CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-697

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/Serial Number:	21-697/N-000
Drug Name:	VAPRISOL™ (conivaptan hydrochloride injection)
Indication(s):	The treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients
Applicant:	Yamanouchi Pharma America, Inc.
Date(s):	Received 01/30/04; user fee (10 months) 11/30/04
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Cynthia Liu, MA
Concurring Reviewer(s):	Karl K. Lin, Ph.D., Expert Mathematical Statistician (Applications in Pharmacology and Toxicology)
Medical Division:	Div. of Metabolic and Endocrine Drug Products (HFD-510)
Pharmacology Team:	Fred Alavi, Ph.D., Pharmacological Reviewer
	Karen Davis-Bruno, Ph.D., Team Leader
Project Manager:	Lina Aljuburi
Keywords:	NDA review, carcinogenicity studies, survival, neoplastic lesions

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Summary of Statistical Review

- Statistical reports for the two standard 2-year carcinogenicity studies (rat and mouse) with two sexes each, submitted by the sponsor along with electronic data sets, were reviewed.

- Dose levels for the F344 rat study were 0, 0.3, 1, 3, and 10 mg/kg/day for the males and 0, 1, 3, 10, and 30 mg/kg/day for the females. Dose levels for the B6C3F1 mouse study were 0, 3, 10, and 30 mg/kg/day for the males and 0, 1, 3, and 10 for the females. Route of administration was oral gavage for both species.

- This reviewer's results of the survival and tumor analyses for both rat and mouse studies agree with the sponsor's.

- There were at least 70% of male and female animals surviving in both studies at the beginning of Week 80, indicative of sufficient number of animals with adequate exposure to the treatment.

- In the rat study, there was a significant dose-response in mortality in either sex, which was associated with significantly increased mortality rates in the intermediate and/or high dose groups when compared to the control. No significant treatment-related increases in neoplastic lesions were observed in both sexes.

- In the mouse study, no significant positive trends or group comparisons in mortality or tumor incidences were observed in either of the two sexes.

- There were no analyses of combining tumors, tissues, and/or related hyperplastic lesions requested by the reviewing pharmacologist.

Introduction

The sponsor has submitted two carcinogenicity studies (rat and mouse) conducted by [redacted] for the new drug application (NDA 21-697) for VAPRISOL™ (conivaptan hydrochloride injection). There were two sexes in each study. The purpose of these studies was to evaluate the carcinogenic potential of test article YM087 when administrated once daily by oral gavage to rats and mice for at least 104 weeks.

This reviewer has performed her own independent statistical analyses on survival and neoplastic lesions, using the electronic data sets submitted by the sponsor on 1/30/2004. The data files and study reports this reviewer reviewed are located in \\Cdsesub1\n21697\N_000\2004-01-30\pharmtox\datasets and \\Cdsesub1\n21697\N_000\2004-01-30\pharmtox\tox. The 4 study designs are briefly described below, followed by this reviewer's analysis methods and discussion in regard to the differences, if any, between the sponsor and reviewer's results.

Study Design

The group designation, dose level, and number of animals per group for the rat and mouse studies are provided below. The strains of rats and mice were CDF®(F-344) BR and B6C3F1/ [redacted]BR VAF/Plus®, respectively.

Rat				Mouse			
Group Designation and Dose Level (mg/kg/day)		Animals per group		Group Designation and Dose Level (mg/kg/day)		Animals per group	
		Male	Female			Male	Female
1 = Control	0	60	60	1 = Control	0	60	60
2 = Low	0.3	60	-	2 = Low	1	-	60
3 = Mid-Low	1	60	60	3 = Mid	3	60	60
4 = Mid	3	60	60	4 = Mid-High	10	60	60
5 = Mid-High	10	60	60	5 = High	30	60	-
6 = High	30	-	60				

Reviewer's Analysis Methods

Survival. Evaluations of dose-response trend in mortality and group comparisons were conducted using Cox-Tarone binary regression (parametric) and Gehan-Breslow (nonparametric) tests. The former method is weighted more heavily toward late incidences and the latter method is weighted more heavily toward early incidences due to treatment. As a result, both are valuable tools for incidence data with onset times. Kaplan-Meier product limit survival curves were a supplementary tool to examine the survival distribution patterns

among the study groups. Two-sided tail probabilities for trend and group comparisons are evaluated at the 5% significance level.

Neoplastic Lesions. The occult tumors (incidental and/or fatal) were analyzed by interval-based exact permutation test incorporating cause of death information. The cut-off points used for the intervals were Weeks 0-52, 53-78, 79-92, 93-before terminal sacrifice, and terminal sacrifice, which are based on the suggestions from National Toxicology Program (NTP). The palpable (superficial) tumors were also analyzed by interval-based exact permutation test as in the case of fatal tumors, using the first palpation time (provided in the sponsor's electronic data files) as the tumor onset time. SAS PROC MULTTEST (1999) was used to implement the interval-based exact permutation test. Comparisons of control versus treated groups were performed only if there was a significant trend (at $p \leq 0.05$, 1-sided) in the incidence data.

The benign and malignant neoplastic lesions were evaluated individually as well as combined. In the cases of multiple-organ findings (e.g., hemangioma, hemangiosarcoma, endometrial stromal polyp, and endometrial stromal sarcoma), the incidences were counted and evaluated by animal as well as by tissue type. The statistical results for these cases may be biased because not all the animals were examined for every tissue. This reviewer has selected combined tumor types and/or combined organ types, where appropriate, for the analyses based on the work of McConnell et al. (1986) and her past experience. There were no combining cases requested by the reviewing pharmacologist.

Since whether tumor incidence rates increase as doses increase is the main concern of the FDA/CDER pre-clinical review team regardless of the real direction indicated by the data, upper-tailed probabilities (p-values) were, therefore, always computed in testing for positive trend and group comparisons. The following table provides the criterion for determining the statistical significance according to the FDA's Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (May 2001).

	Test for Positive Trend	Control-High Pairwise Comparisons
Standard 2-Year Studies with 2 Species and 2 Sexes	Common and rare tumors are tested at 0.005 and 0.025 significance levels, respectively.	Common and rare tumors are tested at 0.01 and 0.05 significance levels, respectively.

Common tumor is defined as a tumor type with background (control) rate >1% and rare tumor with background (control) rate ≤1%. The concurrent control and historical control (where applicable) data were both taken into consideration in determining commonality of a tumor.

There are some differences between the sponsor and reviewer's analysis methods. For example, arithmetic (true) dose levels were used in this reviewer's analyses as opposed to ordinal dose levels (e.g., 0, 1, 2, 3, etc.) in the sponsor's. This reviewer performed interval-based exact permutation test for the analyses of neoplastic lesions, while the sponsor used logistic regression and Cox-Tarone binary regression for the incidental and fatal/palpable tumors, respectively.

Results and Discussion

In general, this reviewer's results of the survival analyses for the rat and mouse studies agree with the sponsor's. Despite the differences in the methods of tumor analysis, no major discrepancies in the results were observed for both studies.

The Rat Study

Survival. There was a significant positive trend ($p = 0.0000$) in mortality in the male rats (Table 1), which was driven by the significantly higher mortality in the high-dose group (10 mg/kg/day) when compared to the control ($p = 0.0001$). The female rats also showed a significant positive trend in mortality ($p = 0.0000$, Table 2) which was associated with significantly increased mortality rates in the mid-, mid-high-, and high-dose groups (3, 10, and 30 mg/kg/day, respectively) when compared to the control (all $p < 0.02$). The Kaplan-Meier product limit survival curves for the males (Figure 1) and females (Figure 2) depicted the findings clearly. In addition, at least 70% of the male rats and female rats in each group were still surviving at the beginning of Week 80, indicating that a sufficient number of animals were exposed to treatment adequately according to the FDA's guidance (May 2001).

Neoplastic Lesions. There were no significant positive trends in the incidences of any common tumors at the $p \leq 0.005$ significance level and of any rare tumors at the $p \leq 0.025$ significance level in either of the two sexes in the rat study. The summary incidences can be found in Table 13 of r087-tx-047.pdf, the sponsor's rat report.

The Mouse Study

Survival. As indicated in Tables 3 (male) and 4 (female), there were no significant positive trends or group comparisons in mortality in either of the two sexes in the mouse study. According to the Kaplan-Meier product limit survival curves, there were at least 90% of the

male mice (Figure 3) and 80% of the female mice (Figure 4) in each group still surviving at the beginning of Week 80. This indicates that a sufficient number of animals were exposed to treatment adequately according to the FDA's guidance (May 2001).

Neoplastic Lesions. There were no significant positive trends in the incidences of any common tumors at the $p \leq 0.005$ significance level and of any rare tumors at the $p \leq 0.025$ significance level in either of the two sexes in the mouse study. The summary incidences can be found in Table 13 of r087-tx-054.pdf, the sponsor's mouse report.

Conclusion

In the rat study, there were significant positive trends in mortality in both sexes. Specifically, the male high dose group (10 mg/kg/day) and the female intermediate to high dose groups (3, 10, and 30 mg/kg/day) all showed a significantly increased mortality when compared to the control. In the mouse study, no significant positive trends or group comparisons were observed for the survival data in either sex. Based on the examinations of the validity of the study designs, the majority of the rats and mice were exposed to treatment adequately.

No significant positive trends in the incidences of any common or rare tumors were observed in either sex of the rat and mouse studies.

Labeling Comments

The highest doses for the male and female mice were 30 and 10 mg/kg/day, respectively. The sponsor had the dose levels reversed in the text.

Prepared by: Cynthia Liu, MA, Statistical Reviewer

Concurred by: Karl K. Lin, Ph.D., Expert Mathematical Statistician (Applications in Pharmacology and Toxicology)

CC: HFD-510/LAljuburi, KDavisbruno, FAlavi
HFD-715/ENevius, KLin, TSahlroot, CLiu
HFD-700/CAnello

Table 1 – Results of Statistical Analyses of Mortality Data for Male Rats

Group	1	2	3	4	5
Dose (mg/kg/day)	0	0.3	1	3	10
Number of Deaths					
Weeks 0-52	0	0	0	0	2
Weeks 53-78	2	3	2	5	13
Weeks 79-92	7	7	2	10	12
Weeks 93-before term sac	12	12	14	13	14
Terminal Sacrifice Weeks	39	38	42	32	19
Unadjusted Mortality	21/60	22/60	18/60	28/60	41/60
Kaplan-Meier Estimate (Final)	0.350	0.367	0.300	0.467	0.683
Cox-Tarone Test (two-sided p)	0.0000 + **	0.9764 +	0.5406 –	0.2234 +	0.0001 + **
Gehan-Breslow Test (two-sided p)	0.0000 + **	0.8508 +	0.3543 –	0.1592 +	0.0001 + **

Figure 1 – Kaplan-Meier Product Limit Survival Curves for Male Rats

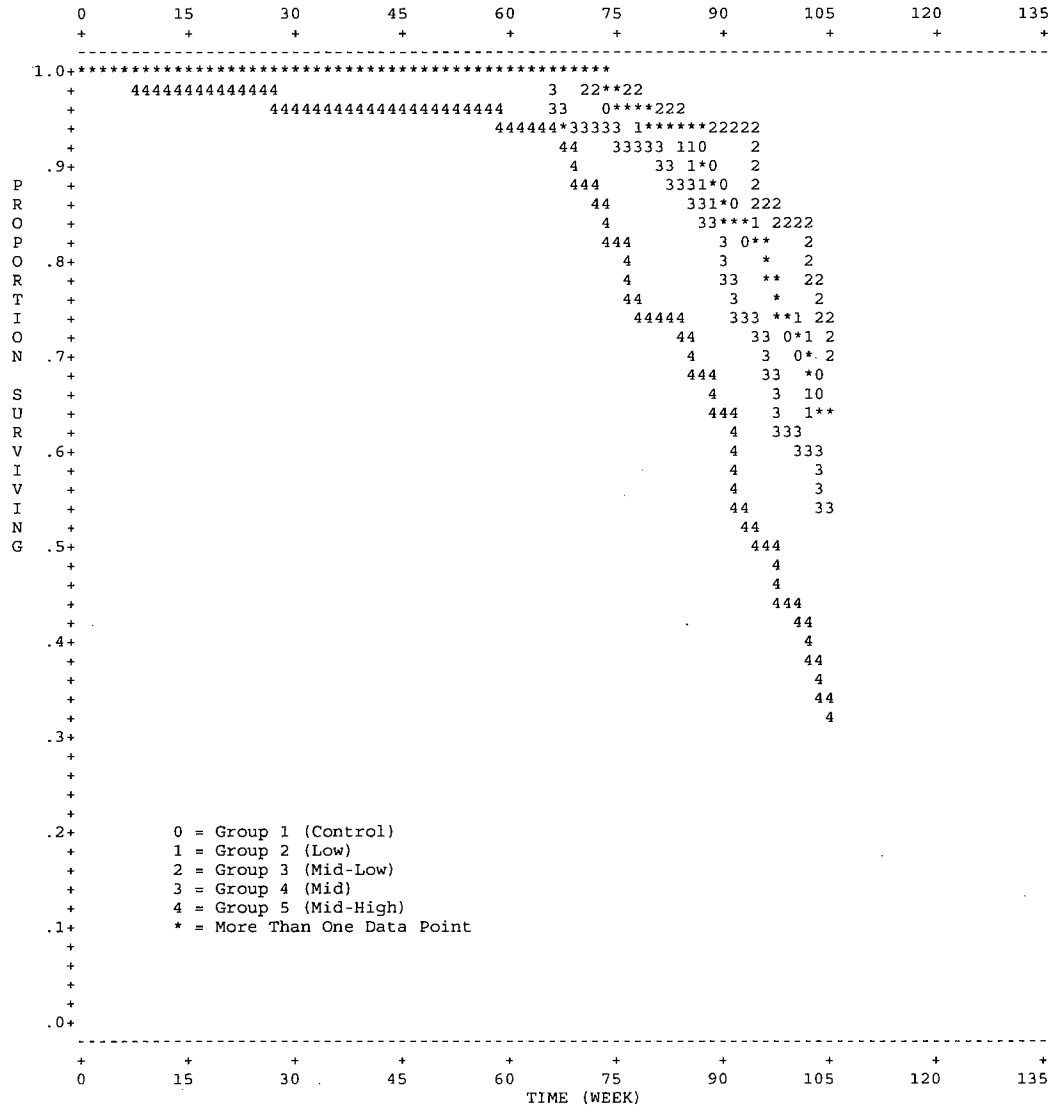


Table 2 – Results of Statistical Analyses of Mortality Data for Female Rats

Group	1	3	4	5	6
Dose (mg/kg/day)	0	1	3	10	30
Number of Deaths					
Weeks 0-52	2	3	2	0	1
Weeks 53-78	1	1	4	8	10
Weeks 79-92	0	3	8	10	17
Weeks 93-before term sac	12	9	12	13	15
Terminal Sacrifice Weeks	45	44	34	29	17
Unadjusted Mortality	14/60	16/60	26/60	31/60	42/60
Kaplan-Meier Estimate (Final)	0.237	0.267	0.433	0.517	0.703
Cox-Tarone Test (two-sided p)	0.0000 + **	0.7738 +	0.0195 + *	0.0009 + **	0.0000 + **
Gehan-Breslow Test (two-sided p)	0.0000 + **	0.5808 +	0.0079 + **	0.0003 + **	0.0000 + **

Figure 2 – Kaplan-Meier Product Limit Survival Curves for Female Rats

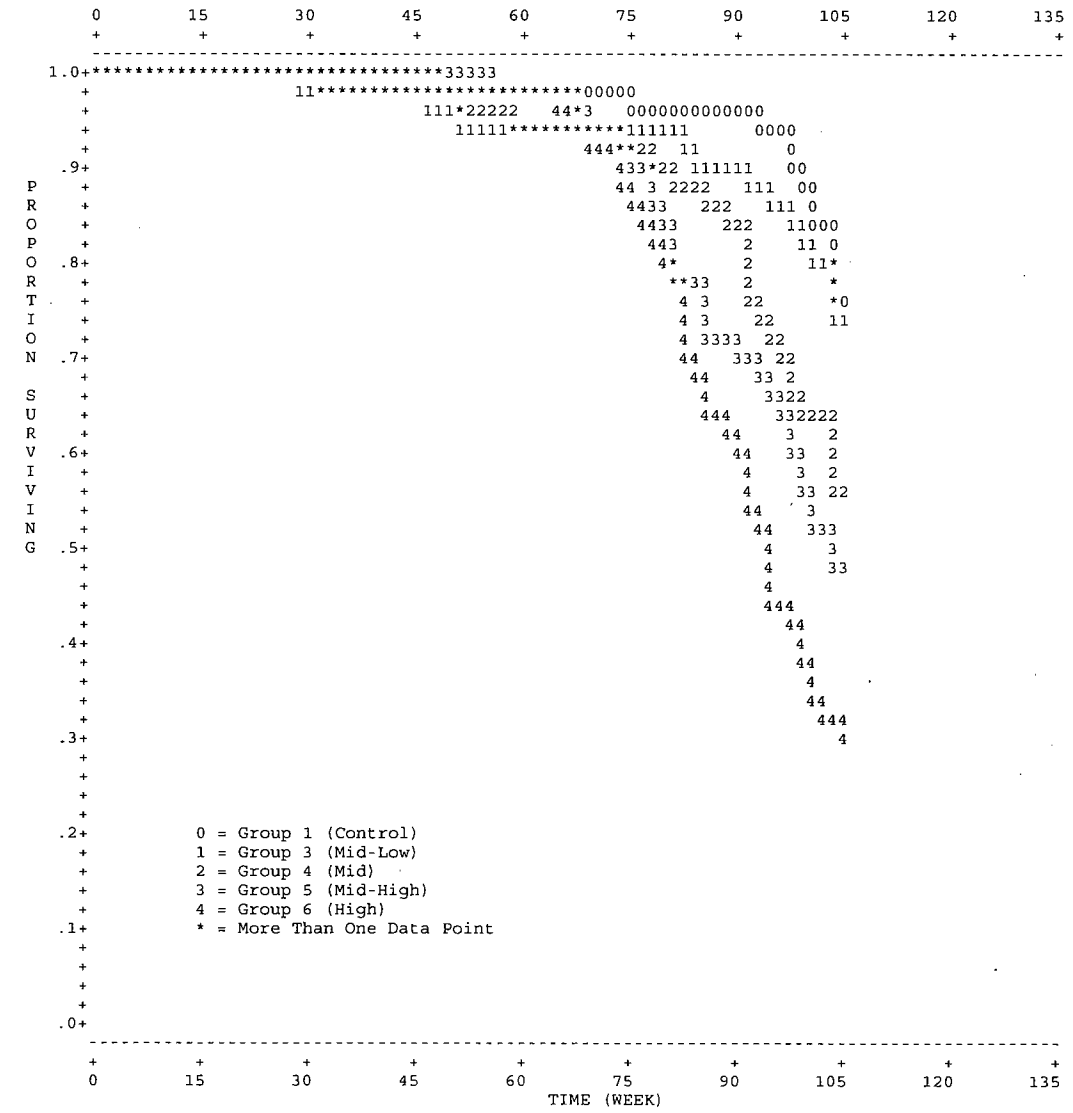


Table 3 – Results of Statistical Analyses of Mortality Data for Male Mice

Group	1	3	4	5
Dose (mg/kg/day)	0	3	10	30
Number of Deaths				
Weeks 0-52	1	2	2	1
Weeks 53-78	2	4	1	1
Weeks 79-92	4	1	3	3
Weeks 93-before term sac	5	5	3	8
Terminal Sacrifice Weeks	48	48	51	47
Unadjusted Mortality	12/60	9/60	9/60	13/60
Kaplan-Meier Estimate (Final)	0.200	0.155	0.150	0.217
Cox-Tarone Test (two-sided p)	0.6240 +	0.6759 –	0.6333 –	0.9202 +
Gehan-Breslow Test (two-sided p)	0.6905 +	0.5308 –	0.5044 –	0.9985 +

Figure 3 – Kaplan-Meier Product Limit Survival Curves for Male Mice

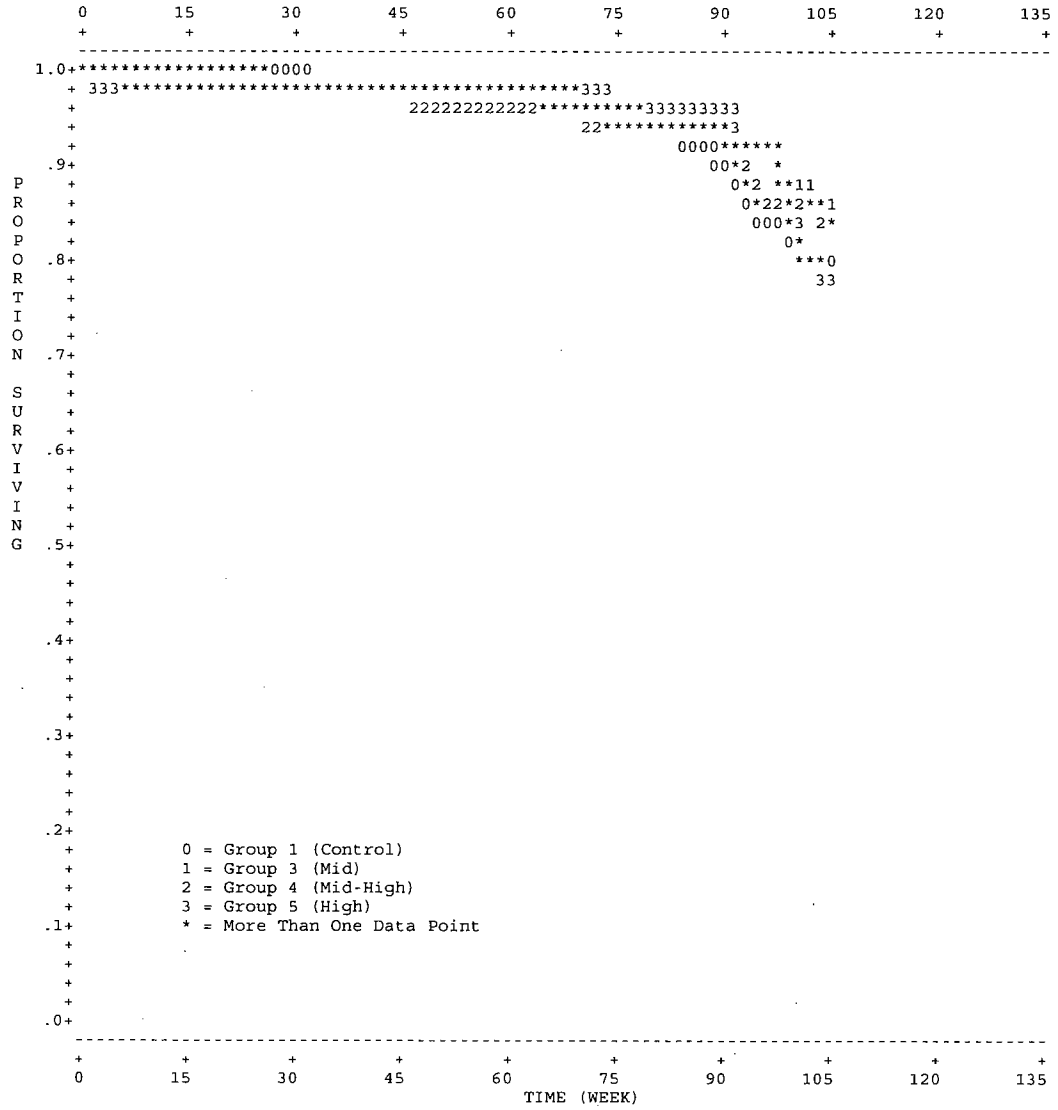
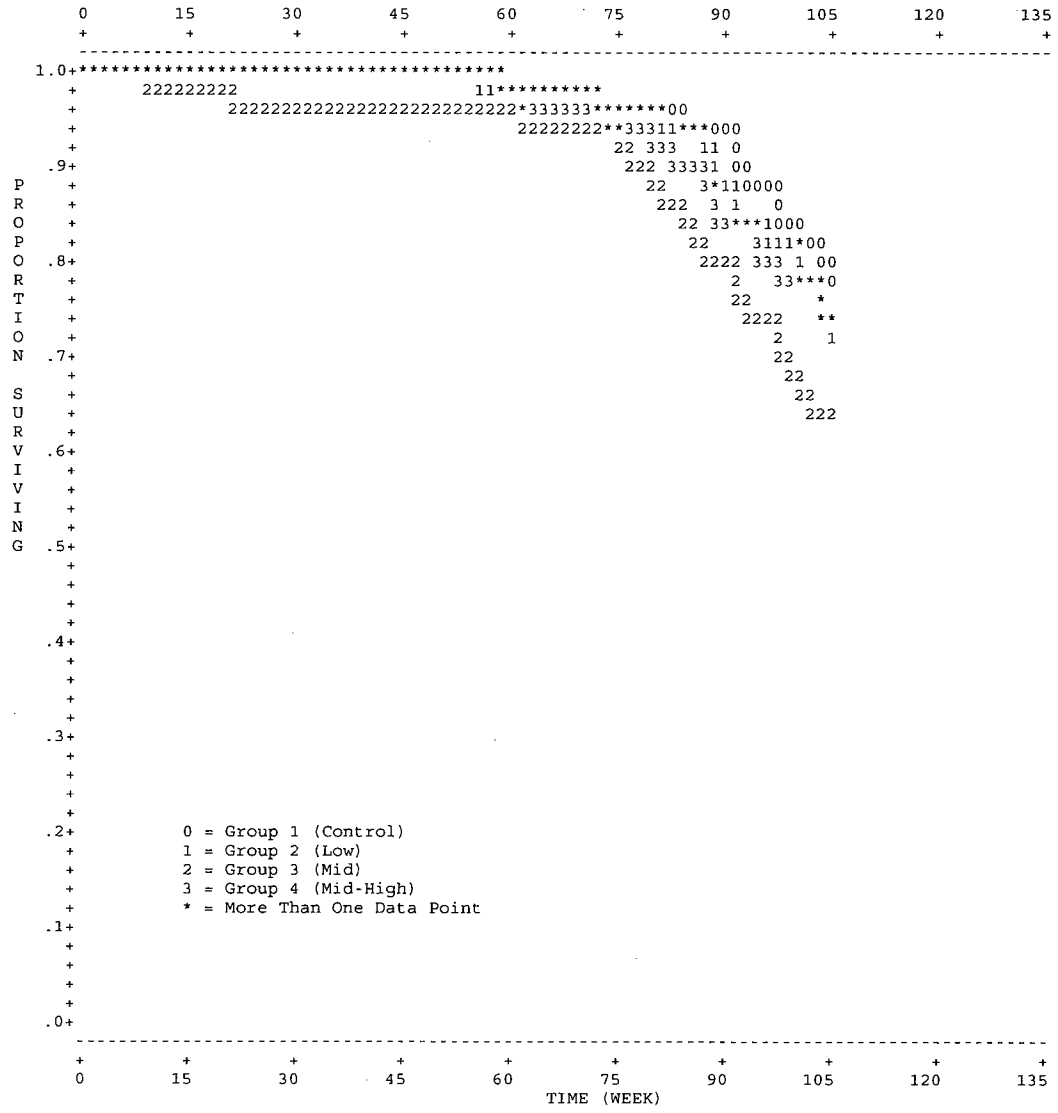


Table 4 – Results of Statistical Analyses of Mortality Data for Female Mice

Group	1	2	3	4
Dose (mg/kg/day)	0	1	3	10
Number of Deaths				
Weeks 0-52	1	0	2	0
Weeks 53-78	2	2	4	4
Weeks 79-92	4	7	8	6
Weeks 93-before term sac	8	8	8	5
Terminal Sacrifice Weeks	45	43	38	45
Unadjusted Mortality	13/60	17/60	22/60	15/60
Kaplan-Meier Estimate (Final)	0.221	0.283	0.367	0.250
Cox-Tarone Test (two-sided p)	0.9776 +	0.5600 +	0.0911 +	0.7809 +
Gehan-Breslow Test (two-sided p)	0.8894 +	0.4523 +	0.0507 +	0.5781 +

Figure 4 – Kaplan-Meier Product Limit Survival Curves for Female Mice



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/s/

Cynthia Liu
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Karl Lin
5/27/04 10:48:04 AM
BIOMETRICS
Concur with review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: 21-697/N_000

Drug Name: Conivaptan hydrochloride IV

Indication(s): The treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients

Applicant: Yamanouchi Pharma America, Inc.

Date(s): Submitted January 30, 2004

User fee goal date: November 30, 2004

Review Priority: Standard (NME)

Biometrics Division: DOB II

Statistical Reviewer: Japobrata Choudhury, Ph.D. (HFD-715)

Concurring Reviewers: Todd Sahlroot, Ph.D. (HFD-715), Stephen Wilson, Dr. P.H. (HFD-715)

Medical Division: Division of Metabolic and Endocrine Drug Products

Clinical Team: Karen Mahoney, M.D. (HFD-510), Mary Parks, M.D. (HFD-510)

Project Manager: Lina Aljuburi, RPM

Keywords: Clinical studies, NDA review

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1. EXECUTIVE SUMMARY

Three (3) controlled studies were designed to evaluate the efficacy and safety of conivaptan HCl in the treatment of patients with euvolemic (for non-medical readers, it means roughly "not too much or too little fluid volume") or hypervolemic hyponatremia in hospitalized patients. These consist of one study (087-CL-027) of intravenously (IV) administered conivaptan HCl in 84 patients and two orally administered studies 087-CL-026 and 087-CL-043. Study 087-CL-027 is considered pivotal since it employed the dose and intravenous route of conivaptan HCl administration proposed for marketing. This study has been reviewed in this document.

From the results provided by the sponsor (not reviewed here), the oral Study 087-CL-043 provided clear statistical evidence in favor of both the 40mg and 80 mg doses (even after Bonferroni adjustment for the two doses); however, oral Study 087-CL-026 only provided clear statistical evidence in favor of 80 mg dose [40mg also showed statistical evidence in favor of its efficacy, if Fisher's LSD method of multiple comparison (which does not provide strong family-wise control of Type I Error)]. Also, the enrollment was stopped before reaching the target (78 randomized instead of 84). Therefore, in general, the oral studies provide support for the claimed efficacy.

Study 087-CL-027 was a double-blind, placebo-controlled, parallel group, multicenter study conducted in the United States, Israel and South Africa, in which either placebo or conivaptan HCl 40 or 80 mg/ day was administered IV for 4 days (with a follow-up of additional 6 to 9 days), after a 20 mg loading dose on Day 1. Hyponatremia was defined as serum sodium <130 mEq/L.

Remaining information on the EXECUTIVE SUMMARY is distributed in the following three sub-sections.

Note: Supplemental New Drug Application is abbreviated by sNDA. Except where specifically mentioned otherwise (as notes, reviewer's comments, conclusions, etc.), all other results and statements in this document are the sponsor's. Sometimes, the sponsor's statements may be slightly changed for brevity or for clarity.

1.1 Conclusions and Recommendations

In the currently proposed labeling, the sponsor has provided only a graph for a secondary efficacy variable (Mean (S.E.) of Change in Serum Sodium Value from Baseline (Hour 0) [1] to each Measurement Time [2] by Treatment Group, Full Analysis Set) and that also only for 40mg conivaptan. Although 80mg is numerically more efficacious than c

a The sponsor has not provided the results of the primary efficacy variable in the labeling. The sponsor clarified in the July 2, 2004 amendment, the sentence in the labeling (Clinical Studies Section), "Patients had a mean serum sodium of 123.3 mEq/L at study entry,"

by: "Patients in the 40 mg/day group had a mean serum sodium of 123.3 at baseline, i.e., study entry,"

By the sponsor's many analyses and this reviewer's own analyses, this reviewer (statistical) does not have any concern about the efficacy of the two doses tested (details are in Section 5.1 "Statistical Issues and Collective Evidence" of this document).

1.2 Brief Overview of Clinical Studies

Three (3) controlled studies were designed to evaluate the efficacy and safety of conivaptan HCl in the treatment of patients with euvolemic or hypervolemic hyponatremia in hospitalized patients. These consist of one "adequate and well-controlled" study (087-CL-027) of intravenously (IV) administered conivaptan HCl in 84 patients and two adequate and well-controlled studies (087-CL-026 and 087-CL-043) of orally administered conivaptan HCl in 74 and 82 patients, respectively. Study 087-CL-027 is considered pivotal since it employed the dose and intravenous route of conivaptan HCl administration proposed for marketing. This study has been reviewed in this document.

Note: The expression "Adequate and well-controlled" was used by the sponsor.

Study 087-CL-027 was a double-blind, placebo-controlled, parallel group, multicenter study in 84 patients with euvolemic or hypervolemic hyponatremia, conducted in the United States, Israel and South Africa, in which either placebo or conivaptan HCl 40 or 80 mg/ day was administered IV for 4 days, after a 20 mg loading dose on Day 1. In each of the three studies, hyponatremia was defined as serum sodium <130 mEq/L, and serum sodium was also used as a primary response variable. The primary endpoint in these studies was Area Under the Curve (AUC) for change from baseline in serum sodium. Secondary efficacy measurements in these studies included, among others, change from baseline to the last outcome result for serum sodium and Free Water Clearance (FWC).

Ref: Clinical Overview under Summary of the NDA.

1.3 Statistical Issues and Findings

There were really no important statistical issues and findings that would impact conclusions regarding the demonstration of efficacy of the drug.

This study has provided statistical evidence in favor of the efficacy of both 40 mg and 80 mg of conivaptan (YM087), IV. Conivaptan was statistically significantly superior to placebo in the change from baseline in serum sodium over the duration of treatment as measured by the AUC (from beginning through end of treatment) corrected for baseline serum sodium (primary endpoint). Baseline-adjusted AUCs were approximately 8-fold

and 11-fold greater for patients in the 40 mg/d and 80 mg/d, respectively, than for patients in the placebo group.

Although there was a statistically significant treatment by baseline volume status interaction, treatment effects (vs placebo) in both hypervolemic and euvolemic patients were statistically significant. Therefore, the interaction is not a concern for the overall efficacy of the drug. A figure for the 95% confidence intervals for euvolemic and hypervolemic patients has been presented in Section 4.2 Other Special/Subgroup Populations. Mean effect (vs placebo) among hypervolemic patients was more than that among euvolemic patients, especially in the 80 mg group. [redacted]

The sponsor provided numerous analyses, including nonparametric analyses (Supplemental Table S1.1 in Section 14.4 of the NDA Study Report) and many subset analyses. These have been referred to in 11.4.1.1 (especially, on pages 130 to 136). Most of these are presented in Sections 14.2 and 14.4 of the NDA study report. All results provide highly statistically significant evidence in favor of the efficacy of the drug.

The sponsor stated in Section 11.4.1.1 (page 130) of the NDA Study Report, "... although the statistical relationship between Baseline serum sodium levels and Baseline-adjusted AUC *(Note: This is covariation)* was significant in all populations (i.e., PPS, FAS, FAS-as-planned-randomized, and FAS-as-randomized), there was no significant interaction with treatment. In the FAS population, there was a significant interaction between treatment and Baseline volume status."

The sponsor stated, "IV YM087 was statistically significantly superior to placebo with respect to the secondary efficacy parameters: time from the first dose of study medication to a confirmed ≥4 mEq/L increase from baseline in serum sodium; total time from the first dose of study medication to the end of treatment during which patients have a serum sodium ≥4 mEq/L higher than that observed at baseline; change in serum sodium from baseline to the end of treatment; and number of patients who obtain a confirmed ≥6 mEq/L increase from baseline in serum sodium or a confirmed normal serum sodium level (≥135 mEq/L)." *Note: These results were not reviewed.*

2. INTRODUCTION

2.1 Overview

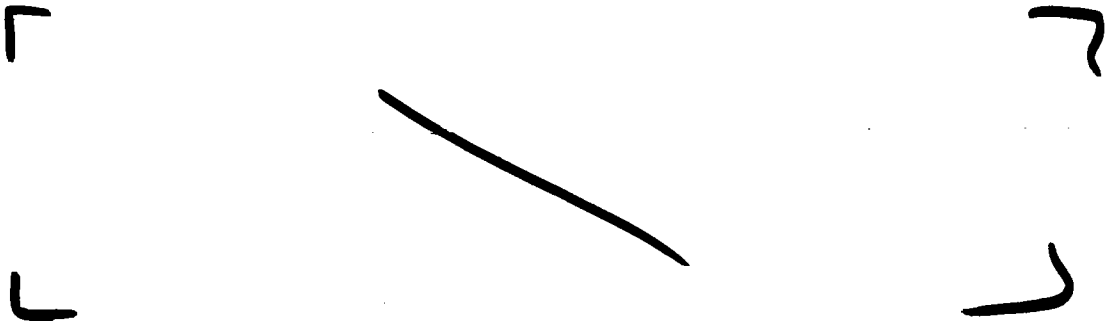
Conivaptan hydrochloride* (conivaptan HCl) was developed under the compound designations [redacted]
and as YM087, YM-35087, and AVA-300 by Yamanouchi Pharmaceutical Co, Ltd (YPCL), Yamanouchi Europe (YEU) and Yamanouchi Pharma America, Inc (YPA).

* United States Adopted Name (USAN) Council

Pharmacologic class and mode of action:

Conivaptan HCl is a nonpeptide dual antagonist of arginine vasopressin (AVP) with nanomolar affinity for V1a and V2 receptors.

Proposed clinical use:



Ref: Introduction under Summary

Three (3) controlled studies were designed to evaluate the efficacy and safety of conivaptan HCl in the treatment of patients with euvolemic or hypervolemic hyponatremia in hospitalized patients. These consist of one "adequate and well-controlled" study (087-CL-027) of intravenously (IV) administered conivaptan HCl in 84 patients and two "adequate and well-controlled studies" (087-CL-026 and 087-CL-043) of orally administered conivaptan HCl in 74 and 82 patients, respectively. [*Note: All statements in this Section are the sponsor's. For the IV study, the only one reviewed, this reviewer did not find anything to contradict the expression, "adequate and well-controlled".*] Study 087-CL-027 is considered pivotal since it employed the dose and intravenous route of conivaptan HCl administration proposed for marketing. This study has been reviewed in this document.

It was a double-blind, placebo-controlled, parallel group, multicenter study in 84 patients (29 in the placebo, 29 in the iv YM087 40 mg/d group, and 26 in the iv YM087 80 mg/d group, respectively) with euvolemic or hypervolemic hyponatremia, conducted in the United States, Israel and South Africa, in which either placebo or conivaptan HCl 40 or 80 mg/ day was administered IV for 4 days, after a 20 mg loading dose on Day 1. In each of the three studies, hyponatremia was defined as serum sodium <130 mEq/L, and serum sodium was also used as a primary response variable. The primary endpoint in these studies was Area Under the Curve (AUC) for change from baseline in serum sodium. Secondary efficacy measurements in these studies included, among other things, change from baseline to the last outcome result for serum sodium and Free Water Clearance (FWC).

Eighty-four patients comprised the safety population (SAF) and the full analysis set (FAS) for efficacy evaluation. The per protocol set (PPS) comprised 69 patients (24 from

the placebo, 22 from the iv YM087 40 mg/d, and 23 from the iv YM087 80 mg/d groups, respectively).

A total of 51 study sites participated in the study, including 3 sites in Canada, 10 sites in Israel, 10 sites in South Africa and 28 sites in the United States. Only one site in Canada enrolled patients (3 patients). There were 32 patients enrolled in Israel, 18 patients in South Africa, and 51 in U.S.A. (Ref: Text Table 16-1).

A total of 51 study sites were initiated in this study (Section 16.1.4). Of these, 25 randomized at least 1 patient, and 24 sites had patients that went on to receive CTM (Site 28 enrolled a single patient who was randomized prematurely and failed study entry criteria during Baseline and therefore did not go on to receive CTM). All the four patients who were randomized but did not receive any treatment, are described below. The 24 study sites enrolling at least 1 patient were pooled into 6 centers. One site, enrolling 14 patients stood alone; the remaining 23 sites were grouped according to geographic location for study sites outside North America and by numerical site order for study sites within North America, as outlined in Text Table 9-3 and defined in Section 9.7.1.1 (of the NDA study Report).

Patient 076705 was prematurely randomized and did not get single-blind placebo during Baseline or double-blind CTM after randomization. Patient 070701 received single-blind placebo during Baseline and was randomized but never received study drug because of poor venous access and withdrawal of informed consent after multiple lab attempts. Patient 076903 received single-blind placebo during Baseline and was randomized, but then was noted to no longer meet entry criteria because of renal insufficiency and postural hypotension. Patient 077202 received single-blind placebo during Baseline and was randomized, but withdrew consent prior to receiving any CTM.

2.2 Data Sources

Location of the NDA in EDR (electronic documents room):

\\CDSESUB1\N21697\N_000\2004-01-30

Amendments:
Related data provided are in the electronic document room: \\CDSESUB1\N21697\N_000\2004-01-30\crt

The July 2, 2004 submission was in hard copy only.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The subsections in this Section are: **Study Design and Endpoints; Patient Disposition, Demographic and Baseline Characteristics; Statistical Methodologies; Results and Conclusions.**

A list of abbreviations and definition of terms has been provided on page 30 of the report for Study 087-CL-027 in the NDA (after the list of Figures) and is reproduced in this document as Appendix II.

Study Design and Endpoints

Study 087-CL-027 was a double-blind, placebo-controlled, parallel group, multicenter study in 84 patients (29 in the placebo, 29 in the iv YM087 40 mg/d group, and 26 in the iv YM087 80 mg/d group, respectively) with euvolemic or hypervolemic hyponatremia, conducted in the United States, Israel and South Africa, in which either placebo or conivaptan HCl 40 or 80 mg/ day was administered IV for 4 days, after a 20 mg loading dose on Day 1. In each of the three studies, hyponatremia was defined as serum sodium <130 mEq/L, and serum sodium was also used as a primary response variable. The primary endpoint in these studies was Area Under the Curve (AUC) for change from baseline in serum sodium. Secondary efficacy measurements in these studies included, among others, change from baseline to the last outcome result for serum sodium and Free Water Clearance (FWC).

This study employed 2 central randomization sequences, 1 for study sites in Israel and South Africa and another for sites in North America. Randomization was done in blocks of 3 patients, stratified by volume status. The randomization schedule was designed to yield an equal distribution of patients from each volume stratum in the 3 treatment groups. Eligible patients were assigned to the next sequential randomization number, from lowest to highest within each randomization stratum. Stratification by volume status was instituted because preliminary findings from Phase 2 studies suggested that volume status affected the efficacy response to YM087. Before Amendment 2, the number of enrolled patients per stratum was not to exceed 60% of the total patient population; this limitation on patient enrollment was dropped with Amendment 2.

Because there were concerns with using a placebo rather than an active control drug in this patient population, the lower limit of serum sodium concentration eligible for entry into the study was set to115 mEq/L and the treatment duration was limited to 4 days. The 4-day Treatment Phase allowed for the assessment of the onset of action of YM087, while minimizing the length of time that the placebo-treated patients went without treatment for

hyponatremia. Although the investigators were blinded to patient treatment assignment, for the safety of the patients, they were not blinded to serum sodium levels. However, because all patients, including placebo recipients, were treated in a similar manner with regard to fluid restriction and prohibition of treatment with alternative therapies for correction of their hyponatremia, any observed changes in serum sodium levels can be attributed to YM087 and not to changes in other treatment strategies that the investigator may have initiated in response to the serum sodium data made available to him or her during the study. There was no signal that on average the conivaptan patients were given more concomitant drugs, which would cause conivaptan to appear more effective than it really is. Patients entered into this study who were not already hospitalized were treated on an inpatient basis to accurately obtain all specified assessments. All patients in the study received the usual care for hyponatremia, which consists primarily of fluid restriction. Patients could enter the study with varying degrees of fluid restriction, but the specific level of fluid restriction established for each patient before Baseline was limited to no more than 2 L. This level of fluid restriction was to be maintained throughout the study, unless changes were made to address safety concerns.

The Medical Officer's thinking regarding the appropriateness of the endpoints studied by the applicant is in short: "A. Primary endpoint (change from baseline in serum sodium over the duration of the treatment phase as measured by the AUC serum sodium effect curve).
Serum sodium is an appropriate endpoint (*Note: variable to study*). …
B. Secondary efficacy parameters:
1. Time to confirmed >/= 4 mEq increase in serum sodium.
A reduction in the amount of time required to safely return a hyponatremic patient toward normonatremia would be a definite improvement over currently used methods. A 4 mEq increase is large enough to be clinically meaningful, especially if the serum sodium is very low (e.g. <120 mEq/L) at presentation. … Changes in neurohormones will be interesting, but it will not independently contribute to proving the efficacy of the drug."

Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition: Of the 104 patients who entered Baseline, 88 met study entry criteria and were randomized into the study (30, 30, and 28 patients in the placebo, iv YM087 40 mg/d, and iv YM087 80 mg/d groups, respectively). Of these 88, 84 went on to be treated with study drug: 29 received placebo, 29 received iv YM087 40 mg/d, and 26 received iv YM087 80 mg/d. Thus, the planned patient enrollment of 84 randomized treated patients was met.

Patient 076705 (80mg) was prematurely randomized and did not get single-blind placebo during Baseline or double-blind CTM after randomization. Patient 070701 (placebo) received single-blind placebo during Baseline and was randomized but never received study drug because of poor venous access and withdrawal of informed consent after multiple lab attempts. Patient 076903 (40mg) received single-blind placebo during Baseline and was randomized, but then was noted to no longer meet entry criteria because of renal insufficiency and postural hypotension. Patient 077202 (80mg) received single-blind placebo during Baseline and was randomized, but withdrew consent prior to receiving any CTM.

Summary of Patients Disposition Data, All Randomized and Treated Patients

Category [1]	Total	Placebo	IV YM087 40 mg	IV YM087 80 mg
Number of Patients Randomized	88	30	30	28
Number of Patients Entering the Study	86	30	29	27
Number of Patients not Entering the Study	2	0	1	1
Reasons for not Entering the Study				
Other/Administration	2	0	1	1
Number of Patients Treated	84	29	29	26
Number of Patients not Treated	2	1	0	1
Reasons for not Treated				
Other/Administration	2	1	0	1
Number of Patients Completed Treatment	66	23	22	21
Number of Patients Early Withdrawal	20	7	7	6
Reasons for Early Withdrawal				
Adverse Event	10	3	2	5
Lack of Efficacy	2	1	1	0
Other/Administration	8	3	4	1
Number of Patients in SAF	84	29	29	26
Number of Patients in FAS	84	29	29	26
Number of Patients in PPS	69	24	22	23

[1] SAF = Safety, FAS = Full Analysis Set, PPS = Per Protocol Set.
Data Source: pstatus.sd2 Program Source: t1_1.sas Listing Source: Listing 1.2.1/1.2.2/1.2.3

Demographic and baseline characteristics:

P-values for pairwise comparisons with respect to demographic and baseline characteristics were provided in the July 2, 2004 amendment. None of them were statistically significant, especially, for the 40mg vs placebo comparison (not presented here).

Summary of Demographic Characteristics by Treatment Group, Full Analysis Set

Parameter	Placebo (N= 29)	IV YM087 40 mg (N= 29)	IV YM087 80 mg (N= 26)	Total (N= 84)	P-value [1]
Sex					
Male	15 (51.7)	12 (41.4)	14 (53.8)	41 (48.8)	0.630
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)	0.092
Black, Non-Hispanic	2 (6.9)	1 (3.4)	6 (23.1)	9 (10.7)	
Hispanic (White or Black)	0 (0.0)	0 (0.0)	1 (3.8)	1 (1.2)	
Other	1 (3.4)	1 (3.4)	0 (0.0)	2 (2.4)	
Age					
<= 65	3 (10.3)	8 (27.6)	7 (26.9)	18 (21.4)	
> 65	26 (89.7)	21 (72.4)	19 (73.1)	66 (78.6)	
n	29	29	26	84	
Mean	75.7	73.8	72.5	74.0	0.626
Std	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	

As shown in the Table, the study population of patients who received double-blind CTM had a mean age of 74 years; 79% of the study population was older than 65 years of age. Overall, the study population was predominantly white (86%). Although there were no statistically significant differences in race distribution among the groups, a higher percentage of the patients in the iv YM087 80 mg/d group were nonwhite (27%) than in the other 2 treatment groups (10% for the placebo group and 7% for the iv YM087 40 mg/d group). Additionally, although men and women were equally represented in the overall and placebo study groups, women composed the majority (59%) of patients in the iv YM087 40 mg/d group and the minority (46%) in the iv YM087 80 mg/d group.

In general, demographic and baseline characteristics for the PPS (Per Protocol Set) were very similar to those of the FAS (Full Analysis Set) (Statistical Tables 3.1.2, 3.1.3, 3.2.2, and 3.2.3 (last two for Baseline Characteristics) in Section 14.1 of the NDA Study Report). However, unlike in the FAS, there were slightly more women than men in the iv YM087 80 mg/d group in the PPS. Nevertheless, no statistically significant differences between the groups in the PPS and FAS were noted in any demographic parameter.

Summary of Baseline Characteristics by Treatment Group, Full Analysis Set

		IV YM087		
Parameter	Placebo (N= 29)	40 mg (N= 29)	80 mg (N= 26)	Total (N= 84)
Inclusion/Exclusion Criteria				
Met	24 (82.8)	27 (93.1)	26 (100.0)	77 (91.7)
Not Met	5 (17.2)	2 (6.9)		7 (8.3)
Smoking Status				
Never Smoked	13 (44.8)	17 (58.6)	14 (53.8)	44 (52.4)
Past Smoker	9 (31.0)	8 (27.6)	7 (26.9)	24 (28.6)
Current Smoker	7 (24.1)	4 (13.8)	5 (19.2)	16 (19.0)
Alcohol Consumption (drink/per week)				
n	28	29	26	83
Mean	2.5	2.6	2.7	2.6
Std	5.47	7.55	7.05	6.67
Min	0	0	0	0
Median	0.0	0.0	0.0	0.0
Max	21	35	30	35

As shown in the Table below, a higher (compared with other treatment groups, especially the 40mg group) percentage of the patients in the placebo group was euvolemic (72.4% vs 62.1%). However, this difference is not statistically significant (checked by this reviewer). Since conivaptan treatment effects (vs placebo) are smaller in euvolemic patients, more euvolemic patients in the study or in any group is not a concern. A higher percentage of the patients in the placebo group was current smokers (24% vs. 14% and 19% in the iv YM087 40 mg/d and iv YM087 80 mg/d groups, respectively); the placebo group had a correspondingly low percentage of people who had never smoked as compared with the other 2 groups (45% for placebo, 59% for iv YM087 40 mg/d, and 54% for iv YM087 80 mg/d). Average alcohol consumption was similar across treatment groups (2.5, 2.6, and 2.7 average drinks per week were consumed by patients in the placebo, iv YM087 40 mg/d, and iv YM087 80 mg/d groups, respectively).

Summary of Medical History - Hyponatremia History by Treatment Group, Safety Analysis Set

Category	Placebo (N= 29)	IV YM087 40 mg (N= 29)	IV YM087 80 mg (N= 26)	Total (N= 84)
Cause of Hyponatremia				
COPD	2 (6.9)	0 (0.0)	0 (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)	3 (3.6)
Other	13 (44.8)	10 (34.5)	9 (34.6)	32 (38.1)
Volume Status at Baseline				
Hypervolemic	8 (27.6)	11 (37.9)	9 (34.6)	28 (33.3)
Euvolemic	21 (72.4)	18 (62.1)	17 (65.4)	56 (66.7)
Time Since Earliest Known Occurrence (day)				
n	23	27	21	71
Mean	485	360	313	387
Std	910.7	1023	715.1	894.7
Min	1	2	1	1
Median	86	60	5	27
Max	3903	5296	3075	5296
Time Since Current Episode (day)				
n	26	29	23	78
Mean	43	15	28	28
Std	123.5	24.9	88.8	87.0
Min	1	1	1	1
Median	5	4	3	4
Max	607	95	423	607

As shown in the Table, approximately 67% of the patient population at Baseline was euvolemic. By treatment group 72%, 62%, and 65% of patients in the placebo, iv YM087 40 mg/d, and iv YM087 80 mg/d, respectively, were euvolemic at Baseline.

The most common cause for hyponatremia was the pooled category of "other" causes. The most common single cause of hyponatremia was CHF (30% of patients), followed by idiopathic hyponatremia (18% of patients), malignancy (8% of patients), and chronic obstructive pulmonary disease (COPD) (2% of patients). A higher percentage of placebo recipients developed hyponatremia from "other" causes than did patients in either the iv YM087 40 mg/d or iv YM087 80 mg/d groups (45% in the placebo group vs. 35% in each YM087 group). Conversely, a lower percentage of patients in the placebo group developed hyponatremia as a result of CHF or any of the other single causes except COPD as compared with patients in the iv YM087 40 mg/d or iv YM087 80 mg/d groups.

Statistical Methodologies

Safety population (SAF)

The SAF included all patients who met the following criteria:

- Have been randomized

▪ Have received any study medication

The SAF was conducted as an as-treated analysis. No treated patients were excluded from SAF. This population was used for some Baseline summaries and all safety summaries and analyses.

Full analysis set (FAS)

The FAS comprised all patients who met the following criteria:

· Had been randomized

· Had received any study medication

· Had at least 1 Baseline (at Hours 4, 6, 10, or at the end of the Baseline Phase [Hours 20 to 28]) serum sodium measurement available

· Had at least 1 on-treatment serum sodium measurement available

The analysis of primary efficacy endpoint was performed using the FAS. The analyses of secondary endpoints were also performed using the FAS. Summaries of Baseline characteristics were developed for this population. Patients in the FAS were analyzed as a "modified intention to treat", according to the treatment indicated by their randomization. Only patients that actually received study medication were included in the analysis. Because the treatment group assignment in the FAS is based on the patient's randomization, the FAS and the FAS-as-randomized populations are identical. In contrast to the SAP, the FAS is referred to as the modified intent-to-treat population in the protocol. Because there were no treatment errors, the SAF and the FAS populations contain identical patients in each treatment group.

The Statistical Analysis Plan stated:

> "The primary efficacy parameter is the Change from Baseline in Serum Sodium over the duration of treatment as measured by the AUC, from the beginning through the end of treatment, corrected for baseline serum sodium. The primary efficacy analysis will be based on the FAS.
>
> The Analyses of Primary Efficacy Parameter
>
> Analysis of covariance (ANCOVA) will be used to provide an overall test of differences among the three treatment groups. The model will include treatment, center and patient's volume status (euvolemic or hypervolemic) as factors, and baseline serum for calculation of the baseline-adjusted AUC sodium value as a covariate.

The treatment-by-baseline serum sodium value, treatment-by-center, and treatment-by-volume status interactions will be examined at the 0.1 significance level. If the treatment-by-baseline serum sodium value interaction is significant, then the means by treatment will be computed at different baseline serum sodium quartiles and the predicted values for each treatment group will be plotted against the baseline serum sodium value to help understand the difference in treatment effects for different baseline serum sodium values. If a statistically significant interaction is observed for treatment-by-center, then center specific differences in treatment means will be examined for systematic trends associated with sample size and geographic location. If the treatment-by-volume status interaction is significant, then the means by treatment and volume status will be computed and presented in the appendix of the CSR to explain the nature of the interaction. If the treatment-by-baseline serum sodium value, treatment-by-center, and treatment-by-volume status interactions are not significant, then they will be removed from the model.

The two treatment contrasts will be of primary interest (i.e., each of the dose groups versus placebo).

Statistical significance of these comparisons will be evaluated using Dunnett's two- sided multiple test procedure performed at the overall significance level $\alpha = 0.05$.

Van Elteren tests will be carried out using the FAS as a secondary, supportive analysis to the ANCOVA or as a primary analysis in the case that normality assumption for ANCOVA model are not met. Across all eligible patients, baseline adjusted area under the serum sodium effect curves will be ranked independently of the baseline values. Midrank scores will be assigned to tied data. To compare treatments in the presence of baseline values, the statistical model will include terms for treatment and ranked values of the baseline data. To compare treatments in the presence of center, the statistical model will include terms for treatment and center. To compare treatments in the presence of baseline volume status, the statistical model will include terms for treatment and baseline volume status. The two IV YM087 versus placebo comparisons derived from Van Elteren tests will be based on a nonparametric analog of Dunn's test."

Calculation Method for the Primary Efficacy Variable (AUC) and Some Extra Details on Statistical Methodology are in Appendix I of this document.

The analysis of primary efficacy endpoint was performed by using the Full Analysis Set (FAS). The analyses of secondary endpoints were also performed by using the FAS. Summaries of Baseline characteristics were developed for this population.

There were two protocol amendments as detailed in Sections 9.8.1.1 and 9.8.1.2 (on pages 88 to 92) of the Study Report. After the blind was broken, several changes to the planned analyses were made as detailed in Section 9.8.2 (page 93) of the Study Report. None of these seem to be serious enough to change the overall conclusions.

Use of an "efficacy subset" of patients:

No patients treated with study medication were dropped from the FAS, the primary population used to test the primary efficacy parameter. To test the robustness of the study conclusions, supportive efficacy analyses of the primary endpoint were conducted by using the FAS-as-randomized, FAS-as-planned-randomized, PPS, and pre- and post-Amendment 2 populations as described in Section 9.7.1.3 of the NDA Study Report.

Results and Conclusions.

Results:

Primary efficacy analysis

As shown in the Table and Figure below, in the FAS population, the iv YM087 40 mg/d and iv YM087 80 mg/d dosing regimens were significantly effective in increasing the Baseline-adjusted AUC over the duration of the 4-day Treatment Phase. The difference in the LS (least squares) mean of Baseline adjusted serum sodium AUC was statistically significant.

Note: The sponsor provided numerous analyses, including nonparametric analyses, and many subset analyses. These have been referred to in 11.4.1.1 (especially, on pages 130 to 136). Most of these are presented in Section 14.2 and 14.4 of the NDA study report. All results provide highly statistically significant evidence in favor of the efficacy of the drug. Only primary results are presented here.

Summary of Baseline-Adjusted Area under the Serum Sodium Effect Curve (AUC, defined in Appendix I) over the Duration of Treatment by Treatment Group, Full Analysis Set:

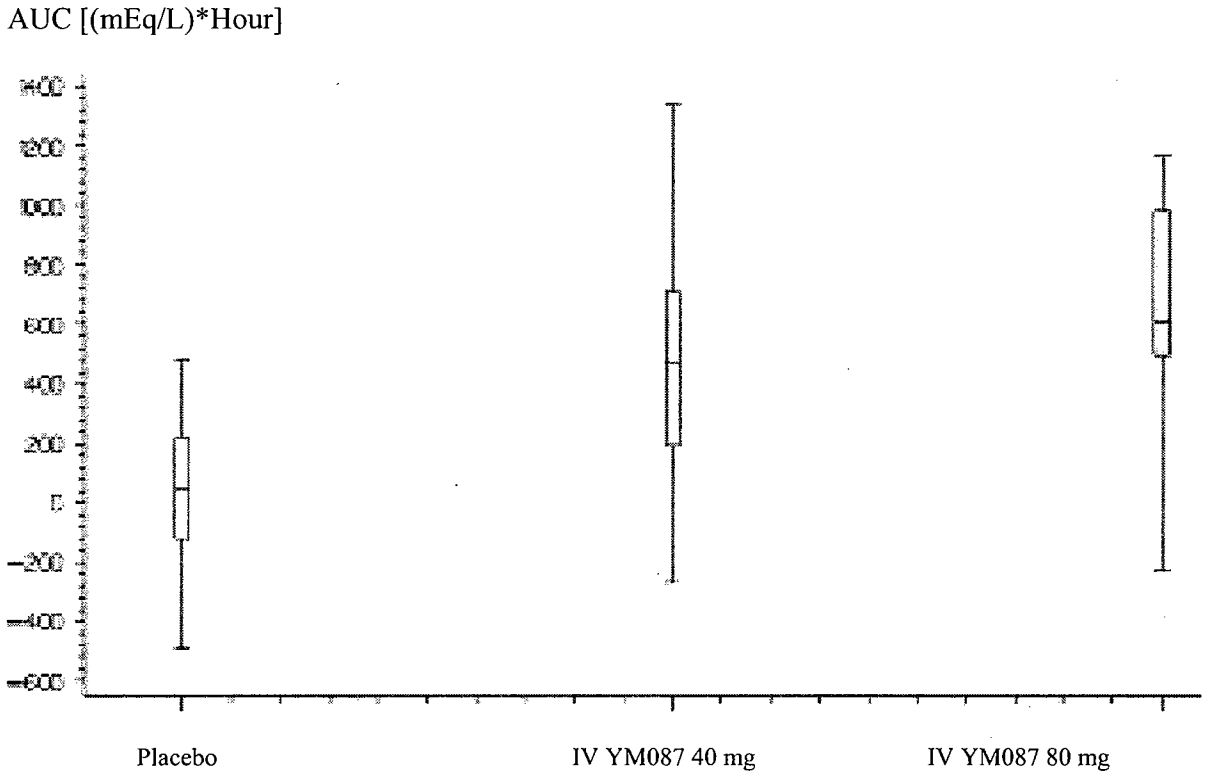
		IV YM087		P-value [1]				
Statistics	Placebo	40 mg	80 mg	Treatment	Baseline	Volume Status	Center	Treatment*Volume Status
AUC for Baseline [2]								
n	29	29	26					
Mean	11929.6	11839.1	11979.2					
Std	388.71	447.36	327.27					
Min	11064.0	10800.0	11275.2					
Median	12000.0	11880.0	11964.0					
Max	12528.0	12504.0	12432.0					
AUC for Treatment Phase								
n	29	29	26					
Mean	11991.0	12339.9	12640.9					
Std	403.87	507.89	358.34					
Min	11053.4	10555.3	11439.0					
Median	12043.0	12410.9	12690.0					
Max	12505.0	13154.4	13180.5					
Baseline Adjusted AUC								
n	29	29	26					
Mean	61.4	500.8	661.7					
Std	242.30	365.46	331.14					
L.S. Mean	12.9	490.9	716.6	0.0000	0.0196	0.4082	0.0727	0.0411
S.E. (L.S. Mean)	61.16	56.79	60.45					
Min	-493.0	-268.7	-225.0					
Median	42.2	470.5	610.5					
Max	483.3	1337.3	1168.2					

	Treatment Difference [3]		
Parameter	L.S. Mean	S.E. (L.S. Mean)	P-value
IV YM087 40 mg vs Placebo	478.0	83.16	0.00010
IV YM087 80 mg vs Placebo	703.6	86.40	0.00010

[1] P-values were from an ANCOVA model including baseline value as a covariate, treatment, volume status, center as factors and the significant(at level 0.1) interaction term(s) between Treatment and baseline value, volume status, center. All P-values were derived from two-sided tests.
[2] Baseline value is the average of serum sodium measurements at hour 4, 6, 10 and at end of the Baseline Phase (Hours 20-28). AUC for Baseline is calculated by the baseline value multiplied by 96 (hours).
[3] P-values for treatment differences were from a Dunnett's test on the difference of least-squares means. All P-values were derived from two-sided tests.

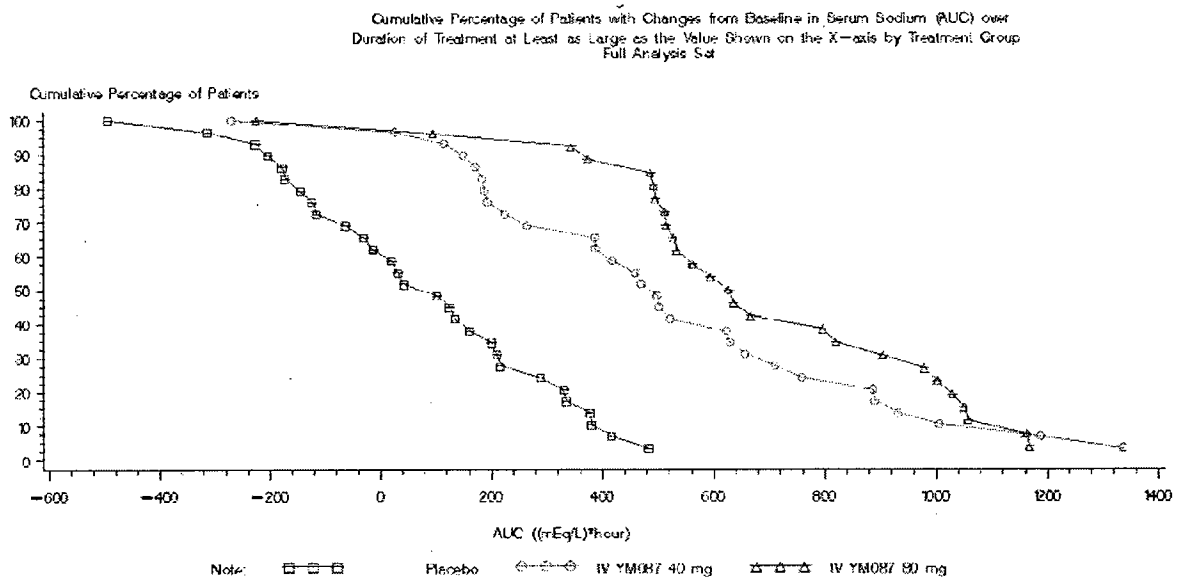
Baseline AUC values were similar for the 3 groups in the FAS population. Treatment with YM087 had a highly significant impact on Baseline-adjusted AUC (overall $P < 0.0001$). Patients in the iv YM087 40 mg/d group had average Baseline-adjusted AUCs that were approximately 8-fold greater than the average value for patients in the placebo group. Patients in the iv YM087 80 mg/d group responded more dramatically, with average Baseline-adjusted AUC values nearly 11-fold higher than the average AUC values for the placebo group.

Figure for Baseline-adjusted Area under the Serum Sodium Effect Curve (AUC) over the Duration of the Treatment by Treatment Group, Full Analysis Set:



Note: The Figures are Box and Whisker Plots. The bottom and top edges of the box are located at the sample 25th and 75th percentiles. The center horizontal line is drawn at the 50th percentile (median).

Note: The upper and lower horizontal lines above and below the vertical lines represent the highest and lowest actual observed values.



A secondary efficacy variable:

Summary of Mean and Mean Change in Serum Sodium from the Baseline to the End of the Treatment and to Day 4, Full Analysis Set:

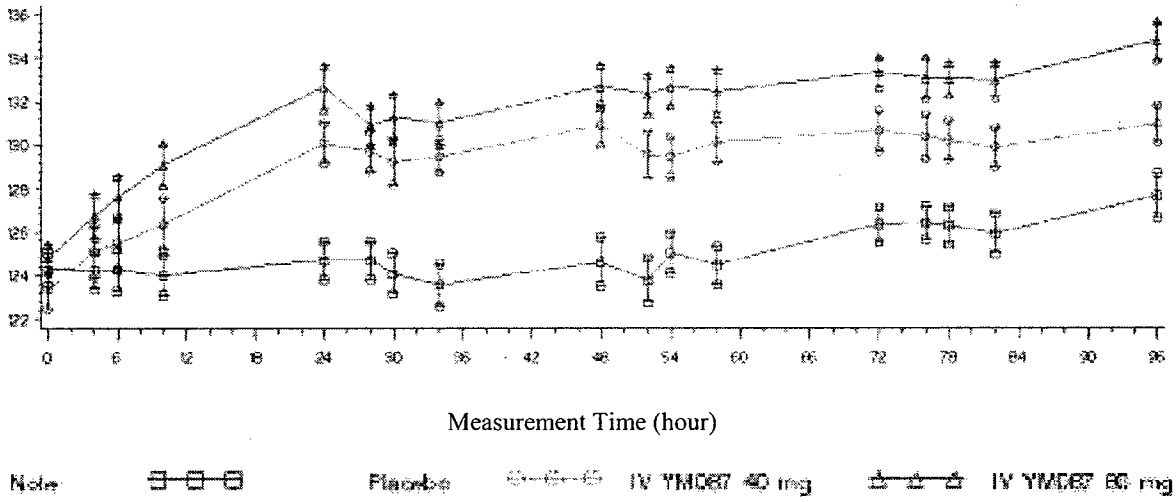
Treatment*Volume Statistics	Placebo	IV YM087		P-value [1]				
		40 mg	80 mg	Treatment	Baseline	Volume Status	Center	Status
At Baseline [2]								
n	29	29	26					
Mean	124.3	123.3	124.8					
Std	4.05	4.66	3.41					
Min	115.3	112.5	117.5					
Median	124.3	123.3	124.8					
Max	130.5	130.3	129.5					
At End of the Treatment[3]								
n	29	29	26					
Mean	125.8	129.8	133.4					
Std	4.94	4.78	3.50					
Min	113.0	116.0	121.5					
Median	125.5	130.6	134.1					
Max	133.0	137.0	137.8					
Change from Baseline to End of the Treatment								
n	29	29	26					
Mean	1.5	6.5	8.6	0.0000	0.0001	0.7171	0.2368	0.0196
Std	4.64	4.43	4.00					
L.S. Mean	0.8	6.3	9.4					
S.E. (L.S. Mean)	0.80	0.74	0.79					
Min	-5.5	-0.3	0.0					
Median	0.8	5.8	8.3					
Max	13.3	18.0	15.5					
At Day 4 of the Treatment Phase								
n	25	24	24					
Mean	126.2	130.6	133.4					
Std	4.47	3.96	3.62					
Min	116.0	121.2	121.5					
Median	125.5	130.6	134.3					
Max	133.0	137.0	137.8					
Change from Baseline to Day 4								
n	25	24	24					
Mean	1.7	7.1	8.7	0.0000	0.0000	0.8921	0.6845	
Std	4.78	4.27	4.13					
L.S. Mean	2.0	6.8	9.0					
S.E. (L.S. Mean)	0.82	0.81	0.80					
Min	-5.5	1.3	0.0					
Median	1.0	7.0	8.9					
Max	13.3	18.0	15.5					

	Treatment Difference [4]					
	Change from Baseline to End of the Treatment			Change from Baseline to Day 4		
Parameter	L.S. Mean	S.E. (L.S. Mean)	P-value	L.S. Mean	S.E. (L.S. Mean)	P-value
IV YM087 40 mg vs Placebo	5.5	1.09	0.0001	4.9	1.12	0.0001
IV YM087 80 mg vs Placebo	8.5	1.13	0.0001	7.0	1.11	0.0001

[1] P-values were from an ANCOVA model including baseline value as a covariate, treatment, volume status, center as factors and the significant (at level 0.1) interaction term(s) between treatment and baseline value, volume status, center. All P-values were derived from two-sided tests.
[2] Baseline value is the average of non-missing serum sodium measurements at hour 4, 6, 10 and at end of the Baseline Phase (Hours 20-28).
[3] The value at the end of the treatment is the average of non-missing serum sodium measurements at end of Treatment Phase.
[4] P-values for treatment differences were from a Dunnett's test. All P-values were derived from two-sided tests.
Data Source: plas.sd2 Program Source: t6_4.sas Listing Source: Listing 16.0
Note: the data presented in this table were generated using OC methods.

Figure for Mean (S.E.) of Change in Serum Sodium Value from Baseline (Hour 0) [1] to Each Measurement Time [2] by Treatment Group, Full Analysis Set:

Serum Sodium (mEq/L)



[1] Baseline Value is the average of serum sodium measured at hour 4, 6, 10, and the end of the Baseline Phase (Hours 20 – 28)

[2] The serum sodium was measured at hour 4, 6, 10 and 24 in study day 1 to 4.

Note: The mean values are joined by straight line. The vertical lines are the ranges from mean – s.e. to mean + s.e. S.E. = the standard error of the mean

Note: The data presented in this figure represented all observed cases.

3.2 Evaluation of Safety

I did not perform any formal safety evaluation. However, I performed a huge number of statistical tests on safety variables for the clinical reviewer.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

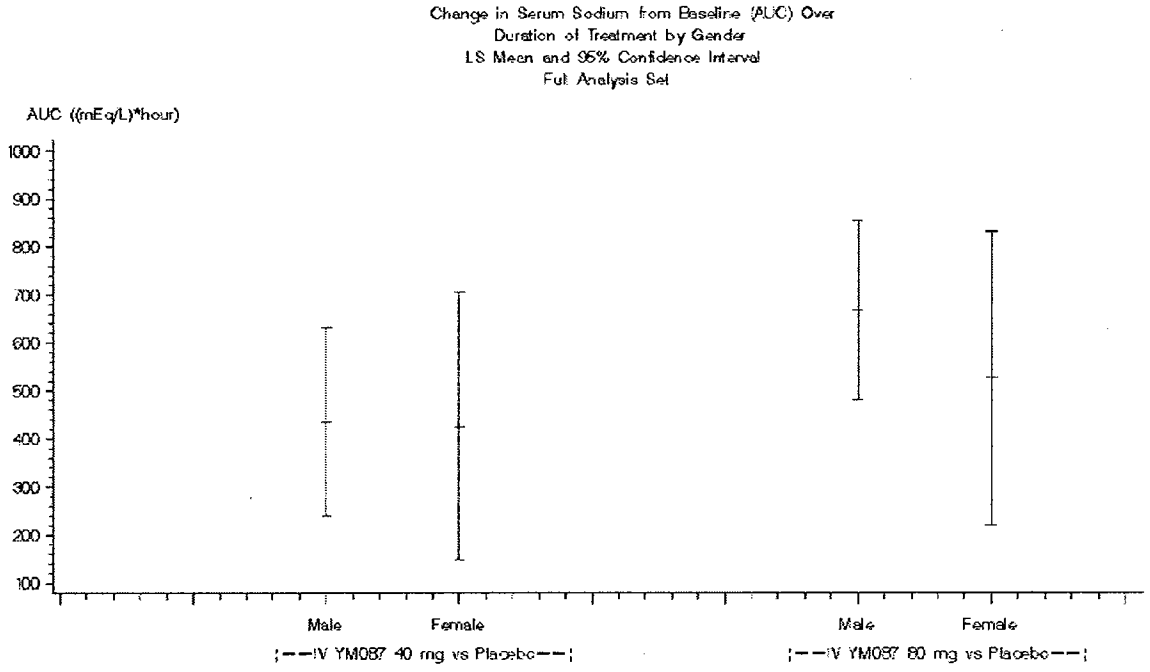
4.1 Gender, Race, and Age

Note: On the one hand, the study is not powered for subgroup results or even interactions. On the other hand, adjustments for so many subgroups cannot be properly done, without pre-specifying which subgroup results will be confirmatory. In general, Dunnett's method of multiple comparison adjustment was employed for the two doses.

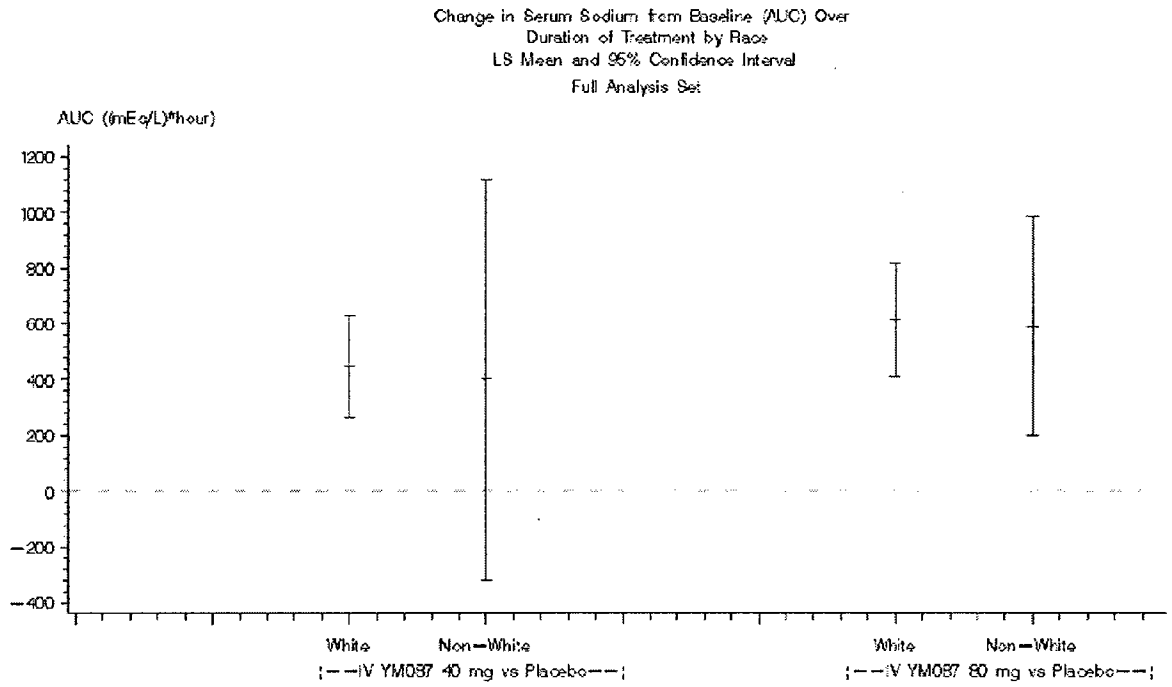
Results of these demographic characteristics (at baseline) were presented before. There were no statistically significant baseline imbalances.

Tables for various subgroup results with p-values are in supplementary Tables s14.1 to s14.21 (Pages 447 to 479) of the NDA study report.

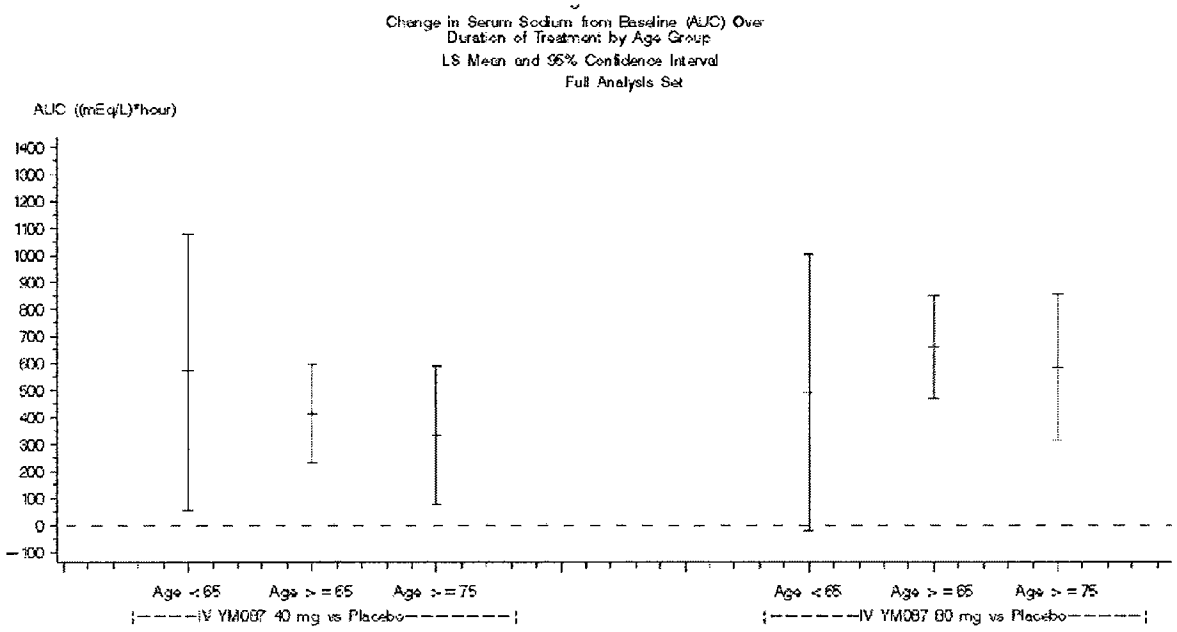
Figures for 95% confidence intervals for subgroups (difference for each dose vs placebo) are presented below.



Treatment by sex interaction p-value was 0.6636 and treatment effects in both males and females were statistically significant (Table s14.1 of the NDA Study Report).



The treatment by race interaction p-value (.9911; 85.7% patients were non-Hispanic Whites) and the treatment effect in the 40mg group for non-White patients (p-value= 0.1839) were statistically non-significant. There is not sufficient power for statistical significance in such small subgroups. Still, differences in treatment effects for Whites vs non-Whites were statistically non-significant (Table s14.2 of the NDA Study Report).

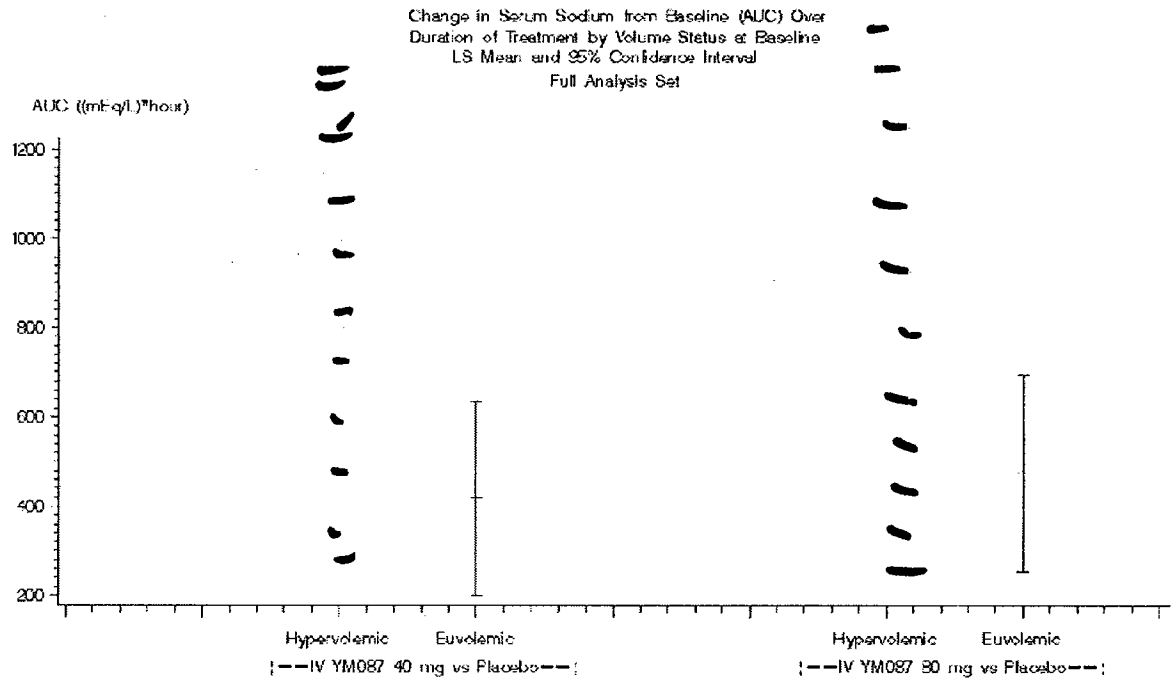


There was a statistically significant quantitative treatment-by-age interaction (interaction significance is tested at .1 level; p-value = .0931 by Table s14.4 of the NDA Study Report).

Three age groups in years were considered: <65, ≥65 (overlapping with the next), and ≥75. Efficacy p-value (vs placebo) for the 80 mg group was not statistically significant (may not have sufficient power for such a small subgroup) in the <65 years subgroup.

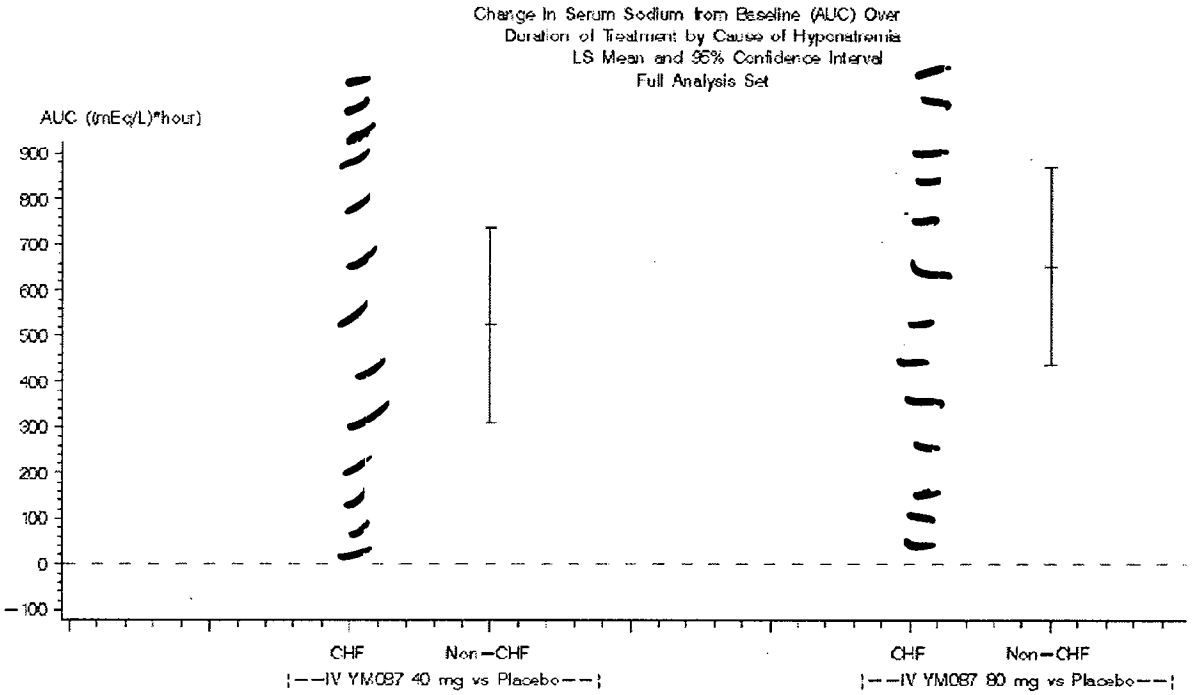
4.2 Other Special/Subgroup Populations

P-values for pairwise comparisons with respect to demographic and baseline characteristics were provided in the July 2, 2004 amendment. None of them were statistically significant, especially, for the 40mg vs placebo comparison.



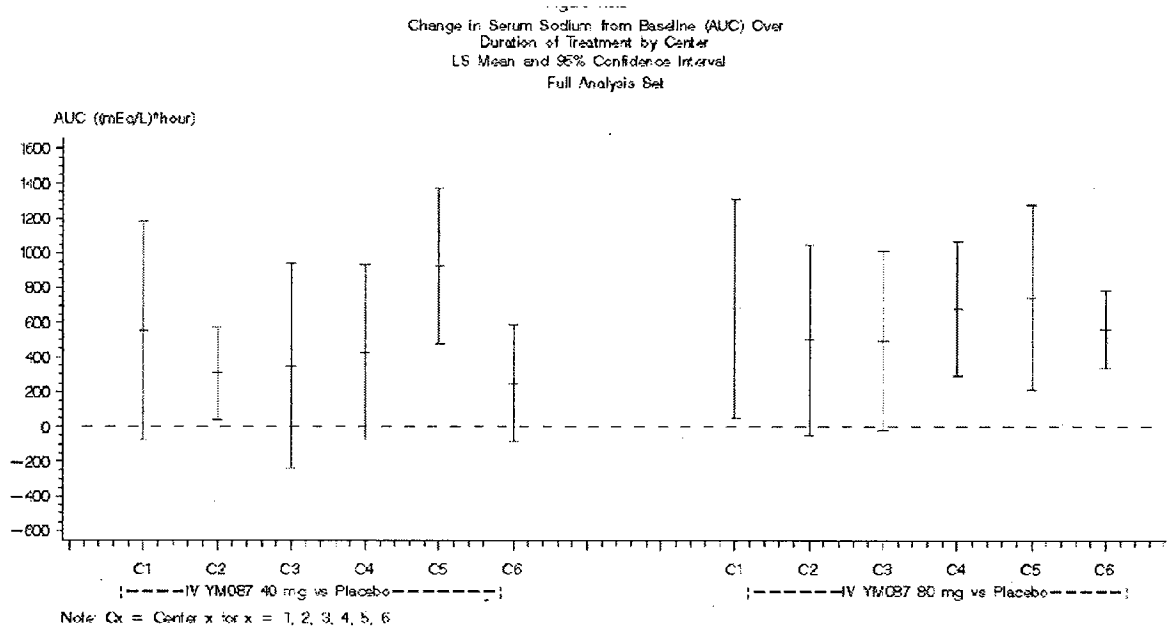
There was a statistically significant quantitative treatment-by-volume status interaction (only in the "Full Analysis Set". Interaction significance is tested at .1 level; p-value = .0851 by Table s14.3 of the NDA Study Report but .0411, when other factors are included in the model as presented in the primary efficacy results (Table) before in this document). Treatment effects in both hypervolemic and euvolemic patients were statistically significant.

From the above figure, [redacted] the euvolemic patients.



The Treatment by cause of hyponatremia interaction was statistically non-significant (p-value = 0.3587; Table s14.5 in the NDA Study Report). The treatment effects in both CHF patients and Non-CHF patients subgroups were statistically significant for both 40mg and 80 mg doses,

§ Detailed Center (grouped) Results are provided in the July 2, 2004 amendment.



The centers were grouped the following way:

Center	Name (site number)	No. of Per Protocol Set Patients
1	[redacted]	14
2		15
3		14
4		13
5		11
6		17

The treatment-by-center interaction was 0.7883 (which is non-significant. See Table s2.1.1 in the clinical study report for Study 087-CL-027 on page 1426 of 3351).

§ There was an amendment, Amendment 2, to the protocol after some patients were treated. All these many changes are in Section 9.8.1.2 (page 90) of the report of this Study in the NDA. The first two changes were:
· The dosing regimen was altered such that both placebo and drug were administered as a 30-minute bolus followed by an approximately 96-hour continuous infusion (comprising four 24-hour continuous infusions of either 40 or 80 mg/d YM087). This elimination of the Study Day 3 bolus was done because from both clinical and pharmacokinetic standpoints it was no longer felt to be justified.
· The limitation of patient enrollment based on volume status was deleted

The sponsor stated (ISE, Section 2.7.3.2.2.1), "Further, the increases in AUC in the IV YM087 40 mg/d and IV YM087 80 mg/d treatment groups, using pre- and post-Amendment 2 as a factor, remained significant compared to placebo (p=0.00010 for both groups). There was no significant interaction between pre- and post-Amendment 2 populations." Although this reviewer did not see anything contrary to what is stated (and really matters), there is an arithmetical error (in p=0.00010 for both groups). In Table s4.2 (of the NDA study report, page 1005), the p-values are slightly bigger than 0.00010:

Partial Table from "Summary of Baseline-Adjusted Area under the Serum Sodium Effect Curve (AUC) over the Duration of Treatment by Treatment Group (Part II of II) Full Analysis Set: Included Patients Enrolled into the Study **Pre-Amendment 2** (Full Analysis Set)"

	Treatment Difference [3]		
Parameter	L.S. Mean	S.E. (L.S. Mean)	P-value
IV YM087 40 mg vs Placebo	579.1	137.29	0.00140
IV YM087 80 mg vs Placebo	716.8	139.81	0.00020

[3] P-values for treatment differences were from a Dunnett's test on the difference of least-squares means.

§ The SIADH (Syndrome of inappropriate antidiuretic hormone secretion) subgroup results for efficacy provided in the 7-2-04 amendment does not pose any concern.

§ The efficacy results for baseline serum sodium subgroups were provided in the 7-2-04 amendment. Baseline serum sodium was a significant covariate and within 80mg group the subgroup of patients with baseline serum sodium $\leq$ 120mEq/L had statistically significantly different efficacy results from those of the other subgroups. However, there was no statistically significant baseline serum sodium by treatment interaction. The only statistically non-significant efficacy comparison between treatment groups was in the subgroup of patients with baseline serum sodium $\leq$ 120mEq/L (only 15 patients in this subgroup) for the 40mg conivaptan vs placebo (11 patients were involved for this comparison).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Study 087-CL-027 is considered pivotal since it employed the dose and intravenous route of conivaptan HCl administration proposed for marketing. This study has been reviewed in this document. Conivaptan (YM087) was evaluated in the well controlled environment of hospitalized patients over a 4-day Treatment Phase. This study has provided statistical evidence in favor of the efficacy of both 40 mg and 80 mg of conivaptan.

Conivaptan (YM087), IV, was statistically significantly superior to placebo in the change from baseline in serum sodium over the duration of treatment as measured by the AUC (from beginning through end of treatment) corrected for baseline serum sodium. Baseline-adjusted AUCs were approximately 8-fold and 11-fold greater for patients in the 40 mg/d and 80 mg/d, respectively, than for patients in the placebo group.

§ P-values for pairwise comparisons with respect to demographic and baseline characteristics were provided in the July 2, 2004 amendment. None of them were statistically significant, especially, for the 40mg vs placebo comparison.

There was a statistically significant treatment by baseline volume status interaction. Since treatment effects (vs placebo) in both hypervolemic and euvolemic patients were statistically significant, this interaction does not pose a concern for the overall efficacy assessment. A figure for the 95% confidence intervals for euvolemic and hypervolemic patients has been presented above in Section 4.2 Other Special/Subgroup Populations. Mean effect (vs placebo) among [redacted] euvolemic patients, especially in the 80 mg group. Dose response [redacted] in the euvolemic patients.

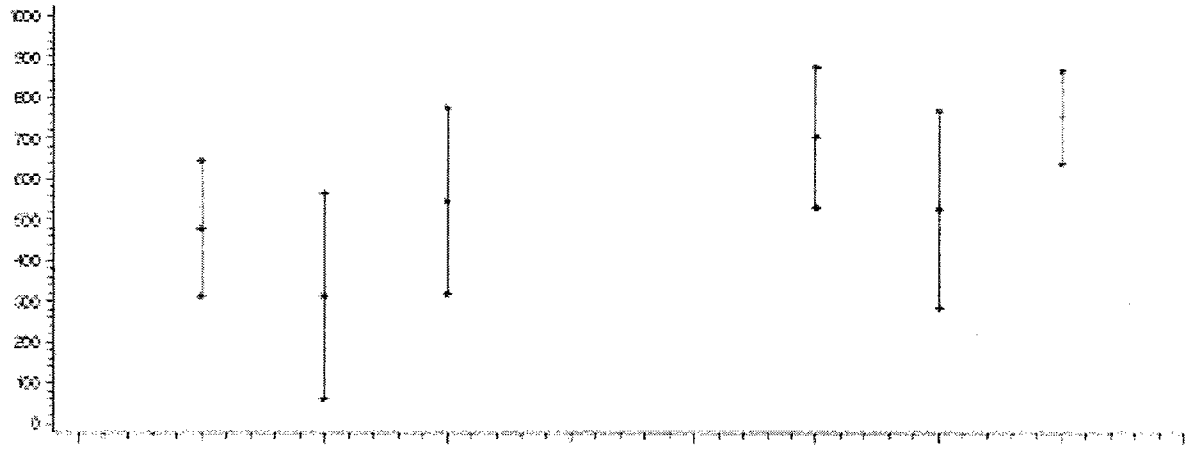
The sponsor provided numerous analyses, including nonparametric analyses (Supplemental Table S1.1 in Section 14.4 of the NDA study report) and many subset analyses. These have been referred to in 11.4.1.1 (especially, on pages 130 to 136) of the NDA study report. Most of these are presented in Section 14.2 and 14.4 of the NDA study report. All results provide highly statistically significant evidence in favor of the efficacy of the drug. Since the placebo results were the worst in Center 1 and the treatment results were the best in Center 5, this reviewer analyzed by excluding Center 1 and Center 5. The overall results, still, provide highly statistically significant evidence in favor of the efficacy of the drug.

The sponsor stated in Section 11.4.1.1 (page 130) of the NDA Study Report, "... although the statistical relationship between Baseline serum sodium levels and Baseline-adjusted AUC was significant in all populations (i.e., PPS, FAS, FAS-as-planned-randomized, and FAS-as-randomized), there was no significant interaction with treatment. In the FAS population, there was a significant interaction between treatment and Baseline volume status."

The following comparison of the results of the primary efficacy results of the IV Study (which has been reviewed) and the two oral studies (not reviewed) is from the sponsors Integrated Summary of Efficacy (ISE, page 79).

Treatment Effect Size Compared with Placebo for the Baseline-adjusted Area Under the Serum Sodium Effect Curve (AUC) over the Duration of the Treatment – LS Mean and 95% CI Individual Pivotal IV and Supportive Oral Phase 3 Hyponatremia Studies - Full Analysis Set

AUC [(mEq/L)*Hour]



Study 027 Study 026 Study 043 Study 027 Study 026 Study 043

----40mg vs placbo----- -----80mg vs placebo--------

Summary of Change in Serum Sodium from Baseline (AUC) over Duration of Treatment - Individual Pivotal IV and Supportive Oral Phase 3 Hyponatremia Studies - Full Analysis Set

	Pivotal IV Hyponatremia								Supportive Oral Hyponatremia			
	027				026				043			
Statistics	Placebo	YM087 40 mg/d	YM087 80 mg/d	P-Value (b)	Plac.	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		23	24	27		30	27	26	
Baseline Adjusted AUC												
Mean	61.4	501	662		329	594	802		129	640	986	
(SD)	(242)	(365)	(331)		(400)	(421)	(473)		(255)	(504)	(606)	
LS Mean (SE)	12.9	490.9	716.6		309.2	621.3	836.2		87.5	634.2	952.7	
	(61.1)	(56.79)	(60.45)		(94.82)	(89.0)	(87.78)		(80.82)	(84.16)	(85.74)	
Treatment Differences												
Across All Treatment Group				0.0000				0.0002				0.0060
40 mg/d YM087 vs Placebo				0.0001				0.0299				0.0001
80 mg/d YM087 vs Placebo				0.0001				0.0001				0.0001

[a] For study 027, baseline value is the average of serum sodium 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, 12 and at 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 significant(at 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: plaslog (026), plaslog(027), plas(043).sd2 Program Source: t27311.sas

5.2 Conclusions and Recommendations

In the currently proposed labeling, the sponsor has provided only a graph for a secondary efficacy variable (Mean and S.E. of Mean) of Change in Serum Sodium Value from Baseline (Hour 0) [1] to each Measurement Time [2] by Treatment Group, Full Analysis Set) and that also only for 40mg conivaptan. Although 80mg has numerically more efficacy than [redacted]. The sponsor has not provided the results of the primary efficacy variable in the labeling. The sponsor clarified in the July 2, 2004 amendment, the sentence in the labeling (Clinical Studies Section), "Patients had a mean serum sodium of 123.3 mEq/L at study entry," by: "Patients in the 40 mg/day group had a mean serum sodium of 123.3 at baseline, i.e., study entry,"

By the sponsor's many analyses and this reviewer's own analyses, this reviewer (statistical) does not have any concern about the efficacy of the two doses tested (details are in the previous Section 5.1).

6. APPENDICES

Appendix I: Statistical Methodology Details

Calculation Method for the Primary Efficacy Variable (AUC) and Some Extra Details on Statistical Methodology:

The Calculation of the Baseline-Adjusted AUC

The following procedure will be used to compute baseline-adjusted AUC:

Step 1: Compute baseline serum sodium value for calculation of the baseline- adjusted AUC

A) Baseline serum sodium value for calculation of the baseline-adjusted AUC

Baseline serum sodium value for calculation of the baseline- adjusted AUC will be defined as the average of baseline measurements at Hours 4, 6, 10, and at the end of the Baseline Phase (Hours 20- 28).

B) Handling of missing baseline serum sodium measurement

Missing baseline serum sodium measurements will not have values imputed. Patients without any baseline serum sodium measurement will be excluded from analyses of the primary efficacy variable.

C) Algorithm for computing baseline serum sodium value for calculation of the baseline-adjusted AUC

Let X 4, X 6, X 12, X 24 be serum sodium measurements obtained during Baseline Phase at Hours 4, 6, 10, and at the end of the Baseline Phase (Hours 20-28) respectively. Then the baseline serum sodium value for calculation of the baseline-adjusted AUC is calculated as the following:

BV_ SS = [(Sum of non-missing X 4, X 6, X 12, X 24) / (Number of non- missing X 4, X 6, X 12, X 24)]

Step 2: Compute the AUC

A) The serum sodium effect curve

The serum sodium effect curve is defined by the last serum sodium measurement obtained before drug administration and consecutive measurements obtained after drug administration through the end of the Treatment Phase (Day 4).

B) Method for imputing the missing serum sodium measurement

There are 17 possible measurements for the serum sodium effect curve. If an intermediate measurement is missing, linear interpolation between the previous (including baseline) and following non-missing measurements will be used to assign a value. If the terminal value is missing, the integral average method (described below in Case 2) will be used to compute the AUC.

The time interval for computing AUC will be normalized from Hour 0 to Hour 96 for all patients.

C) Algorithm for computing the AUC

Let X 0, X 1, ..., X 16, X 17 be serum sodium measurements (observed or imputed) obtained at time T 0, T 1, ..., T 16, T 17 respectively, then the AUC will be calculated as the following:

Case 1: For patients with the last serum sodium measurement (Hour 24 on Day 4)

$AUC\_[0\text{-}96] = \frac{1}{2} [(X\,0 + X\,1)*(T\,1 - T\,0) + \ldots + (X\,16 + X\,17)*(T\,17 - T\,16)]$

Case 2: For patients without the last serum sodium measurement (Hour 24 on Day 4)

AUC_[0- 96] = (AUC* 96hours)) / (Total time, in hours, to the last observed serum sodium measurement),

where AUC is computed as in Case 1 by using all data from the last serum sodium measurement obtained before drug administration through the last serum sodium measurement obtained during the Treatment Phase.

Step 3: Compute the baseline-adjusted AUC

The baseline-adjusted AUC is computed as the following:

AUC_ adj = AUC_[0- 96] - BV_ SS* 96

The 087-CL-027 Statistical Analysis Plan (SAP) will be modified to include the following (Ref: 16.1.9, Statistical Documenttation, of the NDA):

(A few less important ones are omitted.)

Two patients were treated only for 2 days but had 4 days of serum sodium data available. During the BDRM (Blinded Data Review Meeting), the committee decided that all available data should be used in the primary analysis but the 2-day sodium data will be used in a supportive analysis on the FAS of the primary efficacy endpoint. Pooling of study centers, was as defined below. The SAP will be signed off before the database lock and release of treatment codes.

Establish rules for pooling of study centers:

The BDRM committee discussed several different strategies of pooling the study centers. In an attempt to minimize any deleterious effects of the pooling scheme on the ability to analyze the effect of "center" in the PPS, it was decided to delay choice of the final pooling scheme until the effects of each scheme proposed could be determined on the number of patients available for the PPS at each center. When this analysis was completed shortly after the BDRM, members endorsed the scheme below via email because it left adequate numbers at each center in both the FAS and PPS to evaluate any effect of center. The scheme was geographical for sites outside of North America, and in chronological order for sites within North America.

	Description	Sites Included	Total Patients	Number of PPS
Center 1	Israel 1	13	14	14
Center 2	Israel 2	10, 12, 16, 17	15	15
Center 3	South Africa	21, 24, 26, 29	14	14
Center 4	Chronological 1	07, 51, 56, 58 62	14	13
Center 5	Chronological 2	63, 65, 67, 69	12	11
Center 6	Chronological 3	72, 79, 86, 89, 92, 98	17	17

Timeline for Database Lock and Topline Results:

DCRs and review of all of the data will be completed by Thursday, 01 May 2003. Approval by YPA of release of the database and the database lock is scheduled for 01 May 2003. Topline results of the primary efficacy endpoint will be made available on 02 May 2003. All other topline results will be made available on 08 May 2003.

Other "changes to the planned statistical analysis" and "additional analyses" are in Sections 9.8.2. and 9.8.3, respectively, in the NDA Study Report.

Appendix II: List of Abbreviations and Definition of Terms

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase, also known as SGPT
AML	American Medical Laboratories
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase, also known as SGOT
ATC	anatomical therapeutic chemical
AUC	area under the serum sodium effect curve
AVP	arginine vasopressin
BDRM	blind data review meeting
bid	twice daily
bpm	beats per minute
BUN	blood urea nitrogen
CATO	Cato Research
CHF	Congestive heart failure
CI	Confidence interval
COPD	chronic obstructive pulmonary disease
CPK	creatinine phosphokinase
CPMP	Committee for Proprietary Medicinal Products
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CTM	clinical trial material
CYP	Cytochrome P450
D	Day
D5W	5% dextrose and water
EC	ethics committee
ECG	Electrocardiogram
eg	for example
EWC	effective water clearance
FAS	full analysis set
FDA	Food and Drug Administration
FWC	free water clearance
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ie	that is
im	intramuscular
IND	Investigational New Drug
INR	international normalized ratio

IRB	institutional review board
iv, IV	intravenous(ly)
IVRS	interactive voice response system
L	Liter
LDH	lactate dehydrogenase
LOCF	last observation carried forward
LS	least squares
Mayo	Mayo Medical Laboratory
MCH	Mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeterof mercury
NEC	not elsewhere classified
NOS	not otherwise specified
NYHA	New York Heart Association
OC	observed cases
PAC	premature atrial contraction
PBO	placebo
PG/EtOH	propylene glycol and ethanol
PK	pharmacokinetic(s)
po	by mouth
PPS	per protocol set
prn	as needed
PT	prothrombin time
PVC	premature ventricular contraction
qd	once daily
qhs	nightly
qid	four times daily
RBC	red blood cell
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
sc	subcutaneous
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SOC	system organ class
TEAE	treatment-emergent adverse event
TEAV	treatment-emergent abnormal (laboratory) value
TIA	transient ischemic attack
tid	three times daily
U.S.	United States
UTI	urinary tract infection

vs.	versus
WBC	white blood cell
WHODRUG	World Health Organization Drug Dictionary
YM087	conivaptan
YEU	Yamanouchi Europe, B.V.
YPA	Yamanouchi Pharma America, Inc.
YPCL	Yamanouchi Pharmaceutical Co., Ltd

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