CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-697

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-697
Submission Date(s)	6-30-05; 1-30-04
Brand Name	Vaprisol®
Generic Name	Conivaptan IV
Reviewer	Sang M. Chung, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Clinical Pharmacology and Biopharmaceutics II
ORM division	Division of Metabolic and Endocrine Products
Sponsor	Astellas
Submission Type	Amendment as Response to AE
Formulation; Strength(s)	IV solution; 20mg in 4 ml ampoules
Indication	Euvolemic or hypervolemic hyponatremia

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Clinical Pharmacology and Biopharmaceutics II (OCPB/DCPB-II) has reviewed Amendment to NDA21-697 (conivaptan HCl) and finds it acceptable. The Recommendation should be sent to the sponsor as appropriate.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Conivaptan is a non-peptide antagonist of arginine vasopressin (AVP), also known as an antidiuretic hormone (ADH). It will be the first in the class if conivaptan is approved by the Agency.

An approvable letter was issued on November 30, 2004 with several deficiencies including insufficient number of patients for safety analysis. The letter also stated that the sponsor should evaluate an optimal dosage regimen.

The sponsor compiled safety data with a total of 404 patients who received IV conivaptan.

[redacted] The lower effective dose seemed to have comparable efficacy and safety to that of the original proposed dosage regimen (Table 1). [redacted]

Table 1 **Preliminary efficacy results between 20mg/day and 40mg/day infusion**

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%)

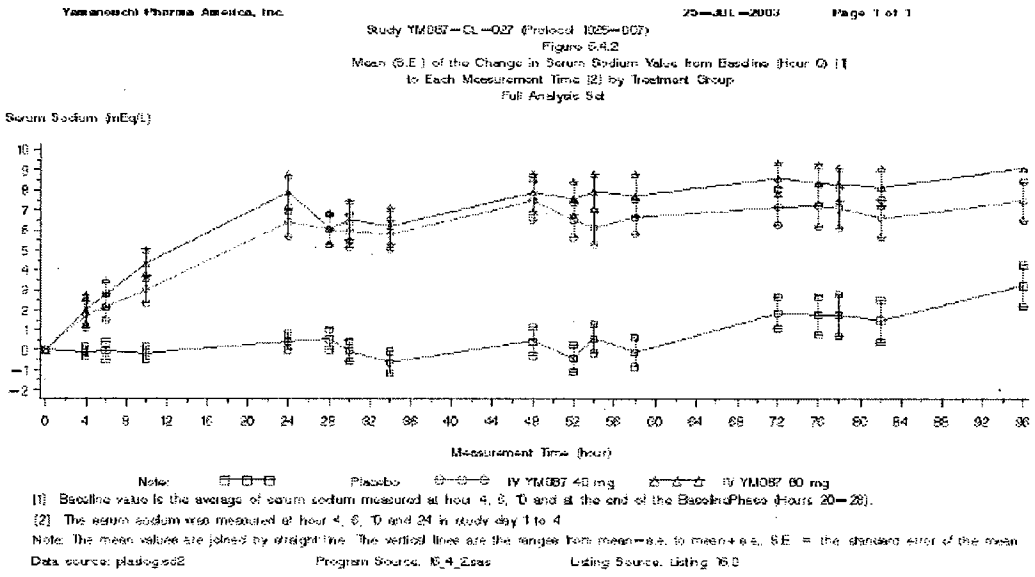

Figure 1 **Mean change in serum sodium concentration from the baseline to each measurement time by treatment**

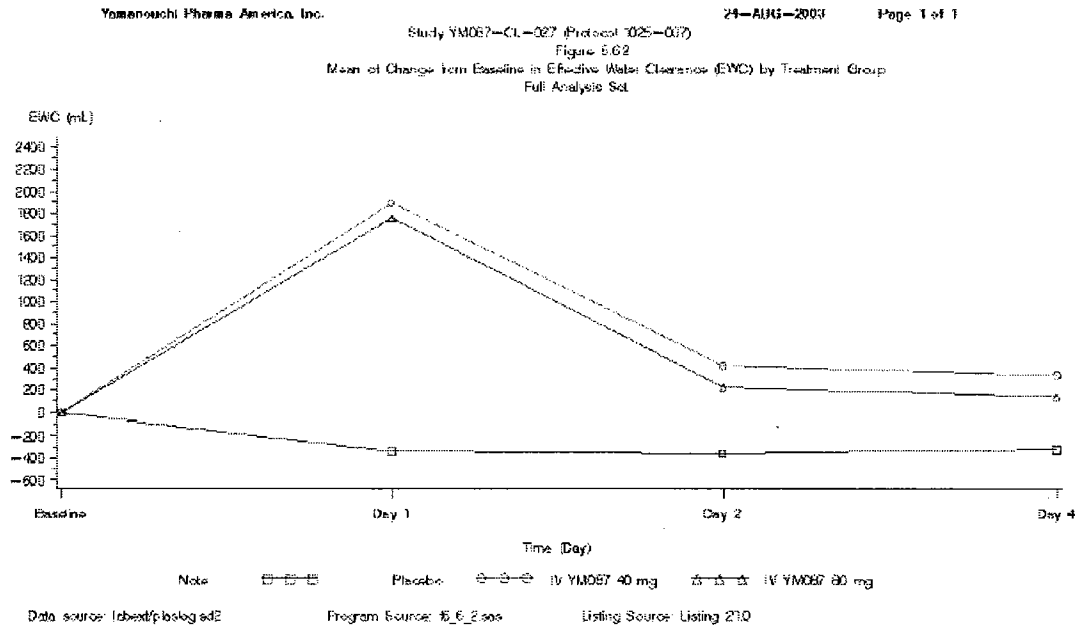

Figure 2 **Mean change from the baseline in effective water clearance by treatment group**

Two recommendations in the AE letter were made by the OCPB in line with evaluation of the optimal dosage regimen; 1) evaluation of the relationship between creatinine clearance and PD endpoints, and 2) evaluation of optimum loading dose. The detailed recommendations and the sponsor's responses were as follows:

OCPB Recommendation 1

The exposure-response relationship for conivaptan may vary with renal function. A systematic analysis of the relationship between pharmacodynamic response (e.g., free water clearance) and creatinine clearance is needed.

Sponsor's Response

The sponsor evaluated the relationship between creatinine clearance and PD endpoints such as free water clearance, effective water clearance, and serum sodium change. Representative results were shown in Figure 3 and 4, and correlation coefficients were summarized in Table 2. There was a modest proportional correlation between creatinine clearance and PD endpoints. The results indicate that the apparent dose-response of conivaptan seems to be shifted to a relationship with reduced efficacy in patients with reduced renal function.

The sponsor proposed no dose adjustment for patients with renal impairment. However, the dose adjustment should be considered based on safety concerns because exposure of

conivaptan may be increased in the patients compared to that of healthy subjects according to results after oral dosing.

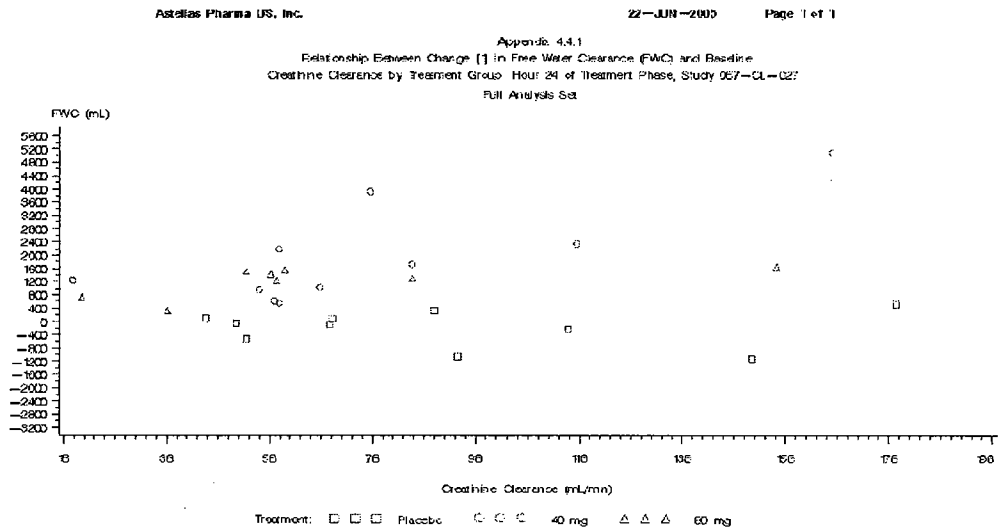

Figure 3 **Free water clearance versus creatinine clearance**

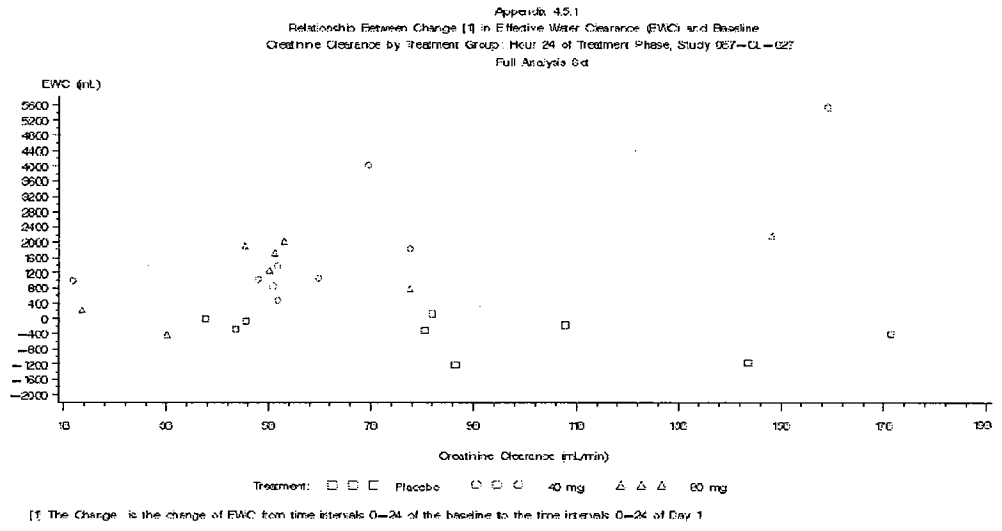

Figure 4 **Effective water clearance versus creatinine clearance**

Table 2 **Correlation between baseline creatinine clearance and PD measurements at 24 hours (Study 087-CL-027)**

		Placebo	Conivaptan 40mg	Conivaptan 80mg
Change in FWC	**N**	11	10	9
	Coefficient	-0.04	0.76	0.56
Change in EWC	**N**	11	10	9
	Coefficient	-0.46	0.84	0.58
Change in serum sodium	**N**	24	27	26
	Coefficient	-0.23	0.14	0.08

OCPB Recommendation 2

The need for an initial intravenous loading dose of conivaptan is not clear, given its pharmacokinetics. Submit data to justify a loading dose (e.g., data on the efficacy with and without an initial bolus dose). Include justification for the dosing used during this bolus.

Sponsor's Response

Conivaptan plasma concentration after the loading dose was about three-fold higher than that after infusion for 4 days, and the high concentration may be related to safety events such as hypotension and injection site reaction. The sponsor proposed a study (with or without a loading dose) as part of a Phase 4 Commitment. In addition, the sponsor claimed that the loading dose did not show clinically significant first-day safety issue. For example, onset day of hypotension was 1.5 day and 2 day during the treatment of 40mg/day and 80mg/day infusion.

There were other recommendations in the AE letter without approvability contingency. The recommendations and the sponsor's responses were as follows:

Recommendation 1

Exploration of methods for decreasing the incidence of infusion site reaction is recommended.

Response

The sponsor proposed the following labeling: "Administration of VAPRISOL through large veins and change of the infusion site every 24 hours is recommended to minimize the potential risk of vascular irritation."

Recommendation 2

Conivaptan exposure in patients treated with the proposed dosage regimen was not well characterized in the NDA. Conivaptan plasma concentrations were measured predominantly at the end of infusion in the pivotal Phase 3 study entitled "A 4-Day, Double Blind, Placebo-controlled Multicenter Study of IV YM087 (CI-1025) to Assess Efficacy and Safety in Patients with Euvolemic or Hypervolemic Hyponatremia." These data are inadequate to characterize the pharmacokinetics of the drug when used as proposed. Please characterize conivaptan exposure in the target population(s) if there are any on-going or planned clinical trials. Sampling every 24 hours during infusion is suggested to characterize conivaptan pharmacokinetics in target patients.

Response

Pharmacokinetics of conivaptan in the target patients after the proposed dosing regimen was characterized in the Study 087-CL-80, and results were summarized in the following table. Blood samples were collected at 1, 4, and 24 hours on Day 1, 24 hours on Day 2, and 1, 2, 7, 12, and 24 hours on Day 5 (post-treatment). Age range was between 63 and 87 years (n=14).

Table 3 Conivaptan pharmacokinetic parameters after 20mg IV loading dose and 40mg/day infusion for 4 days (Study 087-CL-080).

Parameter	IV Conivaptan 40 mg/day§ (n=14)
Conivaptan concentration at 0.5 hours (ng/mL)†	
Mean ± SD	786.36 ± 302.883
Median	781.08
Range	[redacted]
Conivaptan concentration at 96 hours (ng/mL)‡	
Mean ± SD	419.21 ± 488.218
Median	227.51
Range	[redacted]
$AUC_{0\text{-}inf}$ (ng hr/mL)	
Mean ± SD	31465.40 ± 33560.711
Median	19119.07
Range	[redacted]
Elimination Half-life (hr)	
Mean ± SD	10.65 ± 5.549
Median	8.6
Range	[redacted]
Clearance (L/hr)	
Mean ± SD	13.88 ± 12.984
Median	9.51
Range	[redacted]

§ Dosing regimen included a 20 mg loading dose.

† end of the loading dose.

‡ end of the 4-day infusion

Recommendation 3

Special population studies, using the full dose planned for labeling, are needed in the elderly and in patients with hepatic impairment.

Response

Pharmacokinetic parameters in Table 3 were mostly from elderly patients, and the results appear to be comparable to those of healthy subjects. For example, mean conivaptan plasma concentration at the end of infusion was 188 ng/ml and 228 ng/ml for healthy subjects (Day 3) and elderly patients (Day 4), respectively.

The sponsor is evaluating study designs for the pharmacokinetic study in hepatic impaired patients.

Recommendation 4

A warfarin interaction study is recommended, using the full dose proposed for labeling.

Response

A protocol is being developed.

Recommendation 5

Response

The issue was addressed in the sponsor's response to one of Agency's major recommendation.

Recommendation 6

In Study 087-CL-027, multiple protocol violations occurred in which subjects received prohibited CYP3A4-metabolized drugs. The fact that subjects 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 proposing a risk management plan for further reducing the likelihood that patients taking conivaptan will receive other CYP3A4-metabolized drugs.

Response

The sponsor proposed labeling to provide information to health professionals. In addition the sponsor plans to develop a proper Risk Management Plan.

Overall, the sponsor's responses and proposals are acceptable.

5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✔ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

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12/8/2005 01:20:53 PM
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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-697
Submission Date(s)	January 30, 2004; March 31, 2004; May 28, 2004
Brand Name	Vaprisol
Generic Name	Conivaptan IV
Reviewer	Sang M. Chung, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM division	Division of Metabolic and Endocrine Drug Products
Sponsor	Yamanouchi
Relevant IND(s)	56,813 and 55,607
Submission Type; Code	1S
Formulation; Strength(s)	IV solution; 20mg in 4 ml ampules
Indication	Euvolemic or hypervolemic hyponatremia

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB/DPE-II) has reviewed NDA21-697 (conivaptan HCl) and finds it acceptable provided complete responses to CPB Comments be made. The Recommendation and CPB Comments should be sent to the sponsor as appropriate.

CPB Comments

1. 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 exposure-response relationship in patients with significantly decreased renal function (e.g., elderly SIADH patients, or patients with renal impairment). Therefore, it is recommended to 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 efficacy endpoints.

2. The proposed dosage regimen was not justified well as follows:
   - Loading dose and amount of loading dose: In general, loading dose is not recommended for drugs with a short half-life unless there is any clinical benefit. However, the sponsor proposed the loading dose without reasonable justification. For example, one of efficacy points (i.e., serum sodium change from baseline) did not show benefits of a loading dose.
   - Infusion time: The sponsor [redacted] and there was no formal analysis on the optimal infusion time.

   In these regards, it is recommended to provide reasonable justification on the proposed dosage regimen including utility of loading dose and optimum infusion time.

3. Exposures of conivaptan in target patients 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 had limited values due to non-linearity in conivaptan exposure. Therefore, it is recommended to characterize conivaptan exposure in target population(s) if there is any plan for clinical trials or on-going trial(s). Sampling in every 24 hours during infusion is suggested to characterize conivaptan pharmacokinetics in target patients.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Conivaptan is a non-peptide antagonist of arginine vasopressin (AVP). The AVP, also known as antidiuretic hormone, conserves body water by enhancing electrolyte-free water absorption through AVP receptor (V_2) in the renal collecting duct. The AVP is released from the posterior pituitary and three subtypes of AVP receptor have been identified in several tissues: 1) V_2 receptor in the kidney, 2) V_{1A} receptor in smooth muscle including blood vessels, and 3) V_{1B} receptor in the adenohypophysis. Conivaptan is a V_2 antagonist.

[redacted]

The proposed indication is for euvolemic or hypervolemic hyponatremia and conivaptan is the first in that class. Euvolemic hyponatremia is defined as normal total body sodium and increased total body water without signs of edema or volume depletion. Hypervolemic hyponatremia is defined as total body sodium is increased, but total body water is increased to a greater extent. Conivaptan is expected to normalize serum sodium concentration (primary efficacy endpoint, Figure 1) [redacted]

Patients with syndrome of inappropriate antidiuretic hormone (SIADH) have been identified as one of target populations. [redacted]

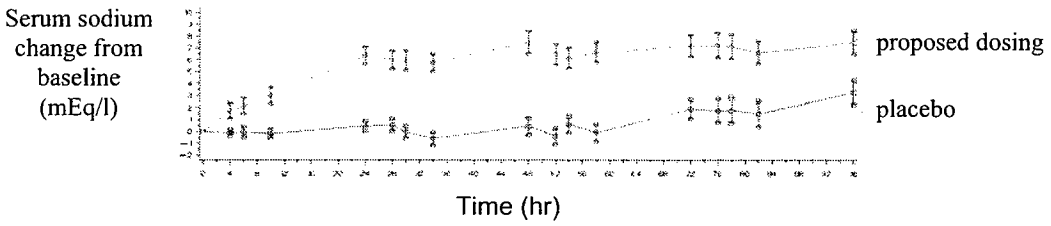


Figure 1 **Mean change of primary efficacy endpoint (serum sodium) after the proposed dosing (data from the proposed labeling)**

The sponsor [redacted] intravenous administration. [redacted]

Agency raised safety concerns on possible drug interaction with strong CYP3A4 inhibition potential of conivaptan. There were three pivotal Phase III studies; one study

with IV dosing (number of patients on conivaptan was about 49), and two studies with oral dosing. The results of two oral studies were to be the major supportive data for safety findings of conivaptan based on assumption of similar exposure between two routes of administration

A total of 37 studies were included for review of the clinical pharmacology and biopharmaceutics (CPB) section in the NDA as follows:

- 10 studies for healthy subject pharmacokinetics (PK),
- 2 studies for patient PK,
- 3 studies for intrinsic factors (elderly, hepatic impairment, and renal impairment),
- 13 studies for extrinsic factors,
- 1 population PK study, and
- 6 studies for patient PD and PK/PD.
- 2 amendments
    - 1 study for the conivaptan effect on QT prolongation
    - 1 study for absolute bioavailability

Of 37 CPB studies, two studies used the same as the proposed dosage regimen and one study used similar to the proposed dosing (20mg loading dose and 40mg/day for 3 days). Several pieces of CPB information were extrapolated from results obtained after oral dosing. A typical conivaptan plasma concentration-time profiles after oral and the proposed dosage regimen were shown in Figure 2 (Study 083).

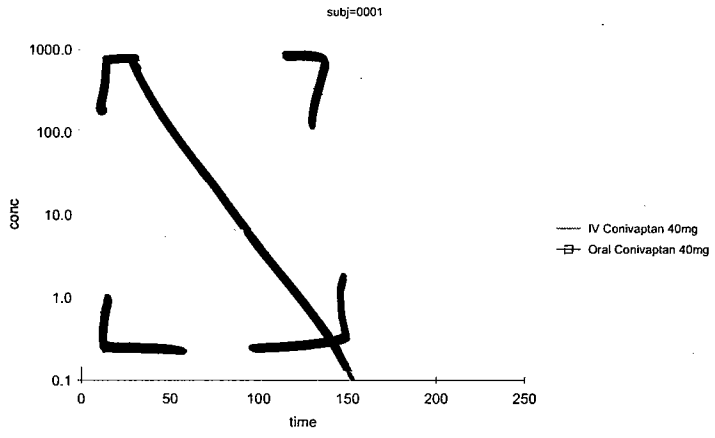


Figure 2 **Representative plasma conivaptan concentration-time profiles from a subject (square for the oral dosing and line for the proposed dosage regimen).**

Representative primary pharmacokinetic (PK) parameters from the IV dosing (i.e., 20mg loading dose for 30minutes and 40/day infusion for 3 days) were summarized in Table 1.

Table 1 **Summary of conivaptan PK parameters (Study 074)**

Parameter	Mean (SD)
C_{max} (ng/ml)	618.93 (104.67)
AUC_{0-96} (ng h/ml)	10640.35 (4314.61)
$T_{1/2}$ (hr)	4.99 (1.37)
AUC_{0-inf} (ng h/ml)	10740.11 (4375.56)
CL (L/h)	15.18 (6.69)

The partial AUCs (AUC at each day) were increased with time and it indicated non-linear PK with time because accumulation was not expected based on the short half-life. In addition, there was non-linearity between steady-state concentrations after infusion ($C_{ss,inf}$) and doses. The non-linearity might be due to auto-inhibition in metabolism and/or p-gp.

The major route of elimination was fecal excretion (about 83% total radioactivity) and about 12% of total radioactivity was found in urine after oral (20-mg solution) and IV (10-mg in 5minutes) administration. The responsible metabolic isozyme was CYP 3A4. Mean absolute oral bioavailability (F) was reported ranging from 28% to 44% in three studies, and it appeared to be dependent on doses due to non-linearity in PK.

The effect of intrinsic and extrinsic factors on conivaptan exposure was shown in Figure 3. Conivaptan exposure was affected by intrinsic and extrinsic factors. Particularly, ketoconazole significantly increased conivaptan exposure (11-fold by AUC) when both were administered orally. In addition, conivaptan increased significantly exposure of sensitive CYP3A4 substrates (e.g., midazolam and simvastatin). The results indicate that conivaptan is a strong CYP3A4 inhibitor as well as a sensitive substrate of CYP3A4.

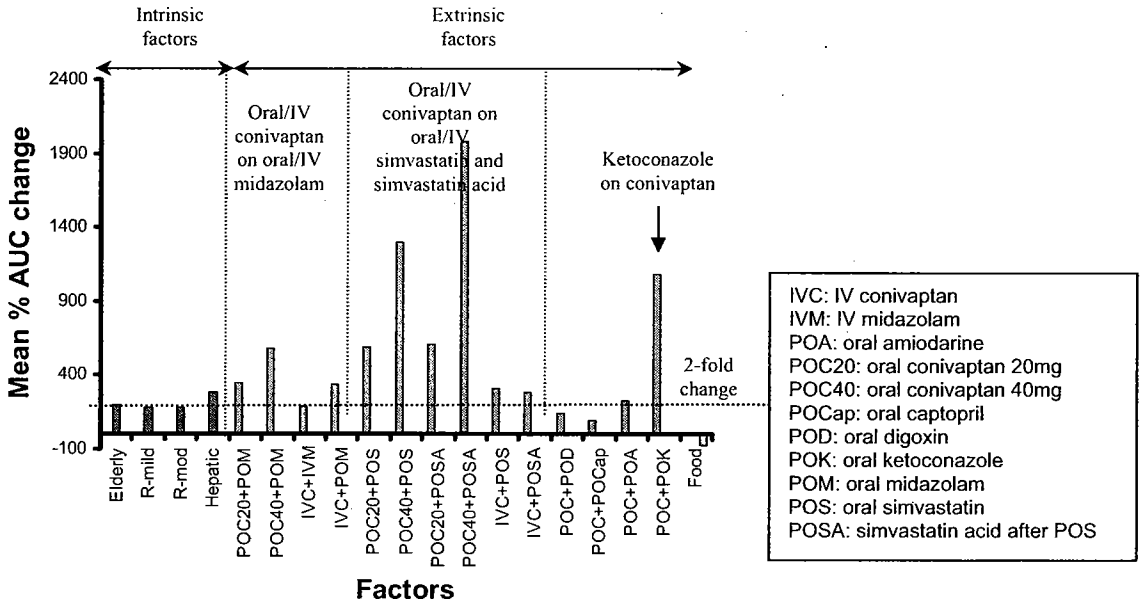


Figure 3 **Conivaptan exposure change (i.e., AUC) by intrinsic and extrinsic factors, and the effect of conivaptan on exposure of other drugs; mean % change compared to AUC in healthy subjects or control.**

Conivaptan was a substrate and inhibitor of p-glycoprotein according to results of *in vitro* studies.

A Phase I clinical study was conducted to estimate the effect of conivaptan on QT prolongation, and results of analyses on heart rate corrected QT and outlier indicated that there was no significant signal for conivaptan on QT prolongation.

Summary of CPB Issues

1. Exposure after the proposed dosing in the target population

Conivaptan exposure was not well characterized in the target population (i.e., SIADH) after the proposed dosing. Sparse conivaptan exposure was measured (i.e., concentration at the end of infusion) in the pivotal Phase III study but those showed limited value because of non-linearity in conivaptan PK. For example, total exposure may not be reasonably estimated using concentrations at the end of infusion.

Results from studies after oral administration indicated that conivaptan exposure in patients was significantly increased compared to that in healthy subjects. However, it was difficult to extrapolate quantitatively results after oral dosing to that after the proposed dosing because degree of non-linearity in pharmacokinetics appeared to be different between the routes of administration.

2. Dosing regimen / Dose-response

Justification on the proposed dosage regimen was not elaborated. For example, the reason for a loading dose (i.e., 20-mg over 30-minutes) was not clear within the provided information. In general, a steady-state will be reached in 24 hours infusion based on conivaptan half-life (i.e., about 5 hours). It might be a clinical need for the loading dose but it was not explicitly demonstrated. In addition, there was no reasonable justification on duration of infusion.

In general, exposure-response was not characterized well particularly using the proposed dosage regimen. According to the reviewing clinical reviewer, a lower effective dose will be recommended to be explored.

3. Effect of intrinsic factors (i.e., age, hepatic impairment, and renal impairment) on conivaptan exposure.

There were the effects of intrinsic factors on conivaptan exposure based on results after 10mg oral dosing. In addition, conivaptan exposure was increased more than 2-fold in the target population compared to that in healthy subject using cross study comparison after oral dosing.

It is difficult to extrapolate the above results in the target population with intrinsic factors (e.g., SIADH patients with renal impairment) to the situation with the proposed dosage regimen primarily because of non-linearity of conivaptan PK and dependency of non-linearity to routes of administration.

4. One dosage regimen without adjustment

There was no proposed dose adjustment even though several factors (e.g., intrinsic factors) increased conivaptan exposure significantly.

2 Question-Based Review (QBR)

2.1 General Attributes

2.1.1 What are the highlights of the physico-chemical properties of conivaptan?

Conivaptan is the first oral non-peptide ADH antagonist and its structure was shown in Figure 4.

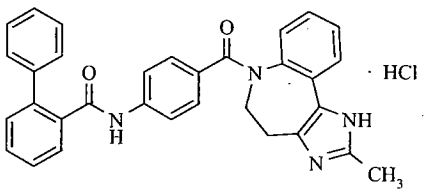
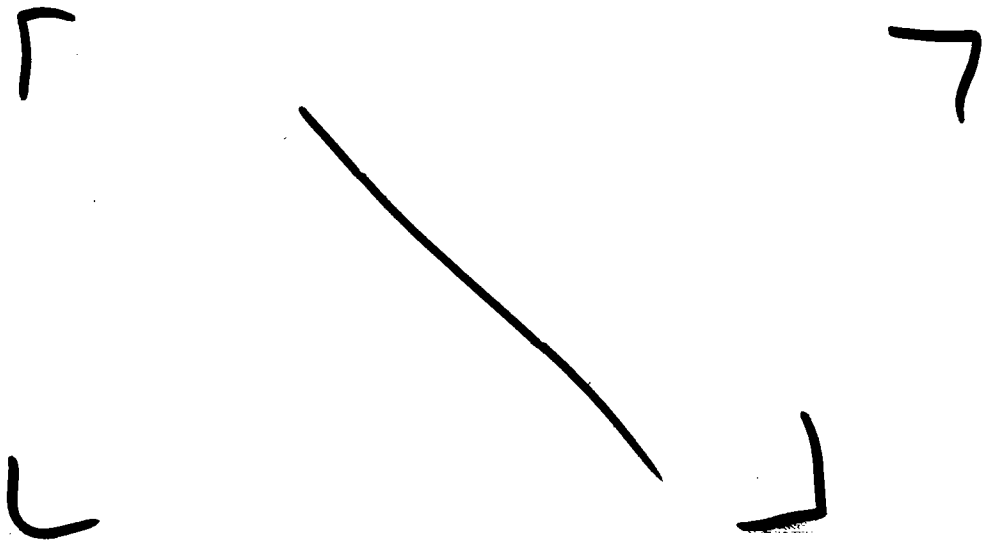


Figure 4 **Molecular structure of conivaptan (Molecular weight; 535.04 as the salt and 498.57 as free base, pKa, 6.4)**

Aqueous solubility was 0.15mg/ml (very slightly soluble) and its solubility in



2.2 General Clinical Pharmacology

2.2.1 What are major findings of *in vitro* studies using human biomaterials?

- PROTEIN BINDING

Plasma protein binding of conivaptan was from [redacted] 99 [redacted]% with conivaptan [redacted] In addition, warfarin and salicylic acid did not interfere with conivaptan protein binding.

- METABOLIC PATHWAY

Based on results of microsomal studies (using specific substrates, and inhibitors), it was concluded that 3A4 was the responsible isozyme for conivaptan metabolism. In addition, conivaptan was a strong CYP 3A4 inhibitor with a submicromolar IC_{50} values. Detailed results of *in vitro* studies are summarized in Section 3.4 Extrinsic Factors. Structures of identified metabolites were shown in Figure 7.

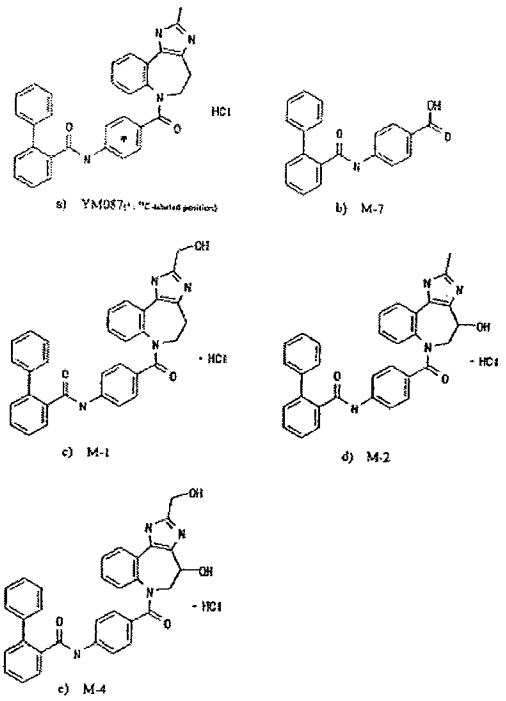


Figure 7 **Chemical structures of metabolites from all studies including preclinical**

Induction potential on metabolic isozymes was not evaluated.

Among metabolites, only M1 showed equal potency to conivaptan in a receptor binding study. Exposure of three metabolites were measurable after IV infusion for 3 days in healthy subjects (Study 074), and AUCs were 120.75, 634.46, 10.24 ng*h/ml (n=8) for M1, M2, M3, respectively. Conivaptan AUC was 10640 ng*h/ml. Therefore, the contribution of active metabolite, M1, was regarded as negligible with minimal *in vivo* exposure (1.1% of conivaptan AUC).

- ACTIVITY ON TRANSPORTER

2.2.2 What are the characteristics of conivaptan pharmacokinetics?

Conivaptan pharmacokinetics were characterized in healthy subjects. Conivaptan appeared to be a low hepatic extraction ratio drug based on comparison of plasma clearance (CL, 0.253 L/min) and the hepatic plasma flow (0.75 L/min) assuming hematocrit as 0.5. Pharmacokinetic parameters based on similar to the proposed dosing were summarized in Table 2.

Table 2 **Summary of conivaptan PK parameters (Study 074, 20mg loading dose over 30minutes and 40mg/day continuous infusion for 3 days)**

Parameter	Mean (SD)
C_{max} (ng/ml)	618.93 (104.67)
AUC_{0-96} (ng h/ml)	10640.35 (4314.61)
$T_{1/2}$ (hr)	4.99 (1.37)
AUC_{0-inf} (ng h/ml)	10740.11 (4375.56)
CL (L/h)	15.18 (6.69)

Conivaptan pharmacokinetics (PK) were characterized after the proposed dosing in Study 083 and PK parameters were summarized in Table 3. Results of oral dosing (20mg BID for 5 days) were included in the table from the same study (Study 083). Detailed exposure comparison between oral and IV dosing is in the section of EXPOSURE COMPARISON BETWEEN ORAL AND IVDOSING

Table 3 **Summary of steady-state PK parameters (Mean (SD))**

Parameter	i.v. Conivaptan n=21	Oral Conivaptan[a] AM Dose n=20	Oral Conivaptan[b] PM Dose n=20	Oral Conivaptan[c] Sum of AM and PM n=20
C_{avg} (ng/mL)	151.31 (72.021)	125.17 (88.304)	73.06 (50.540)	98.11 (66.173)
AUC_{SS} (ng•hr/mL)	3631.43 (1728.49)	1478.09 (1059.65)	876.67 (606.474)	1177.38 (794.07)
Cl or CL/F (L/hour)	12.92 (6.849)	40.56 (27.325)	80.85 (92.468)	49.17 (34.301)
Vd (L)	376.13 (251.273)	N/A	N/A	N/A
λ_Z (Ke) (hour^{-1})	0.0479 (0.03361)	N/A	N/A	N/A
t½ (hour)	21.64 (12.542)	N/A	N/A	N/A
F (AUCss Ratio)	1	0.3778	0.2349	0.3063

[a] C_{avg} and AUC_{SS} results for oral AM dose normalized to 40 mg
[b] C_{avg} and AUC_{SS} results for oral PM dose normalized to 40 mg
[c] Results for sum of AM and PM oral doses
F = Ratio of normalized oral AUCss/IV AUCss
Data Source: Supportive Table 5

The sponsor calculated AUC at steady-state (AUCss) using average concentration at steady-state (Cavg) and dosing interval (tau) with the following equation:

$$AUCss = Cavg*tau$$

The AUC calculation was based on an assumption of linear PK. However, conivaptan showed non-linearity with time (refer the section for PK LINEARITY WITH TIME) and thus PK parameter estimation by the above equation may not be accurate.

2.2.3 Is the major route of elimination identified?

The major route of elimination was identified as fecal excretion after IV and oral dosing. About 80% of dose was found in feces as total radioactivity from both routes of administration. About 0.4% and 1% of oral and IV dose was excreted in urine as conivaptan and there was no quantitative assessment for conivaptan and its metabolites in fecal excretion.

Results of a mass balance study (Study 061) were shown in Figure 8 and summarized in Table 4.

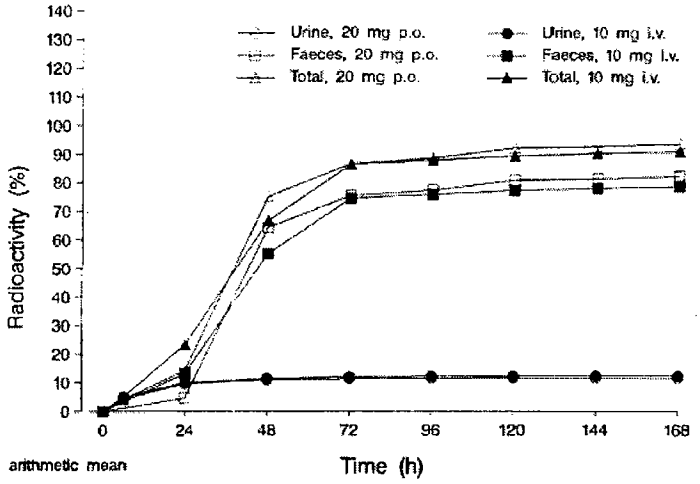


Figure 8 **Cumulative excretion of radioactivity in urine (circle), feces (square), and total (triangle) after IV and oral dosing.**

Table 4 **Summary of conivaptan PK parameters: Geometric mean (min-max)**

Parameter	10mg IV	20mg PO
Cmax (ng/ml)	1010.8	105.7
Tmax (h)	0.08	0.750
T1/2 (h)	5.00 (4.7-5.5)	5.1
AUClast (ng h/ml)	528.82	352.59
AUC0-inf (ng h/ml)	533.19	357.42
Vss (L)	52.1	
CL (l/h)	18.8	
A_{urine} (% dose)*	12.28	11.53
A_{feces} (% dose)*	79.85	83.68

*: total radioactivity

2.2.4 Is conivaptan pharmacokinetics linear?

- With doses

A formal CPB study was not conducted to evaluate PK linearity with the proposed dosing. In a QT study (Study 079), two infusion doses (40mg and 80mg) were used with the same 20mg loading dose, and conivaptan plasma concentrations were measured on Day 4 (n=40/treatment) for 24 hours. The results were shown in Figure 9. Plasma concentrations were ranging from [redacted] and from [redacted] for 40mg/day and 80mg/day infusion, respectively. The ratio (80mg over 40mg) of steady-state concentrations (Css) between two doses were about 4. The results indicate that CL is decreased 50% by doubling the doses based on the following equation:

$$Css = \text{infusion rate} / CL$$

Therefore, it was concluded that there was non-linearity in PK with the proposed dosing.

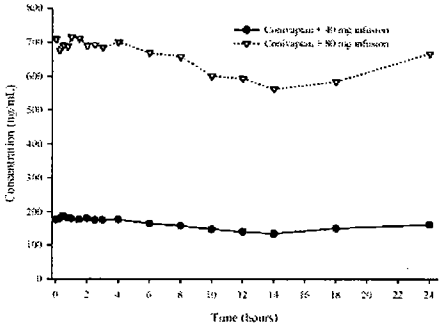


Figure 9 **Mean conivaptan plasma concentration on Day 4**

Results after oral administration showed non-linear PK with doses and degree of non-linearity was higher compared to that with the proposed IV dosing. Summary of the results is in the Appedix.

- With time (Single dose vs. Steady-state)

Formal analysis was not done to evaluate PK linearity with time after the proposed IV dosing. The means of partial AUC (daily AUC) were reported in Study 074 with similar dosing to the proposed method and results were 2572.64, 2844.69, and 3960.92, for intervals of 0-24 hr, 24-48 hr, and 48-72 hr, respectively. Total daily doses were 60mg for Day 1 (20mg loading+40mg infusion), and 40mg for Day 2 and Day 3. The partial AUCs were increased with time and it indicated non-linear PK with time because the accumulation was not predicted with a short half-life of conivaptan.

There was significant accumulation after multiple oral dosing and degree of accumulation was dependent on doses. The results indicated non-linearity with time after oral dosing and results are summarized in the Appendix.

2.2.5 Is conivaptan pharmacokinetics in target population different from that in healthy?

Major target populations are patients with hyponatremia due to syndrome of inappropriate antidiuretic hormone (SIADH) or congestive heart failure. Conivaptan exposure data in the target population was not well characterized.

Average conivaptan plasma concentrations at the end of treatments were reported in the pivotal Phase III study (Study 027) as 376 and 1777 ng/ml after 40mg and 80mg/day infusion, respectively (Section 2.5.3.2.4). The corresponding plasma concentrations in healthy subjects were 161 and 668 ng/ml (Study 079, n=40/treatment). The concentrations in patients were 2.3- to 2.7-fold higher than those in healthy subjects depending on doses after oral or IV bolus administration.

The concentration after 80mg/day infusion was about 4.7-fold higher than that after 40mg/day infusion in patients and the corresponding concentration increase with increasing dose was 4.1-fold in healthy subjects. Therefore, the results indicated that there might be similar non-linearity of conivaptan PK in patients compared to that in healthy subjects.

In conclusion, conivaptan pharmacokinetics was significantly different between healthy subjects and patients. Specifically, conivaptan exposure in patients was larger than that in healthy subjects. However, it should be cautioned to interpret this exposure difference.

2.2.6 What are exposure differences between oral and IV dosing?

Although the proposed dosing was IV administration, exposure comparison between oral and IV dosing was essential for conivaptan because there were two supportive Phase III studies for safety findings after oral doses and major studies for intrinsic and extrinsic factors were based on oral doses. Therefore, exposure comparison was essential to extrapolate appropriately results of oral dosing to those after the proposed dosing.

There were results of five studies for exposure comparison between IV and oral dosing. Three studies were designed for absolute bioavailability estimation and two studies were based on cross study comparison using a population pharmacokinetic approach (Study 075 and 082).

The sponsor withdrew study reports using a population PK approach on July 19, 2004 because the sponsor concluded that the results did not meet objectives with flaws in the modeling.

The sponsor reported absolute bioavailability as 35% (Study 061; IV=10mg in 5 minutes and PO=20mg, n=4), and 44% (Study 015; IV =60mg in 30 minutes, PO=60mg, n=6) based on single doses. In addition, mean AUC ratio (oral/IV) was reported as 0.28 (Study 083). The estimation of absolute bioavailability was based on the same clearance between routes of administration and the assumption was not warranted for conivaptan because of degree of non-linearity and it was dependent on routes of administration.

Representative pharmacokinetic parameters after IV dosing (infusion of 3.0 microgram/kg/ml for 3 hours) were 1548.9 ng*h/ml, 343 ml/min/kg, and 4 hours for AUC, CL, and half-life, respectively (Study 008, n=4). Pharmacokinetics after oral dose was characterized and representative results were summarized in Table 5 (Study 083). A single dose PK was estimated after the first dose of 20mg and steady-state PK was estimated on Day 5 after 20mg BID (q12h). Exposure after oral dose as AUC after normalized by dose was significantly lower than that after the proposed dosing. .

In conclusion, conivaptan exposure after the proposed dosage regimen seemed to be about 3-fold higher than that after similar oral dose.

Table 5 Conivaptan PK parameters after oral dosing

Parameter	AM Dose Day 1 n=21	AM Dose Day 5 n=20	PM Dose Day 5 n=20
C_{max} (ng/mL)			
C_{min} (ng/mL)			
C_{avg} (ng/mL)			
T_{max} (hour)[a]			
AUCI (ng•hr/mL)			
AUC_{12} or AUC_{SS} (ng•hr/mL)			
CL/F (L/hour)			
λ_z (KE) ($hour^{-1}$)			
$t_{1/2}$ (hour)			

[a] Median (range)

2.2.7 What are major findings about exposure-response?

Primary efficacy endpoint is change in serum sodium from baseline over the duration of the treatment phase as measured by the area under the serum sodium effect curve (AUC). Secondary endpoints were serum sodium measurements, free water clearance (FWC), and effective water clearance (EWC). FWC is an adjusted urine output with solutes levels including urea (level of urea is function of diet and renal function). EWC is urine output

adjusted with relevant electrolytes to the treatment effect. The followings are formulae to calculate FWC and EWC:

$$FWC = (Urine\ output) \times \left(1 - \frac{Urine_{osm}}{Plasma_{osm}}\right)$$

$$EWC = (Urine\ output) \times \left(1 - \frac{Urine_{Na} + Urine_{K}}{Plasma_{Na} + Plasma_{K}}\right)$$

Urine output is regarded as a general indicator of efficacy. However, it is confounded by many other factors (e.g., fluid intake, and changes in cardiac function) that are not related to drug treatment.

Major safety issues were injection site reactions, hypotension, thirsty, and renal dysfunction.

The sponsor did not plan to conduct any formal dose-response analyses. Three Phase III studies were conducted as follows:

- Pivotal study; 20mg over 30minutes + 40mg/day or 80mg/day continuous infusion for 4 days (Study 027, n=29 for 40mg/day, n=26 for 80mg/day, and n=29 for placebo)
- Supportive two studies (oral dosing); 20mg BID or 40mg BID for 5 days (Study 026; n=74, and Study 043; n=83)

Results from the pivotal study on the serum sodium from baseline were shown in Figure 1 and results of statistical analysis on the primary efficacy endpoint from all studies were summarized in Table 6. It appeared to be no dose-dependency on the primary efficacy endpoint.

Table 6 **Results of comparison on primary efficacy endpoint (changed in serum sodium AUC from baseline) with doses**

Study	Treatment Group	n	Mean	S.E.	95% Confidence Interval [a]	P-Value for Dose Comparison [b] YM087 80 mg vs YM087 40 mg
087-CL-027	40 mg	29	500.8	67.86	(361.8, 639.8)	0.0925
	80 mg	26	661.7	64.94	(528.0, 795.5)	
087-CL-026	40 mg	24				
	80 mg	27				
087-CL-043	40 mg	27				
	80 mg	26				
3 Studies combined	40 mg	80	575.6	48.21	(479.6, 671.6)	0.0013
	80 mg	79	816.3	55.70	(705.4, 927.2)	

[a] 95% confidence intervals for the means were calculated using the t-values.
[b] P-values were from a two-sided t-test on the difference of the means.
Data Source: ym086auc(026), ym087auc(027), ym043auc(043).sd2 Program Source: s2734bsas

Drug effect after oral doses seemed to be superior to that after IV doses according to the above table, and there was similar trend in urine output according to cross study comparison of Phase I studies as summarized in Figure 10. Time averaged exposure (i.e., AUC) may not explain the difference in the primary efficacy endpoints between routes of administration because AUC after oral administration was lower than that after IV dose. Efficacy might be a function of input rate as it can be exemplified with furosemide and nifedipine.

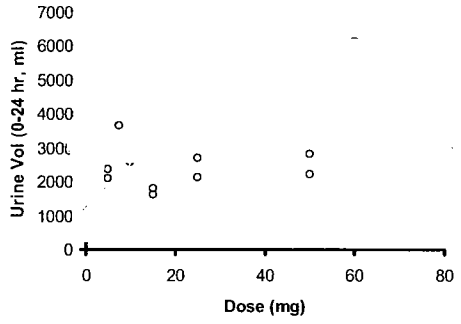


Figure 10 **Cumulative urine volume up to 24 hours after dosing. Closed circle is for oral (Study 009) and open circle is for IV (Study 013) administration**

The sponsor referred Study 025 as a pilot dose exploration study for the pivotal study. In the study, the patients received 20mg loading dose over 30 minutes and subsequent continuous infusion either 20 (n=4), 40 (n=4), or 80mg/day (n=3) for 2-4 days. The results on major efficacy endpoint were summarized in Figure 11.

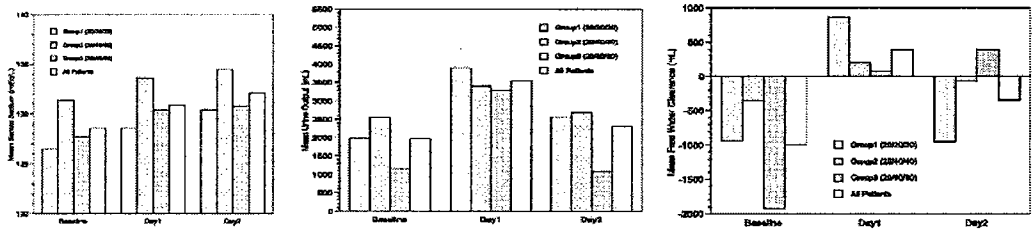


Figure 11 **Average serum sodium levels (left panel), mean urine output (middle panel), and mean free water clearance (right panel) (Study 025)**

It appeared that there was no clear dose-response relationship.

2.2.8 Is there exposure related QT prolongation effect?

Among safety issues, the electrocardiographic (ECG) effect of conivaptan was assessed using a quantitative method (Study 079) and thus included in CPB review.

The effect of conivaptan on QT prolongation was assessed using a placebo- and positive-controlled, parallel study in healthy subjects (n=40/treatment). Individually corrected QT (QTcI) was the primary endpoint, and the major secondary endpoints were Bazett's (QTcB), and Fridericia's (QTcF) formulae corrected QTs.

Study treatments were summarized in Table 7.

Table 7 Description of study treatments

Treatment	Description
conivaptan 20 mg bolus + 40 mg continuous infusion	Single 30-minute IV bolus of 20 mg conivaptan followed by a continuous infusion of 40 mg (1X clinical dose) of conivaptan on Day 1. Continuous infusions of 40 mg/d conivaptan on Days 2 through 4
conivaptan 20 mg bolus + 80 mg continuous infusion	Single 30-minute IV bolus of 20 mg conivaptan followed by a continuous infusion of 80 mg (2X clinical dose) of conivaptan on Day 1. Continuous infusions of 80 mg/d conivaptan on Days 2 through 4
moxifloxacin 400 mg	A single 60-minute IV dose of moxifloxacin 400 mg followed by a 23-hr continuous infusion of placebo on Days 1 through 4
placebo	4 successive 24-hr continuous infusions of placebo on Days 1 through 4

Digital ECGs were obtained as average of triplicate samples at nominal sampling time and methods of data analyses were acceptable. Detailed methods were summarized in the Appendix (4.3.2 Study 079).

Conivaptan 80mg was chosen as a possible maximum tolerable dose in healthy subjects and exposure was predicted to be about 4 times higher than that after 40mg.

Results on the primary and secondary endpoints were summarized in the Appendix. According to moxifloxacin labeling, mean change in QTc from pre-dose was 9 msec on Day 1 and 3 msec on Day 3 after 1 hour infusion. The current results with moxifloxacin were comparable to the labeling information and thus it was concluded that the assay sensitivity was appropriate.

It was concluded that there was no signal of conivaptan effect on QT prolongation. There were no subjects reached the outlier criteria (i.e., absolute QTc of > 500msec, > 60msec change from baseline). According to the reviewing Pharm/Tox reviewer, there was no particular signal in a dog model after acute and chronic (i.e., 52 weeks) dosing.

Regression analysis was performed between conivaptan plasma concentrations and QTcI, and it was concluded that there was no significant relationship between conivaptan plasma concentrations and QTc based on slope = -0.0006 in the pooled data with concentrations and QTcI.

2.2.9 Is there any quantitative PK-PD analyses?

A preliminary PK-PD modeling was attempted by the sponsor between plasma conivaptan concentrations and fluid balance (ml/min) after oral administration without documentation on detailed methods and individual data (Study 010). Fluid balance was calculated as difference between the balance values in active and control periods, and

negative fluid balance indicated a net diuretic effect. Typical sigmoidal Emax model was employed to characterize relationship between fluid balance and plasma conivaptan concentrations using WinNonlin, and EC_{50} of 205 ng/ml, E_0 of 1.0 ml/min, E_{max} of -9.0 ml/min, and a shape factor gamma of 0.86 were estimated. The relationship between fluid balance and conivaptan plasma concentrations were summarized in Figure 12. The physiologic possible E_{max} is reported to be

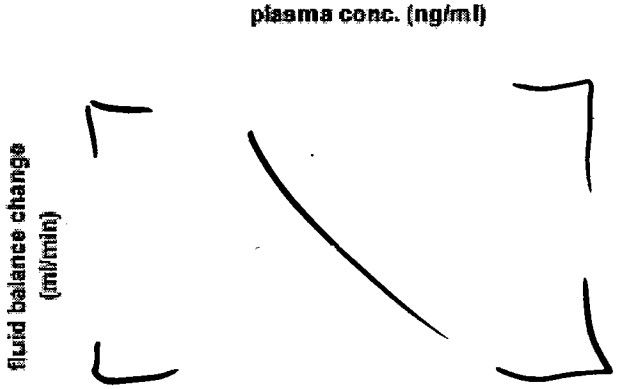


Figure 12 **Relationship between fluid balance and plasma level as mid-point.**

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure?

Conivaptan exposure was increased by three intrinsic factors (age, hepatic impairment, and renal impairment).

2.3.2 What is the exposure difference in elderly healthy subjects compared to exposure in young healthy subjects?

Conivaptan exposure was estimated in elderly healthy subjects (n=6/treatment, age ranging 65 to 90 years) after oral administration of three doses (15mg, 30mg, and 60mg, Study 014). Results were summarized with exposure data of healthy young subjects from other study (Study 010) in Table 8. Exposure in elderly subjects increased disproportional to increasing doses and degree of non-linearity seemed to be higher in elderly subjects compared to that in healthy young subjects.

Elderly subjects have 58% higher exposure as AUC after 60mg oral dose than young subjects. Although exposure difference as AUC was 58% with large inter-subject variability in this study, exposure difference in elderly patients is predicted to be larger than 58% because exposure was significantly higher in patients compared to that in healthy subjects. Therefore, there should be cautions to extrapolate the above results to exposure estimation in elderly patients.

Table 8 **PK parameters of healthy young and elderly subjects**

Pharmacokinetic parameters	Dose YM087	YOUNG subjects [under fasting conditions]	ELDERLY subjects [under fasting conditions]
mean C_{max} (range) ng/ml	15 mg	143	106
	30 mg	234	297 (
	60 mg	593 (	735 (
mean AUC (range) ng.h/ml	15 mg	*393	245 (
	30 mg	*745	961 (
	60 mg	*2417	3812 (

AUCs are expressed in ng.min/ml in the Pharmacokinetic Study Report

2.3.3 What is the exposure difference in patients with hepatic impairment compared to exposure in healthy subjects?

Exposure change in the hepatic impairment patients was evaluated with 10mg oral dose (Study 060, n=8 for healthy subjects, n=12 for patients)

Dose of 10mg tablet was administered on Day1 after breakfast (approximately at 8:00AM), BID during Day 2 and Day 7 after breakfast and dinner, and approximately at 8:00AM on Day 8. Pharmacokinetics were evaluated on Day 1 (0-24 hours) and Day 8 (0-12 hours), and results were summarized in Figure 13 and Table 9. There were mild (n=6) and moderate (n=5) sub-groups by Child-Pugh classification.

Exposure by AUC was up to 2.8-fold higher in patients than that in healthy subjects. There was no apparent protein binding difference between healthy subjects and patients. The sponsor concluded that dosage to hepatic impaired patients should not necessary be reduced.

The study results should be considered with clinical concerns with significant exposure change.

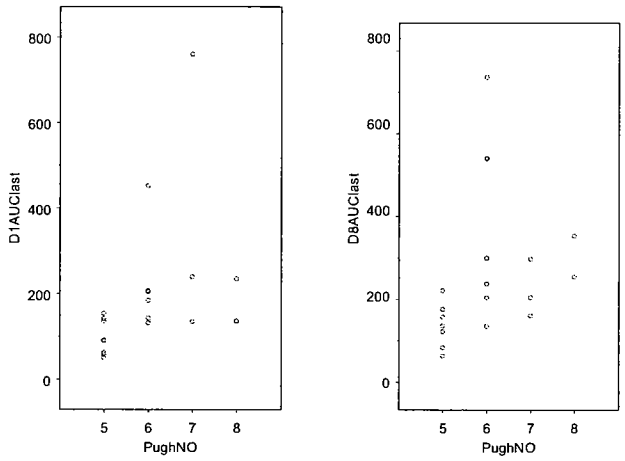


Figure 13 **Relationship between Pugh score and AUC; on D1 (left panel) and on D8 (right panel) (Subject 10 was excluded because of incomplete results from Day 1).**

Table 9 **Summary of PK parameters in healthy subjects and in patients with hepatic impairment. Values in each cell are mean, SD and CV in bracket, range, and median.**

	t_{max} (h)	C_{max} (ng/ml)	AUC_{last} (ng.h/ml)	AUC[1] (ng.h/ml)	$t_{1/2}$ (h)	f_e
Healthy subjects pre-dose	NA	NA	NA	NA	NA	0.61 [illegible] 0.59
Patients pre-dose	NA	NA	NA	NA	NA	0.55 [illegible] 0.57
Healthy subjects day 1	0.95 (0.48, 50%) [illegible] 0.89	40.0 (16.8, 42%) [illegible] 33.7	97.2 (40.8, 42%) 49.7 – 152 90.0	98.8 (40.9, 41%) 50.2 – 153 91.3	5.53 (2.50, 45%) 2.89 – 11.4 5.25	0.47 (0.10, 20%) 0.31 – 0.57 0.51
Patients, excl. 010 day 1	1.84 (3.38, 184%) 0.67 – 12.0 0.73	68.2 (19.9, 29%) 43.6 – 108 66.3	256 (190, 74%) 130 – 760 204	277 (241, 87%) 133 – 945 208	5.91 (1.06, 18%) 4.58 – 8.17 5.99	0.63 (0.18, 29%) 0.38 – 1.02 0.61
Patients, incl. 010 day 1	2.68 (4.35, 162%) 0.67 – 12.0 0.87	62.5 (27.3, 44%) 0.08 – 108 66.0	235 (196, 83%) 0.2 – 760 194	NA*	NA*	NA*
Healthy subjects day 8	0.84 (0.17, 20%) 0.67 – 1.00 0.87	60.0 (24.2, 40%) 24.0 – 88.9 60.8	NA	144 (54.9, 38%) 62.2 – 220 145	3.52 (1.41, 40%) 2.59 – 6.91 3.17	0.62 (0.11, 18%) 0.45 – 0.84 0.62
Patients day 8	1.07 (0.43, 40%) 0.50 – 2.05 1.00	96.8 (59.3, 61%) 35.7 – 225 86.0	NA	328 (182, 56%) 134 – 735 275	3.83 (0.88, 23%) 2.67 – 5.36 3.67	0.68 (0.17, 25%) 0.36 – 1.05 0.68

[1] AUC = $AUC_{0-\infty}$ on day 1, AUC_{0-12h} on day 8

* since in patient 010 no terminal phase was present, no $AUC_{0-\infty}$ or $t_{1/2}$ could be calculated; f_e could not be determined since the concentration of the 2h plasma sample was below LOQ.

2.3.4 What is the exposure difference in patients with renal impairment compared to exposure in healthy subjects?

Dose of 10mg tablet was administered at 8:00AM before breakfast on Day 1, and BID from Day 2 and Day 7 before breakfast and dinner, and before breakfast on Day 8.

Conivaptan PK was estimated on Day 1 (0-24 hours) and Day 8 (0-12 hours). Results of PK parameters were summarized in Figure 14 and Table 10. There was no significant association between CLcr and conivaptan AUC (i.e., r square=0.089). Exposure by AUC was up to 80% higher in moderate and severe renal impaired patients than that in healthy subjects. The sponsor concluded that dosage to renal impaired patients should not be necessarily reduced. However, there should be cautions in the interpretation of results because the kidney is the target organ for conivaptan and PK-PD might be different in the patients compared to that in healthy subjects.

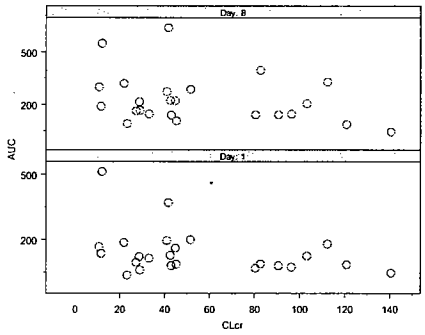


Figure 14 **Relationship between creatinine clearance (CLcr; ml/min) and AUC; AUC on Day 1 (lower panel) and AUC on Day 8 (upper panel).**

Table 10 **Summary of PK parameters**

	t_{max} (h)	C_{max} (ng/ml)	AUC_{last} (ng.h/ml)	AUC[1] (ng.h/ml)	$t_{1/2}$ (h)	f_e (%)
Healthy subjects pre-dose	NA	NA	NA	NA	NA	0.58 (0.06, 11%) 0.49 – 0.66
Patients $30 \le Cl_{cr} < 60$ ml/min.1.73 m^2 pre-dose	NA	NA	NA	NA	NA	0.57 0.56 (0.12, 22%) 0.35 – 0.76
Patients $10 \le Cl_{cr} < 30$ ml/min.1.73 m^2 pre-dose	NA	NA	NA	NA	NA	0.57 0.65 (0.14, 22%) 0.47 – 0.85
Healthy subjects Day 1	0.67 (0.15, 23%) 0.50 – 1.00	46.0 (12.4, 27%) 25.2 – 67.2	92.2 (41.4, 45%) 45.1 – 179	93.7 (42.0, 45%) 45.4 – 182	5.23 (1.42, 27%) 3.45 – 7.29	0.64 0.52 (0.10, 18%) 0.40 – 0.67
Patients $30 \le Cl_{cr} < 60$ ml/min.1.73 m^2 Day 1	0.67 0.81 (0.17, 21%) 0.67 – 1.02 0.71	44.9 67.3 (23.1, 34%) 41.4 – 113 66.1	81.7 166 (93, 56%) 79.5 – 368 143	83.3 168 (95, 56%) 80.1 – 373 146	5.13 4.65 (0.70, 15%) 3.32 – 5.80 4.66	0.51 0.53 (0.12, 22%) 0.30 – 0.68 0.56
Patients $10 \le Cl_{cr} < 30$ ml/min.1.73 m^2 Day 1	0.77 (0.25, 33%) 0.50 – 1.02 0.84	59.2 (28.6, 48%) 30.8 – 115 55.3	163 (150, 92%) 35.0 – 511 127	165 (151, 92%) 35.4 – 517 129	3.98 (1.03, 26%) 2.35 – 5.27 4.20	0.56 (0.10, 18%) 0.42 – 0.71 0.56
Healthy subjects Day 8	0.75 (0.15, 20%) 0.67 – 1.00 0.67	76.4 (41.0, 54%) 23.1 – 138 69.5	NA	184 (120, 65%) 41.7 – 394 141	3.35 (0.45, 13%) 2.67 – 3.88 3.54	0.63 (0.09, 15%) 0.49 – 0.77 0.63
Patients $30 \le Cl_{cr} < 60$ ml/min.1.73 m^2 Day 8	0.84 (0.18, 22%) 0.67 – 1.03 0.84	93.8 (48.9, 52%) 51.6 – 206 83.8	NA	252 (168, 67%) 104 – 637 220	3.43 (0.49, 14%) 2.53 – 4.07 3.44	0.58 (0.11, 19%) 0.44 – 0.76 0.58
Patients $10 \le Cl_{cr} < 30$ ml/min.1.73 m^2 Day 8	0.82 (0.21, 25%) 0.52 – 1.03 0.84	90.8 (27.8, 31%) 60.7 – 148 86.7	NA	247 (143, 58%) 88.0 – 548 200	3.29 (0.57, 17%) 2.49 – 4.23 3.40	0.64 (0.09, 14%) 0.53 – 0.76 0.61

NA: not applicable
[1] AUC = AUC_{0-24} on day 1, AUC_{0-12} on day 8

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence conivaptan exposure?

An inhibitor of CYP 3A4 metabolic isozyme (e.g., ketoconazole) increased conivaptan exposure (e.g., 11-fold) after oral co-administration.

Although the proposed dosing was IV infusion and food effect was not anticipated, food effect was incorporated in this review because some of essential CPB claims were based on results after oral administration and food reduced up to 68% conivaptan exposure. Therefore, meal condition was an important factor in cross study comparison.

2.4.2 What is the effect of a CYP 3A4 inhibitor on conivaptan exposure?

The effect of a 3A4 inhibitor on conivaptan exposure was assessed using ketoconazole 200 BID (q12h) on conivaptan PK (Study 058, n=12). Conivaptan 10mg (one 10mg tablet) was administered on Day 1 and Day 5 under fasting conditions, and ketoconazole 200mg BID (q12h) was administered from Day 4 to Day 6 in healthy subjects. Results were summarized in Figure 15 and Table 11. Ketoconazole increased conivaptan AUC up to 11-fold when both were orally co-administered. Ketoconazole was contraindicated in the proposed labeling.

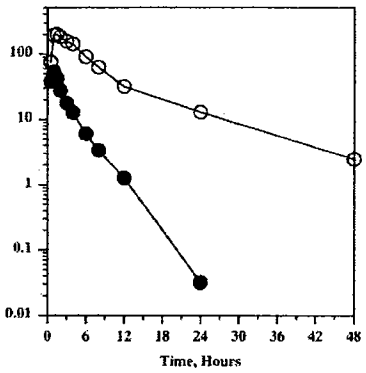


Figure 15 **Mean conivaptan plasma concentration-time profiles; conivaptan alone (closed circle) and when conivaptan was co-administered with ketoconazole (open circle)**

Table 11 **Summary of conivaptan PK parameters**

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Conivaptan 10-mg Tablets Alone (Reference)	Conivaptan 10-mg Tablets with Ketoconazole (Test)		
Cmax, ng/mL	51.4	204	392	335 to 458
tmax, hr	0.96	1.50	157	Not Applicable
AUC(0-tlqc), µg·hr/mL	0.141	1.55	1100	938 to 1290
AUC(0-∞), µg·hr/mL	0.146	1.58	1090	938 to 1270
t½, hr	2.80	9.17	327	Not Applicable
CL/F, mL/min	1220	110	9.07	Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference)

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean

2.4.3 What is the effect of conivaptan on exposure of sensitive 3A4 substrates?

- Effect of conivaptan on simvastatin

The effect of conivaptan on simvastatin exposure was assessed in two studies. In the first study (Study 064), 15mg BID IV conivaptan (approximately 8:00 and 20:00) was administered over 120 minutes for 3 days (Day 3 to Day 5). Simvastatin was administered as 60mg commercially available tablets on Day 1 and Day 5 under fasting condition. PK parameters of simvastatin were estimated using WinNonlin with non-compartmental analyses. Results of mean ratios (90% confidence interval) were summarized in Table 12. There was a significant effect of conivaptan on simvastatin and simvastatin acid exposure.

Table 12 **Summary of statistical results on the effect of conivaptan on simvastatin and simvastatin acid: mean ratio (90% CI) of Day 1 vs. Day 5 (n=4)**

	Simvastatin	**Simvastatin acid**
$AUC_{0\text{-}inf}$	3.12 (0.98-9.92)	2.87 (1.67-4.92)
Cmax	4.22 (1.58-11.27)	2.64 (1.91-3.66)

In the second study (Study 054), the effect of oral conivaptan on oral simvastatin exposure was assessed in healthy subjects (n=4). Simvastatin 60mg (three 20mg tablets) was administered on Day 1 and Day 6 under fasting conditions. Conivaptan 20mg (two 10mg tablets) BID or 40mg (four 10mg tablets) BID was administered from Day 2 to Day 6. Conivaptan significantly increased simvastatin and simvastatin acid. In addition, simvastatin and simvastatin acid exposure were increased with increasing conivaptan dose. For example, simvastatin AUC was increased 6- and 13-fold for 20mg BID and 40mg BID conivaptan, respectively. Results were summarized in the Table 13 and 14.

Table 13 **Summary of simvastatin PK parameters**

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Reference	Test		
	Simvastatin Alone	With 20 mg q12h Conivaptan		
n	16	7		
Cmax, ng/mL	13.0	10.2	79.0	56.1 to 111.2
tmax, hr	3.00	1.34	44.2	Not Applicable
AUC(0-tlqc), ng·hr/mL	72.3	46.4	64.1	42.6 to 96.5
AUC(0-∞), ng·hr/mL	89.8	53.0	59.0	35.4 to 98.5
t½, hr	9.32	7.66	81.6	Not Applicable
	Simvastatin Alone	With 40 mg q12h Conivaptan		
N	16	7		
Cmax, ng/mL	13.0	18.7	144.2	102.5 to 203.1
tmax, hr	3.00	2.02	66.9	Not Applicable
AUC(0-tlqc), ng·hr/mL	72.3	118.0	163.2	108.4 to 245.6
AUC(0-∞), ng·hr/mL	89.8	116.3	129.5	77.6 to 216.2
t½, hr	9.32	5.10	54.8	Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Table 14 **Summary of simvastatin acid PK parameters**

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Reference	Test		
	Simvastatin Alone	With 20 mg q12h Conivaptan		
n	16	7		
Cmax, ng/mL	2.43	19.8	820	568 to 1184
tmax, hr	4.41	3.41	77.3	Not Applicable
AUC(0-tlqc), ng·hr/mL	21.6	16.3	75.4	51.8 to 109.8
AUC(0-∞), ng·hr/mL	27.0	16.5	61.0	41.8 to 89.0
t½, hr	7.49	4.43	59.1	Not Applicable
	Simvastatin Alone	With 40 mg q12h Conivaptan		
N	16	7		
Cmax, ng/mL	2.43	43.7	1808	1253 to 2610
tmax, hr	4.41	5.05	115	Not Applicable
AUC(0-tlqc), ng·hr/mL	21.6	45.6	211.5	145.2 to 308.0
AUC(0-∞), ng·hr/mL	27.0	53.4	197.8	135.7 to 288.5
t½, hr	7.49	7.42	99.1	Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference)

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean

- Effect of conivaptan on midazolam exposure

The effect of conivaptan on midazolam exposure was assessed in two studies. In the first study (Study 074), the effect of IV conivaptan on IV or oral midazolam was evaluated in healthy subjects. Conivaptan was administered 20mg loading dose over 30 minutes and 40mg/day continuous infusion for 3 days (Day 2 to Day 5). Midazolam as a 1mg bolus IV dose or as a 2mg oral dose was administered on Day 1 and on Day 5 at the same time as the conivaptan infusion (n=7).

Conivaptan concentration for infusion was reduced (i.e., from 0.2mg/ml to 0.05mg/ml) and infusion rate was increased through protocol amendments during the study because of tolerability issue by injection site reactions.

Summary of mean ratio and 90% CI were summarized in Table 15.

Table 15 **Summary of statistical results on the effect of conivaptan on midazolam**

	MDZ IV & CON IV (MDZ+CON)/MDZ		MDZ PO & CON IV (MDZ+CON)/MDZ	
Parameter	Ratio	90% CI	Ratio	90% CI
Cmax (ng/mL)	109.03	93.89-126.60	210.75	186.25-238.47
$AUC_{0-\infty}$□ (ng.h/mL)	191.85	174.49-210.94	339.40	288.60-399.14

Two (1-OH and 4-OH) midazolam metabolites were measured in the study and conivaptan increased exposure of 4-OH about 1.6- and 2-fold after midazolam administration to IV and oral route, respectively.

In the second study (Study 052), the effect of oral conivaptan on oral midazolam exposure was assessed in healthy volunteers (n=16). Midazolam 2mg syrup (2mg/ml) was administered from Day 1 to Day 6. Conivaptan 20mg (two 10mg tablets) or 40mg (four 10mg tablets) BID (q12h) were administered under fasting conditions from Day 2 to Day 6.

Results were summarized in Table 16. Conivaptan increased oral midazolam AUC for 2.8- and 3.9-fold after 20mg BID and 40mg BID for 5 days, respectively.

Table 16 **Mean midazolam PK parameters and results of statistical analyses**

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Midazolam Alone (Reference)	with Conivaptan (Test)		
20 mg q12h Conivaptan				
n	16	8		
Cmax, ng/mL	8.82	19.2	218	191-248
tmax, hr	0.62	0.60	96.0	Not Applicable
AUC(0-8), ng hr/mL	18.8	53.0	282	252-315
AUC(0-∞), ng hr/mL	21.7	75.8	349	307-397
$t_{1/2}$, hr	3.22	6.59	204	139-269
CL/F, mL/min	1706	606	35.5	11.7-59.4
40 mg q12h Conivaptan				
n	16	8		
Cmax, ng/mL	8.82	23.4	265	233-302
tmax, hr	0.62	0.90	145	Not Applicable
AUC(0-8), ng hr/mL	18.8	72.8	387	346-433
AUC(0-∞), ng hr/mL	21.7	125	577	507-656
$t_{1/2}$, hr	3.22	9.99	310	245-375
CL/F, mL/min	1706	189	11.1	12.8-35.0

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference)

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean

2.4.4 What are other drugs affected by conivaptan?

- Effect of conivaptan on amlodipine exposure (Study 057)

Conivaptan 40mg (four 10mg tablets) BID was administered before breakfast and dinner under fasting conditions from Day 7 to Day 18. Amlodipine 5mg was administered on Day 1 and Day 11. Amlodipine PK parameters were estimated using up to 192 hours plasma sampling after dosing.

Results were summarized in Table 17. Steady-state conivaptan increased amlodipine mean AUC up to 2.45-fold compared to that without conivaptan.

Table 17 **Summary of amlodipine PK parameters**

Parameter	Mean Values: Amlodipine Alone (Reference)	Mean Values: Amlodipine With Conivaptan (Test)	Ratio	90% Confidence Interval
N	12	12		
Cmax, ng/mL	2.62	3.66	140	131 to 149
tmax, hours	8.67	8.83	102	Not applicable
AUC(0-tlqc), ng hr/mL	109	244	225	210 to 241
AUC(0-∞), ng hr/mL	129	316	245	223 to 270
CL/F, mL/min	660	272	41.2	33.8 to 48.6
t½, hours	46.1	89.0	193	Not applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference

- Effect of conivaptan on warfarin PK and PD (Study 049, n=12)

Conivaptan 40mg (four 10mg tablets) BID was administered under fasting condition for 10 days to patients with stable warfarin treatment for at least 1 month. Initially, International Normalized Ratio (INR) and prothrombin time (PT) were considered to measure the effect of conivaptan on warfarin therapy. Due to large intra-patient variability of INR, PT was selected to evaluate the effect of conivaptan on warfarin through amendment. In addition, warfarin PK was estimated.

It was concluded that multiple dose of 40mg conivaptan did not affect significantly warfarin PK as summarized in Table 18. It was also concluded that conivaptan did not affect PT in patients under stable warfarin treatment (Table 19).

Table 18 **Summary of warfarin PK parameters**

	Least-Squares Mean Predose Warfarin Concentrations			
	Day 1 Without Conivaptan (Reference)	Day 10 With Conivaptan (Test)	Ratio	90% Confidence Interval
N	12	10		
R-Warfarin (µg/mL)	0.651	0.637	97.7	90.3 to 106
S-Warfarin (µg/mL)	0.324	0.291	89.7	81.4 to 98.8

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Table 19 **Summary of the effect of 40mg conivaptan on prothrombin time in patients with stable warfarin treatment.**

Day	N	Mean PT		Mean Change[a] in PT		Ratio[b]	90% CI[c]
		Mean	SD	Difference	SE		
Baseline[d]	48	18.8	2.51	--	--	--	--
-21	12	18.1	1.68	--	--	--	--
-14	12	19.6	2.43	--	--	--	--
-7	12	18.8	3.03	--	--	--	--
1	12	18.9	2.79	--	--	--	--
2	12	19.9	3.60	1.07	1.00	105	(97.0, 114.0)
3	11	19.4	2.09	0.54	1.02	103	(95.1, 112.1)
4	10	18.7	1.47	-0.10	1.05	100	(92.0, 108.9)
5	10	19.3	4.04	0.48	1.05	102	(93.6, 110.8)
6	10	19.8	3.52	0.98	1.05	105	(96.3, 114.0)
7	10	18.4	1.51	-0.46	1.05	98	(90.2, 106.8)
8	10	18.5	2.24	-0.34	1.05	98	(90.5, 107.2)
9	9	19.0	2.15	0.13	1.08	101	(92.6, 110.2)
10	10	17.8	2.06	-1.08	1.05	95	(86.9, 102.9)
11	10	17.2	1.54	-1.61	1.05	92	(84.5, 100.0)
Closeout[e]	12	17.0	1.52	-1.80	1.00	91	(83.9, 98.5)

[a] Difference from Baseline
[b] Mean as a percentage of Baseline
[c] For mean PT as percentage of Baseline
[d] Baseline = mean of Days -21, -14, -7, and 1.
[e] Closeout = off drug for 1 week.

- Effect of conivaptan on digoxin PK in healthy male subjects

The effect of conivaptan on digoxin exposure was assessed in two studies. In the first study (Study 011), the effect of the single oral dose of 20mg (two 10mg capsules) conivaptan on 0.5mg digoxin IV infusion over one hour was evaluated in a two period, double blind, placebo controlled, cross-over study. Conivaptan was administered under fasting conditions (n=7).

Results were summarized in Table 20. The sponsor concluded that there was no significant effect of conivaptan on digoxin PK. There was high intra-subject variability in PK parameters and it may reduce power to detect difference.

Table 20 **Summary of digoxin PK parameters**

Parameters	Geometric mean ratio (Arithmetic mean ratio)	CV(%)	t01(p-value)	t02(p-value)	90% confidence interval	Power (%)
C_{max}	1.18(1.31)*	29.4	3.45(0.003)	-5.08(0.311)	0.96 - 1.45	12.2
$AUC_{(0-48h)}$	1.07(1.11)	16.6	4.55(0.0004)	-2.37(0.019)	0.96 - 1.20	71.6
$AUC_{(0-inf)}$	1.08(1.20)*	29.4	2.68(0.011)	-1.27(0.114)	0.88 - 1.33	32.7
CL_s	0.70(1.02)*	29.4	-1.15(0.863)	-5.10(0.0002)	0.57 - 0.86	28.6
V_{ss}	1.21(1.42)*	44.3	2.48(0.015)	-0.20(0.422)	0.90 - 1.63	7.3

Power : Power estimates under the assumption with alpha=5%, calculated geometric mean of the ratio -1 as a true difference and sample size used in this study
* ; arithmetic mean ratio derived from pharmacometric report
t01, t02 : t-values for the two one-sided t-tests

In the second study (Study 048), the effect of conivaptan on the steady-state digoxin PK was evaluated. Digoxin 0.25mg QD was administered from Day 1 to Day 20 under fasting condition. Conivaptan 40mg (four 10mg tablets) BID (q12h) was administered from Day 11 to Day 20. Digoxin PK was estimated on Day 10 and 20, and conivaptan PK was estimated on day 20 (n=12).

Results were summarized in Table 21. Conivaptan increased digoxin AUC by 43% and Cmax by 79%. The sponsor concluded that the results should be considered when both drugs were to be co-administered.

Table 21 **Summary of digoxin PK parameters**

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Digoxin Alone (Reference)	With Conivaptan (Test)		
N	12	12		
Cmax, ng/mL	1.53	2.75	179	167 to 192
tmax, hr	1.30	0.875	67.1	Not Applicable
AUC(0-24), ng·hr/mL	16.6	23.8	143	135 to 151
Cmin, ng/mL	0.532	0.707	133	125 to 142
CL/F, mL/min	259	180	69.5	62.9 to 76.2
Ae%	47.1	53.1	113	99.4 to 126
CLr, mL/min	122	95.7	78.4	66.7 to 89.8

Ratio – Ratio of treatment mean values, expressed as a percentage (100% × test/reference)
90% Confidence Interval – 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Digoxin is a drug with a narrow therapeutic index and thus it is recommended to carefully monitor patients if combination therapy between conivaptan and digoxin is necessary.

2.4.5 What are other drugs that affect conivaptan exposure?

- Effect of captopril on conivaptan PK (Study 012)

The effect of captopril on conivaptan PK was evaluated in a double blind, randomized cross-over study (n=15). Conivaptan 30mg (three 10mg capsules) and 25mg captopril (one tablet) were administered under fasting conditions. Results were summarized in Table 22 and it was concluded that there was no significant effect of captopril on single oral dose of conivaptan.

Table 22 Summary of conivaptan PK parameters

Pharmacokinetic parameter	YM087 + placebo mean (SD)	YM087 + captopril mean (SD)
t_{max} (h)	1.15 (0.33)	1.28 (0.39)
C_{max} (ng/ml)	175 (89)	175 (92)
t 1/2,a (h)	0.35 (0.15)	0.42 (0.13)
t 1/2,α (h)	1.29 (0.42)	1.15 (0.35)
t 1/2,β (h)	4.38 (1.13)	4.08 (0.82)
$AUC_{0\text{-}24h}$ (ng.h/ml)	530 (297)	581 (357)
$AUC_{0\text{-}inf}$ (ng.h/ml)	537 (302)	586 (362)
Cl_{app} (l/h)	68.3 (36.5)	67.8 (40.0)

- Effect of furosemide on conivaptan exposure in CHF patients (Study 024).

The effect of furosemide on conivaptan exposure was assessed in CHF patients (n=24, 6 patients per treatment). The patients received 40mg or 80mg QD furosemide for 6 days (Day 1 to Day 9) and then conivaptan 20mg or 40mg QD was administered as adds-on dosing for 3 days (Day 7 to Day 9). Both drugs were administered 1 hour before breakfast. The patients were moderate to severe CHF patients with stable background therapy with ACE inhibitor and optional a beta-blocker and digoxin.

Conivaptan PK was estimated by a population PK approach with primarily Day 9 with blood sampling at 2, 4, 6, and 24 hours after dosing. Conivaptan PK was characterized using a two-compartment model with nonlinear [redacted]) elimination. The sponsor concluded that furosemide did not affect significantly conivaptan PK based on the population PK parameter estimates as summarized in Table 23.

Table 23 Pop PK parameter estimates of the basic model

Parameter	θ (95%CI)	Interpatient Variability as CV % (95%CI)
Vmax (mg/hr)	2.78 (2.15-3.41)	5.59 (0-28.1)
V_1 (L)	176 (127-225)	56.8 (28.5-75.2)
Km (mg)	8.26 (6.06-10.5)	29.2 (0-55.5)
K_{12} (hr^{-1})	0.08 (0.06-0.10)	--
K_{21} (hr^{-1})	0.04 (0.01-0.07)	59.9 (0-115)
F_1 (Bioavailability factor)*	1.57 (1.16-1.98)	NA
Residual variability		29.4 (15.5-38.6)

-- Not estimable
NA Not Applicable
*F_1 depends on dose (i.e. F_1 = 1 at 20 mg QD, F_1 = 1.57 at 40 mg QD)

The conclusions were not acceptable because of the following reasons:

1. The above study did not include conivaptan alone and the population PK analyses did not include conivaptan alone, either.
2. There was no sampling during absorption period.

In addition, the sponsor withdrew results of the population PK analysis including non-linear elimination modeling (July 19, 2004 meeting).

2.4.6 Is there an *in vitro* basis to suspect *in vivo* drug-drug interaction?

Potential effect of ketoconazole, a 3A4 inhibitor, on conivaptan was evaluated with microsomal study. In addition, potential effect of conivaptan on simavastatin, a sensitive 3A4 substrate, was evaluated in the same study. Results were summarized in Table 24. The results indicated that a strong 3A4 inhibitor could increase conivaptan exposure at clinically relevant concentrations when both were co-administered. Similarly, conivaptan could increase a sensitive 3A4 substrate.

Table 24 **Summary of K_i values**

Substrate	Inhibitor	K_i*	C_{max}†
Conivaptan	Ketoconazole	0.017 ± 0.005 μM (8.9 ng/mL)	5–20 μM (2.7–11 μg/mL)
Conivaptan	Simvastatin	2.1 ± 0.56 μM (900 ng/mL)	0.01–0.025 μM (4.1–10.5 ng/mL)
Simvastatin	Conivaptan	0.92 ± 0.19 μM (490 ng/mL	0.44–0.61 (234–324 ng/mL)

C_{max} = maximum observed plasma concentration; K_i = inhibition constant

* Data are presented as means ± SD (N = 3)

† Values are representative of the C_{max} attained after relevant pharmacologic dosing with indicated drugs (i.e., 200 to 400 mg ketoconazole,[9] 20 to 40 mg simvastatin,[7,8] 30 mg conivaptan hydrochloride to healthy subjects [087-CL-010], or 20 mg conivaptan hydrochloride to patients with CHF [087-CL-017]).

2.4.7 What are *in vitro* results for identification of the responsible metabolic isozymes?

The major metabolic isozyme was concluded as 3A4 with results of three primary *in vitro* studies: 1) metabolism of conivaptan with cDNA expressed CYP isoforms, 2) correlation between conivaptan metabolism and specific substrates for CYP isoforms, and 3) inhibition of conivaptan metabolism with specific CYP isoforms. Results were summarized in Figure 16 and 17, and Table 25.

2.4.8 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Conivaptan was concluded as a strong 3A4 inhibitor by results of *in vitro* study and the results were summarized in Table 26.

Table 26 **IC_{50} values of conivaptan for major human CYP isozymes as determined in a fluorescence-based high throughput screening assay (Study R087-ME-033)**

CYP Isozyme	IC_{50} (μM)*
CYP1A2	198.3 ± 37.1
CYP2C9	13.3 ± 6.9
CYP2C19	19.2 ± 3.6
CYP2D6	12.6 ± 8.8
CYP3A4	0.47 ± 0.39

IC_{50} = concentration required to produce 50% inhibition.

* Data are presented as means ± SD (N = 4).

Induction potential of conivaptan on metabolic enzymes was not evaluated.

2.4.9 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

The *in vitro* bi-directional rates of conivaptan transport across Caco-2 cells were determined at 5 different concentrations. In addition, involvement of P-gp was assessed with verapamil, a p-gp inhibitor. Results were summarized in Table 27. The results indicated that conivaptan was a p-gp substrate because it showed polarized bi-directional transport, and verapmail significantly reduced polarized transport of conivaptan.

Table 27 **Summary of apparent permeability for the transport of conivaptan across Caco-2 cells. Values were shown for transport in the apical to basolateral (Ap to Bl) and basolateral to apical (Bl to Ap) direction and in the absence and presence of 100 microM verapamil.**

YM087 Concentration (μM)	Ap to Bl ($\times 10^{-6}$ cm/s)	Bl toAp ($\times 10^{-6}$ cm/s)	Ap to Bl + verapamil ($\times 10^{-6}$ cm/s)	Bl toAp + verapamil ($\times 10^{-6}$ cm/s)
0.3	1.29 ± 0.22	71.0 ± 10.5	11.4 ± 1.71	22.1 ± 3.03
1	2.74 ± 1.29	52.7 ± 7.26	12.2 ± 1.62	28.3 ± 3.46
3	3.35 ± 0.61	39.3 ± 4.99	9.82 ± 2.58	20.5 ± 2.01
10	5.31 ± 1.63	25.9 ± 3.79	11.6 ± 2.08	17.8 ± 3.07
15	5.53 ± 0.37	25.9 ± 1.55	11.7 ± 2.10	21.2 ± 1.48

2.5 General Biopharmaceutics

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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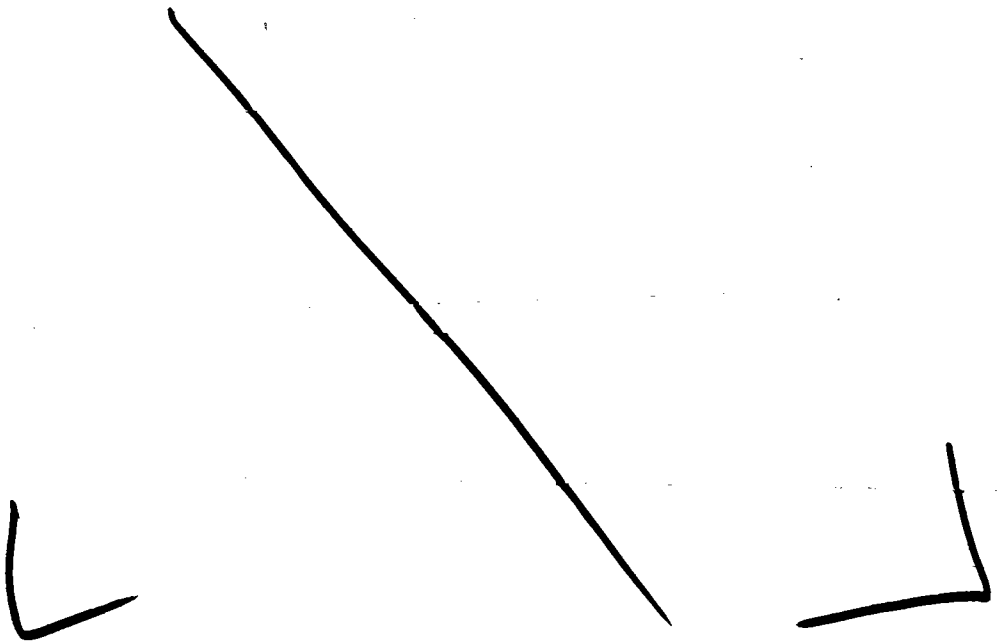

2.6 Analytical

2.6.1 What bioanalytical methods are used to assess concentrations?

Results of bioanalytical method were reviewed from the Study 083, exposure comparison between IV infusion and oral doses, as a representative clinical study.

Conivaptan was measured by HPLC/ . It was reported that there was no particular interfering peak in the study samples.

There were two calibration curves with different limit of quantification (LOQ): BAM-085 for and BAM-009 for range.

The results for accuracy and precision with quality control samples were acceptable. For examples, mean accuracy results ranged from -4.3% to 3.4%, and mean precision ranged from 1.6% to 8.3% for quality control samples from BAM-009

Results of intra-day and inter-day precision were summarized in Table 31.

Table 31 Results of intra- and inter-day precision

level (ng/ml)	pooled intra-day precision (%)	inter-day precision (%)
	[redacted]	

3 Labeling Comments

The sponsor will update the current NDA with supplement data on safety and efficacy after the current review cycle and thus labeling is expected to be updated significantly with the supplement. Therefore, labeling will be reviewed with the update.

21 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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