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RESEARCH**

APPLICATION NUMBER:

22-016

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

| | |
|-------------------------------------|---|
| NDA | 22-016 |
| Submission Date(s) | August 25, 2006 |
| Brand Name | Vaprisol® |
| Generic Name | Conivaptan IV |
| Reviewer | Sang M. Chung, Ph.D. |
| Team Leader | Hae-Young Ahn, Ph.D. |
| OCP Division | Division of Clinical Pharmacology II |
| OND division | Division of Metabolism and Endocrine Products |
| Sponsor | Astellas |
| Submission Type | Response to an AE letter |
| Formulation; Strength(s) | IV solution; 20mg in 4 ml ampoules |
| Indication | Hypervolemic hyponatremia treatment |

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed an amendment to NDA22-016 (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

The sponsor submitted the original NDA 21-697 for Vaprisol[®] with the proposed indication of euvolemic or hypervolemic hyponatremia treatment in hospitalized patients. The Agency approved Vaprisol[®] for the indication of euvolemic hyponatremia treatment on December 29, 2005. For the indication of hypervolemic hyponatremia treatment, the Agency administratively unbundled the original application into NDA 22-016 with an approvable letter indicating that additional analysis is needed on hypervolemic hyponatremia patients with and without underlying congestive heart failure (CHF) because of imbalance in cardiac related adverse events in the sub-population.

This submission is to address issues in the AE letter and the sponsor conducted the conivaptan systemic exposure comparability across sub-patient populations with volume (i.e., euvolemic vs. hypervolemic) and CHF (with and without) status to support insignificant effect of CHF on hypervolemic hyponatremia treatment.

The clinical pharmacology issues are addressed based on the Study report of R087-CL-080 and the study was a 4-day, open-label, multicenter study of intravenous YM087 in patients with euvolemic or hypervolemic hyponatremia for the clinical efficacy, safety, and pharmacokinetic report. Patients received 20mg loading dose over 30 minutes (3.33ml/min) followed by either 4-day continuous infusion (0.175 ml/min) of 20mg/day or 40mg/day. The infusion site was changed every 24 hours. Blood samples were collected by two designs; rich sampling or sparse sampling. For the rich sampling, blood samples were obtained at 0, 0.5 (at the end of loading dose), 1, 4, 24 (Day 1), 48 (Day 2), 72 (Day 3), 96 (Day 4), 97, 98, 103, 108, and 120 hours after the start of dosing in 18 patients. In addition, blood samples were obtained around Day 11 after the dosing in some of the patients. For the sparse sampling, about 5 blood samples per patient were collected at 0, 0.5, 72, 96, and 240 hours after the start dosing in 188 patients. Number of patients in each sub-group is summarized in Table 1.

Table 1 Number of patients in each sub-group (sub-group was based on the source files of econc.xpt and edata080.xpt by the reviewer)

| | Total number of subject | euvolemic | | hypervolemic | |
|-----------------|-------------------------|-----------|----------|--------------|----------|
| | | 20mg/day | 40mg/day | 20mg/day | 40mg/day |
| Rich sampling | 18 | 6 | 3 | 6 | 3 |
| Sparse sampling | 188 | 14 | 124 | 8 | 42 |

Conivaptan plasma concentration-time profiles are shown in Figure 1 and pharmacokinetic parameters are summarized in Table 2. The sponsor included patients by per protocol in the analysis and the reviewer's analysis included all the patients under any treatment. Therefore, there were a few inconsistencies in number of patients by sub-groups and total patients among data.

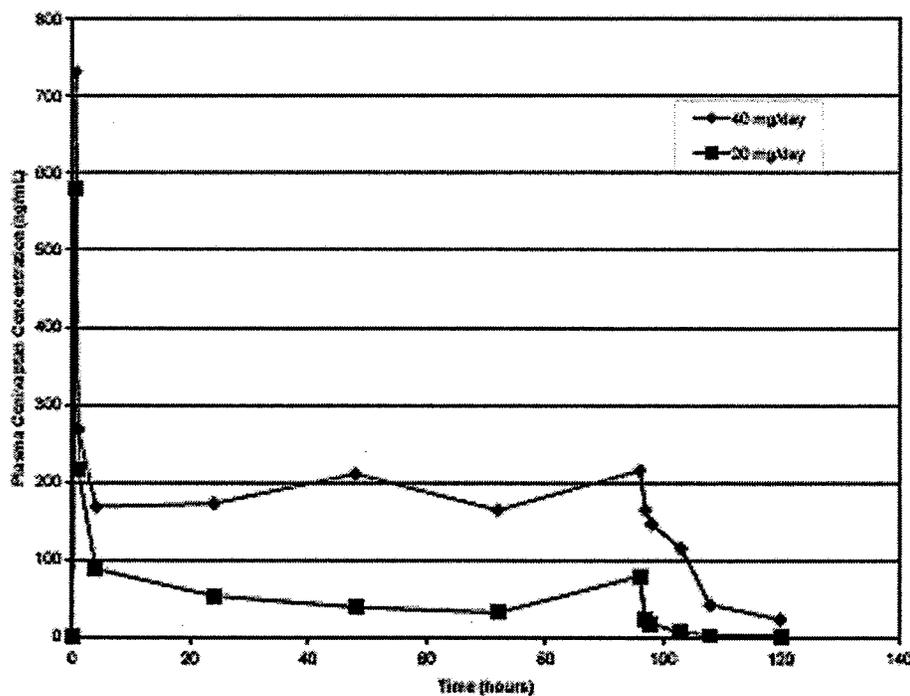


Figure 1 Median conivaptan plasma concentration-time profiles from the rich sampling

Table 2 Conivaptan pharmacokinetic parameters from the rich sampling

| Parameter | Study Population Bases | | | |
|---------------------------------------|------------------------|-------------------|-----------------------------|-------------------|
| | PK-Rich Patients | | PK-Rich Geriatric Patients† | |
| | 20 mg IV YM087 | 40 mg IV YM087 | 20 mg IV YM087 | 40 mg IV YM087 |
| | n = 8 | n = 8 | n = 7 | n = 7 |
| AUC_{0-inf} (hr*ng/mL) | | | | |
| Mean | 6995.90 | 30771.39 | 7496.26 | 31477.18 |
| SD | 3787.658 | 25586.100 | 3794.816 | 27551.902 |
| Median | 6199.77 | 21487.37 | 6213.85 | 17143.87 |
| Range | 2662.8 – 13956.9 | 8595.2 – 85725.8 | 2662.8 – 13956.9 | 8595.2 – 85725.8 |
| Geo Mean | 6129.37 | 23646.41 | 6641.99 | 23349.80 |
| t_{1/2} (hr) | | | | |
| Mean ± SD | 5.30 ± 1.922 | 10.19 ± 6.508 | 5.55 ± 1.932 | 8.43 ± 4.531 |
| Median | 5.26 | 8.12 | 5.47 | 7.36 |
| Range | 3.3 – 9.3 | 4.1 – 22.5 | 3.3 – 9.3 | 4.1 – 15.1 |
| Geo Mean | 5.03 | 8.55 | 5.29 | 7.45 |
| K_{e1} (1/hr) | | | | |
| Mean ± SD | 0.144 ± 0.045 | 0.095 ± 0.054 | 0.137 ± 0.044 | 0.104 ± 0.051 |
| Median | 0.132 | 0.086 | 0.126 | 0.094 |
| Range | 0.074 – 0.207 | 0.030 – 0.169 | 0.074 – 0.207 | 0.045 – 0.169 |
| Geo Mean | 0.137 | 0.081 | 0.131 | 0.093 |
| CL (L/hr) | | | | |
| Mean ± SD | 18.67 ± 10.357 | 9.52 ± 6.260 | 17.24 ± 10.308 | 9.89 ± 6.669 |
| Median | 16.13 | 8.73 | 16.09 | 10.50 |
| Range | 7.2 – 37.6 | 2.1 – 20.9 | 7.2 – 37.6 | 2.1 – 20.9 |
| Geo Mean | 16.31 | 7.61 | 15.06 | 7.71 |

Study Population Base(s):

† PK Rich and Geriatric Patients (Aged 65 Years Old or Older)

Abbreviations: AUC_{0-inf} = area under the concentration time curve from zero to infinity; CL = clearance;

Geo Mean = Geometric Mean; K_{e1} = Elimination Rate Constant; SD = standard deviation

Sources: Tables 13.9-T2.1.1 and 13.9-T2.1.2

Median plasma conivaptan concentration profiles for the 20 mg/day and 40 mg/day dose regimens for all PK-rich patients are shown in Figure 6.

In general, conivaptan showed non-linear pharmacokinetics reflected by clearance and half-life changes with different doses (Table 2 and Figure 2). In addition, between-subject-variability (BSV) was high in conivaptan plasma concentration-time profiles (Figure 2) and pharmacokinetic parameters (Table 2).

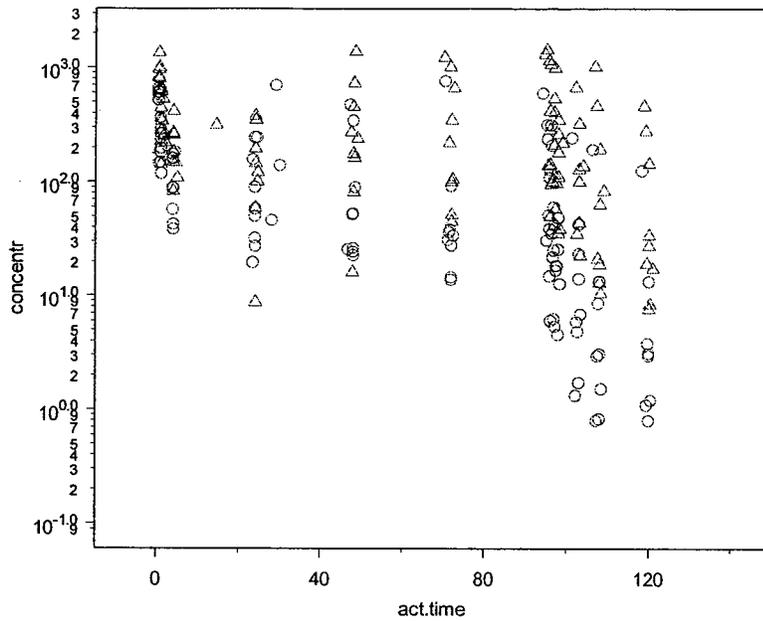


Figure 2 conivaptan plasma concentration-time profiles in the rich sampling patients (circle for 20mg/day; n=9 and triangle for 40mg/day; n=9)

The results from the sparse sampling were comparable to those from the rich sampling. Conivaptan concentrations were measured at 240 hours after the start of dosing in most of the patients and there were measurable levels in many patients at that time; 9 out of 22 patients at 20mg/day dosing and 86 out of 165 patients at 40mg/day dosing (Figure 3).

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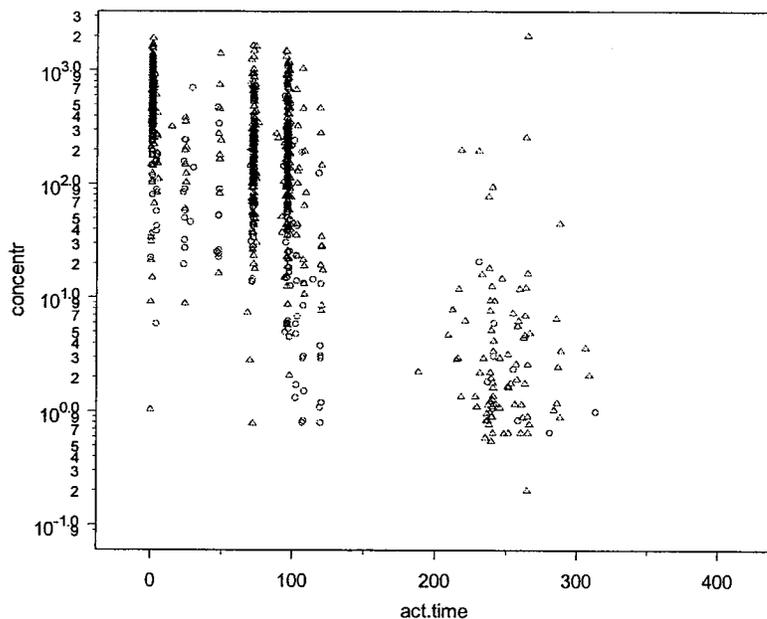


Figure 3 Conivaptan plasma concentration-time profiles in the sparse sampling (n=22 for 20mg/day, n=166 for 40mg/day)

The sponsor concluded no significant difference in conivaptan pharmacokinetics between euvolemic and hypervolemic hyponatremia patients. However, there was no presentation of the results on the analysis for the issue in this amendment. This reviewer conducted the following analyses using data files of econc.xpt, efarm.xtp, and edata080.xpt.

Although BSV of conivaptan plasma concentrations and AUCs was lower in hypervolemic patients compared to those of euvolemic patients (Figure 4 and 5), the number of subjects was small (Table 1) and thus data were not sufficiently large enough to draw for any conclusion based on data from the rich sampling patients.

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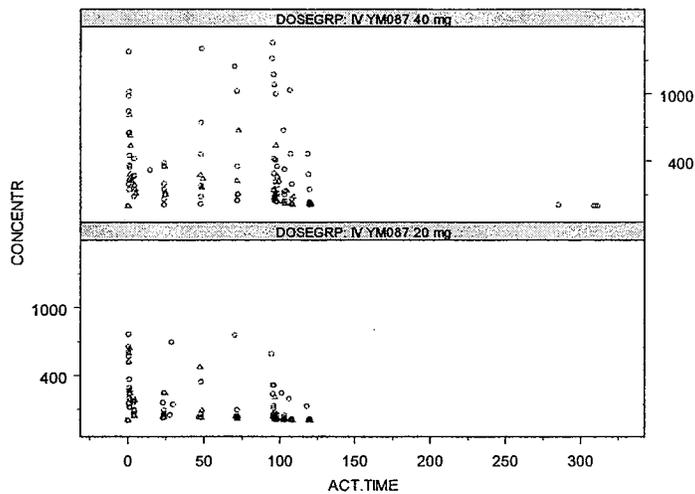


Figure 4 Conivaptan plasma concentration-time profiles by sub-groups in the rich sampling; circles for euvolemic patients, and triangle for hypervolemic patients

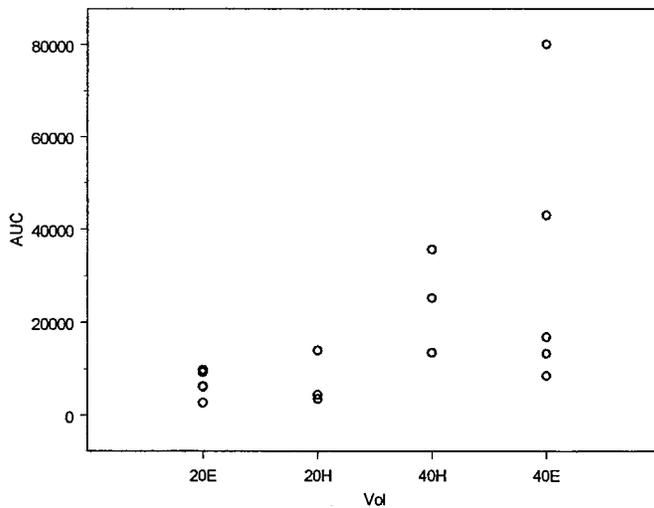


Figure 5 AUC by sub-groups; 20E, 20H, 40H, and 40E indicate 20mg/day in euvolemic (n=5), 20mg/day in hypervolemic (n=3), 40mg/day in euvolemic (n=5), and 40mg/day in hypervolemic (n=3), respectively.

Conivaptan plasma concentrations in sparse sampling are shown in Figure 6 and 7, and the sampling was not intended to estimate the conventional time-averaged pharmacokinetic parameters mainly because of non-linearity of conivaptan with time (auto-metabolic inhibition) and doses. Plasma concentrations at the end of dosing (at 96 hour after start dosing) were selected as a best alternative pharmacokinetic parameter assuming it represents an apparent steady-state. The summary statistics on C_{96} is in Table 3 and there was no significant difference in the parameter between euvolemic and

hypervolemic patients in two doses. Therefore, it is concluded that there is no significant difference in pharmacokinetics between the sub-patient populations.

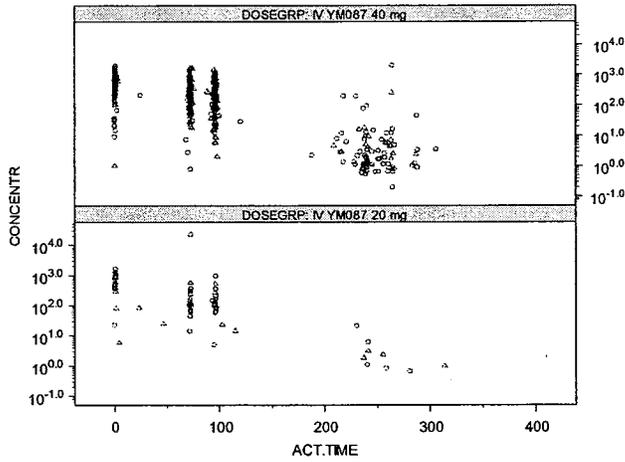


Figure 6 Plasma conivaptan concentrations in sparse sampling; circle for euvolemic and triangle for hypervolemic patients

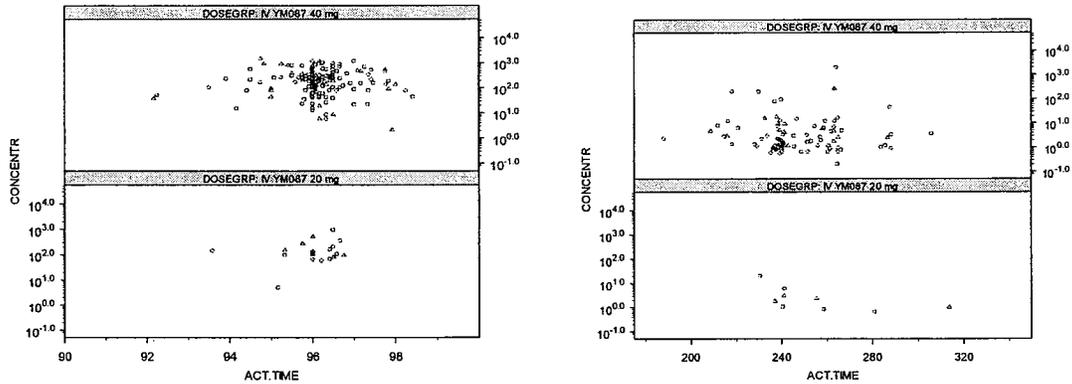


Figure 7 Plasma conivaptan concentrations at Day 4 and in the elimination phase (left) and 10 days after the start of dosing (right)

Table 3 Concentration at 96 hour after the start dosing (C_{96}) by sub-groups with sparse sampling

| | 20mg/day | | 40mg/day | |
|---------------------|-------------------|-------------------|-------------------|-------------------|
| | Euvolemic | Hypervolemic | Euvolemic | Hypervolemic |
| N | 14 | 8 | 124 | 42 |
| C_{96} (ng/ml) | 181.3 (232.35) | 191.9 (155.86) | 292.3 (299.91) | 316.9 (327.62) |

Cardiac related adverse event was the major concern in the AE letter and the pharmacokinetic comparison of conivaptan across sub-groups such as patients with CHF and without CHF is one of important supporting analyses for the issue. The sponsor submitted results of the analysis (December 4, 2006, ATTACHMENT) as a response to the reviewer's request (November 29, 2006). A total of 58 patients were identified as CHF who had PK sampling and it was concluded that conivaptan pharmacokinetics in patients with CHF were comparable to those of patients without CHF (Table 4).

Table 4 Summary of conivaptan concentration in hyponatremia patients (Study 087-CL-080)

| Parameter | IV Conivaptan Hypervolemic Patients with or without CHF | | IV Conivaptan Hypervolemic or Euvolemic Patients with CHF | | IV Conivaptan Hypervolemic Patients with CHF | |
|--|---|-------------|---|-------------|--|-------------|
| | 20 mg/day§ | 40 mg/day§ | 20 mg/day§ | 40 mg/day§ | 20 mg/day§ | 40 mg/day§ |
| Conivaptan concentration at 0.5 hrs† (ng/mL) | | | | | | |
| n | 11 | 42 | 8 | 48 | 7 | 26 |
| Mean±SD | 678 ± 234.2 | 692 ± 259.6 | 685 ± 284.4 | 700 ± 289.6 | 625 ± 246.8 | 706 ± 242.7 |
| Conivaptan concentration at 96 hrs (ng/mL) | | | | | | |
| n | 10 | 44 | 8 | 50 | 7 | 27 |
| Mean±SD | 162 ± 144.0 | 313 ± 320.7 | 163 ± 160.4 | 352 ± 315.3 | 172 ± 171.3 | 337 ± 382.2 |

Lower limit of quantitation: 0.5 ng/mL.

SD: standard deviation; $t_{1/2}$: elimination half-life; CL: clearance

§ Dosing regimen included a 20 mg loading dose.

† End of the loading dose.

Source: Appendix A Tables 9.1.1, 10.1.1 (from August 25, 2006 Complete Response) and Table 2006.12.4 (enclosed)

The sponsor also concluded that age was not a significant covariate to the conivaptan pharmacokinetics based on data in Table 5 and 6. In the analysis, sub-groups were categorized by all patients and geriatric patients. The sub-groups must be categorized by age (i.e., less than 65 vs. geriatrics) because the age effect can be a function of sample size in the sponsor's approach and thus can provide a false negative effect of age on pharmacokinetics. For example, the sponsor concluded no age effect in Table 5 even if number of patient with age less than 65 was one. Therefore, the sponsor's approach based on Table 5 and 6 was not acceptable.

Table 5 Pharmacokinetics by age from the rich sampling

| Parameter | Study Population Bases | | | |
|-------------------------------------|----------------------------|----------------------------|-----------------------------|----------------------------|
| | PK-Rich Patients | | PK-Rich Geriatric Patients† | |
| | 20 mg IV YM087 n = 8 | 40 mg IV YM087 n = 8 | 20 mg IV YM087 n = 7 | 40 mg IV YM087 n = 7 |
| AUC_{0-∞} (hr*ng/mL) | | | | |
| Mean | 6995.90 | 30771.39 | 7496.26 | 31477.18 |
| SD | 3787.658 | 25586.100 | 3794.816 | 27551.902 |
| Median | 6199.77 | 21487.37 | 6213.85 | 17143.87 |
| Range | 2662.8 – 13956.9 | 8595.2 – 85725.8 | 2662.8 – 13956.9 | 8595.2 – 85725.8 |
| Geo Mean | 6129.37 | 23646.41 | 6641.99 | 23349.80 |
| t_{1/2} (hr) | | | | |
| Mean ± SD | 5.30 ± 1.922 | 10.19 ± 6.508 | 5.55 ± 1.932 | 8.43 ± 4.531 |
| Median | 5.26 | 8.12 | 5.47 | 7.36 |
| Range | 3.3 – 9.3 | 4.1 – 22.5 | 3.3 – 9.3 | 4.1 – 15.1 |
| Geo Mean | 5.03 | 8.55 | 5.29 | 7.45 |
| K_e (1/hr) | | | | |
| Mean ± SD | 0.144 ± 0.045 | 0.095 ± 0.054 | 0.137 ± 0.044 | 0.104 ± 0.051 |
| Median | 0.132 | 0.086 | 0.126 | 0.094 |
| Range | 0.074 – 0.207 | 0.030 – 0.169 | 0.074 – 0.207 | 0.045 – 0.169 |
| Geo Mean | 0.137 | 0.081 | 0.131 | 0.093 |
| CL (L/hr) | | | | |
| Mean ± SD | 18.67 ± 10.357 | 9.52 ± 6.260 | 17.24 ± 10.308 | 9.89 ± 6.669 |
| Median | 16.13 | 8.73 | 16.09 | 10.50 |
| Range | 7.2 – 37.6 | 2.1 – 20.9 | 7.2 – 37.6 | 2.1 – 20.9 |
| Geo Mean | 16.31 | 7.61 | 15.06 | 7.71 |

Study Population Base(s):
 † PK Rich and Geriatric Patients (Aged 65 Years Old or Older)
 Abbreviations: AUC_{0-∞} = area under the concentration time curve from zero to infinity; CL = clearance;
 Geo Mean = Geometric Mean; K_e = Elimination Rate Constant; SD = standard deviation
 Sources: Tables 13.9-T2.1.1 and 13.9-T2.1.2

Table 6 Pharmacokinetics by age from the sparse sampling

| | All Patients | | All Geriatric Patients† | |
|--------------------------------|-------------------|-------------------|-------------------------|-------------------|
| | 20 mg IV YM087 | 40 mg IV YM087 | 20 mg IV YM087 | 40 mg IV YM087 |
| Hour 0 | | | | |
| n | n = 31 | n = 173 | n = 27 | n = 134 |
| Mean ± SD | 26.34 ± 99.717 | 17.31 ± 133.531 | 30.24 ± 106.540 | 6.88 ± 58.778 |
| Median | 0.00 | 0.00 | 0.00 | 0.00 |
| Range | 0.00 – 440.80 | 0.00 – 1396.39 | 0.00 – 440.80 | 0.00 – 663.89 |
| Hour 0.5 | | | | |
| n | n = 31 | n = 170 | n = 27 | n = 132 |
| Mean ± SD | 733.33 ± 322.688 | 701.39 ± 342.739 | 683.41 ± 281.775 | 690.33 ± 324.485 |
| Median | 659.36 | 679.51 | 653.75 | 656.31 |
| Range | 144.47 – 1587.55 | 0.00 – 1910.84 | 144.47 – 1274.29 | 0.00 – 1910.84 |
| Hour 0.5 – Loading Dose | | | | |
| n | n = 201 | | n = 159 | |
| Mean ± SD | 706.32 ± 339.139 | | 689.16 ± 316.812 | |
| Median | 670.62 | | 653.75 | |
| Range | 0.00 – 1910.84 | | 0.00 – 1910.84 | |
| Hour 72 | | | | |
| n | n = 30 | n = 173 | n = 26 | n = 133 |
| Mean | 863.70 | 297.43 | 972.17 | 300.94 |
| SD | 3972.609 | 302.507 | 4267.511 | 320.670 |
| Median | 96.64 | 189.32 | 96.64 | 187.57 |
| Range | 13.68 – 21879.0 | 0.00 – 1650.53 | 13.68 – 21879.0 | 0.00 – 1650.53 |
| Hour 96 | | | | |
| n | n = 30 | n = 172 | n = 26 | n = 134 |
| Mean ± SD | 175.99 ± 195.952 | 308.32 ± 321.105 | 178.20 ± 202.597 | 315.01 ± 323.742 |
| Median | 117.55 | 215.66 | 117.55 | 214.63 |
| Range | 4.92 – 938.30 | 2.06 – 1999.30 | 14.67 – 938.30 | 2.06 – 1999.30 |
| Hour 240 | | | | |
| n | n = 20 | 159 | n = 17 | n = 123 |
| Mean ± SD | 1.86 ± 4.619 | 3.34 ± 10.600 | 2.05 ± 4.985 | 2.99 ± 8.600 |
| Median | 0.00 | 0.77 | 0.00 | 0.77 |
| Range | 0.00 – 20.44 | 0.00 – 93.94 | 0.00 – 20.44 | 0.00 – 76.93 |

Study Population Base(s): All Patients and All Geriatric Patients (Aged 65 Years Old or Older)
 Abbreviations: SD = standard deviation
 Sources: Tables 13.9-T1.1.1 and 13.9-T1.1.2

The data from the sparse sampling patients were recaptured by the age and doses as showed in Table 7 and it indicates no significant difference in convaptan pharmacokinetics by age.

Table 7 Conivaptan pharmacokinetics by age

| | 20mg/day | | 40mg/day | |
|-----------------|-------------------|--------------------------|-------------------|--------------------------|
| | Less than 65 | Equal or greater than 65 | Less than 65 | Equal or greater than 65 |
| N | 3 | 18 | 37 | 126 |
| C ₉₆ | 205.5 (178.03) | 181.4 (214.65) | 288.6 (318.14) | 301.4 (303.94) |

In conclusion, there was no significant difference in conivaptan pharmacokinetic between euvolemic and hypervolemic populations and conivaptan pharmacokinetics was not significantly different in geriatrics compared to that of patients' age less than 65 years.

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Attachment

From: Raineri, Donald [mailto:Don.Raineri@us.astellas.com]
Sent: Monday, December 04, 2006 5:15 PM
To: Mahoney, Karen M (CDER/DMEDP)
Cc: Johnson, Jennifer; Chung, Sang
Subject: RE: Heart failure status of 080 hypervolemic patients who had PK sampling

Dear Dr. Mahoney,

Attached you will find our response to your request (below) for the number of hypervolemic patients with CHF who had PK sampling in Study CL-087-080.

Please do not hesitate to contact me if you require additional information.

Kind regards,
Don

Donald L. Raineri, Pharm.D.
Senior Director, Regulatory Affairs
Astellas Pharma US, Inc.
(847) 405-1604 (office)
(847) 317-7286 (fax)
donald.raineri@us.astellas.com

Dear Dr. Mahoney:

The following is our response to your November 29, 2006 e-mail request regarding the number of hypervolemic patients with CHF who had PK sampling in Vaprisol® Study 087-CL-080.

In Study 087-CL-080:

- 69 patients were hypervolemic (14 in the 20 mg/day dose group and 55 in the 40 mg/day dose group)
- Of these 69 hypervolemic patients, 43 had CHF and 26 were non-CHF patients
- In the 40 mg/day dose group there were 55 hypervolemic patients (PK data available for 42), of which 35 had CHF and 20 were non-CHF patients
- In the 20 mg/day dose group there were 14 hypervolemic patients (PK data available for 11), of which 8 had CHF and 6 were non-CHF patients.

Table 1 (Summary of Conivaptan Concentration in Hyponatremia Patients, Study 087-CL-080) tabulates the plasma concentration of conivaptan at 0.5 and 96 hours for (i) hypervolemia, (ii) CHF and (iii) hypervolemia with CHF populations. These data indicate that conivaptan concentration was similar at 0.5 and 96 hours irrespective of the patient's underlying status, including patients with hypervolemia and CHF, and supports the conclusion that exposure in patients with hypervolemia and CHF is not higher than in euvolemic patients. The number of patients with hypervolemia and CHF and rich PK sampling was 2 subjects in both the 20 and 40 mg dose groups and was considered too small to draw meaningful conclusions.

Also enclosed is a table of conivaptan concentrations in patients with hypervolemic hyponatremia and CHF. [Table 2006.12.4 – Summary of Plasma YM087 Concentrations (ng/mL) at 0.5 and 96 Hour in CHF and Hypervolemic Patients; Study 087-CL-080] and a listing of patients with CHF (including conivaptan concentrations) [Listing 2006.12.4 – Listing of Plasma YM087 Concentrations (ng/mL) in CHF Patients; Study 087-CL-080] irrespective of their underlying volume status.

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Table 1: Summary of Conivaptan Concentration in Hyponatremia Patients, Study 087-CL-080

| Parameter | IV Conivaptan Hypervolemic Patients with or without CHF | | IV Conivaptan Hypervolemic or Euvolemic Patients with CHF | | IV Conivaptan Hypervolemic Patients with CHF | |
|--|---|-------------|---|-------------|--|-------------|
| | 20 mg/day§ | 40 mg/day§ | 20 mg/day§ | 40 mg/day§ | 20 mg/day§ | 40 mg/day§ |
| Conivaptan concentration at 0.5 hrs† (ng/mL) | | | | | | |
| n | 11 | 42 | 8 | 48 | 7 | 26 |
| Mean±SD | 678 ± 234.2 | 692 ± 259.6 | 685 ± 284.4 | 700 ± 289.6 | 625 ± 246.8 | 706 ± 242.7 |
| Conivaptan concentration at 96 hrs (ng/mL) | | | | | | |
| n | 10 | 44 | 8 | 50 | 7 | 27 |
| Mean±SD | 162 ± 144.0 | 313 ± 320.7 | 163 ± 160.4 | 352 ± 315.3 | 172 ± 171.3 | 337 ± 382.2 |

Lower limit of quantitation: 0.5 ng/mL.

SD: standard deviation; t_{1/2}: elimination half-life; CL: clearance

§ Dosing regimen included a 20 mg loading dose.

† End of the loading dose.

Source: Appendix A Tables 9.1.1, 10.1.1 (from August 25, 2006 Complete Response) and Table 2006.12.4 (enclosed)

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/s/

Sang Chung
12/18/2006 09:21:35 AM
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Hae-Young Ahn
12/18/2006 09:40:45 AM
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