

The sponsor fitted the data by a non-parametric, model-independent method. Based on this truncated data base, the sponsor calculated the following parameters: (95% CI):

CL = 9.8 ml/min/Kg (7.8-11.8)

V_{ss} = 0.21 L/Kg (0.18-0.24)

T_{1/2} first dose = 0.3 hour (0.27-0.32)

T_{1/2} last dose = 0.29 hour (0.28-0.31)

C_{max} first dose (Normalized to the 5 ug/kg dose) = 36,000 pg/ml (29,600-43,300)

C_{max} Last dose (Normalized to the 5 ug/kg dose) = 38,400 pg/ml (29,200-43,700)

Hemodynamics:

Table 4.4 Baseline Hemodynamics.

Parameter↓	Treatment⇒	Placebo	5 ug/kg Q 4h	10 ug/kg Q6h	10 ug/kg Q 4h	P-Value
PCWP (mm Hg)		25.5 ± 6.4	26.7 ± 6.7	30.4 ± 7.6	24.7 ± 5.1	0.098
Mean RAP (mm Hg)		13.1 ± 6.7	13.6 ± 6.6	14.5 ± 5.3	12.0 ± 7.0	0.77
Systemic Vascular Resistance (Dynes.Sec.cm ⁻⁵)		1655 ± 646	1757 ± 647	1363 ± 493	1473 ± 501	0.28
Cardiac Output (L/min)		3.6 ± 1.0	3.7 ± 1.2	4.1 ± 1.0	4.5 ± 1.4	0.17
Cardiac Index (L/min)		1.8 ± 0.41	1.8 ± 0.5	2.0 ± 0.4	2.1 ± 0.5	0.31
Pulmonary Vascular Resistance (Dynes.Sec.cm ⁻⁵)		329 ± 204	286 ± 148	194 ± 146	234 ± 177	0.16
Systolic Pulmonary Artery Pressure (mm Hg)		57.7 ± 12.8	57.9 ± 14.1	59.6 ± 13.0	52.3 ± 17.2	0.54
Diastolic Pulmonary Artery Pressure (mm Hg)		28.7 ± 6.8	29.0 ± 7.4	29.6 ± 8.4	27.5 ± 8.5	0.90
Systolic Systemic Blood Pressure (mm Hg)		110.8 ± 16.3	118.8 ± 16.3	112.4 ± 16.8	120.3 ± 16.4	0.31
Diastolic Blood Pressure (mm Hg)		66.5 ± 14.3	71.5 ± 13.1	64.3 ± 11.8	74.6 ± 12.3	0.14
Heart Rate (beats/min)		84.3 ± 19	96 ± 11	89 ± 13	89 ± 12	0.08

General Comments: The hemodynamic data for the initial bolus included information from nearly all patients. For the second bolus, hemodynamic data was missing for five of the placebo patients, two of the 5 ug/kg Q 4 hour, one or two of the 10 mg Q 6 hour dose (depending on the particular measurement) and one of the 10 mg Q 4 hour dosing regimens.

PCWP. The effect of repeated single doses of Natrecor on PCWP is shown in Figures 4.3. There appears to be a dose-related decrease in PCWP. The peak effect generally occurs at the first time point. It is not possible to determine if there are substantially greater effects prior to the first measurement. The duration of effect lasts for at least 2 hours, with possibly some residual effect still present at the interdosing interval (based on the kinetics, the 2-hour time point would represent approximately 6 half-lives and the 4-hour time point 12 half-lives).

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Figure 4.3

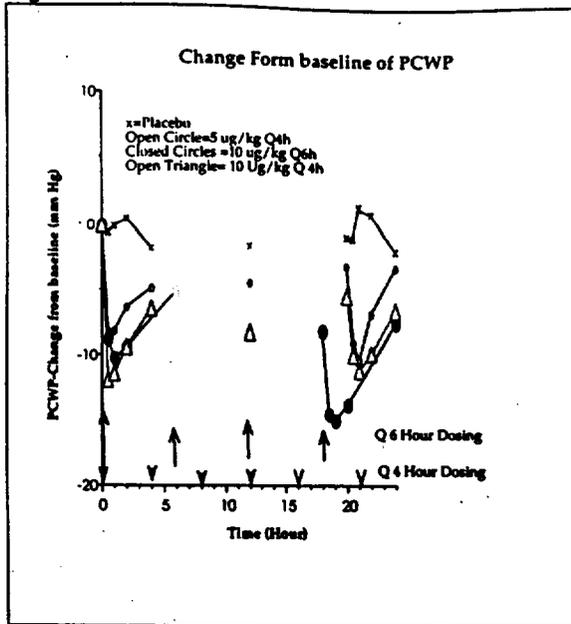
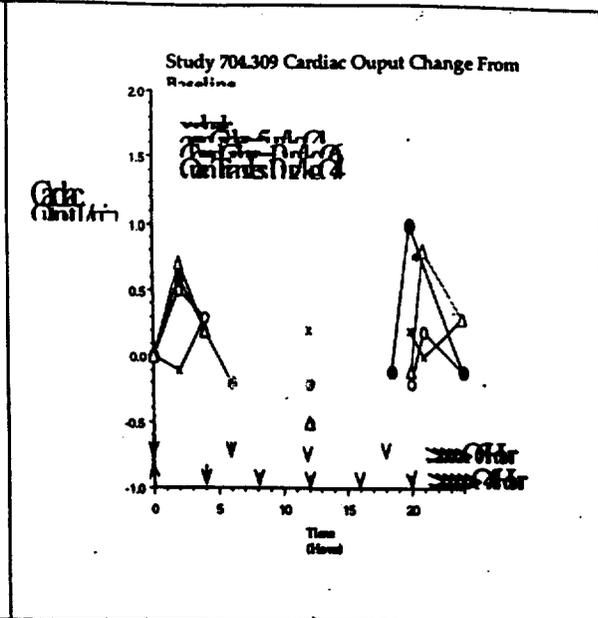


Figure 4.4



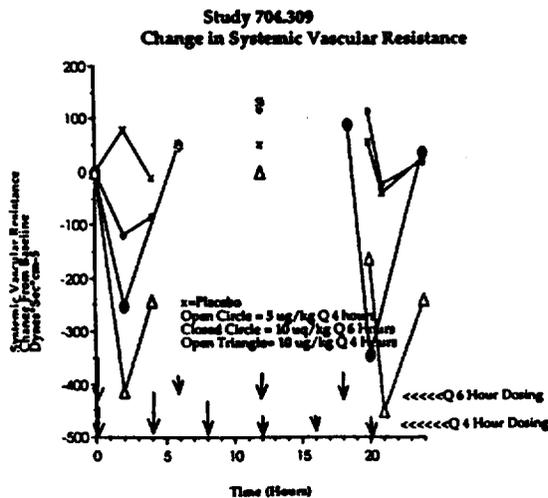
Cardiac Output:

The effect of Natrecor on cardiac output is shown in Figure 4.4. All three doses had an effect on cardiac output greater than placebo at the 2 hour time point, however, this effect was not statistically significant (when corrected for multiple comparisons). There were no differences in cardiac output at the interdosing intervals.

Systemic Vascular Resistance (See Figure 4.5):

Natrecor had an apparent effect at two hours (again this is approximately 6 half-lives) both after the first and last dose. The sponsor did not measure the effect of Natrecor prior to the two hour time point. By the inter-dosing interval, there appears to be little, if any residual effect on SVR.

Figure 4.5



Effect on Pulmonary Artery Pressures and Pulmonary Resistance (Figure 4.6): There appears to be an effect of Natrecor on both pulmonary systolic and diastolic pressure. The magnitude of this effect on pulmonary pressures at 30 minutes to 2 hours after each bolus was approximately (10-15)/(6-10) mm Hg. There was no strong dose relationship (i.e. the 5 mg Q 4 hour dose had effects similar to the 10 mg Q 4 hour and 10 mg Q 6 hour doses).

Figure 4.6

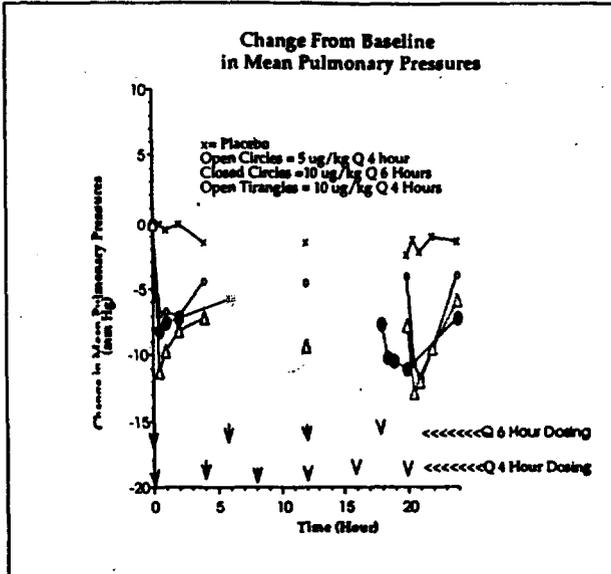
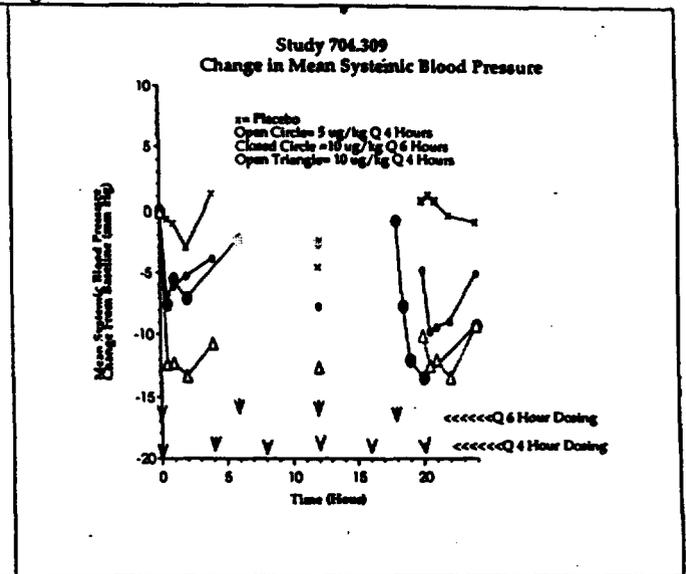


Figure 4.7



Effect on Systemic Vital Signs: Natrecor appears to have an effect on mean systemic blood pressures (Figure 4.7). The 10 ug/kg Q 6 hour dose group appeared to have a decrease systolic blood pressures. The 10 ug/kg Q 4 hour group has an effect on diastolic blood pressure. Heart rate change was variable and did not show a consistent pattern after both the first and last bolus (I did not graph the data).

Renal Function: Fluid intake, urine output and urinary sodium and potassium excretion is shown in the table 4.5:

Table 4.5 Urine Parameters.

Parameter ↓	Dose>	Placebo	5 ug/kg Q 4 H	10 ug/Kg Q 6 H	10 ug/kg Q 4 H
Intake ml/24 H		1923 ± 569	1871 ± 754	1839 ± 605	1915 ± 530
Output (ml/24 Hr)		2455 ± 1041	1762 ± 1250	1640 ± 798	1696 ± 1438
Net (Output-Intake) (ml/24 Hr)		531 ± 954	-109 ± 1294	-199 ± 815	-243 ± 1409
Urine Sodium Excretion (meq/24 Hours)		179 ± 150	98 ± 67	348 ± 769	116 ± 151
Urine Potassium Excretion (meq/24 Hours)		120 ± 44	92 ± 47	177 ± 407	68 ± 39

Only in the placebo group was there an net diuresis. In the other hBNP groups fluid input exceeded urinary excretion.

PK-PD analyses: The sponsor did not provide any PK-PD correlations to any of the hemodynamic parameters.

Safety:

Deaths: There were two deaths that occurred during the observation period of the study (I've looked at both CRFs).

Patient # 381-001 (Placebo). Was a 53 year old white male with a history of NYHA Class IV CHF due to alcoholic cardiomyopathy, diabetes mellitus, chronic renal insufficiency and COPD. The subject died on study day 6. He had a single episode of ventricular fibrillation and cardiac arrest.

Patients # 315-005(5 ug/kg Q 4 H). This was a 65 year old white male with NYHA Class IV CHF, hypertension, and bifasicular heart block and previous supraventricular arrhythmias. He tolerated the infusion well but died on day 30 from worsening pump failure.

Dropouts:

Patient # 315-001(Placebo): This was a 35 year old black female with NYHA Class IV CHF due to post-partum cardiomyopathy. The baseline hemodynamic measurements were a cardiac output of 2.94-3.72 L/min and a wedge pressure of 20 mm Hg. The patient was discontinued after the first bolus. The cardiac output was depressed to 2.51 L/min and the wedge pressure increased to 24 mm Hg. The patient was treated with intravenous dobutamine.

Patient # 315-009 (placebo): This was a 59 year old white male with NYHA class IV CHF, rheumatic heart disease, who was status post valve replacement surgery and VT. The subject had wedges ranging from 20-32 mm Hg and cardiac output ranging from 2.42-3.3 L/min at baseline. At the 1-hour time point the wedge pressure increased to 36 mm Hg and the patient discontinued the study and was treated with dobutamine, dopamine and furosemide.

Patient 315-006 (Placebo). This was a 47 year old female NYHA Class III. Her baseline hemodynamics measurements included a cardiac output of 2.93-3.01 L/min and a wedge of 18-20 mm Hg. When discontinued, her cardiac output was 2.58 L/min and wedge of 30 mm Hg suggesting worsening CHF.

Patient 348-017 (Placebo). This was a 60 year old white male with a history of coronary artery disease, hypertension and cardiomyopathy. He was status post myocardial infarction and abdominal aortic aneurysm repair. Baseline wedge was 28-36 mm Hg and cardiac output was 4.6 to 5.1 l/min. The patient was discontinued because of worsening CHF, but the wedge at the time of discontinuation was 30 mm Hg and the cardiac output was 4.50 L/min. The sponsor claims that there were complaints of nausea and diaphoresis accompanied by a decrease in cardiac output and increasing PCWP? (I can't see a major change in this patient's cardiac status).

Patient # 353-001 (Placebo) This was a 46 year old male with NYHA CHF Class III, coronary artery disease and AICD. The initial wedge pressures were 22-26 mm Hg and the cardiac output was 3.3 to 3.6 L/min. The patient was discontinued after the first bolus for worsening CHF and treated with IV nipride. The wedge pressures at the time of discontinuation was 21 mm Hg and cardiac output was 3.5 L/min. These measurements did not substantially differ from those of baseline.

Patient # 315-003 (5 ug/kg Q 4 hours) This was a 48 year old white male with hypertension and NYHA Class III due to ischemic cardiomyopathy. The patient's initial hemodynamics included a wedge of 20-22 mm Hg and a cardiac output of 3.01-3.20 mm Hg. The patient's hemodynamics at the time of discontinuation for worsening CHF was a wedge of 24 and a cardiac output of 3.2 L/min.

Patient # 355-001 (5 ug/kg Q 4 hours). This was a 35 year old white male NYHA Class III CHF who had idiopathic dilated cardiomyopathy and A-V dissociation which required a pacemaker. The baseline wedge was 19-10 mm Hg and cardiac output ranged from 3.40-4.45 l/min. Prior to the final bolus, the wedge had increased to 24 mm Hg and the cardiac output decreased to 2.89 l/min. The subject was discontinued for worsening CHF and treated with lisinopril and hydralazine.

Patient # 315-002 (hBNP 10 ug/kg Q 6 Hours). This was a 55-year old white male with NYHA Class III CHF and coronary artery disease. He received two doses of intravenous hBNP, but his cardiac output continued to decrease. He was treated with dopamine, dobutamine, nitroprusside and furosemide. His initial wedge pressures were 32-34 mm Hg and the cardiac output was 3.99-4.06 L/min. His final wedge was 32 mm Hg but his cardiac output decreased to 3.24 L/min

Patients 315-004 (hBNP 10 ug/kg Q 4 Hours). This was a 59-year old white male with NYHA Class IV CHF and a history of coronary artery disease and pulmonary hypertension. The subject received 3 intravenous boluses. The patient was discontinued for worsening CHF and treated with dopamine, dobutamine, nitroprusside and furosemide. The initial wedge pressure was 26 mm Hg and the cardiac output was 4.82 L/min. When terminated the wedge pressure was 29 mm Hg and the cardiac output decreased to 3.66 L/min.

Three subjects had severe adverse events but completed the intravenous bolus.

Patient # 360-004 (Placebo) was a 34-year old black male who developed tachycardia, fever and was also noted to have an elevated white count. The patient was presumed to have sepsis. All cultures, however, were negative (including catheter tip). The patient also developed hyponatremia ([Na⁺]=132 meq/l).

Patient # 359-003 (hBNP 10 ug Q 4 hours). This was a 52 year old white male with NYHA Class IV CHF due to ischemic cardiomyopathy and past myocardial infarction. He tolerated the intravenous bolus of hBNP. Four days after the completion of the infusion the subject had an episode of hypotension (systolic blood pressure was 40 mm Hg) and bradycardia (HR=56). He was treated with dopamine and atropine. An intra-abdominal-balloon pump was inserted. (Did the patient have an MI? Cardiac enzymes were apparently not drawn nor were EKGs described).

Patient # 359-002 (10 ug Q 6 hours). This is a 54-year old white female with NYHA Class III CHF and diabetic nephropathy (initial creatinine 2.0 mg/dl). She tolerated the infusion. Her creatinine prior to the infusion was 2.6 mg/dl with a second, subsequent measurement prior to the infusion of 2.0 mg/dl. On day 4 (10/8/95) her urine output decreased and her creatinine rose to 2.6 mg/dl. She was treated with Zaroxolyn and Demadex. The next day her creatinine increased to 3.8 mg/dl and she was treated with renal dose dopamine. On 10/11/95 her urine output further decreased and she was placed on a Bumex drip. Her creatinine increased to 4.3. It did not appear that she was treated with an ACE-inhibitor. She received dialysis and ultrafiltration. She also developed a fever on 10/8/95, the central line was removed and she was started on vancomycin (note that the timing of the diminished renal function antedated vancomycin treatment). On 10/9/95 she was noted to have mild ototoxicity. She also had an episode of A Fib (on 10/11/95) and NSVT on (10/14/95). On 10/13/98 she was noted to have a profound anemia (initially Hct was 8.7 decreased to 5.4). She was transfused with 2 Units of PRBCs. On 10/14/95 she had an episode of hypotension associated with a mental status change.

Adverse Events:

The adverse events through day 14 were rather diffuse. Table 4.5 (derived from Table 32 p 46.277) lists all events in which there were at least 3 subjects in any one group

Table 4.5 Adverse Events Occurring Through Day 14.

Event	Placebo	5 ug/kg Q 4 Hour	10 Uq/Kg q 6Hour	!0 ug/kg Q 4 Hour
Catheter Pain	2	3	5	4
Headache	4	3	3	0
Back Pain	2	0	2	4
Abdominal Pain	1	1	3	1
Hypotension	1	3	3	3
Nausea	3	3	4	2
Vomiting	2	3	2	2
Dizziness	3	3	1	0
Sweating	1	0	0	3

The severity of these events is not described.

Vital Signs: See Figure 4.7 above for blood pressures. Heart rate during the boluses and observation period was not consistently changed.

EKG was not analyzed for intervals.

Laboratory values: No patient developed anti hBNP antibodies (all but 6 active hBNP subjects had a post treatment measurement of anti-hBNP antibodies).

Conclusion. This study is consistent but far from definitive that hBNP caused a hemodynamic effect when given as 4-6 evenly spaced boluses over a 24-hour period. The effect is best described as a drop in both wedge and pulmonary pressures. Any definitive conclusions, however, must be tempered by the poor method of blinding and the lack of significance of the primary stipulated end-point (the effect after the last bolus at the interdosing interval).

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Study # 704.310 Vol. 50 to 53.

Title of Study: A Phase II, randomized, Double-blind, Placebo Controlled, Ascending Dose Response Study of the Effects of a 24-Hour Course of NATRECOR BNP Administered as an Intermittent Intravenous Bolus in Subjects With Congestive Heart Failure.

Investigator, Sites and Number Enrolled.

Table 5.1 Investigator, Sites and Number Enrolled.

Investigator and Sites	#	Investigator and Sites	#	Investigator and Sites	#
Site # 352 Robert C. Bourge, MD University of Alabama Birmingham Birmingham AL	8	Site # 379 Cara East, MD Baylor University Med Center Dallas, TX	2	Site #355 Ray Hersberger, MD Oregon Health Science Center Portland OR	4
Site # 306 Robert Hobbs, MD Cleveland clinic Foundation Cleveland OH	11	Site # 356 Walter Kao, MD Rush Presbyterian-St. Lukes Medical Center Chicago,IL	5	Site # 373 Roberto Lang, MD University of Chicago Chicago IL	9
Site # 359 Kenneth B. Marguiles, MD Temple Univ Health Science Center Philadelphia,PA	3	Site # 315 Leslie Miller, MD St. Louis University Med Center St Louis, MO	2	Site #383 John O'Brien, MD Faifax Hospital Falls Church, VA Joseph Kiernan, MD Co-investigator	1
Site # 360 P. Jacob Varghese, MD George Washington U. Med Center Washington, DC	5	Site # 361 Hector O. Ventura, MD Ochsner Clinic New Orleans, LA 70121	10	Total =60	

Formulations: Two formulations of hBNP were used in this study: Lots # E0013A1 and G0003A1, Both lots were produced by the synthetic peptide methodology. Subjects who were enrolled earliest received the E0013A1 Lot, with the rest receiving lot # G0003A1.

Protocols, Amendments, Line listings and CRFs: A protocol dated 18 July 1994 was submitted. No protocol amendments were submitted. Line listings for much of the data was available and CRFs were available as reproductions on CD-ROM.

Protocol Design: This study is labeled as a double-blind, placebo-controlled, dose ranging study.

Doses: Three doses were planned: 3ug/kg, 5 ug/kg and 10 ug/kg, each dose was administered every four hours for a total of 6 doses/subject. Subjects were initially randomized to the low dose group (or placebo) and only after that group safely completed the bolus were subjects enrolled into sequentially the second highest dose and subsequently the highest dose groups (or placebo).

Number of subjects: Twenty patients were to be enrolled into each group. Within each group fifteen were to receive hBNP and 5 to receive placebo.

Protocol: Patients were eligible for enrollment if they were at least 18 years old with chronic CHF (NYHA II-IV) and demonstrated a ejection fraction ≤ 0.30 (as determined either by 2-D echocardiography or radionuclide ventriculography). Patients were to be on stable regimens of

ACE-inhibitors with or without digoxin and/or diuretics. Stability was defined as the same medication for at least two weeks and the same dose for at least one week.

Specifically excluded were patients with recent MI (2 months) or unstable angina (within 2 weeks). Patients with valvular stenosis, hypertrophic, restrictive or obstructive cardiomyopathy or patients with active myocarditis were not eligible. The protocol also excluded patients with rhythm or conduction abnormalities such as ventricular tachycardia, ventricular fibrillation, Mobitz type II block or third degree heart block (except if patient has permanent pacemaker). Patients who have had a recent stroke (within 3 months) or patients with significant renal disease ($SCr > 3.0$) or who are hypotensive ($SBP < 85$ mm Hg) or had hyponatremia or hypernatremia ($[Na^+] < 125$ or > 160 meq/l) as well as those incapable of discontinuing their cardiac medications (with the exception of antiarrhythmics) were also excluded. In addition, patients with other acute or chronic medical conditions or laboratory abnormalities, which could increase the risk of such patients to Natrecor infusion, were excluded.

Screening: Subjects were screened for eligibility within one week of initiating the treatment procedures. The screen was to include a history (including NYHA class, cause of CHF), physical exam, vital signs, laboratories, ECG and chest X-ray. Patients were to be on stable ACE-inhibitors (either enalapril or lisinopril) for at least 1 week.

Pretreatment: Within 12 hours before of the start of the infusion the subject was to be admitted and placed on continuous telemetry monitoring. All cardiovascular medications except digoxin, diuretic and anti-arrhythmic drugs were withheld. The usual dose of digoxin and diuretics were maintained but were administered approximately 12 hours prior to the study (i.e. 10 PM the night before the infusion). If the subject was on BID-dosing regime for diuretics, the dose could either be held, given at the discretion of the investigator or given in its entirety the night before. Any ACE inhibitor or nitrate was given two hours prior to the first and last bolus of hBNP/placebo.

During the pre-treatment period, a Swan-Ganz catheter was placed. Initial hemodynamic measurements were made at least two hours after insertion of the Swan Ganz is inserted. Only those patients whose PCWP was > 15 mm Hg and also a CI of < 2.5 L/min/m² were to be further enrolled into the study.

Within 1-hour before starting the infusion, several baseline measurements were made. These measurements include vital signs (1 hour and 15 minutes prior to the infusion), hemodynamic measurements (2 sets within 30 minutes). If the measurements were not within $\pm 15\%$ of each other, an additional set of measurements were made, with the average of the last two values serving as baseline). Blood was drawn for baseline chemistry and hematology (within 15 minutes of the infusion). Blood was also drawn for baseline hBNP levels (within 15 minutes of the infusion) and a blood sample to serve as a reference (reference to what?) was also drawn..

Treatment period: After a light breakfast, the subjects received the first of the planned boluses. The following were the proposed measurements and times with respect to the first bolus. All measurements were also to be repeated at the time of any serious event:

Vital signs were measured at 15, 30 and 45 minutes and 1, 1.5, 2, 3, and 4 hours after the first and last boluses. Vital signs were also measured immediately prior to the four middle boluses.

Hemodynamics (with the exception of cardiac output): Were measured at 30 minutes and 2 hour after the first bolus and immediately prior to each bolus. These hemodynamics were measured 30 min and 1, 2, and 4 hours after last bolus.

Cardiac Output: Was measured 2 hours after the first bolus and prior to each bolus. After the last bolus, cardiac output was measured at 2 and 4 hours.

hBNP concentrations: Blood was collected at 2, 5, 15, 60 and 90 minutes after the first and last boluses for hBNP concentrations .

24-hour Urine: was collected beginning at the first bolus. Urine measurements included urine volume and urinary sodium and potassium.

Inputs and outflows: Total fluid intake (intravenous and oral) was measured for the 24-hour period beginning with the fist bolus.

Dosing Guidelines: Subsequent bolus doses were halved if the patient had symptomatic hypotension, which did not require fluid or pressor support. If the hypotension required fluid or pressor intervention, the patient was discontinued from receiving additional boluses. A patient whose status deteriorated was discontinued from the study and received the most appropriate treatment (i.e. diuretics or inotropes) and was declared a treatment failure.

Post treatment. Contact was made with all patients at 7 and 15 days after the infusion by telephone. A clinic visit on day 20 to 30 was also scheduled during which the subject was examined and blood was draw for chemistries and for anti-BNP antibodies.

Statistical Issues: Randomization was stratified by study site. The primary analysis was to be descriptive. The endpoint of interest was PCWP. Endpoints of secondary endpoints included: cardiac index, SVR, mean RAP and heart rate. The time-point of interest was 4 hours after the sixth bolus. For renal endpoints, the metrics of interest are urine output, urine sodium and urine potassium.

The primary metric was analyzed by a one-way ANOVA of the change from baseline. Placebo subjects across all treatments were pooled. The ANOVA included terms for the treatment arm but not investigators. Any differences between treatment arms were analyzed for significance by an omnibus F-Test. Dose trends were tested by linear contrasts using equally spaced scores for the doses.

The significance of the change from baseline at the other time points will also be determined by the significance as determined by an ANOVA model. The sponsor also proposes to test whether the hemodynamic effect after the first and last boluses at the individual time points were different.

Blinding. There was no placebo formulation. The on-site pharmacist formulated the dose and therefore, was aware as to both the nature and dose of treatment. The pharmacist prepared the formulation before the catheter was successfully inserted and before measurements of hemodynamics qualified the individual for the study. If the patient is found ineligible or the catheter could not be inserted the subject is considered as not enrolled.

Results:Demographics:

Summary demographics are shown in Table 5.2 :

Table 5.2 Demographics of study 704.310

Parameter ↓ Dose>	Placebo (n=17)	3 ug/kg (n=14)	5 ug/kg (n=14)	10 ug/kg (n=15)
Age	55 ± 12	48 ± 14	50.5 ± 9	55 ± 13
Race: Black/ Caucasian	8/9	6/8	5/9	6/9
Gender Male/Female	11/6	12/2	10/4	12/3
Height	172 ± 9.6	175 ± 11.3	177 ± 7.6	175 ± 10
Weight	86 ± 21	92 ± 22	89 ± 20	77 ± 22
Signs/Symptoms of CHF				
Rales Yes/No	5/12	7/7	5/9	3/12
S3 Yes/No	7/10	4/10	8/6	6/9
Peripheral Edema Yes/No	8/8	3/8	7/6	5/10
NYHA Class II/III/IV/ND	2/8/7/0	2/6/6/0	0/6/7/1	0/8/7/0
Ejection Fraction (%)	20 ± 7	17 ± 5	21 ± 7.5	18 ± 6

In general, there were differences between those enrolled into this study and the population of CHF patients as a whole. In this study, most patients were male and the median age was approximately 52 years old. In the general population, the CHF group is approximately evenly divided between males and females and the age of onset of CHF is usually > 70 years old.

The majority of the patients enrolled into this study were NYHA Class III-IV. All but six subjects, distributed across all treatment groups, had signs or symptoms of acute CHF as demonstrated by either rales, an S3 or peripheral edema at either screening or pre-treatment physical exam.

Caveats to Data.

The sponsor analyzed the data in two ways. The first is the "All Patients" analysis, which was this reviewer's preferred analysis. This analysis included the information on all patients. The other analysis was the "Per-Protocol" analysis. This analysis excluded 16 patients who did not receive their ACE-inhibitors 2 hours prior to both first and last doses of Natrecor.

[Comment: There were many other subjects who deviated from the protocol whose data was nevertheless, incorporated in the "per-protocol" analysis. The sponsor apparently did not feel that including these subjects sufficiently damaged any resultant conclusions to warrant their exclusion from the analysis. These deviations include subjects who did not fulfill the enrollment criteria, most commonly patients had the measurements of EF outside the specified time window (n=9), or had EFs > than 30% (n=2). Eleven subjects deviated from exclusion criteria in that they received captopril BID (n=7), had SBP < 85 mm Hg (n=2), received hydralazine (n=2), or had cardiac indices greater than 2.5 L/min/m². There did not appear to be overlap between those who had other deviations and those who were excluded from the per protocol analysis.]

Kinetics: The protocol was to assess the kinetics from both the first and last intravenous bolus. However, only plasma concentrations from the first bolus were analyzed. Concentrations of hBNP were analyzed by the an antigen displacement assay. Endogenous hBNP was determined prior to baseline and this value was subtracted from each measurement after the bolus. The data was fit to a non-parametric model. Several cohorts were analyzed separately. These cohorts included: 1) those received hBNP and were also taking enalapril (n=19); 2) those who received hBNP plus any ACEI (n=29); and 3) those taking hBNP with or without ACEI (n=42). The non-parametric values for these three cohorts were essentially the same. Below are the kinetic parameters for the largest of the cohorts:

Table 5.3 kinetic Parameters Study 704.310

Dose ↓ Parameter ⇒	Cmax (ng/ml)*	CL (ml/min/kg)	Varea (l/Kg)	Vss (l/Kg)	k (h-1)	t1/2 (h)
All	36.6 (30-43)	9.8 (8-12)	0.24 (0.20-0.29)	0.21 (0.18-0.24)	2.53 (2.3-2.8)	0.3 (0.27-0.32)

*Normalized to the 5 ug/kg dose

Hemodynamics:

Discontinuations: A total of 10 patients discontinued the study prior to completing all six pre-specified boluses. Those who discontinued are briefly described:

Placebo: One patient (worsening CHF)

3 ug/kg Q 4 Hours: Five Patients (3 patients for hypotension; 1 for bradycardia and 1 for worsening CHF)

5 ug/kg Q 4 hours: 2 patients (one worsening CHF, one hypotension)

10 ug/kg Q 4 Hours: 2 patients (2 with hypotension).

Baseline Hemodynamic measurements are shown in Table 5.4:

Table 5.4 Baseline Hemodynamics Study 704.310

Measurement ↓	Dose →	Placebo	3 ug/kg	5 u/kg	10 ug/kg
PCWP (mm Hg)		25.8 ± 7.2	23.3 ± 7.0	28.1 ± 6.2	21.9 ± 4.98
Cardiac Index (L/min)		2.0 ± 0.67	2.1 ± 0.56	1.9 ± 0.57	2.2 ± 0.56
Systemic Vascular Resistance (Dynes*sec*cm-5)		1559 ± 633	1372 ± 640	1421 ± 522	1535 ± 512
Mean Pulmonary Artery Pressure (mm Hg)					
Mean Right Atrial Pressure (mm Hg)		10.4 ± 7.2	8.8 ± 4.9	10.6 ± 5.4	8.1 ± 5.1
Systemic Pressures:					

PCWP: Baseline wedge pressures are shown in the Table 5.4. The percentage change during the infusion periods is shown in Figure 5.1. There were marginally significant differences in wedge pressure ($p=0.056$) at baseline. The primary end point (the effect 4 hours after the last bolus) was marginally significant using the omnibus test ($p=0.052$) but not on linear trend test ($p=0.7$), Contrasts comparing each of the treatments to placebo showed none of the contrasts reached the level of 0.05.

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Figure 5.1

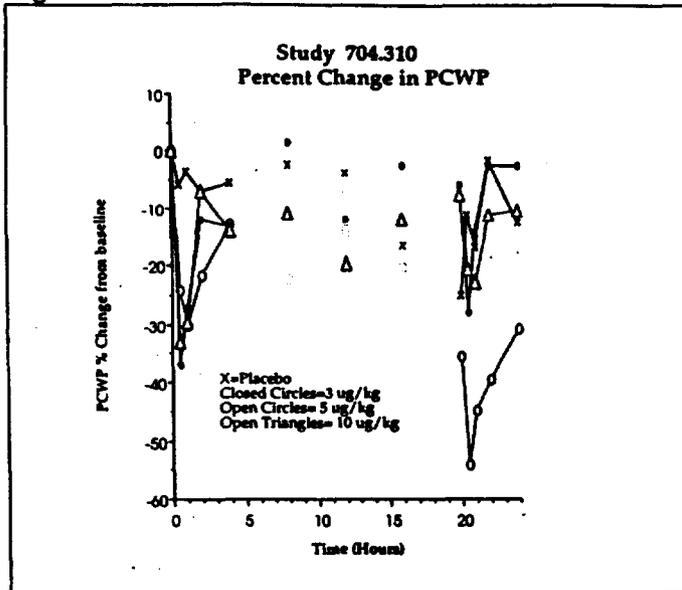
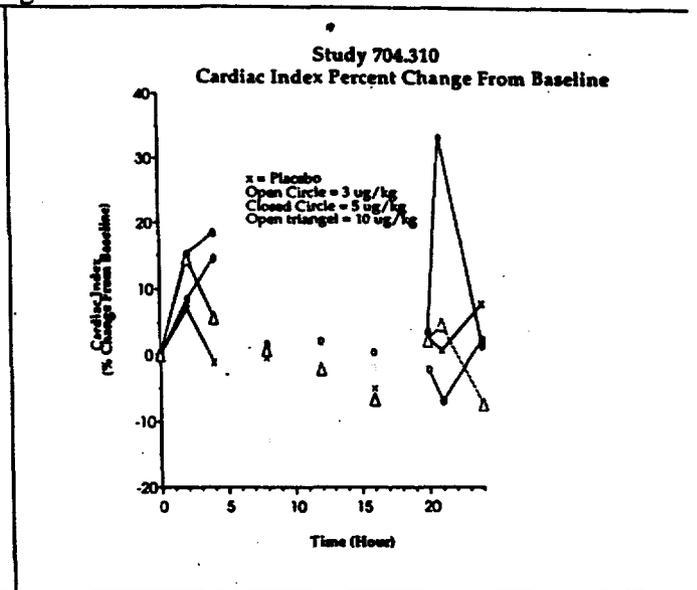


Figure 5.2



From a descriptive point of view (since this was not a prospective primary analysis), Natrecor appeared to decrease PCWP at 0.5 and 1 hours after the first dose relative to placebo. None of the three Natrecor doses appeared to differ from each other. After the last bolus only the 5 ug/kg bolus doses differed from placebo.

Cardiac Index: Baseline Cardiac Index for the three Natrecor treatment groups and placebo is also shown in Table 5.4. The cardiac indices did not differ across groups at baseline. The effect of Natrecor boluses on cardiac index is shown in Figure 5.2. There was no difference in effect on cardiac index at 4 hours after the last bolus (the primary endpoint, Omnibus F-test). There was no consistent effect after the last bolus, with the exception of the 5 ug/kg dose (the middle dose) which had a statistically greater drop in cardiac index relative to placebo. At none of the inter-dosing intervals was even the nominal p value < 0.1 .

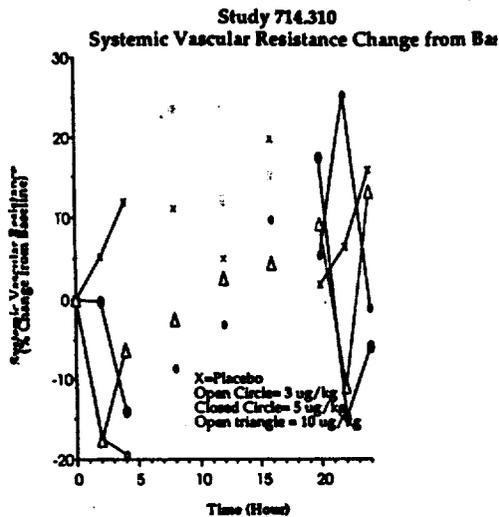
Systemic Vascular Resistances: Baseline Systemic Vascular Resistance is also shown in Table 5.4 for the three doses and placebo. The SVR were the same across groups at baseline. At the interdosing interval of the last bolus there did not appear to be any residual effects and no dose response is observed (Figure 5.3).

Pulmonary Artery Pressures: (Data not graphed). The effect of the various boluses on mean pulmonary artery pressures was variable. The 3 and 5 ug/kg Q- 4 Hour regimens appeared to markedly decrease mean pulmonary artery pressures. The 10 ug/kg Q-4 Hours bolus, however, differed little from placebo.

Systemic Blood Pressures: Systemic blood pressures both systolic and diastolic were generally lower among those who received boluses of Natrecor. The effects were so highly variable, however, that none of the time points approached statistical significance.

Heart Rate: (Data not graphed)

Figure 5.3



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Safety:

Deaths, Dropouts and Discontinuations.

There were no deaths during the study or within 14 days of receiving the infusion.

Two patients died after the 14 day observation period.

Patient 356-103(Placebo) was a 73-year old white male with NYHA Class IV and an ejection fraction of 11%. This subject's underlying cardiac problems included coronary artery disease and hypertension. He tolerated the infusion during the protocol. The patient was apparently found dead at home 19 days after the infusion.

Patient # 373-103 (Natrecor 10 ug/kg dose). This was a 47 year old black male NYHA CHF Class III, with an ejection fraction of 29%. Underlying cardiac problems included CHF, hypertension and sick sinus syndrome. The subject had a pacemaker at baseline. During the study the subject had increased shortness of breath, associated with sweating insomnia and dizziness. The ADR form notes that the nurse thought the pacemaker was not capturing. It is unclear if any procedure was done to rectify the pacemaker. The patient died a sudden death on day 30.

Urine Output: Not submitted for the "All-Patients" Cohort

Discontinuations:

Ten subjects discontinued during active infusion. Seven of these patients discontinued due to adverse events and three due to inadequate response (there was no pre-specified definition what constitutes an inadequate response).

Subject # 352-201 (Placebo). This was a 51-year old white male with NYHA Class IV CHF and EF < 10% whose cardiovascular problems included ischemic heart disease, myocardial infarction x 2. He was status-post CABG. This patient discontinued treatment after two intravenous boluses of placebo for worsening CHF. Qualifying and pre-treatment hemodynamics showed a wedge of between 31-36 mm Hg and a cardiac output output of between 2.8-3.4 L/Min. The subject discontinued due to worsening CHF. Hemodynamics at the time of discontinuation showed a wedge of 30 mm Hg and a cardiac output of 3.4 L/min. (comment: not a major change). The subject received dobutamine.

Subject 361-102 (Natrecor 3 ug/kg). This was a 49 year old white female with NYHA Class II CHF and a ejection fraction of 20-25%. She had a history of coronary artery disease was status-post by a myocardial infarction as well as a CABG. She developed symptomatic hypotension. Her blood pressure decreased from a baseline BP of 104/69 and a pulse of 98 BPM a nadir, of 84/48 with a pulse of 94 BPM. Pulmonary artery pressure also declined from a baseline value of 78/27 mm Hg to a treatment value of 38/16 mm Hg. Fifteen minutes prior to the episode of hypotension she received a dose of nitroglycerine SL, nitropaste and intravenous nitroglycerine to treat an episode of angina. The timing of the nitroglycerine use relative to the hypotensive episode is unclear (The CRF, under **CARDIOVASCULAR MEDICATIONS**, notes the nitroglycerine was given. This entry was subsequently crossed out. The crossed out time was approximately 7 ½ hours after the episode of hypotension).

Subject # 361-103 (3 ug/kg). This is a 64 year old white male NYHA Class IV CHF with an ejection fraction of 15-20%. This subject had a history of cardiomyopathy and atrial fibrillation. Approximately 10 minutes after the second IV bolus of study drug, the subject developed substantial hypotension 117/65 mm Hg pulse 103 BPM at baseline to 56/31 mm Hg with a pulse 102 BPM. The subject had developed asymptomatic hypotension after the first bolus. The subject was treated by placement in the Trendelenberg position.

Subject 359-101 (3 ug/kg). This was a 47 year old black male with NYHA Class IV CHF and an EF of 5-10 %. The patient had a history of dilated cardiomyopathy, hypertension and previous subendocardial infarction. The patient's initial hemodynamics during qualification and pretreatment were a wedge of 32-30 mm Hg and a cardiac output of 3.86-3.0 l/min. The hemodynamics prior to discontinuations are unclear. The last wedge I saw was a wedge of 32 mm Hg but there was no concurrent cardiac output measurement. The last cardiac output measurement was 45 minutes earlier and was 4.02 l/min. The subject received an intravenous push of morphine sulfate approximately 5 minutes before the episode of hypotension. The subject received milrinone but milrinone was not started until approximately 3 1/2 hours after the episode of worsening CHF.

Subject 355-103 (3ug/kg). This was a 63-year old male with NYHA Class III CHF and an ejection fraction of 10%. The subject's cardiovascular history was remarkable for idiopathic cardiomyopathy and atrial fibrillation. The patient discontinued study drug because of asymptomatic hypotension after the administration of the fifth dose. The vital signs that I saw were a BP of 70/50 mm Hg with a pulse of 83 BPM. The subject also had an episode of relative hypotension following the first dose.

The BP was 91/49 mm Hg and pulse 123 BPM. Baseline vital signs were BP=116/65 mm Hg and pulse = 69 BPM.

Subject 360-101 (3 ug/kg). This was a 66-year old white male NYHA Class II CHF and an EF of 18% as a consequence of ischemic cardiomyopathy. Ten minutes after his usual dose of isodril and enalapril, he became hypotensive with a BP of 85/61 mm Hg and a heart rate of 34 BPM. The EKG showed a junctional rhythm. The subject was treated with fluids and atropine. The rhythm and rate recovered. A second episode of junctional bradycardia was noted two weeks later, after treatment with nitroglycerine for a possible myocardial infarction (no cardiac enzymes or EKG were included).

Subject # 373-203 (5 ug/kg). This was a 41-year old black male with NYHA class IV and EF of 10% and an underlying diagnosis of cardiomyopathy and hypertension. The pretreatment vital signs were BP = 71/46 mm Hg with a pulse =102 BPM. During the study the blood pressure dropped to 66/37 mm Hg and the pulse increased to 103 BPM. The medication was discontinued, and he was treated with saline, dopamine and dobutamine.

Subject # 306-304 (10 ug/kg). This was a 73-year old white male with NYHA Class III CHF and an EF of 20 %.. His cardiovascular condition included underlying hypertension and atrial fibrillation. He was status-post aortic valve replacement. Following the first bolus of medication, the subject's blood pressure decreased from 120/76 mm Hg and a pulse of 91 BPM at baseline to a low of 68/38 mm Hg and a pulse of 98 BPM forty five minutes after the initial bolus. The subject was treated with normal saline and Natrecor was stopped. The episode of hypotension lasted 1 ½ hours.

Subject # 361-303 (10 ug/kg) was a 69-year old white male NYHA Class III CHF and an EF of 15-20 %. This subject had a history of atrial and ventricular fibrillation. Following the first intravenous bolus of medication the subject felt light-headed. Pretreatment blood pressure was 100/60 mm Hg and a pulse of 88 BPM. Forty-five minutes after the first bolus, his blood pressure decreased to 73/49 mm Hg with a pulse of 89 BPM. The subject remained hypotensive for an additional one hour. The subject was treated with fluids and dopamine.

Serious Adverse Events:

Three subjects had serious adverse events . The adverse event of **Subject #360-101** was summarized above.

Subject # 306-204 (placebo). This was a 54 year old white male , NYHA Class IV CHF who tolerated the study procedures but was readmitted to the hospital on day 8 for worsening CHF. On day 11 he developed a pulmonary embolus for which he was treated with heparin and then Coumadin. During the hospitalization he developed heart block which required the insertion of a permanent pacemaker.

Subject 315-301 (10ug/kg). this was a 57-year old white male who tolerated the procedures well but on day 4 after discharge from the hospital he was involved in a car accident and sustained a myocardial contusion. It is unclear from the records whether he was the passenger or driver of the car.

Table 5.5 Adverse Events Through Day 14 (At least three events in any group, All patient Cohort).

Event	PBO	3 ug/kg	5 ug/kg	10 ug/kg	Event	PBO	3 ug/kg	5 ug/kg	10 ug/kg
Hypotension	2(12%)	4(29%)	2 (14%)	4 (27%)	Cough Increased	0	3 (21%)	3 (21%)	2 (13%)
Vent. Tachycardia	1 (6%)	1(7%)	4 (29%)	2 (13%)	Dyspnea	1 (6%)	2 (14%)	1 (7%)	4 (27%)
CHF	5 (29%)	1 (7%)	1 (7%)	0 (0%)	Anxiety	2 (12%)	0	3 (21%)	2 (13%)
Catheter Pain	3 (18%)	2 (14%)	4 (29%)	3 (20%)	Insomnia	0	0	3 (21%)	3 (20%)
Headache	1 (12%)	2 (14%)	4 (29%)	3 (20%)	Dizziness	0	0	0	4 (27%)
Pain	1 (6%)	1(7%)	5 (36%)	1 (7%)	Nervousness	0	1(7%)	3 (21%)	0
Chest Pain	0	0	1 (7%)	3 (20%)	Leg Cramps	1 (6%)	0	3 (21%)	1 (7%)
Headache	2 (12%)	2 (14%)	3 (21%)	2 (13%)					

There are far too few people to draw any conclusions about the relationship of drug and adverse events. Moreover, it is unclear if during the entire 14-day period those who assessed adverse events were blinded to treatment.

More placebo patients had evidence of CHF, yet more high dose infusion patients had dyspnea. There doesn't appear to be internal consistency as to whether Natrecor decreases symptoms of CHF. Ventricular Tachycardia was more frequent in the drug dose groups (most common in the 5 ug/kg regimen).

Adverse Events listed as Severe: A total of 10 patients had 11 episodes that were classified as severe. These are listed below:

Table 5.5 Events Classified as Severe

Patient # (Dose)	Event	Patient # (Dose)	Event
306-202 (PBO)	Dysuria	359-101 (3 ug/kg Q 4)*	Worsening CHF
306-203 (5 ug/kg Q4)	Right Side Pleuritic Chest Pain	360-101 (3 ug/kg Q4)*	Bradycardia
306-204 (PBO)*	Worsening CHF, Heart Block	360-103 (3 ug/kg Q4)	Left Foot Pain
315-301 (10 ug/kg Q 4)*	Car accident	361-102 (3 ug/kg Q 4)*	Hypotension
359-101 (3 ug/kg Q 4)*	Worsening CHF	379-101 (PBO)	Pain in Right Knee

* Capsular summaries are contained above either under discontinuations or severe adverse events

Vital Signs: (see above).

EKGs. The only data that was captured by the CRFs was whether the EKGs were normal or abnormal. No rhythm changes or electrocardiographic intervals or changes of these intervals were captured.

Laboratory: Tables 33A-57D (vol. 151 pp. 53-152).

The sponsor analyzes this small study by comparing each of the parameters at a specific time point as well as changes from baseline, number of measurements outside an arbitrarily defined normal range, and shifts to or from this normal range. Although some of the analyses appeared to show differences in one of the treatment groups when compared to placebo, these differences did not appear either consistently drug or dose related.

#6. Study # 704.312 (vol. 75-77).

Title of Study: A Dose ranging Study of NATRECOR hBNP in the Treatment of Postoperative Hypertension After Coronary Artery Bypass Surgery.

Investigator and Sites:

Table 6.1 Investigator, Sites and Number Enrolled.

Dr. R. Davis Portland VA Medical Center Portland OR N=20	Dr. Barbara Tardiff Duke Univ. Med. Center Durham, NC N=4
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Study Summary: This is an open-label, sequential, dose-response study of Natrecor in patients who were post-operative from CABG. Doses of Natrecor ranged from 5 to 25 ug/kg.

Protocol, Line Listings and CRFs. The original protocol and one amendment were supplied, line listings were available, and representations of CRFs were supplied within the CANDAs on CD-ROM.

The study planned to enroll subjects who were hypertensive (SBP > 140 mm Hg for > 15 minutes) within 12 hours of CABG surgery. Subjects were discontinued from any intravenous nitroprusside infusion at least 30 minutes prior defining the subject as hypertensive. Treatment of the patient with low dose nitroglycerine (0.25-0.5 ug/kg/min) was acceptable. At the time of enrollment, all subjects were expected to be instrumented with a Swan-Ganz as well as an arterial line.

Subjects were excluded if they had valvular stenosis or obstructive cardiomyopathy, recent stroke (within 3 months), renal disease (serum creatinine > 3.0 mg/dL), ventricular arrhythmias (multifocal PVCs and VT), EF < 30%, PCWP < 10 mm Hg.

A total of 20 subjects were enrolled, four subjects per treatment group. These subjects were treated with doses of either 5, 10, 15, 20 or 25 ug/kg as a bolus, administered over a 30-60 seconds. Only when the first cohort successfully completes the study will the next cohort be enrolled. Each subject was to receive up to two boluses of drug. The first dose was given upon enrollment, the second bolus, at half the initial dose, was given only if the SBP, fifteen minutes after the initial bolus, was still > 140 mm Hg or if the subject responded initially to Natrecor but then had a recurrence of the elevated blood pressure.

Procedures:

Screening:

Screening procedures, were performed at least one week prior to surgery. The screening included the patient signing an informed consent as well as satisfactorily fulfilling the protocol requirements for medical history, physical exam, preoperative ECG, CXR, UA and hematology and chemistry.

Immediately Prior to Drug administration:

Hemodynamic Measurements included: PAP, RAP, heart rate, PCWP, CO and FiO₂.

Vital Signs included: Systolic, Diastolic and Mean Arterial Pressures.

Blood Gas Studies included: Arterial pO₂, pCO₂, oxygen content, mixed venous blood MvO₂, MvCo₂ and O₂ content

Laboratories include: CBC, serum chemistries and baseline hBNP levels.

Treatment Period:

Vital Signs were measured every 5 minutes for 60 minutes and after the first and, if administered, after the second bolus then every 15 minutes, thereafter.

Hemodynamic Measurements: were measured at 15, 30, 45, 60 minutes and then hourly.

Blood Gas Studies: were measured at 15, 30, 45, 60 and 90 minutes.

Cardiac Rhythm to be constantly monitored

Plasma BNP samples drawn at 1, 4, 8, 15, 30, 60, 90 and 120 minutes.

Post Treatment Period (the hours reflect the time from the initial infusion):

Vital signs were recorded at 9 and 12 hours.

Hemodynamics were recorded at 9 and 12 hours

Routine laboratories were obtained on the day following drug administration.

At 7-days after the treatment the subject was interviewed for adverse events.

Statistics: The primary variable of interest is SBP. No specific time point was defined as the primary metric of interest. SBP was analyzed by a one-way ANOVA. The null hypothesis of a zero intercept was tested. Linear contrasts were constructed and tested. A descriptive analysis was made as to the time to onset of effect and the duration of effect. The time of onset as well as time to offset of effect was predicated on the maintenance of a blood pressure < 140 mm Hg for at least 15 minutes.

Results:

Demographics: A total of 24 subjects were enrolled at two clinical sites, twenty from one site. No subjects were lost to follow up.

These subjects were allocated in the following manner

Table 6.2 Allocation of Subjects Study 704.312

Dose	5 ug/kg	10 ug/kg	15 ug/kg	20 ug/kg	25 ug/kg
N	3	4	4	4	9*

* Includes one subject who mistakenly received a dose of 32 ug/kg.

Twenty-two subjects were male, the mean age (means ± SD) was 63.7 ± 11.4 years., 21 were Caucasian, 1 was black and 2 were Native American, weight (means ± SD) was 85.1 ± 13.7 kg.

Caveats: One subject, allocated to the 5 ug/kg bolus, actually received 32 ug/kg as a single dose. This subject's data was analyzed in conjunction with that of the 25 ug/kg dose. Six subjects received a second dose of hBNP at half the original dose. These doses were administered at times ranging from 18-37 minutes after the initial bolus. An additional three subjects received a second full dose (not ½ the dose as pre-specified in the protocol). These subjects had transient responses to hBNP but then their SBP then increased to > 140 mm Hg. The timing of the second boluses were 35, 38 and 83 minutes after the initial bolus. These three subjects were initially treated with 15 ug/kg (2 subjects) and 25 ug/kg (1 subject).

Six subjects received higher doses of nitroglycerine that were pre-specified. The subjects are listed in Table 6.3

Table 6.3 Subject # and Maximal dose of Nitroglycerine

Subject # ⇒	384003	384009	384011	384014	384018	428024
Maximum NTG Dose ug/kg/min ⇒	2.0	1.0	1.35	1.0	0.90	0.52

The subject, randomized to the 5 ug/kg group who received 32 ug/kg was analyzed with the highest (25 ug/kg) group.

Kinetics:

hBNP was measured by an ELISA method (see Dr. Sadreih's review for details).

The kinetic profiles were best fit to a two-compartment model (with the exception of one subject for whom a one- and two-compartment model was similar). The best estimate of the kinetic parameters are shown in Table 6.4:

Table 6.4 Best Fit Parameters Based on A Two-Compartment Model

	CL ml/min/kg	α min ⁻¹	$t_{1/2\alpha}$ min	β hr ⁻¹	$t_{1/2\beta}$ hr	k_{21} hr ⁻¹	Vc L/Kg	Vss L/kg
mean	9.85	0.537	2.35	2.71	0.307	9.92	0.075	0.17
95% intervals	8.27-11.43	0.28-0.794	1.2-3.35	2.22-3.20	0.242-0.372	5.62-14.2	0.059-0.091	0.133-0.206

CL=clearance; α = first decay constant; $t_{1/2\alpha}$ = the corresponding half life; β = second decay constant,
 $t_{1/2\beta}$ =the corresponding half-life; k_{21} the rate constant from the peripheral to the central compartment;
 Vc= Volume of central compartment; Vss = Steady State Volume of Distribution.

The average fraction of the AUC accounted for by the initial half-life was approximately 30%, that of the terminal half-life was approximately 70%.

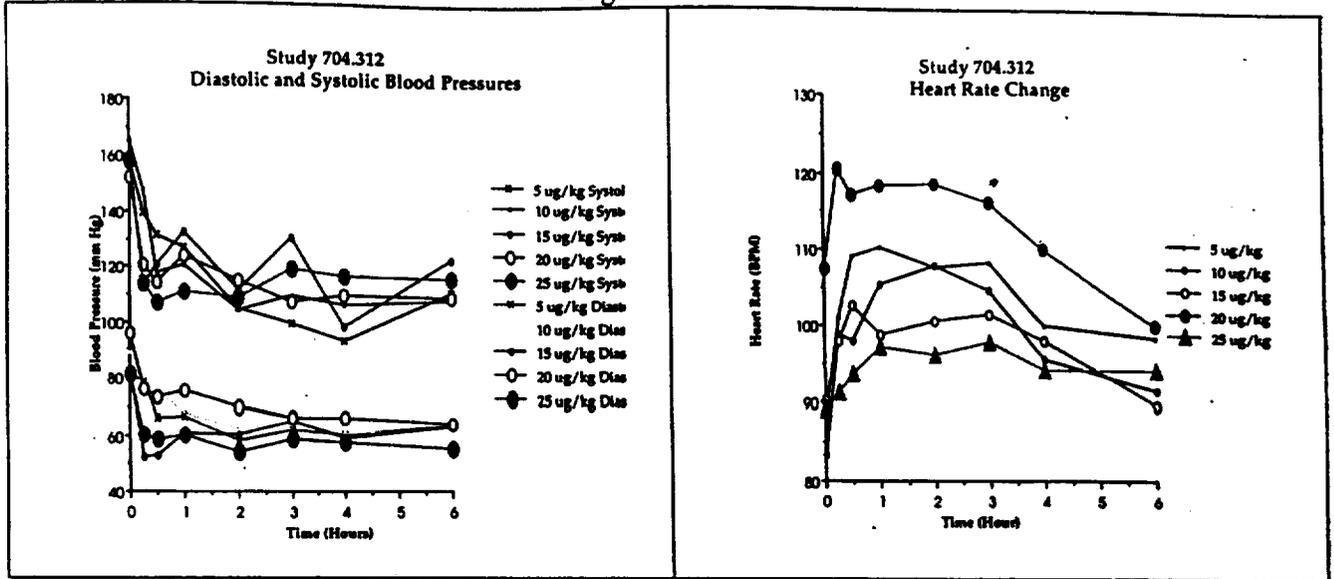
Blood Pressure/Heart Rate Responses:

There was a rapid drop in blood pressure by 15 minutes after the initial bolus of hBNP (Figure 6.1). Blood pressure at the end of the 6-hour observation period was substantially lower than 140 mm Hg. None of the Natrecor doses, however, appeared to differ from each other in the magnitude of blood pressure effect. With respect to heart rate (Figure 6.2), there was a corresponding increase in heart rate also noted within 15 minutes (the first measurement) time point. It should be noted that a large number of subjects had concurrent changes of nitroglycerine infusion rates during the observation period. The vital signs changes (and perhaps the lack of a convincing dose response effect) partly may be attributed to post-operative recovery as well as to changes in nitroglycerine infusion rates.

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Figure 6.1

Figure 6.2



Hemodynamics:

Baseline hemodynamics measurements are shown in Table 6.5. I've also included some impression as to whether there was an effect relative to baseline (Under General Trend). Given the small number of subjects, there was no consistent dose-related effect on hemodynamics.

Figure 6.5 Hemodynamic Parameters 710.312

Parameter ↓	Dose ⇒	5 ug/kg (n=3)	10 ug/kg (n=4)	15 ug/kg (n=4)	20 ug/kg (n=4)	25 ug/kg (n=9)	General Trend
PCWP (mm Hg)		17.7 ± 4.7	13.0 ± 4.8	11.3 ± 1.5	14.3 ± 8.5	14 ± 2.4	↓
Cardiac Index (L/Min/M2)		3.6 ± 1.6	3.1 ± 0.5	2.8 ± 0.5	3.1 ± 1.2	2.8 ± 0.2	⇒
Right Atrial Press (mm Hg)		13.7 ± 1.5	12.8 ± 4.7	10.3 ± 1.9	9.8 ± 1.0	12.5 ± 2.2	⇒↓
Systemic Vascular Resistance (dynes*sec*cm-5)		1208 ± 680	1263 ± 131	1409 ± 295	1450 ± 473	1492 ± 490	↓
Pulmonary Vascular Resistance (dynes*sec*cm-5)		20 ± 76	102 ± 33	118 ± 23	117 ± 112	18 ± 72	⇒
Systolic Pulm Artery Press (mm Hg)		25 ± 3.6	30 ± 10	27 ± 5	33 ± 6	30 ± 7	⇒
Diastolic Pulm Artery Press (mm Hg)		14 ± 3	17 ± 7	16 ± 3	17 ± 6	16 ± 3	⇒

PK-PD Analysis. The sponsor did not attempt a PK-PD analysis of the data.

Safety:

There were no deaths.

One subject (# 384-003) treated with 5 ug/kg hBNP x2, was eventually treated with intravenous nitroprusside when the SBP did not drop below 140 mm Hg. Three subjects # 384-009; # 384-014 and #384-022, treated with 15, 20 and 25 ug/kg hBNP, respectively, had acceptable drops

in blood pressure following two boluses of drug but subsequently redeveloped elevated systolic blood pressure. These subjects were treated with intravenous nitroprusside and esmolol. Two additional subjects required intervention for blood pressure increases within 24 hours of entering the study but after completing the observation periods.

Adverse Events: The sponsor lists a total of 16 subjects with one or more adverse events during the infusion period and within seven days of the infusion period.

Table 6.6 Adverse Events During and Within Seven Days of Natrecor infusion Study 710.312

Pt # (dose)	Event (day)	pt # (dose)	Event (day)	Pt #	Event (day)
384001 (5)	None	384010 (15)	None	384018 (25)	None
384003 (5)	Hypertension (1)	384011 (15)	Oliguria (2)	384019 (25)	Oliguria (2) Hypertension (2)
384004 (5)	None	384012 (15)	None	384020 (25)	Fever (1)
384005 (10)	None	384013 (20)	Atrial fib (3)	428021 (25)	Fever (1) Hypotension (2)
384006 (10)	None	384014 (20)	Sinus Tachycardia (1)	428022 (25)	Hypotension (1) Fever (1) Hypertension (2) Lung Edema (2) Hypoxia (2 and 3) Abdominal Tenderness (3) Atrial Flutter (3) Atrial Fibrillation (4)
384007 (10)	Nausea and Vomiting (2)	384015 (20)	Hemorrhage (1) Oliguria (2) Hypoxia (4)	428023 (25)	Hypotension (1) Confusion (2) Oliguria (3) Bradycardia (3) Insomnia (5)
384008 (10)	Nausea and Vomiting (3)	384016 (20)	Hypotension (1)	428024 (25)	Nausea (1) Lung Disorder (2)=crackles Dyspnea (3)
384009 (15)	none	384017 (25)	Hypertension (3)	384001 (25)	None

Since this was a small data base, with no placebo group, it is not possible to determine if any events are drug related or post-surgery related.

Four patients had oliguria during the one week observation period (#s 384011, 384015, 384019 and 428023). All these subjects received at least 15-ug/kg hBNP and the events occurred on day 2-3 post-operatively. Three of these subjects apparently responded to Lasix. No information was supplied for the fourth. Two subjects (#s 428022, 384013) had some form of supraventricular arrhythmia, one of these, (# 384013) had atrial flutter listed among the previous cardiovascular conditions i.e. the supraventricular arrhythmia was likely a pre-existing condition.

Vital Signs: The group means for vital signs during the infusion are displayed in Figures 6.1 and 6.2. Table 6.7 contains both the highest heart rate as well as the lowest diastolic blood pressure within 6 hours of the bolus. In order to determine if the index measurement is a fluke, I've also included the closest in value heart rate and blood pressure that occurred within ½ hour of the index measurement.

Table 6.7 Study 704.312 Highest Heart rate and Lowest Diastolic Blood Pressures

pt # (Dose)	HR _{max}	HR ₂	DBP _{min}	DBP ₂	pt # (Dose)	HR _{max}	HR ₂	DBP _{min}	DBP ₂
384001(5)	90	89	92/48	110/50	384011 (15)	106	106	153/47	151/50
384002 (25)	113	111	85/49	87/57	384012 (15)	108	106	84/39	85/40
384003 (5)	127	120	90/54	95/58	384013 (20)	132	131	88/55	85/57

384004(5)	132	125	99/60	79/62	384014 (20)	142	137	127/-	132/57
384005 (10)	125	125	105/55	110/55	384015 (20)	122	121	69/42	79/59
384006 (10)	101	96	106/46	80/48	384016 (20)	138	135	96/65	101/68
384007 (10)	94	87	110/41	111/47	384017 (25)	95	94	82/42	83/44
384008(10)	144	140	111/58	96/67	384018 (25)	91	91	101/41	101/44
384009 (15)	107	106	90/49	87/55	384019 (25)	176	141	91/51	100/55
384010 (15)	120	119	126/47	125/48	384020 (25)	155	113	102/54	103/56

HR_{max} = Maximal Heart Rate, HR₂ = Next nearest Heart Rate within ½ hour of index measurement;
 DBP min. = Minimum DBP DBP₂ = Nearest DBP measurement within ½ hour of Index DBP

Tachycardia (usually defined as a heart rate > 100) was fairly common, Diastolic blood pressures < 60 mm Hg was also fairly common.

EKGs. The EKGs were not analyzed except to categorize the EKGs as either normal/abnormal. No information is, therefore, available as to EKG intervals.

Laboratory: Blood was drawn for laboratory values at screening, prior to treatment (this must be post-surgery) and 24 hours after the start of the bolus. The sponsor analyzed the change from baseline for the individual groups by ANOVA , linear trends or shift analysis. All subjects were also combined and change from baseline analyzed. I have tabulated some of the abnormalities in Table 6.8.

Table 6.8 Study 710.312 Laboratory Changes and the analysis (es) which suggested Differences..

Parameter	Direction -method	Sodium	↓ Liner Contrasts Shift Analysis
BUN↔↑↓	↑ All Subject	Potassium	↑ All Subjects
Creatinine	↑ All Subject	Bicarbonate	↑ All Subjects
LDH	↓ All Subject Shift Analysis	Calcium	↓ All Subjects Shift Analysis
SGOT	↑ All Subjects Shift Analysis	Phosphorus	↑ All Subjects Shift Analysis
Magnesium	↑ All Subjects Shift Analysis	Leukocytes	↑ All subjects
Hematocrit	↓ Shift Analysis		

It is hard to determine which of abnormal values is drug related or surgery related.

Conclusion: this was a small, two-center (nearly all subjects, however, were enrolled in one of the centers), open-labeled study in patients shortly after completing cardiac bypass surgery and had a systolic blood pressure was > 140 mm Hg for at least 15 minutes. Subjects were to be on low-dose nitroglycerine, those enrolled were also to receive a single bolus and possibly a second bolus hBNP. The doses of hBNP were 5 ug/kg, 10 ug/kg, 15 ug/kg, 20 ug/kg and 25 ug/kg. There was a steep decrease in both systolic and diastolic blood pressures by the first measurement time point. There was a corresponding increase in heart rate also noted at the first measurement time point. None of the doses, however, differed from each other.