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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
20-920**

Medical Review(s)



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Memorandum

DATE: 6.21.01

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Office of Drug Evaluation 1

SUBJECT: Secondary Review of NDA 20-920

NAME OF DRUG: Nesiritide (Natrecor[®])

SPONSOR: Scios Inc.

DOCUMENTS USED FOR MEMO:

1. Medical Review of current submission by Abraham Karkowsky, M.D., dated 5.15.01.
2. Supplement to Medical Review, by Abraham Karkowsky, M.D., dated 5.15.01.
3. Statistical Review by James Hung, Ph.D., dated 4.18.01.
4. Statistical Addenda by James Hung, Ph.D., dated 4.20.01, 4.23.01, 5.7.01, and 5.16.01.
5. Pharmacology and Biopharmaceutics Review by Angelica Dorantes, Ph.D., dated 6.8.01. and Nakissa Sadrieh, Ph.D., dated 4.24.98.
6. Pharmacology/ Toxicology Review by Belay Tesfamariam, Ph.D., dated 4.9.01. and Tom Papoian, dated 12.9.98.
7. Chemistry, Manufacturing and Controls Reviews by Pardhasaradhi Komanduri, Ph.D., dated 3.20.01, 4.18.01, 6.5.01 and by J.V. Advani dated 6.14.01.
8. Microbiology Reviews #3 and 4 by Brenda Uratani, Ph.D., dated 3.25.99 and 2.16.01.
9. Medical Review by D.C. Throckmorton, M.D., dated 3.4.99 and original Secondary Medical Review by Abraham Karkowsky, dated 3.11.99, of original NDA submission.
10. Memorandum from Avi Karkowsky regarding pediatric studies with nesiritide, dated 6.15.01.

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0.0 OVERVIEW

This memorandum constitutes the Secondary Medical Review and recommendation that NDA 20-920 for Natrecor[®] (nesiritide citrate), be approved for the treatment of acutely decompensated congestive heart failure for patients who are short of breath at rest.

This package is being transmitted with reviews by all of the relevant disciplines. As the current submission represents the second review of NDA 20-920, there are two primary medical reviews by Dr. Throckmorton (original submission) and Dr. Karkowsky (current submission). There is also an earlier secondary medical review by Dr. Karkowsky. The conclusions of reviews by the other relevant review disciplines have been synthesized into the present document and their recommendations regarding labeling incorporated where appropriate. At this time, there are no identified unresolved preclinical issues that could affect the action recommended. The 120-Day Safety Update and Pediatric studies are addressed in appendices.

Natrecor (nesiritide) was initially submitted 4.24.98 and was the subject of an Advisory Committee held 1.29.99. On 4.27.99, the FDA sent a non-approvable letter for NDA 20-920, conveying the following concerns:

- 1) The need for additional safety data 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) The need for data from a broader range of CHF patients, including those with active ischemia, preserved systolic function, and those receiving other IV vasoactive agents.
- 3) The need for an active-control study comparing Natrecor to an IV vasodilator such as nitroglycerin to provide clearer characterization of Natrecor's efficacy and safety profile, especially as it relates to effects on blood pressure and hypotension.
- 4) The need for data pertaining to symptom evaluations including 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) The need for data to support the sustained hemodynamic effects of Natrecor.
- 6) A trial to support the recommendations for the dosing regimen and dose adjustment.
- 7) Data on patients with unrestricted use of diuretics and other cardiac therapies.

In response to this letter, the sponsor designed and conducted the VMAC trial (Vasodilation in the Management of Acute Congestive Heart Failure), which was the subject of a second Advisory Committee meeting 5.25.2001. What follows is a summary of the available data for each of the seven points raised in the non-approvable letter. As part of each summary, the reader is referred for additional details to my summary of the NDA database that follows this overview.

1) The need for additional safety data to better understand the onset and offset characteristics of symptomatic hypotension when Natrecor is added to standard-care therapies in a typical hospital setting.

To address this issue, the VMAC trial removed most of the restrictions on the use of other agents in the treatment of acute heart failure used in earlier trials and studied nesiritide at a lower infusion rate (0.010 $\mu\text{g}/\text{kg}/\text{min}$ IV). In the VMAC trial, the infusion was administered after a bolus of nesiritide (2 $\mu\text{g}/\text{kg}$ over 60 seconds IV) (see trial description, section 7.0 below). The safety data from this trial, as summarized in section 9.0 below, adequately demonstrate that the rate of symptomatic hypotension with this dose is not demonstrably higher than for patients who receive IV nitroglycerin (NTG) as therapy for their decompensated CHF. There is clear evidence, however, that when symptomatic hypotension occurs with nesiritide, it lasts substantially longer than the hypotension associated with NTG. For example, in the VMAC trial, 18/30 episodes (60%) of symptomatic hypotension in nesiritide lasted longer than 120 minutes, compared with 0/12 (0%) in the nitroglycerin group (table 9.1.3 below). There were no detectable differences in terms of the need for additional therapies or need to discontinue therapy as a result of this prolonged hypotension. Similarly, higher doses of nesiritide use in earlier trials were associated with an significantly increased rates of elevated serum creatinine over baseline compared with active controls (table 9.2.1 and 9.2.2), and the need for medical therapy for renal injury (table 9.2.4). In VMAC, the lower dose of nesiritide was associated with a less substantial, numerical excess of elevated creatinine compared with NTG (table 9.2.5).

2) The need for data from a broader range of CHF patients, including those with active ischemia, preserved systolic function, and those receiving other IV vasoactive agents.

The original NDA database included very few patients who used nesiritide in combination with other vasodilators and IV inotropes. The VMAC trial enrolled patients with ongoing cardiac ischemia (61 patients, 12.4% of total, had acute coronary syndrome in the past 7 days, 26 patients 5.1% of total, had MI in past 7 days). The trial also did not use ejection fraction as an entry criteria (64 patients, 15.3%, had EF >40%), and allowed the entry of patients who were using other vasodilators (approximately 20% of subjects used phosphodiesterase (PDE) inhibitors, dopamine or dobutamine within 6 hours of entry into the trial). During the trial, approximately 20% of the patients continued the use of either dobutamine or dopamine, although no patients continued PDE inhibitors.

While these numbers are relatively small, no safety signal was identified when patients who used these agents concomitantly was examined. These data are insufficient to infer anything about the relative contributions to efficacy of these products when they are used together.

3) The need for an active-control study comparing Natrecor to an IV vasodilator such as nitroglycerin to provide clearer characterization of Natrecor's efficacy and safety profile, especially as it relates to effects on blood pressure and hypotension.

The VMAC trial was designed to allow a double-blind, randomized comparison of placebo, NTG and nesiritide on both hemodynamic and symptom endpoints at the end of 3 hours.

With regard to efficacy (see sections 8.1 and 8.5 below), use of nesiritide was associated with both a greater reduction in pulmonary capillary wedge pressure (PCWP) and to a greater improvement in dyspnea than placebo. Nitroglycerin (NTG) also demonstrated a non-significant favorable trend relative to placebo for the same two metrics. At 24 hours, there was a trend for greater improvement in symptoms in nesiritide compared with NTG (table 8.5.8).

All patients received either NTG or nesiritide after 3 hours. With regard to safety (see section 9.0 below) the comparison of particular interest was the incidence of hypotension in the nesiritide and NTG groups. In the VMAC trial, the incidence of symptomatic hypotension was similar in the two groups although there was a numerical excess of symptomatic hypotension in the nesiritide group (table 9.2.5). As summarized above, when hypotension occurred, it lasted longer in the nesiritide group, but this increased duration was not associated with a need for additional therapies or changes in study medications more often than was seen in the NTG group.

A secondary area of concern, also related to the adverse events seen in the original NDA, was the incidence of renal injury. Again, as summarized above, the higher doses of nesiritide used in the original NDA were clearly associated with more renal injury, especially injury detected by increases in serum creatinine. The lower dose used in the VMAC trial and NTG had a similar rate of elevated serum creatinine, although there was a numerical excess of such events in the nesiritide group.

3) The need for an active-control study comparing Natrecor to an IV vasodilator such as nitroglycerin to provide clearer characterization of Natrecor's efficacy and safety profile, especially as it relates to effects on blood pressure and hypotension (cont).

The other adverse event plausibly related to nesiritide use is bradycardia. In animals, this effect has been linked to an increased parasympathetic tone. In the original NDA this adverse even was reported in as many as 5% of the patients who received nesiritide 0.030 µg/kg/min. In the VMAC trial, the rates of bradycardia were similar in the NTG and nesiritide groups (1 and 2% respectively). Nesiritide at the dose used in VMAC and NTG had similar rates of other adverse events,

Mortality for patients in VMAC was collected through six months (see section 9.3). At that time, there had been 44 deaths in the NTG group of 216 patients (20.4%), compared with 67 deaths in the nesiritide group of 273 patients (24.5%). Per the analysis by Dr. James Hung summarized in table 9.3.1, these data cannot exclude a 50% excess in mortality in the nesiritide group relative to NTG. For the entire NDA database, the mortality rates at 6 months for the combined control group (including both vasodilators and inotropes) and the nesiritide group were 94/443 (21.5%) and 154/724 (21.7%) respectively.

4) The need for additional data pertaining to symptom evaluations, including the appropriateness of measuring symptoms in patients without dyspnea at rest and the potential bias created by physician evaluations and the knowledge of hemodynamics.

As summarized in section 8.5 below, the VMAC trial was designed to minimize the possibility of investigator knowledge of the PCWP influencing the clinical assessment of symptoms. In addition to shielding the patients from knowledge of their PCWP, the trial enrolled a cohort who did not have central pressures monitored. The data from these patients sufficiently demonstrate an association between the use of nesiritide and a significant improvement in dyspnea relative to baseline in patients with acutely decompensated CHF and dyspnea at rest. While not a part of the letter, the results from VMAC also reinforced the earlier trial data showing an association between the use of nesiritide and an improvement in PCWP that is significant relative to placebo.

5) The need for data to support the sustained hemodynamic effects of Natrecor to address the issue of tolerance.

After 3 hours, patients in VMAC remained blinded with regard to type of active treatment. In a cohort of these patients, hemodynamic monitoring was followed through at least 24 hours. As discussed below in section 8.1 below, there was no evidence in this cohort of a waning of the hemodynamic effects of nesiritide through 24 hours. After 24 hours, the number of patients with observations is limited. This lack of significant detectable tolerance is in apparent agreement with a pre-clinical experiment performed since the original NDA was submitted, in which rabbits were administered nesiritide continuously for 72 hours. In that experiment, there was evidence of loss of hemodynamic effect (see section 3.0 below).

6) A trial to support the recommendations for the dosing regimen and dose adjustment.

The VMAC trial is adequate to support a dosing regimen for Natrecor as follows: a bolus of 2µg/kg over approximately 60 seconds followed by an infusion of 0.01 µg/kg min for 24 hours. The available data are insufficient to allow for a description of how to adjust the dose of nesiritide. In the VMAC trial a group of individuals were centrally monitored. For this group, their nesiritide dose could be titrated based on hemodynamics (PCWP ≥20, SBP ≥100 mmHg), but the group is too small (62 patients, of whom approximately 25-30 were up-titrated) to assess the safety of these higher doses. In addition, the data from the previous trials clearly suggest a substantial safety risk associated with the use of doses of nesiritide ≥0.010 g/kg/min as initial therapy (hypotension in particular, but also bradycardia and changes in renal function).

7) The need for data in patients with unrestricted use of diuretics and other cardiac therapies.

In the VMAC trial there were some restrictions to concomitant medications, especially during the first 3 hours of the trial (prior to the primary endpoint), but the use of other cardiac therapies was not as restricted as it had been in the earlier trials and more closely reflected usual treatment for these patients (see section . As a result, diuretics, digoxin, aspirin, beta-blockers and non-IV nitrates were all used by >10% of the enrolled population. While no formal mechanism to assess the possible interaction, and the numbers of patients who took combinations of medications is not large, no safety risks were detected associated with the concomitant use of any of these drugs with nesiritide.

In conclusion, the VMAC trial is sufficient to provide a complete response to the identified deficiencies identified in the non-approvable letter, and the combined NDA database supports the approvability of Natrecor for the

treatment of acutely decompensated congestive heart failure in patients who are short of breath at rest. Given the substantial safety concerns that exist for doses of nesiritide greater than 0.010 µg/kg/min from the trials in the original NDA submission, and the lack of sufficient safety information from the VMAC trial when higher doses are used in patients who are centrally-monitored, Natrecor should be approved for use at a single dose of 0.010 µg/kg/min infusion following a bolus of 2µg/kg.

1.0 BACKGROUND

Nesiritide is the first member of a class of naturally-occurring peptides to undergo extensive clinical testing. Information on the basic science of their actions can be found in the list of references at the end of this memorandum. There are at least 3 members of natriuretic peptides (A-, B-, and C-type), each encoded by a unique gene and produced as a pro-drug. Natrecor is identical in amino acid structure to the B-type natriuretic peptide, and is abbreviated hBNP if it is derived from human sources. The levels of hBNP are elevated in congestive heart failure, perhaps related to dilation of the cardiac ventricle, where hBNP is produced. This protein interacts with three receptors, of which two mediate the actions of nesiritide, and the third is a clearance receptor. The clearance of hBNP (and nesiritide) is accomplished via two mechanisms: interaction with the clearance receptor (type C) which is internalized and degraded, and destruction of hBNP by neutral endopeptidases present in the vascular endothelium.

In animals BNP decreases blood pressure and peripheral vascular resistance through two potential mechanism: vasorelaxation and changes in vascular permeability. *Ex vivo*, binding of nesiritide with one of the functional receptors (type A) results in an increase in intracellular cGMP levels, resulting in the activation of a series of cGMP-dependent protein kinases and, ultimately, relaxation of smooth muscle. It isn't known if this effect is more prominent on the arterial or venous vessels, although the receptors for BNP exist in both locations. There is also evidence from animal studies suggesting that these ANP alters the vascular permeability, leading to a shift of fluids from the intravascular to extravascular space.

Natrecor (nesiritide) was initially submitted 4.24.98 and was the subject of an Advisory Committee held 1.29.99. On 4.27.98, the FDA sent a non-approvable letter for NDA 20-920, conveying the following specific concerns:

- 1) The need for additional safety data 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) Broader range of CHF patients, including those with active ischemia, preserved systolic function, and those receiving other IV vasoactive agents.
- 3) The need for an active-control study comparing Natrecor to an IV vasodilator such as nitroglycerin to provide clearer characterization of Natrecor's efficacy and safety profile, especially as it relates to effects on blood pressure and hypotension.
- 4) Questions pertaining to symptom evaluations including 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.
- 6) A trial to support the recommendations for the dosing regimen and dose adjustment.
- 7) Unrestricted use of diuretics and other cardiac therapies.

In response to this letter, the sponsor designed the VMAC trial (Vasodilation in the Management of Acute Congestive Heart Failure), whose results will be summarized below along with the salient features of earlier trials.

2.0 CHEMISTRY

Nesiritide is a 32- amino acid peptide synthesized. In early phase trials, it was synthesized using peptide synthesis columns. The later, pivotal trials, including the most recent trials, used the preparation to be marketed, which was produced using a recombinant technology. The product was identified as to its molecular composition by the following methods: amino-acid sequencing, mass spectroscopy, optical rotation and co-elution of recombinant with reference standards. In addition, a biological assay measuring the production of cGMP by CHOCA5A1S cells is used to assess product activity. During the first submission of the NDA, the chemists concluded that the chemistry, manufacturing and controls (CMC) were satisfactory for approval, and no changes in manufacturing or controls have occurred since that review.

2.0 CHEMISTRY (cont)

In the most recent review by Dr. Advani, the sponsor was asked to tighten the specification limits for related substances in the drug product. This request was incorporated into the final agreed specification for drug product. In the most recent submission, the sponsor also proposed moving to a _____ assay to assess activity (rather than the _____ assay in currently in use); a proposal that was not acceptable to the Review Chemist from HFD-510, who argued that the _____ assay will yield less information than the currently approved _____ assay (see memo from Dr. Komanduri Pardha, dated 4.10.01). This is not an approvability issue.

The final product, Natrecor, is formulated as the citrate salt of hBNP for reconstitution. The quantitative composition of the lyophilized drug per vial is: nesiritide 1.58 mg, mannitol 20.00 mg, citric acid monohydrate 2.10 mg, and sodium citrate dihydrate 2.94 mg.

The microbiology reviewer (Dr. Bryan Riley) recommended approval of the application 'on the basis of product quality microbiology.'

3.0 PRE-CLINICAL PHARMACOLOGY

The pharmacology of nesiritide (hBNP) was extensively evaluated during the initial NDA submission by Dr. Tom Papoian and in the most recent submission by Dr. Belay Tesfamariam.

In the biological systems measured, nesiritide increases cGMP levels. This effect was seen in endothelial and smooth muscle cells as well as conscious rabbits and dogs. The time course for the decay of plasma cGMP levels after stopping drug was estimated at 20.6 ± 5.9 minutes in rabbits given hBNP SQ or IV (see Dr. Papoian's review, page 8). In similar experiments, the pharmacokinetics of hBNP were fit to a two-compartment model, with results as summarized below.

Table 3.0.1 Pharmacokinetics of hBNP^a.

PK Parameter	Rabbit	Canine	Human
T _{1/2} alpha (min)	5.5±0.9	6.9±1.6	1.6±0.6
T _{1/2} beta	27.4±9.7	33.2±6.7	20.7±1.3
CL (L/Hr/kg)	1.54±0.2	1.38±0.007	0.327±0.049

a. Data from review by Tom Papoian, Ph.D., dated 12.9.98, table 3, page 28.

Smooth Muscle Relaxation and Cardiac Effects

The administration of nesiritide causes relaxation of pre-contracted muscle strips, with statistically-significant effects seen in arterial muscle at ≥ 0.03 nM and venous at ≥ 1.0 nM. From these data, the expected effective serum concentration was 1.0 nM (see Dr. Papoian's review, page 11). The EC₅₀ for relaxation was 19 ± 7 nM for human arterial smooth muscle exposed to hBNP.

The administration of hBNP via continuous infusion to rabbits caused a dose-dependent reduction in mean arterial pressure, with a maximal effect on blood pressure after 105 minutes. Following discontinuation of hBNP, mean arterial pressure in these animals rose within 10-15 minutes of discontinuation, but did not return to baseline within the 60 minutes of follow-up (Dr. Papoian's review, Figure 11, page 22).

The administration of hBNP infusion to dogs had no effect on any ECG parameter, including the R-R interval. Nesiritide also had no inotropic effect in either normal rabbits or in explanted human heart tissue from cardiac transplant patients, despite a positive effect seen with dobutamine and isoproterenol (Dr. Papoian review, figure 20, page 35).

A closely-related peptide, atrial natriuretic peptide (ANP), has been shown to induce a translocation of proteins and fluid from the intravascular space to the interstitium in both humans and in animals. This effect (an increase in 'conductance'), which is thought to occur as the result of changes in endothelial permeability to proteins and salts, leads to redistribution of volume away from the intravascular space, and is thought to be one mechanism whereby ANP improves hemodynamics in CHF (refs. 1-3).

Renal Effects

Administration of hBNP to normal rabbits by IV bolus ($3 \mu\text{g}/\text{kg}$) increased urine output and urinary sodium excretion (Dr. Papoian's review, Figure 9, page 18).

Tolerance

The Pharmacology review performed as part of the second submission focused on the issue of tolerance to the effects of nesiritide. The sponsor performed a study infusing nesiritide for 72 hours to anesthetized rabbits with continuous BP monitoring. Infusion of 0.1 µg/kg/min resulted in a sustained increase in plasma BNP levels as well as cGMP levels (3.5-fold over baseline). In rabbits infused with nesiritide for 72 hours and then made acutely hypertensive with norepinephrine, nesiritide retained the ability to lower blood pressure acutely. The pharmacologist (Dr. Belay Tesfamariam) concluded that this experiment was insufficient to exclude the development of partial tolerance to nesiritide after continuous infusion. This was not the view of the supervisory pharmacologist (Dr. Al DeFelicce) who concluded that there was no evidence for the development of tolerance in this model.

4.0 PRE-CLINICAL TOXICOLOGY

Acute and chronic toxicology studies for nesiritide were reviewed as part of the original NDA submission by Dr. Tom Papoian. He concluded that the toxicities observed could be accounted for by the known pharmacology of the compound. As nesiritide is a peptide, antibody formation in rabbits exposed to human nesiritide peptide was tested. No antibody formation was detected, suggesting the protein is not immunogenic in rabbits, and that antibodies in humans are unlikely to develop. With regard to the development of tolerance, he found evidence that the receptors for BNP down-regulated in cell cultures exposed to long-term BNP, but that no clear evidence for or against tolerance was available.

No carcinogenicity or reproductive toxicology studies were conducted with nesiritide. A single assay for mutagenicity was conducted. In an Ames test, no increase in the number of positive revertants was seen in any of the bacterial strains tested in the presence or absence of metabolic activation. Using a pre-exposure method, 'minimally positive' results were seen (1.9-fold increase in revertants) in the *S. typhimurium* tester strain TA98, later felt to be related to the test vehicle.

5.0 CLINICAL PHARMACOKINETICS/ PHARMACODYNAMICS (PK/PD)

Again, the most extensive review of the PK/PD properties of nesiritide was conducted during the initial NDA submission (Nakissa Sadrieh, Ph.D., dated 4.24.98). Regarding the half-life of nesiritide, she concluded that the elimination of a bolus follows a 2-compartment model, with the initial (alpha) phase accounting for 30% of the AUC. The $T_{1/2}$ -alpha is 1.4 minutes and $T_{1/2}$ -beta is 20.2 minutes (Dr. Sadrieh's review, page 20).

Population pharmacokinetics was performed to assess the effects of demographics on PD parameters. Dr. Sadrieh reported that there was no correlation between the clearance of nesiritide and the following variables: age, gender, race/ ethnicity, baseline pulmonary capillary wedge pressure (PCWP) and cardiac index (CI), NYHA class at entry, body weight, serum creatinine or estimated creatinine clearance (see Dr. Sadrieh's report, page 57). Similarly, in modeling done by the sponsor and by the FDA, there was a correlation between steady-state serum concentrations of nesiritide and changes in PCWP, CI and systemic vascular resistance (SVR). The mean C_{50} for PCWP and SVR was 2.4 ng/ml, which was estimated to occur at a dose of 0.02 µg/kg/min IV. The estimated E_{max} from this model was -16 mm Hg for PCWP.

No additional information related to clinical PK/PD was submitted in the recent NDA submission. The recommendations of the Clinical Pharmacology/ Biopharmaceutic reviewer (Angelica Dorantes, Ph.D.) have been incorporated into the labeling recommendations.

6.0 DRUG INTERACTIONS

The concomitant use of enalapril did not affect the clearance of nesiritide. Concomitant use of nesiritide with other intravenous vasodilators (nitroglycerin, nitroprusside, milrinone) have not been studied formally and such patients have not been included in substantial numbers in the available trials.

7.0 OVERVIEW OF CLINICAL STUDIES

Original NDA Submission

In the original NDA there were 9 clinical studies, including 8 trials in CHF, and one in the treatment of post-op hypertension. Two of the trials were pivotal in support of the efficacy of nesiritide: 704.325 and 704.326.

Table 7.0.1 CHF Trials in Original NDA^a.

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

a. Data from original NDA 20-920 submission, volume 1.78

b. Cross-over designed trial.

Table 7.0.2 Non-CHF Trials in Original NDA^a.

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

NDA Resubmission

The second submission of NDA 20-920 contained two trials, of which one is considered pivotal for the approvability decision (704.339, the VMAC trial). This trial, as discussed below, compared the effects of a lowered nesiritide dose (0.010 µg/kg/min) to that of placebo and NTG in patients with decompensated congestive heart failure, collecting hemodynamic and symptom benefit data as well as expanded safety in an effort to address the concerns detailed in the non-approvable letter. A second trial (704.329, PRECEDENT) was ongoing at the time of the original NDA submission, and was included in the resubmission. It.

Table 7.0.3 Trials in NDA Resubmission^a.

	Placebo	Control	Nesiritide	Nesiritide	Trial Design
704.339, VMAC	145	145 (NTG)	208	--	Double-blind, randomized trial in patients with dyspnea at rest and decompensated CHF. Primary endpoint was PCWP and symptom improvement at 3 hours. See below for details.
704.329, PRECEDENT		83 (Dobutamine)	84	79	Open-label, randomized trial of patients with ≥ Class III CHF. comparing the effects of higher doses of nesiritide (0.015 and 0.030 µg/kg/min) to dobutamine on the rates of cardiac ectopy and heart rate. Primary analyses were holter-base: heart rate and cardiac ectopy.

a. Data from Dr. Karkowsky's review.

b. Patients were randomized to one of two nesiritide group 0.015 and 0.030µg/kg/min.

Pivotal Studies

For the present approval decision, the VAMC trial is of primary importance, as it was specifically designed to address the deficiencies noted in the initial submission. What follows is a summary of three long-infusion studies in the first submission (704.311, 704.325, and 704.326) and 704.339 (the VMAC), followed by a discussion of the efficacy and safety data, derived largely from these four trials. The reader is referred to Dr. Karkowsky's review of VMAC and my earlier review of the first NDA submission for the details of the clinical trials.

Study 704.311

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

Study 704.325

This was a randomized, double-blinded, placebo-controlled, multicenter study designed to enroll approximately 120 subjects with symptomatic, decompensated CHF for whom inpatient parenteral therapy was deemed appropriate. After a Swan-Ganz catheter was inserted and baseline hemodynamic measurements were obtained, subjects with PCWP ≥ 18 mm Hg, CI ≤ 2.7 L/min/m² and SBP ≥ 90 mm Hg were randomized to receive either placebo or one of two doses (0.015 or 0.03 $\mu\text{g}/\text{kg}/\text{min}$) of nesiritide (delivered as a loading bolus plus fixed-dose infusion). Cardiac hemodynamics and clinical status were followed for an initial 6-hour blinded evaluation period, during which diuretics and additional parenteral interventions and oral medications for decompensated CHF were to be withheld unless urgently required for worsening CHF not responding to study drug infusion. The primary study efficacy endpoint was the percentage change from baseline in PCWP at 6 hours.

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

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

Study 704.326

This was a multicenter, randomized, open-label, active-controlled study designed to enroll approximately 300 subjects with symptomatic, decompensated CHF for whom inpatient parenteral vasoactive therapy (other than or in addition to parenteral diuretics) was deemed appropriate. Eligible patients were randomized to one of three treatment groups: nesiritide, 0.3 $\mu\text{g}/\text{kg}$ bolus followed by a 0.015 $\mu\text{g}/\text{kg}/\text{min}$ infusion, bolus of 0.6 $\mu\text{g}/\text{kg}$ followed by a 0.03 $\mu\text{g}/\text{kg}/\text{min}$ infusion; or standard care. Nesiritide was administered intravenously as a fixed-dose infusion. The standard care agent was to be a single parenteral vasoactive agent routinely used for the short-term management of decompensated CHF, such as intravenous nitroprusside, nitroglycerin, dobutamine, or milrinone. The choice of standard care agent and its dose was left to the discretion of the investigator. Treatment assignment was open-label with regard to the standard care agent versus nesiritide.

Study 704.326(cont)

The dose of nesiritide subjects, for those patients, was double-blinded. The purpose of the study was to gain additional safety data and clinical experience on the use of nesiritide for the short-term management of decompensated CHF in a setting which reflected the routine treatment of such patients (i.e., with few restrictions on patient management).

Each subject received diuretics as clinically indicated. An arterial line or Swan-Ganz catheter was placed in a subject if it was deemed clinically necessary by the attending physician, although it was not a requirement of the study protocol (and occurred infrequently). The duration of therapy with the initial study drug (nesiritide or standard care agent) varied according to each patient's cardiopulmonary status, as determined by the attending physician. At the discretion of the investigator, a second parenteral vasoactive agent was administered in addition to, or as a substitute for, the initial study drug at any time. The attending physician determined when parenteral vasoactive therapy was discontinued and how the transition from parenteral therapy for CHF to oral therapy was undertaken.

Clinical status (including symptoms and signs of CHF) was assessed at baseline, at 6 and 24 hours and at the end of parenteral therapy. Adverse events were followed through day 14. Blood samples for assessment of serum anti-BNP antibodies were obtained at baseline and at day 21 (for subjects receiving nesiritide). Also at day 21, each subject's clinical course was reviewed with regard to mortality status, duration of initial hospitalization, the need for re-admission, and the need for dialysis and intubation during the 21-day study period.

The VMAC Trial

This was a multi-center, randomized, double-blind trial comparing NTG, placebo, and nesiritide in the treatment of patients requiring hospitalization and IV therapy for decompensated CHF. Important inclusion criteria included dyspnea at rest. Regarding exclusion criteria, patients with acute cardiac ischemia, preserved systolic function, or renal impairment were not excluded. Regarding concomitant therapies:

The following drugs were restricted through the first 3 hours:

1. Continuous infusion of IV diuretics (oral and IV boluses were permitted).
2. Nitroprusside.
3. Unblinded IV NTG.
4. IV ACE inhibitors.
5. Milrinone.
6. Newly-administered dopamine or dobutamine.

The following medications were restricted through the duration of the study drug infusion:

1. Nitroprusside.
2. Unblinded NTG.
3. Milrinone.
4. IV ACE inhibitors.

A total of 480 patient were randomized, stratified according to their use of Swan-Ganz catheterization to receive either placebo, NTG (titrated to effect) or nesiritide (2µg/kg bolus followed by an infusion of 0.01µg/kg/min) to form the following treatment groups as shown schematically below:

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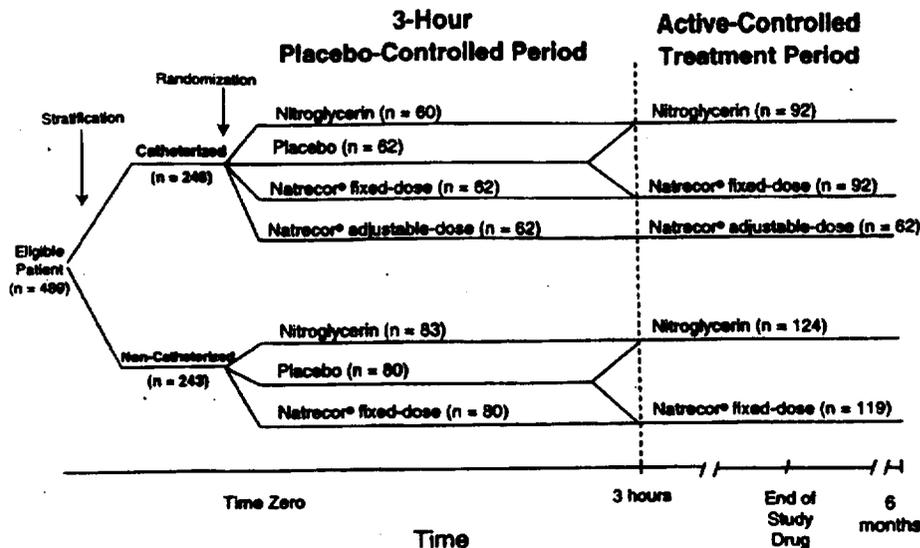


Figure 3-1
Overview of VMAC Trial Design

The two groups were as follows:

240 catheterized patients

1. Group 1 (n=30): Placebo for 3 hours (D5W) followed by IV NTG.
2. Group 2 (n=30): Placebo for 3 hours followed by nesiritide fixed-dose.
3. Group 3 (n=60): IV NTG.
4. Group 5 (n=60): Nesiritide fixed-dose.
5. Group 6 (n=60): Nesiritide adjustable-dose.

240 non-catheterized patients

1. Group 1 (n=30): Placebo for 3 hours (D5W) followed by IV NTG.
2. Group 2 (n=30): Placebo for 3 hours followed by nesiritide fixed-dose.
3. Group 3 (n=60): IV NTG.
4. Group 4 (n=60): Nesiritide fixed-dose.

At the end of 3 hours, after the collection of the primary endpoint data, patients in the placebo group were re-randomized to either nesiritide or NTG for the remainder of the treatment period (≥ 24 hours at the discretion of the investigator). Patients who had cardiac catheterization and were randomized to nesiritide were eligible for dose-escalation. This could only be done at 3-hour intervals and required a SBP ≥ 100 mm Hg and a PCWP ≥ 20 . Under that circumstance, the dose of nesiritide was increased by administering a $1\mu\text{g}/\text{kg}$ bolus followed by an increase in the infusion of $0.005\mu\text{g}/\text{kg}/\text{min}$.

The primary endpoints of VMAC were the change from baseline to 3 hours in:

1. PCWP (catheterized patients only).
2. Dyspnea evaluation (all patients).

The secondary endpoints were to compare the hemodynamic and clinical effects of nesiritide with IV NTG:

1. Effect on PCWP and dyspnea 1 hour after start of study drug infusion.
2. Onset of effect of nesiritide on PCWP.
3. Effect on PCWP at 24 hours.
4. Overall safety profile.

'Other measurements of interest' collected through at least 24 hours included the following:

1. Comparative effects of treatment groups on PCWP, CO, CI, heart rate, BP, RAP.
2. Average hourly NTG dose, compared between catheterized and non-catheterized patients.
3. Clinical change from baseline for global clinical evaluation for the treatment groups.

Safety information included the need for re-hospitalization, the collection of adverse events and serious adverse events through 30 days, and mortality through 6 months.

The demographics of the population enrolled in VMAC are summarized below.

Table 7.0.4 Demographics at baseline in VMAC^a.

Demographic	Catheterized			Non-Catheterized		
	PBO (n=62)	NTG (n=60)	Natrecor (n=124)	PBO (n=80)	NTG (n=83)	Natrecor (n=80)
Age, years (mean + SD)	59 + 16	59 + 15	63 + 12	65 + 15	62 + 14	62 + 13
Ethnicity						
Black	14 (23%)	17 (28%)	30 (24%)	20 (25%)	18 (22%)	20 (25%)
Caucasian	39 (63%)	34 (57%)	76 (61%)	44 (55%)	51 (61%)	42 (53%)
Other	9 (14%)	9 (15%)	18 (15%)	16 (20%)	14 (17%)	18 (22%)
Gender Male	47 (76%)	43 (72%)	95 (77%)	56 (70%)	43 (52%)	53 (66%)
Weight Kg mean + SD	86 + 23	85 + 22	81 + 19	83 + 24	82 + 23	85 + 22
Etiology of Cardiomyopathy						
Ischemic	34 (59%)	27 (48%)	73 (63%)	44 (59%)	34 (42%)	29 (39%)
Idiopathic, dilated	14 (24%)	15 (27%)	24 (21%)	15 (20%)	24 (32%)	21 (28%)
Hypertensive	3 (5%)	7 (13%)	5 (4%)	9 (12%)	8 (11%)	13 (17%)
Hx Coronary Artery Disease	39 (63%)	38 (63%)	91 (73%)	56 (70%)	52 (63%)	43 (54%)
AICD present	18 (29%)	14 (23%)	42 (34%)	18 (23%)	17 (20%)	13 (16%)
Hx of Cardiac Revascularization	25 (40%)	18 (30%)	58 (47%)	34 (43%)	24 (29%)	23 (29%)
Hx Previous MI	28 (45%)	28 (47%)	67 (54%)	42 (53%)	31 (37%)	29 (36%)
MI within last 7 days						
Q-wave	2 (3%)	0	1 (1%)	2 (3%)	1 (1%)	2 (3%)
Non-Q-wave	1 (2%)	5 (8%)	3 (2%)	4 (5%)	4 (5%)	1 (1%)
Acute Coronary Syndrome						
< 7 days	4 (6%)	6 (10%)	10 (8%)	17 (21%)	14 (17%)	10 (13%)
<24 hours	1 (2%)	1 (2%)	5 (4%)	8 (10%)	8 (10%)	5 (6%)

a. From Dr. Karkowsky's review, table 7.

The PRECEDENT Trial

This trial, which is in no way a pivotal efficacy trial, is mentioned here as it relates to the proposed labeling. The trial randomized 255 patients with decompensated CHF requiring hospitalization to either dobutamine or nesiritide at the higher doses used in the early trials of nesiritide (0.015 or 0.030 µg/kg/min infusion without bolus). The primary analysis was change in heart rate and the incidence of cardiac ectopy as detected on Holter monitoring. This trial was not conducted in response to any deficiencies noted in the non-approvable letter and it does not support the safe and effective use of the lower dose of nesiritide used in VMAC. Dr. Karkowsky concluded in his review that nesiritide had less ectopy in the trial than dobutamine, but that the two treatments were not differentiated on the basis of their effects on the symptoms of CHF. He also concluded that there was substantial hypotension and more renal injury in both dose groups of nesiritide compared with dobutamine (pages 94-95 of his review).

8.0 EFFICACY OF NESIRITIDE IN ACUTELY DECOMPENSATED CHF

8.1 Effects of Nesiritide on PCWP

The hemodynamic effects of nesiritide were characterized in the original submission as well as in the VMAC trial. In the original submission, two trials (704.311 and 704.325) measured central hemodynamics in patients with acutely decompensated CHF for up to 24 hours. The effects of nesiritide on systemic blood pressure will be considered in the safety assessment.

Trial 704.311: PCWP at 3 and 24 Hours

Compared with placebo, nesiritide had a significant, dose-dependent effect to lower PCWP, regardless of the population studied. Note that the doses studied in this trial are higher than the dose currently proposed for use.

Table 8.1.1 Changes in PCWP (baseline to 3 hours) in 704.311^a.

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

a. Data from initial NDA submission, volume 54, Appendix 1, Table 17A, 17B.

b. p Value per sponsor.

c. Comparison using T-test for ITT population.

For the patients in the trial with available data, an effect of nesiritide on PCWP persisted through 24 hours.

Table 8.1.2 Changes in PCWP (0- 24 hours) in 704.311^a.

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

a. Data from initial NDA volume 54, Appendix 1, Table 19A, 19B for the 'Evaluable at 24 hours' population.

b. p Value per sponsor.

c. Comparison using T-test.

Trial 704.325: PCWP at 6 hours

In trial 704.325, patient with decompensated CHF were randomized to either placebo or nesiritide (one of two doses). After six hours, nesiritide had a significant effect on the pre-specified primary endpoint relative to placebo (% change from baseline at 6 hours, shaded in the table below), and on the absolute change in PCWP (in mmHg).

Table 8.1.3 Primary Endpoint Analysis for Study 704.325^a.

Median changes from Baseline in PCWP at 6 hours for 'Worst outcome' population	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.0305 n=42	p Value ^b
PCWP at baseline and 6 hours (mm Hg)				
At baseline (mm Hg)	28	27	28	0.76
At 6 hours (mm Hg)	30	23	18.5	<0.001
Median % Change from Baseline (%)	7.3	-20.0	-32.6	<0.001
p Value (change from baseline) ^c	0.010	0.227	<0.001	
p Value (compared with control baseline) ^d	--	0.001	<0.001	
Median Change from Baseline (mm Hg)	1.5	-4.0	-9.5	<0.001
p Value (change from baseline) ^c	0.011	0.222	<0.001	
p Value (compared with control baseline) ^d	---	0.002	<0.001	

a. Data from NDA volume 59, Appendix 1, Table 22A, 22B, and 22C.

b. p Value for primary endpoint by non-parametric ranked analysis (Kruskal-Wallis).

c. p Value compares the 6 hour value for each group individually with the control baseline using 2-Sample Wilcoxon.

d. p Value compares the 6 hour value for each group vs. Baseline using 1-sample Wilcoxon.

Trial 704.339 (VMAC): PCWP at 3 Hours

Measurement of the PCWP at the end of 3 hours was one of the pre-specified primary endpoints of the trial. As shown in the table below, both nesiritide and NTG reduced the mean change from baseline for the PCWP relative to placebo. These data are important as they link the proposed dose of nesiritide to the earlier trials that also looked at changes in PCWP with higher doses of nesiritide.

Table 8.1.4 Change in PCWP at 3 Hours in VMAC^a.

PCWP Measurement (mean±SD)	Placebo N=	NTG N=60	Pooled Nesiritide N=124
Baseline	27.5±5.5	28.0±5.7	27.7±7.0
3-Hour	25.7±6.6	24.2±6.2	21.9±7.4
Mean Change	-2.0±4.2	-3.8±5.3	-5.8±6.5
p-Value vs. Placebo	--	0.087	<0.001
p-Value nesiritide vs. NTG	--	--	0.027

a. Data from Avi Karkowsky's review, table 14.

In data not shown, change in PCWP at earlier timepoints were consistent with these data. The earliest measurement (15 minutes) showed a clear separation of nesiritide from placebo in this regard. For timepoints beyond 3 hours, the effect of both nesiritide and NTG on PCWP appears to persist. At 24 hours, the numbers of patients with available data in the three treatment groups are 84, 86, and 57 respectively.

Table 8.1.5 Change in PCWP Through 24 Hours in VMAC^a.

PCWP Measurement (mean±SD) ^b	NTG N=92 ^c	Nesiritide Fixed Dose N=92	Nesiritide Adjustable Dose N=62
6 Hours	-4.4±0.7	-6.0±0.7	-6.9±0.9
9 Hours	-5.4±0.8	-6.9±0.7	-8.1±0.9
12 Hours	-5.9±0.7	-6.6±0.5	-9.2±0.9
24 Hours	-5.9±0.7	-6.6±0.5	-9.2±0.9

a. Data from Avi Karkowsky's review, table 27.

b. Shown as mean change from baseline ±sd.

c. After 3 hours all placebo patients were re-randomized to get either NTG or nesiritide.

8.2 Effects of Nesiritide on Other Hemodynamic Measurements

The effects of nesiritide on these hemodynamic measures mirrored the effects on PCWP. They were measured in trial 704.311, whose results are summarized in the first table below, 704.325 (summarized in my original review), and VMAC.

Trial 704.311: Hemodynamics at 3 and 24 Hours

Table 8.2.1 Effect of 3 hour Infusion of Nesiritide on Hemodynamic in 704.311^a.

Hemodynamic Parameter (Mean Change from Baseline)	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
MRAP (mm Hg)	-0.8±3.7	-3.73.5	-3.3±4.3	-4.5±6.2	0.024
SVR (Dyne-sec/cm ²) %	-16.4±397	-364±863	-203±493	-500±426	0.017
Cardiac Index (L/min/M ²)	+1.1±20	+28.8±50	+18.2±32	+36.6±38	0.004
Pulmonary Vascular Resistance (Dyne-sec/cm ²)	+54±96	-55±251	-21±186	-47±158	0.110
Systolic BP (mm Hg)	+1.2±9	-7.4±12	-4.3±14	-10.0±14	0.011
Heart Rate (BPM)	+2.6±7.6	-3.7±6.7	-2.2±8.8	+6.2±13.8	0.002

a. Data from original NDA 20-920, vol. 54, Table 20B through 30B. Data are expressed as absolute change from baseline for ITT population.

b. p Value comparing arithmetic means from baseline using ANOVA linear contrast except for heart rate, which used Omnibus F test.

The next table summarizes the same effects on selected hemodynamic measurements at the end of 24 hours. The magnitude of the decrease in mean systolic BP persists through 24 hours, although the magnitude of the effect on mean SVR, PVR, and CI were decreased at 24 hours.

Table 8.2.2 Effect of 24 hour Infusion of Nesiritide on Hemodynamic in 704.311^a.

Hemodynamic Parameters (Mean Change from Baseline)✓	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
MRAP (mm Hg)	-1.4±5	-2.6±4	-3.6±6	-2.9±4	0.493
SVR (Dyne-sec/cm ²) %	-17.6±675	-283±680	-67±776	-354±300	0.266
Cardiac Index (L/min/M ²)	+4.6±18	+16.0±32	+9.7±54	+25.4±21	0.237
Pulmonary Vascular Resistance (Dyne-sec/cm ²)	+3.3±113	-68.3±233	-32.8±182	-31.8±129	0.576
Systolic BP (mm Hg)	+2.1±12	-6.1±12	-3.3±13	-9.0±12	0.021
Heart Rate (BPM)	+4.5±11	-1.0±6.8	-0.2±7.6	+4.0±8.2	0.083

a. Data from original NDA 20-920, vol. 54, Tables 20B through 31B, Data expressed as change from baseline for ITT population.

b. p Value comparing arithmetic means from baseline using ANOVA linear contrast except for heart rate, which used Omnibus F test.

Trial 704.339 (VMAC): Hemodynamics (non-PCWP) at 3 Hours

The table below summarizes some of the salient other hemodynamic effects at 3 hours for VMAC. While many of these parameters improved relative to placebo after 1 hour (data not shown), the effects on these endpoints tended to wane by 3 hours. The effects of nesiritide and NTG were comparable on these endpoints.

Table 8.2.3 Change from Baseline for Selected Hemodynamic Parameters at 3 Hours in VMAC^a.

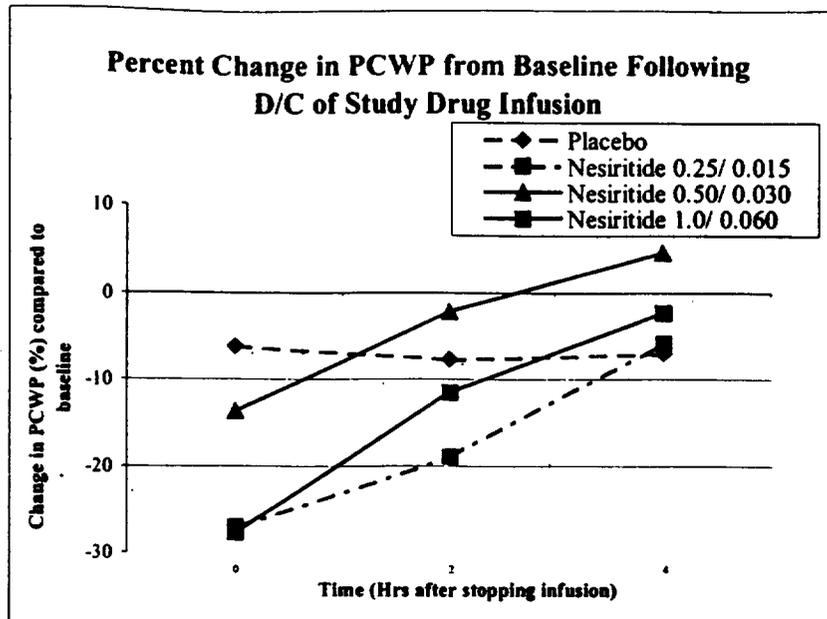
Hemodynamic Parameters (Mean Change from Baseline)	Placebo n=62	NTG N=60	Nesiritide n=124	p Value ^b
MRAP (mm Hg)	0.0±0.6	-2.6±0.6	-3.1±0.4	<0.001
SVR (Dyne-sec/cm ²) %	-44±62	-105±62	-144±43	0.186
Cardiac Index (L/min/M ²)	0.0±0.7	0.2±0.07	0.1±0.05	0.09
Pulmonary Vascular Resistance (Dyne-sec/cm ²)	+21±16	-19±16	-21±21	0.037

a. Data from Dr. Karkowsky's review, page 27.

b. p Value comparing nesiritide with placebo.

Hemodynamic Changes after Discontinuation of Nesiritide

Changes in PCWP following nesiritide discontinuation was examined systematically in only one trial using a long-term infusion strategy: 704.311. The figure below, from my original review, shows the changes in mean PCWP following drug discontinuation. For all study populations in study 704.311, the PCWP had returned to within 10% of the placebo levels in all nesiritide groups by 4 hours, and were intermediate between the last measurement on study drug and the 4-hour post-infusion value. The figure below shows the last recorded value on study drug for the ITT population (shown as time 0), as well as the 2- and 4-hrs post-infusion values (see original NDA submission volume 1.54, table 17C for data). No 'rebound' increases in PCWP to greater than baseline were observed.



8.3 Renal Effects of Nesiritide: Diuresis and Natriuresis

One proposed effect of nesiritide is to promote a natriuresis and diuresis, both through direct action and through the inhibition of aldosterone production. In animals and in normal volunteers, nesiritide has been shown to cause both natriuresis and diuresis in the pre-clinical part of the NDA (see Dr. Papoian's review for details). Of note, patients with cirrhosis and ascites, who have elevated baseline hBNP levels, have a blunted diuretic response to nesiritide (ref. 4). In the clinical database, the pivotal trials in the original submission as well as the VMAC trial measured some aspects of Na⁺ and water excretion as part of their programs. Overall, Natrecor had a small, inconsistent effect on Na⁺ and water excretion.

Changes in Na⁺ and Water Balance in Trial 704.311

The first table below summarizes the effect of nesiritide on fluid intake and urine output in the ITT population, where no significant effect of nesiritide was detected. Instead, there was a trend towards decreased urine volume in the subjects who received nesiritide, which achieved nominal statistical significance for the nesiritide 0.50/0.030 group. Overall, the mean and median fluid balance was positive in all of the nesiritide groups (more fluid in than out). This was a result of less urine output, and not due to differences in the amount of fluids administered to the patients. The difference between the placebo and the high-dose nesiritide groups amounted to approximately 1 liter over a 24 hour period (with more out in the placebo group). Importantly, in this trial there was no significant difference in the study groups with regard to diuretic use, although more subjects in the placebo group received diuretics during study drug administration.

Table 8.3.1 Fluid Intake and Urinary Volume During First 24 Hours in Study 704.311^a.

Measurement (Mean±sd)	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
Fluid Intake (ml/ 24 hrs) p Value compared with placebo ^c	1935±515 --	1836±427 NS	1767±545 NS	2147±1062 NS	0.222
Total Urine Output (ml/ 24 hrs) p Value compared with placebo ^c	2410±1086 --	1745±840 NS	1479±806 <0.05	2011±1845 NS	0.041
Output - Intake (ml/24 hrs) Median p Value compared with placebo ^c	475±1094 547 --	-91±756 -162 NS	-287±848 -434 NS	-136±1872 -407 NS	0.113 0.059

a. Data from original NDA submission volume 54, Appendix 1, Table 34.

b. See statistical section for statistical methods. p Value per sponsor by ANOVA Omnibus F test.

c. Comparison using Dunnet's t-test.

The next table summarizes the excretion of sodium and potassium during the first 24 hours of 704.311. All nesiritide groups had a non-significantly lower mean sodium excretion relative to placebo.

Table 8.3.2 Changes in Na⁺ Excretion During First 24 Hours in Study 704.311^a.

	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
Urine Sodium Excretion (meq/24 hrs)					
Mean±sd	156±91	85±58	104±80	146±285	0.369
Median	146	77	86	46	0.943
p Value compared with placebo ^c	--	NS	NS	NS	

a. Data from original NDA medical review, table 7.0.1e.1.2.

b. See statistical section for statistical methods. p Value per sponsor by ANOVA Omnibus F test.

c. Comparison using Dunnet's t-test.

Changes in Na⁺ and Water Balance in Trial 704.325

In this trial, the sponsor evaluated body volume status in several ways. First, fluid intake and urine output was measured for the periods 0-6 hours and 0-24 hours after start of study drug.

For the period between 0 and 6 hours, subjects who received nesiritide had significantly more out than in, when compared with the placebo subjects. Over a 24 hour period, the difference between the placebo and nesiritide 0.030 group, if sustained, would translate into an increased fluid out of approximately 240 mls.

For the 0 to 24 hour period, however, control subjects had significantly more out, when compared with nesiritide-treated subjects. The increase in net fluid out for the control group was due to increased urine volume (rather than decreased fluid intake). The nesiritide group received fewer diuretics during this initial 24-hour period, which may account for some of this discrepancy.

Table 8.3.3 Change of Volume Status During First 24 Hours in Study 704.325^a.

Volume parameter and period of measurement	Control n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^c
0 to 6 Hour Data				
Fluid Intake (Mean ±SD)	96.5±52	97.0±43	96.4±60	0.998
Urine Output (ml/ hr)	66.8±43	91.7±60	106.2±72	0.010
Output minus Intake (ml/ hr)	-29.7±69	-2.6±70	+9.8±76	0.039
0 to 24 Hour Data				
Fluid Intake (Mean ±SD)	78.6±26	82.1±24	83.0±25	0.702
Urine Output (ml/ hr)	136.2±56	102.6±47	89.9±47	<0.001
Output minus Intake (ml/ hr)	+57.8±60	+20.7±47	+6.9±47	<0.001

a. Data from NDA volume 59, Appendix 1, Tables 57A, and electronic datasets. All subjects with available data are included (≥90% of enrolled subjects for all points).

c. p Value using Omnibus F test.

The next table summarizes the excretion of sodium during the first 24 hours of the 704.311 study. All nesiritide groups had a non-significantly lower mean sodium excretion relative to control.

Table 8.3.4 Changes in Na⁺ Excretion During First 24 Hours in Study 704.311^a.

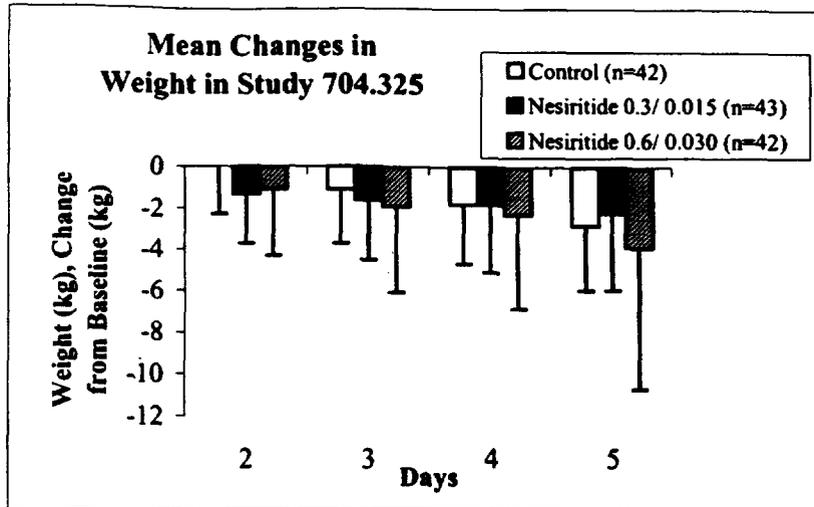
Measurement	Control n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
Urine Sodium Excretion (meq/24 hrs) Mean±sd	156±91	85±58	104±80	146±285	0.369
p Value compared with placebo ^c	--	NS	NS	NS	

a. Data from initial NDA submission, volume 54, Appendix 1, Table 35.

b. See statistical section for statistical methods. p Value per sponsor by ANOVA Omnibus F test.

c. Comparison using Dunnet's t-test.

Trial 704.325 also followed the weights of the subjects during the first 5 days of hospitalization. There was a non-significant trend towards greater weight losses, particularly in the high-dose nesiritide group during days 2 and 3. This difference tended to persist in the high-dose nesiritide group through day 5. At day 5, the control group and the high-dose nesiritide group had lost 2.8 ± 3.2 and 3.9 ± 6.8 kgs, respectively ($p = 0.479$).



Changes in Na⁺ and Water Balance in Trial 704.326

The sponsor also collected data on the changes in weight for each of the three treatment groups in the 704.326 trial, summarized below. At all time points out to 7 days, the mean change in weight from baseline was less in the high-dose nesiritide group than in the 'standard care' group. More subjects in the control group were given diuretics (97% in the control group, 82% in the nesiritide 0.015 group, and 74% in the nesiritide 0.030 group). The reasons for this difference in the amount of diuretics administered cannot be determined, given the open-label nature of the trial.

Table 8.3.5 Changes in Subject Weights in Study 704.326^a.

Vital Signs	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value ^d
Baseline weight	79.7±21	82.9±24	79.0±19	0.401
Weight Change Day 2				
Change from Baseline	-0.9±2	-1.1±3	-0.7±2	0.453
p Value (Chg from Base) ^b	0.001	0.001	0.013	
p Value (Compared to Standard Care) ^c	--	0.496	0.551	
Weight Change Day 4				
Change from Baseline	-2.1±3	-2.1±4	-0.9±4	0.262
p Value (Chg from Base) ^b	0.001	0.001	0.151	
p Value (Compared to Standard Care) ^c	--	0.959	0.148	
Weight Change Day 6				
Change from Baseline	-2.7±6	-4.5±6	-2.6±4	0.475
p Value (Chg from Base) ^b	0.073	0.004	0.021	
p Value (Compared to Standard Care) ^c	--	0.320	0.952	
Weight Change Day 8				
Change from Baseline	-3.0±6	-2.8±4	-1.2±4	0.662
p Value (Chg from Base) ^b	0.182	0.085	0.289	
p Value (Compared to Standard Care) ^c	--	0.948	0.410	

a. Data from NDA volume 66, Appendix table 23.

b. Comparison by T test.

c. Comparison by ANOVA, pairwise contrast.

d. Comparison by ANOVA, omnibus F-test.

Changes in Na⁺ and Water Balance in VMAC (704.329)

The VMAC trial followed fluid intake and output during the first 24 hours, but not Na⁺ excretion. There is no placebo in this comparison, as all patients were converted to active treatment at the end of 3 hours. As summarized below, there was no significant effect of nesiritide on fluid excretion compared with NTG. The comparable NTG and nesiritide groups used similar amounts of diuretics through 24 hours. In similar fashion, the weight lost during the first 24 hours in VMAC was similar in nesiritide and NTG groups.

Table 8.3.6 Change of Volume Status During First 24 Hours in Study 704.339 (VMAC)^a.

Change in Fluid Balance and Weight Through 24 Hours	NTG N=216	All Nesiritide N=273	Nesiritide Fixed-Dose N=211	Nesiritide Adjustable N=62
Output minus Intake (ml/ hr)	-1279±1455	-1257±1657	-1308±1613	-1082±1799
Weight Change from Baseline	-1.1±2.3	-1.4±3.0	-1.4±3.0	-1.3±3.2

a. Data from Dr. Karkowsky's review, page 40.

8.4 Effects of Nesiritide on Hormone levels

Serum Aldosterone Levels

A proposed mechanism for the diuresis and natriuresis seen in animals following nesiritide infusion is the inhibition of aldosterone production. In trial 704.325, while the median aldosterone concentration was decreased at the end of 6 hours in the nesiritide groups compared with placebo, huge patient-to-patient variability limits the interpretation of the data.

Table 8.4.1 Changes in Aldosterone Levels from 0-6 hours in Study 704.325^a.

Aldosterone (ng/dl)	Control n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^a
Baseline	12	11	11	0.976
Hour 6	11.5	4.6	6.2	0.137
Range	0.9 to 120.0	0.9 to 119.0	0.9 to 81.0	
Change from Baseline	+0.6	-2.5	-1.6	0.030
Range				

a. Data from original NDA review table 7.0.1e.1.7.

Serum Epinephrine Levels

In trial 704.325, there were no significant effects of nesiritide on serum epinephrine or norepinephrine levels detected, when compared with placebo for the 0-6 hour time point.

8.5 Effects of Nesiritide on Symptoms of CHF

The effect of nesiritide on the symptoms of CHF were assessed in two trials: 704.325 and 704.339 (VMAC).

Change in CHF Symptoms in Study 704.325

Global Assessment of Clinical Status: Baseline to 6 Hours

Using a non-parametric analysis, as per the primary endpoint analysis, subjects who received nesiritide felt significant improvement in symptoms relative to the control patients at the end of 6. The table below shows the percentage of subjects in each of the assessment categories for the three dose-groups at the end of six hours, showing the higher percentage of subjects in the nesiritide groups who felt markedly better or better, compared with placebo. Note that there is no suggestion of differential effect of the two nesiritide dose groups. Similar data was found if one used the investigator assessments.

Table 8.5.1 Subject Global Assessments at End of Six Hours, from Study 704.325^a.

6 Hour Global Assessment	Placebo N=42	Nesiritide 0.3/ 0.015 n=40	Nesiritide 0.6/ 0.030 n=39	p Value ^c
Markedly Better	0 (0%)	5 (13%)	3 (8%)	<0.001
Better	6 (14%)	19 (48%)	23 (59%)	
No Change	31 (74%)	10 (25%)	9 (23%)	
Worse	2 (5%)	2 (5%)	2 (5%)	
Markedly Worse	3 (7%)	4 (10%)	2 (5%)	

a. Data from original NDA submission, volume 59, Appendix 1, Table 45a and electronic datasets.

c. p Value using Omnibus F test.

Assessment of Individual Signs and Symptoms of CHF from 0-6 hours in Trial 704.325

The sponsor also collected changes in individual signs and symptoms of CHF at 6 hours. These results are summarized below. Nesiritide use was associated with nominally statistically significant improvements in several individual signs and symptoms at the end of 6 hours: breathing difficulty, appetite, fatigue, light-headedness, peripheral edema, and overall CHF score. The relevance of a perceived change in peripheral edema or edema by 6 hours is difficult to establish. Also important to note is the overall lack of any greater effect of the high-dose nesiritide relative to the lower dose. In particular, the Heart Failure Score mean and median was higher in the nesiritide 0.030 group relative to the nesiritide 0.015 group.

Table 8.5.2 Individual Signs and Symptoms of CHF at 6 Hrs in Study 704.325^a.

Signs and Symptoms of CHF at 6 hours (compared with baseline)	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^b
Breathing Difficulty: 6 hour results				
Improved from baseline	5 (12%)	22 (56%)	20 (50%)	<0.001
No change from baseline	27 (64%)	16 (41%)	18 (45%)	
Worse than baseline	10 (24%)	1 (3%)	2 (5%)	
Appetite				
Improved from baseline	3 (7%)	11 (28%)	2 (8%)	0.017
No change from baseline	38 (90%)	27 (69%)	35 (88%)	
Worse than baseline	1 (2%)	1 (3%)	2 (5%)	
Peripheral Circulation				
Improved from baseline	2 (5%)	7 (18%)	6 (15%)	0.271
No change from baseline	40 (95%)	31 (79%)	34 (85%)	
Worse than baseline	0 (0%)	1 (3%)	0 (0%)	
Fatigue				
Improved from baseline	2 (5%)	12 (32%)	15 (38%)	<0.001
No change from baseline	35 (83%)	25 (66%)	24 (60%)	
Worse than baseline	4 (12%)	1 (3%)	1 (3%)	
Lightheadedness				
Improved from baseline	2 (5%)	9 (24%)	4 (10%)	0.023
No change from baseline	39 (93%)	29 (76%)	34 (85%)	
Worse than baseline	1 (2%)	0 (0%)	2 (5%)	
Peripheral Edema				
Improved from baseline	3 (7%)	8 (21%)	9 (23%)	0.028
No change from baseline	36 (86%)	30 (79%)	31 (78%)	
Worse than baseline	3 (7%)	0 (0%)	0 (0%)	

a. Data from NDA volume 59, Appendix 1, Tables 51A through 53A, and electronic datasets. All subjects with available data are included (≥90% of enrolled subjects for all points).

b. p Value using Kruskal-Wallis test per the sponsor.

The sponsor also obtained a 'total' score for the above symptoms, which is shown below.

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Table 8.5.3 Summations of Signs and Symptoms of CHF after 6 hours in Study 704.325^a.

Signs and Symptoms of CHF at 6 hours (compared with baseline)	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^b
CHF Total Score: Baseline				
Mean ±SD	12.4±2.6	13.2±2.7	12.5±2.8	0.315
Median	12.0	13.3	12.0	
Range	8.0 to 20.0	8.0 to 20.0	7.0 to 18.0	
CHF Total Score: 6 hour time-point				
Mean ±SD	12.1±1.1	10.3±1.9	10.8±1.6	<0.001
Median	12.0	10.0	11.0	
Range				

a. Data from NDA volume 59, Appendix 1, Tables 47A through 53A, and electronic datasets. All subjects with available data are included (≥90% of enrolled subjects for all points).

b. p Value using Omnibus F test.

Change in Symptoms of CHF in VMAC (704.339)

In response to the potential blinding issues surrounding 704.325, the sponsor designed VMAC to minimize the possibility that the assessors and/or patients would know about the changes in PCWP at the time of the primary symptom endpoint (3 hours). They also included patients in the trial that did not receive central hemodynamic monitoring, so that no such data could be known.

Changes in Dyspnea through 3 hours

In the trial, patients were asked to rate their change in dyspnea relative to baseline (all patients were dyspneic at rest). The degree of dyspnea at rest is summarized in Dr. Karkowsky's review in table 15. Almost 90% of all treatment groups were dyspneic either 'at rest while sitting' or 'at rest while lying flat or with one pillow.' The change in dyspnea, a pre-specified primary endpoint for the trial, is summarized below.

Table 8.5.4 Changes in Dyspnea at 3 Hours in VMAC^a.

	Placebo N=142	NTG N=143	Natrecor N=204
Markedly Better	25 (18%)	14 (12%)	34 (17%)
Moderately Better	24 (17%)	50 (35%)	54 (27%)
Minimally Better	41 (29%)	37 (26%)	64 (32%)
No Change	46 (32%)	33 (23%)	45 (22%)
Minimally Worse	6 (4%)	5 (3%)	5 (2%)
Moderately Worse	0 (0%)	0 (0%)	1 (<1%)
Markedly Worse	0 (0%)	1 (1%)	0 (0%)
p-Value c/w placebo	--	0.191	0.034
p-Value c/w NTG	--	--	0.6

a. From Dr. Karkowsky's review, table 16.

The FDA performed also an analysis based on whether the patient had central monitoring. A trend towards benefit was present in both post-hoc sub-groups, which was most evident in the catheterized patients.

Table 8.5.5 Changes in Dyspnea at 3 Hours in VMAC: Catheterized Patients^a.

	Placebo N=62	NTG N=60	Natrecor N=124
Markedly Better	9 (15%)	8 (13%)	18 (15%)
Moderately Better	8 (13%)	17 (28%)	33 (27%)
Minimally Better	18 (29%)	14 (23%)	40 (33%)
No Change	23 (37%)	16 (27%)	28 (23%)
Minimally Worse	4 (6%)	4 (7%)	4 (3%)
Moderately Worse	0 (0%)	0 (0%)	0 (0%)
Markedly Worse	0 (0%)	1 (2%)	0 (0%)
p-Value c/w placebo	--	0.31	0.030
p-Value c/w NTG	--	--	0.44

a. From Dr. Hung's statistical addendum dated 4.23.01.

Table 8.5.6 Changes in Dyspnea at 3 Hours in VMAC: Non-catheterized Patients^a.

	Placebo N=80	NTG N=83	Natrecor N=80
Markedly Better	16 (20%)	9 (11%)	16 (20%)
Moderately Better	16 (20%)	33 (40%)	21 (26%)
Minimally Better	23 (29%)	23 (28%)	24 (30%)
No Change	23 (29%)	17 (20%)	17 (21%)
Minimally Worse	2 (3%)	1 (1%)	1 (1%)
Moderately Worse	0 (0%)	0 (0%)	1 (1%)
Markedly Worse	0 (0%)	0 (0%)	0 (0%)
p-Value c/w placebo	--	0.40	0.41
p-Value c/w NTG	--	--	0.96

a. From Dr. Hung's statistical addendum dated 4.23.01.

The primary endpoint was at 3 hours, but patients were asked at earlier timepoints as well. These data are summarized in Dr. Karkowsky's review. The only timepoint where substantial differences between the Natrecor and placebo groups occurred was the 3 hour timepoint.

Changes in Global Clinical Evaluation at 3 hours

The patients also assessed the change in their global clinical state at 3 hours (not a pre-specified endpoint). The results were similar to those shown above for the changes in dyspnea.

Table 8.5.7 Changes in Patient's Global Assessment at 3 Hours in VMAC^a.

	Placebo N=142	NTG N=143	Natrecor N=204
Markedly Better	21 (15%)	16 (11%)	28 (14%)
Moderately Better	26 (18%)	48 (34%)	55 (27%)
Minimally Better	45 (32%)	30 (21%)	69 (34%)
No Change	45 (32%)	41 (29%)	44 (22%)
Minimally Worse	5 (4%)	6 (4%)	7 (3%)
Moderately Worse	0 (0%)	2 (1%)	0 (0%)
Markedly Worse	0 (0%)	0 (0%)	0 (0%)
p-Value c/w placebo	--	0.3	0.07
p-Value c/w NTG	--	--	0.5

a. From Dr. Karkowsky's review, table 24.

Changes in Dyspnea at 24 hours

The VMAC trial collected data on changes in dyspnea through 24 hours. For these summary tables, the combined NTG and Natrecor groups were compared for the as randomized population.

Table 8.5.8 Changes in Dyspnea at 24 Hours in VMAC^a.

	NTG N=216	Natrecor N=273
Markedly Better	67 (31%)	100 (38%)
Moderately Better	76 (35%)	84 (32%)
Minimally Better	39 (18%)	53 (20%)
No Change	29 (13%)	28 (11%)
Minimally Worse	2 (1%)	0 (0%)
Moderately Worse	2 (1%)	1 (1%)
Markedly Worse	0 (0%)	0 (0%)
p-Value c/w NTG	--	0.13

a. From Dr. Hung's statistical addendum dated 4.26.01.

As this was a combination of the catheterized and non-catheterized patients, the FDA performed an analysis of the populations separately. A trend towards benefit was present in both post-hoc sub-groups, but in this case the trend was most evident in the non-catheterized patients.

Table 8.5.9 Changes in Dyspnea at 24 Hours in VMAC: Catheterized Patients^a.

	NTG N=216	Natrecor N=273
Markedly Better	33 (36%)	51 (34%)
Moderately Better	28 (30%)	47 (32%)
Minimally Better	18 (20%)	30 (20%)
No Change	11 (12%)	19 (12%)
Minimally Worse	2 (2%)	0 (0%)
Moderately Worse	0 (0%)	1 (1%)
Markedly Worse	0 (0%)	0 (0%)
p-Value c/w NTG	--	0.94

a. From Dr. Hung's statistical addendum dated 4.26.01.

Table 8.5.10 Changes in Dyspnea at 24 Hours in VMAC: Non-catheterized Patients^a.

	NTG N=216	Natrecor N=273
Markedly Better	34 (28%)	49 (42%)
Moderately Better	48 (39%)	37 (31%)
Minimally Better	21 (17%)	23 (19%)
No Change	18 (15%)	9 (8%)
Minimally Worse	1 (1%)	1 (1%)
Moderately Worse	2 (2%)	0 (0%)
Markedly Worse	0 (0%)	0 (0%)
p-Value c/w NTG	--	0.027

a. From Dr. Hung's statistical addendum dated 4.26.01.

8.6 Other Clinical Measures of Efficacy

Other potential indicators of clinical benefit include the duration of hospitalization, the need for re-hospitalization, and the need for other invasive procedures (e.g., intubation, dialysis). The rate of hospitalization and re-hospitalization was examined in depth in two of the trials in the original NDA submission (704.325 and 704.326) and in the VMAC trial. The need for intubations and dialysis was quite low and did not differ significantly among the treatment groups.

Duration of Hospitalization and Need for Re-Hospitalization in Trial 704.325

The duration of hospitalization prior to entry into 704.325 was similar in the treatment groups: 3.0±2.9, 4.1±4.4 and 5.3±11.4 for the subjects in the control, nesiritide 0.3/ 0.015, and 0.6/ 0.030 groups respectively (p>0.05). The number of patients discharged before day 21 was examined, as was their average duration of hospitalization, and the results summarized in the table below. Note that while 95% of the control group was discharged prior to 21 days, 19% of both nesiritide groups remained hospitalized at 21 days. There was no significant difference in the duration of hospitalization among the treatment groups.

Table 8.6.1 Hospitalization through 21 days in study 704.325^a.

Volume parameter and period of measurement	Control n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value
Total days of hospitalization^d				
Mean±SD	7.6±4.9	7.3±3.9	7.8±4.5	0.891 ^b
Median	6.5	6.0	7.0	
Subjects not discharged as of day 21	2 (5%)	8 (19%)	8 (19%)	0.085 ^c

a. Data from original NDA medical review, table 7.0.2c.1. All subjects with available data are included.

b. p Value using Kruskal-Wallis test.

c. p Value using Fisher's exact test.

d. For subjects D/C'd prior to 21 days.

If the subjects who were hospitalized for >5 days before entering the study were excluded from the analysis, the duration of hospitalization was still similar between the three treatment groups. Similarly, subjects hospitalized >5 days when entering the trial also had similar duration of hospitalization.

There was a non-significant increase in the rate of re-admission through 21 days in the nesiritide groups. The reasons for these admissions, however, were mostly other medical conditions, unrelated to CHF.

Table 8.6.2 Hospital Readmission Through 21 days in Study 704.325^a.

	Control n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value
Subjects discharged prior to day 21	40 (95%)	35 (81%)	34 (81%)	0.085 ^b
If discharged, # of subjects readmitted by day 21	1 (3%)	4 (11%)	4 (12%)	0.229 ^b
If readmitted, primary reason for first readmittance				
CHF recurrence	0 (0%)	1 (25%)	1 (25%)	
Elective, unrelated to CHF	0 (0%)	0 (0%)	0 (0%)	
Medical condition other than CHF	1 (100%)	2 (40%)	1 (25%)	
Other	0 (0%)	2 (40%)	2 (50%)	

a. Data from NDA original medical review, table 7.0.2c.2. Includes all subjects who were discharged before day 21.

b. p Value using Fisher's Exact test.

Duration of Hospitalization and Need for Re-Hospitalization in Trial 704.326

The duration of hospitalization prior to entry into study 704.326 was 1.5±2.4, 1.5±3.5, and 1.7±2.9 for the subjects in the control, nesiritide 0.3/ 0.015, and 0.6/ 0.030 groups respectively (p>0.05). Note that these durations were shorter than for the 704.325 trial. The number of patients discharged before day 21 was also examined, as was their average duration of hospitalization. The results are summarized in the table below. A small percentage of all three groups remained in the hospital at the end of 21 days. There was no significant difference in the duration of hospitalization among the treatment groups.

Table 8.6.3 Hospitalization through 21 days in study 704.326^a.

	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Subjects discharged prior to day 21	97 (95%)	101 (98%)	96 (96%)	0.515

a. Data from original NDA review, table 7.0.2c.3..

For subjects who were discharged prior to day 21 there was a non-significantly lower rate of re-admission through 21 days for the nesiritide groups. The reasons for these admissions, however, were mostly other medical conditions, unrelated to CHF.

Table 8.6.4 Hospital Readmission Through 21 Days in Study 704.326^a.

	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Subjects discharged prior to day 21	97	101	96	
If discharged, # of subjects readmitted by day 21	16 (16%)	8 (8%)	11 (11%)	0.181 ^b

a. Data from original NDA review, table 7.0.2c.

b. p Value using Fisher's Exact test.

Duration of Hospitalization and Need for Re-Hospitalization in Trial 704.339 (VMAC)

VMAC assessed the need for hospitalization differently from the two trials above, and focused on the 30-day endpoint. Once again, no significant differences were seen between the treatment groups.

Table 8.6.5 Hospital Readmission Through 21 Days in Study 704.339 (VMAC)^a.

	NTG N=216	Natrecor Fixed Dose N=211	All Nesiritide N=273	Natrecor Adjustable N=62
Subjects discharged prior to day 30	206 (95%)	194 (92%)	253 (93%)	59 (95%)
Days of Hospitalization through Day 30	8.1±7.0	10.3±8.7	10.0±8.4	8.8±7.2
If discharged, # of subjects readmitted by day 30	48 (23%)	41 (21%)	50 (20%)	9 (15%)

a. Data Dr. Karkowsky's review, table 36.

9.0 SAFETY OF NESIRITIDE IN ACUTELY DECOMPENSATED CHF

There are three 'safety' issues that remain unresolved from the initial NDA submission, of which two represent deficiencies specifically noted in the non-approvable letter. They are the increased incidence of clinically-significant hypotension and renal injury observed in the nesiritide group relative to both placebo and active treatment. The third issue is the effect of nesiritide on mortality, an issue that arises in part as a consequence of the reported beneficial effects of another drug under development for the treatment of acutely decompensated CHF. The other safety concerns have been discussed in an earlier primary and secondary review, where the reader is referred for details.

9.1 Hypotension in the Nesiritide NDA Database

Two aspects of these adverse events were raised in the original non-approvable letter. First, there was a clear association between the doses of nesiritide used in the earlier trials (0.015, 0.030 µg/kg/min) and the occurrence of symptomatic hypotension resulting in significant clinical adverse events, including renal injury. As an example, the first table summarizes the incidence of hypotension, including symptomatic hypotension, in the three 'long-infusion trials' in the original submission.

Table 9.1.1 Hypotensive AEs During the First 24 hours in the 'Long Infusion' Trials^a.

	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Hypotension	15 (9%)	33 (20%)	52 (31%)	7 (27%)	<0.001
Asymptomatic Hypotension	9 (6%)	19 (12%)	29 (17%)	3 (12%)	<0.001
Symptomatic Hypotension	6 (3%)	14 (8%)	23 (14%)	4 (15%)	0.003
Decreased Pulmonary Pressures	0 (0%)	0 (0%)	3 (2%)	5 (19%)	<0.001

a. Data from original review, table 8.0.2a.3. Reflects trials 704.311, 704.325, and 704.326 data.

These data are to be contrasted with the reports of hypotension from the VMAC trial, which used a lower infusion dose of nesiritide.

Table 9.1.2 Hypotensive AEs During the First 24 hours in VMAC^a.

	NTG N=216	Nesiritide Fixed Dose N=211	All Nesiritide N=273
Hypotension	27 (13%)	27 (13%)	24 (12%)
Asymptomatic Hypotension	17 (8%)	17 (8%)	12 (8%)
Symptomatic Hypotension	10 (5%)	10 (5%)	12 (4%)

a. Data from Dr. Karkowsky's review, table 44.

That the lowered dose of nesiritide causes less hypotension seems clear. This is reinforced by a series of analyses the sponsor conducted looking at the changes in systolic and diastolic BP measured during nesiritide infusion. The following is excerpted from a table by Dr. Karkowsky to emphasize that while the incidence of large decreases in BP did not differ between the treatment groups, the duration of hypotension was significantly longer in the patients on nesiritide. The consequences of the hypotension, however, did not appear to be significantly worse than the hypotension reported with NTG.

Table 9.1.3 Hypotensive Episodes During VMAC^a.

	NTG N=216	Nesiritide Fixed Dose N=211	All Nesiritide N=273	Nesiritide Adjustable N=62
Hypotensive Episodes	12 (6%)	13 (6%)	15 (5%)	2 (3%)
Duration of Episode				
<30 Mins	7 (54%)	0	0	0
31-60 Mins	2 (15%)	4 (25%)	4 (22%)	0
61-120 Mins	4 (31%)	5 (31%)	5 (28%)	0
121-180 Mins	0	4 (25%)	5 (28%)	1 (50%)
3-7 Hours	0	3 (19%)	4 (22%)	1 (50%)
Severity of Episode				
Mild	7 (54%)	6 (38%)	6 (33%)	0
Moderate	5 (38%)	8 (50%)	10 (56%)	2 (100%)
Severe	1 (8%)	2 (13%)	2 (11%)	0 (0%)
Effect on Study Drug				
None/ Increased	3 (23%)	1 (6%)	1 (6%)	0
Decrease/ Interrupt ^b	5 (38%)	6 (38%)	8 (44%)	2 (100%)
Discontinued	5 (38%)	9 (56%)	9 (50%)	0 (0%)

a. Data from Dr. Karkowsky's review, table 48. Hypotension refers to pre-defined lowering of BP from baseline.

b. Per protocol, the investigator could restart study drug if patient recovered.

9.2 Renal Injury in the Nesiritide NDA Database

The higher doses of nesiritide used in the original trials were associated with a higher incidence of renal injury than the active control comparison. The first two tables summarize the incidence of pre-specified increases in serum creatinine in study 704.325 and 704.326 from the original submission.

Table 9.2.1 Incidence of Increased Creatinine Values in Trial 704.325^a.

Pre-specified increases in creatinine	Control n=42	Nesiritide 0.3/0.015 n=43	Nesiritide 0.6/0.030 n=42
>1.0 mg/dl Increase	0 (0%)	2 (5%)	4 (10%)
>0.5 mg/dl Increase	2 (5%)	7 (16%)	8 (19%)
>100% Increase	1 (2%)	1 (2%)	4 (10%)
>50% Increase	1 (2%)	5 (12%)	8 (19%)
>25% Increase	7 (17%)	11 (26%)	8 (19%)

a. Data from original NDA medical review, table 8.0.8a.24.

Table 9.2.2 Incidence of Increased Creatinine Values in Trial 704.326^a.

Pre-specified increases in creatinine	Control n=102	Nesiritide 0.3/0.015 n=103	Nesiritide 0.6/0.030 n=100	Nominal p Value ^a
>1.0 mg/dl Increase	3 (3%)	6 (6%)	6 (6%)	0.571
>0.5 mg/dl Increase	9 (9%)	15 (15%)	21 (22%)	0.049
>100% Increase	2 (2%)	3 (3%)	1 (1%)	0.874
>50% Increase	3 (3%)	10 (10%)	14 (15%)	0.013
>25% Increase	14 (14%)	25 (25%)	33 (34%)	0.004

a. Data from original NDA medical review, table 8.0.8a.25.

There was also a greater need for interventions as a result of renal failure in 704.326 and 704.326..

Table 9.2.3 Intervention For Renal Failure in Study 704.325^a.

Intervention for Worsening Renal Fxn	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 N=42
No Intervention	41 (98%)	37 (86%)	33 (79%)
Medical Intervention Without Dialysis	0 (0%)	6 (14%)	7 (17%)
Dialysis	1 (2%)	0 (0%)	2 (5%)

a. Data from NDA medical review, table 6.2.13.5.

Table 9.2.4 Intervention For Renal Failure in Study 704.326^a.

Intervention for Worsening Renal Fxn	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritid 0.6/ 0.03 n=100
Intervention without Dialysis	6 (6%)	12 (12%)	7 (7%)
Dialysis	2 (2%)	1 (1%)	2 (2%)

a. Data from original NDA medical review, table 6.3.12.3.9

In the VMAC trial, no exclusions were included for the presence of elevated serum creatinine at the time of entry. Here, no difference in the rate of elevated serum creatinines was seen between the two treatment groups, although the rate of both new dialysis and abnormal serum creatinine was higher in the nesiritide group. In addendum #1 to his Medical Review, Dr. Karkowsky analyzed the association between hypotension and the development of an abnormal serum creatinine. He concluded that '(t)here was no obvious relationship between hypotension and creatinine changes.'

Table 9.2.5 Incidence of Increased Creatinine Values in Trial 704.339 (VMAC)^a.

Pre-specified increases in creatinine	All NTG N=216	All Natrecor N=211
Need for Dialysis	5 (2%)	9 (3%)
Pre-specified increases in creatinine >0.5 mg/dl Increase	45 (21%)	59 (28%)

a. Data from Dr. Karkowsky's review, tables 42 and 48.

9.3 Mortality in the NDA Database

The other safety issue that needs summarizing here is the available information on the mortality in the various treatment groups. There are two datasets that can be examined reasonably: the entire randomized dataset, which would (roughly) compare the use of nesiritide with the use of a varied group of controls, including dobutamine and NTG. The second dataset of interest, and one that is somewhat more interpretable, comes from the long-term follow-up of the VMAC trial, comparing the use of nesiritide and NTG.

When the entire NDA database is used, incorporating the 724 Natrecor[®] patients, 443 control patients, there is no significant difference between the two groups with regard to overall mortality. Dr. Karkowsky appropriately points out this comparison includes 80 patients who received dobutamine as part of study 704.329 (PRECEDENT).

During the VMAC trial, the potentially beneficial effects of levosimendan were announced, and the sponsor elected to follow the population in VMAC for 6 months to obtain mortality information. The mortality rate is presented in categorical form on the next page. According to an analysis by Dr. Hung, the mortality data from VMAC do not exclude a 50% excess risk of mortality for nesiritide.

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Table 9.3.1 Mortality in VMAC^a.

	Nitroglycerin (NTG) N=216	Natrecor Fixed Dose N=211	All Natrecor N=273
30 Day Mortality			
Deaths	11 (5.1%)	15 (7.1%)	22 (8.1%)
p-Value c/w NTG	--	0.39	0.23
Hazard Ratio Natrecor:NTG (95% C.I.)	--	1/41 (0.65, 3.07)	1.56 (0.75, 3.24)
90 Day Mortality			
Deaths	27 (12.5%)	37 (17.5%)	52 (19.1%)
p-Value c/w NTG	--	0.15	0.078
Hazard Ratio Natrecor:NTG (95% C.I.)	--	1.44 (0.88, 2.37)	1.52 (0.95, 2.43)
180 Day Mortality			
Deaths	44 (20.4%)	46 (21.8%)	67 (24.5%)
p-Value c/w NTG	--	0.62	0.32
Hazard Ratio Natrecor:NTG (95% C.I.)	--	1.11 (0.74, 1.68)	1.22 (0.83, 1.79)

a. Data from Dr. Hung's statistical review, table 7.

The sponsor also compared the mortality rates for all control patients with all nesiritide patients through 6 months. In this analysis the control group includes vasodilators such as NTG (from VMAC) as well as inotropes (especially dobutamine) from the PRECEDENT and the earlier trials of nesiritide. The mortality rates at 6 months for the combined control group and the nesiritide group were 94/443 (21.5%) and 154/724 (21.7%) respectively.

10.0 APPENDIX A: REFERENCES

1. Koller, K.J. and D.V. Goeddel. 1992. Molecular biology of the natriuretic peptides and their receptors. *Circulation* 86:217-224.
2. Rutlen, D.L., G. Christensen, K.G. Helgesen, and A. Ilebekk. 1998. Influence of atrial natriuretic peptide on intravascular volume displacement in pigs. *American Journal of Physiology* 259:H1595-H1600
3. Watenpugh, D.E., Vissing, S.F., et al. 1995. Pharmacologic atrial natriuretic peptide increases human systemic leg filtration, but decreases leg capillary filtration. *J. Cardiovasc. Pharmacol.* 26: 414-419.
4. La Villa, G., Riccardi, D., et al. (1995) Blunted natriuretic response to low-dose brain natriuretic peptide infusion in nonazotemic cirrhotic patients with ascites and avid sodium retention. *Hepatology* 22: 1745-1750.

11.0 APPENDIX B: 120-DAY SAFETY UPDATE

On 3.28.01, the sponsor submitted the available 6-month mortality data from the VMAC trial as a 'Safety Update Report.' No other safety information has been submitted that can be characterized as 120-Day Safety Update. The safety review and labeling recommendations will incorporate the safety data from the original NDA submission as well as the VMAC and PRECEDENT trial data.

12.0 Appendix C: PEDIATRICS

In his memorandum dated 6.15.01, Dr. Karkowsky recommends against pediatric trials with Natrecor at this time. I concur with his recommendation. The justification for not needing these studies is based primarily on data submitted by the sponsor making the following two points:

- 1) CHF in this population is due to different etiologies than adult CHF: left to right shunts or valvular outlet obstruction.
- 2) The population of children admitted to the hospital specifically for exacerbations of CHF is quite small, based on data submitted from HCFA.

13.0 APPENDIX C: PRINTED CARTON LABELING

The proposed printed carton labeling was unacceptable to the Chemistry reviewers, who have proposed changes to the sponsor.

14.0 APPENDIX D: PACKAGE INSERT LABELING

Proposed Package Insert begins on the next page.

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

NDA 20-920 Natrecor® (nesiritide)
Reviewer Abraham Karkowsky, M.D., Ph.D.
Date 4/25/01

/S/

There will be several additional documents that will constitute the completed review. Only studies 704.339 (VMAC) and 704.329 (PRECEDENT) are reviewed in this package. Several analyses have yet to be formally included into this document for the two studies that have been reviewed. There was no attempt to incorporate the results of previous studies into a integrated safety and efficacy document.

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Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Hemodynamic and Clinical Effects of Natrecor® (nesiritide) Compared With Nitroglycerine Therapy for Symptomatic Decompensated CHF (The VMAC trial).

Investigator and Sites:

Table 1. Investigators and sites.

Site # 679 Aaron, M.F., MD and Bourge, RC, MD U of Alabama at Birmingham Birmingham, AL	Site # 615 Abraham, W, MD U. of Cincinnati Med Center Cincinnati, OH	Site # 668 Bank, AJ, MD St. Paul Heart Clinic, PA St Paul MN	Site # 657 Berk, M, MD Cardiovascular Research Institute of Dallas Dallas, TX
Site # 637 Bhat, G., MD U of Louisville Research Foundation Louisville, KY	Site # 638 Browne, K, MD Watson Clinic Lakeland FL	Site # 561 and # 697: Berger, A, MD Beth Israel Deaconess Med Center Boston, MA	Site # 683 Chu, A., MD HeartCare Midwest Peoria, IL
Site # 679: Cobb, FR, MD Durham VA Med Center Durham, NC	Site #674 Cotts, W, MD Northwestern Memorial Hospital Chicago, IL	Site # 620: DeMarco, T, MD U Calif, SF Med Center SF, CA	# 502 Dennish, G, MD San Diego Cardiovascular Research Associates Encinitas, CA
Site # 618: Dinerman, J, MD Jacksonville Heart Center, Jacksonville, FL	# 570 and #676 El Hafi, S, MD Med Tech Research, Inc Houston, TX	# 554 and # 695 Elkayam, U.; MD LA County, USC Med Center LA, CA	# 519 Feldman, R., MD MediQuest Research Group Ocala, FL
# 543 Fishbein, D, MD U of Washington Med Center Seattle, WA	# 585 Ford, LE, MD Roudebush Med Center Indianapolis, IN	Site # 678 Ghali, J, MD Cadiac Ctrs of LA, L.L.C. at Willis Knighton Heart Inst Shreveport, LA	Site # 671 Goldsmith, SS, MD Hennipen County Med Center Minneapolis, MN
Site # 681 Goldsmith, SS, MD U of MD Med System Baltimore, MD	Site # 538 Greenspan, M, MD Buxmont Cardiol Associates Lifemark Medical Center Sellersville, PA	Site # 642 Hall, J, MD Med Reserch Consortium at Winona Memorial Hosp Indianapolis, IN	Site # 357 Hare, J, MD The Johns Hopkins Hospital Baltimore, MD
# Site #524 Harlamert, E, MD Community Hospital East Indianapolis, IN	Site # 543 Hassapoyannes, C, MD Dorn Research Institute Columbia, SC	Site # 663: Haight, WH, MD The Heart Center Huntsville, AL	Site # 355: Hershberger, R., MD Oregon Health Sciences University Portland, OR
Site # 686 Hettleman, BD, MD Dartmouth Hitchcock Med Center Lebanon, NH	Site # 666 Hill, JA, MD U of Florida Health Sci Center Gainesville, FL	Site # 551 Hoagland, PM, MD San Diego Cardiac Center Research Department San Diego, CA	# Site # 382 Johnson, AD, MD Scripps Clinic La Jolla, CA
Site # 356 Kao, W, MD Rush-Presbyterian-St Lukes Med Center Chicago, IL	Site # 567 Karlsberg, R, MD Cardiovascular Res Institute of Southern CA Beverly Hills, CA	Site # 627 Koren, M, MD Jacksonville Center for Clinical Research Jacksonville, FL	Site # 367 Kukin, M, MD Mt Sinai Med Center New York, NY

Site # 693 Lamas, G, MD Mt Sinai Med Center NYC, NY	Site # 369 LeJemtel, T, MD Albert Einstein Hospital Bronx, NY	Site # 605 Liang, C, Ph.d., MD U of Rochester Med Center Rochester, NY	Site #370 Lui, CY, MD U of Ariz Health Science Center Tucson, AZ
Site # 540 Mallon, SM, MD U of Miami/Jackson Memorial Med Center Miami, FL	Site # 516 McGrew, FA, MD The Stern Cardiovascular Center Memphis, TN	Site # 687 and Site # 711 McIvor, ME, MD and Schlyer, G, MD The Heart Inst of St Petersburg St Petersburg, FL	Site # 647 Miller, AB; MD U of Florida Health Science Center Jacksonville, FL
Site # 677 Moskowitz, R, MD Motefiore Med Center Bronx, NY	Site # 572 Oren, R.M, MD Univ of Iowa Hospitals and Clinics Iowa City, IA	Site # 547 Promisloff, S, MD Hillsboro Cardiology Hillsboro, OR	Site # 628 Reddy, H, MD U. of Missouri Health Science Center Colombus, MO
Site # 688 Roark, SF, MD Cardiology Associates of Gainesville Gainesville, FL	Site # 545 Schocken, D, MD USF College of Med Tampa, FL	Site # 675 Silver, MA, MD Christ Hospital Med Center Oak Lawn, IL	Site # 636 Stevenson, LW, MD Brigham and Women's Hospital Boston, MA
Site # 560 Torre, G, MD Baylor Colege of Medicine Houston, TX	Site # 360 Varhese, J, MD George Washington Med Center Washington, DC	Site # 508 Vaska, K, MD U of SD School of Medicine Siouz Falls, SD	Site # 656 Vranian, R, MD Cardiovascular Medicine of Virginia at Pratt Medical Center LTD Fredricksburg, VA
Site # 503 Wagoner, L, MD U of Cincinnati Med Center Cincinnati, OH	Site # 579 Walsh, MN, MD The Care Group LLC Indianapolis, IN	Site # 539 Wilson, D, MD U of Kansas Med Center Kansas City, KS	Site # 580 Wilson, JR, MD Vanderbilt U Med Center Nashville, TN
Site # 667 Young, J, MD The Cleveland Clinic Foundation Cleveland, OH	Site # 680 Zafari, AM, MD, Ph.D VA Medical Center IIIB Decatur GA		

Formulations:

The Natrecor used in this study was produced using recombinant DNA technology (Lot K0003A). The formulation consists of Natrecor (mg), mannitol (20 mg), citric acid monohydrate (mg), and sodium citrate dihydrate (2.94 mg).

Dates of the study:

The specific dates of the protocol are shown in table 2. The amendments were only incorporated before a substantial portion of the subjects was enrolled.

Table 2. Important study dates

Original Protocol	4 August 1999
First Amendment	28 April 2000
Second Amendment	31 August 2000
First Subject Enrolled	26 October 1999
Last Subject Completed	25 August 2000
Blind Broken	12 Sep 2000

Oversight Committees: The protocol stipulated the formation of a Data Safety Monitoring Committee consisting of three experts in the field of either heart failure and/or clinical research and a statistician who are independent of Scios Corporation. The data reported to the DSMB is to include all deaths, myocardial infarctions, cerebrovascular accidents and acute renal failure requiring dialysis that occur within the 30 day period of the start of infusion.

Treatment groups: Subjects are to be stratified, with approximately half the subjects to be catheterized and the other half treated without a catheter in place. Those who enter with a right heart catheter in place are to be included in the catheter stratum. Other subjects will be allocated to either catheter or non-catheter treatment based on the investigator's usual treatment.

There are five different treatments

Group 1: Placebo (3 hours) followed by IV nitroglycerine (after 3 hours).

Group 2: Placebo (3 hours) followed by IV Natrecor (after 3 hours).

Group 3: IV Nitroglycerine

Group 4: IV Natrecor fixed dose

Group 5: IV Natrecor adjustable dose (catheterized stratum only)

Since Natrecor binds to heparin, non-heparin coated intravenous tubing must be used.

The initial dose of Natrecor is to consist of a bolus of 2ug/kg over approximately 60 seconds followed by the constant infusion at 0.01 ug/kg/min. The treatment regimens for both the Natrecor fixed and Natrecor adjustable doses were exactly the same for the first three hours.

After the first three hours, those randomized to the fixed dose regimen received a constant dose of 0.01 ug/kg/min for the duration of therapy. For those who are randomized to the adjustable dose Natrecor, the dose could be increased if the PCWP was ≥ 20 mm Hg and the SBP was ≥ 100 mm Hg. The increase consisted of a bolus of 1 ug/kg over 60 seconds followed by an increase of the infusion rate by 0.005 ug/kg/min. The adjustment can be made every 3 hours to a maximum dose of 0.03 ug/kg/min. Each increase is predicated on the same PCWP and SBP criteria.

For those treated with nitroglycerin, the dose regimen is to reflect the investigator's usual regimen for this drug.

From two hours prior to the start of infusion through the 3-hours placebo controlled period, the following medications must be withheld.

- Continuous intravenous diuretics
- Nitroprusside
- IV ACE inhibitors
- Milrinone
- New infusion of dobutamine
- New infusion of dopamine
- Non-blinded nitroglycerine

Ongoing dobutamine and dopamine may be continued but the dose is not to be increased.

From the end of the 3-hour placebo-controlled period, the following medications should be withheld:

- Nitroprusside
- Milrinone
- IV ACE inhibitors
- Non-blinded nitroglycerine