuropsychiatric SAE Term, "Full Dose" Population

In the subset of subjects (n = 63) who received the full dosing regimen proposed for labeling, one conivaptan subject (1.6%) and no placebo subjects developed any neuropsychiatric SAE. The total size of this subset is inadequate for safety evaluation.

7.1.2.4.5 *Post hoc* SAE Term Groupings

The clinical reviewer also noted a somewhat higher frequency of respiratory and infection adverse events in the full safety population conivaptan group compared to the placebo group.

The higher percentage of respiratory adverse events in the full safety population occurred largely in the oral conivaptan group. The composite consisted primarily of single occurrences of a given event, without any one event implicating conivaptan as causal. There were four cases of pulmonary embolism (0.4%) among conivaptan-treated subjects, compared to one (0.3%) among placebo-treated subjects.

In the subset of subjects who received the full dosing regimen proposed for labeling, there was one case of pneumonia in the conivaptan group and one case of respiratory arrest in the placebo group.

For infection adverse event terms in the full safety population, the composite again consisted primarily of single occurrences of a given type of infection. Pneumonia occurred in five (0.6%) conivaptan subjects compared to one (0.3%) placebo subject. Because aspiration of food material was noted at necropsy in some animals which had

expired in toxicology studies, the clinical reviewer looked at all pneumonia cases for evidence of aspiration as an etiology; one of the conivaptan cases appeared related to aspiration, but this patient was at risk for aspiration because of squamous cell carcinoma of the pyriform sinus (see death narrative for Subject 023-0004001). Four of the five cases of pneumonia in the conivaptan group occurred in subjects who were already seriously ill with other medical disorders. No clear causal relationship can be established for conivaptan and risk for pneumonia or other infection.

In the subset of subjects who received the full dosing regimen proposed for labeling, there was one case of an infected jugular vein and one case of pneumonia, both in the conivaptan group. There were no infection SAEs in the placebo group. The total number of subjects in this subset is inadequate for safety evaluation.

7.1.2.5 Summary of Serious Adverse Events

For the full safety population, the following types of serious adverse events occurred statistically significantly more frequently in conivaptan-treated patients than in placebo-treated patients:

- Serious renal adverse events
- Serious hypovolemia-related events

Serious cardiac failure events among patients with underlying congestive heart failure also occurred more frequently among conivaptan-treated patients than among placebo-treated patients, although the difference was not statistically significant.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

As recorded in the case report forms (CRFs), the most commonly reported reasons for patient withdrawal from study during the treatment phase were lack of compliance, adverse event(s) and lack of efficacy.

Patients who were withdrawn from the study due to adverse events (AEs) were to be followed until resolution of the AE.

The following table indicates general reasons for dropout from Phase 2 and Phase 3 clinical trials. A separate table for Study -027 is included, as this study contained the bulk of study subjects who were exposed to the full dosing regimen planned for labeling.

Table 7.1.3.1.1: Reasons for Dropout- Study -027

Status at End of Treatment		Placebo (N= 29)	IV YM087 40 mg (N= 29)	IV YM087 80 mg (N= 26)	Total (N= 84)
Completed Treatment	n (%)	23 (79.3)	22 (75.9)	21 (80.8)	66 (78.6)
Early Withdrawal	n (%)	6 (20.7)	7 (24.1)	5 (19.2)	18 (21.4)
Reason for Early Withdrawal					
Adverse Events	n (%)	3 (50.0)	2 (28.6)	5 (100.0)	10 (55.6)
Lack of Efficacy	n (%)	1 (16.7)	1 (14.3)	0 (0.0)	2 (11.1)
Other/Administration	n (%)	2 (33.3)	4 (57.1)	0 (0.0)	6 (33.3)

Source: Sponsor's Table 2.1.2, -027 study report

The most common reason for early withdrawal in Study -027 conivaptan groups was an adverse event. The percentage of patients withdrawing for adverse events in each group was 10.3% for the placebo group, 10.3% for the 40 mg/day group (one AE added by clinical reviewer- see below), 19.2% for the 80 mg/day group, and 14.5% for the combined conivaptan dose groups.

The clinical reviewer examined all withdrawals listed as "Other/Administrative". Reasons for those withdrawals are listed in the following table.

Table 7.1.3.1.2: Breakdown of Reasons for Withdrawal Listed as "Administrative/Other", Study -027

	Pbo	Coni 40	Coni 80
Poor Venous Access	1		
Withdrew Consent	1	2	2
"Withdrawal at Patient's Discretion", after Respiratory Arrest		1	
Started Hydrocortisone		1	

Source: Sponsor's Listing 1.2.3, -027 study report

In the clinical reviewer's opinion, the patient in the conivaptan 40 mg/day group who had a respiratory arrest and then withdrew, should be listed as having withdrawn due to an adverse event. The clinical reviewer also noted that two patients who withdrew consent were not listed in the conivaptan 80 mg/day group. This increases the percentage of patients in the 80 mg group who withdrew from study from 19% to 27%.

Table 7.1.3.1.3: Reasons for Dropout- Full Safety Population

	All Phase 2/3 IV Studies (023, 025, 027, 032, 038, 044)		All Phase 2/3 Oral Studies (016, 017, 020, 021, 022, 024, 026, 033, 034, 043, 047)		All Phase 2/3 IV + Oral Studies (016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 032, 033, 034, 038, 043, 044, 047)	
	Placebo n(%)	YM087 Any Dose n(%)	Placebo n(%)	YM087 Any Dose n(%)	Placebo n(%)	YM087 Any Dose n(%)
Patients treated	92	208	240	688	332	896
Completed treatment	84 (91.3)	193 (92.8)	218 (90.8)	641 (93.2)	302 (91.0)	834 (93.1)
Premature discontinuations:	8 (8.7)	15 (7.2)	22 (9.2)	69 (10.0)	30 (9.0)	84 (9.4)
Adverse Event	4 (4.3)	7 (3.4)	11 (4.6)	35 (5.1)	15 (4.5)	42 (4.7)
Lack of Efficacy	2 (2.2)	3 (1.4)	1 (0.4)	5 (0.7)	3 (0.9)	8 (0.9)
Withdrawal of Consent	0	0	1 (0.4)	2 (0.3)	1 (0.3)	2 (0.2)
Lost to Follow-up	0	0	0	0	0	0
Protocol Violation	0	0	2 (0.8)	4 (0.6)	2 (0.6)	4 (0.4)
Patient Died	0	0	0	3 (0.4)	0	3 (0.3)
Lack of Compliance	0	0	0	10 (1.5)	0	10 (1.1)
Other/Admin. Reasons	2 (2.2)	5 (2.4)	7 (2.9)	9 (1.3)	9 (2.7)	14 (1.6)
Satisfactory Response	0	0	0	1 (0.1)	0	1 (0.1)

Source: Sponsor's Table 2.7.4-13

On review of cases where the reason for withdrawal was listed as "Other/Admin", one subject who received 20 mg conivaptan (Subject 020-0050003) and who was listed as having withdrawn due to lack of compliance actually was withdrawn by the primary care physician due to the subject's worsening renal function. Therefore, there is one additional case of withdrawal due to adverse events. The percentage of placebo subjects withdrawing for adverse events was 4.5%, and in the combined conivaptan groups was 4.8%.

It is notable that the percentages of withdrawals due to adverse events in Study -027 were higher than those seen in the overall safety population. Because of the small number of study patients in -027, one cannot make conclusions about the relative safety of the IV formulation when given in full dose. This emphasizes the need for a larger population of study subjects exposed to the full planned dosing regimen.

7.1.3.2 Adverse events associated with dropouts

The following table details the reasons for dropouts due to adverse events. Study -027 is detailed separately because the majority of patients who could have been exposed to the full planned dosing regimen for labeling were in this study. All Phase 2/3 studies are also included.

Table 7.1.3.2: Treatment-emergent Adverse Events Leading to Discontinuation

		-027		All Phase 2/3 Trials	
		Pbo n (%) (n = 29)	**Coni n (%) (n = 55)**	**Pbo n (%) (n = 332)**	**Coni n (%) (n = 896)**

Table 7.1.3.2: Treatment-emergent Adverse Events Leading to Discontinuation					
		-027		All Phase 2/3 Trials	
		Pbo n (%) (n = 29)	Coni n (%) (n = 55)	Pbo n (%) (n = 332)	Coni n (%) (n = 896)
System	MedDRA Term				
Cardiac Disorders		1 (3.4%)	1 (1.8%)	4 (1.2%)	11 (1.2%)
	Angina pectoris			1 (0.3%)	
	Arrhythmia NOS				1 (0.1%)
	Cardiac arrest				1 (0.1%)
	Cardiac failure NOS			1 (0.3%)	3 (0.3%)
	Chest pain				1 (0.1%)
	Congestive cardiac failure aggravated	1 (3.4%)	1 (1.8%)	1 (0.3%)	3 (0.3%)
	Heart rate increased				1 (0.1%)
	V tach			1 (0.3%)	1 (0.1%)
Ear and Labyrinth Disorders				1 (0.3%)	
	Vertigo			1 (0.3%)	
Endocrine Disorders			1 (1.8%)		
	Hypopituitarism		1 (1.8%)		
Gastrointestinal Disorders				1 (0.3%)	8 (0.9%)
	Abdominal pain NOS				2 (0.2%)
	Abdominal pain upper				1 (0.1%)
	Dyspepsia				1 (0.1%)
	Faecal abnormality NOS				1 (0.1%)
	Flatulence				1 (0.1%)
	Oesophagobronchial fistula				1 (0.1%)
	Small intestinal obstruction NOS				1 (0.1%)
	Vomiting NOS			1 (0.3%)	
Immune system disorders				1 (0.3%)	1 (0.1%)
	Drug hypersensitivity			1 (0.3%)	
	Hypersensitivity NOS				1 (0.1%)
Infections and Infestations			3 (5.5%)		4 (0.4%)
	Injection site infection		1 (1.8%)		1 (0.1%)
	Pneumonia NOS		1 (1.8%)		2 (0.2%)
	Sepsis NOS		1 (1.8%)		1 (0.1%)
Injury, Poisoning and Procedural Complications				1 (0.3%)	1 (0.1%)
	Head injury				1 (0.1%)
	Postprocedural haemorrhage			1 (0.3%)	
Investigations			1 (1.8%)	1 (0.3%)	1 (0.1%)
	Blood urea increased		1 (1.8%)		1 (0.1%)
	Liver function test abnormal			1 (0.3%)	
Metabolism and Nutrition Disorders		1 (3.4%)		1 (0.3%)	3 (0.3%)
	Appetite decreased NOS				1 (0.1%)
	Hyperkalaemia				1 (0.1%)
	Hyponatremia	1 (3.4%)		1 (0.3%)	
	Thirst				1 (0.1%)
Musculoskeletal and Connective Tissue Disorders					1 (0.1%)
	Myalgia				1 (0.1%)
Neoplasms					2 (0.2%)
	Oesophageal carcinoma NOS				1 (0.1%)
	Pulmonary mass				1 (0.1%)
Nervous System Disorders				1 (0.3%)	6 (0.7%)
	Cerebrovascular accident				1 (0.1%)
	Dizziness				1 (0.1%)
	Grand mal convulsion				1 (0.1%)
	Headache				1 (0.1%)

Table 7.1.3.2: Treatment-emergent Adverse Events Leading to Discontinuation

		-027		All Phase 2/3 Trials	
		Pbo n (%) (n = 29)	Coni n (%) (n = 55)	Pbo n (%) (n = 332)	Coni n (%) (n = 896)
	Malaise				1 (0.1%)
	Syncope				1 (0.1%)
	Syncope vasovagal			1 (0.3%)	
Psychiatric Disorders		1 (3.4%)		2 (0.6%)	1 (0.1%)
	Confusional state	1 (3.4%)		1 (0.3%)	
	Feeling abnormal				1 (0.1%)
	Insomnia			1 (0.3%)	
Renal and Urinary Disorders		1 (3.4%)	1 (1.8%)	1 (0.3%)	5 (0.6%)
	Renal failure NOS	1 (3.4%)		1 (0.3%)	2 (0.2%)
	Renal failure acute		1 (1.8%)		1 (0.1%)
	Renal impairment NOS				2 (0.2%)
Reproductive System and Breast Disorders					1 (0.1%)
	Erectile dysfunction NOS				1 (0.1%)
Respiratory, Thoracic and Mediastinal Disorders			2 (3.6%)		5 (0.6%)
	Dyspnoea exacerbated				1 (0.1%)
	Nocturnal dyspnoea				1 (0.1%)
	Oxygen saturation decreased		1 (1.8%)		1 (0.1%)
	Pulmonary embolism				1 (0.1%)
	Respiratory arrest		1 (1.8%)		1 (0.1%)
Skin and Subcutaneous Tissue Disorders			1 (1.8%)		2 (0.2%)
	Cyanosis peripheral		1 (1.8%)		1 (0.1%)
	Rash NOS				1 (0.1%)
Vascular Disorders		1 (3.4%)	4 (7.3%)	1 (0.3%)	5 (0.6%)
	Hypotension NOS	1 (3.4%)		1 (0.3%)	1 (0.1%)
	Phlebitis NOS		1 (1.8%)		1 (0.1%)
	Phlebitis superficial		1 (1.8%)		1 (0.1%)
	Phlebitis infusion site		2 (3.6%)		2 (0.2%)

Source: Sponsor's Table 2.7.4-62

Among these reasons for discontinuation, infusion site-related adverse events occurred more frequently in the conivaptan groups than in the placebo groups for both Study -027 and the overall safety population. Infusion site reactions are further discussed in the following section.

7.1.3.3 Other significant adverse events

Please see Section 7.1.5.1 for a discussion of other common adverse events.

Events that were expected to be of special interest for conivaptan, based on its pharmacologic action and preclinical findings, included overly rapid correction of serum sodium, infusion site reactions, hypotension, hepatic toxicity and bone marrow toxicity. Overly rapid correction of serum sodium in hyponatremia has been associated with a variety of adverse outcomes, particularly neurologic outcomes, including the characteristic clinical sequelae of central pontine myelinolysis. Infusion site reactions were noted early in development of conivaptan, and were a limiting adverse event in

some early trials. Hypotension might be expected, based on the markedly elevated urine output that can be seen with the drug. Hepatotoxicity and bone marrow toxicity were possible signals noted in animal studies.

7.1.3.3.1 Overly Rapid Correction of Serum Sodium

The criteria used by the sponsor in its three major efficacy trials (-027, -026 and -043) for identification of overly rapid correction of serum sodium are listed below. The occurrence of any one of these criteria was sufficient to identify a case of overly rapid correction.

- Serum sodium increased by more than 12 mEq/L in 1 day.
- Serum sodium increased by more than 24 mEq/L total.
- Serum sodium exceeded 145 mEq/L.
- The investigator believed serum sodium was correcting too quickly.

A total of 14 patients in all Phase 3 trials met one of the above four criteria. This included no placebo patients, 7/80 (9%) patients from the 40 mg/day conivaptan group, and 7/79 (9%) of patients from the 80 mg/day group. None of these patients experienced AEs that have been associated (in the medical literature) with rapid correction of serum sodium, as described below.

The sponsor approached the evaluation of this adverse event by searching the medical literature for AEs potentially associated with rapid correction of serum sodium. These included:

- renal failure
- encephalopathy
- central pontine myelinolysis
- extrapontine demyelination
- spastic quadriparesis
- pseudobulbar palsy
- mutism dysarthria
- cerebral edema
- aseptic meningitis
- seizures
- transtentorial herniation
- ventricular tachycardia
- ventricular fibrillation
- rhabdomyolysis
- obtundation
- severe headache
- confusion
- agitation
- lethargy
- brain death
- coma.

The sponsor then examined AEs from all their controlled Phase 3 clinical trials. A total of 19 patients experienced at least one of these AEs: 7 (9%) in the placebo group, 7 (9%) in the conivaptan 40 mg/day group, and 5 (6%) in the 80 mg/day group. Among these 19 patients, 8/19 (42%) had renal dysfunction, 6 (32%) had confusion, 3 (16%) had ventricular tachycardia, 2 (11%) had lethargy, 1 (5%) had a convulsion, and 1 (5%) had encephalopathy. None of these 19 patients with identified AEs of interest were among the 14 patients who had overly rapid correction of serum sodium.

The sponsor did not report an examination of AEs that did occur among the 14 patients with overly rapid correction of serum sodium. The clinical reviewer identified these cases and looked for AEs among the patients. The following table details the specific AEs that did occur among patients with overly rapid correction of serum sodium.

Table 7.1.3.3.1.1: Adverse Events Among Study Patients who Experienced Overly Rapid Correction of Serum Sodium in Study -027

Adverse Event	Pbo (Total n = 29) Rapid Correction n = 0	Coni 40 mg (Total n = 29) Rapid Correction n = 2	Coni 80 mg (Total n = 26) Rapid Correction n = 2
Thrombophlebitis	n/a	1	1
Loose stools	n/a		1
Vomiting	n/a		1
Weight Loss	n/a		1
Abdominal Pain	n/a		2
Hypotension NOS	n/a		2
Urinary Incontinence	n/a	1	
Urinary Tract Infection	n/a		1
Increased Creatinine	n/a		1
Shakiness	n/a		1
Hallucination	n/a		1
Insomnia	n/a		1

Source: Listing 14.1, -027 study report

Table 7.1.3.3.1.2: Adverse Events Among Study Patients who Experienced Overly Rapid Correction of Serum Sodium in Phase 3 Controlled Studies

Adverse Event	Pbo (Total n = 82) Rapid Correction n = 0	Coni 40 mg (Total n = 80) Rapid Correction n = 7	Coni 80 mg (Total n = 78) Rapid Correction n = 7
Rash	n/a		1
Thrombophlebitis	n/a	1	1
Loose stools	n/a		1

Table 7.1.3.3.1.2: Adverse Events Among Study Patients who Experienced Overly Rapid Correction of Serum Sodium in Phase 3 Controlled Studies			
Adverse Event	**Pbo (Total n = 82) Rapid Correction n = 0**	**Coni 40 mg (Total n = 80) Rapid Correction n = 7**	**Coni 80 mg (Total n = 78) Rapid Correction n = 7**
LFTs Increased	n/a	1	
Vomiting	n/a		3
Weight Loss	n/a		1
Abdominal Pain	n/a		2
Hypotension NOS	n/a	1	3
Urinary Incontinence	n/a	1	
Urinary Tract Infection	n/a		2
Increased Creatinine	n/a		1
Shakiness	n/a		1
Weakness Severe	n/a	1	
Hallucination	n/a		1
Insomnia	n/a		1
Edema	n/a		1
Edema Increased	n/a	1	1
Chest pain	n/a	1	
Source: Sponsor's Listing 14.1, -027 study report; Table 12-9, -043 study report; Table 12-11, -026 study report			

Thus, although the sponsor did not identify AEs mentioned in the literature as possibly associated with rapid correction of serum sodium among the 14 study patients who experienced overly rapid correction of serum sodium in the Phase 3 controlled hyponatremia trials, one cannot say that this problem was without possible consequences. Some of the observed AEs were possibly neurologic in character, such as hallucination, severe weakness, insomnia and shakiness. Also notable was that 4 of these 14 patients (29%) experienced hypotension, an event that occurred in only 1 placebo patient (1.2%) in all three trials. The majority of adverse events among patients with overly rapid correction of serum sodium occurred in the conivaptan 80 mg/day groups.

The clinical reviewer also examined these 14 patients for the degree of serum sodium change or absolute value achieved. Some patients met more than one criterion, and are listed once for each criterion met.

- Among those patients (n=5) who met the criterion of an increase of more than 12 mEq/L over 24 hours, the absolute increase ranged from 13 mEq/L to 25 mEq/L, with a mean of 17. All of these increases occurred on Treatment Day 1. The patient who had the greatest increase was in Study -027, the "pivotal" IV study.
- One patient met the criterion of an increase of serum sodium >24 mEq/L over duration of study, with an increase from 118 to 143 (+25) over the 5 days of Study -043.
- Two patients had serum sodiums > 145 mEq/L during study, both in Study -043. Despite dosage reductions, their serum sodiums remained >145 from days 2-4 of

study. One patient peaked at 150 mEq/L and one peaked at 155 mEq/L, both on Study Day 3. Both had normal serum sodiums by day 5.

- Seven patients met the criterion of the investigator having the opinion that the rise in serum sodium was too rapid. Among these patients, the rise in serum sodium over the first 24 hours of study was in the sponsor's listing for only two patients, who had increases of 7 and 16 mEq/L over the first 24 hours. The absolute increase among the five patients for whom this value was available ranged from 7-19 mEq/L, with a mean of 15. Peak serum sodiums in the five patients for whom this value was available ranged from 134-142 mEq/L.

Thus, the potential for very rapid correction of serum sodium exists, including one patient in the pivotal IV study who had an increase of 25 mEq/L over the first 24 hours of treatment. Some patients who had rapid correction of serum sodium had other significant adverse events, including hallucination, severe weakness and hypotension. Frequent monitoring of serum sodium, especially on the first day of treatment, will be necessary if conivaptan is approved; the clinical reviewer also recommends the study of lower doses of the IV formulation.

7.1.3.3.2 Infusion Site Reactions

Infusion site reactions were a consistent signal in animal studies. The degree of infusion site vascular inflammation was significant enough to result in termination of a 4 week rat IV infusion study and a dog IV bolus study. Both the PG/EtOH vehicle and conivaptan itself contribute to vascular irritation. In bolus studies in animals, more concentrated formulations caused more severe changes. Rats were more susceptible to this than dogs and rabbits; the sponsor felt this might be due to smaller vessel diameter, and recommends that conivaptan be administered via large veins.

Infusion site reactions were also a common occurrence in humans during the development of the IV formulation of conivaptan. One Phase 1 clinical study (-064) was terminated early due to infusion site reactions. In Phase 1 Study -074, a midazolam interaction study, infusion site reactions occurred at all infusion concentrations (0.05, 0.08, and 0.16 mg/mL), but were more marked with the higher concentrations These reactions included local erythema, phlebitis, edema, pain, and occasionally, pyrexia; six patients discontinued the study due to infusion site reactions.

Among all IV subjects in Phase 2 and Phase 3 trials, 3/92 (3%) of placebo subjects experienced treatment-emergent infusion site reactions, while 43/208 (21%) of conivaptan-treated subjects had such reactions. This difference was statistically significant. In the three controlled Phase 3 hyponatremia trials, infusion site reactions were the most common TEAE leading to discontinuation of study, and all occurred in Study -027, the single Phase 3 intravenous trial for hyponatremia. In Study -027, the "pivotal" IV efficacy study, 2 (7%) of placebo patients had infusion site reactions, while 14 (48%) and 14 (54%), respectively, of conivaptan 40 and 80 mg group patients had infusion site reactions. These differences between conivaptan and placebo were statistically significant. Among all Phase 2 and Phase 3 IV studies, the vast majority of

infusion site reactions occurred at doses of 40 or 80 mg/day. The specific TEAEs reported included phlebitis, thrombophlebitis, DVT, pain, swelling, bruising, erythema and injection site infection. One patient experienced a left external iliac and left common femoral DVT after administration of conivaptan via the left common femoral vein. Another patient experienced DVT of the right popliteal to iliac vein. One patient developed a jugular vein infection after an infusion site reaction. Five Phase 2/3 patients, all in Study -027, discontinued study medication due to infusion site reactions. Four Phase 2/3 subjects had temporary discontinuation of study medication due to infusion site reactions.

In Study -027, volume status at baseline (euvolemic or hypervolemic) was not a predictor of infusion reactions. Infusion reactions occurred in 70% of euvolemic patients, who comprised 67% of the -027 population. Infusion reactions occurred in 30% of hypervolemic patients, who comprised 33% of the -027 population.

In Study -027, the protocol specified that infusions were to be administered via a central line or indwelling arm vein catheter, and not via a hand catheter. Final drug concentrations for infusion were 0.16 mg/mL and 0.32 mg/mL for the conivaptan 40 and 80 mg/day groups respectively. The volume of the initial bolus of 20 mg conivaptan plus D5W was 100 mL. The total volume of D5W and drug administered in each 24 hour infusion bag was 250 mL. The sponsor states that conivaptan cannot be infused in normal saline or lactated Ringer's solution. The clinical reviewer did not note the exploration of a possible effect of dilution in larger volumes of D5W (with resultant lower concentrations) on the incidence of infusion site reactions.

Infusion site reactions were common with conivaptan, despite efforts to administer the drug in arm (not hand) or central veins.

7.1.3.3.3 Hypotension

Serious adverse events possibly related to hypovolemia were discussed above in Section 7.1.2.4.1.

Additional events of hypotension occurred that were not considered serious by the investigators. The sponsor analyzed the occurrences of the event terms "hypotension NOS" and "orthostatic hypotension". In Study -027, the incidence of these terms was 6.9% (2/29) in the placebo group, 24% (7/29) in the conivaptan 40 mg/day group, and 23% (6/26) in the 80 mg/day group. Only one of the cases of hypotension was considered serious by the investigator, but persistent hypotension did occur in three patients who died. The incidence of these terms in the two "pivotal" oral studies was 11.3% (6/53) in the placebo groups, 3.9% (2/51) in the 40 mg/day groups, and 9.4% (5/53) in the 80 mg/day groups.

The clinical reviewer noted other adverse event terms that could be related to hypotension. The following table by the clinical reviewer details all hypotension-related terms, whether deemed serious or not, for the full safety population, and separately for

those studies (-027, -025 and -074) in which the subjects could have received the full dosing regimen proposed for labeling.

Table 7.1.3.3.3: Incidence of Occurrence of Hypotension-related AE Terms, Full Safety Population and "Full-Dose" Studies

	"Full-Dose" Studies		Full Safety Population	
	Pbo n (%) n = 29	Coni n (%) n = 75	Pbo n (%) n = 332	Coni n (%) n = 896
Cardiogenic Shock				1 (0.1%)
Blood Pressure Decreased			1 (0.3%)	2 (0.2%)
Cardiac Index Decreased				1 (0.1%)
Dehydration		2 (2.7%)		9 (1%)
Hypovolaemia	1 (3.4%)	2 (2.7%)	2 (0.6%)	5 (0.6%)
Dizziness Postural		1 (1.3%)	1 (0.3%)	4 (0.4%)
Syncope			2 (0.6%)	9 (1.0%)
Syncope Vasovagal			1 (0.3%)	2 (0.2%)
Loss of Consciousness	1 (3.4%)		1 (0.3%)	1 (0.3%)
Hypotension NOS	2 (6.9%)	11 (14.7%)	15 (4.5%)	41 (4.6%)
Orthostatic Hypotension		4 (5.3%)	4 (1.2%)	9 (1.0%)
Total	4 (13.8%)	20 (26.7%)	27 (8.1%)	84 (9.4%)

Source: Sponsor's Table 12-2, -027 study report; Table 12-3, -074 study report; Table 14, -025 study report

Hypotension and hypotension-related terms occurred commonly in IV studies of conivaptan, with a higher incidence among conivaptan-treated subjects than among placebo-treated subjects. This difference between conivaptan and placebo was not as marked in oral studies. This difference between oral and IV for the incidence of hypotensive events again underscores the need for further IV safety studies. Hypotension is a particularly undesirable adverse event in the CHF population, many of whom have myocardial ischemic disease, and are less likely to tolerate hypotension than those with a healthy heart.

7.1.3.3.4 Hepatotoxicity

The potential for hepatotoxicity was of interest for conivaptan because the drug has significant intersubject variability for achieved concentration of drug, with some subjects reaching plasma concentrations of drug in the range in which hepatotoxicity was seen in animal studies. Accumulation of conivaptan occurs with repeated dosing, and accumulation is more rapid at higher doses. Accumulation is higher in patients than in normal volunteers. Hypervolemic hyponatremic patients have twice the exposure of euvolemic hyponatremic patients.

In the full safety population, which included 332 placebo and 896 conivaptan subjects, the sponsor reported that mean ALT increases from baseline at any time during treatment were 2.5 iU/L for placebo and 6.5 iU/L for conivaptan. Mean increase in bilirubin for these groups was 0.069 for pbo and 0.079 for conivaptan. The incidence of 3-fold increases in ALT was higher in the conivaptan group (2.1%) than in the placebo group (1%). This was seen predominantly in the oral drug group. The incidence of 10 fold increases in ALT was higher in the conivaptan group than in the placebo group, and this was seen in both the IV and oral conivaptan groups.

The sponsor reported that liver-related adverse events occurred in 1% of placebo subjects and 2% of conivaptan subjects, and that most events were increases in liver enzymes.

The clinical reviewer examined all hepatic-related adverse event terms. The incidence of these terms is summarized in the following table. The laboratory abnormalities in this table include only those that were specifically reported as an adverse event. The incidences of all hepatobiliary laboratory abnormalities are presented in separate tables.

Table 7.1.3.3.4.1: Incidence of Hepatobiliary Adverse Events

	Study -027		Full Safety Population	
	Pbo n = 29	**Coni n = 55**	**Pbo n = 332**	**Coni n = 896**
Ascites			1 (0.3%)	
Cholelithiasis			1 (0.3%)	1 (0.1%)
Cholestasis				1 (0.1%)
Hepatic Failure		1 (1.8%)		1 (0.1%)
Hepatitis NOS				1 (0.1%)
Hepatomegaly				1 (0.1%)
ALT incr				5 (0.6%)
AST incr				6 (0.7%)
Alkaline Phosphatase incr			1 (0.3%)	1 (0.1%)
Bilirubin incr			1 (0.3%)	2 (0.2%)
LDH incr				1 (0.1%)
GGT incr			1 (0.3%)	5 (0.6%)
LFT abnl		1 (1.8%)	2 (0.6%)	8 (0.9%)
Total		2 (3.6%)	7 (2.1%)	33 (3.7%)

Source: Sponsor's Table 2.7.4-663; sponsor's Table 12-2, -027 study report

For the events in the above table, none occurred more frequently in conivaptan patients than in placebo patients. When looking at only the reported clinical events (not including the laboratory events), there was no difference in incidence between conivaptan patients and placebo patients.

For the following table of hepatobiliary laboratory abnormalities in Study -027, the clinical reviewer looked at all hepatobiliary chemistry measurements. The clinical

reviewer entered an abnormality into the table if the patient's test was normal at baseline and became abnormal during study treatment, or if the patient's test was abnormal at baseline and became more abnormal during study treatment. For a given patient, only the occurrence that represented the most abnormal value was counted, e.g. a patient who had an increased AST on one day, and then a further increase of AST the next day, was only counted once as having an increased AST.

Table 7.1.3.3.4.2: Incidence of Hepatobiliary Laboratory Abnormalities, Study -027

	Pbo n = 29	Coni n = 55
AST incr	5 (17.2%)	9 (16.4%)
AST incr >3x uln		2 (3.6%)
AST incr >10x uln		2 (3.6%
ALT incr	2 (6.9%)	10 (18.2%)
ALT incr >3x uln		2 (3.6%)
ALT incr >10x uln		1 (1.8%)
LDH incr	4 (13.8%)	7 (12.7%)
Alkaline Phosphatase incr	3 (10.3%)	12 (21.8%)
Alkaline Phosphatase incr >3x uln		1 (1.8%)
Total Bilirubin incr	1 (3.4%)	2 (3.6%)
Total Bilirubin incr >3x uln		2 (3.6%)
Total (# events/ # patients in group)	15 (51.7)	40 (72.7)
Source: Sponsor's Table 16.2.8-114		

For Study -027, the above table illustrates that increases in ALT and alkaline phosphatase occurred with greater frequency in conivaptan patients than in placebo patients. All cases of increases of AST >3x uln and >10x uln, ALT increases >3x uln or >10x uln, alkaline phosphatase >3x uln, and bilirubin >3x uln, occurred in conivaptan patients.

The following table examines the incidence of treatment-emergent abnormalities in liver function tests for the full safety population. For this table, only the end-of-study values were used for comparison to baseline, whereas in the above table for Study -027, emergence of an abnormal value at any time during treatment was counted as an abnormal laboratory occurrence. Also for this table, the percentages expressed are based on the total number of subjects with a laboratory result for the given analysis.

Table 7.1.3.3.4.3: Incidence of Treatment-emergent Abnormal Hepatobiliary Laboratory Values, Full Safety Population

	Pbo n = 332	Coni n = 896
GGT abnl	29 (36.3%)	90 (35.6%)
LDH abnl	71 (23.6%)	214 (25.8%)
AST abnl	74 (24.0%)	178 (20.9%)

Table 7.1.3.3.4.3: Incidence of Treatment-emergent Abnormal Hepatobiliary Laboratory Values, Full Safety Population		
	Pbo n = 332	**Coni n = 896**
AST >3x uln	2 (0.6%)	18 (2.1%)
AST >10x uln		4 (0.5%)
ALT abnl	62 (20.3%)	157 (18.6%)
ALT >3x uln	3 (1.0%)	18 (2.1%)
ALT >10x uln		2 (0.2%)
Bilirubin (total) abnl	52 (16.5%)	120 (13.8%)
Bilirubin (total) >3x uln	2 (0.6%)	8 (0.9%)
Alkaline Phosphatase abnl	42 (13.7%)	148 (17.4%)
Alkaline Phosphatase >3x uln	1 (0.3%)	3 (0.4%)
Total (# events/ # subjects in group)	330 (99.4)	960 (101.2)
Source: Sponsor's Table 2.7.4.3.5-2		

The above table illustrates that for the full safety population, increases in ALT and alkaline phosphatase occurred more frequently in conivaptan patients than in placebo patients. This difference was statistically significant. Increases in AST and ALT of >3x uln occurred more frequently in conivaptan patients than in placebo patients, and increases of AST and ALT of >10x uln occurred only in conivaptan patients.

The clinical reviewer examined the case of hepatic failure, and the cases of liver function tests >10x uln (a total of 3 subjects). The hepatic failure case occurred in a subject who developed multiorgan failure and died in the postoperative period after a failed cardiac transplant. Another subject had metastatic gallbladder cancer. The third subject underwent liver biopsy and had findings consistent with infectious hepatitis.

To summarize the clinical reviewer's findings regarding hepatobiliary events, such events occurred slightly more frequently among conivaptan-treated subjects than among placebo group subjects. The most serious adverse events appear likely to be due to the subjects' underlying other severe diseases. In the single controlled IV Phase 3 study (-027), elevations of ALT and alkaline phosphatase occurred more frequently in conivaptan group patients than in placebo group patients, and the combined incidence of all hepatobiliary laboratory abnormalities was higher in the conivaptan groups than in the placebo group. Few events of transaminases >3x or >10x uln occurred, but all were in the conivaptan groups. In the full safety population, the incidence of elevations in individual hepatobiliary laboratory values was approximately the same for placebo and conivaptan groups. However, the incidence of transaminases >3x uln was higher in the conivaptan groups. Only a few cases of transaminases >10x uln occurred, but all were in the conivaptan groups.

Conivaptan appears to be associated with a small increased risk for elevations of transaminases compared to placebo. The higher overall occurrence of hepatobiliary

laboratory abnormalities in the IV Study -027, when compared to the lower per-patient-exposure full safety population again points to the need for study of more IV conivaptan patients.

7.1.3.3.5 Bone Marrow and Coagulation Events

The clinical reviewer specifically examined bone marrow events because of animal toxicity findings. Coagulation/bleeding events were of interest because of the presence of vasopressin receptors on platelets, and because of the procoagulant effect of the AVP *agonist*, DDAVP. The vasopressin antagonist SR121463 has been found to antagonize DDAVP-induced release of hemostasis factors in dogs (Bernat 1997). The following table summarizes bone marrow and coagulation events.

Table 7.1.3.3.5: Bone Marrow and Coagulation Events

	Study -027			Full Safety Population	
	Pbo n = 29	Coni 40 n = 29	Coni 80 n = 26	Pbo n = 332	Coni All Doses n = 896
Anemia NOS	2 (6.9%)	2 (6.9%)		7 (2.1%)	21 (2.3%)
Coagulopathy					1 (0.1%)
Eosinophilia					1 (0.1%)
Haemorrhagic Disorder				1 (0.3%)	
Leukopenia NOS				1 (0.3%)	2 (0.2%)
Lymphocytosis					1 (0.1%)
Monocytosis					1 (0.1%)
Nephrogenic Anemia					1 (0.1%)
Neutropenia					2 (0.2%)
Normochromic Normocytic Anemia		1 (3.4%)			1 (0.1%)
Reticulocytosis				3 (0.9%)	4 (0.4%)
Thrombocytopenia					2 (0.2%)
Eye hemorrhage NOS					2 (0.2%)
Retinal hemorrhage					2 (0.2%)
Duodenitis hemorrhagic				1 (0.3%)	
Gastrointestinal hemorrhage NOS	1 (3.4%)			1 (0.3%)	
Gingival bleeding					2 (0.2%)
Melaena					1 (0.1%)
Catheter site hemorrhage			1 (3.8%)		1 (0.1%)
Postprocedural hemorrhage				1 (0.3%)	
Blood in stool				1 (0.3%)	
Fecal occult blood positive					1 (0.1%)
Hematocrit decreased				1 (0.3%)	2 (0.2%)
Hemoglobin decreased					5 (0.6%)
Monocyte count increased					1 (0.1%)
Platelet count decreased				2 (0.6%)	1 (0.1%)
Prothrombin time abnormal					1 (0.1%)
Prothrombin time prolonged					1 (0.1%)
Red blood cell decreased					4 (0.4%)
White blood cell count decreased					1 (0.1%)
White blood cell count increased					2 (0.2%)
Cerebrovascular accident					2 (0.2%)
Haematuria	1 (3.4%)			4 (1.2%)	7 (0.8%)
Haemoglobinuria					1 (0.1%)
Metrorrhagia				1 (0.3%)	1 (0.1%)

Table 7.1.3.3.5: Bone Marrow and Coagulation Events					
	Study -027			Full Safety Population	
	Pbo n = 29	Coni 40 n = 29	Coni 80 n = 26	Pbo n = 332	Coni All Doses n = 896
Epistaxis				1 (0.3%)	6 (0.7%)
Haematoma NOS		1 (3.4%)			1 (0.1%)
Total Anemia Events	2 (6.9%)	3 (10.3%)		8 (2.4%)	34 (3.8%)
Total Thrombocytopenia Events				2 (0.6%)	3 (0.3%)
Total Leukopenia Events				1 (0.3%)	4 (0.4%)
Total Bleeding Events	2 (6.9%)	1 (3.4%)	1 (3.8%)	11 (3.3%)	27 (3.0%)
Source: Sponsor's Table 12-2, -027 study report; Sponsor's Table 2.7.4-664					

Anemia (terms including anemia NOS, normochromic normocytic anemia, hematocrit decreased, hemoglobin decreased, red blood cell decreased) occurred somewhat more frequently in conivaptan subjects than in placebo subjects for the full safety population. The number of bone marrow and coagulation events in Study -027 was too small for meaningful comparison, and no comment can be made on dose effect.

Please see Section 7.1.7.3 for details of the effect of conivaptan on PT and INR.

7.1.3.3.6 Muscle Events

Because of the reported occurrence of a case of rhabdomyolysis in the development program, and because of conivaptan's potential for elevation of statin blood levels, the clinical reviewer specifically examined muscle events and CPK abnormalities.

Table 7.1.3.3.6.1: Incidence of CPK Elevations, Study -027				
	Pbo	Coni 40	Coni 80	All Coni
CPK elevated*	2	2	2	4
CPK >3x uln		1	1	2
*CPK nl at baseline to >uln; or CPK >uln at baseline to higher value Source: Sponsor's Table 16.2.8-114				

Table 7.1.3.3.6.2: Incidence of CPK Elevations, Full Safety Population		
	Pbo n = 332	Coni n = 896
Treatment-emergent CPK abnl	51 (17.1%)	115 (13.8%)
CPK >10x uln		4 (0.4%)
Source: Sponsor's Tables 2.7.4-175 and 2.7.4-175-123		

Although the Integrated Summary of Safety states that there were no CPK elevations of clinical concern, Table 2.7.4-175-123 in the Integrated Analysis of Safety reports four cases. The clinical reviewer searched for these cases, which can be summarized as follows:

Subject 034-0018020: 49 year old man with CHF, on oral conivaptan 80 mg/day, who was hospitalized for rhabdomyolysis on Treatment Day 7. He was also taking cerivastatin, rosiglitazone, and gemfibrozil, as well as other cardiac medications. CPK was 9710 IU/L, and diagnosis of rhabdomyolysis was made; the narrative does not discuss the patient's symptoms. Statins and gemfibrozil were discontinued, and patient was released to home on Study Day 14 "with sequelae". Conivaptan was not interrupted.

Subject 034-0047002: 72 year old man with CHF, on oral conivaptan 80 mg/day. On Treatment Day 55, CPK 3587. Had recently received cephalexin for elbow bursitis and had complained of neck and shoulder pain. He was also taking lovastatin. Study medication interrupted for 4 days and lovastatin discontinued. By day 61, CPK 527.

Subject 033-0013002: 69 year old man with CHF, on oral conivaptan 80 mg/day and simvastatin (prohibited medication). Baseline CPK 25. On Study Day 37, CPK 337. On Study Day 87, CPK 6,041. Study drug and simvastatin stopped on Study Day 92. Study Day 92 CPK 3,563. Patient switched to pravastatin and conivaptan resumed Study Day 116.

Subject 020-0001002: 61 year old man with CHF on oral conivaptan 40 mg/day; also on simvastatin. On Treatment Day 88, reported myalgia both legs; CPK 2,474. Study drug permanently discontinued; bedrest for two days. Recovered by Study Day 130.

For myopathy, the clinical reviewer used a case definition of CPK >10x uln and muscle symptoms. It appears that one case of rhabdomyolysis, two cases of myopathy, and one case of significant elevation of CPK occurred. All were in CHF patients taking at least one prohibited statin and oral conivaptan. These cases are likely due to elevation of statin drug levels by conivaptan's inhibition of CYP3A4 metabolism, rather than a primary effect of conivaptan on muscle.

As mentioned earlier, protocol violations concerning administration of prohibited medications were common in the Phase 3 protocols, despite the highly controlled nature of the clinical trial setting. The clinical reviewer recommends that the sponsor give further thought to the management of risk of interactions of conivaptan and CYP3A4-metabolized drugs, particularly statins.

The clinical reviewer wanted to know if rhabdomyolysis could occur in a patient receiving a statin concomitantly with conivaptan given for only four days. A search of the Adverse Event Reporting System (AERS) revealed two cases of rhabdomyolysis occurring after atorvastatin overdose; therefore, acute exposure to high levels of statin has been associated with rare cases of rhabdomyolysis.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The sponsor elicited adverse events by open-ended query of study subjects at each study visit. These and all other adverse events volunteered by study subjects were recorded. For Study -027, this occurred daily during the treatment phase. For patients in CHF studies, a "Living with Heart Failure" instrument was also used to elicit heart failure symptoms and functional status. Investigators also reported any observations. MedDRA terms were used in the NDA.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The clinical reviewer examined many case report forms for evaluation of deaths and adverse events described above. In general, the assigned adverse event term closely resembled the original adverse event term used by the investigator. The clinical reviewer previously described a few cases of discontinuation from study where the reason for discontinuation was listed by the sponsor as "admin/other", but clinical review of the case report revealed that discontinuation was actually due to an adverse event. The clinical reviewer grouped some terms in the previous sections in order to get a better sense of certain types of adverse events, such as hypovolemia-related events, and heart failure-related events. There was no evidence of deliberate splitting or lumping of terms on the part of the sponsor. The coding of adverse events did not appear to differ between placebo and treatment groups.

7.1.5.3 Incidence of common adverse events

Dry mouth, thirst and polyuria were common and were expected events related to the physiology of conivaptan action. The other most commonly reported treatment-emergent adverse events (occurring in >5% of any group) identified by the sponsor in the Phase 3 controlled hyponatremia population were infusion site reactions, hypotension, pyrexia, diarrhea, renal dysfunction and vomiting. These events, presented for Study -027 alone and the full safety population, are detailed in the following table. Please note that the clinical reviewer grouped all related events under the footnoted terms in the table below. This grouping may result in somewhat different incidence rates than those reported by the sponsor.

Table 7.1.5.3: Incidence of Most Common Adverse Events

	Study -027			Full Safety Population	
	Pbo n = 29	Coni 40 n = 29	Coni 80 n = 26	Pbo n = 332	Coni n = 896
Infusion Site Reactions[1]	2 (6.9%)	14 (48.2%)	14 (53.8%)	10 (3.0%)	71 (7.9%)
Hypotension[2]	4 (13.8%)	12 (41.3%)	7 (26.9%)	27 (8.1%)	84 (9.4%)
Pyrexia		3 (10.3%)	2 (7.7%)	2 (0.6%)	14 (1.6%)

Table 7.1.5.3: Incidence of Most Common Adverse Events

	Study -027			Full Safety Population	
	Pbo n = 29	Coni 40 n = 29	Coni 80 n = 26	Pbo n = 332	Coni n = 896
Diarrhea		2 (6.9%)	2 (7.7%)	5 (1.5%)	22 (2.5%)
Renal Dysfunction[3]	2 (6.9%)	2 (6.9%)	4 (15.3%)	14 (4.2%)	46 (5.1%)
Vomiting		2 (6.9%)	1 (3.8%)	6 (1.8%)	8 (0.9%)

Source: Sponsor's Table 12-2, -027 study report; sponsor's Table 2.7.4-663
1 For clinical reviewer's included terms, see Section 7.1.3.3.2. Full safety population includes both oral and IV studies, and therefore dilutes overall incidence of infusion site reactions.
2 For clinical reviewer's included terms, see Section 7.1.3.3.3
3 Clinical reviewer's included terms were renal failure NOS, renal failure aggravated, acute prerenal failure, oliguria, renal failure acute, blood creatinine increased, BUN:Cr ratio increased, blood urea increased, urine output decreased, azotaemia, renal disorder NOS, and renal impairment NOS. Also, please see the SAE Section 7.1.2.4.3 renal case reports; for some events which were coded as other event terms, renal dysfunction also occurred. These additional events may not be reflected in this table, because CRFs were provided only for SAEs.

Infusion site reactions and hypotension are further discussed above in Sections 7.1.3.3.2 and 7.1.3.3.3. These events occurred more commonly among conivaptan treated subjects than among placebo-treated subjects. For hypotension, this difference was more marked in the IV Study -027 than in the full safety population. In Study -027, the single well-controlled IV study, renal dysfunction occurred more frequently among patients in the 80 mg/day conivaptan group than among placebo-treated patients. Pyrexia and diarrhea occurred somewhat more frequently among conivaptan-treated subjects than placebo-treated subjects, while vomiting occurred slightly more frequently among placebo subjects. Diarrhea was mild and self-limited. Pyrexia occurred only among subjects who also experienced infusion site reactions or pneumonia. A full listing of common adverse events in controlled Phase 3 trials follows in Section 7.1.5.4.

7.1.5.4 Common adverse event tables

The following table provides an overall summary of treatment-emergent adverse events for the full safety population, which includes all Phase 2 and Phase 3 studies, both IV and oral, for both hyponatremia and CHF.

Table 7.1.5.4.1: Overall Summary of Treatment-emergent Adverse Events (TEAEs), Full Safety Population[1]

		IV		Oral		IV + Oral	
		Pbo n (%)	Coni n (%)	Pbo n (%)	Coni n (%)	Pbo n (%)	Coni n (%)
Number of Subjects		92	208	240	688	332	896
Number of TEAEs Reported		114	389	554	1848	668	2237
Number of Subjects with TEAEs		57 (62)	144 (69)	151 (63)	445 (65)	208 (63)	589 (66)
Number of Serious TEAEs		23	57	28	160	51	217
Number of Subjects with TEAEs by							

Table 7.1.5.4.1: Overall Summary of Treatment-emergent Adverse Events (TEAEs), Full Safety Population[1]							
		IV		Oral		IV + Oral	
		Pbo n (%)	Coni n (%)	Pbo n (%)	Coni n (%)	Pbo n (%)	Coni n (%)
Severity[3]							
	Mild	22 (24)	60 (29)	66 (27)	186 (27)	87 (26)	246 (27)
	Mod	26 (28)	57 (27)	71 (30)	183 (27)	97 (29)	240 (27)
	Severe	9 (10)	27 (13)	15 (6)	75 (11)	24 (7)	102 (11)
	Severity Unknown	0	0	0	1 (<1)	0	1 (<1)
Number of Subjects Discontinued Due to TEAEs		4 (4)	11 (5)	8 (3)	31 (5)	12 (4)	42 (5)
Number of Deaths Due to TEAEs[2]		7 (8)	9 (4)	2 (1)	17 (2)	9 (3)	26 (3)
Number of Deaths		8 (9)	10 (5)	5 (2)	17 (2)	13 (4)	27 (3)

[1] Studies -016, -017, -020, -021, -022, -023, -024, -025, -026, -027, -032, -033, -034, -038, -043, -044, -047
[2] Sponsor's assessment of deaths as due to TEAEs
[3] Severity assessment by sponsor
Source: Sponsor's Table 2.7.4-18, Module 2, Section 2.7.4, p 86

The sponsor's table 2.7.4-58 details the number and percentage of patients with TEAEs with an incidence of >1% and a higher incidence for conivaptan than placebo, for the Phase 3 controlled studies. This table provides the best comparison between event rates for placebo and conivaptan.

Table 2.7.4-58: Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

	Controlled IV Hyponatremia (027)			Controlled Oral Hyponatremia (026, 043)			All Controlled IV + Oral Hyponatremia (026, 027, 043)	
System Organ Class MedDRA Term	Placebo n(%) (N= 29)	YM087 40/d n(%) (N= 29)	YM087 80/d n(%) (N= 26)	Placebo n(%) (N= 53)	YM087 40/d n(%) (N= 51)	YM087 80/d n(%) (N= 53)	Placebo n(%) (N= 82)	YM087 Any Dose n(%) (N=159)
Blood and lymphatic system disorders	2 (7)	3 (10)	0	3 (6)	4 (8)	4 (8)	5 (6)	11 (7)
Anaemia NOS	2 (7)	2 (7)	0	3 (6)	4 (8)	3 (6)	5 (6)	9 (6)
Nephrogenic anaemia	0	0	0	0	0	1 (2)	0	1 (<1)
Normochromic normocytic anaemia	0	1 (3)	0	0	0	0	0	1 (<1)
Cardiac disorders	5 (17)	5 (17)	2 (8)	5 (9)	7 (14)	2 (4)	10 (12)	16 (10)
Atrioventricular block NOS	0	1 (3)	0	0	0	0	0	1 (<1)
Cardiac failure NOS	0	1 (3)	0	0	3 (6)	0	0	4 (3)
Cardiac failure chronic	0	0	0	0	1 (2)	0	0	1 (<1)
Cardiac failure congestive	0	1 (3)	0	0	0	0	0	1 (<1)
Congestive cardiac failure aggravated	1 (3)	1 (3)	2 (8)	1 (2)	0	1 (2)	2 (2)	4 (3)
Mitral valve incompetence	0	1 (3)	0	0	0	0	0	1 (<1)
Myocardial ischaemia	0	1 (3)	0	0	0	0	0	1 (<1)
Supraventricular tachycardia	0	0	0	0	1 (2)	0	0	1 (<1)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

	Controlled IV Hyponatremia (027)			Controlled Oral Hyponatremia (026, 043)			All Controlled IV + Oral Hyponatremia (026, 027, 043)	
System Organ Class MedDRA Term	Placebo n(%) (N= 29)	YM087 40/d n(%) (N= 29)	YM087 80/d n(%) (N= 26)	Placebo n(%) (N= 53)	YM087 40/d n(%) (N= 51)	YM087 80/d n(%) (N= 53)	Placebo n(%) (N= 82)	YM087 Any Dose n(%) (N=159)
Tachycardia NOS	0	0	0	0	1 (2)	0	0	1 (<1)
Ventricular extrasystoles	0	1 (3)	0	0	0	0	0	1 (<1)
Ventricular tachycardia	0	0	0	1 (2)	1 (2)	1 (2)	1 (1)	2 (1)
Ventricular triguminy	0	0	0	0	1 (2)	0	0	1 (<1)
Endocrine disorders	0	1 (3)	0	0	0	0	0	1 (<1)
Hypopituitarism	0	1 (3)	0	0	0	0	0	1 (<1)
Eye disorders	0	0	1 (4)	3 (6)	1 (2)	1 (2)	3 (4)	3 (2)
Eye pruritus	0	0	1 (4)	0	0	0	0	1 (<1)
Visual disturbance NOS	0	0	0	0	1 (2)	0	0	1 (<1)
Gastrointestinal disorders	7 (24)	7 (24)	5 (19)	9 (17)	6 (12)	9 (17)	16 (20)	27 (17)
Abdominal pain NOS	2 (7)	0	2 (8)	0	0	0	2 (2)	2 (1)
Constipation	2 (7)	0	0	2 (4)	2 (4)	3 (6)	4 (5)	5 (3)
Diarrhoea NOS	0	2 (7)	2 (8)	1 (2)	0	2 (4)	1 (1)	6 (4)
Dry mouth	0	2 (7)	0	0	0	1 (2)	0	3 (2)
Dyspepsia	0	1 (3)	0	0	1 (2)	1 (2)	0	3 (2)
Flatulence	0	0	0	0	0	1 (2)	0	1 (<1)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

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Gastritis NOS	0	1 (3)	1 (4)	0	0	0	0	2 (1)
Gingival bleeding	0	0	0	0	1 (2)	0	0	1 (<1)
Hiatus hernia	0	0	1 (4)	0	0	0	0	1 (<1)
Loose stools	0	0	1 (4)	1 (2)	0	0	1 (1)	1 (<1)
Nausea	2 (7)	0	0	2 (4)	2 (4)	2 (4)	4 (5)	4 (3)
Vomiting NOS	0	2 (7)	1 (4)	2 (4)	0	0	2 (2)	3 (2)
General disorders and administration site conditions	3 (10)	11 (38)	12 (46)	8 (15)	6 (12)	7 (13)	11 (13)	36 (23)
Anasarca	0	1 (3)	0	0	0	0	0	1 (<1)
Application site erytherm	0	2 (7)	1 (4)	0	0	0	0	3 (2)
Application site pain	0	1 (3)	0	0	0	0	0	1 (<1)
Application site reaction NOS	0	0	1 (4)	0	0	0	0	1 (<1)
Application site swelling	0	1 (3)	0	0	0	0	0	1 (<1)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

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Chest pain	0	0	0	0	1 (2)	0	0	1 (<1)
Fatigue	0	0	0	0	0	1 (2)	0	1 (<1)
Feeling hot	0	1 (3)	0	0	0	0	0	1 (<1)
Infusion site inflammation	0	0	1 (4)	0	0	0	0	1 (<1)
Infusion site pain	0	0	1 (4)	1 (2)	0	0	1 (1)	1 (<1)
Infusion site phlebitis	1 (3)	0	3 (12)	0	0	0	1 (1)	3 (2)
Infusion site reaction	0	2 (7)	2 (8)	0	0	0	0	4 (3)
Infusion site swelling	0	0	1 (4)	0	0	0	0	1 (<1)
Injection site bruising	0	0	1 (4)	0	0	0	0	1 (<1)
Injection site erythema	0	0	1 (4)	0	0	0	0	1 (<1)
Injection site inflammation	0	0	1 (4)	0	0	0	0	1 (<1)
Injection site phlebitis	0	3 (10)	1 (4)	0	0	0	0	4 (3)
Injection site swelling	0	2 (7)	0	0	0	0	0	2 (1)
Oedema NOS	0	1 (3)	0	0	1 (2)	0	0	2 (1)
Oedema peripheral	1 (3)	1 (3)	0	1 (2)	1 (2)	3 (6)	2 (2)	5 (3)
Pain NOS	0	0	1 (4)	1 (2)	1 (2)	0	1 (1)	2 (1)
Pyrexia	0	3 (10)	2 (8)	1 (2)	3 (6)	1 (2)	1 (1)	9 (6)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

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Rigors	0	0	1 (4)	0	0	0	0	1 (<1)
Hepatobiliary disorders	0	1 (3)	0	1 (2)	1 (2)	0	1 (1)	2 (1)
Cholestasis	0	0	0	0	1 (2)	0	0	1 (<1)
Hepatic failure	0	1 (3)	0	0	0	0	0	1 (<1)
Infections and infestations	4 (14)	2 (7)	4 (15)	3 (6)	6 (12)	7 (13)	7 (9)	19 (12)
Cellulitis	0	0	0	0	0	1 (2)	0	1 (<1)
Injection site infection	0	0	1 (4)	0	0	0	0	1 (<1)
Nasopharyngitis	0	0	0	0	1 (2)	1 (2)	0	2 (1)
Oral candidiasis	0	0	0	0	1 (2)	0	0	1 (<1)
Pneumonia NOS	0	0	2 (8)	0	2 (4)	1 (2)	0	5 (3)
Sepsis NOS	0	1 (3)	0	0	0	0	0	1 (<1)
Skin fungal infection NOS	0	0	0	0	0	1 (2)	0	1 (<1)
Urinary tract infection NOS	2 (7)	1 (3)	1 (4)	2 (4)	2 (4)	4 (8)	4 (5)	8 (5)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

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System Organ Class MedDRA Term	Placebo n(%) (N= 29)	YM087 40/d n(%) (N= 29)	YM087 80/d n(%) (N= 26)	Placebo n(%) (N= 53)	YM087 40/d n(%) (N= 51)	YM087 80/d n(%) (N= 53)	Placebo n(%) (N= 82)	YM087 Any Dose n(%) (N=159)
Injury, poisoning and procedural complications	0	0	0	1 (2)	3 (6)	5 (9)	1 (1)	8 (5)
Drug toxicity NOS	0	0	0	0	1 (2)	1 (2)	0	2 (1)
Fall	0	0	0	0	1 (2)	2 (4)	0	3 (2)
Foot fracture	0	0	0	0	0	1 (2)	0	1 (<1)
Head injury	0	0	0	0	1 (2)	0	0	1 (<1)
Pneumothorax traumatic	0	0	0	0	0	1 (2)	0	1 (<1)
Investigations	0	0	5 (19)	5 (9)	5 (10)	3 (6)	5 (6)	13 (8)
Alanine aminotransferase increased	0	0	0	0	1 (2)	0	0	1 (<1)
Aspartate aminotransferase increased	0	0	0	0	2 (4)	0	0	2 (1)
Blood creatine increased	0	0	0	0	0	1 (2)	0	1 (<1)
Blood creatine phosphokinase increased	0	0	0	0	0	1 (2)	0	1 (<1)
Blood creatinine increased	0	0	1 (4)	0	0	1 (2)	0	2 (1)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

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Blood glucose increased	0	0	1 (4)	0	0	0	0	1 (<1)
Blood pressure decreased	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (<1)
Blood urea increased	0	0	1 (4)	0	0	0	0	1 (<1)
Body temperature increased	0	0	1 (4)	0	0	0	0	1 (<1)
Faecal occult blood positive	0	0	0	0	0	1 (2)	0	1 (<1)
Liver function test abnormal	0	0	1 (4)	0	1 (2)	0	0	2 (1)
Troponin increased	0	0	0	0	1 (2)	0	0	1 (<1)
Weight decreased	0	0	2 (8)	1 (2)	0	0	1 (1)	2 (1)
White blood cell count increased	0	0	0	0	1 (2)	0	0	1 (<1)
Metabolism and nutrition disorders	6 (21)	6 (21)	6 (23)	5 (9)	7 (14)	2 (4)	11 (13)	21 (13)
Anorexia	0	0	0	0	1 (2)	0	0	1 (<1)
Appetite decreased NOS	0	0	1 (4)	0	0	0	0	1 (<1)
Dehydration	0	2 (7)	0	0	0	0	0	2 (1)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

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Diabetes mellitus non-insulin-dependent	0	0	1 (4)	0	0	0	0	1 (<1)
Electrolyte depletion	0	0	1 (4)	0	0	0	0	1 (<1)
Fluid overload	0	0	0	0	1 (2)	0	0	1 (<1)
Hyperglycaemia NOS	0	1 (3)	0	0	0	0	0	1 (<1)
Hyperkalaemia	1 (3)	0	3 (12)	1 (2)	1 (2)	0	2 (2)	4 (3)
Hypoalbuminaemia	0	0	0	0	1 (2)	0	0	1 (<1)
Hypoglycaemia NOS	0	0	0	1 (2)	1 (2)	1 (2)	1 (1)	2 (1)
Hypokalaemia	2 (7)	2 (7)	0	1 (2)	2 (4)	1 (2)	3 (4)	5 (3)
Hypomagnesaemia	0	0	0	0	1 (2)	0	0	1 (<1)
Hyponatraemia	1 (3)	1 (3)	1 (4)	0	1 (2)	0	1 (1)	3 (2)
Hypovolaemia	1 (3)	1 (3)	1 (4)	1 (2)	2 (4)	0	2 (2)	4 (3)
Musculoskeletal and connective tissue disorders	1 (3)	1 (3)	2 (8)	2 (4)	3 (6)	2 (4)	3 (4)	8 (5)
Arthralgia	0	0	2 (8)	2 (4)	0	1 (2)	2 (2)	3 (2)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

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Muscle atrophy	0	1 (3)	0	0	0	0	0	1 (<1)
Muscle stiffness	0	0	0	0	1 (2)	0	0	1 (<1)
Myalgia	0	0	0	0	0	1 (2)	0	1 (<1)
Pain in extremity	0	0	0	0	1 (2)	0	0	1 (<1)
Pathological fracture	0	0	0	0	1 (2)	0	0	1 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (3)	0	1 (2)	1 (2)	0	1 (1)	2 (1)
Benign cardiac neoplasm	0	1 (3)	0	0	0	0	0	1 (<1)
Lung cancer stage unspecified (excl metastatic tumours to lung)	0	0	0	0	1 (2)	0	0	1 (<1)
Nervous system disorders	5 (17)	4 (14)	2 (8)	4 (8)	7 (14)	3 (6)	9 (11)	16 (10)
Cerebral arterial aneurysm	0	1 (3)	0	0	0	0	0	1 (<1)
Convulsions NOS	0	0	0	0	1 (2)	0	0	1 (<1)
Dizziness	1 (3)	0	1 (4)	1 (2)	1 (2)	2 (4)	2 (2)	4 (3)
Dizziness postural	0	1 (3)	0	0	0	0	0	1 (<1)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

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System Organ Class MedDRA Term	Placebo n(%) (N= 29)	YM087 40/d n(%) (N= 29)	YM087 80/d n(%) (N= 26)	Placebo n(%) (N= 53)	YM087 40/d n(%) (N= 51)	YM087 80/d n(%) (N= 53)	Placebo n(%) (N= 82)	YM087 Any Dose n(%) (N=159)
Encephalopathy	0	1 (3)	0	0	0	0	0	1 (<1)
Headache	2 (7)	1 (3)	0	2 (4)	4 (8)	1 (2)	4 (5)	6 (4)
Somnolence	0	0	0	0	1 (2)	0	0	1 (<1)
Syncope vasovagal	0	0	0	0	1 (2)	0	0	1 (<1)
Tremor	0	0	1 (4)	0	0	0	0	1 (<1)
Psychiatric disorders	3 (10)	2 (7)	3 (12)	3 (6)	3 (6)	2 (4)	6 (7)	10 (6)
Aggression	0	1 (3)	0	0	0	0	0	1 (<1)
Anxiety	0	0	0	0	0	1 (2)	0	1 (<1)
Confusional state	2 (7)	1 (3)	1 (4)	1 (2)	1 (2)	0	3 (4)	3 (2)
Depression	0	0	0	0	1 (2)	0	0	1 (<1)
Hallucination NOS	0	0	1 (4)	0	0	0	0	1 (<1)
Insomnia	0	0	1 (4)	2 (4)	2 (4)	1 (2)	2 (2)	4 (3)
Restlessness	0	0	1 (4)	0	0	0	0	1 (<1)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

	Controlled IV Hyponatremia (027)			Controlled Oral Hyponatremia (026, 043)			All Controlled IV + Oral Hyponatremia (026, 027, 043)	
System Organ Class MedDRA Term	Placebo n(%) (N= 29)	YM087 40/d n(%) (N= 29)	YM087 80/d n(%) (N= 26)	Placebo n(%) (N= 53)	YM087 40/d n(%) (N= 51)	YM087 80/d n(%) (N= 53)	Placebo n(%) (N= 82)	YM087 Any Dose n(%) (N=159)
Renal and urinary disorders	4 (14)	4 (14)	4 (15)	3 (6)	3 (6)	2 (4)	7 (9)	13 (8)
Azotaemia	0	1 (3)	0	0	0	0	0	1 (<1)
Dysuria	0	1 (3)	1 (4)	1 (2)	0	1 (2)	1 (1)	3 (2)
Polyuria	0	1 (3)	0	0	0	0	0	1 (<1)
Renal failure NOS	1 (3)	1 (3)	2 (8)	0	2 (4)	1 (2)	1 (1)	6 (4)
Renal failure acute	0	0	1 (4)	0	0	0	0	1 (<1)
Urinary incontinence	1 (3)	1 (3)	0	0	1 (2)	0	1 (1)	2 (1)
Urinary retention	0	0	0	0	0	1 (2)	0	1 (<1)
Reproductive system and breast disorders	0	0	1 (4)	0	0	1 (2)	0	2 (1)
Balanitis NOS	0	0	0	0	0	1 (2)	0	1 (<1)
Ovarian mass	0	0	1 (4)	0	0	0	0	1 (<1)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

	Controlled IV Hyponatremia (027)			Controlled Oral Hyponatremia (026, 043)			All Controlled IV + Oral Hyponatremia (026, 027, 043)	
System Organ Class MedDRA Term	Placebo n(%) (N= 29)	YM087 40/d n(%) (N= 29)	YM087 80/d n(%) (N= 26)	Placebo n(%) (N= 53)	YM087 40/d n(%) (N= 51)	YM087 80/d n(%) (N= 53)	Placebo n(%) (N= 82)	YM087 Any Dose n(%) (N=159)
Respiratory, thoracic and mediastinal disorders	6 (21)	3 (10)	1 (4)	4 (8)	5 (10)	6 (11)	10 (12)	15 (9)
Bronchitis NOS	0	0	0	0	1 (2)	0	0	1 (<1)
Bronchospasm NOS	0	0	0	0	0	1 (2)	0	1 (<1)
Chronic obstructive airways disease	0	0	1 (4)	0	0	0	0	1 (<1)
Chronic obstructive airways disease exacerbated	0	0	0	0	1 (2)	0	0	1 (<1)
Cough	1 (3)	0	0	0	2 (4)	1 (2)	1 (1)	3 (2)
Dyspnea	1 (3)	0	0	0	0	2 (4)	1 (1)	2 (1)
Dyspnea exacerbated	0	0	0	0	0	1 (2)	0	1 (<1)
Epistaxis	0	0	0	0	0	2 (4)	0	2 (1)
Hyperapnia	0	0	0	0	1 (2)	0	0	1 (<1)
Pharyngolaryngeal pain	2 (7)	0	0	1 (2)	1 (2)	0	3 (4)	1 (<1)
Pulmonary embolism	0	0	0	0	0	1 (2)	0	1 (<1)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

	Controlled IV Hyponatremia (027)			Controlled Oral Hyponatremia (026, 043)			All Controlled IV + Oral Hyponatremia (026, 027, 043)	
System Organ Class MedDRA Term	Placebo n(%) (N= 29)	YM087 40/d n(%) (N= 29)	YM087 80/d n(%) (N= 26)	Placebo n(%) (N= 53)	YM087 40/d n(%) (N= 51)	YM087 80/d n(%) (N= 53)	Placebo n(%) (N= 82)	YM087 Any Dose n(%) (N=159)
Skin and subcutaneous tissue disorders	1 (3)	2 (7)	3 (12)	1 (2)	1 (2)	2 (4)	2 (2)	8 (5)
Cyanosis peripheral	0	0	1 (4)	0	0	0	0	1 (<1)
Ecchymosis	0	1 (3)	0	0	0	0	0	1 (<1)
Erythema	0	0	1 (4)	0	0	0	0	1 (<1)
Purpura NOS	0	0	1 (4)	0	0	0	0	1 (<1)
Rash NOS	1 (3)	1 (3)	0	0	0	2 (4)	1 (1)	3 (2)
Skin disorder NOS	0	0	0	0	1 (2)	0	0	1 (<1)
Surgical and medical procedures	0	0	0	1 (2)	1 (2)	0	1 (1)	1 (<1)
Heart transplant	0	0	0	0	1 (2)	0	0	1 (<1)

Table 2.7.4-58 (cont'd): Number and Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class (Incidence of MedDRA Term>=1% and YM087 > Placebo) Pool 4D: Controlled Phase 2/3 IV + Oral Studies in Hyponatremia (Population: SAF) (026, 027, 043)

	Controlled IV Hyponatremia (027)			Controlled Oral Hyponatremia (026, 043)			All Controlled IV + Oral Hyponatremia (026, 027, 043)	
System Organ Class MedDRA Term	Placebo n(%) (N= 29)	YM087 40/d n(%) (N= 29)	YM087 80/d n(%) (N= 26)	Placebo n(%) (N= 53)	YM087 40/d n(%) (N= 51)	YM087 80/d n(%) (N= 53)	Placebo n(%) (N= 82)	YM087 Any Dose n(%) (N=159)
Vascular disorders	4 (14)	14 (48)	9 (35)	6 (11)	4 (8)	6 (11)	10 (12)	33 (21)
Aortic stenosis	0	1 (3)	0	0	0	0	0	1 (<1)
Deep vein thrombosis	0	2 (7)	0	0	0	0	0	2 (1)
Flushing	1 (3)	2 (7)	0	0	1 (2)	1 (2)	1 (1)	4 (3)
Hypertensive crisis	0	0	0	0	1 (2)	0	0	1 (<1)
Hypotension NOS	2 (7)	4 (14)	5 (19)	3 (6)	2 (4)	2 (4)	5 (6)	13 (8)
Orthostatic hypotension	0	3 (10)	1 (4)	2 (4)	0	3 (6)	2 (2)	7 (4)
Phlebitis NOS	1 (3)	4 (14)	4 (15)	0	0	0	1 (1)	8 (5)
Phlebitis superficial	0	0	1 (4)	0	0	0	0	1 (<1)
Thrombophlebitis	0	3 (10)	0	0	0	0	0	3 (2)

* All indicated doses are in milligrams/day
Note: Patients are assigned to a treatment group based on the nominal dose.
Data Source: TEAE.sd2 Program Source: Query1-3b.sas

7.1.5.5 Identifying common and drug-related adverse events

In addition to the common events noted by the sponsor, the clinical reviewer examined other groups of adverse event terms for the Phase 3 controlled studies in hyponatremia, and for the full safety population. These are detailed in the following table.

Table 7.1.5.5: Adverse Event Groupings for Chest Pain, Arrhythmia, Cardiac Failure, and Infections

	Study -027			Phase 3 Controlled Trials			Full Safety Pop	
	Pbo n = 29	Coni 40 n = 29	Coni 80 n = 26	Pbo n = 82	Coni 40 n = 80	Coni 80 n = 79	Pbo n = 332	All Coni n = 896
Acute Coronary Syndrome							1 (0.3%)	
Angina pectoris							2 (0.6%)	12 (1.3%)
Angina unstable							1 (0.3%)	3 (0.3%)
Chest discomfort							2 (0.6%)	6 (0.7%)
Chest pain					1 (1.3%)		12 (3.6%)	36 (4.0%)
Chest pain aggravated							1 (0.3%)	1 (0.1%)
Chest tightness								1 (0.1%)
All angina and chest pain terms					1 (1.3%)		19 (5.7%)	59 (6.7%)
Arrhythmia NOS								3 (0.3%)
Atrial fibrillation							2 (0.6%)	8 (0.9%)
Atrial flutter								5 (0.6%)
Atrial tachycardia							1 (0.3%)	
Supraventricular arrhythmia NOS							1 (0.3%)	
SVT					1 (1.3%)		1 (0.3%)	2 (0.2%)
Sinus bradycardia								1 (0.1%)
Sinus arrhythmia								1 (0.1%)
Sinus tachycardia							1 (0.3%)	1 (0.1%)
Supraventricular extrasystoles							1 (0.3%)	1 (0.1%)
AV block NOS		1 (3.4%)			1 (1.3%)			1 (0.1%)
AV block complete								1 (0.1%)
AV block first degree							6 (1.8%)	1 (0.1%)
Bradycardia NOS							4 (1.2%)	8 (0.9%)
BBB left							1 (0.3%)	1 (0.1%)
Sick sinus syndrome							1 (0.3%)	
Tachycardia NOS					1 (1.3%)		1 (0.3%)	3 (0.3%)
Ventricular arrhythmia NOS								2 (0.2%)
Ventricular bigeminy								2 (0.2%)
Ventricular extrasystoles		1 (3.4%)					1 (0.3%)	3 (0.3%)
Ventricular fibrillation							2 (0.6%)	1 (0.1%)
V tach				1 (1.2%)	1 (1.3%)	1 (1.3%)	6 (1.8%)	15 (1.7%)
Ventricular trigeminy					1 (1.3%)			1 (0.1%)
All arrhythmia and cardiac conduction system terms		2 (6.9%)		1 (1.2%)	2 (2.5%)		29 (8.7%)	61 (6.8%)
All supraventricular arrhythmia terms							5 (1.5%)	18 (2.0%)

Table 7.1.5.5: Adverse Event Groupings for Chest Pain, Arrhythmia, Cardiac Failure, and Infections

	Study -027			Phase 3 Controlled Trials			Full Safety Pop	
	Pbo n = 29	Coni 40 n = 29	Coni 80 n = 26	Pbo n = 82	Coni 40 n = 80	Coni 80 n = 79	Pbo n = 332	All Coni n = 896
All ventricular arrhythmia terms				1 (1.2%)	2 (2.5%)		9 (2.7%)	24 (2.7%)
Cardiac failure NOS		1 (3.4%)			4 (5.0%)		4 (1.2%)	13 (1.5%)
Cardiac failure acute								1 (0.1%)
Cardiac failure chronic					1 (1.3%)		1 (0.3%)	2 (0.2%)
Cardiac failure congestive		1 (3.4%)					1 (0.3%)	4 (0.4%)
Congestive cardiac failure aggravated	1 (3.4%)	1 (3.4%)	2 (3.8%)	2 (2.4%)		3 (3.8%)	9 (2.7%)	29 (3.2%)
Ischaemic cardiomyopathy								1 (0.1%)
All cardiac failure terms	1 (3.4%)	3 (10.3%)	5 (19.2%)	2 (2.4%)	5 (6.3%)	3 (3.8%)	15 (4.5%)	50 (5.6%)
Infections and infestations	4 (8.1%)	2 (6.9%)	4 (15.3%)	7 (8.5%)	8 (10.0%)	11 (13.9%)	45 (13.5%)	125 (13.9%)
Pneumonia			2 (3.8%)		4 (5.0%)	1 (1.3%)	5 (1.5%)	11 (1.2%)

Source: Sponsor's Table 2.7.4-663; Table 2.7.4-58; -027 study report Table 12-2

In the full safety population, angina and chest pain adverse event terms occurred somewhat more frequently in the conivaptan group than in the placebo group. This difference was not evident in the Phase 3 controlled IV and oral hyponatremia trials. The full safety population was enriched in patients with underlying CHF, and most angina episodes occurred in this population. Cardiac failure terms occurred somewhat more frequently in the conivaptan groups than in placebo groups for the IV Phase 3 hyponatremia Study -027 and in the full safety population. For the IV study, these terms occurred more frequently in the 80 mg conivaptan group than in the 40 mg group, although the overall numbers are small. No clear differences between conivaptan and placebo were noted for incidences of arrhythmias, pneumonia, or infections in general.

Pyrexia also occurred more frequently in conivaptan treated subjects than in placebo patients in the full safety population (1.6% vs 0.3%).

With respect to drug-relatedness of adverse events, causality (based on statistically significant differences between occurrence in conivaptan patients and placebo patients) is likely for serious renal adverse events, serious and nonserious hypovolemia events, serious and nonserious hypotensive events, and infusion site reactions. Such physiologically related effects as thirst and polyuria appear clearly related.

7.1.5.6 Additional analyses and explorations

7.1.5.6.1 Dose dependency of adverse events

No dose dependency for the occurrence of death was demonstrated in the controlled trials of conivaptan.

It is possible that some of the adverse events associated with conivaptan are dose dependent. The clinical reviewer compared the incidence of events for IV vs oral groups; and for lower vs higher doses within the oral and IV groups

Study subjects in the IV trials had a higher incidence of certain events than those in oral trials. This could represent a dose dependency, since the exposure for IV conivaptan was three times higher than that for oral conivaptan, and no subject who took oral conivaptan received equivalent exposure to the dose regimen proposed for labeling. However, differences in incidence of adverse events between IV and oral could be due to some pharmacologic difference other than drug levels/ exposure. Types of serious adverse events occurring more frequently in the IV studies than in oral studies included cardiac failure SAEs (4.3% vs 2.6%), arrhythmia SAEs (2.4% vs 1%), infection SAEs (6.7% vs 1.3%), renal SAEs (4.3% vs 2.6%) and respiratory SAEs (3.4% vs 1.9%). There was no significant difference between IV and oral for hypovolemia SAEs. When examining all AEs, whether deemed serious or not, hypotension-related AEs occurred more frequently in IV conivaptan subjects than in oral conivaptan subjects. Overly rapid correction of serum sodium occurred more frequently among IV conivaptan subjects than oral subjects.

The incidence of overly rapid correction of serum sodium was equal between the IV 40 and 80 mg conivaptan groups. Among IV conivaptan subjects who experienced overly rapid correction of serum sodium, more adverse events were reported in the 80 mg dose group than in the 40 mg dose group. Infusion site reactions appeared to be dose-dependent in Study -027 and in the intensive QTc study submitted during the review cycle (see Section 7.1.12). Cardiac failure-related adverse events occurred more frequently in the Study -027 80 mg IV group (15.6%) than in the 40 mg group (6.9%).

Among oral conivaptan patients in the controlled hyponatremia trials, dose dependency was not noted for any particular event or group of events.

7.1.5.6.2 Explorations to time of onset

When overly rapid correction of serum sodium occurred, it almost always occurred on the first day of treatment. Among those patients who experienced serious renal adverse events, the mean duration of conivaptan therapy prior to first recorded onset of a serious renal adverse event was 31 days. The median time to event, however, was six days, and 12/27 serious renal adverse events (44%) occurred in subjects who had taken conivaptan for 4 or fewer days.

7.1.5.6.3 Demographic interactions for adverse events

Among deaths in the development program, the proportions of men (62% of all deaths) and women (32% of all deaths) were the same as the overall demographic of the full safety program. There was also no difference by race (white vs nonwhite). For age, the percentage of subjects dying who were less than 65 years old was somewhat lower than the overall demographic (42% of deaths vs 58% of overall demographic). Deaths occurred somewhat more frequently among subjects age $\geq$ 65 years (58% of deaths vs 42% of overall demographic) and among subjects age >75 years (38% of deaths vs 17% of demographic). However, the very elderly subjects tended to have severe underlying disease, and several were made "DNR" prior to death.

For anemia terms, cardiac failure terms, hypotension terms and renal impairment terms, there was no difference in incidence by age or gender. This was also true for race, except for renal and urinary disorders in the pool of all IV studies (Source: Sponsor's Tables 2.7.4- 395, -396, -419, -420, -442 and -443). In these IV studies, renal and urinary disorder terms occurred only in white subjects (Source: Sponsor's Table 2.7.4-443).

In the controlled Phase 3 hyponatremia trials, patients who were hypervolemic at entry had a higher overall incidence of TEAEs (78%) when compared with patients who were euvolemic at baseline (66%). For hypervolemic patients, the overall incidence of TEAEs was higher in the conivaptan group (78%) than in the placebo group (61%). This difference was not evident in the euvolemic patients, where the incidence was 66% for conivaptan and 66% for placebo. When considering Study -027 alone (the single controlled Phase 3 IV hyponatremia trial), there was no difference in the incidence of TEAEs when comparing patients who were hypervolemic at baseline to those who were

euvolemic at baseline (82% vs 83%). In the oral Phase 3 hyponatremia studies (-026 and -043), however, the incidence of TEAEs was higher for hypervolemic patients than for euvolemic patients for both the 40 mg/day conivaptan dose (85% for hypervolemic vs 58% for euvolemic) and 80 mg/day conivaptan dose (60% for hypervolemic vs 55% for euvolemic). In the three Phase 3 hyponatremia trials, the groups of patients who were hypervolemic at baseline consisted almost entirely of CHF patients, since cirrhosis patients were excluded by the abnormal liver function test exclusion criterion. This finding of a higher incidence of TEAEs overall for hypervolemic patients further underscores the need for more safety information for CHF patients treated with the proposed IV dosing regimen for hyponatremia.

In the controlled Phase 3 hyponatremia trials, approximately 40% of patients (63 conivaptan patients and 31 placebo patients) carried a baseline diagnosis of CHF. Patients with a baseline diagnosis of CHF who were treated with conivaptan had a higher incidence of treatment-emergent cardiac failure events (cardiac failure NOS, cardiac failure congestive, congestive cardiac failure aggravated) than those who were treated with placebo [8/63 (12.7%) for conivaptan vs 1/31 (3.2%) for placebo]. For the IV Study -027 alone, among CHF patients, more of these same treatment-emergent cardiac failure events occurred in conivaptan-treated patients [5/18 (27.8%)] than in placebo-treated patients [1/9 (11.1%)]. (Source: Sponsor's IAS Table 2.7.4-378-2). This provides yet another signal that more information is needed about the safety of the proposed IV dosing regimen in CHF patients.

7.1.6 Less Common Adverse Events

Less common adverse events of interest have been discussed in previous sections. No other distinctive uncommon adverse events occurred. There was no difference between the conivaptan and placebo groups for the occurrence of malignancy.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Safety laboratory testing for the controlled hyponatremia trials included routine chemistry, hematology, and urinalysis. CPK and liver function tests were also measured. Central laboratories, rather than local laboratories, were generally used in the development program. Abnormal laboratory values were followed to resolution. Some unscheduled laboratory values, such as those obtained while a subject was hospitalized apart from study visits, appeared in summary tables of laboratory values. However, not all laboratory values from hospitalizations, and not all laboratory values from adverse event narratives, were included in laboratory summary tables.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Previous sections (7.1.3.3.4 and 7.1.3.3.5) have discussed the differences in incidence for anemia-related laboratory and hepatobiliary-related laboratory, and these will not be further discussed in the laboratory section. Renal adverse events and creatinine outliers were also previously discussed, but the clinical reviewer will cover creatinine in somewhat greater depth here, as conivaptan appears to cause an increase in mean creatinine. The clinical reviewer also noted some differences between conivaptan and placebo for INR and glucose, and these are presented here. Creatinine and nonfasting glucose were among the studies routinely measured at multiple time points in most studies. INR was not measured repeatedly in all subjects, nor was fasting glucose. Hemoglobin and hematocrit were of interest to the reviewer because of the preclinical findings of bone marrow toxicity, and because of the possible signal of excess anemia events in conivaptan subjects. Clinical coagulation events have been previously discussed. There was no difference in the occurrence of diabetes mellitus between conivaptan and placebo groups.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Table 7.1.7.3.1: Mean Change from Minimum Baseline Value to End of Treatment for Serum Creatinine and Glucose

	Study-027			Controlled Phase 3 Hyponatremia Studies			Full Safety Population	
	Pbo	Coni 40	Coni 80	Pbo	Coni 40	Coni 80	Pbo	Coni
Creatinine (mg/dL)	-0.021	+0.243	+0.361	+0.020	+0.197	+0.263	+0.028	+0.132
Glucose (mg/dL)	+20.8	+40	+13.9	+24.5	+26.8	+14.8	+9.3	+17
Fasting glucose (mg/dL)	-5.9	+24.9	+10	+2.8	+6.4	+11	+2.6	+15.3
Hemoglobin (g/dL)	-0.54	-0.50	-0.44	-0.57	-0.30	-0.23	-0.06	-0.02
Hematocrit (%)	-1.58	-0.64	-1.62	-1.6	-0.33	-0.50	-0.07	+0.17

Source: Sponsor's IAS Tables 2.7.4 -CN3C, -CN4A, -CN4D, -HN3C, -HN4A and -HN4D

Mean serum creatinine consistently increased for conivaptan subjects compared to placebo subjects. In Study -027, this difference in group mean change between placebo and conivaptan was statistically significant (p 0.0001 for the differences from baseline) on Study Day 2 for the 80 mg/day group, and on Study Day 4 for both the 40 and 80 mg/day groups. This finding was dose-related. An accepted definition for a clinically significant rise in serum creatinine for an individual patient is an increase of 0.5 mg/dL or an increase of 25% from baseline (Cox 2002). In Study -027, mean change in creatinine

in the 80 mg/day conivaptan group met the latter criterion, indicating that the average patient in Study 027 had a clinically significant rise in serum creatinine. For the 40 mg/day conivaptan group, mean % increase in serum creatinine was 24%. At Study Day 4 in Study -027, mean changes in BUN were statistically significantly higher in the conivaptan groups (p 0.01), but this was not clearly dose-related. Please see Section 7.1.2.4.3 for a further discussion of serious clinical renal adverse events.

Mean changes in nonfasting glucose were not consistently different between conivaptan and placebo groups. However, mean rise in fasting glucose was consistently higher among conivaptan subjects than among placebo subjects, with marginal statistical significance. Dose dependency was not clearly demonstrated.

The sponsor also reported that mean INR decreased in the conivaptan groups relative to the placebo groups. For the full safety population, these mean changes were -0.061 for placebo vs -0.184 for conivaptan. For the controlled Phase 2/3 studies, these mean changes were +0.055 for placebo vs -0.019 for conivaptan.

Mean hemoglobin and hematocrit declined slightly more in the placebo group than in the conivaptan groups. One would expect end of study hemoglobin and hematocrits to be higher in the conivaptan groups than in the placebo groups if conivaptan caused hemoconcentration. These values do not suggest a significant conivaptan toxicity with regard to erythrogenesis, although the incidence of reported clinical anemia events was higher in the conivaptan groups than in the placebo groups for the full safety population (see Section 7.1.3.3.5).

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 7.1.7.3.2: Number and Percentage of Subjects with Treatment-emergent Abnormalities in Creatinine, Glucose, INR and PT

	-027			Phase 3 Controlled Hyponatremia			Full Safety Population	
	Pbo	Coni 40	Coni 80	Pbo	Coni 40	Coni 80	Pbo	Coni
Creatinine	4 (13.8%)	12 (42.9%)	13 (50.0%)	14 (18.2%)	26 (38.2%)	25 (38.5%)	127 (39.4%)	416 (47.3%)
Glucose	10 (43.5%)	16 (66.7%)	13 (59.1%)	26 (61.9%)	30 (65.2%)	30 (68.2%)	183 (66.8%)	545 (69.8%)
Fasting Glucose	1 (16.7%)	4 (57.1%)	3 (50.0%)	18 (40.0%)	22 (57.9%)	14 (41.2%)	40 (44.8%)	89 (50.6%)
INR	6 (31.6%)	5 (33.3%)	6 (35.3%)	7 (26.9%)	7 (38.9%)	8 (34.8%)	7 (11.1%)	15 (11.0%)
PT	5 (27.8%)	6 (40.0%)	6 (35.3%)	7 (29.2%)	8 (44.4%)	8 (34.8%)	26 (37.7%)	77 (47%)

Source: Sponsor's Tables 2.7.4-47, 2.7.4-175-1, and 2.7.5-175-2

Treatment-emergent abnormalities in serum creatinine occurred more frequently in the conivaptan groups than in the placebo groups; this effect occurred in a dose-dependent fashion. This difference was statistically significant for all three populations in the above table. Abnormal fasting glucose also emerged more frequently in conivaptan subjects than placebo subjects, although this was not clearly dose-dependent.

Treatment-emergent abnormalities in alkaline phosphatase occurred more frequently in conivaptan patients than in placebo patients in the full safety population (17.4% vs 13.7%).

For those subjects who had INR or PT measured, abnormal values were more likely to emerge in conivaptan subjects than in placebo subjects. This was not clearly dose-dependent. When one compares the incidence of abnormal INR between all Phase 2/3 IV studies and all Phase 2/3 oral studies, treatment-emergent INR occurred more frequently in IV subjects in both the conivaptan [11 (34.4%) for IV vs 4 (3.8%) for oral] and placebo groups [6 (31.6%) for IV vs 1 (2.3%) for oral]. When comparing patients in the Phase 2/3 hyponatremia studies to those in the Phase 3 CHF trials, abnormal INR was more likely to emerge among patients in the CHF trials than among patients in the hyponatremia trials, for both and conivaptan and placebo.

Treatment-emergent abnormal alkaline phosphatase values occurred more frequently in orally treated subjects than in IV subjects.

The number of subjects with treatment-emergent abnormalities in hemoglobin and hematocrit did not differ between placebo and conivaptan groups for any of these populations.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Laboratory outliers not previously discussed include those for creatinine (criterion for outlier specified as >1.6 mg/dL) and INR (criterion for outlier specified as >1.5). These are summarized in the following table. The sponsor did not prespecify ranges of clinical concern for glucose and fasting glucose.

Table 7.1.7.3.3: Laboratory Outliers for Creatinine and INR

	-027			Controlled Phase 3 Hyponatremia Studies			Full Safety Population	
	Pbo	**Coni 40**	**Coni 80**	**Pbo**	**Coni 40**	**Coni 80**	**Pbo**	**Coni**
Creatinine	1 (3.4%)	6 (21.4%)	10 (38.5%)	5 (6.5%)	10 (14.7%)	16 (24.6%)	64 (19.9%)	244 (27.7%)
INR	4 (21.1%)	1 (6.7%)	2 (11.8%)	4 (15.4%)	2 (11.1%)	2 (8.7%	4 (6.3%)	4 (2.9%)

Source: Sponsor's Tables 2.7.4-175 -23, -24, and -27

A creatinine value of >1.6 was reached more frequently in conivaptan groups than in placebo groups. This effect appeared dose-dependent, and was more marked in the single controlled IV hyponatremia trial, -027. The difference between placebo and conivaptan was statistically significant for all three populations in the above table. Outliers for increased INR were not consistently more frequent for either placebo or conivaptan; as mentioned earlier, mean INR actually decreased for conivaptan subjects compared to placebo.

The number of outliers of clinical concern for hemoglobin (<11 g/dL for women and <12.5 g/dL for men) and hematocrit (<33% for women and <37% for men) did not differ between placebo and conivaptan groups for any of the above three populations. See Section 7.1.3.3.5 for a discussion of clinical adverse events of anemia.

A clinically significant elevation of alkaline phosphatase (defined as >220 mg/dL) emerged in a higher percentage of conivaptan patients (7.9%) than placebo patients (3.2%) in the three controlled hyponatremia trials. This was not dose-dependent. In the full safety population, an alkaline phosphatase value >220 mg/dL emerged in 12.2% of conivaptan patients and 9.8% of placebo patients.

Three laboratory events were reported to have led to discontinuation from study:

Subject 020-0054002: Discontinued eight months after first onset of elevated liver function tests (LFTs). SGOT 63 IU/L and SGPT 80 IU/L at time of discontinuation.

Subject 027-0072905: Discontinued eight days after noted to have a BUN of 37.3 mg/dL and a creatinine of 2.034 mg/dL.

Subject 034-0013004: Discontinued two weeks after onset of hyperkalemia (K 5.7 mEq/L) and acute renal failure.

7.1.7.4 Additional analyses and explorations

Dose Dependency of Laboratory Abnormalities:

Mean increase in creatinine, incidence of treatment-emergent abnormal creatinine, and incidence of creatinine >1.6 mg/dL all appeared to occur in a dose-dependent fashion.

7.1.7.5 Special assessments

Hepatobiliary laboratory abnormalities were discussed in Section 7.1.3.3.4.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were obtained in all clinical studies of conivaptan.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The clinical reviewer analyzed vital signs for each of three study groupings: Study -027, the single controlled Phase 3 IV hyponatremia study; the pool of the three Phase 3 controlled hyponatremia studies, oral and IV (-027, -026 and -043); and the full safety population of all Phase 2/3 oral and IV studies in hyponatremia and CHF.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

For Study -027, mean supine and standing systolic blood pressures declined significantly in the conivaptan groups compared to the placebo group. These changes are illustrated in the following table:

Table 7.1.8.3.1: Changes in Supine and Standing Systolic Blood Pressures (in mmHg), Study -027

	Pbo	Coni 40	Coni 80	P Value for Difference Between Pbo and all Coni
Mean Baseline Supine SBP	125.0	145.9	125.3	
Mean Change in Supine SBP from Baseline to End of Study	+5.3	-14.4	-3.1	0.002
Mean Baseline Standing SBP	122.1	141.8	120.9	
Mean Change in Standing SBP from Baseline to End of Study	+5.5	-14.6	-7.6	0.008

Source: Sponsor's Table 2.7.4-65

Mean supine and standing SBP increased in the placebo group and declined in both conivaptan groups. Although a greater mean decline occurred in the conivaptan 40 mg/day group, interpretation is hampered by higher mean baseline systolic blood pressures (SBPs) for 40 mg/day group patients. For the full safety population, mean standing systolic blood pressure decreased in the conivaptan group (mean change -6.8 mmHg) and increased in the placebo group (mean change -1.3 mmHg). This difference was more marked among the group of all IV subjects in Phase 2 and Phase 3 trials, where the mean change in the conivaptan groups was -11.4 mmHg and the mean change in the placebo groups was +5.5 mmHg. Degree of change in heart rate and weight did not differ between placebo for Study -027, the group of Phase 3 hyponatremia studies, or for the full safety population.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

As previously discussed (see sections 7.1.2.4.1 and 7.1.3.3.3), hypotension occurred more frequently in subjects taking conivaptan; this effect was more marked in the single Phase 3 hyponatremia study (-027). Significant treatment-emergent changes in heart rate and weight did not occur with greater frequency in conivaptan-treated subjects than in placebo subjects.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

As previously discussed, dropout due to hypotension occurred more commonly in conivaptan-treated subjects than in placebo subjects.

7.1.8.4 Additional analyses and explorations

The declines in mean systolic blood pressure in Study -027 did not show evidence of dose dependency.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

In the preclinical phase, the sponsor conducted a study evaluating the inhibitory effect of conivaptan on the human ether-a-go-go-related gene (HERG) potassium channel expressed in human embryonic kidney cells, using dofetilide as a positive control. The IC50 value of dofetilide was 36 nM for inhibitory effect on relative tail current in HEK293 cells expressing the HERG potassium channel. The IC50 value of conivaptan was 2.92 μM (2,920 nM); the effect was concentration dependent. This modest *in vitro* effect would generally be interpreted as having a low but finite risk of clinical manifestations at the plasma drug concentrations seen in healthy volunteers. Because of this finding, the FDA requested that the sponsor perform an intensive clinical study of the effect of conivaptan on the QT interval. This study is reviewed below in Section 7.1.12.

Electrocardiograms (ECGs) were measured in all clinical trials. In the Phase 3 controlled hyponatremia trials, resting ECGs were performed at the end of the baseline phase and on the last day of treatment (Study Day 4 for -027, and Day 5 for Studies -026 and -043).

Ventricular dysrhythmias did not occur more frequently in conivaptan patients than in placebo patients in Study -027, the pool of controlled Phase 3 hyponatremia trials, or the full safety population. No cases of torsades de pointes were reported in the development program.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

For the pool of all Phase 2/3 studies, ECG results (rate, PR, QRS, QT and QTc) were summarized using mean and standard deviation for each treatment group at baseline and endpoint. Changes from baseline were compared across treatment groups.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

For Study -027, there was no significant change from baseline to endpoint for PR interval, QRS duration or QTc interval. Heart rate declined slightly more numerically in the conivaptan groups than in the placebo groups, but this difference was not statistically significantly different. Uncorrected QT declined more in the conivaptan groups than in the placebo groups, with a p value for the difference between placebo and conivaptan of 0.019. For QT, mean placebo change from baseline to endpoint was +9.9 ± 28.15 msec, mean change for the 40 mg/day conivaptan group was -13 ± 31.31, and mean change for the 80 mg/day group was -24.6 ± 40.61 msec. Because the QTc was not significantly different between conivaptan and placebo, this difference was likely due to the modest decline in heart rate seen in conivaptan patients.

For the pool of all Phase 3 hyponatremia studies, there was no significant change from baseline to endpoint for heart rate, PR interval, QRS duration, QT interval, or QTc interval.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

For Study -027, no patients had a shift in QTc from baseline to endpoint of ≥ 60 msec.

For the pool of all Phase 3 hyponatremia trials, 2/104 patients taking oral conivaptan had a shift in QTc from baseline to endpoint of ≥ 60 msec using the Bazett formula. No placebo patients had a QTc shift of ≥ 60 msec.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

In Study -027, one placebo and three conivaptan patients had a baseline QTc ≥ 500 msec. At end of treatment, no placebo patients and one conivaptan patient had a QTc ≥ 500 msec (Bazett formula).

For the pool of all Phase 3 hyponatremia studies, two placebo and eleven conivaptan patients had a baseline QTc ≥ 500 msec. At end of treatment, two placebo patients and six conivaptan patients had a QTc ≥ 500 msec (Bazett formula).

Source: Sponsor's Table 2.7.4-50

7.1.9.4 Additional analyses and explorations

An intensive QT study was performed and is discussed in Section 7.1.12.

7.1.10 Immunogenicity

Conivaptan is a nonpeptide vasopressin receptor antagonist and therefore likely carries less *a priori* risk of immunogenicity than a therapeutic protein would carry. Specific studies of immunogenicity were not done in humans or animals. There was no evidence to suggest immunogenicity in animals.

7.1.11 Human Carcinogenicity

Please see Dr. Alavi's toxicology review for a complete discussion of the sponsor's carcinogenicity program. The sponsor's extensive animal carcinogenicity studies revealed no clinical concerns for carcinogenic potential of conivaptan.

7.1.12 Special Safety Studies

The sponsor performed an intensive placebo- and positive- controlled study of the ECG effects of intravenous conivaptan in 161 healthy male and female volunteers. This study report was submitted during the review cycle and may be found via the path \\CDSESUB1\N21697\N_000\2004-03-31 .

The study design was evaluated by FDA Biopharmacology prior to the sponsor initiating the study, and was felt to be of adequate design, using the FDA's Concept Paper on the Clinical Evaluation of QT/QTc Prolongation. Subjects were randomized to one of four treatments: placebo, moxifloxacin (positive control), IV conivaptan 40 mg/day, or IV conivaptan 80 mg/day. Digital ECGs were obtained by continuous recorder on Study Day 0, 1 and 4. ECGs from numerous predetermined time points were read using a high-resolution on-screen caliper method.

For the primary endpoint (change from baseline in individually corrected QT interval measured in msec), the lease square mean differences from placebo and 95% CIs were:
Vaprisol 40 mg minus placebo: -2.55 (-5.23, +0.17)
Vaprisol 80 mg minus placebo: -2.58 (-5.29, +0.13)

The QTc changes from baseline for the placebo group on Days 1 and 4 were -1 and -3 msec respectively. The moxifloxacin group demonstrated adequate assay sensitivity, with a placebo-corrected change from baseline QTc of +7 and +10 msec on Days 1 and 4, respectively. For the 40 mg/day conivaptan group, placebo-corrected QTc changes from baseline were -4 and -2 msec on Days 1 and 4, respectively. For the 80 mg/day conivaptan group, placebo-corrected QTc changes from baseline were -3 and -2 msec on Days 1 and 4, respectively.

No subject developed a new absolute QT value of >500 msec. On Day 1, one subject each in the moxifloxacin and 80 mg/day conivaptan groups had >60 msec change from

baseline in QTc. No subjects had a >60 msec change from baseline in QTc at steady state.

Injection site irritation was common in the conivaptan groups, occurring in 19.5% of subjects in the 40 mg/day group, and in 47.5% of subjects in the 80 mg/day group.

In summary, conivaptan does not appear to be associated with QTc prolongation. The small decrease in placebo-corrected QTc seen in the conivaptan groups is unlikely to be of clinical significance (Wever 2004).

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No specific studies of abuse potential or withdrawal phenomena were done for conivaptan. No adverse events related to abuse or withdrawal phenomena were noted. No overdoses occurred. Withdrawal and abuse concerns are low for conivaptan because of the proposal for short-term use in hospitalized patients.

7.1.14 Human Reproduction and Pregnancy Data

No pregnant subjects were treated with conivaptan and no subjects became pregnant while participating in conivaptan trials.

Please see Dr. Alavi's toxicology review for details of the effects of conivaptan on reproduction and pregnancy in animal studies. In rats, conivaptan had effects on estrus cycles, fetal viability and development, parturition , and neonatal growth and development. Conivaptan has antagonistic effects on the rat oxytocin receptor, which could contribute to delayed parturition or inhibition of milk secretion. However, conivaptan did not exhibit these antagonistic effects on the oxytocin receptor in rabbits; the rabbit oxytocin receptor is more similar to the human oxytocin receptor than the rat oxytocin receptor is to the human oxytocin receptor. In rats, conivaptan was distributed to fetus via placental transfer and to neonates via milk.

The clinical need for the use of conivaptan in pregnant women is likely to be very low. Physiologic changes occur during pregnancy, with a reset osmostat and release of vasopressin at lower levels of plasma osmolality for pregnant women than in nonpregnant women. The placenta produces a vasopressinase that rapidly inactivates vasopressin. Vasopressinase levels increase dramatically in normal pregnant women. These changes in water metabolism that occur in pregnancy are physiologic. Occasionally, pregnant women develop a form of diabetes insipidus due to excessive vasopressinase action. However, in this disorder, if serum sodium changes, it would increase rather than decrease.

Drs. Alavi and Davis-Bruno, toxicology reviewers, recommend that conivaptan be in Pregnancy Category C, and the clinical reviewer concurs.

7.1.15 Assessment of Effect on Growth

In humans, conivaptan was studied only in adults. As mentioned above, conivaptan had adverse effects on neonatal growth and development in rats.

7.1.16 Overdose Experience

No cases of conivaptan overdose occurred in the clinical development program. Searches of the medical literature and of the AERS database revealed no reports of conivaptan or other vasopressin receptor antagonist overdose.

7.1.17 Postmarketing Experience

Conivaptan has not been marketed in any country. No other vasopressin receptor antagonist has yet been marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

During the review cycle, the sponsor submitted information regarding an IV vs oral bioequivalence study that revealed that very few study subjects (n = 63) in their development program had actually been exposed to the full proposed dose for labeling. As discussed earlier, during development, the sponsor had elected to pursue only an IV formulation for short-term use in hospitalized patients. This decision occurred because the drug is a potent inhibitor of CYP3A4, and a case of rhabdomyolysis had occurred in a study subject also taking simvastatin. The sponsor wished to do a single IV efficacy study in hyponatremia, and to use oral data to support safety. However, the sponsor based this plan on a pharmacokinetic model that seemed to show dose bioequivalence for the IV and oral formulations. After submission of their marketing application, the sponsor completed an actual bioequivalence study that showed that the oral form is only 1/3 as bioavailable as the IV form. Although there are some factors that affect the accuracy of a direct multiplication of dose, a patient would need to be exposed to an oral dose very near to 120 mg/day for four days in order to have the same exposure as a patient who receives 40 mg IV conivaptan per day for four days (the proposed regimen for labeling). Although the sponsor performed two small studies (-021 and -022, total n = 11) in which study subjects could have received this oral dose, no study subject actually received 120 mg/day for even one day in either of these studies. Therefore, the only study subjects who could have received the full proposed dose for labeling were those in Study -027 (the primary intravenous efficacy study), Study -074 (midazolam interaction study), and -025 (dose-dependent pilot efficacy and safety study). In Study -027, a total of 43 subjects received the dosing regimen proposed for marketing. In Study -074, several protocol changes were made due to problems with infusion site reactions, but it appears that the maximum number of study subjects that could have received the full proposed dosing regimen was 16. In Study -025, four subjects received the full dosing

regimen. Thus, the maximum number of subjects in the entire development program who could have received the full dosing regimen proposed for marketing was 63. This number is inadequate for safety evaluation.

Across the entire development program, 1421 subjects and patients were exposed to conivaptan.

A total of 456 subjects were exposed in Phase 1 studies; 89 received IV conivaptan for durations of 1-7 days. Thirty-eight of these subjects received at least one dose of conivaptan $\geq$ 40 mg. A total of 356 subjects received oral conivaptan for 1-8 days, and an additional 11 subjects received oral or IV conivaptan as a single dose.

For all Phase 2 and Phase 3 trials in both hyponatremia and CHF, 896 patients were exposed to conivaptan. Of these, 208 received IV conivaptan. A total of 525 patients (all in oral studies) had at least 28 days of treatment. Of these, 285 had at least 84 days of treatment and 25 had at least 182 days of treatment. A total of 208 patients received IV conivaptan, 77 in hyponatremia trials and 131 in CHF trials.

The sponsor provided separate information for two Phase 2 Japanese trials (-018 and -019), which included 72 patients exposed to conivaptan.

As of the data cutoff date of 1 Sep 03, 50 patients had been enrolled in the open label extension Study -031, and 86 had been enrolled in the controlled Study -071.

7.2.1.1 Study Type and Design/ Patient Enumeration

The following tables enumerate the subjects exposed to conivaptan in all clinical studies. However, as described above, very few subjects ($n \leq 63$) received the full exposure proposed for labeling.

Table 7.2.1.1.1: Enumeration of Subjects in Phase 1 Studies (Source: Sponsor's Table 2.7.4.3)

Study	All Doses YM087	Placebo
BA Study Reports		
087-CL-015 (95-AVA-07)	7	N/A
087-CL-061 (98-AVA-03)	4	N/A
Comparative BA and BE Study Reports		
087-CL-065 (01-AVA-01)	12	N/A
087-CL-066 (01-AVA-02)	12	N/A
Healthy Subjects PK and Initial Tolerability Study Reports		
087-CL-006 (50872/AS21)	18	9
087-CL-008 (50872/AS23)	15	9
087-CL-013 (95-AVA-05)	8	N/A
087-CL-007 (50872/AS22)	7	4
087-CL-009 (95-AVA-01)	4	N/A
087-CL-002 (50871/ASA1)	18	9
087-CL-003 (50871/ASA2)	8	5
087-CL-004 (50871/ASA3)	6	3
087-CL-005 (50871/ASA4)	12	N/A
087-CL-063 (50871/ASA5)	18	6
Intrinsic Factor PK Study Reports		
087-CL-014 (95-AVA-06)	18	6
087-CL-059 (98-AVA01)	24	N/A
087-CL-060 (98-AVA-02)	21	N/A
Extrinsic Factor Study Reports		
087-CL-001 (50871/AKi1)	8	N/A
087-CL-010 (95-AVA02)	86	N/A
087-CL-052 (1025-032)	16	N/A
087-CL-074	37	N/A
087-CL-057 (1025-037)	12	N/A
087-CL-049 (1025-029)	12	N/A
087-CL-054 (1025-034)	16	N/A
087-CL-064 (00-AVA-01)**	4	N/A
087-CL-058 (1025-038)	12	N/A
087-CL-011 (95-AVA-03)	14	N/A
087-CL-048 (1025-028)	12	N/A
087-CL-012 (95-AVA-04)	15	N/A
TOTALS	**456**	**51**

Table 7.2.1.1.2: Enumeration of Subjects in all Phase 2/3 Trials, IV and Oral, Hyponatremia and CHF (Source: Sponsor's Table 2.7.4-4)

	IV Studies		Oral Studies		IV + Oral Studies	
Study # 087-CL-	YM087 Any Dose	Placebo	YM087Any Dose	Placebo	YM087 Any Dose	Placebo
Phase 3 Controlled Hyponatremia						
027	55	29	---	---	55	29
026	---	---	51	23	51	23
043	---	---	53	30	53	30
Subtotal	55	29	104	53	159	82
Phase 2/3 Uncontrolled Hyponatremia						
023	11	NA	---	---	11	NA
025	11	NA	---	---	11	NA
047	---	---	30 (22)*	NA	30 (22)*	NA
021	---	---	5	NA	5	NA
022	---	---	6	NA	6	NA
Subtotal	22	0	41 (22)*	0	63 (22)*	0
All Phase 2/3 Controlled and Uncontrolled Hyponatremia						
Subtotal Hypo-natremia	77	29	123**	53	200**	82
Phase 2/3 Controlled CHF						
032	104	38	---	---	104	38
038	14	12	---	---	14	12
044	13	13	---	---	13	13
017	---	---	16	8	16	8
020	---	---	230	74	230	74
033	---	---	35	12	35	12
034	---	---	249[a]	93	249	93
Subtotal	131	63	530	187	661	250
Phase 2/3 Uncontrolled CHF						
024	---	---	23	NA	23	NA
016	---	---	12	NA	12	NA
Subtotal	0	0	35	0	35	0
All Phase 2/3 CHF						
Subtotal CHF	131	63	565	187	696	250
All Phase 2/3 IV & Oral Studies in Hyponatremia & CHF						
Grand Total	208	92	688**	240	896**	332

* The number in parentheses represents a count of the patients in that cell who have already been counted as being exposed to YM087 by virtue of having received the drug in controlled study 087-CL-043.
** Unique number of patients
[a] This number does not include Patient 034-0028002, who was excluded from the safety population because he never received study medication. This patient was randomized to treatment, but died due to an AE during his Baseline visit where the first bottle of oral study medication is normally dispensed to the patient.

Table 7.2.1.1.3: Enumeration of Subjects in Phase 2 Japanese Studies (Source: Sponsor's Table 2.7.4-5)

Study	All Doses YM087
087-CL-018	30
087-CL-019	42
Total	**72**

7.2.1.2 Demographics

Because most of the subjects who received the full proposed dose for labeling came from Study -027, demographics for that study are presented in a separate table from the overall demographic.

Table 7.2.1.2.1 Demographic Characteristics by Treatment Group, Full Analysis Set, Study -027

Parameter	Categories	Placebo n = 29	Coni[1] 40 n = 29	Coni 80 n = 26	Total n = 84
Gender					
	Male	15 (51.7%	12 (41.4%)	14 (53.8%)	41 (48.8%)
	Female	14 (48.3%)	17 (58.6%)	12 (46.2%)	43 (51.2%)
Race					
	White, non-Hispanic	26 (89.7%)	27 (93.1%)	19 (73.1%)	72 (85.7%)
	Black, non-Hispanic	2 (6.9%)	1 (3.4%)	6 (23.1%)	9 (10.7%)
	Hispanic	0	0	1 (3.8%)	1 (1.2%)
	Other	1 (3.4%)	1 (3.4%)	0	2 (2.4%)
Age (Years)					
	≤ 65 years	3 (10.3%)	8 (27.6%)	7 (26.9%)	18 (21.4%)
	> 65 years	26 (89.7%)	21 (72.4%)	19 (73.1%)	66 (78.6%)
	Mean	75.7	73.8	72.5	74
	SD	11.61	11.51	13.82	12.22
	Min	42	46	32	32
	Median	75.0	76.0	75.0	75.5
	Max	97	91	95	97

Table 7.2.1.2.2: Demographic Characteristics, All Subjects in Phase 2/3 IV and Oral Studies in Hyponatremia and CHF (Source: Sponsor's Table 2.7.4-15)

	All Phase 2/3 IV Studies (023, 025, 027, 032, 038, 044)		All Phase 2/3 Oral Studies (016, 017, 020, 021, 022, 024, 026, 033, 034, 043, 047)		All Phase 2/3 IV + Oral Studies (016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 032, 033, 034, 038, 043, 044, 047)	
	Placebo n(%)	YM087 Any Dose n(%)	Placebo n(%)	YM087 Any Dose n(%)	Placebo n(%)	YM087 Any Dose n(%)
Number of patients	92	208	240	688	332	896
Age (yrs)						
Mean	66.8	63.4	62.1	61.4	63.4	61.8
SD	14.43	13.59	12.73	12.00	13.37	12.41
Minimum, Maximum	21, 97	24, 95	22, 94	16, 93	21, 97	16, 95
<65	35 (38.0)	116 (55.8)	136 (56.7)	401 (58.3)	171 (51.5)	517 (57.7)
>=65	57 (62.0)	92 (44.2)	104 (43.3)	287 (41.7)	161 (48.5)	379 (42.3)
>=75	27 (29.3)	51 (24.5)	42 (17.5)	103 (15.0)	69 (20.8)	154 (17.2)
Sex						
Male	63 (68.5)	134 (64.4)	174 (72.5)	519 (75.4)	237 (71.4)	653 (72.9)
Female	29 (31.5)	74 (35.6)	66 (27.5)	169 (24.6)	95 (28.6)	243 (27.1)
Race						
Caucasian	68 (73.9)	143 (68.8)	191 (79.6)	580 (84.3)	259 (78.0)	723 (80.7)
Black	20 (21.7)	56 (26.9)	41 (17.1)	85 (12.4)	61 (18.4)	141 (15.7)
Hispanic	3 (3.3)	8 (3.8)	6 (2.5)	14 (2.0)	9 (2.7)	22 (2.5)
Asian	0	0	0	4 (0.6)	0	4 (0.4)
Other	1 (1.1)	1 (0.5)	2 (0.8)	5 (0.7)	3 (0.9)	6 (0.7)

* All indicated doses are in milligrams/day.
Note: No uncontrolled IV studies were performed in CHF
Note: Patients in controlled studies are assigned to a treatment group based on the nominal dose. Patients in uncontrolled studies are assigned to a treatment group based on the dose of maximum duration.
Note: Study 047 was an extension of study 043. Patients are counted only once in the 'YM087 Any Dose' and once in any dose group where the patient was in the same dose group for both studies.
Data Source: demog.sd2, dose.sd2 Program Source: dsmog3.sas

For the full study population, the conivaptan and placebo groups were acceptably balanced for age, race and gender. The conivaptan group contained a slightly higher percentage of patients < age 65 than the placebo group. If these younger conivaptan patients had fewer comorbidities than the overall placebo population, the placebo group could appear to have a somewhat higher adverse event rate. However, the magnitude of the difference between conivaptan and placebo in this regard is relatively small, and did not alter the clinical reviewer's conclusions regarding any safety event.

Demography was similar between Study -027 and the full safety population, except that Study -027 had a smaller percentage of patients ≤ age 65 years.

7.2.1.3 Extent of exposure (dose/duration)

The following table details the exposure to conivaptan during the Phase 3 controlled hyponatremia trials.

Table 7.2.1.3.1: Duration of Exposure, Controlled Phase 3 Studies in Hyponatremia (Source: Sponsor's Table 2.7.4-7)

	All Controlled IV Hyponatremia Studies (027)			All Controlled Oral Hyponatremia Studies (026, 043)		
	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)	Placebo n(%)	YM087 40/d n(%)	YM087 80/d n(%)
# of Patients in Safety Population	29	29	26	53	51	53
Length of Exposure (Days)						
N	29	29	26	53	51	53
Mean	3.6	3.3	3.8	4.6	4.8	5.0
SD	0.78	1.14	0.65	1.05	0.54	0.27
Median	4.0	4.0	4.0	5.0	5.0	5.0
Minimum, Maximum	1, 4	1, 4	2, 4	1, 5	2, 5	3, 5
Number of Patients						
>= 1 Day	29 (100)	29 (100)	26 (100)	53 (100)	51 (100)	53 (100)
>= 2 Days	28 (96.6)	25 (86.2)	26 (100)	52 (98.1)	51 (100)	53 (100)
>= 3 Days	26 (89.7)	22 (75.9)	23 (88.5)	47 (88.7)	50 (98.0)	53 (100)
>= 4 Days	22 (75.9)	20 (69.0)	23 (88.5)	46 (86.8)	49 (96.1)	52 (98.1)
>= 5 Days	0	0	0	45 (84.9)	46 (90.2)	52 (98.1)

* All indicated doses are in milligrams/day.
Note: Patients are assigned to a treatment group based on the nominal dose.
Data Source: demog.sd2, dose.sd2 Program Source: durexp4d.sas

The following table outlines the numbers of subjects exposed in all Phase 2 and Phase 3 studies in hyponatremia and CHF. The vast majority of subjects were exposed to the oral drug, which was only 1/3 as bioavailable as the IV form. No subjects were exposed to more than 4 days of IV drug.

Table 7.2.1.3.2: Duration of Exposure, All Phase 2/3 IV and Oral Studies in Hyponatremia and CHF (Source: Sponsor's Table 2.7.4-8)

	All Phase 2/3 IV Studies (023, 025, 027, 032, 038, 044)		All Phase 2/3 Oral Studies (016, 017, 020, 021, 022, 024, 026, 033, 034, 043, 047)		All Phase 2/3 IV + Oral Studies (016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 032, 033, 034, 038, 043, 044, 047)	
	Placebo n(%)	YM087 Any Dose n(%)	Placebo n(%)	YM087 Any Dose n(%)	Placebo n(%)	YM087 Any Dose n(%)
# of Patients in Safety Population	92	208	240	688	332	896
Length of Exposure (Days)						
N	92	208	240	688	332	896
Mean	1.8	1.8	66.1	69.6	48.3	53.8
SD	1.30	1.21	44.81	44.41	47.75	48.33
Median	1.0	1.0	82.0	82.0	67.5	77.0
Minimum, Maximum	1, 4	1, 4	1, 229	1, 267	1, 229	1, 267
Number of Patients						
>= 1 Day	92 (100)	208 (100)	240 (100)	688 (100)	332 (100)	896 (100)
>= 2 Days	28 (30.4)	66 (31.7)	236 (98.3)	672 (97.7)	264 (79.5)	738 (82.4)
>= 3 Days	26 (28.3)	47 (22.6)	230 (95.8)	671 (97.5)	256 (77.1)	718 (80.1)
>= 4 Days	22 (23.9)	43 (20.7)	229 (95.4)	646 (93.9)	251 (75.6)	689 (76.9)
>= 5 Days	0	0	228 (95.0)	640 (93.0)	228 (68.7)	640 (71.4)
>= 6 Days	0	0	183 (76.3)	556 (80.8)	183 (55.1)	556 (62.1)
>= 7 Days	0	0	183 (76.3)	555 (80.7)	183 (55.1)	555 (61.9)
>= 14 Days	0	0	174 (72.5)	536 (77.9)	174 (52.4)	536 (59.8)
>= 28 Days	0	0	172 (71.7)	525 (76.3)	172 (51.8)	525 (58.6)
>= 84 Days	0	0	96 (40.0)	285 (41.4)	96 (28.9)	285 (31.8)
>= 182 Days	0	0	10 (4.2)	25 (3.6)	10 (3.0)	25 (2.8)

* All indicated doses are in milligrams/day.
Note: No uncontrolled IV studies were performed in CHF.
Note: Patients in controlled studies are assigned to a treatment group based on the nominal dose. Patients in uncontrolled studies are assigned to a treatment group based on the dose of maximum duration.
Note: Study 047 was an extension of study 043. Patients are counted only once in the 'YM087 Any Dose' and once in any dose group where the patient was in the same dose group for both studies.
Data Source: demog.sd2, dose.sd2 Program Source: durexp3e.sas

Study Subject Disposition

The following two tables detail study patient disposition for Study -027 and for the Full Safety Population.

Table 7.2.1.3.3: Disposition of Randomized Study Patients, Study -027

Disposition Category	Reason for Patient Withdrawal at Each Stage	Total	Placebo	Coni 40	Coni 80
# Randomized		88	30	30	28
# Entered Study		86	30	29	27
# did not Enter Study		2	0	1	1
	Administrative/Other[1]	2	0	1	1
# Treated		84	29	29	26
# not Treated		2	1	0	1
	Administrative/Other[1]	2	1	0	1
# Completed Treatment		66	23	22	21
# did not Complete Treatment after Entering Study		20	7	7	6
	Adverse Event	13	3	5[2]	5
	Lack of Efficacy	4	3	1	0
	Withdrawal of Consent	1	1	0	0
	Diagnosis of Hypopituitarism after Initial Study Treatment	1	0	1	0
	Administrative	1	0	0	1
# in Safety Analysis Set[3]		84	29	29	26
# in Full Analysis Set[3]		84	29	29	26
# in Per Protocol Set[3]		69	24	22	23
# Treated but not in Per Protocol Set[4]		15	5	7	3

[1]Reasons for not receiving study drug after randomization included withdrawal of consent (n = 2), "no longer met inclusion/exclusion criteria" (n = 1) and poor venous access (n = 1)
[2]Sponsor's Text Table 10-1 (p 104 of study report) states that 2 patients in the conivaptan 40 mg/day group withdrew due to adverse events. However, medical officer review of the CRFs revealed that 3 of the cases classified as "administrative/other" were actually withdrawals due to adverse events
[3]See Section 4.5.2 for definitions of analysis sets
[4]See Tables 4.5.2.1 and 4.5.2.2 for details of reasons for exclusion from Per Protocol Set.

Table 7.2.1.3.4 Disposition of Patients, Full Safety Population

	All Phase 2/3 IV Studies (023, 025, 027, 032, 038, 044)		All Phase 2/3 Oral Studies (016, 017, 020, 021, 022, 024, 026, 033, 034, 043, 047)		All Phase 2/3 IV + Oral Studies (016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 032, 033, 034, 038, 043, 044, 047)	
	Placebo n(%)	YM087 Any Dose n(%)	Placebo n(%)	YM087 Any Dose n(%)	Placebo n(%)	YM087 Any Dose n(%)
Patients treated	92	208	240	688	332	896
Completed treatment	84 (91.3)	193 (92.8)	218 (90.8)	641 (93.2)	302 (91.0)	834 (93.1)
Premature discontinuations:	8 (8.7)	15 (7.2)	22 (9.2)	69 (10.0)	30 (9.0)	84 (9.4)
Adverse Event	4 (4.3)	7 (3.4)	11 (4.6)	35 (5.1)	15 (4.5)	42 (4.7)
Lack of Efficacy	2 (2.2)	3 (1.4)	1 (0.4)	5 (0.7)	3 (0.9)	8 (0.9)
Withdrawal of Consent	0	0	1 (0.4)	2 (0.3)	1 (0.3)	2 (0.2)
Lost to Follow-up	0	0	0	0	0	0
Protocol Violation	0	0	2 (0.8)	4 (0.6)	2 (0.6)	4 (0.4)
Patient Died	0	0	0	3 (0.4)	0	3 (0.3)
Lack of Compliance	0	0	0	10 (1.5)	0	10 (1.1)
Other/Admin. Reasons	2 (2.2)	5 (2.4)	7 (2.9)	9 (1.3)	9 (2.7)	14 (1.6)
Satisfactory Response	0	0	0	1 (0.1)	0	1 (0.1)

* All indicated doses are in milligrams/day.
Note: No uncontrolled IV studies were performed in CHF.
Note: Patients in controlled studies are assigned to a treatment group based on the nominal dose. Patients in uncontrolled studies are assigned to a treatment group based on the dose of maximum duration.
Note: Study 047 was an extension of study 043. A patient can be included in both completed treatment and the reasons for premature discontinuation categories if the patient completed study 043 and prematurely discontinued in study 047.

As discussed in Section 7.1.3.1, clinical review of all withdrawals listed as "Administrative" or "Other" revealed that one patient in Study -027, and one other subject in the full safety population, actually withdrew due to adverse events.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary sources of clinical data were submitted for review. The clinical reviewer conducted a literature search for evidence of safety concerns with conivaptan or other vasopressin receptor antagonists.

7.2.2.1 Other studies

The sponsor provided separate data for two studies conducted in Japan (Studies -018 and -019); clinical review of these studies revealed no additional safety concerns.

7.2.2.2 Postmarketing experience

Conivaptan is not yet marketed in any country. No other vasopressin receptor antagonist is yet marketed in any country.

7.2.2.3 Literature

The medical literature was referenced during various parts of the review, but a separate literature review was not submitted for review.

7.2.3 Adequacy of Overall Clinical Experience

Due to the small number of study subjects who received the full proposed IV dose for labeling, the overall clinical experience presented in this NDA for conivaptan is not sufficient to allow adequate safety review. The number of subjects exposed to the relevant dose falls far short of ICH guidelines. More information from larger studies of IV use of conivaptan is needed. The clinical reviewer recommends the study of lower doses of conivaptan in order to evaluate the relative adverse event profile of lower doses. In Studies -026 and -043, the oral Phase 3 hyponatremia trials, exposure of approximately 1/3 that attained in Study -027 still resulted in efficacy in correction of hyponatremia. The clinical reviewer also recommends the study of dilution of conivaptan in larger volumes of IV fluid, to see if the high incidence of infusion reactions can be decreased.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please see Dr. Alavi's toxicology review for details of the adequacy of preclinical testing of conivaptan. Of special clinical interest is the HERG channel study described in Section 7.1.12, and the human intensive QTc study done to evaluate this modest preclinical finding. In general, preclinical testing for conivaptan was adequate.

7.2.5 Adequacy of Routine Clinical Testing

The types of routine clinical tests performed in the safety evaluation of conivaptan were adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see Dr. Chung's biopharmacology review for details of the adequacy of the sponsor's biopharmacologic evaluation program. Adequate IV pharmacokinetic data were not provided for patients with hyponatremia.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor made adequate efforts to detect adverse events, including adverse events of special interest for this drug considering its pharmacology and preclinical findings. Details of these events of special interest can be found in Section 7.1.3.3.

7.2.8 Assessment of Quality and Completeness of Data

Aside from the major issue of lack of adequate numbers of subjects receiving the full proposed dose for labeling, the data included in the NDA were generally complete. Organization of parts of the NDA was not always intuitively obvious, but the clinical reviewer was usually able to find desired sections with time. Case report forms were difficult to navigate, and came in multiple formats, but with time, the clinical reviewer

could generally find details of adverse events. For almost all subjects with serious adverse events, followup to resolution of the adverse event was documented.

7.2.9 Additional Submissions, Including Safety Update

A safety update was submitted four months into the review cycle, and may be accessed via the path \\CDESUB1\N21697\N_000\2004-05-28 .

This safety update provided additional safety data on 180 patients and 102 healthy subjects involved in ongoing studies who received conivaptan after the original NDA data cutoff of 1 Sep 03 and before 15 Apr 04. For 136 of these subjects, data had been submitted with the original NDA, and only new information was presented in the safety update. In the additional safety population, 130 patients and 102 healthy subjects received conivaptan IV.

Study -079, the intensive QTc study in healthy volunteers, was previously described in Section 7.1.12. Eighty subjects received IV conivaptan.

Study -083 was the comparative IV/oral bioavailability study which led to the realization that no subjects in the original NDA submission who were treated with oral conivaptan had exposure equivalent to that proposed for the IV label. This study was conducted in healthy subjects and included 22 subjects who received oral conivaptan and 21 who received IV.

Study -031 was an oral extension study of two of the Phase 3 hyponatremia studies. This included 50 patients (20 mg/day n = 7, 40 mg/day = 24, 60 mg/day = 3, and 80 mg/day = 16) Of these 50 patients, 35 completed 12 weeks of oral treatment.

Study -071 was a Phase 2 intravenous study in CHF patients. In this study, 40 patients received conivaptan 40 mg/day, 40 received 80 mg/day, and 43 received 120 mg/day. Infusions lasted two days total.

Study -080 was a Phase 3B open-label intravenous hyponatremia safety study. This study is ongoing and remains blinded.

7.2.9.1 Deaths in Safety Update

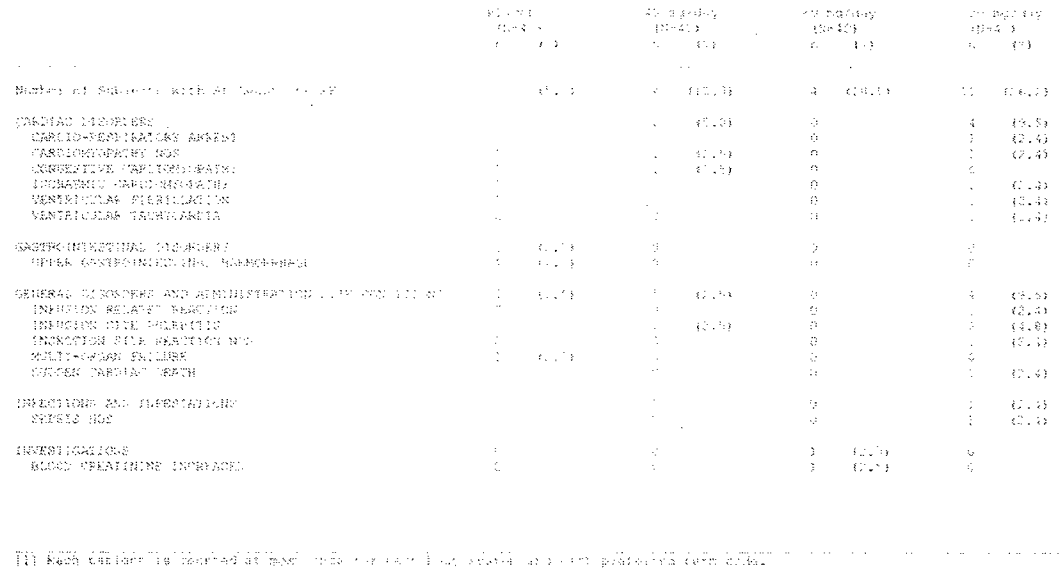
No deaths occurred in Study -079 or -083. Study -080 is still blinded, and no deaths had occurred as of the safety update cutoff. For Study -031, one additional death occurred from CHF; otherwise, all deaths are represented in the Table 7.1.1.1.1 in Section 7.1.1 above. In Study -071, four additional deaths occurred. Subject 071-0000088 had underlying congestive heart failure and was found dead at home. Subject 071-0000089 had postpartum cardiomyopathy and collapsed in hospital. Pulseless electrical activity was noted, and patient did not respond to resuscitation; autopsy revealed cardiomyopathy, but no additional revealing findings. Subject 071-0000096 had congestive heart failure and died at home. Subject 071-0000097 had CHF and suffered an in-hospital cardiac arrest, and could not be resuscitated.

7.2.9.2 Serious Adverse Events in Safety Update

In all IV studies, infusion site reactions were common events. In Study -031, nine subjects experienced serious adverse events; five events were aggravation of underlying CHF. One patient who had an exacerbation of CHF also developed acute renal failure. Two patients experienced worsening of hyponatremia, one subject had a small bowel obstruction, and one subject had pyrexia. In Study -071, two cases of acute renal failure occurred.

One additional dropout due to an SAE occurred in Study -031. This patient withdrew due to thrombocytopenia. For Study -071, the following table summarizes all SAEs leading to death or discontinuation to date, including those before the original NDA submission and those up to the time of the safety update.

Table 7.2.9.2: Study -071 Adverse Events Leading to Discontinuation or Death at any Time During Study (Source: Safety Update Sponsor's Table 14.3.1.7)



In this table, serious cardiac events leading to death or discontinuation occurred exclusively in conivaptan-treated subjects, with none occurring in placebo subjects. Subjects in the 120 mg/day conivaptan group had a higher incidence of discontinuations due to cardiac events than did subjects in the 40 and 80 mg/day groups.

No new types of serious adverse events emerged. However, infusion site reactions, serious cardiac AEs in CHF patients, and renal failure remain concerns.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the full safety population, the following treatment-emergent adverse events occurred more frequently among conivaptan treated subjects than among placebo subjects. The relevant section of the clinical review follows each event:

- serious (statistically significant difference) and nonserious renal adverse events, and acute renal failure (Sections 7.1.2.4.3 and 7.1.5.3)
- serious and nonserious hypovolemia events (statistically significant differences) (Sections 7.1.2.4.1 and 7.1.5.3)
- serious and nonserious hypotensive events (statistically significant differences) (Sections 7.1.2.4.1 and 7.1.3.3.3)
- infusion site reactions (statistically significant difference) and infusion site reactions leading to discontinuation from study (Sections 7.1.3.2 and 7.1.3.3.2)
- angina and chest pain events in patients with underlying CHF (Section 7.1.5.5)
- pyrexia (Section 7.1.5.3)
- diarrhea (Section 7.1.5.3)
- thirst (Section 7.1.5.3)
- polyuria (Section 7.1.5.3)
- anemia events (Section 7.1.3.3.5)
- increases in mean serum creatinine and serum creatinine outliers of clinical significance (statistically significant differences) (Sections 7.1.7.3.1, 7.1.7.3.2, and 7.1.7.3.3)
- increases in mean serum alkaline phosphatase (statistically significant difference) (Section 7.1.7.3.1)
- increases in mean serum ALT, ALT >3x uln, and ALT >10x uln (Section 7.1.3.3.4)
- increases in AST to >3x uln and >10x uln (Section 7.1.3.3.4)
- increased mean fasting glucose and treatment-emergent abnormalities of fasting glucose (Sections 7.1.7.3.1and 7.1.7.3.2)
- treatment-emergent prolongations of prothrombin time in patients who had PT measured (primarily patients taking concomitant warfarin) (Section 7.1.7.3.2)

All cases of acute renal failure occurred in congestive heart failure patients, but the overall incidence of serious renal adverse events was not higher among congestive heart failure patients than among those without congestive heart failure. Serious hypovolemia-related adverse events occurred more commonly in congestive heart failure patients. Infusion site reactions were very common among IV conivaptan subjects, and appear dose-related. One case of rhabdomyolysis, two cases of myopathy, and one additional case of significant CPK elevation occurred in subjects taking oral conivaptan; all were also taking CYP3A4-metabolized statins.

In the three controlled Phase 3 hyponatremia trials, the following events occurred with greater frequency in conivaptan-treated subjects than in placebo subjects:

- serious renal adverse events (Section 7.1.2.4.3)
- serious hypovolemia-related events (Section 7.1.2.4.1)
- infusion site reactions (statistically significant difference) and infusion site reactions leading to discontinuation from study (Sections 7.1.3.2 and 7.1.3.3.2)
- overly rapid correction of serum sodium (Section 7.1.3.3.1)
- serious cardiac failure-related events in patients with underlying CHF (Section 7.1.2.4.2)
- thirst (Section 7.1.5.3)
- polyuria (Section 7.1.5.3)
- increases in mean serum creatinine and serum creatinine outliers of clinical significance (statistically significant differences) (Sections 7.1.7.3.1, 7.1.7.3.2, and 7.1.7.3.3)
- increases in mean fasting plasma glucose (Section 7.1.7.3.1)

It is not clear that serious renal adverse events were always due to prerenal causes, as review of available case data for the Phase 3 hyponatremia trials showed that most of the patients who had serious renal adverse events actually had smaller mean increases in urine output than the mean of the group of all Phase 3 conivaptan and placebo patients combined.

The number of subjects who could have had the full exposure proposed for labeling was inadequate for safety evaluation. However, in these subjects, the following events occurred with greater frequency in conivaptan-treated subjects than in placebo subjects:

- serious renal adverse events (Section 7.1.2.4.3)
- serious and nonserious hypovolemia events (Sections 7.1.2.4.1 and 7.1.5.3)
- overall hypotensive events and hypotensive events leading to discontinuation from study (Section 7.1.3.3.3)
- treatment-emergent serious and nonserious treatment-emergent adverse cardiac failure events among patients with underlying CHF (Sections 7.1.2.4.2 and 7.1.5.5)
- infusion site reactions (statistically significant difference) and infusion site reactions leading to discontinuation from study (Sections 7.1.3.2 and 7.1.3.3.2)
- overly rapid correction of serum sodium (Section 7.1.3.3.1)
- declines in mean standing and supine systolic blood pressure (statistically significant differences) (Section 7.1.8.3.1)
- thirst (Section 7.1.5.3)
- polyuria (Section 7.1.5.3)
- increases in mean fasting plasma glucose and treatment-emergent elevations of fasting plasma glucose (Sections 7.1.7.3.1 and 7.1.7.3.2)
- increases in ALT (Section 7.1.3.3.4)
- increases in alkaline phosphatase (Section 7.1.3.3.4)
- increases in mean serum creatinine (statistically significant difference) and serum creatinine outliers of clinical significance (statistically significant difference) (Sections 7.1.7.3.1, 7.1.7.3.2, and 7.1.7.3.3)

- treatment-emergent prolongations of prothrombin time in patients who had PT measured (primarily patients taking concomitant warfarin) (Section 7.1.7.3.2)

Five out of eighteen patients (27.8%) in Study -027 who had plasma conivaptan levels >1000 ng/mL developed serious renal adverse events.

In Study -027, the pool of controlled hyponatremia trials, and the full safety population overall, death did not occur more frequently among conivaptan patients than among placebo patients. Death occurred slightly more frequently in the sponsor's CHF trials among patients who received conivaptan than among those who received placebo (Section 7.1.1).

Increases in mean creatinine, treatment-emergent abnormal creatinine, and outlier creatinine values all appear dose-related. Infusion-site reactions are dependent on infusion concentration and dose.

Those conivaptan patients who had CHF at baseline, and those patients who were hypervolemic at baseline, had a higher overall incidence of TEAEs than placebo patients with these baseline conditions, for both the full study populations and the pool of Phase 3 controlled hyponatremia trials. Most serious renal adverse events, serious hypovolemia-related events, and instances of treatment-emergent INR occurred in CHF patients. All cases of acute renal failure occurred in CHF patients. Congestive heart failure patients exhibited 8-fold higher conivaptan exposure than healthy subjects. These findings underscore the need for caution regarding administration of conivaptan to congestive heart failure patients, and also the need for establishment of the lowest potentially effective dose of conivaptan.

There were two cases of myopathy, one case of rhabdomyolysis, and one case of significant CPK elevation; all occurred in patients receiving concomitant statins (see Section 7.1.3.3.6). As discussed in the Protocol Deviations section (4.5.2) and the Drug-Drug Interactions Section (8.2) it is worrisome that, even in a highly controlled clinical trial setting, a significant percentage of patients received additional CYP3A4-metabolized drugs. This fact calls into question the likelihood of adequate management of the risk of CYP3A4 interactions via restricted labeling. Although in the preNDA phase, DMEDP had discussed the possibility of restricted labeling as a means of risk management, this protocol deviation information was unavailable to reviewers at the time of that discussion.

A potentially significant limitation of interpretation of the safety of conivaptan is related to blinding. Investigators were blinded to treatment assignment, but not to serum sodium levels, and might have been able to surmise which subjects were receiving conivaptan. It is also quite likely that investigators and other caregivers could tell by signs and symptoms which patients were receiving conivaptan and which were receiving placebo; urine output and thirst were markedly higher in conivaptan-treated patients. This could have resulted in differences in investigator behavior in choice of other treatments and fluids. It could also have influenced handling of adverse event risk and categorization.

For example, a very high urine output could have prompted nursing concern for volume depletion risk, and extra nursing vigilance for orthostatic hypotension and fall prevention. An investigator who could be fairly certain that a patient was receiving conivaptan might be unconsciously less likely to record an adverse event or assign causality for an adverse event to conivaptan. Thus, underrepresentation of adverse event risk of conivaptan could have occurred.

To summarize the adverse event information submitted in this NDA, the size of the relevant full-dose safety population is too small for adequate safety evaluation. Safety signals in this small population, and in the larger population with lower exposure, include renal dysfunction, hypovolemia, hypotension, exacerbations of CHF, infusion site reactions, overly rapid correction of serum sodium, increase in alkaline phosphatase, prolongation of PT (in warfarin-treated patients), and elevation in fasting plasma glucose. Thirst and polyuria occurred frequently and were expected pharmacologic effects; however, these events may have contributed to problems with blinding of treatment assignment. Additional events seen with greater frequency in the full study population included clinical anemia events and increases in transaminases to >3x and >10x uln. The drug's marked inhibition of CYP3A4 presents a significant safety risk. For CHF patients, several types of serious adverse events occurred with greater frequency in conivaptan-treated patients than in placebo-treated patients.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

As noted in the above safety sections, the clinical reviewer pooled data in three ways. The safety information of most relevance for the proposed dosing regimen for labeling came from Study -027, the single controlled Phase 3 intravenous hyponatremia study. In this study, 55 patients received conivaptan, and 29 patients received the full dose intended for labeling. When it was possible and relevant, the clinical reviewer pooled information from the "full dose" population, i.e. the patients from Study -027, 43 of whom received the full dose proposed for labeling; plus the few subjects who received full dosing in Studies -025 (4 subjects) and -074 (up to 16 subjects). This is referred to as the "full dose" population in the clinical review. To explore event rates in well-controlled studies, the clinical reviewer sometimes used the pool of all controlled hyponatremia Phase 3 studies (-027, -026 and -043), oral and IV. However, no subjects in oral conivaptan groups in the development program received the full planned dose for labeling. This pool is referred to as the "Controlled Phase 3 Hyponatremia" pool. To assess for less common events, and to assess the statistical significance of some events, the clinical reviewer used the pool of all Phase 2 and Phase 3 studies, IV and oral, for both hyponatremia and CHF. This population is referred to as the full safety population; again, the oral subjects in this population had considerably lower exposure than IV subjects over the planned dosing period.

7.4.1.2 Combining data

When combining data for the "full-dose" pool, the clinical reviewer combined the number of subjects who received full conivaptan dose for the conivaptan group, and combined all placebo subjects for the placebo group. For the "Controlled Phase 3 Hyponatremia" and "Full Safety" populations, the reviewer simply combined the numbers of conivaptan subjects across all included studies for the conivaptan groups, and the number of placebo subjects across all studies for the placebo group.

7.4.2 Explorations for Predictive Factors

The clinical reviewer explored for predictive factors among demographic variables, dose, time to event, and presence or absence of underlying congestive heart failure.

7.4.2.1 Explorations for dose dependency for adverse findings

Explorations for dose dependency occurred primarily in the Study -027 population, and the population of all Phase 3 controlled studies in hyponatremia (-026, -027 and -043).

7.4.2.2 Explorations for time dependency for adverse findings

Explorations for time dependency occurred through in depth review of serious adverse event case reports for the "Full Safety" population.

7.4.2.3 Explorations for drug-demographic interactions

Explorations for drug-demographic interactions occurred for Study -027, the pool of Phase 3 controlled hyponatremia trials, and the "Full Safety" population.

7.4.2.4 Explorations for drug-disease interactions

Explorations for drug-disease interactions occurred for patients with underlying congestive heart failure.

7.4.2.5 Explorations for drug-drug interactions

Explorations for drug-drug interactions were conducted by review of specific drug-drug interaction studies conducted by the sponsor, and by extraction of information from serious adverse event case reports.

7.4.3 Causality Determination

Causality was explored by comparison of event rates in Study -027 and the 3 pools described above. All events occurring with greater frequency in the conivaptan groups were considered possibly caused by conivaptan. Those events which occurred significantly more frequently in conivaptan subjects than in placebo subjects were considered attributable to conivaptan. For attribution to conivaptan, the clinical reviewer

also considered the likelihood of a relationship between the adverse event and the pharmacologic action of conivaptan.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor states that their recommended IV dosing regimen was based on the following:

- [redacted]
- [redacted]
- [redacted]
- Intravenous doses were initially given as BID boluses of 30 minutes each; serum sodium levels increased somewhat, but did not consistently reach the normal range.
- A change to a 30-minutes bolus followed by a continuous infusion resulted in more consistent increases of serum sodium to the normal range.

However, because of the information that the sponsor submitted during the review cycle that showed that the oral formulation was only 1/3 as bioavailable as the IV formulation, the [redacted] dose of conivaptan may be considerably higher than needed for efficacy.

[redacted] Finally, because it is desirable to know the lowest potentially effective dose, and because some subjects responded to doses as low as 20 mg/day oral conivaptan, it is also desirable for the sponsor to explore doses in the range of 7 mg/day.

While the sponsor asserts that the initial bolus which preceded the continuous infusion resulted in more consistent increases in serum sodium, the half-life of 4 hours for IV conivaptan calls the need for a bolus into question. Intravenous drugs requiring an initial bolus followed by continuous infusion are generally of considerably shorter half-life. Exploration of efficacy without a bolus is desirable. If a comparison between a "bolus" regimen and a "no bolus" regimen is undertaken, exploration of a lower bolus dose is indicated. The effect of a "no bolus" regimen on the incidence of infusion site reactions would also be of interest.

8.2 Drug-Drug Interactions

Please see Dr. Chung's biopharmacology review for detailed discussion of drug-drug interaction studies.

The sponsor conducted ten oral and two IV drug interaction studies. The results of these studies included:

- IV conivaptan, given as 15 mg BID for 3 days concomitantly with 60 mg/day oral simvastatin, increased simvastatin AUC 3-fold.
- Oral conivaptan, 40 mg/day given concomitantly with oral simvastatin for 3 days, increased simvastatin AUC 5.9-fold.
- Oral conivaptan, 80 mg/day, given concomitantly with amlodipine (another CYP3A4-metabolized drug), increased amlodipine AUC 2.4-fold.
- Ketoconazole caused an 11-fold increase in conivaptan drug levels.
- Oral conivaptan modestly inhibited digoxin PK. Conivaptan appears to be both a substrate for and an inhibitor of the p-glycoprotein transporter.
- Oral conivaptan 40 mg/day given for 10 days to patients on stable warfarin therapy did not have a significant effect on R- or S- warfarin concentrations or PT. However, as noted above, clinically significant prolongations of PT occurred in some patients taking conivaptan and warfarin in other studies in the clinical development program. The oral dose used in this warfarin interaction study would be expected to have only 1/3 the exposure seen with the proposed intravenous dose.
- Captopril and furosemide had no effect on conivaptan pharmacokinetics.

Conivaptan is both an inhibitor of CYP3A4 metabolism and a substrate of CYP3A4. As discussed in the Protocol Deviations section (4.5.2) it is worrisome that, even in a highly controlled clinical trial setting, a significant percentage of patients received additional CYP3A4 inhibitors. This fact calls into question the likelihood of management of the risk of CYP3A4 interactions via restricted labeling. Although DMEDP had discussed the possibility of restricted labeling as a means of risk management, this protocol deviation information was unavailable to reviewers at the time of that discussion.

The following table breaks down CYP3A4 interacting drugs as substrates, inducers or inhibitors. The table details the numbers of patients receiving each of these types of CYP3A4 drugs in the three major hyponatremia trials of conivaptan.

Table 8.2.: Numbers of Study Patients Receiving Concomitant CYP3A4 Drugs in Protocols -027, -026 and -043

Type of Compound[4]	Treatment Group	IV Study -027 (total n = 84) n receiving/ n in treatment group (%)	Oral Study -026 (total n = 74) n receiving/ n in treatment group (%)	Oral Study -043 (total n = 83) n receiving/ n in treatment group (%)
CYP3A4 Substrates[2]	Placebo	3/29 (10.3%)	4/23 (17.4%)	13/30 (43.3%)
	Coni[1] 40 mg/day	1/29 (3.4%)	2/24 (8.3%)	7/27 (25.9%)
	Coni 80 mg/day	5/26 (19.2%)	4/27 (14.8%)	12/26 (46.2%)
CYP3A4 Inducers	Placebo	0 (0.0%)	0 (0.0%)	3/30 (10.0%)
	Coni 40 mg/day	0 (0.0%)	0 (0.0%)	2/27 (7.4%)
	Coni 80 mg/day	0 (0.0%)	0 (0.0%)	1/26 (3.8%)
CYP3A4 Inhibitors[3]	Placebo	1/29 (3.4%)	2/23 (8.7%)	2/30 (6.7%)
	Coni 40 mg/day	1/29 (3.4%)	1/24 (4.2%)	3/27 (11.1%)
	Coni 80 mg/day	2/26 (7.7%)	4/27 (14.8%)	3/26 (11.5%)

[1]Conivaptan
[2]Substrates included alprazolam, diazepam, triazolam, diltiazem, simvastatin, lovastatin, amlodipine, felodipine and zoldipem
[3]Inhibitors included alprazolam, diazepam, triazolam and diltiazem
[4]If a patient was taking a compound that interacted with CYP3A4 in more than one way, that patient was counted once for each mode of interaction. If a patient was taking more than one compound with the same mode of interaction, the patient was counted only once for that mode of interaction.

The finding of PT prolongation in warfarin-treated patients in the full clinical safety program, but not in the oral conivaptan-warfarin interaction study, may make an IV conivaptan interaction study with warfarin desirable. Such a study is also desirable because the oral conivaptan dose used in the above warfarin interaction study would be expected to result in only 1/3 the conivaptan exposure seen with the proposed intravenous conivaptan dose.

8.3 Special Populations

Please see Dr. Chung's biopharmacology review for details of special population assessments. The sponsor performed special population studies for elderly subjects, patients with renal dysfunction and patients with hepatic dysfunction. However, because these studies used oral conivaptan and had much lower exposure than the proposed dose for labeling, they are not useful for determining whether dosage adjustment will be needed in these states. Brief summaries of these studies follow.

The sponsor performed a study (-059) in patients with mild-moderate renal dysfunction, using oral conivaptan 10 mg po on Study Day 1, 10 mg po bid on Study Days 2-7, and 10 mg po on Study Day 8. Patients were grouped (8 per group) by creatinine clearance: $\geq$ 80 mL/min; $\geq$ 30 to <60; and $\geq$10 to <30. In that study, after the first dose, C_{max}s for each of those groups were 46.0, 67.3 and 59.2 ng/mL respectively. T_{max}s were 0.67, 0.81 and

0.77 hrs, respectively. Mean $T_{½}$s appeared to decrease, with values of 3.98, 4.65 and 5.23 hrs respectively. $AUC_{0\text{-}inf}$ showed little difference between groups. On Day 8, C_{max} increased in all groups, with values of 76.4, 93.8 and 90.8 ng/mL respectively. T_{max}s and $AUC_{0\text{-}12h}$ were comparable between groups. $T_{½}$s were 3.35, 3.43 and 3.29 respectively. Mean serum creatinine did not increase significantly in any group. The sponsor recommended no dosage adjustment for patients with CrCls as low as 10 mL/min/1.73 m^2, but the oral dose used in the study is too low for meaningful reviewer comment about the need for dosage adjustment with the proposed intravenous dosage regimen for labeling.

The sponsor's study (-060) in patients with impaired hepatic function examined 12 patients with cirrhosis and 8 subjects with normal liver function. Patients with cirrhosis had stable hepatic dysfunction, with a Pugh score >5. Subjects received oral conivaptan 10 mg po on day 1, 10 mg po bid on days 2-7, and 10 mg po on day 8. Plasma concentrations were higher in patients with hepatic impairment compared to healthy subjects. After the first dose, the mean $AUC_{0\text{-}inf}$ values were 144 and 328 ng-h/mL respectively. After the last dose, $AUC_{0\text{-}12h}$ values were 144 and 328 ng-h/mL, respectively. $T_{½}$ on day 1 was 5.53 hrs for healthy subjects and 5.91 for hepatic dysfunction patients. On day 8, $T_{½}$s were 3.53 and 3.83 respectively. C_{max} was also higher in hepatic dysfunction patients than in healthy subjects, and T_{max} was longer. The sponsor does not recommend dose adjustment in hepatic impairment, but the oral dose used in the study is too low for meaningful reviewer comment about the need for dosage adjustment with the proposed intravenous dosage regimen for labeling.

The sponsor's study (-014) in elderly subjects with single oral doses of conivaptan showed that AUCs were comparable between elderly and younger subjects for doses of 15 and 30 mg/day orally, but were two-fold higher in the elderly group for the 60 mg/day oral dose. C_{max} for the 60 mg group was also higher in the elderly (735 ng/mL) than in younger subjects (593 ng/mL). [redacted] However, the oral conivaptan dose used is too low for meaningful comment on the need for dosage adjustment with the proposed intravenous dosage regimen for labeling. Also, systemic exposure was found to be 2.4-fold higher in patients with the target disease states compared to healthy subjects; this would further affect use in the elderly.

No children were studied, and insufficient numbers of nonwhite subjects were studied to make conclusions regarding any need for dose adjustment for pediatric or nonwhite subjects.

In the pool of all IV studies (Source: Sponsor's Tables 2.7.4- 395, -396, -419, -420, -442 and -443), renal and urinary disorder terms occurred only in white subjects (Source: Sponsor's Table 2.7.4-443). Otherwise, no differences in the incidence of any adverse event occurred by race.

In the Phase 3 controlled hyponatremia trials, the incidence of TEAEs was similar between age groups for the placebo group. However, for the conivaptan groups, the

incidence of TEAEs was higher among older patients (≥ 65 years and ≥ 75 years) than among patients <65 years of age. Older patients (≥ 65 years and ≥ 75 years) in the conivaptan group were also more likely to experience TEAEs than placebo patients in the same age groups. Of the seven conivaptan-treated patients who experienced orthostatic hypotension, six were ≥ 75 years old. For the two placebo-treated patients who experienced orthostatic hypotension, one was older than 75 years of age.

No serious safety differences emerged by gender.

8.4 Pediatrics

Conivaptan has not been studied in pediatric patients, and use in children under age 18 is not recommended.

In a 6 Aug 03 preNDA meeting between DMEDP and the sponsor, DMEDP stated it would not require pediatric study prior to submission of the initial NDA. If conivaptan is approved for use in adults, DMEDP will base the decision regarding need for pediatric studies on an assessment of the medical literature for likelihood of benefit in the pediatric population.

8.5 Advisory Committee Meeting

No Advisory Committee meeting was held during this review cycle. An Advisory Committee meeting had been discussed, but after the sponsor submitted its information from Study -083 regarding a lack of dose bioequivalence between the oral and IV forms, it was decided that further safety information would likely be needed for conivaptan. If the sponsor submits further IV safety information, DMEDP will again consider the need for an Advisory Committee meeting.

8.6 Literature Review

A literature review for background information is included in Section 2.6. Otherwise, references to literature are integrated with appropriate sections of the review.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan was submitted by the sponsor.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

Conivaptan, given by continuous intravenous infusion in a dose of 40 mg/day for four days, is effective in raising serum sodium in patients with nonhypovolemic hyponatremia.

However, most of the safety information submitted with the NDA is from oral studies. None of these oral studies include subjects who received doses of conivaptan that would achieve the same exposure over the dose and time period proposed for labeling. The sponsor did not discover this fact until well into the review cycle. Very few subjects received conivaptan in the dose and duration proposed for labeling. From these few subjects, and from the lower exposure oral population, some safety signals have emerged, especially hypotension, renal dysfunction, and infusion site reactions. A question of a higher incidence of adverse events among congestive heart failure patients has also arisen.

In general, the sponsor noted the same adverse event signals as the clinical reviewer. However, the clinical reviewer found evidence of a higher incidence of serious renal adverse events than that noted by the sponsor. In the clinical reviewer's opinion, the changes in serum creatinine seen with conivaptan are potentially clinically significant also; the sponsor did not reach this conclusion. While the clinical reviewer identified a safety signal of a higher incidence of certain serious adverse events among conivaptan-treated CHF patients than among placebo-treated CHF patients, the sponsor did not.

There is too little safety information to support a recommendation for approval at this time. If the sponsor chooses to resubmit for future NDA approval, study of substantial numbers of subjects exposed to IV conivaptan will be needed. The study of lower doses is also recommended, as there is evidence of efficacy in subjects who received lower oral exposures. Information on the lowest effective IV dose is needed.

9.2 Recommendation on Regulatory Action

The clinical reviewer recommends an "approvable" action. Because of the apparent efficacy of conivaptan, and because it would be the first drug product to treat hyponatremia, it is a potentially useful drug. However, insufficient safety information exists. If the sponsor submits substantial evidence of the safety of conivaptan in the dose and regimen proposed for labeling, the drug could potentially be approved in a future review cycle.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Because approval is not recommended at this time, no risk management activity is required. However, the sponsor is encouraged to submit a risk management plan with any future NDA.

9.3.2 Required Phase 4 Commitments

Not applicable.

9.3.3 Other Phase 4 Requests

Not applicable.

9.4 Labeling Review

Not applicable; it is expected that substantial changes will occur in multiple sections of the label once adequate IV safety (and perhaps lower dose efficacy) information is submitted.

9.5 Comments to Applicant

9.5.1 Substantial Issues Affecting Approvability

9.5.1.1 The number of subjects exposed to conivaptan at levels comparable to the dosing regimen proposed for labeling was inadequate for evaluation of safety. If you choose to resubmit a New Drug Application, substantially larger numbers of subjects who received the relevant exposure (i.e. comparable to that proposed for labeling) will need to be submitted for safety evaluation.

9.5.1.2 The lowest effective dose for intravenous conivaptan in the treatment of nonhypovolemic hyponatremia has not been established. There is evidence from your oral conivaptan studies that lower doses of intravenous conivaptan might be effective. If you choose to resubmit a New Drug Application, studies of the lowest potentially effective intravenous dose are needed.

9.5.1.3 The following Chemistry, Manufacturing, and Controls issues affect approvability:

9.5.1.3.1 Regarding the proposed drug substance specifications (S.4.5):

9.5.1.3.1.1 The proposed criterion for [redacted] (NMT [redacted] is not justified by the release data (mean + 3 SD = [redacted]) or by the submitted stability studies (NMT [redacted]). The criterion should be revised to a lower limit to reflect

the observed release and stability data since the material has been shown to have and to maintain low impurity levels.

9.5.1.3.1.2 [redacted]

9.5.1.3.2 Regarding the drug product stability protocols for market lots and future drug substance changes (P.7), there is not yet sufficient commercial scale manufacturing experience to justify a reduction to annual stability testing after the initial 3 production lots. Therefore, thee protocols should be revised to use the sampling intervals proposed in the validation protocol, [redacted]

9.5.1.3.3 The proposed stability criterion for [redacted] in drug product is not justified in that there is no increase over time. We recommend that the release specification (NMT [redacted]) be accepted for both as a release and stability criterion.

9.5.1.3.4 Provide any additional drug product stability data from the primary, site-specific or supporting studies, including compatibility studies that are available.

9.5.2 Other Issues

9.5.2.1 Exploration of methods for decreasing the incidence of infusion site reactions is needed.

9.5.2.2 Exposures of conivaptan in target patient populations were not characterized well with the proposed dosage regimen. Conivaptan plasma concentrations were measured predominantly at the end of infusion in the pivotal Phase III study, and those measurements were of limited value due to the nonlinearity in conivaptan exposure. We recommend that you further characterize conivaptan exposure in target patient populations. Sampling every 24 hours during infusion is suggested to characterize conivaptan pharmacokinetics in target patients.

9.5.2.3 It is not clear that an initial IV bolus of conivaptan is needed for efficacy. In general, a loading dose is not recommended for drugs with a short half-life unless there is a clinical benefit. Your application did not adequately justify a loading dose. DMEDP recommends that you study the efficacy and infusion-site related safety of IV conivaptan with and without the initial bolus. Justification is also needed for the amount of the bolus.

9.5.2.4 Special population studies, using the full dose planned for labeling, are needed in the elderly, in patients with hepatic impairment, and in patients with renal impairment.

9.5.2.5 A warfarin interaction study is needed, using the full dose planned for labeling.

9.5.2.6 The Pharmacology and Toxicology review staff recommends the following changes to your proposed label if you choose to resubmit your application:

"Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard lifetime (104 week) carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of 3, 10, or 30 mg/kg/day in males, and 1, 3, or 10 mg/kg/day in females by gavage. Rats were given oral doses of 0.3, 1, 3, or 10 mg/kg/day in males and 1, 3, 10, or 30 mg/kg/day in females by gavage. No increased incidence of tumors was observed at doses up to 30 mg/kg/day in mice (6X systemic exposure of an IV bolus of 20 mg on day 1 followed by IV infusion 40 mg for 3 days based on AUC comparison) or rats (2X systemic exposure of an IV bolus of 20 mg on day 1 followed by IV infusion 40 mg for 3 days based on AUC comparison).

Conivaptan was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, in human peripheral blood lymphocytes, or *in vivo* rat micronucleus assay.

In fertility studies after 4-weeks treatment by intravenous bolus at 0.5, 1.25 or 2.5 mg/kg/day, male fertility was unaffected. However, in females given IV bolus conivaptan 15 days before mating through gestation day 7 there was prolonged diestrus, decreased fertility and increased pre- and post-implantation loss at 2.5 mg/kg/day (systemic exposures less than the therapeutic dose).

Pregnancy Category C

Conivaptan has been shown to have adverse effects on the fetus when given to animals during pregnancy at systemic exposures less than that achieved at a therapeutic dose based on AUC comparisons. There are no adequate and well-controlled studies in pregnant women. Conivaptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The patient should be apprised of the potential hazard to the fetus. Conivaptan crosses the placenta and is found in fetal tissue. Fetal tissue levels are <10% of maternal plasma concentrations; C

[redacted]]

In female rats given intravenous bolus dose of 0.5, 1.25 or 2.5 mg/kg/day conivaptan before mating and continuing through gestation day 7, there was prolonged diestrus, decreased fertility and increased pre- and post-natal implantation loss at 2.5 mg/kg/day (systemic exposures less than the therapeutic dose).

In pregnant rats given intravenous doses of 0.5, 1.25 or 2.5 mg/kg/day from gestation day 7 through 17 (organogenesis), no significant maternal or fetal effects were observed at systemic exposures less than therapeutic exposure based on AUC comparisons.

In pregnant rats given intravenous doses of 0.1, 0.5, 1.25, or 2.5 mg/kg/day from gestation day 7 through [redacted] decreased pup viability, weaning indices, delayed growth and physical development including sexual maturation and delayed reflex development were observed in pups from groups given 2.5 mg/kg/day by [redacted] (systemic exposures less than therapeutic dose based on AUC comparisons) [redacted]

In pregnant rabbits given intravenous doses of 3, 6, or 12 mg/kg/day from gestation day 6 through 18 (organogenesis), there were no fetal findings; however, maternal toxicity was observed in all groups. Oral doses of ≥0.2 mg/kg to pregnant rabbits during organogenesis also resulted in maternal toxicity (systemic exposures less than the therapeutic dose).

In oral pre- and post- natal studies in rats, maternal behavior, care and lactation were adversely affected (e.g. pups scattered in cage, lack of nursing reflex), resulting in increased neonatal mortality in dams given ≥0.3 mg/kg (systemic exposures less than the therapeutic dose). Delayed parturition was observed at ≥10 mg/kg given orally (systemic exposures equivalent to the therapeutic dose based on AUC comparisons). An absence of milk in the stomach and decreased pup body temperature were observed at ≥10 mg/kg/day. Underdevelopment of mammary gland lactation and absent maternal behavior may relate to the activity of conivaptan on oxytocin receptors. In bolus intravenous postnatal rat studies adverse effects were not observed in maternal care but decreased neonatal viability, decreased weaning indices, delayed growth/physical development and delayed sexual maturation of offspring were observed at 2.5 mg/kg (systemic exposures less than the therapeutic dose).

Labor and Delivery

The effect of conivaptan on labor and delivery has not been studied in humans. Conivaptan delayed delivery in rats given 10 mg/kg/day by oral gavage (systemic exposures equivalent to the therapeutic dose based on AUC comparisons). Administration of conivaptan at 2.5 mg/kg/day intravenously [redacted] increased peripartum pup mortality as a [redacted] mammary gland lactation); systemic exposures were less than the therapeutic dose based on AUC comparisons. These effects may be associated with conivaptan activity on oxytocin receptors in the rat. The relevance to humans is unclear.

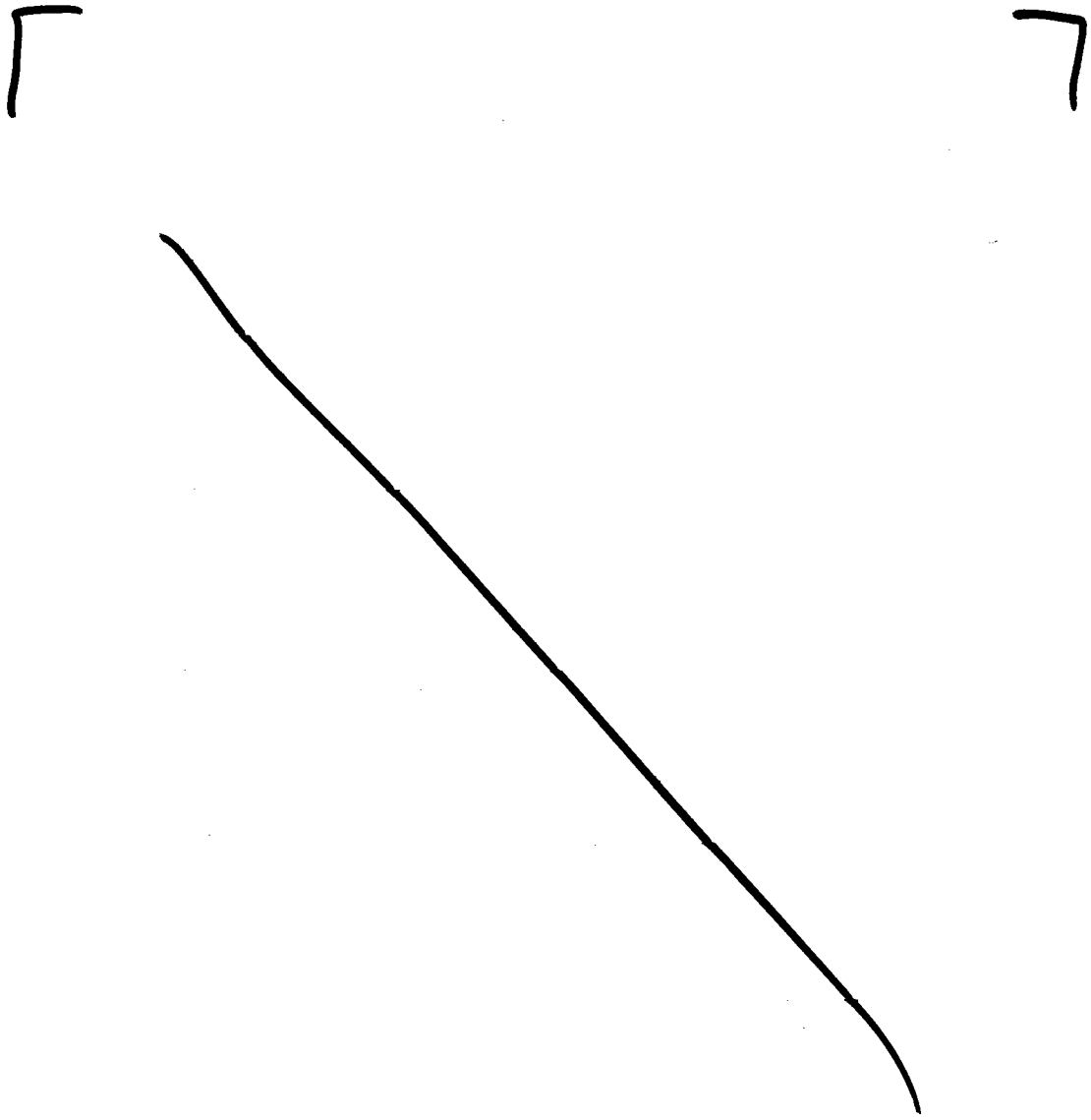
Lactating Women

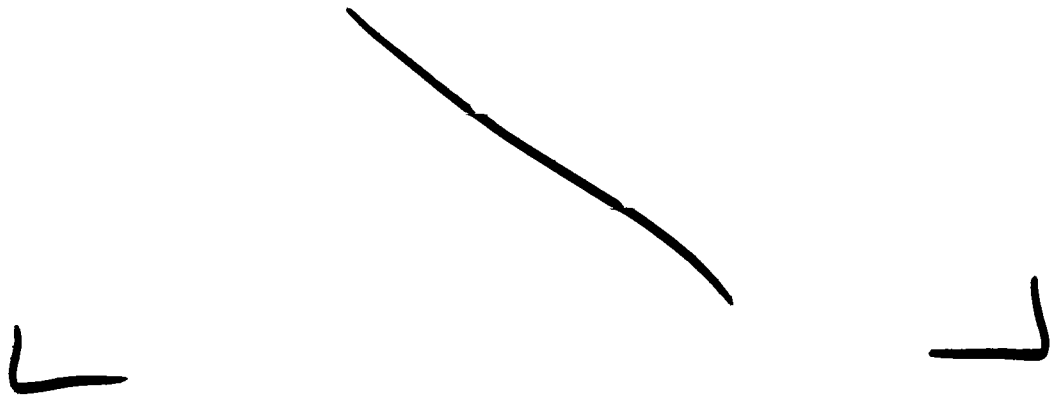
It is not known whether conivaptan is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when conivaptan is administered to a lactating woman. Conivaptan is excreted in milk and detected in neonates when given by intravenous and oral administration to lactating rats. Milk levels in rats reach maximal levels at 1 h post dose following intravenous administrations which are up to 3 times greater than maternal plasma levels. Administration of conivaptan at 2.5 mg/kg/day intravenously or orally ≥0.3 mg/kg/day increased peripartum pup mortality as a function

of impaired maternal behavior, care and lactation (underdeveloped mammary gland lactation); systemic exposures were less than the therapeutic dose based on AUC comparisons."

9.5.2.7 The Division of Medication Errors and Technical Support (DMETS) recommends the following changes to your packaging and labeling (if you choose to resubmit your NDA).

9.5.2.7.1 Container Changes





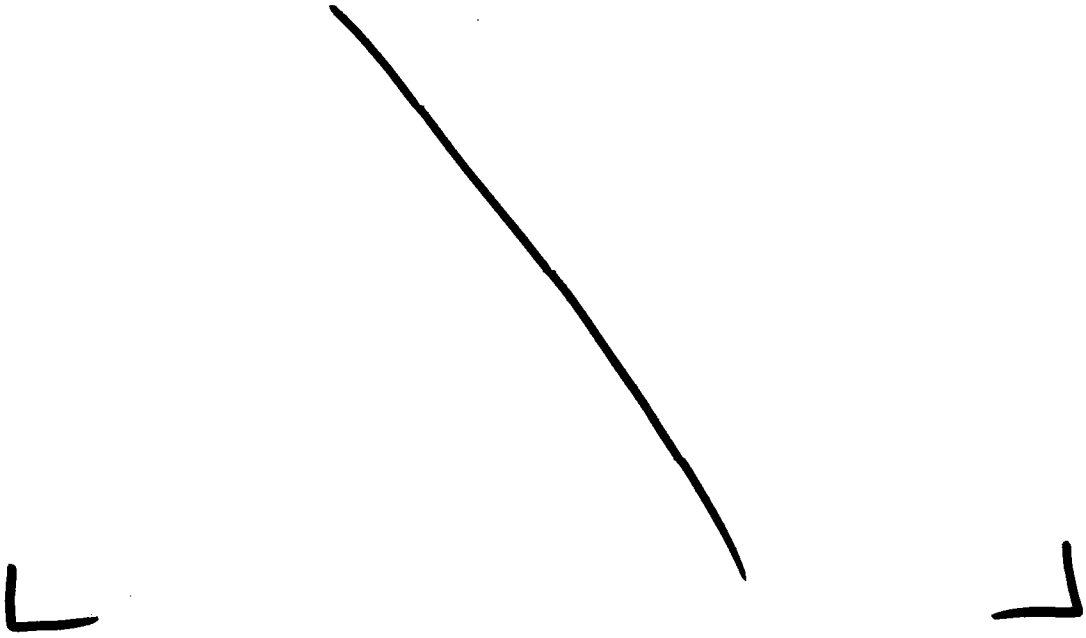
9.5.2.8 The clinical reviewer notes a higher incidence of serious renal adverse events among patients taking conivaptan than among patients taking placebo. Information provided in your application did not permit complete characterization of the etiology of these serious renal adverse events. If you resubmit your application, information will be needed that will allow the clinical reviewer to assess whether these events are related to intravascular volume depletion or nephrotoxicity. For all patients experiencing a decline in renal function, complete information will be needed, including detailed narratives, complete urinalysis information, intake and output records, documentation of followup to resolution, etc.

9.5.2.9 Information is needed about the duration of conivaptan's effect on serum sodium after discontinuation of the proposed intravenous conivaptan regimen. If you resubmit your application, provide information regarding the number of days one can expect to see maintenance of the serum sodium effect after discontinuation of the proposed intravenous regimen of conivaptan.

9.5.2.10 Exposure-response for conivaptan may be changed with renal function because efficacy is likely to be dependent on renal function. It is essential to understand the exposure-response relationship in patients with significantly decreased renal function (e.g. elderly SIADH patients, or patients with renal impairment). Therefore, we recommend you explore an association between efficacy and renal function. The effect of renal function on efficacy may be evaluated using the relationship between creatinine clearance and one of the efficacy endpoints.

9.5.2.11 The Chemistry reviewer requests the following information:

9.5.2.11.1 Regarding the proposed drug substance manufacturing process (S.2.2):



9.5.2.13 In your Phase 3 intravenous study (-027), multiple protocol violations occurred in which patients received prohibited CYP3A4-metabolized drugs. The fact that patients received other CYP3A4-metabolized drugs even in a highly controlled clinical trial setting calls into question whether restriction to short-term use in hospitalized patients will be an effective means of managing the risk of CYP3A4 drug interactions in the less-controlled setting of community use. Consider proposal of a risk management plan for further reducing the likelihood that patients taking conivaptan will other receive CYP3A4-metabolized drugs.

10 APPENDICES

10.1 Review of Individual Study Reports

Clinical Study 087-CL-027 (Protocol 1025-007)

This section contains additional details of study design. Because this was the major intravenous trial of conivaptan, efficacy and safety outcomes for this trial are discussed in detail in the Efficacy and Safety sections of the review (sections 6 and 7).

Title: A Four-day, Double-blind, Placebo-controlled Multicenter Study of IV YM087 (CI1025) to Assess Efficacy and Safety in Patients with Euvolemic or Hypervolemic Hyponatremia

General Methodology:

Randomized, double-blind, multicenter study of 40 or 80 mg per day continuous infusions of YM087 or placebo in the treatment of euvolemic or hypervolemic hyponatremia (serum sodium 115 to <130 mEq/L). A screening phase of up to two weeks was followed by a 20-28 hour baseline phase (Day -1), a four-day double-blind treatment phase, and a posttreatment followup visit on Study Days 10-13. Patients who completed the study had the option to enter an open-label extension study. Patients were screened as in- or out- patients, were hospitalized during baseline and four-day treatment, and had a return posttreatment visit if they were not participating in the extension.

Number and Type of Patients:

Eighty-eight patients were randomized; four of these did not go on to receive any study treatment. A total of 84 patients were treated (29 placebo, 29 in the 40 mg/day group and 26 in the 80 mg/day group). These 84 patients comprised the safety population and the full efficacy analysis set. Sixty-nine of these patients comprised a per-protocol set (24 placebo, 22 in the 40 mg/day group and 23 in the 80 mg/day group). The set of patients who completed the study without discontinuing early included 23 in the placebo group, 22 in the 40 mg/day group, and 21 in the 80 mg/day group, for a total of 69.

All patients were inpatients during the study; those who were not hospitalized at the beginning of the study were admitted.

Inclusion Criteria:

- Euvolemic (defined without pitting edema or ascites) or hypervolemic (defined as edematous).
- Hyponatremic (serum sodium 115- <130 mEq/L)
- Serum osmolality <290 mOsm/kg H_2O

- ≥ 18 years old
- Men and women; women were postmenopausal, surgically sterile, or using barrier birth control.

Exclusion Criteria:

- Evidence of extracellular volume depletion or dehydration
- Fasting blood sugar ≥ 275 mg/dL
- Breast feeding or pregnancy
- "Expected requirement for emergent treatment of hyponatremia during the course of the study"
- Clinical evidence of volume depletion or dehydration
- Supine systolic blood pressure (SBP) < 85 mm Hg
- Orthostatic hypotension (SBP drop of > 20 mm Hg supine to standing or SBP < 80 mm Hg on standing)
- Uncontrolled hypertension
- Uncontrolled brady- or tachy- arrhythmias
- Untreated hypothyroidism, hyperthyroidism or adrenal insufficiency
- Creatinine clearance < 20 mL/min (Cockroft Gault equation, details page 47 of -027 study report)
- Known urinary outflow obstruction, unless the patient could be catheterized during the study
- Serum glutamic pyruvic transaminase (SGPT) or serum glutamic oxaloacetic transaminase (SGOT) >5 times upper limit of normal
- Serum albumin ≤ 1.5 g/dL
- Prothrombin time (PT) >22 seconds or International Normalized Ratio (INR) >2.0 for patients not on anticoagulant therapy, and INR ≥ 3.0 for patients on anticoagulant therapy
- White blood cell count (wbc) < 3,000/μL
- Known HIV or active hepatitis infection

Prohibited Medications:

The original protocol and two amendments addressed prohibited medications:

- In the original protocol (Jan 00) agents known to cause SIADH, agents used to treat hyponatremia, and some agents with CYP3A4 metabolism were prohibited.
- In Protocol Amendment 1 (Jun 00), patients receiving medications used to treat hyponatremia could enter if the agent was discontinued one week prior to initiation. patients receiving CYP3A4-metabolized statins could take be taking them prior to study as long as they were discontinued during the study period. Most other CYP3A4 metabolized drugs could be given with careful observation.
- In Protocol Amendment 2 (Jun 01), the list of prohibited CYP3A4 metabolized drugs was expanded, and warfarin use was restricted

The following table details prohibited medications.

Table 10.1.1 Prohibited Medications, with Changes by Protocol Amendments, Study -027

		Meds Pt Could Not be on to Enter Original Protocol	Changes with Amendment 1	Changes with Amendment 2
Amiodarone		Allowed if pt on it for >3 mo and on <300 mg/day		
Antineoplastic or Chemotherapeutic Agents		y		Specified busulfan, doxorubicin, etoposide, paclitaxel, tamoxifen, vinblastine and vincristine
Astemizole		y		
Atorvastatin		(doses > 40 mg)	Doses > 60 mg allowed if pt stopped during study	
AVP		y		
Azole Antifungals		y		
Barbiturates		y		
Buspirone		y		
BZDs[1]		y	Allowed with close observation	
Calcium Channel Blockers		y	Allowed with close observation	
Carbemazepine		y		
Chlorpropamide		y		No longer on prohibited list
Chronic corticosteroids		y		
Cimetidine		y		No longer on prohibited list
Ciprofloxacin		y		
Cisapride		y		
Clofibrate		y		No longer on prohibited list
Cyclosporine		y		
Demeclocycline		y	Allowed as long as discontinued 1 wk before study	No longer on prohibited list
Desmopressin		y		No longer on prohibited list
Digoxin		Allowed if pt on it > 1 mo		
Florinef		y		No longer on prohibited list
Fluvoxamine		y		
Gestodene		y		No longer on prohibited list
Grapefruit Juice		y		
Lithium		y	Allowed as long as discontinued 1 wk before study	No longer on prohibited list
Lovastatin		y	Allowed if pt stopped during study	
Macrolide Antibiotics[3]		y		
MAOIs[4]		y		No longer on prohibited list
Mifepristone		y		No longer on prohibited list
Narcotic Analgesics[2]		y	Allowed with close	No longer on prohibited list

Table 10.1.1 Prohibited Medications, with Changes by Protocol Amendments, Study -027

		Meds Pt Could Not be on to Enter Original Protocol	Changes with Amendment 1	Changes with Amendment 2
			observation	
Nefazodone		y		
Oxytocin		y		No longer on prohibited list
Phenytoin		y		
Protease Inhibitors		y		
Quinidine		y		
Rifabutin		y		
Rifampin		y		
Sildenafil		y		No longer on prohibited list
Simvastatin		y	Allowed if pt stopped during study	
Tacrolimus		y		
Terfenadine		y		
Trazodone				Added
Troglitazone		y		
Urea		y	Allowed as long as discontinued 1 wk before study	No longer on prohibited list
Warfarin				Careful monitoring required
Zoldipem				Added

[1]Benzodiazepines other than lorazepam, oxazepam and temazepam
[2]Other than codeine, hydrocodone, hydromorphone and morphine
[3]Except azithromycin
[4]Monoamine oxidase inhibitors

Dose:

Patients enrolled prior to Protocol Amendment 2 received a 20 mg IV bolus infusion over 30 minutes on Days 1 and 3. Each bolus was followed by 40 mg/day or 80 mg/day as a continuous infusion for two days. After Protocol Amendment 2, patients received a 20 mg IV bolus on Day 1 followed by a continuous 40 mg/day or 80 mg/day infusion on days 2,3 and 4. Dose selection was based on findings from Phase 1 and 2 studies that showed effectiveness in increasing serum sodium and free water clearance starting at oral doses of 20 mg/day. Doses became intolerable at 120 mg/day due to infusion site reactions. Placebo group patients received D5W as placebo, in the same volume and time administration schedule as patients in the conivaptan groups.

All patients were placed on a two liter per day restriction of total fluid intake.

Efficacy Measures:

Primary Efficacy Endpoint: change from baseline in serum sodium over the duration of the treatment phase as measured by the area under the serum sodium effect curve (from beginning through the end of the scheduled treatment period) corrected for baseline serum sodium [defined as the average of measurements taken at hours 4, 6 and 10, and at the end of the baseline phase (hours 20-28)].

Secondary Efficacy Parameters:

- Time from first dose of study medication to a confirmed $\geq$ 4 mEq/L increase from baseline in serum sodium
- Total time from first dose of study medication to end of treatment during which patients have a serum sodium $\geq$ 4 mEq/L higher than that observed at baseline
- Change in serum sodium from baseline to end of treatment
- Number of patients who obtain a confirmed $\geq$ 6 mEq/L increase from baseline in serum sodium or a confirmed normal serum sodium level ($\geq$ 135 mEq/L)

Other Efficacy Parameters:

Change from baseline in each of the following:
- Free water clearance (FWC)
- Effective water clearance (EWC)
- Net fluid loss
- Serum osmolality
- Urine osmolality
- Urine sodium
- Arginine vasopressin
- Plasma renin activity
- Plasma aldosterone
- Plasma epinephrine
- Plasma norepinephrine

Pharmacokinetic Measurements:

Plasma concentrations of conivaptan at end of Baseline, end of Study Day 2 and end of Study Day 4.

Safety Parameters:

Standard AE, VS and clinical laboratory. Also examined ECGs, volume status, change in body weight, and change in a "thirst index"

Randomization and Blinding:

Randomization was done in blocks of three patients, stratified by volume status. The placebo run-in period was single blind to treatment. The rest of the study was double-

blind to treatment assignment, but the sponsor decided for safety reasons that the investigators would not be blinded to serum sodium levels.

Study Schedule:

Please see sponsor's Figure 9.2 on page 60 of the -027 study report for full details of study events. The following abbreviated table outlines the major events and measurements.

Table 10.1.2: Schedule of Study Procedures, Study -027

	Screen	Baseline	Time Zero	Tx[2] Day 1	Tx Day 2	Tx Day 3	Tx Day 4	Post Visit
	Day -14 to -1	Day -1						10-13 Days Post Tx
Medical History	x[3]							
Physical Exam	x						Hr 24	
Clinical Lab	x		x		Hr 24		Hr 24	
Urinalysis	x						Hr 24	
Orthostatic VS, Wt and Volume Status	x	x	x	Hrs 4, 10 and 24	Hrs 4 and 24	Hr 24	Hr 24	x
Serum Sodium	x	Hrs 0, 4, 6 and 10; and 6 hrs before 1st dose	x	Hrs 4, 6, 10 and 24	Hrs 4, 6, 10 and 24	Hrs 4, 6, 10 and 24	Hrs 4, 6, 10 and 24	x
Thirst Index		x	x	Hrs 6 and 24	Hrs 6 and 24	Hrs 6 and 24	Hrs 6 and 24	x
Serum Potassium		Hrs 0, 4, 6 and 10	x	Hrs 4, 6, 10 and 24	Hrs 4, 6, 10 and 24	Hrs 4, 6, 10 and 24	Hrs 4, 6, 10 and 24	
Serum Osmolality		Hrs 0, 4, and 6	x	Hrs 4, 6, 10, and 24	Hrs 4, 6, 10 and 24	Hrs 4, 6, 10 and 24	Hrs 4, 6, 10 and 24	
Urine Electrolytes and Osm		Hr 6	x	Hrs 6 and 24			Hr 24	
Urine Output		Continuous	Continuous	Continuous	Continuous		Continuous	
ECG			x				Hr 24	
BUN/Cr			x	Hr 24		Hr 24		
Amiodarone Level[1]			x					
Digoxin Level[1]			x					
CXR, T3 and T4			x					
Vasopressin			x		Hr 24		Hr 24	
Neurohormones			x		Hr 24		Hr 24	
Coni or Pbo Bolus			x					
Coni or Pbo Infusion				Continuous	Continuous	Continuous	Continuous	

1 Amiodarone or digoxin levels for patients receiving these medications
2 Treatment
3 "x" indicates the procedure was performed once in the time period for that column. Where relevant, times are given.

10.2 Line-by-Line Labeling Review

Not applicable

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/s/

Karen Mahoney
11/16/04 09:30:24 AM
MEDICAL OFFICER

Mary Parks
11/16/04 11:39:53 AM
MEDICAL OFFICER
concur

MEDICAL TEAM LEADER MEMO OF NDA

NDA #:	21-697
Sponsor:	Yamanouchi
Drug product:	Vaprisol® (conivaptan hydrochloride)
Indication:	Treatment of hyponatremia in non-hypovolemic states
Date of Submission:	January 30, 2004
Primary Medical Reviewer:	Karen M. Mahoney, MD
Statistical Reviewer:	Japo Choudhury, PhD

EXECUTIVE SUMMARY

Introduction and Background

Vaprisol® (conivaptan hydrochloride) is a non-peptide, vasopressin (AVP) antagonist that is under clinical development for the treatment of hyponatremia in euvolemic and hypervolemic patients.

Vasopressin is a hypothalamic neuropeptide that is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and stored in the posterior pituitary where it is released in response to osmotic and non-osmotic stimuli. Vasopressin functions as an antidiuretic hormone (ADH) at physiologic plasma concentrations; vasoconstrictive activity occurs only at higher plasma levels. Release of vasopressin in response to increasing plasma osmolality occurs via stimulation of neurons located in the anterior hypothalamus. Release of AVP secondary to osmolar changes is an extremely sensitive response with only a 1-2% increase in plasma osmolality required to stimulate AVP secreation. In contrast, the release of AVP secondary to changes in blood pressure/volume is mediated via the baroreceptors located in the major blood vessels. The threshold for AVP release in response to changes in blood pressure or effective blood volume is much higher than changes in plasma osmolality. A 5-10% reduction in blood volume or blood pressure is required to stimulate AVP secretion.

Three types of AVP receptors are known: V1a (vascular and hepatic); V1b (anterior pituitary); and V2 (kidney). Of these, the most significant function of vasopressin is at the V2 receptor located on the renal collecting tubules. Stimulation of these receptors results in the renal water conservation to maintain plasma osmolality within a narrow range of 280 to 285 mEq/L. This is accomplished through AVP-mediated insertion of water channels (aquaporins) along the luminal surface of the collecting tubules with subsequent passive reabsorption of solute-free water down the inner medullary

concentration gradient. In the absence of AVP, the distal collecting tubules remain impermeable to water and larger volumes of solute-free water are excreted. Derangements of AVP regulation, synthesis/release, or action result in hypernatremia (deficiency or non-response to hormone activity) or hyponatremia (excessive or inappropriate release for plasma osmolality).

Hyponatremia remains the most common laboratory abnormality in clinical practice. Multiple disease processes can result in hyponatremia and the approach to identifying the cause first focuses on the patient's volume status. Hypovolemic (or extracellular fluid contraction) hyponatremia is due to losses of salt in excess of water. Diarrhea, vomiting, or diuretic use often accompanied by hypotonic fluid replacement are common causes of hypovolemic hyponatremia. In these states, treatment with isotonic fluid replacement typically corrects the hyponatremia.

Hyponatremia in euvolemic and hypervolemic states may also be due to many different disease processes. The syndrome of inappropriate antidiuretic hormone release (SIADH) is the most common cause of euvolemic hyponatremia. AVP release can occur in the setting of malignancies that secrete AVP in an unregulated fashion or due to diseases of the pulmonary or central nervous system. Certain drugs have also been associated with hyponatremia due to stimulation of AVP release (e.g., narcotics, serotonin-reuptake inhibtors) or potentiation of AVP action at the kidneys (e.g., chlorpropamide). Although it is the leading cause of euvolemic hyponatremia, SIADH remains a diagnosis of exclusion after certain conditions have been ruled out (hypothyroidism, hypocortisolism, renal disorders, and diuretic use).

Hypervolemic hyponatremia is found in edematous states such as congestive heart failure (CHF), advanced liver disease, and nephrotic syndrome. In these disease states, AVP may be inappropriately elevated for the degree of plasma osmolality; however, the release of AVP is partly due to the reduced effective circulating volume in these patients (i.e., stimulation of AVP release via the baroreceptors). It important to recognize that in hypervolemic hyponatremia other processes may contribute, if not cause, the hyponatremia. For example, use of angiotensin converting enzyme inhibitors (ACE-inhibitors) or diuretics may cause hyponatremia due to effects on the renin-angiotensin system or renal sodium loss. Recently, several investigators have focused on the role of AVP in the pathogenesis of some of these disease processes. In particular, AVP activity as a contributor to worsening CHF has been evaluated in animal models of heart failure, and clinical studies are currently being conducted in CHF patients with AVP-antagonists. These trials are being conducted under investigational new drug (IND) applications in the Divison of Cardiorenal Drug Products with the primary endpoint including clinical events.

The clinical manifestations of hyponatremia are primarily neurological and reflect the brain cell adaptive process to ECF hypoosmolality. Variable presentations of hyponatremia reflect the magnitude and duration of hyponatremia. With reductions in ECF osmolality, brain cells adapt via losses of electrolytes and organic solutes to reduce the risk of brain edema (fluids shifting from extracellular to intracellular space). Acute

hyponatremia is generally symptomatic as the brain volume has not sufficiently adjusted to the extracellular hypoosmolar state. Chronic hyponatremia is less symptomatic although severe hyponatremia (e.g., < 120-125 mEq/L) may be associated with nausea, headaches, and seizure activity.

The management of hyponatremia must take into consideration the duration of hyponatremia and the presence or absence of symptoms. In general, acute symptomatic hyponatremia can be rapidly corrected without complications. Correction of chronic hyponatremia, particularly asymptomatic states, requires a limited and controlled approach to avoid the neurologic complications of increasing the ECF osmolality in patients whose brain cells have undergone a protective adaptive processes. Rapid correction of serum sodium in this setting increases the risk of rapid fluid shift from the intracellular to extracellular space. Patients may present with tremor, incontinence, hyperreflexia, quadriparesis, quadriplegia, dysarthria, cranial nerve palsies, and mutism. The most severe complication is central pontine myelinolysis, a massive demyelination of descending axons in the pons.

Hyponatremia in both euvolemic and hypervolemic states requires the treatment of the underlying disease process and fluid restriction. Severe or recalcitrant hyponatremia may require other measures outlined in Dr. Mahoney's review. Regardless of the treatment(s) applied, correction is slow and challenging to clinicians and patients as extreme fluid restrictions may be difficult to adhere to and interfere with the medical management of other conditions. As already discussed, choice of treatment must be made with consideration of the degree and duration of hyponatremia to avoid the complications of overly rapid serum sodium correction.

Non-peptide vasopressin antagonists block the effect of AVP at the V2 receptors (selective) and V1A (non-selective). Inhibition of AVP action induces a solute-free diuresis as renal distal collecting tubules remain impermeable to the reabsorption of water resulting in volume depletion, hemoconcentration, and increases in plasma osmolality and serum sodium. Several AVP-antagonists have undergone clinical testing in Phase 2 and 3 studies for the treatment of hyponatremia in nonhypovolemic patients. The clinically development program for conivaptan initially included an intravenous (i.v.) and oral (p.o.) formulation. Conivaptan, a potent CYP3A4 inhibitor, when given with simvastatin in a Phase 2 clinical trial resulted in a serious adverse event of rhabdomyolysis secondary to a drug-drug interaction (DDI). As a result, during an EOP2 meeting with the Division of Metabolic and Endocrine Drug Products, members of the division noted that an indication for chronic use was problematic as the patient population would likely be on multiple medications including those metabolized through CYP3A4. The division also noted that this safety signal was reminiscent of another potent CY3A4 inhibitor, mibefradil, that was approved for chronic treatment of hypertension. Mibefradil was later withdrawn due to serious interactions with drugs such as simvastatin and lovastatin resulting in post-marketing reports of rhabdomyolysis. The Agency's experience in this situation suggested that labeling and post-approval risk management programs would unlikely prevent serious DDIs from occurring in the general population. Shortly after this meeting, the applicant submitted their plans to

discontinue development of an oral formulation. Conivaptan was to be restricted to short-term (4 days), in-patient, intravenous treatment of hyponatremia.

The clinical studies submitted in support of this NDA included three Phase 3 clinical studies: one using the intravenous formulation and two using the oral formulation. All three trials evaluated the [redacted] however, administration and duration were slightly different. The intravenous dosing regimen includes a [redacted] with a [redacted] while the oral dosing regimen did not require a loading dose, and dosing was for 5 days. Other studies included 5 controlled studies in the CHF population, an uncontrolled, open-label extension study in hyponatremic patients, and over 30 clinical pharmacology studies (special population, pK/tolerability studies, etc.). The majority of these studies evaluated the oral dosing of conivaptan. Dr. Mahoney has summarized all clinical studies submitted to the NDA in Tables 4.2.1 through 4.2.8 of her review.

Summary Findings of Clinical Review

In her primary review, Dr. Mahoney identified several concerns in this NDA:

1. Inadequate safety exposure for the proposed intravenous dosing regimen

At the time of NDA submission, the applicant assumed that, based on pharmacokinetic modeling, the oral and intravenous formulations as dosed in Phase 3 trials, produced similar systemic drug exposures. As such, the single intravenous study was considered pivotal to establishing effectiveness while the oral studies were deemed supportive in nature. However, all safety data would be based on studies using both formulations.

After the NDA submission, results from a formal bioequivalence study became available to the applicant. This study compared the pK of the oral versus intravenous formulations of conivaptan and found that oral administration in the Phase 2 studies yielded [redacted] less drug exposure than the IV dosing regimen. Given these findings, the safety results from the po studies cannot be directly extrapolated to the to-be-marketed IV formulation. Out of the 1,421 subjects exposed to conivaptan, only 63 (4.4%) received the proposed IV dosing regimen or an equivalent amount of the oral formulation.

Given the size and clinical heterogeneity of the target population for such a drug (e.g., hyponatremia is the most common laboratory abnormality among hospitalized patients, according to the sponsor), this safety exposure is unacceptable for the purposes of characterizing the spectrum of risks of conivaptan and certainly inadequate as a basis for assessing the balance of risk and benefit for the proposed use.

2. Adverse events occurred more frequently in the conivaptan group than placebo group

Dr. Mahoney identified the following AEs which occurred at a statisticially significantly higher rate in conivaptan group versus placebo.

- serious and nonserious hypovolemia-related events

- serious and nonserious hypotensive events
- serious renal adverse events
- infusion site reactions and infusion site reactions leading to withdrawal from study
- increases in mean serum creatinine, treatment-emergent elevated serum creatinine, and elevated creatinine values of clinical significance
- increases in mean serum alkaline phosphatase
- decreased supine and standing diastolic blood pressure (in pivotal efficacy trial)

While some of these AEs may be related to the pharmacologic effect of conivaptan, these findings, in conjunction with an inadequate safety exposure database, raise the question of whether a thorough dose-response evaluation has been conducted by the applicant.

3. A minimum effective dose has not been proposed for marketing

The purpose of establishing a minimum effective dose is to provide a dosing regimen that lessens the risk of dose-related toxicities (and optimizes risk vs. benefit). The two Phase 3 studies involving the oral formulation demonstrated significant increases in plasma sodium levels. Because the oral formulation provides only [redacted] the amount of drug exposure obtained with intravenous administration and, yet, was still effective, it is reasonable to conclude that a lower dosing regimen than 40 mg IV would also be effective.

4. The efficacy of shorter treatment duration has not been evaluated

Meaningful increases in serum sodium were observed within 24 hours of conivaptan dosing that also correlated with the peak time of free water excretion. Effectiveness of therapy was maintained for approximately 6 to 9 days after treatment cessation. The effect of a shorter duration of treatment (e.g., 2 days infusion) was not evaluated. A shorter treatment duration that is similarly effective to a 4 day infusion may be beneficial because it would decrease time of hospitalization and may decrease toxicities related to conivaptan pharmacokinetics.

Dr. Mahoney and reviewers from the Office of Clinical Pharmacology and Biopharmaceutics have also raised questions regarding the necessity of a loading dose.

Recommendations

This application is approvable. The following deficiencies need to be addressed in the re-submitted application:

1. Provide additional patient exposure data at the proposed intravenous dosing regimen.

   In the current application, only 63 (4.4%) patients out of the cohort of 1,421 conivaptan-treated subjects received the proposed dosing regimen. As several adverse events occurred more frequently in conivaptan-treated patients, more patient data are necessary to better characterize the safety of the proposed dosing regimen.

2. Evaluate the efficacy and safety of lower dosing regimens and shorter duration of infusion. Evaluate the necessity of a loading dose.

   Efficacy was observed at the 40 and 80 mg oral doses of conivaptan in a Phase 3 clinical trial submitted to this NDA. A bioequivalence study demonstrated an approximate ! lower drug exposure level for the oral dose compared to an equivalent intravenous dose. Consequently, intravenous dosing regimens lower than 40 mg daily infusions may adequately treat nonhypovolemic hyponatremia while decreasing dose-related adverse events.

   The Phase 3 studies revealed significant increases in serum sodium levels within the first 24 hrs of drug administration that was accompanied by an increase in free water clearance. The applicant should explore whether administration of therapy for less than 4 days will be effective while decreasing the risk of drug-related adverse events (e.g., infusion-related adverse events).

Labeling will be deferred until the aforementioned deficiencies have been addressed. However, labeling will require extensive discussion on careful patient selection prior to initiating therapy and close monitoring of serum sodium during therapy to avoid the clinical complications of rapid sodium correction.

CLINICAL EFFICACY

Evidence of efficacy was provided in three Phase 3, placebo-controlled, clinical trials of patients with euvolemic or hypervolemic hyponatremia that studied daily doses of 40 mg and 80 mg. Study 027 was the pivotal study for the

[redacted]

Studies 026 and 043 were supportive for efficacy and studied only the oral formulation at 40 and 80 mg administered over 5 days. All three studies were similar in design including patient population selected. Hyponatremia was defined as ≥ 115 mEq/L and < 130 mEq/L. Patients were further stratified by volume status: euvolemic hyponatremia or hypervolemic hyponatremia.

The primary efficacy endpoint was the change in serum sodium from baseline over the duration of treatment, as measured by the area under the serum sodium effect curve (from beginning through end of treatment), corrected for baseline serum sodium.
This efficacy measure was selected because serum sodium levels fluctuate daily and could be affected by measures other than conivaptan administration.

Secondary and tertiary efficacy parameters included measures that would support a conclusion that improvements in serum sodium were a direct effect of conivaptan administration and not due to additional therapeutic interventions (e.g., fluid restriction). These secondary/tertiary measures are more familiar to clinicians treating hyponatremia and include:

- time from first dose of study medication to confirmed ≥ 4 mEq/L increase from baseline in serum sodium

- total time from first dose of study medication to end of treatment during which patients had a serum sodium ≥ 4 mEq/L higher than that observed at baseline
- change in serum sodium from baseline to end of treatment
- number of patients who obtained a confirmed ≥ 6 mEq/L increase from baseline in serum sodium or a confirmed normal serum sodium (≥ 135 mEq/L)
- free water clearance
- effective water clearance

Results from Pivotal Study Evaluating Intravenous Dosing Regimen

Eighty-eight patients were randomized in the pivotal intravenous formulation trial (Study-027). Of these, only 86 patients actually received treatment; 29 received placebo, 26 received conivaptan 40 mg IV, and 26 received conivaptan 80 mg IV. In general, the treatment groups were balanced at baseline. A higher proportion of subjects across all three treatment groups were > 65 years of age (78.6% of cohort > 65 yrs of age) and likely reflect the underlying medical conditions associated with hyponatremia.

Conivaptan 40 mg and 80 mg IV significantly corrected hyponatremia over placebo as measured by the change in serum sodium from baseline over the duration of treatment (Table 1). While the 80 mg dose had a greater mean change than 40 mg, a marked overlap in response was noted between the two dose groups (see Figure 6.1.4.1.3.1.1 from primary medical review).

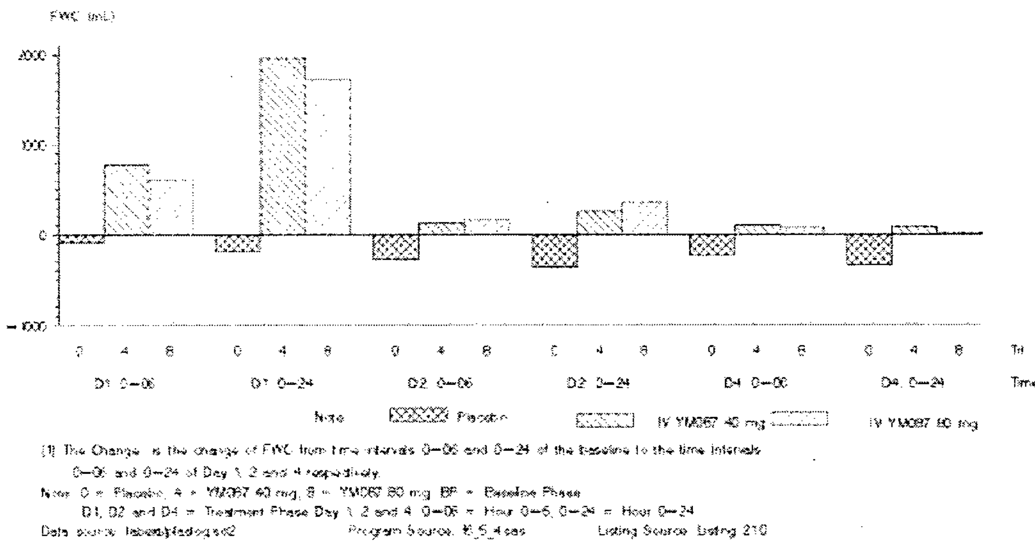
Table 1. Primary Efficacy Results in Study -027

	Placebo n = 29	Conivaptan 40 mg/day n = 29	Conivaptan 80 mg/day n = 26	P-value
Change from baseline in baseline-adjusted serum sodium AUC (mean ± SD, in mEq-hr/L)	61.4 ± 242.3	500.8 ± 365.46	661.7 ± 331.14	Overall: <0.0001 C40[2] vs pbo: <0.0001 C80[3] vs pbo: <0.0001

The mean change in serum sodium from baseline was higher in the conivaptan 40 and 80 mg groups (6.8 and 9.0 mEq/L, respectively) than in the placebo group (2.0 mEq/L). Similarly, a greater percentage of patients in the conivaptan treatment groups achieved a normal serum sodium or had an increase that was ≥ 6 mEq/L. These changes were accompanied by an increase in serum osmolarity and a greater net fluid loss was observed in the conivaptan groups than placebo on Days 1 and 2.

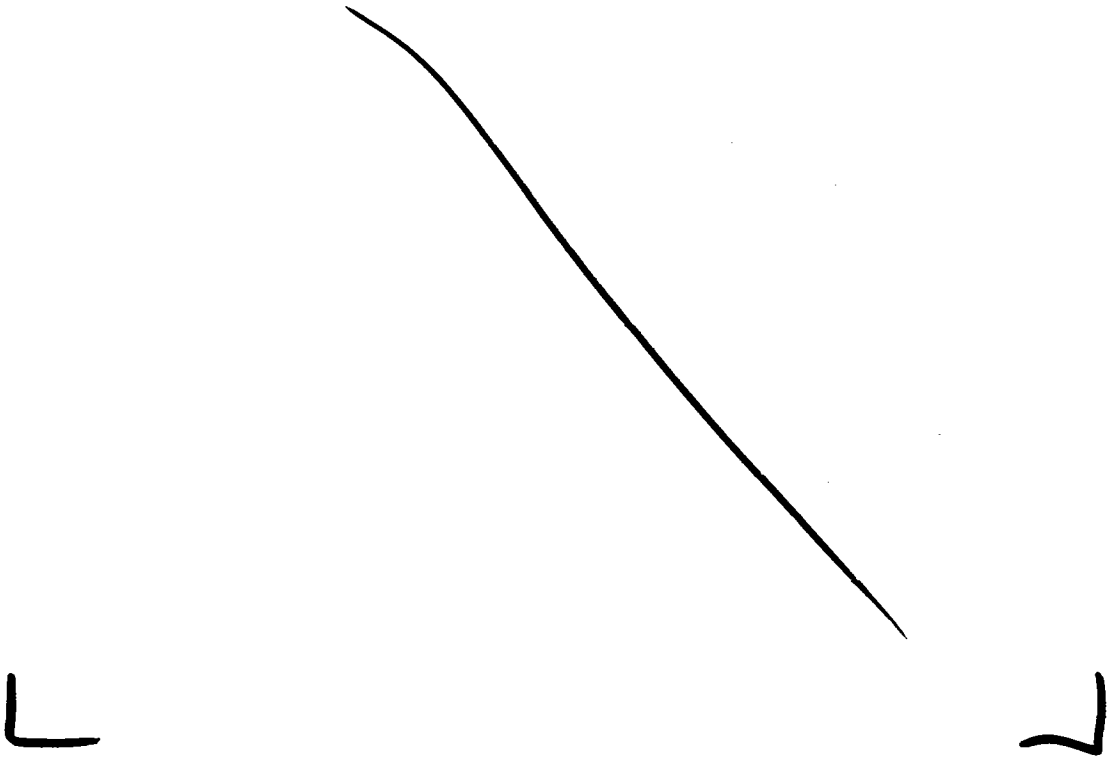
In her review, Dr. Mahoney summarized current approaches to treating [redacted] hyponatremia. Fluid restriction is a mainstay of any treatment regimen and was also a part of the conivaptan treatment algorithm (restriction of < 2 L per day). Dr. Mahoney observed that more patients in the conivaptan groups than placebo had daily fluid intakes exceeding this restricted amount but efficacy was still maintained. A secondary efficacy parameter evaluated the time in which 50% of patients increased their serum sodium level by at least 4 mEq/L. The median time for the placebo treatment group could not be calculated as less than 50% of patients had achieved this degree of

sodium correction. A majority of patients treated with conivaptan 40 and 80 mg achieved a ≥ 4mEq/L correction in serum sodium in approximately one day (mean 23.7 hrs for 40 mg and 23.4 hrs for 80 mg). This time interval also correlated with the effect of conivaptan on free water clearance (see Figure 6.1.4.1.3.3.2 from primary medical review and copied below).



The effectiveness of conivaptan was consistent across several subgroups analyzed including: age, gender, race, baseline volume status, and presence or absence of CHF.

Clinical Efficacy Observed in Studies Using Oral Formulation



CLINICAL SAFETY

A total of 1,421 study participants received conivaptan. Of these, only 63 received conivaptan at the dosing regimen recommended for marketing or an equivalent oral dose. Safety review of only those patients (referred to as the "full dose" population) receiving the equivalent dose of conivaptan 40 mg IV revealed no significant difference between drug and placebo; however, the insufficient number of subjects studied in the full dose population precludes any adequate conclusion on the safety of conivaptan 40 mg IV. Indeed, when the full safety population of patients treated in Phase 2 and 3 was evaluated (placebo-332; conivaptan-896), Dr. Mahoney identified serious adverse events that occurred more frequently in the conivaptan group (See Tables 7.1.2.4 and 7.1.3.3.3. and section 7.1.3.3.2 of primary review).

Table 4. Selected Serious AEs in the Full Safety Population

	Conivaptan n=896	Placebo n=332
Serious renal AEs	16 (1.8%)	1 (0.3%)
Serious hypovolemic-related AEs	25 (2.8%)	4 (1.2%)
Serious and nonserious hypotensive events	84 (9.4%)	27 (8.1%)
Infusion site reactions*	43/208 (21%)	3/92 (3%)

*IV Phase 2 and 3 studies only

A review of the case narratives summarized by Dr. Mahoney makes evident that many of the patients who experienced these AEs were older with serious medical conditions that may decrease their threshold for tolerating the brisk aquaresis obtained with conivaptan. Patients with CHF experienced more treatment related AEs than the non-CHF study population. Several of these events are associated with the pharmacologic effect of the drug (e.g., hypovolemia and hypotension). The serious renal AEs included significant increases in serum creatinine levels and renal failure. Review of the case narratives would also suggest that these abnormalities are, in part, due to the potent diuretic effect of conivaptan resulting in hypovolemia and decreased renal perfusion. Dr. Mahoney did identify 3 patients who did not appear to have a brisk diuresis; however, there are no other clinical data to conclude a direct nephrotoxic effect of conivaptan.

Infusion site reactions were noted early in clinical development and in preclinical studies and was the most common AE in IV studies. In the Phase 2 and 3 IV trials, 21% of conivaptan-treated patients experienced infusion site reactions compared to 3% of the placebo group. Adverse event terms included phlebitis, thrombophlebitis, DVT, swelling, and erythema and injection site infection. All patients discontinuing therapy in the pivotal study (Study 027) reported an infusion reaction. This protocol required that drug be administered through an indwelling arm catheter or central line; administration through hand veins were prohibited.

Rapid correction of serum sodium may result in serious neurologic deficits. The Phase 3 clinical trials defined overly rapid correction as:

- serum sodium increased by more than 12 mEq/L in 24 hrs
- serum sodium increased by more than 24 mEq/L total
- serum sodium exceeded 145 mEq/L
- investigator determined that serum sodium was corrected too quickly

Using these criteria, no placebo patients had overly rapid correction while 7 (9%) of the conivaptan 40 mg group and 7 (9%) of the 80 mg group had rapid serum sodium correction. Dr. Mahoney further evaluated the degree of serum sodium change and

identified increases within a 24 hr period ranging from 13 mEq/L to 25 mEq/L. One patient had an increase from 118 mEq/L to 143 mEq/L over a 5-day treatment period. While no serious clinical complications resulted from these serum sodium changes, the potential of rapid sodium correction with neurologic deficit does exist when employing an AVP-antagonist for the management of chronic hyponatremia.

Increases in ALT/AST and alkaline phosphatase occurred more frequently in conivaptan patients than in placebo patients. Transaminase elevations > 10 x ULN occurred only in conivaptan-treated patients (2 ALT cases and 4 ALT cases). Hepatic failure was reported in three patients. All three had disease processes that likely contributed to the AE (cardiac transplant, metastatic gallbladder cancer, and infection hepatitis).

In conclusion, significantly higher rates were observed in the conivaptan-treated patients for renal adverse events, hypovolemia, and hypotension. Conivaptan intravenous administration was associated with more infusion-related adverse events despite a requirement that drug administration utilize only central veins or antecubital veins. While many of the adverse events can be attributed to the pharmacologic effect of conivaptan, the applicant has submitted insufficient patient exposure data for the proposed dosing regimen. Furthermore, studies using the less bioavailable oral formulation suggests that a lower intravenous dosing regimen may still be effective and have decrease the risk of dose-related adverse events.

RELEVANT FINDINGS FROM OTHER REVIEW DISCIPLINE FINDINGS

Chemistry, Manufacturing, and Controls

Reviews of CMC and microbiology information were found to be acceptable.

Pharmacology/Toxicology

A HERG channel study was reported to be mildly positive which resulted in the requirement that a QTc study be conducted with moxifloxacin included as a positive control. The results of this study were submitted to the NDA and summarized in Dr. Mahoney's review. No significant QTc prolongation was observed in the conivaptan 40 mg and 80 mg treatment groups.

Clinical Pharmacology

Conivaptan is both a CYP3A4 substrate and a CYP3A4 inhibitor. Auto-inhibition appears to contribute to non-linear pharmacokinetics.

Pharmacokinetic studies with CYP3A4 substrates and inhibitors have provided compelling evidence that serious drug-drug interactions may occur in the clinical setting:

- Ketoconazole (potent CYP3A4 inhitor) increases conivaptan drug levels 11-fold.
- Conivaptan increases simvastatin AUC (CYP3A4 substrate) 3-fold (a Phase 2 clinical study has documented rhabdomyolysis in a patient receiving conivaptan and simvastatin)

Other issues raised by the biopharm reviewers included:

- establishing a minimum effective dose
- establishing the need for a loading dose
- explore shorter duration of treatment/infusion
- determine appropriate dosing in special populations (elderly, renal impairment and hepatic impairment)

ADMINISTRATIVE/REGULATORY ISSUES

Dr. Mahoney has reviewed the financial disclosure information and found it adequate.

Clinical site inspections were conducted at two investigator sites and deficiencies noted did not appear to affect the results of this NDA.

A waiver has been granted for the conduct of pediatric studies as the number of pediatric patients affected by nonhypovolemic hyponatremia is too small to adequately study in a well-designed clinical trial.

CONCLUSIONS

Hyponatremia in euvolemic and hypervolemic patients is a common clinical finding. The clinical manifestions of this laboratory abnormality depend on both the magnitude and duration of hyponatremia; however, the neurological signs and symptoms predominate. Correction of hyponatremia reduces the risk of these complications but the treatment, itself, may also result in neurologic symptomatology if the rate of correction is not carefully monitored. Current clinical management includes treatment of underyling disease process, fluid restriction, and the use of several off-label therapies. While effective in most circumstances, these therapies increase sodium levels over the course of days to weeks, are difficult to adhere to (fluid restriction), are associated with toxicities, and/or may be unpalatable.

Use of AVP receptor antagonists to correct nonhypovolemic hypoosmolality takes advantage of the fact that inhibition of the V2 receptor causes a solute free diuresis that effectively increases plasma osmolality and corrects serum sodium levels (and directly addresses a central pathological mechanism in the genesis of the hyponatremic state in the hypovolemic and euvolemic patients targeted). In this application, conivaptan infused at 40 mg daily over a 4 day period significantly increased serum sodium levels with an associated increase free water clearance within 24 hrs of drug administration. Serum sodium increased by a mean of 6.8 mEq/L at the end of study and many patients were able to liberalize their 2 L per day fluid restriction.

While clearly effective, the safety exposure in this NDA was inadequate as the majority of subjects were exposed to the oral formulation of conivaptan. Due to its potent inhibition of CYP3A4 substrates, the chronic, oral use of conivaptan was discontinued during clinical development program after serious drug-drug interactions were reported in Phase 2 studies. The currently [redacted] Only 63 patients received this dosing regimen or an equivalent oral dose. Findings of more serious adverse events in

the conivaptan-treated group that may reflect its potent diuretic effect (e.g., serious hypotension, hypovolemia, and renal events) and infusion-related adverse events require the applicant to provide more patient exposure data for an adequate assessment of risk versus benefit. Efficacy observed with a less bioavailable oral dosing regimen also raises the need for an evaluation of a lower, effective intravenous dosing regimen that may reduce the risk of adverse events noted in the review of this NDA.

Consequently, this application should be approvable with deficiencies summarized under the Recommendation section of this memo.

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/s/

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11/8/04 10:44:56 AM
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Concur with Dr. Parks