

**NDA 20-920  
Cardio-Renal Advisory Committee  
Briefing Document**

**Natrecor<sup>®</sup> (nesiritide) for Injection**

**11 January 1999**

## TABLE OF CONTENTS

	<u>Page</u>
<i>List of Abbreviations</i> .....	iv
1. <i>Executive Summary</i> .....	1
2. <i>Regulatory History of Natrecor®</i> .....	5
3. <i>Overview of Scios Clinical Studies with Natrecor® in CHF</i> .....	7
3.1 Subject Demographics .....	7
3.2 History of Clinical Development .....	8
3.3 Rationale for Recommended Dosing Regimen .....	11
3.4 Duration of Infusion .....	12
4. <i>Clinical Pharmacology and Pharmacokinetics</i> .....	19
4.1 Preclinical Pharmacology .....	19
4.2 Clinical Pharmacology .....	20
4.3 Pharmacokinetics .....	26
5. <i>Efficacy Summary</i> .....	29
5.1 Goals of Therapy in the Short-Term Treatment of Decompensated CHF .....	29
5.2 Assessments of Clinical Efficacy .....	29
5.3 Results .....	31
5.4 Efficacy Conclusions .....	48
6. <i>Safety Summary</i> .....	50
6.1 Safety Evaluations Performed .....	51
6.2 Safety Database Information .....	54
6.3 Mortality .....	58
6.4 Adverse Events in Clinical Trials .....	60
6.5 Clinical Laboratory Evaluations .....	78
6.6 Assay for Anti-hBNP Antibodies .....	80
6.7 Safety Summary of Studies from the Literature or from other Indications .....	80
6.8 Overdose Experience .....	80
6.9 Clinical Effects After Discontinuation of Natrecor® .....	81
6.10 Natrecor® as a Natural Product .....	81

## TABLE OF CONTENTS (cont'd)

	<u>Page</u>
6.11 Safety Conclusions .....	82
7. <i>Experience with Related Compounds</i> .....	86
8. <i>Benefit/Risk Assessment</i> .....	88
8.1 Natrecor® (nesiritide): Therapeutic Profile .....	88
8.2 The Neurohormonal Hypothesis .....	90
8.3 Currently Available Agents for the Short-Term Treatment of CHF and Their Limitations .....	91
8.4 Benefit/Risk Conclusions .....	93
9. <i>Ongoing Natrecor® Studies</i> .....	95
10. <i>Manufacturing Summary</i> .....	96
11. <i>Proposed Indication, Usage, and Dosing</i> .....	97
 <u>Appendices</u>	
<i>Appendix A: Study 704.311 Efficacy Synopsis</i> .....	98
<i>Appendix B: Study 704.325 Efficacy Synopsis</i> .....	113
<i>Appendix C: Study 704.326 Efficacy Synopsis</i> .....	130

## LIST OF ABBREVIATIONS

Abbreviation	Definition	Abbreviation	Definition
ACE	angiotensin converting enzyme	PVC	premature ventricular contraction
ALT	alanine transaminase	PCWP	pulmonary capillary wedge pressure
ANOVA	analysis of variance	PVR	pulmonary vascular resistance
AST	aspartate transaminase (oxaloacetic transaminase)	RBC	red blood cell
AUC	area under the curve	SBP	systolic blood pressure
BP	blood pressure	SD	standard deviation
BUN	blood urea nitrogen	SVR	systemic vascular resistance
CHF	congestive heart failure	$t_{1/2\alpha}$	initial elimination phase
CI	cardiac index	$t_{1/2\beta}$	second elimination phase
CL	clearance	$V_{\text{area}}$	volume of distribution area
CNP	C-type natriuretic peptide	$V_c$	volume of distribution of the central compartment
CO	cardiac output	$V_{\text{ss}}$	volume of distribution at steady-state
cyclic AMP	cyclic adenosine monophosphate	VT	ventricular tachycardia
cyclic GMP	cyclic guanosine 3',5'-monophosphate	WBC	white blood cell
D5W	5% Dextrose Injection, USP		
GC-A	guanylyl cyclase-A		
GFR	glomerular filtration rate		
hANP or ANP	human atrial natriuretic peptide		
hBNP or BNP	human B-type natriuretic peptide		
HR	heart rate		
IV	intravenous		
LVEDP	left ventricular end-diastolic pressure		
MRAP	mean right atrial pressure		
MI	myocardial infarction		
NEP 24.11	neutral endopeptidase enzyme		
NP-C receptor	natriuretic peptide clearance receptor		
NYHA	New York Heart Association		
NTG	nitroglycerin		
NSVT	nonsustained ventricular tachycardia		
PAP	pulmonary artery pressure		

# Item 1

## Executive Summary

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Congestive heart failure (CHF) affects nearly five million Americans. Decompensation of chronic CHF to a more acute stage requiring hospitalization is a frequent event and is the most frequent discharge diagnosis in patients over 65 years of age in the U.S. For the large majority of patients presenting with acutely decompensated CHF, symptoms of congestion predominate and include dyspnea, fatigue, and decreased appetite. These symptoms result from elevated cardiac filling pressures and fluid overload, leading to pulmonary congestion, abdominal congestion, and peripheral edema.

The immediate goal of therapy in these acutely decompensated patients is to rapidly:

- stabilize their cardiac hemodynamics (by lowering cardiac preload and afterload and increasing cardiac output);
- relieve the symptoms of acutely decompensated CHF.

These patients are currently treated with intravenous (IV) diuretics and IV vasoactive agents, such as dobutamine, milrinone, nitroglycerin, or nitroprusside. While these agents are effective, they each are associated with disadvantages. For example, the inotropes dobutamine and milrinone act via stimulation of cyclic adenosine monophosphate (cyclic AMP) and can be associated with adverse effects such as tachycardia and ventricular arrhythmias. They have also been associated with an increase in mortality in patients with CHF when used on a long-term basis. Nitroprusside is a potent vasodilator, but can be difficult to use, particularly without invasive hemodynamic monitoring. Nitroglycerin is a much weaker vasodilator, which can be associated with rapid tachyphylaxis as well as a high incidence of side effects, such as headache and nausea. Thus, there is a need for new therapeutic options for the treatment of decompensated CHF.

Human BNP (hBNP) is an endogenous 32-amino-acid peptide hormone produced in the ventricular myocardium (Figure 1–1). Circulating levels of hBNP are naturally elevated in patients with systolic and diastolic cardiac dysfunction as well as when cardiac hypertrophy is present. In both animal and human studies, IV administration of exogenous hBNP produces vasodilation, natriuresis and diuresis, and suppression of aldosterone levels. It is believed that hBNP may be one of the body's natural mechanisms to augment cardiac function in a failing heart. This suggests that administration of exogenous hBNP would have therapeutic benefit in the short-term treatment of CHF.



- Significantly improves hemodynamics by reducing cardiac preload and afterload, thereby increasing cardiac output (via an improvement in stroke volume, without an increase in heart rate [HR]);
- Produces rapid hemodynamic improvement as early as 30 minutes after the start of therapy. Hemodynamic effects are sustained through at least 24 hours of infusion;
- Decreases the rate-pressure product (heart rate  $\times$  blood pressure), suggesting that Natrecor<sup>®</sup> does not increase cardiac work or myocardial oxygen consumption;
- Produces rapid improvement in clinical status consistent and concurrent with hemodynamic improvement in the majority of subjects. This improvement is evident both as an improvement in global clinical status (as assessed by patient and physician independently) and in specific symptoms of CHF, such as dyspnea and fatigue;
- Produces a significant reduction in levels of plasma aldosterone and no reflex increase in levels of plasma norepinephrine, as might occur following therapy with other vasodilators;
- Produces a mild diuresis with weight loss and a reduced need for diuretic therapy during infusion with Natrecor<sup>®</sup> in acutely decompensated CHF patients.

Natrecor<sup>®</sup> generally has been well tolerated when administered to patients with decompensated CHF and other common significant comorbidities (such as coronary artery disease, arrhythmias, and renal insufficiency) and when administered with medications commonly administered to this population (such as digoxin, angiotensin converting enzyme [ACE] inhibitors, beta-blockers, dopamine, and dobutamine). Natrecor<sup>®</sup> has been administered to subjects with CHF for up to 9 days. The limiting side effect of Natrecor<sup>®</sup> is dose-related hypotension, an extension of the desired pharmacologic effect, and one that is easily monitored and treated in the hospital setting. Symptomatic hypotension was reported in 8% to 14% of subjects receiving the 0.015 and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  doses of Natrecor<sup>®</sup>, respectively. Additional side effects, which have occurred in  $\leq 10\%$  of Natrecor<sup>®</sup> subjects in all clinical studies (at all doses), include nausea, insomnia, confusion, anxiety, nervousness, diaphoresis, bradycardia, oliguria, and mild to moderate increases in serum creatinine. Natrecor<sup>®</sup> can be safely used without invasive hemodynamic monitoring (such as a Swan-Ganz<sup>®</sup> catheter) although blood pressure should be monitored.

Thus, Natrecor<sup>®</sup> has several unique features that are not characteristic of currently available therapies for the short-term treatment of decompensated CHF. Compared to both inotropes and vasodilators, Natrecor<sup>®</sup> uniquely produces a combination of desirable hemodynamic, renal, and neurohormonal effects. Most IV agents, including diuretics, vasodilators, and dobutamine, may be associated with neurohormonal activation, while Natrecor<sup>®</sup> counteracts these systems. Long-term therapies which either inhibit the renin-angiotensin-aldosterone system (ACE inhibitors and spironolactone) or the sympathetic nervous system (beta-blockers) all have been shown to decrease mortality in patients with chronic heart failure. Unlike most available therapeutic agents for CHF, Natrecor<sup>®</sup> is not associated with an increased heart rate

either as a reflex mechanism or as a result of direct sympathetic stimulation. Compared to inotropes specifically, which have been associated with proarrhythmia in the acute setting and increased mortality with long-term use, Natrecor® is not associated with an increased risk of ventricular arrhythmias. Natrecor®'s activity is also not dependent on beta-adrenergic receptors such as is dobutamine. Therefore, Natrecor® may be a useful agent for the increasing population in whom beta-blockers are used as long-term therapy. Natrecor® is also effective when administered as a fixed-dose infusion, obviating the need for dose titration inherent in the use of most other available agents. When administered as a fixed-dose infusion dose range of 0.015 or 0.03 µg/kg/min, Natrecor® is effective in most patients, as evidenced by rapid hemodynamic and symptom improvement, and progressive symptom improvement over the course of therapy.

**Item 2****Regulatory History of Natrecor®**

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On 25 March 1993, Scios representatives attended a pre-IND Meeting with the FDA Division of Cardio-Renal Drug Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research, to discuss the development of Natrecor® as an agent for the short-term treatment of congestive heart failure (CHF). Agreements reached included the following:

- Initial clinical studies could be conducted in CHF patients rather than healthy volunteers.
- The hemodynamic endpoint of reduction in PCWP is an acceptable primary endpoint for demonstrating efficacy for this indication.
- The safety database for NDA filing should include information on approximately 300 to 500 patients treated with Natrecor®.

Scios filed an IND for Natrecor® in November 1993, and initiated clinical studies in patients with CHF in January 1994.

Initial clinical studies in the development program were performed with Natrecor® produced by peptide synthetic methods. In 1996, Scios developed a more cost-effective recombinant DNA manufacturing process for Natrecor® which produced a peptide with an amino acid sequence identical to that of the synthetic peptide and of the endogenous B-type natriuretic peptide (BNP). On 17 April 1996, near the end of Phase II clinical development, Scios met with the Agency to discuss the transition from the synthetic to recombinant drug substance. Agreement was reached on a series of chemistry and preclinical pharmacology, pharmacokinetic, and toxicology studies to be performed to confirm that the synthetic and recombinantly produced peptides were indistinguishable. Data from these studies were submitted to the Agency on 04 December 1996. The FDA agreed that Scios could subsequently utilize the recombinantly produced drug product in the Phase III clinical program.

In addition, at the meeting with the Agency on 17 April 1996, the clinical program completed to date and future plans for Phase III were discussed. The following agreements were reached:

- The safety database for an NDA filing should include information on approximately 500 patients treated with Natrecor®.
- The Phase III program should include, in addition to Scios study 704.311, one additional placebo-controlled, dose-ranging efficacy study performed specifically in the target patient population, patients with decompensated CHF requiring hospitalization.

- In that study, the effects of Natrecor® on cardiac hemodynamics (i.e., a reduction in PCWP) over a short period of time (range of 30 minutes to a few hours) versus placebo would be an acceptable primary endpoint for that confirmatory Phase III clinical trial.
- Information on patient symptoms and clinical status should be collected as well.

In response to this meeting, Scios designed Phase III studies 704.325 and 704.326 to obtain the requested efficacy and safety information. Scios met with the Agency on 23 July 1996 for the End-of-Phase II Meeting to discuss these proposed protocols. It was agreed that:

- In addition to the previously completed studies, the proposed Phase III studies 704.325 and 704.326 were adequately designed to support the submission of an approvable NDA.

On 09 July 1997, Scios attended a Pre-NDA Meeting with the Agency, at which time it was agreed that:

- The format and content of the proposed clinical pharmacokinetics, clinical, statistical, and pharmacology sections of the NDA were acceptable for the submission of an NDA.

The NDA was filed on 24 April 1998.

## Item 3

### Overview of Scios Clinical Studies with Natrecor® in CHF

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Nesiritide has been administered to approximately 785 subjects in clinical studies to date. Of these, 505 subjects with CHF were enrolled in the eight clinical studies in the Natrecor® CHF development program. These studies demonstrate that, as an intravenous (IV) agent for the short-term treatment of CHF, Natrecor® rapidly:

- improves cardiac hemodynamics, and
- improves the clinical status of patients with acutely decompensated CHF.

These eight studies are the focus of Scios NDA 20-920 and this Briefing Document. They are also summarized in tabular form in Table 3–2 at the end of this section.

Throughout the development program, the primary efficacy endpoint has been a reduction in PCWP. Highly statistically significant reductions in PCWP have been demonstrated in multiple randomized, double-blind, placebo-controlled clinical studies, including the two pivotal efficacy studies: 704.311 and 704.325.

#### **3.1 Subject Demographics**

In all CHF studies in NDA 20-920, a total of 721 subjects were enrolled in both the Natrecor® and control treatment groups. Subjects in the Natrecor® database are representative of the target population that would receive Natrecor® in clinical practice. In particular, women, the elderly, and subjects with advanced CHF (such as NYHA Classes III and IV) were well represented.

**Table 3-1**  
**All CHF Studies**  
**Demographics**

<b>Factor</b>	<b>All Subjects (n = 721)</b>	<b>Control (n = 216)</b>	<b>Natrecor® (n = 505)</b>
<b>Age</b>			
Mean (yrs):	59 ± 13	59 ± 13	59 ± 13
≥ 65	252 (35%)	75 (35%)	177 (35%)
<b>Gender</b>			
Male	525 (73%)	155 (72%)	370 (73%)
Female	196 (27%)	61 (28%)	135 (27%)
<b>Race</b>			
White	457 (63%)	133 (62%)	324 (64%)
Black	190 (26%)	54 (25%)	136 (27%)
Hispanic	62 ( 9%)	24 (11%)	38 ( 8%)
Asian	6 ( 1%)	2 ( 1%)	4 ( 1%)
<b>NYHA Class</b>			
I	1 ( 0%)	0 ( 0%)	1 ( 0%)
II	43 ( 6%)	10 ( 5%)	33 ( 7%)
III	417 (58%)	133 (62%)	284 (56%)
IV	259 (36%)	73 (34%)	186 (37%)

### 3.2 History of Clinical Development

Early clinical studies evaluated the safety, pharmacology, and pharmacokinetics of various doses and dosing regimens of Natrecor® in patients with chronic CHF to identify the optimal dosing regimen for this clinical indication. These early studies were all randomized, double-blinded, and placebo-controlled. The effects of IV administration of Natrecor® as both a bolus and a continuous infusion were explored.

In clinical study 704.305 (n = 30), Natrecor® was administered as a single IV bolus at doses ranging from 0.3 to 20 µg/kg to patients with chronic CHF. Bolus doses ≥ 3 µg/kg resulted in dose-related beneficial hemodynamic effects, such as decreases in PCWP and systemic vascular resistance (SVR) and increases in cardiac index (CI), which lasted for up to a few hours at the higher doses. To assess whether repeated boluses would produce sustained effects on hemodynamic parameters over time, Phase II studies 704.309 (n = 60) and 704.310 (n = 60) were performed. In these studies, Natrecor® was administered as a repetitive bolus regimen (every 4 or 6 hours for 24 hours). Favorable acute hemodynamic effects followed each bolus dose, but the effects on some parameters (particularly CI) waned before the time of the next bolus. Thus, a repetitive bolus regimen did not appear to result in stable

hemodynamic effects as would be desired for the short-term management of decompensated CHF and was not further pursued for this indication.

The effects of Natrecor® when administered as a continuous IV infusion were explored in parallel with the aforementioned bolus studies. In study 704.306 (n = 16), Natrecor® was administered as a fixed-dose infusion for 4 hours at doses of 0.025 or 0.05 µg/kg/min. In study 704.307 (n = 20), Natrecor® was administered as an escalating dose infusion at 0.003, 0.01, 0.03, and 0.1 µg/kg/min to patients with chronic, symptomatic CHF. These studies showed that administration of Natrecor® as a continuous infusion resulted in dose-related hemodynamic effects, which were sustained throughout the infusion. However, dose-related symptomatic hypotension limited tolerance of the 0.1 µg/kg/min dose, so only lower doses were pursued in subsequent studies.

To confirm the sustained hemodynamic effects of Natrecor® during administration as a fixed-dose infusion over a longer period of time, Phase II/III study 704.311 (n = 103) was performed. In this randomized, double-blinded, placebo-controlled study, Natrecor® was administered for 24 hours as a fixed-dose infusion at 0.015, 0.03, or 0.06 µg/kg/min (preceded by a small loading bolus [ $\leq 1$  µg/kg]). The primary efficacy endpoint was the change in PCWP at 3 hours. Highly statistically significant reductions in PCWP compared to placebo were observed at 3 and 6 hours ( $p \leq 0.004$ ); the reductions in PCWP were sustained throughout the 24-hour infusion. Reductions in SVR and increases in CI, without increases in heart rate were also observed. Also, Natrecor® significantly reduced the number of treatment failures; 5 placebo subjects (17%) and 0, 1, and 0 subjects (0%, 4%, and 0%) in the 0.015, 0.03, and 0.06 µg/kg/min Natrecor® dose groups, respectively, developed worsening CHF requiring intervention ( $p = 0.021$  [Fisher]). Hypotension limited tolerance of the 0.06 µg/kg/min Natrecor® dose. This study suggested that Natrecor® doses in the range of 0.015 to 0.03 µg/kg/min were safe and effective in the short-term treatment of CHF. Therefore, these two doses were utilized in subsequent Phase III studies.

To confirm the safety and efficacy of Natrecor® in the target population of patients with acutely decompensated CHF, Phase III studies 704.325 (n = 127) and 704.326 (n = 305) were performed. The subjects enrolled in both studies were specifically patients requiring hospitalization for acutely decompensated CHF. Inclusion/exclusion criteria were nonrestrictive, and subjects with concomitant medical conditions common in patients with CHF, such as coronary artery disease, renal insufficiency, and a history of arrhythmias (including atrial fibrillation and ventricular tachycardia) were permitted to enroll in the study. Both studies utilized Natrecor® doses of 0.015 and 0.03 µg/kg/min administered as a continuous infusion (preceded by a small loading bolus [ $\leq 0.6$  µg/kg]); the duration of infusion was based on the clinical status of the patient and left to the discretion of the investigator.

Study 704.325 began with a randomized, double-blinded, placebo-controlled, 6-hour evaluation period, during which hemodynamics, urine output, neurohormones, and clinical status (including a global assessment of status by the subject and by the physician as well as specific

symptoms of CHF) were assessed. The primary efficacy endpoint was the change in PCWP after 6 hours of therapy. Highly statistically significant results ( $p < 0.001$ ) were obtained for this endpoint. Dose-related reductions in SVR and increases in CI were also observed.

In addition, in this study, each subject's global clinical status (as assessed by the subject and by the physician) and specific symptoms of CHF were evaluated during the initial 6-hour double-blinded, placebo-controlled assessment period. Compared to placebo, Natrecor<sup>®</sup> administration resulted in statistically significant improvements in clinical status and symptoms of CHF by 6 hours. Because patients in this study were acutely ill and could not be subjected to placebo infusion for long, study drug assignment (but not Natrecor<sup>®</sup> dose) was unblinded after completion of the 6-hour assessments, and placebo patients were treated thereafter with IV vasoactive agents currently available for the short-term treatment of CHF, such as dobutamine or milrinone. The continuation of Natrecor<sup>®</sup> beyond 6 hours was permitted but not required. Comparisons to placebo were therefore no longer possible after 6 hours; however the clinical status of subjects continued to be followed in the study. By 24 hours after initiation of therapy, over 80% of subjects in the Natrecor<sup>®</sup> groups were reporting an improvement in clinical status.

Study 704.326 was designed to gain safety and clinical experience with Natrecor<sup>®</sup> in a setting which mimics as closely as possible the conditions under which Natrecor<sup>®</sup> would be administered in actual clinical practice. Thus, unlike earlier studies in the program, few restrictions on patient management were imposed by the clinical study protocol. Decisions regarding the use of concomitant medications, the need for study drug dose modifications, the length of parenteral therapy, and the need for invasive central hemodynamic monitoring were left to the discretion of the investigator. Indeed, a Swan-Ganz<sup>®</sup> catheter was utilized for patient management in less than 20% of subjects in the study; hemodynamic parameters were not recorded, although clinical status and symptoms of CHF were followed. Patients were randomized into one of three groups: 0.015 or 0.03  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> or a standard care agent of the investigator's choice for the short-term treatment of CHF (most commonly dobutamine, milrinone, or nitroglycerin). This study was intended primarily to be a safety study, and no efficacy comparisons for Natrecor<sup>®</sup> versus the standard care agents were prespecified in the protocol with regard to proving superiority or equivalence of Natrecor<sup>®</sup> to one or all of the standard care agents. Rather the purpose of the standard care group was to serve as a control group for safety assessments, i.e., to reflect the incidence of underlying adverse experiences in a parallel control group to aid in the interpretation of the incidence of various adverse events reported in the Natrecor<sup>®</sup> groups.

This study showed that Natrecor<sup>®</sup> could be administered safely and effectively to the target population of patients with acutely decompensated CHF without the need for invasive monitoring. It confirmed that Natrecor<sup>®</sup> therapy results in a rapid improvement in clinical status and symptoms of CHF in these patients. Natrecor<sup>®</sup> was used as the sole parenteral vasoactive agent for the short-term treatment of decompensated CHF in 80% of patients assigned to the Natrecor<sup>®</sup> groups.

Thus, the studies in the Natrecor® CHF development program demonstrate that Natrecor® is a safe and effective first-line agent for the short-term treatment of CHF. Natrecor® rapidly improves cardiac hemodynamics, clinical status, and symptoms of CHF in patients with decompensated CHF. Highly statistically significant results were obtained for the primary efficacy endpoint of reduction in PCWP in both pivotal efficacy studies 704.311 and 704.325.

### **3.3 Rationale for Recommended Dosing Regimen**

It is recommended that Natrecor® be administered as a continuous infusion at a rate of 0.015 µg/kg/min for the short-term treatment of CHF.

As previously described, dosing regimens involving IV administration of Natrecor® as both a bolus and a fixed-dose continuous infusion were evaluated in Phase II studies. Both approaches resulted in the rapid onset of desirable hemodynamic effects. However, these effects waned within a few hours following a bolus dose but were sustained throughout the administration of a continuous infusion. Therefore, administration as a continuous infusion was chosen for the short-term treatment of CHF.

An infusion at 0.003 µg/kg/min was found essentially to be a “no effect dose” with minimal effects on hemodynamics. Infusions of 0.06 and 0.1 µg/kg/min resulted in potent hemodynamic effects but use of these doses was limited by the frequent development of symptomatic hypotension. Intermediate infusion doses of 0.015 and 0.03 µg/kg/min produced desirable dose-dependent hemodynamic effects and were well tolerated. These doses were chosen for more extensive evaluation in Phase III studies.

In study 704.311, the 0.015 and 0.03 µg/kg/min doses resulted in similar hemodynamic effects; in study 704.325, the 0.03 µg/kg/min dose clearly resulted in greater hemodynamic effects than the 0.015 µg/kg/min dose did. In Phase III studies 704.325 and 704.326, both doses resulted in rapid and similar improvements in subjects’ clinical status and in specific symptoms of CHF. Thus, both the 0.015 and 0.03 µg/kg/min doses have beneficial effects on efficacy parameters. However, symptomatic hypotension was observed somewhat more frequently at the 0.03 µg/kg/min than at the 0.015 µg/kg/min dose.

Therefore, the dose of 0.015 µg/kg/min administered as a fixed-dose IV infusion was chosen as the recommended initial dose, since it provides the optimal benefit/risk profile for most patients. In patients who are tolerating the 0.015 µg/kg/min infusion well but in whom more pronounced hemodynamic effects are desired, the dose may be increased to 0.03 µg/kg/min. It is recommended that dose increases be made no more frequently than every 3 hours to permit the peak hemodynamic effects of Natrecor® to be achieved prior to additional dosing adjustments.

In studies 704.306 and 704.307, Natrecor® was administered as a continuous infusion without a loading bolus. In studies 704.311, 704.325, and 704.326, a small loading bolus ( $\leq 1$  µg/kg) of Natrecor® was administered before the continuous infusions of Natrecor® were initiated.

The IV bolus was not intended to achieve a hemodynamic effect itself. Indeed, study 704.305 had shown that an IV bolus dose of Natreacor of 1 µg/kg did not produce any recognizable hemodynamic effects. Therefore, the IV loading boluses (at doses ranging from 0.25 to 0.6 µg/kg) used before the 0.015 and 0.03 µg/kg/min infusion doses in the Phase III studies would produce negligible hemodynamic effects. Rather, this loading bolus was utilized with the intent of more rapidly achieving steady-state plasma concentrations and steady-state pharmacodynamic effects of Natreacor<sup>®</sup>. However, a retrospective review of the time course of Natreacor<sup>®</sup>'s effects on PCWP in various clinical studies suggests that the addition of the small loading bolus did not significantly alter the pharmacodynamic profile of Natreacor<sup>®</sup>. Since Natreacor<sup>®</sup> has a relatively short half-life (18 minutes), steady-state levels can be achieved within a clinically appropriate period (within 60 to 90 minutes) with a continuous infusion without the loading bolus. Study 704.306 shows that a continuous infusion of Natreacor<sup>®</sup> without an initial loading bolus results in a rapid onset of hemodynamic effects with a pharmacodynamic profile that is not discernibly different from that seen with comparable infusion doses preceded by a loading bolus in studies 704.311 and 704.325. In addition, in study 704.326, a few patients inadvertently did not receive the loading bolus yet still showed an improvement in clinical status and symptoms of CHF (such as dyspnea) by 6 hours. Thus, it is believed that this small loading bolus does not contribute significantly to the beneficial clinical effects of Natreacor<sup>®</sup> seen in clinical studies but does make drug administration more complicated and can lead to inadvertent dosing errors. A simpler administration regimen without an IV loading bolus is preferred for commercialization. Therefore, Scios recommends that Natreacor<sup>®</sup> be administered as a fixed-dose infusion at 0.015 µg/kg/min without a loading bolus.

### **3.4 Duration of Infusion**

Of the 505 subjects enrolled in the Natreacor<sup>®</sup> CHF development program, 111 subjects with CHF received Natreacor<sup>®</sup> administered as an IV bolus, and a total of 394 subjects with CHF received continuous IV infusions of Natreacor<sup>®</sup> at doses ranging from 0.003 to 0.1 µg/kg/min. Most of the subjects in the CHF development program (71%) received infusions at or above the recommended dose of 0.015 µg/kg/min.

In clinical practice, the duration of IV vasoactive therapy for the short-term management of CHF may range from hours to days, depending upon patients' clinical status at presentation, underlying medical conditions, and responsiveness to therapy. Accordingly, the duration of infusion of Natreacor<sup>®</sup> in Phase III studies 704.325 and 704.326 was largely left to the clinical judgment of the investigators. In study 704.325, Natreacor<sup>®</sup> was administered for an average of 36 hours (range of 3.0 hours to 122.3 hours [5 days]). In study 704.326, Natreacor<sup>®</sup> was administered for an average of 48 hours (range of 2.2 to 283.2 hours [12 days]) including interruptions. The longest infusion without interruption was 214.2 hours (9 days).

The duration of infusion in the Natrecor® CHF clinical studies is summarized in Table 3–2.

**Table 3–2**

**All CHF Studies  
Duration of Natrecor® Infusion Dosing in Patients with CHF  
(Number of Subjects Receiving Each Infusion Dose)**

Duration of Infusion Dosing	Natrecor® Infusion Dose			
	< 0.015 µg/kg/min	0.015 – < 0.020 µg/kg/min	0.020 – < 0.035 µg/kg/min	> 0.035 µg/kg/min
< 24 hours	9	57	63	22
24–72 hours	19	79	80	15
72–120 hours	5	17	14	2
> 120 hours	0	4	5	3
Total Subjects at Each Infusion Dose*	33	157	162	42
Percent of Total CHF Natrecor® Subjects (n = 505)	7%	31%	32%	8%

\* An additional 111 CHF subjects received Natrecor® administered as a single bolus or a repetitive bolus dosing regimen for up to 24 hours.

**Table 3-3**  
**Controlled Clinical Studies:**  
**Natrecor® for the Short-term Treatment of CHF**

Study	Subjects	Dose Administration and Randomization	Study Design	Results
<i>Bolus Administration Studies</i>				
704.305	30 (21/9) <sup>1</sup> (29-65) <sup>2</sup> (24/6/0) <sup>3</sup>	0.3, 1, 3, 10, 15, or 20 µg/kg (n = 4/dose group) or placebo (n = 6) as a single IV bolus	Randomized, double-blind, placebo-controlled, dose-ranging study. Subjects with NYHA Class II, III, or IV CHF received a single IV bolus of Natrecor® or placebo. Effects of study drug on hemodynamics (PCWP, CI, MRAP, PAP, SVR, BP) were followed for at least 4 hours.	Bolus doses of 0.3 and 1 µg/kg had no effect. The four higher doses resulted in acute decreases in preload (PWCP, MRAP) and afterload (SVR), and increases in CI. The magnitude of the response to the 15 and 20 µg/kg doses was not greater than that seen with the 10 µg/kg dose. The hemodynamic effects lasted for 2 to 4 hours.
704.309	60 (44/16) <sup>1</sup> (34-76) <sup>2</sup> (39/21/0) <sup>3</sup>	5 µg/kg q4h (n = 15) 10 µg/kg q6h (n = 14) 10 µg/kg q4h (n = 15) or placebo q4 or q6 (n = 16) repetitive IV bolus regimen × 24 h	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Subjects with symptomatic NYHA Class II, III, or IV CHF received IV bolus injections of Natrecor® or placebo every 4 or 6 hours for 24 hours. Effects of study drug on hemodynamics (PCWP, CI, MRAP, PAP, and SVR) and renal function were followed during the treatment period.	A bolus dose of 5 or 10 µg/kg Natrecor® resulted in decreases in preload (PCWP, MRAP) and afterload (SVR), and increases in CI and stroke volume index. The magnitude of the response was greatest 1-2 hours following each bolus and waned by 4 hours. There was no evidence of tachyphylaxis after subsequent boluses. PCWP was reduced from baseline at the end of the 24-hour dosing period (i.e., 4 or 6 hours after the last bolus), although not statistically significantly. No effect on diuresis or natriuresis was observed.
704.310	60 (45/15) <sup>1</sup> (24-74) <sup>2</sup> (35/25/0) <sup>3</sup>	3 µg/kg q4h (n = 14) 5 µg/kg q4h (n = 14) 10 µg/kg q4h (n = 15) or placebo q4 (n = 17) repetitive IV bolus regimen × 24 h	Randomized, double-blind, placebo-controlled, dose-ranging study. Subjects with symptomatic NYHA Class II, III, or IV CHF on a treatment regimen including ACE inhibitors received IV bolus injections of Natrecor® or placebo every 4 hours for 24 hours. Effects of study drug on hemodynamics (PCWP, CI, MRAP, PAP, and SVR) and renal function were followed during the treatment period.	A bolus dose of 3, 5, or 10 µg/kg Natrecor® resulted in decreases in preload (PCWP, MRAP). The magnitude of the response was greatest 1-2 hours following each bolus and waned by 4 hours. There was no evidence of tachyphylaxis with regard to PCWP reduction after subsequent boluses. Afterload (SVR) and CI were not significantly improved 2 hours after each bolus (the earliest timepoint assessed). Coadministration of an ACE inhibitor did not alter the pharmacokinetics of Natrecor®. No effect on diuresis or natriuresis was observed.

1 Number of males/females  
 2 Age range in years  
 3 Ethnicity (white/black/other)

Table 3–3 (cont'd)

**Controlled Clinical Studies:  
 Natrecor® for the Short-term Treatment of CHF**

Study	Subjects	Dose Administration and Randomization	Study Design	Results
<i>Short Infusion Studies</i>				
704.306	16 (15/1) <sup>1</sup> (33–79) <sup>2</sup> (13/2/1) <sup>3</sup>	0.025 or 0.05 µg/kg/min (n = 6/dose group) or placebo (n = 4) × 4 h as a fixed-dose, continuous IV infusion	Randomized, double-blind, placebo-controlled, dose-ranging study. Subjects with symptomatic NYHA Class II, III, or IV CHF received a 4-hour IV, fixed-dose infusion of Natrecor® or placebo. Effects of study drug on hemodynamics (PCWP, CI, MRAP, PAP, SVR, BP), neurohormone levels and renal function were followed before, during, and for at least 4 hours after study drug infusion.	Dose-related decreases in PCWP, MRAP, and SVR and increases in CI were observed. Renal blood flow and glomerular filtration rate were maintained, although no increase in diuresis was seen. Plasma and urinary cGMP were increased. A decrease in plasma norepinephrine and a trend towards a decrease in serum aldosterone were also noted.
704.307	20 (17/3) <sup>1</sup> (31–71) <sup>2</sup> (12/5/3) <sup>3</sup>	0.003, 0.01, 0.03, and 0.1 µg/kg/min as an escalating-dose IV infusion × 1.5 h at each dose (Natrecor® or placebo on successive days in a crossover design)	Randomized, double-blind, placebo-controlled, dose-escalation crossover study. Subjects with symptomatic NYHA Class II, III, or IV CHF received a 6-hour IV escalating-dose infusion of Natrecor® or placebo on day 1 (and the other on day 2 in a crossover design). Effects of study drug on hemodynamics (PCWP, CI, MRAP, PAP, SVR, BP) and renal function were followed during study drug infusion.	The 0.003 µg/kg/min dose did not cause clinically significant hemodynamic effects. Administration of higher doses resulted in dose-related decreases in preload (PCWP, MRAP), afterload (SVR), and PAP, and increases in CI. Urine output was mildly increased during Natrecor® infusion, although the increase was not statistically significant.

1 Number of males/females  
 2 Age range in years  
 3 Ethnicity (white/black/other)

**Table 3–3 (cont'd)**  
**Controlled Clinical Studies:**  
**Natrecor® for the Short-term Treatment of CHF**

Study	Subjects	Dose Administration and Randomization	Study Design	Results
<i>Long Infusion Studies</i>				
704.311	103 (83/20) <sup>1</sup> (28–85) <sup>2</sup> (56/26/1) <sup>3</sup>	0.25 µg/kg IV bolus followed by 0.015 µg/kg/min (n = 22), or 0.5 µg/kg followed by 0.03 µg/kg/min (n = 26), or 1.0 µg/kg followed by 0.06 µg/kg/min (n = 26), or IV placebo bolus followed by a placebo continuous IV infusion (n = 29) for 24 hours	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Subjects with NYHA Class II, III, or IV CHF received an infusion of Natrecor® or placebo for 24 hours. Effects of study drug on hemodynamics (PCWP, CI, MRAP, PAP, SVR) and renal function were followed during the treatment period and for 4 hours thereafter. The primary efficacy endpoint was the change in PCWP at 3 hours.	Highly statistically significant reductions in PCWP were achieved at 3 hours (p ≤ 0.004). Dose-related decreases in PCWP, MRAP, PAP, and SVR and increases in CI were observed with no effect on heart rate. The effect on hemodynamics was sustained through 24 hours of infusion. No increase in diuresis or natriuresis was observed. Worsening CHF requiring intervention was significantly reduced with Natrecor® therapy compared to placebo (p = 0.021).

1 Number of males/females  
 2 Age range in years  
 3 Ethnicity (white/black/other)

**Table 3–3 (cont'd)**  
**Controlled Clinical Studies:**  
**Natrecor® for the Short-term Treatment of CHF**

Study	Subjects	Dose Administration and Randomization	Study Design	Results
<i>Long Infusion Studies (cont'd)</i>				
704.325	127 (93/34) <sup>1</sup> (19–85) <sup>2</sup> (77/38/12) <sup>3</sup>	0.3 µg/kg IV bolus followed by 0.015 µg/kg/min (n = 43), or 0.6 µg/kg bolus followed by 0.03 µg/kg/min (n = 42) as a fixed-dose IV infusion or placebo for 6 hours followed by an IV vasoactive standard care agent for CHF (n = 42)  Duration of Natrecor® infusion at discretion of investigator (mean 36 hours, range 3.0–122.3 hours)	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Subjects with symptomatic, acutely decompensated CHF requiring inpatient parenteral therapy initially received either Natrecor® or placebo. During a 6-hour, double-blinded, placebo-controlled period, the effects of study drug on hemodynamics (PCWP, CI, MRAP, PAP, SVR, PVR) and symptoms of decompensated CHF were evaluated. Urine output and neurohormones were evaluated at baseline and at 6 hours. The primary efficacy endpoint was the percent change in PCWP at 6 hours.  After the 6-hour blinded period, treatment assignment to Natrecor® or placebo was unblinded (but Natrecor® dose remained blinded). Placebo subjects were subsequently treated with a “standard care” parenteral vasoactive agent (such as dobutamine, milrinone, or nitroglycerin) of the investigator’s choice. The addition of other vasoactive medications and duration of therapy with either Natrecor® or “standard care” was according to the investigator’s discretion.	Highly statistically significant reductions in PCWP were achieved at 6 hours ( p < 0.001). Dose-related decreases in preload (PCWP, MRAP), afterload (SVR), and an increase in CI were observed with no effect on HR. PAP was decreased with both doses, and PVR was significantly decreased with the low dose only. The hemodynamic effects of Natrecor® were sustained through 24 hours of infusion.  Both doses of Natrecor® caused a decrease in aldosterone and an increase in urine output.  Both doses of Natrecor® caused statistically significant improvements in global clinical status as well as specific symptoms of decompensated CHF compared to placebo.

1 Number of males/females  
 2 Age range in years  
 3 Ethnicity (white/black/other)

**Table 3–3 (cont’d)**  
**Controlled Clinical Studies:**  
**Natrecor® for the Short-term Treatment of CHF**

Study	Subjects	Dose Administration and Randomization	Study Design	Results
<i>Long Infusion Studies (cont’d)</i>				
704.326	305 (207/98) <sup>1</sup> (20–92) <sup>2</sup> (201/67/34) <sup>3</sup>	0.3 µg/kg IV bolus followed by 0.015 µg/kg/min (n = 103), or 0.6 µg/kg bolus followed by 0.03 µg/kg/min (n = 100) as a fixed-dose IV infusion or standard care (n = 102)  Duration of infusion at discretion of investigator (mean 48 hours, range 2.2–283.2 hours)	Randomized, open-label, active-controlled, parallel-design, dose-ranging safety study. Subjects with symptomatic, acutely decompensated CHF requiring inpatient parenteral therapy received either Natrecor® or “standard care” (i.e., a parenteral vasoactive agent such as dobutamine, milrinone, or nitroglycerin) for as long as was clinically indicated. Natrecor® dose was double-blinded. The purpose of this study was to gain safety and clinical experience with Natrecor® in a setting mimicking actual clinical practice. Central hemodynamic monitoring was not required. Effects of study drug on clinical status were assessed, including symptoms of decompensated CHF, weight loss, the need for additional parenteral therapies, duration of hospitalization, the need for readmission after discharge, the need for intubation, dialysis, or ultrafiltration, and mortality status.	Both doses of Natrecor® produced statistically significant improvements in global clinical status as well as in specific symptoms of decompensated CHF compared to baseline. Compared to “standard care,” Natrecor® was associated with less need for diuretics. There was no significant difference between treatment groups in length of therapy, length of hospitalization, readmissions, medical interventions, or mortality. In 80% of subjects in the Natrecor® groups, Natrecor® was used as the sole IV vasoactive agent for this episode of decompensated CHF.

1 Number of males/females  
 2 Age range in years  
 3 Ethnicity (white/black/other)

## Item 4

**Clinical Pharmacology and Pharmacokinetics**

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**4.1 Preclinical Pharmacology**

In preclinical studies, hBNP has been shown to be a potent vasodilator without direct inotropic activity. In an in vitro assay system, hBNP demonstrated a potent relaxant effect on both human arterial and venous rings precontracted with endothelin-1 or phenylephrine. In in vivo studies, hBNP administration resulted in a balanced vasodilation, decreasing cardiac preload and afterload. Direct coronary artery infusion of hBNP in anesthetized pigs resulted in vasodilation of both coronary conductance and resistance vessels.

Human BNP has no known direct inotropic activity. In both a Langendorff-perfused rabbit heart assay and in explanted human cardiac ventricular tissue, hBNP exhibited no significant positive or negative inotropic activity.

The effects of hBNP on cardiac electrophysiology were evaluated in healthy conscious dogs. Continuous IV infusion of hBNP (at doses of 0.03 and 0.09  $\mu\text{g}/\text{kg}/\text{min}$ ) had no remarkable effect on surface electrocardiographic intervals (PR, QRS, QT, and QTC intervals) during sinus rhythm, atrial and ventricular effective refractory period, sinus node recovery time, and atrioventricular junction conductance.

Human BNP has diuretic and natriuretic effects in animals. These actions are explained by hBNP's ability to increase glomerular filtration rate (GFR), inhibit sodium reabsorption in the distal tubules, and to reduce plasma aldosterone levels.

Some of hBNP's physiological effects may be mediated by its hormonal interaction with the renin-angiotensin-aldosterone system and on other vasoconstrictive peptides which are known to mediate cardiorenal function. In both animals and humans, hBNP decreases aldosterone, a hormone that promotes renal tubule reabsorption of sodium and water. Indeed, it is known that primary cultures of adrenal cortical cells, the cells that produce aldosterone in response to angiotensin II or adrenocorticotropin hormone, express the biological receptor for hBNP. Aldosterone suppression is likely to be a mechanism of action whereby hBNP increases urine output and urine sodium excretion without increasing urine potassium excretion. In addition, it has been demonstrated that hBNP inhibits endothelial cell release of the vasoconstrictive peptide endothelin-1 when these cells are treated with angiotensin II or thrombin. Some of the vascular relaxant effects of hBNP may be mediated by inhibiting endothelin-1 release. Human BNP's vascular relaxant effect is accentuated in arteries precontracted with endothelin-1, another example of the interaction of hBNP with endogenous neurohormonal systems.

Preclinical studies in rabbits show that the natriuretic peptide clearance (NP-C) receptor and a peptidase present on the vascular luminal surface, neutral endopeptidase 24.11 (NEP 24.11), are involved in the metabolism of hBNP. The NP-C receptor is a cell surface protein located throughout the circulatory system that presumably binds to hBNP and mediates its cellular internalization, delivery to lysosomal compartments, and hydrolysis to inactive fragments and individual amino acids. The kidney is a rich source of both the NP-C receptor and NEP 24.11, is an organ to which a significant amount of hBNP is distributed, and is also involved in the excretion of hBNP by filtration.

## **4.2 *Clinical Pharmacology***

The pharmacological effects of hBNP have been studied in a wide variety of human subjects by Scios or by others and reported in the medical literature. The remainder of this section summarizes the pharmacological profile observed in these studies.

### **4.2.1 *Scios Pharmacology Studies***

Scios performed three randomized, double-blinded, placebo-controlled, dose-ranging pharmacology studies in patients with advanced CHF (studies 704.305, 704.306, and 704.307). All studies focused on hemodynamics, although additional information about renal and neurohormonal effects was also collected in some cases.

Study 704.305 reported the effects of a single IV bolus dose of Natrecor<sup>®</sup> ranging from 0.3 to 20 µg/kg. Study 704.306 studied 4-hour, fixed-dose IV infusions of 0.025 and 0.05 µg/kg/min of Natrecor<sup>®</sup>. Study 704.307 studied a 6-hour escalating dose infusion of Natrecor<sup>®</sup> (escalating doses of 0.003, 0.01, 0.03, 0.1 µg/kg/min × 90 minutes at each dose). Patients enrolled in these studies had a Swan-Ganz<sup>®</sup> pulmonary artery catheter placed before evaluation to allow repeated measurements of hemodynamic endpoints such as PCWP (the principal endpoint of these studies), mean right atrial pressure (MRAP), SVR, and CI, among others.

### **4.2.2 *Hemodynamic Observations***

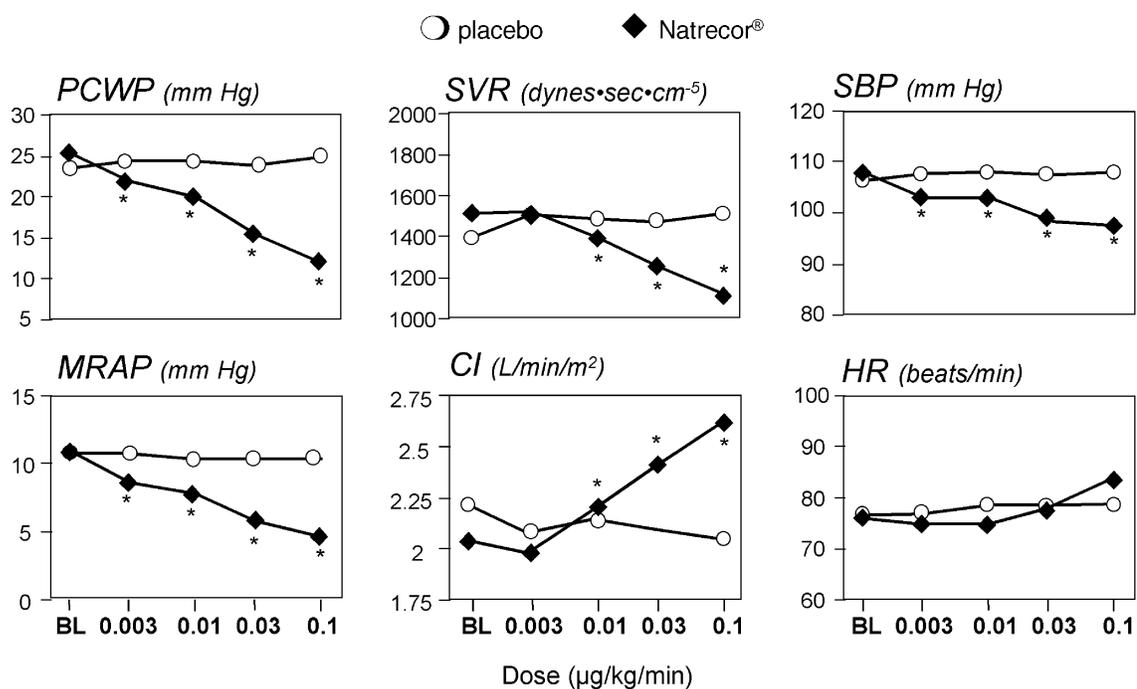
All studies consistently showed a dose-dependent favorable effect of Natrecor<sup>®</sup> on PCWP and MRAP (reduction), SVR (reduction), and CI (increase). Higher doses also produced a decrease in systemic blood pressure, generally without an increase in heart rate. Study 704.305 showed that the effects of a single IV bolus on PCWP lasted for 4 hours or more, but the effects on CI and SVR were more short lived. Continuous infusions of Natrecor<sup>®</sup> (studies 704.306 and 704.307) maintained the hemodynamic benefit for the duration of the infusion. Doses at or below 0.03 µg/kg/min were generally well tolerated; above 0.03 µg/kg/min, the infusion was associated with an increased incidence of symptomatic hypotension.

The effects of Natrecor® on hemodynamic parameters were dose related, as shown in Figure 4-1 and Table 4-1, which summarize hemodynamic data from Study 704.307.

Natrecor® had no significant effect on heart rate.

Figure 4-1

Study 704.307  
Dose-Related Hemodynamic Effects of Natrecor®  
(n = 20)



Plotted values represent treatment group means.

\* p < 0.05 vs. placebo, by a within-dose crossover analysis of change from baseline.

L.S. Marcus et al. Circulation 1996; 94:3184-3189.

**Table 4-1**  
**Study 704.307**  
**Hemodynamic Effects of Natrecor® at Each Completed Dose**

Hemodynamic Parameter	Baseline Value	Absolute (Percent) Change at Each Dose of Natrecor®			
		0.003 µg/kg/min	0.01 µg/kg/min	0.03 µg/kg/min	0.1 µg/kg/min
PCWP (mm Hg)	24.8 ± 5.0	-3.2 ± 3.5 (-12.5%)	-6.0 ± 3.5 (-24.1%)	-10.2 ± 5.2 (-40.9%)	-14.6 ± 4.6 (-56.5%)
MRAP (mm Hg)	11.0 ± 5.1	-2.5 ± 1.9 (-23.9%)	-3.5 ± 1.7 (-35.3%)	-5.5 ± 2.4 (-54.6%)	-6.2 ± 2.7 (-63.9%)
SVR (dynes·sec·cm <sup>-5</sup> )	1514 ± 385	7 ± 236 (2.2%)	-121 ± 348 (-6.1%)	-261 ± 348 (-15.6%)	-449 ± 361 (-25.7%)
CI (L/min/m <sup>2</sup> )	2.1 ± 0.4	0.0 ± 0.3 (-1.0%)	0.2 ± 0.4 (10.4%)	0.4 ± 0.6 (20.9%)	0.6 ± 0.4 (33.5%)
SBP (mm Hg)	108 ± 14	-5 ± 4 (-4.4%)	-5 ± 5 (-4.6%)	-10 ± 8 (-8.6%)	-11 ± 8 (-10.1%)
HR (beats/min)	75 ± 15	-0.5 ± 2.6	-0.5 ± 4.4	2.9 ± 7.9	11.5 ± 9.2

Results are presented as mean change (or percent change) ± standard deviation.

#### **4.2.3 Renal Effects**

In study 704.306, renal blood flow and GFR were maintained during a 4-hour Natrecor® infusion; no effect on urine output was observed. In study 704.307, a mild increase in urine output and urinary sodium excretion was noted during Natrecor® infusion although the increase was not statistically significant. There was no increase in urinary potassium excretion.<sup>(1)</sup> In a larger study (study 704.325) involving 127 patients, there was a statistically significant, dose-dependent higher urine output during the first 6 hours of infusion in the 0.015 and 0.03 µg/kg/min Natrecor® treatment groups compared to placebo.

#### **4.2.4 Neurohormonal Effects**

Study 704.306 made a prospective effort to assess the effects of Natrecor® on plasma levels of norepinephrine and aldosterone. Although the sample size was small, the data suggest a reduction in plasma aldosterone and show a statistically significant reduction of norepinephrine levels in Natrecor®-treated patients. In a large placebo-controlled study (704.325) involving 127 patients, both the 0.015 and the 0.03 µg/kg/min Natrecor® dose groups showed a statistically significant decrease in aldosterone during study infusion and a neutral effect on norepinephrine levels.

#### **4.2.5 Studies in the Literature**

Nesiritide has been administered to healthy volunteers as well as subjects with CHF, hepatic cirrhosis, hypertension, and cardiac disease in a number of pharmacology studies

published in the literature. The physiologic effects observed when nesiritide is administered to humans include diuresis, natriuresis, decreases in renin and aldosterone, vasodilation, coronary artery dilation, and improved diastolic function.

In several placebo-controlled human clinical studies reported in the literature, IV administration of nesiritide (0.007 µg/kg/min or 0.014 µg/kg/min for 1 to 3 hours) to healthy subjects has been associated with increases in urine flow rate, effective renal blood flow, GFR, urine sodium excretion, and with decreases in plasma renin and aldosterone.<sup>(2,3,4,5)</sup> In one of the studies,<sup>(2)</sup> increases in hematocrit and plasma albumin were noted, suggesting that nesiritide administration may be associated with a decrease in plasma volume.

In a placebo-controlled study of 8 normal subjects, Cargill et al<sup>(6)</sup> showed that nesiritide (0.035 µg/kg/min) significantly reduced the pressor effect of angiotensin II. When subjects received a 60-minute infusion of nesiritide or placebo with a concomitant infusion of angiotensin II (6 nmol/kg/min) for the last 30 minutes, there was a significant attenuation of the increase in systemic BP (systolic, diastolic, and mean) and of the increase in plasma aldosterone observed with nesiritide infusion, as compared to placebo.

In patients with CHF, Yoshimura<sup>(7)</sup> showed that a 30-minute infusion of nesiritide (0.1 µg/kg/min) significantly decreased PCWP and SVR and significantly increased stroke volume index. The infusion of nesiritide also significantly increased urine volume and sodium excretion, and decreased plasma aldosterone.

Studies by Clarkson showed that IV infusions of nesiritide improved diastolic function, as evidenced by improved echocardiographic measures of diastolic function as well as by an attenuation of the rise in PCWP that occurred during exercise. In a placebo-controlled crossover trial in healthy human volunteers, nesiritide (0.002 through 0.017 µg/kg/min) significantly reduced left ventricular isovolumic relaxation time and improved transmitral Doppler flow profiles (peak E/A velocity), with no associated effect on BP or HR.<sup>(8)</sup> In a placebo-controlled crossover study of patients with isolated diastolic dysfunction, an infusion of nesiritide (0.017 µg/kg/min) significantly attenuated the expected rise in PCWP (23 versus 16 mm Hg, placebo versus nesiritide, respectively) and MRAP that occurred during exercise, without affecting HR, systemic BP, or stroke volume.<sup>(9)</sup> In both of these studies, nesiritide also suppressed plasma aldosterone compared to placebo.

Okumura et al<sup>(10)</sup> studied 13 subjects with normal coronary arteries and left ventricular function. Nesiritide was infused at a dose of 0.5 µg/kg/min for 4 minutes into the left main coronary artery (n = 6) or the pulmonary artery (n = 7). Direct infusion into the coronary artery decreased coronary vascular resistance, and increased coronary artery luminal diameter. The effect was felt to be preferentially evident in the epicardial system.

Kato<sup>(11)</sup> demonstrated that an intravenous infusion of nesiritide blocked hyperventilation-induced anginal attacks in patients with a history of variant angina. In this study, patients with a history of variant angina reproducibly induced by hyperventilation

received infusions of saline or nesiritide (0.05 µg/kg/min) in a crossover design on consecutive days and then were requested to hyperventilate during each infusion. All 11 subjects experienced hyperventilation-induced angina during saline infusion, but none did during the nesiritide infusion.

#### ***4.2.6 Discussion of Clinical Pharmacology***

In studies conducted across a range of human subjects, from normal volunteers to patients with CHF, nesiritide has been shown to reliably produce certain pharmacological effects. The most notable effect, particularly in volume-overloaded patients with high peripheral resistance (i.e., patients with CHF), is a balanced vasodilatation, with a reduction in both preload and afterload. Nesiritide infusion in the dose range of 0.01 to 0.1 µg/kg/min produced dose-related reductions in PCWP, MRAP, SVR, and pulmonary artery pressure (PAP), and increases in CI and stroke volume index.

These hemodynamic effects of nesiritide are produced by either bolus administration or by continuous infusion and are dose-related. Preload reduction produced by bolus administration lasts for several hours, whereas afterload reduction and increases in CI last for only a couple of hours. Hemodynamic effects produced by infusion generally last for the duration of the infusion. The optimal effective dose range is 5 to 25 µg/kg by bolus and 0.01 to 0.03 µg/kg/min by infusion. The principal adverse effect is an excess of the pharmacological vasodilating activity, leading to hypotension, usually at the higher doses. Studies also suggest that nesiritide infusion maintains or improves coronary blood flow and improves diastolic filling.

The increase in CI is most likely an indirect effect due to nesiritide's reduction of preload and afterload, rather than a direct inotropic effect, since in preclinical studies nesiritide has been shown to be a potent vasodilator but to have no direct inotropic activity. Natrecor® improves CI by augmenting stroke volume index, not by increasing HR. This suggests that Natrecor® improves cardiac hemodynamics without an increase in the metabolic cost to the heart.

Generally, the decreases in preload and afterload and increases in CI with nesiritide administration have not been accompanied by a reflex tachycardia, as is seen with most other vasodilating agents. Preclinical studies indicated no remarkable effect of nesiritide on cardiac conduction. Therefore, the lack of increased heart rate in association with nesiritide administration may be explained by either a decrease in sympathetic tone and/or an increase in parasympathetic tone. Increased vagal efferent effects on the heart have been documented with administration of a related peptide, atrial natriuretic peptide (ANP). Nesiritide administration is usually accompanied by a decrease or neutral effect on plasma norepinephrine levels.

Nesiritide is also found to produce reductions in plasma aldosterone. Evidence for suppression of other neurohormones, such as renin, is limited, although it appears that a reflex increase in the norepinephrine and renin does not occur. Moderate diuretic and natriuretic properties have

been demonstrated in some studies and is likely due to nesiritide's effect on sodium handling at the distal renal tubule, mediated at least in part via nesiritide's effects on aldosterone.

Thus, in preclinical and clinical pharmacology studies, administration of Natrecor® has resulted in hemodynamic, renal, and neurohormonal effects which would be desirable in an agent used for the short-term treatment of CHF.

#### ***4.2.7 References***

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### 4.3 Pharmacokinetics

When Natrecor<sup>®</sup> is administered to patients with CHF, the mean volume of distribution of the central compartment ( $V_c$ ) of Natrecor<sup>®</sup> is estimated to be approximately 0.073 L/kg, and the mean steady-state volume of distribution ( $V_{ss}$ ) is estimated to be approximately 0.19 L/kg. The mean volume of distribution area ( $V_{area}$ ) was estimated to be approximately 0.25 L/kg. The estimate of  $V_c$  is just less than twice plasma volume and the estimate of  $V_{ss}$  is approximately the same as that of extracellular water, both of which are consistent with Natrecor<sup>®</sup> being a 32-amino-acid peptide. Estimates of volume of distribution did not differ significantly among dose groups, suggesting that no volume of distribution parameter is dose dependent.

After IV bolus dosing in patients with CHF, the Natrecor<sup>®</sup> concentration versus time can be described with a two-compartment open model. Approximately two thirds of the area under the curve (AUC) is associated with the longer terminal phase of elimination. The arithmetic mean of the terminal elimination half-life ( $t_{1/2\beta}$ ) of Natrecor<sup>®</sup> is estimated to be approximately 18 minutes and that of initial elimination phase ( $t_{1/2\alpha}$ ) is estimated to be approximately 2 minutes.

In patients with CHF, the mean estimate of clearance (CL) of Natrecor<sup>®</sup> is approximately 9.2 mL/min/kg without evidence of dose dependence with single IV bolus doses ranging from 0.3 to 20  $\mu$ g/kg and IV infusion doses ranging from 0.003 to 0.1  $\mu$ g/kg/min.

Based on a terminal half-life of 18 minutes, at least 90% of steady-state plasma level is expected to be reached in 1 hour. A person with an average clearance (9.2 mL/min/kg) given a constant rate infusion of 0.015  $\mu$ g/kg/min is predicted to have a steady-state plasma concentration of hBNP of 1630 pg/mL above baseline levels.

#### 4.3.1 Effects of Demographic and Clinical Variables

Clearance did not vary significantly with age, gender, race/ethnicity, baseline hemodynamic status (as defined by baseline PCWP or CI), endogenous hBNP concentration, or NYHA classification of CHF. Clearance was found to vary proportionally with body weight, supporting the administration of weight-adjusted dosing of Natrecor<sup>®</sup> (i.e., administration on a  $\mu$ g/kg basis).

The pharmacokinetic analysis of data from study 704.325 showed a trend of a positive relationship between creatinine clearance and hBNP clearance and a trend of a negative relationship between serum creatinine and hBNP clearance. In a population analysis of data from study 704.311, no statistically significant effect of creatinine clearance or serum creatinine on hBNP clearance was detected. In that study, analyses suggested that hBNP clearance decreases no more than approximately 10.9% for each 10 mL/min decrease in creatinine clearance. Thus, relative to the average patient with a creatinine clearance of

70 mL/min, a patient with a creatinine clearance of 40 mL/min would be expected to have a decrease in hBNP clearance of no more than approximately 33%.

The effect of renal insufficiency on the safety and efficacy of Natrecor<sup>®</sup> were assessed in Phase III clinical studies. In study 704.325, the effects of Natrecor<sup>®</sup> on PCWP, CI, and systolic blood pressure (BP) were not significantly different for patients with or without chronic renal insufficiency (with serum creatinines from 2 mg/dL to 4.3 mg/dL). This suggests that patients with renal insufficiency do not have an exaggerated response to the drug (as might be expected if its clearance was significantly reduced). This was confirmed in study 704.326, in which the incidence of hypotension was not greater in patients with renal insufficiency (with serum creatinines from 2 to 15.3 mg/dL) than in patients without renal insufficiency; this is consistent with a preclinical study that showed that in rabbits subjected to complete bilateral renal artery ligation, steady-state hBNP levels were increased by only 1.9-fold. Thus, these studies suggest that dosing of Natrecor<sup>®</sup> does not need to be adjusted based on renal dysfunction.

#### **4.3.2 Effects of Concomitant Medications**

The estimates of CL,  $V_{\text{area}}$ ,  $V_{\text{ss}}$ , terminal  $t_{1/2}$ , terminal rate constant of elimination, and peak concentration (normalized to dose) in subjects who were receiving enalapril (or any angiotensin converting enzyme [ACE] inhibitor) concomitantly with Natrecor<sup>®</sup> (in study 704.310) did not differ significantly from the estimates in subjects who did not receive an ACE inhibitor (in study 704.309). This is consistent with the findings of a Scios-sponsored preclinical study, which showed that the ACE inhibitor captopril does not alter the pharmacokinetics of Natrecor<sup>®</sup> in dogs and an in vitro study, which showed that Natrecor<sup>®</sup> is not a substrate for human ACE.

Preclinical studies showed that heparin did not affect the pharmacokinetics of Natrecor<sup>®</sup>.

#### **4.3.3 Pharmacokinetics Conclusions**

The elimination of hBNP is characterized by a relatively short half-life (18 minutes). This short half-life is reflected in steady-state plasma concentrations being reached quickly with continuous IV infusion (the dosing regimen recommended for labeling) and in a relatively short duration of pharmacological effects of hBNP observed after termination of an infusion or after bolus administration. In addition, the plasma concentrations with constant IV infusion are proportional to dose. These characteristics of Natrecor<sup>®</sup> are desirable for its use in the short-term treatment of CHF. The target therapeutic plasma concentration can be achieved quickly with a constant intravenous infusion and, in the event of an undesired effect, the plasma drug levels decline relatively quickly after the infusion is terminated. The pharmacokinetics of hBNP in humans are consistent with what has been derived from preclinical studies.

Clearance was found to vary proportionally with body weight, supporting the administration of weight-adjusted dosing of Natrecor®. Clearance is not influenced significantly by age, gender, race/ethnicity, baseline endogenous hBNP concentration, severity of CHF (as indicated by baseline PCWP, baseline CI, or NYHA classification), or concomitant administration of an ACE inhibitor. Although the kidney likely plays some role in Natrecor® clearance, clinical data suggest that dose adjustment is not required in patients with renal insufficiency, presumably because clearance via other mechanisms is occurring.

# Item 5

## Efficacy Summary

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### Table Of Contents

	<u>Page</u>
5.1 Goals of Therapy in the Short-Term Treatment of Decompensated CHF .....	29
5.2 Assessments of Clinical Efficacy .....	29
5.2.1 Hemodynamics .....	29
5.2.2 Clinical Status .....	30
5.3 Results .....	31
5.3.1 Effects on Cardiac Hemodynamics .....	31
5.3.1.1 Pulmonary Capillary Wedge Pressure (PCWP) .....	31
5.3.1.2 Sustained Hemodynamic Effects .....	35
5.3.1.3 Other Hemodynamic Parameters .....	37
5.3.2 Clinical Status .....	39
5.3.2.1 Global Clinical Status .....	39
5.3.2.2 Improvement in Specific Symptoms of CHF .....	41
5.3.2.3 Sustained Effects on Clinical Status .....	43
5.3.3 Diuresis and Diuretic Usage .....	47
5.3.4 Other Clinical Outcomes of Interest .....	47
5.4 Efficacy Conclusions .....	48

## ***5.1 Goals of Therapy in the Short-Term Treatment of Decompensated CHF***

Decompensation of chronic CHF to a more acute condition requiring hospitalization is a frequent event and is the most frequent discharge diagnosis in patients over 65 years of age in the U.S.

The prototypical hemodynamic abnormalities that characterize decompensated CHF include:

- increased cardiac filling pressures (referred to as preload, and assessed by measurement of PCWP and MRAP);
- increased SVR (referred to as afterload);
- poor cardiac output.

The combination of cardiac dysfunction and fluid overload leads to symptoms of heart failure, such as dyspnea, fatigue, lightheadedness, and decreased appetite.

The therapeutic goals for acutely decompensated CHF requiring hospitalization include:

- rapid improvement of cardiac hemodynamics;
- rapid relief of fluid and sodium retention;
- rapid relief of the symptoms associated with cardiac decompensation and fluid overload.

Therefore, the clinical studies in the Natrecor® CHF development program focused on demonstration of these attributes.

## ***5.2 Assessments of Clinical Efficacy***

### ***5.2.1 Hemodynamics***

Throughout the clinical development of Natrecor® as an IV therapy for the short-term treatment of CHF, reduction in PCWP has been the primary efficacy endpoint.

PCWP was chosen as the primary efficacy endpoint for Natrecor® because PCWP is an important clinical variable which is regularly used, when available, in the management of patients. An elevated PCWP is one of the hallmark hemodynamic abnormalities in CHF. The elevation is believed to be responsible for many of the syndrome's debilitating symptoms, such as shortness of breath, orthopnea, and exercise intolerance. A decrease in PCWP represents a direct measurement of Natrecor®'s primary mode of action: vasodilation.

However, no one hemodynamic measurement is of sole importance in consideration of cardiac physiology. The interpretation of a pharmacologic effect on any one hemodynamic measurement must always be done in the context of the overall hemodynamic profile. Therefore, in all Natrecor® studies involving hemodynamic measurements, extensive

monitoring and analysis of pulmonary and systemic pressures and resistances, stroke volume and cardiac index, and heart rate were conducted. The derived product of heart rate and systolic blood pressure, otherwise known as the rate pressure product, was also calculated as an indirect estimate of myocardial oxygen demand.

### 5.2.2 Clinical Status

One of the major goals of the treatment of decompensated CHF is to rapidly improve clinical status and specific symptoms of CHF. Studies 704.325 and 704.326 assessed the effect of Natrecor® on subjects' clinical status and clinical symptoms of CHF. Two types of assessments were established by the Sponsor. These were developed as, and intended to be, supplements to the principal hemodynamic endpoints.

One scoring system assessed the subject's overall global clinical status compared to baseline. Both the subject and the physician were asked to evaluate the subject's clinical status independently at various time points following the initiation of study drug administration and to rate it in one of the following categories as compared to pretreatment:

- markedly better
- better
- no change
- worse
- markedly worse

These assessments were performed 6 hours and 24 hours after the initiation of therapy and at the end of parenteral therapy.

The physician, with input from the subject, also was requested to assess each subject's status at baseline with regard to four symptoms of decompensated CHF. The four specific symptoms of acutely decompensated CHF assessed were:

- dyspnea
- fatigue
- lightheadedness
- decreased appetite

Each of these symptoms were then assessed 6 hours and 24 hours after the initiation of therapy and at the end of parenteral therapy and rated as one of the following:

- improved from baseline
- no change from baseline
- worse than baseline

### **5.3 Results**

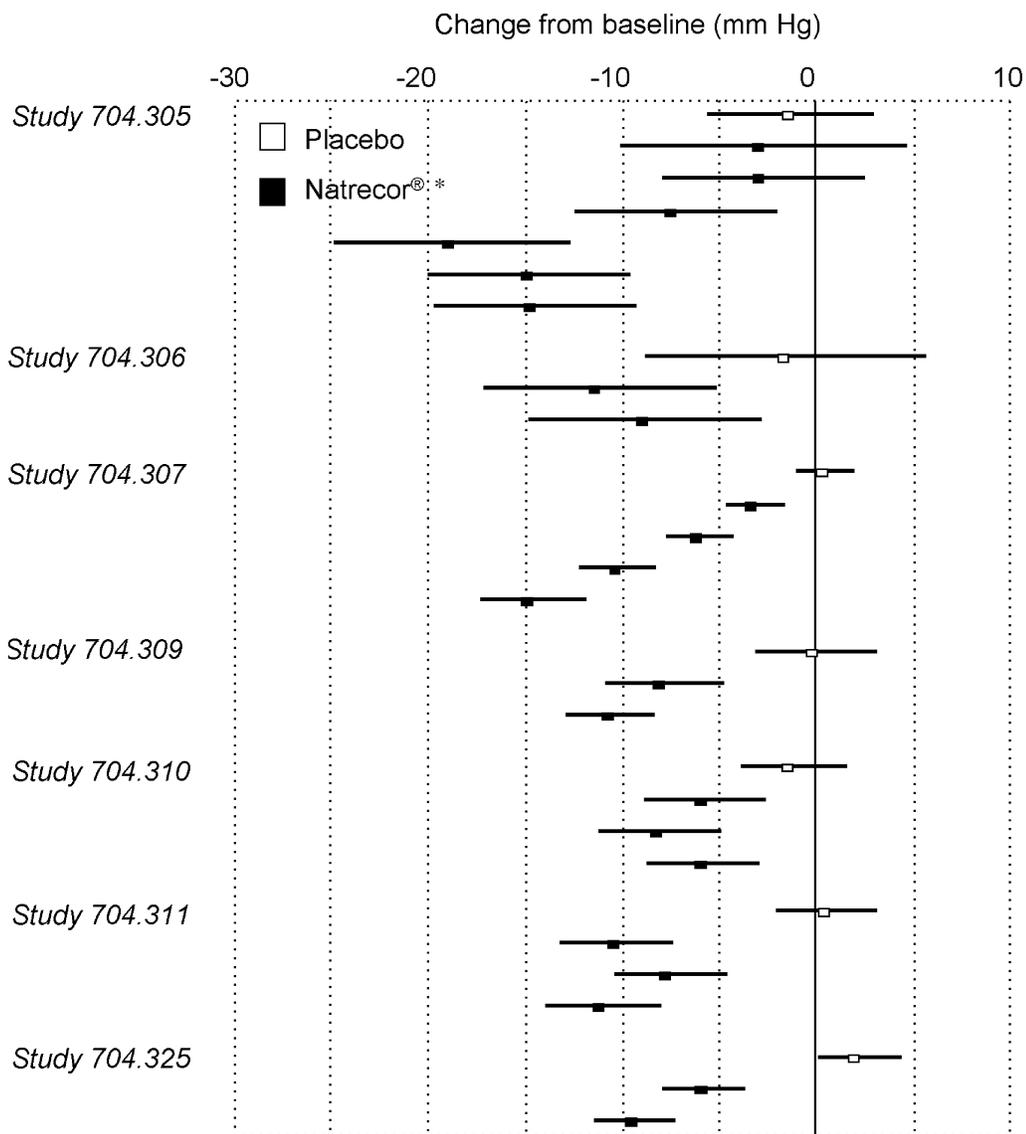
#### **5.3.1 Effects on Cardiac Hemodynamics**

##### **5.3.1.1 Pulmonary Capillary Wedge Pressure (PCWP)**

The effects of Natrecor<sup>®</sup> on PCWP have been assessed in seven randomized, double-blinded, placebo-controlled clinical studies in patients with CHF performed by the Sponsor. In each of these studies, IV administration of Natrecor<sup>®</sup>, as a bolus or infusion at various doses, has consistently resulted in reductions in PCWP compared to placebo, as depicted in Figure 5–1.

Figure 5-1

All CHF Studies  
 Mean Change in PCWP  
 95% Confidence Intervals



\* Depicts results at various Natrecor® doses.

The two pivotal efficacy studies were studies 704.311 and 704.325. Both were randomized, double-blind, placebo-controlled studies in which the primary efficacy endpoint was the effect on PCWP at 3 or 6 hours, respectively, after initiating study drug.

The design of the two studies are briefly summarized in Table 5–1. A more detailed description of each study’s design, methodology, and results can be found in Appendices A and B, respectively.

**Table 5–1**  
**Design of Pivotal Studies 704.311 and 704.325**

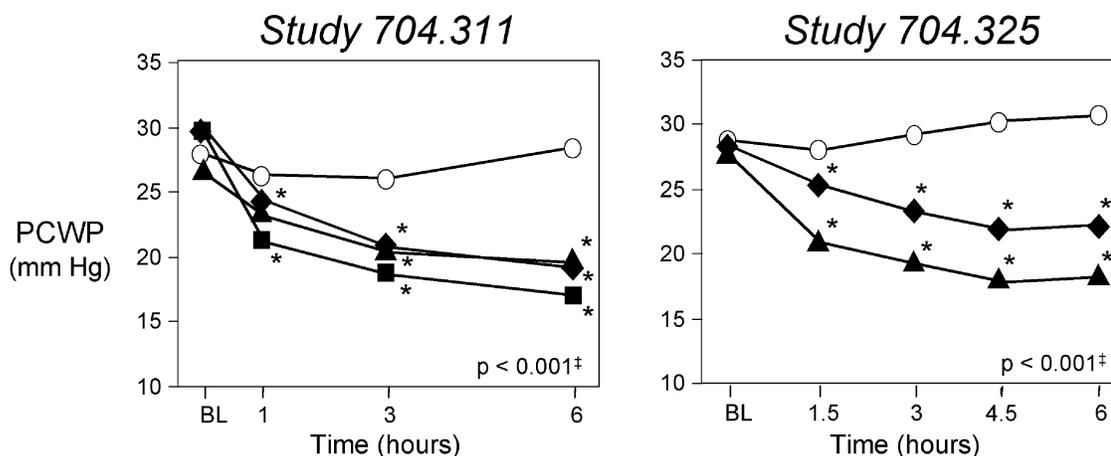
	<b>Study 704.311</b>	<b>Study 704.325</b>
Design	randomized, double-blind, placebo-controlled	randomized, double-blind, placebo-controlled
Subjects	n = 103 subjects with symptomatic CHF	n = 127 subjects with symptomatic CHF requiring hospitalization and IV vasoactive therapy
Inclusion Criteria:		
PCWP	≥ 18 mm Hg	≥ 18 mm Hg
CI	≤ 2.7 L/min/m <sup>2</sup>	≤ 2.7 L/min/m <sup>2</sup>
Ejection Fraction	≤ 35%	no restriction
Dose Groups	placebo (infusion preceded by loading bolus) Natreacor® 0.015 µg/kg/min (0.25 µg/kg bolus) Natreacor® 0.03 µg/kg/min (0.50 µg/kg bolus) Natreacor® 0.06 µg/kg/min (1.00 µg/kg bolus)	placebo (infusion preceded by loading bolus) Natreacor® 0.015 µg/kg/min (0.3 µg/kg bolus) Natreacor® 0.03 µg/kg/min (0.6 µg/kg bolus)
Dosing Duration	24 hours	placebo: 6 hours Natreacor®: at discretion of investigator (mean ~ 36 hrs)
Primary Efficacy Endpoint	Reduction in PCWP at 3 hours	Reduction in PCWP at 6 hours

In both studies, highly statistically significant results were obtained for the effects of Natreacor® on PCWP compared to placebo. Figure 5–2 and Table 5–2 depict the results of the two studies at 6 hours when analyzed using an intent-to-treat, carry-forward analysis of all enrolled subjects.

Figure 5-2

Studies 704.311 and 704.325  
PCWP

○ Placebo    ◆ Natrecor® 0.015 µg/kg/min    ▲ Natrecor® 0.03 µg/kg/min    ■ Natrecor® 0.06 µg/kg/min



Plotted values represent treatment group means.

† ANOVA F-test for both absolute and percent change at 6 hours.

\* p < 0.05 vs. placebo, by pairwise contrast within carry-forward ANOVA of change from baseline.

Table 5-2

Studies 704.311 and 704.325  
Change (and Percent Change) in PCWP at 6 Hours  
(Intent-to-Treat, Carry-Forward Analyses)

	Placebo	Natrecor®			Treatment Inference
		0.015 µg/kg/min	0.03 µg/kg/min	0.06 µg/kg/min	
<b>Study 704.311</b>	n = 29	n = 22	n = 26	n = 26	
PCWP at baseline (mm Hg)	27.8	29.8	27.3	29.4	
PCWP at 6 Hours					
Change (mm Hg)	+0.5	-10.7	-6.8	-12.5	p < 0.001 <sup>a</sup>
Percent change	+3.0%	-34.1%	-23.8%	-43.3%	
Pairwise inference	–	p < 0.001 <sup>b</sup>	p < 0.001 <sup>b</sup>	p < 0.001 <sup>b</sup>	
<b>Study 704.325</b>	n = 42	n = 43	n = 42	–	
PCWP at baseline (mm Hg)	28.5	28.1	27.5	–	
PCWP at 6 Hours					
Change (mm Hg)	+2.0	-5.8	-9.6	–	p < 0.001 <sup>a</sup>
Percent change	+8.4%	-20.1%	-35.3%	–	
Pairwise inference	–	p < 0.001 <sup>b</sup>	p < 0.001 <sup>b</sup>	–	

Results are presented as treatment group means.

<sup>a</sup> Omnibus F test; p-value applies to analysis of both change and percent change.

<sup>b</sup> Pairwise comparison to placebo, by pairwise contrast within ANOVA; p-value applies to analysis of both change and percent change.

In each of studies 704.311 and 704.325, the protocol-specified primary efficacy analysis also achieved highly statistically significant results. In Study 704.311, the protocol-specified primary efficacy endpoint was the absolute change in PCWP at 3 hours after initiation of study drug for subjects remaining on the study drug regimen of randomization; treatment effect was assessed by means of a linear contrast in treatment group. In study 704.325, the protocol-specified primary endpoint was PCWP expressed as a percentage change from baseline at 6 hours after initiation of study drug; treatment effect was assessed by means of a worst outcome, nonparametric, intent-to-treat analysis. The results of these analyses are presented in detail in the study synopses in Appendices A and B, respectively. Both of these protocol-specified primary analyses yielded results very similar to the aforementioned intent-to-treat, carry forward analyses and were highly statistically significant ( $p = 0.004$  and  $p < 0.001$  for studies 704.311 and 704.325, respectively).

Thus, highly statistically significant results were achieved for the primary efficacy endpoints for all doses of Natrecor<sup>®</sup> tested in the two pivotal efficacy studies 704.311 and 704.325 when analyzed via either an intent-to-treat, carry-forward analysis or via the protocol-specified primary analyses.

### 5.3.1.2 Sustained Hemodynamic Effects

Study 704.311 demonstrated that, when Natrecor<sup>®</sup> is administered as a continuous intravenous infusion, it has sustained hemodynamic effects through at least 24 hours of infusion (the last hemodynamic time point assessed on study drug). Table 5–3 depicts changes from baseline in PCWP at 24 hours of infusion in the placebo and Natrecor<sup>®</sup> 0.015  $\mu\text{g}/\text{kg}/\text{min}$  dose group from that study.

**Table 5–3**  
**Study 704.311**  
**Change (and Percent Change) in PCWP at 24 Hours**

	Placebo (n = 29)	Natrecor <sup>®</sup> 0.015 $\mu\text{g}/\text{kg}/\text{min}$ (n = 22)	Treatment Inference
<b>Subjects Enrolled:</b>			
<b>Subjects Summarized:</b>	(n = 25)	(n = 21)	
PCWP At Baseline (mm Hg)	27.8	29.8	
PCWP at 24 hours			
Change (mm Hg)	–1.8	–8.3	$p \leq 0.002^a$
Percent change	–6.2%	–27.1%	
	$p \geq 0.169^b$	$p < 0.001^b$	

Subjects are analyzed according to the treatment group of randomization. For inclusion in the analysis, PCWP must have been recorded while the subject was still receiving study drug and within  $24 \pm 3$  hours after start of study drug. Results are presented as treatment group means. P-values apply to the analysis of both “change” and “percent change.”

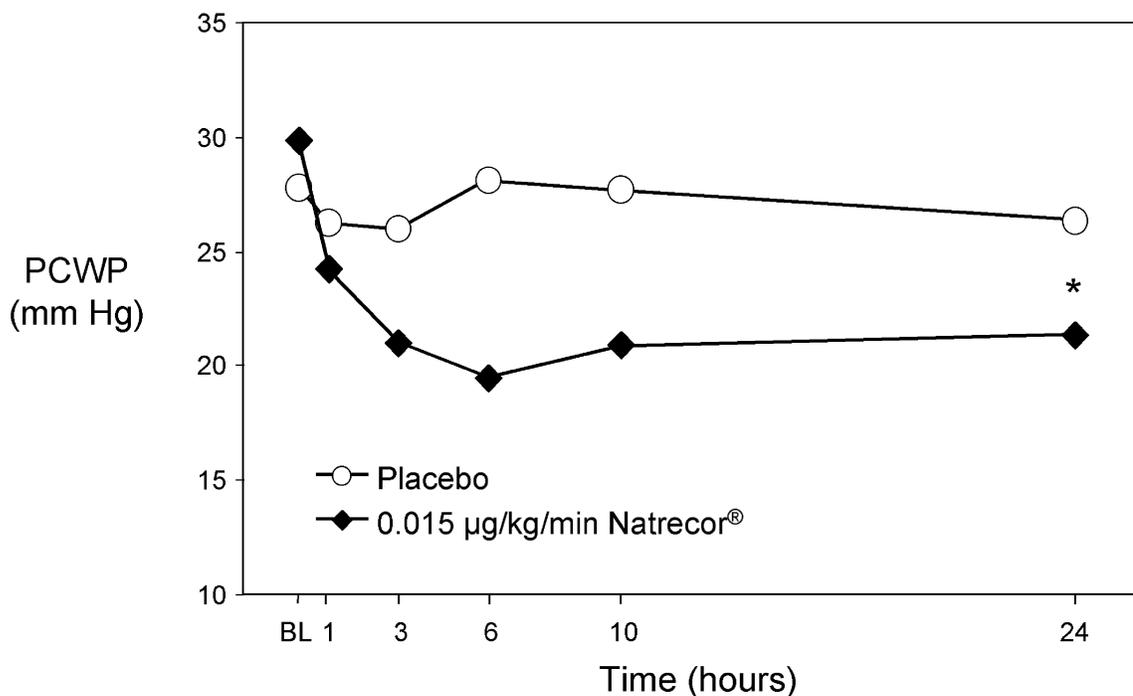
<sup>a</sup> pairwise contrast within ANOVA framework

<sup>b</sup> one-sample t-test of change from baseline

This change from baseline in PCWP at 24 hours in the Natrecor® group is highly statistically significant compared to placebo ( $p \leq 0.002$  [pairwise contrast]). These changes in PCWP over time are shown graphically in Figure 5-3. Thus, Natrecor® continues to have sustained effects on PCWP through 24 hours of infusion.

Figure 5-3

Study 704.311  
Sustained Hemodynamic Effects



Plotted values represent treatment group means.

\*  $p = 0.001$  at 24 hours, by pairwise contrast within ANOVA of change from baseline

In studies 704.309 and 704.310, subjects with CHF continued to exhibit hemodynamic responses to doses of Natrecor® when administered as repetitive boluses every 4 or 6 hours for 24 hours (data not shown).

This evidence of sustained effects with prolonged administration in patients with CHF is consistent with the results from preclinical studies, in which Natrecor® continued to have sustained hemodynamic effects through at least 2 weeks of continuous IV infusion.

### 5.3.1.3 Other Hemodynamic Parameters

The effects of Natrecor® on other hemodynamic parameters, such as MRAP, SVR, and CI were also assessed in studies 704.311 and 704.325. The results for these assessments at 6 hours in both studies are shown in Table 5–4. Hemodynamic results for studies 704.311 and 704.325 are shown graphically in Figures 5–4 and 5–5.

**Table 5–4**  
**Studies 704.311 and 704.325**  
**Percent Changes in MRAP, SVR, and CI at 6 Hours**  
**(Intent-to-Treat, Carry-Forward Analyses)**

		Placebo	Natrecor®			Treatment Inference
			0.015 µg/kg/min	0.03 µg/kg/min	0.06 µg/kg/min	
<b>Study 704.311</b>						
MRAP	Baseline (mm Hg)	13.0	13.4	16.1	13.0	
	% change at 6 Hours	7%	–27%	–28%	–40%	p = 0.001 <sup>a</sup>
	Pairwise inference	–	p = 0.006 <sup>b</sup>	p = 0.003 <sup>b</sup>	p < 0.001 <sup>b</sup>	
SVR	Baseline (dynes·sec·cm <sup>–5</sup> )	1704	1782	1662	1719	
	% change at 6 Hours	1%	–13%	–5%	–26%	p = 0.001 <sup>a</sup>
	Pairwise inference	–	p = 0.046 <sup>b</sup>	p = 0.372 <sup>b</sup>	p < 0.001 <sup>b</sup>	
CI	Baseline (L/min/m <sup>2</sup> )	1.9	1.8	1.9	1.9	
	% change at 6 Hours	–1%	22%	20%	38%	p = 0.005 <sup>a</sup>
	Pairwise inference	–	p = 0.041 <sup>b</sup>	p = 0.055 <sup>b</sup>	p < 0.001 <sup>b</sup>	
<b>Study 704.325</b>						
MRAP	Baseline (mm Hg)	14.2	14.8	14.3	–	
	% change at 6 Hours	9%	–11%	–41%	–	p < 0.001 <sup>a</sup>
	Pairwise inference	–	p = 0.008 <sup>b</sup>	p < 0.001 <sup>b</sup>	–	
SVR	Baseline (dynes·sec·cm <sup>–5</sup> )	1524	1592	1687	–	
	% change at 6 Hours	13%	–12%	–18%	–	p < 0.001 <sup>a</sup>
	Pairwise inference	–	p < 0.001 <sup>b</sup>	p < 0.001 <sup>b</sup>	–	
CI	Baseline (L/min/m <sup>2</sup> )	2.0	1.8	1.9	–	
	% change at 6 Hours	–4%	18%	28%	–	p < 0.001 <sup>a</sup>
	Pairwise inference	–	p = 0.003 <sup>b</sup>	p < 0.001 <sup>b</sup>	–	

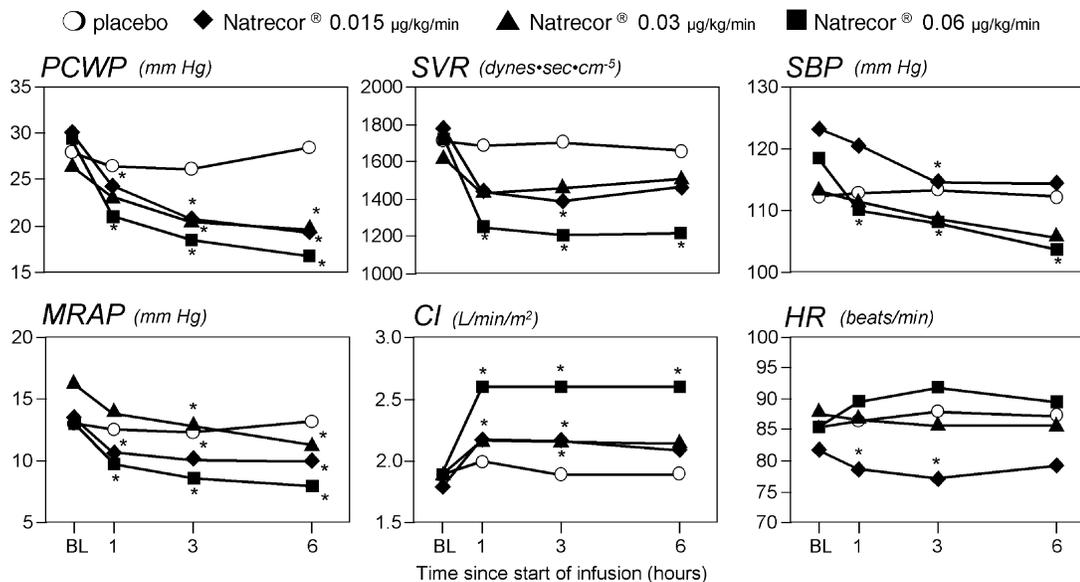
Results are presented as treatment group means.

<sup>a</sup> Omnibus F test.

<sup>b</sup> pairwise comparison to placebo, by pairwise contrast within ANOVA.

Figure 5-4

**Studies 704.311**  
**Hemodynamic Effects of Natrecor®**  
**(n = 103)**

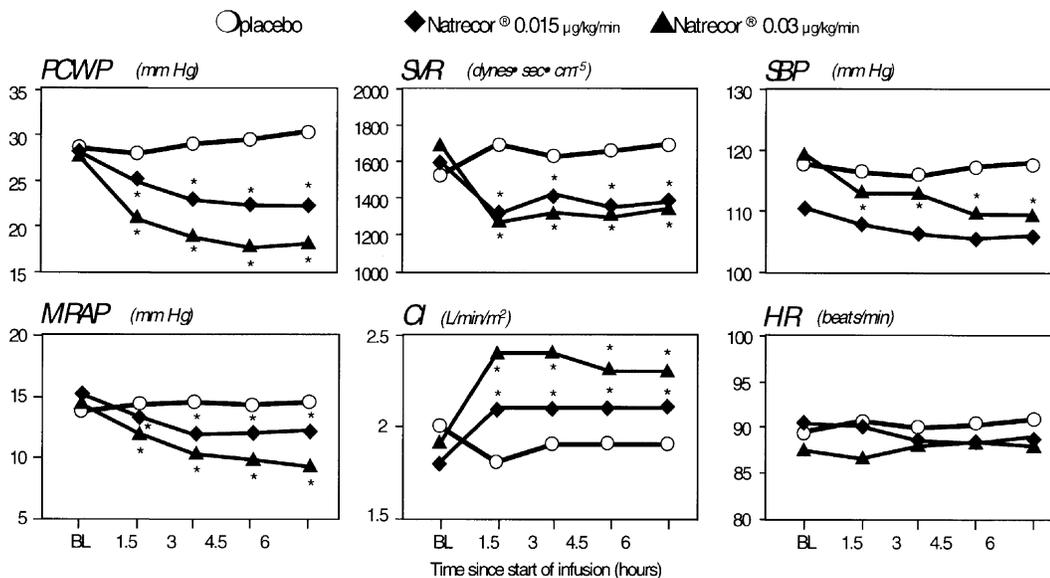


Plotted values represent treatment group means.

\* p < 0.05 vs. placebo, by pairwise contrast within carry forward ANOVA of change from baseline

Figure 5-5

**Studies 704.325**  
**Hemodynamic Effects of Natrecor®**  
**(n = 127)**



Plotted values represent treatment group means.

\* p < 0.05 vs. placebo, by pairwise contrast within carry forward ANOVA of change from baseline

Thus, in both pivotal efficacy studies (as well as the earlier studies in the development program), desirable effects on multiple hemodynamic parameters were observed, such as a reduction in preload (i.e., PCWP and MRAP), a reduction in afterload (i.e., SVR), and an increase in CI.

### 5.3.2 *Clinical Status*

#### 5.3.2.1 *Global Clinical Status*

In both studies 704.325 and 704.326, administration of Natrecor® resulted in rapid improvements in global clinical status as assessed by both the subjects and their physicians.

In study 704.325, clinical status was assessed during the initial 6-hour double-blind, placebo-controlled assessment period. The subject's self-assessment of clinical status 6 hours after start of study drug is shown in Table 5-5.

**Table 5-5**  
**Study 704.325**  
**Global Assessment of Clinical Status by the Subject at 6 Hours**

	Percentage of Subjects With Each Response		
	Placebo (n = 42)	Natrecor® 0.015 µg/kg/min* (n = 43)	Natrecor® 0.03 µg/kg/min* (n = 42)
<b>Subjects Enrolled:</b>			
<b>Subjects Summarized:</b>	(n = 42)	(n = 40)	(n = 39)
Markedly Better	0%	13%	8%
Better	14%	48%	59%
No Change	74%	25%	23%
Worse	5%	5%	5%
Markedly Worse	7%	10%	5%

Subjects are summarized according to the treatment group of randomization. Assessments made 5 1/2 to 7 hours after start of study drug infusion were eligible for summarization.

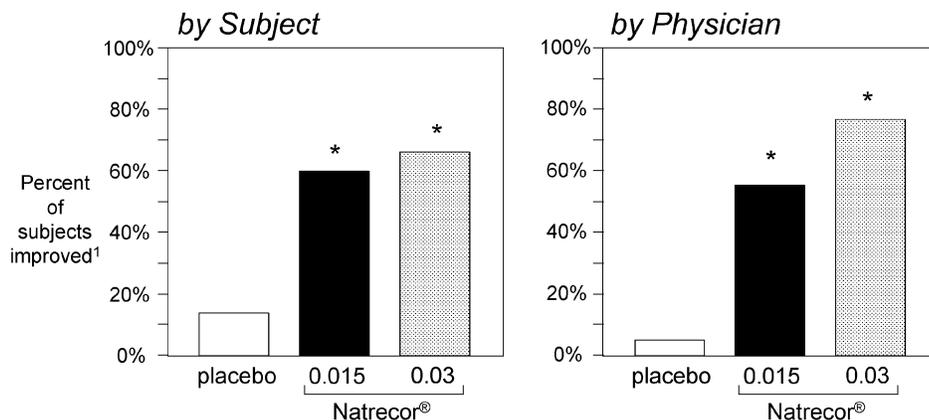
\*  $p \leq 0.001$  for pairwise comparisons of each Natrecor® dose group to placebo [2-sample Wilcoxon]

By 6 hours (the first time point assessed), the majority (> 60%) of subjects in both Natrecor® dose groups reported feeling better or much better compared to only 14% of placebo subjects. This rapid improvement in clinical status was statistically significant for each of the two Natrecor® treatment groups when compared to placebo ( $p \leq 0.001$  for both groups [2-sample Wilcoxon]).

Similar results were obtained when the physician was asked to assess each subject's clinical status at 6 hours as shown in Figure 5-6.

Figure 5-6

**Study 704.325**  
**Global Assessment of Clinical Status at 6 Hours**



\*  $p \leq 0.001$  compared to placebo (2-sample Wilcoxon test on 5-category ordinal variable.)

<sup>1</sup> percent of subjects reporting feeling “better” or “markedly better”

Thus, in study 704.325, Natrecor<sup>®</sup> resulted in improvements in clinical status as assessed by both the subject and the physician by 6 hours after initiation of therapy. Highly statistically significant improvements compared to placebo were obtained for both the 0.015 and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> dose groups.

The beneficial effects of both doses of Natrecor<sup>®</sup> on clinical status were confirmed in study 704.326. This was an active-controlled observational study performed to obtain additional safety and clinical experience with Natrecor<sup>®</sup> in the treatment of decompensated CHF. Subjects were randomized to receive one of two doses of Natrecor<sup>®</sup> (0.015 or 0.03  $\mu\text{g}/\text{kg}/\text{min}$ ) in a double-blinded manner — or a standard care IV vasoactive agent for the treatment of decompensated CHF of the investigator’s choosing, such as dobutamine (open-label). A more detailed description of this study’s design, methodology and results can be found in Appendix C.

As shown in Table 5-6, in study 704.326, the majority of subjects treated with Natrecor<sup>®</sup> reported an improvement in clinical status by 6 hours after the initiation of therapy (the first assessment performed). The percentages of Natrecor<sup>®</sup> and standard care subjects reporting an improvement by 6 hours were comparable. These improvements relative to baseline were highly statistically significant ( $p < 0.001$  [1-sample Wilcoxon]) for all three treatment groups.

**Table 5–6**  
**Study 704.326**  
**Global Assessment of Clinical Status by the Subject at 6 Hours**

	Percent of Subjects With Each Response		
	Standard Care* (n = 102) Subjects Enrolled: Subjects Summarized: (n = 84)	Natreacor® 0.015 µg/kg/min* (n = 103) (n = 86)	Natreacor® 0.03 µg/kg/min* (n = 100) (n = 82)
Markedly Better	10%	12%	5%
Better	55%	56%	55%
No Change	32%	30%	35%
Worse	4%	2%	5%
Markedly Worse	0%	0%	0%

Subjects are summarized according to the treatment administered. Assessments made 5 1/2 to 7 hours after start of study drug infusion were eligible for summarization.

\* p < 0.001 compared to pretreatment (1-sample Wilcoxon)

Similar results were obtained when the physician's assessment of global clinical status at 6 hours was analyzed (data not shown).

Thus, in both studies 704.325 and 704.326, administration of Natreacor® was associated with a rapid improvement in clinical status as assessed by the subjects or by their physicians at 6 hours. In study 704.326, the improvement was comparable to that observed with standard care.

### ***5.3.2.2 Improvement in Specific Symptoms of CHF***

Administration of Natreacor® also resulted in the rapid improvement of specific symptoms of CHF in both studies 704.325 and 704.326.

In study 704.325, prior to the initiation of therapy, 93% of subjects had dyspnea, 96% had fatigue, 27% had lightheadedness, and 48% had decreased or absent appetite. In this randomized, double-blinded, placebo-controlled study, the percentage of subjects who reported an improvement in each of these symptoms as early as 6 hours after start of therapy (first assessment time point) is shown in Table 5–7. Dyspnea and fatigue were most notably improved.

**Table 5-7**  
**Study 704.325**  
**Symptoms of CHF at 6 Hours**

Subjects Enrolled: Subjects Summarized:	Percent Reporting Improvement			Treatment Inference
	Placebo (n = 42)	Natreacor®		
		0.015 µg/kg/min (n = 43)	0.03 µg/kg/min (n = 42)	
Dyspnea	12%	56% p < 0.001 <sup>b</sup>	50% p < 0.001 <sup>b</sup>	p < 0.001 <sup>a</sup>
Fatigue	5%	32% p = 0.001 <sup>b</sup>	38% p < 0.001 <sup>b</sup>	p < 0.001 <sup>a</sup>
Lightheadedness	5%	24% p = 0.010 <sup>b</sup>	10% p = 0.713 <sup>b</sup>	p = 0.023 <sup>a</sup>
Decreased Appetite	7%	28% p = 0.023 <sup>b</sup>	8% p = 0.771 <sup>b</sup>	p = 0.017 <sup>a</sup>

Subjects are summarized according to the treatment group of randomization. Assessments made 5 1/2 to 7 hours after start of study drug infusion were eligible for summarization.

<sup>a</sup> Kruskal-Wallis test on 3-category ordinal variable (worse, no change, improved).

<sup>b</sup> pairwise comparison to placebo, two-sample Wilcoxon test on 3-category ordinal variable.

In study 704.326, an active-controlled study of Natreacor® (0.015 and 0.03 µg/kg/min), at baseline, 99% of subjects had dyspnea, 97% had fatigue, 43% had lightheadedness, and 58% had decreased or absent appetite. Both doses of Natreacor® resulted in rapid improvement in each of these symptoms by 6 hours. The percent of subjects who reported an improvement in each symptom by 6 hours after start of therapy is shown in Table 5-8.

**Table 5–8**  
**Study 704.326**  
**Symptoms of CHF at 6 Hours**

	Percent Reporting Improvement			Treatment Inference
	Standard Care (n = 102) (n = 84–85)	Natreacor®		
Subjects Enrolled: Subjects Summarized:		0.015 µg/kg/min (n = 103) (n = 88–89)	0.03 µg/kg/min (n = 100) (n = 79–80)	
Dyspnea	61%	63% p = 0.726 <sup>b</sup>	55% p = 0.515 <sup>b</sup>	p = 0.583 <sup>a</sup>
Fatigue	30%	30% p = 0.662 <sup>b</sup>	33% p = 0.505 <sup>b</sup>	p = 0.787 <sup>a</sup>
Lightheadedness	13%	19% p = 0.594 <sup>b</sup>	14% p = 0.340 <sup>b</sup>	p = 0.369 <sup>a</sup>
Decreased Appetite	23%	27% p = 0.531 <sup>b</sup>	20% p = 0.621 <sup>b</sup>	p = 0.534 <sup>a</sup>

Subjects are summarized according to the treatment administered. Assessments made 5 1/2 to 7 hours after start of study drug infusion were eligible for summarization.

<sup>a</sup> Kruskal-Wallis test on 3-category ordinal variable (worse, no change, improved).

<sup>b</sup> Pairwise comparison to standard care, two-sample Wilcoxon test on 3-category ordinal variable.

In study 704.326, both doses of Natreacor® caused a rapid improvement in each of these symptoms compared to baseline. Generally, the percent of subjects with an improvement in symptoms with Natreacor® administration was comparable to the standard care group.

Thus, in both studies 704.325 and 704.326, initiation of therapy with Natreacor® resulted in a rapid improvement in symptoms of CHF.

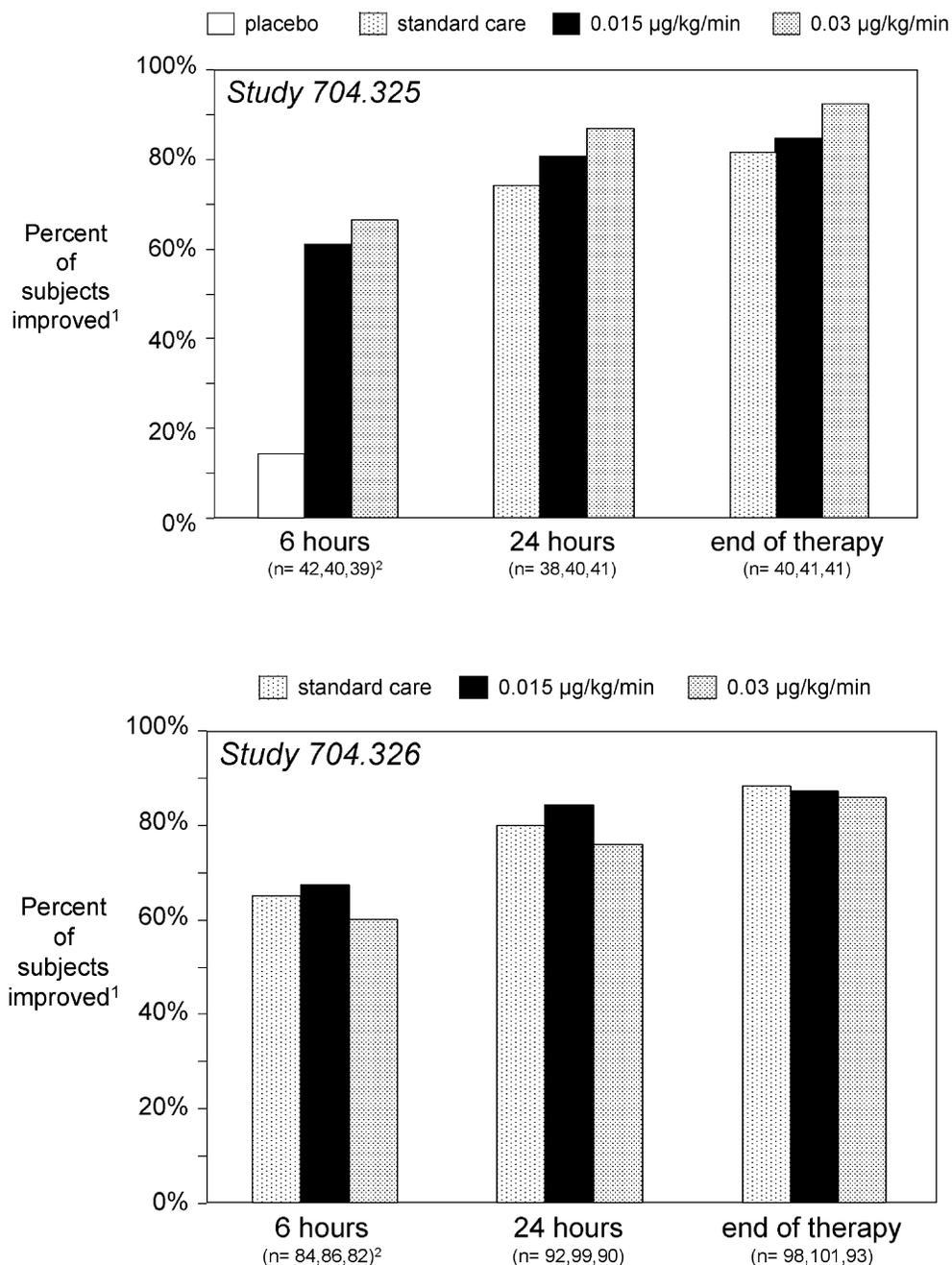
### 5.3.2.3 Sustained Effects on Clinical Status

In clinical practice, the duration of IV vasoactive therapy for the short-term management of CHF may range from hours to days, depending upon patients' clinical status at presentation, underlying medical conditions, and responsiveness to therapy. Because of this, the duration of infusion of Natreacor® in Phase III studies 704.325 and 704.326 was left to the clinical judgment of the investigators. In study 704.325, Natreacor® was administered for an average of 36 hours (range of 3.0 hours to 122.3 hours [5 days]). In study 704.326, Natreacor® was administered for an average of 48 hours (range of 2.2 to 283.2 hours [12 days]) including interruptions. In Phase III, the longest infusion without interruption was 214.2 hours (9 days).

In both studies 704.325 and 704.326, beyond 6 hours, the number of Natreacor® subjects with an improvement in clinical status (as assessed by both the subject and the physician) continued to increase with time. This is shown graphically in Figure 5–7. As can be seen, by 24 hours after the initiation of therapy with Natreacor®, over 80% of the subjects were reporting an improvement in clinical status. By the last available assessment at the end of therapy, close to 90% of the Natreacor® subjects were improved. This suggests that Natreacor® therapy continues to have beneficial effects on clinical status with extended therapy.

Figure 5-7

**Studies 704.325 and 704.326**  
**Global Assessment of Clinical Study by Subject**  
**at 6 Hours, 24 Hours, and End of Therapy**



<sup>1</sup> Percent of subjects reporting feeling “better” or “markedly better.”

<sup>2</sup> Number of subjects summarized in the control, 0.015, and 0.03 µg/kg/min Natrecor® groups, respectively. Assessments made 5 1/2 to 7 hours, 20–28 hours, or at least 20 hours after start of study drug infusion were eligible for summarization at 6 hours, 24 hours, or end of therapy, respectively.

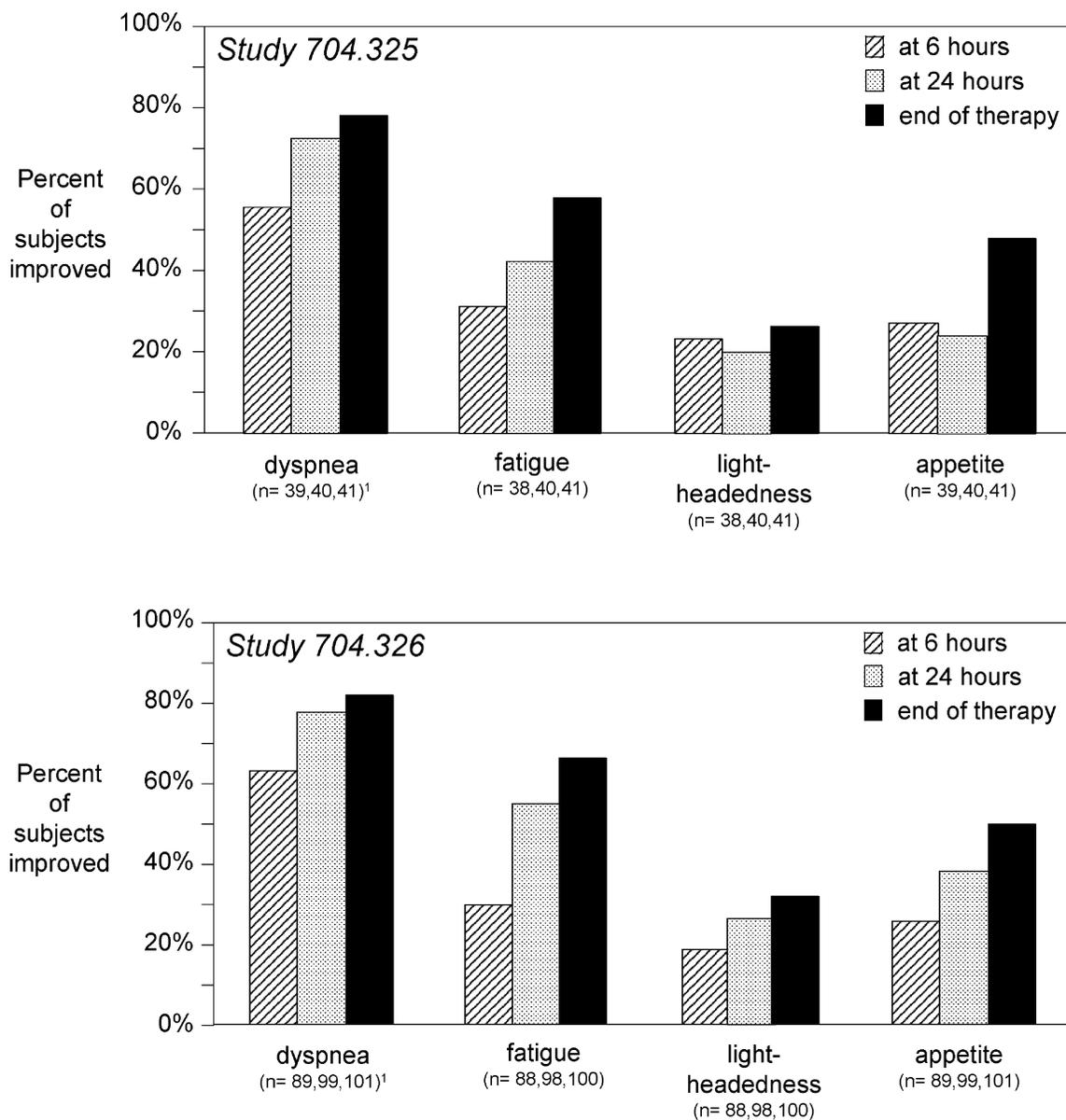
Because of the active-control design of studies 704.325 (which is active-controlled after 6 hours) and 704.326, neither study permits a comparison of the effects of Natrecor® to placebo on clinical status after 6 hours. In addition, neither study had the objective of demonstrating superiority or equivalence of Natrecor® to standard care agents after 6 hours. Therefore, the effects of Natrecor® and the standard care agents can only be compared descriptively after 6 hours. In studies 704.325 and 704.326, the percentage of active control/standard care subjects reporting an improvement in clinical status at the end of therapy was 81% and 89%, respectively. The percentage of Natrecor® subjects reporting an improvement was generally very similar to the percentage of standard care subjects reporting improvement at 24 hours and at the end of therapy.

Figure 5–8 shows, for subjects receiving the 0.015 µg/kg/min dose of Natrecor® in studies 704.325 and 704.326, the percentage of subjects reporting an improvement in specific symptoms of CHF. Again, a progressive increase in the percentage of subjects showing an improvement over time can be seen. Similar results were obtained for subjects in the Natrecor® 0.03 µg/kg/min dose group and active control/standard care group (data not shown). This again supports a sustained beneficial effect of Natrecor® on clinical symptoms of CHF over time.

Thus, in both studies 704.325 and 704.326, extended therapy with Natrecor® was accompanied by progressive improvement over the course of therapy in both global clinical status and in specific symptoms of CHF.

Figure 5–8

**Studies 704.325 and 704.326**  
**Symptoms of CHF**  
**at 6 Hours, 24 Hours, and End of Therapy**  
**(Natrecor® 0.015 µg/kg/min dose group)**



<sup>1</sup> Number of subjects summarized in the 0.015 µg/kg/min Natrecor® group at 6 h, 24 h, and end of therapy, respectively. Assessments made 5 1/2 to 7 hours, 20–28 hours, or at least 20 hours after start of study drug infusion were eligible for summarization at 6 hours, 24 hours, or end of therapy, respectively.

### 5.3.3 *Diuresis and Diuretic Usage*

In study 704.311, the administration of the subject's usual chronic doses of diuretics was permitted, as clinically indicated. In that study, Natrecor® administration was not associated with an increase in diuresis compared to placebo, although there was a trend toward less administration of diuretics to the Natrecor® subjects than to the placebo subjects. In study 704.325, which enrolled patients with decompensated CHF requiring hospitalization and parenteral therapy (and in which diuretics were initially withheld), Natrecor® administration did increase urine output compared to placebo. Among those subjects who did not receive diuretics during the initial 6-hour urine collection period, the mean urine output per hour in the placebo and 0.015 and 0.03 µg/kg/min Natrecor® treatment groups was 63.9, 92.0, and 109.9 mL/h, respectively (p = 0.004 [omnibus F test]).

In both studies 704.325 and 704.326, Natrecor® administration was associated with progressive weight loss consistent with a net diuresis. It is interesting to note that this was not a result of increased diuretic usage. Actually, fewer Natrecor® subjects required diuretics compared to “standard care” in both studies, as shown in Table 5–9.

**Table 5–9**

**Studies 704.325 and 704.326  
Diuretic Usage During Study Drug Infusion**

Study	% of Subjects Receiving Diuretics			p value <sup>2</sup>
	Control	Natrecor® 0.015 µg/kg/min	Natrecor® 0.03 µg/kg/min	
704.325 <sup>1</sup>	90% (38/42)	72% (31/43)	50% (21/42)	p < 0.001
704.326	97% (99/102)	82% (84/103)	74% (74/100)	p < 0.001

<sup>1</sup> During first 24 hours only.

<sup>2</sup> Comparison of three treatment groups [Fisher's Exact Test].

### 5.3.4 *Other Clinical Outcomes of Interest*

In study 704.311, clinical status and symptoms of CHF were not assessed directly. However, 5 placebo subjects (17%) but only 0, 1, and 0 subjects (0%, 4%, and 0%) in the 0.015, 0.03, and 0.06 µg/kg/min Natrecor® dose groups, respectively, terminated study drug infusion prematurely due to worsening CHF, required intervention with other parenteral agents, and were therefore categorized as treatment failures (p = 0.021 [Fisher's exact test]). Thus, study 704.311 supports a beneficial effect of Natrecor® on clinical status.

Study 704.326 most closely depicts the likely usage of Natrecor® during commercialization. In that study, medical management decisions regarding Natrecor® use (including duration of therapy and the need for central hemodynamic monitoring) were left solely to the discretion of

the investigator rather than being dictated by the protocol. In that study, in addition to the aforementioned beneficial effects observed on clinical status, it is interesting to note that:

- 83% of the subjects in the 0.015 µg/kg/min Natreacor<sup>®</sup> dose group and 76% of the subjects in the 0.03 µg/kg/min Natreacor<sup>®</sup> dose group completed the entire course of therapy for acutely decompensated CHF with Natreacor<sup>®</sup> as the sole parenteral vasoactive agent.
- A Swan-Ganz<sup>®</sup> catheter was utilized in only 18% of subjects receiving Natreacor<sup>®</sup>, showing that Natreacor<sup>®</sup> can be used without central hemodynamic monitoring.

Thus, study 704.326 supports a role for Natreacor<sup>®</sup> as a first-line IV agent for the treatment of decompensated CHF.

#### **5.4 Efficacy Conclusions**

Natreacor<sup>®</sup> has been studied in 8 controlled studies in patients with CHF. The studies in the Natreacor<sup>®</sup> development program demonstrate that Natreacor<sup>®</sup> exhibits the characteristics desired in an agent for the short-term treatment of decompensated CHF. When administered to patients with decompensated CHF, Natreacor<sup>®</sup> (compared to placebo) has been shown:

- to improve cardiac hemodynamics, by:
  - reducing preload (i.e., PCWP and MRAP)
  - reducing afterload (SVR), and
  - increasing cardiac index
  - without increasing heart rate.
- to improve clinical status, as assessed by:
  - the subjects' self-assessment of global clinical status
  - the physician's assessment of global clinical status
  - the assessment of specific symptoms of CHF, such as dyspnea and fatigue.

Table 5–10 summarizes the efficacy results from clinical studies 704.311, 704.325, and 704.326 in the Natreacor<sup>®</sup> development program. Of note, highly statistically significant results were achieved for the primary efficacy endpoint (reduction in PCWP) in the two pivotal efficacy studies: 704.311 and 704.325.

Table 5–10

**Studies 704.311, 704.325, and 704.326  
Summary of Efficacy Results**

<b>Outcome of Interest</b>	<b>Study 704.311</b>	<b>Study 704.325</b>	<b>Study 704.326</b>
Reduction in PCWP	Yes (p = 0.004)	Yes (p < 0.001)	Not Assessed
Improvements in other hemodynamic parameters (such as MRAP, SVR and CI)	Yes	Yes	Not Assessed
Diuretic effect and/or reduced diuretic usage	No	Yes	Yes
Improvement In Clinical Status	Fewer treatment failures with Natrecor® as compared to placebo	Improvement in global clinical status per subject	Improvement in global clinical status per subject
		Improvement in global clinical status per physician	Improvement in global clinical status per physician
		Improvement in symptoms of CHF	Improvement in symptoms of CHF

These beneficial effects were achieved:

- without an increase in heart rate or cardiac work;
- without the need to titrate the dose;
- without the need for central hemodynamic monitoring (such as with a Swan-Ganz® catheter);
- and with reduced need for concomitant diuretics.

More details on clinical studies 704.311, 704.325, and 704.326 can be found in Appendices A, B, and C, respectively.

## Item 6

### Safety Summary

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To date, approximately 785 subjects have received nesiritide in clinical studies either sponsored by Scios or published by other investigators. Scios' NDA 20-920 contains data from eight studies in which Natrecor<sup>®</sup> was administered to 505 patients with CHF.

In Scios-sponsored clinical trials, Natrecor<sup>®</sup> has been administered to a broad spectrum of subjects with CHF. In early studies, subjects were often patients with chronic stable CHF who volunteered for study participation or who were already hospitalized for either decompensated CHF or cardiac transplantation evaluation. Study 704.311 (n = 103) was a placebo-controlled study which included a 24-hour infusion of Natrecor<sup>®</sup> or placebo in patients with symptomatic CHF. In the two largest studies in the development program (studies 704.325 [n = 127] and 704.326 [n = 305]), the subjects enrolled were patients requiring hospitalization and therapy with an IV vasoactive agent for acutely decompensated CHF. Additionally, in study 704.326, subjects could not have already received an IV vasoactive agent for the treatment of CHF for more than 4 hours. Inclusion/exclusion criteria in both studies were nonrestrictive. Subjects with concomitant medical conditions common in patients with CHF, such as coronary artery disease, renal insufficiency, and arrhythmias (including atrial fibrillation and ventricular arrhythmias) were permitted to enroll in the study, and indeed made up a large percentage of the study population. Thus, these studies assess the safety and efficacy of Natrecor<sup>®</sup> as a first-line agent in the target population of patients who are likely to receive Natrecor<sup>®</sup> during commercialization.

Study 704.326 (n = 305 subjects) in particular was designed to mimic as closely as possible the conditions under which Natrecor<sup>®</sup> would be administered in actual clinical practice. Few restrictions on patient management were imposed by the clinical study protocol. Decisions regarding the use of concomitant medications (oral or IV), the need for study drug dose modifications, the length of therapy, and the need for invasive monitoring were left to the discretion of the investigator. A Swan-Ganz<sup>®</sup> catheter was used for patient management in less than 20% of subjects in the study.

Thus, the safety information on Natrecor<sup>®</sup> obtained from these clinical studies provides a useful database for evaluating the safety profile of Natrecor<sup>®</sup> in the target population of patients likely to receive Natrecor<sup>®</sup> during commercialization, i.e., patients with decompensated CHF requiring hospitalization.

### ***6.1 Safety Evaluations Performed***

In the clinical development program for Natreacor<sup>®</sup> for the short-term treatment of CHF, adverse events were recorded through day 14 in all studies. Mortality status was collected as of day 15 or day 21, depending on the study. All subjects underwent single-lead ECG cardiac monitoring during study drug administration to permit the evaluation of treatment-emergent arrhythmias. At least one set of hematology and general chemistry laboratory tests was performed before and after study drug infusion in each study. Blood was assayed for the potential development of anti-hBNP antibodies in all studies. The design of each of the CHF studies in the development program and key safety monitoring performed in each study are summarized in Table 6-1.

**Table 6-1**

**Clinical Safety Assessments of Natrecor® in Patients with CHF**

Study	No. of Subjects in Study	Study Design	Natrecor® Dosing	AEs Reported Through	Mortality Status as of	Labs <sup>1</sup> Obtained At	Anti-hBNP Antibodies Assessed At
704.305	30	Randomized, double-blind, placebo-controlled, ascending dose	0.3, 1, 3, 10, 15, or 20 µg/kg hBNP as a single bolus (n = 4/dose) or placebo (n = 6)	day 14	day 15	baseline day 1 day 2	baseline day 21 day 42
704.306	16	Randomized, double-blind, placebo-controlled, ascending dose	0.025 or 0.05 µg/kg/min hBNP or placebo × 4 h as a fixed-dose continuous IV infusion	day 14	day 15	baseline day 1 day 2 day 7–10	baseline day 21 day 42
704.307	20	Randomized, double-blind, placebo-controlled, dose-escalation crossover study	0.003, 0.01, 0.03, and 0.1 µg/kg/min as an escalating-dose IV infusion × 1.5 h at each dose (hBNP and placebo on successive days in a crossover design)	day 14	day 15	baseline day 1 day 2 day 3 day 7–10	baseline day 21 day 42
704.309	60	Randomized, double-blind, placebo-controlled, parallel design	5 µg/kg hBNP q4h 10 µg/kg hBNP q6h 10 µg/kg hBNP q4h or placebo q4-6h repetitive bolus regimen × 24 h	day 14	day 15	baseline day 2 day 20–30	baseline day 20–30
704.310	60	Randomized, double-blind, placebo-controlled, ascending dose	3 µg/kg hBNP q4h 5 µg/kg hBNP q4h 10 µg/kg hBNP q4h or placebo as repetitive bolus regimen × 24 h	day 14	day 15	baseline day 2 day 20–30	baseline day 20–30
704.311	103	Randomized, double-blind, placebo-controlled, parallel design	0.015, 0.03, or 0.06 µg/kg/min BNP or placebo continuous IV infusion × 24 h	day 14	day 15	baseline day 2 day 20–30	baseline day 20–30

<sup>1</sup> Complete blood cell count, general chemistry panel

<sup>2</sup> Na, K, CO<sub>2</sub>, CL, BUN, creatinine only obtained daily during parenteral CHF therapy

**Table 6–1 (cont'd)**  
**Clinical Safety Assessments of Natrecor® in Patients with CHF**

Study	No. of Subjects in Study	Study Design	Natrecor® Dosing	AEs Reported Through	Mortality Status as of	Labs <sup>1</sup> Obtained At	Anti-hBNP Antibodies Assessed At
704.325	127	Randomized, double-blind, placebo-controlled, parallel design study for first 6 hours, then active-controlled, open-label study thereafter	0.015 or 0.03 µg/kg/min hBNP as a fixed-dose IV infusion for up to 5 days or placebo/standard care	day 14	day 21	baseline daily for up to 5 days <sup>2</sup> within 24 h of end of parenteral CHF therapy	baseline day 21
704.326	305	Randomized, open-label, active-controlled, parallel design	0.015 or 0.03 µg/kg/min hBNP as a fixed-dose IV infusion for up to 12 days or standard care	day 14	day 21	baseline daily for up to 7 days <sup>2</sup> within 24 h of end of parenteral CHF therapy	baseline day 21

<sup>1</sup> Complete blood cell count, general chemistry panel

<sup>2</sup> Na, K, CO<sub>2</sub>, CL, BUN, creatinine only obtained daily during parenteral CHF therapy

## 6.2 Safety Database Information

### 6.2.1 Safety Analysis Populations

To facilitate the evaluation of the safety profile of Natrecor® in patients with CHF, three primary safety analysis populations have been defined, as presented in Table 6–2. For the purpose of safety evaluation, subjects were summarized according to the treatment administered as opposed to the treatment of randomization.

Table 6–2

#### Safety Analysis Populations

Studies	All CHF Studies (n = 721)	Placebo-Controlled Studies (n = 289)	Long Infusion Studies (n = 509)
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
704.325	x		x
704.326	x		x
Treatment Groups for Analysis	control <sup>1</sup> Natrecor® <sup>2</sup>	placebo Natrecor® <sup>2</sup>	control <sup>1</sup> Natrecor® 0.015 µg/kg/min Natrecor® 0.03 µg/kg/min

<sup>1</sup> Placebo and active control groups pooled

<sup>2</sup> All Natrecor® doses pooled

The “All CHF Studies” analysis population includes all subjects in all CHF studies in the Natrecor® development program. All of these studies were controlled studies; however, as delineated in Table 6–2, the control subjects received placebo in some studies and an active control agent for the treatment of decompensated CHF (such as dobutamine or milrinone) in others. All control subjects are compared to all Natrecor® subjects. A total of 721 subjects are included in this analysis population, including 505 subject exposures to Natrecor® and 235 subject exposures to control (nineteen subjects who received both Natrecor® and placebo in crossover study 704.307 are summarized in both groups).

The “Placebo-controlled” analysis population includes all subjects in all CHF studies that were strictly placebo-controlled (studies 704.305, 704.306, 704.307, 704.309, 704.310, and 704.311). Subjects in Phase III study 704.326 are not included because the study was active-controlled. Subjects in Phase III study 704.325 are also not included in this population because this study was placebo-controlled for only the first 6 hours and was active-controlled after 6 hours. All placebo subjects are compared to all Natrecor® subjects. A total of 289 subjects are included in this analysis population, including 217 subject exposures to Natrecor® and 91 subject

exposures to placebo (nineteen subjects who received both Natrecor<sup>®</sup> and placebo in crossover study 704.307 are summarized in both groups).

The “Long Infusion Studies” analysis population includes subjects in studies 704.311, 704.325, and 704.326. This analysis population is made up primarily of subjects who best represent the target population for Natrecor<sup>®</sup> use, i.e., patients with acutely decompensated CHF requiring hospitalization. These subjects also received the longest exposure to Natrecor<sup>®</sup> (generally  $\geq 24$  hours) in the dose range recommended for labeling (0.015 to 0.03  $\mu\text{g}/\text{kg}/\text{min}$ ).

All control subjects (whether receiving placebo, an active control agent or both) are combined for summarization. Subjects on Natrecor<sup>®</sup> are presented by dose group, except that the 26 subjects who received the 0.06  $\mu\text{g}/\text{kg}/\text{min}$  dose of Natrecor<sup>®</sup> from study 704.311 are generally excluded from these analyses. A total of 509 subjects are included in this analysis population, including 336 subject exposures to 0.015 or 0.03  $\mu\text{g}/\text{kg}/\text{min}$  of Natrecor<sup>®</sup> and 173 subject exposures to control.

### ***6.2.2 Extent of Exposure***

A total of 787 subjects have received nesiritide in clinical studies to date. Of these, 258 subjects received nesiritide in pharmacology studies which have been published in the literature. Another 24 patients received Natrecor<sup>®</sup> in an uncontrolled, dose-ranging pilot study for the treatment of acute postoperative hypertension. An additional 505 subjects were enrolled in the Natrecor<sup>®</sup> CHF development program. These latter subjects were the focus of NDA 20-920.

The extent of exposure to Natrecor<sup>®</sup> is summarized in Tables 6–3 and 6–4. In the Natrecor<sup>®</sup> CHF development program, 111 subjects with CHF received Natrecor<sup>®</sup> administered as an IV bolus. Natrecor<sup>®</sup> was administered as a single IV bolus at doses ranging from 0.3 to 20  $\mu\text{g}/\text{kg}$  to subjects with CHF. Natrecor<sup>®</sup> has also been administered to subjects with CHF as a repetitive bolus regimen at doses up to 10  $\mu\text{g}/\text{kg}$  every 4 hours for 24 hours.

A total of 394 subjects with CHF received continuous IV infusions of Natrecor<sup>®</sup> at doses ranging from 0.003 to 0.1  $\mu\text{g}/\text{kg}/\text{min}$ . Most of these subjects ( $n = 361$ ) received infusions at an average dose at or above the recommended dose of 0.015  $\mu\text{g}/\text{kg}/\text{min}$ . The majority of subjects ( $n = 243$ ) received infusions for longer than 24 hours. The longest infusion of Natrecor<sup>®</sup> to date (without interruption) has been 214.2 hours (~ 9 days). The longest exposure (including interruptions) has been 283.2 hours (~ 12 days).

Table 6-3

## Nesiritide Safety Database

Total Exposure	Number of Patients
Total Nesiritide Exposure	<b>787</b>
Pharmacology studies (literature)	258
Natreacor® (non-CHF study)	24
Natreacor® CHF studies	505
<b>Dosing Duration</b>	
Natreacor® CHF patients	<b>505</b>
IV Bolus (≤ 24 hours):	111
Infusion for:	
< 24 hours	151
24–72 hours	193
72–120 hours	38
> 120 hours	12

Table 6-4

## Subject Exposure to Natreacor® by Mean Dose

	Mean Dose of Natreacor® (µg/kg/min)				Total
	< 0.015	≥ 0.015 – < 0.020	0.020 – < 0.035	> 0.035	
Number of subjects exposed to dose	33	157	162	42	394
% of all subjects who received an infusion (n = 394)	8%	40%	41%	11%	100%

### 6.2.3 *Baseline Demographics and Medical History*

Baseline demographic information pertaining to the Long Infusion Studies population (studies 704.311, 704.325, and 704.326) is presented in Table 6-5. This particular study population was selected since it best represents the target population that would receive Natreacor® in clinical practice. These study protocols had the fewest restrictions on inclusion and exclusion criteria and, generally, involved at least a 24-hour infusion of Natreacor® within the recommended dose range (0.015 to 0.03 µg/kg/min). The table demonstrates that these studies included a high percentage of subjects who were elderly or female. Approximately 50% of subjects had heart failure due to ischemic cardiomyopathy and 94% of subjects had NYHA Class III or IV CHF.

Table 6-5

**Studies 704.311, 704.325, and 704.326**  
**Demographics**  
**Long Infusion Studies**

Factor	All Subjects* (n = 509)	Control (n = 173)	Natrecor® µg/kg/min	
			0.015 (n = 169)	0.03 (n = 167)
<b>Demographics</b>				
Mean Age (yrs):	61	61	61	63
≥ 65	216 (42%)	70 (40%)	69 (41%)	77 (46%)
% Female	149 (29%)	46 (27%)	49 (29%)	54 (32%)
<b>CHF Etiology</b>				
Ischemic	264 (52%)	89 (51%)	88 (52%)	87 (52%)
<b>NYHA Class</b>				
II	30 (6%)	8 (5%)	8 (5%)	14 (8%)
III	285 (56%)	107 (62%)	97 (57%)	81 (49%)
IV	193 (38%)	58 (34%)	64 (38%)	71 (43%)

\* Subjects dosed at 0.06 µg/kg/min Natrecor® are not included.

In Studies 704.325 and 704.326, additional information about the subjects' baseline medical history was collected since patients with comorbidities which are common in CHF patients were permitted to enroll in these studies. Table 6-6 demonstrates that a high percentage of subjects in these studies had a history of hypertension, a previous myocardial infarction, diabetes, chronic renal insufficiency, atrial fibrillation, and ventricular arrhythmias.

Table 6-6

**Studies 704.325 and 704.326**  
**Medical History**

Factor	All Subjects (n = 432)	Control (n = 144)	Natrecor® µg/kg/min	
			0.015 (n = 146)	0.03 (n = 142)
<b>Medical History</b>				
Hypertension	278 (64%)	88 (61%)	96 (66%)	94 (66%)
Previous MI	224 (52%)	76 (53%)	78 (53%)	70 (49%)
Diabetes	179 (41%)	61 (42%)	58 (40%)	60 (42%)
Chronic renal insufficiency	150 (35%)	51 (35%)	45 (31%)	54 (38%)
<b>Arrhythmias</b>				
Atrial fibrillation	172 (40%)	62 (43%)	55 (38%)	55 (39%)
Frequent PVC	155 (36%)	50 (35%)	53 (36%)	52 (37%)
Nonsustained VT	105 (24%)	32 (22%)	38 (26%)	35 (25%)
Sustained VT	35 (8%)	10 (7%)	7 (5%)	18 (13%)

#### 6.2.4 *Concomitant Cardiac Medications*

Table 6–7 demonstrates that cardiac medications that are commonly used in general practice to treat patients with CHF were also commonly administered during infusion of Natrecor®. It should be noted that, in Study 704.311, medications other than diuretics, digoxin, or antiarrhythmics were not permitted.

**Table 6–7**

**Studies 704.311, 704.325, and 704.326  
Concomitant Cardiac Medications  
Long Infusion Studies**

Medication	Natrecor® Subjects* (n = 362)	
Diuretics	244	(67%)
Digoxin	210	(58%)
ACE inhibitors	160	(44%)
Non-IV nitrates	97	(27%)
Class III antiarrhythmics	51	(14%)
Calcium channel blockers	33	(9%)
β-blockers	20	(6%)
Other antiarrhythmics	12	(3%)
Angiotensin II receptor antagonists	16	(4%)
Hydralazine	14	(4%)

\* Includes all dose groups

#### 6.3 *Mortality*

A total of 28 deaths occurred in all treatment groups during the protocol-specified reporting periods of all Natrecor® CHF clinical studies. An additional six deaths which occurred after the study reporting periods were reported to the Sponsor. Three of the additional deaths occurred in subjects who had received placebo only and the other three additional deaths occurred in subjects who had received Natrecor®.

In both placebo-controlled and active-controlled studies, there was no evidence of an increase in mortality with Natrecor® use. The reported cause of death for most patients was generally end-stage CHF or a related event such as cardiac arrest, sudden death, or arrhythmias.

No deaths occurred during Natrecor® administration or that were believed to be associated with Natrecor® administration. Figure 6–1 presents the Kaplan-Meier estimates of mortality for the Placebo-controlled Studies and the Long Infusion Studies (includes all dose groups). Note that 15-day mortality is presented for the Placebo-Controlled Studies since all of the protocols specified a 2-week follow up period. For the Long Infusion Studies, 21-day mortality is presented since the protocol-specified follow up periods were either two weeks

(study 704.311) or 3 weeks (studies 704.325 and 704.326). In study 704.311, 21 day follow up information was available for 97 of the 103 total subjects. Four placebo subjects and 2 Natrecor® subjects were censored. Table 6–8 shows the numbers of deaths which occurred.

Figure 6–1

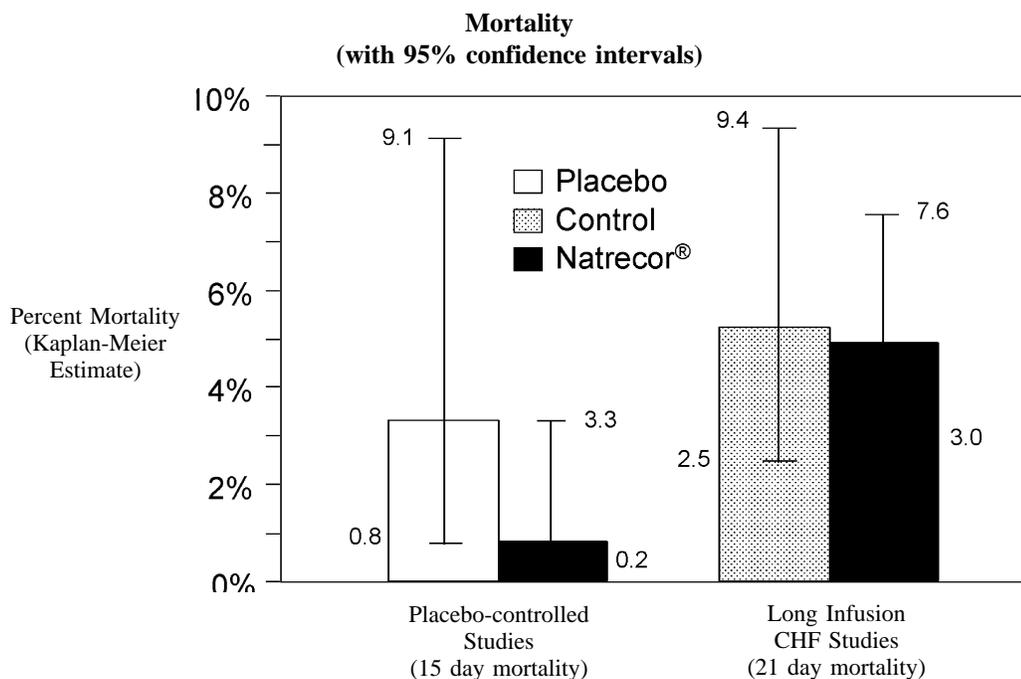


Table 6–8

**Mortality**

	Control	Natrecor®	Treatment Inference <sup>a</sup>
<b>Placebo-Controlled Studies<sup>b</sup></b>	<b>n = 91</b>	<b>n = 217</b>	
Deaths through Day 15	3	2	
15-Day Mortality Rate	3.3%	0.9%	p = 0.269
95% CI	(0.8%, 9.1%)	(0.2%, 3.3%)	(-6.6%, 1.8%)
<b>Long Infusion Studies<sup>c</sup></b>	<b>n = 173</b>	<b>n = 362</b>	
Deaths through Day 21	9	18	
21-Day Mortality Rate	5.3%	5.0%	p = 0.895
95% CI	(2.5%, 9.4%)	(3.0%, 7.6%)	(-4.4%, 3.8%)

Mortality estimation and inference are based on Kaplan-Meier methods and Peto's estimate of variance.

<sup>a</sup> Test of the equality of mortality rates, and 95% CI on rate differences (Natrecor®-Control).

<sup>b</sup> All subjects were observed through Day 15; no observations were censored.

<sup>c</sup> All subjects in studies 704.325 and 704.326 were observed through Day 21; 4 control subjects and 2 Natrecor® subjects from study 704.311 were censored between Day 15 and Day 21.

#### **6.4 Adverse Events in Clinical Trials**

From the 721 patients enrolled in the All CHF studies, all adverse events reported in 2.5% or more of Natrecor<sup>®</sup> subjects through day 14 are shown in Table 6–9. Hypotension, bradycardia, confusion, nervousness, and sweating occurred somewhat more frequently in the Natrecor<sup>®</sup> groups than in the control group ( $p < 0.05$ ), which is comprised of both placebo and active control groups. In addition, there is a suggestion that nausea and increased creatinine occurred more frequently with Natrecor<sup>®</sup>, although the differences were not statistically significant. It is notable that arrhythmias, worsening CHF, and electrolyte abnormalities were not more common in the Natrecor<sup>®</sup> group.

**Table 6-9**  
**All CHF Studies**  
**Adverse Events<sup>1</sup> Through Day 14**  
**(Number [Percent] of Subjects)**

<b>Body System/Adverse Events</b>	<b>Control (n = 235)</b>		<b>Natrecor® (n = 505)</b>		<b>p value<sup>2</sup></b>
<b>Cardiovascular</b>					
hypotension	35	(15%)	152	(30%)	< 0.001
symptomatic hypotension	16	(7%)	76	(15%)	0.001
ventricular tachycardia	36	(15%)	75	(15%)	0.912
sustained ventricular tachycardia	6	(3%)	9	(2%)	0.576
worsening congestive heart failure	20	(9%)	48	(10%)	0.785
angina pectoris	11	(5%)	36	(7%)	0.257
ventricular extrasystoles	13	(6%)	22	(4%)	0.464
bradycardia	2	(1%)	26	(5%)	0.003
atrial fibrillation	5	(2%)	14	(3%)	0.804
<b>Body as a Whole</b>					
headache	43	(18%)	80	(16%)	0.398
pain	19	(8%)	50	(10%)	0.498
catheter pain	16	(7%)	42	(8%)	0.558
abdominal pain	16	(7%)	38	(8%)	0.879
back pain	16	(7%)	26	(5%)	0.395
noncardiac chest pain	8	(3%)	28	(6%)	0.271
fever	12	(5%)	21	(4%)	0.569
asthenia	8	(3%)	19	(4%)	1.000
sepsis	6	(3%)	14	(3%)	1.000
<b>Digestive</b>					
nausea	29	(12%)	90	(18%)	0.067
vomiting	15	(6%)	44	(9%)	0.310
constipation	18	(8%)	25	(5%)	0.176
diarrhea	13	(6%)	21	(4%)	0.451
dyspepsia	6	(3%)	22	(4%)	0.302
<b>Nervous</b>					
insomnia	19	(8%)	58	(11%)	0.196
dizziness	16	(7%)	43	(9%)	0.469
anxiety	11	(5%)	28	(6%)	0.725
confusion	5	(2%)	33	(7%)	0.011
nervousness	3	(1%)	23	(5%)	0.030
<b>Respiratory</b>					
dyspnea	15	(6%)	40	(8%)	0.548
cough increased	5	(2%)	20	(4%)	0.275
<b>Metabolic and Nutritional</b>					
hypokalemia	10	(4%)	20	(4%)	0.843
BUN increased	7	(3%)	15	(3%)	1.000
<b>Urogenital</b>					
creatinine increased	7	(3%)	29	(6%)	0.141
urinary tract infection	8	(3%)	15	(3%)	0.821
oliguria	2	(1%)	13	(3%)	0.164
<b>Skin and Appendages</b>					
sweating	3	(1%)	21	(4%)	0.044
pruritis	4	(2%)	15	(3%)	0.454
<b>Musculoskeletal</b>					
leg cramps	11	(5%)	13	(3%)	0.179

1 Occurring in 2.5% or more of Natrecor® subjects

2 Fisher's Exact Test

Table 6–10 summarizes by treatment group the incidence of selected adverse events during the first 24 hours in the Long Infusion Studies (Studies 704.311, 704.325, 704.326). These three studies best represent the target population for Natrecor® and subjects generally were treated for at least 24 hours using the recommended dose range for labeling (0.015 to 0.03 µg/kg/min). The adverse events shown are those which tended to consistently occur more frequently in Natrecor® subjects than control subjects or selected events that are important in CHF patients.

**Table 6–10**

**Studies 704.311, 704.325, and 704.326  
Selected Adverse Events by Dose Group  
During the First 24 Hours of Infusion**

Adverse Events	Control (n = 173)	Natrecor® µg/kg/min		p value*
		0.015 (n = 169)	0.03 (n = 167)	
Symptomatic Hypotension	6 (3%)	14 (8%)	23 (14%)	0.003
Bradycardia	0 (0%)	6 (4%)	9 (5%)	0.003
Nausea	9 (5%)	17 (10%)	19 (11%)	0.092
Increased Creatinine	1 (1%)	3 (2%)	4 (2%)	0.331
Sustained VT	2 (1%)	1 (1%)	0 (0%)	0.777
Cardiac Arrest	1 (1%)	0 (0%)	0 (0%)	1.000
Ventricular Extrasystoles	6 (3%)	7 (4%)	4 (2%)	0.713
Headache	21 (12%)	16 (9%)	9 (5%)	0.086

\* Fisher's Exact Test

As shown in Table 6–10, the frequency of symptomatic hypotension appears to be dose-related. Adverse events other than symptomatic hypotension, which tended to be associated with Natrecor® administration during the first 24 hours of infusion, such as bradycardia, nausea, and increased creatinine, did not tend to occur more frequently in the 0.03 µg/kg/min Natrecor® group than in the 0.015 µg/kg/min Natrecor® group.

If one considers observations from study 704.311 only, which studied Natrecor® doses up to 0.06 µg/kg/min, the frequency of symptomatic hypotension during study drug administration in the 0.015, 0.03, and the 0.06 µg/kg/min dose groups was 5%, 4%, and 15%, respectively. Nausea occurred in 9%, 0%, and 15% of subjects receiving the 3 respective doses.

Selected adverse events are discussed in more detail in the ensuing sections.

#### ***6.4.1 Reductions in Blood Pressure***

A continuous infusion of Natrecor® is associated with dose-related decreases in blood pressure. For example, 6 hours after the start of study drug infusion in study 704.325 (n = 127), the mean change in systolic blood pressure in the placebo and the 0.015 and 0.03 µg/kg/min

Natrecor<sup>®</sup> dose groups was +0.3, -4.4, and -9.3 mm Hg ( $p = 0.001$ , omnibus F-test). A decrease in blood pressure is a desired effect of Natrecor<sup>®</sup>, in that a reduction of systemic arterial pressures (due to afterload reduction) contributes to an increase in cardiac output in patients with CHF. An excessive decrease in blood pressure is an intrinsic risk of any vasodilator and is inextricably linked to its mechanism of action. It is therefore unlikely that the benefits of vasodilators (such as preload and afterload reduction) could be derived without exposing some patients to a reduction in blood pressure that is greater than desired.

Hypotension, the most frequent adverse event associated with Natrecor<sup>®</sup> administration, is therefore an extension of the drug's pharmacologic effect as a potent vasodilator. To interpret the clinical significance of the incidence of hypotension, it should be remembered that in the Natrecor<sup>®</sup> development program, there was no prespecified definition for the adverse event of "hypotension." Therefore, the reporting of hypotension as an adverse event does not reflect a drop in blood pressure of a defined magnitude or necessarily a clinically relevant adverse event. In some studies, the protocol mandated that the study drug infusion be reduced in response to a decrease in systolic blood pressure below 80–85 mm Hg and that, in such a case, hypotension should be reported as an adverse event on the Case Report Form regardless of its clinical impact. In actual clinical practice, dose adjustment in response to a decrease in blood pressure is considered a conventional way in which to administer a vasoactive agent — not necessarily an adverse experience. For this reason, most of the remaining discussion will focus on symptomatic hypotension (i.e., a decrease in blood pressure accompanied by symptoms or signs of excessively decreased blood pressure) only.

To help illuminate how changes in blood pressure during Natrecor<sup>®</sup> administration may relate to symptomatic hypotension, Tables 6–11 and 6–12 were devised. Table 6–11 summarizes the maximum decrease in systolic blood pressure that occurred at any time during the first 24 hours of infusion in subjects from the Long Infusion studies (studies 704.311, 704.325, and 704.326). Table 6–12 summarizes the same information from the subset of subjects from those studies who experienced symptomatic hypotension during the first 24 hours. Both tables also show the numbers of subjects whose minimum systolic blood pressure was within various blood pressure ranges.

Examination of Tables 6–11 and 6–12 together demonstrates some important points. From the entire study population summarized in Table 6–11, it is clear that most Natrecor<sup>®</sup> subjects (regardless of dose) maintain a blood pressure that is at least 90 mm Hg. Subjects who experienced symptomatic hypotension in the control and the 0.015  $\mu\text{g}/\text{kg}/\text{min}$  dose groups tended to have somewhat lower baseline blood pressure than the whole treatment group cohort. Maximum decreases in blood pressure appear to be dose-related. However, the maximum decreases in blood pressure for the 0.015  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> dose group were not much greater than those of the control group (difference of 7 mm Hg). Finally, the fact that there were several subjects who experienced a minimum systolic blood pressure as low as 70 mm Hg without experiencing symptoms suggests that there is no minimum blood pressure or range of blood pressures that is reliably predictive of symptomatic hypotension.

Table 6–11

**Minimum Systolic Blood Pressure During First 24 Hours  
All Subjects  
(Studies 704.311, 704.325, and 704.326)**

	Natrecor® µg/kg/min			p value <sup>2</sup>
	Control (n = 173)	0.015 (n = 169)	0.03 (n = 167)	
Baseline SBP <sup>1</sup>	116	117	116	0.666
range	84–181	79–198	79–205	
Maximum decrease in SBP <sup>1</sup>	15	22	24	< 0.001
Minimum SBP <sup>1</sup>	101	95	92	< 0.001
Subjects with minimum SBP:				
≥ 100 mm Hg	98 (56%)	64 (38%)	58 (35%)	
90–99 mm Hg	46 (27%)	51 (30%)	44 (26%)	
80–89 mm Hg	24 (14%)	40 (24%)	36 (22%)	
70–79 mm Hg	3 (2%)	13 (8%)	19 (11%)	
< 70 mm Hg	1 (1%)	1 (1%)	10 (6%)	

<sup>1</sup> mm Hg, treatment group medians

<sup>2</sup> Kruskal-Wallis test

Table 6–12

**Minimum Systolic Blood Pressure During First 24 Hours  
Subjects with Symptomatic Hypotension  
(Studies 704.311, 704.325, and 704.326)**

	Natrecor® µg/kg/min			p value <sup>2</sup>
	Control (n = 6)	0.015 (n = 14)	0.03 (n = 23)	
Baseline SBP <sup>1</sup>	110	105	120	0.027
range	90–134	90–150	81–170	
Maximum decrease in SBP <sup>1</sup>	20	27	40	0.005
Minimum SBP <sup>1</sup>	90	80	78	0.244
Subjects with minimum SBP:				
≥ 100 mm Hg	2	0	2	
90–99 mm Hg	1	2	3	
80–89 mm Hg	1	6	5	
70–79 mm Hg	1	6	6	
< 70 mm Hg	1	0	7	

<sup>1</sup> mm Hg, treatment group medians

<sup>2</sup> Kruskal-Wallis test

In order to better understand and describe the clinical impact of symptomatic hypotension during Natrecor® therapy, additional summaries were prepared. Table 6–13 summarizes several clinical characteristics of the symptomatic hypotension that occurred during the first 24 hours of infusion of the 0.015 and 0.03 µg/kg/min Natrecor® doses in the Long Infusion Studies. The onset of symptomatic hypotension rarely occurred within 1 hour after the start of the infusion. It occurred between 1 to 6 hours after the start of Natrecor® in approximately half of cases.

Table 6–13

**Studies 704.311, 704.325, and 704.326**  
**Clinical Characteristics of First Onset of Symptomatic Hypotension Within the First 24 Hours**  
**Number of Subjects With Symptomatic Hypotension**

	Natrecor® (µg/kg/min)	
	0.015 (n = 169)	0.03 (n = 167)
<b>Subjects with Symptomatic Hypotension</b>	14	23
<b>Time of Onset</b>		
< 1 hour	0	1
1– < 3 hours	4	3
3– < 6 hours	3	7
6–24 hours	7	11
unknown	0	1
<b>Severity</b>		
Mild	5	4
Moderate	9	12
Severe	0	7
<b>Duration</b>		
≤ 30 minutes	5	5
31–60 minutes	2	5
61–120 minutes	2	2
> 2–7 hours	4	8
> 7 hours	1	3
<b>Greatest Impact on Dosing</b>		
No effect on Natrecor® dose	3	1
Dose decreased	3	8
Discontinued	8	14
<b>Dobutamine/Dopamine Added</b>	0	3

As shown in Table 6–13, within the first 24 hours of therapy with 0.015 µg/kg/min of Natrecor®, symptomatic hypotension occurred in 14 (8%) subjects. All of these cases were described as mild or moderate in severity. Three of the cases were managed with no change in the Natrecor® dose, 3 resulted in a dose decrease, and 8 cases ultimately resulted in the discontinuation of Natrecor®. None of these cases were considered emergencies and only 1 of the discontinuations occurred immediately after the onset of symptomatic hypotension. The other 7 discontinuations occurred sometime between 1.5 and 20 hours after the onset of symptomatic hypotension, suggesting that patients did not deteriorate precipitously. Most cases were resolved within a few minutes to a couple hours after the onset of symptomatic hypotension. No pressors were administered. These data suggest that with the 0.015 µg/kg/min dose of Natrecor®, symptomatic hypotension should be easily detected with routine blood pressure monitoring and easily managed with dose adjustment or discontinuation of Natrecor®, if necessary.

Table 6–13 shows that symptomatic hypotension was more frequently observed with the 0.03 µg/kg/min dose and tended to be more often described as moderate or severe. Most cases of symptomatic hypotension categorized as severe occurred during infusion of this dose. Ultimate dose discontinuation occurred in nearly two-thirds of the cases and a decrease in the Natrecor® dose occurred in one-third of cases. As with the 0.015 µg/kg/min dose of Natrecor®, most cases of symptomatic hypotension were resolved within a few minutes to a few hours after their onset. Dobutamine or dopamine was administered in response to symptomatic hypotension in 3 of the 23 cases that occurred with the 0.03 µg/kg/min dose. These data suggest that, although symptomatic hypotension may be more frequent with the 0.03 µg/kg/min dose and may require more intervention than the lower dose, this potential adverse event can also be safely managed with routine blood pressure monitoring and dose adjustment or ultimate discontinuation of Natrecor®, if necessary, in most patients.

Table 6–14 summarizes the frequency of symptomatic hypotension by subgroups based on age, gender, NYHA class, CHF etiology, and baseline systolic blood pressure. There does not appear to be a difference in the frequency of symptomatic hypotension based on age, gender, NYHA class, or CHF etiology during Natrecor® therapy. In particular, there does not appear to be a clear relationship between baseline systolic blood pressure and the incidence of symptomatic hypotension although blood pressure should be monitored in all patients.

**Table 6–14**  
**Studies 704.311, 704.325, and 704.326**  
**Symptomatic Hypotension Reported Within the First 24 Hours,**  
**by Demographic Subgroup and Baseline Systolic Blood Pressure**  
**(Long Infusion Population)**

Subgroup	Control	All Natrecor®	Natrecor® (µg/kg/min)	
			0.015	0.03
<b>All Subjects</b>	3% (6/173)	11% (37/336)	8% (14/169)	14% (23/167)
<b>Age</b>				
< 65 years old	5% (5/103)	11% (21/190)	8% (8/100)	14% (13/90)
≥ 65 years old	1% (1/70)	11% (16/146)	9% (6/69)	13% (10/77)
<b>Gender</b>				
male	4% (5/127)	9% (20/233)	8% (9/120)	10% (11/113)
female	2% (1/46)	17% (17/103)	10% (5/49)	22% (12/54)
<b>NYHA Class</b>				
III	5% (5/107)	11% (20/178)	9% (9/97)	14% (11/81)
IV	2% (1/58)	11% (15/135)	6% (4/64)	15% (11/71)
<b>CHF Etiology</b>				
Ischemic	2% (2/89)	10% (18/175)	9% (8/88)	11% (10/87)
IDC <sup>1</sup>	5% (2/38)	16% (12/75)	10% (4/40)	23% (8/35)
<b>Baseline SBP<sup>2</sup></b>				
≤ 100 mm Hg	9% (3/34)	10% (6/59)	19% (5/26)	3% (1/33)
101–139 mm Hg	3% (3/115)	12% (24/199)	8% (8/101)	16% (16/98)
≥ 140 mm Hg	0% (0/23)	7% (5/67)	3% (1/35)	13% (4/32)

<sup>1</sup> Idiopathic, dilated cardiomyopathy

<sup>2</sup> Systemic systolic blood pressure

In summary, Natrecor<sup>®</sup> is a potent vasodilator and generally results in a desired reduction in preload and afterload. In some patients, excessive vasodilatation may result in symptomatic hypotension. However, no long-term or significant adverse sequelae such as myocardial infarction, stroke, or death have been associated with Natrecor<sup>®</sup>-induced hypotension to date. The majority of subjects tolerate moderate dose-related decreases in blood pressure well and experience an overall beneficial clinical response to Natrecor<sup>®</sup> therapy. Natrecor<sup>®</sup> should be administered in a clinical setting in which blood pressure can be adequately monitored and dose reduction instituted as clinically indicated.

## **6.4.2 *Arrhythmias***

### **6.4.2.1 *Bradycardia***

The natriuretic peptides are believed to modulate autonomic tone, including both decreasing sympathetic and increasing parasympathetic tone. This may explain why reflex tachycardia, an undesirable feature of therapy with other vasodilators, does not accompany Natrecor<sup>®</sup> infusion. It may also contribute to a low but increased incidence of reported bradycardia during Natrecor<sup>®</sup> infusion. When Natrecor<sup>®</sup> was administered at doses of 0.015 and 0.03 µg/kg/min, bradycardia (i.e., reported events of bradycardia, sinus bradycardia, or junctional bradycardia) was reported during therapy (or within 1.5 hours after discontinuation of Natrecor<sup>®</sup>) in 4% and 6% of subjects, respectively. These events have generally resolved spontaneously or have been self-limited after discontinuation of Natrecor<sup>®</sup>. No reports of bradycardia were noted among the 26 subjects who received the 0.06 µg/kg/min dose of Natrecor<sup>®</sup>. It is important to note that Natrecor<sup>®</sup> does not appear to be associated with an increased incidence of AV node conduction abnormalities, such as first degree, second degree, or complete heart block.

Table 6–15 summarizes the 7 cases of bradycardia that were reported during treatment with the 0.015 µg/kg/min dose of Natrecor<sup>®</sup>. Bradycardia associated with this dose is usually asymptomatic and short-lived, and usually resolves spontaneously. For example, five of the 7 cases were classified as mild. The 2 other cases were described as moderate, probably because both cases were associated with hypotension (systolic blood pressure was 71 and 84 mm Hg for these 2 cases). One case that involved bradycardia and hypotension ultimately resulted in discontinuation of Natrecor<sup>®</sup>. No case required the administration of atropine or pressors.

Table 6-15

Bradycardia Reported During Infusion of 0.015 µg/kg/min Natrecor®

Patient Number	AE Verbatim	Hour of Onset	Total Hours on Natrecor®	AE Duration (hrs)	AE Severity	AE Action	Effect on Natrecor® Dosing	BL HR	HR with Bradycardia	BL SBP	Hypotension with Bradycardia?	Minimum SBP	Relevant Concomitant Medications
369019	ASYMPTOMATIC BRADYCARDIA	19	24	1 min	mild	none	none	90	unknown	100	no	80	furosemide, digoxin, enalapril
533002	SYMPTOMATIC BRADYCARDIA	20.22	26.08	intermittent for 13 hours	moderate	none	discontinued 5.5 hours after onset of event	74	unknown, minimum known HR = 70	107	yes	71	furosemide, amiodarone, digoxin, isosorbide mononitrate, lisinopril
535005	BRADYCARDIA	8.25	13.5	4 minutes	mild	none	interrupted, restarted at half dose	127	58	150	no	101	losartan, digoxin, nitroglycerin patch
554001	BRADYCARDIA (ASYMPTOMATIC)	1.45	24.03	1 minute	mild	none	none	76	44	93	no	85	furosemide, zaroxolyn, captopril, digoxin
554037	BRADYCARDIA	2.5	15.58	1 minute	moderate	none	none	66	42	99	yes	84	furosemide, captopril, isosorbide dinitrate, metoprolol, sublingual nitroglycerin
587003	BRADYCARDIA	25	72.42	a few minutes	mild	digoxin discontinued	none	64	unknown, minimum known HR 60	150	no	132	furosemide, captopril, digoxin
369001	ASYMPTOMATIC 2.2 SECOND PAUSE	3.33	50	1 min	mild	none	none	73	NA	112	no	100	captopril, digoxin, isosorbide mononitrate

Bradycardia was reported during therapy (or within 1.5 hours after discontinuation of therapy) with the 0.03 µg/kg/min dose of Natrecor® in 9 subjects. Six of these cases were described as bradycardia or sinus bradycardia, two were reported as junctional bradycardia, and one was an idioventricular rhythm. In general, since hypotension was more frequent with the higher dose of Natrecor®, bradycardia associated with this dose was also more likely to be associated with hypotension and to result in discontinuation of Natrecor®. One of the 9 cases resulted in the administration of atropine.

Possible explanations for the bradycardia that occurs in the setting of hypotension with Natrecor® include alterations in autonomic tone or, more rarely, the Bezold-Jarisch reflex. Although the precise mechanism of the Bezold-Jarisch reflex is not known, it is generally believed that rapid decreases in cardiac preload stimulate ventricular C fibers which, in turn, cause bradycardia either by increased parasympathetic tone and/or decreased sympathetic tone. A similar mechanism has been implicated with nitroglycerin therapy, rapid hemorrhage, or with syncope that results during tilt-table testing.

Table 6–16 summarizes the frequency of reported bradycardia by subgroups based on age, gender, NYHA class, and CHF etiology. There does not appear to be a clear difference in the frequency of bradycardia based on age, gender, NYHA class, or CHF etiology. Bradycardia occurring with the 0.03 µg/kg/min dose may occur more commonly in the elderly. The table also suggests that subjects with a baseline heart rate less than 80 beats per minute may experience bradycardia during Natrecor® therapy more frequently than patients with a higher baseline heart rate.

Table 6–16

**Studies 704.311, 704.325, and 704.326**  
**Bradycardia<sup>1</sup> Reported Within the First 24 Hours**  
**by Demographic Subgroup and Baseline Heart Rate**  
**(Long Infusion Population)**

Subgroup	All Natrecor <sup>®</sup>	Natrecor <sup>®</sup> (µg/kg/min)	
		0.015	0.03
<b>All Subjects</b>	4% (15/336)	4% (6/169)	5% (9/167)
<b>Age</b>			
< 65 years old	3% (5/190)	3% (3/100)	2% (2/90)
≥ 65 years old	7% (10/146)	4% (3/69)	9% (7/77)
<b>Gender</b>			
male	4% (9/233)	2% (2/120)	6% (7/113)
female	6% (6/103)	8% (4/49)	4% (2/54)
<b>NYHA Class</b>			
III	3% (6/178)	3% (3/97)	4% (3/81)
IV	5% (7/135)	5% (3/64)	6% (4/71)
<b>CHF Etiology</b>			
Ischemic	4% (7/175)	3% (3/88)	5% (4/87)
IDC <sup>2</sup>	4% (3/75)	5% (2/40)	3% (1/35)
<b>Baseline HR<sup>3</sup></b>			
≥ 80 bpm	3% (6/200)	2% (2/100)	4% (4/100)
< 80 bpm	7% (9/126)	6% (4/63)	8% (5/63)

<sup>1</sup> Includes bradycardia, sinus bradycardia, or nodal arrhythmia.

<sup>2</sup> Idiopathic, dilated cardiomyopathy.

<sup>3</sup> Heart rate; beats per minute.

Table 6–17 summarizes the frequency of bradycardia occurring by subgroups that were administered digoxin and beta-blockers during study drug therapy. The table summarizes data from studies 704.325 and 704.326 only since the use of these medications was permitted in these studies. Bradycardia may be more frequent in Natrecor<sup>®</sup> patients who are also taking digoxin. It is difficult to draw any conclusions about the frequency of bradycardia in subjects concomitantly administered beta-blockers, since both the use of beta-blockers and the number of bradycardic events in subjects who received beta-blockers were low. The low use of beta-blockers during Natrecor<sup>®</sup> therapy corresponds to the low chronic use of beta-blockers in these patients (only 10% of subjects were receiving beta-blockers chronically).

Table 6–17

**Studies 704.325 and 704.326**  
**Frequency of Bradycardia<sup>1</sup> Reported During the First 24 Hours,**  
**by Concomitant Medication Use<sup>2</sup>**

Subgroup	All Natrecor® (n = 288)	Natrecor® (µg/kg/min)	
		0.015 (n = 146)	0.03 (n = 142)
<b>Digoxin</b>			
yes	7% (10/142)	7% (5/74)	7% (5/68)
no	4% (3/72)	3% (1/31)	2% (1/41)
<b>Beta-Blockers</b>			
yes	8% (2/26)	6% (1/18)	13% (1/8)
no	5% (12/258)	4% (5/126)	5% (7/132)

<sup>1</sup> Includes bradycardia, sinus bradycardia, or nodal arrhythmia.

<sup>2</sup> “Yes” indicates medication was administered within 24 hours before starting study drug.

“No” indicates medication was not administered either within 24 hours before study drug or during study drug.

In summary, bradycardia occurred in approximately 5% of subjects who received Natrecor® and the frequency of bradycardia does not appear to be dose related. Bradycardia that occurred during the 0.015 µg/kg/min dose of Natrecor® was usually mild and self limited. Bradycardia that occurred with the 0.03 µg/kg/min dose of Natrecor® was more likely to be associated with hypotension and to require Natrecor® discontinuation. No patient has required placement of a pacemaker and no long-term adverse sequelae have resulted from the Natrecor®-induced bradycardia to date. Natrecor® does not appear to be associated with an increased incidence of atrioventricular (AV) node conduction abnormalities such as first degree, second degree, or complete heart block.

#### 6.4.2.2 Ventricular Arrhythmias

Natrecor® administration has not been associated with an increase in other arrhythmias such as ventricular tachycardia (VT). This appears to be the case in spite of the fact that in the two largest studies (704.325 and 704.326), subjects with ventricular ectopy or ventricular tachycardia or those treated with antiarrhythmic medications were included in the study. In fact, 50% and 30% of all subjects in the two respective studies had a history of frequent premature ventricular contractions (PVCs) before entry into the studies. A history of nonsustained VT was present in 36% and 19% of all subjects before entry in the two respective studies. This high prevalence of clinically significant ventricular arrhythmias at baseline signifies that the studies were conducted in a patient population at high risk for the manifestation of ventricular arrhythmias at any time.

In the placebo-controlled analysis population, the frequency of VT during the first 24 hours was 2% in each of the placebo and the Natrecor® treatment groups. Ventricular extrasystoles occurred in 0% and 1% of the placebo and Natrecor® groups, respectively. In the All CHF

population, through the first 24 hours of study drug administration, the frequency of VT in the control and Natrecor<sup>®</sup> groups was 7% and 5%, respectively, and the frequency of ventricular extrasystoles was 3% in each of the control and Natrecor<sup>®</sup> groups.

Thus, there does not appear to be an increased frequency of ventricular ectopy or VT with Natrecor<sup>®</sup> therapy, even in a population of subjects who exhibit a high frequency of these arrhythmias at baseline. The lack of association of Natrecor<sup>®</sup> with ventricular arrhythmias may be explained by the following corroborating points: (1) Natrecor<sup>®</sup> is not an inotrope and its activity does not depend on the generation of cyclic AMP or on stimulation of  $\beta$ -adrenergic receptors; (2) Natrecor<sup>®</sup> may decrease sympathetic and increase parasympathetic tone, as is supported by the lack of a reflex increase in heart rate or plasma norepinephrine during Natrecor<sup>®</sup> administration; (3) Natrecor<sup>®</sup> appears to improve cardiac hemodynamics without increasing myocardial oxygen consumption (as supported by the decrease in the rate-pressure product).

#### 6.4.3 Serum Creatinine

Using serum creatinine values available at the time of NDA submission, for the Natrecor<sup>®</sup> treated population as a whole, there were no clinically significant changes in serum creatinine, compared to the control group. For example, in the All CHF population, the mean change from baseline in serum creatinine at the time of the last laboratory value in the control (n = 235) and the Natrecor<sup>®</sup> (n = 505) treated groups was 0.0 mg/dL and +0.1 mg/dL, respectively (p = 0.001, [omnibus F test]). Similarly, in the Long Infusion Studies, in the control and the 0.015 and 0.03  $\mu$ g/kg/min Natrecor<sup>®</sup> groups, the mean change in serum creatinine from baseline at day 2 was -0.1, 0.0, and +0.1 mg/L, respectively (p < 0.001 [omnibus F test]), and at the last available time point was -0.1, +0.1, and +0.1 mg/dL, respectively (p = 0.001 [omnibus F test]).

Serum creatinine was further evaluated by reviewing all serum creatinine values observed during the entire study period for each subject (Table 6–18). In the Long Infusion Studies, more Natrecor<sup>®</sup> subjects than control subjects had a serum creatinine value  $\geq 2$  mg/dL and at least 50% increased from baseline **at any time during the entire study period**, and this phenomenon appeared to be dose-related. However, clinically significant renal dysfunction during the entire study period such as a greater than 100% increase in creatinine or renal failure requiring dialysis was not more frequent in Natrecor<sup>®</sup> subjects than in control subjects. After the Natrecor<sup>®</sup> NDA was submitted, the Sponsor obtained additional follow up creatinine values for patients in studies 704.325 and 704.326 only in order to determine whether the increases in creatinine were transient or not. Using this additional follow up data, Table 6–18 demonstrates that, for the subset of subjects who had a creatinine value  $\geq 2$  mg/dL and > 50% increased from baseline, there was no evidence of a higher rise in creatinine at follow up in the Natrecor<sup>®</sup> groups versus control, although the median creatinine values were still above baseline in all treatment groups.

**Table 6–18**  
**Studies 704.311, 704.325, and 704.326**  
**Changes in Serum Creatinine**  
**Long Infusion Studies**

	Natrecor® µg/kg/min		
	Control	0.015	0.03
All Subjects <sup>1</sup>	173	169	167
Baseline creatinine <sup>2</sup>	1.3	1.2	1.3
Change from baseline <sup>2</sup> (last value)	0.0	0.0	0.0
≥ 2 mg/dL and increased by > 50% <sup>1</sup>	3 (2%)	10 (6%)	17 (10%)
Change from baseline <sup>2</sup> (last value)	0.7	0.4	0.4
> 100% increased <sup>1</sup>	4 (2%)	5 (3%)	6 (4%)
Acute renal failure requiring dialysis <sup>1</sup> (704.325, 704.326 only)	3 (2%) n = 144	1 (< 1%) n = 146	4 (3%) n = 142

<sup>1</sup> number of subjects

<sup>2</sup> Median Value (mg/dL)

Using additional creatinine values obtained after NDA submission, Table 6–19 shows that the increases in creatinine were transient in almost all subjects. “Transient” is defined as a minimum creatinine observed on follow up that was not increased from baseline by more than 0.5 mg/dL. From study 704.311, there were 5 patients who met the criteria of a creatinine value ≥ 2 mg/dL and > 50% increased from baseline during the entire study period (these patients are included in Table 6–18). All of these maximum creatinine values occurred sometime between study day 17 to 29, and there were no subsequent creatinines values available for any of these cases.

Table 6–20 is provided to allow review of the creatinine data for the 25 subjects from studies 704.325 and 704.326 with rises in serum creatinine. Please note that the last column in Table 6–20 is provided to help cross reference how each case was categorized in Table 6–19.

**Table 6–19**  
**Categorization of Subjects with Increased Creatinine**  
**(Studies 704.325 and 704.326)**

Category	Control	0.015	0.03
<b>Creatinine value ≥ 2 mg/dL and &gt; 50% increased from baseline</b>	<b>2</b>	<b>9</b>	<b>14</b>
Transient <sup>1</sup>	1	7	12
Not transient <sup>2</sup>	0	0	1
Insufficient follow-up available	1	2	1

<sup>1</sup> Follow-up creatinine ≤ 0.5 mg/dL above baseline creatinine.

<sup>2</sup> Follow-up creatinine > 0.5 mg/dL above baseline creatinine.

Table 6–20

**Follow-Up Information on the Subset of Subjects  
with a Creatinine Value  $\geq 2$  mg/dL and  $> 50\%$  Increased**

Subject Number	Time on Drug (Days)	Baseline Creatinine	Maximum Creatinine <sup>1</sup>	Follow-Up Creatinine <sup>2</sup>	Comment	Categorization of Creatinine Increases
<b>Control Group</b>						
493019	3.8	1.2	2.5 (SD 5)		Dies SD 5 due to cardiopulmonary arrest and endstage ischemic cardiomyopathy.	3
543002	21	1.5	3.0 (SD 7)	1.2 (SD 30)		1
<b>Natreacor 0.015 Group</b>						
352003	4.9	1.3	2.0 (SD 6)	1.2 (SD 17)		1
382013	1.9	2	3.2 (SD 4)		80 year old receives dobutamine for 7 days up to entry into study. Patient's CHF is refractory to Natreacor®, dobutamine, dopamine, and milrinone and all treatment is withheld on SD 3. Subject dies SD 5 of end-stage heart disease and progressive renal insufficiency.	3
488004	1	1.8	5.5 (SD 5)	2.0 (SD 35)	Creatinine increase due to bladder obstruction and resolution due to treatment with foley placement.	1
498001	0.25	1.3	2.1 (SD 6)	1.5 (SD 8)		1
524004	11.8	1.9	4.1 (SD 3)	1.6 (SD 44)	Fluid depleted. Patient also treated with captopril and hydralazine.	1
536002	5	1	2.5 (SD 6)	1.0 (SD 10)		1
536013	4.5	1.8	2.7 (SD 6)	2.3 (SD 20)		1
538010	2.7	2.2	3.5 (SD 5)	3.1 (SD 6)	89 year old develops sepsis and acidosis on SD 5, is made DNR on SD 6, and dies SD 9 due to endstage heart failure, mitral regurgitation, and atrial fibrillation	3
547003	2	1	2.3 (SD 4)	1.0 (SD 13)		1
<b>Natreacor 0.03</b>						
357001	1	1.5	3.4 (SD 2)	1.3 (SD 28)	Subject with chronic pancreatitis develops small bowel obstruction 18 hours into Natreacor® infusion.	1
367004	1	1.4	2.4 (SD 5)	1.5 (SD 18)		1
373004	3.8	1.7	4.4 (SD 8)	2 (SD 12)	Hospitalized for 1 month for treatment of CHF, asthma, and renal insufficiency prior to entry into study. Received 1 month of inotrope treatment up to entry into study.	1
488001	1	0.7	2.2 (SD 4)	2.1 (SD 5)		3
524007	0.8	2.4	3.9 (SD 3)	2.7 (SD 6)		1
525002	6.5	1.3	2.1 (SD 8)	1.1 (SD 39)		1

<sup>1</sup> Within 7 after discontinuation of study drug;

<sup>2</sup> Minimum creatinine observed on follow-up.

Gray row shows the one subject whose follow-up creatinine value does not meet the definition for "transient".

Table 6–20 (cont'd)

**Follow-Up Information on the Subset of Subjects  
with a Creatinine Value  $\geq 2$  mg/dL and  $> 50\%$  Increased**

Subject Number	Time on Drug (Days)	Baseline Creatinine	Maximum Creatinine <sup>1</sup>	Follow-Up Creatinine <sup>2</sup>	Comment	Categorization of Creatinine Increases
533005	3.3	1.5	2.4 (SD 7)	1.5 (SD 15)	Subject develops urosepsis on SD 3 from an indwelling urinary catheter for treatment of chronic obstructive uropathy.	1
547001	0.1	1.2	2.1 (SD 3)	1.4 (SD 46)		1
554049	1	1.4	2.5 (SD 6)	1.2 (SD 23)		1
559001	0.9	1.6	2.7 (SD 2)	2 (SD 3)		1
561004	2	1.4	2.6 (SD 3)	1.6 (SD 4)		1
561006	2.7	1.5	2.4 (SD 8)	1.7 (SD 14)	Prerenal azotemia SD 6–11.	1
572001	0.9	1.2	3.3 (SD 8)	1.8 (SD 17)	Dobutamine begun SD 2. Subject develops atrial tachycardia SD 5 and subsequent hypotension, oliguric renal failure, MI, hyponatremia, and a GI bleed before his death on SD 20 due to endstage heart failure.	2
580006	1.2	1.5	2.3 (SD 5)	1.4 (SD 8)		1

<sup>1</sup> Within 7 after discontinuation of study drug;

<sup>2</sup> Minimum creatinine observed on follow-up.

Gray row shows the one subject whose follow-up creatinine value does not meet the definition for “transient”.

Thus, Natrecor® administration may be associated with a transient, modest increase in serum creatinine in a minority of subjects (~ 6% of Natrecor® subjects receiving the 0.015  $\mu\text{g}/\text{kg}/\text{min}$  dose) but does not appear to be associated with marked increases in serum creatinine or increases in clinically significant acute renal failure.

A number of subgroup analyses were run to evaluate possible factors that might predispose patients to exhibit a rise in creatinine with Natrecor® administration. These analyses were done in studies 704.325 and 704.326 only since these protocols had the least restrictive protocols. Table 6–21 illustrates that no clear pattern emerges. Of note, increased age, NYHA Class IV, a history of chronic renal insufficiency, baseline creatinine  $\geq 2$  mg/dL, low baseline systolic blood pressure, systolic blood pressure  $< 85$  mm Hg during the first 24 hours of therapy, or concomitant ACE inhibitor use did not appear to increase the likelihood of a rise in serum creatinine with Natrecor®.

**Table 6–21**  
**Studies 704.325 and 704.326**  
**Increased Creatinine (To a Value  $\geq 2$  mg/dL and  $> 50\%$  Increased)**  
**During Entire Study Period by Subgroup**

Subgroup	Control (n = 144)	All Natrecor® (n = 288)	Natrecor® (µg/kg/min)	
			0.015 (n = 146)	0.03 (n = 142)
<b>All Subjects</b>	1% (2/144)	8% (23/288)	6% (9/146)	10% (14 /142)
<b>Age</b>				
< 65 years old	1% (1/76)	8% (12/152)	6% (5/82)	10% (7/70)
≥ 65 years old	1% (1/68)	8% (11/136)	6% (4/64)	10% (7/72)
<b>Gender</b>				
Male	2% (2/106)	7% (14/194)	5% (5/102)	10% (9/92)
Female	0% (0/38)	10% (9/94)	9% (4/44)	10% (5/50)
<b>Race</b>				
White	2% (2/94)	9% (16/184)	4% (4/91)	13% (12/93)
Black	0 % (0/32)	10% (7/73)	13% (5/39)	6% (2/34)
<b>NYHA Class</b>				
II	0% (0/8)	11% (2/18)	0% (0/6)	17% (2/12)
III	1% (1/86)	7% (10/151)	5% (4/81)	9% (6/70)
IV	2% (1/50)	9% (11/118)	8% (5/59)	10% (6/59)
<b>History of Diabetes</b>				
Yes	3% (2/61)	9% (11/118)	5% (3/58)	13% (8/60)
No	0% (0/83)	7% (12/170)	7% (6/88)	7% (6/82)
<b>History of Hypertension</b>				
Yes	1% (1/88)	9% (17/190)	8% (8/96)	10% (9/94)
No	2% (1/56)	6% (6/98)	2% (1/50)	10% (5/48)
<b>Baseline SBP<sup>1</sup></b>				
≤ 100 mm Hg	0% (0/28)	6% (3/50)	4% (1/25)	8% (2/25)
101–139 mm Hg	2% (2/93)	7% (12/167)	5% (4/84)	10% (8/83)
≥ 140 mm Hg	0% (0/22)	13% (8/61)	13% (4/31)	13% (4/30)
<b>SBP &lt; 85 mm Hg During First 24 Hours</b>				
No	2% (2/130)	8% (16/209)	5% (6/112)	10% (10/97)
Yes	0% (0/14)	9% (9/79)	9% (3/34)	9% (4/45)
<b>Baseline Creatinine</b>				
< 2.0 mg/dL	2% (2/107)	9% (20/233)	6% (7/118)	11% (13/115)
≥ 2.0 mg/dL	0% (0/36)	6% (3/53)	7% (2/28)	4% (1/25)
<b>Baseline BUN:Cr Ratio</b>				
< 40	2% (2/132)	8% (20/258)	6% (8/136)	10% (12/122)
≥ 40	0% (0/10)	11% (3/27)	11% (1/9)	11% (2/18)
<b>ACE inhibitors<sup>2</sup></b>				
Yes	3% (2/72)	7% (11/164)	4% (4/89)	9% (7/75)
No	0% (0/43)	12% (9/77)	9% (3/33)	14% (6/44)

<sup>1</sup> systemic systolic blood pressure

<sup>2</sup> during 24 hours before study drug

In preclinical studies, there has been no observed adverse effects of Natrecor® on laboratory measures of renal function or renal histopathology even when administered at very high doses. For example, in some of these studies, Natrecor® was administered as a continuous infusion for 2 weeks to primates at doses up to 3 µg/kg/min (a dose more than 200-fold higher than the recommended clinical dose of 0.015 µg/kg/min). Thus, the transient rises in serum creatinine observed in Phase III clinical studies in some subjects with CHF is most likely not due to a direct toxic effect of Natrecor® on the kidney. This phenomenon might be related to the effect of Natrecor® inhibiting the renin-angiotensin system in a small group of patients dependent on that system's effects for adequate renal perfusion, similar to the increase in serum creatinine observed following institution of ACE inhibitor therapy in some patients.

#### 6.4.4 Summary of Clinical Safety of Natrecor®

Overall, Natrecor® is not associated with an adverse effect on mortality or on the frequency of serious adverse events. Table 6–22 demonstrates that events categorized as serious which occurred through study day 14 in the Long Infusion Studies were no more frequent for Natrecor® subjects than for control subjects.

**Table 6–22**

**Serious Adverse Events Through 14 Days  
(Studies 704.311, 704.325, and 704.326)**

Serious Adverse Event	Control (n = 173)	Natrecor® µg/kg/min		p value*
		0.015 (n = 169)	0.03 (n = 167)	
Cardiovascular	12 (7%)	9 (5%)	19 (11%)	0.110
Congestive Heart Failure	3 (2%)	3 (2%)	7 (4%)	0.280
Bradycardia	1 (1%)	0 (0%)	1 (1%)	0.774
Hypotension	1 (1%)	0 (0%)	1 (1%)	0.774
Body as a Whole	1(1%)	3 (2%)	2 (1%)	0.539
Sepsis	0 (0%)	2 (1%)	2 (1%)	0.402
Urogenital	3 (2%)	0 (0%)	2 (1%)	0.294
Acute Kidney Failure	3 (2%)	0 (0%)	1 (1%)	0.279
Kidney Function Abnormal	0 (0%)	0 (0%)	1 (1%)	0.328

\* Fisher's Exact Test

An infusion of Natrecor® has been associated with an increased frequency of symptomatic hypotension, bradycardia, and transient mild to moderate elevations of serum creatinine. To place these in context, it is useful to review the comparative safety profile of Natrecor® and those agents routinely used in the "standard care" of patients with CHF who require IV vasoactive therapy. The most appropriate database from the Natrecor NDA for this comparison is study 704.326 which was prospectively designed as a safety study and which includes over 60% of patients in the Long Infusion Studies population. Subjects were not randomized to each standard care agent, rather subjects were randomized to Natrecor® or

“standard care,” and the investigator selected the IV vasoactive agent of choice for each standard care subject. For example, of the 102 control subjects, 58 received dobutamine, 19 received milrinone, and 18 received nitroglycerin as study drug. Given the limitation of this retrospective analysis, Table 6–23 allows for a comparison of the relative frequency of symptomatic hypotension, bradycardia, and increased creatinine observed in this study, as well as other adverse events commonly associated with the comparative agents.

**Table 6–23**  
**Study 704.326**  
**Selected Adverse Events During Drug Infusion**

Adverse Event	Control				Natreacor® (µg/kg/min)	
	dobutamine (n = 58)	milrinone (n = 19)	nitroglycerin (n = 18)	All Control (n = 102)	0.015 (n = 103)	0.03 (n = 100)
Symptomatic hypotension	5%	11%	0%	5%	12%	18%
Bradycardia	2%	0%	0%	1%	6%	4%
Nausea	14%	0%	22%	12%	17%	16%
Increased creatinine	3%	0%	0%	3%	4%	4%
Sustained VT	7%	0%	0%	4%	0%	2%
Cardiac arrest	5%	0%	0%	3%	0%	0%
Ventricular extrasystoles	7%	16%	0%	7%	1%	2%
Headache	16%	16%	50%	22%	14%	10%

It is noteworthy in this regard that symptomatic hypotension was observed in 11% of patients who received milrinone and in 5% of patients who received dobutamine. Also, increased creatinine is reported as frequently in patients who received dobutamine as in those who received Natreacor®. Dobutamine is also associated with a higher incidence of serious ventricular arrhythmias such as sustained ventricular tachycardia and cardiac arrest. Nitroglycerin produced a very high incidence of headaches. (The absence of symptomatic hypotension in patients who received nitroglycerin may reflect its relative weakness as an arterial dilator.) Pooling the adverse effects in this control group had the tendency of masking many of the adverse events associated with individual agents.

### 6.5 Clinical Laboratory Evaluations

Other than the mild to moderate increases in creatinine which may occur in a small subset of patients who receive Natreacor® therapy, there are no clinically significant changes in laboratory values associated with Natreacor® therapy. Changes in laboratory parameters from baseline on or before day 2 for all placebo-controlled CHF studies are summarized in Table 6–24.

Table 6–24

**Placebo-Controlled CHF Studies**  
**Mean Change from Baseline for Laboratory Parameters on Day 2**

Chemistry/Hematology Parameter (units)	Placebo (n = 91)			Natrecor® (n = 217)			p value <sup>1</sup>
	n	Baseline	Change	n	Baseline	Change	
sodium (mEq/L)	70	137.1	-1.4	151	136.5	-1.3	0.923
potassium (mEq/L)	71	4.1	0.0	154	4.1	0.0	0.793
chloride (mEq/L)	70	99.7	-0.2	153	99.5	0.2	0.467
bicarbonate (mEq/L)	70	26.0	-0.2	152	26.0	-0.7	0.303
glucose (mg/dL)	66	146.0	-14.4	141	142.9	-7.8	0.411
blood urea nitrogen (mg/dL)	70	27.4	-4.1	153	27.6	-1.9	0.013
creatinine (mg/dL)	70	1.2	-0.1	153	1.3	0.0	0.082
uric acid (mg/dL)	61	9.0	-0.9	135	8.9	-0.4	0.019
protein, total (g/dL)	66	6.9	-0.2	143	6.8	-0.3	0.183
albumin (g/dL)	66	3.8	-0.2	142	3.7	-0.2	0.396
bilirubin, total (mg/dL)	62	1.1	0.1	131	1.2	0.0	0.513
alkaline phosphatase (U/L)	62	102.1	-2.1	131	108.1	-5.5	0.162
LDH (U/L)	60	270.5	34.9	129	308.2	2.9	0.223
AST (SGOT) (U/L)	62	31.2	-3.4	132	34.5	-6.9	0.449
ALT (SGPT) (U/L)	61	31.5	-3.0	129	33.7	-3.5	0.642
calcium (mg/dL)	63	8.9	-0.2	136	8.9	-0.2	0.817
phosphorus (mg/dL)	61	3.6	0.0	133	3.5	0.0	0.668
magnesium (mg/dL)	62	2.1	0.0	127	2.1	-0.1	0.351
WBC ( $\times 10^3/\text{mm}^3$ )	65	7.6	0.8	141	7.7	1.0	0.330
RBC ( $\times 10^6/\text{mm}^3$ )	65	4.5	-0.0	142	4.5	0.1	0.010
hemoglobin (g/dL)	65	12.9	-0.1	142	13.0	0.2	0.008
hematocrit (%)	69	38.4	-0.3	154	38.8	0.4	0.033
platelets ( $\times 10^3/\text{mm}^3$ )	64	219.2	-25.3	141	218.8	-16.7	0.040

<sup>1</sup> Omnibus F test of Natrecor® versus placebo with respect to change from baseline.

It should be noted that Natrecor® is a member of the family of peptides referred to as “natriuretic peptides” and has been shown to have modest diuretic and natriuretic properties in clinical studies in the medical literature (see section 3). Natrecor® is also known to reduce aldosterone levels. It therefore would be expected that Natrecor® therapy might result in some alterations in serum electrolytes in some patients. However, in the laboratory evaluations for the All CHF Studies and the Placebo-Controlled Study populations, there was no clinically significant difference between treatment groups with regard to changes in serum sodium or potassium or the number of subjects who had normal serum sodium or potassium levels at baseline which became abnormal at later time points. Thus, Natrecor® may have modest natriuretic properties, but this does not appear to result in clinically significant hyponatremia.

## 6.6 Assay for Anti-hBNP Antibodies

Natreacor<sup>®</sup> has an amino acid sequence identical to that of the endogenous hBNP hormone peptide and therefore would not be expected to be antigenic. Of the 505 CHF subjects treated with Natreacor<sup>®</sup>, 354 were evaluated for the development of anti-hBNP antibodies following Natreacor<sup>®</sup> administration. None of these subjects developed anti-hBNP antibodies.

Of note, 6 CHF subjects received Natreacor<sup>®</sup> in more than one clinical study and did not develop anti-hBNP antibodies upon repeat administration. These findings are consistent with the results of a preclinical study in which rabbits received 8-hour infusions of Natreacor<sup>®</sup> at monthly intervals for 3 months without the development of anti-hBNP antibodies.

## 6.7 Safety Summary of Studies from the Literature or from other Indications

Other than the 505 subjects in the Natreacor<sup>®</sup> CHF program included in the NDA, there are 258 patients who received nesiritide in studies conducted by other investigators<sup>(1-24)</sup>, and 24 patients who received Natreacor<sup>®</sup> (nesiritide) in a Scios sponsored study of post-operative hypertension.<sup>(25)</sup> In general, in these studies, the report of side effects with nesiritide was infrequent and consistent with the profile seen with Natreacor<sup>®</sup> (nesiritide) in NDA 20-920. That is, the most common adverse findings noted were related to decreases in blood pressure. Other events mentioned included bradycardia, facial itching, and a sensation of heat on the face.

There was one case report in which 3 subjects with iatrogenically-induced hypoxemia developed an apparent profound vagal response, characterized by hypotension and bradycardia, during nesiritide infusion.<sup>(14)</sup> In 2 of these cases (both healthy volunteers), prompt spontaneous recovery with no lasting symptoms ensued after discontinuation of nesiritide infusion and reversal of iatrogenically induced hypoxemia. In the third case (a 66-year-old man with exertional dyspnea and suspected diastolic dysfunction), the episode was responsive to IV fluids and atropine and had no sequelae. The etiology of these episodes was unclear, although a nonspecific autonomic response to vasodilation (known as the Bezold-Jarisch reflex) or a direct stimulation of vagal afferents was proposed.

## 6.8 Overdose Experience

In clinical studies, Natreacor<sup>®</sup> has been administered to subjects with CHF at doses as high as 0.1 µg/kg/min as a continuous infusion. At this higher dose, symptomatic hypotension was frequent.

There is no clinical experience with Natreacor<sup>®</sup> administered as an infusion at doses above 0.1 µg/kg/min. However, Natreacor<sup>®</sup> has been administered to patients with CHF as a bolus at doses up to 20 µg/kg, which achieves quite high plasma hBNP levels for a short period of time; no adverse experiences other than decreases in blood pressure accompanied this bolus administration.

In preclinical studies, Natrecor® has been administered to rats as a continuous infusion for 2 weeks at doses as high as 20 µg/kg/min (a dose more than 1000-fold higher than the recommended clinical dose) and to monkeys at doses up to 3 µg/kg/min (200-fold higher than the recommended clinical dose). A decrease in blood pressure was observed throughout the 2 week infusion period, but there was no evidence of adverse effects on clinical status, laboratory parameters, or electrocardiography.

### 6.9 Clinical Effects After Discontinuation of Natrecor®

Natrecor® is intended for use for the short-term treatment of CHF. It is important to note that Natrecor® does not appear to be associated with more bad outcomes, such as emergent intubations, hospital readmissions, or death within 21 days, versus control. Table 6–25 summarizes clinical events and outcomes which occurred both during the study hospitalization as well as after hospital discharge through day 21 in studies 704.325 and 704.326.

**Table 6–25**  
**Clinical Outcomes Within 21 Days**  
**Studies 704.325 and 704.326**

	Control (n = 144)	Natrecor® µg/kg/min		p value
		0.015 (n = 146)	0.03 (n = 142)	
During Study Hospitalization:				
Median length of stay (days)	6	6	6	0.678 <sup>1</sup>
Emergency intubations	6 (4%)	2 (1%)	7 (5%)	0.183 <sup>2</sup>
Deaths	5 (3%)	8 (5%)	6 (4%)	0.736 <sup>2</sup>
After Hospital Discharge:				
Emergency intubations	2 (1%)	1 (< 1%)	1 (< 1%)	0.849 <sup>2</sup>
Readmitted-all causes <sup>3</sup>	17 (12%)	12 (9%)	15 (12%)	0.632 <sup>2</sup>
Readmitted-recurrent CHF <sup>3</sup>	9 (7%)	5 (4%)	5 (4%)	0.534 <sup>2</sup>
Deaths	2 (1%)	0 (0%)	2 (1%)	0.402 <sup>2</sup>

1 Kruskal-Wallis

2 Fisher's Exact Test

3 Percentage of patients discharged by Day 21 presented

### 6.10 Natrecor® as a Natural Product

It is generally accepted that rare or unusual adverse reactions can be overlooked in clinical development due to the relatively small number of patients studied, compared with the much larger number exposed to drug during commercialization. In that regard, it is reassuring that hBNP is a natural product that circulates in fairly high concentration in patients with CHF. The Natrecor® peptide is identical to the endogenous peptide. Therapeutic infusions of Natrecor® in the dose range recommended in the proposed label produce plasma concentrations in the range of 2,000 to 6,000 pg/mL for the duration of the infusion. Patients with advanced

CHF who are likely to be treated with intravenous administration of Natrecor® have endogenous BNP levels in the range of several hundred pg/mL up to 1,000 pg/mL. Thus patients with CHF are continually exposed to hBNP, and administering Natrecor® to these patients increases circulating levels of the hBNP peptide. Therefore, idiosyncratic adverse reactions to exogenous BNP are far less likely than might be the case with a new chemical entity that is foreign to the body.

It is important to note that Natrecor® is metabolized and eliminated via the same mechanisms as endogenous hBNP. That is, Natrecor® is metabolized via two mechanisms: 1) binding to a natriuretic peptide clearance receptor present throughout the vasculature, and 2) proteolytic cleavage. After binding to the cell surface clearance receptor, the natriuretic peptides undergo endocytosis and intracellular lysosomal hydrolysis. The clearance receptors are then recycled to the cell surface. A second metabolic pathway for BNP (and ANP) is proteolytic cleavage and inactivation by a neutral endopeptidase (NEP24.11), which is present on the vascular luminal surface. These dual and ubiquitous clearance mechanisms add to the overall safety profile of Natrecor® since its clearance would not be significantly altered by any organ dysfunction, which often occurs in this acutely ill target population.

### **6.11 Safety Conclusions**

To date, approximately 785 subjects have received nesiritide intravenously in clinical studies. Natrecor® has been administered to a broad spectrum of patients with CHF (n = 505) in eight Scios-sponsored clinical studies. The adverse event profile of Natrecor® has been well defined and Natrecor® generally has been well tolerated when administered to patients representative of those likely to receive Natrecor® during commercialization, i.e., patients with decompensated CHF and other common significant comorbidities, such as coronary artery disease, underlying arrhythmias, and renal insufficiency. Demographic factors (age, gender, ethnicity), severity of CHF (NYHA Class III, NYHA Class IV), and renal insufficiency do not appear to markedly alter the safety profile of Natrecor®.

Natrecor® administration is associated with dose-related decreases in blood pressure. This is an expected effect of the drug, given Natrecor®'s potent vasodilating properties. These decreases in blood pressure are most often asymptomatic and often do not require intervention (or can be managed by dose reduction, if indicated). When Natrecor® is administered as a continuous infusion at a dose of 0.015 µg/kg/min, symptomatic hypotension during the first 24 hours of therapy has been reported in 8% of subjects. No long-term adverse sequelae have been clearly associated with Natrecor®-induced hypotension to date. The majority of subjects tolerate moderate dose-related decreases in blood pressure well and experience an overall beneficial clinical response to Natrecor® therapy. Natrecor® should be administered in a clinical setting in which blood pressure can be monitored and dose adjustment instituted as clinically indicated.

Other clinically significant adverse events are infrequent. During the first 24 hours after initiation of Natrecor<sup>®</sup> infusion at a dose of 0.015 µg/kg/min, the following adverse events were reported: nausea (10%), insomnia (8%), bradycardia events (4%), confusion (4%), nervousness (4%), and sweating (2%). When bradycardia occurs with the 0.015 µg/kg/min dose, it is usually mild, short-lived, and resolves spontaneously. Bradycardia which occurs with the 0.03 µg/kg/min dose is more likely to be accompanied by hypotension and to require a dose reduction or discontinuation of Natrecor<sup>®</sup>. However, no patient required placement of a pacemaker and no long-term adverse sequelae have resulted from the Natrecor<sup>®</sup>-induced bradycardia to date. Natrecor<sup>®</sup> administration has not been associated with an increase in cardiac AV node conduction abnormalities or ventricular arrhythmias and does not significantly increase heart rate.

Although Natrecor<sup>®</sup> has been shown to have mild diuretic and natriuretic properties and to lower aldosterone, Natrecor<sup>®</sup> does not appear to cause clinically significant changes in serum sodium or potassium. Moderate rises in serum creatinine at some point during the study period have been observed in approximately 6% and 10% of subjects receiving the 0.015 and 0.03 µg/kg/min dose of Natrecor<sup>®</sup>, respectively, and these increases are transient in most patients. No other significant effects on laboratory parameters have been observed.

Administration of Natrecor<sup>®</sup> does not appear to be associated with any long-term safety concerns. For example, there was no significant difference in all-cause mortality between the Natrecor<sup>®</sup> and control subjects. The length of hospitalization was comparable for Natrecor<sup>®</sup> and control subjects. Finally, after discontinuation of Natrecor<sup>®</sup> therapy, there does not appear to be an increased incidence of recurrent hospital readmissions for either all-causes or for CHF.

Thus, the clinical studies of Natrecor<sup>®</sup> support a role for Natrecor<sup>®</sup> as a safe and effective agent for the short-term treatment of CHF.

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## Item 7

### Experience with Related Compounds

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Endogenous hBNP belongs to a family of peptides which are often referred to as “natriuretic peptides.” Another recognized member of this family is ANP. Both of these peptides share a similar 17-membered ring structure but differ somewhat in their amino acid sequence and length. They are also the product of separate genes. ANP is produced primarily in the cardiac atria while BNP is produced primarily in the cardiac ventricles.

Both BNP and ANP are believed to bind to the same GC-A receptor, thereby activating cyclic GMP as a second messenger. Both also bind to the same clearance receptor. However, the pharmacokinetics of ANP and BNP differ in that BNP has a lower affinity for the natriuretic peptide clearance receptor and is more resistant to degradation by neutral endopeptidase than is ANP, resulting in lower clearance and a longer plasma half-life than ANP. A review of the safety experience with this related compound was performed while preparing the NDA for Natrecor®.

#### Anaritide

A total of 923 subjects have received anaritide, a 25-amino acid form of ANP, in clinical studies in the U.S. Intravenous anaritide has been administered to healthy volunteers as well as patients with hepatic cirrhosis, CHF, nephrotic syndrome, hypertension, chronic renal failure, acute renal failure, radio-contrast induced nephropathy, and asthma. In these studies, anaritide was administered intravenously as either a continuous infusion (at doses of 0.003 to 0.6 µg/kg/min) or as a bolus (at doses of 0.5 to 6 µg/kg). The most common adverse event observed in these studies was hypotension. In placebo-controlled studies enrolling 726 patients with acute renal failure, in which anaritide was administered for 24 hours at a dose of 0.2 µg/kg/min for treatment of acute renal failure, hypotension was reported in 50% of anaritide and 23% of placebo patients ( $p < 0.001$  [Fisher]). Tachycardia and premature ventricular contractions were each reported in 6% of anaritide patients and 2% of placebo patients ( $p \leq 0.02$  [Fisher]). No other clinically significant adverse events or changes in laboratory parameters were observed. Mortality was followed for 60 days and was comparable in the placebo and anaritide groups (42% and 44%, respectively).

### Carperitide

Carperitide, a 28-amino-acid form of ANP, was approved for marketing in Japan by Suntory Ltd. in May 1995 as an IV agent for the short-term management of acute CHF. Approval was based upon a series of clinical studies in which carperitide was administered to a total of 396 subjects, including 219 subjects with CHF. These studies demonstrated that carperitide had beneficial effects on cardiac hemodynamics, such as a reduction in preload and afterload (PCWP and SVR) and increase in cardiac output. Symptoms of CHF were also followed in some studies. The most commonly reported adverse event was hypotension, reported in 7% of CHF subjects. Bradycardia was reported in 1% of CHF subjects.

Since marketing approval in 1995, approximately 1.5 million 1-mg vials of carperitide have been sold. Assuming that each patient received the recommended dose of 0.1 µg/kg/min for approximately 48 hours, this would suggest that approximately 75,000 patients with CHF have received carperitide during commercialization in Japan to date.

Thus, in addition to the Natrecor® safety database presented in NDA 20-920, there is fairly extensive information on the safety profile of a related peptide. Review of available information on this related compound suggests a safety profile similar to that observed for Natrecor® and has not revealed any new safety issues relevant to the approval of Natrecor®.

## Item 8

### Benefit/Risk Assessment

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Natreacor<sup>®</sup> has been developed as an IV agent for the short-term treatment of CHF. Natreacor<sup>®</sup> represents a new drug class which exhibits a unique combination of beneficial hemodynamic, renal, and neurohormonal effects. Natreacor<sup>®</sup> is identical to the endogenous hBNP molecule, a naturally occurring compound that is elevated in the plasma of patients with CHF. Scientific knowledge about the pharmacology and metabolism of endogenous hBNP is applicable to Natreacor<sup>®</sup>.

#### **8.1 Natreacor<sup>®</sup> (nesiritide): Therapeutic Profile**

##### **8.1.1 Benefits**

Natreacor<sup>®</sup> is a balanced vasodilator, dilating both veins and arteries as well as coronary arteries. It has no direct inotropic activity and is not dependent on beta-adrenergic receptors or the production of cAMP for its activity. In several studies in patients with CHF, Natreacor<sup>®</sup> has been shown to:

- Significantly improve hemodynamics by reducing PCWP (a measure of preload) and SVR (a measure of afterload), thereby increasing CI;
- Improve CI by improving stroke volume index, not by increasing heart rate;
- Decrease the rate pressure product (HR times systolic BP), suggesting that Natreacor<sup>®</sup> does not increase cardiac work or myocardial oxygen consumption;
- Produce rapid hemodynamic improvement as early as 30 minutes after starting therapy with persistence of the effect through at least 24 hours of therapy (the last time point assessed with hemodynamic monitoring).
- Produce rapid and significant symptomatic improvement consistent and concurrent with hemodynamic improvement in the majority of subjects. Symptom improvement is evident both as improvement in global clinical status (as assessed by patient or physician) and with regard to specific symptoms of CHF, such as dyspnea and fatigue;
- Produce a significant reduction in levels of plasma aldosterone, and to prevent a reflex increase in levels of plasma norepinephrine, as might occur following therapy with other vasodilators;
- Produce a mild diuresis with weight loss and a reduced need for diuretic therapy during infusion with Natreacor<sup>®</sup>.

Thus, clinical studies have shown that Natrecor® possesses the desirable effects of an IV agent for the short-term treatment of CHF without many of the undesirable characteristics of existing therapeutic agents. For example, Natrecor® is not associated with an increase in heart rate, either as a reflex mechanism or as a result of direct sympathetic stimulation. Natrecor® also is not associated with an increase in mortality or increased risk of ventricular arrhythmias. Natrecor®'s activity is not dependent on beta-adrenergic receptors (such as is dobutamine), and therefore may be a useful agent for the increasing number of patients with CHF for whom beta-blockers are used as long-term therapy. Natrecor® can be used safely and effectively without invasive hemodynamic monitoring (such as a Swan-Ganz® catheter) although blood pressure should be monitored during use. Natrecor® is also effective when administered as a fixed-dose infusion, reducing the need for dose titration that is characteristic of many of the other available agents for this indication. When administered as a fixed-dose infusion at a dose of 0.015 or 0.03 µg/kg/min, Natrecor® is effective in most patients, as evidenced by rapid hemodynamic and symptom improvement, and progressive symptom improvement over the course of therapy.

### **8.1.2 Risks**

Natrecor® has been studied and generally well tolerated in the target population that would receive Natrecor® in clinical practice. In particular, the adverse event profile of Natrecor® has been very well defined within a safety database population that included a high proportion of patients with advanced CHF and a history of other comorbidities such as coronary artery disease, arrhythmias, and renal insufficiency. The following summarizes the profile of the most important adverse events that may be associated with Natrecor® therapy:

- **Hypotension:** When Natrecor® was administered at doses of 0.015 and 0.03 µg/kg/min, symptomatic hypotension was reported as an adverse event during the first 24 hours after initiation of therapy in 8% and 14% of subjects, respectively. In most cases, the decrease in blood pressure could be safely managed with dose reduction or discontinuation of infusion for a period of time. No long term or significant adverse sequelae have been associated with Natrecor®-induced hypotension to date. The majority of subjects tolerate moderate dose-related decreases in blood pressure well and experience an overall beneficial clinical response to Natrecor® therapy. Natrecor® should be administered in a clinical setting in which blood pressure can be adequately monitored and dose reduction instituted as clinically indicated.
- **Bradycardia:** The natriuretic peptides are believed to modulate autonomic tone, including both decreasing sympathetic and increasing parasympathetic tone. This may contribute to an increased incidence of reported bradycardia during Natrecor® infusion. When Natrecor® was administered at doses of 0.015 and 0.03 µg/kg/min, bradycardia (i.e., reported events of bradycardia, sinus bradycardia or nodal arrhythmia) was reported during the first 24 hours after initiation of therapy in 4% and 5% of subjects, respectively. Bradycardia which occurred during the 0.015 µg/kg/min dose generally

was short lived and resolved spontaneously. Bradycardia occurring during the 0.03 µg/kg/min dose tended to be associated with hypotension and to result in the discontinuation of Natrecor®. Natrecor® does not appear to be associated with an increased incidence of AV node conduction abnormalities, such as first degree, second degree, or complete heart block.

- **Increases in serum creatinine:** When all available serum creatinine measurements for the 21 days following initiation of therapy were reviewed, more Natrecor® patients than control patients had a modest, and usually transient increase in creatinine from baseline (to a value  $\geq 2$  mg/dL and increased by  $>50\%$ ) at some point ( $< 5\%$  of control patients, 6% to 10% of Natrecor® patients). However, clinically significant renal dysfunction such as a greater than 100% increase in creatinine or renal failure requiring dialysis was not more frequent in Natrecor® subjects than in control subjects. Of note, increased age, baseline creatinine greater than 2 mg/dL, or concomitant ACE inhibitor use did not appear to increase the likelihood of a rise in serum creatinine with Natrecor®. In preclinical toxicology studies, there is no evidence of a direct toxic effect of Natrecor® on renal function or histopathology. This laboratory phenomenon may be related to Natrecor®'s inhibition of the renin-angiotensin-aldosterone (RAAS) system in a small group of patients dependent on that system's effects for adequate renal perfusion, similar to the increase in serum creatinine observed following institution of ACE inhibitor therapy in some patients.
- **Additional Adverse Events:** Other clinically significant adverse events were infrequent. During the first 24 hours after initiation of Natrecor® infusion at a dose of 0.015 µg/kg/min, the following adverse events were reported: nausea (10%), insomnia (8%), confusion (4%), nervousness (4%), and sweating (2%).

## 8.2 *The Neurohormonal Hypothesis*

Within the framework of the neurohormonal hypothesis of CHF, Natrecor® is a therapeutic agent which makes clinical and scientific sense. Although the role of neurohormonal suppression in the acute management of CHF is not as clear as in the chronic setting, this may be due to the fact that neurohormonal suppression is not characteristic of the commercially available agents for the short-term management of CHF. Indeed, most widely used IV vasoactive agents for CHF, including dobutamine, nitroglycerin, and nitroprusside, may activate vasoconstrictive hormones. Even IV diuretics enhance hormone-mediated vasoconstriction. The potentially beneficial effect of Natrecor® on neurohormonal suppression appears to be an intrinsic property of the drug, rather than a withdrawal of reflex sympathetic activation, since a comparable improvement in cardiac hemodynamics which may occur with other vasodilating agents may be associated with activation of both the autonomic and RAAS systems.

The clinical benefits that may result from Natrecor®'s effect on neurohormonal suppression are as follows. First, the lack of a reflex tachycardia with nesiritide therapy contributes to the

decrease in the rate pressure product (the double product), suggesting that nesiritide decreases cardiac work and myocardial oxygen consumption. Second, neurohormonal suppression, as well as decreased myocardial oxygen consumption, may help to establish a cardiac environment which protects against the predisposition to ventricular arrhythmias which occur so commonly during acute hemodynamic decompensation. Improved autonomic tone with nesiritide therapy is further supported by recent evidence that the natriuretic peptides, as a drug class, favorably affect heart rate variability, an electrocardiographic measurement which estimates the relative contribution of sympathetic and parasympathetic tone to overall autonomic tone. Finally, direct neurohormonal suppression likely facilitates both venous and arterial vasodilation, leading to balanced systemic vasodilation characterized by both preload and afterload reduction.

### **8.3 *Currently Available Agents for the Short-Term Treatment of CHF and Their Limitations***

Firstline therapy for the acute management of CHF almost always includes IV diuretics. The next line of therapy includes agents which fall into two general categories: 1) the IV inotropes, including dobutamine or milrinone, and 2) the IV vasodilators, including nitroglycerin or nitroprusside. Table 8–1 summarizes the limitations of the commercially available agents for this indication.

Many of the limitations listed in Table 8–1 are shared by several of the agents. For example, hypotension is a recognized risk of all of the vasoactive agents listed. The risk of hypotension is highest with the vasodilators; nitroprusside, in particular, may require invasive hemodynamic monitoring (with a Swan-Ganz® catheter and/or arterial line) to safely administer the agent. Hypotension may also occur during milrinone and dobutamine therapy. An increase in heart rate is common during therapy with several of the agents, either due to a reflex tachycardia which may occur with the vasodilators or via a direct effect which may occur with the inotropes. The inotropes are also associated with ventricular arrhythmias and recent reports suggest that long-term intermittent therapy with inotropes may increase mortality. Tolerance is a recognized limitation of dobutamine, nitroglycerin, and diuretics.

Table 8-1

## Limitations of Commonly Used IV Agents for CHF

Limitations	Dobutamine	Milrinone	Nitroglycerin	Nitroprusside	IV Diuretics
Hypotension	+/-	+	+	+	-
Ventricular Arrhythmias	+	+	-	-	+/-
Increased Heart Rate	+	+	+	+/-	-
Neurohormone Activation	+	-	+	+/-	+
Toxic Metabolites	-	-	-	+	-
Electrolyte Abnormalities	-	-	-	-	+
Tolerance	+	-	+	-	+

In a retrospective ad hoc analysis from the safety study, Study 704.326 (n = 305), a comparison of the short-term outcomes that resulted with the Natrecor® dose groups, versus the dobutamine subgroup, suggests that Natrecor® may have a clinical advantage over dobutamine. Figures 8-1 and 8-2 show that the length of IV vasoactive therapy, all-cause readmissions, and readmissions for CHF specifically, were all reduced in the Natrecor® groups compared to the dobutamine group, although these results did not always reach statistical significance.

Figure 8-1

**Study 704.326**  
**Duration of Treatment**  
**Retrospective Subgroup Analysis: Dobutamine vs. Natrecor®**

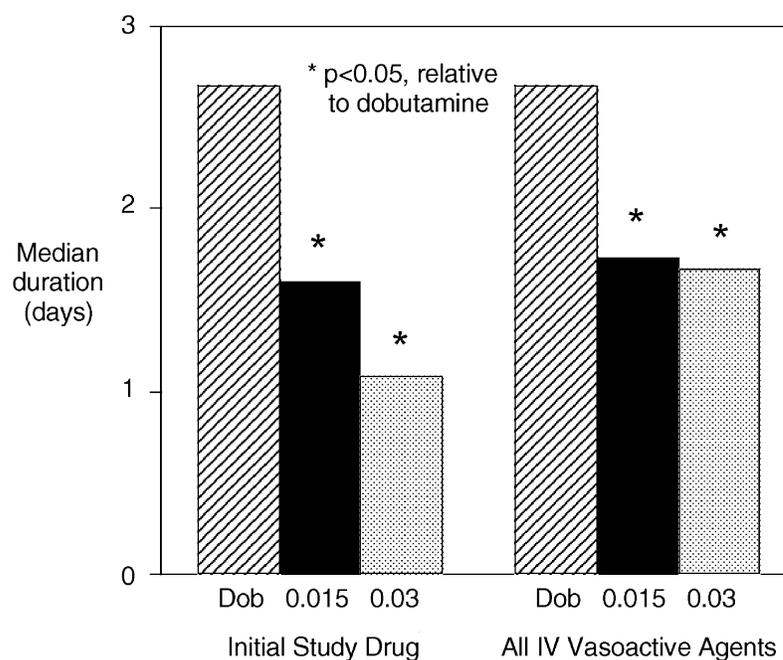
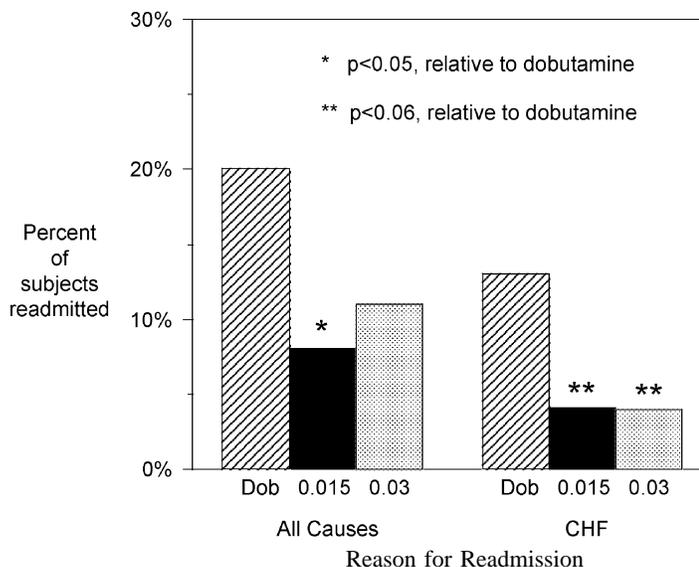


Figure 8-2

**Study 704.326**  
**21-Day Hospital Readmissions**  
**Retrospective Subgroup Analysis: Dobutamine vs. Natrecor®**



Finally, although IV diuretics are used almost universally for this indication, they are not without side effects. Diuretics are associated with significant renin activation, electrolyte disturbances, and prerenal azotemia. In both studies 704.325 and 704.326, Natrecor® therapy was associated with decreased use of diuretics. In fact, approximately 20% of patients were not administered diuretics at any time during their hospital course of therapy. Since Natrecor® itself is associated with diuresis and improvements in the symptoms of congestion, the synergistic effects of Natrecor® and diuretics may decrease the need for diuretics, reducing their inherent risk.

#### 8.4 Benefit/Risk Conclusions

A continuous Natrecor® infusion produces rapid and sustained hemodynamic and clinical improvement in patients with decompensated CHF. The hemodynamic improvement consists of reductions in PCWP and SVR and increases in CI, which are accomplished without producing a reflex tachycardia or an increase in norepinephrine. Concurrent with these effects is a significant, yet mild, increase in diuresis which may allow for fewer diuretics to be used to effect the same clinical goals. For the majority of patients with acutely decompensated heart failure, a vasodilator such as Natrecor® may be the optimal therapeutic strategy since the symptoms which lead to their hospitalization almost universally are due to increased cardiac filling pressures and fluid overload. Symptomatically, patients feel better rapidly following initiation of Natrecor® therapy, especially with regard to symptoms such as dyspnea and fatigue.

The safety database for Natrecor<sup>®</sup> is very representative of the target population that would use Natrecor<sup>®</sup> once commercially available. Natrecor<sup>®</sup> generally has been well tolerated when administered to patients with decompensated CHF and other common significant comorbidities, such as coronary artery disease, underlying arrhythmias, and renal insufficiency. The safety profile of Natrecor<sup>®</sup> is not markedly altered by age, gender, NYHA class, or renal insufficiency. The limiting side effect is dose-related hypotension, an extension of the pharmacologic effect of the drug, and one that is easily monitored in the inpatient clinical setting in which these patients are treated. A moderate increase in serum creatinine occurs in 6–10% of patients, and bradycardia has been reported in 5% of patients. Other adverse events are infrequent and include confusion, nervousness, and sweating.

Natrecor<sup>®</sup> has several features that are not characteristic of currently available therapies. Compared to both inotropes and vasodilators, Natrecor<sup>®</sup> uniquely produces a combination of desirable hemodynamic and neurohormonal effects. Unlike most available therapeutic agents for CHF, Natrecor<sup>®</sup> is not associated with tachycardia due to a reflex mechanism nor as a result of direct sympathetic stimulation. Natrecor<sup>®</sup> is not associated with an increase in mortality or increased risk of ventricular arrhythmias. Natrecor<sup>®</sup>'s activity is also not dependent on beta-adrenergic receptors, such as is dobutamine, and therefore may be an ideal agent for the population for whom beta-blockers are used as chronic therapy. Natrecor<sup>®</sup> can be safely used without invasive hemodynamic monitoring (such as a Swan-Ganz<sup>®</sup> catheter or arterial line) although blood pressure should be monitored. When administered as a fixed-dose infusion within a dose range of 0.015 to 0.03 µg/kg/min, Natrecor<sup>®</sup> is effective in most patients, as evidenced by rapid hemodynamic and symptom improvement, and progressive symptom improvement over the course of therapy.

Natrecor<sup>®</sup> is indicated for the short-term IV treatment of patients with CHF. In these patients, Natrecor<sup>®</sup> rapidly reduces PCWP and SVR and increases CI. It also causes rapid and sustained symptomatic improvement. Blood pressure should be monitored during Natrecor<sup>®</sup> therapy.

**Item 9****Ongoing Natrecor® Studies**

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Currently Scios has one ongoing study, protocol 704.329 (n = 240), entitled Natrecor® (nesiritide) Versus Dobutamine Therapy for Symptomatic, Decompensated CHF: Safety Study Using 24-Hour Holter Monitoring. The objective of this study is to gain additional safety information about the effects of Natrecor® versus dobutamine in the treatment of decompensated CHF. Of particular interest are the effects during the first 24 hours of therapy relative to pretreatment on (1) average heart rate, (2) average hourly premature ventricular beats, and (3) average hourly repetitive beats. In this randomized, multicenter, active-controlled study, baseline data are collected on a 24-hour Holter tape obtained during the 24-hours preceding treatment. On-treatment data are collected during a 24-hour Holter tape obtained during the first 24 hours of treatment with Natrecor® or dobutamine. Other endpoints of interest include an assessment of symptoms and neurohormones 3 and 24 hours after the start of therapy. A final report for this study is expected to be completed in mid-1999.

## Item 10

### Manufacturing Summary

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Natreacor<sup>®</sup> (nesiritide) has the same amino acid sequence as endogenous hBNP (see Figure 1–1), a 32-amino-acid peptide hormone produced in the cardiac ventricle. Natreacor<sup>®</sup> drug substance is manufactured using recombinant DNA technology developed by Scios. Natreacor<sup>®</sup> drug product is manufactured as a sterile lyophilized powder in stoppered vials. The quantitative composition of Natreacor<sup>®</sup> per vial is 5.25 mg nesiritide, 40 mg mannitol, 4.2 mg citric acid, and 5.8 mg sodium citrate dihydrate.

**Item 11****Proposed Indication, Usage, and Dosing**

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***Proposed Indication and Usage Statement***

Natrecor<sup>®</sup> is indicated for the short-term IV therapy of CHF. In patients with CHF, Natrecor<sup>®</sup> rapidly reduces PCWP and SVR and increases CI. It also causes rapid symptomatic improvement.

***Proposed Dosage and Administration Statement***

Natrecor<sup>®</sup> for injection is for intravenous use only. It should be administered as a continuous intravenous infusion at a dose of 0.015 µg/kg/min. In controlled clinical studies, most patients receiving this dose as a fixed-dose infusion showed an improvement in hemodynamic status (i.e., a decrease in PCWP, SVR, and an increase in CI) and an improvement in clinical status (i.e., an improvement in global clinical status and symptoms of CHF).

For patients who are tolerating the 0.015 µg/kg/min infusion well but in whom more pronounced hemodynamic effects are desired, the infusion rate may be increased up to 0.03 µg/kg/min. It is recommended that dose increases be made no more frequently than every 3 hours to permit the peak hemodynamic effects of Natrecor<sup>®</sup> to be achieved prior to further dose adjustments. In clinical studies, infusion rates at or above 0.03 µg/kg/min have resulted in greater reductions in PCWP and SVR and increases in CI than observed at the 0.015 µg/kg/min dose but have also been associated with a higher incidence of symptomatic hypotension.

Blood pressure should be monitored during Natrecor<sup>®</sup> administration. No dosage adjustments are necessary for renal impairment.

# Appendix A

## Study 704.311 Efficacy Synopsis

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### Table Of Contents

	<u>Page</u>
1. <i>Objectives</i> .....	98
2. <i>Study Design</i> .....	98
3. <i>Key Inclusion/Exclusion Criteria</i> .....	99
4. <i>Statistical Methods</i> .....	99
4.1 Objectives and Endpoints .....	99
4.2 Analysis Populations .....	100
4.3 Analysis Methods .....	100
5. <i>Subject Enrollment, Dosing, and Disposition</i> .....	101
5.1 Subject Enrollment and Disposition .....	101
5.2 Study Drug Dosing .....	101
6. <i>Subject Demographics and Baseline Characteristics</i> .....	102
7. <i>Efficacy Results</i> .....	103
7.1 Pulmonary Capillary Wedge Pressure .....	103
7.1.1 Primary Efficacy Endpoint: PCWP at 3 Hours .....	103
7.1.2 PCWP at 24 Hours .....	105
7.2 Other Hemodynamic Endpoints .....	106
7.3 Diuresis and Natriuresis .....	108
7.4 Treatment Failures .....	108
7.5 Subgroup Analyses .....	108
7.6 Statistical Considerations .....	111
7.6.1 Multiple Comparisons .....	111
7.6.2 Enrollment .....	111
8. <i>Efficacy Conclusions for Study 704.311</i> .....	112

## Study 704.311

### **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**

#### ***1. Objectives***

The primary objective of study 704.311 was to evaluate the dose-response effects of several doses of Natrecor® (versus placebo) on central hemodynamic parameters (especially PCWP) in patients with CHF when administered via a 24-hour fixed-dose IV infusion. The primary efficacy endpoint for this objective was defined as the change in PCWP, relative to baseline, at the nominal 3-hour time point for evaluable subjects.

A key secondary objective was to evaluate whether the beneficial effects of Natrecor® could be sustained during the 24-hour treatment period. The study also assessed the natriuretic and diuretic effects, safety, and pharmacokinetic profile of the drug when administered as a 24-hour continuous IV infusion to these CHF patients.

#### ***2. Study Design***

This was a randomized, double-blinded, placebo-controlled, multicenter study designed to enroll approximately 80 subjects (a minimum of 20 subjects in each of 4 treatment groups) with symptomatic NYHA Class II, III, or IV CHF. Subjects were admitted to the hospital and had a Swan-Ganz catheter placed. Prior to study drug administration,  $\beta$ -blockers and calcium channel blockers were withheld for 48 hours, and vasodilators, hydralazine, and ACE inhibitors were withheld for 12 to 24 hours. During study drug infusion, ACE inhibitors, vasodilators,  $\beta$ -blockers, and calcium channel blockers were withheld. Digoxin, diuretics, and antiarrhythmics were administered as per the protocol if clinically indicated.

Subjects were randomized to receive placebo (5% Dextrose Injection, USP, [D5W]) or one of three doses of Natrecor® administered as a small loading bolus followed by a 24-hour, fixed-dose, continuous IV infusion. Treatment groups were:

- Placebo: IV bolus followed by an infusion
- Natrecor®: 0.25  $\mu\text{g}/\text{kg}$  IV bolus followed by an infusion of 0.015  $\mu\text{g}/\text{kg}/\text{min}$
- Natrecor®: 0.5  $\mu\text{g}/\text{kg}$  IV bolus followed by an infusion of 0.03  $\mu\text{g}/\text{kg}/\text{min}$
- Natrecor®: 1.0  $\mu\text{g}/\text{kg}$  IV bolus followed by an infusion of 0.06  $\mu\text{g}/\text{kg}/\text{min}$

Central hemodynamic (PCWP, MRAP, SVR, CI, and PAP), BP, and HR measurements were obtained at baseline, during the study drug infusion (at 1, 3, 6, 10, and 24 hours), and at 2 and

4 hours postinfusion. Total fluid intake and urine output were collected for 24 hours following the initiation of study drug.

Blood was obtained for serum chemistry and hematology studies at baseline, within 24 hours after discontinuation of study drug, and between days 20 and 30. Blood for plasma hBNP levels was obtained at baseline and at various times during and for 4 hours after infusion of the study drug. Blood was obtained for anti-BNP antibody levels at baseline and between days 20 and 30.

Four hours after discontinuation of the study drug infusion, the pulmonary wedge catheter was removed if appropriate, and all previously prescribed medications could resume. Subjects were observed and discharged after a follow-up examination. A follow-up telephone call was made on day 7 and day 15.

### ***3. Key Inclusion/Exclusion Criteria***

Subjects had to be at least 18 years old with a diagnosis of chronic symptomatic NYHA Class II, III, or IV CHF. Subjects were to be on a regimen of oral cardiac medication for the treatment of chronic CHF (e.g., ACE inhibitors, nitrates, or hydralazine, etc. with or without oral digoxin/diuretic therapy) for at least 1 month, and on stable doses of these medications for at least 48 hours prior to study participation. During the baseline evaluation, potential subjects must have also had a PCWP  $\geq$  18 mm Hg and a CI  $\leq$  2.7 L/min/m<sup>2</sup> to proceed with study enrollment.

Patients with any of the following were not eligible for this study: significant valvular obstruction, hypertrophic, restrictive, or obstructive cardiomyopathy, constrictive pericarditis, primary pulmonary hypertension or active myocarditis, active myocardial ischemia, sustained ventricular tachycardia or ventricular fibrillation within the previous 2 weeks, second-degree (Mobitz type II block) or third-degree heart block (unless the subject has a permanent pacemaker), stroke within 3 months, serum sodium concentration  $\leq$  125 or  $\geq$  160 mEq/L, serum creatinine  $>$  3.0 mg/dL, need for  $\beta$ -blockers and/or calcium channel blockers within 48 hours before initiation of study drug administration, or the 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.

### ***4. Statistical Methods***

#### ***4.1 Objectives and Endpoints***

Statistical analysis focused on the effect of Natrecor® on hemodynamics, particularly PCWP. The protocol's statistical methods identified two goals of analysis, corresponding to the study's primary and secondary hemodynamic objectives:

1. To demonstrate a statistically significant dose-response effect with respect to reduction in PCWP at steady-state plasma levels of study drug.

The primary endpoint, for the purposes of the primary dose-response objective, was prospectively defined as the change in PCWP, relative to baseline, at the nominal 3-hour assessment. The protocol specified that, if a subject did not receive the randomized treatment regimen through this assessment period, or if the 3-hour value was otherwise missing, the patient was not eligible for this analysis.

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

For the 24-hour analysis, the endpoint was prospectively defined as the absolute change in PCWP relative to baseline, at the nominal 24-hour assessment. The protocol specified that to be eligible for this analysis, the nominal 24-hour value must have been observed 22 to 26 hours after start of study drug infusion and either while the patient was receiving study drug or within 15 minutes of termination of study drug.

#### **4.2 Analysis Populations**

Subjects eligible for the two analyses described above are called “evaluable at Hour 3” and “evaluable at Hour 24,” respectively. Both of these protocol-specified analyses are “per protocol” analyses, in that only subjects who meet prespecified criteria are eligible for analysis.

A “subjects as randomized” dataset was also analyzed. Subjects are analyzed according to the treatment group to which they were randomized. No subjects are explicitly excluded from this population. Some subjects may not be included in analysis because of data constraints (for example, some analyses require that observations be made within a given time window).

Supplemental “intent-to-treat” datasets were analyzed subsequent to NDA submission at the request of the FDA. Subjects are summarized according to the treatment group to which they were randomized. Analyses include all subjects in analysis by imputing values for missing data, when necessary, using a “last value carried forward” strategy.

#### **4.3 Analysis Methods**

The effect of treatment group was analyzed within the framework of one-way analysis of variance (ANOVA). The protocol specified that the dose-response effect would be examined by means of a linear contrast in treatment effect using equally spaced scores, tested at a two-sided significance level of  $\alpha = 0.05$ . An overall comparison of the four treatment groups was also made with the omnibus F test.

For assessment of the 24-hour PCWP endpoint, the protocol specified that each Natrecor<sup>®</sup> treatment group would be compared to the placebo treatment group using Dunnett's *t* test at a two-sided significance level of  $\alpha = 0.05$ . Pairwise contrasts were also constructed and tested.

In some analyses, hemodynamic observations were required to have been made within pre-specified time intervals around the nominal assessment time being summarized; this will be called a "windowed" analysis. The Hour 3 window was 3 hours  $\pm$  90 minutes, and the Hour 24 window was 24 hours  $\pm$  180 minutes. Observations were additionally required to have been made while the subject was receiving study drug (or within 10 minutes of discontinuation).

## **5. Subject Enrollment, Dosing, and Disposition**

### ***5.1 Subject Enrollment and Disposition***

In this study, 103 patients were enrolled at 15 clinical sites in the U.S. Twenty-nine subjects were enrolled in the placebo treatment group, and 22, 26, and 26 subjects were enrolled in the Natrecor<sup>®</sup> 0.015, 0.003, and 0.06  $\mu\text{g}/\text{kg}/\text{min}$  dose groups, respectively. No patients were lost to follow-up; all patients were followed for the full 14-day study period.

### ***5.2 Study Drug Dosing***

Early in the study, while the sponsor was reviewing study drug accountability at the clinical sites, it was realized 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 Natrecor<sup>®</sup> dose groups, respectively. Three underdosed subjects were in the 0.015  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> dose group, and 2 were in the 0.03  $\mu\text{g}/\text{kg}/\text{min}$  dose group.

In addition, one subject was randomized to the 0.015  $\mu\text{g}/\text{kg}/\text{min}$  dose group but actually received the 0.03  $\mu\text{g}/\text{kg}/\text{min}$  dose.

Fourteen subjects terminated study drug infusion prematurely (i.e., prior to completion of the 24-hour dosing period). Premature termination of study drug infusion occurred in 5 (17%), 0 (0%), 3 (12%), and 6 (23%) subjects in the placebo and 0.015, 0.03, and 0.06  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> dose groups, respectively. Five subjects terminated study drug infusion prior to the 3-hour assessment time point. 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  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> doses who developed an excessively decreased PCWP or hypotension. Table A-1 identifies the subjects who terminated study drug infusion prematurely and the reason for premature termination.

**Table A-1**  
**Study 704.311**  
**Premature Termination of Study Drug Infusion**

Time of Premature Termination	Placebo (n = 29)		Natrecor® 0.015 µg/kg/min (n = 22)		Natrecor® 0.03 µg/kg/min (n = 26)		Natrecor® 0.06 µg/kg/min (n = 26)	
	Subjects	Reason	Subjects	Reason	Subjects	Reason	Subjects	Reason
Prior to 2 h, 50 min	none	—	none	—	380-004	CHF	017-008	↓ BP
					389-006	↓ BP	369-005	↓ PCWP
						bradycardia	369-014	↓ BP
Prior to 24 h*	017-010	CHF	none	—	373-007	↓ PCWP	373-003	↓ PCWP
	369-006	CHF					376-021	↓ BP
	370-005	CHF					388-001	↓ PCWP
	370-006	CHF						
	373-006	CHF						

\* Subjects classified as terminating prior to 22 hours of infusion; all completed at least 2 hours, 50 minutes of infusion.

CHF = worsening CHF

↓ PCWP = PCWP < 10 mm Hg

↓ BP = hypotension

Dose reductions were more frequent in the Natrecor®-treated subjects than in the placebo subjects. The dose was reduced in 2 (7%), 6 (27%), 8 (31%), and 12 (46%) subjects in the placebo and 0.015, 0.03, and 0.06 µg/kg/min Natrecor® dose groups, respectively. However, the most frequent reason for dose reduction was compliance with the protocol-specified requirement that the study drug dose be reduced if the PCWP decreased to less than 10 mm Hg, regardless of whether the decrease was accompanied by an actual adverse event.

## 6. Subject Demographics and Baseline Characteristics

A total of 103 subjects (83 men and 20 women) were enrolled in the study. The mean age ( $\pm$  standard deviation [SD]) for all enrolled subjects was 56.2 years  $\pm$  11.1 years, with 20% of subjects age 65 or greater. Of enrolled subjects, 56 (54%) were white, 26 (25%) were black, 16 (16%) were Hispanic, and 2 (2%) were Asian. Mean weight ( $\pm$  SD) was 81.3  $\pm$  21.1 kg.

Six (6%) subjects were classified as NYHA Class II, 63 (61%) as NYHA Class III, and 34 (33%) as NYHA Class IV. Mean ejection fraction ( $\pm$  SD) for all subjects was 21%  $\pm$  7%.

Baseline mean hemodynamic parameters ( $\pm$  SD) were: PCWP 28.5  $\pm$  6.3 mm Hg, MRAP 13.9  $\pm$  7.2 mm Hg, SVR 1704  $\pm$  738 dynes·sec·cm<sup>-5</sup>, CI 1.9  $\pm$  0.4 L/min/m<sup>2</sup>, and systolic blood pressure (SBP) 116  $\pm$  20 mm Hg.

Baseline characteristics by treatment group are summarized in Table A-2:

**Table A-2**  
**Study 704.311**  
**Subject Demographics and Baseline Characteristics**

Subjects Enrolled:	Placebo n = 29	Natrecor® 0.015 µg/kg/min n = 22	Natrecor® 0.03 µg/kg/min n = 26	Natrecor® 0.06 µg/kg/min n = 26	p value
<b>Gender</b>					
Male	78%	82%	81%	88%	0.537 <sup>1</sup>
Female	28%	18%	19%	12%	
<b>Age</b>					
mean ± SD (years)	53.7 ± 8.0	56.7 ± 11.9	56.7 ± 12.8	58.2 ± 11.6	0.504 <sup>2</sup>
% ≥ 65 years	7%	18%	23%	35%	0.078 <sup>1</sup>
<b>NYHA Class</b>					
II	0%	9%	8%	8%	0.514 <sup>1</sup>
III	72%	64%	50%	58%	
IV	28%	27%	42%	35%	
<b>Hemodynamic Parameters</b>					
PCWP (mm Hg)	27.8 ± 5.8	29.8 ± 7.7	27.3 ± 4.6	29.4 ± 6.7	0.424 <sup>2</sup>
MRAP (mm Hg)	13.0 ± 6.4	13.4 ± 6.1	16.1 ± 7.8	13.0 ± 8.1	0.327 <sup>2</sup>
SVR (dynes·sec·cm <sup>-5</sup> )	1704 ± 683	1782 ± 757	1619 ± 821	1719 ± 739	0.913 <sup>2</sup>
CI (L/min/m <sup>2</sup> )	1.9 ± 0.4	1.8 ± 0.4	1.9 ± 0.5	1.9 ± 0.4	0.787 <sup>2</sup>
SBP (mm Hg)	112 ± 16	123 ± 22	113 ± 17	119 ± 23	0.174 <sup>2</sup>

<sup>1</sup> Fisher's Exact Test

<sup>2</sup> Omnibus F test

## 7. ***Efficacy Results***

### 7.1 ***Pulmonary Capillary Wedge Pressure***

#### 7.1.1 ***Primary Efficacy Endpoint: PCWP at 3 Hours***

The protocol-specified primary efficacy endpoint was the absolute change in PCWP at 3 hours after the initiation of study drug for those subjects defined as “evaluable at 3 hours” (see sections 4.1 and 4.2). Eighty of the 103 enrolled subjects were summarized in this analysis. The remainder of subjects were excluded due to dosing errors or dosing modifications prior to the nominal 3-hour assessment, or did not have a PCWP measurement in the 3-hour assessment window. The results of this analysis (as well as the percent change at 3 hours) are shown in Table A-3. Highly statistically significant reductions in PCWP were achieved in this analysis (p = 0.004).

Table A-3

**Study 704.311**  
**Protocol-Specified Primary Analysis**  
**Change in PCWP at 3 Hours**  
**(Subjects Evaluable at 3 Hours; Windowed Analysis)**

	Placebo (n = 29)	Natrecor®			Treatment Inference
		0.015 µg/kg/min (n = 22)	0.03 µg/kg/min (n = 26)	0.06 µg/kg/min (n = 26)	
Subjects Enrolled:	(n = 29)	(n = 22)	(n = 26)	(n = 26)	
Subjects Summarized:	(n = 29)	(n = 16)	(n = 17)	(n = 18)	
PCWP at baseline (mm Hg)	27.8	30.9	27.8	30.8	
Change at 3 hours (mm Hg)	-1.8	-10.0	-6.8	-9.9	p = 0.004 <sup>a</sup>
	—	p = 0.001 <sup>b</sup>	p = 0.030 <sup>b</sup>	p = 0.001 <sup>b</sup>	
Percent change at 3 hours	-6%	-30%	-22%	-32%	p = 0.001 <sup>a</sup>
	—	p < 0.001 <sup>b</sup>	p = 0.014 <sup>b</sup>	p < 0.001 <sup>b</sup>	

Results are expressed as treatment group means.

<sup>a</sup> linear contrast across treatment groups

<sup>b</sup> pairwise comparison to placebo, by pairwise contrast within ANOVA

An intent-to-treat, carry-forward analysis including all enrolled subjects (n = 103) was also conducted at 3 hours. It yielded similar results which were also highly statistically significant (p < 0.001), as shown in Table A-4.

Table A-4

**Study 704.311**  
**Change in PCWP at 3 Hours**  
**(Intent-to-Treat, Carry-Forward)**

	Placebo (n = 29)	Natrecor®			Treatment Inference
		0.015 µg/kg/min (n = 22)	0.03 µg/kg/min (n = 26)	0.06 µg/kg/min (n = 26)	
Subjects Enrolled:	(n = 29)	(n = 22)	(n = 26)	(n = 26)	
Subjects Summarized:	(n = 29)	(n = 22)	(n = 26)	(n = 26)	
PCWP at baseline (mm Hg)	27.8	29.8	27.3	29.4	
Change at 3 hours (mm Hg)	-1.8	-9.1	-5.9	-10.9	p < 0.001 <sup>a</sup>
	—	p = 0.001 <sup>b</sup>	p = 0.042 <sup>b</sup>	p < 0.001 <sup>b</sup>	
Percent change at 3 hours	-6%	-29%	-20%	-37%	p < 0.001 <sup>a</sup>
	—	p < 0.001 <sup>b</sup>	p = 0.022 <sup>b</sup>	p < 0.001 <sup>b</sup>	

Results are expressed as treatment group means.

<sup>a</sup> linear contrast across treatment groups

<sup>b</sup> pairwise comparison to placebo, by pairwise contrast within ANOVA

Thus, highly statistically significant results were obtained for the primary efficacy endpoint of change in PCWP at 3 hours by both the protocol-specified “per protocol” analysis and the intent-to-treat, carry-forward analysis.

### 7.1.2 *PCWP At 24 Hours*

A key secondary objective of the study was to demonstrate that at least one of the three Natrecor® treatment regimens produced a reduction in PCWP which was sustained through 24 hours of infusion. The protocol specified that this analysis would be done for those subjects defined as “evaluable at 24 hours” (see sections 4.1 and 4.2). Eighty of the 103 subjects were summarized in this analysis. The remainder of subjects were excluded due to dosing errors or drug discontinuation prior to the nominal 24-hour assessment, or did not have a PCWP measurement in the 24-hour assessment window. The results of this analysis are shown in Table A–5. Both the 0.015 and 0.06 µg/kg/min Natrecor® dose groups demonstrated a highly statistically significant reduction in PCWP compared to placebo at 24 hours, and all three Natrecor® groups exhibit a significant reduction compared to baseline ( $p \leq 0.035$  [one-sample  $t$  tests]).

**Table A–5**  
**Study 704.311**  
**Change in PCWP at 24 Hours**  
**(Subjects Evaluable at 24 Hours; Windowed Analysis)**

	Placebo (n = 29) Subjects Enrolled: (n = 25) Subjects Summarized:	Natrecor®			Treatment Inference
		0.015 µg/kg/min (n = 22) (n = 17)	0.03 µg/kg/min (n = 26) (n = 19)	0.06 µg/kg/min (n = 26) (n = 19)	
PCWP at baseline (mm Hg)	28.1	30.5	27.3	30.0	
At 24 Hours					
Change (mm Hg)	–1.8	–8.8	–3.8	–8.4	$p \leq 0.005^a$
Percent change	–6%	–28%	–14%	–28%	
Within-group inference <sup>b</sup>	$p \geq 0.169$	$p < 0.001$	$p \leq 0.035$	$p < 0.001$	
Pairwise inference <sup>c</sup>	—	$p \leq 0.004$	$p \leq 0.328$	$p = 0.002$	
Pairwise inference <sup>d</sup>		significant	not significant	significant	

Results are presented as treatment group means. P values apply to the analysis of both “change” and “percent change”.

<sup>a</sup> Omnibus F test

<sup>b</sup> one-sample  $t$  test

<sup>c</sup> pairwise comparison to placebo, by pairwise contrast within ANOVA

<sup>d</sup> pairwise comparison to placebo, by Dunnett’s  $t$  test run at an overall significance level of  $\alpha = 0.025$

As shown in Table A–6, similar results were obtained when an “as randomized” analysis was conducted on all enrolled subjects (regardless of dosing errors or modifications) with 24-hour on-drug PCWP assessments; no values were imputed (i.e., carried forward) for missing data.

**Table A-6**  
**Study 704.311**  
**Change in PCWP at 24 Hours**  
**(Subjects as Randomized; Windowed Analysis)**

	Natrecor®				Treatment Inference
	Placebo (n = 29) Subjects Enrolled: Subjects Summarized:	0.015 µg/kg/min (n = 22) (n = 21)	0.03 µg/kg/min (n = 26) (n = 21)	0.06 µg/kg/min (n = 26) (n = 19)	
PCWP at baseline (mm Hg)	27.8	29.8	27.3	29.4	
At 24 Hours					
Change (mm Hg)	-1.8	-8.3	-3.7	-8.4	p ≤ 0.003 <sup>a</sup>
Percent change	-6.2%	-27.1%	-13.3%	-27.7%	
Within-group inference <sup>b</sup>	p ≥ 0.169	p < 0.001	p ≤ 0.025	p < 0.001	
Pairwise inference <sup>c</sup>	—	p ≤ 0.002	p ≤ 0.322	p ≤ 0.002	
Pairwise inference <sup>d</sup>		significant	not significant	significant	

Subjects are analyzed according to the treatment group of randomization. For inclusion in the analysis, PCWP must have been recorded while the subject was still receiving study drug and within 24 ± 3 hours after start of study drug.

Results are presented as treatment group means. P values apply to the analysis of both “change” and “percent change”.

<sup>a</sup> Omnibus F test

<sup>b</sup> one-sample *t* test

<sup>c</sup> pairwise comparison to placebo, by pairwise contrast within ANOVA

<sup>d</sup> pairwise comparison to placebo, by Dunnett’s *t* test run at an overall significance level of α = 0.025

Thus, PCWP remained significantly below baseline levels through 24 hours of dosing in both the 0.015 and 0.06 µg/kg/min Natrecor® groups compared to placebo when assessed by either the protocol-specified “per protocol” analysis or the “subjects as randomized” analysis.

## 7.2 *Other Hemodynamic Endpoints*

IV infusion of Natrecor® resulted in statistically significant reductions in MRAP, SVR, PAP, and SBP, and increases in CI, stroke volume, and stroke volume index in all three dose groups. Pulmonary vascular resistance (PVR) also tended to decrease during infusion of all three doses of Natrecor®, although these changes did not reach statistical significance. HR did not change appreciably during Natrecor® infusion, although there was a trend towards a decrease in HR during infusion in the 0.015 and 0.03 µg/kg/min dose groups and an increase in the 0.06 µg/kg/min dose group.

Absolute and percent changes from baseline at 3 hours of study drug infusion for selected hemodynamic parameters are shown in Table A-7.

Table A-7

**Study 704.311**  
**Percent Change in MRAP, SVR, and CI at 3 Hours**  
**(Intent-to-Treat, Carry-Forward Analysis)**

		Placebo (n = 29)	Natrecor®			Treatment Inference
			0.015 µg/kg/min (n = 22)	0.03 µg/kg/min (n = 26)	0.06 µg/kg/min (n = 26)	
<b>MRAP</b>	Baseline (mm Hg)	13.0	13.4	16.1	13.0	p = 0.042 <sup>a</sup>
	% change at 3 hours	0%	-26%	-18%	-35%	
	Pairwise inference	—	p = 0.046 <sup>b</sup>	p = 0.148 <sup>b</sup>	p = 0.006 <sup>b</sup>	
<b>SVR</b>	Baseline (dynes·sec·cm <sup>-5</sup> )	1704	1782	1662	1719	p < 0.001 <sup>a</sup>
	% change at 3 hours	+4%	-12%	-8%	-26%	
	Pairwise inference	—	p = 0.016 <sup>b</sup>	p = 0.054 <sup>b</sup>	p < 0.001 <sup>b</sup>	
<b>CI</b>	Baseline (L/min/m <sup>2</sup> )	1.9	1.8	1.9	1.9	p = 0.003 <sup>a</sup>
	% change at 3 hours	1%	27%	18%	35%	
	Pairwise inference	—	p = 0.009 <sup>b</sup>	p = 0.068 <sup>b</sup>	p < 0.001 <sup>b</sup>	

Results are presented as treatment group means.

<sup>a</sup> Omnibus F test.

<sup>b</sup> Pairwise comparison to placebo, by pairwise contrast within ANOVA.

At 3 hours of infusion, the mean change in systolic blood pressure in the placebo and Natrecor® 0.015, 0.03, and 0.06 µg/kg/min dose groups was +1.2, -7.2, -4.3, and -12.6 mm Hg (+1%, -6%, -3%, and -10%), respectively (p = 0.002 [omnibus F test]). The mean change in heart rate in the four treatment groups was +2.6, -3.5, -2.2, and +5.5 beats per minute (p = 0.004 [omnibus F test], p = 0.228 [linear contrast]).

These changes in hemodynamic parameters with time are shown graphically in Item 5, Figure 5-4.

Throughout the 24-hour study drug infusion, mean MRAP and SVR remained below both baseline and placebo values in all three Natrecor® groups. Although these differences were not always statistically significant, sustained drug activity is supported by the finding that within hours of the discontinuation of Natrecor® infusion, hemodynamics returned to near baseline levels. For example, in the 0.015 µg/kg/min Natrecor® dose group, mean MRAP at baseline was 13.4 mm Hg. After 3 and 24 hours of Natrecor®, mean MRAP had decreased to 10.0 and 10.1 mm Hg, respectively; within 4 hours of discontinuing Natrecor® infusion, MRAP had increased to 11.6 mm Hg. Similarly, in the 0.015 µg/kg/min Natrecor® dose group, mean SVR at baseline was 1782 dynes·sec·cm<sup>-5</sup>. After 3 and 24 hours of Natrecor® infusion, mean SVR was reduced to 1401 and 1445 dynes·sec·cm<sup>-5</sup>, respectively; within 4 hours of discontinuing Natrecor® infusion, mean SVR had returned to 1812 dynes·sec·cm<sup>-5</sup>.

Mean CI also increased over baseline values in all three Natrecor® dose groups throughout the 24 hours of infusion but returned to baseline values within hours of discontinuing the infusion. For example, in the 0.015 µg/kg/min Natrecor® dose group, mean CI at baseline was

1.8 L/min/m<sup>2</sup>. After 3 and 24 hours of Natrecor<sup>®</sup>, mean CI had increased to 2.2 and 2.1 L/min/m<sup>2</sup>, respectively; within 4 hours of discontinuing Natrecor<sup>®</sup> infusion, mean CI had decreased to 1.9 L/min/m<sup>2</sup>.

### 7.3 *Diuresis and Natriuresis*

During the 24-hour treatment period, neither net urine output nor urine sodium or potassium excretion were greater in any of the Natrecor<sup>®</sup> groups than in the placebo group. Actually, net fluid output was slightly lower for Natrecor<sup>®</sup> subjects than for placebo subjects. This may be explained by more concomitant diuretic administration during study drug infusion for placebo subjects compared to Natrecor<sup>®</sup> subjects. During the study drug dosing period, in the placebo and 0.015, 0.03, and 0.06 µg/kg/min Natrecor<sup>®</sup> groups, concomitant diuretics were administered to 66%, 50%, 54%, and 46% of subjects (p = 0.512 [Fisher]).

### 7.4 *Treatment Failures*

As shown in Table A–8, 5 of the 29 placebo subjects (17%) but only 1 of 74 Natrecor<sup>®</sup> subjects (1%) developed worsening CHF during the 24-hour study drug infusion period which required intervention with an IV vasoactive agent. These subjects were categorized as treatment failures.

**Table A–8**

**Study 704.311**  
**Subjects Developing Worsening CHF**  
**Requiring Pharmacological Intervention**  
**During Study Drug Infusion**  
**(All Subjects / Intent-to-Treat)**

<b>Placebo</b> <b>(n = 29)</b>	<b>Natrecor<sup>®</sup></b> <b>0.015 µg/kg/min</b> <b>(n = 22)</b>	<b>Natrecor<sup>®</sup></b> <b>0.03 µg/kg/min</b> <b>(n = 26)</b>	<b>Natrecor<sup>®</sup></b> <b>0.06 µg/kg/min</b> <b>(n = 26)</b>	<b>p value*</b>
5	0	1	0	0.021
(17%)	(0%)	(4%)	(0%)	

\* Fisher's Exact Test

This further supports a benefit of Natrecor<sup>®</sup> on clinical status in these patients.

### 7.5 *Subgroup Analyses*

The effect of demographic factors, cardiac history, baseline cardiac status, and digoxin use on changes in PCWP, CI, and SBP was assessed. Generally, no major differences were observed between subgroups with regard to responsiveness to Natrecor<sup>®</sup>. All subgroups examined had a decrease in PCWP in response to Natrecor<sup>®</sup> infusion, even at the lowest dose tested (0.015 µg/kg/min). Of note, subjects with the most severely decompensated CHF at

enrollment (as defined by NYHA Class IV, PCWP > 26 mm Hg or CI < 2.0 L/min/m<sup>2</sup>) also had a beneficial response to Natrecor<sup>®</sup> administration.

The response to Natrecor<sup>®</sup> appears to correlate directly with baseline PCWP and inversely with baseline CI. Subjects with a higher baseline PCWP tended to have a greater decrease in PCWP during Natrecor<sup>®</sup> infusion than subjects with a lower baseline PCWP. Similarly, subjects with a lower baseline CI tended to have a greater increase in CI during Natrecor<sup>®</sup> infusion than subjects with a higher baseline CI.

Subjects with low BP at enrollment also tolerated Natrecor<sup>®</sup> well. The subgroup of subjects with SBP ≤ 100 mm Hg at enrollment actually had an increase in mean SBP during 0.015 µg/kg/min Natrecor<sup>®</sup> infusion, presumably due to an improvement in overall cardiac function.

These subgroup results for the Natrecor<sup>®</sup> 0.015 µg/kg/min dose group are shown in Table A-9.

Table A-9

**Study 704.311**  
**Subgroup Analysis:**  
**Effects of Demographics, Baseline Cardiac Status, and Digoxin Use**  
**on Changes in PCWP, CI, and SBP at 3 Hours**  
**(0.015 µg/kg/min Natrecor® Dose Group [n = 22])**

Factor	n	PCWP		CI		SBP	
		Baseline (mm Hg)	% Change	Baseline (L/min/m <sup>2</sup> )	% Change	Baseline (mm Hg)	% Change
<b>Age</b>							
< 65 years	18	27.5	-31%	1.74	16%	116	-6%
≥ 65 years	4	31.0	-21%	1.84	24%	133	-12%
<b>Gender</b>							
male	18	28	-31%	1.75	16%	118	-5%
female	4	26	-22%	1.83	23%	126	-17%
<b>Ethnicity</b>							
white	15	30	-25%	1.76	18%	118	-8%
black	6	23	-33%	1.74	41%	121	-10%
Hispanic	1	25	-32%	2.46	1%	118	2%
<b>NYHA Class</b>							
II	2	26	-23%	1.43	29%	111	-11%
III	14	28	-29%	1.78	16%	117	-11%
IV	6	27	-27%	1.74	23%	128	-2%
<b>Etiology of CHF</b>							
ischemic	11	28	-26%	1.76	21%	124	-6%
IDM*	5	25	-20%	1.76	16%	116	-12%
<b>Baseline PCWP</b>							
< 26 mm Hg	7	24	-24%	1.75	16%	124	-14%
≥ 26 mm Hg	15	30	-30%	1.76	21%	113	-3%
<b>Baseline MRAP</b>							
< 13 mm Hg	10	26	-31%	1.89	16%	117	-12%
≥ 13 mm Hg	11	28	-26%	1.75	20%	121	-1%
<b>Baseline CI</b>							
< 2.0 L/min/m <sup>2</sup>	15	28	-31%	1.72	28%	117	-7%
≥ 2.0 L/min/m <sup>2</sup>	7	28	-19%	2.30	9%	131	-6%
<b>Baseline SBP</b>							
≤ 100 mm Hg	2	27	-14%	1.60	19%	94	5%
101-139 mm Hg	15	28	-32%	1.75	21%	117	-11%
≥ 140 mm Hg	4	25	-9%	2.19	18%	153	-3%
<b>On Digoxin**</b>							
yes	9	28	-33%	1.75	28%	124	-8%
no	13	28	-25%	2.02	10%	113	-6%

\* Idiopathic dilated cardiomyopathy.

\*\* As a prior med.

Treatment group medians are presented. Medians are calculated from the "subjects as randomized," windowed dataset.

## 7.6 *Statistical Considerations*

### 7.6.1 *Multiple Comparisons*

The Sponsor intended PCWP at 3 hours to be the primary efficacy endpoint for this study and for PCWP at 24 hours to be a key secondary endpoint; this is consistent with the wording of the study objectives in the protocol. An FDA reviewer has questioned whether the wording of the protocol's statistical section suggests dual primary endpoints (PCWP at 3- and 24-hours), therefore calling for an adjustment of p-values.

Fortunately, this issue is moot, in that both the 3- and 24-hour results remain highly significant after adjustment for dual endpoints. A conservative Bonferroni adjustment would dictate that each of the two analyses needs to be assessed at the  $\alpha = 0.025$  level to maintain an overall significance level of  $\alpha = 0.05$ . The primary analysis of 3-hour PCWP produces a linear contrast p-value of  $p = 0.004$ ; corroborative analyses typically produce p-values of  $p < 0.001$ . Similarly, the Dunnett's analysis of 24-hour PCWP, run at an overall significance level of  $\alpha = 0.025$ , continues to show that the 0.015 and 0.06  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> dose groups are each significantly different from placebo, with the nominal p-values from pairwise contrasts being  $p = 0.002$  or smaller.

### 7.6.2 *Enrollment*

An FDA reviewer has questioned the study's enrollment of 103 subjects given the protocol's statement that "approximately 80" subjects would be studied. Enrollment of 103 subjects is, in fact, consistent with the protocol as explained below.

The study was powered under the assumption of 20 analyzable subjects in each of the four treatment groups. Scios prospectively recognized that the study's site-stratified randomization might produce an imbalanced enrollment among treatment groups, especially if several sites proved to be low-enrollers. In order to preserve the intended statistical power, the protocol carefully stated that "each group will consist of at least 20 subjects...Scios Nova will monitor enrollment across sites. Once 20 subjects have been enrolled into each group, Scios Nova will notify sites to cease enrollment. Thus, there will be a minimum of 20 subjects randomized in each group." Upon the decision to terminate enrollment, subjects already identified for study participation were allowed to complete study procedures. Thus, the actual enrollment of 103 subjects (22 to 29 subjects per group) is consistent with the protocol.

Furthermore, a supplemental analysis was conducted of the first subjects enrolled until enrollment of exactly 20 subjects in the smallest group (total enrollment of 94 subjects). Results of this analysis are essentially the same (including statistical inferences) as those from the original analysis of all 103 subjects.

## 8. Efficacy Conclusions for Study 704.311

Continuous IV infusion of Natrecor® at doses of 0.015 to 0.06 µg/kg/min resulted in significant decreases in PCWP which were apparent as early as 1 hour after the initiation of infusion (the earliest time point evaluated in this study) and were sustained throughout the 24-hour infusion. Highly significant results were achieved for the protocol-specified primary efficacy endpoint of reduction in PCWP at 3 hours. PCWP remained significantly reduced below baseline values after 24 hours of infusion in both the 0.015 and 0.06 µg/kg/min Natrecor® dose groups.

Significant dose-related reductions in MRAP, SVR, PAP, and SBP and increases in CI, volume, and stroke volume index were also observed. PVR also tended to decrease during infusion of all three doses of Natrecor®, although these changes did not reach statistical significance.

The hemodynamic responses in the 0.06 µg/kg/min Natrecor® dose group were usually greater than the hemodynamic responses seen in the two lower dose groups; however, the responses in the 0.03 µg/kg/min dose group were not consistently greater than those in the 0.015 µg/kg/min group (and were frequently less pronounced). The reason for this phenomenon is unclear but it may be a result of pharmacy errors in drug preparation leading to marked underdosing, which was noted at some sites. This phenomenon has not been observed in other studies. In both studies 704.307 and 704.325, for example, the 0.03 µg/kg/min dose has produced greater hemodynamic effects than did the 0.015 µg/kg/min dose.

The 0.06 µg/kg/min Natrecor® dose resulted in greater effects on central hemodynamic parameters, such as PCWP, SVR, and CI. However, it was associated with a higher incidence of hypotension, which frequently required premature discontinuation of dosing. Thus, subsequent clinical studies focused on the 0.015 and 0.03 µg/kg/min doses.

In this study, diuresis and natriuresis were not greater during Natrecor® infusion than during placebo infusion. However, pretreatment urine output and sodium excretion were not assessed, obviating the ability to assure that pretreatment urine outputs were comparable in the four treatment groups; also, concomitant diuretic use was permitted in all treatment groups, possibly further confounding the interpretation of these results. There was a trend of more diuretic usage during study drug infusion among placebo subjects than Natrecor® subjects.

Five placebo subjects but only 0, 1, and 0 subjects in the 0.015, 0.03, and 0.06 µg/kg/min Natrecor® dose groups, respectively, terminated study drug infusion prematurely due to worsening CHF ( $p = 0.021$  [Fisher's Exact Test]), supporting a beneficial effect of Natrecor® therapy on clinical status in these subjects.

# Appendix B

## Study 704.325 Efficacy Synopsis

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### Table Of Contents

	<u>Page</u>
1. <i>Objectives</i> .....	113
2. <i>Study Design</i> .....	113
3. <i>Key Inclusion/Exclusion Criteria</i> .....	114
4. <i>Statistical Methods</i> .....	115
4.1 Objective and Endpoint .....	115
4.2 Analysis Populations .....	115
4.3 Analysis Methods .....	115
4.3.1 Worst Outcome .....	115
4.3.2 Hemodynamic Parameters .....	116
5. <i>Subject Enrollment, Dosing, and Disposition</i> .....	117
6. <i>Demographic and Baseline Characteristics</i> .....	117
7. <i>Efficacy Results</i> .....	119
7.1 Pulmonary Capillary Wedge Pressure .....	119
7.1.1 Primary Efficacy Endpoint: PCWP at 6 Hours .....	119
7.1.2 Other Hemodynamic Parameters .....	120
7.2 Clinical Status .....	122
7.3 Symptoms of CHF .....	124
7.4 Neurohormones .....	126
7.5 Diuresis and Diuretic Usage .....	126
7.6 Other Assessments .....	126
7.7 Mortality .....	127
7.8 Subgroup Analyses .....	127
8. <i>Efficacy Conclusions for Study 704.325</i> .....	128

## Study 704.325

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

#### ***1. Objectives***

The primary objective of this study was to assess the efficacy of two distinct IV doses of Natrecor® in decreasing PCWP in patients with symptomatic, decompensated CHF, as measured by a blinded comparison to placebo after 6 hours of treatment.

Additional objectives were to evaluate the effects of Natrecor® on other hemodynamic endpoints, clinical symptoms, and neurohormone levels in patients with symptomatic, decompensated CHF, as well as to gain additional information on the safety profile of Natrecor® in patients with symptomatic, decompensated CHF who require hospitalization.

#### ***2. Study Design***

This was a randomized, double-blinded, placebo-controlled, multicenter study designed to enroll 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  $\geq 18$  mm Hg, CI  $\leq 2.7$  L/min/m<sup>2</sup>, and SBP  $\geq 90$  mm Hg received one of the following three regimens:

- Placebo: bolus followed by infusion (D<sub>5</sub>W)
- Natrecor®: IV bolus of 0.3 µg/kg followed by a 0.015 µg/kg/min infusion
- Natrecor®: IV bolus of 0.6 µg/kg followed by a 0.03 µg/kg/min infusion

Cardiac hemodynamics and clinical status were followed for an initial 6-hour, double-blinded evaluation period during which diuretics and additional parenteral interventions and oral medications for decompensated CHF were withheld unless urgently required for worsening CHF not responding to study drug infusion. The primary study efficacy endpoint was the percentage change in PCWP from baseline at 6 hours in the Natrecor® groups compared to the placebo group.

After the 6-hour blinded evaluation was completed, treatment assignment for all subjects was unblinded with regard to whether the subject was receiving placebo or Natrecor®. Placebo subjects then received “standard care,” consisting of the initiation of a parenteral agent of the investigator’s choice routinely used for the short-term management of decompensated CHF (such as IV nitroprusside, nitroglycerin [NTG], dobutamine, or milrinone). These subjects thereafter served primarily as a control group for safety monitoring purposes. Natrecor® subjects could have been continued on their fixed-dose Natrecor® regimens (still blinded as to

specific dose group assignment) for up to a maximum infusion 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 (including PCWP, CI, MRAP, SVR, SBP, HR, and PAP) 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 hours for subjects still receiving Natrecor® if a Swan-Ganz catheter was still in place). All concomitant medications were recorded. Specific symptoms of decompensated CHF were assessed at baseline; clinical status (i.e., global assessment and specific symptoms) was assessed, relative to baseline status, at the end of the 6-hour blinded evaluation period, at 24 hours, and at the end of parenteral therapy. Urine output, fluid intake, and weight were assessed daily. Plasma hBNP 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 assessment of serum anti-hBNP 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 readmission, and mortality status.

### ***3. Key Inclusion/Exclusion Criteria***

To be eligible for participation in the study, subjects must have been at least 18 years of age, had a previous history of chronic CHF and presented with symptomatic, decompensated CHF for which in-patient parenteral therapy was deemed appropriate. After placement of a Swan-Ganz catheter, subjects must have had a PCWP  $\geq 18$  mm Hg, CI  $\leq 2.7$  mL/min/m<sup>2</sup>, and SBP  $\geq 90$  mm Hg to proceed with the study. There was no protocol-specified restriction regarding cardiac ejection fraction.

Potential subjects with any of the following were not eligible for this study: myocardial infarction (MI) within the previous 48 hours or ongoing unstable angina; significant valvular stenosis; hypertrophic, restrictive or obstructive cardiomyopathy; constrictive pericarditis; primary pulmonary hypertension; biopsy-proven active myocarditis, or complex congenital heart disease; stroke within 3 months or other evidence of significantly compromised central nervous system perfusion; ongoing treatment with a parenteral vasoactive agent (i.e., an inotrope or vasodilator) for this episode of decompensated CHF which could not be discontinued for an appropriate washout period to permit the reassessment of baseline hemodynamics and clinical status prior to initiating study drug; or 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).

## **4. Statistical Methods**

### **4.1 Objective and Endpoint**

The primary objective of the statistical analysis of this study was to demonstrate a statistically significant treatment effect of either dose of Natreacor®, relative to placebo, on PCWP, after 6 hours of treatment.

The primary endpoint was PCWP, expressed as a percentage change from baseline, 6 hours after initiation of study drug.

### **4.2 Analysis Populations**

The primary analysis population was the “intent-to-treat” population. Subjects are summarized according to the treatment group to which they were randomized. Analyses include all subjects in analysis by imputing values for missing data, when necessary, using a “worst outcome” or “last value carried forward” strategy.

A “subjects as randomized” dataset was also analyzed. Subjects are analyzed according to the treatment group to which they were randomized. No subjects are explicitly excluded from this population. Some subjects may not be included in analysis because of data constraints (for example, some analyses require that observations be made within a given time window).

### **4.3 Analysis Methods**

#### **4.3.1 Worst Outcome**

Administration of parenteral diuretics or vasoactive agents (other than study drug) during the 6-hour double-blinded evaluation period might alter the 6-hour PCWP measurement. Unblinding prior to completion of the 6-hour assessment could also introduce bias. Therefore, a per protocol “worst outcome” analysis plan was developed.

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.

For purposes of the primary efficacy analysis, very rigorous and conservative definitions of intervention and unblinding were utilized. Any subject receiving any parenteral diuretic or

parenteral vasoactive agent was to be classified as “worst outcome,” even if the subject’s status was not worsening and/or the agent had been administered accidentally. Also, a subject was considered to have been unblinded prematurely if, during site monitoring, there was not clear documentation that the 6-hour measurements were made prior to unblinding.

Despite repeated site education on these issues, a number of deviations from these instructions occurred. Five, 4, and 2 subjects in the placebo and 0.015 and 0.03 µg/kg/min Natrecor® treatment groups, respectively, were categorized as having been unblinded prematurely; in some of these cases, the primary efficacy measurements were made during the same minute as the call to the Automated Telephone Unblinding System and thus the site staff may not have actually known the treatment assignment until after completing their evaluation; however, this could not be documented. Also, in some cases, parenteral agents were administered before the 6-hour assessments, either inadvertently or for a reason other than CHF. However, for the purposes of the primary efficacy analysis, all of these subjects were categorized as “worst outcome.” Subjects categorized as “worst outcome” are summarized in Table B-1. In most cases, it is not clear these subjects actually represented patients with an actual worsening of clinical status requiring intervention.

**Table B-1**

**Study 704.325  
Subjects Categorized as Worst Outcome\***

Placebo		Natrecor® 0.015 µg/kg/min		Natrecor® 0.03 µg/kg/min	
Subjects	Reason	Subjects	Reason	Subjects	Reason
356-001	U	352-001	I, U	017-003	I
368-006	U	352-003	U	356-002	U
369-018	I	352-009	I	498-002	U
487-003	U	360-002	U	498-003	I
503-001	I, U	370-006	I		
503-004	U	487-001	I, U		
503-008	I	487-002	I		

\* Subjects classified as worst outcome prior to obtaining an eligible 6-hour PCWP measurement

U = possible premature unblinding

I = cardiovascular intervention

#### **4.3.2 Hemodynamic Parameters**

Hemodynamic endpoints were analyzed at baseline and 1.5, 3, 4.5, 6, and 24 hours after initiation of study drug. The primary analysis of 6-hour PCWP was a “worst outcome” nonparametric analysis.

For subjects not classified “worst outcome,” the 6-hour analysis value was obtained by considering all blinded, preintervention hemodynamic assessments between 5.5 and 7 hours after start of study drug. Of these, the observation recorded closest to 6 hours was selected for

analysis. Determination of the analysis values at 1.5, 3, and 4.5 hours was by a similar algorithm.

Subjects classified “worst outcome” as of the given assessment time (through the 6-hour assessment) were assigned an arbitrarily poor analysis value for all hemodynamic endpoints. Because analysis was by rank-based nonparametric methods, the “worst outcome” value is arbitrary except that (1) it must be the same for all worst outcome subjects and (2) it must be worse than any value actually observed across all subjects in the study.

The three treatment groups were tested for nonspecific differences with the Kruskal-Wallis test, and for dose-related differences with the Jonckheere-Terpstra test. Each Natrecor<sup>®</sup> treatment group was compared to the placebo treatment group with a 2-sample Wilcoxon test. When the endpoint was represented as change or percentage change from baseline, the hypothesis of a nonzero change from baseline was tested with a 1-sample Wilcoxon test.

Two additional analyses were employed to evaluate the robustness of the hemodynamic results: (1) a “carry forward” parametric analysis and (2) a “windowed” parametric analysis. In the windowed analyses, hemodynamic observations were required to have been made within prespecified time intervals around the nominal assessment time being summarized. The window for Hour 6 was 6 hours  $\pm$  180 minutes.

All reported p values are two sided.

## ***5. Subject Enrollment, Dosing, and Disposition***

In this study, 127 subjects were enrolled by 23 clinical investigators in the U.S. Forty-two, 43, and 42 subjects were enrolled in the placebo/standard care group and the 0.015 and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> groups, respectively. All but 1 subject was followed through the 21-day study period. One subject in the 0.015  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> treatment group was lost to follow-up on day 8 as of NDA filing but was subsequently located and found to be alive as of day 21.

The median duration of Natrecor<sup>®</sup> infusion in the study (excluding interruptions) in the 0.015 and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> treatment groups was 24.0 hours (range, 3.0 to 119.8 hours) and 24.5 hours (range, 4.3 to 122.3 hours), respectively. Most Natrecor<sup>®</sup> subjects who required parenteral therapy for CHF beyond 24 hours were switched from Natrecor<sup>®</sup> to a standard care agent after completing the protocol-specified 24-hour assessments.

## ***6. Demographic and Baseline Characteristics***

Of the 127 subjects enrolled, 93 were men and 34 were women. The mean age ( $\pm$  standard deviation [SD]) for all enrolled subjects was 58.8 years  $\pm$  13.5 years (range, 19 to 85 years). Forty-six subjects (36%) were  $\geq$  65 years old. Of enrolled subjects, 77 (61%) were white, 38 (30%) were black, and 12 (9%) were Hispanic. Mean weight ( $\pm$  SD) was 81.4  $\pm$  17.5 kg (range, 47.1 to 150.2 kg).

Before this hospitalization, 3 subjects (2%) were classified as NYHA Class II, 67 (53%) as NYHA Class III, and 57 (45%) as NYHA Class IV. Mean ejection fraction ( $\pm$  SD) for all subjects was  $22 \pm 7\%$  (range, 5% to 41%). The primary etiology of the subjects' chronic CHF was ischemic cardiomyopathy in 58 subjects (46%) and idiopathic dilated cardiomyopathy in 35 subjects (28%); in the remainder of the subjects, the etiology of CHF was hypertensive, alcohol- or drug-induced cardiomyopathy, valvular heart disease, or was unknown.

Baseline mean hemodynamic parameters ( $\pm$  SD) for all subjects were as follows:

PCWP  $28.0 \pm 6.5$  mm Hg (range, 18 to 52 mm Hg), MRAP  $14.5 \pm 6.6$  mm Hg (range, 2 to 36 mm Hg), SVR  $1603 \pm 555$  dynes·sec·cm<sup>-5</sup> (range, 572 to 3248 dynes·sec·cm<sup>-5</sup>), CI  $1.9 \pm 0.5$  L/min/m<sup>2</sup> (range, 0.8 to 3.0 L/min/m<sup>2</sup>), and SBP  $116 \pm 18$  mm Hg (range, 79 to 164 mm Hg). The groups were well matched with regard to their baseline hemodynamic status, except that the 0.015  $\mu$ g/kg/min Natrecor<sup>®</sup> group tended to have a lower BP at baseline than the other two groups. At baseline, mean SBP in the placebo, 0.015, and 0.03  $\mu$ g/kg/min Natrecor<sup>®</sup> treatment groups was 118, 110, and 120 mm Hg, respectively ( $p = 0.045$  [omnibus F test]).

These baseline parameters are summarized by treatment group in Table B-2.

**Table B-2**  
**Study 704.325**  
**Subject Demographics and Baseline Characteristics**

Baseline Parameter	Placebo (n = 42)	Natrecor® 0.015 µg/kg/min (n = 43)	Natrecor® 0.03 µg/kg/min (n = 42)	All Subjects (n = 127)	p value
<b>Gender</b>					
male	79%	81%	60%	73%	0.055 <sup>1</sup>
female	21%	19%	40%	27%	
<b>Age</b>					
Mean ± SD (years)	59.0 ± 14	56.6 ± 15	60.8 ± 12	58.8 ± 14	0.357 <sup>2</sup>
% ≥ 65 years	38%	30%	40%	36%	0.624 <sup>1</sup>
<b>NYHA Class</b>					
II	5%	0%	2%	2%	0.196 <sup>3</sup>
III	60%	56%	43%	53%	
IV	36%	44%	55%	45%	
<b>Hemodynamic Parameters</b>					
PCWP (mm Hg)	28.5 ± 6.8	28.1 ± 6.5	27.5 ± 6.4	28.0 ± 6.5	0.818 <sup>2</sup>
MRAP (mm Hg)	14.2 ± 6.3	15.1 ± 6.9	14.3 ± 6.8	14.5 ± 6.6	0.817 <sup>2</sup>
SVR (dynes·sec·cm <sup>-5</sup> )	1524 ± 493	1598 ± 582	1687 ± 589	1603 ± 555	0.407 <sup>2</sup>
CI (L/min/m <sup>2</sup> )	2.0 ± 0.4	1.8 ± 0.5	1.9 ± 0.5	1.9 ± 0.5	0.159 <sup>2</sup>
SBP (mm Hg)	118 ± 17	110 ± 16	120 ± 19	116 ± 18	0.045 <sup>2</sup>
<b>Symptoms of CHF</b>					
Fatigue	95%	98%	95%	96%	0.253 <sup>3</sup>
Dyspnea	93%	95%	90%	93%	0.628 <sup>3</sup>
Lightheadedness	24%	33%	24%	27%	0.592 <sup>3</sup>
Decreased appetite	47%	53%	43%	48%	0.626 <sup>3</sup>

<sup>1</sup> Fisher exact test

<sup>2</sup> Omnibus F test

<sup>3</sup> Kruskal-Wallis test on the 3- or 4-category ordinal variable

## 7. *Efficacy Results*

### 7.1 *Pulmonary Capillary Wedge Pressure*

#### 7.1.1 *Primary Efficacy Endpoint: PCWP At 6 Hours*

The protocol-specified primary efficacy endpoint was the percent change in PCWP at 6 hours after the initiation of therapy as assessed by the “worst case” analysis. An intent-to-treat, carry-forward analysis was also conducted. The results of these two analyses are shown in Table B-3.

Table B-3

**Study 704.325**  
**Primary Efficacy Endpoint**  
**Percent Change in PCWP at 6 Hours**  
**(Intent-to-Treat)**

	Placebo (n = 42)	Natrecor® 0.015 µg/kg/min (n = 43)	Natrecor® 0.03 µg/kg/min (n = 42)	
Subjects Enrolled:	(n = 42)	(n = 43)	(n = 42)	
Subjects Summarized:	(n = 42)	(n = 43)	(n = 42)	p value
Baseline PCWP (median) (mm Hg)	28.0	27.0	28.0	
<b>Percent Change from Baseline:</b>				
Worst Outcome Analysis (median)	+7.3%	-20.0%	-32.6%	p < 0.001 <sup>1</sup>
	—	p = 0.001 <sup>2</sup>	p < 0.001 <sup>2</sup>	
Carry-Forward Analysis (mean)	+8.4%	-20.1%	-35.3%	p < 0.001 <sup>3</sup>
	—	p < 0.001 <sup>4</sup>	p = 0.001 <sup>4</sup>	

<sup>1</sup> Kruskal-Wallis test.

<sup>2</sup> Pairwise comparison to placebo, by 2-sample Wilcoxon test.

<sup>3</sup> Omnibus F test.

<sup>4</sup> Pairwise comparison to placebo, by pairwise contrast within ANOVA.

Both analyses yield highly statistically significant results ( $p < 0.001$ ) for the primary efficacy endpoint.

### ***7.1.2 Other Hemodynamic Parameters***

IV infusion of Natrecor® resulted in statistically significant reductions in MRAP, SVR, PAP, and SBP, and increases in CI, stroke volume, and stroke volume index in both treatment groups. PVR decreased during study drug infusion in the 0.015 Natrecor® group but not in the placebo or 0.03 µg/kg/min Natrecor® group. HR did not change appreciably during Natrecor® infusion.

Absolute and percentage changes from baseline at 6 hours after start of study drug for MRAP, SVR, and CI are shown in Table B-4.

**Table B-4**  
**Study 704.325**  
**Percent Change in MRAP, SVR, and CI at 6 Hours**  
**(Intent-to-Treat, Carry Forward Analysis)**

		Placebo (n = 42)	Natrecor®		Treatment Inference
			0.015 µg/kg/min (n = 43)	0.03 µg/kg/min (n = 42)	
MRAP	Subjects Enrolled:				
	Subjects Summarized:				
	Baseline (mm Hg)	14.2	14.8	14.3	
	% change at 6 hours	9%	-11%	-41%	p < 0.001 <sup>a</sup>
	Pairwise inference	—	p = 0.008 <sup>b</sup>	p < 0.001 <sup>b</sup>	
SVR	Subjects Enrolled:				
	Subjects Summarized:				
	Baseline (dynes-sec-cm <sup>-5</sup> )	1524	1592	1687	
	% change at 6 hours	13%	-12%	-18%	p < 0.001 <sup>a</sup>
	Pairwise inference	—	p < 0.001 <sup>b</sup>	p < 0.001 <sup>b</sup>	
CI	Subjects Enrolled:				
	Subjects Summarized:				
	Baseline (L/min/m <sup>2</sup> )	2.0	1.8	1.9	
	% change at 6 hours	-4%	18%	28%	p < 0.001 <sup>a</sup>
	Pairwise inference	—	p = 0.003 <sup>b</sup>	p < 0.001 <sup>b</sup>	

Results are presented as treatment group means.

<sup>a</sup> Omnibus F test

<sup>b</sup> Pairwise comparison to placebo, by pairwise contrast within ANOVA

These changes in hemodynamic parameters with time, as well as the effects on blood pressure and heart rate, are shown graphically in Item 5, Figure 5-5. At 6 hours of infusion, the mean change in systolic blood pressure in the placebo and Natrecor® 0.015 and 0.03 µg/kg/min dose groups was +0.7, -4.1, and -10.1 mm Hg (1%, -3%, and -8%), respectively (p ≤ 0.001 [omnibus F test]).

Mean HR did not change appreciably during Natrecor® infusion, suggesting that any increase in CI was due to an increase in stroke volume index rather than an increase in HR. Mean changes in HR from baseline at 6 hours in the placebo, 0.015, and 0.03 µg/kg/min Natrecor® treatment groups were +1.5, -1.5, and +0.5, respectively (p = 0.203 [omnibus F test]).

Six hours after administration of study drug began, mean changes from baseline in mean PAP in the placebo, 0.015, and 0.03 µg/kg/min Natrecor® treatment groups were +1.8, -6.3, and -7.8 mm Hg, respectively (p < 0.001 [omnibus F test]). Mean changes from baseline in pulmonary vascular resistance in the three treatment groups were +18.3, -60.3, and -1.7 dynes-sec-cm<sup>-5</sup> (p = 0.031 [omnibus F test]).

The observation that Natrecor® increases CI without increasing HR suggests that Natrecor® improves cardiac function without increasing cardiac work and myocardial oxygen consumption. Although these latter parameters were not directly measured in this study, the cardiac pressure rate index was calculated as a surrogate for cardiac work at baseline and at 6 hours. The pressure rate index is obtained by multiplying SBP by HR for each subject at each time point under evaluation. Six hours after start of study drug, the pressure rate index

had increased somewhat in the placebo group but had decreased in the two Natrecor® groups in a dose-related manner. Six hours after start of therapy, in the placebo, 0.015, and 0.03 µg/kg/min Natrecor® treatment groups, the pressure rate index had changed from baseline by 260, -535, and -809 mm Hg × beats/min, respectively (p = 0.001 [omnibus F test]).

## 7.2 Clinical Status

At 6 and 24 hours after the initiation of study drug, as well as at the end of parenteral therapy, both the subject and the physician were asked to evaluate the subject's overall clinical status compared to baseline and to categorize it as markedly better, better, no change, worse, or markedly worse. Compared to placebo, administration of both the 0.015 and 0.03 µg/kg/min doses of Natrecor® resulted in a statistically significant rapid improvement in overall clinical status, as assessed by both the physician and the subject.

The subjects' self-assessment of clinical status 6 hours after start of study drug is shown in Table B-5.

**Table B-5**  
**Study 704.325**  
**Global Assessment of Clinical Status by the Subject at 6 Hours**  
**(Subjects as Randomized; Windowed Analysis)**

	Percentage of Subjects With Each Response		
	Placebo	Natrecor® 0.015 µg/kg/min*	Natrecor® 0.03 µg/kg/min*
<b>Subjects Enrolled:</b>	<b>(n = 42)</b>	<b>(n = 43)</b>	<b>(n = 42)</b>
<b>Subjects Summarized:</b>	<b>(n = 42)</b>	<b>(n = 40)</b>	<b>(n = 39)</b>
Markedly Better	0%	13%	8%
Better	14%	48%	59%
No Change	74%	25%	23%
Worse	5%	5%	5%
Markedly Worse	7%	10%	5%

Subjects are summarized according to the treatment group of randomization. Assessments made 5 1/2 to 7 hours after start of study drug infusion were eligible for summarization.

\* p ≤ 0.001 for pairwise comparisons of each Natrecor® dose group to placebo [2-sample Wilcoxon]

This rapid improvement in clinical status was statistically significant for both Natrecor® treatment groups when compared to pretreatment (p = 0.019 and p < 0.001, respectively [1-sample Wilcoxon]) or to placebo (p ≤ 0.001 for both groups [2-sample Wilcoxon]).

Comparable results were obtained at 6 hours based upon the physician's double-blinded assessment of each subject's overall clinical status, as shown in Table B-6.

Table B-6

**Study 704.325**  
**Global Assessment of Clinical Status by the Physician at 6 Hours**  
**(Subjects as Randomized; Windowed Analysis)**

	Percentage of Subjects With Each Response		
	Placebo	Natrecor® 0.015 µg/kg/min*	Natrecor® 0.03 µg/kg/min*
<b>Subjects Enrolled:</b>	(n = 42)	(n = 43)	(n = 42)
<b>Subjects Summarized:</b>	(n = 42)	(n = 40)	(n = 39)
Markedly Better	0%	13%	10%
Better	5%	43%	67%
No Change	67%	25%	15%
Worse	21%	10%	3%
Markedly Worse	7%	10%	5%

Subjects are summarized according to the treatment group of randomization. Assessments made 5 1/2 to 7 hours after start of study drug infusion were eligible for summarization.

\* p ≤ 0.001 for pairwise comparisons of each Natrecor® dose group to placebo [2-sample Wilcoxon]

This improvement in clinical status, as assessed by the physician, was statistically significant for both the 0.015 and 0.03 µg/kg/min Natrecor® treatment groups when compared to placebo (p < 0.001 for both groups [2-sample Wilcoxon]).

After 6 hours of placebo infusion, the control subjects received therapy with active-control standard care agents (such as IV dobutamine or milrinone). Table B-7 summarizes the percentage of patients in each treatment group reporting feeling better or markedly better at 24 hours after initiation of study drug and at the end of parenteral therapy. At both time points, the percent of subjects in the Natrecor® groups reporting an improvement was at least as high as the percentage of active control subjects.

Table B-7

**Study 704.325**  
**Global Assessment of Clinical Status by the Subject**  
**at 24-Hours after Start of Study Drug and at End of Parenteral Therapy**  
**Percentage of Patients Reporting Feeling Better or Markedly Better**  
**(Subjects as Randomized; Windowed Analysis)**

	Percentage of Subjects Reporting Feeling Better or Markedly Better		
	Active Control	Natrecor® 0.015 µg/kg/min	Natrecor® 0.03 µg/kg/min
<b>Subjects Enrolled:</b>	(n = 42)	(n = 43)	(n = 42)
At 24 hours	74% (28/38)	80% (32/40)	88% (36/41)
At end of therapy	80% (32/40)	85% (35/41)	93% (38/41)

Subjects are summarized according to the treatment group of randomization. Assessments made 20–28 hours or at least 20 hours after start of study drug were eligible for summarization at 24 hours or end of therapy, respectively.

Within each treatment group, these data showed a statistically significant improvement relative to baseline ( $p < 0.001$  [1-sample Wilcoxon test on the 5-category ordinal variable] in all cases). There were no statistically significant between-group differences.

### 7.3 Symptoms of CHF

Subjects were also assessed for the presence of specific symptoms of CHF at baseline, at 6 and 24 hours after the initiation of study drug, and at the end of all parenteral therapy. At baseline, 93% had dyspnea, 96% had fatigue, 27% had lightheadedness, and 48% of subjects had decreased or absent appetite.

Administration of Natrecor® resulted in a rapid improvement in many of these symptoms, most notably dyspnea and fatigue. The percentage of subjects who reported an improvement in these symptoms as early as 6 hours after start of study drug is shown in Table B–8.

**Table B–8**  
**Study 704.325**  
**Symptoms of CHF at 6 Hours**  
**(Subjects as Randomized; Windowed Analysis)**

	Percent Reporting Improvement			Treatment Inference
	Placebo (n = 42)	Natrecor®		
		0.015 µg/kg/min (n = 43)	0.03 µg/kg/min (n = 42)	
<b>Subjects Enrolled:</b>				
<b>Subjects Summarized:</b>	(n = 42)	(n = 38–39)	(n = 40)	
Dyspnea	12%	56% $p < 0.001^b$	50% $p < 0.001^b$	$p < 0.001^a$
Fatigue	5%	32% $p = 0.001^b$	38% $p < 0.001^b$	$p < 0.001^a$
Lightheadedness	5%	24% $p = 0.010^b$	10% $p = 0.713^b$	$p = 0.023^a$
Decreased Appetite	7%	28% $p = 0.023^b$	8% $p = 0.771^b$	$p = 0.017^a$

Subjects are summarized according to the treatment group of randomization. Assessments made 5 1/2 to 7 hours after start of study drug infusion were eligible for summarization.

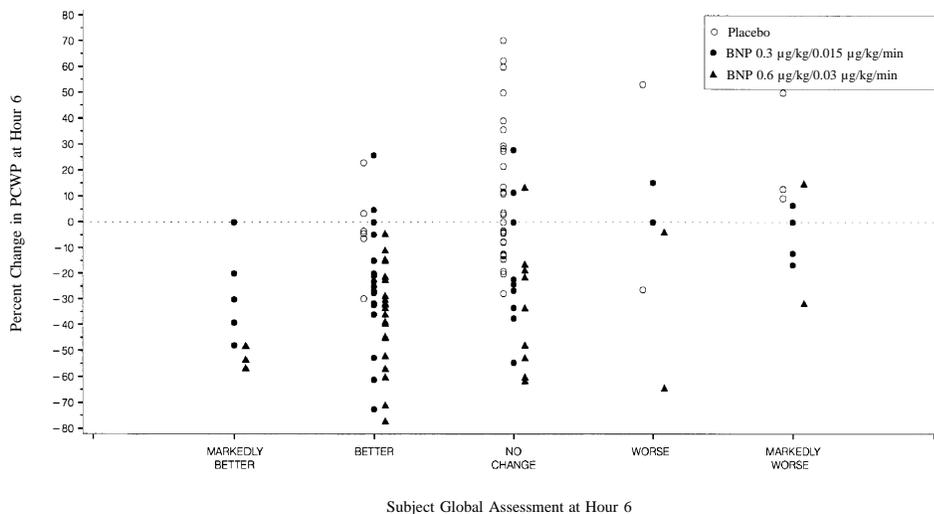
<sup>a</sup> Kruskal-Wallis test on 3-category ordinal variable (worse, no change, improved).

<sup>b</sup> pairwise comparison to placebo, two-sample Wilcoxon test on 3-category ordinal variable.

Thus, compared to placebo, Natrecor® administration results in improvements in cardiac hemodynamics, global clinical status, and specific symptoms such as dyspnea. In order to explore the relationship of improvements in hemodynamics with improvements in clinical status, the percentage change from baseline in each subject's PCWP at 6 hours was plotted against his/her global clinical status rating and dyspnea rating at 6 hours. The results are shown in Figures B–1 and B–2.

Figure B-1

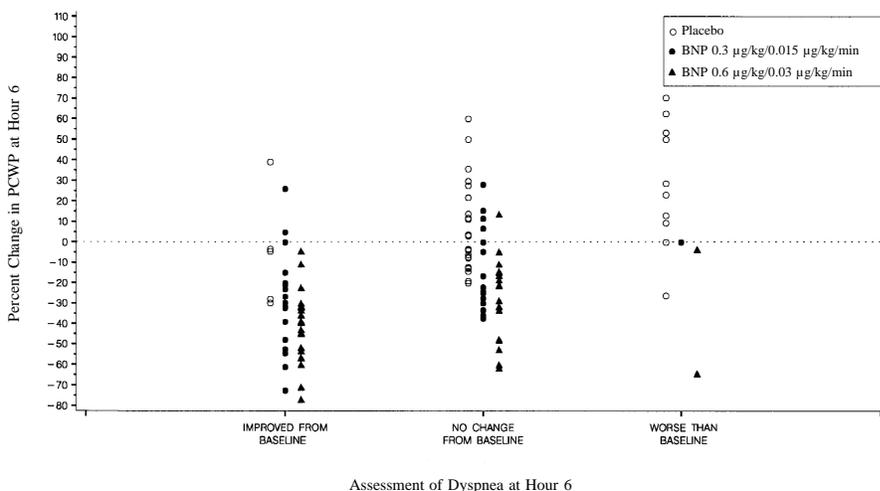
Study 704.325  
Global Assessment of Clinical Status by Subject versus PCWP  
at 6 Hours



Subjects are summarized according to the treatment group of randomization. Global assessments made 5 1/2 to 7 hours after start of study drug are presented. PCWP values are obtained from the carry-forward dataset.

Figure B-2

Study 704.325  
Dyspnea versus PCWP  
at 6 Hours



Subjects are summarized according to the treatment group of randomization. Global assessments made 5 1/2 to 7 hours after start of study drug are presented. PCWP values are obtained from the carry-forward dataset.

Generally, regardless of treatment group, subjects who reported improvements in dyspnea tended to also have reductions in PCWP. Also, Natrecor<sup>®</sup> subjects tended to have improvements in both dyspnea and PCWP, while placebo subjects tended to have no change or a worsening of dyspnea by 6 hours as well as an increase in PCWP. While this does not prove a causal relationship between hemodynamic changes and clinical status, there does appear to be a general correlation between these outcome parameters in this study.

#### **7.4 Neurohormones**

Plasma aldosterone levels were reduced from baseline in both Natrecor<sup>®</sup> treatment groups 6 hours after start of study drug administration. In the placebo, 0.015, and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> treatment groups, median changes from baseline in plasma aldosterone levels were +0.6, -2.5, and -1.6  $\mu\text{g}/\text{dL}$ , respectively ( $p = 0.030$  [Kruskal-Wallis]). Median aldosterone was reduced with Natrecor<sup>®</sup> administration both in subjects receiving ACE inhibitors prior to study drug as well as in subjects not receiving ACE inhibitors prior to study drug.

Median changes from baseline in plasma norepinephrine levels 6 hours after start of study drug administration were +36, -75, and +8  $\text{pg}/\text{mL}$  in the placebo and 2 Natrecor<sup>®</sup> dose groups, respectively ( $p = 0.370$  [Kruskal-Wallis]).

Plasma renin levels were not analyzed due to technical problems with sample collection and assay.

#### **7.5 Diuresis and Diuretic Usage**

Among those subjects who did not receive diuretics during the initial 6-hour urine collection period, the mean urine output per hour in the placebo, 0.015, and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> treatment groups was 63.9, 92.0, and 109.9  $\text{mL}/\text{h}$ , respectively ( $p = 0.004$  [omnibus F test]). The mean net urine output (i.e., urine output minus fluid intake) for this period for the three respective groups was -32.3, -3.3, and +15.9  $\text{mL}/\text{h}$  ( $p = 0.013$  [omnibus F test]).

Over the first day of therapy, the Natrecor<sup>®</sup> treatment groups tended to have a greater weight loss than the control group, presumably due to a greater net diuresis. Mean changes in weight from baseline to day 2 were 0.0, -1.3, and -1.1  $\text{kg}$ , respectively ( $p = 0.109$  [omnibus F test]).

During the first 24 hours of treatment, there was less need for diuretic therapy in the Natrecor<sup>®</sup> groups than in the control group. During this period, 90%, 72%, and 50% of subjects in the control, 0.015, and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> treatment groups, respectively, received diuretics ( $p < 0.001$  [Fisher]).

#### **7.6 Other Assessments**

Neither the length of hospitalization (i.e., from the initiation of study drug through initial hospital discharge) nor the need for readmission after discharge (through day 21) differed between treatment groups. The median length of the initial hospitalization was 7, 8, and

7 days in the placebo/control group, 0.015, and 0.03 µg/kg/min Natrecor® dose groups, respectively ( $p = 0.281$  [Kruskal-Wallis]).

Among those subjects discharged by day 21 of the study, 1, 4, and 4 subjects in the three treatment groups, respectively, were readmitted for any reason by day 21 ( $p = 0.229$  [Fisher]). Most of these admissions were not related to recurrence of CHF, but rather were due to unrelated or pre-existing medical conditions, such as emphysema, diabetes, deep venous thromboses, or infections. In the three treatment groups, 0, 1, and 1 subjects were readmitted for recurrent CHF by day 21.

In the control, 0.015, and 0.03 µg/kg/min Natrecor® treatment groups, 1, 1, and 5 subjects, respectively, required emergent intubation by day 21 ( $p = 0.195$  [Fisher]). These intubations were usually not due directly to worsening of CHF but rather due to other acute adverse events that were believed to be unrelated to Natrecor®.

Ultrafiltration for fluid overload was instituted by day 21 in 0, 0, and 1 subject in the three treatment groups, respectively ( $p = 1.000$  [Fisher]). Dialysis was instituted in 1, 0, and 2 subjects in the three treatment groups, respectively. None of the events leading to these interventions were believed to be related to Natrecor® administration.

### **7.7 Mortality**

All-cause mortality through day 21 was 5% for all subjects and was identical across the three treatment groups. Two (5%), 2 (5%), and 2 (5%) subjects in the control and two Natrecor® dose groups, respectively, died by day 21.

### **7.8 Subgroup Analyses**

The effect of demographics and various parameters of baseline status and prior use of medication on hemodynamic responses (PCWP, CI, and SBP) utilizing a carry-forward analysis were assessed.

In general, all subgroups examined had a beneficial hemodynamic response to Natrecor® infusion. Of note, even subjects with the most severely decompensated CHF at enrollment (as defined by NYHA Class IV, PCWP  $\geq 26$  mm Hg or CI  $< 2.0$  L/min/m<sup>2</sup>) had an improvement in cardiac function during Natrecor® administration. It is also interesting to note that subjects with low SBPs at baseline respond to study drug infusion well, exhibiting beneficial effects on PCWP and CI accompanied by an increase in BP during Natrecor® infusion (presumably due to an increase in CI).

Prior ACE inhibitor usage did not significantly alter the hemodynamic effects of Natrecor® or increase the incidence of symptomatic hypotension reported during the first 24 hours. Similarly, usage of digoxin or beta-blockers also did not significantly alter the hemodynamic effects of Natrecor®.

Subjects with renal insufficiency, defined as baseline creatinine  $\geq 2.0$  mg/dL, did not have an altered hemodynamic response to Natrecor<sup>®</sup> or an increased incidence of symptomatic hypotension.

## **8. Efficacy Conclusions for Study 704.325**

Infusion of both the 0.015 and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  doses of Natrecor<sup>®</sup> resulted in rapid decreases in PCWP that were evident by the time of the first hemodynamic assessment in this study (1.5 hours). According to the protocol-specified “worst outcome” analysis, at the primary efficacy evaluation time point (i.e., 6 hours), median PCWP had actually increased from baseline by 7.3% in the placebo group (reflecting the acutely decompensated medical status of these subjects) but had decreased by 20.0% and 32.6% in 0.015 and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> treatment groups, respectively ( $p < 0.001$  [Kruskal-Wallis]). Similar results were obtained utilizing a carry-forward analysis. Thus, highly statistically significant results were achieved for the primary efficacy endpoint.

IV infusion of Natrecor<sup>®</sup> resulted in rapid and statistically significant reductions in MRAP, SVR, PAP, and SBP compared to placebo. Dose-related increases in CI, stroke volume, and stroke volume index also occurred during Natrecor<sup>®</sup> treatment without an increase in heart rate. Thus, Natrecor<sup>®</sup> increases cardiac output without increasing the work of the heart (i.e., without increasing the heart rate times pressure product).

Compared to placebo, administration of both the 0.015 and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  doses of Natrecor<sup>®</sup> resulted in a rapid and significant improvement in overall clinical status in the majority of subjects, as assessed by both the physician and the subject. Six hours after the initiation of study drug administration, 60% and 67% of subjects in the 0.015 and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> treatment groups reported an improvement in clinical status compared to only 14% in the placebo group ( $p < 0.001$  [Kruskal-Wallis]). Compared to placebo, Natrecor<sup>®</sup> administration also resulted in a rapid improvement in specific symptoms of CHF, such as dyspnea, fatigue, lightheadedness, and decreased appetite. Clinical status improvement generally correlated with hemodynamic improvement.

With longer Natrecor<sup>®</sup> treatment, the number of patients reporting an improvement in clinical status and specific symptoms of CHF continued to increase. Twenty-four hours after start of study drug, 80% and 88% of subjects in the 0.015 and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> treatment groups reported an improvement in clinical status (i.e., reported feeling better or markedly better) compared to pretreatment. As of the last recorded assessment available, 80%, 85%, and 93% of subjects in the active control, 0.015, and 0.03  $\mu\text{g}/\text{kg}/\text{min}$  Natrecor<sup>®</sup> treatment groups reported an improvement in clinical status.

Administration of both doses of Natrecor<sup>®</sup> was also associated with a reduction in plasma aldosterone levels, even in subjects on ACE inhibitor therapy. This effect on aldosterone may result in enhanced diuretic and relative potassium-sparing properties of Natrecor<sup>®</sup>. Indeed, during the initial 6-hour evaluation period, administration of Natrecor<sup>®</sup> was also associated

with an increase in urine output compared to placebo. During the first 24 hours of therapy, Natrecor® administration was also associated with an increase in weight loss and a reduced need for concomitant diuretics compared to control.

Thus, this study demonstrates that, when administered to patients with acutely decompensated CHF requiring hospitalization, Natrecor® therapy results in a rapid improvement in both hemodynamics and clinical status, as assessed by both the patients themselves or their physician.

# Appendix C

## Study 704.326 Efficacy Synopsis

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### Table Of Contents

	<u>Page</u>
1. <i>Objective</i> .....	130
2. <i>Study Design</i> .....	130
3. <i>Key Inclusion/Exclusion Criteria</i> .....	131
4. <i>Statistical Methods</i> .....	131
4.1 Objectives .....	131
4.2 Analysis Population .....	132
4.3 Analysis Methods .....	132
5. <i>Subject Enrollment, Dosing, and Disposition</i> .....	132
6. <i>Subject Demographics and Baseline Characteristics</i> .....	133
7. <i>Efficacy Results</i> .....	134
7.1 Global Assessment of Clinical Status .....	134
7.2 Symptoms of CHF .....	135
7.3 Changes in Weight and Diuretic Usage .....	136
7.4 Parenteral Vasoactive Therapy .....	136
7.5 Intubation, Dialysis, and Central Hemodynamic Monitoring .....	137
7.6 Length of Hospital Stay and Need for Readmission .....	137
7.7 Mortality .....	138
7.8 Subgroup Analyses .....	138
8. <i>Efficacy Conclusions for Study 704.326</i> .....	139

## Study 704.326

### A Randomized, Open-Label, Active-Controlled, Multicenter Phase III Safety Study of Two Doses of Natrecor® hBNP Administered as a Continuous Infusion in the Treatment of Decompensated CHF

#### 1. Objective

The objective of study 704.326 was to gain additional safety and clinical experience with Natrecor® in the treatment of decompensated CHF requiring inpatient parenteral vasoactive therapy.

#### 2. Study Design

This was a multicenter, randomized, open-label, active-controlled Phase III safety study designed to enroll 300 subjects with symptomatic, decompensated CHF for whom inpatient parenteral vasoactive therapy (other than, or in addition to, parenteral diuretics) was deemed appropriate. Eligible patients were randomized to one of three treatment groups:

- A standard care agent for the treatment of CHF.
- Natrecor®: IV bolus of 0.3 µg/kg followed by a 0.015 µg/kg/min infusion.
- Natrecor®: IV bolus of 0.6 µg/kg followed by a 0.03 µg/kg/min infusion.

Natrecor® was to be administered intravenously as a fixed-dose infusion, although dose increases or decreases were permitted if clinically indicated. The standard care agent was to be a single parenteral vasoactive agent routinely used for the short-term management of decompensated CHF, such as IV nitroglycerin (NTG), dobutamine, or milrinone; the choice of standard care agent and its dose was left to the discretion of the investigator. Treatment assignment to standard care or Natrecor® was open-label; for Natrecor® subjects, assignment to the 0.015 or 0.03 µg/kg/min dose was double-blinded.

Each subject was permitted to receive diuretics as clinically indicated. Each subject may have had an arterial line or Swan-Ganz catheter if it was deemed clinically necessary by the attending physician, although it was not a requirement of the study protocol. The duration of therapy with the initial study drug (Natrecor® or standard care agent) varied according to each patient's cardiopulmonary status as determined by the attending physician. At the discretion of the investigator, a second parenteral vasoactive agent may have been added to, or substituted for, the initial study drug at any time. The attending physician determined when parenteral vasoactive therapy was discontinued and how the transition from parenteral therapy for CHF to oral therapy should be undertaken.

Specific symptoms of decompensated CHF were assessed at baseline; clinical status (i.e., global assessment and specific symptoms) was assessed, relative to baseline status, at 6 hours, 24 hours, and at the end of parenteral therapy. A general chemistry panel and complete blood cell count were obtained pretreatment and within 24 hours after discontinuation of all parenteral therapy for this episode of decompensated CHF. Adverse events were followed through day 14. Blood samples for assessment of serum anti-BNP antibodies were obtained at baseline and at day 21 (for subjects receiving Natrecor®). Also at day 21, each subject's clinical course was reviewed with regard to mortality status, duration of initial hospitalization, the need for readmission, and the need for dialysis and intubation during the 21-day study period.

### **3. Key Inclusion/Exclusion Criteria**

Subjects must have been at least 18 years of age, with a previous history of chronic CHF, now presenting with symptomatic, decompensated CHF for which in-patient vasoactive parenteral therapy (other than, or in addition to, diuretics) was deemed appropriate.

Potential subjects with any of the following were not eligible for this study: ongoing myocardial ischemia; significant valvular stenosis, obstructive cardiomyopathy, constrictive pericarditis, primary pulmonary hypertension, biopsy-proven active myocarditis, or complex congenital heart disease; recent stroke or significantly compromised central nervous system perfusion; cardiogenic shock, systolic blood pressure consistently less than 90 mm Hg or other evidence of significant hemodynamic instability which required the immediate institution of inotropic/pressor support.

In addition, potential subjects already being treated with a parenteral vasoactive agent (i.e., an intravenous inotrope or vasodilator) for this episode of decompensated CHF were excluded from the study if they had received this therapy for more than 4 hours or could not discontinue it for the protocol-specified washout period.

### **4. Statistical Methods**

#### **4.1 Objectives**

The primary purpose of the statistical summarization of this study was to facilitate the clinical assessment of drug safety. To this end, statistical inference was conducted largely as a screening tool.

A secondary purpose was the evaluation of various measures of clinical outcome. Clinical outcomes of particular interest were the global assessments of clinical status and the symptoms of CHF evaluated over time within each group. The assessment of the equivalence or superiority of Natrecor® to standard care agents was not an objective of the protocol.

## 4.2 *Analysis Population*

Analyses summarized subjects “as treated,” that is, according to the treatment actually received. There were two subjects with treatment assignment errors. Both subjects were randomized to 0.03 µg/kg/min Natrecor®; one subject was treated with standard care, the other with 0.015 µg/kg/min Natrecor®. No subjects were explicitly excluded from analysis, though not all subjects are represented in all analyses because of data constraints (e.g., an analysis may require that observations be made within a given time window).

## 4.3 *Analysis Methods*

Within-group changes from baseline were tested with either a one-sample *t* test, one-sample Wilcoxon test, or the binomial test, as appropriate for the endpoint.

Though not specified by protocol, between-group comparisons were made for exploratory purposes. Non-specific treatment group differences were tested (using, for example, the omnibus F test, Kruskal-Wallis test, or the generalized Fisher exact test, as appropriate), followed by pairwise comparisons (e.g., pairwise contrasts, two-sample Wilcoxon, or Fisher’s exact test). No adjustments were made for multiple comparisons.

All reported p values are two-sided.

## 5. *Subject Enrollment, Dosing, and Disposition*

In this study, 305 subjects were enrolled by 46 clinical investigators in the U.S. Four (1%) of the 305 subjects were lost to follow-up before day 21; one of these subjects was in the standard care group and 3 were in the 0.015 µg/kg/min Natrecor® treatment group. Seventeen subjects died by day 21. All other subjects were followed through the complete 21-day study period. (Note: After NDA filing, each of these 4 subjects lost to follow-up was subsequently located and found to be alive through day 21.)

One-hundred-two subjects were analyzed in the standard care group. These subjects received a number of different agents as their initial standard care agent (i.e., study drug): 58 (57%) received dobutamine, 19 (19%) received milrinone, 18 (18%) received nitroglycerin, 6 (6%) received dopamine, and 1 (1%) received amrinone as their initial standard care agent. In the control group, the median length of therapy with the initial standard care agent (including interruptions) was 47.0 hours (range, 0.5 hours to beyond study day 21 [504 hours]).

One-hundred-three and 100 subjects were treated with 0.015 and 0.03 µg/kg/min Natrecor®, respectively. The median length of Natrecor infusion in these two treatment groups was 40.0 hours (range, 2.3 to 283.2 hours) and 25.6 hours (range, 2.2 to 169.0 hours), respectively.

## 6. Subject Demographics and Baseline Characteristics

Of the 305 subjects enrolled, 207 were men and 98 were women. The mean age ( $\pm$  standard deviation [SD]) for all enrolled subjects was 63.9 years  $\pm$  13.1 years, and 158 subjects (52%) were  $\geq$  65 years of age. Of enrolled subjects, 201 (66%) were white, 67 (22%) were black, 31 (10%) were Hispanic, and 3 (1%) were Asian. Mean weight ( $\pm$  SD) was 80.7  $\pm$  21.5 kg.

Prior to this hospital admission, 1 ( $<$  1%) subject was classified as NYHA Class I, 23 (8%) were classified as NYHA Class II, 170 (56%) were NYHA Class III and 111 (36%) as NYHA Class IV.

Baseline characteristics are summarized in Table C-1.

**Table C-1**  
**Study 704.326**  
**Subject Demographics and Baseline Status**

Baseline Parameter	Standard Care (n = 102)	Natrecor® 0.015 $\mu$ g/kg/min (n = 103)	Natrecor® 0.03 $\mu$ g/kg/min (n = 100)	All Subjects (n = 305)	p value
<b>Gender</b>					
Male	72%	65%	67%	68%	0.610 <sup>1</sup>
Female	28%	35%	33%	32%	
<b>Age</b>					
mean $\pm$ SD (years)	63.2 $\pm$ 13.6	63.3 $\pm$ 13.6	65.3 $\pm$ 12.1	63.9 $\pm$ 13.1	0.453 <sup>2</sup>
% $\geq$ 65 years	51%	50%	55%	52%	0.723 <sup>1</sup>
<b>NYHA Class</b>					
I	0%	0%	1%	0%	0.647 <sup>3</sup>
II	6%	6%	11%	8%	
III	60%	55%	52%	56%	
IV	34%	39%	36%	36%	
<b>Symptoms of CHF</b>					
Dyspnea	100%	98%	98%	99%	0.597 <sup>3</sup>
Fatigue	98%	94%	100%	97%	0.050 <sup>3</sup>
Lightheadedness	44%	44%	41%	43%	0.868 <sup>3</sup>
Decreased appetite	58%	63%	52%	58%	0.351 <sup>3</sup>

<sup>1</sup> Fisher's Exact Test

<sup>2</sup> Omnibus F test

<sup>3</sup> Kruskal-Wallis test on the 3- or 4-category ordinal variable

Many subjects had a history of cardiac arrhythmias; 30% had a history of frequent premature ventricular contractions (PVCs), 19% had a history of nonsustained ventricular tachycardia (NSVT), and 8% had a history of sustained ventricular tachycardia or ventricular fibrillation, and 40% of subjects had a history of atrial fibrillation. Also, 68% of subjects had a history of hypertension, 70% had a history of coronary artery disease, and 38% had a history of chronic renal insufficiency.

## 7. Efficacy Results

### 7.1 *Global Assessment of Clinical Status*

Natrecor® administration (at both the 0.015 and 0.03 µg/kg/min doses) resulted in a rapid improvement in overall clinical status, as assessed independently by both the physician and the subject. The subjects' assessment of global clinical status 6 hours after start of study drug is shown in Table C-2.

**Table C-2**

**Study 704.326**  
**Global Assessment of Clinical Status by the Subject at 6 Hours**  
**(Subjects as Treated; Windowed Analysis)**

	Percent of Subjects With Each Response		
	Standard Care*	Natrecor® 0.015 µg/kg/min*	Natrecor® 0.03 µg/kg/min*
<b>Subjects Enrolled:</b>	<b>n = 102</b>	<b>n = 103</b>	<b>n = 100</b>
<b>Subjects Summarized:</b>	<b>n = 84</b>	<b>n = 86</b>	<b>n = 82</b>
Markedly Better	10%	12%	5%
Better	55%	56%	55%
No Change	32%	30%	35%
Worse	4%	2%	5%
Markedly Worse	0%	0%	0%

Subjects are summarized according to the treatment administered. Assessments made 5 1/2 to 7 hours after start of study drug infusion were eligible for summarization.

\* p < 0.001 compared to pretreatment (1-sample Wilcoxon)

These assessments relative to baseline status (i.e., test of “no change”) were highly statistically significant (p < 0.001 [1-sample Wilcoxon]) at 6 hours for all three treatment groups. The majority of subjects (≥ 60%) in each of the three groups were improved by 6 hours. The assessment of clinical status by the physician at 6 hours yielded similar results (data not shown).

By 24 hours after start of study drug, most subjects were improved. For example, the subjects' self-assessments of global clinical status (for subjects in the Natrecor® 0.015 µg/kg/min treatment group) at various time points are shown in Table C-3:

**Table C-3**  
**Study 704.326**  
**Global Assessment of Clinical Status by the Subject at Various Time Points**  
**(0.015 µg/kg/min Natrecor® Group)**

	Percent of Subjects With Each Response		
	At 6 Hours	At 24 Hours	End of Therapy
<b>Subjects Enrolled:</b>	<b>n = 103</b>	<b>n = 103</b>	<b>n = 103</b>
<b>Subjects Summarized:</b>	<b>n = 86</b>	<b>n = 99</b>	<b>n = 101</b>
Markedly Better	12%	23%	34%
Better	56%	61%	54%
No Change	30%	14%	5%
Worse	2%	2%	7%
Markedly Worse	0%	0%	0%

Subjects are summarized according to the treatment administered. Assessments made 5 1/2 to 7 hours, 20 to 28 hours, or at least 20 hours after start of study drug were eligible for summarization at 6 hours, 24 hours, or end of therapy, respectively.

These assessments relative to baseline (i.e., test of “no change”) were highly statistically significant ( $p < 0.001$  [1-sample Wilcoxon]) at all three assessment time points. Similar results were obtained in the 0.03 µg/kg/min Natrecor® dose group and standard care group or when the physicians’ assessments were analyzed.

The improvement in global clinical status overtime for all 3 treatment groups is shown graphically in Item 5, Figure 5–7.

## 7.2 Symptoms of CHF

Subjects were also assessed for the presence and severity of specific symptoms of CHF at baseline, and for their severity relative to baseline (improved, no change, worse) at 6 and 24 hours after the initiation of study drug and at the end of all parenteral vasoactive therapy. At baseline, 99% had dyspnea, 97% had fatigue, 43% had lightheadedness, and 58% of subjects had decreased or absent appetite.

Both doses of Natrecor® resulted in a rapid improvement in each of these symptoms. The percent of subjects who reported an improvement in each symptom only 6 hours after start of study drug is shown in Table C-4.

**Table C-4**  
**Study 704.326**  
**Symptoms of CHF at 6 Hours**  
**(Subjects as Treated; Windowed Analysis)**

Subjects Enrolled: Subjects Summarized:	Percent Reporting Improvement			Treatment Inference
	Standard Care (n = 102) (n = 84–85)	Natrecor®		
		0.015 µg/kg/min (n = 103) (n = 88–89)	0.03 µg/kg/min (n = 100) (n = 79–80)	
Dyspnea	61%	63% p = 0.726 <sup>b</sup>	55% p = 0.515 <sup>b</sup>	p = 0.583 <sup>a</sup>
Fatigue	30%	30% p = 0.662 <sup>b</sup>	33% p = 0.505 <sup>b</sup>	p = 0.787 <sup>a</sup>
Lightheadedness	13%	19% p = 0.594 <sup>b</sup>	14% p = 0.340 <sup>b</sup>	p = 0.369 <sup>a</sup>
Decreased Appetite	23%	27% p = 0.531 <sup>b</sup>	20% p = 0.621 <sup>b</sup>	p = 0.534 <sup>a</sup>

Subjects are summarized according to the treatment administered. Assessments made 5 1/2 to 7 hours after start of study drug infusion were eligible for summarization.

<sup>a</sup> Kruskal-Wallis test on 3-category ordinal variable (worse, no change, improved).

<sup>b</sup> Pairwise comparison to standard care, two-sample Wilcoxon test on 3-category ordinal variable.

The percent of subjects with an improvement in symptoms with Natrecor® administration was generally at least as high as the percent of subjects in the standard care group showing improvement at each time point assessed.

The percentage of subjects reporting improvement in these symptoms continued to increase over the course of therapy in all three treatment groups (see Item 5, Figure 5–8 on page 43).

### 7.3 Changes in Weight and Diuretic Usage

All three treatment groups exhibited a statistically significant mean decrease in weight during the hospitalization, presumably reflecting a net diuresis. By day 2, for example, the mean decrease in weight in the standard care and 0.015 and 0.03 µg/kg/min Natrecor® treatment groups was 0.9, 1.1, and 0.7 kg, respectively (p = 0.453 [omnibus F test]).

There was less need for diuretic administration in the Natrecor® treatment groups than in the standard care group. In the standard care and in the 0.015 and 0.03 µg/kg/min Natrecor® treatment groups, diuretics were administered during study drug infusion in 97%, 82%, and 74% of subjects, respectively (p < 0.001 [Fisher]).

### 7.4 Parenteral Vasoactive Therapy

The median total duration of treatment with any vasoactive parenteral agent (i.e., initial study drug or any additional vasoactive agent) was 48.0 hours (range, 3.0 hours to > 21 days) for the standard care group, 42.4 hours (range, 2.3 hours to > 21 days) for the 0.015 µg/kg/min

Natreacor<sup>®</sup> group, and 41.3 hours (range, 2.2 hours to > 21 days) in the 0.03 µg/kg/min Natreacor<sup>®</sup> group (p = 0.421 [Kruskal-Wallis]).

In all three treatment groups, most subjects stayed on their initial parenteral vasoactive agent (i.e., the initial standard care agent for the control group or Natreacor<sup>®</sup>) as the sole parenteral therapeutic agent until they were improved clinically and could be transitioned to oral medications. Only 2 (2%), 9 (9%), and 12 (12%) subjects in the standard care and 0.015 and 0.03 µg/kg/min Natreacor<sup>®</sup> groups discontinued therapy with their respective initial agents and then were treated with another parenteral vasoactive agent. Also, additional parenteral vasoactive agents were added to the initial agent in only 8 (8%), 8 (8%), and 12 (12%) of the subjects in the standard care and 0.015 and 0.03 µg/kg/min Natreacor<sup>®</sup> groups, respectively. Thus, the use of additional parenteral vasoactive agents in addition to, or instead of, the initial agent was infrequent in all groups. Among subjects assigned to the 0.015 and 0.03 µg/kg/min Natreacor<sup>®</sup> groups, 83% and 76%, respectively were treated with Natreacor<sup>®</sup> as the sole parenteral vasoactive agent during this hospitalization.

### ***7.5 Intubation, Dialysis, and Central Hemodynamic Monitoring***

Fewer subjects in the Natreacor<sup>®</sup> groups than in the standard care group required emergent intubation for respiratory support. Eight (8%), 2 (2%), and 4 (4%) subjects in the standard care and 0.015 and 0.03 µg/kg/min Natreacor<sup>®</sup> dose groups were intubated by day 21 (p = 0.126 [Fisher]).

No subjects required ultrafiltration and few subjects in any group required dialysis for worsening renal function or fluid overload. Two (2%), 1 (1%), and 2 (2%) subjects in the standard care and two Natreacor<sup>®</sup> dose groups were dialyzed by day 21 (p = 0.610 [Fisher]).

A Swan-Ganz catheter was utilized in the care of 20 (20%), 13 (13%), and 23 (23%) subjects in the standard care and two Natreacor<sup>®</sup> dose groups. No central hemodynamic data were collected in this study.

### ***7.6 Length of Hospital Stay and Need for Readmission***

The length of hospitalization (i.e., from the initiation of study drug through initial hospital discharge) did not differ significantly among treatment groups. The median length of the initial hospitalization was 5, 6, and 5 days in the standard care and 0.015 and 0.03 µg/kg/min Natreacor<sup>®</sup> dose groups, respectively (p = 0.743 [Kruskal-Wallis]).

Among those subjects discharged by day 21, there was a trend towards fewer readmissions through day 21 in the Natreacor<sup>®</sup> groups compared to the standard care group. In the standard care and 0.015 and 0.03 µg/kg/min Natreacor<sup>®</sup> treatment groups, 16 of 97 (16%), 8 of 101 (8%), and 11 of 96 (11%) discharged subjects, respectively, were readmitted for any reason by day 21 (p = 0.181 [Fisher], p = 0.082 for comparison of standard care versus the 0.015 µg/kg/min Natreacor<sup>®</sup> group).

There were also fewer readmissions by day 21 for recurrent CHF in the Natrecor<sup>®</sup> dose groups than in the standard care group. In the standard care and 0.015 and 0.03 µg/kg/min Natrecor<sup>®</sup> treatment groups, 9 (9%), 4 (4%), and 4 (4%) subjects, respectively, were readmitted by day 21 for recurrent CHF ( $p = 0.238$  [Fisher]).

These and other measures of medical intervention are summarized in Table C–5.

**Table C–5**  
**Study 704.326**  
**Medical Interventions**

<b>Baseline Parameter</b>	<b>Standard Care (n = 102)</b>	<b>Natrecor<sup>®</sup> 0.015 µg/kg/min (n = 103)</b>	<b>Natrecor<sup>®</sup> 0.03 µg/kg/min (n = 100)</b>	<b>p value</b>
Duration of parenteral therapy for CHF (median) (hours)	48.0	42.4	41.3	0.421 <sup>1</sup>
Length of hospital stay (median) (days)	5	6	5	0.743 <sup>1</sup>
Need for dialysis through day 21	2%	1%	2%	0.610 <sup>2</sup>
Need for emergent intubation through day 21	8%	2%	4%	0.126 <sup>2</sup>
Subjects not discharged by day 21	5%	2%	4%	0.515 <sup>2</sup>
Readmission <sup>3</sup> through day 21 (all-cause)	16%	8%	11%	0.181 <sup>2</sup>
Readmission <sup>3</sup> through day 21 (for CHF)	9%	4%	4%	0.238 <sup>2</sup>

1 Kruskal-Wallis test

2 Fisher's Exact Test

3 Percentages are calculated relative to the number discharged.

## 7.7 Mortality

All-cause mortality through day 21 was comparable among the three treatment groups. Five (5%), 6 (6%), and 6 (6%) of the subjects in the standard care and two Natrecor<sup>®</sup> dose groups, respectively, died by day 21.

## 7.8 Subgroup Analyses

To evaluate the effects of disease severity on responsiveness to Natrecor<sup>®</sup> therapy, the global assessment of clinical status by the subject was analyzed for the subgroup of subjects with NYHA Class III and NYHA Class IV CHF. The percentage of subjects in each subgroup reporting an improvement (i.e., reporting feeling better or markedly better) by 6 hours is shown in Table C–6.

Table C-6

**Study 704.326**  
**Global Assessment of Clinical Status by the Subject at 6 Hours**  
**Subgroups: NYHA Class III and IV CHF**

	Percent of Subjects Reporting an Improvement in Clinical Status		
	Standard Care	Natreacor® 0.015 µg/kg/min	Natreacor® 0.03 µg/kg/min
NYHA Class III	66% (35/53)	64% (29/45)	72% (33/46)
NYHA Class IV	57% (16/28)	69% (25/36)	50% (13/26)

Subjects are summarized according to the treatment administered. Assessments made 5 1/2 to 7 hours after start of study drug infusion were eligible for summarization.

Thus, subjects with both NYHA Class III and NYHA Class IV CHF showed a rapid improvement in clinical status with Natreacor® therapy.

### ***8. Efficacy Conclusions for Study 704.326***

This study demonstrated that, when administered in a conventional hospital setting to patients with acutely decompensated CHF, Natreacor® in doses of 0.015 or 0.03 µg/kg/min resulted in rapid improvements in overall clinical status, as assessed by both the physician and the subject. Within 6 hours after start of infusion, the majority (≥ 60%) of Natreacor® subjects showed an improvement in clinical status; by 24 hours of therapy, most subjects were improved. Natreacor® administration was also associated with rapid improvement in specific symptoms of CHF, such as dyspnea, fatigue, lightheadedness, and decreased appetite. The percent of subjects with an improvement in symptoms with Natreacor® administration was generally at least as high as the percent of subjects in the standard care group showing improvement at each time point assessed.

For most subjects (80%), Natreacor® was administered as the sole vasoactive parenteral agent for the short-term treatment of CHF. A Swan-Ganz catheter was utilized in the management of only 18% of the Natreacor® subjects in this study, demonstrating that the drug can be used safely and effectively without central hemodynamic monitoring. There was less concomitant diuretic administration in the Natreacor® groups than in the standard care group. Fewer subjects in the Natreacor® groups than in the standard care group required emergent intubation for respiratory support. Neither all-cause mortality nor the need for dialysis through day 21 differed significantly between the Natreacor® groups and the standard care group. By day 21, hospital readmissions for recurrent CHF or other events had occurred less frequently for subjects administered Natreacor® than for those administered standard care agents.

Thus, this study supports a role for Natreacor® as a first-line parenteral agent for the short-term treatment of CHF.