**Table 1**

**Estimates of hBNP Clearance at 6 Hours in 65 Evaluable Subjects with Congestive Heart Failure after an Intravenous Infusion Dose**

| Infusion | | | Infusion | | | Infusion | | |
|---|---|---|---|---|---|---|---|---|
| Subject ID | Rate μg/kg/min | Clearance mL/kg/min | Subject ID | Rate μg/kg/min | Clearance mL/kg/min | Subject ID | Rate μg/kg/min | Clearance mL/kg/min |
| 324-001 | 0.0300 | 5.58 | 369-002 | 0.0300 | 9.21 | 382-005 | 0.0300 | 15.05 |
| 324-002 | 0.0300 | 8.50 | 369-004 | 0.0150 | 6.98 | 382-008 | 0.0300 | 6.52 |
| 324-004 | 0.0300 | 6.89 | 369-006 | 0.0150 | 5.17 | 382-009 | 0.0150 | 5.12 |
| 352-001 | 0.0150 | 9.40 | 369-007 | 0.0150 | 6.63 | 382-011 | 0.0150 | 11.51 |
| 352-002 | 0.0150 | 6.57 | 369-008 | 0.0150 | 9.29 | 382-013 | 0.0150 | 6.64 |
| 352-004 | 0.0300 | 11.07 | 369-009 | 0.0300 | 4.69 | 470-001 | 0.0300 | 7.34 |
| 352-007 | 0.0300 | 9.78 | 369-011 | 0.0300 | 8.43 | 470-003 | 0.0150 | 7.80 |
| 352-008 | 0.0300 | 14.62 | 369-013 | 0.0150 | 6.29 | 487-001 | 0.0150 | 5.26 |
| 352-009 | 0.0150 | 8.20 | 369-015 | 0.0300 | 6.59 | 487-002 | 0.0150 | 4.95 |
| 352-010 | 0.0150 | 13.55 | 369-017 | 0.0300 | 8.24 | 488-003 | 0.0150 | 23.26 |
| 352-011 | 0.0075 | 14.91 | 369-019 | 0.0075 | 7.87 | 498-001 | 0.0150 | 4.64 |
| 352-012 | 0.0300 | 8.73 | 370-002 | 0.0300 | 9.09 | 498-002 | 0.0300 | 4.78 |
| 352-013 | 0.0300 | 15.05 | 370-003 | 0.0150 | 5.85 | 498-003 | 0.0300 | 5.05 |
| 357-001 | 0.0300 | 7.02 | 370-004 | 0.0150 | 3.02 | 503-003 | 0.0150 | 15.54 |
| 367-001 | 0.0150 | 7.02 | 370-005 | 0.0300 | 9.63 | 503-005 | 0.0300 | 9.71 |
| 367-002 | 0.0150 | 14.42 | 370-006 | 0.0150 | 7.83 | 523-002 | 0.0300 | 5.39 |
| 367-003 | 0.0150 | 4.80 | 373-002 | 0.0150 | 12.72 | 523-003 | 0.0150 | 4.86 |
| 367-004 | 0.0300 | 7.71 | 373-003 | 0.0150 | 7.82 | 532-001 | 0.0300 | 5.34 |
| 368-002 | 0.0150 | 9.23 | 373-004 | 0.0300 | 6.69 | 588-001 | 0.0300 | 7.29 |
| 368-003 | 0.0300 | 8.45 | 374-001 | 0.0150 | 2.98 | 588-002 | 0.0150 | 12.44 |
| 368-004 | 0.0150 | 11.66 | 382-001 | 0.0300 | 5.86 | 588-004 | 0.0150 | 12.80 |
| 368-007 | 0.0150 | 10.94 | 382-002 | 0.0150 | 6.93 | — | — | — |

Mean CL = 8.51 ml /kg/min; standard deviation of CL = 3.66 mL/kg/min

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Table 2

**Plasma hBNP Concentrations (pg/mL) at Baseline and 6 and 24 Hours for Subjects Evaluable at 24 Hours (n = 29)**

| Subject Number | $C_0$ | 6-Hour Concentration (n = 29) | 24-Hour Concentration (n = 29) |
|---|---|---|---|
| **0.015 μg/min/kg** | | | |
| 352001 | 1214 | 2809 | 1982 |
| 352002 | 928 | 3211 | 2986 |
| 352010 | 453 | 1560 | 1945 |
| 367002 | 321 | 1361 | 1865 |
| 368007 | 973 | 2344 | 1227 |
| 369008 | 752 | 2366 | 2005 |
| 370004 | 687 | 5661 | 1864 |
| 370006 | 630 | 2546 | 1878 |
| 374001 | 2053 | 7091 | 6730 |
| 382002 | 768 | 2931 | 1952 |
| 488003 | 1028 | 1673 | 1111 |
| 503003 | 836 | 1801 | 1933 |
| Mean | 887 | 2946 | 2290 |
| SD | 423 | 1655 | 1408 |
| **0.030 μg/min/kg** | | | |
| 324001 | 1017 | 6393 | 6882 |
| 324002 | 773 | 4303 | 4361 |
| 324004 | 1531 | 5882 | 3057 |
| 352007 | 1113 | 4179 | 2816 |
| 352008 | 1417 | 3469 | 3589 |
| 352012 | 1508 | 4945 | 3035 |
| 352013 | 615 | 2608 | 2530 |
| 367004 | 1391 | 5282 | 6285 |
| 368003 | 1332 | 4881 | 4083 |
| 369002 | 1253 | 4509 | 2977 |
| 369015 | 1601 | 6154 | 6981 |
| 370002 | 917 | 4216 | 3426 |
| 382001 | 956 | 6072 | 7475 |
| 283005 | 3228 | 5221 | 4589 |
| 470001 | 1596 | 5682 | 4494 |
| 532001 | 1315 | 6932 | 6219 |
| 588001 | 2505 | 6620 | 3517 |
| Mean | 1416 | 5138 | 4489 |
| SD | 612 | 1136 | 1595 |

Table 3

**Plasma CL at 6 and 24 Hours of Infusion for Subjects Evaluable at 24 Hours (n = 29)**

| Subject Number | Dose (μg/kg/min) | CL at 6 h (mL/kg/min) (n = 29) | CL at 24 h (mL/kg/min) (n = 29) |
|---|---|---|---|
| 324001 | 0.03 | 5.58 | 5.12 |
| 324002 | 0.03 | 8.50 | 8.36 |
| 324004 | 0.03 | 6.89 | 19.66 |
| 352001 | 0.015 | 9.40 | 19.53 |
| 352002 | 0.015 | 6.57 | 7.29 |
| 352007 | 0.03 | 9.78 | 17.62 |
| 352008 | 0.03 | 14.62 | 13.81 |
| 352010 | 0.015 | 13.55 | 10.05 |
| 352012 | 0.03 | 8.73 | 19.65 |
| 352013 | 0.03 | 15.05 | 15.67 |
| 367002 | 0.015 | 14.42 | 9.72 |
| 367004 | 0.03 | 7.71 | 6.13 |
| 368003 | 0.03 | 8.45 | 10.91 |
| 368007 | 0.015 | 10.94 | 59.06 |
| 369002 | 0.03 | 9.21 | 17.40 |
| 369008 | 0.015 | 9.29 | 11.97 |
| 369015 | 0.03 | 6.59 | 5.58 |
| 370002 | 0.03 | 9.09 | 11.96 |
| 370004 | 0.015 | 3.02 | 12.74 |
| 370006 | 0.015 | 7.83 | 12.02 |
| 374001 | 0.015 | 2.98 | 3.21 |
| 382001 | 0.03 | 5.86 | 4.60 |
| 382002 | 0.015 | 6.93 | 12.67 |
| 382005 | 0.03 | 15.05 | 22.04 |
| 470001 | 0.03 | 7.34 | 10.35 |
| 488003 | 0.015 | 23.26 | 180.72 |
| 503003 | 0.015 | 15.54 | 13.67 |
| 532001 | 0.03 | 5.34 | 6.12 |
| 588001 | 0.03 | 7.29 | 29.64 |
| | Mean: | 9.48 | 19.91 |
| | SD: | 4.37 | 32.66 |

Tables 4 shows the clinical characteristics of the 65 evaluable subjects at the 6-hour time point and table 5 shows the slopes and corresponding 95% confidence intervals obtained from the linear regression of CL

versus, weight, creatinine clearance, serum creatinine, age, cardiac index and pulmonary capillary wedge pressure.

**Table 4**

**Summary of Characteristics of 65 Subjects Evaluable at 6 Hours**

| Variable | Mean | Standard Deviation | Minimum | Maximum |
|---|---|---|---|---|
| WT (kg) | 80.0 | 19.2 | | |
| $CL_{cr}$ (mL/min) | 43.6 | 21.2 | | |
| CR (mg/dL) | 1.42 | 0.62 | | |
| Age (yrs) | 58.9 | 13.7 | | |
| CI (L/min/$m^2$) | 1.82 | 0.48 | | |
| PCWP (mm Hg) | 27.8 | 6.2 | | |

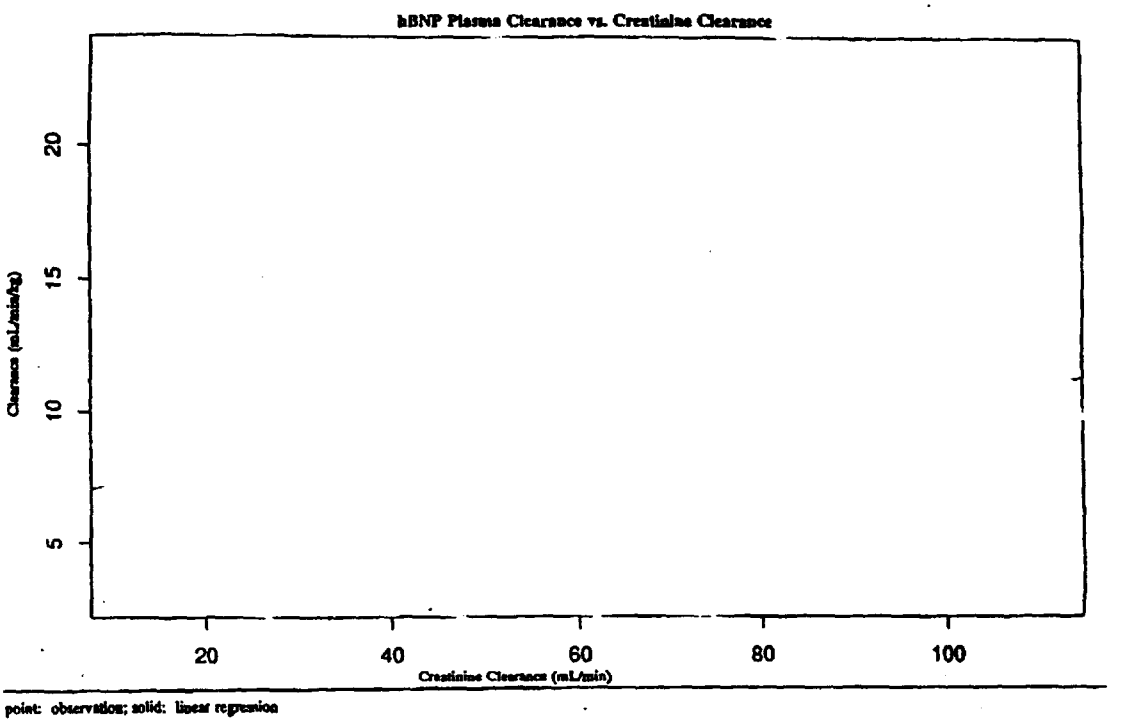
**Table 5**

**Estimates of Slope for Regression Equations of CL vs. WT, $CL_{cr}$, CR, Age, CI, and PCWP**

| Linear Regression | Slope | 95% Confidence Interval |
|---|---|---|
| CL vs. WT | -0.0229 | (-0.0696, 0.0238) |
| CL vs. $CL_{cr}$ | 0.0391 | (-0.0024, 0.0807) |
| CL vs. CR | -1.33 | (-2.74, 0.07) |
| CL vs. age | -0.053 | (-0.118, 0.012) |
| CL vs. CI | -1.41 | (-3.25, 0.43) |
| CL vs. PCWP | 0.059 | (-0.085, 0.203) |

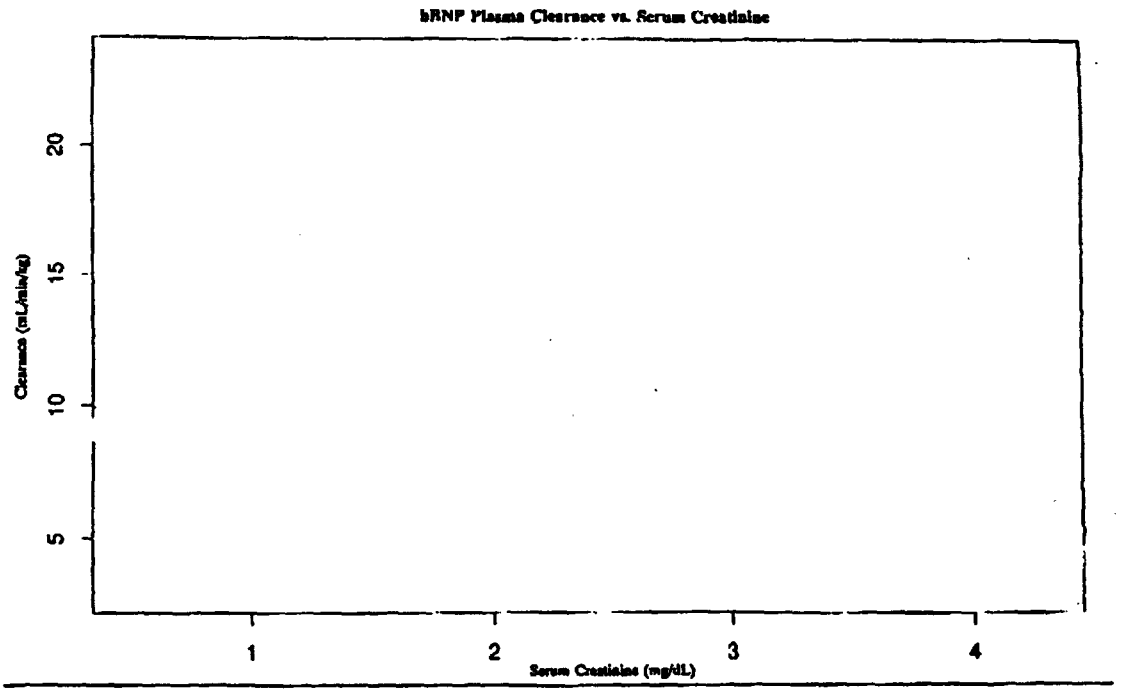
Since all the confidence intervals include zero, the null hypothesis cannot be rejected, therefore there is no significant correlation between clearance and any of the parameters listed. However, the sponsor does note that there may be a trend towards a correlation between plasma clearance and renal function, with plasma clearance decreasing with increasing serum creatinine and decreasing creatinine clearance. Figures 2 and 3 illustrate the trend.

Figure 2




point: observation; solid: linear regression

Figure 3




point: observation; solid: linear regression

Table 6 lists the mean clearances (and 95% confidence intervals) for varying disease states, ethnicity, gender and production method of administered hBNP. There were no statistically significant differences detected in the means of the groups with respect to the 4 variables disease state, ethnicity, gender and production method of Natrecor.

**Table 6**

**hBNP Clearance versus NYHA Classification, Ethnicity, Gender, and hBNP Production Method**

| | | | hBNP Clearance (mL/min/kg) | |
|---|---|---|---|---|
| Variable | Category | No. of Subjects | Mean | 95% Confidence Interval |
| NYHA | II | 1 | 4.72 | (−∞, +∞) |
| | III | 30 | 8.56 | (7.23, 9.91) |
| | IV | 34 | 8.57 | (7.25, 9.89) |
| Ethnicity | Black | 18 | 7.95 | (6.51, 9.40) |
| | White | 39 | 9.00 | (7.63, 10.36) |
| | Hispanic | 8 | 7.40 | (6.21, 8.59) |
| Gender | male | 45 | 8.84 | (7.69, 9.99) |
| | female | 20 | 7.78 | (6.27, 9.28) |
| Production Method | synthetic | 14 | 8.54 | (7.04, 10.05) |
| | recombinant | 51 | 8.50 | (7.40, 9.60) |

## Conclusions:

In this continuous infusion study of Natrecor at 0.015 and 0.03 µg/kg/min, following a loading dose of either 0.3 or 0.6 µg/kg/min, the clearance of Natrecor at 6 hours after the start of infusion was estimated at 8.51 ml/min/kg in subjects with congestive heart failure. The values of the clearances at 24 hours after the start of infusion were not to be relied upon for several reasons. The first reason is that many data points were excluded from the analysis (40 subjects). Additionally, there was a possibility of changes in the levels of endogenous hBNP with the improvement in the health of the patients over the course of the 24 hours treatment with Natrecor, which for the sake of the calculations of CL was assumed to be a constant.

No correlation was found between plasma clearance of Natrecor and body weight, creatinine clearance, serum creatinine, age, cardiac index, pulmonary capillary wedge pressure, disease state, method of production of Natrecor, ethnicity or gender. A trend was however reported for a decrease in plasma clearance as serum creatinine increases and as creatinine clearance decreases.



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## Appendix 8

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**Pharmacokinetic analysis of plasma concentrations of Natrecor hBNP from study 704.312 (IND ) "A dose-ranging study of Natrecor hBNP in the treatment of postoperative hypertension after coronary artery bypass surgery"**

**Study No. 704.312** **Volume 1.33** **Pages 59-118**
**Report No. 00283**

Report date: December 1st, 1997 (revised)

**Investigators:** Richard F. Davis, M.D. (Portland, Oregon)
Barbara Tardiff, M.D. (Durham, North Carolina)

**PK data analyzed by:** Nancy Sambol, PharmD (UCSF)
Chui Yu Liu

**Objectives:**

To determine the PK of hBNP at various dose levels.

**Medication:**

Natrecor: 5 mg lyophilized powder reconstituted in 5% dextrose in water (lot # G0003A1 and G0004A1). The Natrecor was produced by synthetic peptide methodology.

Placebo: 5% dextrose in water.

**Dose level:**

Subjects were treated with an IV bolus dose of Natrecor at 5 (n=3), 10 (n=4), 15 (n=4), 20 (n=4), or 25 µg/kg (n=8). One subject received 32.5 µg/kg Natrecor. A second bolus of Natrecor was administered during the 6-hour treatment evaluation period at the same or lower dose if the initial response was deemed inadequate or if hypertension recurred (if systolic pressure was greater than 140 mm Hg at 15 minutes

posttreatment or if the systolic pressure returned to 140 mm Hg 30 minutes after treatment).

**Study population:**

Twenty four subjects with postoperative hypertension after coronary bypass surgery.

**Design:**

Plasma samples for PK analysis were collected just before the first bolus dose and 1, 4, 8, 15, 30, 60, and 90 minutes after the first dose.

**Assay procedures:**

The methodology used was an ELISA that is described in Appendix 9. Briefly,

The LOQ was pg/ml.

**Data analysis:**

The model fit to the data (including the predose data) included a term for endogenous hBNP concentration and a two-compartment open model (with instantaneous input) to describe drug disposition. Endogenous hBNP and the PK parameters were estimated using the weighted least squares regression analysis of

The goodness of fit of the two-compartment model was compared to that of a one-compartment model using weighted squared residuals and the Akaike criteria. For fitting purposes, the primary parameters of the two-compartment model are the predicted predose concentration of the endogenous hBNP (Co), the rate constant of the first phase of the concentration decline (α), the rate constant of the second phase of the concentration decline ( ß), the rate constant from the peripheral compartment to the central compartment (k21), and the volume of

distribution of the central compartment (Vc). The secondary parameters are CL, t ½ α, t ½ ß and Vss.

The dependence of CL, Vc and Vss on dose was investigated by using linear regression with the null hypothesis that the slope is zero. If zero was included in the 95% confidence interval, the null hypothesis could not be rejected and there was no correlation between the parameters evaluated.

**Results:**

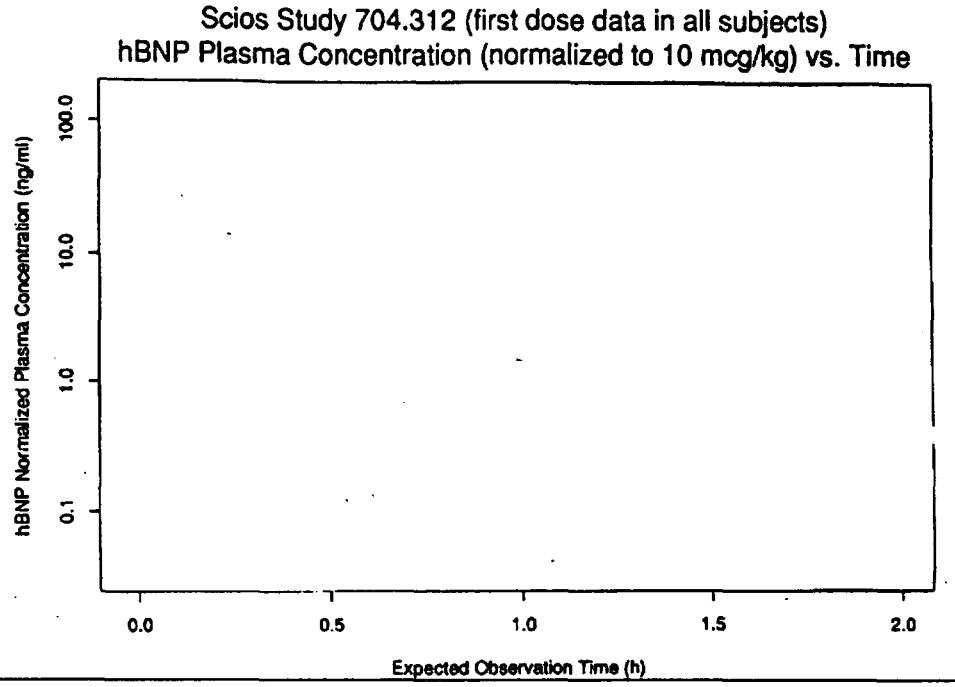
The data from all the subjects were described by a 2-compartment model. Data from 2 of the subjects were omitted from the analysis due to discrepancies in the plasma levels of Natrecor at various time points. The following is a list of the values for the mean PK parameters for the 22 evaluable subjects:

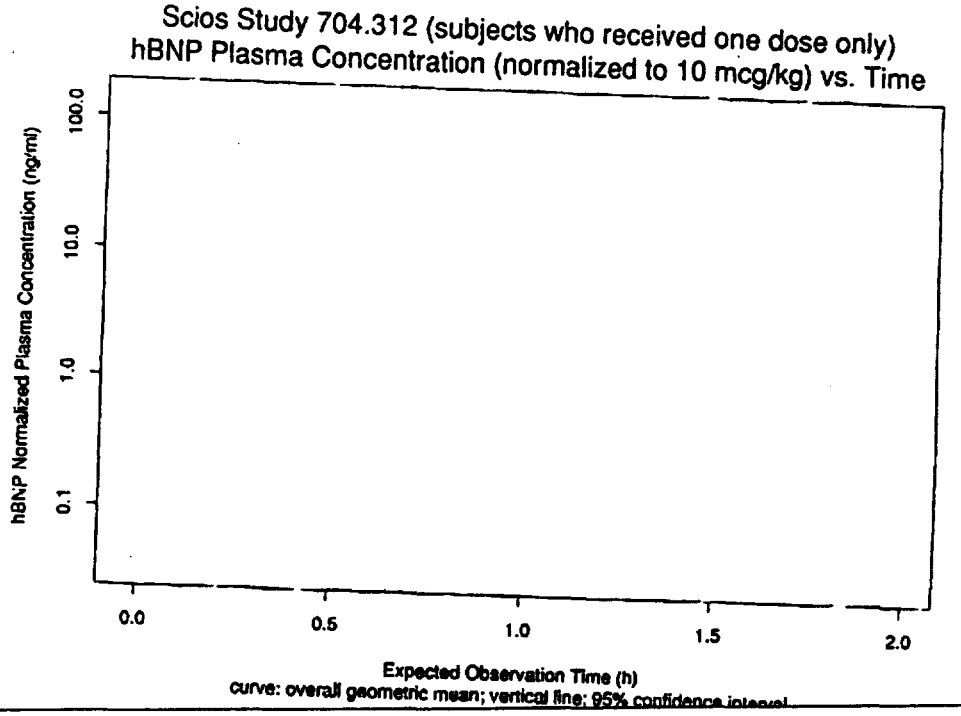
| | |
|---|---|
| CL (ml/min/kg) | 9.85 ± 0.76 |
| α ($min^{-1}$) | 0.537 ± 0.124 |
| t ½ α (min) | 2.35 ± 0.30 |
| (A/α)/(A/α+B/ß) | 34.0 ± 4.0 % |
| ß ($h^{-1}$) | 2.71 ± 0.23 |
| t ½ ß (h) | 0.307 ± 0.031 |
| (B/ß)/(A/α+B/ß) | 66.0 ± 4.0 % |
| k21 ($h^{-1}$) | 9.92 ± 2.07 |
| Vc (L/kg) | 0.75 ± 0.008 |
| Vss (L/kg) | 0.170 ± 0.018 |

The relationships of CL, Vc and Vss with dose were investigated and in each case, the slope of the line was not significantly different from zero, therefore, the null hypothesis could not be rejected and no significant correlation was established. The slopes (and 95% CI) are as follows:

| | |
|---|---|
| For CL vs. dose | -0.0219 (-0.2279, 0.1840) |
| For Vc vs. dose | -0.0002 (-0.0023, 0.0019) |
| For Vss vs. dose | -0.0001 (-0.0048, 0.1840) |

The following figures show the concentration time profile for Natrecor in study 704.312:


Scios Study 704.312 (first dose data in all subjects)
hBNP Plasma Concentration (normalized to 10 mcg/kg) vs. Time
hBNP Normalized Plasma Concentration (ng/ml)
100.0
10.0
1.0
0.1
0.0
0.5
1.0
1.5
2.0
Expected Observation Time (h)


Scios Study 704.312 (subjects who received one dose only)
hBNP Plasma Concentration (normalized to 10 mcg/kg) vs. Time
hBNP Normalized Plasma Concentration (ng/ml)
100.0
10.0
1.0
0.1
0.0
0.5
1.0
1.5
2.0
Expected Observation Time (h)
curve: overall geometric mean; vertical line: 95% confidence interval

**Conclusions:**

In the present study, a bolus dose of Natrecor at 5, 10, 15, 20 and 25 µg/kg/min was administered to patients with pulmonary hypertension after coronary artery bypass surgery. In all 24 patients, the data were fit to a 2-compartment model. 2 of the subjects were not used in the final analysis of the data due to discrepant data points.

The PK estimates obtained are as follows:

| | |
|---|---|
| CL (ml/min/kg) | 9.85 ± 0.76 |
| α ($min^{-1}$) | 0.537 ± 0.124 |
| t ½ α (min) | 2.35 ± 0.30 |
| (A/α)/(A/α+B/ß) | 34.0 ± 4.0 % |
| ß ($h^{-1}$) | 2.71 ± 0.23 |
| t ½ ß (h) | 0.307 ± 0.031 |
| (B/ß)/(A/α+B/ß) | 66.0 ± 4.0 % |
| k21 ($h^{-1}$) | 9.92 ± 2.07 |
| Vc (L/kg) | 0.75 ± 0.008 |
| Vss (L/kg) | 0.170 ± 0.018 |

These data are consistent with those obtained in subjects with CHF. Additionally, no dose-dependency was found between CL, Vc or Vss and dose.

## Appendix 9

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**Assay:**

The methodology used was an ELISA. The BNP enzyme immunoassay is an antigen displacement in which the constant region (Fc) specific anti-murine antibodies are used to capture BNP-specific mouse monoclonal antibodies onto microtiter wells.

Optical densities are measured using 2 instruments:

**System suitability:**

For the validation protocol, 2 analysts performed the assays on 2 separate days, therefore 4 separate assays were performed. The acceptance criteria for all the plates are that hBNP standard curve ½ maximum values be between 80-160 pg/ml. The working range of the curve was between 40-320 pg/ml. The curves of the optical density versus concentration obtained were not linear, therefore, the concentrations were log transformed in order to linearize the curves. This yielded curves with a negative slope and with a linear section that usually was between 40-320 pg/ml.

The ½ maximal values for the system suitability for the 2 analysts ranged from 98-114 for the 2 analysts on both test days.

A calibrator solution was tested in various positions on the plate in 4 separate assays. The mean value of the 21 calibrator aliquots was 158 pg/ml. The sponsor determined that the values for the calibrator solution would meet the criteria for suitability if the concentrations obtained for the calibrator was between 126-190 pg/ml (158 pg/ml ± 20%). In fact each aliquot of the calibrator solution was tested in triplicate wells during 2 days of testing and by 2 separate analysts. The values obtained in the 4 separate assays were between 153 and 177 pg/ml. This is within the limit of acceptability set forth by the sponsor.

*However, the reviewer thinks that a 20% margin around the mean of 158 pg/ml is too generous and perhaps a 10 or 15% deviation from this mean would be more rigorous. In fact the sponsor's results show that the greatest deviation from 158 pg/ml was in fact 12% (177 pg/ml on day 1 by analyst 1).*

**Instrument to instrument equivalency:**

A comparison of the 2 instruments
was carried out. The ½ maximal values for the plate readers and the mean calibrator values were within the acceptable margins set forth at the outset by the sponsor and described above.

**Accuracy:**

The accuracy of the method for determining plasma hBNP levels was determined. Three concentrations of hBNP were spiked into plasma diluent and were tested in triplicate on days 1 and 2. An analyst to analyst comparison and an instrument to instrument comparison were conducted. All data obtained were within % of the expected values. The method was deemed accurate for hBNP from 39-300 pg/ml.

## Precision:

The %CV range for analysts and instruments were as follows:

| | % CV | |
|---|---|---|
| | Day 1 | Day 2 |
| Analyst 1 | | |
| Analyst 2 | | |
| Instrument | | |

**Repeatability:**

The average values of 3 spiked samples were compared on days 1 and 2 for each analyst. These values were within % of the expected value *(although the sponsor states that the values would be acceptable within 20% of the expected values).*

Interplate consistency was tested and it was found that the assay test results did not vary significantly based on plate position. When one of

the samples was tested on seven different plate positions, the calculated hBNP concentrations were within 3 standard deviations from the mean concentration.

Three freeze-thaw cycles did not have a significant effect on the recovery of hBNP. The percent CV for all triplicates analyzed during the freeze-thaw cycle analysis was less than 10%, except for one sample where it was 22% (sample 5, but this sample was not used because the hBNP levels were below the working range of the assay.

**LOQ= pg/ml**

# Appendix 10

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**Pharmacodynamic analysis of Natrecor hBNP: estimated with study 704.309 and predicted for studies 704.305 and 704.307.**

The analysis was submitted on February 22nd, 1999.

The analysis was conducted by Chui Yu Liu under the direction of Nancy Sambol, Pharm.D. at UCSF.

The objective of the analysis was to develop a PK/PD model relating hBNP to PCWP using data from study 309, which was an intermittent bolus study. Study 305 (a bolus dose study) and study 307 (an infusion study) served to check the predictions of the model.

**Study design:**

For information regarding the details of study 309, 305 and 307, please refer to appendices 1, 2 and 5 of this review.

Briefly, study 309 was an intermittent bolus dose study where subjects with congestive heart failure received 5 μg/kg every 4 hours (n=15), 10 μg/kg every 4 hours (n=15) and 10 μg/kg every 6 hours (n=14).

Study 305 was an IV bolus dose study in subjects with congestive heart failure. Subjects received a single IV bolus of 0.3 (n=4), 1.0 (n=4), 3.0 (n=4), 10.0 (n=3), 15 (n=4) and 20 (n=4) μg/kg.

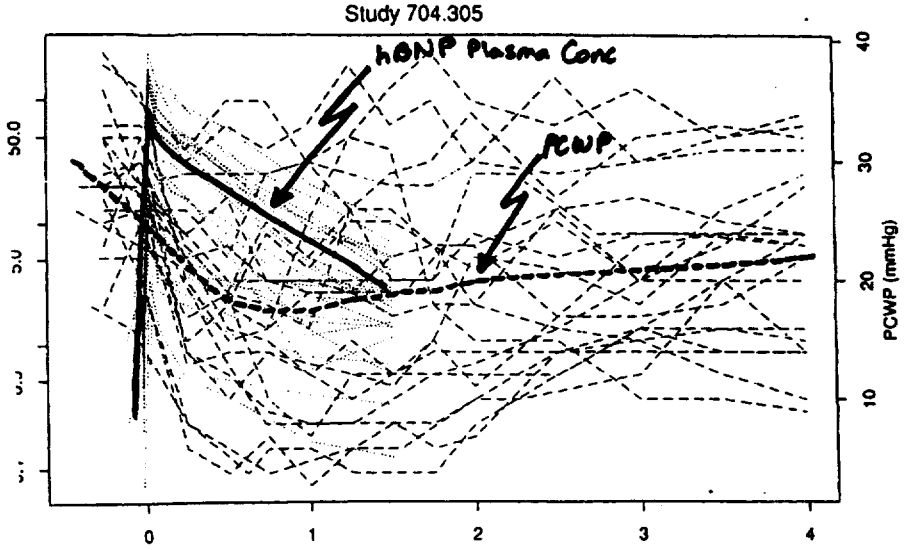
Study 307 was an IV infusion in subjects with congestive heart failure. Natrecor was given at an infusion rate of 0.003 μg/kg/min and was incrementally increased every 1.5 hours to 0.01 μg/kg/min then 0.03 μg/kg/min. Seven subjects were maintained at the 0.03 μg/kg/min dose for 3 hours but the other 13 subjects had their dose escalated to 0.1 μg/kg/min after 1.5 hours.

**Data analysis:**

For the data analysis, NONMEM was used.

For study 309, data were modeled to a two-compartment open model. The following figure shows the observed PCWP vs time in study 305. The data suggest that there is a delay in the effect relative to the concentration.

Figure 1. Observed hBNP Plasma Concentration and PCWP vs. Time
Study 704.305




dotted: hBNP plasma concentration, dashed: PCWP; thin: individual curve, thick: smooth curve

The plasma concentration were convolved to produce "effect site" concentrations, Ce, and the pharmacodynamics of study 309 were modeled as:

$$P=P_0 - Emax.Ce^{\gamma}/Ce^{\gamma}50+Ce^{\gamma}$$

Where P is the predicted PCWP, $P_0$ is the observed baseline PCWP, Emax is the maximum effect and $\gamma$ is the sigmoidicity factor. Keo was used to link C with Ce:

$$(Ce^{ss}=Cp^{ss}.(1-exp^{-keot})$$

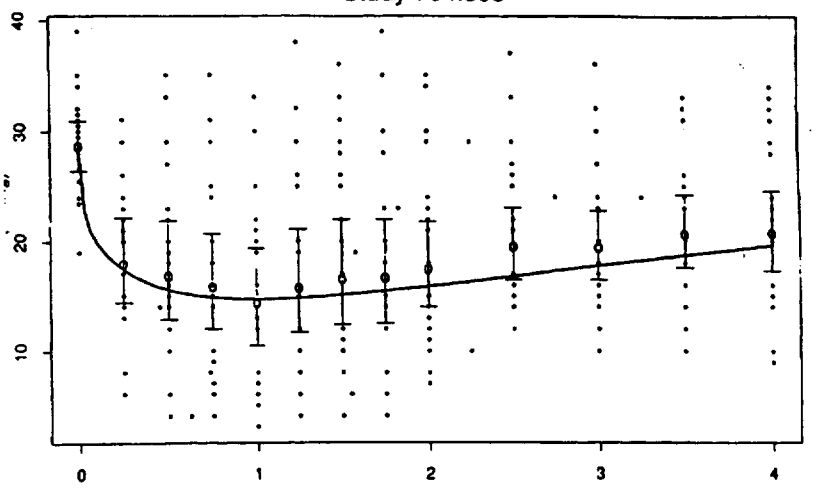
For the PD, the geometric means were estimated as follows:

- half-life related to keo= 2.45 hours (2.30, 2.61)
- Ce50= 6.35 ng/ml (5.77, 6.99)
- $\gamma$=1.03 (1.00, 1.06)

For predictions in study 305, PK parameters were estimated from the data from study 305, but population estimates of the PD parameters from study 309 were applied.

The following graph shows the predicted and the observed PCWP versus time. The predictions fell within the 95% confidence intervals, however, the PCWP values were overestimated.

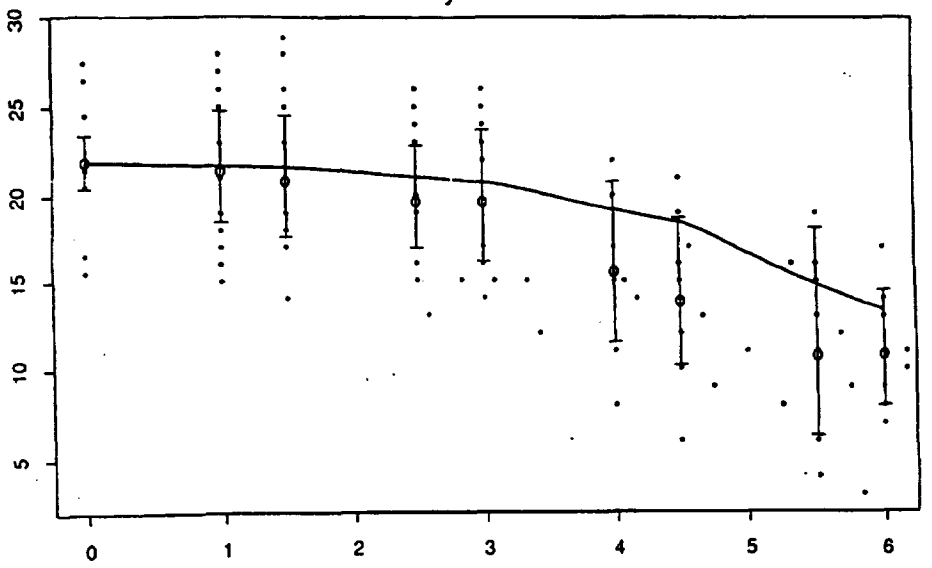
Figure 5. Observed and Predicted PCWP vs Time
Study 704.305




point: individual observation; circle: mean observation; vertical line: 95% confidence interval of mean; curve: mean prediction based on population pharmacokinetic parameter estimates of Study 704.305 and population pharmacodynamic parameter estimates of Study 704.309.

For predictions in study 307, population estimates of both PK and PD parameters of study 309 were used. Again, the predictions fell within the 95% confidence intervals of the data, however, in this case, the PCWP predictions were underestimated:

Figure 6. Observed and Predicted PCWP vs Time
Study 704.307

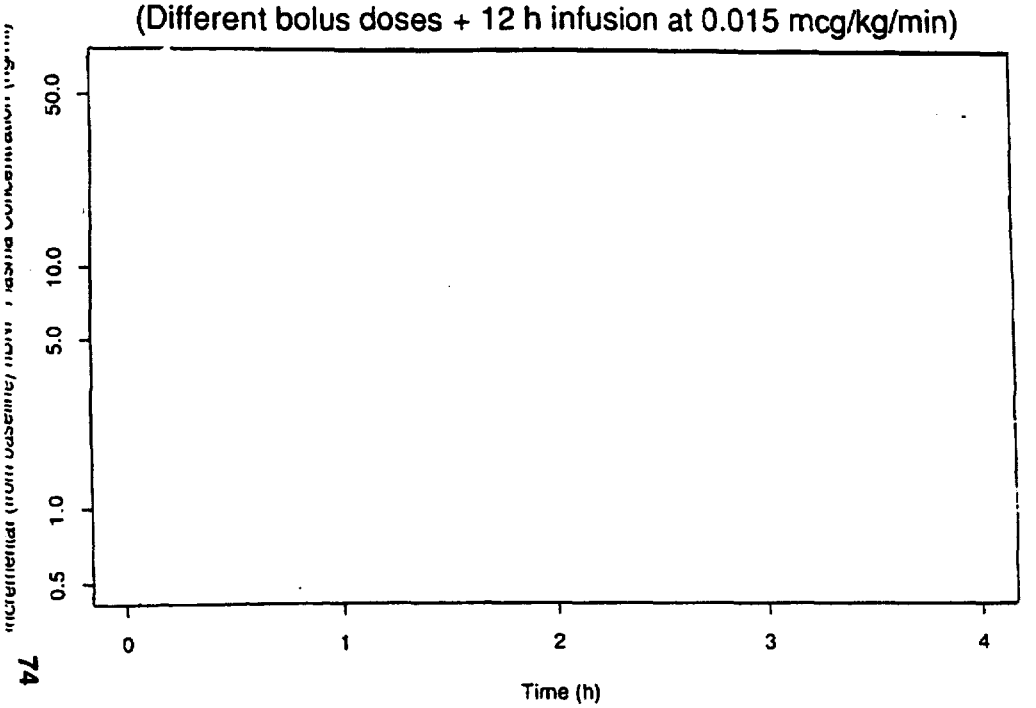



point: individual observation; circle: mean observation; vertical line: 95% confidence interval of mean; curve: mean prediction based on population pharmacokinetic and pharmacodynamic parameter estimates of Study 704.309.

Simulated values of PCWP for a 12-hour intravenous infusion (0.015 µg/kg/min) preceded by various intravenous bolus doses (from 0-6 µg/kg) were obtained using PK and PD parameter estimates of study 309.

Without a bolus dose, 90% of steady state was reached at 0.7 hours after starting the IV infusion.

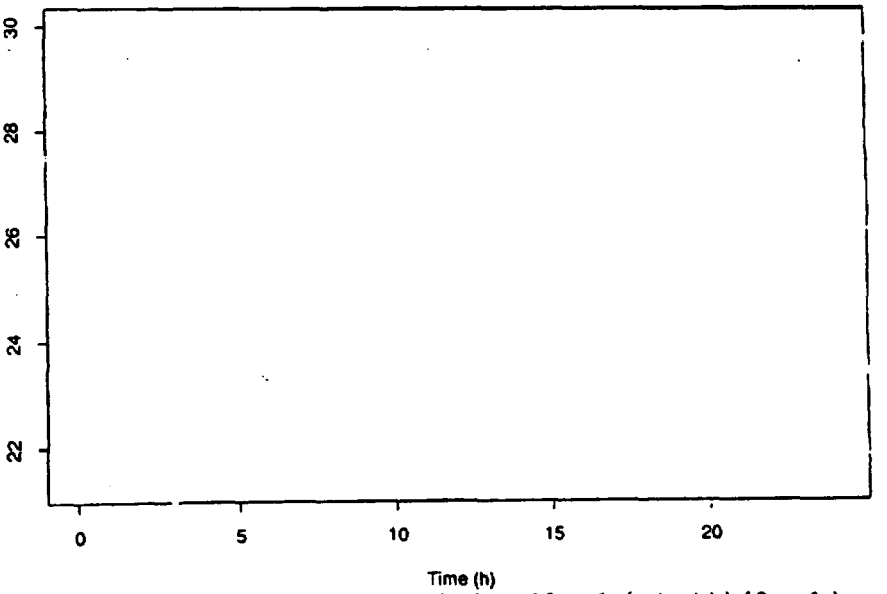
Figure 7. Simulated Pharmacokinetic Profile of hBNP
(Different bolus doses + 12 h infusion at 0.015 mcg/kg/min)




dotted: without bolus dose; increment of bolus dose = 0.3 mcg/kg (up to a total of 6 mcg/kg)

With continuous infusion and no preceding bolus dose, PCWP values were at 90% of steady-state values in 7.9 hours and at 50% of steady state in 2.5 hours.

Figure 8. Simulated Pharmacodynamic Profile of hBNP
(Different bolus doses + 12 h infusion at 0.015 mcg/kg/min)




dotted: without bolus dose; increment of bolus dose = 0.3 mcg/kg (up to a total of 6 mcg/kg)

**Conclusions from the PK/PD analysis of study 309:**

1. The relationship between the decrement in PCWP and hBNP plasma concentration can be described with a sigmoid Emax model with an equilibrium rate constant for delay of 2.45 hours.

2. Predictions of PCWP fell within the 95% CI of the data for studies 305 and 307 (with overestimation and underestimation, respectively).

3. Simulated values of PCWP for a 12-hour intravenous infusion of Natrecor (0.015 μg/kg/min) with no preceding bolus suggest 90% of the steady state values are reached in approximately 7.9 hours and 50% of the steady state values are reached in 2.5 hours.

4. Simulations indicate that bolus doses less than 1 μg/kg contribute little to an earlier decrement in PCWP despite early plasma concentrations exceeding those achieved at steady state.

5. With a bolus dose of 3 μg/kg, PCWP values are at 90% of their steady state values in approximately 50 minutes and at 50% of their steady state values in approximately 10 minutes.

# Appendix 11

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**Pharmacokinetic-pharmacodynamic model of Natrecor hBNP: estimated with studies 704.305, 704.307 and 704.309 and predicted for study 704.311.**

Study report submitted on March 12th, 1999

The analysis was carried out by Chui Yu Liu under the direction of Nancy Sambol, Pharm.D., University of California, San Francisco.

The objective of the analysis was to establish models for the concentration vs. PCWP and concentration vs. systolic blood pressure (SBP) of hBNP.

**Study designs:**

For specific information regarding the details regarding the design of studies 305, 307, 309 and 311, please refer elsewhere in this review.

Briefly, study 309 was an intermittent bolus dose study where subjects with congestive heart failure received 5 μg/kg every 4 hours (n=15), 10 μg/kg every 4 hours (n=15) and 10 μg/kg every 6 hours (n=14).

Study 305 was an IV bolus dose study in subjects with congestive heart failure. Subjects received a single IV bolus of 0.3 (n=4), 1.0 (n=4), 3.0 (n=4), 10.0 (n=3), 15 (n=4) and 20 (n=4) μg/kg.

Study 307 was an IV infusion in subjects with congestive heart failure. Natrecor was given at an infusion rate of 0.003 μg/kg/min and was incrementally increased every 1.5 hours to 0.01 μg/kg/min then 0.03 μg/kg/min. Seven subjects were maintained at the 0.03 μg/kg/min dose for 3 hours but the other 13 subjects had their dose escalated to 0.1 μg/kg/min after 1.5 hours.

Study 311 was conducted in 103 subjects with congestive heart failure. The subjects were administered 0.25 μg/kg IV bolus followed by 0.015 μg/kg/min IV infusion for 24 hours, 0.5 μg/kg IV bolus followed by 0.03 μg/kg/min for 24 hours or 1 μg/kg IV bolus followed by 0.06 μg/kg/min IV infusion for 24 hours.

**Data analysis methods:**

A population approach using the NONMEM program was used to develop the PK and PD models.

The PK of hBNP for studies 305 and 309 were modeled with a two-compartment open model. For study 307, the data were insufficient, therefore population estimates of k21, α, ß and Vc with study 309 were used as estimates of the structural PK parameters.

The pharmacodynamics for studies 305, 307 and 309 were modeled as a sigmoid Emax model as follows:

$$P(t)=P_0 - Emax \cdot Ce(t)^{\gamma}/Ce(t)^{\gamma} + Ce50^{\gamma}$$

The constraint imposed is that Emax is less than or equal to $P_0$, which is the observed baseline effect. The plasma concentrations, C(t), were convolved to obtain the effect site concentration, Ce, attributable to Natrecor. Therefore, the rate constant for the distribution and elimination of drug from the effect compartment, keo, was used to link C with Ce.

The goodness-of-fit of the model to the corresponding data were tested by comparing the observed means with their 95% CI. The goodness of fit was presumed to be acceptable if the predictions pass through the 95% CI at all time points.

Alternative PD models where Ce50 was fixed to either 0.00001 or 100000 were also tested. These were considered to be reduced (or nested) models.

In order to check the model predictions against study 704.311 data, PK parameter estimates were obtained for study 311 and PD parameters estimates were obtained for predicted PCWP and SBP. The geometric mean of the individual posterior estimates obtained from the PK analysis of study 311 were taken as the population PK parameter estimates. The geometric mean of the individual posterior estimates obtained from the pharmacodynamic analysis of studies 305, 307 and 309 combined, were taken as the population estimates of keo, Ce50 and gamma.

**Results:**

**1. Pharmacokinetics:**

For study 305, the t ½ α was estimated to be 1.03 min, the geometric means of t ½ ß was estimated to be 19.9 min, for k21, it was 8.59 $h^{-1}$, for Vc it was 0.032 L/kg and for CL, it was 5.1 ml/min/kg.

For study 309, t ½ α was estimated to be 1.58 min, t ½ ß was estimated to be 13.8 min, for k21, it was 11.8 $h^{-1}$, for Vc it was 0.083 L/kg and for CL, it was 9.3 ml/min/kg.

For study 307, t ½ α was estimated to be 1.51 min, t ½ ß was estimated to be 17.0 min, for k21, it was 11.6 $h^{-1}$, for Vc it was 0.090 L/kg and for CL, it was 8.7 ml/min/kg.

**2. Pharmacodynamics:**

For PCWP from studies 305, 309 and 307 combined, the geometric means were as follows (the numbers in parenthesis correspond to the 95% confidence intervals):

- Keo=0.38 $h^{-1}$ (0.32, 0.44 $h^{-1}$ )
- Half-life for keo=1.83 hours (1.56, 2.43 h)
- Ce50=6.07 ng/ml (5.07, 7.27 ng/ml)
- γ=0.95 (0.86, 1.04)
- Emax=26.3 mm Hg (25.1, 27.7 mm Hg)

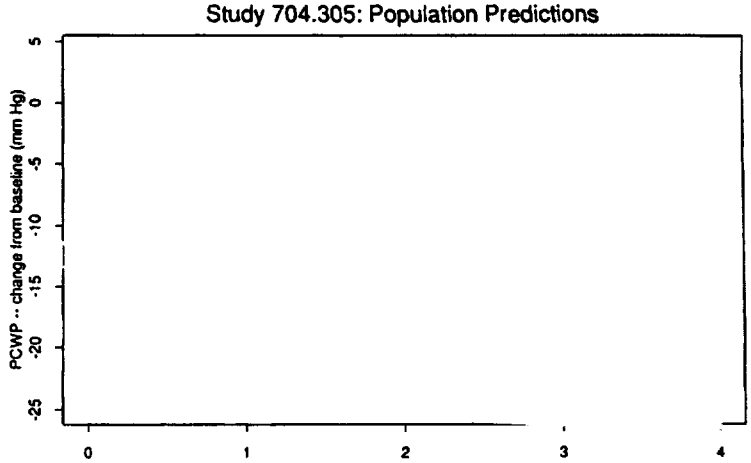
For SBP from studies 305, 307 and 309 combined, the geometric means were as follows:

- Baseline SBP=113.2 mm Hg
- Emax= 21.2 mm Hg (18.5, 24.3 mm Hg)
- Keo=0.18 $h^{-1}$ (0.15, 0.22 $h^{-1}$ )
- Half-life for keo=3.89 hours (3.18, 4.78 h)
- Ce50=3.17 ng/ml (2.96, 3.39 ng/ml)
- γ=1.19 (0.95, 1.51)

### 3. Checking the model predictions against the modeled data:

The following three figures show the predictions of PCWP based on population parameter estimates, relative to the data from study 305 (figure 6.2), study 307 (figure 7.2) and study 309 (figure 8.2):

*Figure 6.2.* Observed and Predicted PCWP vs. Time
Study 704.305: Population Predictions




point: individual observation; circle: mean observation; vertical line: 95% confidence interval of mean; curve: population predictions based on population pharmacokinetic parameter estimates and population pharmacodynamic parameter estimates.

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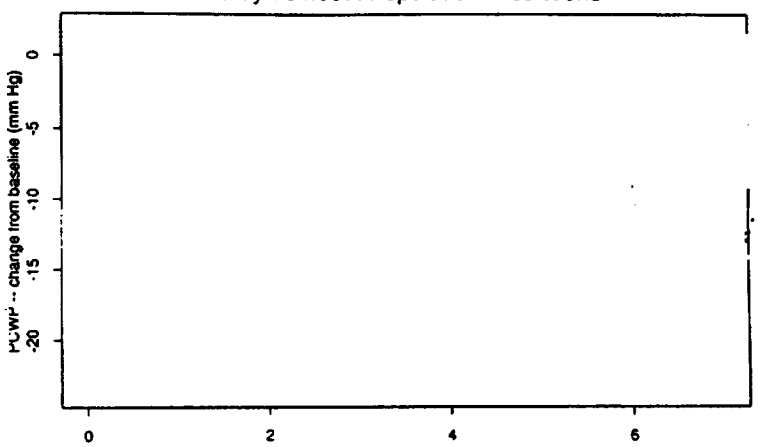
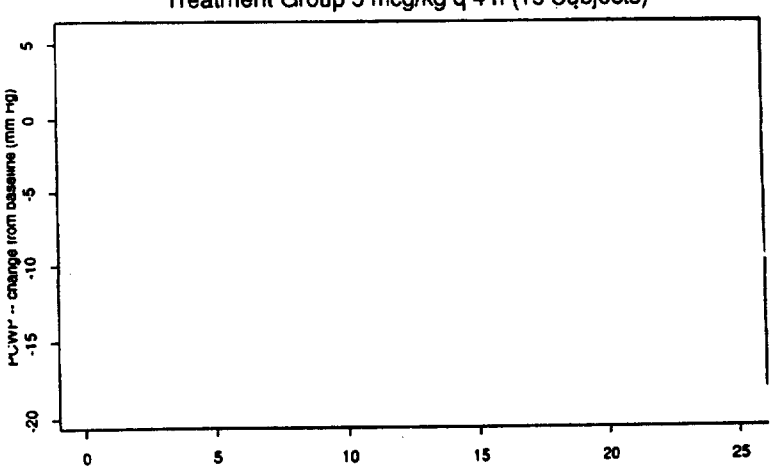
Figure 7.2. Observed and Predicted PCWP vs. Time
Study 704.307: Population Predictions




point: individual observation; circle: mean observation; vertical line: 95% confidence interval of mean; curve: population predictions based on population pharmacokinetic and pharmacodynamic parameter estimates.

Figure 8.2. PCWP vs. Time, Study 704.309
Treatment Group 5 mcg/kg q 4 h (15 Subjects)



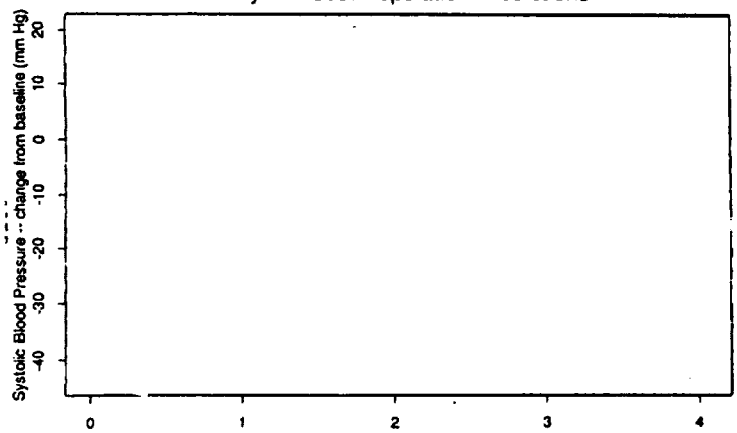

points: individual observations; curve: population predictions

In all cases, the predictions fall within the 95% confidence intervals of the means, thus indicating a reasonable goodness-of-fit.

Figures 9.2, 10.2 and 11.2 show the predictions of systolic blood pressure (SBP) based on the population parameter estimates, relative to the data for study 305, 307 and 309, respectively.

The data show that the predictions fall within the 95% confidence intervals of the means.

Figure 9.2. Observed and Predicted Systolic Blood Pressure vs Time
Study 704.305: Population Predictions




point: individual observation; circle: mean observation; vertical line: 95% confidence interval of mean; curve: population predictions based on population pharmacokinetic parameter estimates and population pharmacodynamic parameter estimates.

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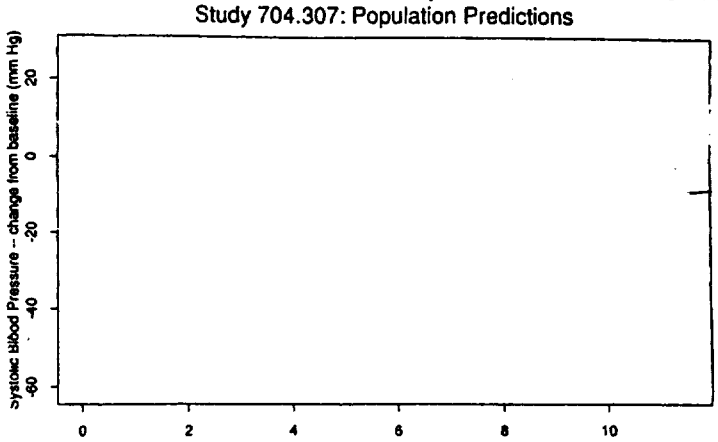
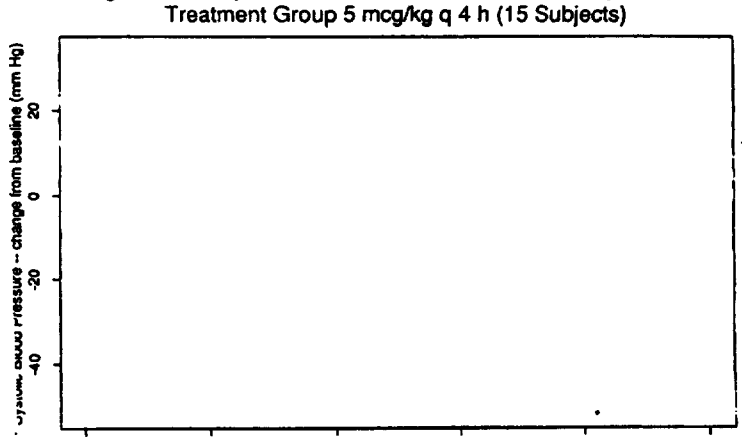
Figure 10.2. Observed and Predicted Systolic Blood Pressure vs Time
Study 704.307: Population Predictions




point: individual observation; circle: mean observation; vertical line: 95% confidence interval of mean;
curve: population predictions based on population pharmacokinetic and
pharmacodynamic parameter estimates.

Figure 11.2. Systolic Blood Pressure vs. Time, Study 704.309
Treatment Group 5 mcg/kg q 4 h (15 Subjects)




points: individual observations; curve: population predictions

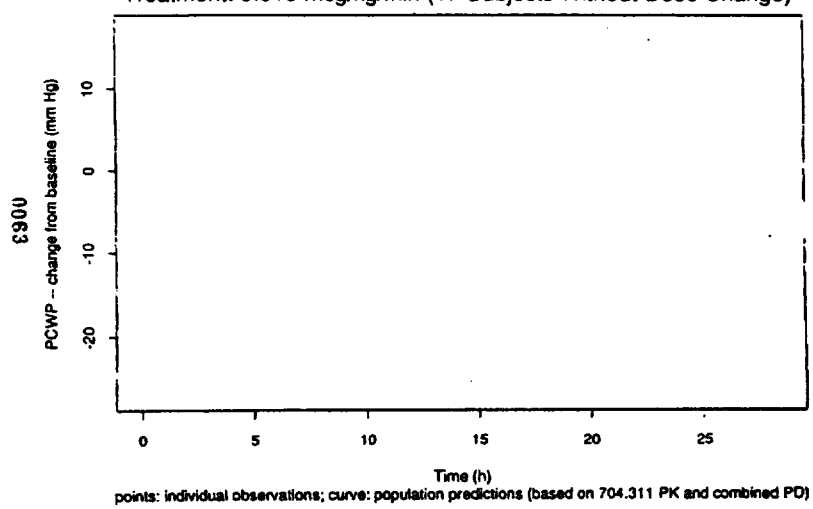
## 4. Checking the model predictions against study 704.311:

For study 311, the mean estimate of α is reported to be 1.46 min, the geometric mean of t ½ ß was estimates at 24.4 min (23.1, 25.6 min), the geometric mean of $k_{21}$ was 4.49 $h^{-1}$ (4.44, 4.54 $h^{-1}$), the geometric mean for Vc was 0.058 L/kg (0.051, 0.065 L/kg) and the geometric mean for CL was 10.4 ml/min/kg (9.1, 12.0 ml/min/kg).

Predictions of PCWP and SBP were obtained for the 3 infusion regimens used in study 311, based on population PK parameter estimates for study 311 and population pharmacodynamic parameter estimates for studies 305, 307 and 309 combined.

The following 3 figures illustrate the PCWP vs. time in study 311, for the 0.015 µg/min/kg, 0.03 µg/min/kg and 0.06 µg/min/kg regimens.

Figure 12.1. PCWP vs. Time, Study 704.311
Treatment: 0.015 mcg/kg/min (17 Subjects Without Dose Change)




points: individual observations; curve: population predictions (based on 704.311 PK and combined PD)

Figure 12.2. PCWP vs. Time, Study 704.311
Treatment: 0.030 mcg/kg/min (15 Subjects Without Dose Change)

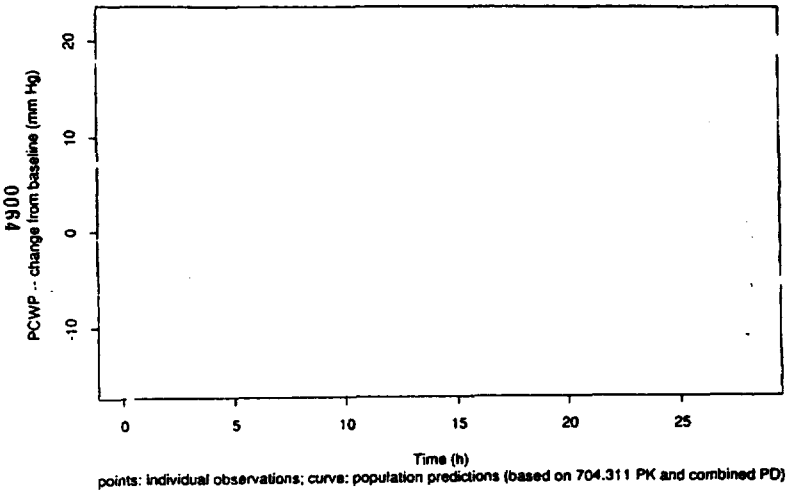
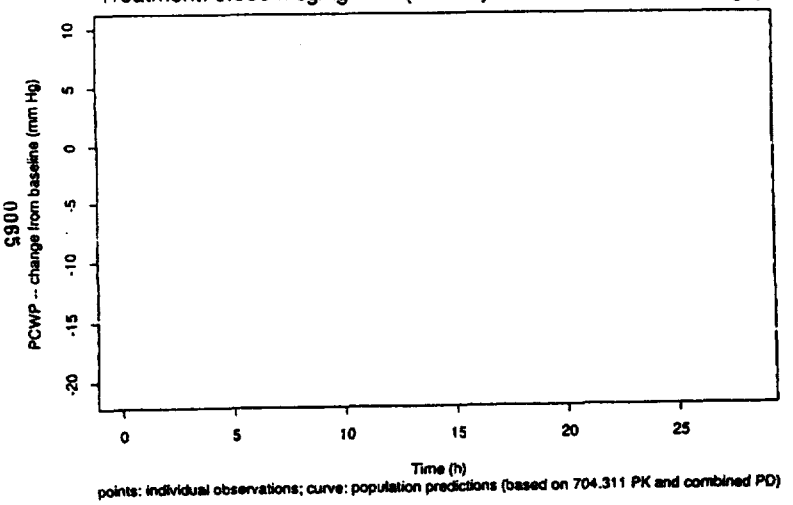



Figure 12.3. PCWP vs. Time, Study 704.311
Treatment: 0.060 mcg/kg/min (14 Subjects Without Dose Change)



The following 3 figures illustrate the SBP vs. time in study 311, for the 0.015 µg/min/kg, 0.03 µg/min/kg and 0.06 µg/min/kg regimens.

Figure 13.1. Systolic Blood Pressure vs. Time, Study 704.311
Treatment: 0.015 mcg/kg/min (17 Subjects Without Dose Change)

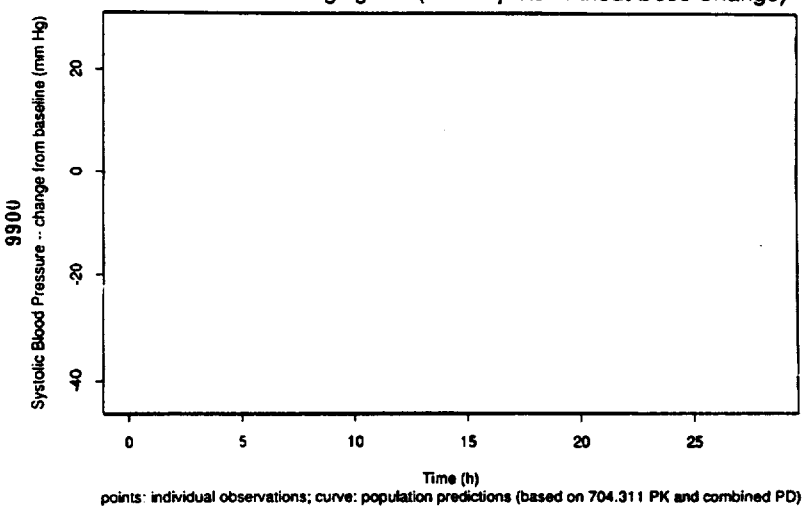



Figure 13.2. Systolic Blood Pressure vs. Time, Study 704.311
Treatment: 0.030 mcg/kg/min (15 Subjects Without Dose Change)

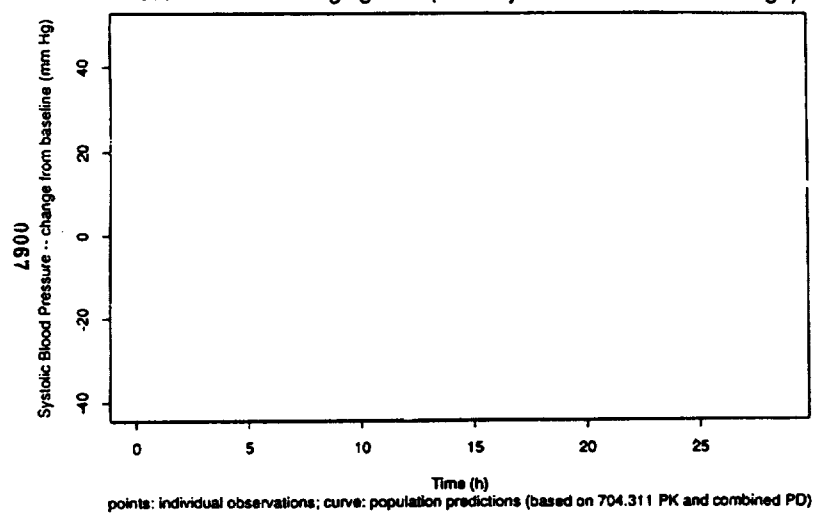
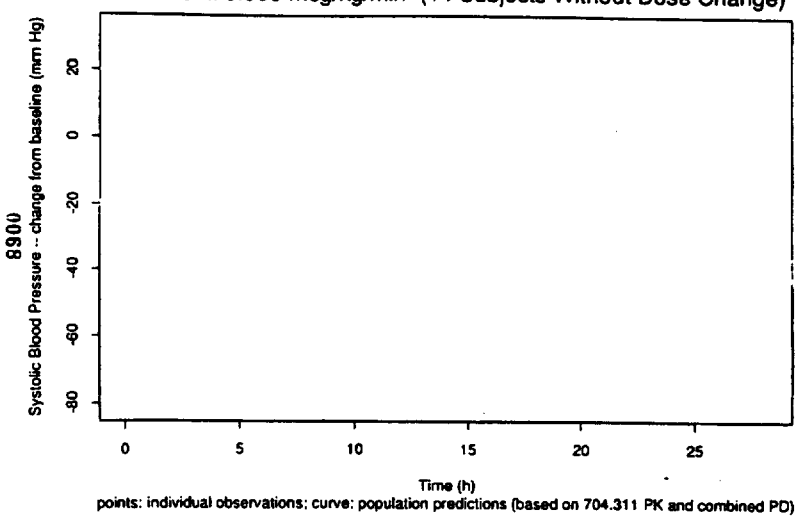
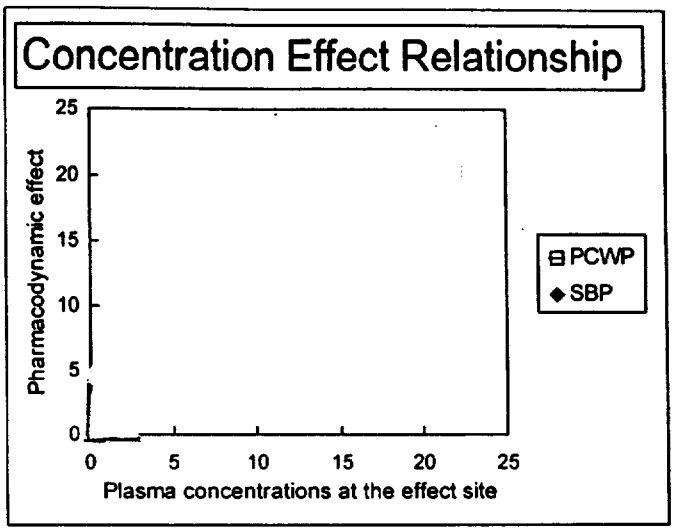


Figure 13.3. Systolic Blood Pressure vs. Time, Study 704.311
Treatment: 0.060 mcg/kg/min (14 Subjects Without Dose Change)




In both cases, for PCWP and SBP, at the 0.015 µg/min/kg dose, the predictions did not fall within the 95% confidence intervals of the observations. At the infusion rate of 0.015 µg/min/kg, the predictions for PCWP and SBP seem to underpredict the decrease in PCWP and SBP at all time points. However, at the higher doses of 0.03 and 0.06 µg/min/kg, the predicted line seemed to fall within the 95% confidence intervals of the observations for both endpoints. It should however be noted that at the infusion rates of 0.03 and 0.06 µg/min/kg, the predictions for PCWP do not seem to be compatible with the observations at the later time points (from 24 hours post infusion till the end of measurements). In the latter situation, the predictions seem to overpredict the decrease in PCWP, ie, the observations are less pronounced that the predictions. Similarly, for SBP, the predictions seem to overestimate the decrease in systolic blood pressure after the 10-hour time point post-infusion. The sponsor suggests that the results indicate some tolerance to the effects of Natrecor with respect to the effects of both PCWP and SBP. The sponsor also adds that the model developed does not however provide information regarding the long-term effects of Natrecor.

The following graph shows the concentration-response relationship for PCWP and SBP using the model described above:




The graph shows that for the same plasma concentration, the effect on blood pressure is slightly more pronounced that the effect on the PCWP. This can be attributed to the slightly larger gamma (0.95 for PCWP vs. 1.19 for SBP). A significant decrease in PCWP will only occur with a significant decrease in SBP, since the plasma concentration-effect relationship for SBP is to the left of the effect on PCWP

The following 3 graphs show results from simulation studies of Natrecor at 0.015 μg/kg/min for 6 hours. The first graph (17.1) shows the plasma profile of hBNP, the second graph (17.2) shows the PCWP response and the third graph (17.3) shows the SBP response as a function of time.

Figure 17.1. Simulated Pharmacokinetic Profile of hBNP
(Different bolus doses + 6 h infusion at 0.015 mcg/kg/min)

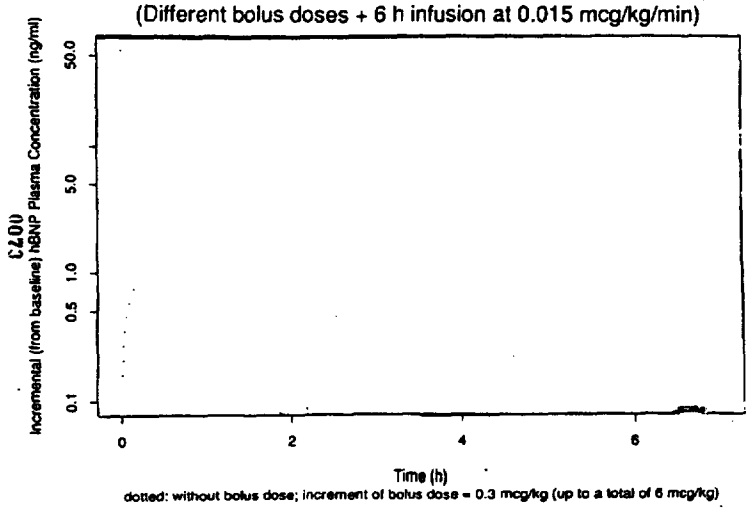



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Figure 17.2. Simulated hBNP Pharmacodynamic Profile: PCWP
(Different bolus doses + 6 h infusion at 0.015 mcg/kg/min)

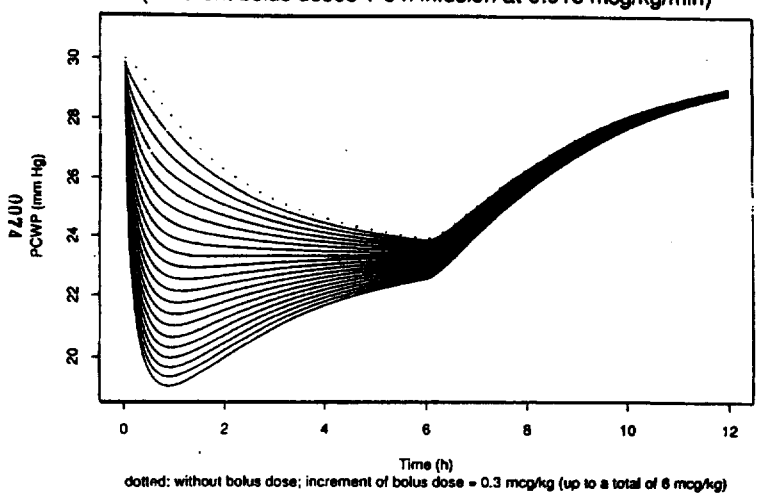
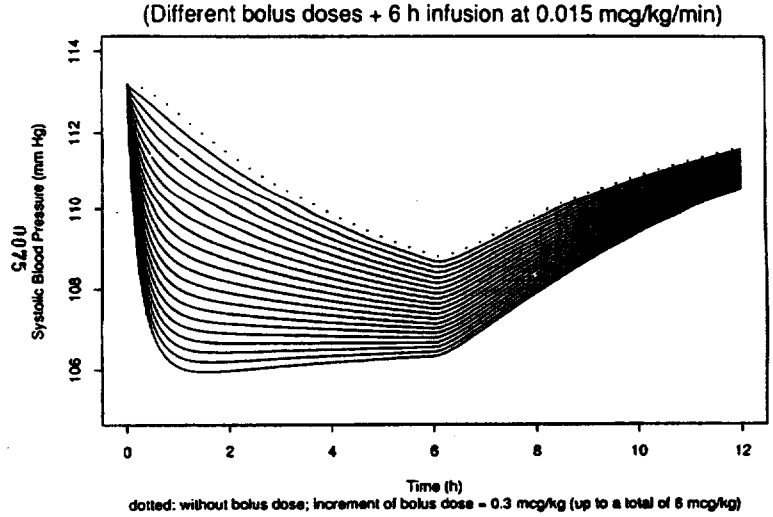



Figure 17.3. Simulated hBNP Pharmacodynamic Profile: SBP
(Different bolus doses + 6 h infusion at 0.015 mcg/kg/min)




Please note that even though the decrease in SBP seems to lag behind the decrease in PCWP (due to a keo for SBP), this means that once the infusion stops, it will take longer for the SBP to recover back to baseline

values. This can be clearly seen by superimposing the above 2 graphs, where the slope of the recovery curve after the stop of infusion is much smaller than that for the recovery of PCWP back to baseline values. This means that the subjects will have returned to baseline values of PCWP, while at the same time they will be experiencing hypotension. Such a scenario is far from ideal in subjects with CHF disease.

**Conclusions from the study and reviewer's comments:**

1. The objective of the analysis was to establish models for the concentration vs. PCWP and concentration vs. systolic blood pressure (SBP) of hBNP. A population approach using NONMEM was used and the pharmacodynamics for studies 305, 307 and 309 were modeled as a sigmoid Emax model.

2. The model predictions were checked against data from study 704.311, with the PK parameter estimates being from study 311 and the PD parameter estimates were obtained from the pharmacodynamic analysis of studies 305, 307 and 309 combined.

3. For PCWP from studies 305, 309 and 307 combined, the geometric means were as follows (the numbers in parenthesis correspond to the 95% confidence intervals):

- Keo=0.38 $h^{-1}$ (0.32, 0.44 $h^{-1}$ )
- Half-life for keo=1.83 hours (1.56, 2.43 h)
- Ce50=6.07 ng/ml (5.07, 7.27 ng/ml)
- $\gamma$=0.95 (0.86, 1.04)
- Emax=26.3 mm Hg (25.1, 27.7 mm Hg)

4. For SBP from studies 305, 307 and 309 combined, the geometric means were as follows:

- Baseline SBP=113.2 mm Hg
- Emax= 21.2 mm Hg (18.5, 24.3 mm Hg)
- Keo=0.18 $h^{-1}$ (0.15, 0.22 $h^{-1}$ )
- Half-life for keo=3.89 hours (3.18, 4.78 h)
- Ce50=3.17 ng/ml (2.96, 3.39 ng/ml)
- $\gamma$=1.19 (0.95, 1.51)

5. The PD parameters obtained from the modeling study indicate that a 50% decrease in systolic blood pressure will be reached at half the plasma concentrations of hBNP (Ce50=3 ng/ml) as compared to a 50% decrease in PCWP (Ce50=6 ng/ml).

6. Additionally, based on the values for keo, it appears that the half-life for the lag in decrease of systolic blood pressure is twice as long as that for a decrease in PCWP. This indicates that once hypotension is observed, it will take twice as long to recover from the adverse event as it would to return to baseline PCWP values. Therefore, based on the severity of the hypotension, one may have to wait 20 hours (5 times 4 hours) in order to return to steady state for hypotension, before one can attempt to dose with either Natrecor or another drug for CHF.

7. When the predictions from the model developed with combined data of studies 305, 307 and 309 was checked with the observed PD data from study 311, neither predicted PCWP nor predicted SBP fell within the 95% confidence intervals of the mean observations for the lowest dose tested (0.015 μg/kg/min). The sponsor attributes this to an "abnormal" dose-response relationship in study 311, where the response (decrement in PCWP and SBP) were greater at 0.015 μg/kg/min versus the values at 0.03 μg/kg/min.

8. The model "reasonably" predicts the decrease in PCWP and SBP for the first 6 hours of infusion of hBNP at the 0.03 and 0.06 μg/kg/min infusion rate. However, the model did not predict the mean observations for neither the PCWP nor the SBP during the offset phase of the dynamic effect, ie, at and after the 24-hour time point. Tolerance to the effects of hBNP cannot be ruled out at this point. Since tolerance was not built into the model, conclusive evidence regarding tolerance does not exist. However, there does appear to be an attenuation of the response for PCWP at time points beyond 10 hours.

9. Simulation studies indicate that bolus doses less than 1 μg/kg would contribute little to a decrement in PCWP despite an immediate increase in plasma hBNP levels. With a bolus dose of 3 μg/kg, the values for PCWP are at 90% of steady state (24 mm Hg) at 50 minutes, and at 50% of steady state at 10 minutes post dose.

10. Simulation studies also show that whilst the decrease in SBP seems to lag behind the decrease in PCWP (due to a larger keo for SBP decrease), the recovery back to baseline after the stop of infusion will take twice as long for SBP, as compared to PCWP. This means that if a patient develops hypotension during dosing with Natrecor and the infusion is stopped because of this adverse event, the PCWP values will return to baseline pre-Natrecor levels twice as fast as the return of the blood pressure to baseline levels. In other words, a patient may be suffering from hypotension concurrently with a high PCWP resulting from CHF.

## Appendix 12

**(Package insert)**

15 pages redacted from this section of the approval package consisted of draft labeling

WILLARD
MAR 11 1999

Natrecor® (Nesiritide, hBNP) NDA 20-920

# Global Review

Abraham Karkowsky, M.D.; Ph.D /S/ MD, Ph.D.

cc. HFD-110 file/CSO/Dthrockmorton/LCui/Nsadrieh/Papoian