2.1 Indication

Natrecor is proposed for the short term intravenous therapy of congestive heart failure. In these patients, the sponsor claims that ...'Natrecor rapidly reduces PCWP and SVR and increases CI. It also causes rapid symptomatic improvement.'

2.2 Administrative History

3.25.93 Pre-IND meeting with the Division of Cardio-Renal Drug Products (DCRDP). Hemodynamic endpoint accepted for primary endpoint for efficacy of nesiritide. Long-term toxicity, carcinogenicity, and reproductive studies waived by Division due to the short-term nature of the therapy.

4.17.96 End of Phase II meeting with DCRDP. Discussion of switch from synthetic to recombinant nesiritide.

7.23.96 End of Phase II meeting with DCRDP. Discussion of additional phase III trials proposed by sponsor.

During this meeting Dr. Temple expressed a preference for an analysis of the clinical data using a last value carried forward analysis. This was out of concern for the non-parametric nature of the primary analysis proposed for the pivotal efficacy trials.

7.9.97 Pre-NDA meeting with DCRDP.

1.27.98 Advisory Committee meeting, discussing IV therapy for CHF.

10.98 Advisory Committee meeting, discussing Guidelines for CHF therapy.

2.3 Proposed Labeling

--from proposed labeling, submitted by the sponsor 4.24.98.

2.3.1 Proposed Indications

Natrecor is indicated for intravenous therapy of congestive heart failure (CHF). In these patients, Natrecor reduces PCWP.

2.3.2 Proposed Contraindications

None known.

2.3.3 Proposed Dosing Schedule

Nesiritide should be administered as a continuous IV at a dose of μg/kg/min. The rate may be adjusted according to hemodynamic and clinical response, although it is recommended that dose increases be made no more frequently than every 3 hours to permit peak hemodynamic effects of nesiritide to be achieved. In the clinical trials, nesiritide was administered for up to 9 days, although 83% of patients received it for <72 hours.

No dose adjustment is proposed for patients with renal impairment.

2.3.4 Proposed Language Regarding Drug Interactions, Special Safety Concerns And Populations, And Monitoring

Parenteral administration of recombinant products should be attended by appropriate precautions in case an allergic or untoward reaction occurs. No serious allergic or anaphylactic reactions have been reported with Natrecor.

Natrecor is not recommended in patients who are sensitive to nesiritide, *E. coli* derived products, or to any component of the product.

2.3.4a Drug Interactions

There was no evidence of drug interactions in clinical studies in which Natrecor was administered concurrently with other drugs, including diuretics, digoxin, ACE inhibitors, beta blockers, dobutamine, dopamine, nitrates, calcium channel blockers, angiotensin II receptor antagonists, and Class III antiarrhythmic agents.

However, the vasodilating effects of Natrecor may be additive to those of other vasodilating agents. Therefore caution should be exercised when combining Natrecor with other vasodilators.

2.3.4a Drug Interactions (cont)

Chemical/ Physical Interactions

Some brands of thermodilution and central line catheters (Swan- Ganz, etc.) are manufactured with unfractionated heparin coating the inner surface of the catheter. Natrecor may bind with the surface of these catheters and lead to a reduction in the amount of Natrecor delivered to the patient. It is recommended that Natrecor be given through a peripheral IV line or a nonheparin- coated central catheter. In a preclinical study in rabbits, IV heparin used at a therapeutically relevant dose did not affect the biological activity of hBNP.

Drug/ Laboratory Test Interactions

No laboratory test interactions with Natrecor have been identified.

2.3.4b Precautions

a. Cardiovascular

As with most vasodilators, Natrecor may produce hypotension. It should be used with caution in patients who would be unusually compromised by undue hypotension. During treatment with Natrecor, blood pressure should be monitored and the rate of Natrecor infusion reduced or stopped in patients showing excessive decreases in blood pressure.

Natrecor is not recommended for patients with significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, pericardial tamponade, or other conditions where cardiac output is dependent upon venous return, patients suspected to have low cardiac filling pressures or for other patients for whom vasodilating agents are not appropriate.

Since Natrecor is not an inotrope, it should not be used as primary therapy for patients with cardiogenic shock or other conditions requiring pressor agents.

No clinical studies have been conducted to date in patients in the acute phase of myocardial infarction. Natrecor lowers plasma aldosterone and may produce modest diuretic, natriuretic, and potassium- sparing effects. Improvements in cardiac function with resultant diuresis may necessitate a reduction in the dose of diuretic. Consideration should be given to monitoring fluid and electrolyte status during therapy. As a consequence of inhibiting the renin- angiotensin- aldosterone system, changes in renal function may occur in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin- angiotensin- aldosterone system, treatment with Natrecor may be associated with progressive azotemia and/ or oliguria. Moderate increases in serum creatinine during or after treatment were reported in 6% of all CHF patients receiving Natrecor compared to 3% of control patients. However, an increase in serum creatinine of 100% or acute renal failure did not occur more frequently in Natrecor patients than in control patients.

b. Pregnancy:

Category C

Animal reproductive studies have not been conducted with Natrecor. It is also not known whether Natrecor can cause fetal harm when administered to pregnant women or can affect reproductive capacity. Natrecor should be used during pregnancy only if the potential benefit justifies any possible risk to the fetus.

c. Nursing Mothers

Caution should be exercised when Natrecor is administered to nursing women, since it is not known whether it is excreted in human milk.

d. Pediatrics

The safety and effectiveness of Natrecor in pediatric patients has not been established.

e. Geriatrics

Of the total number of subjects in clinical trials with Natrecor, 35% were aged 65 years or older, while 13% were 75 or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Pharmacokinetic analyses have not disclosed any age- related effects on the pharmacokinetics of Natrecor.

2.3.4b Precautions

f. Carcinogenesis, mutagenesis, impairment of fertility

Long term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility of Natrecor. Studies to determine mutagenicity (Ames test) were negative at all concentrations tested.

2.4 Foreign Marketing

As of 7.30.98, nesiritide has not received marketing approval in any country. Additionally, marketing approval of nesiritide has not been withdrawn, rejected, or applied for, in any foreign country.

3.0 Chemistry, Manufacturing, and Controls

There are no known clinical implications of chemistry, manufacturing and control identified in consultation with the assigned manufacturing and control reviewer.

4.0 Pharmacology

4.0.1 Pre-Clinical Pharmacology

For details of the pre-clinical and clinical pharmacology, the reader is referred to Dr. Papoian's review. The majority of the information in the following section is derived from the summaries provided by the sponsor.

4.0.2 Pre-clinical Pharmacokinetics

a. Absorption

The absorption of nesiritide was not studied, as it is to be administered intravenously.

b. Distribution

The tissue distribution of hBNP was assessed in rabbits using [^{14}C]-labeled synthetic peptide. At 10 minutes following intravenous bolus administration of 30 µg/kg to rabbits, [^{14}C] label distributed (expressed as a percent of total dose) to skeletal muscle (21.5%), liver (13%), large intestine (10%), small intestine (8.5%), kidneys (7.5%), and fat (3.5%). Significant [^{14}C] label was found in the bile and urine, suggesting that the liver and kidney are important routes of excretion. There were no remarkable differences between male and female animals.

c. Pharmacokinetics & Metabolism

In rabbits and monkeys, hBNP is administered as an intravenous infusion, plasma concentrations quickly reach a steady-state level that is generally proportional to dose. Upon terminating the infusion, the plasma concentration rapidly declines. These observations are consistent with the short duration of biological effects of hBNP observed in animal studies after an IV bolus injection or after cessation of infusion.

In preclinical studies, data pertaining to the elimination of plasma hBNP typically fit a two-compartment model that assumes the drug concentrations decline biexponentially following linear kinetics. The $t_{1/2}$ (half-life of the initial phase) and the $t_{1/2}$ (half-life of the terminal phase) derived from multiple studies ranged from 3.1 to 6.9 minutes and from 12.5 to 33.2 minutes, respectively. Clearance (C_L) of the parent compound ranged from 15 to 26 mL/min/kg.

It is generally believed that the natriuretic peptide clearance (NP-C) receptor is involved in the metabolism of ANP and BNP. The NP-C receptor is a cell surface protein that binds both ANP and BNP and mediates the peptide's cellular internalization and delivery to lysosomal compartments where the peptide is hydrolyzed to inactive fragments and individual amino acids. The avidity of the receptor for BNP is significantly less than for ANP, and BNP is removed from the serum more slowly. In addition, there is indirect evidence to suggest that NP-C receptor binding to BNP may be down-regulated in patients with CHF (ref. 14).

Regarding the role of endopeptidases and the NP-C receptor in BNP clearance, pharmacological blockade of the NP-C receptor in rabbits increased by 1.9-fold the plasma steady-state level of hBNP resulting from a continuous intravenous infusion. Thus, the NP-C receptor plays a role in the elimination of hBNP in rabbits. Pharmacological inhibition of neutral endopeptidase (NEP) increased by 1.7-fold the plasma steady-state level of hBNP in rabbits resulting from a continuous intravenous infusion. The sponsor concluded that endopeptidases also play a role in the metabolism of hBNP in rabbits.

4.0.2 Pre-clinical Pharmacokinetics

Using a continuous IV infusion, the steady-state plasma level of hBNP increased 1.9-fold 1 hour following complete kidney blood flow restriction. Furthermore, with an IV bolus, the clearance of hBNP was reduced by half in animals subjected to complete renal blood flow restriction. Thus, the kidney is involved in the elimination of hBNP from the plasma compartment in rabbits. Complete kidney blood flow restriction by bilateral renal artery ligation represents a worst-case scenario for the effects of impaired renal blood flow on hBNP metabolism.

Studies in cultures of vascular smooth muscle, in DOCA-salt hypertensive rats, and in patients with mild to severe CHF have shown that chronic exposure to elevated levels of BNP is associated with down regulation of hBNP receptors, which may occur in a matter of hours. This down-regulation of receptors has been associated with a decrease in the cGMP-mediated vasodilation. See Dr. Papoian's review for details of these data.

In Vitro Protein Binding

No information was submitted by the sponsor regarding the extent of protein binding by hBNP.

Excretion

As discussed above, both renal and hepatic routes of excretion have been posited, based on studies using [^{14}C]-labeled synthetic peptide.

4.0.3 Pre-Clinical and Clinical Pharmacodynamics

Preclinical studies have demonstrated that hBNP is a balanced vasodilator and reduces cardiac preload and afterload. In particular, hBNP treatment of conscious dogs (0.05 μg/kg/min) reduces mean right atrial pressure (MRAP) and pulmonary capillary wedge pressure (PCWP). There were no detected effects of hBNP on cardiac electrophysiology when measured in conscious dogs. Given this, the sponsor suggests that the bradycardia seen in association with hBNP treatment may be explained by either decreasing sympathetic tone and/or increasing parasympathetic tone. Increased vagal afferent effects on the heart have been documented with administration of the related peptide, ANP(ref. 4). In addition, there is no evidence that hBNP has a direct effect on cardiac contractility. In an isolated Langendorff-perfused rabbit heart preparation, hBNP did not affect the rate of cardiac contraction or contractile function as measured by the maximum rate of pressure increase (+dP/dt max) and maximum rate of relaxation (–dP/dt max). Furthermore, using isolated human ventricle trabeculae tissue, hBNP treatment had no effect on contractility. However, hBNP has been shown to increase coronary artery lumen diameter and endothelin-stimulated coronary artery blood flow in anesthetized pigs. The primary effects of hBNP seen in the animal studies, then, were on the pre- and after-load, as measured by PCWP and MRAP. There may be an additional effect to vasodilate coronary arteries. It has also been reported that in a dog model of CHF, the natriuretic effect of hBNP is attenuated, while the hemodynamic effects are enhanced (ref. 3).

Other reported effects of hBNP include an inhibition of release of both renin and aldosterone. Since there is some overlap between the structures of hBNP and angiotensin II, there may also be interactions between these two molecules at the receptor level within the kidney, adrenal, and vasculature. The decrease in aldosterone is thought to be the explanation for the observed increases in urine sodium and water excretion seen following hBNP infusion. It may also play a role in the decreased systemic blood pressure observed following hBNP infusion in animals. The possibility that hBNP has an effect on vascular permeability, similar to what has been described for ANP has not been examined to the knowledge of this reviewer. Other clinical effects of nesiritide reported include natriuresis and diuresis in normal subjects. This effect is greatly attenuated in subjects with ascites and cirrhosis. The authors of the paper speculated that this was related to sodium and water-avidity by the patients (ref. 15).

4.1 Toxicology/ Genotoxicity/ Carcinogenicity

a. Single-dose Studies/ Repeated-Dose Studies

In single-dose studies, synthetic hBNP caused no signs of toxicity up to 500 and 3000μg/kg, when administered as a bolus to monkeys and rats, respectively. Following 2 week infusion studies at doses of up to 3 and 20μg/kg/min in monkey and rats, respectively, no evidence of treatment-dependent effects on body weight, food consumption, physical clinical observations, ECG, hematology, or microscopic examination. In a study comparing synthetic and recombinant hBNP infusion in monkeys for 2 weeks, the sponsor detected no 'notable' differences.

Repeated infusion of hBNP failed to elicit an antibody response in rabbits and monkeys.

c. Genotoxicity/Mutagenicity/ Carcinogenicity

Given the short-term nature of the nesiritide infusion, limited carcinogenicity has been performed. The sponsor reports that recombinant hBNP is non-mutagenic in the Ames assay at concentrations up to 1790μg/ml.

d. Reproductive Toxicity

Given the short-term nature of the infusion, limited carcinogenicity has been performed.

5.0 Description of Clinical Data Sources

The data source for this primary medical and statistical review of NDA 20-920 comes from the computer-assisted New Drug Application (CANDA) submitted by the sponsor containing the entire NDA, along with the paper submission consisting of 89 volumes. These sources were discussed in section 1.1 above.

In addition, the sponsor submitted data not included in the NDA for several aspects of efficacy or safety, at the request of the medical or statistical reviewers. These materials are identified as to source where appropriate.

5.1 Primary Source Data (Development Program)

There are nine clinical studies submitted in support of the nesiritide NDA. Among these, there are two clinical trials that primarily support the efficacy of the drug: 1) A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Ranging Study to Evaluate the Safety and Efficacy of a 24 Hour Intravenous Infusion of Natrecor hBNP in Subjects with Congestive Heart Failure (Trial #704.311); and 2) A Randomized, Double-Blinded, Placebo-Controlled Study of Two Doses of Natrecor hBNP Administered as a Constant Infusion in Subjects with Decompensated CHF (Trial #704.325). A third, open-label trial was also performed which included a substantial fraction of the total patient database, and focused on the safety of nesiritide in the decompensated CHF population (Trial #704.326).

5.1.1 Study Type and Design/Patient Enumeration

The tables below summarize the studies submitted as part of the NDA according to the type of study (Phase I, II or III), and according to the type and number of subjects enrolled. Note that all of the trials save one enrolled subjects with CHF. This review focused on the results from the three 'long infusion' trials. Dr. Karkowsky reviewed the results from the dose-ranging studies in CHF listed below with the exception of 704.311, which is included with the 'long infusion' studies.

Table 5.1.1.1 Number of subjects in the trials submitted as part of the NDA database, grouped according the study drug administered[a].

Protocol	Control	Nesiritide	Trial Design
Phase II Dose-Ranging Studies			
704.305	6	24	Randomized, double-blind, placebo-controlled, single-dose bolus(0.3, 1,3, 10 or 15 μg/kg/min vs. placebo) study measuring hemodynamics.
704.306	4	12	Randomized, double-blind, placebo-controlled, four hour infusion (0.025 or 0.05 μg/kg/min vs. placebo) study measuring hemodynamics, neurohormone levels and renal function.
704.307	N/A (19)[b]	20	Randomized, double-blind, placebo-controlled, cross-over, escalating dose-infusion (0.003, 0.01, 0.03, and 0.1 μg/min) study measuring hemodynamics and renal function.
704.309	16	44	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Three doses (5 or 10 μg/kg q4 hours for 24 hours or 10 μg/kg q6 hours) were compared with placebo for effects on hemodynamics and renal function.
704.310	17	43	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Three doses (3, 5, or 10 μg/kg q4 hours for 24 hours) were compared with placebo for effects on hemodynamics and renal function.
704.311	29	74	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Three doses (0.25 μg/kg bolus, then 0.015 μg/kg/min,0.5 μg/kg bolus, then 0.03 μg/kg/min, or 1.0 μg/kg bolus, then 0.06 μg/kg/min) as a 24-hour fixed dose infusion were compared with placebo for an effect on hemodynamics and renal function.
Phase III Clinical Efficacy & Safety Studies			
704.325	42	85	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Two doses (0.3 μg/kg bolus, then 0.015 μg/kg/min, or 0.6 μg/kg bolus, then 0.03 μg/kg/min for 24 hours of continuous infusion) were compared with placebo (for 6 hours, followed by active control) for effects on hemodynamics and renal function, and symptomatic improvement in CHF.
704.326	102	203	Randomized, open-label, parallel-design, dose-ranging study. Two doses (0.3 μg/kg bolus, then 0.015 μg/kg/min, or 0.6 μg/kg bolus, then 0.03 μg/kg/min via continuous infusion) were compared with 'standard care' for effects on renal function, weight loss, duration of hospitalization, need for additional parenteral therapies, need for readmission, need for intubation, need for dialysis or ultrafiltration, and symptomatic improvement in CHF. Duration of infusion at discretion of individual investigators.
Total	**216 (235)**	**505**	

a. Data from NDA volume 1.78

b. Cross-over designed trial.

5.1.1 Study Type and Design/Patient Enumeration

In addition, another trial was performed in a non-CHF population, examining the treatment of post-operative hypertension.

Table 5.1.1.2 Number of subjects in the non-CHF trial submitted as part of the NDA database[a].

Tx of Post-Op Hypertension (non-CHF trial)	Control	Nesiritide	Trial Design
704.312	0	24 (total)	Open-label, uncontrolled, ascending-dose, dose-response study. Six doses were examined (5, 10, 15, 20, 25, and 32.5 µg/kg) administered as 1 or 2 IV boluses over 30-60 secs. during a 6-hour period

The sponsor has divided the study population from these trials into three groups for purposes of the safety review. The first is all subjects with CHF who received study drug during the NDA program. The second are those patients with CHF who received study drug as part of a randomized, blinded trial with placebo control for the entire study period. In general, these trials enrolled stable CHF patients, who received study drug for <24 hours. The third group of patients summarized by the sponsor had CHF and received study drug as a continuous, prolonged infusion. In general, these trials enrolled patients with decompensated CHF requiring hospitalization, the target population proposed for nesiritide use. The table below summarizes this information.

Table 5.1.1.3 Patient subject groups in NDA 20-912[a].

Study #	All CHF Studies	Placebo-controlled Studies[c]	Continuous, Long-infusion Studies[d]
704.305	X	X	
704.306	X	X	
704.307	X	X	
704.309	X	X	
704.310	X	X	
704.311	X	X	X[b]
704.325	X		X
704.326	X		X

a. Data from sponsor, NDA vol. 78, p. 70.

b. Initially excluded subjects who received nesiritide 0.6µg/kg/min. These were later added to analysis at Medical Reviewer's request.

c. Trials comparing nesiritide with placebo.

d. Trials comparing nesiritide with both placebo and active control during continuous infusion.

5.1.2 Demographics

The next section compares the demographics of the study populations. The first table shows the demographics of all trials that enrolled CHF subjects (excluding only study 704.312). Information on the prevalence of secondary diagnoses (i.e., hypertension, hypercholesterolemia, diabetes) were not collected uniformly in all trials, and so were not summarized for this table. Overall, the demographics were well-balanced.

Table 5.1.2.1 Combined demographics for the 'all CHF' studies in the NDA database[a].

Demographic	Control n=235	Nesiritide n=505	Total n=721	p Value[b]
Gender				
Female	64 (27%)	135 (27%)	196 (27%)	0.929
Male	171 (73%)	370 (73%)	525 (73%)	
Race				
White	145 (62%)	324 (64%)	457 (63%)	0.246
Black	58 (25%)	136 (27%)	190 (26%)	
Asian	3 (1%)	4 (1%)	6 (1%)	
Hispanic	26 (11%)	38 (8%)	62 (9%)	
Other	3 (1%)	3 (1%)	6 (1%)	
Age (mean±sd)	59.0±12.7	59.1±13.2	59.2±13.1	0.923
Range	20, 91	19, 92	19, 92	
<65 years of age	158 (67%)	328 (65%)	469 (65%)	0.561
≥65 years of age	77 (33%)	177 (35%)	252 (35%)	
NYHA Class of CHF				
Class I	0 (0%)	1 (<1%)	1 (<1%)	0.363
Class II	12 (5%)	33 (7%)	43 (6%)	
Class III	148 (63%)	284 (56%)	417 (58%)	
Class IV	75 (32%)	186 (37%)	259 (36%)	
Unknown	0 (0%)	1 (<1%)	1 (<1%)	

a. Data from the sponsor, NDA vol. 1 (p. 263), and vol. 78 (p. 201-204).
b. p Value calculated using T-Test, Kruskal-Wallis, or Fisher's Exact Test as appropriate

Next, the demographics for the placebo-controlled trials in CHF are summarized. This population represent 289/721 (40.1%) of all subjects in the NDA with CHF. Note that a higher % of subjects in the placebo group were <65 and female, when compared with the nesiritide group.

Table 5.1.2.2 Combined demographics for the placebo-controlled CHF studies in the NDA database[a].

Demographic	Placebo n=91	Nesiritide n=217	Total n=289	p Value[b]
Gender				
Female	26 (29%)	41 (19%)	64 (22%)	0.070
Male	51 (56%)	140 (65%)	179 (62%)	
Race				
White	51 (56%)	140 (65%)	179 (62%)	0.080
Black	26 (29%)	63 (29%)	85 (29%)	
Asian	1 (1%)	3 (1%)	3 (1%)	
Hispanic	10 (11%)	11 (5%)	19 (7%)	
Other	3 (3%)	0 (0%)	3 (1%)	
Age (mean±sd)	54.3±9	54.5±11.6	54.3±11	
Range	31, 73	24, 85	24, 85	
<65 years of age	82 (90%)	176 (81%)	241 (83%)	0.062
≥65 years of age	9 (10%)	41 (19%)	48 (17%)	
NYHA Class				
Class I	0 (0%)	0 (0)%)	0 (0%)	0.746
Class II	4 (4%)	15 (7%)	17 (6%)	
Class III	62 (68%)	133 (61%)	180 (62%)	
Class IV	25 (27%)	68 (31%)	91 (31%)	
Unknown	0 (0%)	1 (<1%)	1 (<1%)	

a. Data from the sponsor, NDA vol. 1 (p. 263), and vol. 78 (p. 201-204).
b. p Value calculated using T-Test or Kruskal-Wallis test as appropriate.

Finally, the sponsor summarized the demographics of the subjects who received nesiritide as a continuous, long-term infusion, usually in the setting of decompensated CHF. This population represent 509/721 (70.6%) of all subjects in the NDA with CHF. This group roughly corresponds to the phase III trial population. Overall, the two treatment groups were well-balanced with regard to race, age, sex, and NYHA class.

Table 5.1.2.3 Combined demographics for the 'long infusion' studies in decompensated CHF in the NDA database[a].

Demographic	Control n=173	Nesiritide 0.015µg/kg/min n=169	Nesiritide 0.030µg/kg/min n=167	Total n=509	p Value[b]
Gender					
Female	46 (27%)	49 (29%)	54 (32%)	149 (29%)	0.511
Male	127 (73%)	120 (71%)	113 (68%)	360 (71%)	
Race					
White	104 (60%)	107 (63%)	106 (63%)	317 (62%)	0.714
Black	41 (24%)	45 (27%)	40 (24%)	126 (25%)	
Asian	2 (1%)	1 (1%)	1 (1%)	4 (1%)	
Hispanic	23 (13%)	14 (8%)	19 (11%)	56 (11%)	
Other	3 (2%)	2 (1%)	1 (1%)	6 (1%)	
Age (mean±sd)	60.6±13	60.8±14	62.8±12	61.4±13	0.248
Range	20, 91	19, 89	21, 92	19, 92	
<65 years of age	103 (60%)	100 (59%)	90 (54%)	293 (58%)	0.505
≥65 years of age	70 (40%)	69 (41%)	77 (46%)	216 (42%)	
NYHA Class					
Class I	0 (0%)	0 (0%)	1 (1%)	1 (<1%)	0.565
Class II	8 (5%)	8 (5%)	14 (8%)	30 (6%)	
Class III	107 (62%)	97 (57%)	81 (49%)	285 (56%)	
Class IV	58 (34%)	64 (38%)	71 (43%)	193 (38%)	
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

a. Data from the sponsor, NDA vol. 1 (p. 263), and vol. 78 (p. 201-204).
b. p Value calculated using ANOVA or Kruskal-Wallis tests as appropriate.

5.1.3 Extent of Exposure (dose/duration)

Natrecor Dose and Duration Exposure

The numbers of patients exposed to nesiritide at specified doses and durations are summarized in the tables below. Overall, 361 patients (71% of all subjects who got nesiritide) received ≥0.015 µg/kg/min of nesiritide (the dose proposed for use by the sponsor). In addition, a total of 394/505 (78%) of the patients who received nesiritide got it in an infusion. The longest continuous infusion of nesiritide was 214.2 hours (approximately 9 days), and the longest interrupted exposure to nesiritide was 283.2 hours (approximately 12 days). The first table summarizes the data for the subjects who received study drug (nesiritide or control) as an infusion.

Table 5.1.3.1 Subjects enrolled in nesiritide infusion studies in NDA 20-920[a].

Duration of Infusion	Control		Infusion Nesiritide[b]			
	Placebo	Std. Care	<0.015	≥0.015-<0.020	0.020-<0.035	≥0.035
0-12 hrs	26	5	3	25	36	20
12-26 hrs	26	33	17	71	62	16
26-50 hrs		28	8	27	33	
50-100 hrs		48	4	23	21	3
>100 hrs		30	1	11	10	3
Total	52	144	33	157	162	42
% of all Nesiritide subjects (n=505)	--	--	6%	31%	31%	8%

a. Data from NDA volume 78, page 192, and supplemental material requested from sponsor.
b. Mean infusion dose in µg/kg/min. Any subject who received nesiritide at 0.015 µg/kg/min, and had their dose reduced at any time were counted in the <0.015 group (there were 18 such patients).

5.1.3 Extent of Exposure (dose/duration)

The next table summarizes the data for the subjects who received study drug as a bolus during any of the studies in the NDA.

Table 5.1.3.2 Subjects in bolus studies with nesiritide in NDA 20-920[a].

	Control		Bolus Nesiritide	
Bolus Studies	Placebo	Std. Care	<21 µg/kg	≥21 µg/kg
	39	0	45	66
% of all Nesiritide subjects (n=505)	--	--	9%	13%

a. Data from NDA volume 78, page 192, and supplemental material requested from sponsor.

Type of Nesiritide Used

Two forms of nesiritide were used in the trials. The initial studies were done with nesiritide produced using 'synthetic peptide technology.' The sponsor later developed a method to produce nesiritide using recombinant DNA technology (which will be the form used in any commercial product). The nesiritide from both methods of production has the same peptide sequence and are chemically identical (see Chemistry Review). The table below summarizes the exposure to the two forms of nesiritide in the clinical studies.

Table 5.1.3.3 Subjects who received nesiritide, according to type of nesiritide administered[a].

Study	Synthetic Nesiritide	Recombinant Nesiritide	Total
704.305	24	0	24
704.306	12	0	12
704.307	20	0	20
704.309	44	0	44
704.310	43	0	43
704.311	74	0	74
704.325	16	69	85
704.326	0	203	203
Total	233	272	505

5.2 Relevant Information from Related INDs/ NDAs and Published Material

5.2.1 Information from Related INDs/ NDAs

Auriculin (human atrial natriuretic peptide, hANP) is another compound in the same family of cardiac peptides. The available safety and efficacy information for this compound is summarized below.

5.2.2 Published Literature from Related INDs/ NDAs

Auriculin (human atrial natriuretic peptide, ANP) is another compound in the same family of cardiac peptides. It has been used extensively in human trials, especially are a renoprotective and as therapy following acute renal failure. The available safety and efficacy information for this compound is summarized below.

ANP has been studied in a variety of clinical situations. In CHF, an increased serum level of ANP has been correlated with a larger left atrium and decreased left ventricular function, including LV ejection fraction ANP has also been used as a therapy in the setting of acute renal failure. In the largest trial to date, ANP administration did not reduce the use of dialysis following acute renal failure. The ANP group also had a higher incidence of both hypotension and premature ventricular contractions (PVCs). More serious arrhythmias were less common, and 'were evenly distributed between the treatment groups'. In another recently published trial, the administration of ANP to patients with oliguric renal failure (urine output ≤212 ml/day, creatinine clearance 5 ml/min) was associated with a trend towards a lower incidence of dialysis (64% vs. 77% in controls, p=0.054). Mortality was unaffected through 60 days (refs. 1, 8).

An effect of ANP to induce a translocation of proteins and fluid from the intravascular space to the interstitium has been demonstrated in both humans and in animals. This effect (an increase in 'conductance'), which is thought to occur as the result of changes in endothelial permeability to proteins and salts, leads to redistribution of volume away from the intravascular space, and is thought to be one mechanism whereby ANP improves hemodynamics in CHF. It has been reported in humans and in animals (refs. 7,10,13).

5.2.2 Post-Marketing Experience

Nesiritide has not been previously marketed.

5.2.3 Literature

Two approaches were used to identify relevant published literature relevant to the current submission.

First, an independent literature review, through a keyword search of Medline, was conducted by this reviewer. Terms used in the search included: congestive heart failure; human clinical trials; atrial natriuretic peptide and hormone.

Second, the sponsor has provided a literature review, which was cross-referenced with the above reviews to assure completeness. The cut-off for consideration of articles in this NDA was approximately January of 1998. This literature review has been incorporated into the background section of this introduction, and into the integrated safety summary where appropriate.

5.2.4 Advisory Committees

A recent Advisory Committee meeting discussed a 'Proposed Guidelines for the Clinical Evaluation of Drugs for the Treatment of Heart Failure'. In it, approval of an agent for short-term use in CHF is to be based on the demonstration in controlled clinical trials that the following 4 conditions are met:

'1) The drug produces favorable hemodynamic effects that can reasonably be expected to be associated with symptomatic improvement over a relevant period of treatment (typically 24-48 hours). If it is expected that physicians might select a dose based on the drug's ability to produce a specific hemodynamic effect, a wide range of doses will need to be evaluated to define the relation of dose to effect.

2) Use of the drug within a defined therapeutic range produces (1) an improvement in symptoms and/or stabilization of clinical status; (2) a meaningful improvement in end-organ function that is deemed to be clinically relevant; (3) a decrease in the need for or duration of intensive care, specialized interventions or hospitalization; and/or (4) a reduction in the risk of death.

3) Withdrawal of the drug or substitution of oral therapy (with any agent) for the drug is not associated with relapse or rebound phenomena, so that any short-term benefit can be sustained.

4) Short- and long-term follow-up of patients treated with the drug for short periods does not reveal important safety concerns that would discourage its use.'

(From Proposed Guidelines for the Clinical Evaluation of Drugs for the Treatment of Heart Failure, Oct. 22, 1998 draft).

The guidance also stated the following:

1) Long-term safety data (particularly with respect to any effect on risk of major clinical events) are important, even if the sponsor is not seeking an indication for long-term use, since short-term use may have important effects and since physicians may prescribe a new drug for periods longer that those indicated in approved labeling. If long-term data are not available, the labeling may emphasize that such data are lacking and that an adverse effect has not been excluded. Alternatively, the lack of long-term data may be of such concern that approval of the drug cannot be granted; this is particularly likely if the drug can easily be prescribed long-term if it were available for clinical use (e.g., because it is an oral formulation).

2) For the approval for short-term use, it is estimated that 1000-1500 patients should be exposed to the drug, with an adequate number being exposed for periods up to 2 weeks.

5.3 Comment on Adequacy of Clinical Experience

The database includes a total of 529 subjects in 9 clinical studies. A total of 505 subjects were enrolled in 8 clinical studies in the CHF developmental program. This review will focus on the CHF population in the NDA database.

First, with regard to the number of subjects exposed, a total of 361/505 subjects (71%) received nesiritide at a mean dose of ≥0.015μg/kg/min, the proposed starting dose. The remainder received a lower dose, or received it in the form of a bolus, rather than continuous infusion. Forty-two subjects received nesiritide at a dose of ≥0.035μg/kg/min.

With regard to the route of administration proposed for use, a total of 394 subjects (78%) received nesiritide in the form of a continuous IV infusion. The remainder received it in single or multiple boluses. A total of 310 subjects received nesiritide for ≥12 hours via continuous infusion.

Finally, with regard to the type of nesiritide administered, recombinant Natrecor, the formulation of nesiritide to be marketed, was administered to 272/505 enrolled subjects (54%).

5.4 Comment on Data Quality and Completeness

Specifics regarding the completeness of the database for NDA 20-920 will be made during each trial review. Overall, follow-up for subjects was adequate for the primary endpoint and its components in each of the phase III trials. Follow-up for abnormal laboratories was dependent on the individual investigators, and the submitted lab data did not include some analyses of interest. At the request of the reviewers, however, the sponsor performed additional analyses that added materially to the analysis of the database.

The Case Report Forms were submitted for all subjects who withdrew from the studies, including both medical and non-medical drop-outs.

The datasets were submitted both in SAS and hardcopy.

In summary, the data quality and completeness is acceptable for a medical and statistical review. Specific problems regarding the adequacy of the data are noted as well at appropriate points in the review document.

APPEARS THIS WAY
ON ORIGINAL

6.1 Review of the Protocol 704.311

6.1.1 Title of Study

A randomized, double-blind, placebo-controlled, multicenter, dose-ranging study to evaluate the safety and efficacy of a 24 hours intravenous infusion of Natrecor (hBNP) in subjects with congestive heart failure.

6.1.2 Sites of Investigation and Investigators

The list of investigators and sites is found in NDA vol. 36, starting on page 13. Study 704.311 was a multicenter investigation, with 15 investigators at 15 sites in the U.S.

Table 6.1.2.1 Investigators and # of enrolled subjects in protocol 704.311[a].

Investigator	# of Subjects Enrolled	# of Subjects Discontinued
Abraham, W.	2	0
Chatterjee, K.	10	2
East, C.	2	0
Hood, W.	9	0
Johnson, A.	4	0
Kao, W.	3	0
Katz, S.	2	0
Kukin, M.	2	0
Lang, R.	7	3
Lejemtel, T.	20	4
Lui, C.	6	2
Mills, R.	23	1
Rosenzweig, B.	4	1
Silver, M.	6	0
Udhojl, V.	3	1

a. Data from sponsor, NDA vol. 36, p. 29-30.

6.1.3 Background

This study was designed to evaluate the hemodynamic effects of three doses of nesiritide in patients with symptomatic CHF. Nesiritide, administered as a 24 hours IV infusion, was compared with placebo with regard to its effects on hemodynamic parameters (especially PCWP). The natriuretic and diuretic effects, pharmacokinetics, and safety of nesiritide were also evaluated.

The sponsor used the results of study 704.307 to determine the three nesiritide doses used in the trial. Per their analysis of that trial, the lowest dose in that study (0.003µg/kg/min) had insignificant effect on hemodynamics, while the highest dose (0.1 µg/kg/min) caused excessive decreases in systolic blood pressure. Using this data, the sponsor chose 0.015, 0.030, and 0.060µg/kg/min as the rates of infusion for the current study.

The choice of a 3 hour time point for the primary endpoint was, per the sponsor, selected from data that suggested that the nesiritide levels would achieve steady-state by this time. The sponsor followed the subjects for 24 hours, as they felt this was the 'longest placebo-controlled period which could ethically justified in patients with symptomatic decompensated CHF.'

Initial protocol

The initial protocol was submitted to the FDA on 11.16.94, with one amendment.

Amendments

The first amendment was on 5.20.95, which revised the reconstitution directions for the pharmacists to correct the dose calculation table.

The sponsor also specified that the trial would continue until at least 20 evaluable subjects in each of the four drug groups were enrolled. Due to significant under-dosing of many initial subjects, this required an increase to over 100 total subjects enrolled. The sponsor also specified that the under-dosed subjects would not be included in the evaluable subjects.

In early 11.94, the sponsor reassessed the enrollment status, and determined that, despite enrolling >100 subjects, the four groups were still unbalanced. It was decided to terminate the enrollment at that time.

6.1.4 Study Design

General

This was a multicenter, randomized, parallel, double-blind study that planned to enroll 80 subjects with symptomatic NYHA Class II, III or IV CHF. Subjects were admitted to the hospital and had a Swan-Ganz catheter placed. After withholding other cardiac medications for 24-48 hours (except for diuretics and antiarrhythmics), subjects were randomized to receive on of three doses of nesiritide or placebo. The infusion lasted 24 hours, during which time hemodynamics (PCWP, SVR, MRAP, and CI) blood pressure and heart rate were monitored. Four hours after discontinuation of infusion the Swan-Ganz catheter was removed, as appropriate, and all previous medications restarted. Subjects were followed until time of discharge, and follow-up phone calls were made on days 7 and 15.

6.1.5 Primary and Secondary Objective/ Endpoint

Primary Objective

1. 'To evaluate the effects and dose response relationships of several doses of Natrecor (vs. Placebo) administered via a 24 hour infusion on central hemodynamic parameters (especially PCWP) in congestive heart failure (CHF) subjects.' (IND vol. 3.1, page 5).

Primary Endpoint

The primary endpoint for study 704.311 was described in more than one way. The first statements come from the final IND protocol.

1. 'To evaluate the effects and dose response relationships of several doses of Natrecor (vs. Placebo) administered via a 24 hour intravenous infusion on central hemodynamic parameters (especially PCWP) in congestive heart failure (CHF) subjects.' (Study Objectives section (2.1) of IND protocol for 704.311, IND vol. 3.1, pages 5-6).

2. 'The primary endpoint, for purposes of the dose-response objective, is the absolute change in PCWP, relative to baseline, at the nominal 3-hour assessment. If a subject did not receive the randomized treatment regimen throughout this assessment, or if the 3-hour value is otherwise missing, the subject will not be eligible for this analysis.'

'For the 24 hour analysis, the primary endpoint is the absolute change in PCWP relative to baseline at the nominal 24 hour assessment. It is additionally required that the value have been observed (1) 22-26 hours after start of the study drug infusion and (2) either while the subject was receiving study drug or within 15 minutes after termination of the study drug.' (Statistical Considerations section (8.1) of IND protocol for 704.311, IND vol. 3.1, page 17).

In the NDA, the sponsor stipulated that the following was the 'primary efficacy endpoint.'

1. The primary endpoint was the change in PCWP relative to baseline, at approximately 3 hours following start of study drug. The protocol specified that to be eligible for the primary analysis, subjects had to have received the randomized treatment, without dose modification, for the duration of this period.

Secondary Objective

1. 'To determine whether the beneficial effects of Natrecor can be sustained for a 24 hour treatment period during which the drug is administered as a continuous intravenous infusion.' (Protocol for 704.311, Study Objectives section (2.2), IND vol. 3.1, page 6).

2. 'To evaluate the ability of a continuous 24 hour intravenous infusion of Natrecor (vs. Placebo) to stimulate a natriuresis and diuresis in subjects with CHF.

3. 'To assess the safety of continuous 24 hour intravenous infusion of Natrecor vs. placebo.

4. 'To determine the pharmacokinetic profile of Natrecor when administered as a continuous intravenous infusion.'

APPEARS THIS WAY
ON ORIGINAL

Secondary Endpoints

'In addition to PCWP, other hemodynamic endpoints will be analyzed. Of particular interest are cardiac index, systemic vascular resistance, mean right atrial pressure, and heart rate. The relationship between selected hemodynamic endpoints and nesiritide plasma concentrations will be examined. Adverse events and laboratory data will also be analyzed.' (Secondary Endpoints section 8.6 of 704.311 protocol, IND vol. 3.1, page 18).

During the NDA review, the sponsor stipulated that the following is the 'lead secondary endpoint:'

1. The 'lead secondary endpoint' was PCWP, expressed as the change relative to baseline after 24 hours. The protocol specified that to be eligible for the analysis, subjects had to have received study drug for the duration of this period.

6.1.6 Number of Subjects/ Randomization

Ultimately, 103 subjects were enrolled at 15 clinical sites between 5.15.95 and 8.16.96. Data was collected through 9.11.96, and no subjects were lost to follow-up.

6.1.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

Subjects who met the following criteria were eligible for participation in the study:

1. At least 18 years of age, with chronic New York Heart Association Class II, III, or IV CHF.
2. Male; or female that is surgically sterile, post menopausal, or using effective. contraception.
3. Left ventricular systolic dysfunction, as evidenced by left ventricular ejection fraction of 35% or less (by either two-dimensional echocardiography or radionuclide or contrast ventriculography within the last 12 months).
4. On a standard treatment regimen for chronic CHF (such as ACE inhibitors, nitrates, or hydralazine, with or without oral digoxin/diuretic therapy) for at least 1 month, and on stable doses of these medications for at least 48 hours.
5. Fully understands all elements of and has signed the Informed Consent Form before initiation of protocol-specified procedures.
6. Hemodynamic criteria: PCWP >18 mm Hg; CI <2.5 ml/min/m^2.

Exclusion Criteria

Potential subjects with any of the following were not eligible for participation in the study:

1. Myocardial infarction within the past 2 months, unstable angina within the past 4 weeks, or any clinical evidence of active myocardial ischemia.
2. Significant valvular stenosis, hypertrophic, restrictive or obstructive cardiomyopathy, constrictive pericarditis, primary pulmonary hypertension, biopsy-proven active myocarditis, or complex congenital heart disease.
3. Sustained ventricular tachycardia or ventricular fibrillation within the past 2 weeks.
4. Second-degree (Mobitz type II) or third-degree heart block, unless the subject had a permanent pacemaker.
5. Stroke within 3 months or other evidence of significantly compromised central nervous system perfusion.
6. Significant renal impairment (e.g., serum creatinine > 3.0 mg/dL).
7. Serum sodium concentration < 125 mEq/L or > 160 mEq/L.
8. Requiring beta blockers and/or calcium channel blockers within 48 hours prior to initiation of study drug administration.
9. Inability to withhold ACE inhibitors, nitrates, and/or hydralazine for the protocol-specified time period prior to study drug administration through completion of the 24-hour study drug infusion.
10. Therapy with another investigational drug within one month prior to entry into the study.
11. Any other acute or chronic medical condition or laboratory abnormality that may increase the risks associated with study participation/study drug administration or may interfere with the interpretation of study results.
12. Unwilling or unable to comply with study requirements.
13. Inability to place a Swan-Ganz catheter in the patient.

6.1.8 Dosage/ Administration

There were three treatment groups in study 704.311:

Group 1: Nesiritide: IV bolus of 0.25 μg/kg followed by a 0.015 μg/kg/min infusion.
Group 2: Nesiritide: IV bolus of 0.50 μg/kg followed by a 0.030 μg/kg/min infusion.
Group 3: Nesiritide: IV bolus of 1.0 μg/kg followed by a 0.060 μg/kg/min infusion.
Group 3: IV bolus of placebo followed by a placebo infusion.

6.1.9 Duration/ Adjustment of Therapy

Prior to study initiation, ß-blockers and calcium channel blockers were withheld for 48 hours. Vasodilators, hydralazine, and ACE inhibitors were withheld for 12-24 hours prior to study drug administration.

Following placement of a central venous catheter, nesiritide or placebo were administered for 24 hours. Four hours after discontinuation of the study drug, the central venous catheter was removed, and previously prescribed medications re-started. Dose of study drug could be adjusted for hypotension (systolic BP <85 mmHg) or a decrease in PCWP to <10. In the event of symptomatic hypotension requiring fluids and/or pressor support or any serious or unexpected adverse event, the infusion was discontinued.

6.1.10 Safety and Efficacy Measurements

The table below details the type and timing of the clinical information collected during protocol 704.311.

Table 6.1.10.1 Timetable for clinical observations and lab measurements in trial 704.311[a].

	Pre-infusion	Start infusion				Stop Infusion	Post-Infusion			
Time (hrs)		**0**	**6**	**12**	**24**	**24-48**	**24**	**Day 7**	**Day 15**	**Day 20-30**
Infusion										
ASA										
History & Physical	X						X			
Vital Signs	X									
ECG (screening)	X									
Urine Collection (24 hr)										
CXR[a]	X									
Swan-Ganz catheter	X									
CPK with isoenzymes										
Laboratories[c]	X						X			X
Hematology[c]	X						X			X
Plasma nesiritide		X	X	X	X	X	X			
Plasma nesiritide Ab										X
F/U Telephone call								X	X	
Adverse Events (AEs)										

a. Data from NDA volume 54, page 24.

b. Swan-Ganz catheter discontinued 4 hours after completion of infusion or when medically appropriate.

c. Labs and hematology collected include: CBC (hemoglobin, hematocrit, WBC count and differential, platelet count); serum chemistries (BUN, creatinine, total bilirubin, AST/ALT, glucose, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol); urinalysis; and stool for occult blood.

6.1.11 Statistical Considerations

General statistical approach

See section 6.1.5 for a discussion of the endpoints specified in the final IND protocol and in the NDA. The following is the statistical plan from the NDA submission.

The statistical analysis had one primary objectives:

1) to demonstrate a statistically significant dose effect with respect to reduction in PCWP at steady state plasma levels.

2) to demonstrate that at least one of the nesiritide treatment regimens produced a statistically significant reduction in PCWP after 24 hours of study drug infusion, as compared with placebo.

All reported p Values were 2-sided, and considered nominally significant if <0.05.

6.1.11 Statistical Considerations (cont)

Analytical methods

Two populations were defined: intent to treat (ITT) at 3 and 24 hours, and evaluable at 3 and 24 hours.

The ITT population included all subjects enrolled. Analysis for this group was performed according to the group each subject was randomized, without regard to actual study drug dosing.

Subjects were excluded from the 'evaluable at three hours' population if: 1) study drug was found to have been administered 'at a grossly incorrect dose because of pharmacist error,' or 2) they terminated study drug before 2 hours 50 minutes of therapy; or 3) they modified the randomized dose of study drug before 2 hours 50 minutes.

Subjects were excluded from the 'evaluable at 24 hours' population if: 1) study drug was found to have been administered 'at a grossly incorrect dose because of pharmacist error;' or 2) they terminated study drug before 22 hours of therapy.

Hemodynamic Parameters

All hemodynamic endpoints were analyzed using the ITT population. PCWP at the end of 3 hours was evaluated using the 'evaluable at 3 hours' population.

Treatments within groups were analyzed within the framework of analysis of variance (ANOVA). Details of analyses are specified in the results section as appropriate.

Renal Parameters

Urine output and fluid intake were standardized to units of mL/24 hours. Urinary Na^+ and K^+ output were standardized to mEq/24 hours. All endpoints were analyzed using ANOVA.

Interim Analyses and sample size estimation

Interim analyses were performed in the spring of 1996 and fall of 1996, summarizing the results from the first 55 subjects and 92 subjects respectively. Per the sponsor, the purpose for the second interim analysis was 'to support discussions with potential corporate partners.' The sponsor also states that these analyses 'were not performed for consideration of early study termination.' (NDA volume 54, page 39).

Sample size was estimated based on the ability of the study to detect a significant difference between groups in PCWP at the end of 3 hours. Study enrollment was increased during the trial, as described above in the amendments section.

6.1.12 Efficacy Outcomes

6.1.12.1 Patient Demographics & Baseline Characteristics

The next set of tables summarizes several key baseline characteristics of the subjects enrolled in the trial. A total of 103 subjects (83 men and 20 women) enrolled in the trial. The mean entry ejection fraction was lower in the placebo group, which also had a lower percentage of white subjects enrolled. Otherwise, the four groups were well-balanced. In data not shown, the etiology for the CHF were balanced between the four groups, with the majority of subjects having ischemic cardiac disease.

Table 6.1.12.1.1 Demographics of the 704.311 trial[a].

Demographic	Placebo n=29	Nesiritide 0.015 µg/kg/min n=22	Nesiritide 0.030 µg/kg/min n=26	Nesiritide 0.060 µg/kg/min n=26	p Value
Gender					0.537
Female	8 (28%)	4 (18%)	5 (19%)	2 (12%)	
Male	21 (72%)	18 (82%)	21 (81%)	23 (88%)	
Race					
White	[illegible]	[illegible]	[illegible]	[illegible]	0.156
Black	9 (31%)	6 (27%)	6 (23%)	5 (19%)	
Asian	0 (0%)	0 (0%)	1 (4%)	1 (4%)	
Hispanic	7 (24%)	1 (5%)	5 (19%)	3 (12%)	
Other	3 (10%)	0 (0%)	0 (0%)	0 (0%)	
NYHA Class at entry					
II	0 (0%)	2 (9%)	2 (8%)	2 (8%)	0.514
III	21 (72%	14 (64%)	13 (50%)	15 (58%)	
IV	8 (28%)	6 (27%)	11 (42%)	9 (35%)	

a. Data from NDA volume 54, appendix table 2 and 4.

6.1.12.1 Patient Demographics & Baseline Characteristics (cont)

Table 6.1.12.1.2 Demographics of the 704.311 trial[a].

Clinical Characteristic at Baseline	Placebo n=29	Nesiritide 0.015 µg/kg/min n=22	Nesiritide 0.030 µg/kg/min n=26	Nesiritide 0.060 µg/kg/min n=26	p Value
Ejection Fraction (%)					
Mean±SD					
Range					
PCWP (mm Hg) Mean ±SD	27.8±5.8	29.8±7.7	27.3±4.6	29.4±6.7	0.424
Mean Right Atrial Pressure (MRAP, mm Hg)	13.0±6	13.4±6	16.1±8	13.0±8	0.327
Mean Systolic BP (mm Hg)	112.±16	123±22	113±17	119±23	0.174
Rales Present	11 (41%)	11 (58%)	11 (42%)	10 (45%)	0.682
Peripheral Edema Present	11 (42%)	11 (58%)	12 (46%)	13 (62%)	0.517
S3 Present	20 (74%)	12 (63%)	20 (77%)	11 (50%)	0.194
Tachycardia (>100 PM)	2 (7%)	3 (15%)	6 (23%)	6 (26%)	0.286

a. Data from NDA volume 54, appendix table 6, 17A, 20A, and 30A.

Aside from two drug classes, the groups were well-balanced with regard to medications used by the subjects prior to entry into the trial. More subjects in all three nesiritide group were using ACE-inhibitors at time of entry. There was also a trend towards a greater use of diuretics in the nesiritide groups.

Table 6.1.12.1.3 Medications used at time of entry into trial 704.311[a].

Medication	Placebo n=29	Nesiritide 0.015 µg/kg/min n=22	Nesiritide 0.030 µg/kg/min n=26	Nesiritide 0.060 µg/kg/min n=26	p Value[b]
Diuretics	13 (45%)	15 (68%)	19 (73%)	16 (62%)	0.165
ACE Inhibitors	7 (24%)	9 (41%)	13 (50%)	15 (58%)	0.068
Digoxin	8 (28%)	9 (41%)	13 (50%)	8 (31%)	0.318
Class III anti-arrhythmics	4 (14%)	2 (9%)	3 (12%)	5 (19%)	0.798
Beta Blockers	2 (7%)	2 (9%)	0 (0%)	1 (4%)	0.548

a. Data from NDA volume 54, page 112.
b. p Value using Fisher's Exact Test.

6.1.12.2 Disposition and Follow-up of Subjects

Disposition

The table below shows the disposition of the subjects in the trial. Note that significantly more subjects in the 0.060 µg/kg/min group discontinued for adverse events. Fourteen subjects terminated study drug infusion prematurely (i.e., prior to completion of the 24-hour dosing period). Five subjects terminated study drug infusion prior to the 3-hour assessment time point, one because of worsening CHF and four because of adverse events (hypotension, excessively decreased PCWP, bradycardia); all of these subjects were in the 0.03 and 0.06 µg/kg/min nesiritide groups. An additional 9 subjects terminated infusion before completion of the 24 hour dosing period; of these, 5 were placebo subjects who developed worsening CHF and 4 were subjects receiving the 0.03 and 0.06 µg/kg/min nesiritide groups who developed an excessively decreased PCWP or hypotension.

Table 6.1.12.2.1 Disposition of subjects randomized in the 704.311[a].

Patient Disposition	Placebo	Nesiritide 0.25/ 0.015	Nesiritide 0.5/ 0.030	Nesiritide 1.0/ 0.060
Randomized/ Enrolled	29	22	26	26
Completed	24 (83%)	22 (100%)	23 (88%)	20 (77%)
Discontinued (Total)	5 (17%)	0 (0%)	3 (12%)	6 (23%)
Adverse Event[b]				
Inadequate Therapeutic Response[c]	5 (17%)	0 (0%)	1 (4%)	0 (0%)
Other reasons	0 (0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 54, page 108.
b. Difference between treatment groups significant (0.004) by Fischer's Exact Test.
c. Difference between treatment groups significant (0.021) by Fischer's Exact Test.

6.1.12.2a Subject Selection

No information is available to this reviewer regarding the selection of subjects for this trial.

6.1.12.2b Protocol Violations & Deviations

Incorrect study drug dosing

Early in the study, the sponsor found that a series of pharmacy reconstitution errors had been made, resulting in marked underdosing of at least 5 subjects. Based on a review of pharmacy records, it was estimated that these subjects received the correct loading bolus dose but then received an infusion dose that was 1% and 2% of the correct dose in the lowest and middle nesiritide dose groups, respectively.

Three underdosed subjects were in the 0.015 µg/kg/min group (subjects 368-009, 380-003, and 389-001), and 2 were in the 0.03 µg/kg/min group (subjects 382-003, 389-002).

In addition, subject 369-009 was randomized to the 0.015 µg/kg/min dose group but actually received the 0.030 µg/kg/min dose.

Missing PCWP measurements

Two subjects, 376-017 and 388-002, had no PCWP measurements recorded after baseline, and so are not included in any PCWP analyses. Both subjects were in the nesiritide, 0.030µg/kg/min group.

Miscellaneous other protocol violations

Several other violations were noted by the sponsor, but felt to be clinically insignificant and not likely to affect the outcome of the trial. These are listed in NDA vol. 54, page 23, and will be considered later as deemed relevant by this reviewer. In particular, two individuals with marked elevations in creatinine at entry will be examined further.

6.1.12.2c Concomitant Therapies used after Trial Initiation

The use of concomitant medications during the trial is summarized for selected classes of drugs below. In general, the four groups were balanced in their use of these agents.

Table 6.1.12.2c.1 Concomitant medications used during nesiritide administration in trial 704.311[a].

Medication	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value[b]
Diuretics	19 (66%)	11 (50%)	14 (54%)	12 (46%)	0.512
ACE Inhibitors	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0.718
Digoxin	15 (52%)	9 (41%)	10 (38%)	14 (54%)	0.623
Class III anti-arrhythmics	4 (14%)	4 (18%)	4 (15%)	5 (19%)	0.952
Beta Blockers	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1.00

a. Data from NDA volume 54, page 114.
b. p Value using Fisher's Exact Test.

6.1.12.3 Analysis of Primary Endpoint and 'Lead Secondary Endpoint' from Trial 704.311

See section 6.1.5 above for a discussion of the pre-specified 'primary' and 'secondary' endpoints in this trial. In this section, the absolute change from baseline for PCWP at the end of 3 and 24 hours will be examined in the 'Evaluable at 3 Hours' population. Other statistical analyses will follow.

'Evaluable at 3 Hours' population analysis

Per the sponsor's analysis, the PCWP fell significantly in all nesiritide groups, compared with control, at the 3 hour time-point in this population. Note, however, that the PCWP remained significantly elevated over normal in all groups.

Table 6.1.12.3.1 Changes in PCWP (mm Hg) from baseline to 3 hours in the 'Evaluable at 3 Hours' population [a].

Measurement (mm Hg)	Placebo n=29	Nesiritide 0.25/ 0.015 n=17	Nesiritide 0.5/ 0.030 n=19	Nesiritide 1.0/ 0.060 n=18
Baseline PCWP	27.8±5.8	30.9±9.3	27.8±4.7	30.8±6.4
3-hour PCWP	26.0±5.8	21.1±6.8	21.1±5.6	20.9±9.6
p Value (Dunnett) [b]	--	NS	NS	NS
p Value (P/W Con) [b]	--	0.028	0.026	0.019
Change from Baseline (0-3 hrs)	-1.8±4.6	-10.0±9.4	-6.8±7.5	-9.9±8.9
p Value (Chng from Baseline) [c]	0.042	0.001	0.002	0.001
p Value (Dunnett) [b]	--	<0.05	NS	<0.05
p Value (P/W Con) [b]	--	0.001	0.030	0.001

a. Data from NDA volume 54, Appendix 1, Table 18A, 18B
b. See statistical section for statistical methods. p Value per sponsor.
c. Comparison using T-test.

'Evaluable at 24 Hours' population analysis

Similar to the 3 hour timepoint, the nesiritide groups had a significantly lower PCWP than the control group in this population. As before, the PCWP remained significantly elevated above normal in all groups, although the magnitude of the changes in PCWP was decreased from the 0-3 hour results. Note also that there was no significant decrease in PCWP from 3 to 24 hours (that is, all of the decrease occurred from 0-3 hours of the nesiritide infusion)

Table 6.1.12.3.2 Changes in Mean PCWP from baseline to 24 hours in the 'Evaluable at 24 Hours' population[a].

Measurement	Placebo n=25	Nesiritide 0.25/ 0.015 n=18	Nesiritide 0.5/ 0.030 n=21	Nesiritide 1.0/ 0.060 n=20
Baseline PCWP	28.1±6	30.5±8	27.3±4.8	30.0±6.8
24-hour PCWP	26.3±8.4	21.4±6.4	23.6±7.8	22.0±8.1
p Value (Dunnett) [b]	--	NS	<0.05	NS
p Value (P/W Con) [b]	--	0.050	0.050	0.074
Change from Baseline (0-24 hrs)	-1.8±6.4	-8.8±6.8	-3.8±6.7	-8.4±6.4
p Value (Chng from Baseline) [c]	0.169	<.001	0.024	<0.001
p Value (Dunnett) [b]	--	<0.05	NS	<0.05
p Value (P/W Con) [b]	--	0.001	0.328	0.002

a. Data from NDA volume 54, Appendix 1, Table 19A, 19B
b. See statistical section for statistical methods. p Value per sponsor.
c. Comparison using T-test.

6.1.12.4 Analysis of Secondary Endpoints from Trial 704.311

There were two 'secondary endpoints' in trial 704.311: the effects of nesiritide on other hemodynamic endpoints (cardiac index: systemic vascular resistance; right atrial pressure; and heart rate); and the relationship between hemodynamic changes and plasma nesiritide concentrations (see section 6.1.5).

The Effects of Nesiritide on Other Hemodynamic Endpoints

The sponsor examined the effect of nesiritide on several other hemodynamic markers. The following tables summarizes those effects after 3 and 24 hours for the ITT population.

Table 6.1.12.4.1 Effect of 3 hour infusion of nesiritide on identified hemodynamic parameters[a].

Hemodynamic Parameter	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value[b]
MRAP (mm Hg)	-0.8±3.7	-3.73.5	-3.3±4.3	-4.5±6.2	0.024
SVR (Dyne-sec/cm²)	-16.4±397	-364±863	-203±493	-500±426	0.017
Cardiac Index (L/min/M²)	+1.1±20	+28.8±50	+18.2±32	+36.6±38	0.004
Pulmonary Vascular Resistance (Dyne-sec/cm²)	+54±96	-55±251	-21±186	-47±158	0.110
Systolic BP (mm Hg)	+1.2±9	-7.4±12	-4.3±14	-10.0±14	0.011
Heart Rate (BPM)	+2.6±7.6	-3.7±6.7	-2.2±8.8	+6.2±13.8	0.002

a. Data from NDA 20-920, vol. 54, Table 20B through 30B. Data are expressed as absolute change from baseline for ITT population.
b. p Value comparing arithmetic means from baseline using ANOVA linear contrast except for heart rate, which used Omnibus F test.

The next table summarizes the same effects on selected hemodynamic measurements at the end of 24 hours. Note that the effect of nesiritide on SVR from 0 to 3 hours is largely lost at the 24 hour time-point, although the effect on systolic BP persists. The significance of the difference relative placebo are also lost for several of the endpoints.

Table 6.1.12.4.2 Effect of 24 hour infusion of nesiritide on identified hemodynamic parameters[a].

Change in Hemodynamic Parameters from Baseline	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value[b]
MRAP (mm Hg)	-1.4±5	-2.6±4	-3.6±6	-2.9±4	0.493
SVR (Dyne-sec/cm²) %	-17.6±675	-283±680	-67±776	-354±300	0.266
Cardiac Index (L/min/M²)	+4.6±18	+16.0±32	+9.7±54	+25.4±21	0.237
Pulmonary Vascular Resistance (Dyne-sec/cm²)	+3.3±113	-68.3±233	-32.8±182	-31.8±129	0.576
Systolic BP (mm Hg)	+2.1±12	-6.1±12	-3.3±13	-9.0±12	0.021
Heart Rate (BPM)	+4.5±11	-1.0±6.8	-0.2±7.6	+4.0±8.2	0.083

a. Data from NDA 20-920, vol. 54, Tables 20B through 31B, Data are expressed as absolute change from baseline for ITT population.
b. p Value comparing arithmetic means from baseline using ANOVA linear contrast except for heart rate, which used Omnibus F test.

The Relationship Between Hemodynamic Changes and Plasma Nesiritide Concentrations

The sponsor performed an analysis of the steady-state pharmacokinetics of nesiritide at more than one dose level as part of the current trial. For a full discussion of the results, please see the biopharmacologist's review.

After 3 hours of infusion, mean plasma nesiritide levels in the placebo and 0.25/ 0.015, 0.5/ 0.03, and 1.0/ 0.06 μg/kg/min dose groups were 835, 2985, 3711, and 6456 pg/mL, respectively. This reflects a linear relationship between dose and 3 hour mean nesiritide level ($R^2 = 0.9578$, $p<0.05$).

6.1.12.5 Subgroup & Post-hoc Analyses of trial 704.311

The sponsor also analyzed the data for the 'Intent-to-Treat population', which included all subjects who received study drug for at least 2 hrs 50 minutes. In this analysis, patients were analyzed in the group to which they were enrolled, regardless of what treatment they actually received. The numbers of patients in the two groups are summarized in the first table below.

Table 6.1.12.5.0 Patient in 'Evaluable at 3 hours' and 'Intent-to-treat' populations in 704.311.

Population	Placebo	Nesiritide 0.25/ 0.015	Nesiritide 0.5/ 0.030	Nesiritide 1.0/ 0.060
Evaluable at 3 Hours	25	18	21	20
Intent-to-Treat	29	22	26	26

Changes in PCWP in the Intent-to-Treat Population

In this population, at the end of 3 hours, nesiritide also had a significant, dose-related effect to decreases PCWP, as summarized in the table below both as absolute numbers and as changes from baseline.

Table 6.1.12.5.1 Changes in PCWP from baseline to 3 hours in the ITT population[a].

Measurement	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26
Baseline PCWP	27.8±5.8	29.8±7.7	27.3±4.6	29.4±6.7
3-hour PCWP	26.0±5.8	21.0±6.8	21.3±6.6	18.8±9.2
p Value (Dunnett)[b]	--	<0.05	NS	<0.05
p Value (P/W Con)[b]	--	0.018	0.021	0.001
Change from Baseline (0-3 hrs)	-1.8±4.6	-8.9±8.7	-6.0±7.9	-10.8±8.3
p Value (Chng from Baseline)[c]	0.042	<0.001	0.002	<0.001
p Value (Dunnett)[b]	--	<0.05	NS	<0.05
p Value (P/W Con)[b]	--	0.001	0.048	<0.001

a. Data from NDA volume 54, Appendix 1, Table 17A, 17B.
b. See statistical section for statistical methods. p Value per sponsor.
c. Comparison using T-test.

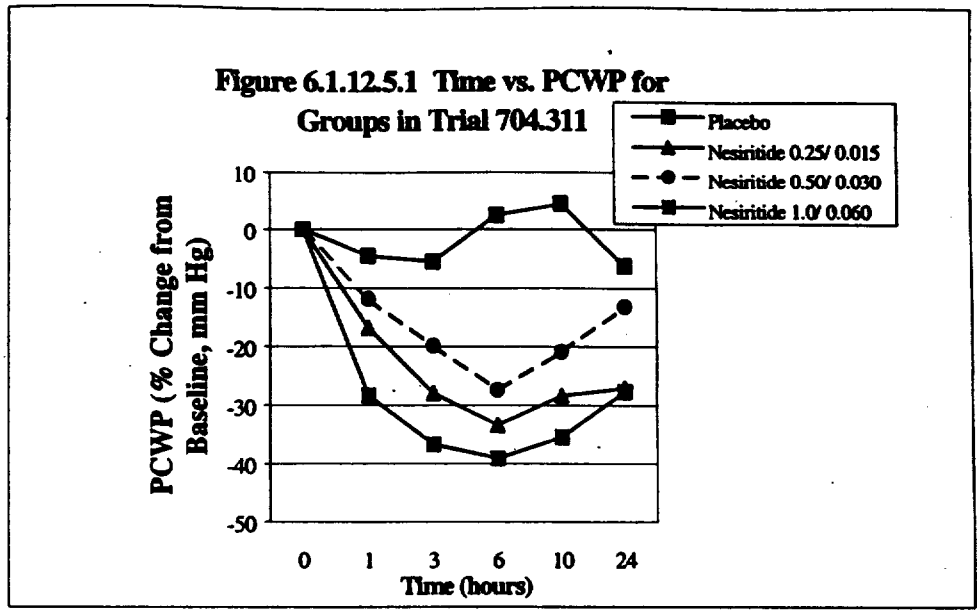
The FDA statistical reviewer also performed several statistical analyses based on the ITT population. The first analysis used the first 80 patients enrolled (the original proposed trial size), using the last value carried forward or worst rank imputation. The reductions in mean PCWP among the treatment groups were compared using three statistical methods: 1) ANOVA, 2) Kruskal-Wallis (non-parametric), and 3) worst rank. A similar analysis was also done using 103 patients. The results are shown in the table below. Pairwise comparisons show 'a significantly larger reduction at 0.015 and 0.060 nesiritide doses as compared to placebo, based on the ITT population. There was also a numberically larger reduction for the nesiritide 0.030 group, relative to placebo.

Table 6.1.12.5.2a (from 16.3) Mean change in PCWP from baseline for 80 & 103 subjects in study 704.311 at hours 3 and 24.

Analysis	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value (ANOVA)	Nominal p Value (Kruskal-Wallis)	Nominal p Value (Kruskal-Wallis/WR)[a]
80 Subjects at 3 hours	-3.8 (n=23)	-7.0 (n=17)	-7.1 (n=18)	-11.2 (n=21)	0.0027	0.0010	0.0079
80 Subjects at 24 hours	-3.7 (n=23)	-8.7 (n=17)	-5.3 (n=18)	-11.1 (n=21)	0.0037	0.0025	0.1601
103 Subjects at 3 hours	-1.7 (n=29)	-8.0 (n=22)	-7.3 (n=24)	-10.2 (n=26)	<0.001	<0.001	0.0014
103 Subjects at 24 hours	-1.9 (n=29)	-8.9 (n=22)	-5.9 (n=24)	-10.6 (n=26)	<0.001	<0.001	0.0128

a. Kruskal-Wallis using worst rank.

The graph below shows the effects of the various doses of nesiritide on mean PCWP during the first 24 hours of treatment for the ITT population. Note that the average effect of nesiritide, 0.25/0.015, was greater than the average effects of nesiritide 0.50/ 0.030 at all time-points. There was also a trend towards a return to baseline by the end of 24 hours in all three treatment groups.



Changes in PCWP in the Last-Value-Carried Forward Population

The sponsor performed an additional analysis of the data from the ITT population, using the last-value – carried forward to look at effects on PCWP and other hemodynamics for up to 24 hours. Again, at the 3 and 24-hour time-points all three nesiritide groups lowered PCWP relative to the placebo group. The intermediate dose, however, did not achieve statistical significance when compared with baseline at 24 hours. The shape of the curve over 24 hours (not shown) was similar to the curve shown above for the ITT population, with a slight decline in effect by 24 hours, especially in the two higher-doses of nesiritide. The table below summarizes the 3 and 24-hour data for this population. Change from baseline is shown as mean of individual differences.

Changes in PCWP in the Last-Value-Carried Forward Population (cont)

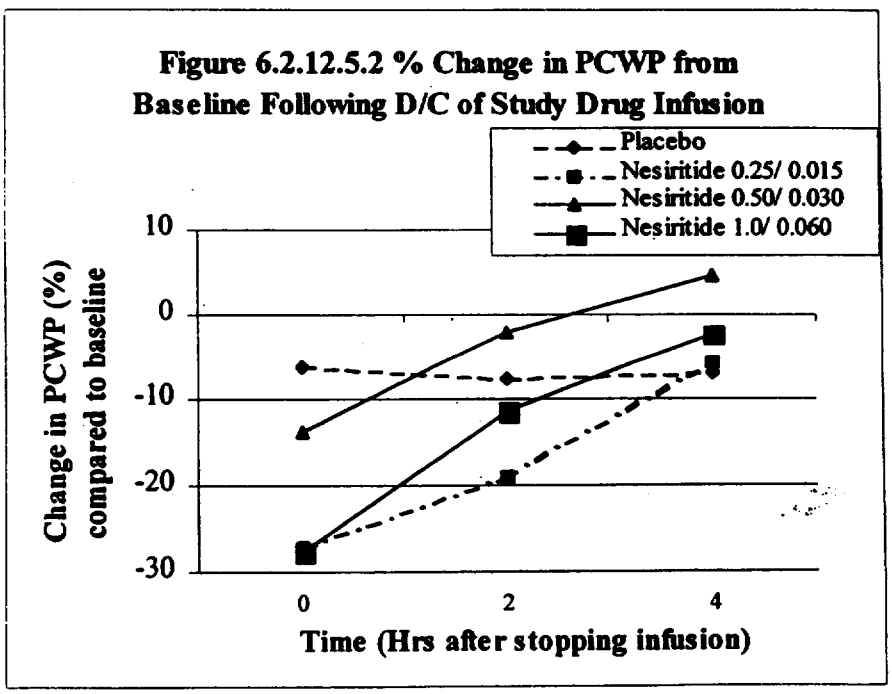
Table 6.1.12.5.3 Changes in PCWP from baseline to 3 and 24 hours in the ITT population[a].

Measurement	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value[b]
Baseline PCWP	27.8±5.8	29.8±7.7	27.3±4.6	29.4±6.7	
3-hour PCWP	26.0±5.8	21.3±7	20.9±7	18.5±9	0.002
p Value (Dunnett) [b]	--	NS	<0.05	<0.05	
p Value (P/W Con) [b]	--	0.024	0.012	<0.001	
24-hour PCWP	26.7±8	21.3±7	23.5±8	19.0±9	0.004
p Value (Dunnett) [b]	--	<0.05	NS	<0.05	
p Value (P/W Con) [b]	--	0.018	0.144	<0.001	
Change from Baseline (0-3 hrs)	-1.8±4.6	-8.5±9	-6.4±8	-10.9±8	<0.001
p Value (Chng from Baseline) [c]	0.042	<0.001	0.001	0.0001	
p Value (Dunnett) [b]	--	<0.05	NS	<0.05	
p Value (P/W Con) [b]	--	0.002	0.027	<0.001	
Change from Baseline (0-24 hrs)	-1.1±6	-8.3±6	-4.0±7	-10.4±8	<0.001
p Value (Chng from Baseline) [c]	0.375	<0.001	0.011	<0.001	
p Value (Dunnett) [b]	--	<0.05	NS	<0.05	
p Value (P/W Con) [b]	--	<0.001	0.130	0.0001	

a. Data from sponsor at FDA request.
b. See statistical section for statistical methods. p Value per sponsor.
c. Comparison using T-test.

Effect of Nesiritide Withdrawal on Hemodynamics

Hemodynamics were measured after 2 and 4 hours following discontinuation of nesiritide. For all study populations, the PCWP had returned to placebo levels in all nesiritide groups by 4 hours, and were intermediate between the last measurement on study drug and the 4-hour post-infusion value. The figure below shows the last recorded value on study drug for the ITT population (shown as time 0), as well as the 2- and 4-hrs post-infusion values (see NDA volume 1.54, table 17C for data).



In data not shown, other hemodynamic markers of interest (SVR, CI, RAP) also returned to baseline in the same period. There was no evidence of an 'over-shoot' to a PCWP > baseline (although the patients received diuretics, which might obscure such an occurrence).

Effects of Nesiritide on Urinary Indices

One proposed effect of nesiritide is to promote a natriuresis and diuresis, both through direct action and through the inhibition of aldosterone production. The first table below summarizes the effect of nesiritide on fluid intake and urine output, where no significant effect of nesiritide was detected. Instead, there was a trend towards decreased urine volume in the subjects who received nesiritide, which achieved nominal significance for the nesiritide 0.50/ 0.030 group. Overall, the mean and median fluid balance was positive in all of the nesiritide groups (more fluid in than out) in the ITT population. This was a result of less urine output, and not due to differences in the amount of fluids administered to the patients. There was no significant difference in the study groups with regard to diuretic use, although a higher percentage of placebo subjects received diuretics during study drug administration during study drug administration (see table 6.1.12.2c.1 above).

Table 6.1.12.5.4 Changes in Fluid intake and urinary volume during first 24 hours in the ITT population of study 704.311[a].

Measurement	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value[b]
Fluid Intake (ml/ 24 hrs) Mean±sd	1935±515	1836±427	1767±545	2147±1062	0.222
p Value compared with placebo[c]	--	NS	NS	NS	
Total Urine Output (ml/ 24 hrs) Mean±sd	2410±1086	1745±840	1479±806	2011±1845	0.041
p Value compared with placebo[c]	--	NS	<0.05	NS	
Output – Intake (ml/24 hrs) Mean ±sd	475±1094	-91±756	-287±848	-136±1872	0.113
Median	[illegible]	[illegible]	[illegible]	[illegible]	0.059
p Value compared with placebo[c]	--	NS	NS	NS	

a. Data from NDA volume 54, Appendix 1, Table 34.
b. See statistical section for statistical methods. p Value per sponsor by ANOVA Omnibus F test.
c. Comparison using Dunnet's t-test.

The next table summarizes the excretion of sodium and potassium during the first 24 hours of the study. All nesiritide groups had a lower mean sodium excretion relative to control.

Table 6.1.12.5.5 Changes in sodium and potassium excretion during first 24 hours in the ITT population of study 704.311[a].

Measurement	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value[b]
Urine Sodium Excretion (meq/24 hrs) Mean±sd	156±91	85±58	104±80	146±285	0.369
Median	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
p Value compared with placebo[c]	--	NS	NS	NS	
Urine Potassium Excretion (meq/24 hrs) Mean±sd	85±56	66±34	63±19	81±42	0.166
Median	70	56	63	74	0.694
p Value compared with placebo[c]	--	NS	NS	NS	

a. Data from NDA volume 54, Appendix 1, Table 35.
b. See statistical section for statistical methods. p Value per sponsor by ANOVA Omnibus F test.
c. Comparison using Dunnet's t-test.

Effect of Nesiritide on Miscellaneous Other Endpoints

More subjects were withdrawn from the study due to worsening CHF in the placebo group (5/29, 17%) than in the nesiritide groups (1/74, 1.3%); p=0.014 by trend test.

Sub-Group Analyses: Effects of Demographics and Baseline Cardiac Status on Hemodynamics at 3 hours in the 0.50/ 0.015 group and the 1.0/ 0.060 group

The effect of demographics and baseline cardiac status was examined retrospectively for several key hemodynamic measures, as summarized in the two tables below. Note the extremely small numbers of subjects in several of the sub-groups, limiting the power of this analysis.

Table 6.1.12.5.6 Effect of demographics and baseline hemodynamics on change in PCWP, CI, and SBP in the nesiritide 0.50/ 0.015 group in study 704.311[a].

Demographic	PCWP		CI		SBP	
	Baseline	% Change	Baseline	% Change	Baseline	% Change
Age						
<65 (n=18)	27	-31%	1.4	16%	116	-6%
≥65 (n=4)	31	-21%	1.8	24%	133	-12%
Gender						
Male (n=18)	28	-31%	1.8	16%	118	-5%
Female (n=4)	26	-22%	1.8	23%	126	-17%
Ethnicity						
White (n=15)	30	-25%	1.8	18%	118	-8%
Black (n=6)	23	-33%	1.7	41%	121	-10%
Hispanic (n=1)	25	-32%	2.5	1%	118	2%
NYHA Class						
II (n=2)	26	-23%	1.4	29%	111	-11%
III (n=14)	28	-29%	1.8	16%	117	-11%
IV (n=6)	27	-27%	1.7	23%	128	-2%
Etiology of CHF						
Ischemic (n=11	28	-26%	1.8	21%	124	-6%
Idiopathic (n=5	25	-20%	1.8	16%	116	-12%
Other (n=6	29	-31%	1.7	1%	111	-3%
Baseline PCWP						
<26 mm Hg (n=7	24	-24%	1.8	16%	124	-14%
≥26 (n=15	30	-31%	1.8	21%	113	-3%
Baseline CI						
<2.0 L/min/m² (n=15)	28	-31%	1.7	28%	117	-7%
≥2.0 (n=7)	28	-26%	2.3	9%	131	-6%
Baseline SBP						
≤100 mm Hg (n=2)	27	-14%	1.6	19%	94	5%
101-139 (n=15)	28	-32%	1.8	21%	117	-11%
140 (n=4)	25	-9%	2.2	18%	153	-3%
On Digoxin						
Yes (n=9)	28	-33%	1.8	28%	124	-8%
No (n=13)	28	-24%	2.0	10%	113	-6%

a. Data from NDA volume 54, text table 3.

APPEARS THIS WAY ON ORIGINAL

Sub-Group Analyses: Effects of Demographics and Baseline Cardiac Status on Hemodynamics at 3 hours in the 0.50/ 0.015 group and the 1.0/ 0.060 group (cont)

Table 6.1.12.5.7 Effect of demographics and baseline hemodynamics on change in PCWP, CI, and SBP for the nesiritide 1.0/ 0.060 group in study 704.311[a].

Demographic	PCWP		CI		SBP	
	Baseline	% Change	Baseline	% Change	Baseline	% Change
Age						
<65 (n=17)	33	-42%	2.0	30%	104	-8%
≥65 (n=9)	28	-23%	1.5	34%	114	-2%
Gender						
Male (n=23)	30	-39%	2.0	36%	112	-7%
Female (n=3)	22	-6%	1.5	49%	138	-2%
Ethnicity						
White (n=17)	30	-39%	2.0	36%	112	-7%
Black (n=5)	22	-52%	2.0	25%	138	-14%
Hispanic (n=3)	34	-12%	1.5	3%	98	0%
NYHA Class						
II (n=2)	22	-52%	1.9	4%	135	-16%
III (n=15)	30	-45%	1.9	34%	110	-4%
IV (n=9)	30	-10%	1.9	34%	117	-4%
Etiology of CHF						
Ischemic (n=16)	32	-39%	2.0	31%	111	-5%
Idiopathic (n=5)	22	-36%	1.8	64%	104	-3%
Other (n=5)	26	-35%	1.9	34%	117	-4%
Baseline PCWP						
<26 mm Hg (n=7)	22	-33%	1.9	35%	104	-6%
≥26 (n=19)	33	-41%	1.9	33%	112	-5%
Baseline CI						
<2.0 L/min/m² (n=16)	30	-33%	1.7	38%	107	-3%
≥2.0 (n=10)	32	-57%	2.2	28%	116	-15%
Baseline SBP						
≤100 mm Hg (n=5)	28	-39%	1.8	34%	95	-3%
101-139 (n=15)	30	-38%	1.9	31%	112	-4%
140 (n=6)	28	-35%	2.0	31%	153	-12%
On Digoxin						
Yes (n=8)	30	-33%	2.0	28%	113	-3%
No (n=18)	32	-39%	1.9	34%	111	-5%

a. Data from NDA volume 54, text table 4.

APPEARS THIS WAY
ON ORIGINAL

6.1.13 Safety Outcomes

The deaths, serious adverse events, and adverse events by body system will be considered in section 8.1 and 8.2 below. The section below will comment on the following specific safety parameters: deaths; subject discontinuations; and cardiovascular AEs. The first table summarizes the adverse clinical events that occurred in the trial within the first 14 days. Note the increased incidence of SAEs and discontinuations due to hypotension in the nesiritide groups.

Table 6.1.13.1 Clinical adverse experience (AE) summary from the trial 704.311[a].

Clinical event	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value
With any AE	15 (52%)	8 (36%)	16 (62%)	14 (54%)	0.387[d]
With Serious AE (SAE)	0 (0%)	1 (4%)	2 (8%)	2 (8%)	
Deaths	1 (3%)	0 (0%)	1 (4%)	1 (4%)	
Dose-Reduction of Study Drug[b]	2 (7%)	6 (27%)	8 (31%)	12 (46%)	
Discontinuation for any reason	5 (17%	0 (0%)	3 (12%)	6 (23%)	
Discontinued due to an AE prior to hour 3	0 (0%)	0 (0%)	2 (8%)	3 (12%)	
Discontinued due to an AE between hours 3 & 24	5 (17%)	0 (0%)	1 (4%)	3 (12%)	
Discontinuation due to hypotension	0 (0%)	0 (0%)	2 (8%)	6 (23%)	
Symptomatic hypotension during study drug infusion	2 (7%)	1 (5%)	1 (4%)	4 (15%)	0.350[e]
Hypotension during study drug infusion[c]	2 (7%)	1 (5%)	3 (12%)	7 (27%)	0.027[e]

a. Data from NDA volume 54, Section 4.
b. Dose reduction could be done for a decrease in PCWP to >10 mm Hg, regardless of symptoms, as well as for adverse events.
c. Includes both symptomatic and asymptomatic hypotension.
d. Using Fischer exact test.
e. Using Cochran-Armitage trend test.

6.1.13.1 Comparisons of Defined Safety Endpoints

The deaths, serious adverse events, and adverse events by body system will be considered in section 8.1 and 8.2 below. The section below will comment on the following specific safety parameters from the 704.311 trial: deaths, subject discontinuations, and cardiovascular adverse events (AEs). A discussion of the most common, dose-limiting adverse event, related to excess vasodilation.

6.1.13.2 Comments on Specific Safety Parameters

Deaths

Three deaths occurred during the 15-day study follow-up period, one each in the placebo group, the nesiritide 0.03 µg/kg/min group, and the nesiritide 0.06 µg/kg/min group. Two additional deaths were reported after day 15, both in the placebo group. A line listing for the deaths appears below, and a narrative summary for each of these deaths can be found in appendix two: narratives of subject deaths.

Table 6.1.13.2.1 Deaths in study 704.311[a].

Subject #	Treatment	Day of Death	Cause of Death	Notes
376-016	Placebo	9	Sudden death	Hx COPD, CAD, PVCs, AODM, HTN
376-022	Placebo	21	Sudden death	Hx pacemaker placement
370-006	Placebo	46	End-stage CHF	S/p cardiac aneurysmectomy
017-007	0.5/ 0.030	8	Renal Failure, Respiratory Failure	S/p cardiac cath
382-004	1.0/ 0.060	8	Sudden death	Hx pacemaker placement (for rheumatic heart disease)

a. Data from NDA vol. 54, section 6.2 and Case Report Forms.

Serious Adverse Events

Five subjects, all treated with nesiritide, experienced adverse events which resulted in rehospitalization or a prolongation of hospitalization. Four of these subjects developed recurrent decompensated CHF after hospital discharge that resulted in rehospitalization. One subject developed pre-renal azotemia that lengthened his hospitalization. The table below summarizes the SAEs. A narrative description for each event is in appendix three.

Table 6.1.13.2.2 Serious Adverse Events in study 704.311[a].

Subject #	Treatment	Day	SAE	Notes
369-009	Nesiritide 0.25/ 0.015	13	CHF decompensation, re-hospitalization	
369-004	Nesiritide 0.5/ 0.030	11	CHF decompensation, re-hospitalization	
376-008	Nesiritide 0.5/ 0.030	9	CHF decompensation, re-hospitalization	
324-001	Nesiritide 1.0/ 0.060	4, 14	Renal failure	Peak creatinine 4.2 on day 14, dx 'Interstitial Nephritis,' no dialysis needed
367-003	Nesiritide 1.0/ 0.060	7	CHF decompensation, re-hospitalization	

a. Data from NDA vol. 54, section 6.3 and Case Report Forms.

The narrative for the patient who developed renal failure is below.

Subject 324-001 (0.06 µg/kg/min Nesiritide) Subject 324-001 is a 67-year-old white woman with NYHA Class III CHF, idiopathic dilated cardiomyopathy, hypertension, mild pulmonary hypertension, and hypothyroidism. She received the full 24-hour infusion of study drug (0.06 µg/kg/min Nesiritide) without incident. On day 4, she was reported to have a decrease in urine output and was diagnosed with acute renal failure due to poor cardiac output (i.e., pre-renal azotemia). No serum creatinine data is available for this period. She was treated with IV dobutamine, dopamine, furosemide, and fluids. Her renal dysfunction resolved by day 9, and she was discharged with a serum creatinine of 1.9 mg/dL. On day 14, she was noted to have an elevated serum creatinine of 4.2 mg/dL and was readmitted with the diagnosis of interstitial nephritis. A follow-up serum creatinine on day 28 was 1.5 mg/dL.

Subject discontinuations

Fourteen subjects terminated study drug infusion prematurely due to an adverse event or an inadequate therapeutic response (i.e., worsening CHF requiring additional therapy). The table below summarizes the reasons for discontinuation. A narrative summary for each of these subjects is in appendix four.

Table 6.1.13.2.3 Subject discontinuations in study 704.311[a].

Subject #	Day of D/C	Cause of Discontinuation	Notes
Placebo Group			
017-010	1 (22 hrs)	CHF worsening,	PCWP 28 to 32 mm Hg
369-006	1 (9hrs)	CHF worsening	PCWP 24 to 30 mm Hg
370-005	1 (12hrs)	CHF worsening, Renal failure	Creatinine increased 1.4 to 4.1 at peak
370-006	1 (3 hrs)	CHF worsening, SVT	Reported to have died on day 46
373-006	1 (4 hrs)	CHF worsening,	PCWP 32 to 34 mm Hg
Nesiritide 0.5/ 0.030			
380-004	1 (2 hrs)	CHF worsening,	PCWP 25 to 28 mm Hg
389-006	1 (1.5 hrs)	Symptomatic hypotension and decreased PCWP	PCWP decreased 13 to 5. SBP 120 to 80 mm Hg.
373-007	1 (9 hrs)	Excess decrease in PCWP	PCWP decreased 24 to 6.
Nesiritide 1.0/ 0.060			
017-008	1 (1 hr)	Symptomatic hypotension	Systolic BP 103 to 62 mm Hg, required dopamine.
369-005	1 (2 hrs)	Symptomatic hypotension and decreased PCWP	PCWP decreased 18 to 6. Systolic BP 150 to 70 mm Hg.
369-014	1 (1 hrs)	Symptomatic hypotension	Systolic BP 138 to 58 mm Hg. Required dopamine.
373-003	1 (3 hrs)	Asymptomatic hypotension and decreased PCWP	PCWP decreased 26 to 6. Systolic BP 166 to 114 mm Hg.
376-021	1 (2 hrs)	Asymptomatic hypotension	Systolic BP 112 to 67 mm Hg
388-001	1 (2 hrs)	Decreased PCWP	PCWP decreased 34 to 2 (!). Experienced abdominal cramping and nausea.

a. Data from NDA vol. 54, section 6.4 and Case Report Forms.

6.1.14 Trial 704.311-Efficacy Summary

This was a trial in patients hospitalized for decompensated CHF. The patients were not acutely severely decompensated, as evidenced by their ability to have other cardiac medications withheld for 24 to 48 hours.

The treatment groups had some significant imbalances. Most important, the placebo group had a lower average ejection fraction, and were less likely to be taking ACE inhibitors and diuretics at time of entry (tables 6.1.12.1.2, 6.1.12.1.3).

1. The primary endpoint for the 704.311 trial was the change in PCWP from baseline to 3 hours. Regardless of the population analyzed (ITT, 'last-value carried forward', 'evaluable at 3 hours'), nesiritide use was associated with a significantly greater decrease in PCWP when compared with placebo(e.g., table 6.1.12.3.1). Within the limitations of the relatively small trial enrollment, this effect was consistent across the demographic sub-groups, including analyses for age, gender, ethnicity, prior NYHA class, and cause of CHF (table 6.1.12.5.6).

2. Over the dose-range studied, there appeared to be a dose-related effect of nesiritide to lower PCWP which persisted to 10 hours (see Fig. 6.1.12.5.1). There was a suggestion that the magnitude of the effect diminished between 10 and 24 hours, but the overall significance of the nesiritide effect on PCWP remained (tables 6.1.12.3.2, 6.1.12.4.2). The effect of the intermediate dose on PCWP was not statistically significant when examined in the ITT and 'last-value carried forward' analyses (tables 6.1.12.5.3).

3. Following discontinuation of nesiritide, the PCWP and other hemodynamics markers returned to baseline within 2-4 hours (see figure 6.1.12.5.2).

4. The effect of nesiritide on the PCWP was coupled with significant beneficial effects on other important hemodynamic parameters: mean right atrial pressure (MRAP); systemic vascular resistance (SVR); cardiac index (CI). It was also associated with a significantly greater decrease in systolic BP (table 6.1.12.4.1, 6.1.12.4.2).

5. In the first 24 hours, patients receiving nesiritide retained more water and sodium on average (with very broad patient-patient variability, see table 6.1.12.5.4, 6.1.12.5.5). The decreased fluid output in the nesiritide groups was a result of less urine output, and not due to differences in the amount of fluids administered to the patients. There was no significant difference in the use of diuretics among the treatment groups (which is used in another trial in this NDA to account for an observed difference in Na^+ and water excretion).

6.1.15 Trial 704.311 Safety Summary

1. A majority of the patients who entered the trial completed the first 24 hours of treatment. Of those who discontinued, the most common cause of discontinuation in the placebo group was worsening CHF (5/5 discontinuations). The most common cause of discontinuation in the nesiritide groups was symptomatic hypotension/ excessive decrease in PCWP (8/9 discontinuations) (table 6.1.13.1).

2. There were 5 deaths in the trial: 3 in placebo; and one each in the 0.5/0.030 and 1.0/ 0.060 groups (table 6.1.13.2).

3. There were five serious adverse events in the trial, all in patients who received nesiritide. The most common cause was decompensation of CHF requiring re-hospitalization (4/5 events). One other patient developed renal failure, not requiring dialysis (table 6.1.13.2.2).

6.1.16 Overall Summary of 704.311

This trial investigated the effects of nesiritide in patients with decompensated CHF severe enough to require hospitalization but not so severe as to preclude the withholding of cardiac meds for 24-48 hours. Within this population, there was a clear effect of nesiritide to improve hemodynamics, especially to acutely decrease PCWP. This hemodynamic effect was rapid in onset (0-3 hours). Within 4 hours of nesiritide withdrawal, the PCWP returned to the level of the placebo group.

Nesiritide also had a beneficial effect on other hemodynamics that paralleled the changes in PCWP. Nesiritide did have a significant effect to lower BP, relative to placebo.

The use of nesiritide was associated with both sodium and water retention during the first 24 hours of infusion. This appears to have been the result of decreased urine output in the nesiritide groups.

With regards to safety, more subjects in the nesiritide group dropped out due to symptomatic hypotension and/or excessive decreases in PCWP, and more patients in the nesiritide groups had serious adverse events (SAEs).

In summary, in the present trial, nesiritide exerted an acute beneficial effect on hemodynamics that reversed within 4 hours of discontinuing infusion. Nesiritide did not, however, return the PCWP to normal, or near normal, values. This effect was coupled with some potentially significant adverse effects, including a greater hypotensive effect, and a tendency towards both sodium and water retention in the first 24 hours. There were also several patients in the nesiritide group who had acute worsening of their CHF shortly after completing the trial.

APPEARS THIS WAY
ON ORIGINAL

6.2 Review of the Protocol 704.325

6.2.1 Title of Study

A Randomized, Double-blinded, Placebo-controlled Study of Two Doses of NATRECOR® hBNP Administered as a Continuous Infusion in Subjects with Decompensated CHF.

6.2.2 Sites of Investigation and Investigators

Trial 704.325 was a multicenter investigation, with 23 investigators in the U.S. The table below summarizes those investigators. A total of 127 subjects enrolled in the trial.

Table 6.2.2.1 Investigators for the 704.325 study[a].

Investigator Name	# of Subjects Enrolled (% of Total Enrollment)
LEJEMTEL, T.	19 (15%)
BOURGE, R.	13 (10%)
JOHNSON, A.	13 (10%)
ABRAHAM, W.	9 (7%)
WAGONER, L.	8 (6%)
GIVERTZ, M.	7 (6%)
HOOD, W.	7 (6%)
DENNISH, G.	6 (5%)
LUI, C.	6 (5%)
LANG, R.	5 (4%)
PEPINE, C.	5 (4%)
VARGHESE, P.	5 (4%)
KUKIN, M.	4 (3%)
BIJOU, R.	3 (2%)
CHATTERJEE, K.	3 (2%)
DONOHUE, T.	3 (2%)
HARE, J.	3 (2%)
KAO, W.	2 (2%)
VENTURA, H.	2 (2%)
HERSHBERGER, R.	1 (1%)
PLEHN, J.	1 (1%)
ROUSH, K.	1 (1%)
UDHOJI, V.	1 (1%)
Total	127 (100%)

a. Data from NDA Volume 59, Appendix one, Table 1.

6.2.3 Background

Original Submission: 6.28.96

Amendment One: 12.20.96

Clarified the definition of the primary endpoint and how it would be analyzed. In particular, the protocol amendment clarified that that the 6-hour PCWP measurement used for the primary efficacy analysis must be made while study staff is still blinded. It also clarified how the order of events occurring during the 5.5- to 6-hour period of time after the start of study drug (such as the primary endpoint measurement, unblinding, and cardiovascular intervention) would impact the analysis.

Also: 1. Instructed that the subject's respiratory status and intubation status be monitored throughout the blinded evaluation period,

2. Clarified that an intervention with parenteral diuretics or cardiovascular medications during the 6-hour blinded evaluation period was only to occur if a subject's clinical condition worsened. (If a subject's clinical status remained stable during this period, no intervention was to be instituted.).

3. Clarified the type and timing of clinical assessments.

4. Added instructions for collecting information on intubation, dialysis, and ultrafiltration.

during the 21-day follow-up period.

Study Dates for Subject Enrollment: 10.22.96 to 4.29.97

6.2.4 Study Design

This was a randomized, double-blinded, placebo-controlled, multicenter study designed to enroll approximately 120 subjects with symptomatic, decompensated CHF for whom inpatient parenteral therapy was deemed appropriate. After a Swan-Ganz catheter was inserted and baseline hemodynamic measurements were obtained, subjects with PCWP ≥18 mm Hg, CI ≤2.7 L/min/m^2 and SBP ≥ 90 mm Hg were randomized to receive either placebo or one of two doses (0.015 or 0.03 μg/kg/min) of nesiritide (delivered as a loading bolus plus fixed-dose infusion). Cardiac hemodynamics and clinical status were followed for an initial 6-hour blinded evaluation period, during which diuretics and additional parenteral interventions and oral medications for decompensated CHF were to be withheld unless urgently required for worsening CHF not responding to study drug infusion. The primary study efficacy endpoint was the percentage change from baseline in PCWP at 6 hours.

After the 6-hour blinded evaluation was completed (including the collection of the PCWP for the primary endpoint determination), treatment assignment for all subjects was unblinded. Placebo subjects then received "standard care," consisting of the initiation of a parenteral agent routinely used for the short-term management of decompensated CHF (such as IV nitroprusside, nitroglycerin, dobutamine, or milrinone). These subjects thereafter served primarily as an unblinded control group for safety monitoring purposes. Nesiritide subjects could be continued on their fixed-dose regimens (still blinded as to specific dose group assignment) for up to a maximum duration of 5 days (with or without the addition of other parenteral agents) or switched to a "standard care" agent, at the discretion of the investigator.

Cardiac and systemic hemodynamics (PCWP, CI, MRAP, SVR, blood pressure [BP], heart rate [HR], stroke volume index [SVI], pulmonary artery pressures) were assessed at baseline and at 1.5, 3, 4.5, and 6 hours following the initiation of study drug administration in all subjects (and at 24, 36, and 48 hours for subjects still receiving nesiritide, if the Swan-Ganz catheter was still in place). All concomitant medications administered through day 5 were recorded. Clinical status (i.e., global clinical status and specific symptoms and signs of decompensated CHF) was assessed at baseline, at the end of the 6-hour blinded evaluation period, at 24 hours (unblinded), and at the end of parenteral therapy (unblinded). Urine output, fluid intake, and weight were assessed daily. Plasma nesiritide levels and blood samples for assessment of renin, aldosterone, and norepinephrine levels (at selected sites) were obtained at baseline and at 6 and 24 hours after the initiation of study drug infusion. Blood samples for assessments of serum anti-nesiritide antibodies were obtained at baseline and at day 21. Also, at day 21, follow-up patient status was assessed, including duration of initial hospitalization, length of time on parenteral CHF therapy, the need for re-admission, and mortality status.

The sponsor felt that some subjects might not be able to tolerate study drug infusion for even 6 hours, and might require parenteral vasoactive agents prior to the primary endpoint at 6 hours. This would mean that their PCWP at 6 hours would reflect the effects of both study drug and other vasoactive agent. Rather than simply exclude these subjects, the sponsor designed a 'worst outcome' strategy. If a cardiovascular intervention or unblinding occurred before the 6-hour assessment for PCWP (the primary endpoint), that subject was defined as 'worst outcome.' The actual PCWP was to be disregarded for purposes of primary endpoint analysis; instead a PCWP that was worse than any true observed value would be assigned. Analysis as then by non-parametric, rank-based statistical methods.

6.2.5 Primary and Secondary Endpoints

Primary endpoint

1. The primary endpoint was PCWP, expressed as a percentage change from baseline, 6 hours after initiation of study drug (704.325 protocol in IND vol. 7.1, 8.16.96 submission, page 15). The population for this analysis was the 'worst outcome' population (see Statistical Considerations section 6.2.11 below).

6.2.6 Number of subjects/ randomization

No information regarding the number of subjects screened for the study is available.

6.2.7 Inclusion/ Exclusion Criteria

Subjects must have met all of the following criteria to be eligible for participation in the study.

1. Be at least 18 years old.
2. Previous history of chronic CHF.
3. Present with symptomatic, decompensated CHF for which in-patient parenteral therapy was deemed appropriate.
4. Have documentation of PCWP ≥18 mm Hg, CI ≤2.7 mL/min/m^2 , and systolic blood pressure ≥90 mm Hg with consistent baseline hemodynamic measurements.
5. Fully understand all elements of, and had signed, the written Informed Consent Form before the initiation of protocol-specified procedures.

Exclusion Criteria for study 704.325

Potential subjects with any of the following were not eligible for this study:

1. Myocardial infarction within the previous 48 hours or ongoing unstable angina.
2. Significant valvular stenosis, hypertrophic, restrictive or obstructive cardiomyopathy, constrictive pericarditis, primary pulmonary hypertension, biopsy-proven active myocarditis, or complex congenital heart disease.
3. Stroke within 3 months or other evidence of significantly compromised central nervous system perfusion.
4. Ongoing treatment with a parenteral vasoactive agent (i.e., an IV inotrope or vasodilator) for this episode of decompensated CHF, that could not be discontinued for an appropriate washout period to permit the reassessment of baseline hemodynamics and clinical status before initiation of study drug.
5. Clinical status so acutely unstable that it was felt the potential subject could not tolerate Swan-Ganz catheter placement, a brief baseline assessment off parenteral medications, and/or a short placebo infusion (should they be assigned to the placebo group).
6. Therapy with another investigational drug at the time of study entry that had not been pre-approved by the sponsor.
7. Unwillingness or inability to comply with study requirements.

6.2.8 Dosage/ Administration

Study Drug Administration

There were three treatment groups in study 704.325:

Group 1: Nesiritide: IV bolus of 0.3 μg/kg followed by a 0.015 μg/kg/min infusion.
Group 2: Nesiritide: IV bolus of 0.6 μg/kg followed by a 0.030 μg/kg/min infusion.
Group 3: IV bolus of placebo followed by a placebo infusion.

Each subject received an initial IV loading bolus of the study drug followed by a continuous IV infusion for at least 6 hours. After 6 hours, placebo subjects received 'standard care' consisting of the initiation of a parenteral agent routinely used for the short-term management of decompensated CHF (i.e., IV nitroprusside, nitroglycerin, dobutamine, milrinone) for the remainder of the first 24 hours. Subjects in the nesiritide group could continue to receive nesiritide for up to 5 days.

Blinding

Study site personnel responsible for subject treatment and/or assessment were to remain blinded to study drug assignment until the 6-hour blinded evaluation period was completed. To maintain blinding, study drug was provided to study personnel by the pharmacist in an IV bag labeled "NATRECOR® hBNP or placebo". After completion of the 6-hour blinded evaluation period, the investigator contacted the Automated Telephone Response System to learn the subject's study drug assignment. To avoid premature or inappropriate unblinding, the investigator was required to enter the start time for study drug administration and to confirm that the 6-hour blinded assessments of hemodynamics and clinical status had been obtained. Only then was information on the subject's study drug assignment provided. Study staff and the sponsor remained blinded throughout the study as to whether nesiritide subjects were initially assigned to the 0.015 or 0.030 μg/kg/min treatment group.

In discussions with the sponsor, it became clear that the investigator who filled out the 'investigator's assessment' of symptoms would have had knowledge of the 6 hour PCWP. A review of the Case Report Forms also found that the same investigator filled out the patient's assessments (presumably asking each patient how he or she felt relative to baseline). Finally, in some cases the Investigator's and patients assessments were filled out more than one hour after the patients were unblinded. These facts greatly undermine the independence of the symptom and hemodynamic data in this study.

Prior and Concomitant Therapy

The last dose of oral cardiac medications (other than anti-arrhythmic agents) was to be at least 4 hours (2 hours for sublingual NTG) before study drug initiation. These medications were to be held at least through the 6-hour blinded evaluation period. Thereafter, oral cardiac medications could have been administered as clinically indicated to subjects in all treatment groups.

The last dose of diuretics (oral or parenteral) also was to be at least 4 hours before study drug initiation, and diuretics were to be held through the 6-hour blinded evaluation period, if possible.

Prior and Concomitant Therapy (cont)

Parenteral diuretics were only to be given during the 6-hour blinded evaluation period if urgently required to treat worsening CHF not responding to study drug. Parenteral vasodilators or inotropes such as nitroprusside, NTG, dobutamine, or dopamine were to be held from at least 1 hour prior to the baseline assessments through completion of the 6-hour blinded evaluation period, if possible. Milrinone was to be held beginning 2 hours before study drug infusion through completion of the 6-hour blinded evaluation period, if possible. These parenteral vasoactive agents were only to be administered during the 6-hour blinded evaluation period if urgently required for the treatment of worsening CHF not responding to study drug alone (or for pressure support in the case of dopamine). Thereafter, they could have been administered to subjects in all treatment groups as medically indicated.

6.2.9 Duration/ Adjustment of Therapy

Discontinuation of therapy

If a subject had symptomatic hypotension or a drop in systolic BP to <85 mm Hg, the study drug infusion was stopped and then restarted at half the initial infusion rate.

If additional vasoactive parenteral therapy was required during the initial 6 hours of study drug infusion, the following guidelines applied. If the agent initiated was nitroprusside, NTG, milrinone, or other strong vasodilator, study drug was to be discontinued prior to initiation of that drug. Dopamine or dobutamine could be added to the study drug infusion or substituted for it.

Administration of parenteral vasoactive compounds

All parenteral and oral vasoactive agents (including diuretics) were only to be administered during the 6-hour blinded evaluation period if urgently required for the treatment of worsening CHF not responding to study drug alone (or for pressure support in the case of dopamine). Thereafter, they could have been administered to subjects in all treatment groups as medically indicated.

6.2.10 Safety and Efficacy Measurements

1. Hemodynamic endpoints analyzed at baseline and 1.5, 3, 4.5, 6, and 24 hours after initiation of study drug: PCWP, MRAP, SVR, CI, and SBP. Measurements were also made after 24 hours for those subjects with Swan-Ganz catheters still functioning.
2. Clinical status at 6 and 24 hours, and at the end of parenteral therapy. This included an analysis of global clinical status and status related specifically to CHF.
3. Fluid status, including urine output, fluid intake, and weight.
4. Plasma aldosterone and norepinephrine levels (selected sites).
5. Nesiritide antibody levels at 21 days.
6. Clinical markers: duration of initial hospitalization, length of time on parenteral therapy, need for re-admission, and mortality.

The table on the next page details the type and timing of the clinical information collected during study 704.325.

Table 6.2.10.1 Timetable for clinical observations and lab measurements in study 704.325[a].

Procedure	Screening	Baseline	Treatment Period											Post-Treatment		
Time			0	1.5	3	4.5	6	24	36	48	Day 3	Day 4	Day 5	<24 hrs after IV Tx	14	21
Med Hx, Physical Exam														X		
ECG	X															
CSR	X															
Hold cardiac meds[c]	X	X	X	X	X	X	X									
Swan-Ganz Catheter	X	X	X	X	X	X	X	X[d]								
Vital Signs	X	X	X	X	X	X	X	X	X	X						
PCWP, SVR, CI	X	X	X	X	X	X	X	X	X	X[d]						
CBC, Chemistries[b]	X													X		
Plasma hBNP levels		X					X	X[e]								
Renin, aldo, norepi levels		X					X	X[f]								
hBNP Antibody level																X
I/Os, weights			X	X	X	X	X	X	X	X	X	X	X			
Na, K, CO_2, Cl, Crt, BUN								X		X	X	X	X			
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	
F/U Visit																X
Study Drug			X	X	X	X	X	X	X	X	X	X	X[g]			

a. Data from NDA volume.

b. Labs and hematology collected include: CBC (hemoglobin, hematocrit, WBC count and differential, platelet count); serum chemistries (BUN, creatinine, total bilirubin, AST/ALT, glucose, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol); urinalysis; and stool for occult blood.

c. See Dosage/ Administration section above for description of protocol for withholding cardiac meds.

d. Swan-Ganz to be removed after 24 hours if medically appropriate. Cardiac measurements to be done as long as S-Ganz present.

e. Nesiritide subjects only.

f. Norepinephrine levels at selected sites only

g. Administration after 24 hours at discretion of investigator.

6.2.11 Statistical Considerations

General statistical approach

The primary population for analysis was the 'worst outcome' Intent-to-Treat population.

Analysis Populations

Primary Statistical Analysis

Many of the analyses, including the primary efficacy analysis, were performed on the 'worst outcome' population. A subject was classified as "worst outcome" if any of the following conditions were met:

1) the subject received cardiovascular intervention or the investigator unblinded the subject's treatment assignment less than 5.5 hours after start of study drug;

2) the subject received cardiovascular intervention or the investigator unblinded treatment between 5.5 and 6 hours after start of study drug and before obtaining a PCWP reading at least 5.5 hours after start of study drug; or

3) the subject died less than 6 hours after start of study drug.

The protocol defined cardiovascular intervention to be a parenteral diuretic or parenteral vasoactive agent given either for worsening CHF or for treatment of an adverse event. The definition excluded intravenous anti-arrhythmic agents administered in response to an arrhythmia.

The primary analysis for the 6-hour PCWP was done on the 'worst outcome' population using non-parametric, rank-based methods. For those subjects not classified as 'worst outcome,' the PCWP chose for ranking was that PCWP recorded pre-intervention between 5.5 and 7 hours after start of study drug. If more than one existed, the one closest to 6 hours was chosen. For the subjects classified as 'worst outcome,' they were arbitrarily assigned an arbitrarily poor analysis value for all hemodynamic data. Because the analysis was rank-based, the 'worst outcome' value was arbitrary, except that it must: 1) be the same for all 'worst outcome' subjects; and 2) that the value must be worse than any true value measured for the subjects who completed the 6 hours without intervention (non-'worst outcome' subjects).

The proportion of subjects classified as "worst outcome," the earliest event leading to "worst outcome" classification, all events leading to "worst outcome" classification, the study time of the earliest event, and the medications associated with cardiovascular intervention were descriptively summarized. Inferences were conducted only on the proportion of subjects classified as 'worst outcome', and treatment groups were tested for non-specific differences with the generalized Fisher exact test, and dose-related differences with the Cochran-Armitage trend test.

Secondary Statistical Analyses

Two additional analyses were conducted to further evaluate the 'worst outcome' hemodynamics analysis: 1) a parametric analysis using 'last data carried forward'; and 2) a parametric analysis using a 'data as available' dataset. The last value carried forward analysis was specifically recommended to the company by Dr. Temple at the end-of-phase II meeting, 7.23.96.

Statistical Methods for Individual Endpoints

Hemodynamic Data

Hemodynamic endpoints were analyzed at baseline and 1.5, 3, 4.5, 6, and 24 hours after initiation of study drug. Endpoints were represented in terms of the observed value and the change from baseline (i.e., arithmetic difference). Selected endpoints (PCWP, MRAP, SVR, CI, and SBP) were also represented in terms of the percentage change from baseline. The primary analysis of 6-hour PCWP was a "worst outcome" non-parametric analysis. This strategy was applied to the endpoints PCWP, MRAP, SVR, and CI, through the nominal 6-hour assessment. This strategy, as well as other analysis strategies employed by the sponsor, are discussed in Appendix 5 of the overall document.

Global Assessment of Clinical Status

A global assessment of clinical status was to be made separately by the subject and by the investigator at 6 and 24 hours after initiation of study drug and, if parenteral therapy exceeded 24 hours, within 24 hours after discontinuation of all parenteral therapy. Clinical status was evaluated relative to baseline status on a 5-category ordinal scale. Summaries were prepared of the 6-hour assessment, the 24-hour assessment, and the last recorded assessment more than 20 hours after initiation of study drug.

The protocol specified that the 6-hour assessment was to be made before treatment unblinding; this was not required for inclusion in the analysis.