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01 May 2001

Advisors and Consultants Staff
Food and Drug Administration
Attention: Lanise Chiles
5630 Fishers Lane, HFD-21
Rockville, MD 20857

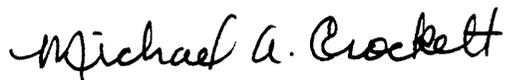
**Reference: NDA 20-920
Natrecor® (nesiritide)
Cardiovascular and Renal Drugs Advisory Committee Briefing Document**

Dear Ms. Chiles:

Please find enclosed 40 letters that are being provided to inform the advisory committee members that Scios' briefing documents for the Natrecor® NDA 20-920 are available for public disclosure without redaction, despite the confidential marker on each page.

These letters are being provided as agreed to by Joan Standert, Executive Secretary for the Cardiovascular and Renal Drugs Advisory Committee. Should you have any questions regarding this submission, or require additional copies, please contact Klara Dickinson of my staff at (408) 616-8591.

Sincerely,



Michael A. Crockett,
Associate Director, Regulatory Affairs



**NDA 20-920
Cardiovascular and Renal Drugs
Advisory Committee
Briefing Document**

Natreacor[®] (nesiritide) for Injection

25 May 2001

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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_{area}	volume of distribution area
CNP	C-type natriuretic peptide	V_c	volume of distribution of the central compartment
CO	cardiac output	V_{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		
PVB	premature ventricular beats		

Item 1

Executive Summary

Clinical Background

Human BNP is an endogenous 32-amino-acid peptide hormone produced by the ventricular myocardium. Natrecor® (nesiritide) is a recombinantly manufactured preparation of human B-type natriuretic peptide (hBNP). Natrecor® has the same 32-amino-acid sequence as the endogenous hBNP hormone.

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 produced 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 profile of effects suggests that administration of exogenous hBNP would have therapeutic benefit in the short-term treatment of CHF. Human BNP is believed to exert many of its actions by binding to the cell surface guanylyl cyclase-A receptor (the GC-A receptor), resulting in the synthesis of cyclic guanosine 3',5'-cyclic monophosphate (cyclic GMP) as a second messenger, which leads to smooth muscle cell relaxation and subsequent vasodilation. As the GC-A receptor is present both in endothelial cells as well as in smooth muscle cells, hBNP is an endothelial cell-independent vasodilator. Human BNP has no direct inotropic nor chronotropic activity.

Human BNP is metabolized by internalization by the natriuretic peptide clearance receptor as well as via hydrolysis by neutral endopeptidases that are present on the vascular luminal surface. As a result of the ubiquitous presence of these dual clearance pathways, the clearance of BNP is not hampered in patients with end-organ failure such as kidney or liver failure.

Scios Inc. has developed Natrecor® as an IV agent for the short-term treatment of patients with acute decompensated CHF. Throughout the development program, the primary efficacy endpoint has been pulmonary capillary wedge pressure (PCWP). Highly statistically significant reductions in PCWP have been achieved in each of the 7 studies in which PCWP was measured, including the pivotal efficacy studies: studies 704.311, 704.325, and the VMAC Trial (study 704.339). Natrecor® has also been associated with statistically significant improvements in the symptoms of acute decompensated CHF (study 704.325 and the VMAC trial).

The Natrecor® NDA was filed with the Agency on April 24, 1998 for the short-term treatment of patients with acute decompensated CHF. On January 29, 1999, Scios presented the Natrecor® development program before the Cardiovascular and Renal Drugs Advisory

Committee, and the committee voted to recommend that Natrecor® be approved by a vote of 5 to 3. In April 1999, Scios received a non-approval letter from the Agency that raised a number of issues: 1) Expansion of the safety database: in particular, additional experience was desired to better understand the onset and offset characteristics of symptomatic hypotension when Natrecor® is added to standard-care therapies in a typical hospital setting; 2) Need for broader range of CHF patients: including those with active ischemia, preserved systolic function, and those receiving other IV vasoactive agents; 3) Need for an active-controlled study: comparing Natrecor® to an IV vasodilator such as nitroglycerin to provide a clearer characterization of the efficacy and safety profile of Natrecor®, especially as it relates to effects on blood pressure and hypotension; 4) Questions pertaining to symptom evaluations included: the appropriateness of measuring symptoms in patients without dyspnea at rest and the potential bias created by physician evaluations and the knowledge of hemodynamics; 5) Data to support the sustained hemodynamic effects of Natrecor® should be collected; 6) Recommendations for the dosing regimen and dose adjustment should be supported by the trial; 7) The use of IV diuretics and other cardiac therapies should not be restricted.

FDA's Bottom Line

“In such a study, Nesiritide would need to be shown to be as useful as nitroglycerin in attaining clinical benefit without adverse consequence of its more sustained (hemodynamic) effects.”

Scios conducted the VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial, 704.339, to address the issues delineated in the FDA letter. Based on pharmacodynamic modeling, Scios modified the Natrecor® dose to a standard dose of 2 µg/kg bolus, followed by a 0.01 µg/kg/min infusion. This dose utilizes a larger bolus dose and a 33% to 67% lower infusion dose than the doses studied in the pivotal phase III trials summarized in the original NDA.

In addition, the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor® Therapy) trial, 704.329, was completed during the NDA review. The PRECEDENT trial was not directly designed to respond to issues related to the FDA's letter. Rather, the purpose of the PRECEDENT trial was to compare the effects of fixed dose infusions of Natrecor® (0.015 µg/kg/min and 0.03 µg/kg/min) and dobutamine on arrhythmogenesis and heart rate. The results of both trials were submitted in January 2001 as a part of the NDA Amendment.

Response to Clinical Issues

Data from the VMAC trial confirm the efficacy profile of Natrecor® as it was demonstrated in the original NDA. The VMAC data also provide a more sophisticated understanding of the overall safety of Natrecor®, including the relative incidence and characteristics of symptomatic

hypotension, compared to that which occurs with IV nitroglycerin. The VMAC trial fully addressed the Agency’s concerns expressed in the April 1999 letter, as well as those raised by the Cardiovascular and Renal Drugs Advisory Committee.

With the additional Natrecor® experience obtained in the VMAC and the PRECEDENT trials, the Natrecor® clinical development program has demonstrated the following:

Number of subjects: Including the 436 Natrecor® subjects enrolled in the VMAC and PRECEDENT trials, the total number of subjects who have received IV Natrecor® to date is 965.

Range of subjects: The patient population treated with Natrecor® included a broad range of CHF patients, including those with acute coronary syndromes, preserved systolic function, significant arrhythmias, and renal insufficiency.

Concomitant medication: Multiple “real-world” studies in the Natrecor® CHF program have resulted in significant experience with the concomitant administration of Natrecor® with common cardiac medications such as ACE inhibitors, digoxin, diuretics, nitrates, antiarrhythmics, dobutamine, and dopamine.

Safety profile: In the VMAC trial, Natrecor® is better tolerated when compared to nitroglycerin. During the first 24 hours of treatment, fewer subjects treated with Natrecor® experienced side effects overall, and fewer Natrecor® subjects reported headache and abdominal pain, compared to those treated with nitroglycerin (Table 1–1).

Table 1–1

**Selected Adverse Events During the First 24 Hours
Number (%) of Subjects**

	Nitroglycerin (n = 216)	Natrecor® Fixed-Dose (n = 211)	All Natrecor® (n = 273)	p-value*
Any Adverse Event	146 (68%)	105 (50%)	140 (51%)	
Headache	44 (20%)	19 (9%)	21 (8%)	< 0.001
Asymptomatic Hypotension	17 (8%)	17 (8%)	23 (8%)	0.869
Symptomatic Hypotension	10 (5%)	10 (5%)	12 (4%)	1.00
Abdominal Pain	11 (5%)	2 (1%)	4 (1%)	0.032

* Fisher’s Test: All Natrecor® compared to nitroglycerin.

Characteristics of symptomatic hypotension: The characteristics of the effects on blood pressure observed with Natrecor® are clearly defined. Symptomatic hypotension occurred at a rate of 4% in all Natrecor® subjects, compared to 5% in nitroglycerin subjects within the first 24 hours of therapy. There were no significant differences in the time of onset, severity, or the need for interventions for symptomatic hypotension compared to nitroglycerin. The duration of symptomatic hypotension was longer with Natrecor®,

although blood pressure improvement was evident within 15 minutes of a dose reduction or dose discontinuation. No hypotension event led to adverse sequelae.

Efficacy: Data from the VMAC trial demonstrated that Natrecor® significantly lowered PCWP faster (within the first 15 minutes after start of study drug, Figure 1–1) than nitroglycerin or placebo and maintained this significant effect compared to nitroglycerin for at least 24 hours (Figure 1–2). Natrecor® produced a sustained lowering of PCWP for at least 48 hours with no evidence of tachyphylaxis.

Figure 1–1

**Primary Endpoint: 3-Hour Change from Baseline in PCWP
(All Treated Catheterized Subjects, as Randomized)
The VMAC Trial**

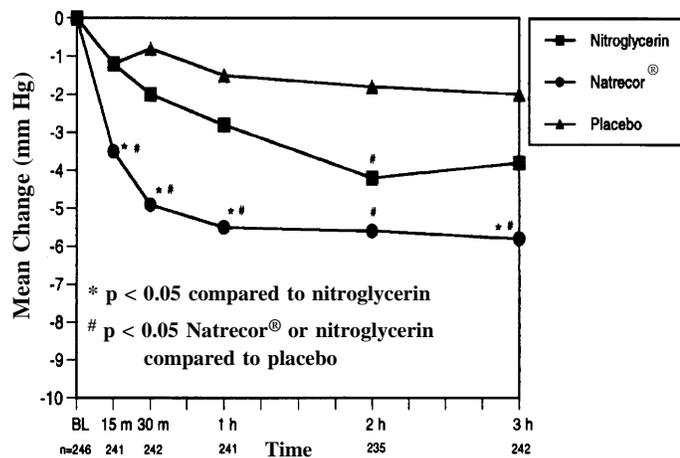
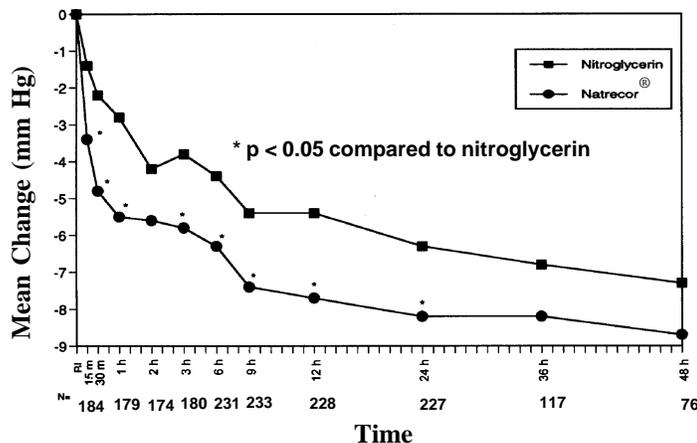


Figure 1–2

**PCWP through 48 Hours (Change from Baseline)
(All Treated Catheterized Subjects, As Randomized)
The VMAC Trial**



Note: Placebo subjects crossed over to double-blinded active treatment after 3 hours.

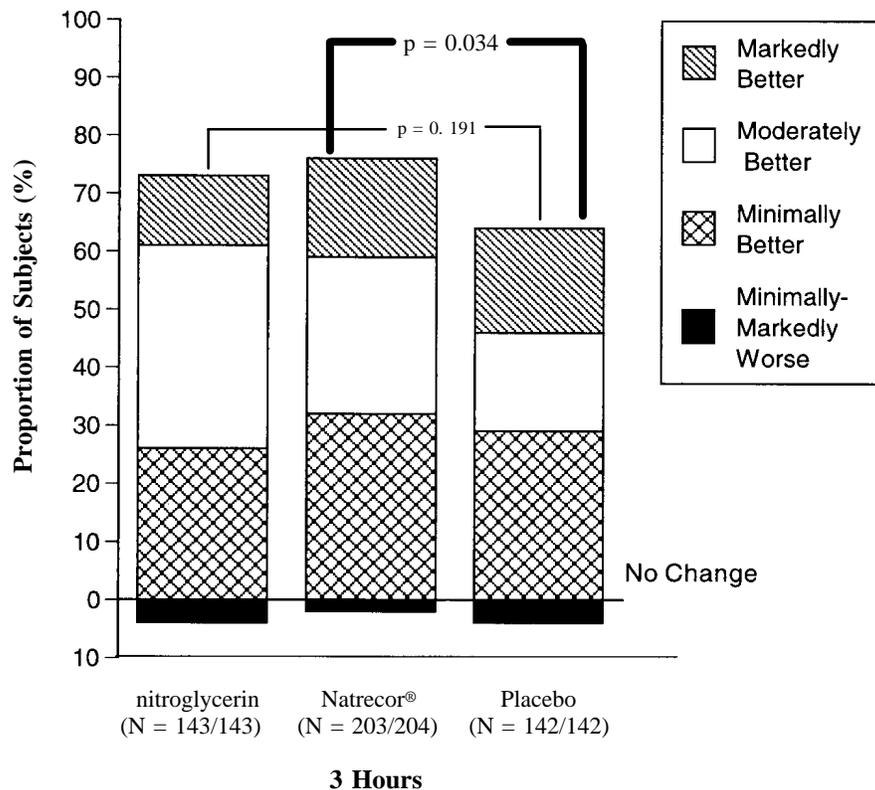
Ease of use: The predictable hemodynamic effects of a fixed dose of Natrecor® should lead to greater ease of use in the clinical setting, compared to the titration strategy that must be used with nitroglycerin.

Blinding: The methodology used to measure clinical benefit in the VMAC trial prospectively sought to minimize bias and to maximize the blinded nature of the assessments. Subjects performed their own assessments without assistance from the Investigator or study staff and without the knowledge of their cardiac hemodynamics.

Rapid symptomatic improvement: Clinical benefit compared to placebo was demonstrated under blinded conditions at the prespecified primary endpoint time point of 3 hours (Figure 1–3). Significantly more Natrecor® subjects experienced an improvement in dyspnea compared to placebo. The differences observed between nitroglycerin and placebo are not statistically significant.

Figure 1–3

Dyspnea through 3 Hours
(All Treated Subjects, as Randomized)



Dosing: The adjustable dose of Natrecor® in the VMAC trial demonstrated that the dose of Natrecor® can be adjusted when clinically indicated without significantly increasing risk to the patient. For example, the frequency of symptomatic hypotension in the first

24 hours observed with the fixed-dose of 0.01 µg/kg/min (preceded by a 2 µg/kg bolus) and the adjustable dose groups was 5% and 3%, respectively.

Monitoring requirements: Due to the safety profile and effectiveness of the standard fixed-dose Natrecor[®], treatment does not necessitate invasive hemodynamic monitoring.

Arrhythmogenesis: In the PRECEDENT study (704.329), Holter monitoring confirmed that Natrecor[®] therapy does not affect heart rate or increase ventricular ectopy or significant ventricular arrhythmias. The control agent, dobutamine, was significantly proarrhythmic and significantly increased heart rate during therapy. Natrecor[®] is associated with a decrease in estimated myocardial oxygen consumption.

Other effects: Natrecor[®] is associated with a decrease in plasma aldosterone.

Diuresis: Natrecor[®] therapy was associated with a reduced need for diuretics.

In summary, the cumulative Natrecor[®] safety database, including the VMAC and PRECEDENT trials, provides a high level of confidence that the risks associated with Natrecor[®] are understood, especially compared to the commonly used agents for this indication, IV nitroglycerin, and dobutamine. The VMAC trial responded in full to the issues outlined in the Agency's non-approval letter. The VMAC trial demonstrated that the efficacy profile of Natrecor[®] was superior to both placebo and IV nitroglycerin. The safety data from VMAC demonstrate that Natrecor[®] is better tolerated by patients than is IV nitroglycerin. The PRECEDENT trial better quantifies the known proarrhythmic effect that is associated with dobutamine therapy and confirms that Natrecor[®] does not increase arrhythmias or heart rate.

The recommended indication statement for Natrecor[®] is as follows:

Natrecor[®] (nesiritide) is indicated for the initial intravenous treatment of patients with decompensated congestive heart failure, regardless of systolic function or primary etiology or the presence of acute coronary syndromes. Natrecor[®] improves dyspnea and overall clinical status, reduces pulmonary capillary wedge pressure and pulmonary artery pressures, and is associated with dose-dependent increases in cardiac index and stroke volume, without inducing tachyarrhythmia or an increase in heart rate. Natrecor[®] can be used alone or in conjunction with other standard therapies such as diuretics, ACE inhibitors, beta-blockers, dopamine, dobutamine, digoxin, and oral nitrates. Natrecor[®] has been studied in a broad range of patients, including the elderly, women, minorities, and patients with a history of significant chronic morbidities such as hypertension, diabetes, and atrial and ventricular arrhythmias.

Item 2

Introduction and Overview of Clinical Development Program

Including studies from the original NDA (Table 2–1) and the VMAC and PRECEDENT trials (Table 2–2), a total of 11 clinical studies of Natrecor[®] (nesiritide) have been completed totalling 965 subjects. In 10 of these studies, Natrecor[®] was administered to 941 patients with decompensated CHF, 11 of whom received Natrecor[®] in more than one study (for a total of 930 unique CHF subjects). An additional pilot study (704.312, n = 24) was also performed for another clinical indication, the treatment of post-operative hypertension.

Since 1994, Scios Inc. has undertaken the clinical development of Natrecor[®] (nesiritide) for the treatment of acute decompensated congestive heart failure (CHF). There were 505 subjects from 8 acute CHF clinical trials included in the dataset that supported the NDA for Natrecor[®], which Scios filed in April 1998. One study included in the NDA was conducted in post-operative hypotension (Study 704.312). This study is not part of this discussion. Studies described in the NDA, which were conducted between 1994 and 1998, involved intravenous (IV) administration of Natrecor[®] using both bolus and fixed-dose regimens.

On January 29, 1999, Scios presented the Natrecor[®] development program before the Cardiovascular and Renal Drugs Advisory Committee and the committee voted to recommend that Natrecor[®] be approved by a vote of 5 to 3. In April 1999, Scios received a letter from the Food and Drug Administration (FDA) which raised a number of issues as discussed in Item 1. Scios conducted the VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial, 704.339, to address the issues delineated in the FDA letter. In addition, the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor[®] Therapy) trial, 704.329, was completed during the NDA review. The PRECEDENT trial was not designed as a direct response to the FDA letter. The purpose of the PRECEDENT trial was to compare the effects of fixed-dose infusions of Natrecor[®] (0.015 µg/kg/min and 0.03 µg/kg/min), and dobutamine on arrhythmogenesis and heart rate. Both studies were submitted as a part of the NDA Amendment. The following tables outline the studies in the clinical development program.

Table 2–1

Natrecor® Clinical Studies in CHF Submitted in the Original NDA

Study	No. of Subjects	Study Design	Natrecor® Dosing
704.326*	305	Randomized, open-label, active-controlled, parallel design	0.015 or 0.03 µg/kg/min as a fixed-dose IV infusion (preceded by a small bolus) for up to 7 days
704.325*	127	Randomized, double-blind, placebo-controlled, parallel design for first 6 hours, then active-controlled, open-label study thereafter	0.015 or 0.03 µg/kg/min as a fixed-dose IV infusion (preceded by a small bolus) for up to 5 days
704.311*	103	Randomized, double-blind, placebo-controlled, parallel design	0.015-, 0.03-, or 0.06-µg/kg/min continuous IV infusion (preceded by a small bolus) for 24 hours
704.310	60	Randomized, double-blind, placebo-controlled, ascending dose	3 µg/kg q4h 5 µg/kg q4h 10 µg/kg q4h as repetitive-bolus regimen for 24 hours
704.309	60	Randomized, double-blind, placebo-controlled, parallel design	5 µg/kg q4h 10 µg/kg q6h 10 µg/kg q4h as repetitive-bolus regimen for 24 hours
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 for 1.5 h at each dose (Natrecor® and placebo on successive days in a crossover design)
704.306	16	Randomized, double-blind, placebo-controlled, ascending dose	0.025 or 0.05 µg/kg/min Natrecor® for 4 hours as a fixed-dose continuous IV infusion
704.305	30	Randomized, double-blind, placebo-controlled, ascending dose	0.3, 1, 3, 10, 15, or 20 µg/kg as a single bolus (n = 4/dose) or placebo (n = 6)

* Phase III pivotal trials

Table 2–2

Natrecor® Clinical Studies in the NDA Amendment

Study	No. of Subjects	Study Design	Natrecor® Dosing
704.339 (VMAC)	489	Randomized, double-blind, parallel design, placebo- and nitroglycerin-controlled, for first 3 hours, then crossover of placebo patients for double-blind active-control period	2-µg/kg IV bolus, followed by a fixed-dose infusion of 0.01 µg/kg/min. An adjustable-dose treatment arm permitted dose increases every 3 hours up to a maximum infusion dose of 0.03 µg/kg/min. No maximum infusion duration.
704.329 (PRECEDENT)	246	Randomized, open-label, dobutamine-controlled, parallel design	0.015 or 0.030 µg/kg/min as a fixed-dose IV infusion (not preceded by a bolus) with no maximum infusion duration

Item 3

The VMAC Trial: Primary Response to Non-Approval Issues

Introduction

The VMAC trial was designed to address comprehensively the issues raised by the FDA and the Cardiovascular and Renal Drugs Advisory Committee that led to the non-approval of Natrecor® in April 1999. The Agency did not question the efficacy of Natrecor®. Rather, the following questions pertaining to the size and makeup of the safety database and to the pharmacodynamic profile of Natrecor® were raised:

- Expansion of the safety database: in particular, additional experience was desired to better understand the onset and offset characteristics of symptomatic hypotension when Natrecor® was added to standard-care therapies in a typical hospital setting.
- A broader range of CHF patients: patients with active ischemia, preserved systolic function, and those receiving other IV vasoactive agents should not be excluded.
- An active-controlled study: comparing Natrecor® to an IV vasodilator such as nitroglycerin would provide a clearer characterization of the efficacy and safety profiles of Natrecor®, especially as they relate to effects on blood pressure and hypotension.
- Issues pertaining to symptom evaluations included: the appropriateness of measuring symptoms in patients without dyspnea at rest and the potential bias created by physician evaluations and the knowledge of hemodynamics.
- Data to support the sustained effects of Natrecor® should be collected.
- Recommendations for the dosing regimen and dose adjustment should be supported by the trial.
- The use of diuretics and other cardiac therapies should not be restricted.

Study Objectives

The primary objective of the VMAC study was to compare the hemodynamic and clinical effects of Natrecor® to placebo when added to standard care, in the treatment of acutely decompensated CHF. The primary endpoints were the changes from baseline, 3 hours after the start of study drug, in:

- Pulmonary capillary wedge pressure (PCWP) (catheterized subjects only)
- The subjects' self-evaluation of dyspnea (all subjects).

The secondary objective was to compare the hemodynamic and clinical effects of Natrecor® with IV nitroglycerin and placebo. Specific endpoints of interest included the:

- Onset of effect on PCWP
- Effect on PCWP and dyspnea 1 hour after the start of study drug
- Effect on PCWP 24 hours after the start of study drug
- Overall safety profile.

Additional objectives included a comparison of the use of other IV vasoactive agents and/or IV diuretics and the effects on other hemodynamic variables.

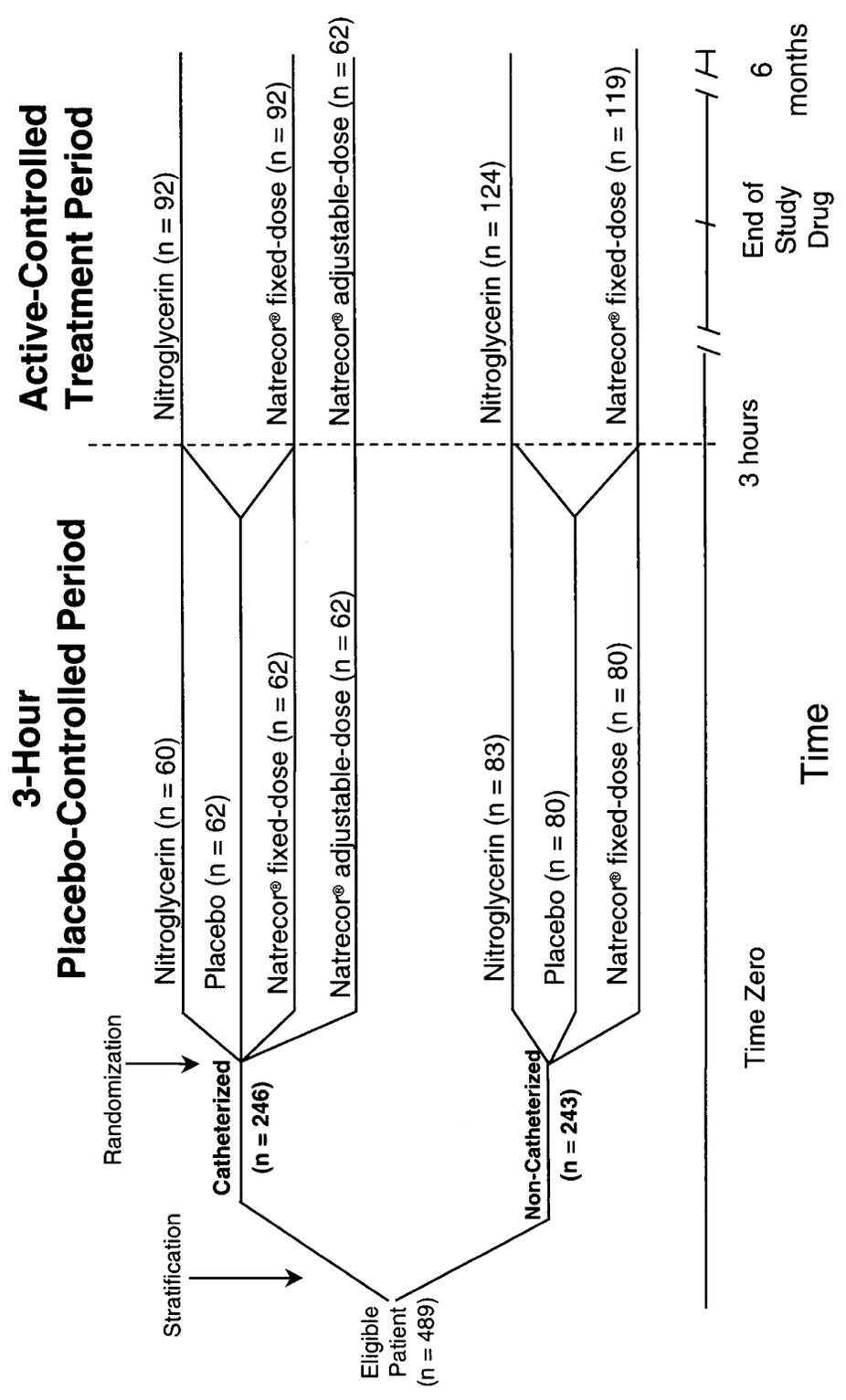
Overview and Rationale for Study Design

This multicenter, randomized, double-blinded and active-controlled clinical trial compared the hemodynamic, clinical, and safety effects of the addition of Natrecor®, placebo, or IV nitroglycerin to standard care for the treatment of acutely decompensated CHF in a typical hospital setting (Figure 3–1). Standard care may have included IV or oral diuretics, dobutamine, dopamine, and any other long-term cardiac or non-cardiac therapies. The first 3 hours were placebo- and nitroglycerin-controlled; the subsequent active-controlled period compared Natrecor® with IV nitroglycerin.

Rationale: Intravenous nitroglycerin was chosen as the active-control agent so that the relative efficacy and safety of Natrecor® could be compared to another commonly used IV vasodilator. A short (3-hour) placebo-controlled period was also used to compare the relative efficacy and safety of the two active agents to placebo. Three hours was chosen as the time for the primary endpoints in order to allow for a treatment effect on symptoms and to avoid a longer placebo-controlled period in extremely ill patients. To compare a fixed-dose regimen of Natrecor® to a standard dosing regimen of nitroglycerin (i.e., titrated regimen) in a double-blinded fashion, a double-dummy study-drug administration design was used. Also, because there is no standard dose or dosing range for nitroglycerin that is typically used for decompensated heart failure, all dosing of nitroglycerin was left to the Investigators' discretion.

Figure 3-1

Overview of VMAC Trial Design



Eligible patients were those requiring hospitalization and IV therapy for acutely decompensated CHF for at least 24 hours. Patients must have had dyspnea at rest, clinical evidence of heart failure as the cause of dyspnea, and elevated cardiac filling pressures (by clinical estimation or by a measured baseline PCWP \geq 20 mm Hg). Excluded patients were those with a baseline systolic blood pressure (SBP) consistently $<$ 90 mm Hg, those requiring mechanical ventilation, those receiving IV nitroglycerin that could not be withheld, and those for whom administration of an IV vasodilator was contraindicated. Patients with decompensated CHF in the setting of an acute coronary syndrome, relatively preserved systolic function (ejection fraction $>$ 40%), atrial or ventricular arrhythmias, renal insufficiency, patients already being administered dobutamine or dopamine, and cardiac transplant candidates were not excluded.

Rationale: The inclusion and exclusion criteria were not restrictive in order to ensure that a typical patient population with acutely decompensated CHF would be studied. Study drug could be added to ongoing therapy with dobutamine or dopamine as long as patients continued to have dyspnea at rest and met all other entry criteria. Because one of the primary endpoints was the dyspnea evaluation, patients had to have dyspnea at rest at baseline. This requirement was to mitigate any potential confusion about how dyspnea could be improved in a patient *without* dyspnea at rest who is confined to a hospital bed.

Randomization was stratified by the Investigators' clinical decision to use a right heart catheter to facilitate the clinical management of the CHF (hereafter referred to as catheterized or non-catheterized subjects). Approximately 240 catheterized patients were to be randomized to one of five treatment groups: 1) 3 hours placebo followed by IV nitroglycerin; 2) 3 hours placebo followed by Natrecor[®] fixed dose; 3) IV nitroglycerin; 4) Natrecor[®] fixed dose; and 5) Natrecor[®] adjustable dose. Approximately 240 non-catheterized patients were to be randomized to one of four treatment groups: 1) 3 hours placebo followed by IV nitroglycerin; 2) 3 hours placebo followed by Natrecor[®] fixed dose; 3) IV nitroglycerin; and 4) Natrecor[®] fixed dose. The end of the 3-hour placebo-controlled period was marked by a partial unblinding that revealed whether a subject had been receiving placebo or active therapy during the first 3 hours; knowledge of whether the active therapy was IV nitroglycerin or Natrecor[®] remained double blinded. After the partial unblinding, placebo subjects crossed over to double-blinded therapy with a titration regimen of nitroglycerin or Natrecor[®] fixed dose. Study drug was to be administered for at least 24 hours. The total duration was left to the Investigators' discretion.

Rationale: To enroll a balanced and clinically appropriate proportion of catheterized and non-catheterized subjects, the randomization was stratified by the Investigators' clinical decision whether or not to use a right heart catheter. The trial sample size of approximately 480 was selected to adequately power the trial to show significant effects on dyspnea, compared to placebo plus standard care, *in the total study population*, not necessarily within each stratum. Both the sponsor and the Agency

anticipated that significant symptom improvement would be observed in the placebo group due to the optimal administration of standard-care therapies, such as IV diuretics, permitted by the protocol. Based on the results of previous trials with Natrecor[®] as well as predictions from pharmacodynamic modeling, the trial was more than adequately powered to show significant hemodynamic differences between Natrecor[®] and placebo. To increase the power of the study to show effects differential between nitroglycerin and Natrecor[®] beyond 3 hours, placebo patients crossed over to active therapy with either nitroglycerin or Natrecor[®] fixed dose.

All doses of nitroglycerin/placebo were determined by the Investigator. Nitroglycerin/placebo was to be titrated to achieve the desired clinical effects. For the first 3 hours, Natrecor[®]/placebo was administered as a 2- $\mu\text{g}/\text{kg}$ bolus, followed by a fixed-dose infusion of 0.01 $\mu\text{g}/\text{kg}/\text{min}$. For the Natrecor[®] fixed-dose group, the infusion dose could not be increased above the initial dose. For the Natrecor[®] adjustable-dose group, after the first 3 hours, the Natrecor[®] dose could be increased at 3-hour intervals if the subjects had an SBP ≥ 100 mm Hg and a PCWP ≥ 20 mm Hg at the time of the dose increase. The regimen for increasing the Natrecor[®] dose included a 1- $\mu\text{g}/\text{kg}$ bolus, followed by an increase in the infusion dose by 0.005 $\mu\text{g}/\text{kg}/\text{min}$ above the previous infusion dose, up to a maximum dose of 0.03 $\mu\text{g}/\text{kg}/\text{min}$.

Rationale: The VMAC trial utilized a 2- $\mu\text{g}/\text{kg}$ bolus followed by a 0.01- $\mu\text{g}/\text{kg}/\text{min}$ infusion of Natrecor[®]. This was a larger bolus dose and a lower infusion dose than previously studied. Scios selected the new dose based on pharmacodynamic-modeling studies that predicted that the new dose would lead to a rapid reduction in PCWP, with 90% of the peak effect achieved within 30 minutes from dose initiation; that a clinically meaningful reduction in PCWP would be sustained for at least 24 hours; that peak effects on SBP would be observed within 45 minutes from dose initiation; and that the overall probability of an SBP < 90 mm Hg would be lower than with higher doses. Also based on pharmacodynamic modeling, an adjustable-dose Natrecor[®] arm was included for catheterized patients to evaluate the safety of increasing the dose of Natrecor[®]. It was believed that a prescription to increase the dose would allow for the known dose-dependent hemodynamic effects of Natrecor[®] in patients who had tolerated the 0.01- $\mu\text{g}/\text{kg}/\text{min}$ Natrecor[®] dose.

During the 3-hour placebo-controlled period, in catheterized patients only, PCWP and pulmonary artery pressures (PAP) were measured at 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours. In addition, cardiac output (CO) and mean right atrial pressure (MRAP) were measured at 1 and 3 hours. In all subjects, vital signs and symptoms (dyspnea and global clinical evaluations) were assessed at 15 minutes and 30 minutes, and at 1, 2, and 3 hours after the start of study drug. Dyspnea and global assessments were to be taken prior to hemodynamic evaluations; Investigators were instructed not to discuss hemodynamic results within hearing distance of the subjects.

Rationale: To help obtain the least biased symptom evaluations, each subject, rather than the Investigator, independently evaluated his/her dyspnea and global clinical status at each time point. The Investigators and study staff were instructed not to help the subject with the evaluation. In addition, if the subject was catheterized, symptoms were to be collected before the hemodynamic measurements were obtained at each time point. The hemodynamic results were not to be discussed with the subject or within the hearing of the subject. After agreement with the Agency, Scios decided to use a 7-point ordinal scale for both the dyspnea and global clinical evaluations (markedly improved, moderately improved, minimally improved, no change, minimally worse, moderately worse, and markedly worse). Due to the anticipation of significant improvement in the placebo (plus standard care) subjects, it was believed that a 7-point scale would be most sensitive to incremental levels of improvement between the treatment groups.

After the initial 3 hours, in catheterized subjects only, PCWP and PAP were obtained through 48 hours. In all subjects, vital signs were assessed every 3 hours for the duration of study drug infusion and frequently for the first 2 hours after any dose change, discontinuation, or restarting of the infusion. Dyspnea and global clinical evaluations were obtained at 6 and 24 hours after the start of study drug, and at the time of discontinuation of study drug. Total fluid intake and urine output were recorded for the first 24 hours after the start of study drug.

Serum creatinine was obtained daily through 2 days after discontinuation of study drug, and at study days 14 and 30. General adverse events were assessed through study day 14. Serious adverse events were assessed through study day 30. All-cause mortality was collected through 6 months.

Rationale: After the original protocol (dated 4 August 1999) was finalized, the Agency suggested that mortality be followed prospectively for 6 months. The Sponsor and Agency agreed that mortality was not a concern of the Agency at the time of non-approval of Natrecor®, nor should it be a major endpoint of the trial. Rather, long-term mortality was considered useful safety information that would help provide confidence for approval of an agent for this short-term indication.

Pharmacodynamic Modeling

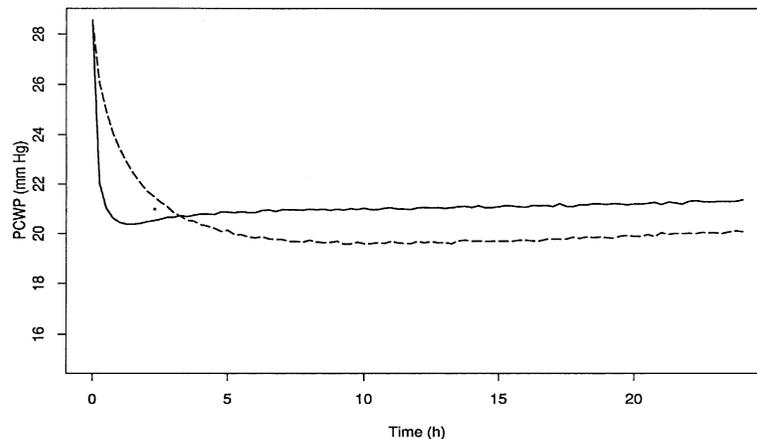
As part of the ongoing dialog between Scios and the Agency in developing the VMAC trial, Scios was interested in modifying the Natrecor® dose so that the peak effects of Natrecor® would be observed earlier and that the maximal effects on SBP would be less than with previously used regimens. Pharmacodynamic models for the effects of Natrecor® on PCWP and SBP were developed using pharmacokinetic and hemodynamic data from a previous IV bolus study and a 24-hour continuous-infusion study. The models were used to predict PCWP and SBP responses of a modified Natrecor® dosing regimen to be used in the VMAC trial, a 2-µg/kg bolus followed by a 0.01-µg/kg/min fixed-dose infusion, compared with the observed

effects of the lowest infusion dose studied in the Phase III studies in the NDA (Figures 3–2, 3–3, and 3–4). The model predicted the following:

- The modified regimen should result in a rapid reduction of PCWP, achieving 90% of the peak effects within 30 minutes from initiation (Figure 3–2).
- The modified regimen should achieve a clinically meaningful reduction in PCWP for at least 24 hours (Figure 3–2).
- The modified regimen should result in 90% of peak effects on SBP being observed within 45 minutes from initiation (Figure 3–3).
- Overall, the predicted probability of an SBP < 90 mm Hg was lower with the modified regimen compared to the 0.25- μ g/kg bolus plus 0.015- μ g/kg/min infusion. The predicted probability of an SBP < 90 mm Hg at earlier time points (within the first 3 to 4 hours) was greater with the modified regimen compared to the 0.25- μ g/kg bolus plus 0.015- μ g/kg/min infusion regimen; thereafter, the predicted probability of an SBP < 90 mm Hg was lower with the modified regimen (Figure 3–4).

Figure 3–2

**Simulated PCWP vs. Time
(10,000 Simulated Subjects for Each Treatment)**

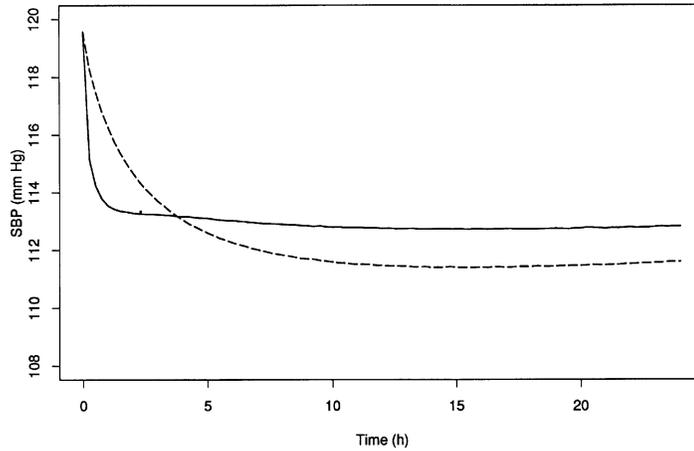


----- = 0.25 μ g/kg + 0.015 μ g/kg/min (lowest infusion dose in NDA)

_____ = 2 μ g/kg + 0.01 μ g/kg/min (VMAC trial dose)

Figure 3-3

**Simulated SBP vs. Time
(10,000 Simulated Subjects for Each Treatment)**

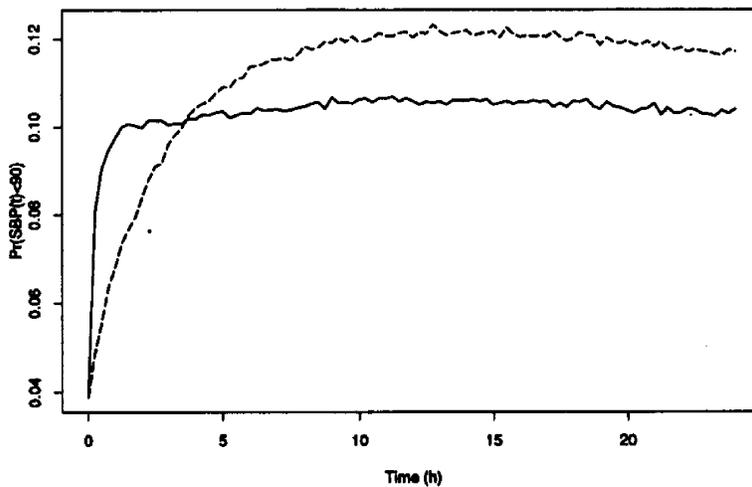


----- = 0.25 $\mu\text{g}/\text{kg}$ + 0.015 $\mu\text{g}/\text{kg}/\text{min}$ (lowest infusion dose in NDA)

_____ = 2 $\mu\text{g}/\text{kg}$ + 0.01 $\mu\text{g}/\text{kg}/\text{min}$ (VMAC trial dose)

Figure 3-4

**Probability of SBP(t) < 90 vs. Time
(10,000 Simulated Subjects for Each Treatment)**



----- = 0.25 $\mu\text{g}/\text{kg}$ + 0.015 $\mu\text{g}/\text{kg}/\text{min}$ (lowest infusion dose in NDA)

_____ = 2 $\mu\text{g}/\text{kg}$ + 0.01 $\mu\text{g}/\text{kg}/\text{min}$ (VMAC trial dose)

In the VMAC trial, the predictions of the pharmacodynamic modeling were very close to what was observed. The modified Natrecor[®] dose (2- $\mu\text{g}/\text{kg}$ bolus, followed by an infusion of 0.01 $\mu\text{g}/\text{kg}/\text{min}$) was associated with a rapid onset of PCWP reduction that was significantly

greater than both placebo and nitroglycerin within 15 minutes. At 30 minutes, 84% of the 3-hour effect was observed; 95% of the 3-hour effect was observed by 1 hour. By 15 minutes, 70% of the 3-hour effect on SBP was observed, and nearly 60% of the 3-hour effect was observed by 1 hour. Natrecor® produced sustained PCWP reduction through 48 hours. The effect on PCWP was significantly greater than that observed with nitroglycerin through 24 hours.

Blinding

The pharmacist learned of each subject's treatment assignment or treatment series during the randomization call to the Automated Telephone Randomization System, which generally took place within 2 hours before the start of study drug. During the 3-hour placebo-controlled period, treatment assignment was double blinded.

After the 3-hour dyspnea and global clinical evaluations and hemodynamic measurements (catheterized subjects only) were performed, the Investigator or study coordinator called the Automated Telephone Randomization System to ascertain whether the subject had been receiving placebo or active treatment; knowledge of treatment assignment of IV nitroglycerin or Natrecor® remained double blinded. Placebo subjects then crossed over to double-blinded treatment with either nitroglycerin or Natrecor®, as had been predetermined during the initial randomization. Subjects who had been receiving nitroglycerin or Natrecor® during the first 3 hours of the study were to continue the original study-drug infusions. For the duration of the study, the study staff, subject, and Sponsor remained blinded to whether the active therapy was Natrecor® or nitroglycerin.

To ensure that the primary endpoints were obtained while the blind was intact, study staff could not carry out the partial unblinding until the result of the PCWP measurement and/or the dyspnea and global clinical evaluations, and dates and times that they were obtained, were entered into the central telephone system during the unblinding call.

Definition of Symptomatic Hypotension

Symptomatic hypotension was prospectively defined as a significant decrease in or sufficiently low blood pressure that was also associated with one or more of the following symptoms spontaneously volunteered by or elicited from the subject:

- Lightheadedness
- Feeling faint
- Dizziness
- Blurred vision

If a subject developed symptomatic hypotension at any time during study-drug administration, both study-drug infusions were to be discontinued. Once the symptoms of hypotension resolved and the SBP stabilized above 90 mm Hg, study drug could be restarted at a flow rate

that was 30% lower than the infusion rate administered when the symptomatic hypotension began. The Natrecor[®]/placebo bolus was not to be re-administered.

Statistical Methods

During the placebo-controlled period, comparisons were made among three groups: nitroglycerin, Natrecor[®], and placebo. During the active-controlled period or post-treatment period, overall comparisons of all subjects were made between two treatment groups: all nitroglycerin and Natrecor[®] fixed-dose, or all nitroglycerin and all Natrecor[®] (including both the fixed-dose and adjustable dose Natrecor[®] groups).

Primary Efficacy Measures

For the first primary efficacy parameter, the mean change in PCWP at 3 hours, the analysis included all catheterized subjects randomized to and treated with placebo or Natrecor[®]. A pairwise contrast within the framework of a one-way analysis of variance (ANOVA) was used for the 3-hour change in PCWP from baseline.

The second primary efficacy parameter, the subject's dyspnea evaluation, was evaluated at 3 hours and was represented as a 7-point ordinal response relative to immediately before the start of study drug. The primary analysis was the comparison between Natrecor[®] and placebo using pairwise contrast of a two-way ANOVA model in all subjects (catheterized and non-catheterized). For the purpose of the analysis, each dyspnea response was assigned a score as follows: markedly better (3), moderately better (2), minimally better (1), no change (0), minimally worse (-1), moderately worse (-2), and markedly worse (-3).

The treatment groups were also compared using a stratified two-sample Wilcoxon procedure (van Elteren's test), stratified on right heart catheter use, at a two-sided significance level of $\alpha = 0.05$. This analysis was pre-specified as a supplemental analysis to test the robustness of the primary analysis *and* was recommended by the Agency as a more appropriate analysis of this type of data than a parametric analysis. Because the protocol allowed for the administration of standard care (IV diuretics, oral cardiac medications, dobutamine, dopamine, etc.) during the first 3 hours, this resulted in a heightened placebo effect and a skewed distribution toward more subjects reporting improvement. A non-parametric test was considered to be more appropriate for the analysis of the dyspnea data.

Enrollment

In the VMAC trial, 498 subjects were randomized at 55 U.S. clinical sites between October 26, 1999 and July 27, 2000. Nine of the 498 randomized subjects were not treated because they did not meet all study inclusion/exclusion criteria at the time study-drug infusion was to begin. The protocol pre-specified the "All Treated Subjects, as Randomized" population (n = 489) as the primary analysis population.

Results

Demographics

Differences Between Catheterized and Non-Catheterized Subjects

Important differences in baseline demographics and clinical presentation existed between the catheterized and non-catheterized strata (Table 3–1). A higher percentage of catheterized subjects was male ($p = 0.003$). Within the 24-hour period before entering into the study, more catheterized subjects had been receiving an IV vasoactive medication than the non-catheterized subjects (27% versus 21%). Study drug also was added to ongoing therapy with dobutamine more often in catheterized subjects (16%) than non-catheterized subjects (12%). Mean baseline systolic BP was lower in the catheterized subjects (118 versus 125 mm Hg), and fewer catheterized subjects were hypertensive (SBP ≥ 140 mm Hg) at baseline (17% versus 26%, $p = 0.055$).

Table 3–1

**Baseline Demographics and Clinical Presentation
(All Treated Subjects, by Strata)**

Characteristics	Catheterized (n = 246)	Non-Catheterized (n = 243)	All Subjects (n = 489)	p-value
Age¹	61 \pm 14	63 \pm 14	62 \pm 14	0.135 ²
≥ 65 years old	97 (39%)	113 (47%)	210 (43%)	
Ethnicity				
White	149 (61%)	137 (56%)	286 (58%)	
Black	61 (25%)	58 (24%)	119 (24%)	0.106 ³
Hispanic	33 (13%)	36 (15%)	69 (14%)	
Other	3 (1%)	12 (5%)	15 (3%)	
Gender: Male	185 (75%)	152 (63%)	337 (69%)	0.003 ³
Screening Dyspnea at Rest	246 (100%)	243 (100%)	489 (100%)	
Physical Exam				
Rales	173 (70%)	186 (77%)	359 (73%)	0.126 ³
Pedal edema	160 (65%)	196 (81%)	356 (73%)	<0.001 ³
ACS Within 7 days	20 (8%)	41 (17%)	61 (12%)	0.004 ³
Ongoing Treatment with Dobutamine	40 (16%)	29 (12%)	69 (14%)	NA
Baseline Hemodynamics				
Systolic BP (mm Hg)¹	118 \pm 20	125 \pm 24	121 \pm 22	
≤ 100 mm Hg	46 (19%)	44 (18%)	90 (18%)	
101–139 mm Hg	157 (64%)	135 (56%)	292 (60%)	
≥ 140 mm Hg	43 (17%)	64 (26%)	107 (22%)	0.055 ³
Heart rate (bpm)¹	84 \pm 15	84 \pm 16	84 \pm 15	
Baseline Creatinine ≥ 2.0 mg/dL	54 (22%)	50 (21%)	104 (21%)	

Tables 23.1, 24.1, 25.1, 26.1, 27.1, 32.1, 44.1, 44.2, 44.3, 81.1, 81.2, 81.3, 88.1, 88.2, 88.3, 120.2, and 120.3.

¹Mean \pm Standard Deviation

²T-Test

³Fisher's Test

In contrast to catheterized subjects, whose underlying hemodynamic profile was more likely to be unclear, non-catheterized subjects had a more convincing clinical presentation of fluid overload associated with their CHF, as evidenced by a higher frequency of pedal edema ($p < 0.001$, Fisher) on physical examination, and more hypertension at baseline. As would be expected, subjects with evidence of an acute coronary syndrome (ACS) were more commonly managed without a right heart catheter ($p = 0.004$, Fisher).

The differences in clinical profile between the catheterized and non-catheterized subjects were representative of the reasons why a right heart catheter would be used in clinical practice. Important differences in cardiac and medical history also were apparent between the catheterized and non-catheterized strata. More catheterized subjects had ischemic cardiomyopathy as the primary etiology of their chronic CHF, whereas more non-catheterized subjects had hypertensive cardiomyopathy ($p = 0.030$, chi square test). As a result, more catheterized subjects had a previous history of a myocardial infarction or an invasive intervention for coronary artery disease, although these differences were not statistically significant. Catheterized subjects had more advanced systolic dysfunction, as evidenced by a lower baseline ejection fraction (25% versus 29%, $p = 0.001$, t-test) than non-catheterized subjects and fewer catheterized subjects had preserved systolic function (10% versus 19% with $EF > 40\%$; $p = 0.010$, Fisher). As may have been predicted by the fact that catheterized subjects had poorer systolic function, these subjects also had a significantly higher reported history of all forms of ventricular arrhythmias than did the non-catheterized subjects.

The differences just summarized lead to the general conclusion that the catheterized stratum was composed of patients with more severe chronic cardiac disease than the non-catheterized stratum. However, all subjects had acutely decompensated heart failure with dyspnea at rest at presentation. Although the catheterized subjects had worse systolic dysfunction, worse underlying ischemic cardiac disease, more life-threatening arrhythmias, and more need at baseline for dobutamine or dopamine therapy, each of these conditions was also common in non-catheterized subjects.

Differences between Active-Treatment Groups

Of the total 489 treated subjects, 216 were treated with nitroglycerin and 273 were treated with Natrecor® during the active-controlled period. The greater total number of Natrecor® subjects in the trial was due to the presence of an additional Natrecor® treatment group in the catheterized stratum. As a result, 56% (154 of 273) of all Natrecor® subjects were catheterized, whereas only 43% (92 of 216) of all nitroglycerin subjects were catheterized. Not surprisingly, the differences previously noted between the catheterized and non-catheterized subjects translate to significant differences between the Natrecor® and nitroglycerin subjects.

More Natrecor® subjects were male ($p = 0.039$), were receiving chronic therapy with a Class III antiarrhythmic medication ($p = 0.025$), received an IV vasoactive medication within

24 hours before study drug ($p = 0.004$), and had study drug added to ongoing therapy with dobutamine or dopamine ($p = 0.013$ and $p = 0.003$, respectively). The Natrecor[®] group also had more subjects with NYHA Class IV chronic CHF, whereas nitroglycerin subjects had more NYHA Class I/II chronic CHF. More subjects in the Natrecor[®] group had a history of significant ventricular arrhythmias (Table 3–2).

Table 3–2

**Differences in Baseline Characteristics Between
Active-Controlled Treatment Groups
(All Treated Subjects, as Randomized)**

Characteristics	Nitroglycerin (n = 216)	Natrecor [®]		p-value ¹
		Fixed Dose (n = 211)	All Natrecor [®] (n = 273)	
Gender: Male	138 (64%)	156 (74%)	199 (73%)	0.039 ²
Chronic NYHA Classification				
No Chronic CHF	18 (8%)	15 (7%)	21 (8%)	
I, II	24 (11%)	14 (7%)	17 (6%)	0.142 ³
III	90 (42%)	85 (40%)	115 (42%)	
IV	84 (39%)	97 (46%)	120 (44%)	
Arrhythmia History				
Sudden Death	14 (6%)	21 (10%)	27 (10%)	0.192 ²
Ventricular Fibrillation	9 (4%)	15 (7%)	22 (8%)	0.093 ²
Sustained VT	21 (10%)	33 (16%)	41 (15%)	0.100 ²
Nonsustained VT	39 (18%)	49 (23%)	68 (25%)	0.078 ²
Long-Term Medications				
Class III Antiarrhythmics	25 (12%)	37 (18%)	52 (19%)	0.025 ²
Clinical Presentation				
IV Vasoactive Rx* within 24 Hours before Study Drug	38 (18%)	57 (27%)	79 (29%)	0.004 ²
Dobutamine continued at baseline	21 (10%)	35 (17%)	48 (18%)	0.013 ²
Dopamine continued at baseline	3 (1%)	11 (5%)	19 (7%)	0.003 ²

Tables 13.1, 18.1, 19.1, 20.1, 21.1, 42.1B, and 44.1

*Dobutamine, dopamine, IV nitroglycerin, nitroprusside, and PDE Inhibitors

²Fisher

³Chi square test

¹p-value nitroglycerin compared to All Natrecor[®]

Natrecor[®] Dosing

The mean and median infusion dose of Natrecor[®] administered at every time point through 48 hours in both Natrecor[®] fixed-dose and Natrecor[®] adjustable-dose subjects was 0.01 µg/kg/min. This would be expected during the first 3 hours, because no dose increases of Natrecor[®] were permitted in the adjustable-dose group until after the 3-hour endpoint measurements were taken. After 3 hours, however, Natrecor[®] doses in this group could be increased at the Investigators' discretion based on available central hemodynamic or other clinical information.

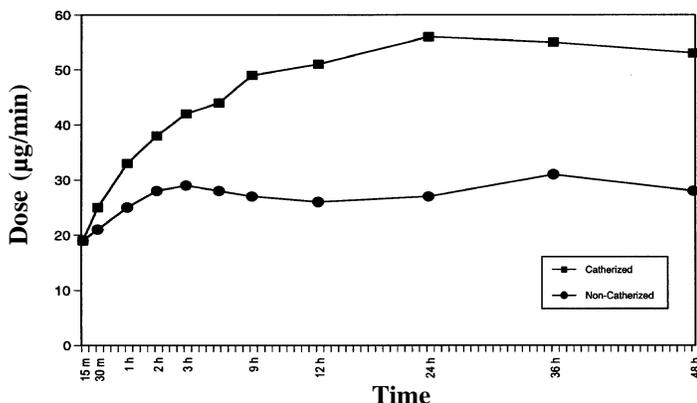
Of the 62 subjects receiving the Natrecor[®] adjustable dose, 35 (56%) received an initial infusion dose of 0.01 $\mu\text{g}/\text{kg}/\text{min}$ and did not have the dose increased. Four subjects received an initial dose of 0.015 $\mu\text{g}/\text{kg}/\text{min}$ (due to dosing errors) and did not have the dose increased. Of the 23 subjects who had their doses increased, 10 subjects received a maximum Natrecor[®] dose of 0.015 $\mu\text{g}/\text{kg}/\text{min}$, 4 received a maximum Natrecor[®] dose of 0.02 $\mu\text{g}/\text{kg}/\text{min}$, 5 received a maximum Natrecor[®] dose of 0.025 $\mu\text{g}/\text{kg}/\text{min}$, and 4 subjects received a maximum Natrecor[®] dose of 0.03 $\mu\text{g}/\text{kg}/\text{min}$.

Nitroglycerin Dosing

One important objective of the trial was to compare the effects of nitroglycerin and Natrecor[®] on blood pressure. To avoid a protocol-driven bias against nitroglycerin, dose adjustments for the nitroglycerin/placebo infusion were to be made “to clinical effect” and were left to the discretion of the Investigators. During both the placebo-controlled and active-controlled periods, the nitroglycerin infusion was titrated to higher maximum doses in catheterized subjects than in non-catheterized subjects. Figure 3–5 shows that at the 3-hour time point, when the primary endpoints were measured, a mean dose of 42 ± 61 $\mu\text{g}/\text{min}$ of nitroglycerin was administered to catheterized subjects, whereas a mean dose of 29 ± 38 $\mu\text{g}/\text{min}$ of nitroglycerin was administered to non-catheterized subjects. From 3 hours to 24 hours, the mean dose of nitroglycerin administered to catheterized subjects was increased from 42 ± 61 $\mu\text{g}/\text{min}$ to 56 ± 64 $\mu\text{g}/\text{min}$ ($p = 0.003$, paired t-test). However, by 24 hours in non-catheterized subjects, the mean nitroglycerin dose of 27 ± 31 $\mu\text{g}/\text{min}$ was essentially no different from the dose that was being administered at the 3-hour time point (29 ± 38 $\mu\text{g}/\text{min}$). These data suggest that, when central hemodynamics are known to the Investigators, nitroglycerin continues to be titrated to higher mean doses over the first 24 hours.

Figure 3–5

Mean Nitroglycerin Dose in Catheterized versus Non-Catheterized Subjects



There was no upper limit to the dose of nitroglycerin that could be administered. Investigators were to select optimal doses of nitroglycerin based on either desired hemodynamic effects or to avoid excessive decreases in blood pressure.

PCWP

PCWP through Hour 3

By the 3-hour time point, Natrecor[®] added to standard care significantly decreased PCWP compared to placebo added to standard care ($p < 0.001$, pair-wise contrast). Natrecor[®] added to standard care also caused a significantly greater reduction in PCWP at 3 hours than did nitroglycerin added to standard care ($p = 0.027$, pair-wise contrast) (Table 3–3).

Table 3–3

Effects on PCWP through 3 Hours (All Treated Catheterized Subjects)				
Time Points	Nitroglycerin (n = 60)	Natrecor[®] (n = 124)	Placebo (n = 62)	p-value (F-Test)
Observed PCWP (mm Hg) Values:				
Baseline (mean ± SD)	28.0 ± 5.7	27.7 ± 7.0	27.7 ± 5.4	0.961
Change from Baseline				
15 minutes	-1.2 ± 3.8	-3.5 ± 5.3*†	-1.2 ± 3.6	
30 minutes	-2.0 ± 4.3	-4.9 ± 5.5*†	-0.8 ± 3.6	
1 hour	-2.8 ± 4.1	-5.5 ± 6.3*†	-1.5 ± 4.8	
2 hours	-4.2 ± 4.8†	-5.6 ± 6.4†	-1.8 ± 5.0	≤ 0.001 ¹
3 hours (Primary Endpoint)	-3.8 ± 5.3	-5.8 ± 6.5*†	-2.0 ± 4.2	

Table 50

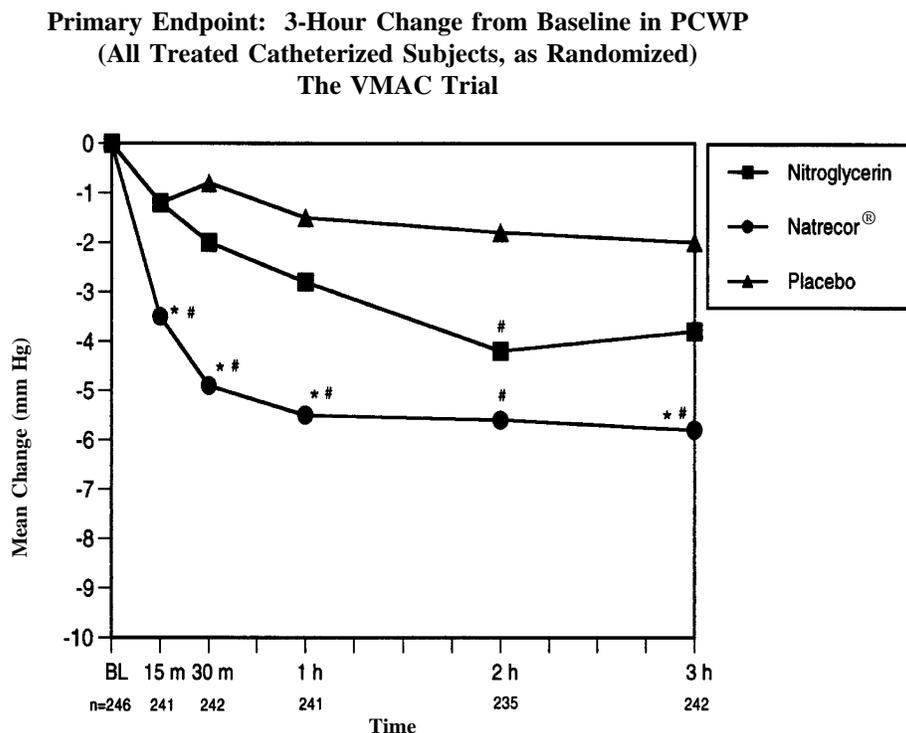
* $p < 0.05$ Natrecor[®] compared to nitroglycerin, one way ANOVA with pair-wise contrast on mean change from baseline.

† $p < 0.05$ Natrecor[®] or nitroglycerin compared to placebo, one-way ANOVA with pair-wise contrast.

¹p-value applies to all time points.

Data from the VMAC trial demonstrated that Natrecor® significantly lowered PCWP faster (within the first 15 minutes after start of study drug) than nitroglycerin or placebo. As Figure 3–6 shows, Natrecor® was associated with a significantly greater reduction in PCWP than nitroglycerin at all time points through 3 hours (except at 2 hours).

Figure 3–6



$p < 0.05$ Natrecor® or nitroglycerin compared to placebo
 * $p < 0.05$ compared to nitroglycerin

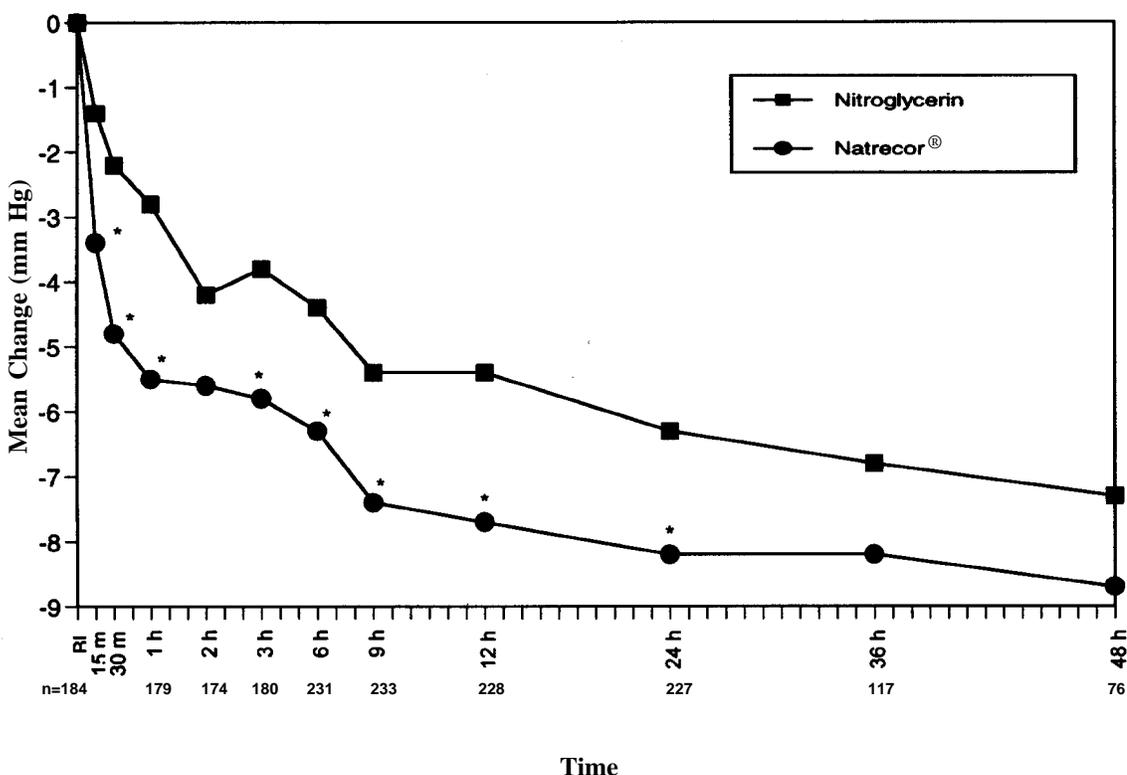
PCWP through Hour 48

Through 48 hours, the pooled Natrecor® dose group experienced sustained reductions in PCWP and showed no evidence of an attenuation of the effect on PCWP over time. At every time point from 15 minutes through 24 hours (except at 2 hours), the reductions in PCWP were significantly greater with Natrecor® than nitroglycerin (Figure 3–7). At 36 and 48 hours, PCWP continued to be reduced by a greater magnitude with Natrecor® than with nitroglycerin. However, the statistical significance was no longer maintained. This may be because PCWP was obtained in only about 50% of catheterized subjects at 36 hours and in only one-third of subjects at 48 hours. These missing data are due to the fact that the Investigators could not always clinically justify keeping a right heart catheter in place for longer than 24 hours. Recall that for the catheterized strata, nitroglycerin continued to be uptitrated in dose from a mean dose of 42 µg/min at the 3-hour time point to a mean dose of 56 µg/min at 24 hours.

The mean and median Natrecor® dose administered in both the fixed-dose and the adjustable-dose arms at every time point through 48 hours was 0.01 µg/kg/min.

Figure 3–7

PCWP through 48 Hours
(Change from Baseline)
(All Treated Catheterized Subjects)



* p < 0.05 compared to nitroglycerin

Dyspnea

Dyspnea through 3 Hours

The prespecified primary analysis of the subject’s dyspnea evaluation was a parametric analysis using a two-way ANOVA model, with treatment and catheter use as two factors. The robustness of the response was also tested using the nonparametric, stratified two-sample Wilcoxon procedure (Van Elteren’s test), stratified on right heart catheter use.

At 3 hours, Natrecor® added to standard care was associated with a more favorable dyspnea evaluation score than was placebo added to standard care (p = 0.050 based on two-way ANOVA and p = 0.034 based on Van Elteren test stratified on catheterized use) (Tables 3–4 and 3–5). In contrast, the effect of nitroglycerin added to standard care on dyspnea at 3 hours was not statistically significantly different from placebo added to standard care (p = 0.285, ANOVA, and p = 0.191, Van Elteren).

Table 3-4

**Primary Endpoint: Subject's Dyspnea Evaluation
Parametric Analysis
(All Treated Subjects, as Randomized)**

	Nitroglycerin (n = 143)	Natrecor® (n = 204)	Placebo (n = 142)
3-hour value (mean ± SD)	1.3 ± 1.1	1.3 ± 1.1	1.1 ± 1.2
(LSMEAN ± SE)	(1.2 ± 0.1)	(1.3 ± 0.1)	(1.1 ± 0.1)
¹ p-value, compared to placebo	0.285	0.050	
¹ p-value, Natrecor® compared to nitroglycerin		0.414	

Table 49.1

¹p-value is based on two-way ANOVA (treatment and catheter use as two factors) with pair-wise contrast.

Table 3-5

**Primary Endpoint: Subject's Dyspnea Evaluation
Non-Parametric Analysis
(All Treated Subjects, as Randomized)**

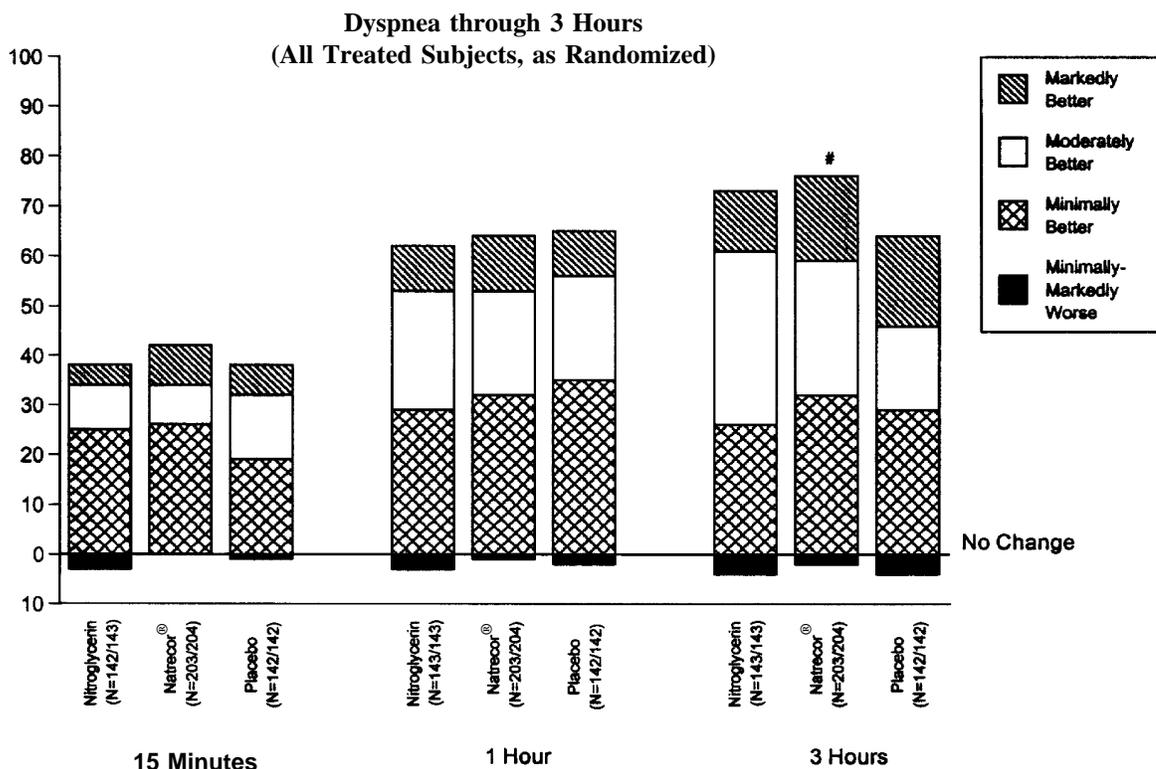
Dyspnea Evaluation	Nitroglycerin (n = 143)	Natrecor® (n = 204)	Placebo (n = 142)
3-Hour Evaluation			
Markedly better (3)	17 (12%)	34 (17 %)	25 (18%)
Moderately better (2)	50 (35%)	54 (27%)	24 (17%)
Minimally better (1)	37 (26%)	64 (32%)	41 (29%)
No change (0)	33 (23%)	45 (22%)	46 (32%)
Minimally worse (-1)	5 (3%)	5 (2%)	6 (4%)
Moderately worse (-2)	0 (0%)	1 (± <1%)	0 (0%)
Markedly worse (-3)	1 (1%)	0 (0%)	0 (0%)
¹ p-value, compared to placebo	0.191	0.034	
¹ p-value, Natrecor® compared to nitroglycerin		0.565	

Table 49.1

¹p-value is based on Van Elteren's test stratified on right heart catheter use.

In all three treatment groups, more subjects reported improvements in dyspnea from baseline and fewer subjects reported worsening of dyspnea from baseline at 3 hours (Figure 3–8). As a result, the normality assumption was compromised and, as suggested by the Agency, a non-parametric analysis was deemed to be a more appropriate statistical test for these data.

Figure 3–8



p < 0.05 Natrecor® or nitroglycerin compared to placebo, Van Elteren's test

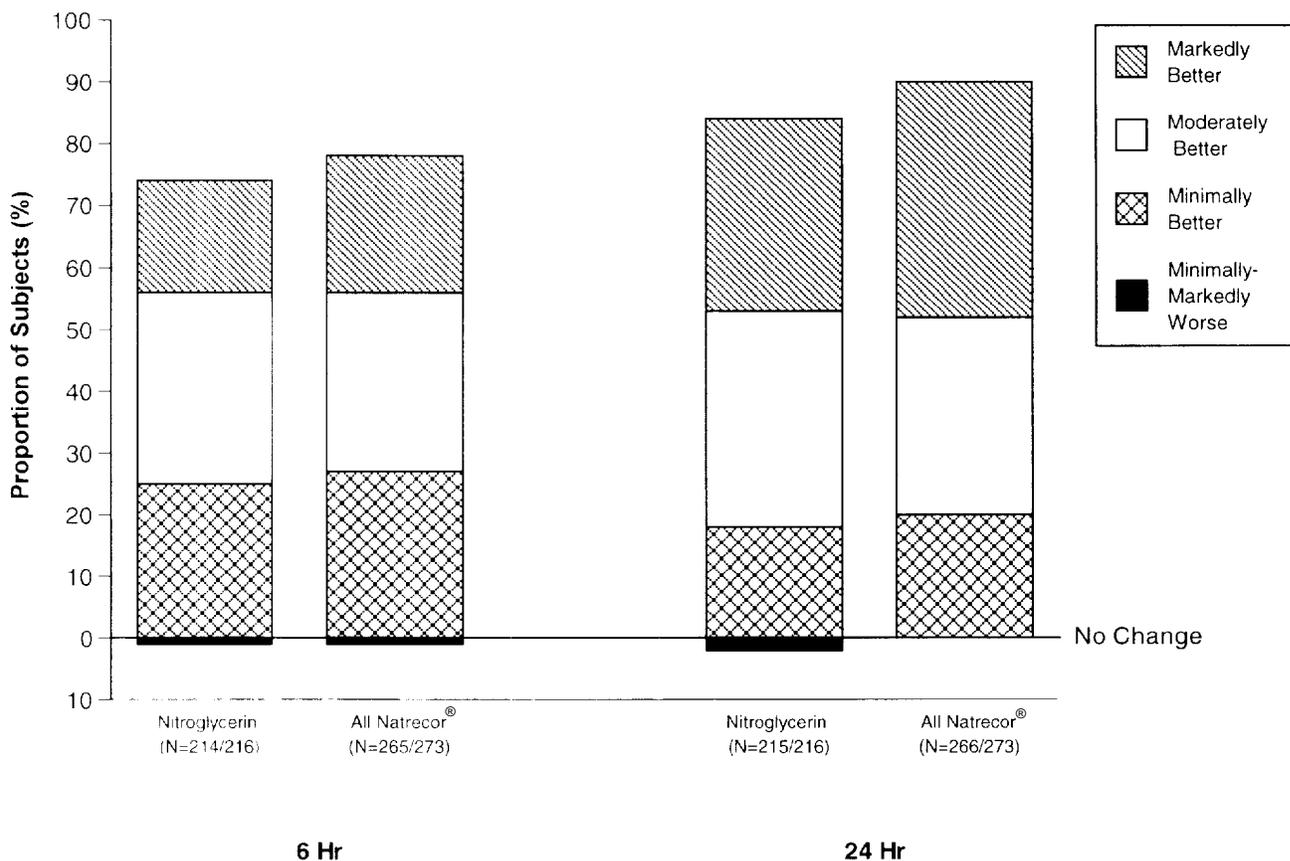
This distribution of responses, in particular the improvements in dyspnea observed in many placebo patients, may be explained by the fact that study drug (nitroglycerin, Natrecor®, or placebo) was added to standard care, which may have included dobutamine, dopamine, IV or oral diuretics, and other cardiac medications. Therefore, Natrecor® therapy added to standard care was associated with a further improvement in dyspnea beyond that which occurred with standard care alone (plus placebo).

Dyspnea through 24 Hours

Through 24 hours, there was evidence of progressive improvement in dyspnea over time in all treatment groups (Figure 3–9). No significant differences were observed between Natrecor[®] and nitroglycerin ($p = 0.126$, Van Elteren’s test) in the whole study population. However, within the non-catheterized stratum, Natrecor[®] significantly improved dyspnea compared to nitroglycerin ($p = 0.018$, t-test; $p = 0.027$ Wilcoxon) at 24 hours.

Figure 3–9

**Dyspnea at 6 and 24 Hours
(All Treated Subjects, as Randomized)**

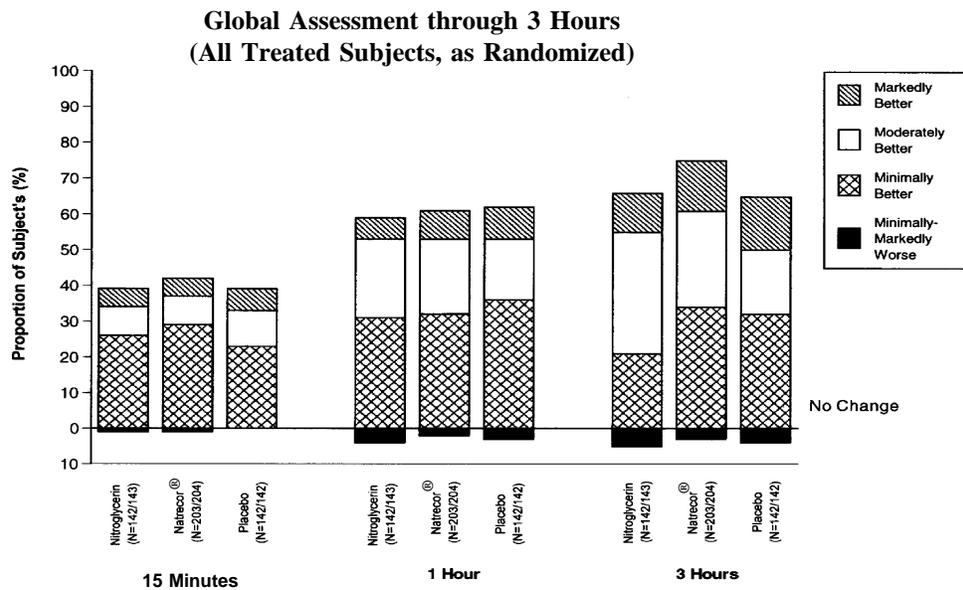


Global Clinical Status

Global Clinical Status through 3 Hours

Global clinical status over the 3-hour placebo-controlled period exhibited a pattern of progressive improvement over time (Figure 3–10). At the 3-hour time point, there was a strong trend toward significant improvement in global clinical status in the Natrecor® group, compared to placebo ($p = 0.068$ [Van Elteren’s test]). There were no significant differences in global clinical status between nitroglycerin and placebo or Natrecor® through 3 hours.

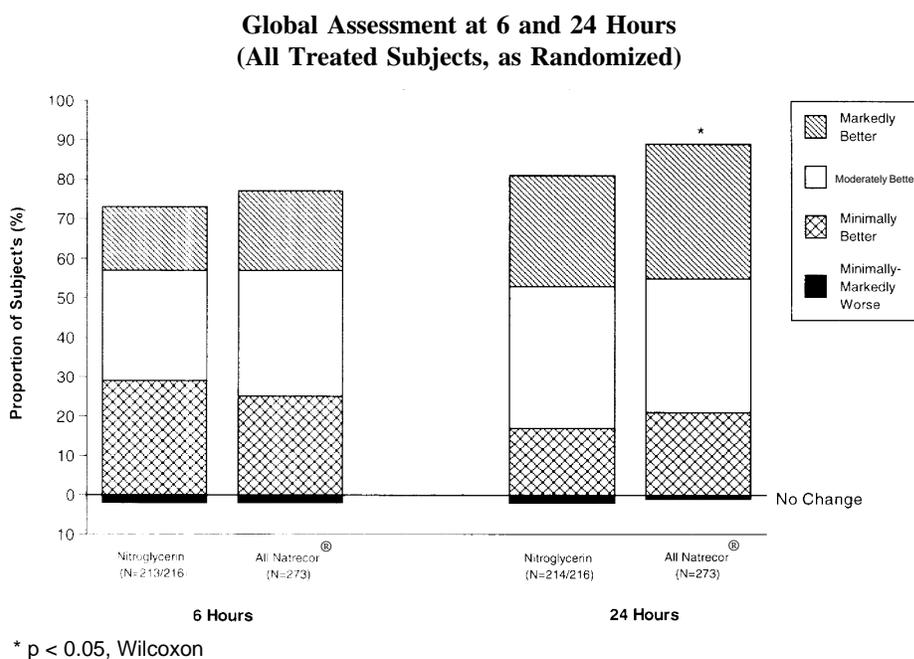
Figure 3–10



Global Clinical Status through 24 Hours

Through 24 hours, a similar pattern of progressive improvement was observed for global clinical status with both treatment groups. At 24 hours, Natrecor® was associated with significant improvement in global clinical status, compared to nitroglycerin ($p = 0.044$, two-way ANOVA, Figure 3–11). In the non-catheterized stratum specifically, Natrecor® significantly improved the global assessment compared to nitroglycerin ($p = 0.009$, [t-test]; $p = 0.013$ [Wilcoxon]) at 24 hours.

Figure 3–11



As stated previously, the VMAC trial was powered to show differential effects on symptoms in the whole study population, not necessarily within each stratum. The demonstration of statistically significant differences between Natrecor® and nitroglycerin in non-catheterized subjects represents a robust demonstration of clinical benefit in a setting that could not have been influenced by the knowledge of hemodynamic measurement.

Effects on Blood Pressure and Heart Rate

Effects on Blood Pressure

During the 3-hour placebo-controlled period, both nitroglycerin and Natrecor® significantly decreased SBP compared to placebo, although these differences were not statistically significant at every time point (Table 3–6). The effect of Natrecor® on SBP was evident within 15 minutes ($p = 0.013$, compared to placebo [pairwise contrast]), at which time 70% of the 3-hour effect was observed. By 30 minutes, nitroglycerin was associated with significant

mean decreases in SBP compared to placebo ($p = 0.005$ [pairwise contrast]), an effect that persisted through the 3-hour time point ($p = 0.043$, compared to placebo [pairwise contrast]). There were no significant differences between nitroglycerin and Natrecor® in their effects on SBP through 3 hours.

Table 3-6

**Effects on SBP through 3 Hours
(All Treated Subjects, as Randomized)**

Placebo-Controlled Period	Nitroglycerin (n = 143)	Natrecor® (n = 204)	Placebo (n = 142)	p-value
Baseline SBP (mm Hg)	124 ± 23	120 ± 23	121 ± 21	0.522
Change From Baseline				
15 minutes	-3.1 ± 11.1	-4.0 ± 11.4*	-1.2 ± 11.2	0.044
30 minutes	-4.4 ± 12.5*	-3.7 ± 11.2*	-0.6 ± 11.2	0.010
1 hour	-6.3 ± 13.9*	-3.2 ± 12.7	-1.5 ± 12.6	0.008
2 hours	-5.8 ± 14.5*	-5.1 ± 13.2*	-2.1 ± 12.0	0.027
3 hours	-5.7 ± 14.9*	-5.6 ± 12.9*	-2.5 ± 11.2	0.039

Table 81.1

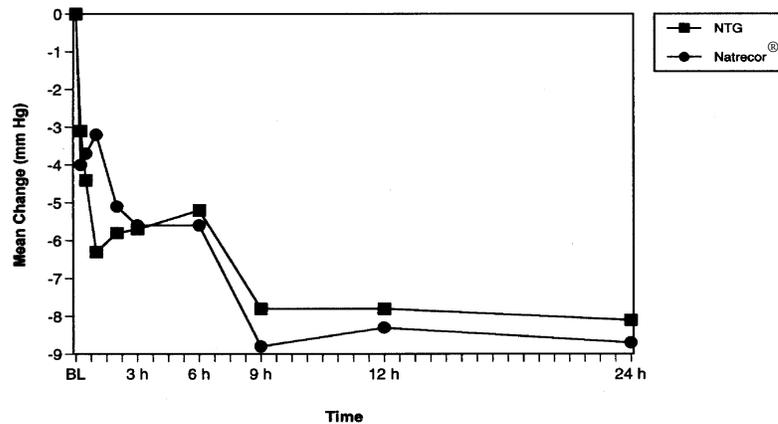
* $p < 0.05$ Natrecor® or nitroglycerin compared to placebo, two-way ANOVA (treatment and catheter use as two factors) with pair-wise contrast test.

[†]two-way ANOVA

Over the first 24 hours, there were no significant differences in the effects on SBP between nitroglycerin and Natrecor® (Figure 3-12). At every time point from 6 to 24 hours, both agents were associated with significant mean decreases in SBP compared to baseline ($p < 0.001$ [paired t-test]).

Figure 3-12

**SBP through 24 Hours
(All Treated Subjects, as Randomized)**



The similar effects of Natrecor[®] and nitroglycerin on SBP over 24 hours is important because Natrecor[®] was associated with significantly greater effects on PCWP during the same period. The apparent effects of nitroglycerin on SBP confirms the physiological activity of nitroglycerin. The effect of nitroglycerin on SBP may have also impacted how actively the nitroglycerin dose was titrated.

Effect on Heart Rate

Neither nitroglycerin nor Natrecor[®] was associated with clinically significant changes in heart rate through 3 hours. For example, at 3 hours the change in heart rate was -1.0 ± 7.3 , -0.1 ± 8.9 , and 0.0 ± 8.5 in the nitroglycerin, Natrecor[®], and placebo groups, respectively ($p = 0.558$, F-test).

Nitroglycerin Dose Subgroups: Effects on PCWP and SBP

The differences between the effects of Natrecor[®] and nitroglycerin on PCWP reduction may not merely reflect a difference in potency of the two IV vasodilators, but may represent a difference in the relative effects of these agents on preload and afterload at the doses studied. Although the Investigators were permitted to dose nitroglycerin *ad libitum*, rather than subjects being randomized to certain dose targets, it is informative to examine the observed hemodynamic effects of different doses of nitroglycerin. This may be especially useful in interpreting the hemodynamic benefit-to-risk profile of nitroglycerin in non-catheterized subjects in whom lower doses of nitroglycerin were administered.

Based on a review of the effects of different doses of nitroglycerin on PCWP and SBP through 3 hours (Table 3–7), it appears that 0.01 µg/kg/min of Natrecor® leads to greater effects on pulmonary hemodynamics than nitroglycerin, without being accompanied by greater effects on the systemic circulation. The mean 1- and 3-hour effects of Natrecor® on PCWP reduction were comparable to the magnitude of effect that occurred with at least 60 µg/min of nitroglycerin. However, the mean reductions in SBP that occurred with at least 60 µg/min of nitroglycerin exceeded the mean effect on SBP that was observed with the 0.01-µg/kg/min dose of Natrecor® at those time points.

Table 3–7

**Hemodynamic Effects by Nitroglycerin Dose Subgroups
Placebo-Controlled Period
(All Treated Catheterized Subjects)**

	Nitroglycerin (µg/min)				Natrecor®	Placebo
	All nitroglycerin	≤ 30	31–60	> 60		
Change in PCWP (mm Hg):						
1 hour	-2.8 ± 4.1 (n = 58)	-2.4 ± 4.3 (n = 44)	-2.9 ± 2.9 (n = 8)	-5.2 ± 4.3 (n = 6)	-5.5 ± 6.3 (n = 121)	-1.5 ± 4.8 (n = 62)
3 hours	-3.8 ± 5.3 (n = 59)	-3.4 ± 5.4 (n = 43)	-2.3 ± 2.7 (n = 6)	-6.6 ± 5.0 (n = 10)	-5.8 ± 6.5 (n = 121)	-2.0 ± 4.2 (n = 62)
Change in SBP (mm Hg):						
1 hour	-4.0 ± 13.0 (n = 60)	-3.2 ± 12.4 (n = 47)	-2.4 ± 6.7 (n = 7)	-11.7 ± 21.0 (n = 6)	-3.0 ± 11.9 (n = 124)	-0.1 ± 11.8 (n = 62)
3 hours	-3.8 ± 14.4 (n = 60)	-4.0 ± 14.3 (n = 44)	2.3 ± 13.9 (n = 6)	-6.6 ± 15.3 (n = 10)	-4.9 ± 12.2 (n = 124)	-2.0 ± 10.8 (n = 62)

Tables 68 and 69.2

Less than 60 µg/min of nitroglycerin led to effects on PCWP that were similar to those of placebo. Yet, the effects of the 0.01-µg/kg/min dose of Natrecor® on SBP were similar to those observed with less effective doses of nitroglycerin. Therefore, although both Natrecor® and nitroglycerin are vasodilators, the relative effects of the two agents on PCWP and SBP suggest that the 0.01-µg/kg/min dose of Natrecor® had a better hemodynamic benefit-to-risk profile. That is, Natrecor® led to greater preload reduction than nitroglycerin, without a corresponding increased risk for excessive effects on systolic BP.

Diuretics and Other Vasoactive Agents

During the first 24 hours of study drug, as well as during the total course of therapy with study drug, significantly fewer All Natrecor® subjects received diuretics than did nitroglycerin subjects (Table 3–8).

Table 3–8

**Diuretic Use during Study-Drug Administration
(All Treated Subjects, as Randomized)**

	Nitroglycerin (n = 216)	Natrecor® Fixed Dose (n = 211)	All Natrecor® (n = 273)
During the First 24 Hours			
Diuretics	198 (92%)	183 (87%)	232 (85%)*
IV Diuretics	163 (75%)	145 (69%)	186 (68%)
Non-IV Diuretics	103 (48%)	97 (46%)	117 (43%)
During Study Drug			
Diuretics	204 (94%)	182 (86%)*	232 (85%)*
IV Diuretics	167 (77%)	150 (71%)	192 (70%)
Non-IV Diuretics	119 (55%)	97 (46%)	118 (43%)*

Tables 44.1 and 45.1

*p < 0.05 compared to nitroglycerin, Fisher's Exact Test

In spite of the lower use of diuretics with Natrecor® therapy, net urine output and weight loss through 24 hours after the start of study drug were similar in nitroglycerin and Natrecor® subjects. The mean net urine output through 24 hours was 1279 ± 1455 and 1257 ± 1657 mL in the nitroglycerin and All Natrecor® group ($p = 0.877$, t-test), respectively. The change in weight through 24 hours after the start of study drug was a loss of 1.1 ± 2.3 kg in nitroglycerin subjects and a loss of 1.4 ± 3.0 kg in All Natrecor® subjects ($p = 0.232$, t-test).

Safety

Natreacor[®] was well tolerated in the VMAC trial and appeared to be better tolerated than nitroglycerin. The analysis of adverse events through the placebo-controlled period and during the first 24 hours after the start of study drug demonstrates that there was no adverse event that occurred in significantly more Natreacor[®] subjects than nitroglycerin subjects. In contrast, significantly more nitroglycerin subjects reported adverse events overall during the placebo-controlled period, as well as during the first 24 hours after the start of study drug. A similar frequency of asymptomatic hypotension and symptomatic hypotension was reported in nitroglycerin and Natreacor[®] subjects through each period summarized.

Adverse Events during the Placebo-Controlled Period

During the placebo controlled period, adverse events overall, headache, hypotension, and abdominal pain were reported in significantly more nitroglycerin subjects (Table 3–9). Compared to placebo, more Natreacor[®] subjects reported headache and asymptomatic hypotension. Symptomatic hypotension was rare during the placebo-controlled period in any treatment group.

Table 3–9

**Adverse Events during Placebo-Controlled Period
(All Treated Subjects, as Randomized)**

Adverse Event	Nitroglycerin (n = 143)	Natreacor[®] (n = 204)	Placebo (n = 142)	p-value¹
Any Adverse Event	39 (27%)	36 (18%)	20 (14%)	0.015
Headache	17 (12%)	11 (5%)	3 (2%)	0.003
Hypotension	6 (4%)	5 (2%)	0 (0%)	0.031
Symptomatic Hypotension	2 (1%)	1 (< 1%)	0 (0%)	0.481
Abdominal Pain	4 (3%)	0 (0%)	0 (0%)	0.014

Table 99.1

¹Fisher's Test

Adverse Events during the First 24 Hours

During the first 24 hours of therapy, significantly more nitroglycerin subjects reported adverse events overall, as well as the specific events of headache, abdominal pain, and catheter pain.

Table 3–10 summarizes adverse events that occurred in at least 3% of subjects in any treatment group.

Table 3–10

**Adverse Events during First 24 Hours after Start of Study Drug
(All Treated Subjects, as Randomized)**

Adverse Event	Nitroglycerin (n = 216)	Natrecor® Fixed Dose (n = 211)	All Natrecor® (n = 273)
Any Adverse Event	146 (68%)	105 (50%)**	140 (51%)**
Body as a whole			
Headache	44 (20%)	19 (9%)**	21 (8%)**
Pain	11 (5%)	8 (4%)	11 (4%)
Back Pain	7 (3%)	9 (4%)	10 (4%)
Abdominal Pain	11 (5%)	2 (1%)*	4 (1%)*
Catheter Pain	11 (5%)	3 (1%)	4 (1%)*
Digestive			
Nausea	13 (6%)	7 (3%)	10 (4%)
Cardiovascular			
Asymptomatic Hypotension	17 (8%)	17 (8%)	23 (8%)
Symptomatic Hypotension	10 (5%)	10 (5%)	12 (4%)
Non-Sustained VT	11 (5%)	6 (3%)	9 (3%)
Ventricular Extrasystoles	2 (1%)	4 (2%)	7 (3%)
Nervous			
Insomnia	9 (4%)	3 (1%)	6 (2%)
Anxiety	6 (3%)	6 (3%)	8 (3%)
Dizziness	4 (2%)	7 (3%)	7 (3%)

Table 100.1

*p < 0.05, compared to nitroglycerin (Fisher's test)

**p ≤ 0.001, compared to nitroglycerin (Fisher's test)

The frequency of reported asymptomatic and symptomatic hypotension was similar between nitroglycerin and Natrecor[®] subjects. Symptomatic hypotension occurred in 10 (5%), 10 (5%), and 12 (4%) subjects in the nitroglycerin, Natrecor[®] fixed-dose, and All Natrecor[®] groups, respectively. It is noteworthy that the frequency of symptomatic hypotension was similar between nitroglycerin and the All Natrecor[®] group, even though the All Natrecor[®] group included the additional 62 Natrecor[®] adjustable-dose subjects. Twenty-seven adjustable-dose subjects received a higher dose of Natrecor[®] than 0.01 µg/kg/min. Of the 2 adjustable-dose subjects who developed symptomatic hypotension within the first 24 hours, 1 subject was receiving 0.01 µg/kg/min, and the other was receiving 0.015 µg/kg/min at the time of the event. No symptomatic hypotension event resulted in adverse sequelae (such as MI or stroke) in any treatment group.

For nitroglycerin subjects, headache was the most common adverse event reported within the first 24 hours (20%), followed by asymptomatic hypotension (8%), nausea (6%), symptomatic hypotension (5%), pain (5%), abdominal pain (5%), catheter pain (5%), and nonsustained VT (5%). For All Natrecor[®] subjects, adverse events that were reported in at least 5% of subjects included asymptomatic hypotension (8%) and headache (8%).

Characteristics of Symptomatic Hypotension: Natrecor[®] versus Nitroglycerin

One important objective of the VMAC trial was to describe the differences in the pharmacodynamic profiles of nitroglycerin and Natrecor[®], especially as they relate to onset and offset of effects and their impact on safety events. This section discusses how differences in the pharmacodynamic profiles of nitroglycerin and Natrecor[®] impacted the characteristics of symptomatic hypotension that occurred within the first 24 hours after the start of study drug. Events occurring within this timeframe are the focus of this discussion because these are the events that are most likely to be related to either drug.

Incidence: During the first 24 hours after start of study drug, symptomatic hypotension was reported in 10 (5%), 10 (5%), and 12 (4%) subjects in the nitroglycerin, Natrecor® fixed-dose and All Natrecor® subjects, respectively (Table 3–11).

Table 3–11

**Clinical Characteristics of Symptomatic Hypotension
Within the First 24 Hours
(All Treated Subjects, as Randomized)**

	Nitroglycerin n = 216	Natrecor® Fixed Dose n = 211	All Natrecor® n = 273	p-value¹
Subjects with Symptomatic Hypotension	10 (5%)	10 (5%)	12 (4%)	1.000 ²
Number of Episodes	12	13	15	
Time of Onset (Episode)				
≤ 1 hour	0 (0%)	0 (0%)	0 (0%)	
> 1–3 hours	1 (8%)	0 (0%)	0 (0%)	
> 3–6 hours	3 (25%)	5 (38%)	5 (33%)	0.906 ³
> 6–24 hours	8 (67%)	8 (62%)	10 (67%)	
Severity of Episode				
Mild	6 (50%)	4 (31%)	4 (27%)	
Moderate	5 (42%)	8 (62%)	10 (67%)	0.319 ³
Severe	1 (8%)	1 (8%)	1 (7%)	
Duration of Episode				
≤ 30 minutes	7 (58%)	0 (0%)	0 (0%)	
31–60 minutes	2 (17%)	3 (23%)	3 (20%)	0.001 ³
61–120 minutes	3 (25%)	5 (38%)	5 (33%)	
121–180 minutes	0 (0%)	3 (23%)	4 (27%)	
> 3–7 hours	0 (0%)	2 (15%)	3 (20%)	0.001 ³
> 7 hours	0 (0%)	0 (0%)	0 (0%)	0.001 ³
Greatest Impact on Dosing				
No effect on dose	3 (30%)	1 (10%)	1 (8%)	
Dose decreased	3 (30%)	3 (30%)	5 (42%)	0.412 ³
Discontinued	4 (40%)	6 (60%)	6 (50%)	
Dopamine Initiated	1 (7%)	0 (0%)	0 (0%)	0.444 ²
Inotrope/Pressor Added	0 (0%)	1 (7%)	1 (6%)	1.000 ²

Table 108.1

¹Nitroglycerin compared to all Natrecor®.

²Fisher

³Wilcoxon

Time to Onset: There were no significant differences in the time to onset of symptomatic hypotension between the treatment groups. No symptomatic hypotension occurred within the first hour of study-drug administration in either treatment group, and only 1 nitroglycerin subject reported symptomatic hypotension within the first 3 hours of study-drug administration. The majority of the events occurred between 6 and 24 hours after the start of study drug in both nitroglycerin and Natrecor® subjects. A plausible reason why the time to onset of symptomatic hypotension may not directly correlate with each agent's half-life may be that symptomatic hypotension is also closely correlated with the administration of diuretics and other long-term therapies throughout the course of therapy. This observation suggests that any differences in the half-lives and pharmacodynamic profiles of nitroglycerin and Natrecor® do not translate into differences in the time to onset of symptomatic hypotension.

Severity of Events: There were no significant differences between treatment groups in the severity of symptomatic hypotension events that occurred within 24 hours or in the need for interventions in response to the events. In addition, no event of symptomatic hypotension led to adverse sequelae in any treatment group. Most events were considered mild or moderate, and only 1 subject in each treatment group experienced an event that was classified as severe.

Need for Intervention: Most events resolved either spontaneously or with an IV volume challenge of 250 mL (or less), or Trendelenburg positioning. In approximately half of the subjects, the events led to no change in study-drug dose or a decrease in the dose. In the other half of subjects, study drug was discontinued due to the event. Therefore, among all subjects in the study, study drug was discontinued due to symptomatic hypotension that occurred within the first 24 hours in only 2% of subjects treated with either nitroglycerin or Natrecor®. There was no significant difference between Natrecor® and nitroglycerin in the need for the dose reduction, dose discontinuation, or the initiation of dobutamine or dopamine in response to symptomatic hypotension.

Duration of Events: The differences in half-life between nitroglycerin and Natrecor® translate to differences in the duration of symptomatic hypotension. Seven of the 12 events of symptomatic hypotension in nitroglycerin subjects resolved within 30 minutes, 2 resolved within 1 hour, and the 3 remaining events resolved within 2 hours. In All Natrecor® subjects, 3 of the 15 events resolved within 1 hour, an additional 4 events resolved within 1 hour, 20 minutes. In 1 event (lasting 4 hours), symptoms occurred intermittently during the total duration of the event and led to a decrease in the dose of Natrecor®, with no other intervention required. Among the other events that lasted longer than 2 hours, 4 events led to a decrease in dose of Natrecor® only, 1 event led to the discontinuation of Natrecor®, and 1 event led to a decrease in dose and the initiation of dobutamine. No event led to adverse sequelae. Although the duration of symptomatic hypotension events was shorter with nitroglycerin, the fact that some events in the nitroglycerin group lasted for up to 2 hours suggests that the duration of the events that occurred with either agent can not be explained by half-life alone. If symptomatic hypotension occurs during Natrecor® therapy, it is recommended that the Natrecor® infusion dose be decreased or interrupted until the symptoms resolve and blood

pressure has stabilized. If interrupted, the Natrecor® infusion may be restarted (without a bolus) at a dose that is 30% lower than the dose that was administered at the time of the event.

Duration of event is defined as the time from the onset of symptoms to the time that the last symptom resolved (see Table 3–11). Therefore, a review of the changes in SBP that occurred after the onset of symptomatic hypotension provides additional information about the duration of the hypotensive events. The protocol specified that study drug was to be discontinued, at least temporarily, if symptomatic hypotension occurred, and that study drug could be restarted whenever the symptoms resolved and the SBP was stable above 90 mm Hg. Therefore, Table 3–12 represents the changes in SBP that occurred after study drug was interrupted in the setting of symptomatic hypotension.

Table 3–12
Systemic SBP (mm Hg) after Onset of Symptomatic Hypotension
(All Treated Subjects, as Randomized)

	Nitroglycerin (n = 12)	Natrecor® Fixed Dose (n = 13)	All Natrecor® (n = 15)
SBP at or Before Event (Baseline)	79.3 ± 12.3	80.0 ± 15.4	80.4 ± 14.6
Change from Baseline			
15 min	+22.3 ± 24.5	+4.1 ± 6.6	+4.3 ± 6.3
30 min	+23.2 ± 21.4	+9.8 ± 11.6	+8.8 ± 11.0
45 min	+19.6 ± 23.5	+6.1 ± 17.2	+5.3 ± 15.4
60 min	+22.3 ± 23.0	+15.3 ± 13.51	+15.7 ± 14.9
90 min	+24.7 ± 19.3	+17.3 ± 20.3	+15.8 ± 19.7
120 min	+26.5 ± 19.2	+18.3 ± 19.5	+16.7 ± 18.6

Table 111.1

The mean SBP measured at or just prior to the symptomatic hypotension events was similar in nitroglycerin and All Natrecor® subjects. Within 15 minutes, reduction or discontinuation of both drugs was associated with a significant increase in SBP from before the event. However, the increase in SBP that occurred in nitroglycerin subjects was significantly greater than in Natrecor® subjects ($p = 0.042$, two-way ANOVA). (The increase in SBP within 15 minutes was 22 mm Hg in nitroglycerin subjects [$p = 0.013$, compared to SBP before the event, paired t-test] and 4 mm Hg in Natrecor® subjects [$p = 0.049$, compared to SBP before the event, paired t-test]). By 1 hour, the increase in SBP in Natrecor® subjects was similar to that of nitroglycerin subjects.

These SBP data show that the offset effect of Natrecor® on blood pressure is longer than with nitroglycerin. Given that the half-life of Natrecor® is 18 minutes, the data support the expectation that blood pressure recovery would be evident within 15 minutes after dose

reduction or discontinuation of Natrecor®. These data also show that the timing of the offset of SBP effects does not exactly correlate with the timing of the resolution of symptoms of hypotension. The duration of symptoms associated with hypotension is affected by many factors that may include the drug's half-life, the use of concomitant medications that may cause hypotension, the subject's hydration status and cardiac output, and biological variability.

Maximum Effects on SBP and HR: Table 3–13 summarizes the maximal effects of nitroglycerin and Natrecor® on SBP and HR in subjects who developed symptomatic hypotension during the first 24 hours after start of study drug. There were no significant differences between the two treatment groups in baseline SBP, lowest SBP observed, maximum decreases and maximum percentage decreases in SBP, or in the change in heart rate observed at the time of the minimum SBP.

Table 3–13

Systolic BP and Heart Rate in Subjects with Symptomatic Hypotension during the First 24 Hours

	Nitroglycerin (n = 10)	Natrecor® Fixed Dose (n = 10)	All Natrecor® (n = 12)
Baseline SBP (mm Hg)	122 ± 20	113 ± 26	113 ± 24
Lowest SBP (mm Hg)	75 ± 13	72 ± 17	74 ± 16
< 70 mm Hg	5 (50%)	3 (30%)	3 (25%)
70 – < 80	1 (10%)	6 (60%)	7 (58%)
80 – < 90	3 (30%)	0 (0%)	0 (0%)
90 – < 100	0 (0%)	0 (0%)	1 (8%)
100 – < 110	1 (10%)	1 (10%)	1 (8%)
≥ 110	0 (0%)	0 (0%)	0 (0%)
Maximum Decrease in SBP (mm Hg)	47 ± 23	41 ± 15	40 ± 14
Maximum % Decrease in SBP	37 ± 14 %	36 ± 10 %	35 ± 9 %
Change in Heart Rate at time of Minimum SBP (bpm)	–12 ± 18	–8 ± 14	–8 ± 13

Table 115.1

Adverse Events Leading to Study-Drug Discontinuation

There were no significant differences between the All Natrecor® group and the nitroglycerin group in the reasons for study-drug termination (Table 3–14). “Dose adjustment to clinical effect” was the most common reason for study-drug termination (approximately 75% of all subjects), followed by “inadequate clinical response” (approximately 15% of all subjects), then “adverse events” (approximately 10% of all subjects).

Table 3–14

**Reasons for Study-Drug Termination
(All Treated Subjects, as Randomized)**

All Subjects	Nitroglycerin (n = 216)	Natrecor® Fixed Dose (n = 211)	All Natrecor® (n = 273)	p-value
Dose Adjustment to Clinical Effect	157 (73%)	161 (76%)	207 (76%)	
Adverse Event	12 (6%)	21 (10%)	24 (9%)	0.222 ¹
Inadequate Clinical Response	37 (17%)	25 (12%)	35 (13%)	0.200 ²
Other	10 (5%)	4 (2%)	7 (3%)	

Tables 39.1–39.3

¹Fisher’s Test based on two categories: AE or not; all Natrecor® compared to nitroglycerin

²Fisher’s Test based on two categories: Inadequate clinical response or not; all Natrecor® compared to nitroglycerin

There were no significant differences between treatment groups in the number of subjects who discontinued study drug due to an adverse event, or in the types of adverse events that led to study-drug discontinuation. Table 3–15 includes events leading to study-drug discontinuation that occurred in at least 2 subjects in either treatment group.

Table 3–15

**Selected Adverse Events Leading to Study-Drug Discontinuation
through Study Day 14
(All Treated Subjects, as Randomized)**

	Nitroglycerin (n = 216)	Natrecor® (n = 273)	p-value¹
Any Adverse Event	12 (6%)	24 (9%)	0.222
Cardiovascular System			
Asymptomatic Hypotension	2 (1%)	8 (3%)	0.197
Symptomatic Hypotension	5 (2%)	9 (3%)	0.594
Non-Sustained VT	0 (0%)	2 (1%)	0.506
Body as a Whole			
Headache	2 (1%)	0 (0%)	0.195
Nervous System			
Confusion	2 (1%)	1 (< 1%)	0.586
Urogenital System			
Kidney Function Abnormal	0 (0%)	2 (1%)	0.506

Table 104.1

¹Fisher

Other Serious, Significant, or Unusual Adverse Events

Through 30 days, there were also no significant differences between treatment groups in the overall frequency of Serious Adverse Events (SAEs) or in the frequency of any particular event (Table 3–16). The most common body system affected was cardiovascular, and the most common event was CHF. For example, 31 (14%) and 33 (12%) nitroglycerin and Natrecor[®] subjects, respectively, experienced CHF as an SAE through day 30. These CHF events were deemed as serious usually because they led to hospital readmission for an acute exacerbation of CHF, an outcome through 30 days that was not unexpected in this population with advanced CHF.

Table 3–16

**Serious Adverse Events (SAEs) through Study Day 30
(All Treated Subjects, as Randomized)**

	Nitroglycerin (n = 216)	Natrecor[®] Fixed Dose (n = 211)	All Natrecor[®] (n = 273)
Subjects with Any SAE	62 (29%)	66 (31%)	83 (30%)
Body System			
Cardiovascular	42 (19%)	39 (18%)	49 (18%)
CHF	31 (14%)	25 (12%)	33 (12%)
Urogenital	11 (5%)	14 (7%)	20 (7%)
Respiratory	14 (6%)	9 (4%)	13 (5%)
Digestive	5 (2%)	8 (4%)	8 (3%)
Metabolic/Nutritional	7 (3%)	7 (3%)	7 (3%)
Body as a Whole	5 (2%)	7 (3%)	7 (3%)

Table 106.1

Acute Coronary Syndrome

Sixty-one subjects with an acute coronary syndrome (ACS) within 7 days of admission were enrolled into the study (34 in the nitroglycerin group and 27 in the All Natrecor® group). The relative incidence of adverse events in these subjects was similar to the pattern of adverse events reported in the larger study population (Table 3–17). In particular, regardless of treatment group, subjects with an ACS did not experience significantly more symptomatic hypotension, angina pectoris, or ventricular arrhythmia within the first 24 hours of therapy compared to those without an ACS.

Table 3–17

Selected¹ Adverse Events during the First 24 Hours after Start of Study Drug Subgrouped by Subjects with Acute Coronary Syndrome (ACS) within 7 Days before Study Drug (All Treated Subjects, as Randomized)

Adverse Event	Nitroglycerin (n = 216)		Natrecor® Fixed Dose (n = 211)		All Natrecor® (n = 273)	
	ACS (n = 34)	No ACS (n = 182)	ACS (n = 23)	No ACS (n = 188)	ACS (n = 27)	No ACS (n = 246)
Any Adverse Event	27 (79%)	119 (65%)	14 (61%)	91 (48%)**	16 (59%)	124 (50%)*
Body as a Whole						
Headache	8 (24%)	36 (20%)	1 (4%)	18 (10%)*	1 (4%)*	20 (8%)*
Abdominal Pain	3 (9%)	8 (4%)	0 (0%)	2 (1%)	0 (0%)	4 (2%)
Cardiovascular						
Hypotension	3 (9%)	22 (12%)	3 (13%)	21 (11%)	4 (15%)	27 (11%)
Symptomatic Hypotension	1 (3%)	9 (5%)	1 (4%)	9 (5%)	2 (7%)	10 (4%)
Angina Pectoris	1 (3%)	4 (2%)	0 (0%)	4 (2%)	0 (0%)	5 (2%)
Ventricular Tachycardia	0 (0%)	11 (6%)	1 (4%)	5 (3%)	1 (4%)	8 (3%)
Digestive						
Nausea	5 (15%)	8 (4%)	2(9%)	5 (3%)	2 (7%)	8 (3%)

Table 162

¹Selected = ...

*p < 0.05 vs. nitroglycerin (Fisher)

**p ≤ 0.001 vs. nitroglycerin (Fisher)

Through 30 days, there was also no difference in the later occurrence of an MI or death in the ACS patients. There was 1 nitroglycerin subject (561-501) with an ACS who developed an MI on study day 4 and 1 Natrecor® fixed-dose subject (554-545) with an ACS who developed an MI on study day 6. There were 2 ACS subjects who died during follow up (subjects 627-506 [Natrecor® fixed-dose] and 538-405 [nitroglycerin]).

Six-Month Mortality

Prospectively collected six-month mortality data is presented in Item 5.

Discussion and Overall Conclusions from VMAC

The VMAC trial comprehensively addressed the issues raised by the FDA and the Cardiovascular and Renal Drugs Advisory Committee. VMAC was a randomized, double-blinded trial that evaluated a new dose of Natreacor[®] (a 2- μ g/kg bolus followed by a fixed-dose infusion of 0.01 μ g/kg/min) in severely ill patients with acute decompensated CHF, dyspnea at rest, and many significant comorbidities, including acute coronary syndromes, preserved systolic function, significant ventricular arrhythmias and renal insufficiency. The study was conducted in patients who were receiving standard-care medications during study-drug infusion such as IV or oral diuretics, beta-blockers, dobutamine, dopamine, and other long-term cardiac therapies. Therefore, the efficacy and safety profile of Natreacor[®] observed in the VMAC trial should be representative of what would be observed in the target population that would be treated with Natreacor[®].

The VMAC trial confirmed that the 0.01- μ g/kg/min dose of Natreacor[®] (preceded by a 2- μ g/kg bolus) leads to rapid (within 15 minutes) and sustained decreases in PCWP. The effect of Natreacor[®] on PCWP was superior to both placebo and nitroglycerin through every time point from 15 minutes to the primary endpoint time point at 3 hours (except at 2 hours, compared to nitroglycerin). The only time point at which nitroglycerin could be distinguished from placebo was at 2 hours. The effect of Natreacor[®] on PCWP was sustained through at least 48 hours and was significantly greater than the effect of nitroglycerin through 24 hours.

At 3 hours, subjects receiving Natreacor[®] reported significant improvements in dyspnea that were in excess of what was observed with standard care alone (placebo) in all subjects. By 24 hours, Natreacor[®] therapy was associated with a significant improvement in the global assessment, compared to nitroglycerin plus standard care in all subjects. In non-catheterized subjects, Natreacor[®] significantly improved both dyspnea and the global assessment compared to nitroglycerin at 24 hours. The emergence of significant differences in clinical benefit between Natreacor[®] and nitroglycerin at the 24-hour time point may represent the clinical manifestation of tachyphylaxis in subjects receiving nitroglycerin. These data also confirm that the beneficial clinical effects of Natreacor[®] were sustained for at least 24 hours, and that objective symptomatic improvement occurred in a setting that was not biased by the knowledge of hemodynamic effects.

The safety profile of Natrecor[®] observed in the VMAC trial should be representative of what would be observed in the target population that would be treated with Natrecor[®]. The 0.01- $\mu\text{g}/\text{kg}/\text{min}$ dose of Natrecor[®] generally was well tolerated, even in severely ill patients with multiple comorbidities, and in those taking multiple concomitant cardiac medications. Natrecor[®] was better tolerated than nitroglycerin, as evidenced by the significantly greater percentage of nitroglycerin subjects who experienced any adverse event, as well as headache and abdominal pain. There was no adverse event clearly associated with Natrecor[®] that occurred significantly more frequently in Natrecor[®] subjects. Increased doses of Natrecor[®] in those subjects who tolerated the 0.01- $\mu\text{g}/\text{kg}/\text{min}$ dose also were well tolerated. Symptomatic hypotension was less frequent with the 0.01- $\mu\text{g}/\text{kg}/\text{min}$ dose of Natrecor[®] than has been reported when patients began treatment with Natrecor[®] at higher initial doses. In the VMAC trial, symptomatic hypotension was reported in 5% and 4% of nitroglycerin and Natrecor[®] subjects, respectively, within the first 24 hours of therapy. Blood pressure should be routinely monitored during Natrecor[®] therapy.

In summary, the VMAC trial confirms the hemodynamic and clinical efficacy of Natrecor[®] that was demonstrated in previous Natrecor[®] trials. The 0.01 $\mu\text{g}/\text{kg}/\text{min}$ (preceded by a 2 $\mu\text{g}/\text{kg}$ bolus) dose of Natrecor[®] led to less hypotension than was observed with higher doses in previous trials. The VMAC trial demonstrates that a fixed-dose strategy of administering Natrecor[®] at a dose of 0.01 $\mu\text{g}/\text{kg}/\text{min}$ (preceded by a 2- $\mu\text{g}/\text{kg}$ bolus) was more effective than a titration strategy with IV nitroglycerin, without adverse consequences of its more potent and sustained hemodynamic and clinical effects. Natrecor[®] led to more rapid hemodynamic improvement that was consistently greater than that of nitroglycerin through at least 24 hours. Natrecor[®] also led to clinical benefit by 3 hours compared to placebo, and by 24 hours, compared to nitroglycerin. A fixed-dose administration of Natrecor[®] leads to predictable hemodynamic and clinical effects in typical acutely decompensated patients with dyspnea at rest, suggesting that Natrecor[®] administration does not necessitate invasive monitoring unless dictated by the clinical condition of the patient.

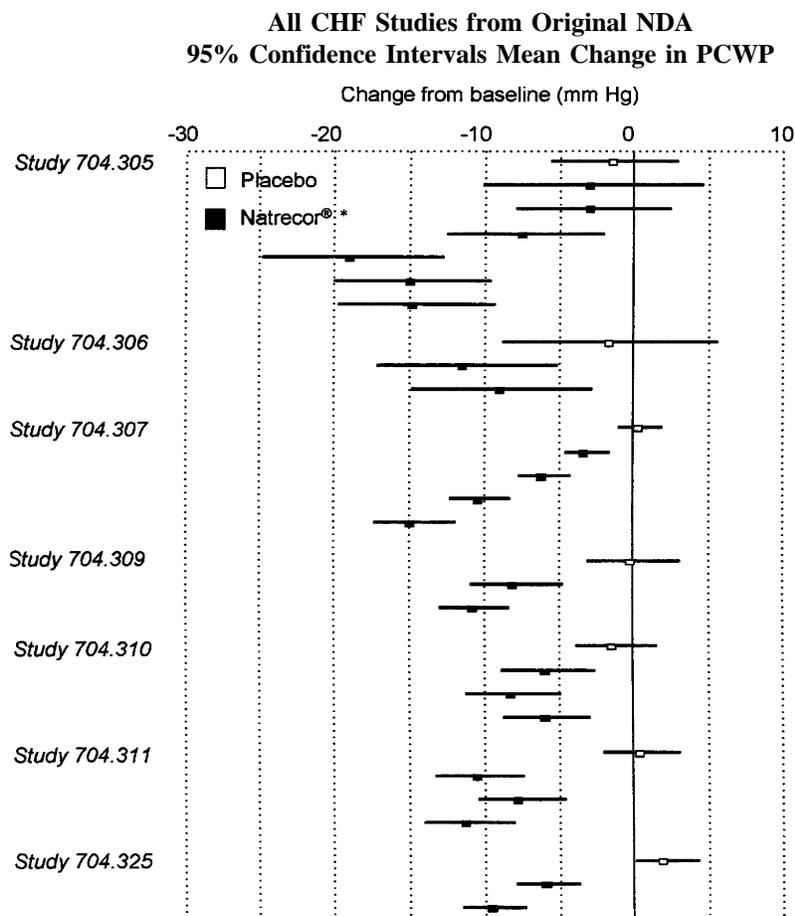
Item 4

Efficacy Supported by the Original NDA

Efficacy Supported by NDA

In 7 placebo-controlled clinical trials that studied Natrecor[®] as an IV therapy for the short-term treatment of acute decompensated CHF, reduction in PCWP was the primary efficacy endpoint. In each of these 7 studies, Natrecor[®] significantly reduced PCWP compared to placebo, at each protocol-specified primary efficacy time point. Figure 4–1 summarizes the mean change (\pm 95% confidence intervals) in PCWP with each Natrecor[®] dose studied in each of these Natrecor[®] trials.

Figure 4–1



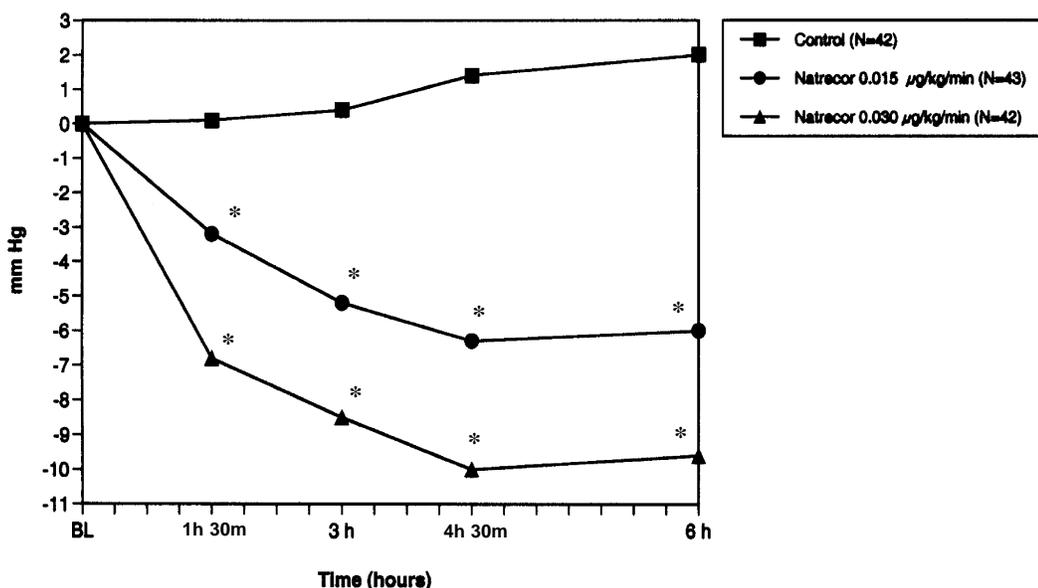
* Depicts results at various Natrecor[®] doses.

One of the pivotal efficacy studies in the NDA development program, study 704.325, was a randomized, double-blind, placebo-controlled study that enrolled 127 subjects. In this study, symptomatic CHF subjects requiring hospitalization and IV vasoactive therapy who had systolic or preserved systolic function, and with a PCWP ≥ 18 mm Hg and a CI ≤ 2.7 L/min/M², were enrolled. Patients were randomized to treatment with placebo, a Natrecor[®] 0.3- μ g/kg bolus followed by a 0.015- μ g/kg/min infusion, or a Natrecor[®] 0.6- μ g/kg bolus followed by a 0.03- μ g/kg/min infusion. At the end of the 6-hour placebo-controlled period, the primary endpoint, PCWP, was measured. At 6 hours, the Investigator and subject also evaluated the subject's global clinical status.

In this study, statistically significant and dose-related effects on PCWP were observed with Natrecor[®] compared to placebo ($p < 0.001$). Figure 4-2 depicts the mean change in PCWP from baseline through 6 hours. Both doses of Natrecor[®] significantly reduced PCWP compared to placebo at every time point measured through 6 hours.

Figure 4-2

**Study 704.325
PCWP
Mean Change from Baseline**



Plotted values represent treatment-group means.

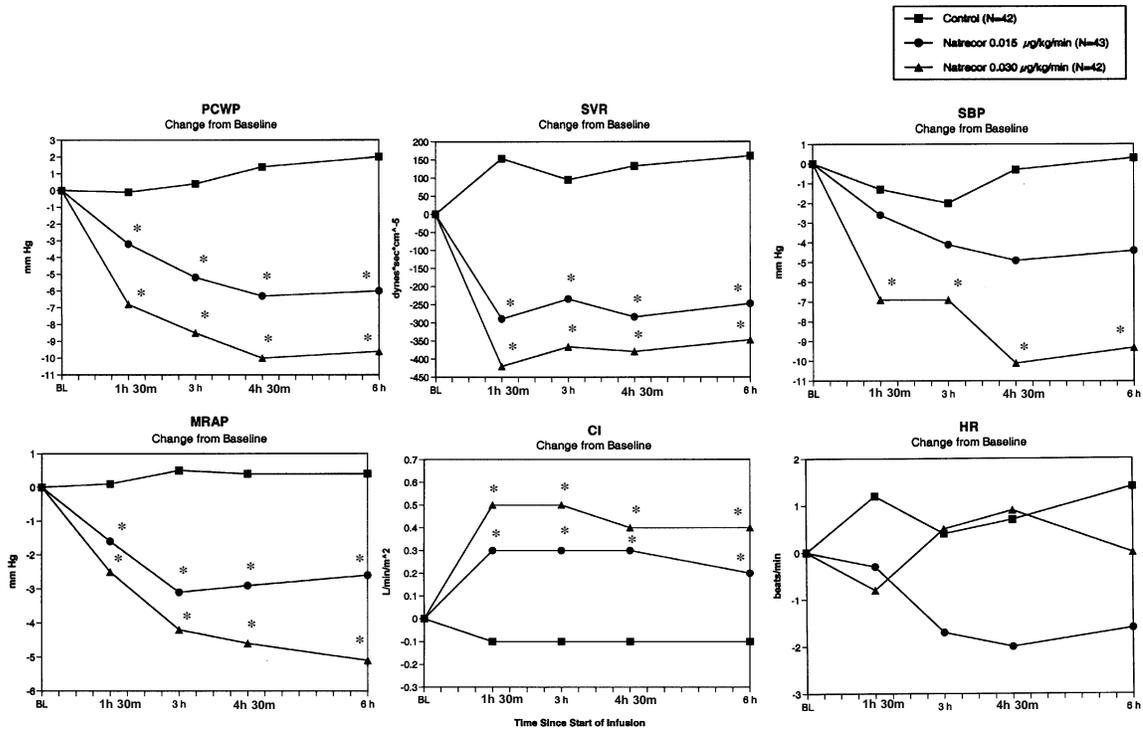
* $p < 0.05$ vs. placebo, by pairwise contrast within carry-forward ANOVA of change from baseline.

Other Hemodynamic Effects Supported by the NDA

In the 704.325 trial, desirable effects on multiple hemodynamic variables were observed, such as a reduction in preload (i.e., PCWP and mean RAP), and afterload (i.e., SVR), and an

increase in cardiac index, without affecting heart rate (Figure 4–3). These effects were consistently dose dependent.

Figure 4–3
Study 704.325
Hemodynamic Effects of Natrecor®
Mean Change from Baseline



Plotted values represent treatment-group means.

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

Global Clinical Status Supported by the NDA

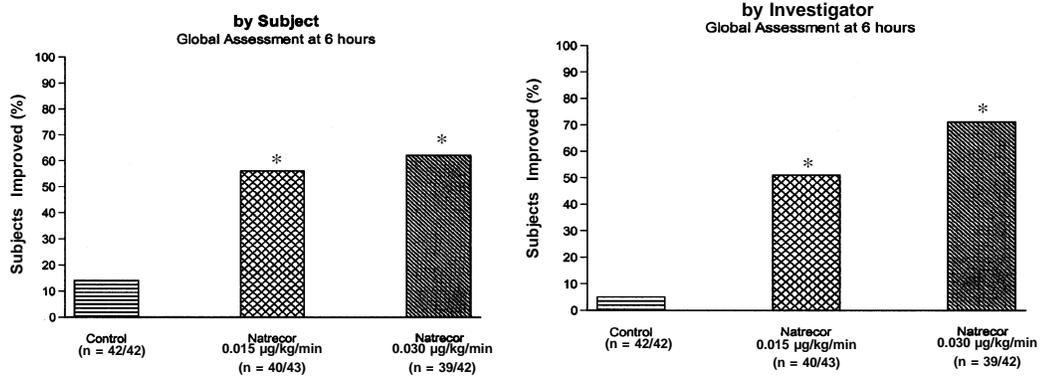
In study 704.325, global clinical status was assessed by means of a non-parametric intent-to-treat analysis. At the 6-hour and 24-hour time points, the subject and physician independently assessed the subjects' global clinical status. Evaluations employed a 5-point ordinal scale that included the following responses: markedly better, better, no change, worse, or markedly worse as compared to baseline.

Administration of Natrecor® resulted in improvements in global clinical status compared to placebo, as assessed by both the subjects and their physicians at 6 hours (Figure 4–4). By 6 hours (the first time point assessed), the majority of subjects (> 60%) in both Natrecor® dose groups reported feeling better or markedly better, compared to only 14% of placebo subjects. During this 6-hour assessment, diuretics were withheld. 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 each group [2-sample Wilcoxon]). Similar results were obtained when the physician was asked to assess each subject's clinical status at 6 hours.

Figure 4-4

**Study 704.325
Global Assessment of Clinical Status at 6 Hours¹**



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

¹ percentage of subjects reporting feeling "better" or "markedly better"

Item 5

Integrated Summary for Safety

Introduction

Subsequent to the original Natrecor® NDA No. 20–290, filed with the Agency on April 27, 1998, two additional clinical trials (704.329, the PRECEDENT trial, and 704.339, the VMAC trial) were completed.

The goals of these two trials, with respect to safety, were to better demonstrate the relative safety of Natrecor® compared to the standard care parenteral CHF therapies, dobutamine (the PRECEDENT trial) and nitroglycerin (the VMAC trial). In addition, better definition of the time constants of the pharmacodynamic effects of Natrecor® on hemodynamics, including systemic blood pressure, was sought. In particular, the VMAC trial attempted to define the pharmacodynamic profile of a lower Natrecor® dose than was administered in the PRECEDENT trial and the Phase III trials from the NDA. Further, the VMAC trial was designed to better define the safety of Natrecor® when used in conjunction with other parenteral IV therapies such as dobutamine or dopamine. Finally, both the PRECEDENT and VMAC trials included patients with preserved systolic function, and the VMAC trial included patients with acute coronary syndromes.

The VMAC Trial, *Vasodilation in the Management of Acute CHF* (Study 704.339) was the largest Natrecor® study (n = 489 treated patients) to date, and enrolled severely ill hospitalized patients with acute decompensated CHF and dyspnea at rest. Approximately 25% of subjects had already demonstrated an inadequate response to at least one standard parenteral agent for the study-related episode of decompensated CHF. The goal of the study was to compare the hemodynamic and clinical effects of a new Natrecor® dose (a 2-µg/kg IV bolus, followed by a 0.01-µg/kg/min continuous IV infusion) to both placebo and nitroglycerin. Eligible patients had dyspnea at rest due to acutely decompensated CHF requiring hospitalization. Patients with renal insufficiency and end-stage renal disease, preserved systolic function, significant atrial or ventricular arrhythmias, and acute coronary syndromes were not excluded.

In this trial, Natrecor®, IV nitroglycerin, or placebo was added to a background of standard-care oral, and sometimes, parenteral therapies (IV diuretics, dobutamine, and dopamine) for CHF for the first 3 hours, followed by a crossover of the placebo-treated patients to either Natrecor® or nitroglycerin for as long as was clinically indicated. Nitroglycerin was titrated (in a double-dummy fashion) at the discretion of the Investigators and according to usual practice.

All CHF Studies

This amended ISS presents the safety profile of Natrecor® from all 10 CHF studies within the Natrecor® clinical development program, referred to as the All CHF studies. However, the focus of the amended ISS is the Long Infusion population, which best represents the expected safety profile of the recommended dose range of Natrecor® in the target population. The All CHF studies are included in select analyses of adverse events and in tables of drug exposure, demography, and concomitant medications.

Long Infusion Studies

In clinical trials, Natrecor® has been administered to a broad spectrum of subjects with CHF (Tables 2–1 and 2–2). In early studies, subjects often were patients with chronic stable CHF who volunteered to participate or who were already hospitalized for either decompensated CHF or cardiac transplantation evaluation. These early studies were placebo controlled. In the final five studies in the development program (704.311 [n = 103], 704.325 [n = 127], 704.326 [n = 305], 704.329 [n = 246], and 704.339 [n = 489]), the subjects enrolled were patients requiring hospitalization for acutely decompensated CHF. For purposes of the ISS, these five studies are classified as Long Infusion studies. Only study 704.311 was entirely placebo controlled for 24 hours. In the later four studies, patients were more acutely ill and could not tolerate placebo infusions for more than a short period of time. Therefore, these studies were primarily active controlled. The control subjects received an IV vasoactive agent such as dobutamine, nitroglycerin, milrinone, or nitroprusside, at the time of study entry (in studies 704.326 and the PRECEDENT trial), or after 6 hours of placebo infusion (in study 704.325). In the VMAC trial, the first 3 hours were placebo-and-nitroglycerin-controlled. After 3 hours, placebo patients crossed over to treatment with either nitroglycerin or Natrecor®. The VMAC trial enrolled patients with dyspnea at rest. Because of the possibility that some patients would not have been able to tolerate too long a period of time without receiving a standard IV vasoactive therapy, the protocol permitted patients to receive dopamine, dobutamine, diuretics, and other oral cardiac therapies during the placebo-controlled period.

Studies 704.326 (n = 305), the PRECEDENT trial (n = 246), and the VMAC trial (n = 489) were intended to be studies that mimicked as closely as possible the conditions under which Natrecor® would be administered in actual clinical practice. Thus, unlike other studies in the program, few restrictions on patient management were imposed by the clinical study protocol. Decisions regarding the use of most concomitant medications, the need for standard-therapy dose adjustments, the duration of parenteral therapy (no upper limit in the VMAC trial, maximum duration of 7 days for Natrecor® in the PRECEDENT trial and 704.326), and the need for invasive monitoring were left to the discretion of the Investigators. Similarly, inclusion/exclusion criteria were nonrestrictive, and subjects with concomitant medical conditions common in patients with CHF, such as coronary artery disease, renal insufficiency, a history of arrhythmias (including atrial fibrillation and ventricular tachycardia), and patients

with preserved systolic function were permitted to enroll in these studies. As recommended by the Agency, patients with acute coronary syndromes were not excluded from the VMAC trial.

In summary, the development program for Natrecor[®] started with the study of relatively stable CHF patients who could tolerate a placebo infusion for a long period of time (Phase I and II). It progressed to the study of more acutely and severely ill patients who could tolerate only short placebo infusions, to the study of patients who were, in some instances, too ill to receive placebo for any period of time, and for whom Natrecor[®] needed to be co-administered with standard care IV vasoactive agents. The use of Natrecor[®] in these trials was as a first-line parenteral therapy in the management of decompensated CHF.

Extent of Exposure

In clinical practice, the duration of IV vasoactive therapy for the short-term management of CHF may range from hours to days, depending upon a patient's clinical status at presentation, underlying medical conditions, and responsiveness to therapy. Accordingly, the duration of infusion of Natrecor[®] in Phase III studies (704.325 and 704.326) and studies performed after NDA submission (the PRECEDENT [704.329] and VMAC [704.339] trials) was largely left to the clinical judgment of the Investigators. Of the 755 subjects (Table 5-1) whose mean Natrecor[®] infusion dose was within the recommended dose range from 0.01 to 0.03 µg/kg/min, the majority (n = 431 [57%]) received infusions for longer than 24 hours; 358 (47%) of these subjects received recommended doses for 24 to 72 hours, and 73 (10%) received the recommended dose for longer than 72 hours. The longest infusion was 161 days in an NYHA Class IV patient (subject 636-502 in the VMAC trial [704.339]) who responded well to long-term Natrecor[®] therapy while awaiting a cardiac transplant.

Table 5-1

**All CHF Studies
Duration of Natrecor[®] Infusion within Recommended Dose Range
(Number of Subjects Receiving Mean Infusion Dose)**

Duration of Infusion Dosing	0.01 µg/kg/min	0.015 µg/kg/min	0.02 µg/kg/min	0.025–0.03 µg/kg/min
≤ 24 hours	103	104	27	90
24–72 Hours	130	110	17	101
> 72 Hours	17	33	4	19
Total	250	247	48	210
Percentage of All CHF Natrecor [®] Subjects	27%	26%	5%	22%

Demographic Characteristics

Baseline demographic characteristics of the Natrecor® patients were similar to those of the control population in the Long Infusion studies (Table 5–2), as well as in the All CHF studies. The Long Infusion Studies population represented typical patients with acutely decompensated CHF. Natrecor® subjects were an elderly population composed of 328 (42%) patients who were at least 65 years of age and 152 (20%) patients who were at least 75 years of age. The population included a relatively high percentage of women and minorities for a heart failure clinical trial database. Approximately one third of patients were women and approximately 40% were minorities.

Table 5–2
Demographics
Long Infusion Studies

Demographics	All Control (n = 472)	All Natrecor® (n = 772)
Mean Age (yr):	61 ± 14	62 ± 13
≥ 65	199 (42%)	328 (42%)
≥ 75	87 (18%)	152 (20%)
Gender: Female	154 (33%)	228 (30%)
Race		
White	282 (60%)	454 (59%)
Black	115 (24%)	197 (26%)
Hispanic	62 (13%)	101 (13%)
Other	13 (3%)	20 (3%)

The baseline medical history of patients in the Long Infusion Studies population provides an understanding of the severity, pathophysiology, and etiology of their CHF and common comorbid conditions.

Mean ejection fraction was similar in the Natrecor® and control groups from the Long Infusion Studies and a substantial percentage of patients had severely depressed ejection fractions (< 20%). The Long Infusion Studies population also included patients with relatively preserved systolic function (ejection fraction > 40%) and CHF; therefore, the safety of Natrecor® has been assessed within this important and pathophysiologically distinct subset of CHF patients (Table 5–3). The largest Phase III studies (704.325, 704.326, 704.329, and 704.339) did not exclude patients on the basis of a baseline ejection fraction (EF); however, baseline EF was not collected in all patients in the first three studies. As requested by the Agency, patients with decompensated heart failure in the setting of an acute coronary syndrome (ACS) were not excluded from the VMAC trial. A total of 61 patients (27 Natrecor®, 34 nitroglycerin) with an ACS within 7 days before the study was enrolled.

Table 5-3

**Baseline Cardiac and Medical History
Long Infusion Studies**

	All Control (n = 472)	All Natrecor® (n = 772)
Ejection Fraction (EF)	(n = 256)	(n = 373)
Mean EF (%)	26 ± 14	25 ± 12
EF < 20%	96 (38%)	127 (34%)
EF > 40% ¹	31 (12%)	35 (9%)
NYHA Class	(n = 472)	(n = 772)
No Previous CHF History	18 (4%)	21 (3%)
I/II	32 (7%)	40 (5%)
III	249 (53%)	420 (54%)
IV	173 (37%)	291 (38%)
Primary Etiology of CHF	(n = 455)	(n = 755)
Ischemic	232 (51%)	400 (53%)
Idiopathic Dilated Cardiomyopathy	113 (25%)	170 (23%)
Hypertensive	43 (9%)	68 (9%)
Valvular or Rheumatic Heart Disease	21 (5%)	37 (5%)
All Other	46 (10%)	80 (10%)
Coronary Artery Disease	(n = 360)	(n = 561)
	233 (65%)	373 (66%)
Previous Myocardial Infarction	(n = 443)	(n = 724)
	210 (47%)	365 (50%)
Acute Coronary Syndromes within 7 Days	(n = 216)	(n = 273)
	34 (16%)	27 (10%)
Arrhythmias	(n = 443)	(n = 724)
Atrial Fib/Fib/Flutter	164 (37%)	246 (34%)
Nonsustained Ventricular Tachycardia (VT)	96 (22%)	182 (25%)
Sustained VT/V. Fibrillation	41 (9%)	87 (12%)
AICD or Pacemaker	(n = 401)	(n = 639)
	70 (17%)	114 (18%)
Medical History	(n = 443)	(n = 724)
Hypertension	293 (66%)	488 (67%)
Diabetes	209 (47%)	317 (44%)
Baseline Creatinine ≥ 2.0 mg/dL	(n = 467)	(n = 765)
	96 (21%)	147 (19%)

¹ From studies 704.325 and 704.339 only.

Throughout the Natrecor® CHF program, the NYHA classifications of patients' chronic CHF before the study-related hospitalization were collected. At the time of the study-related hospitalization, the severity of patients' specific symptoms was collected, rather than applying an NYHA classification to those symptoms. For example, in the VMAC trial (study 704.339), all patients had dyspnea at rest or NYHA Class IV symptoms at the time of entry into the study. However, chronic CHF was classified as NYHA III or IV in 205 (42%) and 204 (42%) VMAC patients, respectively. In the Long Infusion Studies, more than 90% of patients had chronic CHF before the study-related hospitalization that was classified as NYHA Class III or IV.

The Long Infusion Studies also enrolled substantial numbers of patients with the types of comorbidities that are common in patients with severe CHF, such as a history of myocardial infarction (MI), atrial and ventricular arrhythmias, diabetes mellitus, hypertension, and renal insufficiency (19% of patients had a baseline serum creatinine of at least 2.0 mg/dL). The presence of these serious comorbid conditions in the trial populations ensured that the safety of Natrecor® was rigorously tested in patients most susceptible to adverse effects of drug therapies of any kind. The severity of illness in the patient population is highlighted by the presence of sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) in 12% of patients treated with Natrecor®. Because of the growing awareness of the arrhythmogenic potential of commonly used CHF therapies, it is particularly important to evaluate the safety of any new agent for this indication in patients with pre-existing ectopy, those who would be expected to be most vulnerable to such adverse effects. The Natrecor® and Control groups were well balanced with respect to these common comorbid conditions.

Use of Concomitant Drugs During Study-Drug Infusion

As may be expected in this population of patients with severe CHF, there was a high frequency of concomitant use of orally administered cardiac medications such as diuretics, digoxin, ACE inhibitors, nitrates, and beta-blockers with Natrecor®. As such concomitant medication use is what would be in the target population for Natrecor® if Natrecor® is commercialized, the safety profile from the Long Infusion Studies, with respect to drug interactions, should predict what will be observed in the target population. If approved, it is also anticipated that commercial use of Natrecor® would include the most severely ill CHF patients, some of whom will receive multiple parenteral agents (particularly dopamine and dobutamine) with Natrecor®. Therefore, it is important that the Long Infusion Studies allowed for the concomitant use of these agents.

There is insufficient safety experience with the co-administration of Natrecor® with milrinone, nitroprusside, or IV nitroglycerin. Due to the potential of hypotension that may occur with these agents, it is anticipated that the concomitant use of Natrecor® with these agents would lead to synergistic effects on blood pressure and a substantial increase in the risk of hypotension. The concomitant administration of Natrecor® with these agents is not recommended.

In general, use of concomitant medications, by drug class, was comparable in the All Natrecor[®] and All Control patients in the Long Infusion Studies (Table 5–4). However, use of concomitant diuretics at any time during study-drug administration was lower in the All Natrecor[®] group compared to the All control group (79% vs. 85%). In the Long Infusion population, there is a suggestion that diuretics were administered less frequently with increasing doses of Natrecor[®]. The frequency of concomitant diuretic use by increasing Natrecor[®] doses was as follows: 86%, 78%, and 75% in the 0.01-, 0.015-, and 0.030- μ g/kg/min dose groups, respectively. This may be due to a dose-dependent effect of Natrecor[®] on diuresis and natriuresis or on achieving adequate preload reduction.

Table 5–4
Concomitant Medication Use during Study-Drug Infusion
Long Infusion Studies

Medication	All Control (n = 472)	All Natrecor [®] (n = 772)
Diuretics	399 (85%)	613 (79%)
Digoxin	285 (60%)	479 (62%)
ACE Inhibitors	255 (54%)	426 (55%)
Aspirin	183 (39%)	305 (40%)
Non-IV Nitrates	174 (37%)	248 (32%)
Anticoagulants*	193 (41%)	323 (42%)
Statins	99 (21%)	140 (18%)
Class III Antiarrhythmics	53 (11%)	120 (16%)
Dobutamine	101 (21%)	119 (15%)
Beta-Blockers	91 (19%)	116 (15%)
Calcium Channel Blockers	42 (9%)	86 (11%)
Hydralazine	43 (9%)	52 (7%)
Angiotensin II Receptor Antagonists	39 (8%)	47 (6%)
Other Antihypertensives	11 (2%)	34 (4%)
Dopamine	22 (5%)	32 (4%)
Other Antiarrhythmics	18 (4%)	25 (3%)
IIb/IIIa Inhibitors	9 (2%)	14 (2%)
Phosphodiesterase Inhibitor (milrinone or amrinone)	24 (5%)	3 (< 1%)
Nitroprusside	2 (< 1%)	3 (< 1%)
IV Nitroglycerin	20 (4%)	2 (< 1%)

* Heparin, warfarin, and low molecular weight heparins

In the VMAC trial, which was the most recently conducted trial and the one that enrolled the most severely ill patients, concomitant medication use overall was higher, as expected, than in previous Natrecor[®] studies (Table 5–5). Significantly more patients randomized to Natrecor[®] were unable to be weaned from dobutamine before study drug started, compared to patients randomized to nitroglycerin (18% versus 10%, respectively; $p = 0.013$ [Fisher]). A similar pattern was apparent for the use of dopamine at baseline (Natrecor[®], 7%, and nitroglycerin, 1%; $p = 0.003$ [Fisher]). Significantly more Natrecor[®] patients had a history of significant ventricular arrhythmias requiring Class III antiarrhythmic medications ($p = 0.001$ [Fisher]).

Table 5–5
Concomitant Medication Use During Study-Drug Infusion
Study 704.339
(All Treated Subjects, as Randomized)

Medication	Nitroglycerin (n = 216)	All Natrecor [®] (n = 273)
IV Medications at Baseline		
Dobutamine	21 (10%)	48 (18%)
Dopamine	3 (1%)	19 (7%)
During Study Drug		
Diuretics	204 (94%)	232 (85%)
Digoxin	129 (60%)	161 (59%)
ACE Inhibitors	128 (59%)	157 (58%)
Aspirin	100 (46%)	122 (45%)
Nitrates	78 (36%)	88 (32%)
Beta-Blockers	61 (28%)	70 (26%)
Statins	56 (26%)	73 (27%)
Dobutamine	38 (18%)	74 (27%)
Warfarin	35 (16%)	40 (15%)
Class III Antiarrhythmics	21 (10%)	57 (21%)
AII Receptor Antagonists	21 (10%)	18 (7%)
Hydralazine	20 (9%)	24 (9%)
Calcium Channel Blockers	18 (8%)	38 (14%)
Other Antiarrhythmics	9 (4%)	8 (3%)
IIb/IIIa Inhibitors	8 (4%)	6 (2%)
Dopamine ¹	7 (3%)	20 (7%)
Other Antihypertensives	4 (2%)	13 (5%)
PDE ² Inhibitors	0 (0%)	1 (< 1%)

¹PDE = Phosphodiesterase (i.e., milrinone or amrinone)

General Adverse Events in Long Infusion Studies

Examination of dose dependency of adverse events (AEs) in trials that enrolled “real-world,” acutely ill patients provides a basis for prediction of the tolerability and safety profile of Natrecor® in the intended population. A comparison of the AEs that occur during Natrecor® therapy at the recommended dose range of 0.010–0.030 µg/kg/min to the safety profile of standard-care therapies provides a benchmark for what might be expected if Natrecor® were to be commercialized. Adverse events during the first 24 hours of study-drug infusion that occurred with at least a 2% difference in frequency between the All control and All Natrecor® groups are shown in Table 5–6.

Table 5–6
Adverse Events During the First 24 Hours
Long Infusion Studies

Adverse Event*	All Control (n = 472)	Nitroglycerin 704.339 (n = 216)	All Natrecor® (n = 772)	Natrecor® (µg/kg/min)			
				Adjusted Dose 0.01 (n = 211)	Adjusted Dose 0.015 (n = 253)	Adjusted Dose 0.03 (n = 246)	
Cardiovascular							
Asymptomatic Hypotension	30 (6%)	17 (8%)	103 (13%)	17 (8%)	6 (10%)	31 (12%)	49 (20%)
Symptomatic Hypotension	18 (4%)	10 (5%)	82 (11%)	10 (5%)	2 (3%)	28 (11%)	42 (17%)
Nonsustained VT	34 (7%)	11 (5%)	42 (5%)	6 (3%)	3 (5%)	24 (9%)	9 (4%)
Bradycardia Events	2 (<1%)	1 (<1%)	24 (3%)	2 (1%)	1 (2%)	8 (3%)	13 (5%)
Body As a Whole							
Headache	67 (14%)	44 (20%)	61 (8%)	19 (9%)	2 (3%)	23 (9%)	17 (7%)
Abdominal Pain	21 (4%)	11 (5%)	18 (2%)	2 (1%)	2 (3%)	6 (2%)	8 (3%)
Catheter Pain	14 (3%)	11 (5%)	11 (1%)	3 (1%)	1 (2%)	4 (2%)	3 (1%)
Nervous							
Insomnia	16 (3%)	9 (4%)	36 (5%)	3 (1%)	3 (5%)	15 (6%)	15 (6%)
Dizziness	11 (2%)	4 (2%)	35 (5%)	7 (3%)	0 (0%)	16 (6%)	12 (5%)
Digestive							
Nausea	25 (5%)	13 (6%)	67 (9%)	7 (3%)	3 (5%)	24 (9%)	33 (13%)
Vomiting	6 (1%)	4 (2%)	20 (3%)	3 (1%)	1 (2%)	6 (2%)	10 (4%)
Musculoskeletal							
Leg Cramps	12 (3%)	3 (1%)	7 (1%)	2 (1%)	0 (0%)	4 (2%)	1 (< 1%)

*AEs with at least 2% difference in frequency between the All Control and All Natrecor® groups.

Definitions of the treatment groups in the ISS AE tables are as follows:

All Control: Includes the 472 control subjects from all five Long Infusion studies. Treatments may have included the control standard care IV vasoactive agent (such as nitroglycerin, dobutamine, milrinone, dopamine, or nitroglycerin).

Nitroglycerin 704.339: Includes the 216 subjects from the VMAC trial who were treated with nitroglycerin. Review of the nitroglycerin group allows for relative comparisons of Natrecor® and nitroglycerin as IV vasodilators. Nitroglycerin is also the agent with which the Natrecor® program has the most head-to-head comparative safety information, second to dobutamine.

All Natrecor®: Includes all 772 subjects treated with Natrecor® in the five Long Infusion Studies.

Natrecor® 0.01: Includes the 211 subjects from the VMAC trial who were treated with fixed dose of Natrecor® (a bolus of 2 µg/kg followed by an infusion of 0.01-µg/kg/min).

Natrecor® Adjusted Dose: Includes the 62 subjects from the VMAC trial who initially were treated with the 0.01-µg/kg/min dose, but were permitted to undergo dose increases up to a maximum infusion dose of 0.03 µg/kg/min.

Natrecor® 0.015: Includes the 253 subjects from four of the Long Infusion Studies who were treated with the 0.015-µg/kg/min infusion dose (with or without a preceding IV bolus).

Natrecor® 0.03: Includes the 246 subjects from four of the Long Infusion Studies who were treated with the 0.03-µg/kg/min infusion dose (with or without a preceding IV bolus).

Within the first 24 hours of therapy, the frequency of AEs in the Natrecor® 0.01-µg/kg/min and Natrecor® adjustable-dose groups was, in general, very similar to the frequency reported in the All Control group (Table 5–6). There was no AE that was reported significantly more frequently in the Natrecor® 0.01-µg/kg/min dose group or the Natrecor® adjustable-dose group when compared to the IV vasodilator nitroglycerin. In contrast, AEs that were reported in significantly more nitroglycerin subjects than in the Natrecor® 0.01-µg/kg/min subjects included headache ($p = 0.001$ [Fisher]) and abdominal pain ($p = 0.021$ [Fisher]).

Asymptomatic and symptomatic hypotension were reported by a similar percentage of subjects treated with nitroglycerin (8% and 5%, respectively) and either the Natrecor® 0.01-µg/kg/min (8% and 5%, respectively) or the Natrecor® adjustable-dose group (10% and 3%, respectively). These events were also similarly reported in the All Control group (6% and 4%, respectively). Asymptomatic and symptomatic hypotension were reported with increasing frequency with increasing Natrecor® doses, which is consistent with Natrecor®'s known dose-dependent hemodynamic effects.

Other events that were reported at a similar frequency with the 0.01- $\mu\text{g}/\text{kg}/\text{min}$ dose of Natrecor[®] and nitroglycerin, but were reported with apparent dose-dependency with increasing Natrecor[®] doses, included bradycardia, insomnia, dizziness, nausea, and vomiting. Interestingly, headache, the most common adverse event associated with nitroglycerin therapy, did not increase in frequency with higher Natrecor[®] doses. This suggests that Natrecor[®] and nitroglycerin have differing effects on different vascular beds; nitroglycerin may be a more potent vasodilator of the cerebral circulation.

The frequency of non-sustained VT, headache, abdominal pain, catheter pain, and leg cramps was higher in the All Control group than in the All Natrecor[®] group by at least 2%. The decreased frequency of non-sustained VT with Natrecor[®] therapy is well corroborated by the PRECEDENT trial (study 704.329), a randomized trial that compared the effects of Natrecor[®] (0.015 or 0.03 $\mu\text{g}/\text{kg}/\text{min}$) with dobutamine on arrhythmogenesis, as directly measured by Holter monitoring during the first 24 hours of therapy. The frequency of premature ventricular beats, repetitive beats, VT, and couplets was significantly lower in the Natrecor[®]-treated subjects compared to dobutamine subjects. In addition, the related AEs, VT and tachycardia, were reported in significantly more dobutamine subjects within the first 24 hours of therapy. Asymptomatic hypotension and symptomatic hypotension were reported in significantly more Natrecor[®] than dobutamine subjects.

Increasing the Natrecor[®] dose from the recommended standard dose (0.01 $\mu\text{g}/\text{kg}/\text{min}$ preceded by a bolus of 2 $\mu\text{g}/\text{kg}$) after allowing for adequate observation of the patient at steady state would be expected to reduce the frequency of AEs observed at higher doses from that observed if Natrecor[®] were started at higher doses. In the Natrecor[®] adjustable-dose arm ($n = 62$), the frequency of asymptomatic hypotension (10%), symptomatic hypotension (3%), and nausea (5%) was comparable to the frequency of these events in the 0.010- $\mu\text{g}/\text{kg}/\text{min}$ Natrecor[®] group. One explanation for this may be that most patients in the adjustable-dose group (56%) did not require an increase in the Natrecor[®] dose above the 0.01- $\mu\text{g}/\text{kg}/\text{min}$ dose. However, among the 27 subjects who did receive doses of Natrecor[®] above 0.01 $\mu\text{g}/\text{kg}/\text{min}$, symptomatic hypotension was reported in 1 subject during administration of the 0.015- $\mu\text{g}/\text{kg}/\text{min}$ dose, and in no subjects during administration of doses ranging from 0.02 to 0.03 $\mu\text{g}/\text{kg}/\text{min}$.

Summary of General Adverse Events

The profile of side effects that occurred in the 965 patients who received Natrecor[®] therapy in clinical trials has been well characterized. The recommended dose of Natrecor[®] is a standard dose of 0.01 $\mu\text{g}/\text{kg}/\text{min}$ (preceded by a 2- $\mu\text{g}/\text{kg}$ bolus). In those patients who have tolerated the standard dose and who might benefit from the positive dose-dependent effects of Natrecor[®] on hemodynamic variables, Natrecor[®] may be incrementally increased (every 3 hours) to a maximum dose of 0.03 $\mu\text{g}/\text{kg}/\text{min}$. Blood pressure should be closely monitored after each dose increase.

When administered as such, Natrecor[®] is a well tolerated drug and one that is associated with fewer arrhythmias, and less tachycardia, headache, abdominal pain, and leg cramps than standard care IV vasoactive therapies. Dose-dependent hypotension, much of which was asymptomatic, was the most common Natrecor[®]-associated AE, as would be expected from the pharmacodynamic effect of the drug. Both asymptomatic and symptomatic hypotension occurred with equal frequency at the recommended initial dose of Natrecor[®] and during treatment with the IV vasodilator nitroglycerin.

Six-Month Mortality from Studies 704.325, 704.326, 704.329, and 704.339

In the Natrecor[®] program, mortality through 6 months was collected retrospectively in three of the Long Infusion Studies (704.325, 704.326, and 704.329), and was collected prospectively in the VMAC trial. From an integrated analysis of four studies, there was no significant difference in 6-month mortality for the All Control and All Natrecor[®] groups (21.5% versus 21.7%, respectively) (Figure 5–1, Table 5–7). This degree of mortality within a 6-month period is indicative of a study population with advanced heart failure and many significant comorbidities.

Figure 5–1

**Kaplan-Meier Estimate of Mortality by Treatment Group
Studies 704.325, 704.326, 704.329, 704.339
(All Treated Subjects, as Treated)**

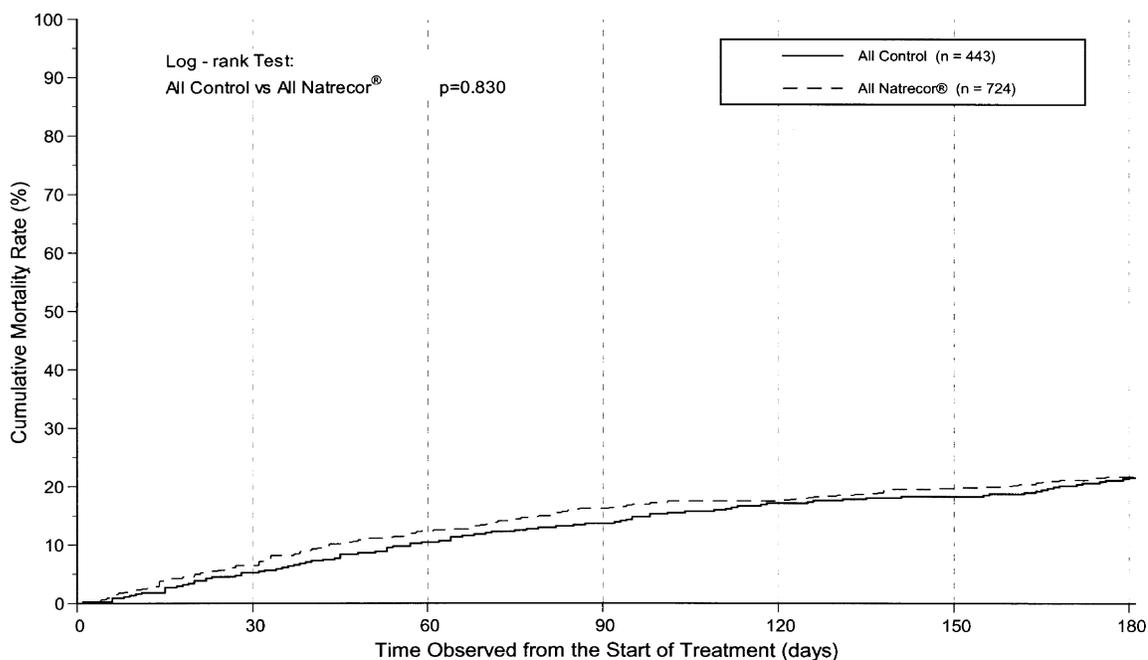


Table 5-7
Mortality through 6 Months
Studies 704.325, 704.326, 704.329, and 704.339
(All Treated Subjects, as Randomized)

	All Control (n = 443)	All Natrecor® (n = 724)
One Month		
Deaths	23	47
Mortality	5.2%	6.5%
95% C.I. (Peto's)	3.4% to 7.6%	4.8% to 8.5%
p-value ¹ (Compared to control)	—	0.347
Risk Ratio ² (Natrecor®/Control)	—	1.3
95% C.I.	—	0.8 to 2.1
Censored ³ before 1 Month	2	8
% Censored ³ before 1 Month	<1%	1%
Six Months		
Deaths	94	154
Mortality	21.5%	21.7%
95% C.I. (Peto's)	17.8% to 25.5%	18.7% to 24.8%
p-value ¹ (compared to control)	—	0.830
Risk Ratio ² (Natrecor®/Control)	—	1.0
95% C.I.	—	0.8 to 1.3
Censored ⁴ before 6 months	12	24
% Censored ⁴ before 6 months	3%	3%

Table 29B dtd 07mar2001

Mortality is based on Kaplan-Meier estimate.

¹p-value is based on log-rank test.

²Risk ratio is based on proportional hazards model.

³Subjects censored are subjects who were lost to follow-up on or before study day 30.

⁴Subjects censored are subjects who were lost to follow-up on or before study day 180.

Six-Month Mortality from The VMAC Trial (704.339)

Six-month follow-up information for 469 (96%) of the total 489 treated subjects is presented in Table 5–8 and Figure 5–2; data for 20 (4%) of the All treated subjects (8 [4%] of the nitroglycerin subjects and 12 [4%] of the All Natrecor[®] subjects) was censored before 6 months.

Table 5–8

**Mortality
VMAC Trial
(All Treated Subjects, as Randomized)**

	Nitroglycerin (n = 216)	Natrecor [®] Fixed Dose (n = 211)	All Natrecor [®] (n = 273)	Inference Method
1 Month				
Deaths	11	15	22	
Mortality	5.1%	7.1%	8.1%	
95% C.I. (Peto's)	2.7% to 8.6%	4.1% to 11.2%	5.2% to 11.8%	
p-value ¹ (compared to nitroglycerin)	—	0.387	0.230	Slogrnk
Risk Ratio ² (Natrecor [®] /nitroglycerin)		1.408	1.560	Scoxreg
95% C.I.		0.647 to 3.067	0.751 to 3.239	
Censored ³ before 1 Month	1	2	3	
% Censored ³ before 1 Month	< 1%	1%	1%	
6 Months				
Deaths	44	46	67	
Mortality	20.8%	22.3%	25.1%	
95% C.I. (Peto's)	15.5% to 26.5%	16.8% to 28.2%	20.0 to 30.5%	
p-value ¹ (compared to nitroglycerin)	—	0.616	0.319	Slogrnk
Risk Ratio ² (Natrecor [®] /nitroglycerin)		1.112	1.216	Scoxreg
95% C.I.		0.735 to 1.681	0.828 to 1.785	
Censored ⁴ before 6 months	8	10	12	
% Censored ⁴ before 6 months	4%	5%	4%	

Table 33.1

¹p-value is based on stratified log-rank test stratified on catheter use.

²Risk ratio is based on stratified proportional hazards model stratified on catheter use.

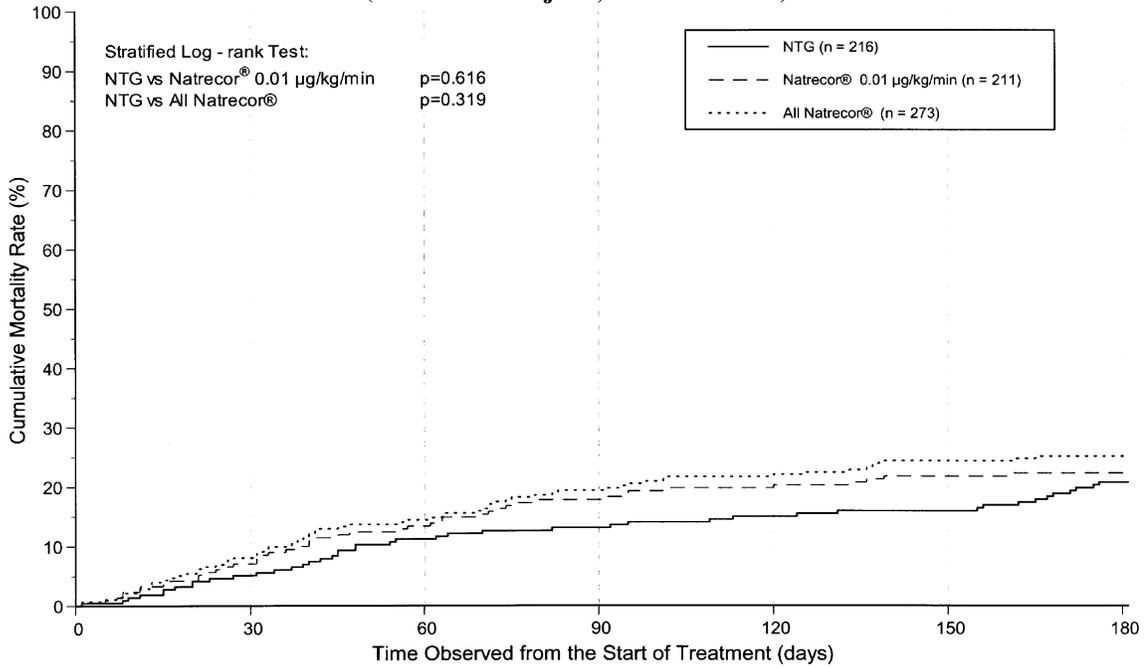
³Subjects censored are subjects who were lost to follow-up on or before study day 30.

⁴Subjects censored are subjects who were lost to follow-up on or before study day 180.

One hundred eleven (23.2%) subjects died on or before study day 180, a mortality that is consistent with a population with advanced CHF. Through 6 months, there were no significant differences in mortality between the nitroglycerin group and either the Natrecor[®] fixed-dose or the All Natrecor[®] groups.

Figure 5-2

**Kaplan-Meier Estimate of Mortality Rate by Treatment Group
The VMAC Trial (Study 704.339)
(All treated subjects, as randomized)**



NOTE: P-VALUE IS BASED ON STRATIFIED LOG-RANK TEST STRATIFIED ON CATHETER USE.

In the VMAC trial, study drug could be added to ongoing therapy with dobutamine or dopamine as long the subject still exhibited dyspnea at rest and met all other study entry criteria. These subjects were refractory to treatment with dobutamine or dopamine. Those subjects who had study drug added to ongoing therapy with dobutamine or dopamine had a worse prognosis and a higher 6-month mortality rate, regardless of treatment group.

For example, in the nitroglycerin treatment group, the 6-month mortality for subjects who were receiving ongoing therapy with dobutamine or dopamine was 32.4%, whereas the 6-month mortality for nitroglycerin subjects who *were not* receiving ongoing therapy with dobutamine or dopamine was 19.4% (Table 5–9). Similarly, the 6-month mortality for Natrecor[®] fixed-dose or All Natrecor[®] subjects who were receiving ongoing therapy with dobutamine or dopamine was 29.8% and 38.4%, respectively, whereas the 6-month mortality in the respective Natrecor[®] treatment groups for subjects who *were not* receiving ongoing therapy with dobutamine or dopamine was 20.5% and 21.5%.

Table 5–9

Mortality by Subgroup of Subjects Receiving Dobutamine or Dopamine at Start of Study Drug (All Treated Subjects, as Randomized)

Baseline Dobutamine/ Dopamine — Yes	Nitroglycerin n = 22	Natrecor[®] Fixed Dose n = 41	All Natrecor[®] n = 58
Deaths (Mortality¹)			
1 month	3 (13.6%)	5 (12.2%)	10 (17.2%)
p-value ²	—	0.863	0.672
6 months	7 (32.4%)	12 (29.8%)	22 (38.4%)
p-value ²	—	0.954	0.462
Baseline Dobutamine/ Dopamine — No	Nitroglycerin n = 194	Natrecor[®] Fixed Dose n = 170	All Natrecor[®] n = 215
Deaths (Mortality¹)			
1 month	8 (4.1%)	10 (5.9%)	12 (5.6%)
p-value ²	—	0.442	0.494
6 months	37 (19.4%)	34 (20.5%)	45 (21.5%)
p-value ²	—	0.741	0.666

Table 147.1

1. Based on Kaplan-Meier estimate.
2. Relative to nitroglycerin.

Because more subjects who were receiving ongoing therapy with dobutamine or dopamine were randomized to a Natrecor[®] treatment group, these data support the theory that subjects in the Natrecor[®] treatment groups had more advanced disease and a worse prognosis at baseline than the nitroglycerin group. Study drug was added to ongoing therapy with dobutamine or dopamine in 22 (10%) nitroglycerin subjects, 41 (19%) Natrecor[®] fixed-dose subjects, and in 58 (21%) All Natrecor[®] subjects ($p < 0.01$ Fisher’s test comparing nitroglycerin and All Natrecor[®]). It is likely that the subjects’ baseline acuity of illness and baseline prognostic factors were the main determinants of 6-month mortality in the VMAC trial, rather than the specific study drug that subjects received.

Six-Month Mortality from The PRECEDENT Trial (704.329)

In the PRECEDENT trial, a randomized comparison of Natrecor® (0.015 and 0.03 µg/kg/min) and dobutamine, 6-month mortality data were retrospectively collected. There were no significant differences in mortality between the dobutamine group and the two Natrecor® groups. The point estimates of mortality through 6 months were 22.2%, 15.9%, and 16.7% in the dobutamine group, and the 0.015- and 0.03-µg/kg/min Natrecor® dose groups, respectively (Table 5–10 and Figure 5–3).

Table 5–10

**Mortality through 6 Months
The PRECEDENT Trial (704.329)
(All Treated Subjects, as Randomized)**

	Dobutamine (n = 83)	Natrecor® 0.015 µg/kg (n = 84)	Natrecor® 0.03 µg/kg (n = 79)
One Month			
Deaths	5	3	3
Mortality	6.1%	3.6%	3.8%
95% C.I. (Peto's)	2.2% to 12.6%	1.0% to 9.3%	1.0% to 9.8%
p-value ¹ (comp to dobutamine)	—	0.472	0.524
One Month (cont'd)			
p-value (0.015 comp to 0.03)	—	—	0.941
Censored ² before one month	1	2	1
% Censored before one month	1%	2%	1%
Six Months			
Deaths	18	13	13
Mortality	22.2%	15.9%	16.7%
95% C.I. (Peto's)	13.8% to 31.8%	8.9% to 24.7%	9.4% to 25.8%
p-value ³ (comp to dobutamine)	—	0.317	0.432
p-value (0.015 comp to 0.03)	—	—	0.865
Censored ⁴ before 6 months	3	3	2
% Censored before 6 months	4%	4%	3%

Mortality is based on Kaplan-Meier estimate.

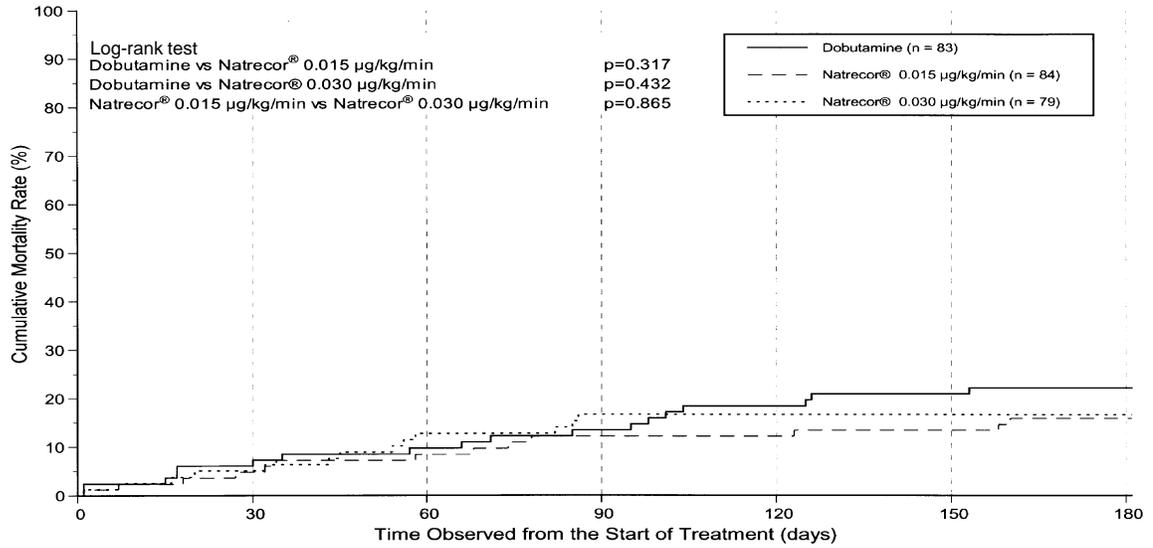
¹p-value is based on log-rank test.

²Subjects censored are subjects who were lost to follow-up on or before study day 30.

³Subjects censored are subjects who were lost to follow-up on or before study day 180.

Figure 5-3

**Kaplan-Meier Estimate of Mortality by Treatment Group
The PRECEDENT Trial (704.329)
(All Treated Subjects, as Treated)**

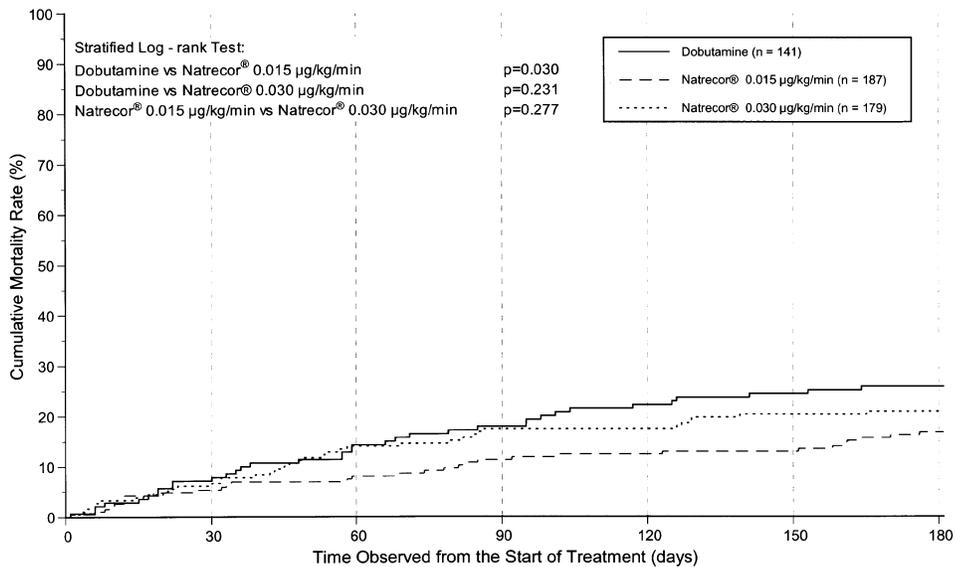


In one of the studies presented in the original NDA (study 704.326), a large percentage of the control patients were treated with dobutamine as study drug (58 [57%] of the 102 control subjects). An analysis of mortality in dobutamine-treated subjects (n = 141) from studies 704.326 and 704.329, compared to Natrecor® subjects (0.015 [n = 187] and 0.03 [n = 179] µg/kg/min) is presented in Figure 5–4. Compared to 0.015-µg/kg/min dose of Natrecor®, dobutamine therapy was associated with a significant increase in mortality. The point estimates for 6-month mortality were 25.8%, 16.8%, and 20.9% in the dobutamine, and the 0.015- and 0.03-µg/kg/min dose groups (p = 0.030, dobutamine compared to the 0.015-µg/kg/min dose group [stratified log-rank test]; p = 0.231, dobutamine compared to the 0.03-µg/kg/min dose group [stratified log-rank test]).

In all of these studies, none of the deaths was attributed to the use of Natrecor®. The most commonly cited cause of death was worsening or end-stage cardiomyopathy.

Figure 5–4

**Kaplan-Meier Estimate of Mortality by Treatment Group
Natrecor® vs. Dobutamine Studies 704.326 and 704.329
(All Treated Subjects, as Treated)**



NOTE: P-VALUE IS BASED ON STRATIFIED LOG-RANK TEST STRATIFIED ON STUDY PROTOCOLS.

Other Serious Adverse Events

There was no significant difference in the frequency of serious adverse events (SAEs) within 14 days between the All Control group and the All Natrecor[®] group (Table 5–11). Also, there was also no clear trend of dose dependency in the frequency of SAEs within 14 days with Natrecor[®] therapy. Cardiovascular was the most common body system in which an SAE occurred, and CHF was the most common event, occurring in 3%–6% of patients in each treatment group. As chronic advanced CHF is a disease characterized by frequent exacerbations leading to hospital readmission, the latter finding is wholly expected.

Table 5–11

**Serious Adverse Events through Study Day 14
Long Infusion Studies**

Adverse Event	All Control (n = 472)	Nitroglycerin 704.339 (n = 216)	All Natrecor [®] (n = 772)	Natrecor [®] (µg/kg/min)			
				Adjusted Dose 0.01 (n = 211)	Adjusted Dose 0.015 (n = 253)	Adjusted Dose 0.03 (n = 246)	
Subjects with any SAE	62 (13%)	34 (16%)	112 (15%)	40 (19%)	10 (16%)	25 (10%)	37 (15%)
Cardiovascular	42 (9%)	22 (10%)	71 (9%)	21 (10%)	3 (5%)	19 (8%)	28 (11%)
CHF	20 (4%)	13 (6%)	38 (5%)	12 (6%)	2 (3%)	10 (4%)	14 (6%)
Urogenital	9 (2%)	6 (3%)	21 (3%)	10 (5%)	6 (10%)	2 (1%)	3 (1%)
Kidney Function Abnormal	4 (1%)	4 (2%)	12 (2%)	6 (3%)	5 (8%)	0 (0%)	1 (<1%)
Respiratory	13 (3%)	7 (3%)	17 (2%)	7 (3%)	4 (6%)	3 (1%)	3 (1%)
Dyspnea	6 (1%)	3 (1%)	7 (1%)	3 (1%)	1 (2%)	1 (<1%)	2 (1%)
Digestive	3 (1%)	2 (1%)	5 (1%)	5 (2%)	0 (0%)	0 (0%)	0 (0%)
Hepatic Failure	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Metabolic/Nutritional	5 (1%)	3 (1%)	7 (1%)	4 (2%)	0 (0%)	3 (1%)	0 (0%)
Dehydration	1 (<1%)	1 (<1%)	4 (1%)	4 (2%)	0 (0%)	0 (0%)	0 (0%)
Body as a Whole	4 (1%)	3 (1%)	10 (1%)	4 (2%)	0 (0%)	3 (1%)	3 (1%)
Sepsis	0 (0%)	0 (0%)	7 (1%)	3 (1%)	0 (0%)	2 (1%)	2 (1%)

In All CHF Studies, the pattern of SAEs reported within 14 days was similar to that reported in the Long Infusion Studies population. There was no difference in the overall frequency of SAEs in the All Control and All Natrecor[®] groups. The cardiovascular body system, and more specifically, CHF, was the most commonly reported SAE in both groups.

Effect on Arrhythmias

The natriuretic peptides are believed to have some effects on autonomic tone, including both decreased sympathetic and increased parasympathetic tone. This may explain why Natrecor® infusion is not accompanied by reflex tachycardia, an undesirable feature that may occur in the setting of potent vasodilation. Natrecor® has been associated with a dose-dependent increase in bradycardia that was self limited, either spontaneously or following Natrecor® discontinuation. However, at the 0.01- $\mu\text{g}/\text{kg}/\text{min}$ Natrecor® dose, bradycardia was not reported more commonly than the All Control or nitroglycerin groups.

The exact mechanism for the bradycardia that occurred with higher doses of Natrecor® is not known. Occasionally, the bradycardia was accompanied by Natrecor®-induced hypotension. The bradycardia that occurs with potent vasodilation due to Natrecor® may be due to the known phenomenon by which vasodilators can lead to bradycardia, the Bezold-Jarisch reflex. Although the precise mechanism of the 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.

Effects on autonomic tone and the lack of a direct inotropic effect may contribute to the fact that Natrecor® administration has not been associated with an increase in atrial or ventricular tachy-arrhythmias. This appears to be the case in spite of the fact that in the four largest studies (704.325, 704.326, 704.329, and 704.339), subjects with a history of ventricular tachycardia or those treated with antiarrhythmic medications, pacemaker, or AICD were not excluded from entry into the study.

The placebo-controlled analysis population (from the ISS in the original NDA) represents the true potential association of Natrecor® with ventricular arrhythmias. Through the first 24 hours of study-drug administration in this analysis population, the frequency of VT 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. Also in these earlier dose-ranging studies (whether bolus or infusion studies), there has been no evidence of a dose-related effect of Natrecor® on ventricular arrhythmias.

In the Long Infusion Studies population, through the first 24 hours of study-drug administration, VT was reported in 7% and 5% of the All Control and all Natrecor® group, respectively. In the All CHF Studies population, the frequency of VT within 24 hours was 8% and 6% of the All Control and all Natrecor® group, respectively.

In the PRECEDENT trial (study 704.329), the effects of Natrecor® and dobutamine on the provocation or aggravation of existing ventricular arrhythmias were compared using Holter monitoring. Patients who were hospitalized for acutely decompensated CHF who could undergo the first 24 hours of treatment with IV diuretics and chronic cardiac therapies, but not an IV vasoactive agent, were enrolled (n = 246). A 24-hour baseline Holter tape was obtained, followed by a second 24-hour Holter tape during the first 24 hours of treatment with dobutamine or Natrecor® (0.015 or 0.03 µg/kg/min).

Table 5–12 shows that subjects in the study had a significant prevalence of PVBs and VT during the baseline Holter tape. During the 24-hour Treatment Holter Tape, dobutamine was associated with a significant mean increase in PVBs and VT overall, as well as by pair-wise comparison to either dose of Natrecor®. Dobutamine subjects experienced a mean increase of 69 PVBs per hour during the 24-hour treatment period, whereas Natrecor® subjects experienced a mean decrease in PVBs on average. More importantly, dobutamine subjects also experienced a significant mean increase of 48 episodes of VT during the 24-hour treatment period. Twenty-five percent of dobutamine subjects experienced an increase of at least 3 episodes of VT during the treatment period. In contrast, both doses of Natrecor® appeared to have had a neutral effect on the aggravation of pre-existing VT.

Table 5–12
PVBs and Ventricular Tachycardia
Changes Observed between 24-Hour Baseline and Treatment Holter Tapes
The PRECEDENT Trial (704.329)

Endpoint	Dobutamine (n = 83)	Natrecor® (µg/kg/min)		p-value
	0.015 (n = 84)	0.03 (n = 79)		
Baseline Holter Tape				
Average hourly PVBs				
Mean ± SD	192 ± 338	110 ± 170	165 ± 265	0.330
Median (25 th , 75 th ile)	39 (13, 218)	35 (5, 145)	50 (8, 200)	
VT (events per 24 hours)				
Mean ± SD	30 ± 144	13 ± 39	27 ± 89	0.224
Median (25 th , 75 th ile)	0 (0, 5)	1 (0, 3)	1 (0, 8)	
Treatment Holter Tape				
Change from Baseline to Treatment Tapes				
Mean ± SD	+69 ± 214	-13 ± 83	-5 ± 96	0.001
Median (25 th , 75 th ile)	4 (-7, +107)	-1 (-24, +3)	-1 (-29, +5)	
p-values, vs. dobutamine	—	0.001	0.002	
VT (events per 24 hours)				
Mean ± SD	+48 ± 205	-6 ± 17	+2 ± 60	< 0.001
Median (25 th , 75 th ile)	+0 (+0, +3)	+0 (-2, +0)	+0 (-1, +0)	
p-values, vs. dobutamine	—	< 0.001	< 0.000	

¹p-values are based on stratified Wilcoxon procedure (Van Elteren Test) controlled for the history of VT strata.

Thus there does not appear to be an increased frequency of ventricular ectopy or ventricular tachycardia with Natrecor[®] therapy in a population of subjects who exhibited a high frequency of these arrhythmias at baseline or were known to have the substrate for these arrhythmias. This may be explained by the following: (1) Natrecor[®] is not an inotrope and its activity does not depend on the generation of cyclic AMP or on stimulation of β -adrenergic receptors; (2) Natrecor[®] may affect autonomic tone (i.e., decrease sympathetic and increase parasympathetic tone), as is supported by the lack of a reflex tachycardia or a reflex increase in norepinephrine during Natrecor[®] administration; (3) Natrecor[®] appears to improve cardiac hemodynamics without increasing estimated myocardial oxygen consumption (as supported by the decrease in the pressure-rate index). The effect on ventricular arrhythmias is an important aspect of the safety profile for a new drug for this indication and represents a distinct safety benefit over other commonly used agents for this indication, such as dobutamine or milrinone.

Effect on Serum Creatinine

In the Long Infusion studies from the original NDA, serum creatinine was not prospectively collected in all subjects for longer than the short-term treatment period for each study. Available follow-up serum creatinine data were collected retrospectively in Natrecor[®] subjects, but not in control subjects, who exhibited an increase in serum creatinine during the original treatment periods. In the VMAC and PRECEDENT trials, serum creatinine was prospectively collected in all subjects through 30 days and 14 days, respectively. Therefore, these trials provide a prospective comparison of the effects of various doses of Natrecor[®] to those observed with nitroglycerin and dobutamine in patients with acute decompensated CHF.

In both the VMAC or PRECEDENT trials, subjects with any degree of renal insufficiency or those receiving chronic dialysis were not excluded from participating. Similarly, there was no baseline serum creatinine value that excluded patients from the studies. As a result, the serum creatinine data observed in these two studies should be representative of the effects on serum creatinine that would be observed in actual practice.

In the VMAC trial, there was no significant difference in mean baseline serum creatinine values between nitroglycerin and Natrecor[®] subjects (Table 5–13). The range of baseline serum creatinine values in All Natrecor[®] subjects was 0.4 to 11.1 mg/dL. Forty four (20%) nitroglycerin subjects and 60 (22%) Natrecor[®] subjects had a baseline serum creatinine greater than or equal to 2.0 mg/dL.

Table 5–13

**Serum Creatinine
The VMAC Trial
(All Treated Subjects, as Randomized)**

	Nitroglycerin 704.339 (n = 216)	Natrecor® Fixed Dose (n = 211)	All Natrecor® n = 273
Baseline Creatinine			
Mean ± SD	1.6 ± 0.99	1.6 ± 1.12	1.6 ± 1.06
Range	0.5 – 9.5	0.4 – 11.1	0.4 – 11.1
Change from Baseline			
Day 2	–0.0 ± 0.31	+0.0 ± 0.43	+0.0 ± 0.41
Day 5	+0.0 ± 0.42	+0.1 ± 0.53	+0.1 ± 0.59
Day 14	+0.2 ± 0.60	+0.2 ± 0.89	+0.2 ± 0.85
Day 30	+0.1 ± 0.73	+0.1 ± 0.70	+0.1 ± 0.75
Increased Creatinine Criteria¹			
Day 2	3 (1%)	5 (2%)	7(3%)
Day 5	3 (2%)	9 (5%)	11(5%)
Day 14	14 (9%)	18 (11%)	22 (11%)
Day 30	6 (4%)	10 (6%)	12 (6%)

Tables 121.1 and 122.1

¹Increased to ≥ 2.0 mg/dL and increased by at least 50% from baseline.

Note: No statistically significant differences compared to nitroglycerin were noted at $\alpha = 0.05$ level.

Through study day 30, there were no significant differences between the nitroglycerin and Natrecor® groups in the changes in serum creatinine from baseline values (Table 5–13). Similarly, there were no significant differences in the percentage of subjects whose follow-up creatinine was at least 50% increased from baseline to a value that was at least 2.0 mg/dL (hereafter referred to as the increased creatinine criteria). It is clear from the review of the changes in creatinine that both nitroglycerin and Natrecor® were associated with gradual and mild mean increases in serum creatinine over 14 days, at which time the greatest percentage of subjects who met the increased creatinine criteria was observed. These effects appeared to be transient, as evidenced by the fact that fewer patients met the increased creatinine criteria by study day 30.

Based on these data, it is unclear whether these mild and transient increases in creatinine are due to the natural history of renal dysfunction for patients with decompensated CHF, or whether these effects are specific to IV vasodilators. Clearly, there are no significant differences between nitroglycerin and Natrecor® when serum creatinine were prospectively followed.

The PRECEDENT trial allowed for a prospective head-to-head comparison of the effects of higher doses of Natrecor® (0.015 and 0.03 µg/kg/min) to the inotrope dobutamine on serum creatinine through day 14 (Table 5–14). There were no significant differences between treatment groups in baseline serum creatinine values or in the changes from baseline in serum creatinine through day 14. Although the numbers of subjects who met the increased creatinine criteria at any time were few in any treatment group, Natrecor® may have been associated with more subjects meeting the increased creatinine criteria as of day 2, whereas dobutamine may have been associated with more subjects meeting the criteria through days 5 and 14. None of these differences was statistically significant.

Table 5–14
Serum Creatinine
The PRECEDENT Trial (704.329)
(All Treated Subjects, as Randomized)

	Dobutamine = 83	Natrecor®		p-value
		0.015 (n = 84)	0.03 (n = 79)	
Baseline Creatinine				
Mean ± SD	1.5 ± 0.66	1.6 ± 0.84	1.5 ± 0.91	0.923 ¹
Range	0.6–4.1	0.6–5.4	0.7–6.9	
Change from Baseline				
Day 2	+0.0 ± 0.26	+0.1 ± 0.36	+0.1 ± 0.30	0.067 ¹
Day 5	+0.1 ± 0.48	–0.0 ± 0.46	+0.0 ± 0.36	0.713 ¹
Day 14	+0.1 ± 0.44	+0.1 ± 0.40	+0.1 ± 0.60	0.821 ¹
Creatinine Increased Criteria*				
Day 2	0 (0%)	4 (5%)	3 (4%)	0.142 ²
Day 5	3 (9%)	1 (4%)	0 (0%)	0.460 ²
Day 14	5 (7%)	3 (4%)	3 (5%)	0.739 ²

*Increased to ≥ 2.0 mg/dL and increased by at least 50% from baseline.

¹Omnibus test

²Fisher's exact test

It remains unclear whether any mild and transient increases in creatinine that occurred in these populations were due to the natural history of renal dysfunction within the month following hospitalization for decompensated CHF patients, or whether these effects were directly related to the agents in question. When creatinine was prospectively followed through 14 and 30 days, there were no significant differences between various doses of Natrecor® and either dobutamine or nitroglycerin.

Conclusions about the Interactions of Concomitant Medications

In order to determine whether the frequency of adverse events that occur with nitroglycerin or Natrecor® is affected by the concomitant administration of common cardiac medications, an analysis of the frequency of hypotension, symptomatic hypotension, nausea, and headache was done based on whether or not subjects were taking ACE inhibitors, digoxin, beta-blockers, or non-IV nitrates.

ACE inhibitors appeared to be associated with a higher incidence of symptomatic hypotension and hypotension in both nitroglycerin and Natrecor® subjects than in subjects who were not taking ACE inhibitors (Table 5–15). There did not appear to be a difference in the increased risk of hypotension or symptomatic hypotension with ACE inhibitors between the nitroglycerin and Natrecor® groups. Therefore, the increased incidence of these events in subjects who were taking ACE inhibitors was either directly due to the ACE inhibitors themselves, due to the combination of an IV vasodilator and an ACE inhibitor, or was a marker for those subjects who would be more likely to develop hypotension and symptomatic hypotension.

Table 5–15

**Effect of ACE Inhibitors on Selected Adverse Events through 24 Hours
The VMAC Trial (704.339)
(All Treated Subjects as Randomized)**

		Natrecor®			
		Nitroglycerin (n = 216)	Fixed Dose (n = 211)	Adjustable Dose (n = 62)	All Natrecor® (n = 273)
Symptomatic Hypotension¹		n = 10	n = 10	n = 2	n = 12
ACE Inhibitors:	Yes	8 (80%)	9 (90%)	2 (100%)	11 (92%)
	No	2 (20%)	1 (10%)	0 (0%)	1 (8%)
No Symptomatic Hypotension²		n = 206	n = 201	n = 60	n = 261
ACE Inhibitors:	Yes	125 (61%)	132 (66%)	36 (60%)	168 (64%)
	No	81 (39%)	69 (34%)	24 (40%)	93 (36%)
Hypotension¹		n = 25	n = 24	n = 7	n = 31
ACE Inhibitors:	Yes	20 (80%)	20 (83%)	4 (57%)	24 (77%)
	No	5 (20%)	4 (17%)	3 (43%)	7 (23%)
No Hypotension²		n = 191	n = 187	n = 55	n = 242
ACE Inhibitors:	Yes	113 (59%)	121 (65%)	34 (62%)	155 (64%)
	No	78 (41%)	66 (35%)	21 (38%)	87 (36%)
Nausea^{1,3}		n = 13	n = 8	n = 3	n = 11
ACE Inhibitors:	Yes	4 (31%)	7 (88%)	1 (33%)	8 (73%)
	No	9 (69%)	1 (13%)	2 (67%)	3 (27%)
No Nausea²		n = 203	n = 203	n = 59	n = 262
ACE Inhibitors:	Yes	129 (64%)	134 (66%)	37 (63%)	171 (65%)
	No	74 (36%)	69 (34%)	22 (37%)	91 (35%)
Headache¹		n = 44	n = 19	n = 2	n = 21
ACE Inhibitors:	Yes	23 (52%)	12 (63%)	1 (50%)	13 (62%)
	No	21 (48%)	7 (37%)	1 (50%)	8 (38%)
No Headache²		n = 172	n = 192	n = 60	n = 252
ACE Inhibitors:	Yes	106 (62%)	128 (67%)	37 (62%)	165 (65%)
	No	66 (38%)	64 (33%)	23 (38%)	87 (35%)

Tables 116.1, 116.2, 117.1, 117.2, 118.1, 118.2, 119.1, and 119.2

¹ACE inhibitors used prior to the event

²ACE inhibitors used within 24 hours before or after the start of study drug

³Nausea includes preferred terms “nausea” and “nausea and vomiting”

There does not appear to be any relationship between the concomitant administration of digoxin, beta-blockers, or non-IV nitrates and the incidence of hypotension, symptomatic hypotension, nausea, or headache in either nitroglycerin or Natrecor® subjects.

Safety Conclusions

The tolerability and overall safety of Natrecor® has been well characterized from a safety database that is representative of typical patients with acutely decompensated CHF. The database includes 965 subjects, of whom 941 were enrolled in the Natrecor® CHF development program. The Natrecor® database is composed of elderly patients (42% and 19% were at least 65 or 75 years of age, respectively). Approximately one-third were women and approximately 40% were minorities. More than 90% had chronic CHF (before the study hospitalization) that was classified as NYHA Class III or IV. Most subjects had systolic dysfunction, due to ischemic cardiomyopathy or idiopathic dilated cardiomyopathy, but patients with preserved systolic function were not excluded from any of the Phase III trials. The Natrecor® database also includes patients with typical comorbidities that are common to patients with severe CHF such as atrial and ventricular arrhythmias, diabetes, hypertension, significant renal insufficiency, and acute coronary syndromes. The presence of these serious comorbid conditions in the trial populations ensures that the safety of Natrecor® has been rigorously tested in patients most susceptible to adverse effects of drug therapies of any kind. Because of the nonrestrictive nature of the Natrecor® Phase III study designs, the use of concomitant cardiac medications (such as diuretics, digoxin, ACE inhibitors, nitrates, beta-blockers, hydralazine, dobutamine, and dopamine) during the studies was also representative of medications that would be used in the target population for Natrecor®, if approved. Thus, the safety profile from the Natrecor® database should be predictive of what would be observed in a larger target population.

The profile of side effects that occurred with Natrecor® therapy has been well characterized. When administered within the recommended dose range (initial dose of 0.01 µg/kg/min; maximum dose 0.03 µg/kg/min), Natrecor® is a well tolerated agent and one that is associated with less ventricular tachycardia, general tachycardia, headache, abdominal pain, and leg cramps than the IV vasodilator nitroglycerin. Within 24 hours, compared to IV nitroglycerin, there was no AE that was reported significantly more frequently in the Natrecor® 0.01-µg/kg/min dose group or the Natrecor® adjustable-dose group. In contrast, AEs that were reported in significantly more nitroglycerin than Natrecor® subjects included headache and abdominal pain. Headache did not increase in frequency with higher Natrecor® doses. This suggests that Natrecor® and nitroglycerin have differing effects on different vascular beds; nitroglycerin may be a more potent vasodilator of the cerebral circulation.

In the entire Natrecor® database, dose-dependent hypotension, much of which was asymptomatic, was the most common Natrecor®-associated AE, as would be expected due to the pharmacodynamic effects of the drug. However, both asymptomatic and symptomatic hypotension were reported with equal frequency during a fixed-dose infusion of Natrecor® as to what was reported during a titratable dosing regimen of nitroglycerin. Other events that were reported at a similar frequency in the 0.01-µg/kg/min Natrecor® dose group and nitroglycerin group, but that were reported with apparent dose dependency with increasing

Natreacor[®] doses, included bradycardia, insomnia, dizziness, nausea, vomiting, and increased creatinine.

In the VMAC trial, in which Natreacor[®] was administered either as a fixed-dose infusion of 0.01 µg/kg/min preceded by a bolus, or as an adjustable-dose regimen, asymptomatic and symptomatic hypotension were reported at a lower frequency than previously reported with higher doses of Natreacor[®]. Symptomatic hypotension events generally were mild or moderate in severity, and no event led to significant sequelae. Although Natreacor[®] has a longer half-life than nitroglycerin, there was no significant difference between the two drugs in the time to onset of hypotension, severity of hypotension events, the maximum effects on SBP, or the need for interventions in response to the hypotension events.

The adjustable-dose regimen of Natreacor[®] used in the VMAC trial (n = 62) was well tolerated. In particular, hypotension (asymptomatic or symptomatic) and other events were reported in a similar number of adjustable-dose subjects as was reported with nitroglycerin or the standard Natreacor[®] dose (0.01 µg/kg/min, preceded by a 2 µg/kg bolus). The adjustable-dose regimen of Natreacor[®] helps to ensure that higher doses of Natreacor[®] are used only when needed to achieve a maximal hemodynamic response in patients who have tolerated the initial 0.01 µg/kg/min dose. This regimen also provides cardiologists with a better tolerated regimen to optimize Natreacor[®] dosing in some patients, as opposed to starting Natreacor[®] at higher doses unnecessarily.

Effects on autonomic tone, and the fact that Natreacor[®] has no direct effects on contractility, may contribute to the lack of association between Natreacor[®] administration and an increase in other arrhythmias such as supraventricular or ventricular tachycardia or a reflex tachycardia. This appears to be the case, in spite of the fact that in the four largest studies (studies 704.325, 704.326, 704.329, and 704.339), subjects with ventricular tachycardia or those treated with antiarrhythmic medications were not excluded from entry. Compared to dobutamine specifically, Natreacor[®] was not associated with the significant increases in heart rate, ventricular ectopy, and the more clinically important ventricular tachycardia that occurred with dobutamine therapy. Doses of Natreacor[®] higher than the 0.01-µg/kg/min dose may be associated with dose-dependent bradycardia that is generally mild and self limited.

In most of the Natreacor[®] database, patients with any degree of renal insufficiency or patients who were receiving long-term dialysis were not excluded. In addition, medications that are known to acutely affect renal function, such as diuretics, were not restricted. When creatinine was prospectively followed through 14 and 30 days, there were no significant differences between Natreacor[®] and either dobutamine or nitroglycerin in the changes from baseline in creatinine or in the frequency of subjects who developed clinically significant increases in creatinine. Natreacor[®] and both control agents were associated with gradual and mild mean increases in serum creatinine over 14 days.

At the 30-day follow-up (in the VMAC trial only), these increases were transient with both Natrecor[®] and nitroglycerin therapy in most patients. The data do not resolve whether these mild and transient increases in creatinine were due to the natural history of renal dysfunction in patients with decompensated CHF, or whether these effects were directly related to the agents in question. When data from the entire database were considered, Natrecor[®] was associated with a dose-dependent increase in the frequency of increased creatinine reported as an AE. More serious renal events such as acute renal failure did not occur significantly more frequently with Natrecor[®] therapy than with any control agent. Because most patients with decompensated CHF have some degree of renal insufficiency, creatinine should be monitored during Natrecor[®] therapy, as it would be routinely monitored with any IV vasoactive agent.

Longer term outcomes, other than general tolerability, that were assessed included serious adverse events (usually resulting in hospital readmission) through 14 days and mortality through 6 months. There were no significant differences in the incidence of serious AEs through 14 days between the All Control, nitroglycerin, and the All Natrecor[®] groups. Similarly, there was no significant difference in 6-month mortality between Natrecor[®] and the All Control group in the entire database, or between Natrecor[®] and nitroglycerin in the VMAC trial. None of the deaths were attributed to therapy with Natrecor[®].

In summary, the standard dose of Natrecor[®] (2- μ g/kg bolus followed by a 0.01- μ g/kg/min infusion) generally was well tolerated, even in severely ill patients with multiple comorbidities, and in those taking multiple concomitant cardiac medications. Natrecor[®] was better tolerated than nitroglycerin, as evidenced by the significantly greater percentage of nitroglycerin subjects who experienced headache and abdominal pain. There was no adverse event clearly associated with Natrecor[®] that occurred significantly more frequently than in nitroglycerin subjects. Increasing doses of Natrecor[®] in those subjects who tolerated the standard dose, and had a systolic BP \geq 100 mm Hg before the dose increases, were also well tolerated. Because Natrecor[®] should be administered as a bolus followed by a fixed-dose infusion in most patients, consistent effects may be anticipated regardless of whether or not patients are being invasively monitored. Blood pressure should be monitored periodically during Natrecor[®] therapy.

Item 6**Benefit/Risk Profile for Natrecor®**

Introduction

Natrecor® has been developed as an IV agent for the short-term treatment of CHF. Representing a new drug class, Natrecor® exhibits a unique combination of beneficial clinical and hemodynamic effects. Natrecor® is identical to the endogenous human B-type natriuretic peptide (hBNP) molecule, a naturally occurring compound that is elevated in the plasma of patients with CHF.

Benefits

Natrecor® is a balanced vasodilator, dilating both veins and arteries, including coronary arteries. It has no direct inotropic activity and is not dependent on beta-adrenergic receptors or the production of cyclic AMP for its activity. The Natrecor® clinical development program in acute CHF supports the following:

- Benefits described in the original NDA have been confirmed by the VMAC (704.339) and the PRECEDENT (704.329) studies.
 - Natrecor® significantly improves hemodynamics by reducing pulmonary capillary wedge pressure (PCWP, a measure of preload) and systemic vascular resistance (SVR, a measure of afterload), thereby increasing cardiac index (CI).
 - Natrecor® produces significant symptom improvement consistent and concurrent with hemodynamic improvement: The symptom improvement is both global (as assessed by patient and physician independently) and particular with regard to prespecified symptoms of CHF, such as dyspnea.
 - Natrecor® is not associated with an increase in tachyarrhythmias.
- Benefits demonstrated by the standard Natrecor® dosing regimen (2-µg/kg bolus, followed by a 0.01-µg/kg/min infusion) plus standard care, were shown in the VMAC study.
 - Produces more rapid hemodynamic improvements, measurable as soon as 15 minutes after the start of therapy, compared to nitroglycerin or placebo.
 - Produces reductions in PCWP that are sustained through at least 48 hours of therapy.
 - Significantly improves dyspnea compared to placebo plus standard therapy at 3 hours.
 - At 24 hours, Natrecor® plus standard therapy significantly improves global clinical status compared to nitroglycerin plus standard therapy.

- In non-catheterized patients, at 24 hours, Natrecor[®] plus standard care significantly improved both dyspnea and the global assessment compared to nitroglycerin.
- While not routinely necessary, doses of Natrecor[®] may be safely increased for greater hemodynamic efficacy in certain patients, under the guidelines provided.
- Natrecor[®] decreases the rate pressure product (HR multiplied by SBP), suggesting that Natrecor[®] does not increase cardiac work or estimated myocardial oxygen consumption.
- Natrecor[®] is associated with a reduced need for diuretic therapy.
- Natrecor[®] produces a reduction in levels of plasma aldosterone.

Thus, clinical trials have shown that Natrecor[®] possesses the desirable effects of a first line 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[®] is not associated with an increase in mortality or increased risk of ventricular arrhythmias. The physiology of Natrecor[®] is not dependent on beta-adrenergic receptors (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 periodically during use.

Natrecor[®] is effective when administered as a fixed-dose infusion, reducing the need for the dose titration that is characteristic of many of the other available agents for this indication. When administered at the standard dose, a 2- $\mu\text{g}/\text{kg}$ bolus followed by a 0.01- $\mu\text{g}/\text{kg}/\text{min}$ fixed-dose infusion, Natrecor[®] is effective, as evidenced by rapid hemodynamic and symptom improvement, and progressive hemodynamic and symptom improvement through at least 24 hours of therapy. There is no evidence for an attenuation of Natrecor[®]'s effect on PCWP through at least 48 hours. The VMAC trial also provided experience with a regimen for a dose increase, should the physician feel that greater clinical effect is desired.

Risks

In the VMAC study, in which Natrecor[®] was administered either as a fixed-dose infusion of 0.01 $\mu\text{g}/\text{kg}/\text{min}$ or as an adjustable-dose regimen, asymptomatic and symptomatic hypotension were reported at a lower frequency than previously reported with higher doses of Natrecor[®]. Symptomatic hypotension events generally were mild or moderate in severity, and no event led to significant sequelae. Although Natrecor[®] has a longer half-life than nitroglycerin, there was no significant difference in the time to onset of hypotension between the two drugs. There were also no significant differences in severity of hypotension events, the maximum effects on SBP, or the need for interventions in response to the hypotension events in the 0.01- $\mu\text{g}/\text{kg}/\text{min}$ Natrecor[®] and nitroglycerin groups.

The duration of symptomatic hypotension events was longer in Natrecor® than in nitroglycerin subjects. However, for both agents blood pressure increased significantly within 15 minutes after dose reduction or discontinuation in response to the onset of the event. When Natrecor® was initiated at higher doses (0.015 or 0.03 µg/kg/min) from the start of infusion (in previous trials), dose-dependent effects on blood pressure and severity of hypotension were observed. If symptomatic hypotension should occur or if systolic BP decreases to less than 90 mm Hg during Natrecor® therapy, the infusion dose should be reduced by 30% or discontinued until the symptoms resolve and blood pressure stabilizes. After resolution of symptomatic hypotension, Natrecor® infusion may be restarted (without a bolus) at a previously tolerated dose or at a dose that is one-third less than the previously administered dose.

The natriuretic peptides are believed to have some effects on autonomic tone, including both decreased sympathetic and increased parasympathetic tone. This may explain why Natrecor® infusion is not accompanied by reflex tachycardia and why it may contribute to an increased incidence of dose-dependent bradycardia reported during Natrecor® infusion. Bradycardia was not reported more commonly with the 0.01-µg/kg/min dose of Natrecor® than with nitroglycerin in the first 24 hours of therapy. At doses of 0.015 and 0.03 µg/kg/min, bradycardia events were reported within 24 hours in 3% and 5% of Natrecor® subjects, respectively. These events generally have been self limited, either spontaneously or following Natrecor® discontinuation. Bradycardia accompanying Natrecor®-induced hypotension may be explained by the Bezold-Jarisch reflex, which has also been implicated in a similar effect that can occur with nitroglycerin, rapid hemorrhage, or during tilt-table testing.

When prospectively measured through 14 days (compared to dobutamine) or through 30 days (compared to nitroglycerin), creatinine was not significantly affected by various doses of Natrecor®. Both Natrecor® and nitroglycerin were associated with a mild increase in creatinine that was transient in most patients. When Natrecor® infusion was started at higher doses (as in previous trials), there was a dose-related increase in increased creatinine reported as an adverse advent. Because most patients with decompensated CHF have some degree of renal insufficiency, creatinine should be monitored during Natrecor® therapy, as it would be routinely monitored with any IV vasoactive agent.

Natrecor® as a Natural Product

It is generally accepted that rare and unusual adverse reactions may not be detected during 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 B-type natriuretic peptide is a natural product that circulates in fairly high concentration in patients with congestive heart failure. Patients with advanced CHF of the severity likely to be subject to treatment with intravenous Natrecor® have endogenous BNP levels in the range of several hundred pg/mL up to 1,000 pg/mL. Thus, these patients are continually exposed to BNP, and idiosyncratic adverse reactions are far less likely than might be the case with a new chemical entity.

Agents Currently Available for the Short-Term Treatment of CHF

When IV therapy is indicated for the short-term treatment of patients with acute decompensated CHF, the agents currently used include nitroglycerin, dobutamine, milrinone, and nitroprusside.

Nitroglycerin and nitroprusside are nitrovasodilators and work as nitric oxide donors producing vasorelaxation. Nitroglycerin is indicated for the treatment of CHF accompanying myocardial ischemia, and nitroprusside as an agent for reducing BP, but both have found widespread use for the short-term treatment of CHF when physicians determine that the patient would benefit from reduction in preload or afterload. Both are administered by titration to a desired effect on PCWP or BP or both. The side effects of the nitrovasodilators are hypotension (with nitroprusside capable of producing profound hypotension), reflex tachycardia, accumulation of thiocyanate and cyanide in the blood following high doses or prolonged administration (nitroprusside only), and rapid tachyphylaxis requiring rest periods and frequent increases in dose to maintain an effect (nitroglycerin only). In addition, nitroglycerin interacts with certain types of IV tubing, requiring its own infusion set. Nitroprusside administration almost always requires invasive hemodynamic monitoring (with a Swan-Ganz® catheter and arterial line) and has also been shown to inhibit platelet function.

Dobutamine is an inotropic agent that acts by stimulating beta-adrenergic receptors, leading to an increase in intracellular concentrations of cyclic AMP. It is indicated when parenteral therapy is necessary for inotropic support in the short term treatment of patients with cardiac decompensation due to systolic dysfunction related to organic heart disease or following surgery. Side effects include increased heart rate (which can increase myocardial oxygen demand and aggravate myocardial ischemia), accelerated atrioventricular conduction (a concern in patients with atrial fibrillation, a common condition in patients with CHF), and increased ventricular ectopy (including nonsustained and sustained ventricular tachycardia). Chronic intermittent therapy with dobutamine has been associated with an increase in mortality in patients with CHF.

Milrinone is an inotropic agent with vasodilating properties. It acts by inhibiting phosphodiesterase and subsequently increasing intracellular concentrations of cyclic AMP. It is indicated for the short term IV therapy of CHF. Its main side effects are hypotension and increases in ventricular ectopy, including nonsustained and sustained ventricular tachycardia. In addition, there is evidence that renal impairment significantly increases the terminal elimination half-life of milrinone. Chronic administration of phosphodiesterase inhibitors has been associated with increased mortality in patients with CHF.

Conclusion

Natrecor[®] infusion produces unequivocal rapid hemodynamic and clinical improvement in patients with decompensated CHF. The hemodynamic improvement consists of dose dependent reductions in PCWP and SVR and increases in CI, which are accomplished without producing a reflex tachycardia or an increase in norepinephrine. Symptomatically, patients feel better rapidly, especially with regard to symptoms such as dyspnea. Ancillary benefits include inhibition of aldosterone, mild diuresis, less need for diuretics, and lack of arrhythmogenesis.

Natrecor[®] has generally been well tolerated when administered to patients with acute decompensated CHF and other common significant comorbidities, such as coronary artery disease, acute coronary syndrome, underlying arrhythmias and renal insufficiency. The safety profile of Natrecor[®] is not markedly altered in the presence of concomitant medications commonly used by patients with CHF, such as digoxin, ACE inhibitors, beta-blockers, and inotropes or significantly altered by age, gender 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 for in the inpatient clinical setting in which these patients are treated. However, the frequency of symptomatic hypotension that occurred with the recommended dose of Natrecor[®] was similar to that observed with IV nitroglycerin in the VMAC study.

Natrecor[®] possesses several features not found in therapy currently available, such as a combination of desirable hemodynamic, renal and neurohormonal effects. Natrecor[®] is not associated with a reflex tachycardia either as a reflex mechanism or as a result of direct sympathetic stimulation. It can be safely used without invasive monitoring (such as a Swan-Ganz[®] catheter). When administered as a fixed-dose infusion at a dose of 0.01 µg/kg/min, preceded with a 2 µg/kg bolus, Natrecor[®] is effective in most patients, obviating the need for initial dose titration or frequent dose adjustments. Human BNP is an endothelial cell-independent vasodilator, and, unlike inotropic agents that have been associated with increased mortality with chronic use, its activity is not dependent on cAMP levels or beta-adrenergic receptors. With the growing use of beta-blockers in heart failure, Natrecor[®] may be the preferred agent during acute exacerbation that may occur in these patients.

Natrecor[®] is indicated for the short-term IV treatment of patients with acute decompensated CHF. In these patients, Natrecor[®] rapidly reduces PCWP and improves dyspnea. A fixed dose infusion preceded by a bolus causes predictable clinical and hemodynamic effects. Compared to titratable drugs, the effectiveness and ease of use of Natrecor[®] is most beneficial in patients who do not require invasive hemodynamic monitoring. Blood pressure should be monitored during Natrecor[®] therapy.

Item 7

Recommended Indication

Natreacor[®] (nesiritide) is indicated for the initial intravenous treatment of patients with decompensated congestive heart failure, regardless of systolic function or primary etiology or the presence of acute coronary syndromes. Natreacor[®] improves dyspnea and overall clinical status, reduces pulmonary capillary wedge pressure and pulmonary artery pressures, and is associated with dose-dependent increases in cardiac index and stroke volume, without inducing tachyarrhythmia or an increase in heart rate. Natreacor[®] can be used alone or in conjunction with other standard therapies such as diuretics, ACE inhibitors, beta-blockers, dopamine, dobutamine, digoxin, and oral nitrates. Natreacor[®] had been studied in a broad range of patients, including the elderly, women, minorities, and patients with a history of significant chronic morbidities such as hypertension, diabetes, and atrial and ventricular arrhythmias.

Appendix A

The VMAC Trial Study Synopsis

Synopsis for Study 704.339

Study Design

Objectives

The primary objective of the VMAC study was to compare the hemodynamic and clinical effects of Natrecor® to placebo, when added to standard care, in the treatment of CHF. There were two primary endpoints for the study: change from baseline in pulmonary capillary wedge pressure (PCWP) in catheterized subjects, and the change from baseline in dyspnea in all subjects, 3 hours after start of study drug.

The secondary objective was to compare the hemodynamic and clinical effects of Natrecor® to those of IV nitroglycerin or placebo added to standard care. Additional objectives included a comparison between treatment groups in the use of other IV vasoactive agents and/or IV diuretics and the effects on other hemodynamic variables.

Study Design

The VMAC trial was a multicenter, randomized, double-blinded clinical trial that enrolled 498 patients and compared the hemodynamic, clinical, and safety effects of Natrecor®, placebo, and IV nitroglycerin when used for the treatment of acutely decompensated CHF in a typical hospital setting.

Randomization of patients was stratified by the Investigator's clinical decision to use a right heart catheter to facilitate the clinical management of the CHF (hereafter referred to as catheterized or non-catheterized subjects). Two hundred forty-six catheterized patients and 243 non-catheterized patients were randomized and treated with one of the following: placebo followed by IV nitroglycerin, placebo followed by Natrecor®, IV nitroglycerin, Natrecor® fixed dose, or Natrecor® adjustable dose (catheterized subjects only). Nine patients were randomized but not treated because they no longer met the inclusion/exclusion criteria.

The first 3 hours of the study were placebo controlled and double blinded, using a double-dummy study drug administration design. Each subject received a bolus of Natrecor®/placebo, followed by simultaneous infusions of "nitroglycerin/placebo" AND "Natrecor®/placebo" through two separate study drug infusion sets (double-dummy design). The Investigator was to assume that each infusion set contained active drug. The initial and

all subsequent doses of nitroglycerin/placebo were determined by the Investigator. Subjects receiving Natrecor®/placebo were administered a 2-µg/kg IV bolus followed by an infusion of 0.01 µg/kg/min. In the Natrecor® adjustable-dose arm, if a subject had a PCWP \geq 20 mm Hg and a systolic blood pressure (SBP) \geq 100 mm Hg, and required additional vasodilation, the Natrecor® dose could be incrementally increased every 3 hours up to a maximum dose of 0.03 µg/kg/min.

After the 3-hour placebo-controlled period, placebo subjects crossed over to double-blinded treatment with active therapy (nitroglycerin or Natrecor® fixed dose). Study drug infusion was to continue for at least 24 hours; the total duration of study drug infusion beyond 24 hours was left to the Investigators' discretion.

During the first 3 hours of study drug administration, vital signs, symptoms (dyspnea and global clinical status) and hemodynamics (including PCWP and pulmonary artery pressures [PAP]) were measured frequently. Additional vital signs were obtained throughout study drug infusion; PCWP and PAP were obtained through 48 hours after the start of study drug. Dyspnea and global clinical status were evaluated at 6 and 24 hours after the start of study drug. Total fluid intake and urine output were recorded for the first 24 hours after the start of study drug.

Serum creatinine was obtained at baseline and at various times through day 30. Adverse events were assessed through study day 14; serious adverse events were assessed through study day 30. Mortality was assessed through 6 months.

Key Inclusion/Exclusion Criteria

Eligible patients were at least 18 years of age and required hospitalization and IV therapy for acutely decompensated CHF for at least 24 hours. Patients had dyspnea at rest; clinical evidence of heart failure as the primary etiology of the dyspnea; and elevated cardiac filling pressures, either by clinical estimation or by a measured baseline PCWP \geq 20 mm Hg. Patients with CHF in the setting of an acute coronary syndrome, with relatively preserved systolic function (ejection fraction $>$ 40%), significant ventricular arrhythmias or renal insufficiency, patients already being administered dobutamine or dopamine, and cardiac transplant candidates were not excluded from participation in the study.

Potential patients with an SBP consistently below 90 mm Hg, patients requiring mechanical ventilation, patients receiving IV nitroglycerin that could not be withheld (e.g., IV nitroglycerin for management of an acute coronary syndrome), and patients for whom administration of an IV vasodilator was contraindicated were excluded.

Significant Changes in Study Conduct or Analysis

The protocol was amended twice during the course of the study. The primary purpose of the first protocol amendment was to extend the follow-up period for mortality assessment from

30 days to 6 months after the start of study drug, per the FDA's suggestion. The statistical section was also amended to make it consistent with the final statistical analysis plan that had previously been submitted and discussed with the FDA.

The primary purpose of the second protocol amendment was to allow subjects who had responded favorably to study drug, and had completed 30 days of therapy, to cross over to open-label Natrecor®. No subjects were treated under the second amendment.

Results

Subject Enrollment and Disposition

Four hundred ninety-eight subjects were randomized at 55 U.S. clinical sites between October 26, 1999 and July 27, 2000; study data were collected through November 22, 2000. Nine of the 498 randomized subjects were not treated. Of the total 489 randomized and treated subjects, 246 were in the catheterized stratum and 243 were in the non-catheterized stratum.

Subject Demographics and Baseline Characteristics

Among the 489 treated subjects (69% men and 31% women) in the VMAC study, the mean age (\pm standard deviation [SD]) was 62 ± 14 years; 57% of subjects were at least 65 years of age and 25% were older than 72 years. One hundred fifty-two (31%) subjects were female; of the 203 (42%) minority subjects, 119 (24%) were Black, 69 (14%) were Latino, and 15 (3%) were categorized as either Asian, or Other.

All subjects had dyspnea at rest or NYHA class IV symptoms at study entry. The majority (84%) had chronic CHF that was classified as NYHA class III or IV. The subjects' physical examination findings supported the intent of the trial to enroll patients with acutely decompensated CHF in the setting of clinically evident fluid overload. Other important clinical findings at baseline included an acute coronary syndrome (12%) and evidence of preserved systolic function (15%). Finally, many subjects had a history of significant arrhythmias including atrial fibrillation or fib/flutter (35%), non-sustained ventricular tachycardia (VT) (22%), sudden death (8%), ventricular fibrillation (6%), and sustained VT (13%).

Efficacy Evaluation

At 3 hours, the addition of Natrecor® to standard care led to significant improvement in dyspnea, compared to the addition of placebo to standard care ($p = 0.034$, van Elteren's test). At 3 hours, Natrecor® also led to a significant reduction in PCWP compared to both placebo and nitroglycerin added to standard care ($p < 0.001$, compared to placebo; $p = 0.027$, compared to nitroglycerin).

The 0.01- $\mu\text{g}/\text{kg}/\text{min}$ dose of Natrecor[®] (preceded by a 2- $\mu\text{g}/\text{kg}$ bolus) led to rapid (within 15 minutes) and sustained decreases in PCWP. At 15 minutes, 60% of the 3-hour effect of Natrecor[®] on PCWP was observed; 95% of the 3-hour effect on PCWP reduction was observed by 1 hour. Natrecor[®]'s effect on PCWP was statistically significant, compared to both placebo and nitroglycerin through every time point from 15 minutes to the primary endpoint time point at 3 hours (except at 2 hours, compared to nitroglycerin). Natrecor[®]'s effect on PCWP was sustained through 48 hours and was significantly greater than the effects of nitroglycerin through 24 hours.

At 3 hours, the beneficial effect of Natrecor on dyspnea was significant, compared to standard care plus placebo, in all subjects ($p = 0.034$, van Elteren's test) as well as in the catheterized stratum ($p = 0.030$, van Elteren's test). In addition, at 24 hours compared to nitroglycerin, Natrecor[®] therapy led to a significant improvement in global clinical status in all subjects ($p = 0.044$, ANOVA) and in both dyspnea and global clinical status, in non-catheterized subjects ($p \leq 0.018$, van Elteren and $p \leq 0.013$, ANOVA dyspnea and global clinical assessment, respectively).

In the Natrecor[®] adjustable-dose subjects who underwent a dose increase to 0.015 $\mu\text{g}/\text{kg}/\text{min}$ or higher at any time, the dose increases led to greater reductions in PCWP over time, without leading to excessive effects on SBP.

Consistent with what has previously been described, in this double-blinded comparison, diuretics were administered to fewer Natrecor[®] than nitroglycerin subjects. Urine output through 24 hours and weight loss were similar between the two groups.

Safety Evaluation

Natrecor[®] was well tolerated in this study. There was no adverse event that occurred in significantly more Natrecor[®] subjects than nitroglycerin subjects through the placebo-controlled period or during the first 24 and 48 hours after the start of study drug. Through these same time periods, significantly more nitroglycerin subjects reported any adverse event. Significantly more nitroglycerin subjects also reported abdominal pain and headache through 24 and 48 hours, respectively.

In all Natrecor[®] subjects, adverse events that were reported in at least 5% of subjects within the first 24 hours, in order of decreasing frequency, included hypotension (11%), asymptomatic hypotension (8%), and headache (8%). In contrast, within the first 24 hours in nitroglycerin subjects, headache (20%) was the most common adverse event reported, followed by asymptomatic hypotension (8%), nausea (6%), symptomatic hypotension (5%), pain (5%), abdominal pain (5%), catheter pain (5%), and nonsustained VT (5%).

Through 30 days there were no significant differences in the frequency of serious adverse events or pattern of changes in serum creatinine that occurred in nitroglycerin or Natrecor[®] subjects.

There were no significant differences in the 1-month and 6-month mortality in nitroglycerin and Natrecor® subjects.

Conclusions

The VMAC trial comprehensively addressed the issues raised by the FDA and the Cardiovascular and Renal Drugs Advisory Committee. VMAC was a randomized, double-blinded trial that studied a new dose of Natrecor®, a 2- $\mu\text{g}/\text{kg}$ bolus followed by a fixed-dose infusion of 0.01 $\mu\text{g}/\text{kg}/\text{min}$, in severely ill patients with acute decompensated CHF, dyspnea at rest, and many significant comorbidities including acute coronary syndromes, preserved systolic function, significant ventricular arrhythmias, and renal insufficiency. The study was conducted in patients who were receiving standard-care medications during study drug infusion such as diuretics, β -blockers, dobutamine, dopamine, and other oral cardiac therapies. Therefore, the efficacy and safety profile of Natrecor® observed in the VMAC study should be representative of what would be observed in the target population that would be treated with Natrecor®.

At 3 hours, Natrecor® led to significant improvements in dyspnea that were in excess of what was observed with standard care alone (placebo) in all subjects, as well as in catheterized subjects. At 24 hours, compared to nitroglycerin, Natrecor® therapy led to a significant improvement in global clinical status in all subjects, and in both dyspnea and global clinical status in non-catheterized subjects. The emergence of significant differences in clinical benefit between Natrecor® and nitroglycerin at the 24-hour time point support the conclusion that the beneficial clinical effects of Natrecor® were sustained for at least 24 hours and that objective symptom improvement occurred in a setting that was not biased by the knowledge of hemodynamic effects.

The 0.01- $\mu\text{g}/\text{kg}/\text{min}$ dose of Natrecor® (preceded by a 2- $\mu\text{g}/\text{kg}$ bolus) led to rapid (within 15 minutes) and sustained decreases in PCWP. At 15 minutes, 60% of the 3-hour effect of Natrecor® on PCWP was observed; 95% of the 3-hour effect on PCWP reduction was observed by 1 hour. Natrecor®'s effect on PCWP was statistically significant, compared to both placebo and nitroglycerin through every time point from 15 minutes to the primary endpoint time point at 3 hours (except at 2 hours, compared to nitroglycerin). Natrecor®'s effect on PCWP was sustained through 48 hours and was significantly greater than the effects of nitroglycerin through 24 hours. In clinical practice, in those patients who require a greater hemodynamic effect, it would be appropriate to incrementally increase the dose of Natrecor® to take advantage of its dose-dependent hemodynamic effects.

The safety profile of Natrecor® observed in the VMAC trial should be representative of what would be observed in the target population that would be treated with Natrecor®. The 0.01- $\mu\text{g}/\text{kg}/\text{min}$ dose of Natrecor® generally was well tolerated, even in severely ill patients with multiple comorbidities and those taking multiple concomitant cardiac medications. Natrecor® was better tolerated than nitroglycerin as evidenced by the significantly greater

percentage of nitroglycerin subjects who experienced any adverse event, as well as headache and abdominal pain. There was no adverse event clearly associated with Natrecor[®] that occurred significantly more frequently in Natrecor[®] subjects. Increasing doses of Natrecor[®] in those subjects who tolerated the 0.01- $\mu\text{g}/\text{kg}/\text{min}$ dose also were well tolerated. Symptomatic hypotension was less frequent with the 0.01- $\mu\text{g}/\text{kg}/\text{min}$ dose and the adjustable dose of Natrecor[®] than has been reported when patients began treatment with Natrecor[®] at higher initial doses. In VMAC, symptomatic hypotension was reported in 5% and 4% of nitroglycerin and Natrecor[®] subjects, respectively, within the first 24 hours of therapy. Blood pressure should be monitored during Natrecor[®] therapy. There were no significant differences in serious adverse events or in mortality through 6 months.

In summary, a fixed-dose strategy of administering Natrecor[®] at a dose of 0.01 $\mu\text{g}/\text{kg}/\text{min}$ (preceded by a 2- $\mu\text{g}/\text{kg}$ bolus) led to an efficacy profile superior to that of a titration strategy with IV nitroglycerin without additional safety concerns. Natrecor[®] led to more rapid hemodynamic improvement that was consistently greater than that of nitroglycerin through at least 24 hours. Natrecor[®] also led to meaningful clinical benefit by 3 hours, compared to placebo, and by 24 hours compared to nitroglycerin subjects. A fixed-dose administration of Natrecor[®] leads to predictable hemodynamic and clinical effects in typical acutely decompensated patients, suggesting that Natrecor[®] administration does not need to be accompanied by invasive monitoring unless dictated by the clinical condition of the patient.

Appendix B

The PRECEDENT Trial Study Synopsis

Synopsis for Study 704.329

Objectives

The primary objective of this study was to compare the effects on heart rate and ventricular arrhythmias of two doses of Natrecor[®] to dobutamine, during the first 24 hours of treatment of decompensated CHF. The primary endpoints were (1) average heart rate, (2) average hourly premature ventricular beats, and (3) average hourly repetitive beats, all expressed as a change from baseline, as measured by Holter monitoring.

Additional objectives included exploring the effects of Natrecor[®] and dobutamine on other Holter endpoints such as couplets, triplets, and ventricular tachycardia (VT), and the evaluation of ventricular ectopy by the application of specific proarrhythmic criteria. Clinical symptoms were also measured.

Study Design

This was a multicenter, randomized, open-label, active-controlled safety study designed to enroll approximately 240 subjects with symptomatic (New York Heart Association [NYHA] Class III or IV), decompensated CHF, for whom treatment with dobutamine or Natrecor[®] was deemed appropriate. After a 24-Hour Baseline Holter Monitoring Period, subjects were randomized to dobutamine or Natrecor[®] (0.015 or 0.03 $\mu\text{g}/\text{kg}/\text{min}$). The randomization was stratified by whether or not the subjects had a known history of VT (nonsustained or sustained). Treatment assignment was open label with regard to the study drug (dobutamine or Natrecor[®]); assignment to the two Natrecor[®] dose groups was double blinded. Dobutamine was to be administered at a dose of at least 5 $\mu\text{g}/\text{kg}/\text{min}$. During the first 24 hours of study drug, each subject underwent Holter monitoring.

Study drug (dobutamine or Natrecor[®]) was to be administered for at least 24 hours as the single IV vasoactive agent for symptomatic, decompensated CHF. Other IV vasoactive agents such as milrinone, nitroprusside, nitroglycerin, and/or any dose of dopamine were not to be added to study drug during the first 24 hours of therapy. Dobutamine was not to be added to the Natrecor[®] infusion during the first 24 hours of therapy. Diuretics and all long-term cardiac therapies were permitted.

After 24 hours, the Holter monitor was removed, and subjects could remain on study drug, if appropriate. Natrecor[®] subjects could continue on their fixed-dose Natrecor[®] regimens (still

blinded to specific dose-group assignment) for up to a maximum of 7 days (with or without the addition of other parenteral agents) or could switch to whatever treatment was appropriate, at the discretion of the Investigators. Subjects in the dobutamine treatment group could continue on study drug as long as appropriate, at the discretion of the Investigators.

Systemic hemodynamics (blood pressure [BP] and heart rate [HR]) were assessed at baseline, at 15 and 30 minutes, and at 3, 8, 16, and 24 hours following the initiation of study drug. Clinical symptoms (i.e., global clinical status and specific signs and symptoms of decompensated CHF) were assessed at baseline and at 3 and 24 hours after the start of study drug. Laboratory tests were measured at baseline, 24 hours (if study drug continued more than 24 hours), within 24 hours after termination of study drug or on study day 7, and once between study days 10 and 14. General and serious adverse events were assessed through study day 14. Mortality was assessed through 6 months.

Key Inclusion/Exclusion Criteria

Eligible patients must have been at least 18 years of age, presenting with symptomatic, decompensated CHF for which inpatient therapy with either dobutamine or Natrecor®, administered as a single IV vasoactive agent with or without diuretics, was deemed appropriate. Patients must have had a chronic CHF classification of NYHA Class III or IV and have received stable doses of oral antiarrhythmic medications for at least the 48 hours before starting study drug, or received no antiarrhythmic medications.

Potential patients with an SBP consistently below 85 mm Hg, unable to tolerate a 24-Hour Baseline Holter Monitoring Period without IV vasoactive medications, requiring an IV antiarrhythmic during the 48 hours before starting study drug, and patients for whom administration of an IV vasodilator was contraindicated were excluded.

Significant Changes in Study Conduct or Analysis

No protocol amendments or significant changes occurred in the conduct of the study.

The study was initially designed to follow subject mortality for 14 days. After the study was completed, subject mortality through 6 months was collected (retrospectively), per the suggestion of the FDA.

Results

Subject Enrollment and Disposition

Two hundred fifty five subjects were randomized at 46 clinical sites between August 5, 1998 and December 30, 1998; study data were collected through February 16, 1999. Nine of the 255 subjects were randomized but not treated. The largest number of subjects randomized and treated at a single site was 20 (8% of total study population).

Study Demographics and Baseline Characteristics

A total of 255 subjects (170 [67%] men and 85 [33%] women) were randomized in the study. The mean age (\pm standard deviation [SD]) for all enrolled subjects was 61 ± 14 years (range 21 to 93 years). One hundred five subjects (41%) were at least 65 years old. Of randomized subjects, 136 (53%) were Caucasian, 71 (28%) were Black, and 40 (16%) were Hispanic, with remaining subjects were classified as either Asian or Other.

The chronic classification of CHF before this hospitalization was NYHA class III in 188 (74%) subjects and NYHA class IV in 67 (26%) subjects. The primary etiology of the subjects' chronic CHF was ischemic cardiomyopathy in 130 (51%) subjects and idiopathic dilated cardiomyopathy in 59 (23%) subjects; in the remainder of subjects, the etiology of CHF was hypertensive, diabetic, alcohol or drug induced cardiomyopathy, valvular heart disease, or was unknown. There were no significant differences between treatment groups in CHF etiology.

Many subjects had a history of cardiac arrhythmias. For example, 35% of subjects had a history of frequent premature ventricular contractions, 27% had a history of nonsustained ventricular tachycardia (NS-VT), 8% had a history of sustained VT, and 4% had a history of ventricular fibrillation. Twenty-eight percent of subjects had a history of atrial fibrillation or fib/flutter, and 5% of the subjects had a history of atrial flutter.

The treatment groups were generally well balanced for demographic characteristics and medical history, except that more dobutamine subjects had NYHA Class IV CHF than did subjects in the two Natrecor[®] groups (36%, 20%, and 23% in the dobutamine, Natrecor[®] 0.015- and Natrecor[®] 0.03- μ g/kg/min treatment groups, respectively, $p = 0.043$ [Fisher].)

Efficacy Evaluation

The PRECEDENT trial studied a population of decompensated heart failure patients with objective evidence of ventricular ectopy before entry into the study — that is, a relevant population that was at risk for the exacerbation of pre-existing substrates for ventricular arrhythmias. The trial demonstrated that the lower dose of Natrecor[®] (0.015 μ g/kg/min) was associated with a significant decrease in all measures of ventricular ectopy (PVBs, repetitive beats, couplets, and episodes of VT) from baseline. The 0.03- μ g/kg/min dose did not lead to significant changes from baseline. The neutral effect of the higher dose on heart rate and ventricular ectopy, a dose that is known to produce dose-dependent hemodynamic improvements in preload and afterload, suggests that the beneficial effect on ectopy that occurred with the lower dose is not likely due to hemodynamic improvement alone.

The PRECEDENT trial quantified the magnitude of the effect of dobutamine on heart rate and the stimulation of ventricular ectopy and VT. Dobutamine subjects experienced a significant increase in average heart rate as well as heart rate of at least 100 beats per minute, for a significantly longer period of time during the first 24 hours of treatment than the subjects receiving the 0.015 µg/kg/min Natrecor® dose ($p < 0.001$). By every measure of ventricular ectopy, either by the number of beats (PVBs or repetitive beats) or the number of events (couplets or VT), dobutamine significantly increased ventricular ectopy from that which was observed on the 24-hour baseline tape. Also, in subjects who had no VT on the baseline tape, dobutamine induced VT during treatment in more subjects than did Natrecor®. The corresponding effect in subjects who did have VT on their baseline tape was that significantly more Natrecor® subjects experienced the resolution or lack of VT during the first 24 hours of treatment than did dobutamine subjects.

When 2 different proarrhythmia criteria were applied, dobutamine was significantly more proarrhythmic than Natrecor®. The Velebit criterion was met in 17 (23%) dobutamine subjects, compared to only 3 (2%) Natrecor® subjects ($p < 0.001$). The CAPS criterion was met in 7 (10%) dobutamine subjects and in no Natrecor® subject ($p = 0.001$, Fisher).

The effects of dobutamine in increasing heart rate and ventricular ectopy were significant in those subjects without a history of VT. This suggests that the proarrhythmic effects of dobutamine in patients with CHF (or structural heart disease) may be due to the sympathetic activation of a dormant substrate for ventricular arrhythmia.

Both dobutamine and Natrecor® led to improvements in global clinical status in approximately one-third of subjects by 3 hours, and in approximately 75% of subjects by 24 hours. There were no significant differences between the treatment groups. Specific symptoms, and most notably dyspnea, were similarly improved with both therapies.

In summary, the PRECEDENT trial demonstrated that both dobutamine and Natrecor® lead to clinical improvement as measured by symptom evaluations during the first 24 hours of therapy. However, Natrecor® subjects did not experience the increase in heart rate or ventricular ectopy that occurred with dobutamine therapy. The 0.015 µg/kg/min dose of Natrecor® was associated with significant decreases in all measures of ventricular ectopy from the 24 hour period preceding therapy with Natrecor®.

Safety Evaluation

Natrecor® administration at both the 0.015 and 0.03 µg/kg/min doses was generally well tolerated by these subjects with symptomatic, decompensated CHF. A decrease in blood pressure (i.e., asymptomatic or symptomatic hypotension) was the most common adverse event associated with Natrecor® administration. During the first 24 hours of study drug infusion, symptomatic hypotension was reported in 2 (2%), 14 (17%), and 19 (24%) subjects in the dobutamine group and the 0.015 and 0.03 µg/kg/min Natrecor® groups, respectively ($p < 0.001$ [Fisher]).

Sinus bradycardia and nausea also occurred in significantly more Natrecor[®] than dobutamine subjects through 24 hours. Other events that were reported in more Natrecor[®] subjects, through 24 hours, but did not reach statistical significance, were headache, dizziness, and vomiting. Through 14 days, headache and sinus bradycardia were reported in significantly more Natrecor[®] than dobutamine subjects.

The exact mechanism for the increased sinus bradycardia that occurred in Natrecor[®] subjects is not known. The events were short-lived and generally resolved spontaneously. It is notable that there was no significant change in the duration of time in bradycardia between the baseline and treatment tape with Natrecor[®]. Natrecor[®]-associated bradycardia may be due to the known phenomenon by which vasodilators can lead to bradycardia, the Bezold-Jarisch reflex. A similar mechanism has been implicated with nitroglycerin therapy, rapid hemorrhage, or with syncope that results during tilt-table testing.

Through 24 hours, tachycardia was reported in significantly more dobutamine than Natrecor[®] subjects. Tachycardia occurred in 11 (13%), 1 (1%), and 2 (3%) subjects in the dobutamine and the 2 Natrecor[®] dose groups, respectively ($p = 0.001$, Fisher). Through 24 hours, nonsustained VT, ventricular extrasystoles, injection site pain, and leg cramps were reported in more dobutamine subjects. However, the differences between treatment groups were not statistically significant. Through 14 days, tachycardia, pain, and injection site reaction were reported in significantly more dobutamine than Natrecor[®] subjects.

Natrecor[®] therapy may be associated with mild and transient increases in BUN and creatinine that resolve within a few days. There were no significant differences in longer term measures of safety such as hospital length of stay, hospital readmissions, or mortality through 6 months.

Conclusions

The PRECEDENT trial was a large, prospective, randomized, dobutamine-controlled trial that characterized the relative risks of dobutamine and Natrecor[®] as therapies for acutely decompensated CHF. Dobutamine was associated with a significant increase in tachycardia, ventricular ectopy, and the more clinically significant VT. Natrecor[®] was associated with dose-dependent hypotension, nausea, and sinus bradycardia. The trial studied a population of decompensated heart failure patients with objective evidence of ventricular ectopy before entry into the study, that is, a relevant population that is at risk for the exacerbation of pre-existing substrates for ventricular arrhythmias.

The trial objectively confirmed, via Holter monitoring, that Natrecor[®] does not have an effect on heart rate, nor is it associated with an increase in ventricular ectopy or more clinically meaningful arrhythmic events. The lower dose of Natrecor[®] (0.015 $\mu\text{g}/\text{kg}/\text{min}$) was associated with a significant decrease in all measures of ventricular ectopy (PVBs, repetitive beats, couplets, and episodes of VT) from baseline, whereas the 0.03 $\mu\text{g}/\text{kg}/\text{min}$ dose had a neutral effect.

The decrease in ectopy associated with the lower dose may be due to the gradual removal of stimuli for ventricular ectopy as the patient becomes more hemodynamically compromised over the first 24 hours of therapy with Natrecor®. Alternatively, Natrecor® does not directly effect contractility and may have direct effects on autonomic tone which may include a decrease in sympathetic tone, an increase in parasympathetic tone, or both.

The PRECEDENT trial also confirmed, as is generally believed to be true in clinical practice, that dobutamine significantly increases heart rate and stimulates the development of ventricular ectopy and VT. Through 24 hours, tachycardia occurred in significantly more dobutamine than Natrecor® subjects. Through 14 days, pain and injection site reaction were reported in significantly more dobutamine than Natrecor® subjects.

The clinical implication of the effect on heart rate is that estimated myocardial oxygen demand likely increases with dobutamine therapy and may even contribute to the increase in ventricular arrhythmias that are observed with dobutamine. By every measure of ventricular ectopy, either by the number of beats (PVBs or repetitive beats) or the number of events (couplets or VT), dobutamine significantly increased ventricular ectopy from that which was observed on the 24-hour baseline tape ($p \leq 0.017$ for each endpoint, compared to each Natrecor® dose). In subjects who had no VT on the baseline tape, dobutamine induced VT during treatment in more subjects than did Natrecor®. In patients who had VT on their baseline tape, significantly more Natrecor® subjects experienced the resolution or lack of VT during the first 24 hours of treatment than did dobutamine subjects. When 2 different proarrhythmia criteria were applied, dobutamine was deemed to be significantly more proarrhythmic than Natrecor®.

Dobutamine increased heart rate and ventricular ectopy in subjects without a known history of VT, suggesting that the proarrhythmic effects of dobutamine in patients with CHF may be due to the sympathetic activation of a dormant substrate due to existing structural changes in the diseased myocardium.

Natrecor® administration at both the 0.015 and 0.03 $\mu\text{g}/\text{kg}/\text{min}$ doses was generally well tolerated in the trial. However, the frequency of both asymptomatic and symptomatic hypotension was higher than what has been observed previously in Natrecor® trials. Both asymptomatic and symptomatic hypotension were reported in significantly more Natrecor® than dobutamine subjects. Sinus bradycardia (possibly due to the Bezold-Jarisch reflex) and nausea also occurred in significantly more Natrecor® than dobutamine subjects through 24 hours. Through 14 days, headache and sinus bradycardia were reported in significantly more Natrecor® than dobutamine subjects. Natrecor® therapy also may be associated with mild and transient increases in BUN and creatinine that resolve within a few days.

The increased hypotension rate in this trial may be explained by the fact that subjects were identified for the study at least 24 hours before study drug began and most subjects underwent inpatient treatment of their decompensated CHF with diuretics and other oral therapies. It is possible that, by the time study drug was started, many patients may not have had elevated cardiac filling pressures. Finally, both doses were administered from the start of the infusion. In clinical practice, it would be preferable to begin with a lower dose, to increase the dose only in those subjects who have not adequately responded to the initial dose, and in those who clearly have evidence of elevated cardiac filling pressures and an adequate blood pressure. This trial supports the conclusion that the 0.015 µg/kg/min dose or lower would be the optimal initial infusion dose of Natrecor® in most patients. It may also be beneficial to begin the Natrecor® administration with a loading bolus, to achieve peak pharmacodynamic effects sooner.

There were no significant differences in longer term measures of safety such as hospital length of stay, hospital readmissions, or mortality through 6 months.

In summary, the PRECEDENT trial demonstrated that dobutamine increases heart rate and leads to significant proarrhythmia in patients with decompensated CHF. Both the induction of new episodes of VT and the aggravation of existing ventricular ectopy occurred with dobutamine therapy. Natrecor® was not associated with the effect on heart rate or ventricular ectopy that occurred with dobutamine therapy. The 0.015 µg/kg/min dose of Natrecor® was associated with significant decreases in all measures of ventricular ectopy from baseline. Given the trade-off of the risk of ventricular arrhythmia and tachycardia with dobutamine or the risk of hypotension with Natrecor®, Natrecor® may be a better tolerated therapeutic option for most acutely decompensated CHF patients. Blood pressure should be monitored periodically with Natrecor® therapy.