

DF

MAR 3 - 1999

**Combined Medical & Statistical Review
Natrecor[®] Injection
(Nesiritide Citrate)**

NDA 20-920

Division of Cardiovascular and Renal Drugs

February 26, 1999

Table of Contents

NDA 20-920 (Nesiritide)	Page #
Tables of Contents	ii - v
General Information	1
0.0 Overall Summary	2-4
1.0 Materials Utilized in Review	5
2.0 Background	5
2.1 Proposed Indication	6
2.2 Administrative History	6
2.3 Proposed Labeling	6-8
2.4 Foreign Marketing	8
3.0 Chemistry, Manufacturing, and Controls	8
4.0 Pre-Clinical Pharmacology/ Pharmacokinetics	8-9
4.1 Toxicology/ Genotoxicity/ Carcinogenicity	9
5.0 Description of Clinical Data Sources	10
5.1 Primary Source Data (Development Program)	10-14
5.1.1 Study Type and Design/Patient Enumeration	10-11
5.1.2 Demographics	11-13
5.1.3 Extent of Exposure (dose/duration)	13-14
5.2 Relevant Information from Related INDs/ NDAs and Published Material	14-15
5.3 Comment on Adequacy of Clinical Experience	15
5.4 Comment on Data Quality and Completeness	16
6.0 Reviews of Individual Studies	
6.1 Study 704.311 ^a	17-35
6.2 Study 704.325 ^a	36-68
6.3 Study 704.326 ^a	69-89
7.0 Integrated Review of Efficacy	90-124
7.0.1 Physiologic Efficacy of Nesiritide	90-100
7.0.1a Effect of Nesiritide on PCWP ^b	90-95
7.0.1b Effect of Nesiritide on Other Hemodynamic Markers	96-100
7.0.1c Durability of the Effect of Nesiritide on PCWP and Other Hemodynamic Measures	101-103
7.0.1d The Relationship Between Plasma Nesiritide Concentrations and Hemodynamic Changes	104
7.0.1e Other Physiologic Effects of Nesiritide	105-109
7.0 Integrated Review of Efficacy (cont)	
7.0.2 Clinical Efficacy of Nesiritide	110-125
7.0.2a Effect of Nesiritide on Mortality	110-111
7.0.2b Effect of Nesiritide on Signs and Symptoms of CHF ^c	111-122
7.0.2c Effect of Nesiritide on Hospitalization Rates	123-124
7.0.2d Effect of Nesiritide on Need for Invasive Medical Interventions	124-125
7.1 Medical Reviewer's Conclusion's Regarding Nesiritide Efficacy	125

a. A detailed tables of contents for this trial or section appears below.

b. PCWP = pulmonary capillary wedge pressure.

c. CHF = congestive heart failure.

Table of Contents (c)

NDA 20-920 (Nesiritide)	Page #
8.0 Integrated Review of Safety	126-184
8.0.1 Occurrence of Adverse Events by Body System	127
8.0.2 Adverse Events in the Cardiovascular System	128-150
8.0.3 Adverse Events in the 'Body as a Whole' System	151
8.0.4 Adverse Events in the Digestive System	151-153
8.0.5 Adverse Events in the Nervous System	153-156
8.0.6 Adverse Events in the Metabolic System	156-167
8.0.7 Adverse Events in the Respiratory System	167
8.0.8 Adverse Events in the Urogenital System	168-177
8.0.9 Adverse Events in the Skin & Appendage System	178
8.0.10 Adverse Events in the Musculoskeletal System	178
8.0.11 Adverse Events in the Hemic & Lymphatic System	179-183
8.0.12 Adverse Events in the Special Senses System	184
8.1 Medical Reviewer's Conclusions Regarding Nesiritide Safety	185
9.0 Recommendations of Medical Reviewer	186-190
10.0 References	191
Appendices	
11.0 Appendix One: Methodologies Used for Safety Review^a	192
11.1 Appendix One: Background Database for Safety Review^a	192-227
12.0 Appendix Two: Narratives for Subjects Who Died	228-232
13.0 Appendix Three: Listing of Subjects With SAEs	233-236
14.0 Appendix Four: Listing of Subjects with Clinical AEs Leading to Discontinuation	237-240
15.0 Appendix Five: Statistics for Study 704.235	241-242
16.0 Appendix Six: FDA Statistical Analysis	243-248
17.0 Appendix Seven: Relationship between PCWP and CHF Signs and Symptoms	249
18.0 Appendix Eight: Individuals with severe and symptomatic hypotension	250-253

a. A detailed tables of contents for this trial or section appears below.

b. PCWP = pulmonary capillary wedge pressure.

c. CHF = congestive heart failure.

Table of Contents For Study 704.311

Trial 704.311	Page #
6.1.1 Title of Study	17
6.1.2 Sites of Investigation and Investigators	17
6.1.3 Background	17
6.1.4 Study Design	18
6.1.5 Primary And Secondary Objective/Endpoints	18-19
6.1.6 Number Of Subjects/ Randomization	19
6.1.7 Inclusion/ Exclusion Criteria	19
6.1.8 Dosage/ Administration	20
6.1.9 Duration/ Adjustment of Therapy	20
6.1.10 Safety and Efficacy Endpoint Measured	20
6.1.11 Statistical Considerations	20-21
6.1.12 Efficacy Outcomes	
6.1.12.1 Patient Demographics and Baseline Characteristics	21-22
6.1.12.2 Disposition and Follow-up for Subjects	22
6.1.12.2a Subject Selection	23
6.1.12.2b Protocol Violations and Deviations	23
6.1.12.2c Concomitant Therapies Used After Trial Initiation	23
6.1.12.3 Analysis of Primary Endpoint	24
6.1.12.4 Analysis of Secondary Endpoints from Trial 704.311	25
6.1.12.5 Subgroup & Post-hoc Analyses of trial 704.311	26-31
6.1.13 Safety Outcomes	32-33
6.1.14 Efficacy Summary For Trial 704.311	34
6.1.15 Safety Summary For Trial 704.311	34
6.1.16 Overall Summary for Trial 704.311	35

Tables of Contents For Study 704.325

Trial 704.325	Page #
6.2.1 Title of Study	36
6.2.2 Sites of Investigation and Investigators	36
6.2.3 Background	36
6.2.4 Study Design	37
6.2.5 Primary And Secondary Objective/Endpoints	37
6.2.6 Number Of Subjects/ Randomization	37
6.2.7 Inclusion/ Exclusion Criteria	37-38
6.2.8 Dosage/ Administration	38-39
6.2.9 Duration/ Adjustment of Therapy	39
6.2.10 Safety and Efficacy Endpoint Measured	39-40
6.2.11 Statistical Considerations	41-42
6.2.12 Efficacy Outcomes	
6.2.12.1 Patient Demographics and Baseline Characteristics	42-43
6.2.12.2 Disposition and Follow-up for Subjects	44
6.2.12.2a Subject Selection	44
6.2.12.2b Protocol Violations and Deviations	44-45
6.2.12.2c Concomitant Therapies Used After Trial Initiation	45-47
6.2.12.3 Analysis of Primary Endpoint	47-48
6.2.12.4 Analysis of Secondary Endpoints from Trial 704.325	49-50
6.2.12.5 Subgroup & Post-hoc Analyses of trial 704.325	51-64
6.2.13 Safety Outcomes	65-67
6.2.14 Efficacy Summary for Trial 704.325	68-69
6.2.15 Safety Summary For Trial 704.325	69
6.2.16 Overall Summary for Trial 704.325	69

Tables of Contents For Study 704.326

Trial 704.326	Page #
6.3.1 Title of Study	70
6.3.2 Sites of Investigation and Investigators	70
6.3.3 Background	70
6.3.4 Study Design	71
6.3.5 Primary And Secondary Objective/Endpoints	71
6.3.6 Number Of Subjects/ Randomization	71
6.3.7 Inclusion/ Exclusion Criteria	71-72
6.3.8 Dosage/ Administration	72
6.3.9 Duration/ Adjustment of Therapy	72
6.3.10 Safety and Efficacy Endpoint Measured	73
6.3.11 Statistical Considerations	73
6.3.12 Efficacy Outcomes	
6.3.12.1 Patient Demographics and Baseline Characteristics	74-75
6.3.12.2 Disposition and Follow-up for Subjects	75
6.3.12.2a Subject Selection	75
6.3.12.2b Protocol Violations and Deviations	75
6.3.12.2c Concomitant Therapies Used After Trial Initiation	76-78
6.3.12.3 Analysis of Efficacy Endpoint	78-83
6.3.13 Safety Outcomes	84-87
6.3.14 Efficacy Summary For Trial 704.326	88
6.3.15 Safety Summary For Trial 704.326	89
6.1.16 Overall Summary for Trial 704.326	89

**Tables of Contents For Appendix 11:
Methodologies & Background for Safety Review**

Table Of Contents (Cont)	Page #
11.0 Methodologies Used for Safety Review	192
11.0.2 Source Materials for the Integrated Safety Review	192-196
11.0.3 Extent Of Subject Exposure to Study Gas	193
11.0.4 General Methodologies Used for the Integrated Safety Review	197-200
11.1 Background Data For Safety Review	
11.1.1 Deaths	200-202
11.1.2 Other Serious Adverse Events	203
11.1.3 Adverse Events Related to Clinical Findings	204-208
11.1.3.1a Drug-Demographic Interactions	208
11.1.3.1b Drug-Disease Interactions	208-209
11.1.3.2 Selected Analyses of AEs of Particular Interest	209-210
11.1 Background Data For Safety Review (cont)	
11.1.4 Adverse Events related to Laboratory Findings and Special Examinations	210-225
11.1.4.1 Standard Analyses and Explorations of Laboratory Data	210
11.1.4.2 Analyses Focused on Changes in Mean Laboratory Measurements	211-212
11.1.4.3 Analyses Focused on Extreme Laboratory Values	212-219
11.1.4.4 Vital Signs (Heart rate and Blood Pressure)	219-221
11.1.4.5 ECGs, Holters, and Urinalyses	221
11.1.5 Subject Discontinuations	222-225
11.1 Background Data For Safety Review (cont)	
11.1.6 Special Studies	225-227
11.1.6.1 Special Studies: Tolerance & Withdrawal	226
11.1.6.2 Special Studies: Abuse Potential	226
11.1.6.3 Special Studies: Human Reproduction Data	226
11.1.6.4 Special Studies: Overdose	226
11.1.6.5 Special Studies: Allergic Reactions/ Antibody Formation	227

INTEGRATED MEDICAL & STATISTICAL REVIEW
OF NEW DRUG APPLICATION 20-920

NDA: 20-920

DRUG NAME: Nesiritide citrate

TRADE NAME: Natrecor®

FORMULATION: For intravenous infusion

SPONSOR: Scios Inc.

TYPE OF DOCUMENT: New Drug Application

MEDICAL REVIEWER: Douglas C. Throckmorton, M.D.

Division of Cardio-Renal Drug Products (DCRDP), HFD-110

STATISTICAL REVIEWER: Lu Cui, Ph.D.

Division of Biometrics-I, HFD-710

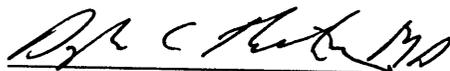
PROPOSED INDICATION: Natrecor is proposed for short term treatment of congestive heart failure.

DATE OF NDA SUBMISSION: 4.24.98

DATE ASSIGNED: 4.29.98

DATE FINAL REVIEW COMPLETED: 2.26.99

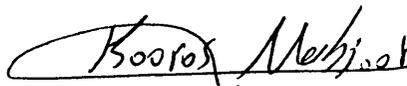
REVIEWER'S SIGNATURES



Douglas C. Throckmorton, M.D.
Medical Reviewer



Lu Cui, Ph.D.
Statistical Reviewer



Concur: Kooros Mahjoob, Ph.D.
George Chi, Ph.D.



0.0 Overall Nesiritide NDA Summary

Human B-type natriuretic peptide (hBNP) is a 32-amino acid peptide produced mainly in the cardiac ventricle, with vasodilatory, diuretic, natriuretic, and neurohormonal actions. Natrecor (nesiritide) is a preparation containing the purified peptide produced by recombinant DNA technology, with an amino acid sequence identical to that of naturally occurring hBNP. It is proposed for intravenous administration in the short term treatment of decompensated congestive heart failure (CHF).

There are nine clinical studies submitted in support of the nesiritide NDA. Among these, there are two clinical trials that primarily support the efficacy of the drug:

1) A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Ranging Study to Evaluate the Safety and Efficacy of a 24 Hour Intravenous Infusion of Natrecor hBNP in Subjects with Congestive Heart Failure (Trial 704.311); and

2) A Randomized, Double-Blinded, Placebo-Controlled Study of Two Doses of Natrecor hBNP Administered as a Constant Infusion in Subjects with Decompensated CHF (Trial 704.325).

A third trial examined the safety of nesiritide in a large, open-label cohort of patients with decompensated CHF:

3) A Randomized, Open-Label, Active-Controlled, Multicenter Phase III Safety Study of Two Doses of Natrecor hBNP Administered as a Continuous Infusion in the Treatment of Decompensated CHF (Trial 704.326).

Trial 704.311

This trial investigated the effects of nesiritide in patients with decompensated CHF severe enough to require hospitalization but not so severe as to preclude the withholding of cardiac medications for 24-48 hours. Three doses of nesiritide were compared with placebo for effect on hemodynamics and safety. At the end of 3 hours, there was a significant, dose-dependent effect of nesiritide to improve hemodynamics, especially to acutely decrease PCWP. This hemodynamic effect took 4-6 hours to reach maximal effect and persisted through 24 hours. After discontinuation, the PCWP returned to within 10% of the level of the placebo group after 4 hours.

Nesiritide also had a beneficial effect on other hemodynamics that paralleled the changes in PCWP, including a significant, dose-dependent effect to lower blood pressure more than placebo.

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

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

Trial 704.325

This trial investigated the effects of nesiritide in patients with decompensated CHF who were severe enough to require hospitalization, yet able to withhold other cardiac medications for 4 hours. Two doses of nesiritide were compared with placebo for the first 6 hours and with active control thereafter. At the end of 6 hours, nesiritide improved hemodynamics significantly, especially PCWP, when compared with placebo. These hemodynamic effects of nesiritide were dose-dependent.

With regard to the signs and symptoms of CHF, the trial found a beneficial effect of nesiritide at the end of 6 hours, relative to placebo. The strength of these data is undermined by difficulties in blinding that are discussed in the trial review. At the 6 hour timepoint, nesiritide also had acute positive effects on several individual signs and symptoms of CHF, including breathing difficulty, fatigue, lightheadedness, and peripheral edema. These significant differences between nesiritide and the active control group also did not persist to 24 hours. Finally, there was a small effect of nesiritide to reduce the median respiratory rate, relative to placebo, from 0 to 6 hours.

The use of nesiritide was associated with both sodium and water retention during the first 24 hours of infusion as the result of decreased urine output, perhaps due in part to an imbalance in the diuretic use. Over 5 days, there was no significant difference between the treatment groups with regard to weight loss.

With regards to safety, more subjects in the nesiritide group dropped out due to symptomatic hypotension and/or excessive decreases in PCWP, and more patients in the nesiritide groups had serious adverse events. Included in these SAEs were three cases of renal failure, associated with two deaths.

Trial 704.326

This was a trial in patients with acutely decompensated CHF, comparing the effects of standard care (i.e., dobutamine, and nitroprusside) with two doses of nesiritide. The primary goal of the trial was to collect safety information regarding the use of nesiritide in the acutely decompensated CHF population. The patients in this trial were required to be off of their other parenteral vasoactive medications for 4 hours, as in the 704.325 study. Patients were randomly assigned to receive either nesiritide or standard therapy in open-label fashion. For subjects assigned to one of the two nesiritide groups, investigators and patients were blinded to the dose of nesiritide administered.

With regard to clinical efficacy, nesiritide appeared as effective as, but not superior to, the active comparators in relieving the symptoms of CHF at the end to 6 and 24 hours. There was no tendency for the high-dose nesiritide to be more effective than the low-dose nesiritide as regards symptomatic benefit.

The physiological effects of nesiritide were similar to what were seen in the earlier trials, and both doses of nesiritide lowered mean systolic blood pressure more than the active control at the end of 6 and 24 hours. There was no trend towards greater weight loss in either of the nesiritide groups relative to active control.

No other clinical benefits of nesiritide were measurably superior to the active comparators.

With regard to safety, the incidence of hypotension was again significantly greater in the nesiritide groups. The severity of the hypotension was also greater in the nesiritide groups.

Efficacy Summary

The data clearly demonstrate a significant hemodynamic effect of nesiritide that is dose-dependent and persists for at least 24 hours. Following discontinuation of nesiritide, hemodynamics return to baseline within 4 hours, without evidence for 'rebound.' While the magnitude of the nesiritide effect on mean hemodynamics (especially PCWP) appears to decrease by the end of 24 hours, the overall effects of nesiritide on hemodynamics compared with placebo persist through 24 hours. The pharmacodynamic half-life of nesiritide is significantly longer than the pharmacokinetic half-life, reflected in the time to maximal effect on PCWP (4-6 hours) and time to return to baseline after discontinuation of nesiritide (2-4 hours).

The link between nesiritide administration and clinical benefits is more tenuous, with a single study (704.325) supporting a greater acute effect of nesiritide than placebo on the signs and symptoms of CHF through 6 hours. These data are weakened by the fact that the investigators were aware of the PCWP values when performing their assessments. Additionally, the same investigator elicited the patient-assessments, introducing a potential bias in the symptom score data. This potential bias also undermines the observed link between the clear effects of nesiritide on PCWP and the observed improvement in signs and symptoms of CHF. The data from trial 704.326 suggests that the effects of nesiritide on CHF signs and symptoms is comparable to the active controls with regard to symptomatic relief over the first 24 hours of therapy. No other beneficial or adverse clinical effect of nesiritide (i.e., re-hospitalization rate, mortality rate) was suggested by the data.

Insufficient data are available in the NDA to comment on the following critical aspects of use:

- 1) information about the use of nesiritide in patients who are already taking other parenteral CHF therapies (especially other vasodilators),
- 2) information regarding the use of nesiritide in patients with CHF and myocardial infarction (these patients were excluded from the three pivotal trials),
- 3) information regarding the titration of nesiritide to achieve desired clinical effect,
- 4) information regarding the development of tolerance beyond 24 hours (where tolerance to nitrates develops), and
- 5) information about the effects of nesiritide at infusion doses below 0.015 µg/kg/min.

Safety Summary

Regarding overall mortality, there was no suggestion of either an adverse or beneficial effect of nesiritide on mortality rates over the period of follow-up in the trials.

Regarding overall safety, the nesiritide administration is associated with the occurrence of adverse events that are likely to be clinically significant and lead to increased patient morbidity. Of the adverse events, hypotension was most worrisome to this reviewer. The data suggest that hypotension requiring drug discontinuation will be more common in patients treated with nesiritide, when compared with current therapies. The data also suggest that the nesiritide use is associated with both clinically severe and prolonged hypotension. Unfortunately, no risk factors to identify patients at high risk for these hypotensive episodes were found.

The clinical database suggests that patients receiving nesiritide are also at increased risk for other clinically significant adverse events related to bradycardia and abnormal renal function. While more data is needed to place the risk of these adverse events into clinical context, the NDA does suggest that some patients may suffer significant clinical consequences related to nesiritide administration. With regard to less common adverse events, further data are needed to fully assess the clinical consequences of some of the adverse events associated with nesiritide use.

Recommendations of Medical Reviewer

Nesiritide has a demonstrated hemodynamic effect that is superior to placebo and persists through at least 24 hours. There is a suggested effect of nesiritide to relieve some of the acute symptoms of CHF, similar to currently available therapies. The available data are insufficient to demonstrate superiority of nesiritide to placebo with regard to symptom relief, which appears at best to be similar to the effects of other currently available parenteral therapies. Nesiritide use is associated with several clinically relevant adverse effects, especially hypotension. The prolonged pharmacodynamic half-life of nesiritide predicts that this hypotension will be more difficult to manage than for currently available therapies that work by the same intracellular mechanism (NTG, nitroprusside). Finally, the database is inadequate to address several important questions regarding its use: the concomitant use of other parenteral vasodilators, potential dose titration, the use in patients with acute myocardial ischemia, the potential effect of nesiritide on vascular permeability, and the potential for the development of tolerance beyond 24 hours, and effective lower dose. With the availability of other therapies also working through the cGMP-dependent protein kinase to cause vasodilatation that have a shorter pharmacodynamic half-life, the presence of significant safety concerns, and the inadequate database to describe its safe and effective use, nesiritide is not approvable.

1.0 Materials Utilized in Review

1.1 Materials from NDAs/ INDs

1. NDA 20-920 (nesiritide): volumes 1.1 through 1.89.
2. Nesiritide computer-assisted NDA (CANDA), including case report forms (CRFs). The CRFs were submitted electronically by the sponsor in the following categories:
 - a. Deaths.
 - b. Discontinued from therapy due to an adverse experience.
 - b1. Discontinued due to an adverse experience.
 - b2. Discontinued due to a clinical endpoint.
 - c. Discontinued from therapy for any other reason.
 - d. Serious adverse experiences.
3. IND 43,998 (nesiritide).
4. INDs for Atrial Natriuretic Peptide: 34,187; 26,034; 33,534; 33,598; 34,337; 38,456; 40,706; 33,276; 34,455; 34,714; 51,028; and 54,569.

1.2 Related Reviews & Consults

No outside reviews or consultants were obtained, and no related reviews utilized as part of this NDA review.

1.3 Other Resources

Four outside resources were reviewed, and relevant portions included in section 5.2.:

1. The printed transcript of the FDA Cardio-Renal Advisory Committee meeting on IV therapy for CHF (1.27.98).
2. The draft guidelines for the clinical evaluation of drugs for the treatment of congestive heart failure, written by Milton Packer for the Cardio-Renal Advisory Committee (12.7.87).
3. The published literature of for all atrial- and ventricular-derived natriuretic peptides.
4. The draft guidelines for the clinical evaluation of drugs for the treatment of congestive heart failure, discussed at the Cardio-Renal Advisory Committee (10.22.98).

2.0 Background

Human B-type natriuretic peptide (hBNP) is a 32-amino acid peptide, which was originally discovered in the brain (hence, B-type). It is produced mainly in the cardiac ventricle, and has vasodilatory, diuretic, natriuretic, and neurohormonal actions, similar to atrial natriuretic peptide, which is found in the atria of the heart (ref. 5). These peptides were first identified in the late 70's. Natrecor (nesiritide citrate) is a preparation containing the purified hBNP peptide produced by recombinant DNA technology, with an amino acid sequence identical to that of naturally occurring hBNP. In animals, hBNP causes vasodilation, and increases urinary sodium and water excretion. Similar natriuretic effects have been reported in humans, perhaps through inhibition of proximal sodium reabsorption (refs. 5, 12).

The effects of hBNP in patients with decompensated congestive heart failure (CHF) were studied as part of this NDA submission. CHF is characterized by abnormalities in cardiac function, renal water and salt handling, and peripheral vascular resistance. The latter abnormalities reflect an attempt by the body to compensate for decreased cardiac function, to maintain cardiac output. Ultimately, these compensatory mechanisms become maladaptive, and contribute to the progression of disease in CHF. Increased sympathetic tone leads to activation of the renin-angiotensin-aldosterone axis, and increased peripheral vascular resistance and sodium/ water retention by the kidney.

Patients with CHF have a combination of poor cardiac output (with decreased stroke volume and cardiac index), increased peripheral resistance with increased cardiac filling pressures (pre-load). This leads to increases in pulmonary artery pressures (PAP), pulmonary capillary wedge pressures (PCWP), and mean right atrial pressures (MRAP). Per the sponsor, the aim of therapy for the treatment of acutely decompensated CHF, such as nesiritide, is to improve the symptoms of CHF as well as any abnormalities in the cardiac hemodynamics, blood pressure and fluid retention. Decompensated CHF is a serious problem, and accounts for approximately one million hospitalizations per year in the U.S. It is now the most common discharge diagnosis for patients >65 years old. The incidence of CHF has also been rising in the U.S., and continues to carry a poor prognosis for survival, despite advances in therapy. This prognosis is worsened by the high prevalence of concomitant diseases in patients with CHF: diabetes; atrial fibrillation; ventricular arrhythmias; coronary artery, renal, and pulmonary disease. These patients also have elevated circulating levels of both ANP and hBNP (ref. 9).

The vasodilatory and natriuretic/diuretic properties of hBNP suggested that it might have therapeutic benefit in patients with CHF (ref. 12). Based on the submitted data, the sponsor proposes the use of hBNP for the treatment of decompensated CHF.

2.1 Indication

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

2.2 Administrative History

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

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

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

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

7.9.97 Pre-NDA meeting with DCRDP.

1.27.98 Advisory Committee meeting, discussing IV therapy for CHF.

10.98 Advisory Committee meeting, discussing Guidelines for CHF therapy.

2.3 Proposed Labeling

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

2.3.1 Proposed Indications

Natrecor is indicated for the short term intravenous therapy of congestive heart failure (CHF). In these patients, Natrecor rapidly reduces PCWP and SVR and increases CI. It also causes rapid symptomatic improvement.

2.3.2 Proposed Contraindications

None known.

2.3.3 Proposed Dosing Schedule

Nesiritide should be administered as a continuous IV infusion at a dose of 0.015 µg/kg/min. The infusion rate may be adjusted according to hemodynamic and clinical response, although it is recommended that dose increases be made no more frequently than every 3 hours to permit peak hemodynamic effects of nesiritide to be achieved. In the clinical trials, nesiritide was administered for up to 9 days, although 83% of patients received it for <72 hours.

No dose adjustment is proposed for patients with renal impairment.

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

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

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

2.3.4a Drug Interactions

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

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

2.3.4a Drug Interactions (cont)

Chemical/ Physical Interactions

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

Drug/ Laboratory Test Interactions

No laboratory test interactions with Natrecor have been identified.

2.3.4b Precautions

a. Cardiovascular

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

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

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

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

b. Pregnancy:

Category C

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

c. Nursing Mothers

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

d. Pediatrics

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

e. Geriatrics

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

2.3.4b Precautions

f. Carcinogenesis, mutagenesis, impairment of fertility

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

2.4 Foreign Marketing

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

3.0 Chemistry, Manufacturing, and Controls

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

4.0 Pharmacology

4.0.1 Pre-Clinical Pharmacology

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

4.0.2 Pre-clinical Pharmacokinetics

a. Absorption

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

b. Distribution

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

c. Pharmacokinetics & Metabolism

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

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

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

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

4.0.2 Pre-clinical Pharmacokinetics

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

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

In Vitro Protein Binding

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

Excretion

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

4.0.3 Pre-Clinical and Clinical Pharmacodynamics

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

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

4.1 Toxicology/ Genotoxicity/ Carcinogenicity

a. Single-dose Studies/ Repeated-Dose Studies

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

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

c. Genotoxicity/Mutagenicity/ Carcinogenicity

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

d. Reproductive Toxicity

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

5.0 Description of Clinical Data Sources

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

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

5.1 Primary Source Data (Development Program)

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

5.1.1 Study Type and Design/Patient Enumeration

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

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

Protocol	Control	Nesiritide	Trial Design
Phase II Dose-Ranging Studies			
704.305	6	24	Randomized, double-blind, placebo-controlled, single-dose bolus(0.3, 1.3, 10 or 15 µg/kg/min vs. placebo) study measuring hemodynamics.
704.306	4	12	Randomized, double-blind, placebo-controlled, four hour infusion (0.025 or 0.05 µg/kg/min vs. placebo) study measuring hemodynamics, neurohormone levels and renal function.
704.307	N/A (19) ^b	20	Randomized, double-blind, placebo-controlled, cross-over, escalating dose-infusion (0.003, 0.01, 0.03, and 0.1 µg/min) study measuring hemodynamics and renal function.
704.309	16	44	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Three doses (5 or 10 µg/kg q4 hours for 24 hours or 10 µg/kg q6 hours) were compared with placebo for effects on hemodynamics and renal function.
704.310	17	43	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Three doses (3, 5, or 10 µg/kg q4 hours for 24 hours) were compared with placebo for effects on hemodynamics and renal function.
704.311	29	74	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Three doses (0.25 µg/kg bolus, then 0.015 µg/kg/min, 0.5 µg/kg bolus, then 0.03 µg/kg/min, or 1.0 µg/kg bolus, then 0.06 µg/kg/min) as a 24-hour fixed dose infusion were compared with placebo for an effect on hemodynamics and renal function.
Phase III Clinical Efficacy & Safety Studies			
704.325	42	85	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Two doses (0.3 µg/kg bolus, then 0.015 µg/kg/min, or 0.6 µg/kg bolus, then 0.03 µg/kg/min for 24 hours of continuous infusion) were compared with placebo (for 6 hours, followed by active control) for effects on hemodynamics and renal function, and symptomatic improvement in CHF.
704.326	102	203	Randomized, open-label, parallel-design, dose-ranging study. Two doses (0.3 µg/kg bolus, then 0.015 µg/kg/min, or 0.6 µg/kg bolus, then 0.03 µg/kg/min via continuous infusion) were compared with 'standard care' for effects on renal function, weight loss, duration of hospitalization, need for additional parenteral therapies, need for readmission, need for intubation, need for dialysis or ultrafiltration, and symptomatic improvement in CHF. Duration of infusion at discretion of individual investigators.
Total	216 (235)	505	

a. Data from NDA volume 1.78

b. Cross-over designed trial.

5.1.1 Study Type and Design/Patient Enumeration

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

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

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

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

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

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

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

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

c. Trials comparing nesiritide with placebo.

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

5.1.2 Demographics

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

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

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

a. Data from the sponsor, NDA vol. 1 (p. 263), and vol. 78 (p. 201-204).

b. p Value calculated using T-Test, Kruskal-Wallis, or Fisher's Exact Test as appropriate

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

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

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

a. Data from the sponsor, NDA vol. 1 (p. 263), and vol. 78 (p. 201-204).

b. p Value calculated using T-Test or Kruskal-Wallis test as appropriate.

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

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

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

a. Data from the sponsor, NDA vol. 1 (p. 263), and vol. 78 (p. 201-204).

b. p Value calculated using ANOVA or Kruskal-Wallis tests as appropriate.

5.1.3 Extent of Exposure (dose/duration)

Natrecor Dose and Duration Exposure

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

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

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

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

b. Mean infusion dose in µg/kg/min. Any subject who received nesiritide at 0.015 µg/kg/min, and had their dose reduced at any time were counted in the <0.015 group (there were 18 such patients).

5.1.3 Extent of Exposure (dose/duration)

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

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

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

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

Type of Nesiritide Used

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

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

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

5.2 Relevant Information from Related INDs/ NDAs and Published Material

5.2.1 Information from Related INDs/ NDAs

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

5.2.2 Published Literature from Related INDs/ NDAs

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

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

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

5.2.2 Post-Marketing Experience

Nesiritide has not been previously marketed.

5.2.3 Literature

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

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

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

5.2.4 Advisory Committees

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

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

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

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

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

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

The guidance also stated the following:

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

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

5.3 Comment on Adequacy of Clinical Experience

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

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

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

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

5.4 Comment on Data Quality and Completeness

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

The Case Report Forms were submitted for all subjects who withdrew from the studies, including both medical and non-medical drop-outs. These were submitted as PDF files on optical discs.

The datasets were submitted both in SAS and hardcopy.

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

6.1 Review of the Protocol 704.311

6.1.1 Title of Study

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

6.1.2 Sites of Investigation and Investigators

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

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

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

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

6.1.3 Background

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

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

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

Initial protocol

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

Amendments

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

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

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

6.1.4 Study Design

General

This was a multicenter, randomized, parallel, double-blind study that planned to enroll 80 subjects with symptomatic NYHA Class II, III or IV CHF. Subjects were admitted to the hospital and had a Swan-Ganz catheter placed. After withholding other cardiac medications for 24-48 hours (except for diuretics and antiarrhythmics), subjects were randomized to receive 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.

6.1.5 Primary and Secondary Objective/ Endpoint

Primary Objective

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

Primary Endpoint

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

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

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

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

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

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

Secondary Objective

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

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

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

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

Secondary Endpoints

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

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

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

6.1.6 Number of Subjects/ Randomization

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

6.1.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

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

1. At least 18 years of age, with chronic New York Heart Association Class II, III, or IV CHF.
2. Male; or female that is surgically sterile, post menopausal, or using effective contraception.
3. Left ventricular systolic dysfunction, as evidenced by left ventricular ejection fraction of 35% or less (by either two-dimensional echocardiography or radionuclide or contrast ventriculography within the last 12 months).
4. On a standard treatment regimen for chronic CHF (such as ACE inhibitors, nitrates, or hydralazine, with or without oral digoxin/diuretic therapy) for at least 1 month, and on stable doses of these medications for at least 48 hours.
5. Fully understands all elements of and has signed the Informed Consent Form before initiation of protocol-specified procedures.
6. Hemodynamic criteria: PCWP >18 mm Hg; CI <2.5 ml/min/m².

Exclusion Criteria

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

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

6.1.8 Dosage/ Administration

There were three treatment groups in study 704.311:

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

6.1.9 Duration/ Adjustment of Therapy

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

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

6.1.10 Safety and Efficacy Measurements

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

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

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

a. Data from NDA volume 54, page 24.

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

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

6.1.11 Statistical Considerations

General statistical approach

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

The statistical analysis had one primary objectives:

- 1) to demonstrate a statistically significant dose effect with respect to reduction in PCWP at steady state plasma levels.
- 2) to demonstrate that at least one of the nesiritide treatment regimens produced a statistically significant reduction in PCWP after 24 hours of study drug infusion, as compared with placebo.

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

6.1.11 Statistical Considerations (cont)

Analytical methods

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

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

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

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

Hemodynamic Parameters

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

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

Renal Parameters

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

Interim Analyses and sample size estimation

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

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

6.1.12 Efficacy Outcomes

6.1.12.1 Patient Demographics & Baseline Characteristics

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

Table 6.1.12.1.1 Demographics of the 704.311 trial^a.

Demographic	Placebo n=29	Nesiritide 0.015 µg/kg/min n=22	Nesiritide 0.030 µg/kg/min n=26	Nesiritide 0.060 µg/kg/min n=26	p Value
Gender					0.537
Female	8 (28%)	4 (18%)	5 (19%)	2 (12%)	
Male	21 (72%)	18 (82%)	21 (81%)	23 (88%)	
Race					0.156
White	10 (34%)	15 (68%)	14 (54%)	17 (65%)	
Black	9 (31%)	6 (27%)	6 (23%)	5 (19%)	
Asian	0 (0%)	0 (0%)	1 (4%)	1 (4%)	
Hispanic	7 (24%)	1 (5%)	5 (19%)	3 (12%)	
Other	3 (10%)	0 (0%)	0 (0%)	0 (0%)	
NYHA Class at entry					0.514
II	0 (0%)	2 (9%)	2 (8%)	2 (8%)	
III	21 (72%)	14 (64%)	13 (50%)	15 (58%)	
IV	8 (28%)	6 (27%)	11 (42%)	9 (35%)	

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

6.1.12.1 Patient Demographics & Baseline Characteristics (cont)

Table 6.1.12.1.2 Demographics of the 704.311 trial^a.

Clinical Characteristic at Baseline	Placebo n=29	Nesiritide 0.015 µg/kg/min n=22	Nesiritide 0.030 µg/kg/min n=26	Nesiritide 0.060 µg/kg/min n=26	p Value
Ejection Fraction (%)					
Mean ±SD	18.5±7	22.4±7	19.4±7	24.2±7	0.011
Range	9 to 32	9 to 35	10 to 35	10 to 33	
PCWP (mm Hg)					
Mean ±SD	27.8±5.8	29.8±7.7	27.3±4.6	29.4±6.7	0.424
Mean Right Atrial Pressure (MRAP, mm Hg)	13.0±6	13.4±6	16.1±8	13.0±8	0.327
Mean Systolic BP (mm Hg)	112.±16	123±22	113±17	119±23	0.174
Rales Present	11 (41%)	11 (58%)	11 (42%)	10 (45%)	0.682
Peripheral Edema Present	11 (42%)	11 (58%)	12 (46%)	13 (62%)	0.517
S3 Present	20 (74%)	12 (63%)	20 (77%)	11 (50%)	0.194
Tachycardia (>100 PM)	2 (7%)	3 (15%)	6 (23%)	6 (26%)	0.286

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

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

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

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

a. Data from NDA volume 54, page 112.

b. p Value using Fisher's Exact Test.

6.1.12.2 Disposition and Follow-up of Subjects

Disposition

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

Table 6.1.12.2.1 Disposition of subjects randomized in the 704.311^a.

Patient Disposition	Placebo	Nesiritide 0.25/ 0.015	Nesiritide 0.5/ 0.030	Nesiritide 1.0/ 0.060
Randomized/ Enrolled	29	22	26	26
Completed	24 (83%)	22 (100%)	23 (88%)	20 (77%)
Discontinued (Total)	5 (17%)	0 (0%)	3 (12%)	6 (23%)
Adverse Event ^b	0 (0%)	0 (0%)	2 (8%)	6 (23%)
Inadequate Therapeutic Response ^c	5 (17%)	0 (0%)	1 (4%)	0 (0%)
Other reasons	0 (0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 54, page 108.

b. Difference between treatment groups significant (0.004) by Fischer's Exact Test.

c. Difference between treatment groups significant (0.021) by Fischer's Exact Test.

6.1.12.2a Subject Selection

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

6.1.12.2b Protocol Violations & Deviations

Incorrect study drug dosing

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

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

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

Missing PCWP measurements

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

Miscellaneous other protocol violations

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

6.1.12.2c Concomitant Therapies used after Trial Initiation

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

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

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

a. Data from NDA volume 54, page 114.

b. p Value using Fisher's Exact Test.

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

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

'Evaluable at 3 Hours' population analysis

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

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

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

a. Data from NDA volume 54, Appendix 1, Table 18A, 18B

b. See statistical section for statistical methods. p Value per sponsor.

c. Comparison using T-test.

'Evaluable at 24 Hours' population analysis

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

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

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

a. Data from NDA volume 54, Appendix 1, Table 19A, 19B

b. See statistical section for statistical methods. p Value per sponsor.

c. Comparison using T-test.

6.1.12.4 Analysis of Secondary Endpoints from Trial 704.311

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

The Effects of Nesiritide on Other Hemodynamic Endpoints

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

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

Hemodynamic Parameter	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
MRAP (mm Hg)	-0.8±3.7	-3.73.5	-3.3±4.3	-4.5±6.2	0.024
SVR (Dyne-sec/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 NDA 20-920, vol. 54, Table 20B through 30B. Data are expressed as absolute change from baseline for ITT population.
b. p Value comparing arithmetic means from baseline using ANOVA linear contrast except for heart rate, which used Omnibus F test.

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

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

Change in Hemodynamic Parameters from Baseline	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
MRAP (mm Hg)	-1.4±5	-2.6±4	-3.6±6	-2.9±4	0.493
SVR (Dyne-sec/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 NDA 20-920, vol. 54, Tables 20B through 31B. Data are expressed as absolute change from baseline for ITT population.
b. p Value comparing arithmetic means from baseline using ANOVA linear contrast except for heart rate, which used Omnibus F test.

The Relationship Between Hemodynamic Changes and Plasma Nesiritide Concentrations

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

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

6.1.12.5 Subgroup & Post-hoc Analyses of trial 704.311

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

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

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

Changes in PCWP in the Intent-to-Treat Population

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

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

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

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

b. See statistical section for statistical methods. p Value per sponsor.

c. Comparison using T-test.

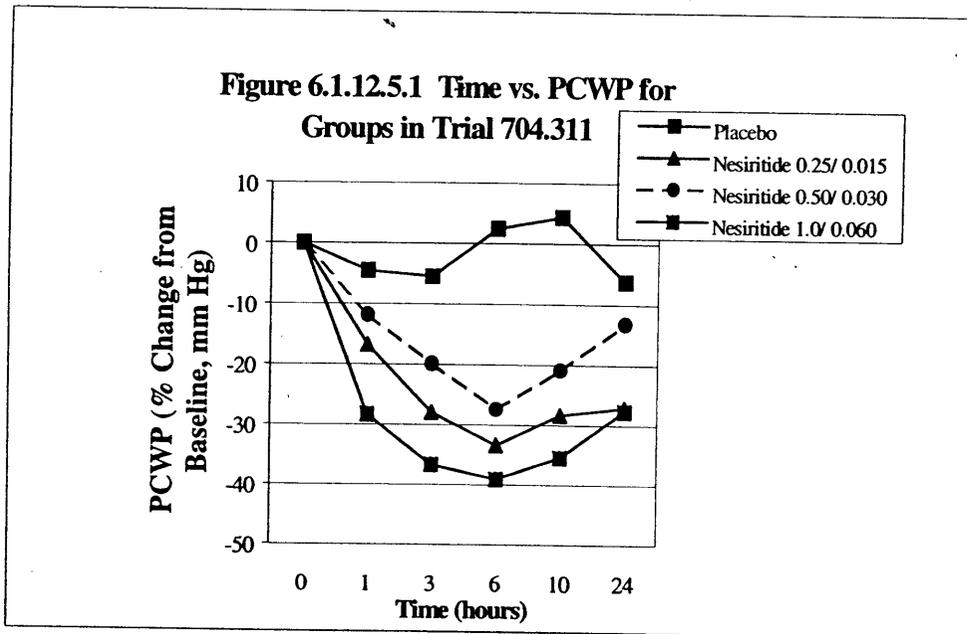
The FDA statistical reviewer also performed several statistical analyses based on the ITT population. The first analysis used the first 80 patients enrolled (the original proposed trial size), using the last value carried forward or worst rank imputation. The reductions in mean PCWP among the treatment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

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

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

a. Kruskal-Wallis using worst rank.

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



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

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

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

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

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

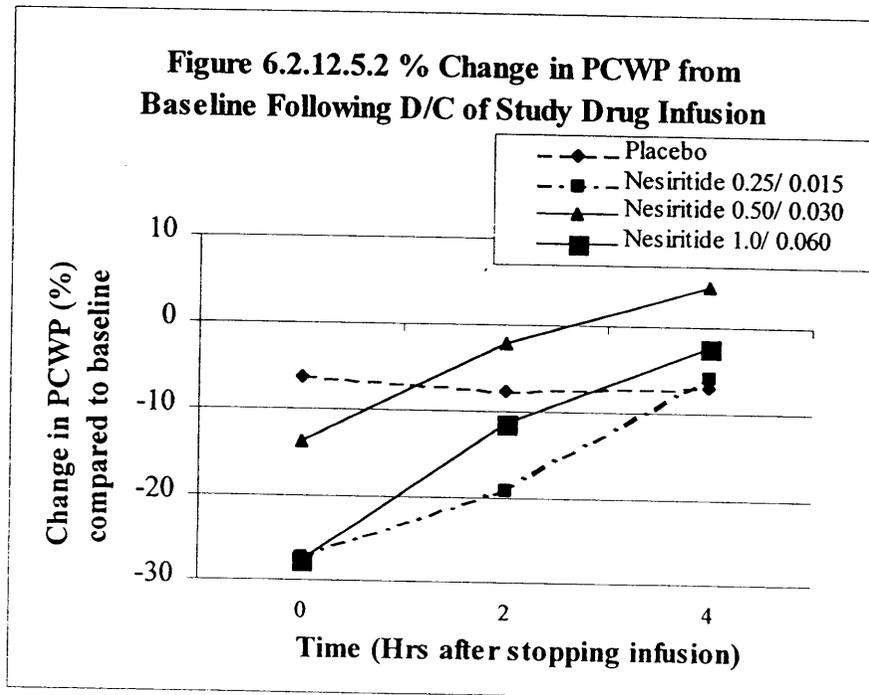
a. Data from sponsor at FDA request.

b. See statistical section for statistical methods. p Value per sponsor.

c. Comparison using T-test.

Effect of Nesiritide Withdrawal on Hemodynamics

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



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

Effects of Nesiritide on Urinary Indices

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

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

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

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

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

c. Comparison using Dunnet's t-test.

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

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

Measurement	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
Urine Sodium Excretion (meq/24 hrs) Mean±sd	156±91	85±58	104±80	146±285	0.369
Median	146	77	86	46	0.943
p Value compared with placebo ^c	--	NS	NS	NS	
Urine Potassium Excretion (meq/24 hrs) Mean±sd	85±56	66±34	63±19	81±42	0.166
Median	70	56	63	74	0.694
p Value compared with placebo ^c	--	NS	NS	NS	

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

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

c. Comparison using Dunnet's t-test.

Effect of Nesiritide on Miscellaneous Other Endpoints

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

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

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

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

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

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

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

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

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

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

6.1.13 Safety Outcomes

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

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

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

a. Data from NDA volume 54, Section 4.

b. Dose reduction could be done for a decrease in PCWP to >10 mm Hg, regardless of symptoms, as well as for adverse events.

c. Includes both symptomatic and asymptomatic hypotension.

d. Using Fischer exact test.

e. Using Cochran-Armitage trend test.

6.1.13.1 Comparisons of Defined Safety Endpoints

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

6.1.13.2 Comments on Specific Safety Parameters

Deaths

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

Table 6.1.13.2.1 Deaths in study 704.311^a.

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

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

Serious Adverse Events

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

Table 6.1.13.2.2 Serious Adverse Events in study 704.311^a.

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

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

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

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

Subject discontinuations

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

Table 6.1.13.2.3 Subject discontinuations in study 704.311^a.

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

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

6.1.14 Trial 704.311 Efficacy Summary

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

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

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

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

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

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

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

6.1.15 Trial 704.311 Safety Summary

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

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

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

6.1.16 Overall Summary of 704.311

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

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

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

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

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

6.2 Review of the Protocol 704.325

6.2.1 Title of Study

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

6.2.2 Sites of Investigation and Investigators

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

Table 6.2.2.1 Investigators for the 704.325 study^a.

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

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

6.2.3 Background

Original Submission: 6.28.96

Amendment One: 12.20.96

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

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

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

3. Clarified the type and timing of clinical assessments.

4. Added instructions for collecting information on intubation, dialysis, and ultrafiltration. during the 21-day follow-up period.

Study Dates for Subject Enrollment: 10.22.96 to 4.29.97

6.2.4 Study Design

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

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

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

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

6.2.5 Primary and Secondary Endpoints

Primary endpoint

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

6.2.6 Number of subjects/ randomization

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

6.2.7 Inclusion/ Exclusion Criteria

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

1. Be at least 18 years old.
2. Previous history of chronic CHF.
3. Present with symptomatic, decompensated CHF for which in-patient parenteral therapy was deemed appropriate.
4. Have documentation of PCWP ≥ 18 mm Hg, CI ≤ 2.7 mL/min/m², and systolic blood pressure ≥ 90 mm Hg with consistent baseline hemodynamic measurements.
5. Fully understand all elements of, and had signed, the written Informed Consent Form before the initiation of protocol-specified procedures.

Exclusion Criteria for study 704.325

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

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

6.2.8 Dosage/ Administration

Study Drug Administration

There were three treatment groups in study 704.325:

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

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

Blinding

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

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

Prior and Concomitant Therapy

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

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

Prior and Concomitant Therapy (cont)

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

6.2.9 Duration/ Adjustment of Therapy

Discontinuation of therapy

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

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

Administration of parenteral vasoactive compounds

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

6.2.10 Safety and Efficacy Measurements

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

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

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

Procedure	S c r e e n i n g	Baseline	Treatment Period											Post-Treatment				
			0	1.5	3	4.5	6	24	36	48	Day 3	Day 4	Day 5	<24 hrs after IV Tx	14	21		
Time																		
Med Hx, Physical Exam																		
ECG	X																	
CSR	X																	
Hold cardiac meds ^c	X	X	X	X	X	X	X	X	X	X ^d								
Swan-Ganz Catheter	X	X	X	X	X	X	X	X	X	X ^d								
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PCWP, SVR, CI	X	X	X	X	X	X	X	X	X	X	X	X ^d						
CBC, Chemistries ^b	X	X	X	X	X	X	X	X	X	X	X	X ^d						
Plasma hBNP levels		X						X	X ^e									X
Renin, aldo, norepi levels		X						X	X ^f									
hBNP Antibody level																		
I/Os, weights			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Na, K, CO ₂ , Cl, Cr ^g , BUN			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F/U Visit			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Data from NDA volume.
 b. Labs and hematology collected include: CBC (hemoglobin, hematocrit, WBC count and differential, platelet count); serum chemistries (BUN, creatinine, total bilirubin, AST/ALT, glucose, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol); urinalysis; and stool for occult blood.
 c. See Dosage/ Administration section above for description of protocol for withholding cardiac meds.
 d. Swan-Ganz to be removed after 24 hours if medically appropriate. Cardiac measurements to be done as long as S-Ganz present.
 e. Nesiritide subjects only.
 f. Norepinephrine levels at selected sites only.
 g. Administration after 24 hours at discretion of investigator.

6.2.11 Statistical Considerations

General statistical approach

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

Analysis Populations

Primary Statistical Analysis

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

- 1) the subject received cardiovascular intervention or the investigator unblinded the subject's treatment assignment less than 5.5 hours after start of study drug;
- 2) the subject received cardiovascular intervention or the investigator unblinded treatment between 5.5 and 6 hours after start of study drug and before obtaining a PCWP reading at least 5.5 hours after start of study drug; or
- 3) the subject died less than 6 hours after start of study drug.

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

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

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

Secondary Statistical Analyses

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

Statistical Methods for Individual Endpoints

Hemodynamic Data

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

Global Assessment of Clinical Status

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

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

The next table shows selected baseline clinical characteristics for the subjects in the study. There were no statistically significant differences between the treatment groups. Note, however, the higher incidence of ischemic CHF in the nesiritide groups and lower incidence of Class IV NYHA CHF in the placebo group.

Table 6.2.12.1.2 Baseline clinical characteristics in the Study 704.325^a.

Demographic	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	All Subjects n=127	p Value
Etiology of CHF					
Ischemic	15 (36%)	24 (56%)	19 (45%)	58 (46%)	0.377 ^b
Idiopathic	16 (38%)	7 (16%)	12 (29%)	35 (28%)	
Hypertensive	1 (2%)	0 (0%)	2 (5%)	3 (2%)	
Other ^c	10 (24%)	12 (28%)	9 (21%)	31 (24%)	
NYHA Class Prior to Hospitalization					
I	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.196 ^d
II	2 (5%)	0 (0%)	1 (2%)	3 (2.4%)	
III	25 (60%)	24 (56%)	18 (43%)	67 (53%)	
IV	15 (36%)	19 (44%)	23 (55%)	57 (45%)	
Reason for Current Decompensation					
Medication Noncompliance	5 (12%)	4 (9%)	5 (12%)	14 (11%)	0.882 ^b
Dietary Noncompliance	7 (17%)	7 (16%)	3 (7%)	17 (13%)	0.370
Arrhythmia	1 (2%)	2 (5%)	3 (7%)	6 (5%)	0.698
Hypertensive Crisis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---
Intercurrent infection	0 (0%)	3 (7%)	2 (5%)	5 (4%)	0.369
Recent Cardiac Surgery	0 (0%)	0 (0%)	1 (2%)	1 (<1%)	0.661
Recent Noncardiac Surgery	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---
Recent Myocardial Infarction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---
Other	16 (38%)	11 (26%)	9 (21%)	36 (28%)	0.234
Unknown	19 (45%)	23 (53%)	23 (55%)	65 (51%)	0.697
Pre-study systolic BP (mm Hg)	118	111	120		0.045

a. Data from NDA volume 59, Appendix 1, table 4.

b. p Value calculated using Fishers exact test.

c. Includes alcoholic, valvular/rheumatic, diabetic, drug-induced and miscellaneous causes for heart failure.

d. p Value calculated from Kruskal-Wallis test.

In data not shown, the three groups were well balanced with regard to past medical history of hypertension, MI, coronary artery disease, and previous CABG/ angioplasty. No subject had a history of MI within the 7 days prior to admission into the study. One subject in the placebo group had a history of sudden death within the previous 7 days. The treatment groups were also balanced with regard to history of other medical disease, including: Atrial fibrillation/flutter; frequent PVCs; ventricular tachycardia/fibrillation; A-V blocks; renal or hepatic insufficiency; lung disease; malignancies; anemia and blood disorders; and other serious medical conditions.

The next table summarizes the physical exams of the subjects on admission into the study. Note the higher % of 'rales present' and 'pedal edema present' in the placebo group. This will be compared with physical exams following therapy.

Table 6.2.12.1.3 Baseline physical exam findings in the Study 704.325^a.

Demographic	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^b
Tachycardia (≥100 BPM) Present	11 (26%)	10 (23%)	9 (21%)	0.901
Rales Present	30 (71%)	22 (51%)	24 (57%)	0.149
S3 Present	36 (86%)	36 (84%)	31 (74%)	0.386
S4 Present	10 (24%)	7 (16%)	9 (21%)	0.677
Jugular Venous Distension Present	31 (74%)	28 (65%)	34 (81%)	0.251
Pedal Edema Present	31 (74%)	27 (63%)	24 (57%)	0.275

a. Data from NDA volume 59, Appendix 1, table 9.

b. p Value calculated using Fishers exact test.

Finally, the use of other cardiovascular medications, including diuretics, was similar in the three groups prior to entering the study (see NDA vol. 59, appendix 1, table 18 for list). The most commonly prescribed drugs were diuretics, prescribed in 62% of all subjects, and ACE inhibitors, prescribed in 46% of subjects.

6.2.12.2 Disposition and Follow-up of Subjects

Disposition

The table below summarizes the disposition of the subjects enrolled in study 704.325, including the reasons for subject discontinuation. All but one of the subjects were followed for the full 21 days of the study. Subject 369-008 (in the 0.30/ 0.015 nesiritide group) was lost to F/U on day 8.

Table 6.2.12.2.1 Disposition of subjects randomized in the study 704.325^a.

Patient Disposition	Placebo	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030
Randomized and Enrolled	42	43	42
Completed	41	42	39
Discontinued prior to 5.5 hrs after start of infusion	1 (2%)	1 (2%)	3 (7%)
D/C due to AE	1 (2%)	1 (2%)	3 (7%)
Other reasons	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 59, section 4.2.

Subject Follow-up

The table below summarizes the follow-up available for subjects by treatment group, depicted as the last day with available data. No subjects were lost to follow-up before 21 days, and with few outliers (especially in the 0.3/0.015 group) the groups had similar follow-up.

Table 6.2.12.2.2 Follow-up of subjects (in days) randomized in the study 704.325^a.

Patient Disposition ^b	Placebo	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030
Alive (mean±sd) Range	25.1±6 21 to 47 (n=40)	35.6±36 21 to 234 (n=40)	27.1±8 21 to 56 (n=40)
Dead (mean±sd) Range	16.5±1 16 to 17 (n=2)	4.5±1 () 4 to 5 (n=2)	17.5±4 15 to 20 (n=2)

a. Data from NDA volume 59, Appendix 1, Table 11.

b. Data shown as last follow-up day, by subject's last clinical status.

6.2.12.2a Subject Selection

Twelve subjects were randomized but not enrolled because they did not meet all of the study inclusion/exclusion criteria. One was too unstable, and the other 11 failed one or more of the hemodynamic criteria for inclusion.

6.2.12.2b Protocol Violations & Deviations

Three subjects had protocol violations related to entry criteria. None of these deviations were considered by the sponsor to be clinically significant or likely to materially affect the outcome of the study.

1. Subject 017-002 was permitted to enroll although baseline hemodynamic measurements varied by slightly more than 15%.

2. Subject 588-001 was permitted to enroll with a baseline cardiac index of 2.98 mL/min/m².

3. Subject 360-002 did not have a previous history of chronic CHF; however, he had been admitted to the hospital with dyspnea and was diagnosed with CHF prior to study enrollment.

One investigator inadvertently was unblinded to the treatment group assignment of a subject (subject 470-001, 0.03 µg/kg/min nesiritide group) approximately 24 hours after the initiation of study drug when she entered the pharmacist's code number, rather than her own, into the Automated Telephone Randomization System. This mistake obviously did not affect the primary endpoint analysis.

Most significantly, 11 subjects were categorized as having been unblinded prematurely (i.e., the 6-hour PCWP was obtained after learning the subject's treatment group). Eleven subjects also received IV vasoactive intervention prior to 6 hours. The table below lists these subjects. Overall, these 18 subjects were listed as 'worst outcomes' for analysis, per the protocol.

Table 6.2.12.2.3 Subjects classified as 'worst outcomes' in study 704.325^a.

Treatment Group And Subject ID #	Reason and Time of Worst Case Classification ^b	Comments
Placebo		
356-001	Unblinding (5:55)	Subject had (ineligible) PCWP reading at 5:55.
368-006	Unblinding (5:58)	Subject had (ineligible) PCWP reading at 6:00.
369-018	CV intervention (3:10)	Subject received 80 mg lasix by IV bolus.
487-003	Unblinding (5:57)	Subject had (ineligible) PCWP reading at 6:00.
503-001	CV intervention (5:54); Unblinding (5:54)	Subject received 40 mg lasix by IV bolus and 2.5 µg/kg/min dopamine by IV infusion.
503-004	Unblinding (5:54)	Subject had (ineligible) PCWP reading at 6:00.
503-008	CV intervention (5:15)	Subject had (ineligible) PCWP reading at 6:00. Subject received 200 mg lasix by IV bolus.
Nesiritide 0.3/ 0.015 µg/kg/min		
352-001	Unblinding (5:16); CV intervention (5:35)	Subject received 2.0 µg/kg/min dobutamine by IV infusion.
352-003	Unblinding (5:26)	Subject had (ineligible) PCWP reading at 6:00.
352-009	CV intervention (2:45); CV intervention (3:00)	Subject received 5 µg/kg/min dobutamine by IV infusion, and then received 100 mg IV demadex.
360-002	Unblinding (5:38)	Subject had (ineligible) PCWP reading at 5:38.
370-006	CV intervention (0:51)	Subject received 10 µg/kg/min dobutamine by IV infusion.
487-001	CV intervention (3:15); Unblinding (5:57)	Subject received 100 mg lasix by IV bolus.
487-002	CV intervention (3:05)	Subject had (ineligible) PCWP reading at 6:00. Subject received 60 mg lasix by IV bolus.
Nesiritide 0.6/ 0.03 µg/kg/min		
017-003	CV intervention (5:30)	Subject received 100 mg lasix by IV bolus. Subject had (ineligible) PCWP reading at 6:00.
356-002	Unblinding (5:39)	Subject had (ineligible) PCWP reading at 6:00.
498-002	Unblinding (5:44)	Subject had (ineligible) PCWP reading at 5:44.
498-003	CV intervention (4:25)	Subject received 300 mg lasix by IV bolus.

a. Data from NDA study report for 704.325, Appendix 2, section 3.1.

b. Time given as hours:minutes after start of study drug infusion.

6.2.12.2c Concomitant Therapies used after Trial Initiation

Infusion of Study Drug

The table below summarizes the infusion of study drug during the initial 5.5-6 hours of therapy (up to the time of the primary endpoint). Several points can be made. First, while the majority of subjects remained on study drug for the entire period ≥93% for all study groups, a significantly higher % of subjects in the high-dose nesiritide group had their doses reduced or terminated for an adverse event such as hypotension. There were also more subjects in the high-dose nesiritide group who had their dose of study drug reduced for clinical improvement.

Table 6.2.12.2.4 Study drug infusion in study 704.325^a.

Characteristic of infusion	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42
Subjects receiving study drug at end of 5.5 hours	41 (98%)	42 (98%)	39 (93%)
Subjects terminated due by 5.5 hours for:			
Adverse event	1 (2%)	0 (0%)	3 (7%)
Inadequate therapeutic response	0 (0%)	1 (2%)	0 (0%)
Subjects with dose modifications prior to primary endpoint (6 hrs):			
Dose reduction	0 (0%)	3 (7%)	7 (17%)
Dose interruption	0 (0%)	0 (0%)	0 (0%)
Dose termination	1 (2%)	0 (0%)	3 (7%)
Reasons for dose modifications prior to primary endpoint (6 hrs):			
Clinical improvement	0 (0%)	1 (2%)	4 (10%)
Hypotension	0 (0%)	2 (5%)	2 (5%)
Worsening CHF	0 (0%)	0 (0%)	0 (0%)
Other adverse events	1 (2%)	1 (2%)	3 (7%)
Other	0 (0%)	0 (0%)	2 (5%)

a. Data from NDA volume 59, Appendix I, Tables 13 and 14.

Infusion of Nesiritide

The duration of nesiritide infusion in the two dose groups was similar: 33.4±35 hrs in the 0.3/ 0.015 nesiritide group; and 38.8±32 hrs in the 0.6/ 0.030 nesiritide group.

The amount of nesiritide infused was significantly different, as would be expected: 29.5±31 µg/kg in the 0.3/ 0.015 nesiritide group; and 59.9±53 µg/kg in the 0.6/ 0.030 nesiritide group.

Infusion of other vasoactive medications

The sponsor summarized the administration of vasoactive medication and diuretics in several ways. First, the duration of all parenteral cardiovascular treatments was not significantly different between the three groups, although there was a trend towards a greater duration of administration in the nesiritide groups.

Table 6.2.12.2.5 Duration of parenteral CV medication infusion in study 704.325^a.

Duration of parenteral cardiovascular treatments	Control n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42
Mean±sd	81.5±45	92.9±50	90.8±47
Median	72.7	92.9	109.8
Range	6 to 144	6 to 144	4.5 to 144

a. Data from NDA volume 59, Appendix I, Table 16 and electronic datasets.

For some subjects in the nesiritide groups, no other parenteral cardiovascular (CV) agent was administered during the hospitalization, while for other nesiritide was discontinued and another agent started, or another agent was added to nesiritide. The table below summarizes these groups.

Table 6.2.12.2.6 Infusion of nesiritide and other parenteral cardiovascular meds in study 704.325^a.

Medications administered	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42
Subjects who received only nesiritide	N/A	7 (16%)	10 (24%)
Subjects who D/C'd nesiritide and started another agent			
First CV med added after nesiritide D/C'd	N/A	20 (47%)	18 (43%)
Dobutamine	N/A	9 (45%)	13 (72%)
Dobutamine/Dopamine	N/A	1 (5%)	2 (11%)
Milrinone	N/A	5 (25%)	2 (11%)
Nitroglycerin	N/A	1 (5%)	0 (0%)
Nitroprusside alone	N/A	2 (10%)	0 (0%)
Other combinations	N/A	2 (10%)	1 (6%)
Subjects who received nesiritide in combination with another agent	N/A	16 (37%)	14 (33%)
Agent combined with nesiritide			
Dobutamine alone		14 (88%)	11 (79%)
Other combinations		2 (12%)	3 (21%)

a. Data from NDA volume 59, Appendix 1, Table 17.

Concomitant medication use during study drug administration

A significantly higher percentage of subjects used diuretics during the first 24 hours following initiation of study drug in the placebo group than in either of the nesiritide groups. Diuretics were used in 38 (90%), 31 (72%), and 21 (50%) of the placebo, nesiritide 0.3/0.015, and nesiritide 0.6/ 0.030 groups respectively (p Value <0.001 using Fischer's exact test).

6.2.12.3 Primary Analyses of the Study 704.325 Results

The primary endpoint was pulmonary capillary wedge pressure (PCWP), expressed as a percentage change from baseline, 6 hours after initiation of study drug for the 'worst outcome' population. The company also performed two other analysis of the PCWP data: 1) a parametric analysis using 'last data carried forward', and 2) a parametric analysis using a 'data as available' dataset. These analyses were discussed with Dr. Temple at the end-of-phase II meeting, 7.23.96.

The FDA statistician performed a series of analyses on the primary endpoint, which have been incorporated below and is also presented in full in appendix six: FDA statistics review. Based on those analyses, the statistical reviewer made the following conclusions:

1. Statistically significance treatment difference among the treatment groups exists with regard to changes in PCWP from baseline through 6 hours, using both the 'Worst-Outcome Population' and the 'Last Value Carried-Forward' Population.
2. Both dose regimens of nesiritide effectively lower PCWP as compared to the control.
3. The numerical trend of the nesiritide treatment effect to lower PCWP appears consistent across all investigators.
4. Nesiritide lowers PCWP significantly in both women and men through 6 hours.

Worst-Outcome Population

For this population, the difference between placebo and either of the two nesiritide dose-groups was highly statistically significant at the 6 hour time-point. This result was true for the pre-specified primary endpoint analysis (% change from baseline at 6 hours, shaded in the table below), or for the absolute change in PCWP (in mm Hg).

Table 6.2.12.3.1 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) ^c	---	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	

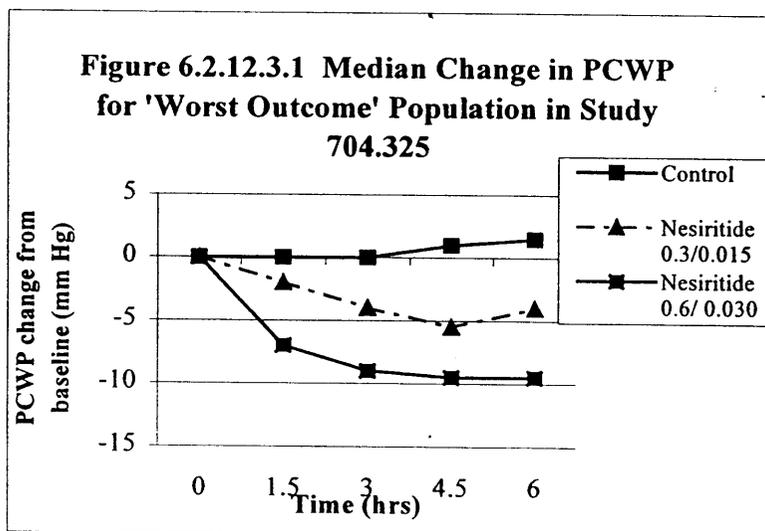
a. Data from NDA volume 59, Appendix 1, Table 22A, 22B, and 22C.

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 compare the 6 hour value for each group vs. Baseline using 1-sample Wilcoxon.

This data is also presented below, along with the change from baseline at earlier and later timepoints for the same study population. There was a clear trend in the 'worst-case' population for greater decreases in PCWP in the high-dose nesiritide group. The change from baseline achieved nominal significance for both of the nesiritide dose-groups at the 1.5 hr time-point and all subsequent time-points. Given the non-parametric nature of this analysis, no mean data (or standard deviations) are possible, and the graph illustrates median values.



6.2.12.4 Non-Primary Analyses of Study 704.325: Changes in PCWP

'Last Data Carried-Forward' population.

The sponsor also performed a parametric analysis of the PCWP data, using a 'carried forward' population (see Appendix 5 for details). The table below summarizes the results of these analyses for PCWP. Again, the nesiritide groups were significantly different from placebo at 6 hours.

Table 6.2.12.4.1 Analysis of change in PCWP using 'last value carried forward' population from study 704.325^a.

Mean and median change from Baseline for PCWP at 6 hours for 'last value carried forward' population	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^b
PCWP at baseline and 6 hours (mm Hg)				
At baseline, mean ±sd (mm Hg)	28.5±7	28.1±6	27.5±6	0.818 ^c
At 6 hours, mean ±sd (mm Hg)	30.4±8	22.1±6	18.0±8	<0.001
Range at 6 hours	13 to 52	7 to 44	6 to 38	
p Value at 6 hours (compared with control baseline) ^c	---	<0.001	<0.001	
Mean±SD (% Change from Baseline-6 hrs)				
p Value (change from baseline) ^c	+8.8±26%	-20.6±23%	-35.2±22%	<0.001
p Value (compared with control baseline) ^d	---	<0.001	<0.001	

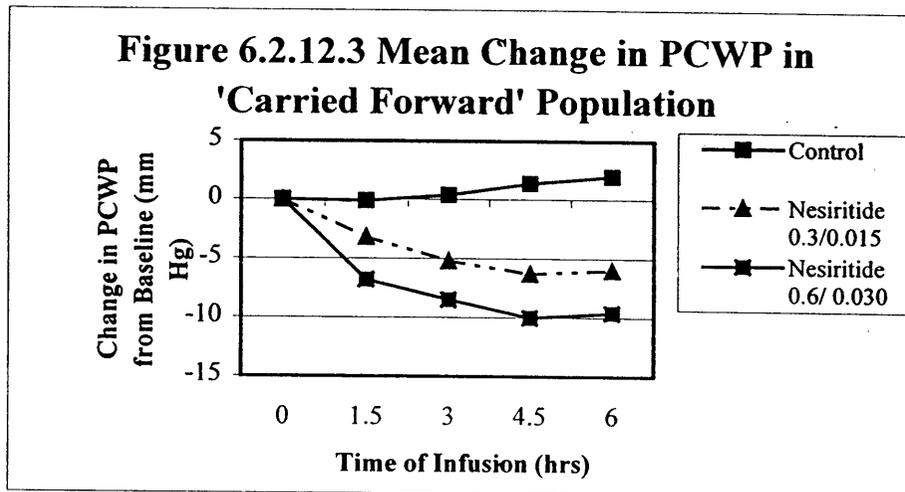
a. Data from NDA volume 59, Appendix 1, Table 26A and 26C.

b. p Value using Omnibus F test.

c. p Value compares the 6 hour value for each group vs. Baseline using t-test.

d. p Value compares the 6 hour value for each group individually with the control using pairwise contrasts.

The data from baseline to 6 hours in the 'last data carried forward' population is shown below. The trend towards greater effect in the two nesiritide groups persists.



'Data as Available' population

Finally, the sponsor performed an analysis of the PCWP using a 'data as available' population (see Appendix 5 for details). Note the broad range of changes in PCWP within all three groups.

Table 6.2.12.4.2 Analysis of change in PCWP using 'data as available' population from study 704.325^a.

Mean and median change from Baseline for PCWP at 6 hours for 'last value carried forward' population ^a	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^b
PCWP at baseline and 6 hours (mm Hg)				
At baseline (mm Hg)	28.5±7	28.1±7	27.5±6	
At 6 hours (mm Hg)	30.4±8	21.4±8	17.8±7	<0.001
% Change from baseline Mean±SD	7.8±26	-21.9±24	-35.5±22	<0.001
Median	0	-24.6	-33.3	
Range	-29.7 to +70.4	-72.5 to +28.0	-78.6 to +13.6	
p Value (change from baseline) ^c	0.061	<0.001	<0.001	
Change from Baseline (mm Hg) Mean±SD	1.8±7	-6.3±7	-9.8±6	<0.001
Median	0	-6	-10	
p Value (change from baseline) ^c	0.126	<0.001	<0.001	
p Value (compared with control) ^d	---	<0.001	<0.001	

a. Data from NDA volume 60, appendix 2, tables 1A, 1B, and 1C.

b. p Value using Omnibus F test.

c. p Value compares the 6 hour value for each group vs. Baseline using 1-sample t test.

d. p Value compares the 6 hour value for each group individually with the control baseline using pairwise contrast.

6.2.12.4 Non-Primary Analyses of Study 704.325: Hemodynamic Data

6-Hour Hemodynamic Data

The sponsor also collected and analyzed data on several other hemodynamic measures, and these are presented in the table below. For ease of interpretation, the population shown is the 'carried forward' population. Where significant differences exist in the findings in this population with the other two analyzed populations ('worst outcome' and 'data as available') these will be noted in a footnote to the table. Overall, the significant effects of nesiritide on hemodynamics are also seen in this population.

Table 6.2.12.4.3 Summary of changes in selected hemodynamic measurements using 'last value carried forward' population from study 704.325^a.

Hemodynamic Parameter	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^b
<u>Right Atrial Pressure (RAP), mm Hg</u>				
RAP at baseline and 6 hours (mm Hg)				
At baseline (mm Hg)	14.2±6	15.1±7	14.3±7	0.817
At 6 hours (mm Hg)	14.6±6	12.1±7	9.1±6	0.001
p Value (compared to control) ^d	---	0.076	<0.001	
% Change in RAP from baseline at 6 hrs (%)				
Mean±SD	+8.1±29	-12.0±42	-39.4±31	<0.001
Median	0	-20	-40	
Range	-53 to +93.8	-48 to +200	-100 to +58	
p Value (change from baseline) ^c	0.076	0.081	<0.001	
p Value (comp. to control) ^d	---	0.010	<0.001	
<u>Systemic Vascular Resistance(SVR) dynes/sec/cm²</u>				
SVR at baseline and 6 hours				
At baseline	1524±493	1598±582	1686±589	0.407
At 6 hours	1693±633	1386±539	1340±511	0.010
p Value (compared to control) ^d	---	0.014	0.005	
% Change in SVR from baseline at 6 hrs (%)				
Mean±SD	+12.8±30	-12.6±25	-17.7±26	<0.001
Median	11.2	-9.2	-20.2	
Range	-52 to +84	-68 to +73	-62 to +51	
p Value (change from baseline) ^c	0.010	0.004	<0.001	
p Value (comp. to control) ^d	---	<0.001	<0.001	
<u>Cardiac Index (CI), L/min/m²</u>				
CI at baseline and 6 hours				
At baseline	2.0±0.4	1.8±0.5	1.9±0.5	0.159
At 6 hours	1.9±0.5	2.1±0.5	2.3±0.6	0.002
p Value (compared to control) ^d	---	0.165	<0.0001	
% Change in CI from baseline at 6 hrs (%)				
Mean±SD	-4.4±26	16.2±33	27.5±40	<0.001
Median	-2.6	12.1	21.4	
Range	-43 to +88	-28 to +159	-40 to +110	
p Value (change from baseline) ^c	0.269	0.004	<0.001	
p Value (comp. to control) ^d	---	0.006	<0.001	

a. Data from NDA volume 59, Appendix 1, Table 27, 28, and 30 (A and C).

b. p Value using Omnibus F test.

c. p Value compares the 6 hour value for each group individually with the control baseline using 1-sample t test.

d. p Value compares the 6 hour value for each group individually with the control baseline using pairwise contrasts.

The next continues to summarize hemodynamic effects of nesiritide, emphasizing the systemic effects of study drug. Of note, there was a highly significant decrease in systemic mean arterial pressure that appeared to be dose-related, but no increase in heart rate.

Table 6.2.12.4.4 Summary of changes in selected hemodynamic measurements using 'last value carried forward' population from study 704.325 (cont)^a.

Hemodynamic Parameter	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^b
<i>Pulmonary Vascular Resistance</i> <i>(PVR), dynes/sec/cm²</i>				
PVR at baseline and 6 hours				
At baseline	278.8±200	293.8±183	242.2±201	0.472
At 6 hours	305.1±303	232.4±155	240.1±139	0.227
p Value (compared to control) ^d	---	0.116	0.163	
Change in PVR from baseline at 6 hrs (mm Hg)				
Mean±SD	+26.3±197	-62.2±100	-2.0±142	0.033
Median	10.3	-53.2	-8.3	
Range	-393 to +540	-296 to +148	-218 to +459	
p Value (change from baseline) ^d	0.392	<0.001	0.928	
<i>Mean Pulmonary Artery Pressure (MPAP) mm Hg</i>				
MPAP at baseline and 6 hours				
At baseline	41.1±9	39.6±9	38.3±8	0.338
At 6 hours	43.1±11	33.0±9	30.6±10	<0.001
p Value (compared to control) ^d	---	<0.001	<0.001	
Change in MPAP from baseline at 6 hrs (mm Hg)				
Mean±SD	+2.0±5.8	-7.0±6.9	-7.7±7.6	<0.001
Median	2.5	-5.0	-8.8	
Range	-11 to +18	-23 to +4.0	-23 to +10	
p Value (change from baseline) ^d	0.031	<0.001	<0.001	
<i>Mean Systemic Arterial BP (MAP), mm Hg</i>				
MAP at baseline and 6 hours				
At baseline	86.2±12.6	81.2±10.0	85.4±11.3	0.103
At 6 hours	86.7±13.1	76.2±11.4	76.8±10.2	<0.001
p Value (compared to control) ^d	---	<0.001	<0.001	
Change in MAP from baseline at 6 hrs (mm Hg)				
Mean±SD	0.5±7.8	-5.1±11.0	-3.6±8.0	0.001
Median	-1.3	-4.5	-8.7	
Range	-17 to +19	-44 to +20	-24 to +11	
p Value (change from baseline) ^c	---	0.005	<0.001	
p Value (comp. to control) ^d	---	0.008	<0.001	
<i>Heart Rate (HR), BPM</i>				
HR at baseline and 6 hours				
At baseline	89.5±12.8	90.3±14.6	87.4±16.7	0.640
At 6 hours	90.9±15.4	88.8±14.5	87.5±16.0	
p Value (compared to control) ^d	---	0.516	0.300	
Change in HR from baseline at 6 hrs (mm Hg)				
Mean±SD	1.4 ±7	-1.6±7	0.0±9	0.218
Median	0.5	-3.0	0.0	
Range	-16 to +24	-16 to +14	-28 to +28	
p Value (change from baseline) ^c	0.240	0.149	0.972	
p Value (comp. to control) ^d	---	0.082	0.435	

a. Data from NDA volume 59, Appendix 1, Tables 33, 36, 39, and 40 (A and B).

b. p Value using Omnibus F test.

c. p Value compares the 6 hour value for each group individually with the control baseline using 1-sample t test.

d. p Value compares the 6 hour value for each group individually with the control baseline using pairwise contrasts.

Change in Respiratory Rate Through 6 hours

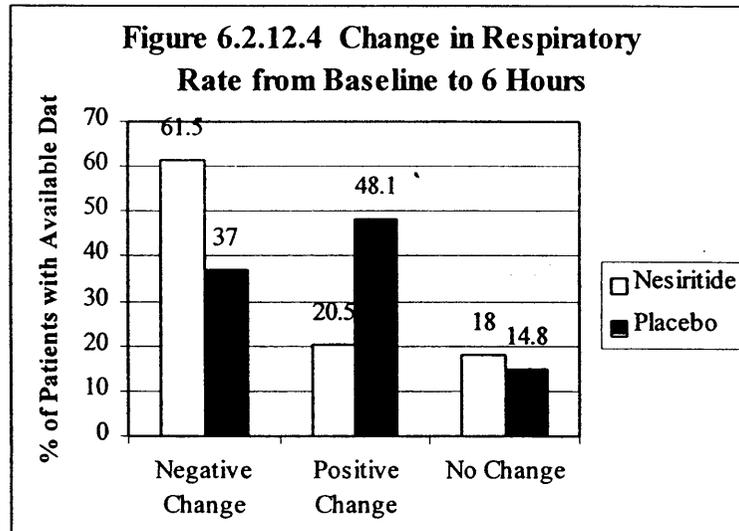
One of the symptoms of CHF, which tends to improve with successful treatment, is ‘breathlessness’, which often results in an increase in respiratory rate. While there are obviously many other causes of tachypnea, if a drug is successful at lowering the respiratory rate in patients with decompensated CHF, this would suggest it has some beneficial effect on ‘breathlessness.’

The table below summarizes the data from 704.325 for changes in respiratory rate between 0 and 6 hours for the nesiritide group (combining both doses) and placebo. For the entire population, as well as those patients who started with tachypnea (≥ 20 respirations per minute), there was a small decrease in the mean and median respiratory rates in the nesiritide group. This decrease was not seen in the placebo group.

Table 6.2.12.4a Summary of changes in respiratory rate (RR) using ‘last value carried forward’ population with respiratory rate ≥ 20 RPM from study 704.325^a.

Parameter of Respiratory Rate (RR) (respirations per minute)	Placebo N=27	Nesiritide N=39
Mean \pm SD	+2.86 \pm 2.8	-1.69 \pm 3.6
Median	0	-2
Patients with Decreased RR (0-6 hours) (n, %)	10 (37.0%)	24 (62%) ^b
Patients with Increased RR (0-6 hours) (n, %)	13 (48%)	8 (20%)
Patients with Unchanged RR (0-6 hours) (n, %)	4 (15%)	7 (18%)

a. Data from Medical Officer analysis of individual Case Report Forms, not independently confirmed by sponsor.
b. p Value comparing incidence of decreased RR using Fisher’s Exact test =0.08.



A similar trend was seen when the entire population of study 704.325 was analyzed, irrespective of their baseline respiratory rate.

Table 6.2.12.4b Summary of changes in respiratory rate (RR) using ‘last value carried forward’ population from study 704.325^a.

Parameter of Respiratory Rate (RR) (respirations per minute)	Placebo N=43	Nesiritide N=83
Mean \pm SD	+0.70 \pm 3.2	-0.34 \pm 3.9
Median	+1	-1
Patients with Decreased RR (0-6 hours) (n, %)	11 (25.6%)	42 (50.6%)
Patients with Increased RR (0-6 hours) (n, %)	24 (55.8%)	31 (37.3%)
Patients with Unchanged RR (0-6 hours) (n, %)	8 (18.0%)	10 (12.0%)

a. Data from Medical Officer analysis of individual Case Report Forms, not independently confirmed by sponsor.

24-Hour Hemodynamic Data

The sponsor also summarized the hemodynamic data (where available) through 24 hours. See Appendix 5 for details of this analysis. Since this analysis did not include the control subjects, its greatest utility is in examining the hemodynamic changes that occurred between 6 and 24 hours for subjects treated with nesiritide. To highlight this, the data is shown from 0 to 6 hours and from 6 to 24 hours. Almost all of the detected hemodynamic effect of nesiritide occurred in the first 6 hours of therapy.

Table 6.2.12.4.5 Summary of changes in selected hemodynamic measurements using 'all nesiritide subjects with a 24 hour evaluation' population from study 704.325^a.

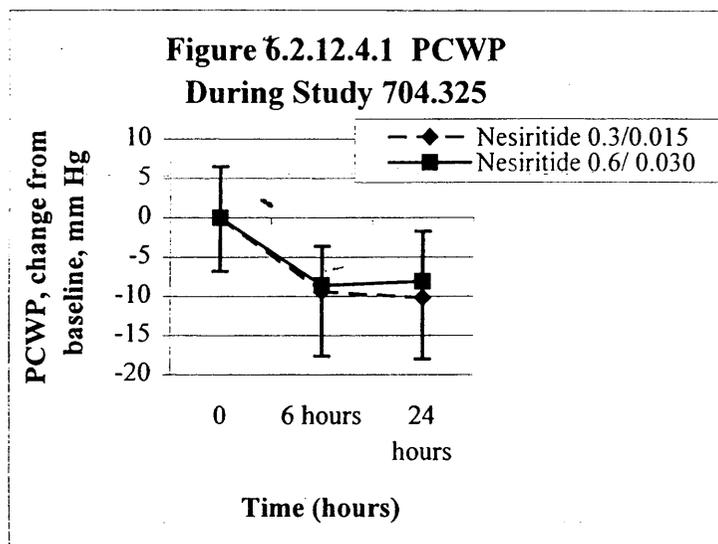
Hemodynamic Parameter	Nesiritide 0.3/ 0.015 n=37	Nesiritide 0.6/ 0.030 n=38
<u>Pulmonary Capillary Wedge Pressure (mm Hg)</u>		
Baseline	28.7±6.5	27.4±6.5
Change in PCWP from 0 to 6 hours		
Mean±SD	-6.8±7.7	-9.5±5.4
Range	-29 to +36	-20 to +3.0
Change in PCWP from 6 to 24 hours		
Mean±SD	-0.6±7	-0.3±5.8
Range	-13 to +15	-13 to +11
Change in PCWP from 0 to 24 hours		
Mean±SD	-7.0±9	-9.9±6
Range	-26 to +13	-21 to +5
<u>Systemic Vascular Resistance (SVR)</u>		
Change in SVR from 0 to 6 hours		
Mean±SD	-318.4±513	-279.8±481
Range	-1933 to +299	-1218 to +865
Change in SVR from 6 to 24 hours		
Mean±SD	-229.1±474	-1.2±404
Range	-1652 to +544	-992 to +1318
Change in SVR from 0 to 24 hours		
Mean±SD	-489.5±630	-345.0±372
Range	-2244 to +685	-1238 to +865
<u>Cardiac Index (CI), L/min/m²</u>		
Change in CI from 0 to 6 hours		
Mean±SD	0.3±0.6	0.4±0.7
Range	-0.6 to 1.8	-1.0 to 1.9
Change in CI from 6 to 24 hours		
Mean±SD	0.2±0.7	0.1±0.7
Range	-1.0 to +2.2	-2.0 to +1.6
Change in CI from 0 to 24 hours		
Mean±SD	0.5±0.6	0.5±0.7
Range	-0.9 to +1.8	-1.0 to +3.2

a. Data from NDA volume 59, Appendix 1, Table 42A, 443A and 44A.

a. Data from NDA volume 59, Appendix 1, Table 42A, 443A and 44A.

b. p Value using Omnibus F test.

This lack of additional effect of nesiritide beyond the effect seen at the end of the 6 hour time-point was also seen in the subset of subjects who received only nesiritide during the first 24 hours (no other parenteral vasoactive medications, a sort of 'responder-analysis'). The graph below is representative of the hemodynamic data for that subset, showing the changes in PCWP from 0 to 6 and 6 to 24 hours for the two nesiritide groups. In absolute terms, the PCWP declined from 30.1 to 20.7, and from 27.0 to 18.4 at 6 hours in the 0.3/0.015 and 0.6/ 0.030 groups respectively.



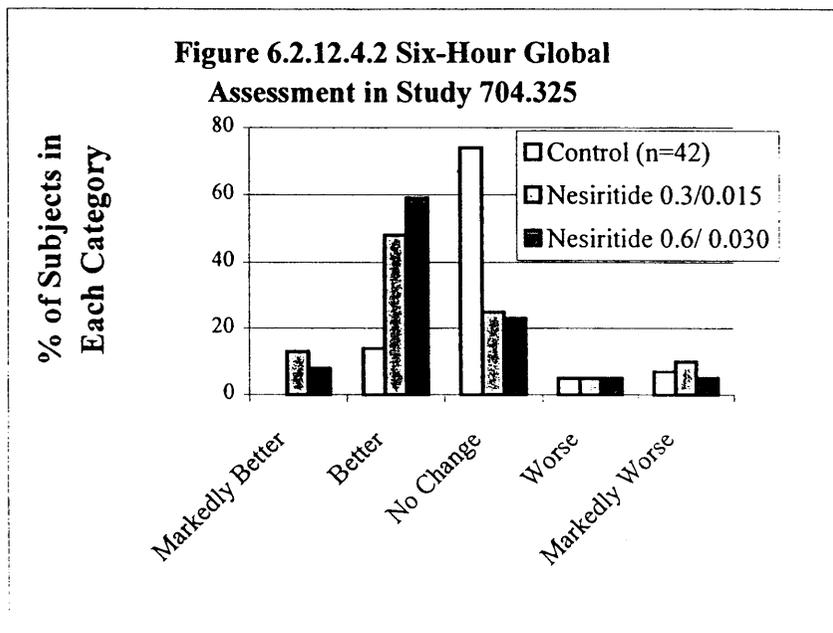
Global Assessment of Clinical Status (Intent-to-Treat Population)

After six and 24 hours, and within 24 hours after discontinuation of all parenteral therapy for the episode of decompensated CHF (or on day 5, whichever occurred first), the subject and the physician were to assess the subject's overall clinical status and rate it: markedly better; better; no change; worse; or markedly worse as compared to baseline. Subjects who received a cardiovascular intervention for worsening CHF during the 6-hour blinded period were to be automatically assigned a rating of markedly worse for all subsequent assessments. The global assessments at the three time points are shown in table 6.2.12.4.4 below, followed by a summary of the individual time points.

It is important to remember that the investigator who filled out the investigator's and patient's assessments also knew the PCWP at the 6 hour time point, as discussed in section 6.2.8 above (Blinding).

6 Hours

Using a non-parametric analysis, as per the primary endpoint analysis, subjects who received nesiritide felt significant improvement relative to the control patients at the end of 6. The graph below shows the % of subjects in each of the assessment categories for the three dose-groups at the end of six hours, showing the higher % of subjects in the nesiritide groups who felt markedly better or better, compared with control. For this time point, the control subjects received placebo, and all study drugs were administered in double-blinded fashion per protocol.



Numerically, the investigator and patient's assessments agreed well. The percentage of the exact agreements between the two assessments averaged 71.1% (73.8%, 67.5%, 71.8% for placebo, 0.03, and 0.06 Natrecor groups, respectively). If allow at most one category difference, overall agreement rate of the assessments is 98.8% (100.0% for placebo, 97.5% and 97.4% for 0.03 and 0.06 Natrecor groups).

The percentage of patients who had Hour 6 assessment scores by patient or investigator indicating an improvement (better or markedly better) is much higher for the Natrecor treated group as compared to placebo. The difference is nominally statistically significant.

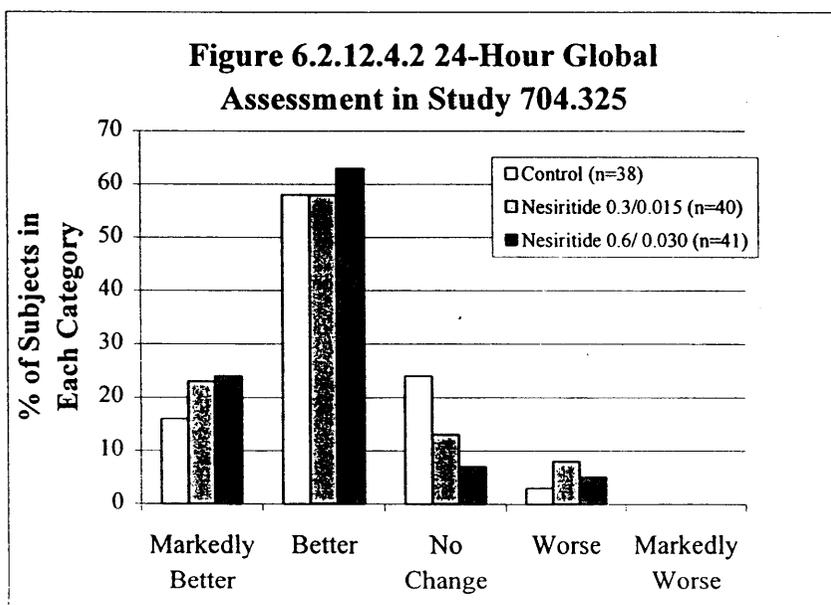
Table 6.2.12.4.6 Improvement in global assessment of clinical status at hour 6 in trial 704.325.

Treatment	Assessment n (%)		Total	p Value
	Not improved	Improved		
<i>Investigator Assessment</i>				
Placebo	40 (95.8%)	2 (4.8)	42	0.001 ^a
Nesiritide 0.3/ 0.015	18 (45%)	22 (55.0)	40	
Nesiritide 0.6/ 0.030	9 (23.1%)	30 (76.9)	39	
<i>Patient Assessment</i>				
Placebo	36 (85.7%)	6 (14.3)	42	0.001 ^a
Nesiritide 0.3/ 0.015	16 (40%)	24 (60.0)	40	
Nesiritide 0.6/ 0.030	13 (33.3%)	26 (66.7)	39	

a. Overall difference, two-sided chi-squared-test per the sponsor.

24 Hours

The global clinical status of all three study groups were much more similar at the 24 hour time-point, even though the average subject continued to receive nesiritide for >30 hours (see section 6.2.12.2c above). There was an increase in the % of nesiritide patients who felt 'markedly better,' but the greatest changes occurred in the control group, where the % of patients who felt 'markedly better' or 'better' increased substantially. It is important to remember that after 6 hours patients in all groups could receive other therapies (i.e., diuretics, ACE inhibitors) unblinded.



Numerically, slightly higher percentage of nesiritide patients had improvement in clinical status at Hour 24 (with a score better or markedly better) for both investigator evaluation and patient evaluation. While there was good agreement between the investigator- and subject-derived scores of clinical status at 24 hours, recall that the same investigator filled out the investigator's assessment and recorded the patient's responses.

Table 6.2.12.4.7 Improvement in global assessment of clinical status at Hour 24 in trial 704.325.

Treatment	Assessment N (%)		Total	p Value
	Not improved	Improved ^b		
<i>Investigator Assessment</i>				
Control ^c	10 (26.3%)	28 (73.7%)	38	0.406 ^a
hBNP 0.3/ 0.015	8 (20%)	32 (80.0%)	40	
hBNP 0.6/ 0.030	6 (14.3%)	36 (85.7%)	42	
<i>Patient Assessment</i>				
Control ^c	10 (26.3%)	28 (73.7%)	38	0.281 ^a
hBNP 0.3/ 0.015	8 (20%)	32 (80.0%)	40	
hBNP 0.6/ 0.030	5 (12.2%)	36 (87.8%)	41	

a. overall difference, two-sided chi²-test.

b. Includes either 'markedly improved' or 'improved'. All others are considered Not Improved.

c. Placebo for 0-6 hours and active control from 6-24 hours.

Finally, when the Global Assessment was performed after discontinuation of all parenteral vasoactive substances (or at day 5), no significant difference between the three groups was seen. This data, along with the numbers corresponding to the graph points above, are presented in tabular form below. The table below shows the data results of the assessment done by the subjects. The investigators also obtained similar data, not shown, for each subject. Again, the only significant difference between control and nesiritide occurred at the 6 hour evaluation (see NDA vol. 59, Appendix 1, table 46A for details).

The table below summarizes the global assessments performed by the patients at 6 and 24 hours, and at day 5 (or after discontinuation of parenteral therapy).

Table 6.2.12.4.8 Subject global assessments at end of parenteral vasoactive administration, from study 704.325^a.

Hemodynamic Parameter	Control ^d	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030	p Value ^c
<u>6 Hour Global Assessment</u>				
Markedly Better	n=42 0 (0%)	n=40 5 (13%)	n=39 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%)	
<u>24 Hour Global Assessment</u>				
Markedly Better	n=38 6 (16%)	n=40 9 (23%)	n=41 10 (24%)	0.337
Better	22 (58%)	23 (58%)	26 (63%)	
No Change	9 (24%)	5 (13%)	3 (7%)	
Worse	1 (3%)	3 (8%)	2 (5%)	
Markedly Worse	0 (0%)	0 (0%)	0 (0%)	
<u>Last Recorded Global Assessment^b</u>				
Markedly Better	n=40 15 (38%)	n=41 16 (39%)	n=41 15 (37%)	0.852
Better	17 (43%)	19 (46%)	23 (56%)	
No Change	8 (20%)	5 (12%)	2 (5%)	
Worse	0 (0%)	2 (2%)	1 (2%)	
Markedly Worse	0 (0%)	0 (0%)	0 (0%)	

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

b. Global assessment must be made at least 20 hours after start of study drug.

c. p Value using Omnibus F test.

d. Control comparator was placebo for first 6 hours and active control at 24 hours.

The FDA statistician performed a series of analyses on the measured changes in global status, which have been incorporated into the presentation above, and is also presented in full in appendix six: FDA statistics review. Based on those analyses, the statistical reviewer made the following conclusions:

1. There was a statistically significant difference between placebo and both nesiritide dose groups with regard to global assessment of clinical status at Hour 6 by investigators or by patients.
2. Numerically, slightly higher percentage of nesiritide patients had improvement in clinical status at Hour 24 (with a score of 'better' or 'much better') for both investigator evaluation and patient evaluation, compared with the control group (placebo-treated 0-6 hours, active control-treated 6-24 hours).

Assessment of Individual Signs and Symptoms of CHF

The sponsor also assessed a set of clinical symptoms and signs of decompensated CHF at baseline, at 6 and 24 hours after the initiation of study drug, and within 24 hours after discontinuation of all parenteral therapy for this episode of decompensated CHF (or on day 5, whichever occurred first). Like the Global Assessments discussed above, these were performed by physicians with knowledge of the patient's clinical status, including their PCWP readings through 6 hours. The following symptoms and signs of CHF were assessed at baseline: appetite, breathing difficulty (dyspnea), peripheral circulation, fatigue, lightheadedness, and peripheral edema. At each follow-up time point, each symptom or sign of CHF was assessed as to whether it had improved, remained unchanged, or worsened from baseline. In order to aid in the interpretation of the data, it is presented in three tables, each summarizing one time point (6 hrs., 24 hrs., or last recorded assessment). As for the global symptom assessment, the only significant effects of nesiritide were seen at the 6 hour time-point.

1. Signs and Symptoms of CHF at the End of 6 Hours

The sponsor also collected changes in individual signs and sxs of CHF at 6 and 24 hours. These results are summarized below. Nesiritide use was associated with nominally* statistically significant improvements in several individual signs and sxs at the end of 6 hours: breathing difficulty, appetite, fatigue, light-headedness, peripheral edema, and overall CHF score.

Table 6.2.12.4.9 Assessment of individual signs and sxs of CHF after 6 hrs of study drug 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
<u>Breathing Difficulty: Baseline</u>				
No breathing difficulty	3 (7%)	2 (5%)	4 (10%)	0.628
Breathing difficulty with moderate activity	7 (17%)	5 (12%)	4 (10%)	
Breathing difficulty with minimal activity	22 (52%)	23 (53%)	21 (50%)	
Breathing difficulty at rest	10 (24%)	13 (30%)	13 (31%)	
<u>Breathing Difficulty: 6 hour results</u>				
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%)	
<u>Appetite: Baseline</u>				
Good appetite	22 (52%)	20 (47%)	24 (57%)	0.626
Decreased appetite	14 (33%)	19 (44%)	15 (36%)	
No appetite	6 (14%)	4 (9%)	3 (7%)	
<u>Appetite: 6 hour results</u>				
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%)	

a. Data from NDA volume 59, Appendix 1, Tables 47A and 48A. All subjects with available data are included (≥90% of enrolled subjects for all points).

b. p Value using Kruskal-Wallis test.

Table 6.2.12.4.10 Assessment of individual signs and symptoms of CHF after 6 hours of study drug 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
Peripheral Circulation: Baseline				
Extremities warm and well-perfused	26 (62%)	18 (42%)	26 (62%)	0.106
Extremities cool with decreased perfusion	12 (29%)	21 (49%)	15 (36%)	
Extremities cold and vasoconstricted	4 (10%)	4 (9%)	1 (2%)	
Peripheral Circulation: 6 hour time-point				
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: Baseline				
No fatigue	2 (5%)	1 (2%)	2 (5%)	0.253
Fatigue with moderate activity	9 (21%)	7 (16%)	4 (10%)	
Fatigue with minimal activity	21 (50%)	22 (51%)	20 (48%)	
Fatigue at rest	10 (24%)	13 (30%)	16 (38%)	
Fatigue: 6 hour time-point				
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%)	

a. Data from NDA volume 59, Appendix 1, Tables 49A through 50A. All subjects with available data are included (≥90% of enrolled subjects for all points).

b. p Value using Kruskal-Wallis test.

Table 6.2.12.4.11 Assessment of individual signs and symptoms of CHF after 6 hours of study drug 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
Lightheadedness: Baseline				
No lightheadedness	32 (76%)	29 (67%)	32 (76%)	0.592
Lightheadedness with moderate activity	4 (10%)	5 (12%)	2 (5%)	
Lightheadedness with minimal activity	5 (12%)	5 (12%)	3 (7%)	
Light headedness at rest	1 (2%)	4 (9%)	5 (12%)	
Lightheadedness: 6 hour results				
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: Baseline				
None	13 (31%)	13 (30%)	19 (45%)	0.382
Mild	19 (45%)	15 (35%)	13 (31%)	
Moderate	6 (14%)	12 (28%)	6 (14%)	
Severe	4 (10%)	3 (7%)	4 (10%)	
Peripheral Edema: 6 hour results				
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.

Table 6.2.12.4.12 Assessment of individual signs and symptoms of CHF after 6 hours of study drug 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	9.0 to 14.0	7.0 to 14.0	7.0 to 14.0	

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.

2. Signs and Symptoms of CHF at the End of 24 Hours

At the end of 24 hours, there were non-significant trends towards greater improvement in fatigue and lightheadedness in the nesiritide groups, but no other differences between the two treatment groups. The overall CHF total score was quite similar for all three groups at the end of 24 hours.

Table 6.2.12.4.13 Assessment of individual signs and symptoms of CHF after 24 hours of study drug in study 704.325^a.

Signs and Symptoms of CHF at 24 hours (compared with baseline)	Active Control n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.0305 n=42	p Value ^c
Breathing Difficulty: 24 hour results				
Improved from baseline	25 (66%)	29 (73%)	33 (79%)	0.513
No change from baseline	12 (32%)	9 (23%)	7 (17%)	
Worse than baseline	1 (3%)	2 (5%)	2 (5%)	
Appetite: 24 hour results				
Improved from baseline	10 (26%)	10 (25%)	14 (33%)	0.804
No change from baseline	27 (71%)	29 (73%)	26 (62%)	
Worse than baseline	1 (3%)	1 (3%)	2 (5%)	
Peripheral Circulation: 24 hour time-point				
Improved from baseline	9 (24%)	11 (28%)	10 (24%)	0.849
No change from baseline	29 (76%)	29 (73%)	31 (74%)	
Worse than baseline	0 (0%)	0 (0%)	1 (2%)	
Fatigue: 24 hour time-point				
Improved from baseline	12 (32%)	17 (43%)	25 (60%)	0.062
No change from baseline	24 (63%)	21 (53%)	15 (36%)	
Worse than baseline	2 (5%)	2 (5%)	2 (5%)	
Lightheadedness: 24 hour results				
Improved from baseline	3 (8%)	8 (20%)	6 (14%)	0.211
No change from baseline	34 (89%)	32 (80%)	36 (86%)	
Worse than baseline	1 (3%)	0 (0%)	0 (0%)	
Peripheral Edema: 24 hour results				
Improved from baseline	21 (55%)	18 (45%)	21 (50%)	0.612
No change from baseline	17 (45%)	21 (53%)	20 (48%)	
Worse than baseline	0 (0%)	1 (3%)	1 (2%)	
CHF Total Score: 24 hour time-point				
Mean ±SD	10.0±2.0	9.8±2.0	9.6±1.8	0.493
Median	10.0	10.0	10.0	
Range	7.0 to 16.0	6.0 to 14.0	7.0 to 16.0	

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).

c. p Value using Omnibus F test.

3. Signs and Symptoms of CHF after 5 Days (or Last Evaluable)

Similarly, at the last recorded assessment of symptoms (or after 5 days, if the patient remained hospitalized), there was no trend towards greater improvement in the nesiritide group.

Table 6.2.12.4.14 Assessment of individual signs and symptoms of CHF for last recorded assessment in study 704.325^a.

Signs and Symptoms of CHF at time of last recorded assessment (or 5 days).	Active Control n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^b
Breathing Difficulty: last recorded assessment				
Improved from baseline	34 (83%)	32 (78%)	33 (79%)	0.789
No change from baseline	7 (17%)	7 (17%)	8 (19%)	
Worse than baseline	0 (0%)	2 (5%)	1 (2%)	
Appetite: last recorded assessment				
Improved from baseline	22 (54%)	20 (49%)	20 (48%)	0.789
No change from baseline	19 (46%)	20 (49%)	21 (50%)	
Worse than baseline	0 (0%)	1 (2%)	1 (2%)	
Peripheral Circulation: last recorded assessment				
Improved from baseline	16 (39%)	18 (44%)	13 (31%)	0.582
No change from baseline	24 (59%)	22 (54%)	29 (69%)	
Worse than baseline	1 (2%)	1 (2%)	0 (0%)	
Fatigue: last recorded assessment				
Improved from baseline	24 (59%)	24 (59%)	31 (74%)	0.240
No change from baseline	16 (39%)	14 (34%)	10 (24%)	
Worse than baseline	1 (2%)	3 (7%)	1 (2%)	
Lightheadedness: last recorded assessment				
Improved from baseline	5 (12%)	11 (27%)	9 (21%)	0.203
No change from baseline	35 (85%)	30 (73%)	32 (76%)	
Worse than baseline	1 (2%)	0 (0%)	1 (2%)	
Peripheral Edema: last recorded assessment				
Improved from baseline	28 (68%)	27 (66%)	22 (52%)	0.263
No change from baseline	13 (32%)	13 (32%)	19 (45%)	
Worse than baseline	0 (0%)	1 (2%)	1 (2%)	
CHF Total Score: last recorded assessment				
Mean ±SD	8.9±1.8	9.0±2.3	9.1±1.7	0.796
Median	9.0	9.0	9.0	
Range	8.0 to 10.0	7.0 to 10.0	8.0 to 10.0	

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 Kruskal-Wallis test.

Relationship Between Changes in PCWP and Changes in CHF Signs and Symptoms

The sponsor performed an analysis seeking to link the changes in PCWP to changes in symptomatic relief. The results of this analysis are shown in Appendix 17. Given the knowledge of the clinical status of the patients, including PCWPs, by the investigators who performed the symptom assessments, the power of these analyses are limited.

Effect of Study Drug on Volume Status

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. In the Intent to Treat population, for the period between 0 and 6 hours, subjects who received nesiritide had significantly more out than in, when compared with the control subjects. For the 0 to 24 hour period, however, control subjects had significantly more out, when compared with nesiritide-treated subjects. In both cases, the increase in net fluid out was due to increased urine volume (rather than decreased fluid intake). It needs to be remembered that the nesiritide group received fewer diuretics during this initial 24-hour period, which may account for some of this discrepancy.

Table 6.2.12.4.15 Assessment 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.

In support of this possibility, if the subjects who received diuretics during the first 6 hours were removed, there remained significant differences in overall volume status at the end of 6 hours between control and nesiritide groups, except that in this case, there was more net output in the nesiritide groups relative to placebo. Over 24 hours, this difference would amount to approximately 200 mls.

Table 6.2.12.4.14 Assessment of volume status during first 6 hours in study 704.325^a.

Volume parameter and period of measurement	Control n=39	Nesiritide 0.3/ 0.015 n=38	Nesiritide 0.6/ 0.030 n=39	p Value ^c
0 to 6 Hour Data				
Fluid Intake (Mean ±SD)	96.2±53	98.3±41	94.1±58	0.936
Urine Output (ml/ hr)	63.9±41	92.9±61	110.7±73	0.001
Output minus Intake (ml/ hr)	-32.3±70	-3.6±70	+15.9±71	0.013

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

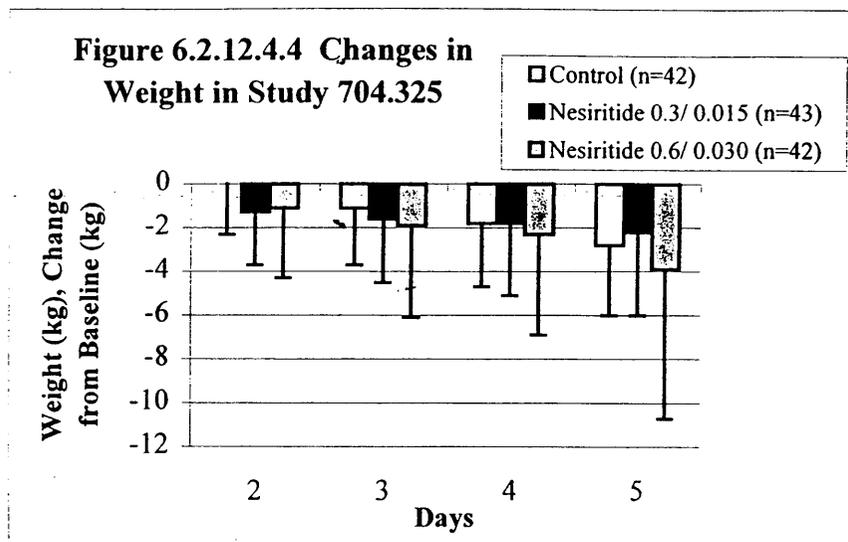
c. p Value using Omnibus F test.

Plasma aldosterone and norepinephrine levels

A proposed mechanism for the diuresis and natriuresis seen in animals following nesiritide infusion is the inhibition of aldosterone production. In support of this possibility, the median aldosterone concentration was decreased at the end of 6 hours in the nesiritide group, compared with controls. For the control group, aldosterone levels rose 0.6 ng/dl (+5%), compared with a decrease of 1.2 ng/dl in the nesiritide 0.015 group (-11%) and -1.6 ng/dl in the nesiritide 0.030 group (-14.5%), p=0.030. This trend was also true if the subjects who did not receive ACE inhibitors before the trial were examined. There were no significant effects, and no discernable trend towards an effect of nesiritide on norepinephrine levels at the end of six hours.

Changes in subject weight during hospitalization

Finally, the sponsor 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).



Effect of Study Drug on Hospitalization

The effect of study drug on hospitalization was examined in several ways. First, the duration of hospitalization prior to entry into the study was 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 ($p > 0.05$). One individual in the high-dose nesiritide group accounted for most of the numerical increase in duration of hospitalization.

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. 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 6.2.12.4.17 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
Subjects discharged prior to day 21	40 (95%)	35 (81%)	34 (81%)	
Total days of hospitalization for subjects D/C'd prior to 21 days				
Mean \pm SD	7.6 \pm 4.9	7.3 \pm 3.9	7.8 \pm 4.5	0.891 ^b
Median	6.5	6.0	7.0	
Time to discharge				
2-3 days	10 (24%)	5 (12%)	5 (12%)	
4-5 days	8 (19%)	10 (23%)	5 (12%)	
6-7 days	5 (12%)	6 (14%)	13 (31%)	
8-14 days	11 (26%)	13 (30%)	8 (19%)	
15-21 days	6 (14%)	1 (2%)	3 (7%)	
Subjects not discharged as of day 21	2 (5%)	8 (19%)	8 (19%)	0.085 ^c

a. Data from NDA volume 59, Appendix I, Tables 59 and 60. All subjects with available data are included ($\geq 90\%$ of enrolled subjects for all points).

b. p Value using Kruskal-Wallis test.

c. p Value using Fisher's exact test.

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. In data not shown, subjects hospitalized > 5 days when entering the trial also had similar duration of hospitalization.

Effect of Study Drug on Hospital Readmission

As shown above, more subjects in the nesiritide groups were not discharged before day 21 (see table 6.2.12.2e.5). If one looks just at those subjects who were discharged, however, there was a non-significant increase in the rate of re-admission through 21 days. The reasons for these admissions, however, were mostly other medical conditions, unrelated to CHF.

Table 6.2.12.4.18 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 volume 59, Appendix 1, Tables 60. Includes all subjects who were discharged before day 21.

b. p Value using Fisher's Exact test.

6.2.13 Safety Outcomes

The deaths, serious adverse events, and adverse events by body system will be considered in section 8.1 and 8.2 below. The section below will comment on the following specific safety parameters from the Study 704.325: deaths; SAEs; and subject discontinuations. Given the potential nephrotoxicity of this compound, the renal effects of nesiritide in the trial will also be summarized. The first table summarizes the adverse clinical events that occurred in the Study 704.325 within the first 21 days of follow-up. In general, adverse events were common in this acutely ill population, with an excess of SAEs (by percentage) occurring in the high-dose nesiritide group. Deaths were balanced in the three groups.

Table 6.2.13.1 Clinical adverse experience (AE) summary from the Study 704.325^a.

Clinical event	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42
With any AE	0 (0%)	0 (0%)	0 (0%)
With Serious AE (SAE) ^b	2 (5%)	4 (10%)	9 (21%)
Discontinued due to an AE ^c	1 (2%)	1 (2%)	3 (7%)
Lost to Follow-up	0 (0%)	1 (2%)	0 (0%)
Deaths ^b	2 (5%)	2 (5%)	2 (5%)

a. Data from NDA volume 59, sections 6.3-6.4, and Appendix 62.

b. Data through 21 day period.

c. Subjects who discontinued the trial prior to 5.5 hours.

Deaths

Two deaths occurred in each of the three treatment groups (six total). The narrative summaries for these deaths can be found in appendix two. All of the deaths in the nesiritide groups occurred after discontinuation of nesiritide. Three other deaths occurred in the nesiritide 0.6/ 0.030 group at days 29, 30 and 31 respectively.

Table 6.2.13.2 Deaths in study 704.325^a.

Subject #	Treatment	Day of Death	Cause of Death	Notes
368-001	Control	15	Ventricular Fibrillation ARF	Hx recent tricuspid valve repair, CABG
503-001	Control	17	Ventricular Fibrillation End-stage CHF Pneumonia	
374-001	Nesiritide 0.3/0.015	4	CHF DNR	
382-013	Nesiritide 0.3/0.015	5	CHF DNR	
357-002	Nesiritide 0.6/0.030	15	AMI (in ER)	Discharged from hospital day 2
370-002	Nesiritide 0.6/0.030	20	Acute cardiac decompensation	

a. Data from NDA vol. 59, section 6.2 and Case Report Forms.

SAEs

Sixteen subjects were reported with SAEs during their 21 day follow-up. Narratives for these events can be found in Appendix 3. Percentage-wise, the high-dose nesiritide group had the most SAEs reported (9/42, 21% of subjects).

Table 6.2.13.3 Serious Adverse Events in study 704.325^a.

Subject #	Treatment	Day of Event	SAE	Notes
502-001 369-018	Placebo “	3 1 (0.5 hrs)	CVA V. Tach	
352-009 360-006 373-002 523-003	Nesiritide 0.3/ 0.015 “ “ “	1 (3 hrs) 1 (6.5 hrs) 3 7, 14	Worsening CHF Worsening CHF Line Sepsis Hyperglycemia, Syncope/ bradycardia	Led to study drug discontinuation Led to study drug discontinuation Day 27, permanent pacemaker placed
324-001 352-007 357-001 368-003 369-009 373-004 382-001 523-004	Nesiritide 0.6/ 0.030 “ “ “ “ “ “ “	3 3 1 (18 hrs) 7, 29 11, 30 2 13 3	Cardiac arrest 3 rd -degree heart block Apnea Subclavian vein thrombosis Ileus Hypotension Septic shock Death (day 29) Acute Renal Failure Sepsis Cardiogenic shock Death (day 30) Acute Renal Failure Hypotension Death (day 31) Acute Renal Failure Hypotension Bacteremia	Received tracheostomy Bowel resection required Occurred on nesiritide infusion S/p femoral arterial occlusion, CABG Received nesiritide twice, the second time associated with atrial fibrillation

a. Data from NDA vol. 59, section 6.3 and Case Report Forms.

The narratives for the two individuals who had hypotensive SAEs while on nesiritide are below.

1. *Subject 357-001 (Nesiritide, 0.03 µg/kg/min)* Subject 357-001 is a 60-year-old white man with a history of NYHA Class IV CHF, idiopathic, dilated cardiomyopathy, pancreatitis, and small bowel obstruction requiring several surgical bowel resections. After 18 hours of nesiritide therapy, he developed an ileus believed to be an exacerbation of his underlying abdominal condition. Worsening of the small bowel obstruction over the subsequent hours resulted in a severe hypotensive crisis, requiring electrical cardioversion, intubation, and treatment with dopamine, dobutamine, norepinephrine, nitroglycerin, and an intra-aortic balloon pump. The subject recovered completely from this episode within 72 hours and was discharged to home on day 14.

2. *Subject 373-004 (Nesiritide, 0.03 µg/kg/min)* Subject 373-004 was a 51-year-old black woman with NYHA Class IV CHF and chronic renal insufficiency. For 1 month before entering the study, she had been hospitalized for asthma and CHF exacerbations and had developed progressive renal failure, presumably due to progressive heart failure. After 24 hours, the nesiritide infusion was interrupted due to respiratory distress and hypotension. Milrinone and renal dose dopamine were started. On day 2, she developed oliguria and became hemodynamically refractory to milrinone; thus, the milrinone was replaced with dobutamine. The following day, nesiritide was also restarted but was discontinued on day 5. On day 5, due to deteriorating chronic renal failure, the patient was started on hemodialysis. Thereafter, she was treated with dobutamine for progressive endstage heart failure for nearly 1 month. She died on day 31 due to endstage heart failure, while awaiting cardiac transplantation.

Subject discontinuations

Five subjects discontinued prior to hour 5.5 of the study drug infusion. Their narratives can be found in Appendix Four.

Table 6.2.13.4 Subject discontinuations in study 704.325^a.

Subject #	Treatment	Day of D/C	AE	Notes
369-018	Placebo	1 (0.5 hrs)	V. Tach	
352-009	Nesiritide 0.3/ 0.015	1 (3 hrs)	Worsening CHF	Led to study drug discontinuation
356-002	Nesiritide 0.6/ 0.030	1 (4.5 hrs)	Symptomatic hypotension	Later died (see above)
357-002	"	1 (4.5 hrs)	Nausea PCWP = 6 mm Hg	
498-003	"	1 (4 hrs)	Oliguria	

a. Data from NDA vol. 59, section 6.24 and Case Report Forms. Discontinuations reported for 0-5.5 hours of study drug infusion.

Medical Interventions

The number of patients intubated at baseline and during the 21 day follow-up is shown below. Note the 5 subjects in the high-dose nesiritide group intubated before day 21 compared with 1 in the control and low-dose nesiritide groups.

Table 6.2.13.5 Requirement for intubations in study 704.325^a.

Intubations	Control n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42
# Intubated at start of study	1 (2%)	1 (2%)	2 (5%)
# Intubated for cardiac reasons through day 21	1 (2%)	1 (2%)	5 (12%)

a. Data from NDA vol. 59, Appendix 1, Table 61.

Of these 7 patients, all but 2 in the nesiritide 0.030 group were intubated >10 days after start of study drug infusion.

1. Patient 324-001 was a 50 y/o WM with sleep apnea and CHF. He received nesiritide 0.030 µg/kg/min for 4 days, without hypotension or bradycardia. On 11.4.96 he suffered a cardiopulmonary arrest associated with hypoxia and somnolence, while receiving nesiritide, which required intubation and study drug discontinuation.

2. Patient 357-001 was a 63 y/o WM with CHF. He received nesiritide 0.030 µg/kg/min for 2 days, until 30 minutes prior to cardiopulmonary arrest with electromechanical dissociation for 'hypotensive crisis' (recorded BP 68/42 mm Hg). His blood pressures recorded 2 hours prior to the cardiac arrest showed a decline in his systolic BP from a baseline of approximately 130 to 88 mm Hg. The reason recorded for discontinuation of study drug was 'hypotension.' During nesiritide infusion the patient also developed a worsening of his tachycardia (118 at baseline to 144 BPM at the end of 6 hours). The patient was treated with levophed and dopamine and intubated, but his blood pressure remained <70 systolic for approximately 2 hours. The next day his creatinine was increased from a baseline of 1.5 to 3.4, for which he received renal dose dopamine. His last recorded BUN/creatinine were 106/3.0 mg/dl.

Renal Adverse Events

In addition to the subjects listed above, some of whom experienced renal AEs (e.g., subject 498-003, oliguria). The sponsor also reported on the incidence of several other renal adverse events of interest.

1. Ultrafiltration for fluid overload

Only one subject, in the high-dose nesiritide group, required ultrafiltration for fluid overload.

2. Intervention for worsening renal function

Three subjects, one in placebo and two in high-dose nesiritide, required dialysis. A total of 13 other subjects required non-dialytic intervention (i.e., IV fluid boluses, medication changes) specifically for renal insufficiency. All of these individuals were in one of the nesiritide groups, as summarized in the table below.

Table 6.2.13.6 Requirement for intervention due to worsening renal failure in study 704.325^a.

Intervention for worsening renal function	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 vol. 59, Appendix 1, Table 61, and Case Report Forms.

6.2.14 Study 704.325 Efficacy Summary

This was a trial in decompensated CHF. That subjects were enrolled after withholding other cardiac drugs for only 2-4 hours suggests that the subjects were more acutely ill than those in study 704.311.

The demographics of the study were balanced as regards race, age, cause of CHF, physical findings on admission, and other medications. There was a higher proportion of women in the high-dose nesiritide group (see table 6.2.12.1.1). Subjects in the nesiritide 0.3/0.015 group also tended to have a lower pre-study systolic blood pressure (table 6.2.12.1.2).

The duration of administration of vasoactive cardiac medications (i.e., dobutamine, nesiritide, milrinone) was not different in the treatment groups. Significantly more subjects in the placebo group received diuretics during the first 24 hours.

1. The primary endpoint for the 704.325 trial was the change in PCWP expressed as a % of baseline after 6 hours of study drug administration. Regardless of the population analyzed ('worst-outcome', 'last-value carried forward', 'data as available'), nesiritide use was associated with a significantly greater decrease in PCWP when compared with placebo. This reduction in PCWP did not result in the normalization of PCWP for most subjects.

2. For the two doses of nesiritide studied, there appeared to be a dose-related effect of nesiritide to lower PCWP which persisted to 6 hours (see Fig. 6.2.12.3.1). There was no augmentation of the effect of nesiritide on PCWP between 6 and 24 hours in any analysis (see table 6.2.12.4.5).

3. No data were collected in this study regarding the changes in hemodynamics following the discontinuation of nesiritide.

4. The effect of nesiritide on the PCWP was coupled with significant beneficial effects on other important hemodynamic parameters: mean right atrial pressure (MRAP); systemic vascular resistance (SVR); cardiac index (CI). While nesiritide was also associated with a significantly greater decrease in systolic BP, there was no significant effect on heart rate (table 6.2.12.4.4). Patients who received nesiritide did have a small decrease in their median respiratory rate from 0-6 hours, compared with placebo (tables 6.2.12.4.4a and 6.2.12.4.4b).

5. In the first 24 hours, patients receiving nesiritide retained more water and sodium on average (with very broad patient-patient variability, see table 6.2.12.4.15). The decreased fluid output in the nesiritide groups was a result of less urine output, and not due to differences in the amount of fluids administered to the patients. There was a no significant trend towards greater weight loss in the nesiritide groups relative to control through 5 days (figure 6.2.12.4.4). This may have occurred, in part, due to decreased diuretic use in the nesiritide groups.

6. With regard to changes in the symptoms of CHF, the sponsor performed both a global assessment as well as an analysis of individual symptoms of CHF.

Global Assessment of Clinical Status

The assessment of clinical status is flawed by the knowledge of the investigator of the PCWP for the patients at the time of their assessment (section 6.8.2). Compared with placebo, at the end of 6 hours nesiritide administration was associated with a significant improvement in the overall Global Assessment score, as judged by either the patient or the investigator (see table 6.2.12.4.6, figure 6.2.12.4.2). The two doses of nesiritide had similar effects, with no discernable dose-response.

Compared with Active Control, at the end of 24 hours, and following discontinuation of parenteral therapy, there were no relevant or significant differences between the three study groups. (table 6.2.12.4.7, figure 6.2.12.4.3).

At the end of 6 hours, nesiritide administration was also associated with a significant improvement in the 'CHF Total Score' compared with Placebo. (table 6.2.12.4.12). Again, there was no indication of a dose-response for the two nesiritide doses. Similar to the Global Assessment Score, this difference between active control and nesiritide did not persist to 24 hours (table 6.2.12.4.13).

6.2.14 Study 704.325 Efficacy Summary (cont)

Assessment of Individual Signs and Symptoms of CHF

When the individual signs and symptoms of CHF were examined, there was a significant benefit of nesiritide at 6 hours for the following: breathing difficulty; fatigue; lightheadedness; peripheral edema (table 6.2.12.4.9 and 6.2.12.4.10). No effect on peripheral circulation was detected.

After 24 hours, all three treatment groups had similar effects on the individual signs and symptoms (table 6.2.12.4.13). There was a trend towards a greater improvement in fatigue in the nesiritide groups ($p=0.062$).

At the time of discontinuation of parenteral therapy ('last recorded assessment'), there were no significant differences between the treatment groups evident with regard to CHF signs and symptoms.

7. There was no significant effect of nesiritide on duration of hospitalization (see table 6.2.12.4.17). There was a non-significant trend towards increased re-admission prior to day 21 in the nesiritide groups (table 6.2.12.4.18).

6.2.15 Study 704.325 Safety Summary

1. A majority of the patients who entered the trial completed the first 24 hours of treatment. There was one discontinuation in the placebo group (V Tach), one in the nesiritide 0.3/ 0.015 group (worsening CHF) and three in the nesiritide 0.6/ 0.030 group (symptomatic hypotension, hypotension, and oliguria). One of the high-dose nesiritide subjects who were discontinued later died (table 6.2.13.4).

2. There were 2 deaths in each of the treatment groups (6 total, table 6.2.13.1). The majority of these were related to progressive CHF.

3. There were 14 serious adverse events in the trial through day 21, one in placebo, 4 in the nesiritide 0.3/ 0.015 group and 8 in the nesiritide 0.6/ 0.030 group (table 6.2.13.3). Three of the subjects in the high-dose group developed renal failure (one following hypotension), and two of these subjects later died. There were also more medical interventions for renal insufficiency/ failure in both the nesiritide groups; 0, 14 and 17% in the placebo, nesiritide 0.3/ 0.015 and 0.6/ 0.030 groups respectively (table 6.2.13.6).

6.2.16 Overall Summary of 704.325

This trial investigated the effects of nesiritide in patients with decompensated CHF severe enough to require hospitalization and able to withhold cardiac meds for 2-4 hours. Within this population, there was a clear effect of nesiritide to improve hemodynamics, especially to acutely decrease PCWP. This hemodynamic effect was rapid in onset (0-6 hours), and persisted, without augmentation, through 24 hours in the subset of patients who received only nesiritide. Nesiritide also lowered systemic BP and increased cardiac output, but didn't cause rebound tachycardia.

The use of nesiritide was associated with both sodium and water retention during the first 24 hours of infusion, as the result of decreased urine output, perhaps due in part to an imbalance in the diuretic use. Over 5 days, there was no significant difference between the treatment groups with regard to weight loss.

With regard to the signs and symptoms of CHF, the data are open to investigator bias, and cannot be seen as independent of the hemodynamic results. Through 6 hours, nesiritide administration had an acute, beneficial effect (relative to placebo). This effect did not persist to 24 hours, at which time all treatment groups showed similar degrees of improvement. Nesiritide also had acute positive effects on several important individual signs of CHF, including breathing difficulty; fatigue; lightheadedness; and peripheral edema. This difference between nesiritide and the active control group also did not persist to 24 hours. Some of the reported improvements (e.g., changes in edema by hours) are difficult to justify/ highly unexpected, and may reflect the investigator bias. A possible effect of nesiritide to improve respiration in patients with CHF was supported by the observed, small decrease in respiratory rate between 0 and 6 hours, relative to placebo.

With regards to safety, more subjects in the nesiritide group dropped out due to symptomatic hypotension and/or excessive decreases in PCWP, and more patients in the nesiritide groups had serious adverse events (see patient narratives). Included in these SAEs were three cases of renal failure, associated with two deaths. There was also a trend towards more subjects with a return of their decompensated CHF requiring re-hospitalization within 2 weeks of hospital discharge.

Overall, then, nesiritide again has a beneficial, acute effect on PCWP and other hemodynamics. This was associated with a short term improvement in symptoms relative to placebo. No beneficial effect on volume status, such as change in weight, was detected. These effects of nesiritide were associated with some potentially significant adverse effects, including a greater incidence of hypotension. There were also several patients in the nesiritide group who had acute worsening of their CHF shortly after completing the trial, and more patients in the nesiritide group requiring non-dialytic intervention for renal failure.

6.3 Review of the Protocol 704.326

6.3.1 Title of Study

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

6.3.2 Sites of Investigation and Investigators

The list of investigators and sites is found in the table below. Trial 326 was a multicenter investigation, with 46 investigators.

6.3.2.1 Investigators and enrollment in trial 704.326^a.

Investigator Name	# of Subjects Enrolled (% of Total Enrollment)
ELKAYAM, U.	54 (18%)
NEIBAUR, M.	25 (8%)
HAUGHT,	23 (8%)
GHALI, J.	17 (6%)
GREENSPAN, M.	11 (4%)
FELDMAN, R.	10 (3%)
BURGER, A.	9 (3%)
EL HAFI, S.	9 (3%)
WILSON, J.	9 (3%)
HOAGLAND, P.	8 (3%)
LANZA, S.	8 (3%)
TENAGLIA, A.	8 (3%)
BOLSTER, D.	7 (2%)
HARLAMERT, E.	7 (2%)
GANDY, W.	6 (2%)
KARLSBERG, R.	6 (2%)
MALLON, S.	6 (2%)
VASKA, K.	6 (2%)
ARENDT, M.	5 (2%)
CARLEY, J.	5 (2%)
OKEN, K.	5 (2%)
OREN, R.	5 (2%)
FORD, L.	4 (1%)
PROMISLOFF, S.	4 (1%)
WILSON, D.	4 (1%)
BOWLES, M.	3 (1%)
EL SHAHAWY, M.	3 (1%)
JOHNSON, A.	3 (1%)
LEJEMTEL, T.	3 (1%)
SCHWARTZ, D.	3 (1%)
SILVER, M.	3 (1%)
WAGONER, L.	3 (1%)
WALSH, M.	3 (1%)
BOURGE, R.	2 (1%)
12 Other Investigators	18 (6%)
TOTAL	305

a. Data from NDA volume 66, Table 1A.

6.3.3 Background

Initial protocol: 7.12.96

General

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 µg/kg bolus followed by a 0.015 µg/kg/min infusion, bolus of 0.6 µg/kg followed by a 0.03 µg/kg/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.

General (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.

6.3.5 Primary and Secondary Endpoints

Primary endpoint (combined endpoint)

Per the sponsor, the primary aim of the study was to collect safety data in the described population of patients with decompensated CHF. 'The standard care group was intended to serve as a control group for safety assessments, i.e., to reflect the incidence of underlying adverse experiences in a parallel group to aid in the interpretation of the incidence of various adverse events reported in the nesiritide groups.'

Per the sponsor, efficacy comparisons were not specified. However, several assessments of clinical efficacy were to be collected, including: global assessment of clinical status; length of use of parenteral therapy; length of hospital stay; readmissions; and 21-day mortality.

6.3.6 Number of subjects/ randomization

A total of 305 subjects were enrolled at 46 clinical sites between 1.7.97 and 7.3.97. Study data were collected through 12.12.97.

Subjects were randomized to one of the three treatment groups in a 1:1:1 ratio. The randomization employed blocking of size twelve. The randomization did not stratify based on investigative site or any other factor.

Patients were randomized to receive either nesiritide or active control therapy. If the subject was randomized to nesiritide, the investigator remained blinded as to the dose of nesiritide (0.015 or 0.030 mg/kg/min).

6.3.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

All of the following criteria must be met:

1. At least 18 years of age.
2. Previous history of chronic CHF.
3. Presented with symptomatic, decompensated CHF for which inpatient vasoactive parenteral therapy (other than or in addition to diuretics) was deemed appropriate.
4. Fully understood all elements of, and has signed, the written Informed Consent Form prior to initiation of protocol-specified procedures.

Exclusion Criteria

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

1. Myocardial infarction within the past 48 hours or ongoing unstable angina.
2. Significant valvular stenosis, obstructive cardiomyopathy, constrictive pericarditis, primary pulmonary hypertension, biopsy-proven active myocarditis, or complex congenital heart disease.
3. Recent stroke within 1 month or other evidence of significantly compromised central nervous system perfusion that would contraindicate the administration of an agent with potent vasodilating properties.
4. Patients already being treated with a parenteral vasoactive agent (an intravenous inotrope or vasodilator) for more than 4 hours for this episode of decompensated CHF.

Exclusion Criteria (cont)

5. Patients already being treated with a parenteral vasoactive agent for less than 4 hours for this episode of decompensated CHF that could not be discontinued for the protocol-specified washout period to permit the reassessment of baseline clinical status prior to initiating study drug.

6. Cardiogenic shock, systolic blood pressure consistently less than 90 mm Hg, or other evidence of significant hemodynamic instability which required the immediate institution of inotropic/pressor support.

7. Therapy with another investigational drug at the time of study entry which had not been pre-approved by the sponsor.

8. Unwillingness or inability to comply with study requirements.

6.3.8 Dosage/ Administration

There were three treatment groups:

Group 1: Nesiritide: IV bolus of 0.3 µg/kg followed by a 0.015 µg/kg/min infusion.

Group 2: Nesiritide: IV bolus of 0.6 µg/kg followed by a 0.03 µg/kg/min infusion.

Group 3: A standard care agent (see below).

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, nitroglycerine, dobutamine, or milrinone. Low dose ("renal dose") dopamine was generally not considered a vasoactive agent for the treatment of CHF. However, for those subjects who received dopamine as the sole initial parenteral agent for the treatment of CHF, dopamine was defined as the standard care agent. The standard care agent was supplied by the pharmacy at each site. The specific agent, dose, and infusion strategy was determined by the attending physician according to standard clinical practice.

6.3.9 Duration/ Adjustment of Therapy

Duration

The duration of therapy with nesiritide was determined by the attending physician; with a maximum infusion permitted by the protocol of 7 days. In cases where it was clinically indicated to continue the nesiritide infusion longer than 7 days, approval must have been obtained from the sponsor.

Discontinuation/ Adjustment of therapy

If a subject receiving nesiritide experienced symptomatic hypotension or a drop in systolic blood pressure to < 85 mm Hg, the nesiritide infusion could be stopped and then restarted at half of the previous infusion rate.

If a subject developed worsening CHF or did not respond adequately to the initial nesiritide infusion dose, the attending physician had the option of increasing the nesiritide infusion dose. Nesiritide must have been administered for a minimum of 6 hours and the subject must have tolerated the nesiritide well throughout the infusion up to that point. The infusion dose was then allowed to be increased according to the following guidelines:

1) The infusion dose was allowed to be sequentially increased by 50% of the initial infusion dose, no more frequently than every 3 hours, up to a maximum dose that was double the initial infusion dose.

2) With each increase in the infusion dose, blood pressure was required to be obtained every 15 minutes for 2 hours, then every 30 minutes for 1 hour, then hourly for 2 hours, and at least every 4 hours thereafter.

3) If additional parenteral vasoactive therapy was required for the treatment of decompensated CHF during nesiritide infusion, other vasoactive agents could have been instituted with the following guidelines. If the agent to be administered was nitroprusside, nitroglycerin, milrinone, or any other agent that has strong vasodilating properties, nesiritide administration was discontinued before initiation of this other agent. Dopamine or dobutamine may have been either added to the nesiritide regimen or substituted for it, as per the clinical judgment of the investigator/attending medical staff.

6.3.10 Safety and Efficacy Measurements

The table below details the type and timing of the clinical information collected during study 704.326.

Table 6.3.10.1 Timetable for clinical observations and lab measurements in the study 326^a.

Procedure	Pre-infusion	Study Drug Infusion						Post-Infusion		
		0	1	2	4	6	6+ ^e		Within 24 hrs	Day 14
Informed Consent	X							X		
Medical History/ PE	X									
ECG	X									
Holter Monitors ^f	See Note									
CXR	X									
D/C Parenteral Cardiac Meds	X ^b									
Vital Signs	X	X	X	X	X	X	X ^c			
CBC, Chemistries ^d								X		
Anti-BNP antibody level	X									X
Assess Signs/ Sxs of CHF	X					X	X	X		
Assess Global Clinical Status						X	X	X		
Study Drug Administration		X	X	X	X	X	X	X		
Daily Weight							X			
Daily Na, K, CO ₂ , Cl, Cr _t , and BU _{id}							X			
Adverse Event Collection										
F/U Visit										X

a. Data from NDA volume 67, page 155.

b. Parenteral meds to be discontinued only if taken for <4 hours. Patients who received parenteral therapy for CHF for >4 hours before entry were not eligible for the study.

c. Vital signs were obtained every 4 hours during the parenteral therapy.

e. Includes tests performed during extended parenteral therapy (>6 hours to 7 days).

f. Holter monitors were performed at 15 sites for a maximum period during 72 hours of infusion.

6.3.11 Statistical Considerations

General statistical approach

Per the sponsor, statistical analysis was conducted largely as a screening tool to facilitate the clinical assessment of drug safety.

A secondary objective was to facilitate the evaluation of various measures of clinical outcome. Per the sponsor, endpoints of particular interest were the global assessments of clinical status and the symptoms and signs of CHF.

Study Population Analyzed

All enrolled subjects were included in the analysis. Subjects with initial treatment errors were summarized within the treatment group that most reasonably approximated the actual treatment received. This was considered the primary analysis population and is identified as the "all subjects" population. Enrolled subjects were not excluded from any analysis unless a relevant data point was missing or unless the subject did not qualify for inclusion in a subgroup analysis.

Analytical methods

The general analysis strategy was to test for nonspecific differences between the three treatment groups, followed by pairwise comparisons of treatment groups. No adjustment was made for multiple comparisons. Continuous data were typically analyzed by the omnibus F test followed by pairwise contrasts, ordinal data by the Kruskal-Wallis test followed by pairwise 2-sample Wilcoxon procedures, and categorical data by the generalized Fisher's Exact test followed by pairwise Fisher exact tests. Within-group changes from baseline were tested with either a paired *t* test, 1-sample Wilcoxon test, or binomial test, as appropriate for the endpoint.

Interim Analyses/ Sample size re-estimation

No interim analyses were performed for efficacy, and the sample size was not adjusted.

Statistical Methods for Individual Endpoints (cont)

Signs and Symptoms of CHF

Six symptoms and signs of CHF (reduced appetite, breathing difficulty, decreased peripheral circulation, fatigue, lightheadedness, and peripheral edema) were scored at baseline, at 6 and 24 hours after initiation of study drug, and if parenteral therapy exceeded 24 hours, within 24 hours after discontinuation of all parenteral therapy. At baseline, evaluation was on either a three- or four-category ordinal scale unique to each symptom or sign. At follow-up, symptoms and signs were evaluated relative to baseline status on a common 3-category ordinal scale ('improved', 'no change,' or 'worse'). Each symptom or sign, and a composite score incorporating all six symptoms and signs, were summarized at the 6-hour assessment, the 24-hour assessment, and the last recorded assessment, done within 24 hours after discontinuation of all parenteral vasoactive medication and more than 20 hours after initiation of study drug.

Individual symptoms and signs were analyzed by non-parametric methods, as previously described for the "worst outcome" hemodynamic analyses, except that the within-group assessment of change from baseline employed a binomial test conditioned on subjects either worsening or improving, rather than using an unconditional one-sample Wilcoxon test. Total score was analyzed by non-parametric methods, as previously described for the "worst outcome" population analyses.

Other Efficacy and Safety Analyses

Analyses on blood and physical measurements (labs, hormone levels, weights, fluid intake) were compared between groups using the Omnibus F test. Within each group, a 1-sample t-test was used on the change from pre-treatment to test for significant changes.

Interim analyses and sample size simulation

No formal interim analyses were proposed or conducted.

Sample size was estimated by determining the # of subjects needed to detect a difference between the treatment groups in the 6-hour 'worst outcome' PCWP group with 90% power at a level of <0.05 for nominal significance. The calculation assumed that the mean difference between two groups would be 25%, with a standard deviation of 28.4%.

6.2.12 Efficacy Outcomes

6.2.12.1 Patient Demographics & Baseline Characteristics

The demographics of the 127 subjects enrolled at 23 sites are summarized in the table below. Note that there was a higher proportion of females in the high-dose nesiritide group, relative to the other two study groups (especially placebo).

Table 6.2.12.1.1 Demographics of the study 704.325^a.

Demographic	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value
Gender				
Female	9 (21%)	8 (19%)	17 (40%)	0.055 ^b
Male	33 (79%)	35 (79%)	25 (60%)	
Race				0.469 ^b
White	25 (60%)	30 (70%)	22 (52%)	
Black	13 (31%)	11 (26%)	14 (33%)	
Asian	0 (0%)	0 (0%)	0 (0%)	
Hispanic	4 (10%)	2 (5%)	6 (14%)	
Other	0 (0%)	0 (0%)	0 (0%)	
Age (Mean±SD)	59.0±14	56.6±14	60.8±12	0.357 ^c
<65 Years old	26 (62%)	30 (70%)	25 (60%)	
≥65 Years old	16 (38%)	13 (30%)	17 (40%)	

a. Data from NDA volume 59 Appendix, Tables 1-4.

b. p Value calculated using Fishers exact test.

c. p Value calculated using ANOVA omnibus F test.

6.3.12.1 Patient Demographics & Baseline Characteristics (cont)

Some of the significant physical exam results are summarized in the next table. There were no significant differences between the three study groups.

Table 6.3.12.1.3 Further demographics in study 704.326^a.

Demographic	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value ^b
Tachycardia >100 BPM	15 (15%)	19 (18%)	17 (17%)	0.779
Rales	66 (65)	68 (66%)	69 (69%)	0.795
S3	51 (50%)	51 (50%)	56 (56%)	0.602
S4	25 (25%)	22 (21%)	22 (22%)	0.858
Jugular Venous Distension	66 (67%)	61 (60%)	59 (59%)	0.482
Pedal Edema	73 (72%)	76 (71%)	71 (71%)	0.899

a. Data from NDA volume 66, table 10.

b. p Value using appropriate statistical method per sponsor.

Medications taken prior to study initiation

There were no significant differences in the use of other cardiac medications prior to study drug administration among the three treatment groups. The most common other medications included diuretics (>80%), digoxin (≥56%), ACE inhibitors (≥55%) and non-IV nitrates (≥44%).

6.3.12.2 Disposition and Follow-up of Subjects

Disposition

The table below summarizes the disposition of the subjects enrolled in study 326, including the reasons for subject discontinuation. Four potential subjects were randomized by the pharmacist but were not subsequently enrolled by the investigator for the following reasons: inability to confirm the diagnosis of CHF, SBP below 80 mm Hg, and failure to obtain consent to participate in the study (in two cases). None of these potential subjects received study drug.

Table 6.3.12.2.1 Disposition of subjects randomized in the study 704.326 at the end of 21 days^a.

Patient Disposition	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100
Enrolled	102	103	100
Completed (to 6 hours)	100 (98%)	101 (98%)	95 (95%)
Discontinued			
D/C prior to 6 hours ^b	2 (2%)	2 (2%)	5 (5%)
D/C due to hypotension	0 (0%)	2 (2%)	5 (5%)
D/C due to arrhythmia	2 (2%)	0 (0%)	1 (1%)
Alive	96 (94%)	94 (91%)	94 (94%)
Dead	5 (5%)	6 (6%)	6 (6%)
Lost to F/U	1 (1%)	3 (3%)	0 (0%)

a. Data from NDA volume 66, section 6.4 and appendix table 11.

b. 6-hour time point represents the end of the blinded analysis in the earlier trial 704.325.

6.3.12.2a Subject Selection

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

6.3.12.2b Protocol Violations & Deviations

1. Subject 538-008 was randomized to the 0.6/ 0.03 µg/kg/min nesiritide group but was given standard care (dobutamine) through a nursing error.

2. Subject 550-001 was randomized to nesiritide 0.6/ 0.03 µg/kg/min but received nesiritide 0.015 µg/kg/min because of pharmacy error.

3. Subject 493-088 was not formally randomized but received the 0.3/ 0.015 µg/kg/min nesiritide treatment after several failed attempts by the pharmacist to correctly access the automated telephone randomization system.

Per the sponsor, there were also a number of minor dosing errors in this study. For example, a number of subjects did not receive the nesiritide loading bolus. In other cases, incorrect subject weights were used to prepare the study drug. None of these dosing deviations were considered by the sponsor to be clinically significant or likely to affect the interpretation of the study.

6.3.12.2c Concomitant Therapies used after Trial Initiation

Administration of study drug

Per protocol, the 'Standard Care' group was to receive a single parenteral vasoactive product, which was to be identified as the 'standard care' for a give subject. The table below summarizes the 'standard care' used by the three groups.

Table 6.3.12.2c.1 Drugs used as 'standard care' in study 704.326^a.

Study Drug	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100
Dobutamine	58 (57%)	--	--
Dopamine	6 (6%)	--	--
Milrinone	19 (19%)	--	--
Nitroglycerin	18 (18%)	--	--
Other	1 (1%)	--	--
Nesiritide	--	103 (100%)	100 (100%)

a. Data from NDA volume 66, table 13.

The sponsor also summarized the length of time each subject received the 'standard care' drugs, and reported that the nesiritide group received their drug (nesiritide) for significantly less time than the Standard Care group (see below).

Table 6.3.12.2c.2 Duration of standard drug infusion in study 704.326^a.

Study Drug	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Elapsed time of infusion Mean±SD	73.7±93	51.3±44	44.1±38	0.015
<6 hour	2 (2%)	2 (2%)	6 (6%)	
6-12 hours	0 (0%)	2 (2%)	5 (5%)	
12-36 hours	36 (35%)	43 (42%)	45 (45%)	
36-100 hours	49 (48%)	46 (45%)	35 (35%)	
>100 hours	15 (15%)	10 (10%)	9 (9%)	

a. Data from NDA volume 66, table 14.

However, if the duration of all parenteral vasoactive cardiovascular medications was compared, there were no significant differences detected among the three treatment groups.

Table 6.3.12.2c.3 Duration of all parenteral cardiovascular drug infusions in study 704.326^a.

Study Drug Infusion	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Elapsed time of infusion Mean±SD	80.4±102	64.6±76	64.9±77	0.421
<24 hours	18 (19%)	18 (17%)	20 (20%)	
24-72 hours	50 (52%)	55 (53%)	51 (51%)	
72 – 120 hours	14 (15%)	21 (20%)	15 (15%)	
120 – 168 hours	4 (4%)	5 (5%)	9 (9%)	
>168 hours	10 (10%)	4 (4%)	5 (5%)	

a. Data from NDA volume 66, table 15.

In data not shown, subjects in the nesiritide groups were more likely to remain on their initial dosing regimen, when compared with the 'standard care' group. The reasons for this change in regimen were complex. Of interest, subjects in the nesiritide groups were more likely to have their initial therapy discontinued, and a new therapy started. The majority of subjects (94 to 98% in the three groups) were continuing to receive their initial therapy (nesiritide or 'standard care' drug) at the end of 6 hours.

Concomitant therapies

The table below summarizes the concomitant therapies utilized during study drug administration. Aside from the use of nesiritide or vasoactive cardiovascular meds such as milrinone or dobutamine, the nesiritide groups received significantly fewer diuretics during the study drug infusion period.

Table 6.3.12.2c.4 Drugs used during study drug administration in study 704.326, including initial agents^a.

Study Drug	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Nesiritide	--	103 (100%)	100 (100%)	<0.001
Dobutamine	61 (60%)	5 (5%)	11 (11%)	<0.001
Phosphodiesterase Inhibitors	24 (24%)	1 (1%)	0 (0%)	<0.001
IV Nitroglycerin	20 (20%)	1 (1%)	1 (1%)	<0.001
Nitroprusside	2 (2%)	2 (2%)	0 (0%)	0.551
Dopamine	13 (13%)	1 (1%)	2 (2%)	<0.001
Diuretics	99 (97%)	84 (82%)	74 (74%)	<0.001
Digoxin	75 (74%)	69 (67%)	63 (63%)	0.266
ACE Inhibitors	67 (66%)	70 (68%)	54 (54%)	0.091
Non-IV Nitrates	51 (50%)	41 (40%)	46 (46%)	0.340
Class III Anti-arrhythmics	15 (15%)	14 (14%)	10 (10%)	0.590
Beta Blockers	11 (11%)	9 (9%)	7 (7%)	0.632
Calcium Channel Blockers	17 (17%)	12 (12%)	18 (18%)	0.412
Other antihypertensive	2 (2%)	6 (6%)	3 (3%)	0.373

a. Data from NDA volume 66, table 20.

For some subjects in the nesiritide groups, no other parenteral cardiovascular (CV) agent was administered during the hospitalization, while for other nesiritide was discontinued and another agent started, or another agent was added to nesiritide. The table below summarizes these groups. More patients started on nesiritide were switched to other parenteral therapies.

Table 6.3. 12.2c.5 Infusion of nesiritide and other parenteral cardiovascular meds in study 704.326^a.

Medications administered	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Subjects who received only initial vasoactive agent	92 (90%)	86 (83%)	76 (76%)	0.027
Subjects who D/C'd study drug & started another agent	2 (2%)	9 (9%)	12 (12%)	0.013
First CV med added after nesiritide D/C'd				
Dobutamine	2 (2%)	7 (7%)	10 (10%)	0.041
Milrinone	0 (0%)	1 (1%)	1 (1%)	1.000
Nitroglycerin	0 (0%)	1 (1%)	0 (0%)	
Subjects who received other parenteral agent while continuing study drug	8 (8%)	8 (9%)	12 (12%)	0.511
Agent combined with study drug				
Dobutamine alone	3 (3%)	5 (5%)	11 (11%)	0.054
Milrinone	1 (1%)	1 (1%)	0 (0%)	1.000
Nitroglycerin	1 (1%)	1 (1%)	1 (1%)	1.000
Nitroprusside	1 (1%)	1 (1%)	0 (0%)	1.000

a. Data from NDA volume 59, Appendix 1, Table 17. P Value per sponsor.

6.3.12.3 Analyses of Study 704.326 Results

The focus of this trial was on the safety results, and these will be discussed in the Safety Outcomes Section below. In this section those analyses not related to safety will be presented.

Effect of Study Drug on Vital Signs

While at baseline the vital signs of the three study groups were similar, there were significant differences between the vital signs at the end of 3 hours in the nesiritide and the standard care groups.

Table 6.3.12.3.1 Changes in vital signs from baseline to 3 hours 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
Systolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	120.7±20	127±25	124±26	0.197
Change from Baseline to 3 hours	-2.3±16	-9.3±16	-11.2±16	<0.001
p Value (Chg from Base) ^b	0.183	0.001	0.001	
p Value (Compared to Standard Care) ^c	--	0.003	0.001	
p Value (Compared to Low-dose BNP) ^c	--	--	0.426	
Diastolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	70±13	71±15	68±15	0.477
Change from Baseline to 3 hours	-5.9±12	-4.5±12	-8.6±11	0.051
p Value (Chg from Base) ^b	0.001	0.001	0.001	
p Value (Compared to Standard Care) ^c	--	0.376	0.125	
p Value (Compared to Low-dose BNP) ^c	--	--	0.016	
Heart Rate (BPM)				
Baseline (mean±sd)	85±15	83±18	84±15	0.823
Change from Baseline to 3 hours	+3.5±15	-0.6±9	+0.6±10	0.053
p Value (Chg from Base) ^b	0.029	0.501	0.569	
p Value (Compared to Standard Care) ^c	--	0.018	0.107	
p Value (Compared to Low-dose BNP) ^c	--	--	0.469	

a. Data from NDA volume 66, table 21.

b. Comparison by T test.

c. Comparison by ANOVA, pairwise contrast.

d. Comparison by ANOVA, omnibus F-test.

Effect of Study Drug on Subject Weight

The sponsor also collected data on the changes in weight for each of the three treatment groups, which is 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. Recall that significantly more subjects in the control group were given diuretics.

Table 6.3.12.3.2 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	
p Value (Compared to Low-dose BNP) ^c	--	--	0.209	
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	
p Value (Compared to Low-dose BNP) ^c	--	--	0.162	
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	
p Value (Compared to Low-dose BNP) ^c	--	--	0.277	
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	
p Value (Compared to Low-dose BNP) ^c	--	--	0.496	

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.

Effect of Study Drug on Symptomatic Relief

Global assessments at 6 and 24 hours of treatment were compared for the three study groups. While all three treatment groups improved significantly over baseline to 6 hours, there was not a significant difference between the Global Assessment Scores between the three groups. There was also no difference between the two nesiritide groups.

Table 6.3.12.3.3 Global assessment, by subjects, of their clinical status at 6 and 24 hours in study 704.326^a.

Global Assessment	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
6 Hour Assessment	n=84	n=86	n=82	0.318 ^c
Markedly Better	8 (10%)	10 (12%)	4 (5%)	
Better	46 (55%)	48 (56%)	45 (55%)	
No Change	27 (32%)	26 (30%)	29 (35%)	
Worse	3 (4%)	2 (2%)	4 (5%)	
Markedly Worse	0 (0%)	0 (0%)	0 (0%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.569	0.358	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.133	
24 Hour Assessment	n=92	n=99	n=90	0.302 ^c
Markedly Better	17 (18%)	23 (23%)	15 (17%)	
Better	57 (62%)	60 (61%)	54 (60%)	
No Change	16 (17%)	14 (14%)	17 (19%)	
Worse	2 (2%)	2 (2%)	4 (4%)	
Markedly Worse	0 (0%)	0 (0%)	0 (0%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.370	0.515	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.128	
Last Recorded Assessment	n=98	n=101	n=93	0.628 ^c
Markedly Better	27 (28%)	34 (34%)	25 (27%)	
Better	60 (61%)	55 (54%)	55 (59%)	
No Change	8 (8%)	5 (5%)	10 (11%)	
Worse	3 (3%)	7 (7%)	2 (2%)	
Markedly Worse	0 (0%)	0 (0%)	1 (1%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.532	0.728	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.354	

a. Data from NDA volume 66, Appendix table 24a. Shown for 'All subjects' population.

b. Comparison by 1-Sample Wilcoxon.

c. Comparison by Kruskal-Wallis.

d. Comparison using 2-Sample Wilcoxon.

The sponsor also looked at the effect of the study drugs on individual signs/ sxs of CHF. The first symptom, 'breathing difficulty' was improved by 6 hours in all three treatment groups, with no difference between the three group.

Table 6.3.12.3.4 Assessment of 'breathing difficulty', by subjects, at 6 and 24 hours in study 704.326^a.

Global Assessment of Breathing Difficulty	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
6 Hour Assessment				
Improved from Baseline	52 (61%)	56 (63%)	44 (55%)	0.583 ^c
No Change from Baseline	30 (35%)	32 (36%)	35 (44%)	
Worse than Baseline	3 (4%)	1 (1%)	1 (1%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.726	0.515	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.302	
24 Hour Assessment				
Improved from Baseline	77 (80%)	77 (78%)	63 (70%)	0.230 ^c
No Change from Baseline	14 (15%)	18 (18%)	20 (22%)	
Worse than Baseline	5 (5%)	4 (4%)	7 (8%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.726	0.112	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.199	

a. Data from NDA volume 66, Appendix table 27a. Shown for 'All subjects' population.

b. Comparison by 1-Sample Wilcoxon.

c. Comparison by Kruskal-Wallis.

d. Comparison using 2-Sample Wilcoxon.

The next table summarizes the changes in 'lightheadedness' at 6 and 24 hours. While all subjects in all three treatment groups, on average, improved by 6 hours, there was no difference between treatment groups discerned. The sponsor also looked at the treatment effects only in those subjects with lightheadedness at entry (roughly 40% of each group). In data not shown, no difference between the treatment groups was seen.

Table 6.3.12.3.5 Assessment of 'lightheadedness', by subjects, at 6 and 24 hours in study 704.326^a.

Global Assessment of Lightheadedness	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Baseline				
No lightheadedness	57 (56%)	56 (56%)	58 (59%)	0.868 ^c
Lightheadedness with moderate activity	12 (12%)	20 (20%)	15 (15%)	
Lightheadedness with minimal activity	25 (25%)	17 (17%)	17 (17%)	
Lightheadedness at rest	7 (7%)	7 (7%)	8 (8%)	
6 Hour Assessment				
Improved from Baseline	11 (13%)	17 (19%)	11 (14%)	0.369 ^c
No Change from Baseline	72 (86%)	67 (76%)	64 (77%)	
Worse than Baseline	1 (1%)	4 (5%)	7 (9%)	
p Value (test of 'No Change') ^b	0.006	0.007	0.481	
p Value (comp with standard care group) ^d	--	0.594	0.340	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.193	
24 Hour Assessment				
Improved from Baseline	25 (26%)	26 (27%)	18 (20%)	0.742 ^c
No Change from Baseline	67 (70%)	66 (67%)	68 (76%)	
Worse than Baseline	4 (4%)	6 (6%)	3 (3%)	
p Value (test of 'No Change') ^b	<0.001	0.001	0.001	
p Value (comp with standard care group) ^d	--	0.886	0.450	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.560	

a. Data from NDA volume 66, Appendix table 27a. Shown for 'All subjects' population.

b. Comparison by 1-Sample Wilcoxon.

c. Comparison by Kruskal-Wallis.

d. Comparison using 2-Sample Wilcoxon.

Finally, the sponsor examined the changes in 'peripheral edema' at hours 6 and 24 of study drug. At the end of 6 hours, there was a trend towards greater improvement of peripheral edema in the nesiritide groups (but no apparent difference between the two nesiritide doses).

Table 6.3.12.3.6 Assessment of 'peripheral edema', by subjects, at 6 and 24 hours in study 704.326^a.

Global Assessment of Peripheral Edema	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Baseline				
None	29 (29%)	28 (28%)	29 (30%)	0.342 ^c
Mild	33 (33%)	23 (23%)	27 (28%)	
Moderate	32 (32%)	33 (33%)	30 (31%)	
Severe	7 (7%)	17 (17%)	12 (12%)	
6 Hour Assessment				
Improved from Baseline	16 (19%)	30 (34%)	25 (31%)	0.060 ^c
No Change from Baseline	68 (80%)	59 (66%)	54 (68%)	
Worse than Baseline	1 (1%)	0 (0%)	1 (1%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.021	0.076	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.653	
24 Hour Assessment				
Improved from Baseline	49 (51%)	56 (57%)	43 (48%)	0.467 ^c
No Change from Baseline	46 (48%)	43 (43%)	47 (52%)	
Worse than Baseline	1 (1%)	0 (0%)	0 (0%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.406	0.713	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.229	

a. Data from NDA volume 66, Appendix table 31a. Shown for 'All subjects' population.

b. Comparison by 1-Sample Wilcoxon.

c. Comparison by Kruskal-Wallis.

d. Comparison using 2-Sample Wilcoxon.

Effect of Study Drug on Hospitalization

The effect of study drug on hospitalization was examined in several ways. First, the duration of hospitalization prior to entry into the study 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 ($p > 0.05$). 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 % 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 6.3.12.3.7 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
Total days of hospitalization for subjects D/C'd prior to 21 days				
Mean \pm SD	6.4 \pm 3.7	6.2 \pm 3.5	6.6 \pm 4.2	0.914
Median	5	5	5	
Time to discharge				
2-3 days	18 (18%)	29 (28%)	25 (25%)	
4-5 days	36 (35%)	22 (21%)	26 (26%)	
6-7 days	13 (13%)	24 (23%)	9 (9%)	
8-14 days	27 (26%)	21 (20%)	26 (26%)	
15-21 days	3 (3%)	5 (5%)	10 (10%)	
Subjects not discharged as of day 21	5 (5%)	2 (2%)	4 (4%)	

a. Data from NDA volume 66, Appendix 1, Tables 33, and electronic datasets.

Effect of Study Drug on Hospital Readmission

As shown above, no difference exists between the treatment groups regarding discharge before day 21 (see table 6.2.12.2e.5). If one looks just at those subjects who were discharged, however, 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 6.3.12.3.8 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
If readmitted, primary reason for first readmittance				
CHF recurrence	8 (50%)	4 (50%)	4 (36%)	
Elective, unrelated to CHF	1 (6%)	0 (0%)	1 (9%)	
Medical condition other than CHF	6 (38%)	2 (25%)	6 (55%)	
Other	1 (6%)	2 (25%)	0 (0%)	
If readmitted, primary reason for all readmittance				
CHF recurrence	9 (53%)	4 (44%)	6 (46%)	
Elective, unrelated to CHF	1 (6%)	0 (0%)	1 (8%)	
Medical condition other than CHF	6 (35%)	2 (22%)	6 (46%)	
Other	1 (6%)	3 (33%)	0 (0%)	

a. Data from NDA volume 66, Appendix 1, Table 34. Includes all subjects discharged before day 21.

b. p Value using Fisher's Exact test.

Effect of Study Drug on Need for other Invasive Interventions through 21 Days

The number of interventions for renal failure, including hemodialysis/ hemofiltration, and the need for intubation were also examined. No subjects required hemofiltration. The need for other interventions was overall balanced in the three treatment groups, although there was a non-significant decrease in the number of intubations in the nesiritide group.

Table 6.3.12.3.9 Need for selected medical interventions through 21 days in study 704.326^a.

Intervention	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Medical Intervention for Worsening Renal Function				
Intervention without Dialysis	6 (6%)	12 (12%)	7 (7%)	0.610
Dialysis	2 (2%)	1 (1%)	2 (2%)	
Intubation	8 (8%)	2 (2%)	4 (4%)	0.126
Swan-Ganz catheter placement	20 (20%)	13 (13%)	23 (23%)	0.140
Intra-arterial line	3 (3%)	1 (1%)	3 (3%)	0.575

a. Data from NDA volume 66, Appendix 1, Table 35. Includes all subjects discharged before day 21. p Value per sponsor.

6.3.13 Safety Outcomes

The deaths, serious adverse events, and adverse events by body system will be considered in the integrated safety summary (sections 8.1 and 8.2). The section below will comment on the following specific safety parameters from the study 326: deaths; subject discontinuations; serious AEs. The first table summarizes the adverse clinical events that occurred during the trial. Narrative summaries for the death, SAEs and discontinuations are to be found in their respective appendices.

Table 6.3.13.1 Clinical adverse experience (AE) summary from trial 704.326^a.

Clinical event	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100
Serious AE (SAE) within 24 hrs of drug infusion	4 (4%)	0 (0%)	3 (3%)
Serious AE (SAE) after ≥ 24 hrs of drug infusion	12 (12%)	9 (9%)	14 (14%)
Completed trial (to 6 hours)	100 (98%)	101 (98%)	95 (95%)
Discontinued			
D/C prior to 6 hours ^b	2 (2%)	2 (2%)	5 (5%)
D/C due to hypotension	0 (0%)	2 (2%)	5 (5%)
D/C due to arrhythmia	2 (2%)	0 (0%)	1 (1%)
Deaths	5 (5%)	6 (6%)	6 (6%) ^b

a. Data from NDA volume 1.42, ref. 5, table 32, and electronic datasets.

b. Another patient in this group died on day 22 of the study.

6.3.13.1 Comparisons of Defined Safety Endpoints

The sponsor focused on several aspects of safety in their review of study 326, and these endpoints will be summarized in this section.

6.3.13.2 Comments on Specific Safety Parameters

Deaths

Seventeen subjects in this study died by day 21. Five (5%), 6 (6%), and 6 (6%) subjects in the standard care and 0.015 and 0.03 nesiritide treatment groups, respectively, died by day 21. One additional death in the 0.03 µg/kg/min nesiritide group occurred on day 22. Narratives for the individual deaths are to be found in appendix 2.

Table 6.3.13.2.1 Deaths in study 704.326^a.

Subject #	Day of Death	Cause of Death	Notes
<u>Standard care: dobutamine</u>			
493-019	5	End-stage CHF	Cardiac arrest on day 3
493-021	18	End-stage CHF	
509-001	21	Renal failure, AMI	
538-011	9	Renal failure, Respiratory arrest,	
585-002	21	End-stage CHF End-stage CHF	
<u>Nesiritide, 0.015 µg/kg/min</u>			
369-003	8	End-stage CHF	Nesiritide for 3 hours
493-008	14	End-stage CHF	Nesiritide for 3 days
504-003	11	AMI, end-stage CHF	Nesiritide for 7 days
538-010	9	End-stage CHF, renal failure, sepsis	Nesiritide for 65 hours
550-002	14	End-stage CHF,	Nesiritide for 3 days
559-005	7	AMI, tricuspid endocarditis, end-stage CHF	Nesiritide for 5 days
<u>Nesiritide, 0.03 µg/kg/min</u>			
382-002	3	End-stage CHF	Nesiritide for 1 day, severe hypotension starting 6 hours after nesiritide stopped
508-004	2	End-stage CHF, Neurologic compromise	Nesiritide for 2 days
509-002	6	Renal failure, CHF	Nesiritide for 5 days
524-005	5	V Fib	Nesiritide for 3 days, discharged on day 4
528-001	22	Arrhythmia	Nesiritide for 3 days. Renal failure starting day 5.
572-001	20	Multi-system organ failure, inc. renal failure	Nesiritide for 1 day
585-003	13	End-stage CHF	Nesiritide for 2 days

a. Data from NDA vol. 66, section 6.2 and Case Report Forms.

Serious Adverse Events

SAEs during study drug administration

Seven patients had serious adverse events that occurred within 24 hours of study drug infusion. Narratives for these patients can be found in appendix 3. Review of these does not reveal any episodes of severe hypotension, renal failure or arrhythmia, with the exception of the following case, in the nesiritide 0.6/ 0.030 group.

Subject 519-002 (Nesiritide, 0.03 µg/kg/min) Subject 519-002 is a 77-year-old black woman with a history of NYHA Class III CHF, hypertensive cardiomyopathy and a previous myocardial infarction. At the time of admission, as part of the routine work-up for CHF, cardiac enzymes were obtained and were normal. She received nesiritide, which was interrupted after 40 minutes of infusion because of hypotension, restarted, and then discontinued after 4.5 hours for hypotension. At no time did she have chest pain. The following morning, she was diagnosed with a non-Q wave myocardial infarction based on an elevation of routinely ordered cardiac enzymes. In retrospect, because of elevated myoglobin (myoglobin = 162 ng/mL; normal 12–76 ng/mL) upon admission, her physicians concluded that she had an evolving MI before entering the study. She was clinically stable throughout and required no treatment for this event.

SAEs following study drug discontinuation

In the absence of safety reports, some events occurred which were classified by the sponsor as serious, that occurred >24 hours after drug discontinuation. These are summarized in the table below.

Table 6.3.13.2.2 Serious Adverse Events in study 704.326^a.

Subject #	Day of Event	SAE
Standard Care Group		
354-001	19	UTI
493-006	11, 15	Pneumonia requiring intubation
521-010	7, 21	CHF recurrence/ rehospitalization
521-012	17	SVT, CHF recurrence
525-003	7	Syncope
539-001	6, 14	CHF
539-004	20	CHF
554-019	6	Acute Renal Failure, HD (required day 13) Perforated GI Ulcer (day 13)
554-047	19	CHF
580-001	14	CHF, Hyperkalemia
580-004	5	Syncope, V. Fib.
580-009	21	CHF

a. Data from NDA vol. 66 appendix 8 and Case Report Forms.

Table 6.3.13.2.3 Serious Adverse Events in study 704.326^a.

Subject #	Day of Event	SAE
Nesiritide 0.3/0.015 Group		
369-001	17	Dehydration
521-005	8	CHF, pneumonia
536-005	14	CHF
540-004	9	CHF
554-008	17	UTI
554-013	9	CHF, VT
570-001	19	CHF
574-001	4	V. Fib

a. Data from NDA vol. 66, appendix 8.

Table 6.3.13.2.4 Serious Adverse Events in study 704.326^a.

Subject #	Day of Event	SAE/ Notes
Nesiritide 0.6/0.030 Group		
524-007	16	Hyperkalemia, Renal failure
534-003	20	Urosepsis
536-014	5	Bacteremia
538-004	6	CHF
547-004	--	Mis-diagnosis, ARDS
554-010	14	Arterial thrombosis (foot)
554-022	5, 7, 9	CHF
554-028	21	CHF
554-029	17	UGI bleed
554-041	9	Junctional Bradycardia
556-002	13	CHF
570-008	18	CVA
570-009	20	Angina
571-004	17	CHF
579-002	11	V Fib, Hypotension on nesiritide

a. Data from NDA vol. 66, appendix 8.

SAEs requiring re-hospitalization

Several patients required rehospitalization within 21 days of starting the study, including one patient, in the standard care group, who was hospitalized several times, including twice for CHF. The table below summarizes the reasons for rehospitalization. A higher number of patients in the standard care group required hospitalization during the 21-day follow-up period.

Table 6.3.13.2.5 Serious Adverse Events requiring rehospitalization in study 704.326^a.

Reason for Readmission	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100
Acute CHF Decompensation	8 (8%)	4 (4%)	4 (4%)
Syncope	2 (2%)	0 (0%)	1 (1%)
Hyperkalemia	1 (1%)	0 (0%)	1 (1%)
Chest pain	0 (0%)	0 (0%)	1 (1%)
Infection	4 (4%)	2 (2%)	1 (1%)
Miscellaneous and elective	1 (1%)	2 (2%)	3 (3%)

a. Data from NDA volume 66.

Subject discontinuations

Nine subjects terminated study drug infusion before 6 hours because of an adverse event. Two subjects in the standard care group terminated early because of sinus tachycardia and non-sustained ventricular tachycardia, respectively. Two nesiritide subjects in the 0.015 µg/kg/min group and 5 subjects in the 0.03 µg/kg/min group terminated before 6 hours because of hypotension and related symptoms. Narrative summaries for these discontinuations can be found in appendix 4.

Table 6.3.13.2.6 Subject discontinuations in study 704.326^a.

Subject #	Day of D/C	Cause of Discontinuation	Notes
Standard Care			
535-001 (dopamine)	30 mins	Sinus Tach	
550-005 (milrinone)	3 hrs	Non-sustained V Tach	
Nesiritide 0.3/ 0.015			
352-001	2 hrs 15 mins	Hypotension	SBP 100 to 84 mm Hg
519-008	3 hrs 15 mins	Hypotension, recurrent on half-dose nesiritide	SBP 99 to 85 mm Hg
Nesiritide 0.6/ 0.030			
504-002	3 hrs 45 mins	Hypotension, recurrent on half-dose nesiritide	SBP 102 to 70 mm Hg
519-002	41 minutes	Hypotension, recurrent on half-dose nesiritide	SBP 170 to 73 mm Hg Later found to have elevated CPK prior to start of nesiritide
521-006	3 hrs 30 mins	Symptomatic hypotension	SBP 138 to 92 mm Hg
562-001	3 hrs 45 mins	Hypotension, Junctional bradycardia	Hx of 1 st degree AV block and LBBB
571-003	25 minutes	Hypotension, recurrent on half-dose nesiritide	SBP 93 to 77 (asymptomatic)

a. Data from NDA vol. 66, section 6.4 and Case Report Forms.

6.3.14 Trial 704.326 Efficacy Summary

This was a trial in patients with decompensated CHF, comparing the effects of standard care with two doses of nesiritide (0.3 µg/kg followed by a 0.015 µg/kg/min infusion or 0.6 µg/kg bolus followed by a 0.03 µg/kg/min infusion). The primary goal of the trial was to collect safety information regarding the use of nesiritide in the decompensated CHF population. The patients in this trial were required to be off of their other parenteral vasoactive medications for 4 hours, just as in the 704.325 study. Patients were randomly assigned to receive either nesiritide or standard therapy in open-label fashion. For subjects assigned to one of the two nesiritide groups, however, investigators were blinded to the dose of nesiritide administered.

Regarding data collection, there was no requirement for use of invasive hemodynamic monitoring (i.e., S-Ganz catheters), so no information regarding changes in PCWP, CI, SVR, etc. was collected (as was done in 704.325). Similar to trial 704.325, however, this trial collected information about changes in the symptoms of CHF. Data was also collected on the duration of hospitalization and the need for invasive procedures such as hemodialysis.

The demographics of the trial were well-balanced as regards race, age, cause of CHF, and physical findings on admission (tables 6.3.12.1.1 through 6.3.12.1.3). The patients in the high-dose nesiritide group were more likely to have had sustained VT and sudden cardiac death. With regard to concomitant medications, significantly fewer patients in the nesiritide groups received diuretics (table 6.3.12.2c.4). Otherwise, the use of ACE inhibitors, beta-blockers, non-IV nitrates, calcium channel blockers were similar in the three groups.

Duration of study drug administration was longer in the standard care group if one only considered the first (or 'standard care') drug (table 6.3.12.2c.2), but not if all vasoactive cardiovascular medications were considered (table 6.3.12.2c.3). Patients were also more likely to start and remain on nesiritide than for other parenteral cardiovascular meds (i.e., dobutamine, and dopamine).

1. With regard to efficacy, there was no pre-specified primary endpoint, as this trial was designed to collect safety data.

2. With regard to blood pressure, nesiritide had a dose-dependent effect to lower systolic BP (SBP) more than the standard care group, with a mean decrease of 11.2 mm Hg in the nesiritide 0.060 group (table 6.3.12.3.1). Mean diastolic blood pressure fell in all three groups; no significant difference between the three groups was detected.

3. With regard to heart rate, no significant differences between the three groups were detected, although the nesiritide 0.030 group had a significantly lower mean heart rate at 3 hours relative to placebo (table 6.3.12.3.1).

4. With regard to changes in body weight, the mean change in weight from baseline was less in the high-dose nesiritide group than in the standard care group at all days measured, up to day 8 (table 6.3.12.3.2). There was no trend at any time for a greater loss of weight in either of the nesiritide groups relative to standard care.

5. With regard to symptomatic relief, all three treatment groups tended to improve by the end of 6 hours, and continued to improve through 24 hours (table 6.3.12.3.3). No difference between the three groups with regard to the global assessment scale was detected. Importantly, the high-dose nesiritide (0.060) infusion was not more effective at improving either the global CHF score or the individual signs and symptoms of CHF, when compared with the nesiritide 0.015 dose. For individual signs and symptoms, there was a trend towards subjects reporting greater improvement in 'peripheral edema' at the end of 6 hours relative to the standard care group, although this difference did not persist to 24 hours (table 6.3.12.3.6).

6. With regard to hospitalization:

a. Duration of hospitalization was similar in all three groups (table 6.3.12.3.7).

b. A non-significant trend exists towards fewer re-admissions within 21 days in the nesiritide groups (table 6.2.12.3.8). Readmissions for CHF occurred equally in all three treatment groups.

7. With regard to need for other invasive medical procedures, no significant differences existed between the three treatment groups (table 6.3.12.3.9). There was a trend towards fewer intubations in the nesiritide groups.

6.3.15 Trial 704.326 Safety Summary

1. Almost all patients enrolled in the trial completed the first 6 hours of the trial. Discontinuations for hypotension during that period were more common in the nesiritide groups (2% and 5% for the two nesiritide groups vs. 0% in standard care, tables 6.3.13.1).
2. Deaths in the trial were balanced in the three groups: 5 (5%), 6 (6%) and 6 (6%) died in the standard care, nesiritide 0.030 and 0.060 groups respectively (table 6.3.13.2 through 6.3.13.4).
3. Serious Adverse Events (SAEs) were balanced between the three treatment groups.
4. See Section 8.0.2a in the Integrated Safety Summary for a discussion of the increased incidence of hypotension in the nesiritide treated patients in this trial.

6.3.16 Overall Summary for Trial 704.326

In conclusion, then, trial 704.326 compared nesiritide with several other approved parenteral therapies for CHF. Importantly, very few patients were treated with other pure vasodilators (nitroprusside, nitroglycerin). With regard to clinical efficacy, nesiritide appeared as effective as the active comparators in relieving the symptoms of CHF at the end to 6 and 24 hours. There was no tendency for the high-dose nesiritide to be more effective than the low-dose nesiritide as regards symptomatic benefit (the only blinded data in this trial).

The physiological effects of nesiritide were similar to what was seen in the earlier trials, and both doses of nesiritide lowered mean systolic blood pressure more than the active control at the end of 6 and 24 hours. There was no trend towards greater weight loss in the either of the nesiritide groups relative to active control.

No other clinical benefits of nesiritide were measurably superior to the active comparators.

7.0 Integrated Efficacy Summary

The integrated efficacy summary will be broken into two parts. First, the ‘physiologic efficacy’ of nesiritide will be compared with the control groups. Next, the ‘clinical efficacy’ of nesiritide will be examined, including effects on the signs and symptoms of CHF, hospitalization, and need for other medical interventions. The majority of the tables and graphs originate in the individual trial reviews or from the FDA Statistical review (Appendix Six), and their original numbering is maintained to aid the reader in locating the relevant portions of the studies.

7.0.1 Physiologic Efficacy of Nesiritide

The hemodynamics section will first summarize the data comparing nesiritide with placebo from studies 704.311 (0-24 hours) and 704.325 (6 hours). Then, the effects of nesiritide at longer time points will be examined. This will include the 704.325 trial beyond 6 hours, and the 704.326. Trial 704.326 did not measure central hemodynamics, so data from that trial will be limited to vital signs.

7.0.1a Effect of Nesiritide on PCWP

7.0.1a.1 Effect of Nesiritide on PCWP Versus Placebo

The effects of nesiritide on PCWP and other hemodynamics were compared with placebo in two long infusion trials: 704.311 (0-24 hours) and 704.325 (0-6 hours). The first section will discuss these time points for both trials.

Trial 704.311 at 3 Hours

Compared with placebo, nesiritide had a significant, dose-dependent effect to lower PCWP, regardless of the population studied: Intent-to-Treat (ITT, shown below), ‘Evaluable at 3 hours’, or ‘Last-value Carried Forward.’

Table 7.0.1a.1 (from 6.1.12.5.1) Changes in PCWP (baseline to 3 hours) in the ITT population 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±4.5	-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 NDA volume 54, Appendix 1, Table 17A, 17B.

b. See statistical section for statistical methods. p Value per sponsor.

c. Comparison using T-test.

FDA Review of 704.311 PCWP Data

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

Table 7.0.1a.2 (from 16.3) Mean change in PCWP from baseline for 80 and 103 subjects in study 704.311 at hours 3.

Analysis	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	p Value (ANOVA)	p Value (Kruskall- Wallis)	p Value (Kruskall- Wallis/WR) ^a
80 Subjects at 3 hours	-3.8 (n=23)	-7.0 (n=17)	-7.1 (n=18)	-11.2 (n=21)	0.0027	0.0010	0.0079
103 Subjects at 3 hours	-1.7	-8.0	-7.3	-10.2	<0.001	<0.001	0.0014

a. Kruskal-Wallis using worst rank.

Trial 704.311 Through 24 Hours

The number of patients enrolled in the treatment groups for 704.311, and the numbers of patients in the 'Evaluable at 24 hours' and 'Intent to Treat' populations are shown below. The comparison through 24 hours remained double-blinded per protocol. There were relatively few drop-outs.

	Placebo	Nesiritide 0.25/ 0.015	Nesiritide 0.5/ 0.030	Nesiritide 1.0/ 0.060
Enrolled Population	29	22	26	26
Evaluable at 24 Hours Population	25	18	21	20
Intent to Treat Population	25	22	20	19

The changes in PCWP in this population are shown below, first from the sponsor's analysis. Similar to the 3 hour timepoint, the nesiritide groups had a significantly lower PCWP compared with the placebo group in this population. Note also that the magnitude of the mean change in PCWP is less at 24 hours than at 3 hours for the nesiritide 0.030 and 0.060 groups.

Table 7.0.1a.3 (from 6.1.12.3.2) Changes in mean PCWP from baseline to 24 hours in the 'Evaluable at 24 Hours' population^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±6.1	-8.8±6.8	-3.6±7.7	-8.0±6.4
p Value (Chng from Baseline) ^c	0.169	<.001	0.024	<0.001
p Value (Dunnett) ^b	--	<0.05	NS	<0.05
p Value (P/W Con) ^b	--	0.001	0.328	0.002

a. Data from NDA volume 54, Appendix 1, Table 19A, 19B

b. See statistical section for statistical methods. p Value per sponsor.

c. Comparison using T-test.

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

Table 16.3 Mean change in PCWP from baseline for 80 & 103 subjects in study 704.311 at hour 24.

Analysis	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	p Value (ANOVA)	p Value (Kruskal- Wallis)	p Value (Kruskal- Wallis/WR) ^a
80 Subjects at 24 hours	-3.7 (n=23)	-8.7 (n=17)	-5.3 (n=18)	-11.1 (n=21)	0.0037	0.0025	0.1601
103 Subjects at 24 hours	-1.9	-8.9	-5.9	-10.6	<0.001	<0.001	0.0128

a. Kruskal-Wallis using worst rank.

The pairwise comparisons show a statistically significant difference (after the Bonferroni adjustment for the multiplicity) in reduction of PCWP between the nesiritide 0.015 or 0.060 groups and placebo at Hour 24, but not for the nesiritide 0.030 group. The nominal p Values for the comparisons are 0.0029 (0.015 vs. Placebo), 0.2950 (0.03 vs. Placebo), and 0.0033 (0.06 vs. Placebo).

Trial 704.325 from Baseline to 6 hours

The sponsor first analyzed the 'worst-outcome' population, where the difference between placebo and either of the two nesiritide dose-groups was highly statistically significant at the 6 hour time-point. This result was true for the pre-specified primary endpoint analysis (% change from baseline at 6 hours, shaded in the table below), or for the absolute change in PCWP (in mm Hg).

Table 7.0.1a.5 (from 6.2.12.3.1) 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	-22.6	<0.001
p Value (change from baseline)^c	0.010	0.227	<0.001	
p Value (compared with control baseline)^c	---	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	

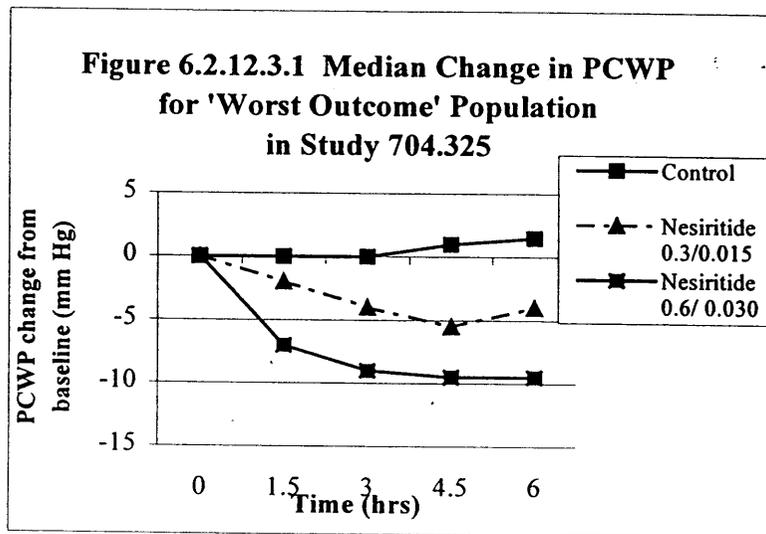
a. Data from NDA volume 59, Appendix 1, Table 22A, 22B, and 22C.

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.

This data is also presented below, along with the change from baseline at earlier timepoints for the same study population. There was a clear trend in the 'worst-case' population for greater decreases in PCWP in the nesiritide groups. The change from baseline achieved nominal significance for both of the nesiritide dose-groups at the 1.5 hr time-point and all subsequent time-points. Given the non-parametric nature of this analysis, no mean data (or standard deviations) are possible, and the graph illustrates median values.



FDA Analysis of 0-6 Hour PCWP Data from 704.325

Analyses for change and percentage change from baseline in PCWP were performed for Intent-to-Treat (ITT) population using worst-score imputation and LVCF imputation. The results, based on worst-score analysis showed a statistically significant treatment difference in change from baseline in PCWP among the three treatment groups starting at Hour 1.5, are summarized below. There were 42 patients in each of the treatment groups, for a total of 126 patients. For details of the FDA statistical review, see Appendix 6.

Table 7.0.1a.6 (from 1.1) Significance of changes in PCWP from baseline for ITT population in 704.325.

Hour	Treatment/ # of Patients	p Value for Absolute Change in PCWP ^a	p Value for % Change in PCWP
1.5	Placebo Nesiritide 0.015 Nesiritide 0.030	0.0001	0.0001
3	Placebo Nesiritide 0.015 Nesiritide 0.030	0.0001	0.0001
4.5	Placebo Nesiritide 0.015 Nesiritide 0.030	0.0001	0.0001
6	Placebo Nesiritide 0.015 Nesiritide 0.030	0.0001	0.0001

a. Kruskal-Wallis test (worst case analysis)

Comparisons of each of the two dosages with the control showed that the active treatment significantly lowered the PCWP, as shown below. In the pair-wise comparisons, no adjustment of p Value for the multiplicity was necessary because of the closure principle.

Table 7.0.1a.7 (from 1.2) Comparison of effect of two nesiritide doses with placebo for change in PCWP from baseline to 6 hours, from ITT population.

Hour	Treatment	p Value for change in PCWP ^a	p Value for % change in PCWP ^a
1.5	Nesiritide 0.015 vs. Placebo	0.0021	0.0020
	Nesiritide 0.030 vs. Placebo	0.0001	0.0001
3	Nesiritide 0.015 vs. Placebo	0.0004	0.0002
	Nesiritide 0.030 vs. Placebo	0.0001	0.0001
4.5	Nesiritide 0.015 vs. Placebo	0.0001	0.0001
	Nesiritide 0.030 vs. Placebo	0.0001	0.0001
6	Nesiritide 0.015 vs. Placebo	0.0019	0.0009
	Nesiritide 0.030 vs. Placebo	0.0001	0.0001

a. Wilcoxon 2-sample test per FDA Statistical Reviewer.

Conclusion Regarding Effects of Nesiritide on PCWP vs. Placebo

Nesiritide exerts a dose-dependent effect to decrease PCWP. This effect of nesiritide was statistically significantly greater than placebo after 3 and 24 hours in the 704.311 trial and for all measured time points up to 6 hours in the 704.325 trial.

The effect was also dose-dependent over the range of nesiritide infusion doses used in the long infusion trials, again at all measured time points up to 6 hours in 704.325 and 24 hours in 704.311. At the 24 hour time-point, the difference between the nesiritide 0.030 dose and placebo was less than for the other nesiritide dose groups.

7.0.1a.2 Effects of Nesiritide on PCWP versus Active Control

The effects of nesiritide on PCWP beyond 6 hours were measured in 704.325, in open-label fashion, using the 'all nesiritide subjects with a 24 hour evaluation' population.

Trial 704.325

In this trial, PCWP data were collected on a subset of individuals in the nesiritide groups beyond 6 hours (the end of the placebo period), but not for the active control group. Of the 42 patients in each of the nesiritide groups, 37 in the nesiritide 0.015 group and 38 in the nesiritide 0.030 group had PCWP data available at the end of 24 hours (making up the 'data as available' population at 24 hours. Note that there was not a significant difference from baseline at the end of 24 hours (although the change in PCWP was numerically similar to the 0-6 hour value). Similarly, there was no significant difference between the PCWP at 6 and 24 hours.

Table 7.0.1a.2.1 (from 6.2.12.4.5) Summary of changes in selected hemodynamic measurements using 'data as available' population from study 704.325^a.

Pulmonary Capillary Wedge Pressure (mm Hg)	Nesiritide 0.3/ 0.015 n=37	Nesiritide 0.6/ 0.030 n=38	p Value^b
Baseline PCWP	28.7±6.5	27.4±6.5	
Change in PCWP from Baseline to 6 hours			
Mean±SD	-6.8±7.7	-9.5±5.4	0.080
Range	-29 to +36	-20 to +3.0	
Change in PCWP from 6 to 24 hours			
Mean±SD	-0.6±7	-0.3±5.8	0.820
Range	-13 to +15	-13 to +11	
Change in PCWP from Baseline to 24 hours			
Mean±SD	-7.0±9	-9.9±6	0.116
Range	-26 to +13	-21 to +5	

a. Data from NDA volume 59, Appendix 1, Table 42A. Shown for all subjects with available 24 hour data.

b. p Value using Omnibus F test.

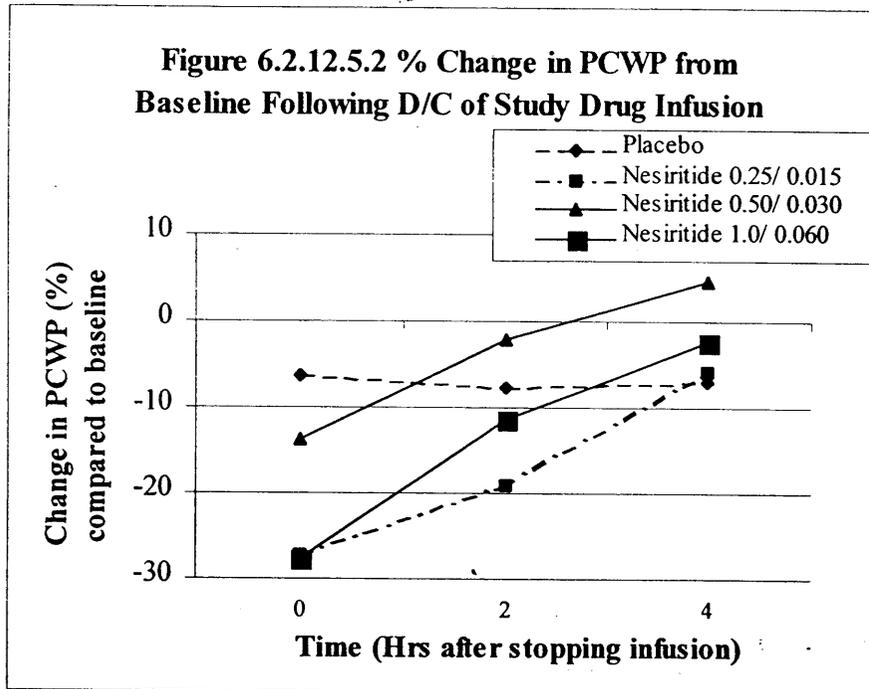
7.0.1a.3 The Demographics of the Effects of Nesiritide on PCWP

The demographics of the short-term effects of nesiritide (0-3 hours) on PCWP were examined in study 704.311. While the number of subjects in some of the sub-groups were quite small, the acute effects of nesiritide on PCWP (0-3 hours) extended across all of the demographics subgroups studied, including grouping by age, sex, race, NYHA class, etiology of CHF, and use of other cardiac medications (i.e., Digoxin, ACE Inhibitors). For details see tables 6.1.12.5.6 and 6.1.12.5.7 in the review of study 704.311.

7.0.1a.4 Changes in PCWP Following Withdrawal of Nesiritide

Trial 704.311 is the only source for information regarding the changes in hemodynamics following withdrawal from nesiritide in the long infusion studies (see review by Dr. Karkowsky for effect of withdrawal of bolus and short-infusion nesiritide).

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 NDA volume 1.54, table 17C for data).



There also did not appear to be an increased incidence of recurrent CHF following nesiritide treatment. In study 704.326, readmissions through day 21 for CHF (or for any cause) were lower in the two nesiritide groups than in the control group.

Conclusion Regarding Withdrawal of Nesiritide Infusion

Based on the data from the 704.311, withdrawal of nesiritide leads to a return of PCWP to within 10% of baseline within 4 hours. After 2 hours, the high-dose nesiritide group had not returned to within 10% of baseline, however. Based on the data from 704.326, no evidence was detected of a 'rebound' phenomenon with regard to PCWP.

7.0.1b Effect of Nesiritide on Other Hemodynamic Markers

7.0.1b.1 Effects of Nesiritide on Other Hemodynamic Markers Compared with Placebo

The effects of nesiritide on PCWP and other hemodynamics were compared with placebo in two long infusion trials: 704.311 (0-24 hours) and 704.325 (0-6 hours).

Study 704.311

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

Table 7.0.1b.1 (from 6.1.12.4.1) Effect of 3 hour infusion of nesiritide on identified hemodynamic parameters^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	-3.7±3.5	-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 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 is decreased at 24 hours.

Table 7.0.1b.1 (from 6.1.12.4.2) Effect of 24 hour infusion of nesiritide on identified hemodynamic parameters^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 NDA 20-920, vol. 54, Tables 20B through 31B. Data are expressed as absolute change from baseline for ITT population.
b. p Value comparing arithmetic means from baseline using ANOVA linear contrast except for heart rate, which used Omnibus F test.

Study 704.325

The hemodynamic effects of nesiritide were compared with placebo for the period between 0 and 6 hours after start of study drug infusion. This analysis uses the 'last value carried forward' population; similar results were obtained using the two other analyzed populations ('worst outcome' and 'data as available'). Significant effects of nesiritide were seen for Right Atrial Pressure, peripheral vascular resistance (PVR), and Cardiac Index. Note also the broad patient-patient variability in response.

Table 7.0.1b.3 (from 6.2.12.4.3) Summary of changes in selected hemodynamic measurements using 'last value carried forward' population from study 704.325^a.

Hemodynamic Parameter	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^b
Right Atrial Pressure (RAP), mm Hg				
RAP at baseline and 6 hours (mm Hg)				
At baseline (mm Hg)	14.2±6	15.1±7	14.3±7	0.817
At 6 hours (mm Hg)	14.6±6	12.1±7	9.1±6	0.001
p Value (compared to control) ^d	---	0.076	<0.001	
% Change in RAP from baseline at 6 hrs (%)				
Mean±SD	+8.1±29	-12.0±42	-39.4±31	<0.001
Median	0	-20	-40	
Range	-53 to +93.8	-48 to +200	-100 to +58	
p Value (change from baseline) ^c	0.076	0.081	<0.001	
p Value (comp. to control) ^d	---	0.010	<0.001	
Systemic Vascular Resistance(SVR) dynes/sec/cm²				
SVR at baseline and 6 hours				
At baseline	1524±493	1598±582	1686±589	0.407
At 6 hours	1693±633	1386±539	1340±511	0.010
p Value (compared to control) ^d	---	0.014	0.005	
% Change in SVR from baseline at 6 hrs (%)				
Mean±SD	+12.8±30	-12.6±25	-17.7±26	<0.001
Median	11.2	-9.2	-20.2	
Range	-52 to +84	-68 to +73	-62 to +51	
p Value (change from baseline) ^c	0.010	0.004	<0.001	
p Value (comp. to control) ^d	---	<0.001	<0.001	
Cardiac Index (CI), L/min/m²				
CI at baseline and 6 hours				
At baseline	2.0±0.4	1.8±0.5	1.9±0.5	0.159
At 6 hours	1.9±0.5	2.1±0.5	2.3±0.6	0.002
p Value (compared to control) ^d	---	0.165	<0.0001	
% Change in CI from baseline at 6 hrs (%)				
Mean±SD	-4.4±26	16.2±33	27.5±40	<0.001
Median	-2.6	12.1	21.4	
Range	-43 to +88	-28 to +159	-40 to +110	
p Value (change from baseline) ^c	0.269	0.004	<0.001	
p Value (comp. to control) ^d	---	0.006	<0.001	

a. Data from NDA volume 59, Appendix 1, Table 27, 28, and 30 (A and C).

b. p Value using Omnibus F test.

c. p Value compares the 6 hour value for each group individually with the control baseline using 1-sample t test.

d. p Value compares the 6 hour value for each group individually with the control baseline using pairwise contrasts.

The next table continues to summarize hemodynamic effects of nesiritide in trial 704.325, emphasizing the systemic effects of study drug. Of note, there was a highly significant decrease in systemic mean arterial pressure that appeared to be dose-related, but no increase in heart rate.

Table 7.0.1b.4 (from 6.2.12.4.4) Summary of changes in selected hemodynamic measurements using 'last value carried forward' population from study 704.325 (cont)^a.

Hemodynamic Parameter	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value ^b
<u>Pulmonary Vascular Resistance (PVR), dynes/sec/cm²</u>				
PVR at baseline and 6 hours				
At baseline	278.8±200	293.8±183	242.2±201	0.472
At 6 hours	305.1±303	232.4±155	240.1±139	0.227
p Value (compared to control) ^d	---	0.116	0.163	
Change in PVR from baseline at 6 hrs (mm Hg)				
Mean±SD	+26.3±197	-62.2±100	-2.0±142	0.033
Median	10.3	-53.2	-8.3	
Range	-393 to +540	-296 to +148	-218 to +459	
p Value (change from baseline) ^d	0.392	<0.001	0.928	
<u>Mean Pulmonary Artery Pressure (MPAP) mm Hg</u>				
MPAP at baseline and 6 hours				
At baseline	41.1±9	39.6±9	38.3±8	0.338
At 6 hours	43.1±11	33.0±9	30.6±10	<0.001
p Value (compared to control) ^d	---	<0.001	<0.001	
Change in MPAP from baseline at 6 hrs (mm Hg)				
Mean±SD	+2.0±5.8	-7.0±6.9	-7.7±7.6	<0.001
Median	2.5	-5.0	-8.8	
Range	-11 to +18	-23 to +4.0	-23 to +10	
p Value (change from baseline) ^d	0.031	<0.001	<0.001	
<u>Mean Systemic Arterial BP (MAP), mm Hg</u>				
MAP at baseline and 6 hours				
At baseline	86.2±12.6	81.2±10.0	85.4±11.3	0.103
At 6 hours	86.7±13.1	76.2±11.4	76.8±10.2	<0.001
p Value (compared to control) ^d	---	<0.001	<0.001	
Change in MAP from baseline at 6 hrs (mm Hg)				
Mean±SD	0.3±7.8	-5.1±11.0	-3.6±8.0	0.001
Median	-1.3	-4.5	-8.7	
Range	-17 to +19	-44 to +20	-24 to +11	
p Value (change from baseline) ^c	---	0.005	<0.001	
p Value (comp. to control) ^d	---	0.008	<0.001	
<u>Heart Rate (HR), BPM</u>				
HR at baseline and 6 hours				
At baseline	89.5±12.8	90.3±14.6	87.4±16.7	0.640
At 6 hours	90.9±15.4	88.8±14.5	87.5±16.0	
p Value (compared to control) ^d	---	0.516	0.300	
Change in HR from baseline at 6 hrs (mm Hg)				
Mean±SD	1.4±7	-1.6±7	0.0±9	0.218
Median	0.5	-3.0	0.0	
Range	-16 to +24	-16 to +14	-28 to +28	
p Value (change from baseline) ^c	0.240	0.149	0.972	
p Value (comp. to control) ^d	---	0.082	0.435	

a. Data from NDA volume 59, Appendix 1, Tables 33, 36, 39, and 40 (A and B).

b. p Value using Omnibus F test.

c. p Value compares the 6 hour value for each group individually with the control baseline using 1-sample t test.

d. p Value compares the 6 hour value for each group individually with the control baseline using pairwise contrasts.

7.0.1b.2 Effects of Nesiritide on Hemodynamics (non-PCWP) Compared with Active Controls
Trial 704.325

The sponsor summarized the hemodynamic data (where available) through 24 hours in trial 704.325. See Appendix 5 for details of this analysis. Since this analysis did not include the control subjects, its greatest utility is in examining the hemodynamic changes that occurred between 6 and 24 hours for subjects treated with nesiritide. To highlight this, the data is shown from 0 to 6 hours and from 6 to 24 hours. Almost all of the detected hemodynamic effect of nesiritide occurred in the first 6 hours of therapy.

Table 7.0.1b.2.1 (from 6.2.12.4.5) Summary of changes in selected hemodynamic measurements using 'all nesiritide subjects with a 24 hour evaluation' population from study 704.325^a.

Hemodynamic Parameter	Nesiritide 0.3/ 0.015 n=37	Nesiritide 0.6/ 0.030 n=38
<u>Pulmonary Capillary Wedge Pressure (mm Hg)</u>		
Baseline	28.7±6.5	27.4±6.5
Change in PCWP from 0 to 6 hours		
Mean±SD	-6.8±7.7	-9.5±5.4
Range	-29 to +36	-20 to +3.0
Change in PCWP from 6 to 24 hours		
Mean±SD	-0.6±7	-0.3±5.8
Range	-13 to +15	-13 to +11
Change in PCWP from 0 to 24 hours		
Mean±SD	-7.0±9	-9.9±6
Range	-26 to +13	-21 to +5
<u>Systemic Vascular Resistance (SVR)</u>		
Change in SVR from 0 to 6 hours		
Mean±SD	-318.4±513	-279.8±481
Range	-1933 to +299	-1218 to +865
Change in SVR from 6 to 24 hours		
Mean±SD	-229.1±474	-1.2±404
Range	-1652 to +544	-992 to +1318
Change in SVR from 0 to 24 hours		
Mean±SD	-489.5±630	-345.0±372
Range	-2244 to +685	-1238 to +865
<u>Cardiac Index (CI), L/min/m²</u>		
Change in CI from 0 to 6 hours		
Mean±SD	0.3±0.6	0.4±0.7
Range	-0.6 to 1.8	-1.0 to 1.9
Change in CI from 6 to 24 hours		
Mean±SD	0.2±0.7	0.1±0.7
Range	-1.0 to +2.2	-2.0 to +1.6
Change in CI from 0 to 24 hours		
Mean±SD	0.5±0.6	0.5±0.7
Range	-0.9 to +1.8	-1.0 to +3.2

a. Data from NDA volume 59, Appendix 1, Table 42A, 443A and 44A.

Trial 704.326

The best source for information comparing the different effects of nesiritide with active controls comes from the 704.326 study. The first table compares nesiritide and active controls for the period from 0-3 hours of study drug infusion (when the fewest changes in drug therapy had taken place, which would greatly complicate the analysis). While at baseline the vital signs of the three study groups were similar, there were significant differences between the vital signs at the end of 3 hours between the nesiritide and the standard care groups for both systolic and diastolic blood pressures. No central hemodynamic measurements were measured in this trial.

Table 7.0.1b.2.2 (from 6.3.12.3.1) Changes in vital signs from baseline to 3 hours in study 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
Systolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	120.7±20	127±25	124±26	0.197
Change from Baseline to 3 hours	-2.3±16	-9.3±16	-11.2±16	<0.001
p Value (Chg from Base) ^b	0.183	0.001	0.001	
p Value (Compared to Standard Care) ^c	--	0.003	0.001	
p Value (Compared to Low-dose BNP) ^c	--	--	0.426	
Diastolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	70±13	71±15	68±15	0.477
Change from Baseline to 3 hours	-5.9±12	-4.5±12	-8.6±11	0.051
p Value (Chg from Base) ^b	0.001	0.001	0.001	
p Value (Compared to Standard Care) ^c	--	0.376	0.125	
p Value (Compared to Low-dose BNP) ^c	--	--	0.016	
Heart Rate (BPM)				
Baseline (mean±sd)	85±15	83±18	84±15	0.823
Change from Baseline to 3 hours	+3.5±15	-0.6±9	+0.6±10	0.053
p Value (Chg from Base) ^b	0.029	0.501	0.569	
p Value (Compared to Standard Care) ^c	--	0.018	0.107	
p Value (Compared to Low-dose BNP) ^c	--	--	0.469	

a. Data from NDA volume 66, table 21.

b. Comparison by T test.

c. Comparison by ANOVA, pairwise contrast.

d. Comparison by ANOVA, omnibus F-test.

Conclusions Regarding the Other Hemodynamic Effects of Nesiritide

Nesiritide has significant effects on systemic and central hemodynamics. Of interest, there was no significant effect of nesiritide on pulmonary vascular resistance, in contrast to the effects on systemic vascular resistance and measures of large-vessel resistance (i.e., Mean Pulmonary Artery Pressure). This may suggest a relative sparing of the pulmonary vasculature as regards vasodilatory effects of nesiritide.

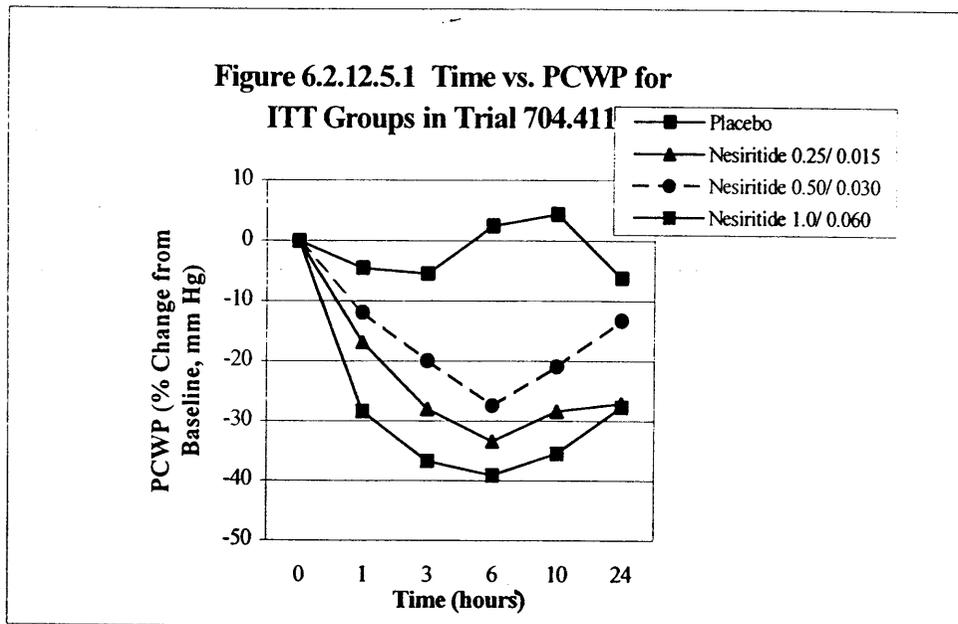
The data from both 704.311 and 704.325 demonstrate that the significant effect of nesiritide on mean and median non-PCWP hemodynamics persists through 24 hours. The data also support a dose-dependent effect on some of the hemodynamic parameters, especially measurements of systemic blood pressure. The acute effects of nesiritide on PCWP extend to all of the demographic sub-groups studied, although conclusions regarding relative magnitude of effect cannot be made because of small numbers.

In conclusion, nesiritide has effects on systemic and central hemodynamics that differ significantly from those seen with both placebo and active-control comparators at the time points measured.

7.0.1c Durability of the Effect of Nesiritide on PCWP and Other Hemodynamic Measures

7.0.1c.1 Durability of Nesiritide Effect on PCWP

The best data for looking at the durability of the effect of nesiritide comes from 704.311, where a majority of the subjects received nesiritide for 24 hours in blinded fashion. The graph below shows the effects of the various doses of nesiritide on PCWP during the first 24 hours of treatment for the ITT population. Note that the average effect of nesiritide, 0.25/0.015, was greater than the average effects of nesiritide 0.50/ 0.030 at all time-points. There was also a trend towards a return to baseline by the end of 24 hours in all three treatment groups, supporting the development of tolerance.



To examine this more fully, the sponsor submitted the serum nesiritide levels at 0, 3 and 24 hours for all patients with available hemodynamic measurements. The table below compares the changes in serum nesiritide levels with the changes in selected hemodynamic markers. Such an analysis is necessarily crude, and the reader is referred to the Biopharmacology review for further details regarding the PK-PD interaction and the development of ‘tolerance.’ Overall, however, the trend in this subset of the study was for a greater decrease in the change in PCWP and other hemodynamic markers relative to the nesiritide serum concentrations. This suggests that a given serum concentration of nesiritide was having a lesser effect on hemodynamics at 24 hours, relative to 3 hours.

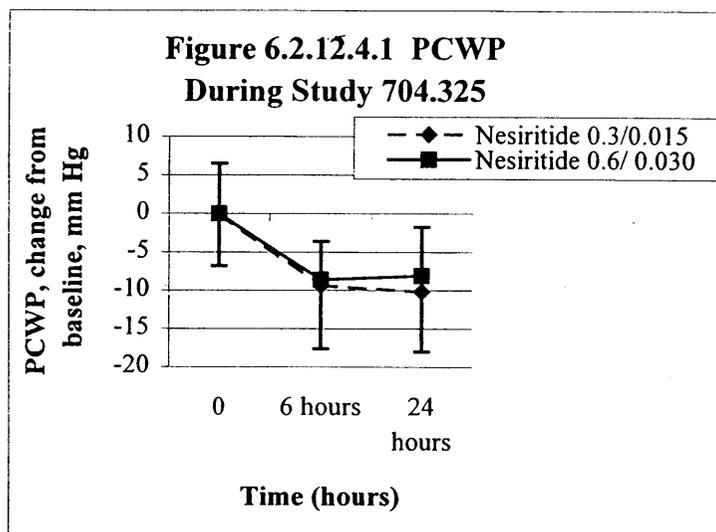
Table 7.0.1b.3 Comparison of changes in serum nesiritide levels and hemodynamic effects between 3 and 24 hours from study 704.311^a.

Measurement	Placebo n=29	Nesiritide 0.015 n=22	Nesiritide 0.030 n=26	Nesiritide 0.060 n=26
% Change in hBNP levels (3-24 hrs)	-28.1%	-10.4%	-12.3%	-18.0%
% Change in PCWP (3-24 hrs)	-1.8 to -1.8 0%	-8.9 to -8.3 -6.7%	-6.0 to -3.7 -38.3%	-10.8 to -8.4 -22.2%
% Change in SVR (3-24 hrs)	-16.4 to -17.6 +6.8%	-364.4 to -283.7 -22.1%	-203.6 to -67.3 -66.9%	-500.2 to -354.5 -29.1%
% Change in CI (3-24 hrs)	0.0 to 0.1 +NA	0.4 to 0.2 -50%	0.3 to 0.0 -100%	0.7 to 0.4 -42.8%
% Change in MPAP (3-24 hrs)	0.4 to -1.2 -400%	-7.4 to -8.4 +13.5%	-6.6 to -6.7 +1.5%	-9.4 to -7.6 -19.1%
% Change in SBP (3-24 hrs)	-0.2 to 0.0 -100%	-5.2 to -5.1 -1.9%	-2.8 to -3.5 +25%	-12.3 to -7.1 -42%

a. Calculated as the difference in the change from baseline at hours 3 and 24, expressed as a % of the hour 3 value. Mean data from sponsor. Mean % changes calculated by Medical Reviewer and not independently verified with sponsor.

Trial 704.325

In trial 704.325, a small number of subjects received only nesiritide during the first 24 hours. (16 in the nesiritide 0.015 group, 21 in the nesiritide 0.060 group). Their mean PCWP at 6 and 24 hours are shown below, showing the decreases in PCWP from 0 to 6 and 6 to 24 hours measured for the two nesiritide groups. The PCWP for the active control group in this study were not collected. In absolute terms, the PCWP declined from 30.1 to 20.7 mm Hg, and from 27.0 to 18.4 mm Hg at 6 hours in the 0.3/0.015 and 0.6/ 0.030 groups respectively. After 24 hours, in this 'responder population', there was no discernable trend towards a return to baseline.



7.0.1c.2 Durability of Nesiritide Effect on Other Hemodynamics

Hemodynamics other than PCWP were also followed in all three long infusion trials. These results are summarized below.

Trial 704.311

Comparing the changes in other hemodynamics from the placebo-controlled data for 704.311, the magnitude of the responses is diminished at 24 hours, relative to 3 hours, although the overall effect remains.

Table 7.0.1c.2.1 (from 6.1.12.4.1) Effect of 3 hour infusion of nesiritide on identified hemodynamic parameters^a.

Hemodynamic Parameter	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
MRAP (mm Hg)	-0.8±3.7	-3.73.5	-3.3±4.3	-4.5±6.2	0.024
SVR (Dyne-sec/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
PVR ^c (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 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.

c. Pulmonary Vascular Resistance.

The next table summarizes the same effects on selected hemodynamic measurements at the end of 24 hours. The magnitude of the decrease in both mean systolic BP and SVR persist through 24 hours. With regard to the PK-PD analyses for changes in hemodynamics other than PCWP, see my discussion in the PCWP section above (Table 7.0.1b.3).

Table 7.0.1c.2.2 (from 6.1.12.4.2) Effect of 24 hour infusion of nesiritide on hemodynamic parameters^a.

Change in Hemodynamic Parameters from Baseline	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
MRAP (mm Hg)	-1.4±5	-2.6±4	-3.6±6	-2.9±4	0.493
SVR (Dyne-sec/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
PVR ^c (Dyne-sec/cm ²)	+3.3±113 ^a	-68.3±233	-32.8±182	-31.8±129	0.576
Systolic BP (mm Hg)	+2.1±12	-6.1±12	-3.3±13	-9.0±12	0.021
Heart Rate (BPM)	+4.5±11	-1.0±6.8	-0.2±7.6	+4.0±8.2	0.083

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

704.325

The data from 704.325 is less useful in determining the durability of the nesiritide effect on hemodynamics, given the small number of subjects who received only nesiritide during the first 24 hours. For those patients who received only nesiritide, and were followed throughout the first 24 hours, the magnitude of the nesiritide effect on other hemodynamics was similar in the nesiritide groups and the active control group. Of significance, the significantly lower mean BP seen at 6 hours in the nesiritide groups persisted through 24 hours (see tables above for details).

704.326

This trial collected only vital signs, summarized through 6 hours in the table above. These data will not address the development of tolerance.

Conclusions Regarding the Durability of the Nesiritide Effect on Hemodynamics

There is animal and cell culture data suggesting the development of tachyphylaxis or drug tolerance, especially to a compound similar to nesiritide, atrial natriuretic peptide (hANP). Reviewing these data, Dr. Papoian came to the following conclusions:

‘Studies in cultures of vascular smooth muscle, in DOCA-salt hypertensive rats, and in patients with mild to severe CHF have shown that chronic exposure to elevated levels of ANP is associated with down regulation of hANP receptors which may occur in a matter of hours.’ These results imply that administration of exogenous hANP, and by extension hBNP (nesiritide), to patients with mild CHF may result in an initial vasodilatory effect. However, sustained exposure may lead to reduced pharmacological activity through (hANP and hBNP) receptor down-regulation. In severe CHF patients (where levels of CHF are elevated up to 6-fold over patients without cardiac disease), whose receptors are already down-regulated, ‘further administration of hBNP may be of limited utility.’ See Dr. Papoian’s review for further details.

Regarding the durability of the effect of long nesiritide infusions on PCWP, the only blinded, randomized data available come from 704.311. In that trial, there is a suggestion for a waning of the effect of nesiritide at the 24 hour time-point, as marked by a return towards baseline of the change in PCWP and other hemodynamic measurements, including SVR and CI. This return towards baseline could not be explained entirely by a decrease in the mean nesiritide concentrations. This trial enrolled a less acutely-ill CHF population than the other two long infusion trials, limiting its general applicability. In study 704.325, the data are more difficult to interpret due to trial design. For the sub-group of patients who remained on nesiritide, and did not receive other parenteral therapies (a sort of responder analysis) there was no apparent decrease in the magnitude of the hemodynamic effects of nesiritide.

While levels of nesiritide are known to be increased at baseline in CHF, no information exists regarding the changes in the hANP/hBNP receptor numbers or affinity following nesiritide infusion in patients with CHF (ref. 9).

In conclusion, the data are inadequate to fully assess the development of tachyphylaxis following long nesiritide infusion. Based on the decrease in the magnitude of the hemodynamic effect of nesiritide in trial 704.311, a degree of tolerance to the hemodynamic effects of nesiritide is possible. This decrease, however, did not reverse the overall significance of the effects of nesiritide on hemodynamics, when compared with placebo through 24 hours. The clinical significance of a ‘lessening’ of the magnitude of hemodynamic effects that nonetheless remain ‘significant’ compared with placebo cannot be determined. It is also important to remember that tolerance to nitrates typically develops after >24 hours of exposure to the drug, where we have no data regarding the maintenance of the hemodynamic effects of nesiritide. Finally, the patients enrolled in trial 704.311 had significantly less ‘acutely’ decompensated CHF relative to those in 704.325 and 704.326, raising issues of generalizability of the data to the severely decompensated CHF population for which the sponsor is seeking a claim.

7.0.1d The Relationship Between Plasma Nesiritide Concentrations and Hemodynamic Changes

In study 704.311, the sponsor performed an analysis of the steady-state pharmacokinetics of nesiritide at more than one dose level. For a full discussion of the results, please see the biopharmacologist's review.

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

There is also a relationship between the plasma nesiritide level and changes in PCWP.

Finally, and of critical importance, the sponsor analyzed the relationship between changes in PCWP and improvement in the symptoms of CHF in study 704.325. The tables for these analyses are reproduced in Appendix 17: Relationship between PCWP and changes in CHF Signs and Symptoms. In short, the greater the percentage decrease in PCWP, the greater the improvement in subject and investigator-derived 'Global Assessment of Well-Being' at hour six. Unfortunately, this analysis is severely undermined by the lack of independence of the collection of the data for hemodynamics and symptom relief.

Conclusions Regarding the Relationship between Changes in PCWP and Clinical Efficacy

Regarding the relationship between nesiritide dose and hemodynamic changes, as reflected by changes in PCWP, a significant relationship between nesiritide dose, nesiritide plasma concentrations, and changes in PCWP was seen in both the 704.311 and 704.325 trials (see study 704.325 for details).

Regarding the relationship between the hemodynamic effects of nesiritide (especially PCWP) and clinical outcomes, there is flawed data, from 704.325, linking decreases in PCWP to improvements in both the global assessment and in the degree of breathlessness. Taken in total, these data weakly support a link between the administered doses of nesiritide and an improvement in the patient's clinical state at the end of 6 hours.

7.0.1e Other Physiologic Effects of Nesiritide

7.0.1e.1 Effects of Nesiritide on Na⁺ and Water Excretion

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. 15). In the clinical database, all three long infusion trials measured some aspects of Na⁺ and water excretion as part of their programs. Overall, nesiritide had a small, inconsistent effect on Na⁺ and water excretion. Note: no information is available about the amount of IV vs. PO diuretics administered during the three trials (only total diuretic use).

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 (see table o.1.12.2c.1).

Table 7.0.1e.1.1 (from 6.1.12.5.5) Changes in fluid intake and urinary volume during first 24 hours in the ITT population of study 704.311^a.

Measurement	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
Fluid Intake (ml/ 24 hrs) Mean±sd	1935±515	1836±427	1767±545	2147±1062	0.222
p Value compared with placebo ^c	--	NS	NS	NS	
Total Urine Output (ml/ 24 hrs) Mean±sd	2106±1086	1745±840	179±806	2012±832	0.059
p Value compared with placebo ^c	--	NS	<0.05	NS	
Output – Intake (ml/24 hrs) Mean ±sd	475±1094	-91±756	-287±848	-136±1872	0.113
Median	547	162	434	407	0.059
p Value compared with placebo ^c	--	NS	NS	NS	

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

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

c. Comparison using Dunnet's t-test.

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

Table 7.0.1e.1.2 (from 6.1.12.5.6) Changes in sodium and potassium excretion during first 24 hours in the ITT population of study 704.311^a.

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

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

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

c. Comparison using Dunnet's t-test.

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 7.0.1e.1.3 (from 6.2.12.4.13) Assessment of volume status during first 24 hours in the ITT population 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.

In support of this possibility, if the subjects who received diuretics during the first 6 hours were removed, there remained significant differences in overall volume status at the end of 6 hours between control and nesiritide groups, except that in this case, there was more net output in the nesiritide groups relative to placebo. This increase in net fluid output, extrapolated over a 24 hour period, would result in a net loss in the nesiritide group of approximately 200 mls per day.

Table 7.0.1e.1.4 (from 6.2.12.4.14) Assessment of volume status during first 6 hours in study 704.325^a.

Volume parameter and period of measurement	Control n=39	Nesiritide 0.3/ 0.015 n=38	Nesiritide 0.6/ 0.030 n=39	p Value ^c
0 to 6 Hour Data				
Fluid Intake (Mean ±SD)	96.2±53	98.3±41	94.1±58	0.936
Urine Output (ml/ hr)	63.9±43	92.0±60	110±73	0.004
Output minus Intake (ml/ hr)	-32.3±70	-3.3±71	+15.9±71	0.013

a. Data from NDA volume 59, Appendix 1, Tables 57B. Includes all subjects with available data (≥90% of enrolled subjects).

c. p Value using Omnibus F test.

The next table summarizes the excretion of sodium and potassium 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 7.0.1e.1.5 (from 6.1.12.5.5) Changes in sodium and potassium excretion during first 24 hours in the ITT population of study 704.311^a.

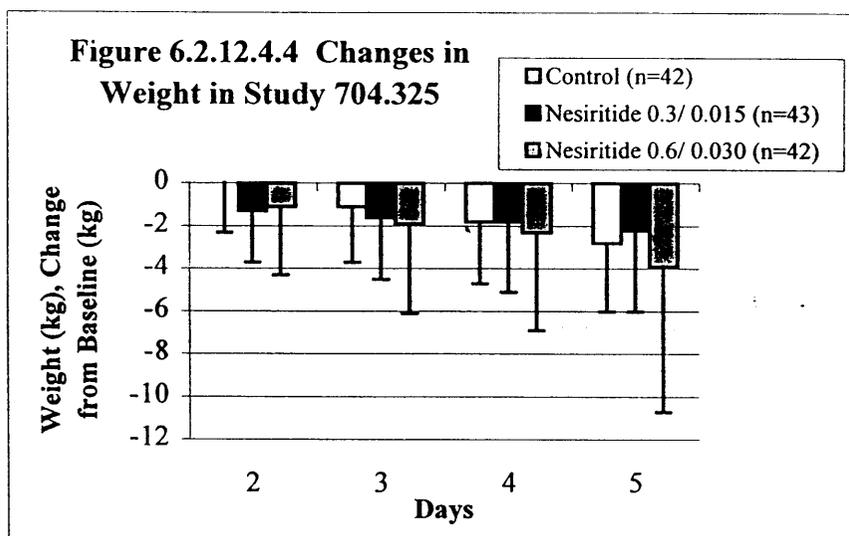
Measurement	Control n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value ^b
Urine Sodium Excretion (meq/24 hrs) Mean±sd	156±91	85±58	104±80	146±285	0.369
Median	146	77	86	46	0.943
p Value compared with placebo ^c	--	NS	NS	NS	

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

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

c. Comparison using Dunnet's t-test.

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. Recall that significantly 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, p<0.001). The reasons for this difference in the amount of diuretics administered cannot be determined, given the open-label nature of the trial.

Table 7.0.1e.1.6 (from 6.3.12.3.2) Changes in subject weights in study 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.

Conclusions Regarding Nesiritide Effects on Na⁺ and Water Excretion

The data regarding the effects of nesiritide on Na⁺ and water excretion are highly study-dependent. In trial (704.311) significantly less Na⁺ and water was lost in all of the nesiritide groups relative to placebo through 24 hours. Importantly, this is the only trial where there was not a significant imbalance with regard to diuretic use between the placebo and nesiritide groups. In the 704.325 trial, for the first 6 hours, those subjects who did not receive diuretics lost more water in the nesiritide groups relative to placebo. For the population as a whole, however, there was more fluid lost in control group than in the nesiritide group. However, because the trial was open-label, the investigators would almost certainly know of the putative natriuretic and diuretic effects of nesiritide. This prevents the use of this data to conclude, as suggested by the sponsor, that the decreased diuretic use reflects a decreased 'need' for diuretics in patients receiving nesiritide. There is also a reported blunting of the natriuretic and diuretic effect of nesiritide, seen in normal volunteers and animals, in patients who are intravascularly depleted (ref. 15).

The data on the changes in subject weights, with broad uncertainties, also suggest that any effect on diuresis and natriuresis by nesiritide has relatively little impact on overall weight change, as a surrogate for fluid loss. In trial 704.326, the high-dose nesiritide group had less weight loss at all time points relative to the active control group. In trial 704.325, there was a small increase in weight loss during the first 24 hours in the nesiritide group relative to control, which tended to diminish with time.

Finally, the literature suggests that ANP stimulates 'translocation' of fluid from the intravascular space (ref. 10). This same phenomenon was suggested by the NDA data with nesiritide (see ISS). If so, movement of salt and water to the interstitial space will prevent its excretion by the kidneys. During aggressive diuresis, the consequence may be an increased risk of renal hypoperfusion and damage. In conclusion, the data do not suggest an effect of nesiritide to increase Na⁺ and water excretion, and instead suggest anti-natriuresis during the first 24 hours. Nesiritide had no clear effect on weight loss in the 'real-world' trial (704.326), and the magnitude of any effect of a 24 hour infusion of nesiritide is likely to be quite limited in this regard.

7.0.1e.2 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, the median aldosterone concentration was decreased at the end of 6 hours in the nesiritide group, compared with placebo. For the control group, aldosterone levels rose 0.6 ng/dl (+5%), compared with a decrease of 1.2 ng/dl in the nesiritide 0.015 group (-11%) and -1.6 ng/dl in the nesiritide 0.030 group (-14.5%), $p=0.030$. This trend was also true if the subjects who did not receive ACE inhibitors before the trial were examined. The table below shows the data, as well as the large patient-to-patient variability of the data.

Table 7.0.1e.1.7 (from 6.2.12.4.16) Changes in serum 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
<i>Baseline</i>	12	11	11	0.976
<i>Hour 6</i>	11.5	4.6	6.2	0.137
<i>Range</i>	0.9 to 120.0	0.9 to 119.0	0.9 to 81.0	
<i>Change from Baseline</i>	+0.6	-2.5	-1.6	0.030
<i>Range</i>	-19.0 to 100.0	-131.0 to +102.0	-111.0 to +34.0	
<i>N (# missing data)</i>	36 (6)	40 (3%)	38 (4)	

a. Data from NDA volume 59, table 54. p Value per sponsor.

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.

Conclusions Regarding Nesiritide Effects on Hormone Levels

In the one trial where serum aldosterone levels were measured, there was a significant decrease in the median serum aldosterone concentrations during the first 6 hours of nesiritide infusion. These data are conflicted by the increased diuretic use in the control group (which would tend to reduce intravascular volume and increase aldosterone). The patient-to-patient variability around these median values, however, was enormous, making application of this data to individual patients impossible.

7.0.2 Clinical Efficacy of Nesiritide

The next portion of the efficacy summary will concentrate on other measures of clinical benefit that are sometimes used to support the clinical efficacy of drugs.

7.0.2a Effect of Nesiritide on Mortality

The demonstration of a mortality benefit is one powerful indicator of clinical efficacy. The effects of nesiritide on mortality will also be examined in section 8.2.1 below.

There were a total of 28 deaths occurred during the reporting periods of the CHF trials. An additional 6 deaths that occurred after the reporting period are also known to the sponsor. The first table summarizes the reported death rates for two relevant patient populations: all known deaths from all studies; and all known deaths from the nesiritide infusion studies (311, 325 and 326). The incidence of deaths during the studies is also tabulated.

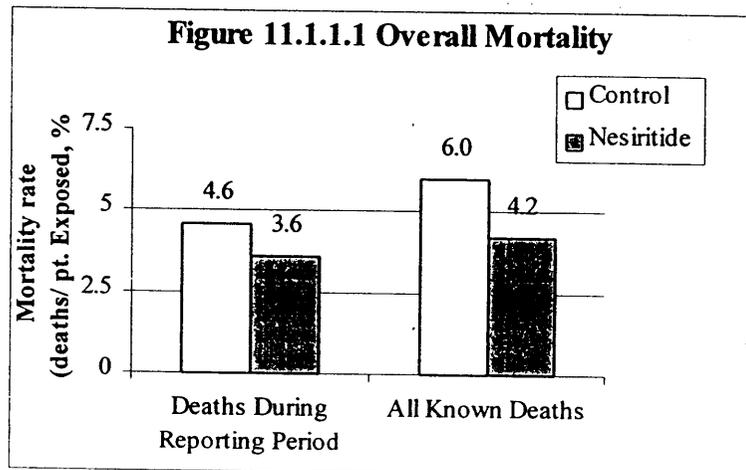
Table 7.0.2a.1 (from 8.1.1.1) Reported deaths in NDA 20-920^a.

Group	Placebo	Active Control	Nesiritide Groups				Total Nesiritide
			Bolus	0.015 µg/kg/min	0.030 µg/kg/min	0.060 µg/kg/min	
	n=114	n=102	n=143	n=169	n=167	n=26	n=505
All Known Deaths	8 (7.0%)	5 (4.9%)	2 (1.4%)	8 (4.7%)	10 (6.0%)	1 (3.8%)	21 (4.2%)
Deaths During Study	5 (4.4%)	5 (4.9%)	0 (0%)	8 (4.7%)	9 (5.4%)	1 (3.8%)	18 (3.6%)
All Known Deaths	n=71	n=102	n=N/A	n=169	n=167	n=26	n=362
From Infusion Studies^b	5 (7.0%)	5 (4.9%)	N/A	8 (4.7%)	10 (6.0%)	1 (3.8%)	19 (5.2%)
Deaths	3 (4.2%)	5 (4.9%)	N/A	8 (4.7%)	9 (5.4%)	1 (3.8%)	18 (5.0%)
During Infusion Studies							

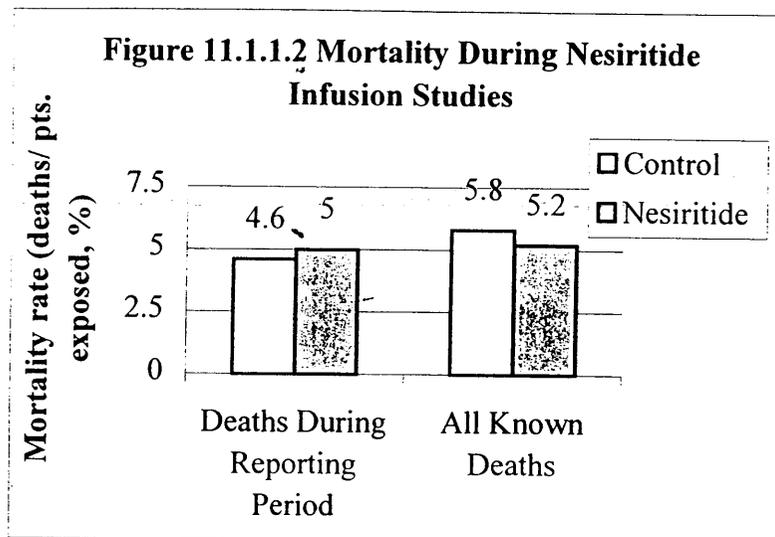
a. Data from Listing 7, NDA vol. 81.

b. Studies 311, 325 and 326.

For all known deaths during the nesiritide NDA, the following graphs summarize the relative incidence of death for nesiritide and control (including both placebo and active control groups). The first graph shows the overall reported mortality for the NDA.



Similarly, the graph below shows the mortality rate during the three infusion studies, where there were 10 known deaths in the control groups (5.8%) compared with 19 deaths in the nesiritide groups (5.2%). Again, there is no evidence of a large benefit of nesiritide regarding mortality.



Finally, in the single largest trial, 704.326, there was a balanced number of deaths reported in the active control and nesiritide groups. Seventeen subjects in this study died by day 21. Five (5%), 6 (6%), and 6 (6%) subjects in the standard care and 0.015 and 0.03 nesiritide treatment groups, respectively. One additional death in the 0.03 $\mu\text{g}/\text{kg}/\text{min}$ nesiritide group occurred on day 22.

Conclusion Regarding the Effect of Nesiritide on Mortality

The data are insufficient to detect a small difference in the mortality rates, but the overall trend in mortality favored nesiritide. No adverse effect of nesiritide on mortality rate is suggested.

7.0.2b Effect of Nesiritide on Signs and Symptoms of CHF

A second area of clinical benefit is relief of symptoms. In the NDA, the sponsor collected information about changes in the signs and symptoms of CHF, as well as an overall assessment of well-being (compared with baseline). The format followed in this summary will be the same as that used for the changes in hemodynamics, with an initial assessment of the blinded, placebo-controlled data, followed by open-label and active-control comparisons.

7.0.2b.1 Effect of Nesiritide on Signs and Symptoms of CHF, Compared with Placebo

The only blinded, placebo-controlled comparison of CHF symptoms took place in trial 704.325 from baseline through 6 hours of study drug infusion.

Trial 704.325

Global Assessment of Clinical Status from trial 704.325 from Baseline to 6 Hours

After six and 24 hours, and within 24 hours after discontinuation of all parenteral therapy for the episode of decompensated CHF (or on day 5, whichever occurred first), the subject and the physician were to assess the subject's overall clinical status and rate it: markedly better, better, no change, worse, or markedly worse as compared to baseline. For the primary analysis, subjects who received a cardiovascular intervention for worsening CHF during the 6-hour blinded period, or were prematurely unblinded, were to be automatically assigned a rating of markedly worse for all subsequent assessments. The problems surrounding the independence of the symptom assessments in study 704.325 have been discussed above (section 6.2.8, Blinding in study 704.325).

6 Hours

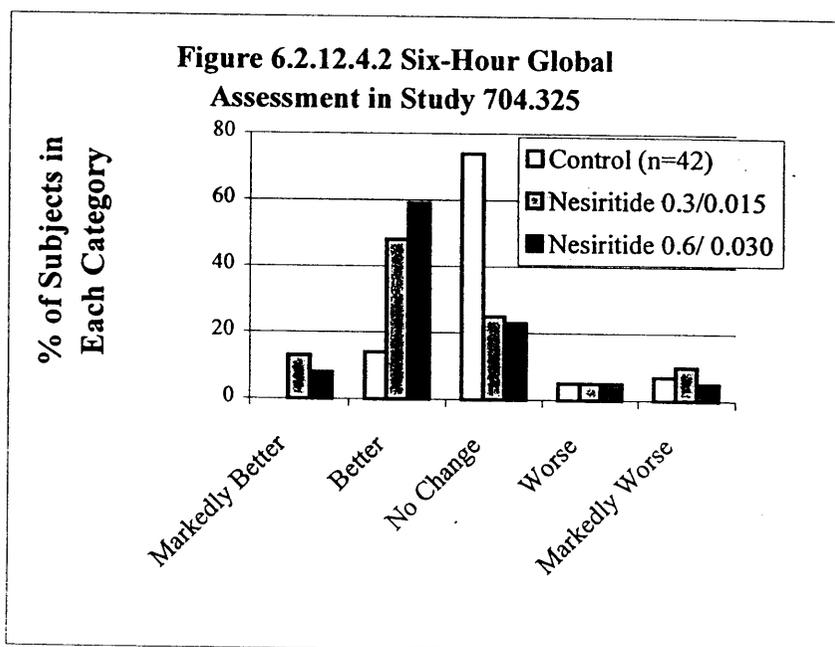
Using a non-parametric analysis, as per the primary endpoint analysis, subjects who received nesiritide felt significant improvement in symptoms relative to the control patients at the end of 6. The graph below shows the percentage of subjects in each of the assessment categories for the three dose-groups 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 (see Appendix 6, FDA Statistician's review for details).

Numerically, the investigator and patient's assessments agreed well. The percentage of the exact agreements between the two assessments averaged 71.1% (73.8%, 67.5%, 71.8% for placebo, 0.030, and 0.060 Natrecor groups, respectively). If allow at most one category difference, overall agreement rate of the assessments is 98.8% (100.0% for placebo, 97.5% and 97.4% for 0.03 and 0.06 Natrecor groups).

Table 7.0.2b.1.1 (from 6.2.12.4.8) Subject global assessments at end of parenteral vasoactive administration, from study 704.325^a.

Hemodynamic Parameter	Placebo	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030	p Value ^c
6 Hour Global Assessment	n=42	n=40	n=39	
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 NDA volume 59, Appendix I, Table 45a and electronic datasets.
- b. Global assessment must be made at least 20 hours after start of study drug.
- c. p Value using Omnibus F test.



As shown in the table on the next page, the percentage of patients who had Hour 6 assessment scores by patient or investigator indicating an improvement (better or markedly better) was also significantly higher for the nesiritide group compared to placebo.

Table 7.0.2b.1.2 (from 6.2.12.4.4) Improvement in global clinical status at hour 6 in trial 704.325.

Treatment	Assessment, n (%)		p Value
	Not improved	Improved	
<i>Investigator Assessment</i>			
Placebo	40 (95.8%)	2 (4.8%)	0.001 ^a
Nesiritide 0.3/ 0.015	18 (45%)	22 (55.0%)	
Nesiritide 0.6/ 0.030	9 (23.1%)	30 (76.9%)	
<i>Patient Assessment</i>			
Placebo	36 (85.7%)	6 (14.3%)	0.001 ^a
Nesiritide 0.3/ 0.015	16 (40%)	24 (60.0%)	
Nesiritide 0.6/ 0.030	13 (33.3%)	26 (66.7%)	

a. Overall difference, two-sided chi-squared-test

The FDA statistician performed a series of analyses on the measured changes in global status, which have been incorporated into the presentation above, and is also presented in full in appendix six: FDA statistics review. Based on those analyses, the statistical reviewer made the following conclusions:

1. There was a statistically significant difference between placebo and both nesiritide dose groups with regard to global assessment of clinical status at Hour 6 by investigators or by patients.

2. Numerically, slightly higher percentage of nesiritide patients had improvement in clinical status at Hour 24 (with a score of 'better' or 'much better') for both investigator evaluation and patient evaluation, compared with the control group (placebo-treated 0-6 hours, active control-treated 6-24 hours).

However, Dr. Cui also concluded that, given the difficulties in the symptom data collection, it is difficult to conclude that Natrecor treatment can improve patient's symptoms based on this study.

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 sxs of CHF at 6 hours. These results are summarized below. Nesiritide use was associated with nominally statistically significant improvements in several individual signs and sxs 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 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 7.0.2b.1.3 (from 6.2.12.4.9) Assessment of individual signs and sxs of CHF at 6 hrs of study drug 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 ^a
<u>Breathing Difficulty: Baseline</u>				
No breathing difficulty	3 (7%)	2 (5%)	4 (10%)	0.628
Breathing difficulty with moderate activity	7 (17%)	5 (12%)	4 (10%)	
Breathing difficulty with minimal activity	22 (52%)	23 (53%)	21 (50%)	
Breathing difficulty at rest	10 (24%)	13 (30%)	13 (31%)	
<u>Breathing Difficulty: 6 hour results</u>				
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%)	
<u>Appetite: Baseline</u>				
Good appetite	22 (52%)	20 (47%)	24 (57%)	0.626
Decreased appetite	14 (33%)	19 (44%)	15 (36%)	
No appetite	6 (14%)	4 (9%)	3 (7%)	
<u>Appetite: 6 hour results</u>				
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%)	

a. Data from NDA volume 59, Appendix I, Tables 47A and 48A. All subjects with available data are included (≥90% of enrolled subjects for all points). p Value using Kruskal-Wallis test.

The next tables continue the summary of nesiritide effects on individual signs and symptoms in 704.325.

Table 7.0.2b.1.4 (from 6.2.12.4.10) Assessment of individual signs and symptoms of CHF after 6 hours of study drug 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
Peripheral Circulation: Baseline				
Extremities warm and well-perfused	26 (62%)	18 (42%)	26 (62%)	0.106
Extremities cool with decreased perfusion	12 (29%)	21 (49%)	15 (36%)	
Extremities cold and vasoconstricted	4 (10%)	4 (9%)	1 (2%)	
Peripheral Circulation: 6 hour time-point				
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: Baseline				
No fatigue	2 (5%)	1 (2%)	2 (5%)	0.253
Fatigue with moderate activity	9 (21%)	7 (16%)	4 (10%)	
Fatigue with minimal activity	21 (50%)	22 (51%)	20 (48%)	
Fatigue at rest	10 (24%)	13 (30%)	16 (38%)	
Fatigue: 6 hour time-point				
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%)	

a. Data from NDA volume 59, Appendix 1, Tables 49A through 50A. All subjects with available data are included (≥90% of enrolled subjects for all points).

b. p Value using Kruskal-Wallis test.

Table 7.0.2b.1.5 (from 6.2.12.4.11) Assessment of individual signs and symptoms of CHF after 6 hours of study drug 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
Lightheadedness: Baseline				
No lightheadedness	32 (76%)	29 (67%)	32 (76%)	0.592
Lightheadedness with moderate activity	4 (10%)	5 (12%)	2 (5%)	
Lightheadedness with minimal activity	5 (12%)	5 (12%)	3 (7%)	
Light headedness at rest	1 (2%)	4 (9%)	5 (12%)	
Lightheadedness: 6 hour results				
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: Baseline				
None	13 (31%)	13 (30%)	19 (45%)	0.382
Mild	19 (45%)	15 (35%)	13 (31%)	
Moderate	6 (14%)	12 (28%)	6 (14%)	
Severe	4 (10%)	3 (7%)	4 (10%)	
Peripheral Edema: 6 hour results				
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.

The next table completes the summary of nesiritide effects on individual signs and symptoms in 704.325.

Table 7.0.2b.1.6 (from 6.2.12.4.12) Assessment of individual signs and symptoms of CHF after 6 hours of study drug 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	9.0 to 14.0	7.0 to 14.0	7.0 to 14.0	

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 Respiratory Rate Through 6 hours from Study 704.325

One of the symptoms of CHF, which tends to improve with successful treatment, is ‘breathlessness’, which often results in an increase in respiratory rate. While there are obviously many other causes of tachypnea, if a drug is successful at lowering the respiratory rate in patients with decompensated CHF, this would suggest it has some beneficial effect on ‘breathlessness.’

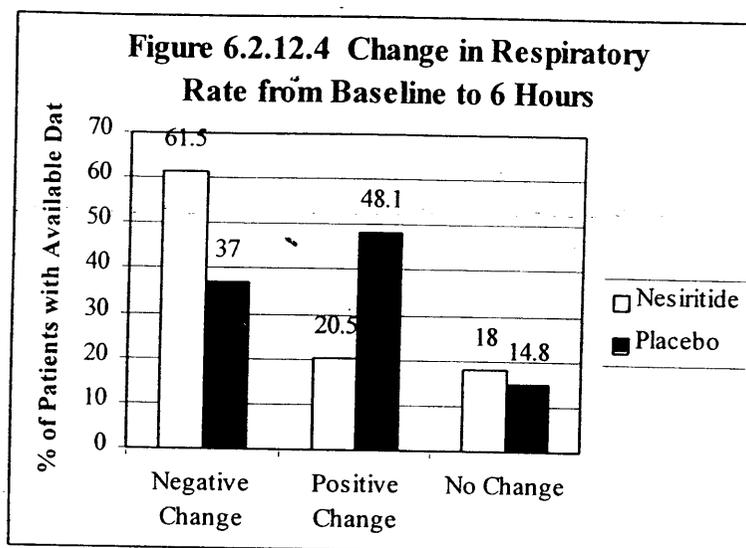
The table below summarizes the data from 704.325 for changes in respiratory rate between 0 and 6 hours for the nesiritide group (combining both doses) and placebo. For the entire population, as well as those patients who started with tachypnea (≥20 respirations per minute), there was a small decrease in the mean and median respiratory rates in the nesiritide group. This decrease was not seen in the placebo group. The sponsor performed a similar analysis (not shown), which agreed in general with these findings. The sponsor also pointed out that the majority of the patients were on supplemental O₂, complicating interpretation of these data.

Table 6.2.12.4.4a Summary of changes in respiratory rate (RR) using ‘last value carried forward’ population with respiratory rate ≥20 RPM from study 704.325^a.

Parameter of Respiratory Rate (RR) (respirations per minute)	Placebo N=27	Nesiritide N=39
Mean±SD	+2.86±2.8	-1.69±3.6
Median	0	-2
Patients with Decreased RR (0-6 hours) (n, %)	10 (37.0%)	24 (62%) ^b
Patients with Increased RR (0-6 hours) (n, %)	13 (48%)	8 (20%)
Patients with Unchanged RR (0-6 hours) (n, %)	4 (15%)	7 (18%)

a. Data from Medical Officer analysis of individual Case Report Forms, not independently confirmed by sponsor.

b. p Value comparing incidence of decreased RR using Fisher’s Exact test =0.08.



A similar trend was seen when the entire population of study 704.325 was analyzed, irrespective of their baseline respiratory rate.

Table 6.2.12.4.b Summary of changes in respiratory rate (RR) using 'last value carried forward' population from study 704.325^a.

Parameter of Respiratory Rate (RR) (respirations per minute)	Placebo N=43	Nesiritide N=83
Mean±SD	+0.70±3.2	-0.34±3.9
Median	+1	-1
Patients with Decreased RR (0-6 hours) (n, %)	11 (25.6%)	42 (50.6%)
Patients with Increased RR (0-6 hours) (n, %)	24 (55.8%)	31 (37.3%)
Patients with Unchanged RR (0-6 hours) (n, %)	8 (18.0%)	10 (12.0%)

a. Data from Medical Officer analysis of individual Case Report Forms, not independently confirmed by sponsor.

7.0.2b.2 Effect of Nesiritide on Signs and Symptoms of CHF, Compared with Active Controls

Information was also collected in open-label fashion comparing the effects of nesiritide to those of active controls in both 704.325 and 704.326. In general, these analyses suffer from the withdrawal of patients who are not improving on therapy, the absence of a placebo group, and the crossing over of patients to other therapies.

Trial 704.325

Overall Assessment of Well-Being from trial 704.325 Beyond 6 Hours

The global clinical status of all three study groups were much more similar at the 24 hour time-point, even though the average subject continued to receive nesiritide for >30 hours (see section 6.2.12.2c*above). There was an increase in the % of nesiritide patients who felt 'markedly better', relative to the 6 hours time point, but the greatest changes occurred in the control group, where the % of patients who felt 'markedly better' or 'better' increased substantially. It is important to remember that after 6 hours patients in all groups could receive other therapies (i.e., diuretics, ACE inhibitors) unblinded.

Finally, when the Global Assessment was performed after discontinuation of all parenteral vasoactive substances (or at day 5), no significant difference between the three groups was seen (see table 6.2.12.4.6 for details).

Table 7.0.2b.2.1 (from 6.2.12.4.8) Subject global assessments at end of parenteral vasoactive administration, from study 704.325^a.

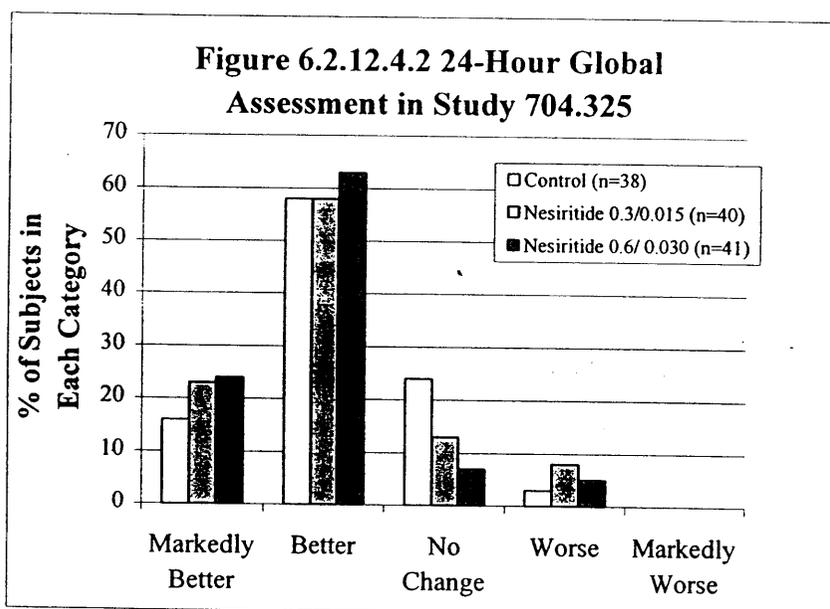
Hemodynamic Parameter	Control ^d	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030	p Value ^c
24 Hour Global Assessment	n=38	n=40	n=41	0.337
Markedly Better	6 (16%)	9 (23%)	10 (24%)	
Better	22 (58%)	23 (58%)	26 (63%)	
No Change	9 (24%)	5 (13%)	3 (7%)	
Worse	1 (3%)	3 (8%)	2 (5%)	
Markedly Worse	0 (0%)	0 (0%)	0 (0%)	
Last Recorded Global Assessment^b	n=40	n=41	n=41	0.852
Markedly Better	15 (38%)	16 (39%)	15 (37%)	
Better	17 (43%)	19 (46%)	23 (56%)	
No Change	8 (20%)	5 (12%)	2 (5%)	
Worse	0 (0%)	2 (2%)	1 (2%)	
Markedly Worse	0 (0%)	0 (0%)	0 (0%)	

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

b. Global assessment must be made at least 20 hours after start of study drug.

c. p Value using Omnibus F test.

d. Control comparator was placebo for first 6 hours and active control at 24 hours.



Numerically, slightly higher percentage of nesiritide patients had improvement in clinical status at Hour 24 (with a score better or markedly better) for both investigator evaluation and patient evaluation. There was good agreement between the investigator- and subject-derived scores of clinical status at 24 hours.

Table 7.0.2b.2.1 (from 6.2.12.4.7) Improvement in global clinical status at Hour 24 in trial 704.325.

Treatment	Assessment N (%)		Total	p Value
	Not improved	Improved ^b		
Investigator Assessment				
Control ^c	10 (26.3%)	28 (73.7%)	38	0.406 ^a
hBNP 0.3/ 0.015	8 (20%)	32 (80.0%)	40	
hBNP 0.6/ 0.030	6 (14.3%)	36 (85.7%)	42	
Patient Assessment				
Control ^c	10 (26.3%)	28 (73.7%)	38	0.281 ^a
hBNP 0.3/ 0.015	8 (20%)	32 (80.0%)	40	
hBNP 0.6/ 0.030	5 (12.2%)	36 (87.8%)	41	

a. overall difference, two-sided χ^2 -test.

b. Includes either 'markedly improved' or 'improved'. All others are considered Not Improved.

c. Placebo for 0-6 hours and active control from 6-24 hours.

Signs and Symptoms of CHF from trial 704.325 Beyond 6 Hours

At the end of 24 hours, there were non-significant trends towards greater improvement in fatigue and lightheadedness in the nesiritide groups, but no other differences between the two treatment groups. The overall CHF total score was quite similar for all three groups at the end of 24 hours. In data shown in the study review, when the signs and symptoms were assessed after discontinuation of all parenteral vasoactive substances (or at day 5), no significant difference between the three groups was seen (see table 6.2.12.4.6 for details).

Table 7.0.2b.2.2 (from 6.2.12.4.13) Assessment of individual signs and symptoms of CHF after 24 hours of study drug in study 704.325^a.

Signs and Symptoms of CHF at 24 hours (compared with baseline)	Active Control n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.0305 n=42	p Value ^b
<u>Breathing Difficulty: 24 hour results</u>				
Improved from baseline	25 (66%)	29 (73%)	33 (79%)	0.513
No change from baseline	12 (32%)	9 (23%)	7 (17%)	
Worse than baseline	1 (3%)	2 (5%)	2 (5%)	
<u>Appetite: 24 hour results</u>				
Improved from baseline	10 (26%)	10 (25%)	14 (33%)	0.804
No change from baseline	27 (71%)	29 (73%)	26 (62%)	
Worse than baseline	1 (3%)	1 (3%)	2 (5%)	
<u>Peripheral Circulation: 24 hour time-point</u>				
Improved from baseline	9 (24%)	11 (28%)	10 (24%)	0.849
No change from baseline	29 (76%)	29 (73%)	31 (74%)	
Worse than baseline	0 (0%)	0 (0%)	1 (2%)	
<u>Fatigue: 24 hour time-point</u>				
Improved from baseline	12 (32%)	17 (43%)	25 (60%)	0.062
No change from baseline	24 (63%)	21 (53%)	15 (36%)	
Worse than baseline	2 (5%)	2 (5%)	2 (5%)	
<u>Lightheadedness: 24 hour results</u>				
Improved from baseline	3 (8%)	8 (20%)	6 (14%)	0.211
No change from baseline	34 (89%)	32 (80%)	36 (86%)	
Worse than baseline	1 (3%)	0 (0%)	0 (0%)	
<u>Peripheral Edema: 24 hour results</u>				
Improved from baseline	21 (55%)	18 (45%)	21 (50%)	0.612
No change from baseline	17 (45%)	21 (53%)	20 (48%)	
Worse than baseline	0 (0%)	1 (3%)	1 (2%)	
<u>CHF Total Score: 24 hour time-point</u>				
Mean ±SD	10.0±2.0	9.8±2.0	9.6±1.8	0.493
Median	10.0	10.0	10.0	
Range	7.0 to 16.0	6.0 to 14.0	7.0 to 16.0	

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.

Trial 704.326

Overall Assessment of Well-Being from Trial 704.326

Global assessments at 6 and 24 hours of treatment were compared for the three study groups. While all three treatment groups improved significantly over baseline to 6 hours, there was not a significant difference between the Global Assessment Scores between the three groups. As was the case for the trial 704.325 data, there was no indication of either a superior or inferior effect of the nesiritide 0.030 group on any signs or symptoms relative to the nesiritide 0.015 group.

Table 7.0.2b.2.3 (from 6.3.12.3.3) Global assessment, by subjects, of their clinical status at 6 and 24 hours in study 704.326^a.

Global Assessment	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
6 Hour Assessment				
Markedly Better	n=84	n=86	n=82	0.318 ^c
Better	8 (10%)	10 (12%)	4 (5%)	
No Change	46 (55%)	48 (56%)	45 (55%)	
Worse	27 (32%)	26 (30%)	29 (35%)	
Markedly Worse	3 (4%)	2 (2%)	4 (5%)	
	0 (0%)	0 (0%)	0 (0%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.569	0.358	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.133	
24 Hour Assessment				
Markedly Better	n=92	n=99	n=90	0.302 ^c
Better	17 (18%)	23 (23%)	15 (17%)	
No Change	57 (62%)	60 (61%)	54 (60%)	
Worse	16 (17%)	14 (14%)	17 (19%)	
Markedly Worse	2 (2%)	2 (2%)	4 (4%)	
	0 (0%)	0 (0%)	0 (0%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.370	0.515	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.128	
Last Recorded Assessment				
Markedly Better	n=98	n=101	n=93	0.628 ^c
Better	27 (28%)	34 (34%)	25 (27%)	
No Change	60 (61%)	55 (54%)	55 (59%)	
Worse	8 (8%)	5 (5%)	10 (11%)	
Markedly Worse	3 (3%)	7 (7%)	2 (2%)	
	0 (0%)	0 (0%)	1 (1%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.532	0.728	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.354	

a. Data from NDA volume 66, Appendix table 24a. Shown for 'All subjects' population.

b. Comparison by 1-Sample Wilcoxon.

c. Comparison by Kruskal-Wallis.

d. Comparison using 2-Sample Wilcoxon.

Signs and Symptoms of CHF from Trial 704.326

The sponsor also looked at the effect of the study drugs on individual signs/ sx's of CHF. The first symptom, 'breathing difficulty' was improved by 6 hours in all three treatment groups, with no difference between the three group.

Table 7.0.2b.2.4 (from 6.3.12.3.4) Assessment of 'breathing difficulty', by subjects, at 6 and 24 hours in study 704.326^a.

Global Assessment of Breathing Difficulty	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Value
6 Hour Assessment				
Improved from Baseline	52 (61%)	56 (63%)	44 (55%)	0.583 ^c
No Change from Baseline	30 (35%)	32 (36%)	35 (44%)	
Worse than Baseline	3 (4%)	1 (1%)	1 (1%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.726	0.515	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.302	
24 Hour Assessment				
Improved from Baseline	77 (80%)	77 (78%)	63 (70%)	0.230 ^c
No Change from Baseline	14 (15%)	18 (18%)	20 (22%)	
Worse than Baseline	5 (5%)	4 (4%)	7 (8%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.726	0.112	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.199	

- a. Data from NDA volume 66, Appendix table 27a. Shown for 'All subjects' population.
- b. Comparison by 1-Sample Wilcoxon.
- c. Comparison by Kruskal-Wallis.
- d. Comparison using 2-Sample Wilcoxon.

The next table summarizes the changes in 'lightheadedness' at 6 and 24 hours. While all subjects in all three treatment groups, on average, improved by 6 hours, there was no difference between treatment groups discerned. The sponsor also looked at the treatment effects only in those subjects with lightheadedness at entry (roughly 40% of each group). In data not shown, no difference between the treatment groups was seen.

Table 7.0.2b.2.5 (from 6.3.12.3.5) Subject assessment of 'lightheadedness', at 6 and 24 hours in 704.326^a.

Global Assessment of Lightheadedness	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Baseline				
No lightheadedness	57 (56%)	56 (56%)	58 (59%)	0.868 ^c
Lightheadedness with moderate activity	12 (12%)	20 (20%)	15 (15%)	
Lightheadedness with minimal activity	25 (25%)	17 (17%)	17 (17%)	
Lightheadedness at rest	7 (7%)	7 (7%)	8 (8%)	
6 Hour Assessment				
Improved from Baseline	11 (13%)	17 (19%)	11 (14%)	0.369 ^c
No Change from Baseline	72 (86%)	67 (76%)	64 (77%)	
Worse than Baseline	1 (1%)	4 (5%)	7 (9%)	
p Value (test of 'No Change') ^b	0.006	0.007	0.481	
p Value (comp with standard care group) ^d	--	0.594	0.340	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.193	
24 Hour Assessment				
Improved from Baseline	25 (26%)	26 (27%)	18 (20%)	0.742 ^c
No Change from Baseline	67 (70%)	66 (67%)	68 (76%)	
Worse than Baseline	4 (4%)	6 (6%)	3 (3%)	
p Value (test of 'No Change') ^b	<0.001	0.001	0.001	
p Value (comp with standard care group) ^d	--	0.886	0.450	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.560	

- a. Data from NDA volume 66, Appendix table 27a. Shown for 'All subjects' population.
- b. Comparison by 1-Sample Wilcoxon.
- c. Comparison by Kruskal-Wallis.
- d. Comparison using 2-Sample Wilcoxon.

Finally, the sponsor examined the changes in 'peripheral edema' at hours 6 and 24 of study drug. At the end of 6 hours, there was a trend towards greater improvement of peripheral edema in the nesiritide groups (but no apparent difference between the two nesiritide doses).

Table 7.0.2b.2.6 (from 6.3.12.3.6) Subject assessment of 'peripheral edema', at 6 and 24 hours in 704.326^a.

Global Assessment of Peripheral Edema	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Baseline				
None	29 (29%)	28 (28%)	29 (30%)	0.342 ^c
Mild	33 (33%)	23 (23%)	27 (28%)	
Moderate	32 (32%)	33 (33%)	30 (31%)	
Severe	7 (7%)	17 (17%)	12 (12%)	
6 Hour Assessment				
Improved from Baseline	16 (19%)	30 (34%)	25 (31%)	0.060 ^c
No Change from Baseline	68 (80%)	59 (66%)	54 (68%)	
Worse than Baseline	1 (1%)	0 (0%)	1 (1%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.021	0.076	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.653	
24 Hour Assessment				
Improved from Baseline	49 (51%)	56 (57%)	43 (48%)	0.467 ^c
No Change from Baseline	46 (48%)	43 (43%)	47 (52%)	
Worse than Baseline	1 (1%)	0 (0%)	0 (0%)	
p Value (test of 'No Change') ^b	<0.001	<0.001	<0.001	
p Value (comp with standard care group) ^d	--	0.406	0.713	
p Value (comp. with low-dose nesiritide group) ^d	--	--	0.229	

a. Data from NDA volume 66, Appendix table 31a. Shown for 'All subjects' population.

b. Comparison by 1-Sample Wilcoxon.

c. Comparison by Kruskal-Wallis.

d. Comparison using 2-Sample Wilcoxon.

Conclusions Regarding Nesiritide Effects on Signs and Symptoms of CHF

If the conclusion is reached that nesiritide is significantly better than either placebo or active control as regard to symptom relief, this will add another piece of data supporting efficacy. To make this argument, the sponsor has submitted data from two trials, of which one portion is 'blinded' and placebo-controlled, while the other is open-label, and compared with active control therapy.

Regarding the placebo-controlled data, it exists in one trial (704.325) from baseline to 6 hours of drug infusion, and reflects the exposure of 79 patients (in two dose groups) to nesiritide compared with 42 patients exposed to placebo. The problems with the data collection in this trial have been summarized above; these limit the strength of any interpretation of the symptom data. In this group of patients from 704.325, a significant effect of nesiritide to reduce the following components of CHF were detected at the end of 6 hours of study drug infusion:

- 1) Global assessment of well-being,
- 2) Individual signs and symptoms of CHF, including breathlessness, fatigue, appetite, fatigue, light-headedness, and peripheral edema, and
- 3) CHF Global score.

There was also a small decrease in the median respiratory rate at the end of 6 hours in the nesiritide groups (2 breathes per minute less than the placebo group).

After 6 hours, these same patients were unblinded with regard to therapy and followed. At the end of 24 hours, no significant differences between treatment groups with regard to any of these parameters were seen, although the % of subjects in the nesiritide groups who were either markedly better or better was slightly higher than the control group. This may have been due to the lag in initiation of parenteral vasoactive therapy in the control group (where none were administered until after the blind was broken). There was also no clear indication that the high-dose nesiritide group had a greater effect on the signs and symptoms of CHF than did the low-dose nesiritide group. This is in contrast to the hemodynamic data, where there was a dose-response effect for nesiritide. Whether this reflects the relative insensitivity of the symptom scales cannot be determined.

Conclusions Regarding Nesiritide Effects on Signs and Symptoms of CHF (cont)

With regard to the comparison between nesiritide and active control therapies, from study 704.326, none of the measured variables suggested any greater or lesser effect of nesiritide on CHF signs and symptoms at any time point. Again, there was no suggestion of a dose-dependent effect of nesiritide in this population.

In conclusion, one placebo-controlled trials supports a significant effect of nesiritide on the signs and symptoms of CHF during a 6-hour infusion period. The data comparing the efficacy of nesiritide and other active controls regarding CHF symptoms and signs suggest that the effects of the two treatment groups on CHF signs and symptoms are similar in magnitude. Again, no dose-response effect for nesiritide was found.

7.0.2c Effect of Nesiritide on Hospitalization Rates

Trial 704.325

The effect of study drug on hospitalization was examined in several ways in 704.325. First, the duration of hospitalization prior to entry into the study 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 ($p > 0.05$). One individual in the high-dose nesiritide group accounted for most of the numerical increase in duration of hospitalization.

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 7.0.2c.1 (from 6.2.12.4.17) 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
Subjects discharged prior to day 21	40 (95%)	35 (81%)	34 (81%)	
Total days of hospitalization for subjects D/C'd prior to 21 days				
Mean±SD	7.6±4.9	7.3±3.9	7.8±4.5	0.891 ^b
Median	6.5	6.0	7.0	
Time to discharge				
2-3 days	10 (24%)	5 (12%)	5 (12%)	
4-5 days	8 (19%)	10 (23%)	5 (12%)	
6-7 days	5 (12%)	6 (14%)	13 (31%)	
8-14 days	11 (26%)	13 (30%)	8 (19%)	
15-21 days	6 (14%)	1 (2%)	3 (7%)	
Subjects not discharged as of day 21	2 (5%)	8 (19%)	8 (19%)	0.085 ^c

a. Data from NDA volume 59, Appendix 1, Tables 59 and 60. All subjects with available data are included ($\geq 90\%$ of enrolled subjects for all points).

b. p Value using Kruskal-Wallis test.

c. p Value using Fisher's exact test.

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. In data not shown, subjects hospitalized >5 days when entering the trial also had similar duration of hospitalization.

Hospital Readmission in 704.325

As shown above, more subjects in the nesiritide groups were not discharged before day 21 (see table 6.2.12.2e.5). If one looks just at those subjects who were discharged, however, 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 7.0.2c.2 (from 6.2.12.4.18) 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 volume 59, Appendix I, Tables 60. Includes all subjects who were discharged before day 21.
b. p Value using Fisher's Exact test.

Trial 704.326

The effect of study drug on hospitalization was examined in several ways in study 704.326. First, the duration of hospitalization prior to entry into the study 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 7.0.2c.3 (from 6.3.12.3.7) 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
Total days of hospitalization for subjects D/C'd prior to 21 days				
Mean±SD	6.4±3.7	6.2±3.5	6.6±4.2	0.914
Median	5	5	5	
Time to discharge				
2-3 days	18 (18%)	29 (28%)	25 (25%)	
4-5 days	36 (35%)	22 (21%)	26 (26%)	
6-7 days	13 (13%)	24 (23%)	9 (9%)	
8-14 days	27 (26%)	21 (20%)	26 (26%)	
15-21 days	3 (3%)	5 (5%)	10 (10%)	
Subjects not discharged as of day 21	5 (5%)	2 (2%)	4 (4%)	

a. Data from NDA volume 66, Appendix 1, Tables 33, and electronic datasets.

Effect of Study Drug on Hospital Readmission in 704.326

As shown above, no difference exists between the treatment groups regarding discharge before day 21 (see table 6.2.12.2e.5). If one looks just at those subjects who were discharged, however, 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 7.0.2c.4 (from 6.3.12.3.8) 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
If readmitted, primary reason for first readmittance				
CHF recurrence	8 (50%)	4 (50%)	4 (36%)	
Elective, unrelated to CHF	1 (6%)	0 (0%)	1 (9%)	
Medical condition other than CHF	6 (38%)	2 (25%)	6 (55%)	
Other	1 (6%)	2 (25%)	0 (0%)	
If readmitted, primary reason for all readmittance				
CHF recurrence	9 (53%)	4 (44%)	6 (46%)	
Elective, unrelated to CHF	1 (6%)	0 (0%)	1 (8%)	
Medical condition other than CHF	6 (35%)	2 (22%)	6 (46%)	
Other	1 (6%)	3 (33%)	0 (0%)	

a. Data from NDA volume 66, Appendix 1, Table 34. Includes all subjects discharged before day 21.

b. p Value using Fisher's Exact test.

Conclusion Regarding the Effect of Nesiritide on Hospitalization

Regardless of the measure, there was no consistent, reproducible beneficial effect of nesiritide on any aspect of hospitalization rates. For instance, in 704.325, a higher percentage of patients who were discharged from the nesiritide groups required re-hospitalization prior to 21 days. This effect was not evident in the larger trial 704.326, where the rate of re-hospitalization was non-significantly reduced in the nesiritide groups relative to the active control group.

As another example, the number of patients re-hospitalized for CHF was higher in the nesiritide groups in 704.311, but slightly lower in the 704.326 study.

In conclusion, the data regarding the effects of nesiritide on hospitalization and re-hospitalization do not demonstrate a benefit for nesiritide relative to the control groups.

7.0.2d Effect of Nesiritide on Need for Invasive Medical Interventions

Trial 704.325

The number of patients intubated at baseline and during the 21 day follow-up is shown below. Note the 5 subjects in the high-dose nesiritide group intubated before day 21. Of these, two in the nesiritide 0.030 group were intubated during or shortly after their nesiritide infusion. The other 5 were intubated >10 days after starting the trial.

Table 7.0.2d.1 (from 6.2.13.6) Requirement for intubations in study 704.325^a.

Intubations	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42
# Intubated at start of study	1 (2%)	1 (2%)	2 (5%)
# Intubated for cardiac reasons through day 21	1 (2%)	1 (2%)	5 (12%)

a. Data from NDA vol. 59, Appendix 1, Table 61.

The need for dialytic intervention is summarized in the table below. Note that interventions for worsening renal failure (short of dialysis) were more nominally significantly more common in the nesiritide groups.

Table 7.0.2d.2 (from 6.2.13.5) Need for intervention due to worsening renal failure in study 704.325^a.

Intervention for Worsening Renal Function	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value
No Intervention	41 (98%)	37 (86%)	33 (79%)	0.033
Medical Intervention Without Dialysis	0 (0%)	6 (14%)	7 (17%)	0.009
Dialysis	1 (2%)	0 (0%)	2 (5%)	--

a. Data from NDA vol. 59, Appendix 1, Table 61.

Trial 704.326

The number of interventions for renal failure, including hemodialysis/ hemofiltration, and the need for intubation are summarized below. No subjects required hemofiltration. The need for other interventions was overall balanced in the three treatment groups, although there was a non-significant decrease in the number of intubations in the nesiritide group.

Table 7.0.2d.3 (from 6.3.12.3.9) Need for selected medical interventions through 21 days in study 704.326^a.

Intervention	Standard Care	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030	p Value
Medical Intervention for Worsening Renal Function				
Intervention without Dialysis	6 (6%)	12 (12%)	7 (7%)	0.610
Dialysis	2 (2%)	1 (1%)	2 (2%)	
Intubation	8 (8%)	2 (2%)	4 (4%)	0.126
Swan-Ganz catheter placement	20 (20%)	13 (13%)	23 (23%)	0.140
Intra-arterial line	3 (3%)	1 (1%)	3 (3%)	0.575

a. Data from NDA volume 66, Appendix 1, Table 35. Includes all subjects discharged before day 21. p Value per sponsor.

Conclusions Regarding the Need for Other Medical Interventions

The data are inconsistent regarding the need for other medical interventions, and do not suggest a clear benefit for nesiritide as regards any specific intervention. The suggested decrease in the rate of intubations in the 704.326 trial was not seen in the 704.325 trial (in which the number of intubations was clearly higher in the high-dose nesiritide group relative to control). There was a suggestion of an increased need for non-dialytic interventions due to renal failure in the 704.325 study, which again was not confirmed in the 704.326 study.

In conclusion, no benefit of nesiritide with regard to the need for medical interventions was demonstrated or strongly suggested.

7.1 Medical Reviewer's Conclusion's Regarding Nesiritide Efficacy

The database adequately demonstrates a significant, dose-dependent effect of nesiritide infusions to decrease PCWP relative to placebo in two trials. The time to peak hemodynamic effect also suggests that the pharmacodynamic half-life of nesiritide is significantly prolonged (2-4 hours) relative to its pharmacokinetic half-life (12-30 minutes). This hemodynamic effect on PCWP was associated significantly with the dose and plasma concentrations of nesiritide. Nesiritide also had significant, dose-dependent effects on other hemodynamics, including systolic blood pressure. The time-course for changes in PCWP and other hemodynamic measurements in study 704.311 through 24 hours suggest a decrease in the magnitude, but not the significance, of the effect of nesiritide on hemodynamics. While these data support the development of some 'tolerance' or 'tachyphylaxis' to nesiritide through 24 hours, they also suggest that nesiritide continues to have a significant hemodynamic effect.

The database demonstrates a nominally significant effect of nesiritide to improve CHF signs and symptoms at the end of 6 hours, when compared with placebo, in one trial. In contrast to the hemodynamic data, this effect was not dose-related. There is also a suggested effect of nesiritide to decrease the median respiratory rate relative to placebo. These data are also flawed by problems relating to their collection, and cannot be interpreted as independent confirmation of nesiritide efficacy, although they are suggestive of benefit. No advantage for nesiritide relative to the 'active control' group with regard to CHF signs and symptoms was demonstrated or suggested by the data from two other trials. The data suggesting a small effect of nesiritide to reduce the respiratory rate does support a beneficial effect of nesiritide on respiration. There was no indication that nesiritide was less effective at improving symptoms than the active control. No other clinical benefits of nesiritide infusion were demonstrated, when compared the active control groups, including: mortality rate, hospitalization rate, or need for other medical interventions.

8.0 Integrated Review of Safety

This section will summarize the critical adverse events identified by the Medical Reviewer for NDA 20-920. Within body systems, the data relating to each adverse event will be summarized, followed by an opinion regarding its association to nesiritide administration. The strength of the association between nesiritide and a given adverse event will be qualified as possible, probable, or definite, based on the conclusions of the Medical Reviewer. The primary data-tables used for this review can be found in Appendix one, section 11.0. Data will be examined in the following order:

- 1) incidence of both AEs and SAEs,
- 2) deaths associated the safety issue, and
- 3) any lab measurements, including vital signs, relevant to the safety issue.
- 4) the demographics of individual AEs and SAEs where possible.
- 5) special studies of relevance to individual AEs. Some of these were performed by the sponsor, or at the request of the FDA. Others were performed by the FDA, and will be identified as such.

The adverse events to be discussed have been included either because, in the opinion of this reviewer, their occurrence is associated with nesiritide administration (e.g., hypotension) or because they are part of a usual safety review (e.g., abnormal LFTs). Those adverse events that are not listed in this section are interpreted as either occurring too rarely to determine their association with nesiritide use or occurred with no evidence of specific association with study drug administration (either control or nesiritide). The critical safety issues where the data were considered insufficient will be identified as such.

In reviewing the database summarized above, this reviewer was careful to examine the data for evidence of events occurring more frequently in the control/placebo group relative to nesiritide, in addition to searching for events linked to nesiritide use. This is important so as to avoid the bias potentially present in any analysis that includes multiple analyses such as the safety review. It is also important to remember that the use of statistics to examine the incidence of rare and unusual events in a safety database is flawed with the same difficulties inherent to multiple looks. The intent of the following sections is to look for trends suggesting an association between a given AE (or group of AEs) and one of the treatment groups, based on multiple lines of evidence. This is, of course, the nature of a safety review.

There are two limiting factors that an NDA places on the detection of renal and cardiac adverse events (AEs): 1) the extent of patient exposure in both controlled and uncontrolled trials, and 2) the potential absence of relevant data. The patients exposed to study drug will be discussed below. Issues relating to the collection of individual data (e.g., Holter monitor data, follow-up abnormal labs) will be addressed in the discussion of each specific safety issue as relevant.

Patient Exposure

Overall, 505 patients were exposed to nesiritide as part of the NDA. The number of patient-years of exposure puts absolute limits on detecting and characterizing the renal and cardiac safety of nesiritide. Using the number 505, and not taking into account the duration of exposure, we can estimate a 95% likelihood of detecting at least one occurrence of adverse events occurring at a rate of between 1/150 and 1/200. As part of the three large infusion trials, 362 patients received nesiritide, compared with 173 control patients (both placebo- and active-control). This smaller number of patients will limit our ability to detect significant adverse events even further. Less information, obviously, will be available regarding the relative rates for adverse events (nesiritide vs. control group). Comparative rates between nesiritide and placebo will be limited by the use of active, open-label controls after short periods of exposure to nesiritide in the infusion trials.

The comparative rates of adverse events for the three nesiritide dose groups also needs to be commented on. With only 26 subjects in the highest nesiritide dose group (0.060 µg/kg/min), adverse event rate comparisons with the other nesiritide dose groups need to be interpreted with great caution.

It is also critical to note that patients who had CHF in combination with an acute MI were not eligible for enrollment in the trial. No direct information is available regarding the safety or efficacy of nesiritide in this population.

A final note needs to be made about the conventions used for the labels in the data summary below. The long infusion trials had small differences in the doses of nesiritide used, especially with regard to the dose of the nesiritide bolus prior to the start of the infusion. These dose groups are summarized on the next page.

Treatment groups in the long infusion trials

704.311

There were four treatment groups in study 704.311:

Group 1: Nesiritide: IV bolus of 0.25 µg/kg followed by a 0.015 µg/kg/min infusion.

Group 2: Nesiritide: IV bolus of 0.50 µg/kg followed by a 0.030 µg/kg/min infusion.

Group 3: Nesiritide: IV bolus of 1.0 µg/kg followed by a 0.060 µg/kg/min infusion.

Group 4: IV bolus of placebo followed by a placebo infusion.

704.325

There were three treatment groups in study 704.325:

Group 1: Nesiritide: IV bolus of 0.3 µg/kg followed by a 0.015 µg/kg/min infusion.

Group 2: Nesiritide: IV bolus of 0.6 µg/kg followed by a 0.030 µg/kg/min infusion.

Group 3: IV bolus of placebo followed by a placebo infusion.

704.326

There were three treatment groups in study 704.326:

Group 1: Nesiritide: IV bolus of 0.3 µg/kg followed by a 0.015 µg/kg/min infusion.

Group 2: Nesiritide: IV bolus of 0.6 µg/kg followed by a 0.03 µg/kg/min infusion.

Group 3: A standard care agent.

In presenting the safety data, the doses of nesiritide have been 'lumped' according to their infusion dose. These will be listed as nesiritide 0.015 or 0.015 µg/kg/min, nesiritide 0.030 or 0.30 µg/kg/min, or nesiritide 0.060/0.060 µg/kg/min. Given the small number of patients available for the safety summary, this 'lumping' was judged by the Medical Reviewer as in the interest of effective review. Where individual trial data is summarized, the bolus information will be included that is correct for the trial in question.

Another note must be made regarding the inclusion of nominal p Values in the tables below. The Medical Reviewer recognizes that few, if any, of these carry any true statistical power (pre-specified, corrected for multiple looks, etc.). Their inclusion in the review is rather to serve as a marker for differences which may (or may not) be clinically relevant, but which bear further scrutiny. As such, all of these p Values should be seen as nominal.

8.0.1 Occurrence of Adverse Events by Body System

First, the relative occurrence of adverse events by body system is summarized from the adverse event table above. Nesiritide administration was associated with a nominally significant increase in the rate of overall adverse events within two systems, and a decreased incidence in one, which are shaded in the table below.

Table 8.0.1.1 (from 11.1.3.2) Adverse Events (AEs) during the first 14 days in the 'long infusion' trials, summarized by body system^a.

Adverse Event	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
Cardiovascular System	93 (54%)	110 (65%)	114 (68%)	14 (54%)	0.027
Body as a Whole	89 (51%)	74 (44%)	69 (41%)	6 (23%)	0.029
Digestive System	52 (30%)	67 (40%)	60 (36%)	7 (27%)	0.242
Nervous System	40 (23%)	67 (40%)	54 (32%)	7 (27%)	0.011
Metabolic & Nutritional	34 (20%)	28 (17%)	34 (20%)	5 (19%)	0.813
Respiratory System	25 (14%)	33 (20%)	36 (22%)	2 (8%)	0.179
Urogenital System	22 (13%)	28 (17%)	35 (21%)	3 (12%)	0.209
Skin & Appendages	15 (9%)	20 (12%)	23 (14%)	0 (0%)	0.114
Musculoskeletal	15 (9%)	10 (6%)	9 (5%)	1 (4%)	0.648
Hemic & Lymphatic	9 (5%)	3 (2%)	8 (5%)	1 (4%)	0.286
Special Senses	3 (2%)	4 (2%)	5 (3%)	1 (4%)	0.602

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

8.0.2 Adverse Events in the Cardiovascular System

The following adverse events within the cardiovascular system will be examined: hypotension, bradycardia, other ventricular and atrial arrhythmias, congestive heart failure, and decreased pulmonary pressure. Adverse events analyzed but not discussed further include hypertension, and myocardial infarct.

8.0.2a Hypotension

AEs

The first two tables summarize the incidence of AEs related to hypotension in the 'all CHF' and the 'long infusion' databases. There was a highly significant increase in the incidence of hypotension, including symptomatic hypotension, in the nesiritide groups, which was dose-dependent in the 'long infusion' trial population.

Table 8.0.2a.1 (from 11.1.3.1) Hypotensive AEs in the 'all CHF' trials from NDA 20-920^a.

Hypotension	Control n=235	Nesiritide n=505	Nominal p Value
Cardiovascular System	116 (49%)	300 (59%)	0.011
Hypotension	35 (15%)	152 (30%)	<0.001
Symptomatic hypotension	16 (7%)	76 (15%)	0.001

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.2a.2 (from 11.1.3.2) Hypotensive AEs in the first 14 days in the 'long infusion' trials^a.

Hypotension	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
Cardiovascular System	93 (54%)	110 (65%)	114 (68%)	14 (54%)	0.027
Hypotension	27 (16%)	45 (28%)	67 (40%)	8 (31%)	<0.001
Symptomatic Hypotension	11 (6%)	20 (12%)	32 (19%)	4 (15%)	0.003
Decreased Pulmonary Pressures	0 (0%)	0 (0%)	3 (2%)	5 (19%)	<0.001
Syncope	2 (1%)	2 (1%)	1 (1%)	0 (0%)	

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

The sponsor also summarized the data for the first 24 hours of the long infusion trials. The incidences of selected AEs from the table above are shown. The majority of the hypotensive AEs occurred during the first 24 hours, during the study drug infusion.

Table 8.0.2a.3 (from 11.1.3.3) Hypotensive AEs during the first 24 hours in the 'long infusion' trials^a.

Hypotension	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	27 (16%)	45 (28%)	67 (40%)	8 (31%)	<0.001
Symptomatic Hypotension	11 (6%)	20 (12%)	32 (19%)	4 (15%)	0.003
Decreased Pulmonary Pressures	0 (0%)	0 (0%)	3 (2%)	5 (19%)	<0.001

a. Data from appendix 8.4, table 12C and from company at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

Hypotensive SAEs

The occurrence of hypotensive SAEs in the 'all CHF' and long infusion trials is summarized below. The SAEs were uncommon.

Table 8.0.2a.4 Hypotensive SAEs through 14 days in the nesiritide NDA database from all CHF trials^a.

Serious Adverse Event	Control n=235	Nesiritide n=505
Hypotension	1 (<1%)	4 (1%)
Hypotension, symptomatic	1 (<1%)	4 (1%)
Syncope	1 (<1%)	2 (<1%)

a. Data from NDA appendix 8.4, table 27A.

Table 8.0.2a.5 (from 11.1.2.2) Hypotensive SAEs through 14 days in the 'long infusion' trials^a.

Serious Adverse Event	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min
Hypotension ^b	1 (1%)	0 (0%)	1 (1%)	0 (0%)

a. Data from appendix 8.4, table 27C and from company at request of reviewer.

b. Includes 'hypotension' and 'symptomatic hypotension.'

Discontinuations

There were significantly more discontinuations for hypotensive adverse events in the nesiritide group, as shown below for both the 'all CHF' and 'long infusion' groups. Dizziness is included as a sign of hypotension that can be misinterpreted, and also leads to discontinuation.

Table 8.0.2a.6 (from 11.1.5.3.1) Discontinuations prior to day 14 for hypotensive AEs in the 'all CHF' population^a.

Hypotension/ Dizziness	Control n=235	Nesiritide n=505	Nominal p Value ^a
Cardiovascular System	15 (6%)	78 (15%)	<0.001
Hypotension	2 (1%)	51 (10%)	<0.001
Symptomatic Hypotension	2 (1%)	32 (6%)	<0.001
Decreased Pulmonary Pressure	0 (0%)	5 (1%)	0.185
Nervous System			
Dizziness	0 (0%)	6 (1%)	0.184

a. Data from NDA appendix 8.4, table 28A.

Table 8.0.2a.7 (from 11.1.5.3.1) Discontinuations for hypotensive AEs in the long infusion trials^a.

Hypotension/ Dizziness	Control	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value ^b
Cardiovascular	9 (5%)	23 (14%)	33 (20%)	6 (23%)	<0.001
Hypotension	1 (1%)	11 (8%)	25 (15%)	2 (8%)	<0.001
Symptomatic Hypotension	1 (1%)	8 (5%)	14 (8%)	2 (8%)	0.002
Decreased Pulmonary Pressure	0 (0%)	0 (0%)	2 (1%)	0 (0%)	<0.001
Dizziness	0 (0%)	0 (0%)	1 (1%)	2 (8%)	0.002

a. Data from supplemental table 28D, with p Value per sponsor.

Hypotensive Deaths

After reviewing both the sponsor's summaries and the case report forms for individual patients, the following deaths were associated with hypotensive episodes. For both patients listed below, there is no apparent association between nesiritide administration and the death.

Table 8.0.2a.8 (from 11.1.1.2) Known deaths associated with hypotension in NDA 20-920^a.

Treatment Group/ Patient #	# of Days After Study Entry	Cause of Death
<u>Placebo</u>		
None	--	--
<u>Active Control^b</u>		
None	--	--
<u>Nesiritide Bolus</u>		
None	--	--
<u>Nesiritide 0.015 µg/kg/min infusion</u>		
382013	5	Progressive Renal Insufficiency CHF
<u>Nesiritide 0.030 µg/kg/min infusion</u>		
357002	15	MI

a. Data from NDA volume 1.81, listing 7, and examination of individual case report forms.

1. *Subject 382-013 (nesiritide, 0.015 µg/kg/min)* subject was an 80-year-old white man with NYHA Class IV CHF due to ischemic cardiomyopathy and progressive renal insufficiency. He had not responded to 7 days of dobutamine therapy before he was enrolled into the study. After 6 hours of nesiritide therapy, his hemodynamics were only minimally improved and dobutamine was restarted. Nesiritide was discontinued on study day 3 due to hypotension and nausea. After a short trial of milrinone added to the dobutamine, it was decided that the subject was refractory to vasoactive medications. The subject was made "Do Not Resuscitate." On day 5, the subject expired due to endstage CHF and progressive renal insufficiency.

Deaths (cont)

2. *Subject 357-002 (Nesiritide, 0.03 µg/kg/min)* Subject was a 54-year-old white man with a history of NYHA Class III CHF due to ischemic cardiomyopathy and chronic angina. Nesiritide was discontinued after 4.5 hours because his PCWP had decreased to 6 mm Hg. However, the subject was symptomatically improved, so no additional parenteral agents for CHF were started and he was discharged on day 2. On day 15, he died in the emergency room from a myocardial infarction after an unsuccessful resuscitation.

Special Studies: Changes in Measured Blood Pressure

In all three long infusion trials there was an association between nesiritide dose and the frequency of hypotension. This reflected an acute effect of nesiritide to lower blood pressure, as shown in the tables below, which come from the individual study reviews.

Table 8.0.2a.9 (from table 6.1.12.4.1) Effect of 3 hour infusion of nesiritide on blood pressure in trial 704.311^a.

Blood Pressure Changes in Study 704.311	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	Nominal p Value ^b
Systolic BP (mm Hg)	+1.2 (+1%)	-7.4 (-6%)	-4.3 (-3%)	-10.0 (-8%)	0.006

a. Data from NDA 20-998, vol. 54, Table 2. Data are expressed as absolute and (%) change from baseline for ITT population.
b. p Value comparing arithmetic means from baseline using ANOVA.

Table 8.0.2a.10 (from table 6.2.12.4.2) Summary of changes in blood pressure using 'last value carried forward' population from study 704.325^a.

Blood Pressure Changes in Study 704.325	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.0305 n=42	Nominal p Value ^b
Mean Systemic Arterial BP (MAP), mm Hg				
MAP at baseline and 6 hours				
At baseline	86.2±12.6	81.2±10.0	85.4±11.3	0.103
At 6 hours	86.7±13.1	76.2±11.4	76.8±10.2	<0.001
Nominal p Value (compared to control)	---	<0.001	<0.001	
Change in MAP from baseline at 6 hrs (mm Hg)				
Mean±SD	0.3±7.3	-5.1±11.0	-8.8±10.9	0.001
Median	-1.3	-4.5	-8.7	
Range	-17 to +19	-44 to +20	-24 to +11	
Nominal p Value (change from baseline) ^c	---	0.005	<0.001	
Nominal p Value (comp. to control) ^c	---	0.008	<0.001	

a. Data from NDA volume 1.59, Appendix 1, Table 26a to 40a and electronic data sets.
b. p Value using Omnibus F test.
c. p Value compares the 6 hour value for each group individually with the control baseline using T-test or 1-sample Wilcoxon.

Table 8.0.2a.11 (from table 6.3.12.3.1) Changes in blood pressure from baseline to 3 hours in 704.326^a.

Blood Pressure Changes in Study 704.326	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal p Value
Systolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	120.7±20	127±25	124±26	0.197
Change from Baseline to 3 hours	-2.8±16	-9.3±16	-11.2±16	<0.001
Nominal p Value (Chg from Base) ^b	0.183	0.0001	<0.001	
Nominal p Value (Compared to Standard Care) ^c	--	0.003	<0.001	
Nominal p Value (Compared to Low-dose BNP) ^c	--	--	0.426	
Diastolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	70±13	71±15	68±15	0.477
Change from Baseline to 3 hours	-5.9±12	-4.5±12	-8.6±11	0.051
Nominal p Value (Chg from Base) ^b	<0.001	<0.001	<0.001	
Nominal p Value (Compared to Standard Care)	--	0.376	0.125	
Nominal p Value (Compared to Low-dose BNP)	--	--	0.016	

a. Data from NDA volume 1.66, table 21.
b. Comparison by T test.
c. Comparison by ANOVA contrasts.

Special Studies: Timing and Severity of Hypotension

The majority of the hypotensive events occurred during the first 24 hours of study drug administration. The sponsor performed further analyses of hypotension.

First, the frequency and severity of all hypotension was summarized. Both the severity of the hypotension and the effect on study drug administration were greatest in the nesiritide group. The effects also tended to be dose-related, with the highest incidence of severe hypotension resulting in drug discontinuation occurring in the nesiritide 0.060 dose group.

Table 8.0.2a.12 (from 11.1.3.2a.1) Severity and effect of all reported hypotension as an AE during the first 24 hours in the 'long infusion' trials in NDA 20-920^a.

Hypotension	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
Greatest Severity					
No hypotension reported	158 (91%)	136 (80%)	115 (69%)	19 (73%)	<0.001
Mild	7 (4%)	14 (8%)	20 (12%)	2 (8%)	
Moderate	7 (4%)	19 (11%)	25 (15%)	2 (8%)	
Severe	1 (1%)	0 (0%)	7 (4%)	3 (12%)	
Greatest Effect on Study Drug Administration^b					
None	10 (6%)	9 (5%)	12 (7%)	2 (8%)	<0.001
Dose Decreased	4 (2%)	12 (7%)	21 (13%)	2 (8%)	
Dose Discontinued	1 (1%)	12 (7%)	19 (11%)	3 (12%)	

a. Data from supplemental data table 23D.2 at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.
 b. p Value for 'Greatest Effect on Drug Administration' performed including data for patients without hypotension.

Next, the sponsor analyzed the incidence of symptomatic hypotension in the long infusion trials. Once again, the severity of the hypotension and the effect on study drug administration were greatest in the nesiritide group. The severity of the hypotension also tended to be dose-related in the three nesiritide doses examined.

Table 8.0.2a.13 (from 11.1.3.2a.1) Severity and effect of symptomatic hypotension as an AE during the first 24 hours in the 'long infusion' trials in NDA 20-920^a.

Symptomatic Hypotension	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
Greatest Severity					
No hypotension reported	167 (97%)	155 (92%)	144 (86%)	22 (85%)	0.004
Mild	2 (1%)	4 (2%)	4 (2%)	1 (4%)	
Moderate	3 (2%)	10 (6%)	12 (7%)	0 (0%)	
Severe	1 (1%)	0 (0%)	7 (4%)	3 (12%)	
Greatest Effect on Study Drug Administration^b					
None	3 (2%)	3 (2%)	2 (1%)	2 (8%)	0.004
Dose Decreased	2 (1%)	5 (3%)	9 (5%)	0 (0%)	
Dose Discontinued	1 (1%)	6 (4%)	12 (7%)	2 (8%)	

a. Data from supplemental data table 23D.2 at request of reviewer. Reflects trials 311, 325, and 326 data.
 b. p Value for 'Greatest Effect on Drug Administration' performed including data for patients without hypotension.

Special Studies: Timing and Severity of Hypotension (cont)

The sponsor analyzed the severity of the hypotension during the first 24 hours in the 704.326 study. There was a higher incidence of hypotension in the nesiritide groups for any SBP <100 mm Hg. Very few patients had extreme hypotension in any group (<60 mm Hg). In data not shown, the time to minimum SBP following start of study drug ranged widely, from 15 minutes to >1400 minutes in all three treatment groups.

Table 8.0.2a.14 (from 11.1.3.2a.2) Severity of hypotension during the first 24 hrs in 704.326^a.

Changes in systolic BP (SBP)	Control n=173	Nesiritide 0.3/0.015 µg/kg/min n=169	Nesiritide 0.6/0.030 µg/kg/min n=167	Nominal p Value
Mean Minimum SBP (mm Hg)	100±17.50	97.9±18	91.0±16	0.001
Median	100.0	94.0	90.0	
Minimum SBP <100	49 (48%)	64 (62%)	71 (71%)	
Minimum SBP <90	20 (20%)	39 (38%)	47 (47%)	
Minimum SBP <80	4 (4%)	13 (13%)	23 (23%)	
Minimum SBP <70	1 (1%)	1 (1%)	7 (7%)	
Minimum SBP <60	1 (1%)	0 (0%)	2 (2%)	

a. Data from NDA appendix 8.4, table 25.

The mean and median decreases in systolic BP were also greater in the nesiritide groups in 704.326, even though the SBP was similar in all three groups at baseline.

Table 11.1.3.2a.15 Severity of hypotension during the first 24 hours in 704.326^a.

Changes in systolic BP (SBP)	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nominal p Value
SBP at Baseline	121±20	127±25	123±26	0.197
Absolute Decrease in SBP (mm Hg)	21.2±16	29.4±16	33.1±19	<0.001
Median Decrease in SBP (mm Hg)	19.0	26.0	29.0	

a. Data from NDA appendix 8.4, table 25.

Finally, the duration of hypotension was examined by the sponsor in the three long infusion studies. Since only one patient in the control or placebo arms was discontinued for hypotension, only those patients in the nesiritide 0.015 and 0.30 groups were included in the analysis. Note that the onset of hypotension was frequently after several hours of nesiritide therapy, that prolonged hypotension was common in both nesiritide dose groups, and that a large majority of the symptomatic hypotension necessitated discontinuation of nesiritide.

Table 11.1.3.2a.16 Clinical features of first onset of symptomatic hypotension within first 24 hours^a.

Symptomatic Hypotension	Nesiritide 0.015 n=14 (of 169 total)	Nesiritide 0.030 n=23 (of 167 total)
Time of Onset (hrs)		
<1 hrs	0	1
1 to <3 hrs	4	3
3 to <6 hrs	3	7
6 to 24 hrs	7	11
Unknown	0	1
Severity		
Mild	5	4
Moderate	9	12
Severe	0	7
Duration		
≤0.5 hrs	5	5
0.5 to <1 hrs	2	5
1 to 2 hrs	2	2
>2 to 7 hrs	4	8
>7 hrs	8	14
Greatest Effect on Drug Dosing		
No Effect	3	1
Dose Decreased	3	8
Nesiritide Discontinued	8	14

a. Data from sponsor at request of Medical Reviewer. A listing of the individual patients with hypotension to varying systolic BPs is found in appendix 18.0.

Demographics of Hypotension

1. Age

Hypotension occurred equally in both the elderly subjects (>65), and for those <65, as shown below for the long infusion trial population. Symptomatic hypotension occurred with equal frequency in the two groups (not shown). Note that in both age groups, hypotension was significantly more common in the nesiritide groups.

Table 8.0.2a.17 Hypotension an AE in the 'long infusion' population according to age^a.

Hypotension	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
>65 Years Old	11/70 (16%)	20/69 (29%)	36/77 (47%)	2/9 (22%)	0.001
<65 Years Old	16/103 (10%)	27/100 (27%)	31/90 (34%)	6/17 (35%)	0.013

a. Data from supplemental data table 13D at request of reviewer. Reflects trials 311, 325, and 326 data.

2. Gender

Symptomatic hypotension occurred more commonly in females.

Table 8.0.2a.18 Hypotension an AE in the 'long population according to gender^a.

Hypotension	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Male	n=127	n=120	n=113	n=23	
Hypotension	15 (12%)	35 (29%)	44 (39%)	7 (30%)	0.0001
Symptomatic Hypotension	8 (6%)	14 (12%)	16 (14%)	3 (13%)	0.190
Female	n=46	n=49	n=54	n=3	
Hypotension	12 (26%)	12 (24%)	23 (43%)	1 (33%)	0.166
Symptomatic Hypotension	3 (7%)	6 (12%)	16 (30%)	1 (33%)	0.009

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data.

3. Other Medications

There was no detected relationship between nesiritide and the use of ACE inhibitors, digoxin, or beta blockers with respect to the occurrence of hypotension or symptomatic hypotension.

Table 8.0.2a.19 Hypotensive AEs by use of other medications in addition to nesiritide from study 704.326.

Occurrence of Hypotensive AEs ^b	Nesiritide 0.3/0.015 and 0.6/0.030 µg/kg/min
ACE Inhibitor Use	
Yes	42/124 (34%)
No	15/49 (31%)
Digoxin Use	
Yes	38/117 (32%)
No	11/45 (24%)
Beta Blockers	
Yes	6/18 (33%)
No	57/183 (31%)

a. Data from ISS table 8-39, reflecting trial 704.326 data.

b. Includes symptomatic and asymptomatic hypotension.

4. NYHA Class III or IV

Hypotensive AEs occurred with equal frequency in Class III and IV NYHA patients. The pattern, with a greater frequency of hypotension in the nesiritide groups, was also evident in both NYHA classes.

Table 8.0.2a.20 Hypotensive AEs in the 'long infusion' population^a according to NYHA Class^a.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Class III	n=107	n=97	n=81	n=15	
Hypotension	12 (11%)	30 (31%)	28 (35%)	5 (38%)	<0.001
Symptomatic Hypotension	6 (6%)	12 (12%)	14 (17%)	1 (7%)	0.067
Class IV	n=58	n=64	n=71	n=9	
Hypotension	11 (19%)	16 (25%)	31 (44%)	2 (22%)	0.014
Symptomatic Hypotension	3 (5%)	7 (11%)	15 (21%)	2 (22%)	0.032

a. Data from supplemental data table 17D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes hypotension and symptomatic hypotension.

5. Etiology of CHF

The sponsor also analyzed the occurrence of AEs by the original etiology of their CHF. With the exception of hypotension due to hypertensive CHF, there was an association between nesiritide and hypotension (both total and symptomatic).

Table 8.0.2b.21 Hypotensive AEs in the 'long infusion' population^a according to etiology of CHF^a.

Hypotension ^b	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Hypertensive CHF	N=13	N=14	N=12	N=3	
Hypotension	3 (23%)	4 (29%)	4 (33%)	2 (67%)	0.582
Symptomatic Hypotension	2 (15%)	2 (14%)	3 (25%)	2 (67%)	0.228
Ischemic CHF	N=89	N=88	N=87	N=16	
Hypotension	10 (11%)	27 (31%)	36 (41%)	5 (31%)	<0.001
Symptomatic Hypotension	5 (6%)	13 (15%)	14 (16%)	2 (13%)	0.102
Idiopathic/Dilated CHF	N=38	N=40	N=11	N=5	
Hypotension	7 (18%)	11 (28%)	19 (54%)	1 (20%)	0.008
Symptomatic Hypotension	3 (8%)	5 (13%)	11 (31%)	0 (0%)	0.038

a. Data from supplemental tables provided at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

Special Studies: Individual Cases

The tables in Appendix 18.0 list all the patients who had severe hypotension by a series of markers during the infusion trials.

The table below summarizes the clinical events for patients who had 'severe' hypotension (as defined by investigators) during the first 24 hours of the long infusion trials. As can be seen, several of the patients had prolonged hypotension, requiring additional medical interventions, including intubation, pressor medications, and IV fluids. The time to onset of the hypotension was also quite variable, ranging from 30 minutes (potentially related to the bolus infusion) to almost 10 hours. Finally, inadequate follow-up labs exist for some patients so determine whether there was renal injury following the hypotension.

A summary of the outcomes for each of the patients can be found in the tables below, along with information regarding the timing of the hypotension relative to study drug use, other medications administered.

Table 8.0.2b.22 (from 18.0.1) Subjects with hypotension in the first 24 hours where the greatest severity was 'severe'^a.

Treatment Group/ Patient ID #	While on Study Drug?	Outcome/ AEs	Duration of Hypotension	Notes
<i>Control</i> 535003	Y/ Dobutamine 1 hr	EMD with Seizure BP 140/- to 0	<5 mins	Study Drug D/C'd No renal failure
<i>Nesiritide 0.030</i> 356002	Y 3 hrs	BP to 86/52	30 mins	Drug D/C'd Tx'd O ₂ , IV fluids
357001	Y 23 hrs	135/78 to 58/48 'Hypotensive Crisis'	9 hrs, 55 mins	Tx'd intubation, levophed, dopamine, IV fluids, Intra-aortic balloon pump
493011	Y/ 7 hrs	BP 150/80 to 90/60 with diaphoresis, LOC	3 hours	IV NS, Trendelenburg, Study Drug D/C'd No renal failure
508004	N	HR from 80-88 to 53 BPM BP 140/70 to 50/30	N/A	Made DNR after OR, Support withdrawn NQWMI
519002	Yes, 40 mins and 4.5 hrs	BP 170/77 to 73/43, then later to 79/32	2 episodes, each <1 hr	
562001	Y 20 mins	BP 152/64 to 80/39 with Junctional rhythm Symptomatic: vomited	3 hrs 45 min	Tx'd with IV D5W, Trendelenburg position
579002	Y 7 hrs 45 mins	BP 108/61 to 88/61 Symptomatic: dizzy	2.5 hrs	Nesiritide discontinued, later developed VTach and Coagulopathy
<i>Nesiritide 0.060</i> 017008	Y 1 hr	BP 98/64 to 62/-	30 minutes	AEs unknown, no lab F/U Pt tx'd with Trendelenburg position
369005	Y 35 mins	BP 98/40 to 70/-, pulse 71	3 hrs	Tx'd Trendelenburg, Atropine, IV NS
369014	Y 1 hr	BP 140/82 to 60/-- Pulse 73 to 61 Symptomatic: light-headed	20 minutes	No Lab F/U Tx'd Dopamine, IV NS No lab F/U

A list of all subjects with discontinuation or severe AEs related to hypotension can be found in appendix 18.0 below. Below are two notable patients from that list, who had hypotension during nesiritide infusion.

Special Studies: Individual Cases (cont)

One patient developed hypotension with a 'hypotensive crisis' requiring intubation while on nesiritide. This necessitated nesiritide discontinuation, and was associated with renal failure.

1. *Subject 357001 (Nesiritide 0.030 µg/kg/min)*, was a 63 y/o WM with CHF who received nesiritide 0.030 µg/kg/min for 2 days, until 30 minutes prior to cardiopulmonary arrest with electromechanical dissociation for 'hypotensive crisis' (recorded BP 68/42 mm Hg). His blood pressures recorded 2 hours prior to the cardiac arrest showed a decline in his systolic BP from a baseline of approximately 130 to 88 mm Hg. The reason recorded for discontinuation of study drug was 'hypotension.' During nesiritide infusion the patient also developed a worsening of his tachycardia (118 at baseline to 144 BPM at the end of 6 hours). After the hypotensive arrest, patient was treated with levophed and dopamine and intubated, but his blood pressure remained <70 systolic for approximately 2 hours. His creatinine rose from a baseline of 1.5 to 3.4, for which he received renal dose dopamine. His last recorded BUN/creatinine were 106/3.0 mg/dl.

Another patient, who the sponsor believes enrolled in the trial despite having a NQWMI, had marked decrease in blood pressure on two occasions associated with bradycardia, ultimately requiring nesiritide discontinuation. Whether this lability of BP/hypotension would occur in other patients with acute MIs treated with nesiritide is unknown.

2. *Subject 519-002 (nesiritide, 0.03 µg/kg/min)* Subject 519-002 is a 77-year-old black woman with NYHA Class III CHF. Nesiritide infusion was interrupted after 41 minutes because of asymptomatic hypotension (decrease in SBP from 170 mm Hg at baseline to 73 mm Hg). Nesiritide infusion was restarted at half of the original dose but at 4 hours, 30 minutes, infusion was terminated because of recurrent asymptomatic hypotension (to SBP of 79 mm Hg). Approximately 30 minutes later, the subject was noted to have sinus bradycardia (heart rate = 48 beats/min) which resolved spontaneously. On day 2, it was discovered that this subject had had elevated cardiac enzymes (myoglobin, with a normal CPK) at enrollment and was diagnosed by the investigator/sponsor as having had a non-Q wave myocardial infarction (before study drug infusion). No follow-up labs are available regarding the development of renal failure, although this is not listed as an adverse event.

Sponsor's Comments Regarding Hypotension

The sponsor felt that while hypotension is the most frequent adverse event associated with nesiritide administration, that this AE is an extension of the pharmacological effect as a vasodilator. They argued that... 'it is therefore unlikely that the benefits of vasodilators (such as preload and afterload reduction) could be derived without exposing some patients to a greater than desired reduction in blood pressure.' They also pointed out that there was no pre-specified definition for hypotension, such that there might be some investigator variability regarding the reporting of hypotension as an AE.

The sponsor sought to determine those demographics that might predict patients who are more likely to develop hypotension. Per the sponsor, 'no single factor assessed emerged as a reliable predictor of the development of symptomatic hypotension, although small sample sizes in many of the subgroups may have confounded this analysis.'

The sponsor concluded that 'no long term or significant adverse sequelae have been clearly associated with nesiritide -induced hypotension to date. The majority of subjects tolerate moderate dose-related decreases in blood pressure well and experience an overall beneficial clinical response to nesiritide therapy. Nesiritide should be administered in a clinical setting in which blood pressure can be adequately monitored and dose adjustment instituted as clinically indicated.'

Reviewer's Conclusions Regarding Hypotension

There is a definite, dose-dependent association between nesiritide administration and the occurrence of hypotension (tables 8.0.2a.9 through 8.0.2a.11). This hypotension was clinically significant, as assessed by the following:

1) the greater incidence of symptomatic hypotension in the nesiritide groups (tables 8.0.2a.1, 8.0.2a.2, and 8.0.2a.3).

2) the increased incidence of discontinuations for decreased BP (tables 8.0.2a.6 and 8.0.2a.7).

3) the greater severity of the hypotension in the nesiritide groups (tables 8.0.2a.12, 8.0.2a.13, and 8.0.2a.14).

4) the presence of individuals who developed hypotension during nesiritide infusion who had clearly adverse clinical outcomes (table 8.0.2a.22).

5) data from trial 704.326, comparing nesiritide with current therapy, which shows that the incidence of hypotension leading to discontinuation of drug within 6 hours of initiation was significantly higher with nesiritide than with the compounds currently being used to treat CHF. These data are of particular interest, since they suggest that the use of nesiritide in practice will lead to significantly more hypotension than is caused by the drugs in current use. This statement is limited by the fact that 704.326 enrolled very few patients who received pure vasodilators (18 patients got IV NTG, none IV nitroprusside). There is, then, no way to know the frequency of these same adverse events for the other pure vasodilators. Given that the pharmacodynamic half-life of these agents is shorter than nesiritide, it is possible that fewer episodes of severe hypotension or renal failure would be seen with these agents.

Further, the time of onset, and duration of hypotension in association with nesiritide is quite variable. Some individuals, however, clearly have sustained hypotension (table 11.1.3.2a.16)

Finally, the sub-group analyses did not reveal any sub-group definitely at increased risk for hypotension, although women had a higher incidence of symptomatic hypotension.

In conclusion, there is a definite association between nesiritide use and a dose-dependent increase in clinically significant hypotension.

8.0.2b Bradycardia

AEs

The first two tables summarize the incidence of AEs related to bradycardia in the 'all CHF' and the 'long infusion' databases. An increase in bradycardic AEs was seen in both sets of trials.

Table 8.0.2b.1 (from 11.1.3.1) Bradycardic AEs in the 'all CHF' trials from NDA 20-920^a.

Bradycardic AEs	Control n=235	Nesiritide n=505
Bradycardic Events^b	2 (1%)	26 (5%)
Bradycardia	2 (1%)	22 (4%)
Sinus Bradycardia	0 (0%)	1 (<1.0%)
AV Node Conduction Abnormalities	4 (2%)	9 (2%)
AV Block, Complete	1 (<1.0%)	0 (0%)
AV Block, First Degree	3 (1%)	5 (1%)
AV Block, Second Degree	1 (<1.0%)	4 (1%)

a. Data from NDA appendix 8.4, table 11A.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

Table 8.0.2b.2 (from 11.1.3.2) Bradycardic AEs in the first 14 days in the 'long infusion' population^a.

Bradycardic AEs	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
Bradycardic Events^b	1 (1%)	9 (5%)	14 (8%)	0 (0%)	0.002
Bradycardia	1 (1%)	9 (5%)	10 (6%)	0 (0%)	0.015
Sinus Bradycardia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Nodal Bradycardia	0 (0%)	0 (0%)	3 (2%)	0 (0%)	0.169
AV Node Conduction Abnormalities	3 (2%)	5 (3%)	4 (2%)	0 (0%)	0.846
AV Block, First Degree	3 (2%)	3 (2%)	2 (1%)	0 (0%)	1.000
AV Block, Second Degree	1 (1%)	2 (1%)	2 (1%)	0 (0%)	0.804

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

The sponsor also summarized the data for the first 24 hours of the long infusion trials. The incidences of selected AEs from the table above are shown. Overall, similar trends in the incidence of AEs were seen in both sets.

Table 8.0.2b.3 (from 11.1.3.3) Bradycardic AEs during the first 24 hours in the 'long infusion' population^a.

Bradycardic AEs	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
Bradycardic Events^b	0 (0%)	6 (4%)	9 (5%)	0 (0%)	0.008
Bradycardia	0 (0%)	6 (4%)	6 (4%)	0 (0%)	0.039

a. Data from appendix 8.4, table 12C and from company at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal bradycardia, and sinus bradycardia.

Bradycardic SAEs

The sponsor also summarized the occurrence of bradycardia as a reported SAE. These events were rarely reported.

Table 8.0.2b.4 (from 11.1.2.1) Bradycardic SAEs through 14 days from 'all CHF' population^a.

Bradycardic SAEs	Control n=235	Nesiritide n=505
Bradycardic events	1 (<1%)	3 (1%)
Bradycardia	1 (<1%)	3 (1%)

a. Data from NDA appendix 8.4, table 27A.

Bradycardic SAEs (cont)

Examination of the list of SAEs identified in the infusion studies found no significant differences between nesiritide and the control group with regard to bradycardic SAEs.

Table 8.0.2b.5 (from 11.1.2.2) The occurrence of bradycardic SAEs through 14 days in the 'long infusion' population^a.

Bradycardic SAEs	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=31	Nominal p Value
Bradycardia ^b	1 (1%)	0 (0%)	2 (1%)	0 (0%)	0.795

^a Data from appendix 8.4, table 27C and from company at request of reviewer.

^b Included 'bradycardic events' and bradycardia.

Discontinuation

Discontinuations for bradycardia were infrequent, and only occurred in the nesiritide groups.

Table 8.0.2b.6 (from 11.1.5.3.1) Discontinuations prior to day 14 due to bradycardic AEs in the 'all CHF' population^a.

Body System/ AE	Control n=235	Nesiritide n=505	Nominal p Value ^a
Cardiovascular System	15 (6%)	78 (15%)	<0.001
Bradycardic Event ^b	0 (0%)	7 (1%)	0.104
Bradycardia	0 (0%)	6 (1%)	0.184
Nodal Arrhythmias	0 (0%)	1 (0%)	1.000

^a Data from NDA appendix 8.4, table 28A.

^b Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

Next, the discontinuations associated with AEs in the long infusion studies are summarized. The rate of discontinuations associated with bradycardia was quite low, and similar in all treatment groups.

Table 8.0.2b.7 (from 11.1.5.3.1) Discontinuations due to bradycardic AEs in the 'long infusion' population^a.

D/Cs with Bradycardia	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
Bradycardic Events ^b	0 (0%)	2 (1%)	4 (2%)	0 (0%)	0.170
Bradycardia	0 (0%)	2 (1%)	3 (2%)	0 (0%)	0.325
Nodal Arrhythmia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361

^a Data from supplemental table 28D, with p Value per sponsor.

^b Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

Bradycardic Deaths

No deaths were attributable to bradycardia induced by study drugs. One death was associated with digoxin toxicity and bradycardia. The narrative of this patient appears below.

1. *Subject 374-001 (nesiritide, 0.015 µg/kg/min)* Subject was a 64-year-old white man with NYHA Class IV CHF due to ischemic cardiomyopathy, diabetes, and chronic renal insufficiency. He responded well to a 24-hour infusion of nesiritide; thereafter, dobutamine was added for inotropic support. The subject's digoxin had been discontinued 1 month earlier due to renal insufficiency. On study day 2, digoxin was reinstated. After receiving his second dose, he developed hypotensive bradycardia (Wenckebach type atrioventricular node block) while sleeping. Atropine was administered, a ventricular pacing wire was placed, and nesiritide was discontinued. Although the heart rate improved with pacing, hypotension persisted due to AV dyssynchrony. Digoxin toxicity was suspected (although digoxin level was 1.1 ng/mL 2 hours earlier) and Digibind was given. Forty minutes later, sinus tachycardia resumed; BP improved within 2 hours. The subject later revealed that he had had a similar event with digoxin in the past and, therefore, had previously been prescribed a low dose of digoxin. His subsequent hospital course included worsening CHF leading to inotrope-dependence and a cardiopulmonary arrest. On day 4, after requesting that all medications be discontinued, the subject died due to endstage heart failure from severe coronary artery disease.

Another subject receiving nesiritide developed marked bradycardia associated with hypotension.

2. Subject 360-101 (nesiritide, 0.030 µg/kg/min) became acutely diaphoretic with bradycardia (ECG, Junctional Bradycardia, rate 34/ min) and hypotension (85/61) during nesiritide administration. Just prior to the event he had received his usual medications: isordil and enalapril, with a BP of 134/76. He recovered with atropine and fluids following discontinuation of nesiritide. He had another episode of bradycardia two weeks later during infusion of IV NTG, which the sponsor suggests may have contributed to the episode.

Special Studies: Heart Rate

The acute effect of nesiritide on heart rate was also compared with control in the three infusion trials. Overall, no clear pattern of effect was discernable, perhaps related to the different controls used in each of the trials (placebo in 704.311, active control in 704.326). Note that the placebo group in 704.311 had an increase in their mean heart rate.

Table 8.0.2b.8 (from table 6.1.12.4.1) Mean change in heart rate from baseline to 3 hours in trial 704.311^a.

Heart Rate in Study 704.311	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	Nominal p Value ^b
Heart Rate (BPM)	+2.6±8	-3.7±7	-2.2±9	+6.2±14	0.002

a. Data from NDA 20-998, vol. 54, Table 2 for ITT population.

b. p Value comparing arithmetic means from baseline using ANOVA.

Table 8.0.2b.9 (from table 6.2.12.4.2) Summary of changes in heart rate using 'last value carried forward' population from study 704.325^a.

Heart Rate in Study 704.325	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.0305 n=42	Nominal p Value ^b
HR at baseline and 6 hours				
At baseline	89.5±12.8	90.3±14.6	87.4±16.7	0.640
At 6 hours	90.9±15.4	88.8±14.5	87.5±16.0	
Nominal p Value (compared to control)	---	0.516	0.300	
Change in HR from baseline at 6 hrs (mm Hg)				0.218
Mean±SD	+1.4 ±7	-1.6±7	0.0±9	
Median	0.5	-3.0	0.0	
Range	-16 to +24	-16 to +14	-28 to +28	
Nominal p Value (change from baseline) ^c	0.240	0.149	0.972	
Nominal p Value (comp. to control) ^c	---	0.082	0.435	

a. Data from NDA volume 1.59, Appendix 1, Table 26a to 40a and electronic data sets.

b. p Value using Omnibus F test.

c. p Value compares the 6-hour value for each group individually with the control baseline using T-test or 1-sample Wilcoxon.

Table 8.0.2b.10 (from table 6.3.12.3.1) Changes in heart rate from baseline to 3 hours in study 704.326^a.

Heart Rate in Study 704.326	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal p Value
Baseline Heart Rate (mean±sd)	85±15	83±18	84±15	0.823
Change from Baseline to 3 hours	+3.5±15	-0.6±9	+0.6±10	0.053
Nominal p Value (Chg from Base) ^b	0.029	0.501	0.569	
Nominal p Value (Compared to Standard Care) ^c	--	0.018	0.107	
Nominal p Value (Compared to Low-dose BNP) ^c	--	--	0.469	

a. Data from NDA volume 1.66, table 21.

b. Comparison by T test.

c. Comparison by ANOVA.

Demographics of Bradycardia

1. Age

No effect of age on the incidence of bradycardic events was detected.

Table 8.0.2b.11 Bradycardic AEs in the 'long infusion' population according to age^a.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
>65 Years Old	n=70	n=69	n=77	n=9	
Bradycardic Events^b	1 (1%)	6 (9%)	8 (10%)	0 (0%)	0.102
Bradycardia	1 (1%)	0 (0%)	5 (6%)	0 (0%)	0.233
Sinus Bradycardia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.000
<65 Years Old	n=103	n=100	n=90	n=17	
Bradycardic Events^b	0 (0%)	3 (3%)	6 (7%)	0 (0%)	0.041
Bradycardia	0 (0%)	3 (3%)	5 (6%)	0 (0%)	0.079

a. Data from supplemental data table 13D at request of reviewer. Reflects trials 311, 325, and 326 data. p Value per sponsor.

b. Includes bradycardia, sinus bradycardia, and nodal arrhythmia.

2. Gender

Bradycardic AEs occurred rarely, and there was no apparent influence of gender on their incidence.

Table 8.0.2b.12 Bradycardic AEs in the 'long infusion' population according to gender^a.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Male	n=127	n=120	n=113	n=23	
Bradycardic Events^b	1 (1%)	5 (4%)	10 (9%)	0 (0%)	0.016
Bradycardia	1 (1%)	5 (4%)	8 (7%)	0 (0%)	0.054
Female	n=46	n=49	n=54	n=3	
Bradycardic Events^b	0 (0%)	4 (8%)	4 (7%)	0 (0%)	0.221
Bradycardia	0 (0%)	4 (8%)	2 (4%)	0 (0%)	0.238

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

3. Other Medications

In study 704.326, the incidence of bradycardia was more frequent in patients taking nesiritide and ACE inhibitors, digoxin, but not beta blockers. The numbers of such patients were quite small, however. The table shows incidences for the 0.015 and 0.030 groups combined (there was no 0.060 group in this study).

Table 8.0.2b.13 Bradycardic AEs arranged by use of other medications in addition to nesiritide from study 704.326^a.

Occurrence of Bradycardic AEs ^b	Nesiritide 0.015 µg/kg/min
ACE Inhibitor Use	
Yes	10/124 (8%)
No	1/49 (2%)
Digoxin Use	
Yes	9/117 (8%)
No	1/45 (2%)
Beta Blockers	
Yes	2/18 (11%)
No	10/183 (5%)

a. Data from ISS VOL. 79, table 8-39, reflecting trial 704.326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

4. NYHA Class III or IV

Bradycardic AEs occurred with equal frequency in Class III and IV NYHA patients.

Table 8.0.2b.14 Bradycardic AEs in the 'long infusion' population^a according to NYHA Class^a.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
NYHA III Bradycardic Events ^b	n=107 7 (7%)	n=97 13 (13%)	n=81 3 (4%)	n=15 0 (0%)	0.094
NYHA IV Bradycardic Events ^b	n=58 0 (0%)	n=64 3 (5%)	n=71 4 (6%)	n=9 0 (0%)	0.413

a. Data from supplemental data table 17D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

5. Etiology of CHF

Bradycardic events occurred with equal frequency regardless of the original etiology of the CHF (with small numbers for analysis).

Table 8.0.2b.15 Bradycardic AEs in the 'long infusion' population^a according to etiology of CHF^a.

Bradycardic Events ^b	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Hypertensive	0/13 (0%)	0/14 (0%)	3/12 (25%)	0/3 (0%)	0.047
Ischemic	0/89 (0%)	5/88 (6%)	8/87 (9%)	0/16 (0%)	0.013
Idiopathic/Dilated	0/38 (0%)	3/40 (8%)	1/35 (3%)	0/5 (0%)	0.383

a. Data from supplemental tables provided at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

Sponsor's Comments

The sponsor argued that the increased incidence of bradycardia in patients who received nesiritide might be due to an effect by nesiritide to both decrease sympathetic and increase parasympathetic tone. Additionally, while bradycardia has accompanied nesiritide -induced hypotension, these events were self-limited following nesiritide discontinuation or have responded to atropine.

The sponsor also argued that nesiritide use was not associated with increases in either ventricular arrhythmias or AV-nodal conduction abnormalities. They pointed out that increases in heart rate are often seen with inotropes such as dopamine and dobutamine.

The sponsor concluded that the association between nesiritide and bradyarrhythmias but not ventricular or nodal arrhythmias, 'is an interesting and important observation for a new drug for this indication and bears further investigation.'

Reviewer's Conclusions Regarding Bradycardia

There is a definite association between nesiritide administration and the development of bradycardia as an adverse event. While the incidence of SAEs related to decreased heart rate is rare, bradycardia caused discontinuation of a higher percentage of nesiritide patients. No sub-groups of patients were identified who were at higher risk of bradycardia. A bradycardic effect of nesiritide has been reported in the literature, where it was associated with profound hypotension leading to loss of consciousness and required atropine and fluids for treatment (ref. 2). For the drug-drug interaction analysis, there was some suggestion that patients on ACE inhibitors, digoxin or beta-blockers were at higher risk, but the patient numbers are simply too small for any firm conclusion.

In conclusion, there is a definite association between nesiritide administration and the development of bradycardia.

8.0.2c Other Ventricular and Atrial Arrhythmias

AEs and SAEs

The occurrence of AEs related to arrhythmias in the two trial populations are summarized below.

Table 8.0.2c.1 (from 11.1.3.1) Arrhythmic AEs in the 'all CHF' population^a.

Arrhythmic AEs	Control n=235	Nesiritide n=505
Ventricular Tachycardia	36 (15%)	75 (15%)
Sustained Ventricular Tachycardia	6 (3%)	9 (2%)
Ventricular Extrasystoles	13 (6%)	22 (4%)
Tachycardia	10 (4%)	12 (2%)
Atrial Fibrillation	5 (2%)	14 (3%)
Supraventricular Tachycardia	5 (2%)	12 (2%)
Bigeminy	3 (1%)	8 (2%)
Syncope	2 (1%)	4 (1%)
Palpitations	1 (0%)	8 (2%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.2c.2 (from 11.1.3.2) Arrhythmic AEs in the first 14 days in the 'long infusion' group^a.

Arrhythmias	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 Values
Ventricular Extrasystoles	13 (8%)	11 (7%)	8 (5%)	0 (0%)	0.477
Ventricular Tachycardia	34 (20%)	42 (25%)	22 (13%)	0 (0%)	0.001
Sustained VT	6 (3%)	5 (3%)	3 (2%)	0 (0%)	0.791
Non-sustained VT	29 (17%)	40 (24%)	22 (12%)	0 (0%)	0.002
Atrial Fibrillation	5 (3%)	2 (1%)	8 (5%)	1 (4%)	0.188
Tachycardia	9 (5%)	5 (3%)	5 (3%)	1 (4%)	0.644
SVT	3 (2%)	4 (2%)	7 (4%)	0 (0%)	0.490
Supraventricular Extrasystoles	2 (1%)	3 (2%)	1 (1%)	0 (0%)	0.781

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

The sponsor also summarized the data for the first 24 hours of the long infusion trials. Of note, less than 50% of the ventricular tachycardias reported took place during the first 24 hours of study drug infusion.

Table 8.0.2c.3 (from 11.1.3.3) Ventricular tachycardia during the first 24 hours in the 'long infusion' trials.

Ventricular Tachycardia	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
Ventricular Tachycardia	14 (8%)	20 (12%)	5 (3%)	0 (0%)	0.007

SAEs Due to Ventricular Arrhythmias

The reported SAEs related to arrhythmias other than bradycardia are summarized below. These events were reported infrequently, at similar rates in both groups.

Table 8.0.2c.4 (from 11.1.2.1) The occurrence of arrhythmic SAEs through 14 days in the nesiritide NDA database from 'all CHF' trials^a.

SAEs related to Arrhythmias	Control n=235	Nesiritide n=505
Heart Arrest	4 (2%)	7 (1%)
Ventricular Tachycardia	2 (1%)	4 (1%)
Sustained Ventricular Tachycardia	2 (1%)	4 (1%)

a. Data from NDA appendix 8.4, table 27A.

Table 8.0.2c.5 (from 11.1.2.2) Occurrence of arrhythmic SAEs through 14 days in the ‘long infusion’ trials^a.

Serious Adverse Event	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
Cardiovascular				
Ventricular Tachycardia	2 (1%)	2 (1%)	2 (1%)	0 (0%)
Sustained VT	2 (1%)	2 (1%)	2 (1%)	0 (0%)

a. Data from appendix 8.4, table 27C and from company at request of reviewer.

Discontinuations

Discontinuations prior to day 14 for ventricular tachycardia were rare, and occurred only in the control group in the ‘CHF trials’ population^a.

Table 8.0.2c.6 (from 11.1.5.3.1) Discontinuations prior to day 14 for ventricular tachycardia in the ‘CHF trials’ population^a.

Body System/ AE	Control n=235	Nesiritide n=505	Nominal p Value ^a
Ventricular Tachycardia	3 (1%)	0 (0%)	0.032

a. Data from NDA appendix 8.4, table 28A.

Next, the discontinuations associated with AEs in the long infusion studies are summarized. Again, the only discontinuations for ventricular tachycardia occurred in the control group.

Table 8.0.2c.7 (from 11.1.5.3.1) Discontinuations due to arrhythmic AEs in the long infusion trials^a.

Arrhythmic AEs associated with Discontinuation	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value ^b
Ventricular Tachycardia	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0.234
Sustained VT	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0.395
Non sustained VT	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1.000
Tachycardia	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1.000

a. Data from supplemental table 28D.

Deaths

Several deaths were associated with arrhythmias, as might be expected in this patient population. The narrative for these patients can be found in Appendix two.

Table 8.0.2c 8 (from 11.1.1.2) Known deaths associated with arrhythmias (non-bradycardic)^a.

Treatment Group/ Patient #	# of Days After Study Entry	Cause of Death
Placebo		
381001	6	Ventricular arrhythmia
356103	19	Dilated cardiomyopathy
376016	6	Ventricular Fibrillation, EMD
376022	21	Sudden Death, CHF
368001	16	Sudden Death, CHF Ventricular Fibrillation, CHF
Nesiritide Bolus		
315005	30	CHF
373301	30	Sudden Cardiac Death Dilated cardiomyopathy
Nesiritide 0.015 µg/kg/min infusion		
538010	9	Mitral regurgitation Chronic atrial flutter
Nesiritide 0.030 µg/kg/min infusion		
524005	5	Ventricular fibrillation
Nesiritide 0.060 µg/kg/min infusion		
3282004	8	Ventricular Arrhythmia Congestive Cardiomyopathy

a. Data from NDA vol. 1.81, listing 7, and examination of individual case report forms.

b. In study 326 subjects were randomized to receive other IV cardiovascular meds.

Demographics of Ventricular Arrhythmias

1. Age

The pattern of non-bradycardic arrhythmias was similar in both > and <65 year olds with the exception of the nesiritide 0.015 dose group, where the incidence of ventricular tachycardia was somewhat higher in the <65 age group. In both groups, the rate of VT was lower in the nesiritide 0.030 group than in control. For rarer AEs, such as atrial fibrillation, the number of cases is too few to justify comparisons (data not shown).

Table 8.0.2c.9 Arrhythmic AEs in the 'long infusion' population according to age^a.

Arrhythmic AEs by Age	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
>65 Years Old	n=70	n=69	n=77	n=9	
Ventricular Tachycardia	15 (21%)	12 (17%)	9 (12%)	0 (0%)	0.249
Sustained VT	4 (6%)	2 (3%)	1 (1%)	0 (0%)	0.481
Non-sustained VT	12 (17%)	11 (16%)	8 (10%)	0 (0%)	0.441
<65 Years Old	n=103	n=100	n=90	n=17	
Ventricular Tachycardia	19 (18%)	30 (30%)	13 (14%)	0 (0%)	0.005
Sustained VT	2 (2%)	3 (3%)	2 (2%)	0 (0%)	0.931
Non-sustained VT	17 (17%)	29 (29%)	12 (13%)	0 (0%)	0.005

a. Data from supplemental data table 13D at request of reviewer. Reflects trials 311, 325, and 326 data. p Value per sponsor.

2. Gender

Arrhythmic AEs occurred in all groups at a higher rate in males, but the pattern of occurrence was similar in both males and females, with a trend towards less non-sustained VT in the high-dose nesiritide groups.

Table 8.0.2c.10 Arrhythmic AEs in the 'long infusion' population according to gender^a.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Male	n=127	n=120	n=113	n=23	
Ventricular Tachycardia	29 (23%)	36 (30%)	16 (14%)	0 (0%)	0.001
Sustained VT	5 (4%)	5 (4%)	2 (2%)	0 (0%)	0.684
Non-sustained VT	24 (19%)	34 (28%)	14 (12%)	0 (0%)	0.001
Female	n=46	n=49	n=54	n=3	
Ventricular Tachycardia	5 (11%)	6 (12%)	6 (11%)	0 (0%)	1.000
Sustained VT	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0.769
Non-sustained VT	5 (11%)	6 (12%)	6 (11%)	0 (0%)	1.000

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data. p Values per the sponsor.

3. NYHA Class III or IV

Ventricular arrhythmias occurred with equal frequency in Class III and IV NYHA patients.

Table 8.0.2c.11 Arrhythmic AEs in the 'long infusion' population^a according to NYHA Class^a.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
NYHA III	n=107	n=97	n=81	n=0	
Ventricular Tachycardia	17 (16%)	27 (28%)	8 (10%)	0 (0%)	0.003
Sustained VT	4 (4%)	4 (4%)	0 (0%)	0 (0%)	0.257
Non-sustained VT	13 (12%)	25 (26%)	8 (10%)	0 (0%)	0.005
NYHA IV	n=58	n=64	n=71	n=0	
Ventricular Tachycardia	15 (20%)	13 (20%)	14 (20%)	0 (0%)	0.394
Sustained VT	1 (2%)	1 (2%)	3 (4%)	0 (0%)	0.704
Non-sustained VT	14 (24%)	13 (20%)	12 (17%)	0 (0%)	0.394

a. Data from supplemental data table 18D at request of reviewer. Reflects trials 311, 325, and 326 data. p Values per the sponsor.

4. Etiology of CHF

Ventricular arrhythmias occurred with equal frequency regardless of the original etiology of CHF. Note the predominance of ischemic etiologies for CHF.

Table 8.0.2b.12 Ventricular tachyarrhythmias as AEs in the 'long infusion' population according to etiology of CHF^a.

Ventricular Tachycardia ^b	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Hypertensive	2/13 (15%)	2/14 (14%)	3/12 (25%)	0/3 (0%)	0.867
Ischemic	16/89 (18%)	19/88 (22%)	12/87 (14%)	0/16 (0%)	0.135
Idiopathic/Dilated	11/38 (29%)	13/40 (33%)	3/35 (9%)	0/5 (0%)	0.034

a. Data from supplemental tables provided at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes sustained and non-sustained VT.

Special Studies: Holter Monitors

Per the sponsor, 15 of the 46 clinical sites in study 704.326 performed pilot Holter monitoring on 45 subjects (15 standard care subjects, and 16 and 14 subjects receiving the 0.015 and 0.030 mg/kg/min nesiritide doses, respectively). No formal analysis of the effects of study drug on arrhythmias was performed, as subjects did not have adequate baseline Holter information to permit a comparative analysis of pre- and on-drug Holter data. The sponsor reported that 'a descriptive review of on-drug Holter information was qualitatively consistent with the investigators' reports of arrhythmic adverse events in that ventricular ectopy (PVCs, couplets, NSVT) was observed less frequently in the nesiritide subjects than in standard care subjects while the reverse trend was found for bradycardia.'

Reviewer's Conclusions Regarding Non-Bradycardic Arrhythmias

The available data support the conclusion that an adverse effect of nesiritide on the incidence of non-bradycardic arrhythmias, especially ventricular arrhythmias, is unlikely. There is, instead, a possible effect of nesiritide to decrease the incidence of non-sustained ventricular tachycardias relative to placebo. This observation is based on the nominally significant decrease in ventricular tachycardia (especially non-sustained VT) in the nesiritide group. Whether this possible effect is related to the bradycardic effects of nesiritide or to other factors is unknown.

In conclusion, an adverse association between nesiritide infusion and ventricular arrhythmias is unlikely.

8.0.2d Congestive Heart Failure

AEs

The incidence of CHF identified as an AE in the two trial populations is summarized below.

Table 8.0.2d.1 (from 11.1.3.1) CHF as an AE in the CHF trials from NDA 20-920^a.

CHF	Control n=235	Nesiritide n=505
Congestive Heart Failure	20 (9%)	48 (10%)

a. Data from NDA appendix 8.4, table 11A.

Examination of the list of AEs identified in the infusion studies (through day 14) found the following.

Table 8.0.2d.2 (from 11.1.3.2) CHF as an AE reported during the first 14 days in the 'long infusion' group^a.

CHF	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
Congestive Heart Failure	11 (6%)	18 (11%)	20 (12%)	3 (12%)	0.274

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

Examination of the list of AEs identified in the infusion studies (through 24 hours) found that the majority of the CHF reported occurred after the first 24 hours in the study.

Table 8.0.2d.3 CHF as an AE reported during the first 24 hours in the 'long infusion' group^a.

CHF	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
Congestive Heart Failure	4 (2%)	5 (3%)	6 (4%)	0 (%)

a. Data from company at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

SAEs

The occurrence of CHF as an SAE was also collected, and is summarized below. No significant differences were detected between the treatment groups.

Table 8.0.2d.4 (from 11.1.2.1) CHF as an SAE through 14 days from 'all CHF' population^a.

CHF	Control n=235	Nesiritide n=505
Congestive Heart Failure	4 (2%)	11 (2%)

a. Data from NDA appendix 8.4, table 27A.

CHF as an SAE was also collected in the 'long infusion' studies.

Table 8.0.2d.5 (from 11.1.2.2) The occurrence of CHF SAEs through 14 days in the 'long infusion' trials^a.

Serious Adverse Event	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
Congestive Heart Failure	3 (2%)	3 (2%)	7 (4%)	1 (4%)

a. Data from appendix 8.4, table 27D and from company at request of reviewer.

Discontinuations

CHF associated with discontinuation is summarized below, again showing no difference between treatment groups with small numbers of subjects.

Table 8.0.2d.6 (from 11.1.5.3.1) Discontinuations for CHF prior to day 14 in the 'all CHF' population^a.

CHF leading to discontinuation	Control n=235	Nesiritide n=505	Nominal p Value
Congestive Heart Failure	7 (3%)	14 (3%)	0.817

a. Data from NDA appendix 8.4, table 28A.

Next, the discontinuations associated with CHF in the long infusion studies are summarized.

Table 8.0.2d.7 (from 11.1.5.3.1) Discontinuations due to CHF AEs in the long infusion trials^a.

AE	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
Congestive Heart Failure	4 (2%)	5 (3%)	5 (3%)	0 (0%)	0.946

a. Data from supplemental table 28D.

Rehospitalizations for CHF

The sponsor collected information about the re-admission through 21 days in trials 704.325 and 704.326. In both, there were more re-admissions for CHF in the nesiritide groups. The data for 704.326 are shown below, and show that there was no difference in the rate of re-hospitalization for CHF between the study groups. Similar data (not shown) was found in 704.325.

Table 8.0.2d.8 (from 6.2.12.2e.7) Hospital readmission through 21 days in study 704.326^a.

Volume parameter and period of measurement	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal p Value
Subjects discharged prior to day 21				
If discharged, # of subjects readmitted by day 21	16 (16%)	8 (8%)	11 (11%)	0.181
If readmitted, primary reason for first readmittance				
CHF recurrence	8 (50%)	4 (50%)	4 (36%)	
Elective, unrelated to CHF	1 (6%)	0 (0%)	1 (9%)	
Medical condition other than CHF	6 (38%)	2 (25%)	6 (55%)	
Other	1 (6%)	2 (25%)	0 (0%)	
If readmitted, primary reason for all readmittance				
CHF recurrence	9 (53%)	4 (44%)	6 (46%)	
Elective, unrelated to CHF	1 (6%)	0 (0%)	1 (8%)	
Medical condition other than CHF	6 (35%)	2 (22%)	6 (46%)	
Other	1 (6%)	3 (33%)	0 (0%)	

a. Data from NDA volume 1.66, Appendix 1, Table 34, and electronic data sets. Includes all subjects discharged before day 21.

Deaths

Several deaths were associated with worsening congestive heart failure, as would be expected for this patient population. None were clearly associated with nesiritide administration. The narrative for these patients can be found in Appendix two.

Demographics

The small number of subjects who had CHF reported as an AE make subset analysis fruitless.

Reviewer's Conclusions Regarding CHF as an AE

The meaning of an adverse event for 'CHF' in trials enrolling only patients with CHF is hard to interpret exactly, but may reflect worsening CHF on therapy. If this is the case, one might expect to see an increase in re-hospitalizations for CHF. This was not seen.

In conclusion, the data suggest an effect of nesiritide on the incidence of 'CHF' as an adverse event is unlikely. The meaning of this AE in the context of the larger trial is unclear, and the data are inadequate to fully resolve this issue. This absence of an effect on 'CHF' as an AE cannot be taken as an indicator of efficacy for the overall trials.

8.0.2e Decreased Pulmonary Pressure

AEs

Examination of the list of AEs identified in the infusion studies (through day 14) found the following incidence of 'decreased pulmonary pressure' as an AE.

Table 8.0.2e.1 (from 11.1.3.2) Decreased pulmonary pressure as an AE in the first 14 days in the nesiritide infusion trials from NDA 20-920^a.

Decreased pulmonary pressure	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
Decreased Pulmonary Pressures	0 (0%)	0 (0%)	3 (2%)	5 (19%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

The sponsor also summarized the data for the first 24 hours of the long infusion trials. Overall, similar trends in the incidence of AEs were seen in both sets, showing that most of the decreased pulmonary pressure occurred during the first 24 hours of nesiritide administration.

Table 8.0.2e.2 Decreased pulmonary pressure as an AE during the first 24 hours in the 'long infusion' trials^a.

Decreased Pulmonary Pressure	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
Decreased Pulmonary Pressures	0 (0%)	0 (0%)	3 (2%)	5 (19%)

a. Data from appendix 8.4, table 12C and from company at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

SAEs

No SAEs were identified as 'decreased pulmonary pressure.'

Discontinuations

Table 8.0.2e.3 (from 11.1.5.3.1) Discontinuations prior to day 14 decreased pulmonary pressure in the 'all CHF' population^a.

	Control n=235	Nesiritide n=505	Nominal p Value ^a
Decreased Pulmonary Pressure	0 (0%)	5 (1%)	0.185

a. Data from NDA appendix 8.4, table 28A. p Value per sponsor.

Next, the discontinuations associated with AEs in the long infusion studies are summarized. The only discontinuations occurred in the nesiritide group.

Table 8.0.2e.4 (from 11.1.5.3.1) Discontinuations due to decreased pulmonary pressure in the 'long infusion' trials^a.

	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value ^b
Decreased Pulmonary Pressure	0 (0%)	0 (0%)	2 (1%)	3 (12%)	<0.001

a. Data from supplemental table 28D, with p Value per sponsor.

Deaths

There were no deaths associated with decreased pulmonary pressures.

Demographics

The small number of subjects who had decreased pulmonary pressure reported as an AE make subset analysis fruitless.

Reviewer's Conclusions Regarding Decreased Pulmonary Pressures

In the context of the other data showing an association between nesiritide and significant effects on systemic blood pressure, the association with decreased pulmonary pressures as AEs can be seen as an extension of the physiological effects of nesiritide. Nonetheless, this AE did result in a significant number of discontinuations, particularly in the highest dose nesiritide group.

In conclusion, there is a definite association between nesiritide administration and the development of clinically significant decreases in pulmonary pressure.

8.0.3 Adverse Events in the 'Body as a Whole' System

The following adverse events within the 'body as a whole' system will be examined: headache. Sepsis will be examined as part of the Hemic and lymphatic system review. Adverse events analyzed but not discussed further include injection site reactions and fever.

8.0.3a Headache

AEs

The occurrence of headaches reported as AEs in the 'all CHF' and 'long infusion' trials is shown below. The reported incidence of headache as an AE was similar in the treatment groups.

Table 8.0.3a.1 (from 11.1.3.1) Headache as an AE in the 'all CHF' trials from NDA 20-920^a.

Headache	Control n=235	Nesiritide n=505
Headache	43 (18%)	80 (16%)

a. Data from NDA appendix 8.4, table 11A.

Incidence of headache in the infusion studies (through day 14) is summarized below.

Table 8.0.3a.2 (from 11.1.3.2) Headache as an AE in the first 14 days in the 'long infusion' trials^a.

Headache	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
Headache	34 (20%)	38 (22%)	22 (13%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs and Deaths

No SAEs or deaths relating to headache were identified in the 'all CHF' or the 'long infusion' trials populations.

Reviewer's Conclusions Regarding Headaches

The data do not support an association between nesiritide administration and an increased incidence of headaches.

8.0.4 Adverse Events in the Digestive System

The following adverse event within the digestive system will be examined: abnormal liver function tests (LFTs), and nausea.

8.0.4a Abnormal Liver Function

This section summarizes the occurrence of AEs related to abnormal LFTs in the NDA.

AEs and SAEs

Table 8.0.4a.1 (from 11.1.3.1) Liver function AEs in the CHF trials from NDA 20-920^a.

Adverse Event	Control n=235	Nesiritide n=505
Abnormal LFTs	2 (1%)	1 (0%)
Jaundice	0 (0%)	1 (1.0%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.4a.2 Liver function AEs in the first 14 days in the nesiritide infusion trials from NDA 20-920^a.

Liver AEs	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
Abnormal LFTs	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Jaundice	0 (0%)	0 (0%)	0 (0%)	1 (4%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

No SAEs were identified referable to abnormal liver function in 'all CHF' or 'long infusion' study populations.

Discontinuations and Deaths With Abnormal LFTs

There were no discontinuations and no deaths associated with abnormal LFTs identified.

Special Studies: Line Listing of Abnormal LFTs

A review of those patients who had abnormal post-baseline AST or ALT, with a normal baseline value, revealed the following patients with marked abnormalities.

Table 8.0.4a.3 Patients with marked F/U LFT abnormalities after a normal baseline, in NDA 20-920^a.

Study/ Treatment	Patient #	Abnormal AST or ALT	Day of abnormal measurement	Notes, F/U
Protocol 326/ Standard Care	555001	AST = 738 ALT = 1346	9	Last study value
Protocol 311/ Nesiritide 0.030	377005	AST = 223	3	Resolved, last AST 22
Protocol 326/ Nesiritide 0.030	572001	AST = 1116	8	Last study value

a. Data from ISS data tables, listing 8, 'Abnormal Post-baseline laboratory values.'

Special Studies: Measured Changes in Lab Values

There was not significant difference in the mean changes from baseline for ALT or AST (see tables 11.1.4.2.1 and 11.1.4.2.2 for details).

In the long infusion trials, there was an unexpected pattern of more patients with increased ASTs in the low-dose nesiritide dose relative to control, but a lower incidence in the high-dose group, relative to the control group. A similar pattern was not seen for ALT. In the 'all CHF trials' population, no differences between the control and nesiritide groups were detected.

Table 8.0.4a.4 (from 11.1.4.3.1a.19) Observed rate of increased ASTs in the 'long infusion' trials^a.

Time of AST above normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	38 (23%)	34 (21%)	21 (13%)	7 (27%)	0.152
Last Available on or before Day 2	5 (16%)	7 (25%)	0 (0%)	0 (0%)	0.003
Last Available on or before Day 5	16 (17%)	23 (24%)	8 (8%)	0 (0%)	0.058
Last Available	23 (20%)	22 (19%)	19 (15%)	2 (8%)	0.814

a. Data from NDA vol. 79, table 44D3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

Reviewer's Conclusions Regarding LFT Abnormalities

The available data do not suggest an adverse effect of nesiritide on the liver, as reflected by changes in LFTs or the incidence of clinically significant liver disease. For clinically significant liver disease, the small number of subjects exposed to nesiritide limits this conclusion.

In conclusion, the data support the conclusion that nesiritide is unlikely to have an adverse effect on the liver, as detected by changes in AST and ALT. The data are inadequate to assess the incidence of severe hepatic injury.

8.0.4b Nausea

The incidences of nausea as an adverse event in the 'all CHF' and 'long infusion' trials are shown below.

Table 8.0.4b.1 (from 11.1.3.1) Nausea as an AE in the 'all CHF' group^a.

Adverse Event	Control n=235	Nesiritide n=505	Nominal p Value
Gastrointestinal System	68 (29%)	168 (33%)	
Nausea	29 (12%)	90 (18%)	0.067
Vomiting	15 (6%)	44 (9%)	0.310

a. Data from NDA appendix 8.4, table 11A.

6.3.12 Efficacy Outcomes

6.3.12.1 Patient Demographics & Baseline Characteristics

The next set of tables summarizes the baseline characteristics of the subjects enrolled in the trial.

Table 6.3.12.1.1 Demographics of study 704.326^a.

Demographic	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Gender				
Female	29 (28%)	36 (35%)	33 (33%)	0.610
Male	73 (72%)	67 (65%)	67 (67%)	
Race				0.580
White	69 (68%)	61 (59%)	71 (71%)	
Black	19 (19%)	28 (27%)	20 (20%)	
Asian	2 (2%)	1 (1%)	0 (0%)	
Hispanic	12 (12%)	11 (11%)	8 (8%)	
Other	0 (0%)	2 (2%)	1 (1%)	
Age (Mean±SD)	63±14	63±14	65±12	0.453
NYHA Class (prior to hospitalization)				0.647
I	0 (0%)	0 (0%)	1 (1%)	
II	6 (6%)	6 (6%)	11 (11%)	
III	61 (60%)	57 (55%)	52 (52%)	
IV	35 (34%)	40 (39%)	36 (36%)	

a. Data from NDA volume 66, table 2. p Values per the sponsor.

Table 6.3.12.1.2 Further demographics in study 704.326^a.

Demographic	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value ^b
Etiology of CHF				0.563
Ischemic	57 (56%)	53 (51%)	54 (54%)	
Idiopathic	19 (19%)	27 (26%)	18 (18%)	
Hypertensive	11 (11%)	12 (12%)	9 (9%)	
Alcohol-induced	2 (2%)	2 (2%)	3 (3%)	
Other and Unknown	13 (13%)	9 (9%)	16 (16%)	
Etiology for Current Decompensation				0.133
Medical Noncompliance	16 (16%)	27 (26%)	17 (17%)	
Dietary Noncompliance	17 (17%)	17 (17%)	15 (15%)	
Arrhythmia	13 (13%)	7 (7%)	11 (11%)	
Hypertensive Crisis	1 (1%)	3 (3%)	2 (2%)	
Intercurrent Infection	9 (9%)	6 (6%)	5 (5%)	
Recent Cardiac Surgery	2 (2%)	2 (3%)	2 (2%)	
Recent Non-Cardiac Surgery	1 (1%)	3 (2%)	4 (3%)	
Recent MI	1 (1%)	3 (2%)	3 (2%)	
Other	21 (21%)	18 (17%)	18 (18%)	
Unknown	44 (43%)	43 (42%)	45 (45%)	
				0.339
				0.704
				0.546
				1.000
				0.648
				0.639
				0.853
				0.896

a. Data from sponsor, for NDA volume 66, supplemental table 4.

b. p Value using appropriate statistical method per sponsor.

In data not shown, the sponsor analyzed the three study groups for significant interactions between the presence or absence of other significant medical diseases. No such interaction was found for the following medical conditions: hypertension; hx of coronary artery disease; hx of prior MI; hx of CABG or angioplasty; hx of valvular heart surgery; hx of cardiac transplantation; hx of sinus node disease or atrial fibrillation/ flutter; PVCs or non-sustained VT. There was also no interaction with a hx of diabetes, chronic renal insufficiency, liver disease, lung disease, bleeding disorder, anemia, or active malignancy. Subjects in the high-dose nesiritide group were nominally significantly more likely to have had sudden death (14%) when compared with the other two groups (8 % in control, 2% in nesiritide 0.015). They were also more likely to have had sustained VT (15%) compared with 6 and 3% in the other two study groups (nominal p=0.005). There was no significant difference in the rate of VT in the past 7 days before admission, however.

8.0.5a Dizziness, Nervousness and Confusion
AEs and SAEs

Table 8.0.5a.1 (from 11.1.3.1) Nervous system AEs in the CHF trials from NDA 20-920^a.

Nervous system AEs	Control n=235	Nesiritide n=505	Nominal p Value
Nervous System	53 (23%)	161 (32%)	
Dizziness	16 (7%)	43 (9%)	0.469
Anxiety	11 (5%)	28 (6%)	0.725
Confusion	5 (2%)	33 (7%)	0.011
Nervousness	3 (1%)	23 (5%)	0.030
Somnolence	4 (2%)	12 (2%)	0.787

a. Data from NDA appendix 8.4, table 11A. p Value per the sponsor.

The same AEs were examined in the long infusion studies.

Table 8.0.5a.2 (from 11.1.3.2) Nervous system AEs in the first 14 days in the 'long infusion' group^a.

Adverse Event	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
Nervous System	40 (23%)	67 (40%)	54 (32%)	7 (27%)	0.011
Insomnia	18 (10%)	25 (15%)	22 (13%)	1 (4%)	0.371
Confusion	5 (3%)	16 (9%)	13 (8%)	1 (4%)	0.059
Dizziness	9 (5%)	17 (10%)	8 (5%)	3 (12%)	0.125
Nervousness	3 (2%)	10 (6%)	5 (3%)	0 (0%)	0.189
Somnolence	3 (2%)	3 (2%)	6 (4%)	0 (0%)	0.663

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs

No SAEs referable to confusion, insomnia, nervousness, or dizziness were reported.

Discontinuations

Discontinuations for dizziness were also considered in the hypotension AE section above.

Table 8.0.5a.3 (from 11.1.5.3.1) Discontinuations prior to day 14 for dizziness in the 'CHF trials' population^a.

	Control n=235	Nesiritide n=505	Nominal p Value
Dizziness	0 (0%)	6 (1%)	0.184

a. Data from NDA appendix 8.4, table 28A. p Value per sponsor.

Next, the discontinuations associated with AEs in the long infusion studies are summarized.

Table 8.0.5a.4 (from 11.1.5.3.1) Discontinuations due to nervous system AEs in the long infusion trials^a.

AE	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
Nervous System	0 (0%)	1 (1%)	3 (2%)	2 (8%)	0.010
Dizziness	0 (0%)	0 (0%)	1 (1%)	2 (8%)	0.002
Nervousness	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Stupor	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Vertigo	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.677

a. Data from supplemental table 28D, with p Value per sponsor.

Deaths

There were no deaths attributable to any of these adverse events.

Table 8.0.4b.2 (from 11.1.3.2) Nausea as an AE in the first 14 days in the 'long infusion' trials^a.

Adverse Event	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
Digestive System	52 (30%)	67 (40%)	60 (36%)	7 (27%)	
Nausea	25 (14%)	36 (21%)	32 (19%)	4 (15%)	0.398
Vomiting	13 (8%)	12 (7%)	17 (10%)	3 (12%)	0.614

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs, Discontinuations, or Deaths

No SAEs, discontinuations, or deaths were associated with nausea as an AE.

Demographics

1. Gender

A lower percentage of the control females reported nausea, resulting in a nominally significant difference relative to the nesiritide group. At the 0.015 and 0.030 dose range, nausea was more common in females relative to males.

Table 8.0.4b.3 (from 8.0.2c.10) Nausea as an AEs in the 'long infusion' population^a according to gender.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Male	n=127	n=120	n=113	n=23	
Nausea	22 (17%)	24 (20%)	15 (13%)	4 (17%)	0.576
Female	n=46	n=49	n=54	n=3	
Nausea	3 (7%)	12 (24%)	17 (31%)	0 (0%)	0.010

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data. p Values per the sponsor.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

2. Age

There was no difference in the incidence of nausea in the <65 and >65 year old age groups.

3. NYHA Class III or IV

There was no difference in the incidence of nausea in NYHA class III or IV groups.

4. Drug Interactions

Small numbers of available patients make it difficult to assess these interactions.

Reviewer's Conclusions Regarding Nausea

Nausea was a commonly reported adverse event in both the control and the nesiritide groups. There was a trend towards more reported nausea in the nesiritide group, for both the 'all CHF' and 'long infusion' populations (especially the 'all CHF' group). With regard to demographics, females had a slightly higher incidence of nausea in the nesiritide groups relative to males.

In conclusion, the data suggest a possible associate between nesiritide administration and a higher incidence of nausea.

8.0.5 Adverse Events in the Nervous System

AEs

The following adverse events within the nervous system will be examined: dizziness, nervousness, and confusion.

Reviewer's Conclusions Regarding Confusion

There was an association between nesiritide use and confusion that tended to be more commonly reported in patients >65 years old.

There was also a nominally significant increase in 'nervousness' in the nesiritide group in the 'all CHF' trial population. The database is too small to draw final conclusions about the clinical significance of the association.

No difference was detected with regard to the other nervous system AEs examined.

In conclusion, the data suggest a possible associate between nesiritide administration and a higher incidence of confusion. The data are inadequate to assess a relationship between nesiritide and nervousness.

8.0.6 Adverse Events in the Metabolic System

The following adverse event within the metabolic system will be examined: hypo- and hyperkalemia, hyperglycemia, hyponatremia, hyper-magnesemia, and changes in serum total protein and albumin. Elevated BUN and Creatinine (Cr) will be examined in the Urogenital System review.

8.0.6a Hyper- and Hypo-kalemia

AEs

The first two tables summarize the changes in potassium reported as AEs in the 'all CHF' and 'long infusion' populations. No significant differences are apparent.

Table 8.0.6a.1 (from 11.1.3.1) Changes in K⁺ as AEs in the 'all CHF' population^a.

K ⁺	Control n=235	Nesiritide n=505
Metabolic & Nutritional System	42 (18%)	83 (16%)
Hypokalemia	10 (4%)	20 (4%)
Hyperkalemia	6 (3%)	12 (2%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.6a.2 (from 11.1.3.2) Changes in K⁺ as AEs in the first 14 days in 'long infusion' population^a.

K ⁺	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
Hypokalemia	9 (5%)	7 (4%)	5 (3%)	3 (12%)	0.216
Hyperkalemia	5 (3%)	6 (4%)	4 (2%)	0 (0%)	0.931

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs

Hyperkalemia as an SAE was rare in the database.

Table 8.0.6a.3 (from 11.1.2.1) Hyperkalemia as an SAE through 14 days in the 'all CHF' group^a.

Hyperkalemia as SAE	Control n=235	Nesiritide n=505
Hyperkalemia	1 (<1.0%)	0 (0%)

a. Data from NDA appendix 8.4, table 27A.

Table 8.0.6a.4 (from 11.1.2.2) Hyperkalemia as an SAEs through 14 days in the 'long infusion' trials^a.

Hyperkalemic SAEs	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
Hyperkalemia	1 (1%)	0 (0%)	0 (0%)	0 (0%)

a. Data from appendix 8.4, table 27D and from company at request of reviewer.

Discontinuations and Deaths

There were no discontinuations or deaths directly attributable to Na⁺ or K⁺ disturbances reported.

Special Studies: Measured Changes in Lab Values

There was a tendency towards a higher mean K⁺ at day two in both the 'all CHF' and the 'long infusion' groups.

Table 8.0.6a.5 (from 11.1.4.2.1) Mean changes in K⁺ from baseline for all subjects in CHF trials^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from: Baseline Day 5	Change from Baseline Day 5
Potassium	-0.1±0.65	-0.0±0.59	0.0±0.69	0.1±0.68

a. Data from NDA volumes 79-80, starting with table 31A1.

Table 8.0.6a.6 (from 11.1.4.2.3.1) Mean changes in serum K⁺ from baseline for the 'long infusion' trials^a.

Lab Test, Change from Baseline to Day 2	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=24
Potassium	-0.2±0.65	-0.0±0.61	0.0±0.63	+0.2±0.41

a. Data from NDA volumes 79-80, starting with table 31A1 and from supplemental data sets submitted at reviewer's request.

Sponsors Comments on Changes in Potassium

In all populations, on day 2, there is a tendency for serum potassium to be decreased from baseline more in the control group than in the nesiritide group. By the last available time point, mean serum potassium tends to have increased slightly over baseline in the nesiritide group compared to the control group. For example, in the Long Infusion Studies, in the control, 0.015-, and 0.03-µg/kg/min nesiritide groups, the change in mean serum potassium from baseline at day 2 is -0.2, -0.0, and 0.0 mEq/L, respectively (p = 0.011) and at the last available timepoint is 0.0, 0.1, and 0.2 mEq/L, respectively (p = 0.020). This moderate potassium-sparing effect may be due to the reduction in aldosterone which accompanies nesiritide administration. There was not an increase in the incidence of the adverse event of hyperkalemia in the nesiritide groups compared to control, even for subjects on ACE inhibitors.

Reviewer's Conclusions Regarding Changes in Serum Potassium

There was no evidence to suggest a clinically adverse effect of nesiritide on serum potassium concentrations, or on the occurrence of adverse events related to serum potassium. At day two, patients who got nesiritide had a slightly higher (0.2 meq/dl) mean change in serum K⁺. Whether this reflects an interaction of nesiritide to decrease aldosterone levels or aldosterone-receptor interaction is not known.

In conclusion, an association between nesiritide administration and clinically relevant changes in serum potassium is unlikely.

8.0.6b Hyponatremia

AEs

The first two tables summarize the incidence of AEs related to serum Na⁺ in the 'all CHF' and 'long infusion' populations. No difference in the incidence of hyponatremia among the treatment groups was detected.

Table 8.0.6b.1 (from 11.1.3.1) Hyponatremia as an AEs in the 'all CHF' population^a.

Adverse Event	Control n=235	Nesiritide n=505
Hyponatremia	6 (3%)	6 (1%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.6b.2 (from 11.1.3.2) Hyponatremia as an AEs in the first 14 days in the 'long infusion' population^a.

Adverse Event	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
Hyponatremia	4 (2%)	0 (0%)	5 (3%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs

No SAEs were identified relating to serum sodium concentrations.

Discontinuations and Deaths

There were no discontinuations or deaths directly attributable to changes in serum Na⁺ reported.

Special Studies: Measured Changes in Lab Values

No effect of nesiritide on changes in mean serum Na⁺ were detected in the 'all CHF' population shown below

Table 8.0.6b.3 (from 11.1.4.2.1) Mean changes in serum Na⁺ from baseline for 'all CHF' group^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Sodium (meq/l)	-0.8±3.3	-1.1±3.2	-1.2±3.8	-1.0±3.7

a. Data from NDA volumes 79-80, starting with table 31A1.

In the 'long infusion' population, there was a trend towards a dose-dependent decrease in mean serum Na⁺ in the nesiritide groups. In data not shown, equal numbers of subjects developed abnormally low serum Na⁺ in this group after starting with normal serum Na⁺.

Table 8.0.6b.4 (from 11.1.4.2.3.1) Mean changes in serum Na⁺ from baseline for all subjects in 'long infusion' groups^a.

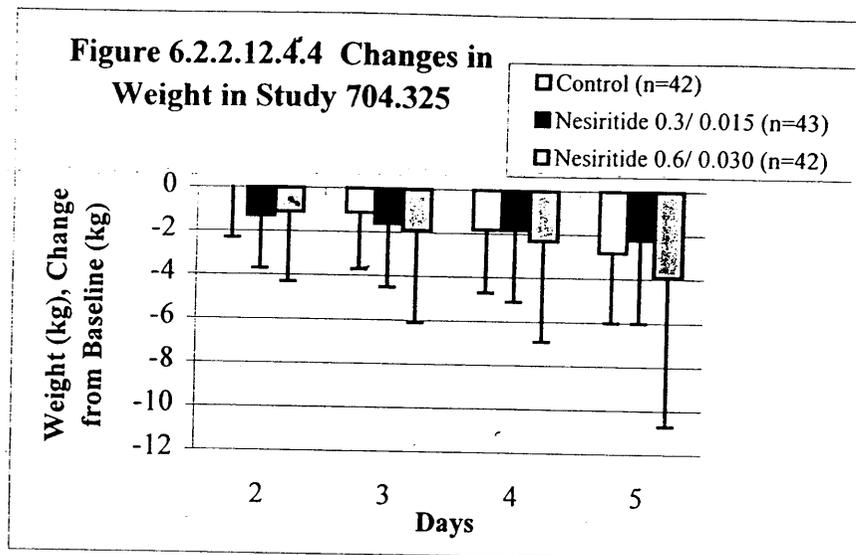
Lab Test, Change from Baseline to Day 2	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=24
Sodium (meq/l)	-0.4±3.3	-0.8±3.0	-1.2±3.3	-1.8±5.3

a. Data from NDA volumes 79-80, starting with table 31A1 and from supplemental data sets submitted at reviewer's request.

Special Studies: Effect on Body Weight and Urine Output

The sponsor measured the fluid balance over the first 24 hours of study drug infusion in study 704.325. If the subjects who received diuretics during the first 6 hours were removed, there was no significant difference in overall volume status at the end of 24 hours between control and nesiritide groups (see NDA volume 1.59, Appendix 1, Tables 57B for details).

The sponsor also followed the weights of the subjects during the first 5 days of hospitalization in study 704.326. 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).



Sponsors Comments on Changes in Sodium

Since nesiritide been shown to have modest natriuretic properties in clinical studies and is also known to reduce aldosterone levels, it would be expected that nesiritide therapy might result in some alterations in serum electrolytes. In the three long infusion studies, there was a suggestion of a dose-related reduction in serum sodium during nesiritide infusion. In the control, 0.015-, and 0.03- $\mu\text{g}/\text{kg}/\text{min}$ nesiritide groups, the change in mean serum sodium from baseline to day 2 is -0.4 , -0.8 , and -1.2 mEq/L, respectively ($p = 0.097$). However, equal numbers of control and nesiritide -treated patients developed hyponatremia after starting with normal baseline serum sodium. Thus, nesiritide ‘may have modest natriuretic properties, but this does not appear to result in clinically significant hyponatremia.’

Reviewer’s Conclusions Regarding Changes in Serum Na^+

The dose-dependent decrease in mean serum Na^+ in the long infusion population suggests an effect of nesiritide on water handling by the kidney, not on sodium as suggested by the sponsor. Decreased serum Na^+ in this population means that, over a 2 day period, more water was retained in the intravascular space in the nesiritide groups. How this possible effect of nesiritide interacts with the effects of nesiritide on increasing intravascular permeability to proteins and other small molecules (see below) is unknown. This anti-diuretic property of nesiritide is worrisome in a patient population with decompensated CHF, although no clinically significant AEs were attributable to this change. One can also draw some reassurance from the lack of an increase in re-admissions for CHF in the nesiritide group (see above). If the clinician relies on changes in body weight to guide his/her diuretic use, however, this fluid in the interstitial space will not be available for excretion, and may make place the patients at increased risk of renal injury to intravascular volume contraction. In conclusion, then, there is a possible effect of nesiritide to decrease water excretion acutely, leading to decreases in serum Na^+ .

8.0.6c Hyperglycemia/ Hypoglycemia

AEs

The sponsor summarized the incidence of hyper- and hypoglycemia in the 'all CHF' and 'long infusion' groups. There was a trend towards a higher incidence of hyperglycemia in both of the nesiritide groups, and a trend towards a higher incidence of hypoglycemia in the 'long infusion' group.

Table 8.0.6c.1 (from 11.1.3.1) Hyperglycemic/ hypoglycemia AEs reported in the 'all CHF' group^a.

Adverse Event	Control n=235	Nesiritide n=505	Nominal p Value
Metabolic & Nutritional System	42 (18%)	83 (16%)	0.673
Hyperglycemia	0 (0%)	10 (2%)	0.036
Hypoglycemia	4 (2%)	8 (2%)	1.000

a. Data from NDA appendix 8.4, table 11A. p Value per the sponsor.

Table 8.0.6c.2 (from 11.1.3.2) Hyperglycemic/ hypoglycemia AEs during the first 14 days in the 'long infusion' group^a.

Adverse Event	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
Metabolic & Nutritional	34 (20%)	28 (17%)	34 (20%)	5 (19%)	0.813
Hyperglycemia	0 (0%)	1 (1%)	5 (3%)	0 (0%)	0.069
Hypoglycemia	2 (1%)	1 (1%)	5 (3%)	2 (8%)	0.051

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data. p Value per sponsor.

SAEs

There were no recorded SAEs related to hypoglycemia. One SAE for hyperglycemia was reported, in the nesiritide 0.030 µg/kg/min group.

Table 8.0.6c.3 (from 11.1.2.1) Hyperglycemic SAEs through 14 days in the 'all CHF' group^a.

Serious Adverse Event	Control n=235	Nesiritide n=505
Hyperglycemia	0 (0%)	1 (<1.0%)

a. Data from NDA appendix 8.4, table 27A.

Examination of the list of SAEs identified in the infusion studies found the following relevant differences.

Table 8.0.6c.4 (from 11.1.2.2) Hyperglycemic SAEs through 14 days in the 'long infusion' trials^a.

Serious Adverse Event	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
Hyperglycemia	0 (0%)	1 (1%)	0 (0%)	0 (0%)

a. Data from appendix 8.4, table 27C and from company at request of reviewer.

Discontinuations and Deaths

There were no discontinuations or deaths due to glucose abnormalities reported.

Special Studies: Measured Changes in Lab Values

The first two tables summarize the mean changes in serum glucose.

Table 8.0.6c.5 (from 11.1.4.2.1) Mean changes in serum glucose from baseline for 'all CHF' group^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Glucose	-9.0±55	-2.7±59	-12.8±55	-8.0±62

a. Data from NDA volumes 79-80, starting with table 31A1.

The next table summarizes the data for the ‘long infusion’ trial population at the end of 2 days. There is a trend towards a dose-dependent increase in mean serum glucose in the nesiritide group.

Table 8.0.6c.6 (from 11.1.4.2.3.1) Mean changes in serum glucose from baseline for subjects in ‘long infusion’ groups^a.

Lab Test, Change from Baseline to Day 2	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=24
Glucose	-6.6±56	+4.9±42	+18.8±79	+26.3±40

a. Data from NDA volumes 79-80, starting with table 31A1 and from supplemental data sets submitted at reviewer’s request.

Special Studies: Lab Shift Analyses

In both the CHF trial as a whole, and in the long infusion studies, a substantial % of patients were hyperglycemic at baseline (54% of both groups in the ‘all CHF’ population). At all timepoints measured, however, there were a small number of patients who were hypoglycemic, with a higher incidence in the nesiritide groups. No effect of nesiritide on the development of hyperglycemia was detected using this same analytic method.

Table 8.0.6c.7 (from 11.1.4.3.1a.3) Observed rate of decreased glucose concentrations in the ‘all CHF’ trials^a.

Time of Glucose Below Normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	4 (2%)	14 (3%)	0.666
Last Available on or before Day 2	1 (1%)	4 (2%)	0.186
Last Available on or before Day 5	2 (1%)	14 (4%)	0.239
Last Available	4 (2%)	22 (5%)	0.299

a. Data from NDA vol. 79, table 35A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was a similar trend in the infusion studies, again with very few patients.

Table 8.0.6c.8 (from 11.1.4.3.1a.4) Observed rate of decreased glucose values in the long infusion trials^a.

Time of Glucose Below Normal	Control n=173	Nesiritide n=0.015 n=169	Nesiritide n=0.030 n=167	Nesiritide n=0.060 n=26	Nominal p Value ^a
Baseline	4 (2%)	7 (4%)	6 (4%)	1 (4%)	0.805
Last Available on or before Day 2	0 (0%)	2 (6%)	1 (3%)	0 (0%)	0.492
Last Available on or before Day 5	2 (2%)	6 (5%)	7 (6%)	0 (0%)	0.712
Last Available	3 (2%)	6 (4%)	9 (6%)	2 (8%)	0.736

a. Data from NDA vol. 79, table 35D3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

Reviewer’s Conclusions Regarding Changes in Serum Glucose

The data presented above are difficult to interpret. Depending on the analysis, there seems to be an effect of nesiritide on ‘glucose handling’ which can result in either an increase in hyper- or hypo-glycemia. The small numbers, and the absence of a putative mechanism for such an effect, make this conclusion less certain. In addition, aside from one SAE reported for hyperglycemia, there were no detected adverse clinical effects of these possible changes in serum glucose.

In conclusion, there is a possible effect of nesiritide on glucose handling in a subset of patients. No clinically significant effects of nesiritide on serum glucose were detected.

8.0.6d Hypermagnesemia

AEs and SAEs

Adverse events related to serum magnesium levels were rare in the database, as summarized below.

Table 8.0.6d.1 (from 11.1.3.1) Changes in serum Mg²⁺ reported as AEs in the 'all CHF' group^a.

Adverse Event	Control n=235	Nesiritide n=505
Metabolic & Nutritional System	42 (18%)	83 (16%)
Hypomagnesemia	4 (2%)	4 (1%)
Hypermagnesemia	1 (1.0%)	0 (0%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.6d.2 (from 11.1.3.2) Changes in serum Mg²⁺ reported as AEs in the first 14 days in the 'long infusion' group^a.

Adverse Event	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
Metabolic & Nutritional	34 (20%)	28 (17%)	34 (20%)	5 (19%)
Hypomagnesemia	4 (2%)	3 (2%)	1 (0.5%)	0 (0%)
Hypermagnesemia	1 (<1.0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

No SAEs related to serum magnesium were reported.

Discontinuations and Deaths

There were no discontinuations directly attributable to changes in serum magnesium reported.

Special Studies: Measured Changes in Lab Values

The first table summarizes the measured changes in Mg²⁺ from baseline at days 2 and 5.

Table 8.0.6d.3 (from 11.1.4.2.1) Mean changes in serum Mg²⁺ from baseline for all subjects in 'all CHF' trials^a.

Change in Mg ²⁺	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Mg ²⁺ (meq/dl)	0.0±0.4	0.0±0.3	0.0±0.3	0.0±0.3

a. Data from NDA volumes 79-80, starting with table 31A1.

Special Studies: Shift Analysis of Lab Abnormalities

In both the 'all CHF' the 'long infusion' populations there were a nominally significant association between nesiritide administration and increased magnesium levels. Note that this small difference persisted to the last available labs in the 'all CHF' studies.

Table 8.0.6d.4 (from 11.1.4.3.1a.20) Observed rate of increased serum Mg²⁺ concentrations in the 'all CHF' trials^a.

Time of Mg ²⁺ Above Normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	19 (9%)	53 (11%)	0.367
Last Available on or before Day 2	5 (6%)	16 (10%)	0.473
Last Available on or before Day 5	13 (8%)	40 (11%)	0.046
Last Available	14 (8%)	53 (13%)	0.060

a. Data from NDA vol. 79, table 48A3 p Value per the sponsor for the entire frequency of high, normal and low lab values.

Table 8.0.6d.5 (from 11.1.4.3.1a.21) Observed rate of increased serum Mg²⁺ levels in 'long infusion' trials^a.

Time of Mg ²⁺ above normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	17 (11%)	20 (13%)	19 (13%)	2 (8%)	0.459
Last Available on or before Day 2	3 (9%)	4 (15%)	6 (21%)	2 (18%)	0.333
Last Available on or before Day 5	10 (10%)	13 (13%)	20 (20%)	2 (10%)	0.008
Last Available	11 (9%)	18 (15%)	22 (18%)	1 (5%)	0.021

a. Data from NDA vol. 79, table 48C3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

There was, however, no clear trend towards the development of elevated Mg²⁺ levels in patients who started with normal levels.

Table 8.0.6d.6 (from 11.1.4.3.1a.22) Patients with increased Mg²⁺ after normal baseline in 'all CHF' trials^{a,b}.

Time of Increased Mg ²⁺	Control n=235	Nesiritide n=505
Last Available on or before Day 2	3 (4%)	8 (5%)
Last Available on or before Day 5	8 (5%)	16 (5%)
Last Available	16 (6%)	23 (6%)

a. Data from NDA vol. 79, table 48B4.

b. Percentages are calculated using all patients with available baseline, regardless of value.

Table 8.0.6d.7 (from 11.1.4.3.1a.23) Observed incidence of increased Mg²⁺ values after normal baseline value in 'long infusion' trials^{a,b}.

Time of Increased Mg ²⁺	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	2 (6%)	3 (11%)	2 (8%)	1 (9%)
Last Available on or before Day 5	6 (6%)	5 (5%)	7 (7%)	1 (5%)
Last Available	7 (6%)	8 (7%)	8 (7%)	0 (0%)

a. Data from supplemental table 48D4.

b. Percentages are calculated using all patients with available baseline, regardless of value.

Reviewer's Conclusions

There was an association between nesiritide administration and the incidence of hyper-magnesemia in both populations reviewed, but this trend was not clearly dose-dependent in the 'long infusion' group. In addition, there was no trend towards elevated Mg²⁺ for those individuals who started with normal serum Mg²⁺ levels, and no change in overall mean serum Mg²⁺ levels.

One interpretation of this finding would be that nesiritide reduces blood flow to the kidney, which in turn reduces the amount of solute delivered to the thick ascending limb (where Mg²⁺ is reabsorbed in regulated fashion). This would lead to increased Mg²⁺ reclamation by the kidney, increasing serum Mg²⁺ levels. Interpretation of these data is also made more difficult by the heavy use of lasix in these trials, which promotes an increased Mg²⁺ excretion by inhibiting the thick ascending limb.

In conclusion, there is the data are inadequate to assess a possible association between nesiritide use and increased serum Mg²⁺.

8.0.6e Changes in Serum Total Protein and Albumin

AEs

The AEs related to changes in serum protein reflect the effects of this loss of oncotic pressure: edema.

Table 8.0.6e.1 (from 11.1.3.1) Changes in serum protein, reported as AEs in the 'all CHF' group^a.

	Control n=235	Nesiritide n=505
Metabolic & Nutritional System	42 (18%)	83 (16%)
Edema	0 (0%)	1 (<1.0%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.6e.2 (from 11.1.3.2) Changes in serum proteins reported as AEs in the first 14 days in the 'long infusion' studies^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
Metabolic & Nutritional	34 (20%)	28 (17%)	34 (20%)	5 (19%)
Peripheral Edema	1 (<1.0%)	2 (1%)	1 (<1.0%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs

No SAEs referable to changes in serum albumin/ total protein, including edema, were reported.

Discontinuations and Deaths

There were no discontinuations or deaths due to changes in serum proteins reported, including edema.

Special Studies: Changes in Measured Lab Values

There was no significant effect of nesiritide on the mean changes in serum total protein or albumin.

Table 8.0.6e.3 (from 11.1.4.2.1) Mean changes in serum chemistries from baseline for the 'all CHF' trials^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Total Protein	-0.3±0.8	-0.3±0.5	-0.2±0.7	-0.3±0.6
Albumin	-0.2±0.3	-0.3±0.3	-0.1±0.3	-0.2±0.4

a. Data from NDA volumes 79-80, starting with table 31A1.

Special Studies: Shift Analysis of Lab Measurements

1. Total Protein

In both the 'all CHF' trials there were a higher % of the nesiritide group that developed a low total protein level. This abnormality was most prominent at days 2 and 5. There was also a higher % of patients with low total proteins at the start of the trial in the nesiritide group.

Table 8.0.6e.4 (from 11.1.4.3.1a.14) Rate of decreased total protein concentrations in the 'all CHF' trials^a.

Time of Total Protein Below Normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	38 (17%)	102 (21%)	0.062
Last Available on or before Day 2	11 (14%)	62 (34%)	0.001
Last Available on or before Day 5	34 (23%)	129 (37%)	0.005
Last Available	32 (19%)	90 (22%)	0.316

a. Data from NDA vol. 79, table 39A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was a similar trend in the 'long infusion' studies, where the trend towards decreased total proteins persisted throughout the measurements. This was most prominent at day two, when the majority of patients were still on study drug.

Table 8.0.6e.5 (from 11.1.4.3.1a.15) Rate of decreased total protein values in the 'long infusion' trials^a.

Time of Total Protein Below Normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	32 (20%)	43 (27%)	40 (26%)	3 (12%)	0.135
Last Available on or before Day 2	4 (13%)	14 (47%)	10 (33%)	8 (36%)	0.038
Last Available on or before Day 5	23 (26%)	38 (39%)	42 (44%)	8 (36%)	0.051
Last Available	27 (25%)	36 (31%)	42 (36%)	1 (4%)	0.038

a. Data from NDA vol. 79, table 39A3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

2. Serum Albumin

In both the 'all CHF' trials there were a higher % of low serum albumin in the nesiritide group. Like the data for the changes in serum total protein, these changes were most prominent at days 2 and 5. Note that

Table 8.0.6e.6 (from 11.1.4.3.1a.16) Observed rate of decreased albumin concentrations in 'all CHF' trials^a.

Time of Albumin Below Normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	86 (38%)	219 (45%)	0.089
Last Available on or before Day 2	25 (31%)	103 (57%)	<0.001
Last Available on or before Day 5	63 (42%)	211 (60%)	<0.001
Last Available	64 (36%)	164 (40%)	0.411

a. Data from NDA vol. 79, table 39A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was a similar trend in the infusion studies, where the differences persisted to the end of the measurement period.

Table 8.0.6e.7 (from 11.1.4.3.1a.17) Observed rate of decreased albumin values in the 'long infusion' trials^a.

Time of Albumin Below Normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	65 (39%)	80 (48%)	76 (48%)	8 (31%)	0.170
Last Available on or before Day 2	6 (19%)	20 (69%)	16 (53%)	7 (50%)	0.001
Last Available on or before Day 5	39 (42%)	62 (66%)	61 (62%)	10 (43%)	0.010
Last Available	49 (43%)	66 (56%)	66 (53%)	3 (12%)	0.001

a. Data from NDA vol. 79, table 40D3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

Similarly, the % of patients who developed decreased albumin after a normal baseline value was higher in the high-dose nesiritide group. This was particularly true at day two, when the nesiritide infusion was continuing in a significant % of the subjects.

Table 8.0.6e.8 (from 11.1.4.3.1a.18) Observed incidence of decreased albumin values after normal baseline value in the long infusion trials^a.

Time of Decreased Albumin	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	1 (3%)	6 (21%)	5 (18%)	4 (29%)
Last Available on or before Day 5	10 (11%)	17 (18%)	16 (17%)	4 (18%)
Last Available	10 (9%)	16 (14%)	17 (14%)	1 (4%)

a. Data from NDA vol. 79, table 37C4.

Reviewer's Conclusions Regarding Changes in Serum Proteins

In the discussion of the changes in hematology (see below), the sponsor posits an effect of nesiritide 'to enhance transcapillary permeability.' This effect has been reported for ANP in animals (refs. 6, 10 and 13). Such an effect, if real, might account for the pattern of changes in serum total protein and albumin seen, with protein transudation from the intravascular space. The association between nesiritide and decreased total protein and albumin, however, persists throughout the hospitalization in the long infusion trials, rather than ending when the nesiritide infusion stops. This suggests a long-term effect, and while no clinical consequences of these changes in serum proteins were detected, a permanent increase in transcapillary permeability might adversely affect intravascular volume regulation. Such a case might occur if clinicians monitor weights as the only measure of fluid loss, and are over-aggressive with diuretics. In such a case, coupled with the loss of proteins and water to the interstitium, would leave the intravascular space depleted risking impaired perfusion of vital organs, including the GI tract and kidneys.

An alternative hypothesis is that nesiritide decreases production of these proteins by the liver, or enhances their destruction. Given the known effects of ANP to alter vascular permeability, such an effect of nesiritide is the more attractive of the two hypotheses.

In conclusion, there is a probable association between the administration of nesiritide and a decrease in serum total protein and albumin, which tended to persist in the long infusion population. No clinical adverse effects were detected as the results of these changes, but the database is inadequate to exclude such effects or to determine the mechanism for the observed changes.

8.0.7 Adverse Events in the Respiratory System

No adverse events were identified that were potentially associated with study drug administration or were a normal part of NDA safety review in this system. Adverse events reviewed included dyspnea and increased cough.

8.0.8 Adverse Events in the Urogenital System

The following adverse events within the Urogenital system will be examined: renal failure (including increases in serum BUN/Crt), and oliguria.

8.0.8a Renal Failure

AEs

The first tables summarize the incidence of urogenital AEs.

Table 8.0.8a.1 (from 11.1.3.1) Renal adverse events (AEs) in the CHF trials from NDA 20-920^a.

Renal AEs	Control n=235	Nesiritide n=505	Nominal p Value
Metabolic & Nutritional System	42 (18%)	83 (16%)	
BUN Increased	7 (3%)	15 (3%)	1.00
Urogenital System	25 (11%)	81 (16%)	0.055
Creatinine Increased	7 (3%)	29 (6%)	0.141
Oliguria	2 (1%)	13 (3%)	0.164
Hematuria	6 (3%)	5 (1%)	0.113
Kidney Function Abnormal	0 (0%)	7 (1%)	0.104
Acute Renal Failure	3 (1%)	6 (1%)	1.000

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.8a.2 (from 11.1.3.2) Renal AEs in the first 14 days in the 'long infusion' trials^a.

Adverse Event	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
Metabolic & Nutritional System					
BUN Increased	7 (4%)	9 (5%)	5 (3%)	0 (0%)	0.615
Urogenital System	22 (13%)	28 (17%)	35 (21%)	3 (12%)	0.813
Creatinine Increased	7 (4%)	10 (6%)	15 (9%)	1 (4%)	0.300
Oliguria	2 (1%)	6 (4%)	6 (4%)	0 (0%)	0.410
Hematuria	4 (2%)	3 (2%)	1 (1%)	0 (0%)	0.697
Acute Kidney Failure	3 (2%)	1 (1%)	3 (2%)	1 (4%)	0.389
Kidney Function Abnormal	0 (0%)	1 (1%)	3 (2%)	0 (0%)	0.249

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

The sponsor also summarized the data for the first 24 hours of the long infusion trials. Very few Urogenital AEs occurred in the first 24 hours.

Table 8.0.8a.3 (from 11.1.3.3) Renal AEs during the first 24 hours in the 'long infusion' trials^a.

Adverse Event	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
Creatinine Increased	1 (1%)	3 (2%)	4 (2%)	0 (0%)
Kidney Function Abnormal	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Acute Kidney Function	0 (0%)	0 (0%)	1 (1%)	0 (0%)
BUN Increased	2 (1%)	2 (1%)	2 (1%)	0 (0%)

a. Data from appendix 8.4, table 12C and from company at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

Urogenital SAEs

Examination of the list of SAEs in both the 'all CHF' and 'long infusion' studies found no difference in the incidence of Urogenital SAEs among the treatment groups. In study 704.325 and 704.326, there was also no difference in the number of patients who required hemodialysis/ hemofiltration (data not shown).

Table 8.0.8a.4 (from 11.1.2.1) Renal SAEs through 14 days in the 'all CHF' trials^a.

Serious Adverse Event	Control n=235	Nesiritide n=505
Urogenital System	3 (1%)	4 (1%)
Kidney Function Abnormal	0 (0%)	1 (<1.0%)
Nephritis	0 (0%)	1 (<1.0%)
Acute Kidney Failure	3 (1%)	2 (0%)

a. Data from NDA appendix 8.4, table 27A.

Urogenital SAEs (cont)

Table 8.0.8a.5 (from 11.1.2.2) Renal SAEs through 14 days in the 'long infusion' trials^a.

Serious Adverse Event	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
Urogenital^c	3 (2%)	0 (0%)	1 (1%)	1 (4%)	0.136
Nephritis	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0.049
Kidney Function Abnormal	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Acute Kidney Failure	3 (2%)	0 (0%)	1 (1%)	0 (0%)	0.410

a. Data from appendix 8.4, table 27C and from company at request of reviewer. p Value per sponsor.

c. Includes nephritis, kidney function abnormal, and acute kidney failure.

Discontinuations

There was an increased incidence of withdrawals with Urogenital AEs in the nesiritide group for both the 'all CHF' and 'long infusion' trials. Note that all of the discontinuations for Urogenital AEs occurred in the nesiritide groups in the 'all CHF' and the 'long infusion' populations.

Table 8.0.8a.6 (from 11.1.5.3.1) Discontinuations prior to day 14 due to renal AEs in the 'all CHF' population^a.

AE associated with discontinuation	Control n=235	Nesiritide n=505	Nominal p Value
Urogenital System	0 (0%)	9 (2%)	0.064
Oliguria	0 (0%)	5 (1%)	0.185
Creatinine Increased	0 (0%)	4 (1%)	0.313
Acute Kidney Failure	0 (0%)	1 (<1.0%)	1.000
Metabolic & Nutritional System	0 (0%)	5 (1%)	0.185
BUN Increased	0 (0%)	4 (1%)	0.313
Hypovolemia	0 (0%)	1 (<1.0%)	1.000

a. Data from NDA appendix 8.4, table 28A.

Table 8.0.8a.7 (from 11.1.5.3.1) Discontinuations due to renal AEs in the 'long infusion' trials^a.

AE associated with discontinuation	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
Urogenital	0 (0%)	2 (1%)	7 (4%)	0 (0%)	0.020
Oliguria	0 (0%)	1 (1%)	4 (2%)	0 (0%)	0.125
Creatinine Increased	0 (0%)	1 (1%)	3 (2%)	0 (0%)	0.249
Acute Kidney Failure	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Metabolic & Endocrine	0 (0%)	2 (1%)	3 (2%)	0 (0%)	0.325
BUN Increased	0 (0%)	2 (1%)	2 (1%)	0 (0%)	0.510
Hypovolemia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361

a. Data from supplemental table 28D, with p Value per sponsor.

Deaths With Renal Failure

The deaths associated with renal failure are listed below. Most occurred distantly from study drug administration. Those deaths whose renal failure worsened during or shortly after study drug administration are summarized following the table.

Table 8.0.8a.8 (from 11.1.1.2) Known deaths associated with renal failure in NDA 20-920^a.

Treatment Group/ Patient #	# of Days After Study Entry	Cause of Death
Placebo 368001	16	Ventricular Fibrillation, CHF
Active Control^b		
509001	21	Suspect large MI
538011	9	LV failure s/p MI
Nesiritide Bolus		
None		
Nesiritide 0.015 µg/kg/min infusion		
382013	5	Progressive Renal Insufficiency CHF
538010	9	Mitral regurgitation Chronic atrial flutter
Nesiritide 0.030 µg/kg/min infusion		
017007	8	Acute Renal Failure, CHF
509002	6	CHF
528001	22	Cardiac arrest Ischemic cardiomyopathy
572001	20	CHF
Nesiritide 0.060 µg/kg/min infusion		
None		

a. Data from NDA vol. 1.81, listing 7, and examination of individual case report forms.

b. In study 326 subjects were randomized to receive other IV cardiovascular meds.

Placebo/ Active Control Group

1. *Subject 538-011 (Standard care: dobutamine)* Subject was a 78-year-old white man with a history of NYHA Class IV CHF, atrial fibrillation, ventricular ectopy, and chronic renal insufficiency. Dobutamine was administered for 8 days. On day 3, he developed acute renal failure. On day 4, he experienced bradycardia and a respiratory arrest requiring intubation and mechanical ventilation. He died on day 9 of severe left ventricular failure.

Nesiritide 0.015 Dose Group

1. *Subject 538-010 (Nesiritide, 0.015 µg/kg/min)* Subject was an 89-year-old white woman with NYHA Class III CHF, coronary artery disease, mitral regurgitation, and chronic atrial fibrillation. Nesiritide was administered for 65 hours, then discontinued because of clinical improvement. On day 4, dobutamine was initiated in response to worsening oliguria. The subject's general condition worsened over the ensuing days. Sepsis was suspected and broad spectrum antibiotics were initiated. Comfort measures only were initiated, and the subject died from a cardiopulmonary arrest on day 9.

Nesiritide 0.030 Dose Group

1. *Subject 509-002 (Nesiritide, 0.03 µg/kg/min)* Subject was a 61-year-old white man with NYHA Class IV CHF due to idiopathic, dilated cardiomyopathy, and a history of non-sustained VT. He received nesiritide for 5 days. For the first few days of the infusion, he responded very well with excellent diuresis and improvement in his congestive symptoms. On day 5, his condition deteriorated with worsening respiratory symptoms and decreased urine output. Nesiritide was discontinued and replaced with dobutamine and dopamine. Later on day 6, the subject died due to worsening CHF.

2. *Subject 528-001 (Nesiritide, 0.03 µg/kg/min)* Subject was a 71-year-old white man with a history of NYHA Class III CHF, ischemic cardiomyopathy, atrial fibrillation, bronchiolitis obliterans, and diabetes. He received nesiritide for 3 days to which he responded very well with diuresis and improvement in CHF symptoms. On day 5, he was noted to have hyperkalemia (K⁺ = 7.6) and an elevated serum creatinine (Cr_t = 3.9 mg/dL). He was diagnosed as having nonoliguric acute renal failure which improved by day 8 (K⁺ = 4.3, Cr_t = 1.5) after the administration of dobutamine, dopamine, and IV furosemide. He died on day 22 due to cardiac arrest.

Demographics (for 'confusion' as an AE)

1. Age

Confusion was more common in the nesiritide group >65 years of age.

Table 8.0.5a.5 Confusion as an AE reported in the 'long infusion' population^a according to age.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
<65 Years Old Confusion	n=103 2 (2%)	n=100 4 (4%)	n=90 3 (3%)	n=17 0 (0%)	0.821
>65 Years Old Confusion	n=70 3 (4%)	n=69 12 (17%)	n=77 10 (13%)	n=9 1 (11%)	0.076

a. Data from supplemental data table 13D at request of reviewer. Reflects trials 311, 325, and 326 data. p Value per sponsor.

2. Gender

Confusion was also more common in the nesiritide group of both men and women, although the small numbers in females make it difficult to draw conclusions about the trend.

Table 8.0.5a.6 Confusion as an AEs in the 'long infusion' population^a according to gender.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Male Confusion	n=127 3 (2%)	n=120 12 (10%)	n=113 9 (9%)	n=23 0 (0%)	0.039
Female Confusion	n=46 2 (4%)	n=49 4 (8%)	n=54 4 (7%)	n=3 1/(33%)	0.297

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data.

3. Other Medications

With small numbers, no drug-drug interaction enhancing the incidence of confusion in study 704.326 was detected.

Table 8.0.5a.7 Confusion as an AEs arranged by use of other medications in addition to nesiritide from study 704.326.

Confusion as an AEs	Nesiritide 0.015 and 0.030 µg/kg/min
ACE Inhibitor Use	
Yes	5/124 (4%)
No	4/49 (8%)
Digoxin Use	
Yes	5/117 (4%)
No	2/45 (4%)
Beta Blockers	
Yes	2/18 (11%)
No	7/183 (4%)

a. Data from ISS table 8-39, reflecting trial 326 data.

4. NYHA Class III or IV

Confusion as an AEs occurred with equal frequency in Class III and IV NYHA patients. There was a trend towards increased incidence of confusion in the nesiritide groups for both NYHA classes.

Table 8.0.5a.8 Confusion as an AEs in the 'long infusion' population^a according to NYHA Class^a.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
NYHA III Confusion	n=107 1 (1%)	n=97 10 (10%)	n=81 7 (9%)	n=15 0 (0%)	0.011
NYHA IV Confusion	n=58 3 (5%)	n=64 6 (9%)	n=71 6 (8%)	n=9 1 (11%)	0.692

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

4. NYHA Class III or IV

Urogenital AEs occurred with equal frequency in Class III and IV NYHA patients.

Table 8.0.2b.12 Urogenital AEs in the 'long infusion' population^a according to NYHA Class^a.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
NYHA III	n=107	n=97	n=81	n=15	
Creatinine Increased	3 (3%)	6 (6%)	7 (9%)	0 (0%)	0.294
Kidney Function Abnormal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	--
Acute Kidney Failure	1 (1%)	1 (1%)	1 (1%)	1 (7%)	0.306
BUN Increased	5 (5%)	4 (4%)	2 (2%)	0 (0%)	0.888
NYHA IV	n=58	n=64	n=71	n=9	
Creatinine Increased	4 (7%)	3 (5%)	7 (10%)	1 (11%)	0.552
Kidney Function Abnormal	0 (0%)	1 (2%)	3 (4%)	0 (0%)	0.493
Acute Kidney Failure	2 (3%)	0 (0%)	2 (3%)	0 (0%)	0.554
BUN Increased	2 (3%)	4 (6%)	2 (3%)	0 (0%)	0.767

a. Data from supplemental data table 17D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

5. Etiology of CHF

Increased creatinine as an AE occurred rarely, with equal frequency regardless of the original etiology of the CHF (with small numbers for analysis).

Table 8.0.8a.13 Increased creatinine as an AE in the 'long infusion' population^a according to cause of CHF^a.

Creatinine Increased as an AE	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Hypertensive	0/13 (0%)	2/14 (14%)	2/12 (17%)	0/3 (0%)	0.527
Ischemic	6/89 (7%)	5/88 (6%)	7/87 (8%)	1/16 (6%)	0.918
Idiopathic/Dilated	0/38 (0%)	0/40 (0%)	5/35 (14%)	0/5 (0%)	0.014

a. Data from supplemental tables provided at request of reviewer. Reflects trials 311, 325, and 326 data.

Special Studies: Measured Changes in Lab Values

At day 2 and 5, the nesiritide group had a smaller decline in mean BUN than the controls in the 'all CHF' and in the 'long infusion' populations.

Table 8.0.8a.14 (from 11.1.4.2.1) Mean changes in renal chemistries from baseline for 'all CHF' trials^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
BUN	-3.6±6.9	-1.4±7.1	-4.3±10.4	-1.4±10.2
Creatinine	-0.1±0.5	0.0±0.3	-0.1±0.5	0.0±0.4

a. Data from NDA volumes 79-80, starting with table 31A1.

Table 8.0.8a.15 (from 11.1.4.2.31) Mean changes in renal chemistries from baseline for 'long infusion' trials^a.

Lab Test, Change from Baseline to Day 2	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=24	Nominal p Value
BUN	-3.3 ± 6.86	-1.8 ± 7.19	-0.7 ± 7.85	-2.5 ± 5.26	0.022
Creatinine	-0.1 ± 0.53	-0.0 ± 0.32	+0.1 ± 0.37	0.0 ± 0.13	<0.001

a. Data from NDA volumes 79-80, starting with table 31A1 and from supplemental data sets submitted at reviewer's request.

Special Studies: Incidence of Development of Elevated BUN and Creatinine

1. Elevated Blood Urea Nitrogen (BUN)

In the CHF trials, the incidence of elevated BUN at baseline was >50% in both the control and the nesiritide group. There was no significant difference in the % of patients with elevated BUN during the trials in this group.

Table 8.0.8a.16 (from 11.1.4.3.1a.5) Observed rate of increased BUN concentrations in 'all CHF' trials^a.

Time of Increased BUN	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	124 (53%)	276 (55%)	0.619
Last Available on or before Day 2	98 (47%)	218 (51%)	0.339
Last Available on or before Day 5	113 (49%)	258 (52%)	0.473
Last Available	119 (51%)	288 (57%)	0.124

a. Data from NDA vol. 79, table 36A4. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was, however, an increased % of patients in the nesiritide group who had normal BUNs at baseline and had elevated BUNs at 2 and 5 days and last available measured.

Table 8.0.8a.17 (from 11.1.4.3.1a.6) Incidence of patients with increased BUN after normal baseline BUN in 'all CHF' trials^a.

Time of Increased BUN	Control n=235	Nesiritide n=505
Last Available on or before Day 2	5 (2%)	23 (5%)
Last Available on or before Day 5	10 (4%)	38 (8%)
Last Available	20 (9%)	62 (12%)

a. Data from NDA vol. 79, table 36A4. p Value per the sponsor for the entire frequency of high, normal and low lab values.

In the long infusion trials, there was again no difference in the incidence of increased BUN (data not shown, see table 36C3 for details). The number of patients with normal BUN at baseline and elevated BUN at time of follow-up was also similar in the treatment groups.

Table 8.0.8a.18 (from 11.1.4.3.1a.7) Observed rate of increased BUN concentrations in the long infusion trials for patients with normal BUN at baseline^a.

Time of BUN Above Normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Last Available on or before Day 2	4 (3%)	8 (5%)	9 (6%)	1 (4%)	NS
Last Available on or before Day 5	10 (6%)	15 (9%)	12 (7%)	1 (4%)	NS
Last Available	13 (8%)	16 (10%)	15 (9%)	3 (12%)	NS

a. Data from supplemental data table 36D4 from sponsor at reviewer's request.

2. Elevated Creatinine

Among all patients enrolled in the CHF trials, there were more with abnormally elevated creatinines at days 2, 5 and at final available assessment in the nesiritide group.

Table 8.0.8a.19 (from 11.1.4.3.1a.8) Observed rate of increased creatinine values in the 'all CHF' trials^a.

Time of Creatinine Below Normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	87 (37%)	186 (37%)	0.837
Last Available on or before Day 2	71 (34%)	165 (39%)	0.134
Last Available on or before Day 5	75 (32%)	200 (40%)	0.032
Last Available	89 (38%)	227 (45%)	0.068

a. Data from NDA vol. 79, table 37A3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

2. Elevated Creatinine (cont)

A higher % of patients with normal creatinines at baseline also had elevated creatinines at follow-up in the nesiritide group.

Table 8.0.8a.20 (from 11.1.4.3.1a.9) Incidence of patients with increased creatinine after normal baseline creatinine in 'all CHF' trials^a.

Time of Increased creatinine	Control n=235	Nesiritide n=505
Last Available on or before Day 2	7 (3%)	33 (8%)
Last Available on or before Day 5	13 (6%)	42 (8%)
Last Available	20 (9%)	64 (13%)

a. Data from NDA vol. 79, table 37A4.

In the long infusion trials, there were a higher percentage of patients with elevated creatinines in the 0.030 dose group, compared with either the 0.015 group or the control group.

Table 8.0.8a.21 (from 11.1.4.3.1a.10) Observed rate of increased creatinine values in 'long infusion' trials^a.

Time of Increased creatinine	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	79 (46%)	62 (37%)	76 (46%)	13 (50%)	0.140
Last Available on or before Day 2	65 (42%)	52 (34%)	77 (52%)	4 (27%)	0.009
Last Available on or before Day 5	69 (41%)	62 (37%)	85 (51%)	10 (40%)	0.060
Last Available	73 (43%)	67 (40%)	90 (54%)	13 (50%)	0.048

a. Data from supplemental table 37C3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

Similarly, the percentage of patients who developed elevated creatinines after a normal baseline value was higher in the 0.030 µg/kg/min nesiritide group.

Table 8.0.8a.22 (from 11.1.4.3.1a.11) Observed incidence of increased creatinine values after normal baseline value in the long infusion trials^a.

Time of Increased creatinine	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	4 (3%)	7 (5%)	18 (12%)	0 (0%)
Last Available on or before Day 5	10 (6%)	12 (7%)	17 (10%)	1 (4%)
Last Available	11 (7%)	16 (10%)	22 (13%)	2 (8%)

a. Data from NDA vol. 79, table 37C4. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

The number of patients with pre-specified increases in serum creatinine also tended to be higher in the nesiritide groups, relative to control. The tables below shows the data for trials 704.311, 704.325, and 704.326. Note that there were relatively few patients with two or more serum creatinines in the 704.311 study.

Table 8.0.8a.23 (from 11.1.4.3.1a.12) Observed incidence of increased creatinine values in trial 704.311^a.

Pre-specified increases in creatinine	Control	Nesiritide 0.25/0.015	Nesiritide 0.50/0.030	Nesiritide 1.0/0.060	Nominal p Value ^a
>1.0 mg/dl Increase	2 (7%)	1 (4%)	1 (4%)	1 (4%)	1.000
>0.5 mg/dl Increase	4 (14%)	4 (17%)	5 (20%)	6 (23%)	0.861
>100% Increase	1 (3%)	1 (4%)	1 (4%)	0 (0%)	0.795
>50% Increase	2 (7%)	4 (17%)	4 (16%)	3 (12%)	0.631
>25% Increase	8 (28%)	10 (43%)	9 (36%)	10 (38%)	0.678

a. Data from the sponsor, table 37D7. p Value per the sponsor.

Table 8.0.8a.24 (from 11.1.4.3.1a.13) Observed incidence of increased creatinine values in trial 704.325^a.

Pre-specified increases in creatinine ^b	Control n=42	Nesiritide 0.3/0.015 n=43	Nesiritide 0.6/0.030 n=42	Nominal p Value ^a
>1.0 mg/dl Increase	0 (0%)	2 (5%)	4 (10%)	0.122
>0.5 mg/dl Increase	2 (5%)	7 (16%)	8 (19%)	0.124
>100% Increase	1 (2%)	1 (2%)	4 (10%)	0.322
>50% Increase	1 (2%)	5 (12%)	8 (19%)	0.049
>25% Increase	7 (17%)	11 (26%)	8 (19%)	0.624

a. Data from NDA vol. 79, table 37D1. p Value for the comparison between the 0.015 and 0.030 nesiritide dose groups and control

Table 8.0.8a.25 (from 11.1.4.3.1a.13) Observed 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 NDA vol. 79, table 37D2. p Value per the sponsor for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

3. Urinary Abnormalities

The sponsor did not perform urinalyses during either the 704.325 or 704.326 trials. In the 704.311 trial only baseline urinalyses were obtained. In the absence of this data, an effect of nesiritide on urinary abnormalities cannot be evaluated or excluded.

Special Studies: Need for Medical Intervention Due to Renal Failure

In trial 704.325, the need for medical intervention, including the need for dialytic intervention was collected, and is summarized in the table below. Note that interventions for worsening renal failure (short of dialysis) were more nominally significantly more common in the nesiritide groups. This trend was less dramatic in trial 704.326.

Table 6.2.13.5 Requirement for intervention due to worsening renal failure in study 704.325^a.

Intervention for worsening renal function	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	Nominal p Value
No Intervention	41 (98%)	37 (86%)	33 (79%)	0.033
Medical Intervention Without Dialysis	0 (0%)	6 (14%)	7 (17%)	0.009
Dialysis	1 (2%)	0 (0%)	2 (5%)	--

a. Data from NDA vol. 59, Appendix 1, Table 61.

Table 6.3.12.3.9 Need for selected medical interventions through 21 days in study 704.326^a.

Intervention for Worsening Renal Function	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal Value
Intervention without Dialysis	6 (6%)	12 (12%)	7 (7%)	0.610
Dialysis	2 (2%)	1 (1%)	2 (2%)	

a. Data from NDA volume 66, Appendix 1, Table 35. Includes all subjects discharged before day 21. p Value per sponsor.

Special Studies: Individual Patient Lab Review with Renal Failure

The following selected patients in trial 704.326 had courses consistent with a severe renal injury during their hospital stays.

Table 8.0.8a.26 Selected patients with marked renal lab abnormalities^a.

Protocol 704.326 Treatment Grp/ Pt. #	Day	BUN/ Cr _t	Notes
Standard Care 493019	0	18 / 1.2	Last lab known, Ultimately died of endstage CHF
	3	24 / 1.5	
	4	32 / 2.0	
	5	41 / 2.5	
Nesiritide 0.015 µg/kg/min 536002	0	14/1.0	F/U creatinine 1.0
	2	12/ 0.9	
	10	10/ 0.9	
	15	15/ 1.0	
	30	30/ 1.9	
	48	48/ 2.4	
547003	0	16/ 1.0	F/U creatinine 1.0
	2	23/ 1.4	
	3	38/ 1.9	
	4	56/ 2.3	
Nesiritide 0.060 µg/kg/min 525002	0	18/ 1.3	F/U creatinine 1.1
	2	28/ 1.9	
	3	32/ 1.5	
	4	32/ 1.4	
	5	30/ 1.4	
	6	31/ 1.4	
	7	36/ 1.6	
	8	51/ 2.1	
572001 (persistent abnormality)	0	18 / 1.2	Last lab known 1.8 (persistent abnormality)
	2	22 / 1.3	
	3	32 / 1.3	
	4	37 / 1.3	
	5	57 / 1.3	
	6	28 / 1.5	
	7	38 / 2.7	
	8	51 / 3.3	

a. Data from individual data listings of patients and electronic data sets.

Following the NDA submission, the sponsor also obtained follow-up serum creatinines for those patients who had abnormal creatinines at last value (≥ 2 mg/dl and 50% increase over baseline). These data are shown below. The single patient who did not resolve his creatinine to within 0.5 mg/dl of baseline is patient 572-001, described in the patient narrative below.

8.0.8a.27 Resolution of elevated serum creatinines from subjects with increased creatinine in studies 704.325 and 704.326^a.

Creatinine ≥ 2 mg/dl and 50% increase over baseline	Control	Nesiritide 0.015	Nesiritide 0.030
Transient	1	7	12
Not Transient ^b	0	0	1
Insufficient Follow-up	1	2	1

a. Data from sponsor's briefing book for Advisory Committee.

b. Follow-up creatinine >0.5 mg/dl above baseline.

1. *Subject 572-001 (Nesiritide, 0.060 µg/kg/min)* This was a 73 year old WM with a history of ischemic cardiomyopathy, 'chronic renal insufficiency' (admitting creatinine 1.2) and previous MI. After receiving nesiritide for one day, he was switched to dobutamine for lack of clinical improvement. He was also later treated with nitroprusside and milrinone, and levophed. His subsequent hospital course was complicated by multifocal atrial tachycardia and hypotension, oliguric acute renal failure, intermittent chest pain, and elevated cardiac enzymes indicative of a myocardial infarction, worsening hyponatremia, gastrointestinal bleed and progressively worsening cardiac and renal function. The subject died on day 20 because of endstage heart failure.

2. *Subject 525-002 (Nesiritide, 0.060 µg/kg/min)* This was a 74 year-old WM with dilated idiopathic cardiomyopathy and CHF. He had a history of hypertension, a fib, acromegaly, and chronic renal insufficiency (baseline creatinine 1.3). He was not on ACE inhibitors, or NSAIDs, but did receive Norvasc, lasix, and Rhythmol. He received nesiritide for 6 days, with no other parenteral vasoactive medications. One the first day of infusion, his creatinine rose to 1.9, followed by a return to near baseline (1.4). On day 7, after completing his nesiritide, his serum creatinine began to rise again, and peaked at time of last value, taken just before discharge (BUN 51, Cr 2.1). At time of last follow-up his creatinine had returned to 1.0 mg/dl.

Another patient in the bolus infusion study 704.309 (reviewed by Dr. Karkowsky) had an adverse renal event resulting in hemodialysis and ultrafiltration, which is summarized below.

1. *Subject 359-002 (Nesiritide, 10 µg/kg bolus q6 hours)* This 54 year old WF had NYHA III CHF due to ischemic cardiomyopathy diabetes mellitus (baseline creatinine 2.0 and 2.1). She tolerated the nesiritide administration. On day 2 her urine output declined and her creatinine rose to 2.6, then 3.8, then 4.3. She was treated with Zaroxilyn and Demadex and renal dose dopamine, but required hemodialysis and ultrafiltration. She later developed central line sepsis, drug-induced ototoxicity, a fib, and anemia.

Sponsor's Comments

In all of the populations analyzed, on day 2, there is a tendency for mean serum BUN and creatinine to be decreased from baseline more in the control group than in the nesiritide group. By the last available time point, mean serum BUN and creatinine tend to have increased slightly over baseline in the nesiritide group compared to control. This phenomenon occurs in a dose-related manner.

Clinically significant renal dysfunction requiring dialysis was not more frequent in nesiritide subjects than in control subjects. Thus, nesiritide administration may be associated with a modest dose-related increase in serum creatinine in a minority of subjects (~10% of nesiritide subjects receiving the 0.015 µg/kg/min dose) but does not appear to be associated with marked increases in serum creatinine or increases in clinically significant acute renal failure. This phenomenon might be related to nesiritide inhibition of the renin-angiotensin system in a small group of patients dependent on that system's effects on renal perfusion.

Reviewer's Conclusions Regarding Urogenital AEs

By several measures, nesiritide use was associated with adverse effects on the kidney. In particular, in the nesiritide group there was an increased percentage of subjects with specified increases in creatinine, and the increased number of subjects withdrawn from the trials for urogenital AEs (all referable to abnormal renal function). The rate of oliguria was also significantly increased in the nesiritide group, suggesting that administration of nesiritide induces a sodium- and water-avid state in susceptible patients, perhaps related to inadequate renal perfusion. While there was no difference in the need for dialysis, such a rare event would be unlikely to be detected in this small database. There were individuals who developed clearly abnormal renal function in association with nesiritide infusion. No demographic was identified in the small database that correlated with increased risk for renal injury, although the sponsor claimed in their briefing documents that a serum creatinine of ≥ 2 mg/dl at trial entry was an independent risk for increased creatinine during nesiritide infusion. In the absence of data regarding urinalyses, renal injuries such as Nephrotic syndrome and Acute Interstitial Nephritis, which would be manifest by the development of urinary abnormalities, cannot be evaluated or excluded. Without the urinalysis data, we are also forced to speculate about the nature of the renal injury that leads to the observed increases in serum creatinine.

In conclusion, the data support a probable association between nesiritide administration and clinically significant renal adverse effects, leading to significant increases in serum creatinine as well as marked, persistent increases in serum creatinine, suggesting permanent renal injury. The database is inadequate to exclude an effect on severe renal injury, such as nephrotic syndrome, papillary necrosis, and interstitial nephritis. It is also inadequate to assess the effect of nesiritide on other renal toxicities that might be detected by urinary abnormalities.

8.0.9 Adverse Events in the Skin & Appendage System

No adverse events were identified that were potentially associated with study drug administration or were a normal part of NDA safety review in this system. Adverse events reviewed included rash and urticaria.

8.0.10 Adverse Events in the Musculoskeletal System

The following adverse event within the Musculoskeletal system will be examined: leg cramps/ myalgia.

8.0.10a Myalgias and Leg Cramps

AEs and SAEs

The two major AEs and SAEs related to the Musculoskeletal system are summarized below for the 'all CHF' and 'long infusion' populations. In the long infusion trials, both overall Musculoskeletal and leg cramps were reported at a lower rate in the nesiritide groups.

Table 8.0.10a.1 (from 11.1.3.1) Adverse Events (AEs) in 'all CHF' trials from NDA 20-920^a.

Adverse Event	Control n=235	Nesiritide n=505
Musculoskeletal System	21 (9%)	30 (6%)
Myalgia	1 (<1.0%)	2 (<1.0%)
Leg Cramps	11 (5%)	13 (3%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.10a.2 (from 11.1.3.2) Musculoskeletal AEs in the first 14 days in 'long infusion' trials^a.

Adverse Event	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
Musculoskeletal	15 (9%)	10 (6%)	9 (5%)	1 (4%)
Myalgia	1 (<1.0%)	1 (<1.0%)	0 (0%)	1 (4%)
Leg Cramps	9 (5%)	5 (3%)	2 (1%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

No SAEs due to leg cramps or myalgias were reported.

Discontinuations and Deaths

No discontinuations or deaths due to myalgias or muscle cramps were reported.

Reviewer's Conclusions Regarding Musculoskeletal AEs

No evidence of an adverse effect of nesiritide on the musculoskeletal system was found. The data are inadequate to interpret the smaller incidence of leg cramps reported in the nesiritide groups.

8.0.11 Adverse Events in the Hemic & Lymphatic System

The following adverse events within the hemic & lymphatic system will be examined: changes in hemoglobin/ hematocrit, WBC count (including sepsis and infections), platelet count, and eosinophil count. Adverse events reviewed but not discussed further include PT and PTT.

8.0.11a Changes in hemoglobin, hematocrit, and RBC count

AEs and SAEs

The occurrence of hemic and lymphatic AEs in the 'all CHF' and 'long infusion' trials is summarized below. No adverse effect of nesiritide is evident.

Table 8.0.11a.1 (from 11.1.3.1) Hemic AEs in the CHF trials from NDA 20-920^a.

Adverse Event	Control n=235	Nesiritide n=505
Hemic & Lymphatic	12 (5%)	17 (3%)
Anemia	4 (2%)	8 (2%)
Ecchymosis	4 (2%)	4 (1%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.11a.2 (from 11.1.3.2) Hemic AEs in the first 14 days in 'long infusion' trials from NDA 20-920^a.

Adverse Event	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
Hemic & Lymphatic	9 (5%)	3 (2%)	8 (5%)	1 (4%)
Anemia	3 (2%)	1 (1%)	5 (3%)	1 (4%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

No SAEs related to changes in hemoglobin/ hematocrit were reported.

Discontinuations and Deaths

No discontinuations or deaths for bleeding or changes in hemoglobin/ hematocrit were reported.

Special Studies: Measured Changes in Lab Values

At the end of 2 and 5 days in the 'all CHF' population there was an increased hematocrit in the nesiritide group.

Table 8.0.11a.3 (from 11.1.4.2.2) Mean changes in RBC labs from baseline for all subjects in CHF trials^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
RBC # (10 ⁶ /mm ³)	+0.0±0.2	+0.1±0.4	+0.0±0.3	+0.0±0.4
HGB (g/dL)	-0.1±0.7	+0.3±0.96	+0.0±0.8	+0.2±0.1
Hematocrit	-0.3±2.1	+0.9±3.0	+0.0±2.7	+0.4±3.1

a. Data from NDA volumes 79-80, starting with table 31A1.

Sponsor's Comments

In the placebo-controlled studies, there is a very subtle trend of a transient increase in RBC count, hemoglobin and hematocrit in the nesiritide group compared to control. 'This phenomenon has been noted occasionally in other studies with natriuretic peptides in the literature and may reflect transient hemoconcentration due to the ability of natriuretic peptides to enhance transcapillary permeability.'

Reviewer's Conclusions Regarding RBC Counts

There was a small effect of nesiritide to increase the mean change in hemoglobin/ hematocrit and RBC count, measured after 2 and 5 days in the 'all CHF' population. This was not associated with any detected AEs. The data are inadequate to test the hypothesis proposed as a mechanism by the sponsor.

In conclusion, the data support a possible effect on RBC concentration, perhaps related to hemoconcentration.

8.0.11c WBC Count/ Infections Including Sepsis

AEs

The first two tables summarize the incidence of AEs related to WBC count, including sepsis, in the 'all CHF' and 'long infusion' trials. No differences are evident among the treatment groups.

Table 8.0.11c.1 (from 11.1.3.1) Hemic & lymphatic AEs in 'all CHF' trials^a.

Adverse Event Related to WBCs	Control n=235	Nesiritide n=505
Hemic & Lymphatic Leukopenia	12 (5%) 1 (0.1%)	17 (3%) 0 (0%)
Body as a Whole Sepsis Line infection	6 (3%) 1 (0.1%)	14 (3%) 1 (0.1%)

a. Data from NDA appendix 8.4, table 11A.

Examination of the list of AEs identified in the infusion studies (through day 14) found the following.

Table 8.0.11c.2 (from 11.1.3.2) Hemic & lymphatic AEs in the first 14 days in the 'long infusion' trials.

Adverse Event Related to WBCs	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
Hemic & Lymphatic Leukopenia Sepsis	9 (5%) 1 (1%) 5 (3%)	3 (2%) 0 (0%) 3 (2%)	8 (5%) 0 (0%) 6 (4%)	1 (4%) 0 (0%) 1 (4%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs

In both the 'all CHF' and the 'long infusion' studies there were more SAEs related to sepsis in the nesiritide groups than in control.

Table 8.0.11c.3 (from 11.1.2.1) Hemic & lymphatic SAEs through 14 days in 'all CHF' trials^a.

Serious Adverse Event	Control n=235	Nesiritide n=505
Sepsis Infection	0 (0%) 1 (<1.0%)	5 (1%) 0 (0%)

a. Data from NDA appendix 8.4, table 27A.

Examination of the list of SAEs identified in the infusion studies found the following relevant differences.

Table 8.0.11c.4 (from 11.1.2.2) Hemic & lymphatic SAEs through 14 days in the 'long infusion' trials^a.

Serious Adverse Event	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=24	Nominal p Value
Sepsis	0 (0%)	2 (1%)	2 (1%)	0 (0%)	0.510

a. Data from appendix 8.4, table 27C and from company at request of reviewer.

Discontinuations

No discontinuations due to sepsis were reported.

Deaths

One death associated with severe infection occurred in the standard care group, and is summarized below.

1. *Subject 509-001 (Standard care: dobutamine)* Subject was a 61-year-old white man with a history of NYHA Class III CHF, a previous myocardial infarction, chronic renal insufficiency, non-sustained VT, and bradycardia. During the study, he was treated with dobutamine for 1 day with no improvement and was discharged to home at his request. On day 10, he was readmitted with bullous cellulitis. On study day 13, he developed worsening renal function and received hemodialysis beginning on day 19. On day 21, he died following a cardiac arrest, presumably associated with a myocardial infarction.

Special Studies: Changes in Mean Hematology Values

The changes in mean WBC count for the ‘all CHF’ and ‘long infusion’ trials are summarized below. In the ‘long infusion’ studies, there was a trend towards greater WBC # after 2 days in the nesiritide groups.

Table 8.0.11c.5 (from 11.1.4.2.2) Mean changes in WBC # from baseline for ‘all CHF’ trials^a.

WBC #	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
WBC #(10 ³ /mm ³)	+0.6±1.4	+0.9±1.6	+0.3±1.8	+0.6±1.9

a. Data from NDA volumes 79-80, starting with table 31A1.

Table 8.0.11c.6 (from 11.1.4.2.4) Mean changes in WBC# from baseline for all subjects in ‘long infusion’ trials^a.

WBC # Change from Baseline Day 2	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=24
WBC #(10 ³ /mm ³)	0.2 ± 1.43	0.9 ± 1.92	0.9 ± 1.66	1.8 ± 1.57

a. Data from supplemental data sets submitted at reviewer’s request.

Special Studies: Incidence of Elevated WBC Counts

In the long infusion population, but not in the CHF trials population, there was an association between dose of nesiritide and incidence of elevated WBC #.

Table 8.0.11c.7 (from 11.1.4.3.1b.1) Observed rate of increased WBC # in the ‘long infusion’ trials^a.

Time of WBC #above normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	14 (8%)	16 (10%)	22 (13%)	3 (12%)	0.408
Last Available on or before Day 2	2 (6%)	5 (14%)	6 (19%)	4 (25%)	0.468
Last Available on or before Day 5	11 (10%)	13 (11%)	24 (20%)	6 (25%)	0.069
Last Available	14 (10%)	16 (11%)	29 (20%)	4 (15%)	0.186

a. Data from NDA vol. 79, table 48C3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

There was also an increased incidence of elevated WBC # after 2 days in patients who started with a normal baseline WBC count in the long infusion studies. This trend was diminished in the later timepoints.

Table 8.0.11c.8 (from 11.1.4.3.1b.2) Observed incidence of increased WBC values after normal baseline value in the ‘long infusion’ trials^a.

Time of Increased WBC	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	2 (6%)	4 (11%)	3 (10%)	3 (19%)
Last Available on or before Day 5	8 (7%)	8 (7%)	10 (8%)	3 (13%)
Last Available	9 (7%)	11 (8%)	15 (10%)	2 (8%)

a. Data from supplemental table 48D4. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

Reviewer’s Conclusions Regarding Changes in WBC Count

Two parts of this review require comment. First, the observed increases in WBC count. While no mechanism for an effect of nesiritide on WBC count is evident, the data are consistent and roughly dose-dependent in the ‘long infusion’ studies. There is also an increase in the % of patients in the nesiritide group who develop elevated WBC counts relative to control (with a small number of patients overall). The data are consistent with the nesiritide causing hemoconcentration, related to the extravasation of fluid and proteins such as was seen for total protein and albumin, but no data exist to test this theory. This is also consistent with the effects reported for ANP.

The second aspect to this body system review that requires comment is the increased # of SAEs due to sepsis in the nesiritide group. While the numbers are provocative (0 cases in control, 5 cases in the nesiritide group), the data are inadequate to either conclude or exclude an effect of nesiritide on this adverse event.

In conclusion, there is a possible effect of nesiritide to increase WBC count. The data are inadequate to determine whether there is an effect of nesiritide on the incidence of sepsis.

8.0.11.d Platelet Count

AEs and SAEs

The incidence of AEs related to platelet function in the 'all CHF' and 'long infusion' trials are summarized below. In the long infusion group, the only patients who developed thrombocytopenia were in the control group.

Table 8.0.11d.1 (from 11.1.3.1) AEs related to platelets in 'all CHF' trials from NDA 20-920^a.

Adverse Event	Control n=235	Nesiritide n=505
Hemic & Lymphatic Thrombocytopenia	12 (5%)	17 (3%)
Ecchymosis	2 (2%)	5 (1%)
	4 (2%)	4 (1%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.11d.2 (from 11.1.3.2) AEs related to platelets in the first 14 days in 'long infusion' trials^a.

Adverse Event	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Hemic & Lymphatic Thrombocytopenia	9 (5%)	3 (2%)	8 (5%)	1 (4%)
Ecchymosis	3 (2%)	0 (0%)	2 (1%)	0 (0%)
	4 (2%)	1 (1%)	3 (2%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

No SAEs related to platelet count or function were reported.

Discontinuations and Deaths

No discontinuations or deaths directly attributable to changes in platelet count were reported.

Special Studies: Measured Changes in Lab Values

The table below summarizes the changes from baseline to 2 and 5 days for platelet count. At both time points the nesiritide group tended to have a higher mean platelet count.

Table 8.0.11d.3 (from 11.1.4.2.2) Mean changes in platelet count from baseline for all subjects in CHF trials^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Platelet #(10 ³ /mm ³)	21.9±27	10.7±30	-16.5±33	-10.9±37

a. Data from NDA volumes 79-80, starting with table 31A1.

Special Studies: Incidence of Abnormal Platelet Counts

There was no trend towards a higher % of either study group developing either abnormally low or high platelet counts.

Reviewer's Conclusions Regarding Platelet Counts

Similar to the data for the WBCs, there is an indication of increased platelet counts in the patients who received nesiritide. This effect, however, did not translate into an increase in abnormal platelet counts. The mechanism of this increase is unknown, but may be related to the hemoconcentration suggested by the sponsor as an explanation for the increase in hemoglobin and hematocrit (and discussed above in the WBC section).

In conclusion, the data support a possible association between nesiritide and a transient increase in platelet count.

8.0.11e Eosinophil Count

AEs and SAEs

There were no AEs or SAEs referable to eosinophilia in the database.

Discontinuations and Deaths

No discontinuations or deaths due to changes in eosinophil count were reported.

Special Studies: Changes in Eosinophil Lab Values

Eosinophil counts were not collected in the database.

Reviewer's Conclusions Regarding Eosinophilia

The database is inadequate to assess possible effects of nesiritide on eosinophil counts.

8.0.11f Allergic Reactions

AEs and SAEs

There were no AEs or SAEs referable to allergic reactions to nesiritide in the database. As an indirect marker for allergic reactions, the occurrence of pruritus and urticaria are summarized below.

Table 11.1.6.5.1 Pruritus, rash and urticaria in the long-infusion studies through day 14^a.

	Control n=173	Nesiritide n=0.015 n=169	Nesiritide n=0.030 n=167	Nesiritide n=0.060 n=26	Nominal p Value
Pruritus	4 (2%)	6 (4%)	6 (4%)	0 (0%)	0.844
Urticaria	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0.593
Rash	5 (3%)	2 (1%)	9 (5%)	0 (0%)	0.150

a. Data from supplemental table 11D per the sponsor.

Discontinuations and Deaths

No discontinuations or deaths due to allergic reactions to nesiritide were reported.

Special Studies: Development of antibodies to Nesiritide

The sponsor collected baseline and day 21 titers of anti-nesiritide antibodies in trial 704.325. A total of 61 subjects who received nesiritide had baseline and follow-up antibody titers measured, and none of the subjects had an increase in anti-BNP antibody titers at day 21, relative to baseline.

Reviewer's Conclusions Regarding Allergic Reactions

An association between nesiritide and allergic reactions, based on the available data, is unlikely.

8.0.12 Adverse Events in the Special Senses System

The following adverse event within the special senses system will be examined: amblyopia.

8.0.12a Amblyopia

AEs and SAEs

The incidence of amblyopia in the 'long infusion' and 'all CHF' trials is shown below. For both groups, the incidence of amblyopia was higher in the nesiritide group.

Table 8.0.12a.1 (from 11.1.3.1) Amblyopia as an AE in the CHF trials from NDA 20-920^a.

Adverse Event	Control n=235	Nesiritide n=505	Nominal p Value
Special Senses	5 (2%)	13 (3%)	0.803
Amblyopia	1 (0.4%)	7 (1.4%)	0.447

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.12a.2 (from 11.1.3.2) Amblyopia as an AE in the first 14 days in the nesiritide infusion trials^a.

Adverse Event	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value
Special Senses	3 (2%)	4 (2%)	5 (3%)	1 (4%)	0.602
Amblyopia	0 (0%)	1 (1%)	3 (2%)	1 (4%)	0.047

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

Discontinuations

The only discontinuation for amblyopia occurred in the nesiritide group.

Table 8.0.12a.3 (from 11.1.5.3.1) Discontinuations due to amblyopia in the long infusion trials^a.

AE	Placebo n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^b
Amblyopia	0 (0%)	1 (<1.0%)	0 (0%)	0 (0%)	0.677

a. Data from supplemental table 28D, with p Value per sponsor.

Deaths

No deaths due to amblyopia were reported.

Reviewer's Conclusions Regarding Amblyopia

Here again we are faced with an adverse event occurring at a higher frequency in the nesiritide group, but with very few overall cases in the database of a very uncommon adverse event. In addition, no animal data or putative mechanism for an effect of nesiritide on the eye is apparent.

In conclusion, the data are inadequate to assess the potential effect of nesiritide on amblyopia.

8.1 Medical Reviewer's Conclusions Regarding Nesiritide Safety

The three tables below summarize the information discussed in the sections above, and reflect this reviewer's judgement regarding the association of each adverse event with nesiritide administration. The strength of the association between nesiritide and a given adverse event is qualified as possible, probable, or definite in the individual reviews above, based on the conclusions of the Medical Reviewer.

Table 8.1.1 Adverse Events Possibly, Probably or Definitely Linked to Nesiritide Administration.

Body System	Adverse Event	Further Information
Cardiovascular	Hypotension	Section 8.0.2a
	Bradycardia	Section 8.0.2b
	Decreased Pulmonary Pressure	Section 8.0.2e
Urogenital System	Renal Failure ^a	Section 8.0.8a
GI System	Nausea	Section 8.0.4b
Nervous System	Confusion	Section 8.0.5a
Metabolic System	Hyponatremia	Section 8.0.6b
	Hyperglycemia/ Hypoglycemia	Section 8.0.6c
	Decreased Serum Total Protein & Albumin	Section 8.0.6e
Hemic & Lymphatic	Increased hemoglobin, hematocrit, & RBC count	Section 8.0.11a
	Increased WBC Count	Section 8.0.11c
	Increased Platelet Count	Section 8.0.11.d

a. Includes increased BUN and creatinine.

Table 8.1.2 Adverse Events that are Unlikely to be Associated with Nesiritide Administration.

Body System	Adverse Event	Further Information
Cardiovascular	Congestive Heart Failure ^b	Section 8.0.2d
	Other Ventricular & Atrial Arrhythmias	Section 8.0.2c
Body as a Whole	Headache	Section 8.0.3a
GI System	Increased AST/ALT	Section 8.0.4a
Metabolic System	Hyper- and Hypo-kalemia	Section 8.0.6a
Hemic & Lymphatic	Allergic Reactions to Nesiritide	Section 8.0.11f
Musculoskeletal System	Myalgias	Section 8.0.10a

a. This refers to CHF reported as an adverse event, not to the efficacy of nesiritide in the treatment of CHF.

Table 8.1.3 Adverse Events for Which Inadequate Data Exist to Determine Association with Nesiritide Administration.

Body System	Adverse Event	Further Information
Cardiovascular System	ECG Abnormalities	Section 11.1.4.5
Nervous System	Dizziness	Section 8.0.5a
	Nervousness	Section 8.0.5a
Urogenital System	Severe Renal Injury ^a	Section 8.0.8a
	Urinary Abnormalities	Section 11.1.4.5
Musculoskeletal System	Leg Cramps	Section 8.0.10a
Metabolic System	Hypermagnesemia	Section 8.0.6d
Hemic & Lymphatic	Sepsis	Section 8.0.11c
	Eosinophil Count	Section 8.0.11e
Special Senses System	Amblyopia	Section 8.0.12a

a. Renal adverse events resulting in permanent loss of renal function, including nephrotic syndrome, need for dialysis, papillary necrosis, and interstitial nephritis.

9.0 Combined Efficacy/ Safety Summary of Medical Reviewer

A recent Advisory Committee meeting discussed a 'Proposed Guidelines for the Clinical Evaluation of Drugs for the Treatment of Heart Failure'. In it, approval of an agent for short-term use in CHF is to be based on the demonstration in controlled clinical trials that 4 conditions are met. Each conditions, as it appears in the draft guidance, will be followed by the Medical Reviewer's opinion about nesiritide's success in meeting that condition.

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

A hemodynamically-significant effect of nesiritide compared with placebo was demonstrated for periods up to 24 hours in two trials. The hemodynamic effects of nesiritide are dose-dependent over a relatively narrow (2-fold) range of nesiritide doses (0.3 µg/kg bolus + 0.015µg/kg/min infusion up to 0.6 µg/kg bolus + 0.030 g/kg/min infusion). In trial 704.325 there was an association between the dose of nesiritide, resultant serum concentration of nesiritide and a decrease in PCWP at the end of 6 hours. The mechanism of this improvement in hemodynamics is likely a combination of the known vasodilatory properties of nesiritide, in combination with an effect of nesiritide to increase the vascular permeability to small molecules, including proteins, allowing for fluid redistribution. The relative contributions of these two effects is unknown.

The available data suggest that the pharmacodynamic effects of a given dose of nesiritide are hard to predict in a given patient, and that several hours (4-6) must pass before the maximal pharmacodynamic effect can be assessed. They also suggest that once nesiritide is discontinued, 2-4 hours pass before the pharmacodynamic effect of nesiritide is lost.

The data available do not suggest the development of 'tolerance' to nesiritide of sufficient magnitude to reverse the overall significant effects of nesiritide in the whole population, although its development in sub-groups cannot be excluded. The data do suggest that the magnitude of the hemodynamic effect decreases between 3 and 24 hours. No hemodynamic data beyond 24 hours is available. Since the primary mechanism of action of nesiritide is the same as that of nitrates, a concern is whether additional data regarding the 24-48 hour period is needed, which is when the majority of the tolerance to IV nitrates develops.

Another aspect of dosing is the interaction between nesiritide and other vasoactive compounds (e.g., nitroprusside). With the exception of IV nitroprusside, data are available on the potential interactions between nesiritide and other parenteral vasoactive compounds in trials 704.325 and 704.326. There are two parts to the data. First, no patient who first received another parenteral agents was then administered nesiritide, either alone or in combination with the other drug. This limits our ability to recommend nesiritide dosing for patients who begin one vasoactive compound, and the physician considers starting nesiritide. Second, there were patients in both trials who were started on other vasoactive compounds after starting nesiritide. For patients stopping nesiritide and starting another agent, there were 59 such patients. For patients being co-administered another vasoactive compound with nesiritide, there were 50 such patients.

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

Use of the drug at doses within a defined therapeutic range

The therapeutic range defined by the trials in the NDA is narrow as discussed above. There is insufficient data to determine if there will be an interaction between nesiritide and other vasodilators that also act through the cGMP-dependent pathways (especially nitrates such as NTG and nitroprusside).. The higher dose of nesiritide (0.060) was not used in the two pivotal infusion studies (704.325, 704.326), related to the increased incidence of hypotension in that population in trial 704.311. Lower doses of nesiritide (<0.015µg/kg/min) were not adequately evaluated to determine their clinical efficacy, although the bolus studies suggest they have hemodynamic effects.

The use of nesiritide is also associated with another potential problem not shared by other available therapies that work by activating the cGMP-dependent protein kinase (NTG, nitroprusside): long pharmacodynamic half-life. Depending on the data used, the half-life of hemodynamic effects for nesiritide is approximately 2-3 hours, compared with minutes in the case of NTG and nitroprusside. This means that once the drug is started, no reasonable inference regarding its peak effect can be made before at least 6 hours has passed. It also means that the drug will have a persistent hemodynamic effect following withdrawal. These two properties will make this drug more difficult to titrate, as well as more difficult to manage any observed side-effect.

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

(1) Improvement in symptoms and/or stabilization of clinical status

Trial 704.325

With regard to improvement in symptoms, nesiritide was significantly better than placebo in one trial at improving the signs and symptoms of CHF through 6 hours. This trial (704.325) compared the effects of nesiritide in 85 patients with placebo in 42 patients. The weaknesses of the data collection in this trial have been discussed above, and these severely limit the independence of the symptom-relief and hemodynamic data for this trial. Since the same investigator who performed the investigator's assessment also filled out the patient's assessment, these data cannot be taken as independent (especially since the investigator also knew the PCWP data). In addition, the trial had some potentially confounding demographic imbalances at baseline, most significantly the higher percentage of females in the nesiritide high-dose group (40%) compared with placebo (21%). There was good agreement between the investigator's and patient's assessments of clinical status, and the symptomatic benefit was seen for both global assessments and for individual signs and symptoms at the end of 6 hours. These improvements, however, extended to 'symptoms' for which a change within 6 hours is highly suspicious (i.e., appetite, edema), again calling into question the validity of the data.

The sponsor also demonstrated an association between the degree of change in PCWP and an improvement in the global assessment score using data from trial 704.325. This, in combination with the earlier association between the dose of nesiritide and the degree of change in hemodynamics (especially PCWP), would support a link between the doses of nesiritide used in the trials, a pharmacodynamic effect (decreased PCWP) and a clinical outcome (improved Global Assessment score after 6 hours). These data suffer from the same problems discussed above.

Finally, the data from trial 704.325 suggest a small effect of nesiritide to decrease the median respiratory rate through 6 hours, relative to placebo. This difference was small (2 breathes per minute).

Thus, while the data, if replicated and convincing, could provide data for a beneficial effect of nesiritide on CHF symptoms, given the problems discussed above, they should be viewed as suggestive, and not definitive.

Trial 704.326

In study 704.326, the effect of nesiritide was compared with the current parenteral standards of care (nitroprusside, dobutamine, and dopamine). Through the end of 24 hours of study drug infusion, the effects of nesiritide on symptomatic benefit were similar to those of the standard agents. Overall, the effects of nesiritide and the active controls on CHF symptoms were similar, with no indication of superiority for nesiritide.

(2) a meaningful improvement in end-organ function that is deemed to be clinically relevant; (3) a decrease in the need for or duration of intensive care, specialized interventions or hospitalization; and/or (4) a reduction in the risk of death.

Nesiritide had no significant or clinically relevant beneficial effects on any end organ function, need for/or duration of intensive care, specialized interventions or hospitalization, or a reduction in the risk of death. As discussed above, there is persuasive evidence for an adverse effect of nesiritide on renal function, as marked by changes in serum creatinine. There is less definite evidence suggesting a beneficial effect of nesiritide to reduce ventricular arrhythmias.

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

In the one long infusion trial, enrolling 'stable' decompensated CHF patients, when the effects of nesiritide withdrawal on PCWP were evaluated (704.311), no evidence of rebound or relapse was detected. In two other trials, which enrolled a more acutely decompensated CHF population (704.325 and 704.326), there was no clear evidence that patients withdrawn from nesiritide had a higher rate of re-hospitalization for CHF, compared with active controls.

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

Follow-up through approximately 21 days revealed that nesiritide administration was possibly, probably, or definitely associated with several safety concerns, both short- and long-term. Of these adverse events, the increased incidence of hypotension, bradycardia, and the development of abnormal renal function are most worrisome.

Hypotension

There is a definite association between nesiritide use and clinically-significant hypotension, as assessed by:

- 1) the greater incidence of symptomatic hypotension in the nesiritide groups.
- 2) the increased incidence of discontinuations for decreased BP.
- 3) the greater severity of the hypotension in the nesiritide groups, as judged by degree of decrease in blood pressure, severity as judged by investigators, or duration.
- 4) the presence of individuals who developed hypotension during nesiritide infusion who had clearly adverse clinical outcomes and/or required additional medical interventions (see table 8.0.2b.20).
- 5) data from trial 704.326, comparing nesiritide with current therapy, which shows that hypotension leading to discontinuation of drug within 6 hours of initiation was significantly more common with nesiritide. These data are of particular interest, since they suggest that the use of nesiritide in practice will lead to significantly more hypotension than is caused by the drugs in current use. This statement is limited by the fact that 704.326 enrolled very few patients who received pure vasodilators (IV 18 got NTG, none NTP). There is, then, no way to know the frequency of these same adverse events for the other pure vasodilators (NTG, NTP). Given that the pharmacodynamic half-life of these agents is significantly shorter, it is possible that fewer episodes of severe hypotension or renal failure would be seen with these agents.

This effect is dose-dependent over the range of nesiritide doses tested in the three long infusion trials, with the highest incidence of severe hypotension seen in the 0.30 and 0.060 nesiritide dose groups.

Bradycardia

With regard to bradycardia, there is a definite association between nesiritide use and bradycardia, including bradycardia requiring medical intervention. More individuals in the nesiritide group were discontinued due to bradycardic events. In addition, some individuals who developed bradycardia with nesiritide required additional medications, including pressors, fluids, and atropine.

Renal Failure

There is a definite association between nesiritide use and the development of abnormal renal function, both assessed by elevated BUN/Creatinine and by the occurrence of adverse renal events. The incidence of a >50% increase in serum creatinine was nominally significantly higher in the nesiritide group in trial 704.326, as was the incidence of increases >0.5 mg/dl. Both of these measures identify populations who have developed significant renal compromise. There were also individuals who developed progressive increases in BUN/Crt consistent with a significant renal insult during and following nesiritide infusion. The clinical consequences of the renal failure are also not yet fully established, but the data suggest the majority of individuals who had renal injury in the infusion trials recovered to near baseline given sufficient follow-up. The database is too small to conclude that no patients will suffer clinically significant adverse renal events associated with the use of nesiritide.

Further, in the absence of urinalyses, some forms of renal injury could not be detected (especially nephrotic syndrome). Further, absent urinalyses, no firm conclusions can be drawn about the etiology of the observed increases in serum creatinine in the nesiritide groups (i.e., interstitial nephritis, acute tubular injury, and 'pre-renal' azotemia).

Another issue that complicates the effects of nesiritide on end-organ perfusion, and by extension on the incidence of renal damage, is the unknown contribution of nesiritide effects on vascular permeability. That effect is real is suggested by the data from ANP, as well as with the observed hemoconcentration that occurred during nesiritide infusion. The effect of this hemoconcentration will be to remove salt and water from the vascular space, where it is 'accessible' to the kidneys (and can then be excreted), and to translocate it to the interstitium. This observation may help explain the anti-natriuresis seen in the first 24 hours in study 704.311. It would also lead to a prediction of increased renal toxicity for patients who begin the trial with marginal perfusion of their kidneys. While such an insult is potentially reversible in most patients, there will likely be an increased incidence of severe renal injury in patients where their volume status is less carefully monitored than was the case in the NDA trials. If investigators follow weights as markers for fluid loss, they will be overly aggressive with their use of diuretics, as they will see no net weight loss. What they will miss is the fluid translocation, which will have the effect of fluid removal from the intravascular space, placing the kidneys at increased risk of injury from inadequate perfusion.

Other Adverse Events

Of the other adverse events, several of them can be linked via an effect of nesiritide to alter vascular permeability (increased RBCs, increased platelet count, increased WBCs, decreased total protein, decreased albumin). If this mechanism is operant, as has been reported for ANP and postulated by the sponsor (refs. 1, 6, 10, 13), then part of the hemodynamic effects of nesiritide may be related not to its vasodilatory properties but rather to its stimulating transudation of proteins (albumin, total protein) followed by water. Depending on the reversibility of this effect following nesiritide withdrawal, this might increase the risk of damage to critical organs (such as the kidney, as discussed above) by decreasing the effective intravascular volume in a way that is not amenable to withdrawal of the drug. In support of this speculation, the effects of nesiritide on total protein and albumin persisted beyond the period of nesiritide infusion (see section 8.0.6e above). Finally, there are some adverse events possibly linked to nesiritide administration, for which the data are inadequate to assess their clinical relevance. These include the small changes in electrolytes, hypo- and hyperglycemia, nausea and confusion.

Recommendations of Medical Officer

The data clearly demonstrate a significant hemodynamic effect of nesiritide that is dose-dependent and persists for at least 24 hours. Nesiritide was assessed over a narrow dose-range that is insufficient to detail the association between a given dose of nesiritide and the anticipated hemodynamic effect. Lower doses of nesiritide, with potential hemodynamic effects, were not explored adequately. The available data does show a dose-response curve for the administration of nesiritide and changes in hemodynamics, especially PCWP. Following discontinuation of nesiritide, hemodynamics return to baseline within 4 hours, without evidence for 'rebound.' While the effect of nesiritide on mean hemodynamics may diminish slightly with time, the significant effects of nesiritide on hemodynamics compared with placebo persist through 24 hours. Insufficient data are available to comment on the following critical aspects of use:

- 1) information about the use of nesiritide in patients who are already taking other parenteral CHF therapies (especially other vasodilators),
- 2) information regarding the use of nesiritide in patients with CHF and myocardial infarction (these patients were excluded from the three pivotal trials),
- 3) information regarding the titration of nesiritide to achieve desired clinical effect,
- 4) information regarding the development of tolerance beyond 24 hours (where tolerance to nitrates develops), and
- 5) information about the effects of nesiritide at infusion doses below 0.015 µg/kg/min.

The link between nesiritide administration and clinical benefits is tenuous, with a single study (704.325) supporting a greater acute effect of nesiritide than placebo on the signs and symptoms of CHF through 6 hours. While this trial also suggest a link between the clear effects of nesiritide on PCWP and the observed improvement in signs and symptoms of CHF, problems in the collection of these data undermine their independence and strength. Another piece of data supporting a salutary effect of nesiritide on CHF is the small decrease in respiratory rate seen in the nesiritide groups, when compared with placebo. The data from trial 704.326 suggests that the effects of nesiritide on CHF signs and symptoms is comparable to the active controls with regard to symptomatic relief over the first 24 hours of therapy, although the data collection was, again, open-label. No other beneficial or adverse clinical effect of nesiritide (i.e., re-hospitalization rate, mortality rate) was suggested by the data in the NDA.

With regard to the safety profile of nesiritide, two features of nesiritide predict that its use will be associated with significant clinical adverse events. First, it operates via the same mechanism as currently available therapies (NTG, nitroprusside) with the added disadvantage of prolonged pharmacodynamic half-life. This prolonged half-life will make its use more difficult than for current therapies, and may increase the risk of adverse events and the need for hospital interventions (e.g., for prolonged hypotension).

Second, the administration of nesiritide under study conditions was associated with clinically significant adverse events at a higher rate than the comparators (either placebo or the active controls). Most concerning in this regard, severe hypotension was significantly more common following nesiritide use, compared with either the currently available parenteral therapies for CHF or with placebo. Unfortunately, no risk factors to identify patients at high risk for these hypotensive episodes were found. Bradycardia and adverse renal events were also more common following nesiritide use. While more data is needed to place the risk of these adverse events into clinical context, the NDA does suggest that some patients taking nesiritide will suffer significant clinical consequences related to these adverse events.

Recommendations of Medical Officer (cont)

Third, with regard to less common adverse events, inadequate data are available to fully assess the clinical consequences of some of the more potentially serious adverse events associated with nesiritide use, as well as for several other adverse events with potential clinical relevance (e.g., hypermagnesemia, hyperglycemia). In particular, the database is insufficient to exclude severe effects on the kidney, in part because of the absence of urinalysis data, and on the liver.

Nesiritide, then, has a demonstrated hemodynamic effect that is superior to placebo and persists through at least 24 hours. There is a suggested effect of nesiritide to relieve some of the acute symptoms of CHF, similar to currently available therapies. The available data are insufficient to demonstrate superiority of nesiritide to placebo with regard to symptom relief, which appears at best to be similar to the effects of other currently available parenteral therapies. Nesiritide use is associated with several clinically relevant adverse effects, especially hypotension. The prolonged pharmacodynamic half-life of nesiritide predicts that this hypotension will be more difficult to manage than for currently available therapies that work by the same intracellular mechanism (NTG, nitroprusside). Finally, the database is inadequate to address several important questions regarding its use: concomitant use of other parenteral vasodilators, potential titratability of nesiritide, the use in patients with acute myocardial ischemia, potential effect of nesiritide on vascular permeability, potential for the development of tolerance beyond 24 hours, and effective lower dose. With the availability of other therapies also working through the cGMP-dependent protein kinase to cause vasodilatation that have a shorter pharmacodynamic half-life, the presence of significant safety concerns, and the inadequate database, nesiritide is not approvable.

10.0 References

1. Allgren, R.L., T.C. Marbury, N. Rahman, J.D. Conger, and M.H. Sayegh. 1997. Aniridine in acute tubular necrosis. *New England Journal of Medicine* 336:828-834.(Abstr.)
2. Cargill, R.I., P.B.M. Clarkson, and T.M. MacDonald. 1995. Profound vagal reactions to brain natriuretic peptide. *Journal of Molecular Medicine* 73:149-150.
3. Clavell, A.L., A.J. Stingo, L.L. Aarhus, and J.C. Burnett. 1993. Biological actions of brain natriuretic peptide in throacic inferior vena caval constriction. *American Journal of Physiology* 265:R1416-R1422
4. Clemo, H.F. and B.S. Stambler. 1996. Atrial natriuretic peptide and cardiac electrophysiology. *Journal of Cardiovascular Electrophysiology* 7:149-162.
5. Eiskjaer, H., Nielsen, C. B., and Pedersen, E. B. Renal and hormonal actions of atrial natriuretic peptide during angiotensin II or noradrenaline infusion in man. *European Journal of Clinical Investigation* 26, 584-595. 1996.
6. Huxley, V.H., V.L. Tucker, K.M. Verburg, and R.H. Freeman. 1987. Increased capillary hydraulic conductivity induced by atrial natriuretic peptide. *Circulation Research* 60:304-307.
7. Koller, K.J. and D.V. Goeddel. 1992. Molecular biology of the natriuretic peptides and their receptors. *Circulation* 86:217-224.
8. Lewis, J.B., M. Salem, F. McGrew, T.C. Marbury, and R.L. Allgren. 1998. Results of the atrial natriuretic peptide clinical trial in oliguric acute renal failure. *J Am Soc Nephrol* 9:134A(Abstr.)
9. McDonagh, T.A., S.D. Robb, D.R. Murdoch, J.J. Morton, and J.J. McMurray. 1998. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 351:9-13.
10. 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
11. Suga, S., K. Nakao, K. Hosoda, Y. Kambayshi, and H. Imura. 1992. Receptor selectivity of natriuretic peptide family, atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide. *Endocrinology* 130:229-239.
12. Yoshimura, M., H. Yasue, and H. Imura. 1991. Hemodynamic, renal, and hormonal responses to brain natriuretic peptide infusion in patients with congestive heart failure. *Circulation* 84:1581-1588
13. Watenpaugh, 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.
14. Lang, C.C., Motsani, J.G., et al. 1992. Clearance of brain natriuretic peptide in patients with chronic heart failure: indirect evidence for a neutral endopeptidase mechanism by against an atrial natriuretic peptide clearance receptor mechanism. *Clinical Science* 82: 619-623.
15. 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.

cc: ORIG: NDA 20-912

HFD-110 Division File

HFD-110/CSO

HFD-110/Medical Officer

HFD-110/Team Leader

HFD-110/Division Director

HFD-110/ Statistical Reviewer

HFD-110/

HFD-110/

Diana Willard

Douglas Throckmorton

Abraham Karkowsky

Raymond Lipicky

Lu Cui

George Chi

Kooros Mahjoob

11.0 Appendix One: Methodologies Used for Safety Review

The safety review is broken into three logical sections, two of which appear in this appendix:

11.0 Methodologies used for Safety Review

11.1 Background Database for Safety Review

The third part of the safety review, the Integrated Review of Safety, is found in section 8.0 above.

11.0 Methodologies Used for Safety Review

11.0.1 Subsections of the Integrated Safety Review and Preliminary Comments

Section 11.0 will use the following outline:

- 1) Source materials for the safety review, including the numbers of subjects exposed in each of the treatment groups, along the extent of exposure;
- 2) General methodologies used to elicit adverse events within the database;
- 3) Specific search strategies used in the nesiritide database.

11.0.2 Source Materials and Methods for the Integrated Safety Review

The nesiritide NDA database includes 8 clinical trials in CHF, as summarized below. Details of the data submitted for each of these trials is to be found in sections 1.1 and 5.1 above, as well as in the reviews of each study. No follow-up safety data collected after submission of the NDA is available to this reviewer.

Table 11.0.2.1 (from table 5.1.1.1) Number of subjects in the trials submitted as part of the NDA database, grouped according the study drug administered^a.

Protocol	Control	Nesiritide	Trial Design
Phase II Dose-Ranging Studies			
704.305	6	24	Randomized, double-blind, placebo-controlled, single-dose bolus (0.3, 1.3, 10 or 15 µg/kg/min vs. placebo) study measuring hemodynamics.
704.306	4	12	Randomized, double-blind, placebo-controlled, four hour infusion (0.025 or 0.05 µg/kg/min vs. placebo) study measuring hemodynamics, neurohormone levels and renal function.
704.307	N/A (19) ^b	20	Randomized, double-blind, placebo-controlled, cross-over, escalating dose-infusion (0.003, 0.01, 0.03, and 0.1 µg/min) study measuring hemodynamics and renal function.
704.309	16	44	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Three doses (5 or 10 µg/kg q4 hours for 24 hours or 10 µg/kg q6 hours) were compared with placebo for hemodynamics & 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	505	

a. Data from NDA volume 78, table 1.

b. Cross-over designed trial.

Demographics of Renal Failure as an AE

1. Age

Adverse events related to renal function^a occurred at equal, low, rates in the < and >65 years of age groups.

Table 8.0.8a.9 Urogenital AEs in the 'long infusion' population^a according to age.

	Control	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
<65 Years Old	n=103	n=100	n=90	n=17	
Creatinine Increased	4 (3%)	3 (3%)	8 (9%)	1 (6%)	0.253
Kidney Function Abnormal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	--
Acute Kidney Failure	2 (2%)	1 (1%)	2 (2%)	0 (0%)	0.899
BUN Increased	4 (4%)	3 (3%)	2 (2%)	0 (0%)	0.948
>65 Years Old	n=70	n=69	n=77	n=9	
Creatinine Increased	3 (4%)	7 (10%)	7 (9%)	0 (0%)	0.499
Kidney Function Abnormal	0 (0%)	1 (1%)	2 (1%)	0 (0%)	0.692
Acute Kidney Failure	1 (1%)	0 (0%)	1 (1%)	1 (11%)	0.132
BUN Increased	3 (4%)	6 (9%)	3 (4%)	0 (0%)	0.553

a. Data from supplemental data table 13D at request of reviewer. Reflects trials 311, 325, and 326 data. p Value per sponsor.

2. Gender

Urogenital AEs occurred rarely, and there was no apparent influence of gender on their incidence.

Table 8.0.2b.10 Urogenital AEs in the 'long infusion' population^a according to age.

	Control	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
Men	n=127	n=120	n=113	n=23	
Creatinine Increased	7 (6%)	6 (5%)	11 (10%)	1 (4%)	0.478
Nephritis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	--
Kidney Function Abnormal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	--
BUN Increased	7 (6%)	6 (5%)	3 (3%)	0 (0%)	0.618
Women	n=46	n=49	n=54	n=3	
Creatinine Increased	0 (0%)	4 (8%)	4 (7%)	0 (0%)	0.221
Nephritis	0 (0%)	0 (0%)	0 (0%)	1 (33%)	0.020
Kidney Function Abnormal	0 (0%)	0 (0%)	2 (4%)	0 (0%)	0.357
Acute Kidney Failure	0 (0%)	0 (0%)	2 (4%)	1 (33%)	0.020
BUN Increased	0 (0%)	3 (6%)	2 (4%)	0 (0%)	0.389

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

3. Other Medications

There were no obvious interactions with nesiritide and other drugs which were associated with increased incidence of elevated creatinine as an AE, although the number of such patients was quite low in any of the trials, even in 704.326.

Table 8.0.2b.11 'Elevated Creatinine' as an AE, arranged by use of other medications in addition to nesiritide from study 704.326.

Elevated Creatinine in 704.326	Nesiritide 0.015 and 0.030 µg/kg/min
ACE Inhibitor Use	
Yes	3/124 (2%)
No	2/49 (4%)
Digoxin Use	
Yes	2/117 (2%)
No	2/45 (4%)
Beta Blockers	
Yes	0/18 (0%)
No	6/183 (3%)

a. Data from ISS table 8-39, reflecting trial 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

Of the eight clinical trials in CHF, there were two clinical trials that primarily support the efficacy of the drug: 1) A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Ranging Study to Evaluate the Safety and Efficacy of a 24 Hour Intravenous Infusion of Natrecor hBNP in Subjects with Congestive Heart Failure (Trial #704.311, abbreviated Trial 311 in this review); and 2) A Randomized, Double-Blinded, Placebo-Controlled Study of Two Doses of Natrecor hBNP Administered as a Constant Infusion in Subjects with Decompensated CHF (Trial #704.325, abbreviated Trial 325 in this review). A third, open-label trial was also performed which included a substantial fraction of the total patient database, and focused on the safety of nesiritide in the decompensated CHF population (Trial #704.326, abbreviated Trial 326 in this review).

11.0.2 Source Materials and Methods for the Integrated Safety Review (cont)

Demographics

The demographics of the NDA population were summarized in section 5.1.2 above. Overall, the populations of the treatment groups were well-balanced, although in the placebo-controlled CHF trials the placebo group had a higher percentage of females and subjects >65 years of age (see table 5.1.2.2).

Natrecor Dose Exposure

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

Table 11.0.3.1 (from 5.1.3.1) Subjects enrolled in nesiritide infusion studies in NDA 20-920^a.

Duration of Infusion	Control		Infusion Nesiritide ^b			
	Placebo	Std. Care	<0.015	≥ 0.015 -<0.020	0.020-<0.035	>0.035
0-12 hrs	26	5	3	25	36	20
12-26 hrs	26	33	17	71	62	16
26-50 hrs		28	8	27	33	
50-100 hrs		48	4	23	21	3
>100 hrs		30	1	11	10	3
Total	52	144	33	157	162	42
% of all Nesiritide subjects (n=505)	--	--	6%	31%	32%	8%

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

b. Mean infusion dose in $\mu\text{g}/\text{kg}/\text{min}$. Any subject who received nesiritide at 0.015 $\mu\text{g}/\text{kg}/\text{min}$, and had their dose reduced at any time were counted in the <0.015 group (there were 18 such patients).

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

Table 11.0.3.2 (from 5.1.3.2) Subjects in bolus studies with nesiritide in NDA 20-920^a.

Bolus Studies	Control		Bolus Nesiritide	
	Placebo	Std. Care	≤ 21 $\mu\text{g}/\text{kg}$	> 21 $\mu\text{g}/\text{kg}$
	39	0	45	66
% of all Nesiritide subjects (n=505)	--	--	9%	13%

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

Collection of safety data

The collection of safety data varied somewhat from trial to trial. The timing of safety data collection for the three largest trials (311,325 and 326) are summarized in the three tables below.

In trial 704.311 adverse events were collected during the infusion and through day 14 after the end of infusion. Collection of other relevant safety data, including labs and vital signs, is shown below.

Table 11.0.3.3 (from 6.1.10.1) Timetable for clinical observations and lab measurements in trial 704.311^a.

Time (hrs)	Pre-infusion	Start infusion				Stop Infusion	Post-Infusion			
		0	6	12	24		48	Day 1	Day 7	Day 15
Drug Infusion										
History & Physical	X						X			
Vital Signs	X									
ECG	X									
Urine Collection (24 hr)										
CPK with isoenzymes										
Laboratories ^c	X	X					X			X
Hematology ^c	X	X					X			X
Plasma nesiritide		X	X	X	X	X	X			
Plasma nesiritide Ab		X								X
F/U Telephone call								X	X	
Adverse Events (AEs)										

a. Data from NDA volume 54, page 24.

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

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

In study 704.325, adverse events were collected through day 14 post-treatment as reported by investigators. Additionally, on day 21, the subject's clinical course was reviewed with regard to the following: mortality status; duration of initial hospitalization; need for re-admission during the 21-day period; length of time on parenteral therapy for CHF; and the need for intubation, dialysis, and ultrafiltration.

Table 11.0.3.4 (from 6.2.10.1) Timetable for clinical observations and lab measurements in study 704.325^a.

Procedure	Screen	Treatment Period										Post-Treatment				
		0	1.5	3	4.5	6	24	36	48	Day 3	Day 4	Day 5	<24 hrs after IV Tx	14	21	
Time																
Med Hx, Physical Exam	X															
ECG	X															
Vital Signs	X	X														
CBC, Chemistries ^b	X	X						X								
Plasma hBNF levels	X				X ^e											
Renin, aldo, nor pi levels	X				X ^f											
hBNP Antibody level	X				X			X								
I/Os, weights	X	X			X			X								
Na, K, CO ₂ , Cl, Crt, BUN	X	X			X			X								
Adverse Events	X	X			X			X								
F/U Visit	X	X			X			X								
Study Drug	X	X			X			X								

a. Data from NDA volume 59, page 25.

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

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

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

e. Nesiritide subjects only.

f. Norepinephrine levels at selected sites only

g. Administration after 24 hours at discretion of investigator.

The table below details the type and timing of the clinical information collected during study 326. In general, AEs were collected through 14 days. Serious adverse events and deaths occurring within 21 days were also to be reported by the investigators.

Table 11.0.3.5 (from 6.3.10.1) Timetable for clinical observations and lab measurements in the study 326^a.

Procedure	Pre-infusion	Study Drug Infusion						Post-Infusion		
		0	1	2	4	6	24 ^e		Within 24 hrs	Day 14
Time (hrs)										
Informed Consent	X									
Medical History/ PE	X									
ECG	X									
Holter Monitors ^f	See Note									
CXR	X									
D/C Parenteral Cardiac Meds	X ^b									
Vital Signs	X	X	X	X	X	X	X ^c			
CBC, Chemistries ^d	X							X		
Anti-BNP antibody level	X									X
Assess Signs/ Sxs of CHF	X						X	X		
Assess Global Clinical Status							X	X		
Study Drug Administration		X	X	X	X	X	X	X		
Daily Weight							X			
Daily Na, K, CO ₂ , Cl, Crt, and BUN							X			
Adverse Event Collection										
F/U Visit										X

a. Data from NDA volume 66, page 14.

b. Parenteral meds to be discontinued only if taken for <4 hours. Patients who received parenteral therapy for CHF for >4 hours before entry were not eligible for the study.

c. Includes period during total period of parenteral therapy. Vital signs were obtained every 4 hours during the parenteral therapy.

e. Includes tests performed during extended parenteral therapy.

f. Holter monitors were performed at 15 sites for a maximum period during 72 hours of infusion.

11.0.4 General Methodologies Used for Safety Review

This section details the examination of AEs in the nesiritide safety database. In general, this was accomplished by examination of two data sets. The first comes from all patients with CHF who received nesiritide as part of the NDA. This will be used especially for overall adverse events incidence and for changes in measured values (labs, vital signs). The other primary data set used for analysis comes from the three 'long infusion' studies, which have been reviewed individually earlier in this review. This set will also be used for AEs, including measured AEs. The examination of dose-response effects of nesiritide will also use this data set. Wherever possible, all AEs potentially linked to the administration of nesiritide are further examined for dose-, time-, sex-, age-, race-dependency. The impact of other medications (ACE inhibitors, beta blockers, and digoxin) and the original etiology of the CHF will also be considered where possible. The small number of adverse events reported for many of the subgroups will complicate these examinations. The sponsor has prepared the majority of the data sets examined, and no independent confirmation of their accuracy has been performed. Any primary analysis performed by FDA reviewers will be identified as such. Unless stated otherwise, all p Values are per the sponsor, and the reader is referred to their documents for details of statistical analysis.

The data tables below have been submitted to the sponsor to allow for correction of typographical or other errors of presentation wherever possible. For all data presentation, nominal statistical significance (relative to placebo or baseline at a $p < 0.05$) will be indicated by the use of shading for the relevant data. In many cases, the sponsor-derived p Value will also be stated. Details of the statistical methodology used by the sponsor to derive individual p Values are to be found in the NDA submission.

The comparative rates of adverse events for the three nesiritide dose groups also requires comment. With only 26 subjects in the highest nesiritide dose group (0.060 $\mu\text{g}/\text{kg}/\text{min}$), adverse event rate comparisons with the other nesiritide dose groups need to be interpreted with great caution.

A note also needs to be made about the conventions used for the labels in the data summary below. The long infusion trials had small differences in the doses of nesiritide used, especially with regard to the dose of the nesiritide bolus prior to the start of the infusion.

704.311

There were four treatment groups in study 704.311:

- Group 1: Nesiritide: IV bolus of 0.25 $\mu\text{g}/\text{kg}$ followed by a 0.015 $\mu\text{g}/\text{kg}/\text{min}$ infusion.
- Group 2: Nesiritide: IV bolus of 0.50 $\mu\text{g}/\text{kg}$ followed by a 0.030 $\mu\text{g}/\text{kg}/\text{min}$ infusion.
- Group 3: Nesiritide: IV bolus of 1.0 $\mu\text{g}/\text{kg}$ followed by a 0.060 $\mu\text{g}/\text{kg}/\text{min}$ infusion.
- Group 4: IV bolus of placebo followed by a placebo infusion.

704.325

There were three treatment groups in study 704.325:

- Group 1: Nesiritide: IV bolus of 0.3 $\mu\text{g}/\text{kg}$ followed by a 0.015 $\mu\text{g}/\text{kg}/\text{min}$ infusion.
- Group 2: Nesiritide: IV bolus of 0.6 $\mu\text{g}/\text{kg}$ followed by a 0.030 $\mu\text{g}/\text{kg}/\text{min}$ infusion.
- Group 3: IV bolus of placebo followed by a placebo infusion.

704.326

There were three treatment groups in study 704.326:

- Group 1: Nesiritide: IV bolus of 0.3 $\mu\text{g}/\text{kg}$ followed by a 0.015 $\mu\text{g}/\text{kg}/\text{min}$ infusion.
- Group 2: Nesiritide: IV bolus of 0.6 $\mu\text{g}/\text{kg}$ followed by a 0.03 $\mu\text{g}/\text{kg}/\text{min}$ infusion.
- Group 3: A standard care agent.

In presenting the safety data, the doses of nesiritide have been 'lumped' according to their infusion dose. These will be listed as nesiritide 0.015 or 0.015 $\mu\text{g}/\text{kg}/\text{min}$, nesiritide 0.030 or 0.30 $\mu\text{g}/\text{kg}/\text{min}$, or nesiritide 0.060/0.060 $\mu\text{g}/\text{kg}/\text{min}$. Given the small number of patients available for the safety summary, this 'lumping' was judged by the Medical Reviewer as in the interest of effective review. Where individual trial data is summarized, the bolus information will be included that is correct for the trial in question.

11.0.4.1 Approach to Eliciting Deaths and Serious Adverse Events

In the nesiritide NDA, an adverse experience (AE) was considered serious if the event resulted in one of the following: death; permanent or substantial disability; inpatient hospitalization; prolongation of existing inpatient hospitalization; cancer; or congenital anomaly. An adverse experience was also considered serious if it was considered to be immediately life-threatening, or was identified as such by the individual investigator. Overdoses (accidental or intentional) were also considered to be serious adverse experiences, whether or not they resulted in any clinical sequelae.

The clinical trials, including 704.311, 704.325, and 704.326, were performed under the auspices of an independent DSMB. As specified in the respective protocols, the DSMBs had access to interim, unblinded safety reports throughout the conduct of the trials. After discharge from the initial hospitalization through the 21-day follow-up period, all events meeting the definition of a serious adverse event were to be reported to the sponsor.

For AEs and SAEs, the two data sets that will be scrutinized include:

- 1) the set of all trials in CHF patients, including 235 control patients and 505 nesiritide, and
- 2) the set of trials using infusions of nesiritide in CHF patients, which enrolled 173 control and 362 nesiritide patients.

The summary tables below will focus on the 'CHF trials' population and the 'long infusion trials'. There were three trials that used infusions of nesiritide lasting ≥ 24 hours (704.311, 704.325, and 704.326), and all have been reviewed elsewhere in this review document. The data from a third set of safety analyses performed by the sponsor, from the 'placebo-controlled CHF trials' will be used infrequently.

11.0.4.2 Approach to Eliciting Adverse Events

Adverse experiences were defined as any unfavorable and unintended change in the structure (signs), function (symptoms), or chemistry (laboratory data) of the body or worsening of a preexisting condition temporally associated with the use of the study drug (active drug, control agents or placebo), whether or not they were considered to be related to the use of the product. Clinical adverse experiences determined by the investigator or volunteered by the patient were recorded throughout the study reporting period. Results from laboratory tests and any special examinations (i.e., physical examinations including vital signs, electrocardiograms, etc.) also were reviewed by the investigator to determine if any of the findings were adverse experiences.

When an adverse experience occurred, the investigator recorded pertinent information about the event on the case report form, including: date and time of onset; whether the event was a serious adverse experience; the relationship of the adverse experience to the study drug; the action taken regarding the test drug (i.e., none or drug discontinued); or whether the adverse experience caused the patient to be discontinued from the study. Additionally, for clinical adverse experiences, the investigator recorded the maximum intensity of the event, the date the adverse experience stopped, and its duration. Maximum intensity was recorded using a three-point scale of intensity: mild (easily tolerated); moderate (interfering with usual activity); or severe (incapacitating). The investigator using a five-point scale as follows graded the relationship between the adverse experience and the test drug: definitely not, probably not, possibly related, probably related, or definitely related.

After discharge from the initial hospitalization through a 14-day follow-up period, all clinical endpoints meeting the definition of adverse events were reported to the sponsor.

11.0.4.3 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

The sponsor mapped the terms used by the individual investigators to describe individual adverse events to COSTART terminology.

11.0.4.4 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

Key adverse event, in this usage, means an adverse event that will be discussed because it may be linked to the use of nesiritide. First, any adverse event identified in the nesiritide safety database occurring in $>1\%$ of the subjects in any group will be tabulated, and the percentage compared. Those AEs that occur with a differential frequency between the treatment and control groups will be examined, and if there is a consistent pattern, discussed further. Other adverse events, normally examined as part of usual NDA review, will also be included.

The occurrence of any adverse event linked to the administration of other natriuretic peptides will be explored. Hypotension is the primary AE identified in this way.

11.0.4.5 Laboratory Adverse Event Incidence

Laboratory safety measurements (hematology, serum chemistry, urinalysis, and miscellaneous) were performed at regular intervals during the clinical trials reported in this submission (see tables above). Since not all patients had all laboratory tests performed, the denominator for a laboratory adverse experience varies, and is the number of patients who had that laboratory test performed. The reporting of any laboratory adverse experience was always dependent on the individual investigator's assessment of its clinical importance. Thus, laboratory values within or outside the normal range could be interpreted as adverse by one investigator and not by another.

11.0.4.5.1 Extent of Laboratory Testing in the Development Program

The table below summarizes the collection of laboratory data in the Phase II-III database.

Table 11.0.4.5.1.1 Timing of laboratory data collection in the trials forming the NDA 20-920 safety database^a.

Study	Complete Lab Values ^c	Hematology ^b	Na ⁺ , K ⁺ , Cl ⁻ , HCO ₃ ⁻ , Cr ⁺ , BUN
311	0 and within 24 hrs of infusion end, and at 20-30 days after infusion	0 and within 24 hrs of infusion end, and at 20-30 days after infusion	--
325	0, and within 24 hrs of infusion end	0, and within 24 hrs of infusion end	24 & 48 hours after start of infusion ^d
326	0, and within 24 hrs of infusion end	0, and within 24 hrs of infusion end	24 hours after start of infusion ^d

a. Data from respective study reviews.

b. Hematology includes hemoglobin & hematocrit.

c. A complete lab evaluation included: CBC with differential; serum chemistries (electrolytes, BUN, creatinine, ALT/AST, albumin, calcium, CPK, glucose, magnesium, phosphate, and bilirubin); urinalysis (for protein, glucose, blood, and bilirubin).

d. Then daily during study drug infusion.

Follow-up for abnormal laboratory findings

Investigators were instructed to provide outcome for all adverse experiences, and it was expected that abnormal laboratory values would be followed through resolution. No specific follow-up criteria were outlined, however, for abnormal laboratory values.

11.0.4.6 Specific Search Strategies Unique to the Nesiritide Review

The majority of the estimates of incidence of specific AEs will be based on the pooled data from the nine studies using nesiritide in patients with CHF. Where relevant, specific explorations for drug-disease interaction (i.e., hypertension, pre-existing hepatic disease), and drug-drug interactions will also be carried. These will utilize subsets of the larger population as appropriate.

11.1 Background Database for Safety Review

In the integrated safety summary, adverse events will be examined in the following order:

- 1) Deaths;
 - 2) Serious Adverse Events (SAEs);
 - 3) Adverse Events (AEs) related to clinical findings;
 - 4) Adverse Events related to laboratory findings and special examinations;
- and
- 5) Subject discontinuations.

Following this, selected adverse events will be examined, using the phase II-III database:

- 1) Special studies, including tolerance, overdose, withdrawal/ rebound, abuse potential, and human reproduction;
 - 2) Selected adverse events linked to the administration of nesiritide or other natriuretic peptides from other INDs/ NDAs, or the literature.
- and
- 3) Selected adverse events examined during normal examination of safety as part of all NDA reviews, including subgroup analyses of adverse events according to gender, race, age, and common clinical characteristics.

The data tables below have been submitted to the sponsor to allow for correction of typographical or other errors of presentation wherever possible. For all data presentation, nominal statistical significance (relative to placebo or baseline at a $p < 0.05$) will be indicated by the use of shading for the relevant data. In some cases, the sponsor-derived p Value will also be stated. Details of the statistical methodology used by the sponsor to derive individual p Values are to be found in the NDA submission.

11.1.1 Deaths in the Nesiritide Safety Database

There were a total of 28 deaths occurred during the reporting periods of the CHF trials. An additional 6 deaths that occurred after the reporting period are also known to the sponsor. The first table summarizes the number of deaths and the number of patients for two relevant patient populations: all known deaths from all studies; and all known deaths from the nesiritide infusion studies (311, 325 and 326). The incidence of deaths during the studies is also tabulated. In this table the placebo patients from 704.325 are included in the placebo group. In that trial, patient in both placebo and nesiritide groups could receive active parenteral therapy after 6 hours.

Table 11.1.1.1 Known deaths in NDA 20-920^a.

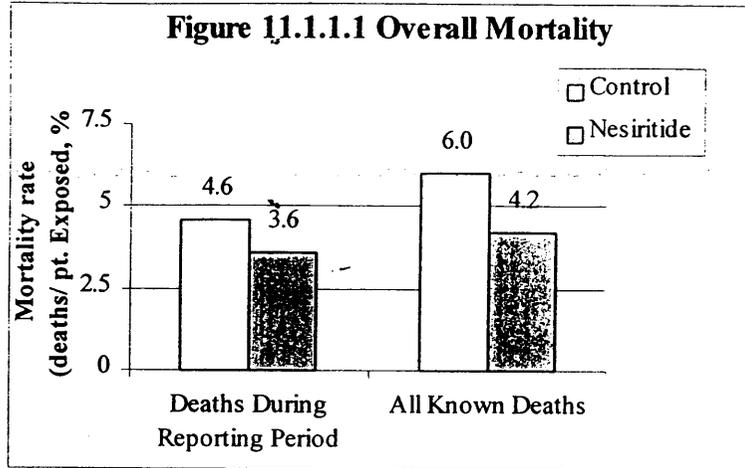
Group	Placebo	Active Control	Nesiritide Groups				Total Nesiritide
			Bolus	0.015 $\mu\text{g}/\text{kg}/\text{min}$	0.030 $\mu\text{g}/\text{kg}/\text{min}$	0.060 $\mu\text{g}/\text{kg}/\text{min}$	
All Known Deaths	n=114 ^c 8 (7.0%)	n=102 5 (4.9%)	n=143 2 (1.4%)	n=169 8 (4.7%)	n=167 10 (6.0%)	n=26 1 (3.8%)	n=505 21 (4.2%)
Deaths During Study	5 (4.4%)	5 (4.9%)	0 (0%)	8 (4.7%)	9 (5.4%)	1 (3.8%)	18 (3.6%)
All Known Deaths From Infusion Studies ^b	n=71 5 (7.0%)	n=102 5 (4.9%)	n=N/A N/A	n=169 8 (4.7%)	n=167 10 (6.0%)	n=26 1 (3.8%)	n=362 19 (5.2%)
Deaths During Infusion Studies ^b	3 (4.2%)	5 (4.9%)	N/A	8 (4.7%)	9 (5.4%)	1 (3.8%)	18 (5.0%)

a. Data from Listing 7, NDA vol. 81.

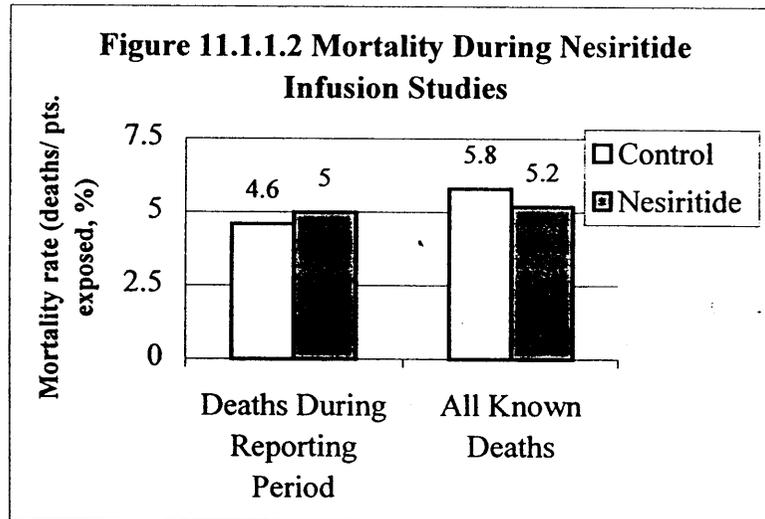
b. Studies 311, 325 and 326.

c. This does not include the 'placebo' group from 704.307, as they also received nesiritide during the trial.

For all known deaths during the nesiritide NDA, the following graphs summarize the relative incidence of death for nesiritide and control (including both placebo and active control groups). There were a total of 13 known deaths in the control groups (5.5%



Similarly, the graph below shows the mortality rate during the three infusion studies, where there were 10 known deaths in the control groups (5.8%) compared with 19 deaths in the nesiritide groups (5.2%).



Narratives for all deaths can be found in appendix two, based on sponsor-supplied narratives and review of individual case report forms by this reviewer. The table below summarizes the cause and timing of all known deaths.

Table 11.1.1.2 Known deaths in NDA 20-920^a.

Treatment Group/ Patient #	# of Days After Study Entry	Cause of Death
Placebo		
324010	15	Failed to wean after heart txp
381001	6	Ventricular arrhythmia Dilated cardiomyopathy
356103	19	Ventricular Fibrillation, EMD
370006	>21	Unknown
376016	6	Sudden Death, CHF
376022	21	Sudden Death, CHF
368001	16	Ventricular Fibrillation, CHF
503001	17	CHF, Bronchopneumonia
Active Control^b		
493019	5	Cardiopulmonary arrest
493021	18	Ischemic cardiomyopathy
509001	21	End-stage cardiomyopathy
538011	9	Suspect large MI
585002	21	LV failure, MI CHF
Nesiritide Bolus		
315005	30	CHF
373301	30	Sudden Cardiac Death Dilated cardiomyopathy
Nesiritide 0.015 µg/kg/min infusion		
374001	4	CHF, ASVD
382013	5	Progressive Renal Insufficiency CHF
369003	8	CHF
493008	14	End-stage Cardiomyopathy
504003	11	Cardiopulmonary arrest, CHF
538010	9	Mitral regurgitation Chronic atrial flutter
550002	14	CHF
559005	7	CHF Tricuspid endocarditis
Nesiritide 0.030 µg/kg/min infusion		
017007	8	Acute Renal Failure, CHF
357002	15	MI
370002	20	Multisystem Organ Failure
382002	3	CHF, Respiratory failure
508004	2	'Poor cardiac function' 'Cardiac standstill'
509002	6	CHF
524005	5	Ventricular fibrillation
528001	22	Cardiac arrest Ischemic cardiomyopathy
572001	20	CHF
585003	13	CHF
Nesiritide 0.060 µg/kg/min infusion		
382004	8	Ventricular Arrhythmia Congestive Cardiomyopathy

a. Data from NDA vol. 81, listing 7, and examination of individual case report forms.

b. In study 326 subjects were randomized to receive other IV cardiovascular meds.

11.1.2 Serious Adverse Events (SAEs) in the Nesiritide Safety Database

The first table shows the SAEs that were identified by investigators through day 14 of each study that occurred at $\geq 1\%$ incidence in either of the treatment groups in the CHF trials.

Table 11.1.2.1 The occurrence of SAEs through 14 days in the nesiritide NDA database from all CHF trials^a.

Serious Adverse Event	Control n=235	Nesiritide n=505
# of Subjects with any SAE	19 (8%)	46 (9%)
Cardiovascular System		
Congestive Heart Failure	4 (2%)	11 (2%)
Heart Arrest	4 (2%)	7 (1%)
Ventricular Tachycardia	2 (1%)	4 (1%)
Sustained Ventricular Tachycardia	2 (1%)	4 (1%)
Hypotension, symptomatic	1 (<1%)	4 (1%)
Hypotension	1 (<1%)	4 (1%)
Bradycardic events	1 (<1%)	3 (1%)
Bradycardia	1 (<1%)	3 (1%)
Syncope	1 (<1%)	2 (<1%)
Body as a Whole		
Sepsis	0 (0%)	5 (1%)
Respiratory: None		
Urogenital System		
Acute Kidney Failure	3 (1%)	4 (1%)
Metabolic and Nutritional System: None		
Nervous System: None		
Digestive System: None		

a. Data from NDA volume 79, appendix 8.4, table 27A.

Examination of the list of SAEs identified in the infusion studies found the following relevant differences between the control and nesiritide groups. None of these differences between nesiritide and the control group achieved nominal statistical significance.

Table 11.1.2.2 The occurrence of SAEs through 14 days in the 'long infusion' trials^a.

Serious Adverse Event	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	Nominal p Value ^a
Cardiovascular	17 (10%)	12 (7%)	25 (15%)	2 (8%)	0.124
Congestive Heart Failure	3 (2%)	3 (2%)	7 (4%)	1 (4%)	0.356
Bradycardia ^b	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0.795
Hypotension ^c	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0.795
Body as a Whole	1 (1%)	3 (2%)	2 (1%)	0 (0%)	0.659
Sepsis	0 (0%)	2 (1%)	2 (1%)	0 (0%)	0.510
Urogenital	3 (2%)	0 (0%)	2 (1%)	1 (4%)	0.136
Acute Kidney Failure ^d	3 (2%)	0 (0%)	2 (1%)	0 (0%)	0.410

a. Data from appendix 8.4, table 27C and from company at request of reviewer. p Value per sponsor.

b. Included 'bradycardic events' and bradycardia.

c. Includes 'hypotension' and 'symptomatic hypotension.'

d. Includes 'acute kidney failure' and 'kidney function abnormal.'

11.1.3 Clinical Adverse Events (AEs) in the Nesiritide Safety Database

The table below summarizes the occurrence of Adverse Events (AEs) in the nesiritide NDA database from all CHF trials for all AEs that occurred with a >1% frequency in any group are of particular interest to the safety review. These AEs were identified by the individual investigators through day 14. Shaded rows are AEs where the difference between control and nesiritide was nominally statistically significant (<0.05) per sponsor.

Table 11.1.3.1 Adverse Events (AEs) in the 'all CHF' trials from NDA 20-920^a.

Adverse Event	Control n=235	Nesiritide n=505	Nominal p Value
Cardiovascular System	116 (49%)	300 (59%)	0.011
Hypotension	35 (15%)	152 (30%)	<0.001
Symptomatic hypotension	16 (7%)	76 (15%)	0.001
Ventricular Tachycardia	36 (15%)	75 (15%)	0.912
Sustained Ventricular Tachycardia	6 (3%)	9 (2%)	0.576
Congestive Heart Failure	20 (9%)	48 (10%)	0.785
Angina Pectoris	11 (5%)	36 (7%)	0.257
Ventricular Extrasystoles	13 (6%)	22 (4%)	0.464
Bradycardic Events	21 (9%)	26 (5%)	0.003
Bradycardia	2 (1%)	22 (4%)	0.012
Sinus Bradycardia	0 (0%)	1 (<0.1%)	1.000
Nodal Arrhythmia	0 (0%)	3 (1%)	0.555
Tachycardia	10 (4%)	12 (2%)	0.169
Atrial Fibrillation	5 (2%)	14 (3%)	0.804
Supraventricular Tachycardia	5 (2%)	12 (2%)	1.000
AV Node Conduction Abnormalities	4 (2%)	9 (2%)	1.000
AV Block, Complete	1 (<0.1%)	0 (0%)	0.318
AV Block, First Degree	3 (1%)	5 (1%)	0.714
AV Block, Second Degree	1 (<0.1%)	4 (1%)	1.000
Bigeminy	3 (1%)	8 (2%)	1.000
Syncope	2 (1%)	4 (1%)	1.000
Palpitations	1 (0%)	8 (2%)	0.285
Vasculitis	0 (0%)	1 (0%)	1.000
Body as a Whole	107 (46%)	107 (21%)	0.026
Headache	43 (18%)	80 (16%)	0.398
Pain	19 (8%)	50 (10%)	0.498
Catheter Pain	16 (7%)	42 (8%)	0.558
Abdominal Pain	16 (7%)	38 (8%)	0.879
Chest Pain	8 (3%)	28 (6%)	0.271
Fever	12 (5%)	21 (4%)	0.569
Sepsis	6 (3%)	14 (3%)	1.000
Allergic Reaction	1 (<0.1%)	0 (0%)	0.318
Gastrointestinal System	68 (29%)	168 (33%)	0.271
Nausea	29 (12%)	90 (18%)	0.067
Vomiting	15 (6%)	44 (9%)	0.310
Constipation	18 (8%)	25 (5%)	0.176
Diarrhea	13 (6%)	21 (4%)	0.451
GI hemorrhage	4 (2%)	7 (1%)	0.750
Abnormal LFTs	2 (1%)	1 (0%)	0.238
Jaundice	0 (0%)	1 (<0.1%)	1.000
Nervous System	53 (23%)	161 (32%)	0.009
Insomnia	19 (8%)	58 (11%)	0.196
Dizziness	16 (7%)	43 (9%)	0.469
Anxiety	11 (5%)	28 (6%)	0.725
Confusion	5 (2%)	33 (7%)	0.011
Nervousness	3 (1%)	23 (5%)	0.030

a. Data from NDA appendix 8.4, table 11A.

Table 11.1.3.1 Adverse Events (AEs) in the 'all CHF' trials from NDA 20-920 (cont)^a.

Adverse Event	Control n=235	Nesiritide n=505	Nominal p Value
Somnolence	4 (2%)	12 (2%)	0.787
Respiratory System	33 (14%)	95 (19%)	0.118
Dyspnea	15 (6%)	40 (8%)	0.548
Cough Increased	5 (2%)	20 (4%)	0.275
Epistaxis	2 (1%)	9 (2%)	0.517
Hypoxia	4 (2%)	7 (1%)	0.750
Metabolic & Nutritional System	42 (18%)	83 (16%)	0.673
Hypokalemia	10 (4%)	20 (4%)	0.843
BUN Increased	7 (3%)	15 (3%)	1.000
Hyperkalemia	6 (3%)	12 (2%)	1.000
Gout	4 (2%)	12 (2%)	0.787
Hypoglycemia	4 (2%)	8 (2%)	1.000
Hyponatremia	6 (3%)	6 (1%)	0.211
Hyperglycemia	0 (0%)	10 (2%)	0.036
Edema	0 (0%)	1 (<0.1%)	1.000
Urogenital System	25 (11%)	81 (16%)	0.055
Creatinine Increased	7 (3%)	29 (6%)	0.141
UTI	8 (3%)	15 (3%)	0.821
Oliguria	2 (1%)	13 (3%)	0.164
Hematuria	6 (3%)	5 (1%)	0.113
Kidney Function Abnormal	0 (0%)	7 (1%)	0.104
Acute Kidney Failure	3 (1%)	6 (1%)	1.000
Skin & Appendages	22 (9%)	58 (11%)	0.446
Sweating	0 (0%)	2 (<0.1%)	0.144
Rash	8 (3%)	12 (2%)	0.467
Pruritus	4 (2%)	15 (3%)	0.454
Musculoskeletal System	21 (9%)	30 (6%)	0.160
Leg Cramps	11 (5%)	13 (3%)	0.179
Arthralgias	8 (3%)	10 (2%)	0.304
Hemic & Lymphatic	12 (5%)	17 (3%)	0.308
Anemia	4 (2%)	8 (2%)	1.000
Thrombocytopenia	4 (2%)	5 (1%)	0.476
Ecchymosis	4 (2%)	4 (1%)	0.272
Special Senses and Endocrine	5 (2%)	13 (3%)	0.803

a. Data from NDA vol. 78, appendix 8.4, table 11A.

Examination of the list of AEs identified in the infusion studies (through day 14) found the following relevant differences. Shaded rows are AEs where the difference between control and nesiritide was nominally statistically significant.

Table 11.1.3.2 Adverse Events (AEs) in the first 14 days in the 'long infusion' trials from NDA 20-920^a.

Adverse Event	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
Cardiovascular System	93 (54%)	110 (65%)	114 (68%)	14 (54%)	0.027
Hypotension	27 (16%)	47 (28%)	67 (40%)	8 (31%)	0.001
Symptomatic Hypotension	11 (6%)	20 (12%)	32 (19%)	4 (15%)	0.003
Decreased Pulmonary Pressures	0 (0%)	0 (0%)	3 (2%)	5 (19%)	0.001
Ventricular Extrasystoles	13 (8%)	11 (7%)	8 (5%)	0 (0%)	0.477
Ventricular Tachycardia	34 (20%)	42 (25%)	22 (13%)	0 (0%)	0.001
Non-sustained VT	29 (17%)	40 (24%)	20 (12%)	0 (0%)	0.002
Congestive Heart Failure	11 (6%)	18 (11%)	20 (12%)	3 (12%)	0.274
Angina Pectoris	8 (5%)	21 (12%)	12 (7%)	0 (0%)	0.025
Bradycardic Events	1 (1%)	9 (5%)	14 (8%)	0 (0%)	0.002
Bradycardia	1 (1%)	9 (5%)	10 (6%)	0 (0%)	0.015
Sinus Bradycardia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Nodal Bradycardia	0 (0%)	0 (0%)	3 (2%)	0 (0%)	0.169
Atrial Fibrillation	5 (3%)	2 (1%)	8 (5%)	1 (4%)	0.188
Tachycardia	9 (5%)	5 (3%)	5 (3%)	1 (4%)	0.644
SVT	3 (2%)	4 (2%)	7 (4%)	0 (0%)	0.490
AV Node Conduction Abnormal	3 (2%)	5 (3%)	4 (2%)	0 (0%)	0.846
AV Block, First Degree	3 (2%)	3 (2%)	2 (1%)	0 (0%)	1.000
AV Block, Second Degree	1 (1%)	2 (1%)	2 (1%)	0 (0%)	0.804
Supraventricular Extrasystoles	2 (1%)	3 (2%)	1 (1%)	0 (0%)	0.781
Body as a Whole	89 (51%)	74 (44%)	69 (41%)	6 (23%)	0.029
Headache	18 (10%)	38 (22%)	22 (13%)	1 (4%)	0.005
Pain	15 (9%)	20 (12%)	15 (9%)	0 (0%)	0.262
Back Pain	11 (6%)	9 (5%)	5 (3%)	1 (4%)	0.507
Sepsis	5 (3%)	3 (2%)	6 (4%)	1 (4%)	0.611
Asthenia	4 (2%)	8 (5%)	5 (3%)	1 (4%)	0.562
Digestive System	52 (30%)	67 (40%)	60 (36%)	7 (27%)	0.242
Nausea	25 (14%)	36 (21%)	32 (19%)	4 (15%)	0.398
Vomiting	13 (8%)	12 (7%)	17 (10%)	3 (12%)	0.614
Constipation	14 (8%)	13 (8%)	9 (5%)	0 (0%)	0.440
Diarrhea	10 (6%)	13 (8%)	4 (2%)	1 (4%)	0.140
GI Hemorrhage	4 (2%)	3 (2%)	4 (2%)	0 (0%)	0.961
Nervous System	40 (23%)	67 (40%)	54 (32%)	7 (27%)	0.011
Insomnia	18 (10%)	25 (15%)	22 (13%)	1 (4%)	0.371
Confusion	5 (3%)	16 (9%)	13 (8%)	1 (4%)	0.059
Dizziness	9 (5%)	17 (10%)	8 (5%)	3 (12%)	0.125
Nervousness	3 (2%)	10 (6%)	5 (3%)	0 (0%)	0.189
Somnolence	3 (2%)	3 (2%)	6 (4%)	0 (0%)	0.663
Metabolic & Nutritional	34 (20%)	28 (17%)	34 (20%)	5 (19%)	0.813
BUN increased	7 (4%)	9 (5%)	5 (3%)	0 (0%)	0.615
Hypokalemia	9 (5%)	7 (4%)	5 (3%)	3 (12%)	0.216
Hyperkalemia	5 (3%)	6 (4%)	4 (2%)	0 (0%)	0.931
Hyperglycemia	0 (0%)	1 (1%)	5 (3%)	0 (0%)	0.069
Hyponatremia	4 (2%)	0 (0%)	5 (3%)	0 (0%)	0.132
Acidosis	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0.795

Table 11.1.3.2 Adverse Events (AEs) in the first 14 days in the 'long infusion' trials from NDA 20-920^a.

Adverse Event	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
Respiratory System	25 (14%)	33 (20%)	36 (22%)	2 (8%)	0.179
Dyspnea	11 (6%)	14 (8%)	14 (8%)	2 (8%)	0.858
Cough Increased	4 (2%)	5 (3%)	4 (2%)	0 (0%)	0.969
Epistaxis	2 (1%)	6 (4%)	3 (2%)	0 (0%)	0.457
Urogenital System	22 (13%)	28 (17%)	35 (21%)	3 (12%)	0.209
Creatinine Increased	7 (4%)	10 (6%)	15 (9%)	1 (4%)	0.300
Oliguria	2 (1%)	6 (4%)	6 (4%)	0 (0%)	0.410
Dysuria	0 (0%)	1 (1%)	4 (2%)	1 (4%)	0.040
Hematuria	4 (2%)	3 (2%)	1 (1%)	0 (0%)	0.697
Acute Kidney Failure	3 (2%)	1 (1%)	3 (2%)	1 (4%)	0.389
Kidney Function Abnormal	0 (0%)	1 (1%)	3 (2%)	0 (0%)	0.249
Skin & Appendages	15 (9%)	20 (12%)	23 (14%)	0 (0%)	0.114
Musculoskeletal	15 (9%)	10 (6%)	9 (5%)	1 (4%)	0.648
Leg Cramps	9 (5%)	5 (3%)	2 (1%)	0 (0%)	0.173
Hemic & Lymphatic	9 (5%)	3 (2%)	8 (5%)	1 (4%)	0.286
Special Senses	3 (2%)	4 (2%)	5 (3%)	1 (4%)	0.602
Amblyopia	0 (0%)	1 (1%)	3 (2%)	1 (4%)	0.047

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

The sponsor also summarized the data for the first 24 hours of the long infusion trials. The incidence of selected AEs from the table above is shown. Overall, similar trends in the incidence of AEs were seen in both sets.

Table 11.1.3.3 Adverse events during the first 24 hours in the 'long infusion' trials in NDA 20-920^a.

Adverse Event	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value
Cardiovascular System	48 (28%)	75 (44%)	73 (44%)	10 (38%)	0.004
Hypotension	15 (9%)	33 (20%)	32 (19%)	4 (15%)	<0.001
Symptomatic Hypotension	5 (3%)	14 (8%)	23 (14%)	4 (15%)	0.005
Decreased Pulmonary Pressures	0 (0%)	0 (0%)	5 (3%)	5 (19%)	<0.001
Ventricular Tachycardia	14 (8%)	20 (12%)	5 (3%)	1 (4%)	0.002
Bradycardic Events	0 (0%)	6 (4%)	9 (5%)	1 (4%)	0.008
Urogenital					
Creatinine Increased	1 (1%)	3 (2%)	4 (2%)	0 (0%)	0.525
Kidney Function Abnormal	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.677
Acute Kidney Failure	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
BUN Increased	2 (1%)	2 (1%)	2 (1%)	0 (0%)	1.000

a. Data from appendix 8.4, table 12C and from company at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

11.1.3.1 Adverse Events in Patient Subgroups

The sponsor performed several analyses examining the effects of gender, age, race, and NYHA class at time of entry.

11.1.3.1a Drug-Demographic Interactions

AEs grouped by age (< or > 65 years old)

This comparison suffered from the small numbers of patients in the >65 years of age category, especially in the nesiritide 0.060 age group (n=9). In both the 24 hour and the 14 day periods, there were no identified AEs in the elderly population which were not seen in the overall population (see supplemental tables 13D and 14D for details). Specific details on the effect of age on specific AEs will be dealt with in the AE summary section 8.2.

Sponsor's Summary

'Hypotension, bradycardia, and confusion were reported somewhat more frequently in elderly subjects' (age 65 years) than younger subjects, particularly at the 0.03 µg/kg/min dose (see table below). 'Generally, however, the safety profile for nesiritide does not appear to be markedly different for subjects < 65 years and those 65 years of age.'

AEs grouped by gender

This group comparison was also limited by the small # of females, especially in the nesiritide 0.060 group (n=3). The only difference of note was the absence of decreased pulmonary pressure as an AE in females, compared with 7 episodes in the nesiritide 0.030 and 0.060 groups in the men. Females in the nesiritide 0.030 dose group were also more likely to have symptomatic hypotension and nausea than men. Specific details on the effect of gender on specific AEs will be dealt with in the AE summary section 8.2.

Sponsor's Summary

Women tended to have a higher incidence of symptomatic hypotension and nausea than did men at the 0.03 µg/kg/min but not at the 0.015 µg/kg/min nesiritide dose. Otherwise, the safety profile for nesiritide 'does not appear to be markedly different for men and women.'

11.1.3.1b Drug-Disease Interactions

AEs in the Patients with Renal Disease

Sponsor's Comments

Preclinical studies have suggested that the kidney may play a role in hBNP clearance (along with other factors such as clearance receptors and metabolism by neutral endopeptidases). This would raise the possibility that patients with renal insufficiency might have reduced clearance of nesiritide and, therefore, an exaggerated response to a given dose. The clinical pharmacokinetic analysis of data from study 704.325 in subjects with CHF (n = 65) showed a trend of a direct relationship between estimated creatinine clearance and hBNP clearance and a trend of an inverse relationship between serum creatinine and hBNP clearance. However, in a population analysis done on data from study 704.311 (n = 54), a statistically significant effect of creatinine clearance or serum creatinine on hBNP clearance was not detected. In that study, analyses suggested that hBNP clearance decreases no more than approximately 10.9% for each 10 ml/min decrease in creatinine clearance. In order to evaluate the clinical impact of renal insufficiency on the efficacy and safety profile of nesiritide, a number of evaluations were performed on data from individual studies. First, in study 704.325, there were no significant differences between the effects of nesiritide on the efficacy parameters in these subjects with or without renal insufficiency (baseline serum creatinine >2 mg/dL). Also, subjects with renal insufficiency did not have greater decreases in blood pressure or an increased incidence of symptomatic hypotension.

Secondly, in study 704.326, the general safety profile of nesiritide was not significantly different in those with and without renal insufficiency. For nesiritide subjects with (n = 41) and without (n = 160) chronic renal insufficiency, the incidence of symptomatic hypotension was 12% and 14%, respectively, nausea 12% and 12%, confusion 12% and 3%, and bradycardia 2% and 6%, respectively.

Baseline renal insufficiency also did not carry an increased risk of worsened renal function during nesiritide infusion. Subjects with baseline serum creatinine >2 mg/dL were not more likely than subjects without renal insufficiency to have at least a 50% rise in serum creatinine following nesiritide administration. Thus, these analyses suggest that nesiritide does not have a significantly different safety profile in patients with and without renal insufficiency.

AEs grouped by NYHA Class III and IV

There were small numbers of patients in the nesiritide 0.060 groups, as in previous analyses. Four episodes of decreased pulmonary pressure occurred in the class III group, all in the nesiritide 0.030 and 0.060 dose-groups ($p < 0.001$ vs. Control). Specific details on the effect of NYHA class (III or IV) on specific AEs will be dealt with in the AE summary section 8.2.

Sponsor's Comments

The adverse event profiles for nesiritide in patients with NYHA Class III and IV CHF appear comparable. For example, in All CHF Studies, the incidence of symptomatic hypotension during the first 24 hours of nesiritide therapy was 11% in subjects with NYHA Class III CHF and 10% in subjects with NYHA Class IV CHF. Similarly, bradycardia events occurred in 3% of subjects with NYHA Class III CHF and in 3% of subjects with NYHA Class IV CHF receiving nesiritide (compared to 0% in both respective control groups).

AEs grouped by Original Etiology of CHF

Specific details on the effect of the original etiology of the CHF on selected AEs will be dealt with in the AE summary section 8.2. The sponsor had no specific comments on the interaction of CHF etiology and AEs.

11.1.3.1c Drug-Drug Interactions

The sponsor analyzed the data from the largest study (704.326) for drug-drug interactions. Specific details on the effect of interactions with ACE inhibitors, digoxin and beta-blockers on specific AEs will be dealt with in the AE summary section 8.2.

Sponsor's Comments

The sponsor examined the incidence of adverse events in patients receiving three other classes of drugs: ACE inhibitors, beta-blockers, and digoxin. None of these three medications appeared to alter the overall incidence of hypotension, although symptomatic hypotension was reported somewhat more frequently in subjects on ACE inhibitors or beta-blockers than in subjects not on these medications. Bradycardia events were also reported somewhat more frequently in nesiritide subjects receiving ACE inhibitors or beta-blockers than those that were not. The sponsor concluded that these data are difficult to interpret, given the low overall incidence of these events and the small sample size for this assessment. In general, however, use of any of these three agents before or during nesiritide administration does not appear to markedly alter the incidence or profile of adverse events.

11.1.3.2 Selected Analyses of AEs of Particular Interest

11.1.3.2a Hypotension

The tables above show a clear dose-related association between nesiritide administration and the incidence hypotension and an adverse event, including symptomatic hypotension and decreases in pulmonary pressures. The majority of these events occurred during the first 24 hours of study drug administration. The sponsor performed further analyses of hypotension.

First, the frequency and severity of hypotension was summarized. Both the severity of the hypotension and the effect on study drug administration were greatest in the nesiritide group. The effects also tended to be dose-related, with the highest incidence of severe hypotension resulting in drug discontinuation occurring in the nesiritide 0.060 dose group.

Table 11.1.3.2a.1 Severity and effect of hypotension as an AE during the first 24 hours in the 'long infusion' trials in NDA 20-920^a.

Hypotension	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
Greatest Severity					
No hypotension reported	167 (97%)	155 (92%)	144 (86%)	22 (85%)	0.004
Mild	2 (1%)	4 (2%)	4 (2%)	1 (4%)	
Moderate	3 (2%)	10 (6%)	12 (7%)	0 (0%)	
Severe	1 (1%)	0 (0%)	7 (4%)	3 (12%)	
Greatest Effect on Study Drug Administration					
None	3 (2%)	3 (2%)	2 (1%)	2 (8%)	0.004
Dose Decreased	2 (1%)	5 (3%)	9 (5%)	0 (0%)	
Dose Discontinued	1 (1%)	6 (4%)	12 (7%)	2 (8%)	

a. Data from data table 23D.2 at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

The sponsor also analyzed the severity of the hypotension that occurred during the first 24 hours in the 704.326 study. As shown below, there was a higher incidence of hypotension in the nesiritide groups for any systolic BP <100 mm Hg. Note that no patients received nesiritide 0.060 µg/kg/min in this study. In data not shown, the time to minimum SBP ranged widely, from 15 minutes to 1400 minutes in all three treatment groups.

Table 11.1.3.2a.2 Severity of hypotension during the first 24 hours in 704.326^a.

Changes in systolic BP (SBP)	Control n=102	Nesiritide 0.015 µg/kg/min n=103	Nesiritide 0.030 µg/kg/min n=100	Nominal p Value
Minimum SBP (mm Hg)	100.1±7.50	97.9±8	91.0±16	0.001
Median	100.0	94.0	90.0	
Minimum SBP <110	79 (77%)	80 (78%)	85 (85%)	
Minimum SBP <100	49 (48%)	64 (62%)	71 (71%)	
Minimum SBP <90	20 (20%)	39 (38%)	47 (47%)	
Minimum SBP <80	4 (4%)	15 (15%)	25 (25%)	
Minimum SBP <70	1 (1%)	1 (1%)	7 (7%)	
Minimum SBP <60	1 (1%)	0 (0%)	2 (2%)	

a. Data from NDA vol. 79, appendix 8.4, table 25.

The mean and median decreases in systolic BP were also higher in the nesiritide groups in 704.326.

Table 11.1.3.2a.3 Severity of hypotension during the first 24 hours in 704.326^a.

Changes in systolic BP (SBP)	Control n=102	Nesiritide 0.015 µg/kg/min n=103	Nesiritide 0.030 µg/kg/min n=100	Nominal p Value
Absolute Decrease in SBP (mm Hg)	21.2±16	29.4±16	33.1±19	<0.001
Median Decrease in SBP (mm Hg)	19.0	26.0	29.0	

a. Data from NDA appendix 8.4, table 25.

11.1.4 Adverse Events Related to Laboratory Findings

11.1.4.1 Collection of Laboratory Data

The collection of laboratory measurements was detailed in section 11.0.4.5 above. Of note, no urinalyses during or after nesiritide administration were performed in any of the three long infusion trials.

11.1.4.2 Analyses Focused on Changes in Mean Laboratory Measurements

The first table summarizes the mean changes from baseline to the last available lab assessment on or before days two and five (separately) for all patients in the CHF trials. Shaded boxes represent differences between control and nesiritide that were nominally statistically significant.

Table 11.1.4.2.1 Mean changes in serum chemistries from baseline for all subjects in 'all CHF' trials^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Sodium	-0.8±3.3	-1.1±3.2	-1.2±3.8	-1.0±3.7
Potassium	-0.1±0.65	-0.0±0.59	0.0±0.69	0.1±0.68
Chloride	-0.3±3.6	-0.1±3.6	-1.3±4.6	-0.4±4.2
Bicarbonate	+0.5±3.4	-0.4±3.4	+1.0±4	+0.3±3.8
Glucose	-9.0±55	-2.7±59	-12.8±55	-8.0±62
BUN	-3.6±6.9	-1.4±7.1	-4.3±10.4	-1.4±10.2
Creatinine	-0.1±0.5	0.0±0.3	-0.1±0.5	0.0±0.4
Uric Acid	-0.7±1.3	-0.3±1.1	-0.3±2.3	-0.2±1.3
Total Protein	-0.3±0.80	-0.3±0.5	-0.2±0.7	-0.3±0.6
Albumin	-0.2±0.3	-0.3±0.3	-0.1±0.3	-0.2±0.4
Total Bilirubin	+0.1±0.29	+0.1±0.6	+0.0±0.4	+0.0±0.8
Alkaline Phosphatase	-1.8±16	-4.6±15	-3.1±16	-7.2±26
LDH	+19.3±132	+3.0±175	-21.2±240	+2.8±149
AST	-5.4±24	-7.2±31	-11.9±61	-5.0±28
ALT	-5.1±19	-4.3±8	-7.8±41	-4.4±15
Calcium	-0.1±0.5	-0.2±0.5	-0.1±0.6	-0.1±0.5
PO ₄	0.0±0.7	0.0±0.7	-0.1±0.9	0.0±0.8
Mg ²⁺	0.0±0.4	0.0±0.3	0.0±0.3	0.0±0.3

a. Data from NDA volumes 79-80, starting with table 31A1.

Table 11.1.4.2.2 Mean changes in hematology from baseline for all subjects in 'all CHF' trials^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
WBC # (10 ³ /mm ³)	0.6±1.4	0.9±1.6	0.3±1.8	0.6±1.9
RBC # (10 ⁶ /mm ³)	0.0±0.2	0.1±0.4	0.0±0.3	0.0±0.4
HGB (g/dL)	-0.1±0.7	0.3±0.96	0.0±0.8	0.2±0.1
Hematocrit	-0.3±2.1	0.9±3.0	0.0±2.7	0.4±3.1
Platelet # (10 ³ /mm ³)	-21.9±27	-10.7±30	-16.5±33	-10.9±37
Prothrombin Time (secs)	-0.6±5	-0.1±3	-0.6±4.8	-0.3±3.2
PTT (secs)	-0.9±8.6	-1.3±17	-1.4±9.2	-1.6±22

a. Data from NDA volumes 79-80, starting with table 31A1.

The next two tables show similar data for mean changes in the long infusion studies, collected on or before the end of study day 2. Shading reflects nominally significant differences between control and nesiritide groups.

Table 11.1.4.2.31 Mean changes in serum chemistries from baseline for all subjects in 'long infusion' trials^a.

Lab Test, change from baseline to day 2	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=24
Sodium	-0.4±3.3	-0.8±3.0	-1.2±3.3	-1.8±5.3
Potassium	-0.2±0.65	-0.0±0.61	0.0±0.63	+0.2±0.41
Chloride	-0.2±3.0	-0.1±3.4	0.0±3.6	-0.7±3.4
Bicarbonate	+0.8±3.5	+0.2±3.1	-0.7±3.8	0.0±1.9
Glucose	-6.6±56	+4.9±42	+18.8±79	26.3±40
BUN	-3.3 ± 6.86	-1.8 ± 7.19	-0.7 ± 7.85	-2.5 ± 5.26
Creatinine	-0.1 ± 0.53	-0.0 ± 0.32	0.1 ± 0.37	0.0 ± 0.13
Uric Acid	-0.2±0.8	-0.2±0.7	+0.1±1.0	-0.2 ± 0.68
Total Protein	-0.3±1.1	-0.2±0.6	-0.3±0.5	-0.2 ± 0.50
Albumin	-0.1 ± 0.30	-0.2 ± 0.38	-0.2 ± 0.29	0.2 ± 0.34
Total Bilirubin	0.0±0.2	0.0±0.5	0.3±1.2	0.2 ± 0.4
Alkaline Phosphatase	2.5±16	-1.8±10	-1.0±13	-4.6 ± 10.0
LDH	-15.1±182	+16.5±66	+13.3±36	+30.6 ± 35.36
AST	-11.1±31	-11.3±17	-2.3±5.1	-2.2 ± 5.16
ALT	-8.5±28	-8.3±13	-3.6±5	-4.7 ± 3.67
Calcium	-0.1 ± 0.52	-0.1 ± 0.73	-0.1 ± 0.60	-0.2 ± 0.31
PO ₄	0.0 ± 0.58	0.2 ± 0.96	-0.0 ± 0.60	-0.2 ± 0.63
Mg ²⁺	0.0 ± 0.40	-0.0 ± 0.30	0.1 ± 0.30	0.2 ± 0.27

a. Data from NDA volumes 79-80, starting with table 31A1 and from supplemented data sets submitted at reviewer's request.

The next table summarizes the mean changes in hematology at or near the end of day 2 for the long infusion trials. Shading reflects nominally significant differences between control and nesiritide groups.

Table 11.1.4.2.4 Mean changes in hematology from baseline for all subjects in 'long infusion' trials^a.

Lab Test, change from baseline day 2	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=24
WBC #(10 ³ /mm ³)	0.2 ± 1.43	0.9 ± 1.92	0.9 ± 1.66	1.8 ± 1.57
RBC # (10 ⁶ /mm ³)	-0.0 ± 0.24	0.3 ± 0.42	0.3 ± 0.42	0.1 ± 0.31
HGB (g/dL)	-0.0 ± 0.64	0.8 ± 1.20	0.8 ± 1.07	0.2 ± 0.93
Hematocrit	-0.2 ± 2.14	2.4 ± 3.88	2.4 ± 3.44	0.8 ± 2.58
Platelet #(10 ³ /mm ³)	-16.8 ± 26.17	8.0± 27.35	-1.4 ± 29.11	-10.3 ± 24.31
Prothrombin Time (secs)	0.2 ± 1.03	-0.5 ± 0.69	-0.2 ± 0.52	0.5 ± 1.72
PTT (secs)	-2.1 ± 13.99	7.9 ± 48.35	-3.3 ± 5.23	-6.6 ± 9.41

a. Data from data sets submitted at reviewer's request.

11.1.4.3 Analyses Focused on Extreme Laboratory Values

11.1.4.3.1 Shift Table Analysis

With the exceptions of the changes discussed below, there were no significant patterns in the shift table analysis. No trends were detected for the following labs: bilirubin, alkaline phosphatase, lactate dehydrogenase, ALT, calcium, or phosphorus.

11.1.4.3.1a Serum Chemistries

Bicarbonate

In the CHF studies, more patients in the nesiritide group had serum HCO₃ values below normal at days 2, 5 and at the last available assessment.

Table 11.1.4.3.1a.1 Observed rate of decreased bicarbonate values in the CHF trials^a.

Time of HCO ₃ below normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	29 (12%)	60 (12%)	0.761
Last Available on or before Day 2	19 (9%)	71 (17%)	0.048
Last Available on or before Day 5	20 (9%)	73 (15%)	0.060
Last Available	21 (9%)	64 (13%)	0.124

a. Data from NDA vol. 79, table 34A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

The trend was less apparent in the infusion studies, although there does appear to be a dose-related increase in the incidence of low bicarbonates at the 2 day point.

Table 11.1.4.3.1a.2 Observed rate of decreased bicarbonate values in the long infusion trials^a.

Time of HCO ₃ below normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	20 (12%)	13 (8%)	22 (14%)	3 (12%)	0.991
Last Available on or before Day 2	10 (6%)	15 (10%)	25 (17%)	1 (7%)	0.286
Last Available on or before Day 5	12 (7%)	19 (11%)	19 (11%)	1 (4%)	0.422
Last Available	13 (8%)	17 (10%)	19 (11%)	4 (15%)	0.170

a. Data from NDA vol. 79, table 34A3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

Serum Glucose

In both the CHF trial as a whole, and in the long infusion studies, a substantial % of patients were hyperglycemic at baseline (54% of both groups in the 'all CHF' population). At all timepoints measured, however, there was a small # of patients who were hypoglycemic, with a higher incidence in the nesiritide groups.

Table 11.1.4.3.1a.3 Observed rate of decreased glucose concentrations in the 'all CHF' groups^a.

Time of Glucose below normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	4 (2%)	14 (3%)	0.666
Last Available on or before Day 2	1 (1%)	4 (2%)	0.186
Last Available on or before Day 5	2 (1%)	14 (4%)	0.239
Last Available	4 (2%)	22 (5%)	0.299

a. Data from NDA vol. 79, table 35A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was a similar trend in the infusion studies, again with very few patients.

Table 11.1.4.3.1a.4 Observed rate of decreased glucose values in the 'long infusion' group^a.

Time of Bicarbonate below normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	4 (2%)	7 (4%)	6 (4%)	1 (4%)	0.805
Last Available on or before Day 2	0 (0%)	2 (6%)	1 (3%)	0 (0%)	0.492
Last Available on or before Day 5	2 (2%)	6 (5%)	7 (6%)	0 (0%)	0.712
Last Available	3 (2%)	6 (4%)	9 (6%)	2 (8%)	0.736

a. Data from NDA vol. 79, table 35D3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

Blood Urea Nitrogen (BUN)

In the CHF trials, the incidence of elevated BUN at baseline was >50% in both the control and the nesiritide group. There was no significant difference in the % of patients with elevated BUNs during the trials in this group.

Table 11.1.4.3.1a.5 Observed rate of increased BUN concentrations in the 'all CHF' population^a.

Time of increased BUN	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	124 (53%)	276 (55%)	0.619
Last Available on or before Day 2	98 (47%)	218 (51%)	0.339
Last Available on or before Day 5	113 (49%)	258 (52%)	0.473
Last Available	119 (51%)	288 (57%)	0.124

a. Data from NDA vol. 79, table 36A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was, however, an increased % of patients in the nesiritide group who had normal BUNs at baseline and had elevated BUNs at 2 and 5 days and last available measured.

Table 11.1.4.3.1a.6 Incidence of patients with increased BUN after normal baseline BUN in the 'all CHF' population^a.

Time of increased BUN	Control n=235	Nesiritide n=505
Last Available on or before Day 2	5 (2%)	23 (5%)
Last Available on or before Day 5	10 (4%)	38 (8%)
Last Available	20 (9%)	62 (12%)

a. Data from NDA vol. 79, table 36A4. p Value per the sponsor for the entire frequency of high, normal and low lab values.

In the long infusion trials, there was again no difference in the incidence of increased BUN (data not shown, see table 36C3 for details). The number of patients with normal BUN at baseline and elevated BUN at time of follow-up was also similar in the treatment groups.

Table 11.1.4.3.1a.7 Observed rate of increased BUN concentrations in the long infusion trials for patients with normal BUN at baseline^{a,b}.

Time of BUN above normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	4 (3%)	8 (5%)	9 (6%)	1 (4%)
Last Available on or before Day 5	10 (6%)	15 (9%)	12 (7%)	1 (4%)
Last Available	13 (8%)	16 (10%)	15 (9%)	3 (12%)

a. Data from supplemental data table from sponsor at reviewer's request.

b. Percentages are calculated using all subjects, regardless of baseline status.

Creatinine

Among all patients enrolled in the CHF trials, there were more with abnormally elevated creatinines at days 2, 5 and at final available assessment in the nesiritide group.

Table 11.1.4.3.1a.8 Observed rate of increased creatinine values in the long infusion trials^{a,b}.

Time of Creatinine below normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	87 (37%)	186 (37%)	0.837
Last Available on or before Day 2	71 (34%)	165 (39%)	0.134
Last Available on or before Day 5	75 (32%)	200 (40%)	0.032
Last Available	89 (38%)	227 (45%)	0.068

a. Data from NDA vol. 79, table 37A3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

b. Percentages are calculated using all subjects, regardless of baseline status.

A higher % of patients with normal creatinines at baseline also had elevated creatinines at follow-up in the nesiritide group.

Table 11.1.4.3.1a.9 Incidence of patients with increased creatinine after normal baseline creatinine in the 'all CHF' trials^a.

Time of increased Creatinine	Control n=235	Nesiritide n=505
Last Available on or before Day 2	7 (3%)	33 (8%)
Last Available on or before Day 5	13 (6%)	42 (8%)
Last Available	20 (9%)	64 (13%)

a. Data from NDA vol. 79, table 37A4. Nominal p Value per the sponsor for the entire frequency of high, normal and low lab values.

In the long infusion trials, there was a higher % of patients with elevated creatinines in the 0.030 dose group, compared with either the 0.015 group or the control group. Note the lower % of elevated creatinines in the nesiritide 0.015 dose group.

Table 11.1.4.3.1a.10 Observed rate of increased creatinine values in the long infusion trials^a.

Time of increased Creatinine	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	79 (46%)	62 (37%)	76 (46%)	13 (50%)	0.191
Last Available on or before Day 2	65 (42%)	52 (34%)	77 (52%)	4 (27%)	0.009
Last Available on or before Day 5	69 (41%)	62 (37%)	85 (51%)	10 (40%)	0.060
Last Available	73 (43%)	67 (40%)	90 (54%)	13 (50%)	0.048

a. Data from supplemental table 37D3 . p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

Similarly, the % of patients who developed elevated creatinines after a normal baseline value was higher in the 0.030 µg/kg/min nesiritide group.

Table 11.1.4.3.1a.11 Observed incidence of increased creatinine values after normal baseline value in the long infusion trials^a.

Time of increased Creatinine	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	4 (3%)	7 (5%)	18 (12%)	0 (0%)
Last Available on or before Day 5	10 (6%)	12 (7%)	17 (10%)	1 (4%)
Last Available	11 (7%)	16 (10%)	22 (13%)	2 (8%)

a. Data from NDA vol. 79, table 37C4. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

The number of patients with pre-specified increases in serum creatinine also tended to be higher in the nesiritide groups, relative to control. The table below shows the data for trials 704.311, 704.325, and 704.326. Note that there were relatively few patients with two or more serum creatinines in the 704.311 study.

Table 11.1.4.3.1a.12 Observed incidence of increased creatinine values in trial 704.311^a.

Pre-specified increases in Creatinine	Placebo n=29	Nesiritide 0.015 n=23	Nesiritide 0.030 n=25	Nesiritide 0.060 n=26	Nominal p Value ^a
>1.0 mg/dl Increase	2 (7%)	1 (4%)	1 (4%)	1 (4%)	1.000
>0.5 mg/dl Increase	2 (7%)	3 (13%)	3 (12%)	4 (15%)	0.798
>100% Increase	1 (3%)	1 (4%)	1 (4%)	0 (0%)	0.795
>50% Increase	1 (3%)	2 (9%)	3 (12%)	3 (12%)	0.635
>25% Increase	6 (21%)	7 (30%)	5 (20%)	7 (27%)	0.804

a. Data from the sponsor. p Value per the sponsor comparing nesiritide dose groups and placebo.

Table 11.1.4.3.1a.13 Observed incidence of increased creatinine values in trial 704.325^a.

Pre-specified increases in Creatinine	Control n=42	Nesiritide 0.015 n=43	Nesiritide 0.030 n=42	Nominal p Value ^a
>1.0 mg/dl Increase	0 (0%)	2 (5%)	4 (10%)	0.122
>0.5 mg/dl Increase	2 (5%)	7 (16%)	8 (19%)	0.124
>100% Increase	1 (2%)	1 (2%)	4 (10%)	0.322
>50% Increase	1 (2%)	5 (12%)	8 (19%)	0.049
>25% Increase	7 (17%)	11 (26%)	8 (19%)	0.624

a. Data from NDA vol. 79, table 37D1. p Value per the sponsor for the comparison between nesiritide dose groups and control.

Table 11.1.4.3.1a.13 Observed incidence of increased creatinine values in trial 704.326^a.

Pre-specified increases in Creatinine	Control n=102	Nesiritide 0.015 n=103	Nesiritide 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 NDA vol. 79, table 37D2. p Value per the sponsor for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

In data not shown, this apparent dose-related increase in elevated creatinine was seen across almost all demographic subsets of studies 704.325 and 704.326: elderly, males/ females, white/black, by NYHA class, presence or absence of hypertension, presence or absence of diabetes, occurrence of hypotension, and use of ACE inhibitors (see tables 37D3 and 37D4 for details).

Total Protein

In both the CHF trials as a whole there was a higher % of the nesiritide group developed low total protein levels. This abnormality tended to resolve by the last available assessment. There was also a slightly higher % of patients with low total proteins at the start of the trial in the nesiritide group.

Table 11.1.4.3.1a.14 Observed rate of decreased total protein concentrations in the 'all CHF' trials^a.

Time of total protein below normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	38 (16%)	62 (12%)	0.110
Last Available on or before Day 2	11 (5%)	17 (3%)	0.003
Last Available on or before Day 5	34 (15%)	49 (10%)	0.003
Last Available	32 (14%)	90 (18%)	0.316

a. Data from NDA vol. 79, table 39A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was a similar trend in the infusion studies.

Table 11.1.4.3.1a.15 Observed rate of decreased total protein values in the long infusion trials^a.

Time of total protein below normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	32 (20%)	43 (27%)	40 (26%)	3 (12%)	0.135
Last Available on or before Day 2	4 (13%)	14 (47%)	10 (33%)	5 (36%)	0.038
Last Available on or before Day 5	23 (26%)	38 (39%)	42 (44%)	8 (36%)	0.051
Last Available	27 (25%)	36 (31%)	42 (36%)	1 (4%)	0.038

a. Data from NDA vol. 79, table 35C3 and 39C3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

Serum Albumin

In both the CHF trials as a whole there was a higher % of the nesiritide group developed low serum albumin.

Table 11.1.4.3.1a.16 Observed rate of decreased albumin concentrations in the 'all CHF' trials^a.

Time of Albumin below normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	86 (38%)	219 (45%)	0.089
Last Available on or before Day 2	25 (31%)	103 (57%)	<0.001
Last Available on or before Day 5	63 (42%)	211 (60%)	<0.001
Last Available	64 (36%)	164 (40%)	0.411

a. Data from NDA vol. 79, table 40A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was a similar trend in the infusion studies.

Table 11.1.4.3.1a.17 Observed rate of decreased albumin values in the 'long infusion' trials^a.

Time of Albumin below normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	65 (39%)	80 (48%)	76 (48%)	8 (31%)	0.170
Last Available on or before Day 2	6 (19%)	20 (69%)	16 (53%)	7 (50%)	0.001
Last Available on or before Day 5	39 (42%)	62 (66%)	61 (62%)	10 (45%)	0.010
Last Available	49 (43%)	66 (56%)	66 (53%)	3 (12%)	0.001

a. Data from supplemental table 40D3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

Similarly, the % of patients who developed decreased albumin after a normal baseline value was higher in the high-dose nesiritide group. This was particularly true at day two, when the nesiritide infusion was continuing in a significant % of the subjects.

Table 11.1.4.3.1a.18 Observed incidence of decreased albumin values after normal baseline value in the long infusion trials^{a,b}.

Time of decreased Albumin	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	1 (3%)	6 (21%)	5 (18%)	4 (29%)
Last Available on or before Day 5	10 (11%)	17 (18%)	16 (17%)	4 (18%)
Last Available	10 (9%)	16 (14%)	17 (14%)	1 (4%)

a. Data from NDA vol. 79, supplemental table 40D4.

b. Percentages are calculated from the total number of patients with available data, regardless of baseline status.

Aspartate Transaminase (AST)

In the long infusion trials, there was an unexpected pattern of more patients with increased ASTs in the low-dose nesiritide dose, but a lower incidence in the high-dose group. A similar pattern was not seen for ALT (see below). In the 'all CHF trials' population, no differences between the control and nesiritide groups was detected.

Table 11.1.4.3.1a.19 Observed rate of increased ASTs in the long infusion trials^a.

Time of AST above normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	38 (23%)	34 (21%)	21 (13%)	7 (27%)	0.152
Last Available on or before Day 2	5 (16%)	7 (25%)	0 (0%)	0 (0%)	0.003
Last Available on or before Day 5	16 (17%)	23 (24%)	3 (8%)	0 (0%)	0.058
Last Available	23 (20%)	22 (19%)	19 (15%)	2 (8%)	0.814

a. Data from NDA vol. 79, table 44C3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

Serum Magnesium

In both the 'controlled CHF' the 'long infusion' populations there were a nominally significant association between nesiritide administration and increased magnesium levels.

The first table shows the controlled CHF studies.

Table 11.1.4.3.1a.20 Observed rate of elevated magnesium concentrations in the 'all CHF' trials^a.

Time of Mg ²⁺ above normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	19 (9%)	53 (11%)	0.367
Last Available on or before Day 2	5 (6%)	16 (10%)	0.473
Last Available on or before Day 5	13 (8%)	40 (11%)	0.046
Last Available	14 (8%)	53 (13%)	0.060

a. Data from NDA vol. 79, table 48A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

A similar trend was seen in the 'long infusion' studies.

Table 11.1.4.3.1a.21 Observed rate of increased serum magnesium levels in the 'long infusion' trials^a.

Time of Mg ²⁺ above normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	17 (11%)	20 (13%)	19 (13%)	2 (8%)	0.459
Last Available on or before Day 2	3 (9%)	4 (15%)	6 (21%)	2 (18%)	0.333
Last Available on or before Day 5	10 (10%)	13 (13%)	20 (20%)	2 (10%)	0.008
Last Available	11 (9%)	18 (15%)	22 (18%)	1 (5%)	0.021

a. Data from NDA vol. 79, table 48D3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

There was, however, no clear trend towards the development of elevated Mg²⁺ levels in patients who started with normal levels.

Table 11.1.4.3.1a.22 % of Patients with increased Mg²⁺ after normal baseline Mg²⁺ in the 'all CHF' trials^a.

Time of increased Mg ²⁺	Control n=235	Nesiritide n=505
Last Available on or before Day 2	3 (4%)	8 (5%)
Last Available on or before Day 5	8 (5%)	16 (5%)
Last Available	10 (6%)	23 (6%)

a. Data from NDA vol. 79, table 48A4. p Value per the sponsor for the entire frequency of high, normal and low lab values.

Table 11.1.4.3.1a.23 Observed incidence of increased Mg²⁺ values after normal baseline value in the 'long infusion' trials^{a,b}.

Time of increased Mg ²⁺	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	2 (6%)	3 (11%)	2 (8%)	1 (9%)
Last Available on or before Day 5	6 (6%)	5 (5%)	7 (7%)	1 (5%)
Last Available	7 (6%)	8 (7%)	8 (7%)	0 (0%)

a. Data from supplemental table 48D4. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

b. Percentages are calculated from the total number of patients with available data, regardless of baseline status.

11.1.4.3.1ba Hematology

No trends were detected for the following hematology labs: erythrocyte count, hemoglobin, hematocrit, platelet count, PT, and PTT.

WBC Count

In the long infusion population, but not in the CHF trials population, there was an association between dose of nesiritide and incidence of elevated WBC count.

Table 11.1.4.3.1b.1 Observed rate of increased WBC # in the 'long infusion' trials^a.

Time of WBC #above normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	14 (8%)	16 (10%)	22 (13%)	3 (12%)	0.408
Last Available on or before Day 2	2 (6%)	5 (14%)	6 (19%)	4 (25%)	0.468
Last Available on or before Day 5	11 (10%)	13 (11%)	24 (20%)	6 (25%)	0.069
Last Available	14 (10%)	16 (11%)	29 (20%)	4 (15%)	0.186

a. Data from supplemental table 49D3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

There was also an increased incidence of elevated WBC # after 2 days in patients who started with a normal baseline count in the long infusion studies. This trend was diminished in the later timepoint, following study drug discontinuation.

Table 11.1.4.3.1b.2 Observed incidence of increased WBC values after normal baseline value in the long infusion trials^{a,b}.

Time of increased WBC	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	2 (6%)	4 (11%)	3 (10%)	3 (19%)
Last Available on or before Day 5	8 (7%)	8 (7%)	10 (8%)	3 (13%)
Last Available	9 (7%)	11 (8%)	15 (10%)	2 (8%)

a. Data from supplemental table 49D4. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

b. Percentages are calculated from the total number of patients with available data, regardless of baseline status.

11.1.4.4 Adverse Events Related to Vital Signs

Blood Pressure

In all three long infusion trials there was an association between nesiritide dose and the frequency of hypotension. This reflected an acute effect of nesiritide to lower blood pressure, as shown in the tables below, which come from the individual study reviews.

Table 11.1.4.1.1 (from table 6.1.12.4.1) Effect of 3 hour infusion of nesiritide on blood pressure in trial 704.311^a.

	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	Nominal p Value ^b
Systolic BP (mm Hg)	+1.2 (+1%)	-7.4 (-6%)	-4.3 (-3%)	-10.0 (-8%)	0.006

a. Data from NDA 20-998, vol. 54, Text Table 2. Data are expressed as absolute and (%) change from baseline for ITT population.

b. p Value comparing arithmetic means from baseline using ANOVA.

Table 11.1.4.1.2 (from table 6.2.12.4.2) Summary of changes in blood pressure using 'last value carried forward' population from study 704.325)^a.

Blood Pressure changes in study 704.325	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	Nominal p Value ^b
Mean Systemic Arterial BP (MAP), mm Hg				
MAP at baseline and 6 hours				
At baseline	86.2±12.6	81.2±10.0	85.4±11.3	0.103
At 6 hours	86.7±13.1	76.2±11.4	76.8±10.2	<0.001
Nominal p Value (compared to control)	---	<0.001	<0.001	
Change in MAP from baseline at 6 hrs (mm Hg)				
Mean±SD	0.3±7.8	-5.1±11.0	-8.6±8.0	<0.001
Median	-1.3	-4.5	-8.7	
Range	-17 to +19	-44 to +20	-24 to +11	
Nominal p Value (change from baseline) ^c	---	0.005	<0.001	
Nominal p Value (comp. to control) ^c	---	0.008	<0.001	

a. Data from NDA volume 1.59, Appendix 1, Table 26a to 40a and electronic data sets.

b. p Value using Omnibus F test.

c. p Value compares the 6 hour value for each group individually with the control baseline using T-test or 1-sample Wilcoxon.

Table 11.1.4.1.2 (from table 6.3.12.3.1) Changes in blood pressure from baseline to 3 hours in study 326^a.

Blood Pressure changes in study 704.326	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal p Value
Systolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	120.7±20	127±25	124±26	0.197
Change from Baseline to 3 hours	-2.3±16	-9.4±16	-11.2±16	<0.001
Nominal p Value (Chg from Base) ^b	0.183	<0.001	<0.001	
Nominal p Value (Compared to Standard Care) ^c	--	0.003	<0.001	
Nominal p Value (Compared to Low-dose BNP) ^c	--	--	0.426	
Diastolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	70±13	71±15	68±15	0.477
Change from Baseline to 3 hours	-3.2±11	-8.3±11	-8.6±11	<0.001
Nominal p Value (Chg from Base) ^b	<0.001	<0.001	<0.001	
Nominal p Value (Compared to Standard Care) ^c	--	0.376	0.125	
Nominal p Value (Compared to Low-dose BNP) ^c	--	--	0.016	

a. Data from NDA volume 1.66, table 21.

b. Comparison by T test.

c. Comparison by ANOVA contrast.

Heart Rate

The acute effect of nesiritide on heart rate was also compared with control in the three infusion trials. Overall, no clear pattern of effect was discernable, perhaps related to the different controls used in each of the trials (placebo in 311, active control in 326).

Table 11.1.4.1.1 (from table 6.1.12.4.1) Mean change in heart rate from baseline to 3 hours in trial 704.311^a.

Heart Rate in study 704.311	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	Nominal p Value ^b
Heart Rate (BPM)	2.6±8	-3.7±7	-2.2±9	+6.2±14	0.002

a. Data from NDA 20-998, vol. 54, Table 2. Data are expressed as absolute and (%) change from baseline for ITT population.

b. p Value comparing arithmetic means from baseline using ANOVA.

Table 11.1.4.1.2 (from table 6.2.12.4.2) Summary of changes in heart rate using 'last value carried forward' population from study 704.325)^a.

Heart Rate in study 704.325	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.0305 n=42	Nominal p Value ^b
HR at baseline and 6 hours				
At baseline	89.5±12.8	90.3±14.6	87.4±16.7	0.640
At 6 hours	90.9±15.4	88.8±14.5	87.5±16.0	0.576
Nominal p Value (compared to control)	---	0.516	0.300	
Change in HR from baseline at 6 hrs (mm Hg)				
Mean±SD	1.4 ±7	-1.6±7	0.0±9	0.218
Median	0.5	-3.0	0.0	
Range	-16 to +24	-16 to +14	-28 to +28	
Nominal p Value (change from baseline) ^c	0.240	0.149	0.972	
Nominal p Value (comp. to control) ^c	---	0.082	0.435	

a. Data from NDA volume 1.59, Appendix 1, Table 26a to 40a and electronic data sets.

b. p Value using Omnibus F test.

c. p Value compares the 6 hour value for each group individually with the control baseline using T-test or 1-sample Wilcoxon.

Table 11.1.4.1.2 (from table 6.3.12.3.1) Changes in vital signs from baseline to 3 hours in 704.326^a.

Heart Rate in study 704.326	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal p Value
Baseline (mean±sd)	85±15	83±18	84±15	0.823
Change from Baseline to 3 hours	+3.5±15	-0.6±9	+0.6±10	0.053
Nominal p Value (Chg from Base) ^b	0.029	0.501	0.569	
Nominal p Value (Compared to Standard Care) ^c	--	0.018	0.107	
Nominal p Value (Compared to Low-dose BNP) ^c	--	--	0.469	

a. Data from NDA volume 1.66, table 21.

b. Comparison by T test.

c. Comparison by ANOVA contrast.

11.1.4.5 Adverse Events Related to Special Examinations

ECGs

No formal analysis of the ECGs was performed by the sponsor beyond the Holter Monitors evaluated as described below.

Holter Monitors

Per the sponsor, 15 of the 46 clinical sites in study 704.326 performed pilot Holter monitoring on 45 subjects (15 standard care subjects, and 16 and 14 subjects receiving the 0.015 and 0.030 mg/kg/min nesiritide doses, respectively). No formal analysis of the effects of study drug on arrhythmias was performed, as subjects did not have adequate baseline Holter information to permit a comparative analysis of pre- and on-drug Holter data. The sponsor reported that 'a descriptive review of on-drug Holter information was qualitatively consistent with the investigators' reports of arrhythmic adverse events in that ventricular ectopy (PVCs, couplets, NSVT) was observed less frequently in the nesiritide subjects than in standard care subjects while the reverse trend was found for bradycardia.'

Urinalyses

Urinalyses were not performed as part of either study 704.325 and 704.326. In study 704.311, the only recorded urinalyses come from the screening period. In the absence of urinalysis data from the long infusion trials, the effect of nesiritide on urinary abnormalities cannot be determined, including: proteinuria, hematuria, pyuria, and glycosuria.

11.1.4.5 Discontinuations

The reasons for discontinuation from the three long infusion trials are summarized in the first three tables below, which are drawn from the individual trial reviews. Note that the time used to calculate 'completion' is short in all three trials (3 to 6 hours).

Table 6.1.12.2.1 Disposition of subjects randomized in the trial 311^a.

Patient Disposition	Placebo	Nesiritide 0.25/ 0.015	Nesiritide 0.5/ 0.030	Nesiritide 1.0/ 0.060
Randomized	29	22	26	26
Completed up to 3 hours	29 (100%)	22 (100%)	25 (96%)	23 (88%)
Discontinued within 24 hours (Total)	5 (17%)	0 (0%)	2 (8%)	6 (23%)
D/C'd due to an AE prior to hour 3	0 (0%)	0 (0%)	1 (4%)	3 (12%)
D/C'd due to an AE between hours 3 & 24	5 (17%)	0 (0%)	1 (4%)	3 (12%)
D/C'd due to hypotension	0 (0%)	0 (0%)	2 (8%)	6 (23%)
D/C'd due to worsened CHF	5 (17%)	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 54, page 108.

Table 6.2.12.2.1 Disposition of subjects randomized in the study 704.325^a.

Patient Disposition	Placebo	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030
Randomized	42	43	42
Completed up to 5.5 hours	41	42	39
Discontinued	1 (2%)	1 (1%)	3 (7%)
D/C'd prior to 5.5 hrs after start of infusion	1 (2%)	1 (1%)	3 (7%)
D/C due to AE	1 (2%)	1 (1%)	3 (7%)
D/C'd due to hypotension ^b	0 (0%)	0 (0%)	2 (5%)
D/C'd due to worsening CHF	0 (0%)	1 (1%)	0 (0%)
D/C'd with other AEs	1 (2%)	0 (0%)	1 (2%)

a. Data from NDA volume 1.59, section 4.2 and electronic data sets.

b. Includes one individual with hypotension and one with PCWP = 6 mm Hg.

Table 6.3.12.2.1 Disposition of subjects randomized in the study 326 at the end of 21 days^a.

Patient Disposition	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100
Randomized	102	103	100
Completed to 6 hours	100 (98%)	101 (98%)	94 (94%)
Discontinued			
D/C prior to 6 hours ^b	2 (2%)	2 (2%)	5 (5%)
D/C due to hypotension	0 (0%)	2 (2%)	5 (5%)
D/C due to arrhythmia	2 (2%)	0 (0%)	1 (1%)
Alive at day 21	96 (94%)	94 (91%)	94 (94%)
Dead	5 (5%)	6 (6%)	6 (6%)
Lost to F/U	1 (1%)	3 (3%)	0 (0%)

a. Data from NDA volume 66, appendix table 11.

b. 6 hour time point represents the end of the blinded analysis in the earlier trial 704.325.

The sponsor also summarized the reasons for study drug withdrawal for the 'CHF trials' population and for the 'long infusion studies' population, as shown below. A higher % of the control group (either placebo or active control) was discontinued per protocol, and a higher % of the nesiritide groups was discontinued for adverse events. The increased % of withdrawals in the nesiritide group in the 'long infusion study' population was dose-related.

Table 11.1.4.3.1.2 Reasons for termination of study drug in the 'all CHF' studies^a.

Reasons for study drug termination	Control n=235	Nesiritide n=505	Nominal p Value ^a
Per Protocol	200 (85%)	386 (76%)	0.006
Adverse Event	6 (3%)	74 (15%)	<0.001
Inadequate Therapeutic Response	20 (9%)	41 (8%)	0.886
Other	9 (4%)	17 (3%)	0.831

a. Data from table 6A per the sponsor. p Values by Fisher's Exact test.

Table 11.1.4.3.1.2 Reasons for termination of study drug in the long-infusion studies^a.

Reasons for study drug termination	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Per Protocol	145 (84%)	126 (75%)	114 (68%)	20 (77%)	0.005
Adverse Event	1 (0%)	23 (14%)	34 (20%)	6 (23%)	<0.001
Inadequate Therapeutic Response	14 (8%)	17 (10%)	18 (11%)	0 (0%)	0.322
Other	9 (5%)	9 (5%)	8 (5%)	0 (0%)	0.875

a. Data from supplemental table 6D per the sponsor.

11.1.5.2 Discontinuations associated with Serious Adverse Events (SAEs)

Discontinuations associated with SAEs are included in the tables below, summarizing all known withdrawals for adverse events, including SAEs.

11.1.5.3 Discontinuations associated with Adverse Events (AEs)

The table below summarizes the discontinuations due to AEs in the CHF trials. The shading indicates a nominally significant difference between the control and nesiritide groups.

Table 11.1.5.3.1 Discontinuations prior to day 14 due to AEs in the 'CHF trials' population^a.

Body System/ AE	Control n=235	Nesiritide n=505	Nominal p Value ^a
Cardiovascular System	15 (6%)	78 (15%)	<0.0001
Hypotension	2 (1%)	51 (10%)	<0.0001
Symptomatic Hypotension	2 (1%)	32 (6%)	<0.0001
Congestive Heart Failure	7 (3%)	14 (3%)	0.817
Bradycardic Event	0 (0%)	7 (1%)	0.104
Bradycardia	0 (0%)	6 (1%)	0.184
Nodal Arrhythmias	0 (0%)	1 (0%)	1.000
Decreased Pulmonary Pressure	0 (0%)	5 (1%)	0.185
Elevated PCWP	2 (1%)	2 (0%)	0.595
Ventricular Tachycardia	3 (1%)	0 (0%)	0.032
Digestive System	1 (0%)	12 (2%)	0.072
Nausea	1 (0%)	10 (2%)	0.188
Vomiting	0 (0%)	3 (1%)	0.555
Nausea and Vomiting	0 (0%)	1 (0%)	1.000
Nervous System: None			
Urogenital System	0 (0%)	9 (2%)	0.064
Oliguria	0 (0%)	5 (1%)	0.185
Creatinine Increased	0 (0%)	4 (1%)	0.313
Acute Kidney Failure	0 (0%)	1 (0%)	1.000
Metabolic & Nutritional System	0 (0%)	5 (1%)	0.185
BUN Increased	0 (0%)	4 (1%)	0.313
Hypovolemia	0 (0%)	1 (0%)	1.000
Respiratory System: None			
Body as a Whole: None			
Skin & Extremities: None			
Special Senses: None			
Amblyopia	0 (0%)	1 (<1%)	1.000

a. Data from NDA appendix 8.4, table 28A.

Next, the discontinuations associated with AEs in the long infusion studies are summarized.

Table 11.1.5.3.1 Discontinuations due to AEs in the long infusion trials^a.

AE	Placebo (n=29)	Nesiritide 0.015 (n=22)	Nesiritide 0.030 (n=26)	Nesiritide 0.060 (n=26)	Nominal p Value ^b
Cardiovascular	9 (5%)	23 (14%)	33 (20%)	6 (23%)	<0.001
Hypotension	1 (1%)	14 (8%)	25 (15%)	3 (12%)	<0.001
Symptomatic Hypotension	1 (1%)	8 (5%)	14 (8%)	2 (8%)	0.002
Congestive Heart Failure	4 (2%)	5 (3%)	5 (3%)	0 (0%)	0.946
Bradycardic Events	0 (0%)	2 (1%)	4 (2%)	0 (0%)	0.170
Bradycardia	0 (0%)	2 (1%)	3 (2%)	0 (0%)	0.325
Nodal Arrhythmia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Decreased Pulmonary Pressure	0 (0%)	0 (0%)	2 (1%)	3 (12%)	<0.001
Ventricular Tachycardia	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0.234
Sustained VT	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0.395
Non-sustained VT	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1.000
Tachycardia	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1.000
Digestive System	0 (0%)	5 (3%)	6 (4%)	1 (4%)	0.036
Nausea	0 (0%)	5 (3%)	4 (2%)	1 (4%)	0.058
Vomiting	0 (0%)	1 (1%)	2 (1%)	0 (0%)	0.326
Nausea and Vomiting	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Urogenital	0 (0%)	2 (1%)	7 (4%)	0 (0%)	0.020
Oliguria	0 (0%)	1 (1%)	4 (2%)	0 (0%)	0.125
Creatinine Increased	0 (0%)	1 (1%)	3 (2%)	0 (0%)	0.249
Acute Kidney Failure	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Body as a Whole	1 (1%)	3 (2%)	0 (0%)	2 (8%)	0.014
Abdominal Pain	0 (0%)	0 (0%)	0 (0%)	2 (8%)	0.002
Headache	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0.291
Asthenia	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0.049
Nervous System	0 (0%)	1 (1%)	3 (2%)	2 (8%)	0.010
Dizziness	0 (0%)	0 (0%)	1 (1%)	2 (8%)	0.002
Nervousness	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Stupor	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Vertigo	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.677
Metabolic & Endocrine	0 (0%)	2 (1%)	3 (2%)	0 (0%)	0.325
BUN Increased	0 (0%)	2 (1%)	2 (1%)	0 (0%)	0.510
Hypovolemia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Respiratory System: None					
Special Sense					
Amblyopia	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.677
Skin and Appendages: None					

a. Data from supplemental table 28D.

11.1.5.4 Discontinuations associated with Laboratory Adverse Events

Discontinuations for laboratory AEs are included in the tables above.

11.1.6 Special Studies

In this section, problems germane to all NDA submissions are reviewed: These include: tolerance, withdrawal/ rebound, abuse potential, human reproductive toxicity, and overdose.

11.1.6.1 Special Studies: Tolerance/ Withdrawal

Tolerance

The potential for tolerance or tachyphylaxis to the vasodilatory effects of nesiritide was discussed in section 7.0.1c (Durability of the Effect of Nesiritide on PCWP and Other Hemodynamic Measures). The reader is referred there for the discussion, which concluded the following: the data are inadequate to fully assess the development of tachyphylaxis following long nesiritide infusion. Based on the decrease in the magnitude of the hemodynamic effect of nesiritide in trial 704.311, a degree of tolerance to the hemodynamic effects of nesiritide is possible. This decrease, however, did not reverse the overall significant effects of nesiritide on hemodynamics, when compared with placebo through 24 hours. The clinical significance of the decreases in mean hemodynamic changes through 24 hours.

Withdrawal

The potential for a withdrawal phenomenon was discussed in section 7.0.1a.4 (Changes in PCWP Following Withdrawal of Nesiritide), with the following conclusion: no evidence was detected of a 'rebound' phenomenon with regard to PCWP. Following withdrawal of nesiritide, the PCWP returned to within 10% of baseline by the end of 4 hours. After 2 hours, the PCWP for the high-dose nesiritide (1.0/ 0.060) group was still approximately 20% below baseline.

11.1.6.2 Special Studies: Abuse Potential

The anticipated abuse potential for nesiritide is low. First, it is administered intravenously in an intensive care unit-setting. Second, it has no known mood-altering properties. There are, however, receptors for nesiritide in the brain. A related compound, atrial natriuretic peptide, has been proposed as a therapy for 'flashbacks' related to Post-Traumatic Stress Syndrome, suggesting some activity on personality and behavior.

11.1.6.3 Special Studies: Human Reproduction Data

Per the sponsor, no pregnant individuals are known to have been exposed to nesiritide during the product development.

11.1.6.4 Special Studies: Overdose

In the three infusion studies, patients were dose on the basis of body weight. Per the sponsor, there have been no observed instances of overdosage during the clinical program and no studies related to overdosage have been conducted.

Sponsor's Comments

The sponsor pointed out that while the proposed nesiritide dose range is 0.015 to 0.03 $\mu\text{g}/\text{kg}/\text{min}$, it has been administered to subjects with CHF at doses as high as 0.1 $\mu\text{g}/\text{kg}/\text{min}$ as a continuous infusion. At this higher dose, symptomatic hypotension was frequent and limited drug tolerance. While the hypotension and accompanying symptoms usually resolved soon after dose reduction or discontinuation of nesiritide infusion, one subject had prolonged symptomatic hypotension and junctional bradycardia following infusion at the 0.1 $\mu\text{g}/\text{kg}/\text{min}$ dose with labile blood pressure for approximately 5.5 hours. During this time he required IV fluids, dopamine and atropine. Nesiritide has been administered as a bolus at doses up to 32 $\mu\text{g}/\text{kg}$, which likely achieves quite high plasma hBNP levels for a short period of time. For these patients, decreases in blood pressure were the only adverse events that accompanied the bolus administration.

Finally, in preclinical studies, nesiritide has been administered to monkeys for 2 weeks at doses as high as 20 $\mu\text{g}/\text{kg}/\text{min}$ (approximately 1000-fold higher than the current clinical dose). A decrease in blood pressure was observed, but there was no evidence of acute adverse effects on clinical status or electrocardiography.

11.1.6.5 Special Studies: Allergic Reactions/ Antibody Formation

In that nesiritide is identical in structure to a naturally-occurring molecule, allergic reactions to it are unlikely. Nesiritide is produced using *E. coli*, which could induce an allergic reaction, despite the extensive process used to both remove and screen for any components of *E. coli* in the finished drug substance. The sponsor reports that there were no reported allergic reactions to either nesiritide or any of the other components of the drug substance. As an indirect marker for allergic reactions, the occurrence of pruritus and urticaria are summarized below.

Table 11.1.6.5.1 Pruritus, rash and urticaria in the long-infusion studies through day 14^a.

	Control n=173	Nesiritide n=0.015 n=169	Nesiritide n=0.030 n=167	Nesiritide n=0.060 n=26	Nominal p Value
Pruritus	4 (2%)	6 (4%)	6 (4%)	0 (0%)	0.844
Urticaria	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0.593
Rash	5 (3%)	2 (1%)	9 (5%)	0 (0%)	0.150

a. Data from supplemental table 11D per the sponsor.

Antibody Formation

Because of the concerns about the potential formation of antibodies against nesiritide, the sponsor collected baseline and day 21 titers of anti-nesiritide antibodies in trial 704.325. A total of 61 subjects who received nesiritide had baseline and follow-up antibody titers measured, and none of the subjects had an increase at day 21, relative to baseline.

12.0 Appendix Two: Narratives of subject deaths in NDA 20-920

Narratives for the 34 deaths known to have occurred in subjects who enrolled in one of the trials in NDA 20-920 are summarized below.

Study 704.306

1. *Subject 324-010 (Placebo)*: Subject was a 57-year-old white man with a history of NYHA Class III CHF due to ischemic cardiomyopathy, mitral and tricuspid valve regurgitation, dobutamine dependence, and pulmonary hypertension; he died on study day 15. This subject was already hospitalized at the time of entry into the study awaiting cardiac transplantation. He tolerated all study procedures well. On study day 15, he underwent a heart transplant after which he was not able to wean from cardiopulmonary bypass and died.

Study 704.309

1. *Subject 381-001 (Placebo)*: Subject was a 53-year-old white man with a history of NYHA Class IV CHF due to alcoholic cardiomyopathy, diabetes mellitus, chronic renal insufficiency, and chronic obstructive lung disease; the subject died on study day 6. This subject tolerated all study procedures well and was considered stable upon completion of study drug dosing. Four days following the termination of study drug dosing, he experienced ventricular fibrillation and cardiac arrest resulting in death despite efforts at cardiopulmonary resuscitation. This death was not considered study related.

2. *Subject 315-005 (Nesiritide, 5 µg/kg q4h)* Subject was a 65-year-old white man with NYHA Class IV CHF, hypertension, bifascicular heart block, and a history of previous episodes of supraventricular arrhythmias. He tolerated the 24-hour dosing period well but subsequently had a complicated hospital course with numerous arrhythmias requiring defibrillation and respiratory distress requiring intubation. He subsequently died of refractory CHF on day 30.

Study 704.310

No deaths occurred in this study during the 14-day study follow-up period. Two deaths on days 19 and 30 were later reported to Scios.

1. *Subject 356-103 (Placebo)* Subject was a 73-year-old white man with a history of NYHA Class IV CHF, coronary artery disease and hypertension. He tolerated all study procedures without incident. He died on day 19 due to ventricular fibrillation and electromechanical dissociation.

2. *Subject 373-301 (Nesiritide, 10 µg/kg)* Subject was a 47-year-old black man with a history of NYHA Class III CHF, hypertension, and sick sinus syndrome requiring a permanent pacemaker. He experienced mild dyspnea, sweating, insomnia, and dizziness during the study drug treatment period, possibly because of problems with capture by his pacemaker. The subject was discharged following the study and was seen in follow-up in clinic a month later without complaints of adverse events. He died two days later (on day 30) at home of sudden cardiac death.

Study 704.311

Three deaths occurred during the 15-day study follow-up period, one in each of the three treatment groups. Two additional deaths were reported after day 15, both in the placebo group.

1. *Subject 376-016 (Placebo)*: Subject was a 60-year-old white man with a history of NYHA Class III CHF, coronary artery disease, ventricular arrhythmias, hypertension, diabetes, and chronic obstructive pulmonary disease (COPD). He presented to clinic with dyspnea and peripheral edema and was enrolled in the study. He tolerated study drug infusion well and had no reported adverse events during his hospital stay. He was discharged to home and was found dead at home on day 6; cause of death was reported as sudden death.

2. *Subject 376-022 (Placebo)* Subject was a 60-year-old white woman with a history of NYHA Class III CHF (with an ejection fraction of 9%), rheumatic heart disease requiring mitral valve replacement, and chronic atrial fibrillation. She tolerated study drug infusion well. The day after study drug infusion, the subject underwent an elective atrio-ventricular (AV) nodal ablation and placement of a pacemaker without complications and was discharged from the hospital soon thereafter. No adverse events were reported during the 15-day study reporting period. The subject was found dead at home on day 21; cause of death was reported as sudden death.

3. *Subject 370-006 (Placebo)* Subject was a 50-year-old man from India with a history of NYHA Class IV CHF, coronary artery disease, a previous ventricular aneurysmectomy and marked cachexia at admission for worsening CHF. He was enrolled in the study but terminated study drug (placebo) infusion prematurely due to worsening CHF after 3 hours 25 minutes of infusion. The subject was then treated with IV dobutamine and furosemide. An episode of supraventricular tachycardia accompanied by chest pain was also reported on day 6. The subject was discharged to home, but was readmitted to another hospital on approximately day 18 with dyspnea and end-stage CHF; he was reported to have died during this hospitalization on approximately day 46, although information on the precise date and cause of death was not available.

4. *Subject 017-007 (0.03 µg/kg/min nesiritide)* Subject was an 85-year-old white man with NYHA Class IV CHF, coronary artery disease, a pacemaker, and atrial fibrillation. He was admitted with a four day history of worsening dyspnea. The subject received the full study drug infusion (0.03 µg/kg/min nesiritide), which was well tolerated. On day 4, the subject underwent elective cardiac catheterization with coronary stent placement. His renal function deteriorated in the days following this procedure, presumably due to contrast administration during the procedure; the adverse events of worsening CHF and acute renal failure were reported on day 8 (with a rise in serum creatinine from 2.4 mg/dL before enrollment to 3.6 mg/dL on day 8), requiring acute dialysis. The subject also required emergent intubation for worsening cardiac and respiratory failure. Due to the subject's generally poor prognosis, the subject and family chose not to pursue further resuscitative measures.

5. *Subject 382-004 (0.06 µg/kg/min nesiritide)* Subject was a 70-year-old white woman with NYHA Class IV CHF and a complex medical history including previous mitral and tricuspid valve replacements for rheumatic heart disease, ventricular pacemaker placement, chronic atrial fibrillation, and renal insufficiency. She was admitted for worsening CHF and enrolled in the study. She tolerated the full 24-hour study drug infusion well. Hypokalemia was reported on day 4, attributed to aggressive diuresis over the few days following study drug. After some improvement in her overall condition, she was discharged but was found dead at home on day 8. Death was attributed to a presumed ventricular arrhythmia and end-stage CHF.

Study 704.325

During the 21-day study reporting period, 6 deaths occurred, two in each of the three treatment groups.

1. *Subject 368-001 (Placebo)* Subject was a 63-year-old white man with NYHA Class IV CHF due to ischemic heart disease and severe mitral and tricuspid valvular disease. After the placebo period, he received dobutamine. On day 3, the subject underwent a surgical cardiac ventricular reduction procedure, coronary artery bypass graft surgery, and mitral and tricuspid valve repair. The subject's postoperative course was complicated by worsening CHF and acute renal failure ultimately requiring dialysis. On day 15, the subject died due to ventricular fibrillation while awaiting cardiac transplantation.

2. *Subject 503-001 (Placebo)* Subject was a 24-year-old white man with NYHA Class IV CHF due to idiopathic dilated cardiomyopathy. After the placebo period, he was treated with dobutamine, dopamine, and milrinone. On day 17, he developed ventricular fibrillation during milrinone infusion. Resuscitation was attempted (including intubation) but was not successful. The cause of death was reported to be endstage CHF and acute bronchopneumonia.

3. *Subject 374-001 (nesiritide, 0.015 µg/kg/min)* Subject was a 64-year-old white man with NYHA Class IV CHF due to ischemic cardiomyopathy, diabetes, and chronic renal insufficiency. He responded well to a 24-hour infusion of nesiritide; thereafter, dobutamine was added for inotropic support. The subject's digoxin had been discontinued 1 month earlier due to renal insufficiency. On study day 2, digoxin was reinstated. After receiving his second dose, he developed hypotensive bradycardia (Wenckebach type atrioventricular node block) while sleeping. Atropine was administered, a ventricular pacing wire was placed, and nesiritide was discontinued. Although the heart rate improved with pacing, hypotension persisted due to AV dyssynchrony. Digoxin toxicity was suspected (although digoxin level was 1.1 ng/mL 2 hours earlier) and Digibind was given. Forty minutes later, sinus tachycardia resumed; BP improved within 2 hours. The subject later revealed that he had had a similar event with digoxin in the past and, therefore, had previously been prescribed a low dose of digoxin. His subsequent hospital course included worsening CHF leading to inotrope dependence and a cardiopulmonary arrest. On day 4, after requesting that all medications be discontinued, the subject died due to endstage heart failure from severe coronary artery disease.

4. *Subject 382-013 (nesiritide, 0.015 µg/kg/min)* Subject was an 80-year-old white man with NYHA Class IV CHF due to ischemic cardiomyopathy and progressive renal insufficiency. He had not responded to 7 days of dobutamine therapy before he was enrolled into the study. After 6 hours of nesiritide therapy, his hemodynamics were only minimally improved and dobutamine was restarted. Nesiritide was discontinued on study day 3 due to hypotension and nausea. After a short trial of milrinone added to the dobutamine, it was decided that the subject was refractory to vasoactive medications. The subject was made "Do Not Resuscitate." On day 5, the subject expired due to endstage CHF and progressive renal insufficiency.

5. *Subject 357-002 (Nesiritide, 0.03 µg/kg/min)* Subject was a 54-year-old white man with a history of NYHA Class III CHF due to ischemic cardiomyopathy and chronic angina. Nesiritide was discontinued after 4.5 hours because his PCWP had decreased to 6 mm Hg. However, the subject was symptomatically improved, so no additional parenteral agents for CHF were started and he was discharged on day 2. On day 15, he died in the emergency room from a myocardial infarction after an unsuccessful resuscitation (including acute intubation).

6. *Subject 370-002 (Nesiritide, 0.03 µg/kg/min)* Subject was a 66-year-old white man with NYHA Class IV CHF and chronic atrial fibrillation. He responded well to 5 days of nesiritide therapy (the maximum allowed infusion duration per protocol). On day 6 (during nesiritide infusion), he developed bilateral femoral artery thromboses (presumably due to the discontinuation of warfarin 8 days earlier) requiring urgent surgical revascularization. On day 20, the subject experienced an acute episode of cardiopulmonary decompensation requiring emergency intubation and pressor support leading to the subject's death later that day.

Study 704.326

Seventeen subjects in this study died by day 21. Five (5%), 6 (6%), and 6 (6%) subjects in the standard care, the 0.015 and 0.03 nesiritide groups, respectively. One additional death in the 0.03 µg/kg/min nesiritide group occurred on day 22.

1. *Subject 493-019 (Standard care: dobutamine)* Subject was a 70-year-old white man with NYHA Class IV endstage ischemic cardiomyopathy. He received dobutamine for 90 hours, which was discontinued due to an inadequate therapeutic response. On day 3, he suffered a cardiopulmonary arrest (requiring acute intubation and defibrillation). On day 5, due to his poor prognosis, support was withdrawn, and he expired.

2. *Subject 493-021 (Standard care: dobutamine)* Subject was a 77-year-old white man with NYHA Class IV CHF and coronary artery disease. He received dobutamine for approximately 13 days and expired on day 18 from endstage cardiomyopathy.

3. *Subject 509-001 (Standard care: dobutamine)* Subject was a 61-year-old white man with a history of NYHA Class III CHF, a previous myocardial infarction, chronic renal insufficiency, Non-sustained VT, and bradycardia. During the study, he was treated with dobutamine for 1 day with no improvement and was discharged to home at his request. On day 10, he was readmitted with bullous cellulitis. On study day 13, he developed worsening renal function and received hemodialysis beginning on day 19. On day 21, he died following a cardiac arrest, presumably associated with a myocardial infarction.

4. *Subject 538-011 (Standard care: dobutamine)* Subject was a 78-year-old white man with a history of NYHA Class IV CHF, atrial fibrillation, ventricular ectopy, and chronic renal insufficiency. Dobutamine was administered for 8 days. On day 3, he developed acute renal failure. On day 4, he experienced bradycardia and a respiratory arrest requiring intubation and mechanical ventilation. He died on day 9 of severe left ventricular heart failure.

5. *Subject 585-002 (Standard care: dobutamine)* Subject was a 72-year-old white man with a history of NYHA Class IV CHF and coronary artery disease. For almost 3 days, he received dobutamine that was then discontinued because of an inadequate therapeutic response. His CHF continued to worsen, resulting in his death on day 21.

6. *Subject 369-003 (Nesiritide, 0.015 µg/kg/min)* Subject was a 88-year-old white woman with NYHA Class III CHF due to ischemic cardiomyopathy. For 31 hours, she received nesiritide that was discontinued due to inadequate clinical response, acute shortness of breath, and sinus tachycardia. On day 2, nesiritide was replaced with milrinone and dobutamine, which were infused for 4 days. After progressive worsening of her heart failure on these agents, she was made "do not resuscitate" and all medications were discontinued on day 6. She died on day 8 due to endstage CHF.

7. *Subject 493-008 (Nesiritide, 0.015 µg/kg/min)* Subject was an 81-year-old white man with NYHA Class IV CHF and ischemic cardiomyopathy. He was admitted 9 days before study entry with a junctional bradycardia. Nesiritide was administered for 3 days and then discontinued by subject request. Dobutamine was initiated on day 3, but all parenteral therapy was discontinued on day 11 by subject request. On day 14, he died of endstage cardiomyopathy.

8. *Subject 504-003 (Nesiritide, 0.015 µg/kg/min)* Subject was a 70-year-old white man with NYHA Class IV CHF, ischemic cardiomyopathy, and ventricular arrhythmias requiring an AICD. He received nesiritide for the 7-day maximum permitted by the protocol; on day 5, dobutamine was added for inotropic support. On day 10 (2 days after nesiritide was discontinued), he experienced a cardiopulmonary arrest for which he was intubated and resuscitated. On day 11, he died due to a recurrent cardiac arrest and endstage cardiomyopathy.

9. *Subject 538-010 (Nesiritide, 0.015 µg/kg/min)* Subject was an 89-year-old white woman with NYHA Class III CHF, coronary artery disease, mitral regurgitation, and chronic atrial fibrillation. Nesiritide was administered for 65 hours, then discontinued because of clinical improvement. On day 4, dobutamine was initiated in response to worsening oliguria. The subject's general condition worsened over the ensuing days. Sepsis was suspected and broad spectrum antibiotics were initiated. Comfort measures only were initiated, and the subject died from a cardiopulmonary arrest on day 9.

10. *Subject 550-002 (Nesiritide, 0.015 µg/kg/min)* Subject was a 73-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy and a history of atrial and ventricular arrhythmias. He was treated with nesiritide for 3 days which was then discontinued because of clinical improvement. On day 14, he developed worsening CHF unresponsive to dobutamine and dopamine. He died on day 14 due to CHF.

11. *Subject 559-005 (Nesiritide, 0.015 µg/kg/min)* Subject was a 58-year-old black man with NYHA Class II CHF due to aortic insufficiency and tricuspid endocarditis. He was treated for 5 days with nesiritide, which was discontinued due to clinical improvement. On day 7, he died after an unsuccessful attempt to resuscitate him during a cardiac arrest. The cause of death was severe cardiomyopathy and tricuspid endocarditis.

12. *Subject 382-002 (Nesiritide, 0.03 µg/kg/min)* Subject was a 73-year-old white woman with NYHA Class IV CHF, ischemic cardiomyopathy and active lung disease at the time of entry into the study. She received nesiritide followed by dobutamine. During placement of a Swan-Ganz catheter, 6 hours after nesiritide was discontinued, she experienced hypotension and respiratory failure requiring intubation and mechanical ventilation. Given the subject's underlying poor prognosis, her status was made "Do Not Resuscitate" on day 2. On day 3, she died due to endstage heart failure and respiratory failure.

13. *Subject 508-004 (Nesiritide, 0.03 µg/kg/min)* Subject was a 69-year-old white man with a history of Class IV CHF, severe ischemic cardiomyopathy, and multiple vascular surgeries. Before entering the study, he underwent cardiac catheterization that revealed that his coronary grafts were occluded and that he was not a candidate for angioplasty or CABG. He initially received nesiritide for 1 day. On day 2, he developed a left femoral thrombosis, due to catheterization of that vessel the day before, requiring emergent thrombectomy. Postoperatively, the nesiritide infusion was restarted at half the original infusion dose and his blood pressure remained stable. Postoperatively, the subject never regained his baseline level of consciousness. Throughout day 2, he developed more difficulty breathing, was made "do not resuscitate", and the nesiritide infusion was discontinued. He expired 2.5 hours later. The cause of death was endstage heart failure.

14. *Subject 509-002 (Nesiritide, 0.03 µg/kg/min)* Subject was a 61-year-old white man with NYHA Class IV CHF due to idiopathic, dilated cardiomyopathy, and a history of Non-sustained VT. He received nesiritide for 5 days. For the first few days of the infusion, he responded very well with excellent diuresis and improvement in his congestive symptoms. On day 5, his condition deteriorated with worsening respiratory symptoms and decreased urine output. Nesiritide was discontinued and replaced with dobutamine and dopamine. Later on day 6, the subject died due to worsening CHF.

15. *Subject 524-005 (Nesiritide, 0.03 µg/kg/min)* Subject was a 61-year-old white man with NYHA Class IV CHF of unknown etiology and a ventricular aneurysm. On day 1, coumadin therapy was begun due to the presence of a left ventricular mural thrombus. He was treated for 3 days with nesiritide that was discontinued because of clinical improvement. The subject was intended to be discharged to home the following day when, 13 hours after discontinuation of nesiritide (day 5), he died due to ventricular fibrillation.

16. *Subject 528-001 (Nesiritide, 0.03 µg/kg/min)* Subject was a 71-year-old white man with a history of NYHA Class III CHF, ischemic cardiomyopathy, atrial fibrillation, bronchiolitis obliterans, and diabetes. He received nesiritide for 3 days to which he responded very well with diuresis and improvement in CHF symptoms. On day 5, he was noted to have hyperkalemia ($K^+ = 7.6$) and an elevated serum creatinine ($Crt = 3.9$ mg/dL). He was diagnosed as having nonoliguric acute renal failure which improved by day 8 ($K^+ = 4.3$, $Crt = 1.5$) after the administration of dobutamine, dopamine, and IV furosemide. He died on day 22 due to cardiac arrest when his pacemaker failed to capture; resuscitation was not attempted due to the wishes of the family.

17. *Subject 572-001 (Nesiritide, 0.03 µg/kg/min)* Subject was a 71-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy. He received nesiritide for 1 day with a good hemodynamic response, but was switched to dobutamine therapy on day 2. His subsequent hospital course was complicated by multifocal atrial tachycardia and hypotension, oliguric acute renal failure, intermittent chest pain, and elevated cardiac enzymes indicative of a myocardial infarction, worsening hyponatremia, gastrointestinal bleed and progressively worsening cardiac and renal function. The subject died on day 20 because of endstage heart failure.

18. *Subject 585-003 (Nesiritide, 0.03 µg/kg/min)* Subject was a 77-year-old white man with NYHA Class IV CHF due to ischemic cardiomyopathy admitted from a nursing home for treatment of decompensated CHF. The subject received nesiritide for 2 days with little improvement. On day 3, he was switched to dobutamine, which he received for 2 days, again with little improvement overall in his clinical condition. On day 5, he was transferred back to the nursing home. During the several subsequent days, the subject developed worsening shortness of breath and a loss of appetite. On day 13, he died due to endstage heart failure.

13.0 Appendix 3: Narratives for Serious Adverse Events

Study 704.311

1. *Subject 369-009 (0.015 µg/kg/min Nesiritide)* Subject 369-009 is a 60-year-old black man with NYHA Class IV CHF, second degree AV block, and hypertension. He received the full 24-hour study drug infusion (0.015 µg/kg/min Nesiritide) with one dose reduction in response to an excessive decrease in PCWP. He subsequently was treated with IV dobutamine and discharged on day 11. On day 13, he was readmitted with decompensated CHF and again was treated with IV dobutamine and diuretics. He was then transferred to another hospital for cardiac transplantation evaluation.

2. *Subject 369-004 (0.03 µg/kg/min Nesiritide)* Subject 369-004 is a 51-year-old black man with NYHA Class III CHF. He received the full 24-hour study drug infusion (0.03 µg/kg/min nesiritide) with one dose reduction in response to an excessive decrease in PCWP, then received therapy with IV milrinone prior to discharge. He presented to the Emergency Department on day 11 with complaints of shortness of breath and fatigue and was readmitted with the diagnosis of decompensated CHF. He was treated with IV inotropes and responded well.

3. *Subject 376-008 (0.03 µg/kg/min Nesiritide)* Subject 376-008 is a 57-year-old white man with a history of NYHA Class III CHF, idiopathic cardiomyopathy, atrial fibrillation, and ventricular arrhythmias. He received the full 24-hour study drug infusion (0.03 µg/kg/min nesiritide) without incident and was discharged. He was readmitted on day 9 with recurrent decompensated CHF and treated with IV dobutamine and furosemide. He was discharged again on day 12.

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

5. *Subject 367-003 (0.06 µg/kg/min Nesiritide)* Subject 367-003 is a 56-year-old black man with NYHA Class IV CHF, idiopathic dilated cardiomyopathy, a pacemaker, and hyponatremia. He received the full 24-hour study drug infusion (0.06 µg/kg/min Nesiritide) with one reduction in dose in response to a decreased PCWP. He was discharged home but presented to the Emergency Department on day 7 with complaints of shortness of breath, nausea, and vomiting; he was readmitted with the diagnosis of CHF and dehydration. His symptoms resolved with hydration and withholding of his digoxin.

Study 704.325

1. *Subject 502-001 (Placebo)* Subject 502-001 is 68-year-old white man with NYHA Class III CHF, chronic atrial fibrillation, hypertension, and peripheral vascular disease who was admitted for treatment of decompensated CHF, with a pre-scheduled femoral-popliteal bypass surgery to follow. His chronic warfarin therapy was discontinued on day 1 in anticipation of the surgery. After the 6-hour placebo infusion, he was treated with dobutamine. On day 2, he underwent femoral-popliteal bypass surgery. On day 3, he sustained a cerebrovascular accident. Cardiac echocardiogram revealed a left ventricular apical thrombosis. He was discharged to home on day 11.

2. *Subject 369-018 (Placebo)* Subject 369-018 is 73-year-old black man with a history of NYHA Class III CHF, dilated cardiomyopathy, chronic atrial fibrillation, and sustained ventricular tachycardia requiring an automatic implantable cardiac defibrillator (AICD). Placebo was discontinued after 25 minutes, when the subject developed sustained ventricular tachycardia (triggering AICD discharge) and loss of consciousness. Two hours later, he experienced a second episode of sustained VT that again resolved after the AICD discharge. He received 5 days of dobutamine therapy and was discharged to home on day 6 with no sequelae from these events.

3. *Subject 352-009 (Nesiritide, 0.015 µg/kg/min)* Subject 352-009 is a 49-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy. After 3 hours of nesiritide therapy, nesiritide was discontinued because of worsening CHF. He was subsequently treated with dobutamine and milrinone for 6 days and was discharged to home on day 12. On day 15, he was rehospitalized for decompensated CHF.

4. *Subject 369-006 (Nesiritide, 0.015 µg/kg/min)* Subject 369-006 is a 73-year-old white woman with NYHA Class III CHF and emphysema. After 6.5 hours, nesiritide was discontinued due to a lack of improvement. She was treated with dobutamine for 5 days, and the subject was discharged on day 12. On day 20, she was readmitted to the hospital for worsening emphysema.

5. *Subject 373-002 (Nesiritide, 0.015 µg/kg/min)* Subject 373-002 is a 68-year-old black man with NYHA Class III CHF due to idiopathic, dilated cardiomyopathy. He responded well to therapy with nesiritide and dobutamine, and was discharged to home on day 3. The following day, he was readmitted for IV antibiotic therapy in response to a bacteremia (presumably due to the indwelling Swan-Ganz catheter used during the study).
6. *Subject 523-003 (Nesiritide, 0.015 µg/kg/min)* Subject 523-003 is a 75-year-old white man with a history of NYHA Class III CHF, ischemic cardiomyopathy, chronic atrial fibrillation, ventricular ectopy, and diabetes. Nesiritide was discontinued after 6.5 hours due to clinical improvement. He was discharged to home on day 6. On day 7, he was rehospitalized for 2 days for management of hyperglycemia due to his underlying diabetes and poor home medication management. On day 14, he was again hospitalized for syncope and bradycardia due to his underlying atrial fibrillation with a slow junctional response. He also developed intermittent episodes of sustained ventricular tachycardia requiring acute intubation, electrical cardioversion, and amiodarone therapy. His dysrhythmias persisted, and, on day 27, a permanent pacemaker was placed. On day 56, he was discharged to a rehabilitation facility.
7. *Subject 324-001 (Nesiritide, 0.03 µg/kg/min)* Subject 324-001 is a 47-year-old white man with NYHA Class III CHF, ischemic cardiomyopathy, obesity, and severe sleep apnea hospitalized for worsening sleep apnea and decompensated CHF. He responded well to therapy with nesiritide, dobutamine, and dopamine. After 60 hours of nesiritide therapy, he experienced a cardiopulmonary arrest precipitated by apnea, hypoxia, and third degree heart block. The subject's physicians believed that this event was due to his underlying sleep apnea. Nesiritide was discontinued, and he was successfully resuscitated. However, he remained intubated and ultimately required a tracheostomy. He was discharged for home ventilatory support on day 25. At follow-up 5 months later, the subject was still requiring respiratory support for apnea.
8. *Subject 352-007 (Nesiritide, 0.03 µg/kg/min)* Subject 352-007 is a 61-year-old white man with a history of NYHA Class IV CHF, ischemic cardiomyopathy, and a previous deep venous thrombosis. After 6 hours of nesiritide therapy, dobutamine was added for inotropic support. On day 3, both infusions were discontinued due to clinical improvement, and the subject was discharged to home. Later that day, he was rehospitalized for anticoagulation therapy for a deep venous thrombosis of the subclavian vein felt to be due to the indwelling Swan-Ganz catheter used during the study. He was discharged to home on day 8.
9. *Subject 357-001 (Nesiritide, 0.03 µg/kg/min)* Subject 357-001 is a 60-year-old white man with a history of NYHA Class IV CHF, idiopathic, dilated cardiomyopathy, pancreatitis, and small bowel obstruction requiring several surgical bowel resections. After 18 hours of nesiritide therapy, he developed an ileus believed to be an exacerbation of his underlying abdominal condition. Worsening of the small bowel obstruction over the subsequent hours resulted in a severe hypotensive crisis, requiring electrical cardioversion, intubation, and treatment with dopamine, dobutamine, norepinephrine, nitroglycerin, and an intra-aortic balloon pump. The subject recovered completely from this episode within 72 hours and was discharged to home on day 14.
10. *Subject 368-003 (Nesiritide, 0.03 µg/kg/min)* Subject 368-003 was a 69-year-old white woman with NYHA Class IV CHF due to ischemic cardiomyopathy who was admitted for a pre-scheduled coronary bypass graft (CABG) surgery but required parenteral therapy for CHF before the procedure. She responded well to a 24-hour infusion of nesiritide and subsequently received dobutamine for inotropic support prior to the CABG procedure. Six days after nesiritide was discontinued, the CABG procedure was performed. Postoperatively she required an intra-aortic balloon pump due to her underlying poor ventricular function. Several hours later, she developed an occlusion of the femoral artery due to the intra-aortic balloon pump, requiring urgent surgical revascularization. On day 29, after a postoperative course complicated by respiratory failure, infections, and renal insufficiency, the subject died due to septic shock.
11. *Subject 369-009 (Nesiritide, 0.03 µg/kg/min)* Subject 369-009 was a 67-year-old Hispanic man with NYHA Class IV CHF due to alcohol-induced cardiomyopathy, chronic renal insufficiency, carotid occlusions, and emphysema. Before entry into the study, he was being treated with dobutamine, which was discontinued before study drug administration. After 6 hours of nesiritide therapy, the infusion was discontinued due to worsening CHF and dobutamine was restarted for 6 days. He was discharged to home on study day 8. On day 11, he was readmitted for treatment of cardiogenic shock, sepsis, and renal failure (serum creatinine = 6.3 mg/dL) due to his underlying endstage CHF. By day 25, his physicians felt that he was dobutamine-dependent; however, he refused home dobutamine therapy and was discharged to home. On day 28, he was readmitted with endstage heart failure. The subject's family refused further treatment and he died on day 30.

12. *Subject 373-004 (Nesiritide, 0.03 µg/kg/min)* Subject 373-004 was a 51-year-old black woman with NYHA Class IV CHF and chronic renal insufficiency. For 1 month before entering the study, she had been hospitalized for asthma and CHF exacerbations and had developed progressive renal failure, presumably due to progressive heart failure. After 24 hours, the nesiritide infusion was interrupted due to respiratory distress and hypotension. Milrinone and renal dose dopamine were started. On day 2, she developed oliguria and became hemodynamically refractory to milrinone; thus, the milrinone was replaced with dobutamine. The following day, nesiritide was also restarted but was discontinued on day 5. On day 5, due to deteriorating chronic renal failure, the patient was started on hemodialysis. Thereafter, she was treated with dobutamine for progressive endstage heart failure for nearly 1 month. She died on day 31 due to endstage heart failure, while awaiting cardiac transplantation.

13. *Subject 382-001 (Nesiritide, 0.03 µg/kg/min)* Subject 382-001 is a 72-year-old white woman with NYHA Class IV CHF due to rheumatic heart disease. Before entry into the study, she underwent an aortic valve replacement that was complicated by postoperative respiratory failure. At study entry, she was mechanically ventilated. She received nesiritide for five days (the maximum allowed by the protocol) with clinical improvement. On day 13 (7 days after nesiritide was discontinued), she developed significant renal failure requiring dialysis. Due to hypotension, dialysis was not tolerated well and pressors (phenylephrine, norepinephrine) were required to maintain adequate blood pressure. Since the subject had previously responded so well to nesiritide, the investigator's request to Scios to re-administer nesiritide was approved on day 19, under an Emergency Use protocol and a physician-sponsored IND. After approximately 15 hours of nesiritide administration, the patient developed atrial fibrillation and the patient's oliguric renal failure had not improved, so nesiritide was discontinued. By day 25, she was hemodynamically more stable and had weaned from the pressors. By day 33, a tracheostomy was performed and the subject was receiving long-term dialysis therapy. She was discharged to home with a tracheostomy on day 40.

14. *Subject 523-004 (Nesiritide, 0.03 µg/kg/min)* Subject 523-004 is a 71-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy. Nesiritide was discontinued after approximately 6 hours and dobutamine was administered for 2 days. The following day he was started on antibiotics for bacteremia, and the Swan-Ganz catheter was removed. He was discharged on day 14 with no sequelae.

15. *Subject 532-001 (Nesiritide, 0.03 µg/kg/min)* Subject 532-001 is a 78-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy, and a history of atrial fibrillation, hypertension, diabetes, chronic renal failure of a solitary kidney (status post nephrectomy due to renal cell carcinoma). He was treated with nesiritide for two days with clinical improvement and was discharged to home on day 7. On day 10, a home health nurse noticed the subject having mental status changes for which he was rehospitalized. A cerebral meningioma was diagnosed by head CT scan. The subject refused treatment for this problem, his mental status changes resolved spontaneously, and he was discharged on day 15.

Study 704.326

1. *Subject 519-006 (Standard care: dopamine)* Subject 519-006 is a 64-year-old white man with NYHA Class III CHF, idiopathic, dilated cardiomyopathy, and acutely decompensated CHF due to subacute myocarditis. He had significant respiratory failure and bilateral pleural effusions at the time of entry into the study. Dopamine (3 µg/kg/min) was administered as the standard care vasoactive agent. A few hours after the dopamine infusion was started, he experienced significant respiratory distress and acute pulmonary edema that required intubation, mechanical ventilation, and additional IV vasoactive medications.

2. *Subject 535-003 (Standard care: dobutamine)* Subject 535-003 is a 23-year-old black man with NYHA Class IV CHF due to idiopathic, dilated cardiomyopathy, and a history of electromechanical dissociation and arrhythmias who was admitted for treatment of decompensated CHF due to an arrhythmia exacerbation. One hour after initiation of dobutamine, he experienced seizure activity and electromechanical dissociation. He was successfully resuscitated and subsequently treated with dobutamine, milrinone, and dopamine. On day 3, he developed hypoxia and acute respiratory failure requiring bronchoscopy and antibiotics. This resolved with treatment and he was discharged to home on day 14.

3. *Subject 536-009 (Standard care: dobutamine)* Subject 536-009 is a 71-year-old white man with NYHA Class IV CHF due to ischemic cardiomyopathy, atrial fibrillation, and pacemaker-dependent bradycardia. He received dobutamine for 6 days. On day 1, he developed severe hemorrhage after a transurethral resection of the prostate that prolonged hospitalization due to the need for colloids, blood and surgical repair. Ultimately, he was discharged to an extended care facility.

4. *Subject 538-008 (Standard care: dobutamine)* Subject 538-008 was an 82-year-old white woman with a history of NYHA Class II CHF, idiopathic, dilated cardiomyopathy, chronic atrial fibrillation, supraventricular tachycardia, and Non-sustained VT who was admitted with shortness of breath and abdominal pain. She was randomized to nesiritide; however, dobutamine was administered instead because of a nursing error. On day 6, during an invasive gastrointestinal procedure, she developed sustained VT and had a respiratory arrest, requiring defibrillation and intubation. On day 9, she was extubated and discharged to a skilled nursing facility on day 26. On day 38 (after the 21-day study reporting period), she died due to progressive heart failure.

5. *Subject 519-002 (Nesiritide, 0.03 $\mu\text{g}/\text{kg}/\text{min}$)* Subject 519-002 is a 77-year-old black woman with a history of NYHA Class III CHF, hypertensive cardiomyopathy and a previous myocardial infarction. At the time of admission, as part of the routine work-up for CHF, cardiac enzymes were obtained and were normal. She received nesiritide, which was interrupted after 40 minutes of infusion because of hypotension, restarted, and then discontinued after 4.5 hours for hypotension. At no time did she have chest pain. The following morning, she was diagnosed with a non-Q wave myocardial infarction based on an elevation of routinely ordered cardiac enzymes. In retrospect, because of elevated myoglobin (myoglobin = 162 ng/mL; normal 12–76 ng/mL) upon admission, her physicians concluded that she had an evolving MI before entering the study. She was clinically stable throughout and required no treatment for this event.

6. *Subject 533-005 (Nesiritide, 0.03 $\mu\text{g}/\text{kg}/\text{min}$)* Subject 533-005 is a 78-year-old white man with NYHA Class IV CHF and a history of Non-sustained VT. He received nesiritide for 4 days and responded favorably. On day 4, the subject developed urosepsis (believed to be caused by an indwelling urinary catheter) which was treated successfully with antibiotics. Also, on day 4, during and after placement of a left subclavian central venous line, he experienced multiple episodes of sustained VT which were successfully treated with electrical cardioversion. These events were considered caused by placement of the central venous line and to the subject's underlying ventricular ectopy due to endstage heart failure.

7. *Subject 561-009 (Nesiritide, 0.03 $\mu\text{g}/\text{kg}/\text{min}$)* Subject 561-009 is a 63-year-old white woman with NYHA Class II CHF due to mitral valve dysfunction requiring mitral valve replacement and severe COPD. After 25 hours of nesiritide infusion, she experienced hemoptysis accompanied by hypotension due to blood loss. Nesiritide was discontinued, neosynephrine was added for pressor support, and the subject received a blood transfusion. A bronchoscopy was performed which located the source of the bleeding. Relevant concomitant medication included coumadin.

14.0 Appendix 4: Narratives of patient discontinuations

Study 704.311

1. *Subject 017-010 (Placebo)* Subject 017-010 is a 55-year-old black man with a history of NYHA Class IV CHF, adriamycin-induced dilated cardiomyopathy, a previous myocardial infarction. He terminated study drug (placebo) infusion after 22 hours due to worsening CHF (i.e., worsening dyspnea, increase in PCWP to 32 mm Hg from 28 mm Hg pretreatment). He was subsequently treated with IV dobutamine and dopamine. No other adverse events were reported.
2. *Subject 369-006 (Placebo)* Subject 369-006 is a 66-year-old Hispanic man with a history of NYHA Class IV CHF, peripheral vascular disease, and hypertension. He terminated study drug (placebo) administration after approximately 9 hours of infusion due to worsening CHF (i.e., worsening dyspnea and increase in PCWP to 30 mm Hg from 24 mm Hg pretreatment). He was subsequently treated with IV dobutamine and furosemide. No other adverse events were subsequently reported.
3. *Subject 370-005 (Placebo)* Subject 370-005 is a 49-year-old Hispanic man with a history of NYHA Class IV CHF, coronary artery disease, diabetes, and ventricular arrhythmias (premature ventricular contractions and bigeminy) at study enrollment. He terminated study drug (placebo) administration after 12 hours, 20 minutes of infusion due to worsening CHF (with an increase in PCWP to 25 mm Hg from 23 mm Hg pretreatment). He was subsequently treated with IV dobutamine and furosemide. His serum creatinine increased from 1.4 mg/dL at baseline to a peak of 4.1 mg/dL on day 10. He also experienced an episode of severe symptomatic hypotension requiring cardiopulmonary resuscitation on day 8. He was subsequently followed through day 27 with no further complications.
4. *Subject 370-006 (Placebo)* Subject 370-006 was a 50-year-old man from India with a history of NYHA Class IV CHF, coronary artery disease, a previous ventricular aneurysmectomy, and marked cachexia at admission for worsening CHF. He was enrolled in the study but terminated study drug (placebo) infusion prematurely after 3 hours, 25 minutes of infusion due to worsening CHF (with an increase in PCWP to 27 mm Hg from 24 mm Hg pretreatment). The subject was then treated with IV dobutamine and furosemide. An episode of supraventricular tachycardia accompanied by chest pain was also reported on day 6. The subject was discharged to home, but was readmitted to another hospital on approximately day 18 with dyspnea and end-stage CHF; he was reported to have died during this hospitalization on approximately day 46, although information on the precise date and cause of death was not available.
5. *Subject 373-006 (Placebo)* Subject 373-006 is a 58-year-old black woman with a history of NYHA Class III CHF, coronary artery disease, supraventricular arrhythmias (treated with electrophysiological ablation), and hypertension. She terminated study drug (placebo) administration after 4 hours, 30 minutes of infusion due to worsening CHF (with an increase in PCWP to 34 mm Hg from 32 mm Hg pretreatment). She was subsequently treated with IV dobutamine and milrinone. No other significant adverse events were reported.
6. *Subject 380-004 (0.03 µg/kg/min Nesiritide)* Subject 380-004 is a 60-year-old Asian man with a history of NYHA Class III CHF, an ejection fraction of 10%, and hypertension. He terminated study drug (0.03 µg/kg/min Nesiritide) administration after 2 hours, 12 minutes of infusion due to worsening CHF (with an increase in PCWP to 28 mm Hg from 25 mm Hg pretreatment). He was subsequently treated with IV diuretics and the resumption of his oral regimen of ACE inhibitors. No other adverse events were reported.
7. *Subject 389-006 (0.03 µg/kg/min Nesiritide)* Subject 389-006 is a 45-year-old Hispanic man with a history of NYHA Class III CHF and hypertension. At baseline, his PCWP was 12 mm Hg, his PAD was 12 mm Hg, and his blood pressure was 120/80 mm Hg. After 90 minutes of study drug (0.03 µg/kg/min Nesiritide) infusion, his PCWP had decreased to 13 mm Hg and his PAD had decreased to 5 mm Hg. The dose of study drug was reduced. At this time, his blood pressure was stable at 120/70 mm Hg with a heart rate of 58 beats/min. After a total of 120 minutes of infusion, the subject developed symptomatic hypotension (systolic blood pressure of 80 mm Hg) accompanied by bradycardia (heart rate of 39 beats/min). Study drug was discontinued. Within 30 minutes, his blood pressure returned to 99/66 mm Hg with a heart rate of 58 beats/min without pharmacological intervention. There were no long-term sequelae of this event.
8. *Subject 373-007 (0.03 µg/kg/min Nesiritide)* Subject 373-007 is a 53-year-old Hispanic woman with a history of NYHA Class II CHF. She was enrolled in the study and had a baseline PCWP of 24 mm Hg and blood pressure of 120/76 mm Hg. After 65 minutes of study drug infusion (0.03 µg/kg/min Nesiritide), her PCWP had decreased to 8 mm Hg (with a blood pressure of 113/71 mm Hg) and the study drug infusion rate was decreased. After 8 hours, 55 minutes of infusion, her PCWP was noted to be 6 mm Hg (with a blood pressure of 103/62 mm Hg); study drug was discontinued, as required by the protocol. No other adverse events were reported during the 14-day study follow-up period.

9. *Subject 017-008 (0.06 µg/kg/min Nesiritide)* Subject 017-008 is a 61-year-old white man with a history of NYHA Class IV CHF and coronary artery disease. At baseline, his blood pressure was 103/58 mm Hg and his PCWP was 30 mm Hg. After 68 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), he developed symptomatic hypotension (dizziness and a systolic blood pressure as low as 62 mm Hg). Study drug infusion was reduced and then discontinued minutes later. He was placed in Trendelenberg position, and IV dopamine was initiated. His blood pressure had returned to 104/89 by the next recorded measurement 20 minutes later. On day 8, the subject developed recurrent asymptomatic hypotension that was attributed to oral vasodilator therapy. The investigator noted that this subject appeared in general to have unexpectedly large changes in blood pressure to small changes in medication doses.

10. *Subject 369-005 (0.06 g/kg/min Nesiritide)* Subject 369-005 is a 44-year-old black man with a history of NYHA Class III CHF, hypertension, and Non-sustained ventricular tachycardia. At baseline, his PCWP was 18 mm Hg and his blood pressure was 150/104 mm Hg. After 30 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), his PCWP had dropped to 10 mm Hg (with a blood pressure of 120/100 mm Hg), and study drug infusion was reduced. After 1 hour, 45 minutes of infusion, his PCWP was noted to be 6 mm Hg (with a blood pressure of 98/70), and study drug was discontinued per protocol guidelines. Thirty-five minutes later, he developed symptomatic hypotension (systolic blood pressure of 70 mm Hg, heart rate 71 beats/min). He was treated with IV fluids and atropine. Within 20 minutes, his systolic blood pressure had returned to 100 mm Hg. There were no long-term sequelae of this event.

11. *Subject 369-014 (0.06 µg/kg/min Nesiritide)* Subject 369-014 is an 84-year-old black woman with NYHA Class IV CHF, chronic atrial fibrillation, and a pacemaker. At baseline, her blood pressure was 138/78 mm Hg and her PCWP was 22 mm Hg. After 65 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), she developed symptomatic hypotension (systolic blood pressure of 82 mm Hg). Study drug was discontinued, but her blood pressure continued to drop to a low of 58 mm Hg. She was treated with IV dopamine, and her blood pressure returned to baseline levels within minutes. There were no long-term sequelae of this event.

12. *Subject 373-003 (0.06 µg/kg/min Nesiritide)* Subject 373-003 is a 40-year-old black man with NYHA Class II CHF and hypertension. At baseline, his PCWP was 26 mm Hg, MRAP was 10 mm Hg, and blood pressure was 166/105 mm Hg. After 3 hours, 45 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), his PCWP was 6 mm Hg, MRAP was 0 mm Hg, and his blood pressure was 127/68 mm Hg; an episode of nausea and vomiting was reported. Study drug infusion was reduced per protocol dosing guidelines. After 6 hours, 35 minutes of infusion, his PCWP remained low at 5 mm Hg with a MRAP of 1 mm Hg (and blood pressure of 114/76 mm Hg). Study drug infusion was terminated. No subsequent adverse events occurred.

13. *Subject 376-021 (0.06 µg/kg/min Nesiritide)* Subject 376-021 is a 48-year-old white man with NYHA Class III CHF and coronary artery disease. At baseline, his PCWP was 35 mm Hg, MRAP was 10 mm Hg, and blood pressure was 112/70 mm Hg. After 2 hours, 5 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), his PCWP was 10 mm Hg and his blood pressure was 81/46 mm Hg. Study drug infusion rate was reduced. After 5 hours of infusion, his PCWP was 15 mm Hg, but his blood pressure was 67/38 mm Hg. Study drug was discontinued. No other adverse events were reported.

14. *Subject 388-001 (0.06 µg/kg/min Nesiritide)* Subject 388-001 is a 52-year-old white man with NYHA Class III CHF, coronary artery disease, and hypertension. At baseline, his PCWP was 34 mm Hg, MRAP was 11 mm Hg, and blood pressure was 103/74 mm Hg. After 2 hours, 19 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), his PCWP was 4 mm Hg with an MRAP of 0 mm Hg (and a blood pressure of 106/62 mm Hg). Study drug infusion rate was reduced. After 4 hours, 4 minutes of infusion, his PCWP was noted to be 2 mm Hg (with a blood pressure of 114/63). The subject also complained of abdominal cramping and nausea. Study drug infusion was terminated. No other adverse events were reported.

Study 704.325

Five subjects terminated study drug prematurely, i.e., prior to completing 5.5 hours of infusion. Narrative summaries for each of these subjects are included below. Note that some of these subjects were also described in the Appendix 3, SAEs.

1. *Subject 369-018 (Placebo)* As Appendix 3, subject 369-018 is a 73-year-old black man with a history of NYHA Class III CHF, dilated cardiomyopathy, chronic atrial fibrillation, and sustained ventricular tachycardia requiring an automatic implantable cardiac defibrillator (AICD). The placebo infusion was discontinued after 25 minutes, when the subject developed sustained ventricular tachycardia (VT) and loss of consciousness that terminated after an AICD discharge. He received 5 days of dobutamine therapy and was discharged to home on day 6.

2. *Subject 352-009 (Nesiritide, 0.015 µg/kg/min)* As described in Appendix 3, subject 352-009 is a 49-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy. After 3 hours of nesiritide therapy, nesiritide was discontinued because of worsening CHF. He was subsequently treated with dobutamine and milrinone for 6 days and was discharged to home on day 12. On day 15, he was rehospitalized for decompensated CHF.

3. *Subject 356-002 (Nesiritide, 0.03 µg/kg/min)* Subject 356-002 is a 54-year-old black woman with NYHA Class IV CHF and idiopathic, dilated cardiomyopathy who was hospitalized for a cardiac transplant evaluation. Before entry into the study, she was being treated with milrinone and nitroprusside, which were discontinued. Nesiritide was administered for 4.5 hours, then discontinued due to symptomatic hypotension and nausea that was treated with IV fluids. Fourteen hours later, milrinone was started and was continued beyond day 6. She remained hospitalized through day 21 awaiting cardiac transplant.

4. *Subject 357-002 (Nesiritide, 0.03 µg/kg/min)* Subject 357-002 was a 54-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy. Nesiritide was discontinued after 4.5 hours because his PCWP had decreased to 6 mm Hg. The subject was symptomatically improved, so no additional therapy for CHF was instituted. He was discharged on day 2. On day 15, he presented to the emergency room with a myocardial infarction and died.

5. *Subject 498-003 (Nesiritide, 0.03 µg/kg/min)* Subject 498-003 is a 69-year-old black woman with NYHA Class III CHF and chronic renal insufficiency. Before entry into the study, she was being treated for oliguria and CHF with dobutamine, which was discontinued before study drug administration. After 4 hours, the nesiritide infusion was discontinued due to worsening oliguria. Dobutamine was restarted, and dopamine was added 7 hours later. Three days later nitroprusside was added. All parenteral vasoactive therapy was discontinued on day 7, and she was discharged on day 14.

Study 704.326

Nine patients discontinued therapy prior to 6 hours in trial 326: two in the standard care, two in the 0.015µg/kg/min group, and five in the 0.03 µg/kg/min group. Narrative prepared by the sponsor for these discontinuations are below.

1. *Subject 535-001 (Standard Care: dopamine)* Subject 535-001 is a 45-year-old white woman with NYHA Class IV CHF. Dopamine was discontinued after 30 minutes because of sinus tachycardia.

2. *Subject 550-005 (Standard Care: milrinone)* Subject 550-005 is a 72-year-old white woman with NYHA Class III CHF. Milrinone was terminated after 3 hours because of Non-sustained ventricular tachycardia.

3. *Subject 352-001 (nesiritide, 0.015 µg/kg/min)* Subject 325-001 is a 64-year-old black man with NYHA Class IV CHF. Nesiritide was discontinued after 2 hours, 15 minutes of infusion because of hypotension (reduction in SBP from 100 mm Hg at baseline to 84 mm Hg). Dopamine was initiated.

4. *Subject 519-008 (nesiritide, 0.015 µg/kg/min)* Subject 519-008 is a 71-year-old white man with NYHA Class III CHF. Nesiritide infusion was interrupted after 3 hours, 15 minutes because of asymptomatic hypotension (decrease in SBP from 99 mm Hg at baseline to 85 mm Hg). Study drug infusion was restarted at half of the original dose but at 5 hours, 45 minutes, infusion was terminated because of recurrent asymptomatic hypotension.

5. *Subject 504-002 (nesiritide, 0.03 µg/kg/min)* Subject 504-002 is a 68-year-old white man with NYHA Class IV CHF. Nesiritide infusion was interrupted after 45 minutes because of asymptomatic hypotension (decrease in SBP from 102 mm Hg at baseline to 70 mm Hg). Study drug infusion was restarted at half of the original dose but at 4 hours, 30 minutes, infusion was terminated because of recurrent asymptomatic hypotension.

6. *Subject 519-002 (nesiritide, 0.03 µg/kg/min)* Subject 519-002 is a 77-year-old black woman with NYHA Class III CHF. Nesiritide infusion was interrupted after 41 minutes because of asymptomatic hypotension (decrease in SBP from 170 mm Hg at baseline to 73 mm Hg). Study drug infusion was restarted at half of the original dose but at 4 hours, 30 minutes, infusion was terminated because of recurrent asymptomatic hypotension. Approximately 30 minutes later, the subject was noted to have sinus bradycardia (heart rate = 48 beats/min) which resolved spontaneously. On day 2, it was discovered that this subject had had elevated cardiac enzymes (myoglobin, with a normal CPK) at enrollment and was diagnosed by the investigator as having had a non-Q wave myocardial infarction (before study drug infusion).

7. *Subject 521-006 (nesiritide, 0.03 µg/kg/min)* Subject 521-006 is a 92-year-old white woman with NYHA Class II CHF. Nesiritide infusion was terminated after 3 hours, 30 minutes because of symptomatic hypotension (decrease in SBP from 138 mm Hg at baseline to 92 mm Hg accompanied by pallor and diaphoresis).

8. *Subject 562-001 (nesiritide, 0.03 µg/kg/min)* Subject 562-001 is a 72-year-old black man with a history of NYHA Class IV CHF due to ischemic cardiomyopathy, first degree heart block, and left bundle branch block. After 3 hours and 45 minutes of the nesiritide infusion, the subject developed symptomatic hypotension (BP = 80/39 mm Hg) accompanied soon thereafter by junctional bradycardia (heart rate of 36 beats/min). nesiritide was discontinued, and fluids and atropine were administered with improvement of the heart rate to a sinus rate of 66 beats per minute. Blood pressure increased to 114/43 mm Hg within approximately 30 minutes. The investigator felt that the event was due to a vagally mediated bradycardia secondary to the hypotension caused by the nesiritide infusion. Nesiritide was not restarted and dobutamine was initiated instead. After the event, the subject was feeling well and there were no sequelae.

9. *Subject 571-003 (nesiritide, 0.03 µg/kg/min)* Subject 571-003 is a 76-year-old white woman with NYHA Class III CHF. nesiritide infusion was interrupted after 25 minutes because of asymptomatic hypotension (decrease in SBP from 93 mm Hg at baseline to 77 mm Hg). Study drug infusion was restarted at a lower dose but at 3 hours, 50 minutes, infusion was terminated because of recurrent asymptomatic hypotension.

15.0 Appendix 5 Analysis Strategies in Study 704.325

The primary endpoint in study 704.235 was of 6-hour PCWP analyzed using a “worst outcome” nonparametric analysis. This strategy was applied to the endpoints PCWP, MRAP, SVR, and CI, through the nominal 6-hour assessment. Two additional analyses were employed, in part, to evaluate the robustness of the “worst outcome” hemodynamic results: (1) a “carry forward” parametric analysis, and (2) a “data as available” parametric analysis. A slightly different “data as available” analysis was applied to the 24-hour data. The four analysis strategies are outlined below.

Worst Outcome Strategy

The endpoints PCWP, MRAP, SVR, and CI were analyzed with a “worst outcome” analysis strategy through the nominal 6-hour assessment. Gould discusses this general approach to the analysis of clinical trials with non-completers.

The 6-hour analysis value was determined as follows: For subjects who were not classified as worst outcome, the set of all hemodynamic observations with non-missing PCWP Values, recorded between 5 1/2 (inclusive) and 7 hours (exclusive) after start of study drug, before cardiovascular intervention and before unblinding, was considered. Assuming that the set was not empty, the observation closest to 6 hours was selected for analysis. If the set was empty, then the set of hemodynamic observations with non-missing PCWP Values, recorded between 2 hours (inclusive) and 5 1/2 hours (exclusive) after start of study drug, before cardiovascular intervention and before unblinding, was considered. Assuming that this set was not empty, the latest observation, i.e., closest to 6 hours, was selected for use in analysis. Subjects classified as worst outcome (who by definition have no blinded, pre-intervention hemodynamic observation after 5 1/2 hours [except for any subjects classified as worst outcome due to death]) were assigned an arbitrarily poor analysis value for all hemodynamic endpoints at all nominal assessments through 6 hours. For example, an appropriate worst outcome value for percent change in PCWP would be +999%, and for percent change in CI, -999%. Because analysis is by rank-based nonparametric methods, the “worst outcome” value is arbitrary except that (1) it must be the same for all worst outcome subjects, and (2) it must be worse than any value actually observed across all subjects in the study. The 1 1/2-, 3-, and 4 1/2-hour analysis values were determined by similar algorithm. Subjects were assigned a worst outcome value if the precipitating event (intervention, unblinding, or death) occurred on or before 1 1/2, 3, and 4 1/2 hours after start of study drug, respectively. Otherwise, a blinded, pre-intervention hemodynamic observations was selected from within the respective windows of (30 min, 2 h 15 min), (1 h, 3 h 45 min), and (2 h, 5 h 15 min); windows were inclusive. The three treatment groups were tested for non-specific differences with a Kruskal-Wallis test, and for dose-related differences with the Jonckheere-Terpstra test. Each nesiritide treatment group was compared to the placebo treatment group with a 2 sample Wilcoxon test. When the endpoint was represented as change or percent change from baseline, the hypothesis of a non-zero change from baseline was tested with a 1-sample Wilcoxon test. The protocol stated that exact, as opposed to asymptotic, inferential methods would be employed. Exact calculations were found to be computationally infeasible for SAS, the analysis software used by the sponsor, and so asymptotic results are reported.

Carry Forward Strategy

All hemodynamic endpoints were analyzed by a “carry forward” analysis strategy, as described below, through the nominal 6-hour assessment. To be eligible for “carry forward” analysis, observations were required to have been recorded prior to both cardiovascular intervention and treatment unblinding. The observation recorded closest to the nominal assessment time being summarized was selected for analysis. If a blinded, pre-intervention observation did not exist in the temporal vicinity of the nominal assessment time, then the last eligible observation, possibly the baseline observation, was extrapolated (i.e., “carried forward”) to the nominal assessment time for analysis. In contrast to the “worst outcome” analysis, all “carry forward” analysis values are *bona fide* hemodynamic measurements. To be considered for “carry forward” analysis at the nominal 1.5, 3-, 4.5-, and 6-hour nominal assessments, observations had to have been observed on or before 2 hours 15 minutes, 3 hours 45 minutes, 5 hours 15 minutes, and 7 hours, respectively. The effect of treatment group was analyzed within the framework of one-way analysis of variance (ANOVA). The three treatment groups were tested for non-specific differences with the omnibus F test, and for dose-related differences with a linear contrast using equally spaced scores. Each nesiritide treatment group was compared to the placebo treatment group with a pairwise contrast. When an endpoint was represented as the change or percent change from baseline, a one-sample *t* test was run within each treatment group to test for a non-zero mean change from baseline. This test used the within-group estimate of variance, not the pooled estimate from the ANOVA model.

Data as Available Strategy

Through 6 Hours the endpoints PCWP, MRAP, SVR, CI, and SBP were also analyzed with a “data as available” analysis strategy, as described below. The resulting summary tables are presented later in this appendix. To be eligible for “data as available” analysis, observations were required to have been recorded prior to both cardiovascular intervention and treatment unblinding. In particular, if a blinded, pre-intervention hemodynamic observation did not exist within a predefined time window around the nominal assessment time being summarized, then that value was considered missing and the subject was effectively excluded from the analysis of that time point. In contrast to the “worst outcome” and “carry forward” analyses, all “data as available” analysis values were required to have been made while the subject was still receiving study drug or within 10 minutes after termination study drug. All “data as available” analysis values are *bona fide* hemodynamic measurements. The effect of treatment group was analyzed within the framework of one-way analysis of variance (ANOVA), as previously described for the “carry forward” analyses.

Data as Available Strategy, through 24 Hours

The selected endpoints of PCWP, MRAP, and SVR were analyzed by a “data as available” strategy, as described below, through the nominal 24-hour assessment. The analysis was restricted to the subset of nesiritide subjects who had a 24-hour hemodynamic observation recorded between 21 and 27 hours (inclusive) after start of study drug. In contrast to the summarizations through the initial 6-hour study period, observations were not required to have been recorded prior to cardiovascular intervention or treatment unblinding. Summaries were prepared of baseline values, change from baseline at 6 hours, change from baseline at 24 hours, and change from 6 hours to 24 hours. Within the restrictions of the above-specified subset, summary tables were prepared on two subject populations: (1) all nesiritide subjects, without regard to dose modification or drug termination, and (2) subjects who received nesiritide, though possibly modifying dose, through (or terminated no earlier than 10 minutes before) the 24-hour hemodynamic observation and received no additional parenteral medication through the 24-hour observation. The effect of treatment group was analyzed within the framework of one-way analysis of variance (ANOVA), as previously described for the “carry forward” analyses.

16.0 Appendix 6: FDA Statistical Comments

16.0.1 Trial 704.311 Statistics Review

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

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

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

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

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

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

Interim analysis, requiring unblinding of the data, was planned before starting the trial. In the protocol, the sponsor states that the interim was to be purely for administrative purposes, but also states that the efficacy would be declared if the p Value from an interim analysis was <0.0027 . The planned final analysis would be tested at $\alpha = 0.05$. The difference in mean PCWP change was to be explored by ANOVA (analysis of variance). The dose response was to be explored by testing of a linear contrast. The effect of each dose at hour 24 was to be compared with placebo using Donnett's test. The protocol specified that the evaluable patient population would be used for the primary analysis even though the intent to treat (ITT) analysis would also be done.

The efficacy results based on the sponsor's analyses are shown in the table below.

Table 16.1 Mean change in PCWP (mm Hg) at hours 3 and 24 in the 'evaluable' and ITT populations of 704.311.

Analysis	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	p Value (Global Diff)	p Value (Linear Trend)
Evaluable at 3 hours	-1.8 (n=29)	-10.0 (n=16)	-6.8 (n=17)	-9.9 (n=18)	0.001	0.004
Evaluable at 24 hours	-1.8 (n=25)	-8.8 (n=17)	-3.8 (n=19)	-8.4 (n=19)	0.001	0.025
ITT at 3 hours	-1.8 (n=29)	-8.9 (n=21)	-6.0 (n=23)	-10.8 (n=24)	<0.001	<0.001
ITT at 24 hours	-1.8 (n=25)	-8.3 (n=21)	-3.7 (n=21)	-8.4 (n=19)	0.001	0.017

The sponsor did two interim analyses, as per above, with the first 55 and 92 patients. The sponsor's results, based on the evaluable and ITT populations, show a significant reduction in mean change in PCWP at hours 3 and 24 after a conservative adjustment of the p Value, for the two primary endpoints at both interim analyses. The first adjustment of the significance level for the multiple endpoints was based on Bonferroni's procedure. The resulting p Value also incorporated the adjustment for the interim analyses (described above). The resulting significance level is $0.05 - (2 \text{ times } 0.0027) = 0.0446$. With this adjustment, a significant increasing trend of reduction in mean PCWP was found at both hour 3 and 24 for the ITT population and at hour 3 for the evaluable patient population. The reductions in mean PCWP in the low and high-dose nesiritide groups were statistically significant as compared to placebo. The reduction is numerically larger for the intermediate (0.030) nesiritide dose as compared to placebo, but was not statistically significant.

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

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

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

a. Kruskal-Wallis using worst rank.

Several subgroup analyses on PCWP at 3 hours were performed with respect to patient's gender, age, race, and baseline ejection fraction. The analyses used all 103 evaluable patients and LVCF imputation for the missing observations. The results are shown below.

Table 16.4 Mean change in PCWP from baseline to 3 hours grouped by demographics in study 704.311.

Analysis	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	p Value (ANOVA)
Gender					
Male	-2.3 (n=21)	-8.0 (n=18)	-6.8 (n=19)	-11.4 (n=23)	0.0006
Female	-2.6 (n=8)	-6.4 (n=4)	-7.3 (n=5)	-2.1 (n=3)	0.3349
Age					
≥65	-3.2 (n=2)	-5.5 (n=4)	-3.5 (n=6)	-5.5 (n=9)	0.8865
<65	-2.2 (n=27)	-8.6 (n=18)	-7.9 (n=20)	-12.7 (n=17)	<0.001
Race					
White	-4.4 (n=10)	-7.0 (n=15)	-7.9 (n=20)	-12.5 (n=17)	0.0222
Non-White	-0.6 (n=19)	-8.3 (n=7)	-6.6 (n=12)	-7.5 (n=9)	0.0079
Baseline LVEF					
>20%	-1.4 (n=9)	-10.1 (n=12)	-6.5 (n=9)	-6.2 (n=15)	0.0587
≤20%	-2.9 (n=20)	-8.7 (n=10)	-7.8 (n=15)	-10.3 (n=11)	0.0108

16.0.2 Trial 704.325 Statistics Review

Based on the analysis as presented below, the FDA statistical reviewer made the following conclusions:

1. Statistically significance treatment difference among the treatment groups exists with regard to changes in PCWP starting at 1.5 hours and persisting through 6 hours.
2. Both dose regimens effectively lower PCWP as compared to the control.
3. The numerical trend of treatment effect appears consistent across all investigators.
4. PCWP was lowered significantly in both women and men at hour 6.

Analysis of Primary Endpoint

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

Analyses for change and percentage change from baseline in PCWP were performed for ITT population using worst-score imputation and LVCF imputation. The results, based on worst-score analysis, showed a statistically significant treatment difference in change from baseline in PCWP among the three treatment groups starting at Hour 1.5 (Table 16.5). The number of subjects in all three treatment groups was 42 (total of 126 subjects).

Table 16.5 Significance of changes in PCWP from baseline for ITT population in 704.325.

Hour	Treatment	Nominal p Value for Absolute Change in PCWPa	p Value for % Change in PCWP
1.5	Placebo 0.015 0.030	0.0001	0.0001
3	Placebo 0.015 0.030	0.0001	0.0001
4.5	Placebo 0.015 0.030	0.0001	0.0001
6	Placebo 0.015 0.030	0.0001	0.0001

a Kruskal-Wallis test (worst case analysis)

Comparisons of each of the two dosages with the control showed that the active treatment significantly lowered the PCWP, as shown below. In the pair-wise comparisons, no adjustment of p Value for the multiplicity was necessary because of the closure principle.

Table 16.6 Comparison of effect of two nesiritide doses with placebo for change in PCWP from baseline to 6 hours, from ITT population.

Hour	Treatment	Nominal p Value for Absolute Change in PCWPa	p Value for Percent Change in PCWPa
1.5	0.015 vs. Placebo	0.0021	0.0020
	0.030 vs. Placebo	0.0001	0.0001
3	0.015 vs. Placebo	0.0004	0.0002
	0.030 vs. Placebo	0.0001	0.0001
4.5	0.015 vs. Placebo	0.0001	0.0001
	0.030 vs. Placebo	0.0001	0.0001
6	0.015 vs. Placebo	0.0019	0.0009
	0.030 vs. Placebo	0.0001	0.0001

a. Wilcoxon 2-sample test

Similar results (Table 16.7) were seen based on LVCF method. In this case, the estimated change or percentage change from baseline was obtained for each treatment group. Since there was a significant baseline effect in most cases, the analyses were done using an Analysis of Covariance (ANCOVA) model with treatment, investigator, and baseline PCWP as factors and covariate respectively. In the analyses, centers missing at least one treatment group were combined. No baseline-by-treatment or investigator-by-treatment were found except for the percentage change at Hour 3 for which a significant baseline-by-treatment interaction was seen. The baseline PCWP readings (means) for the placebo, nesiritide 0.015, and nesiritide 0.030 were 28.45, 28.09, and 27.55 mm Hg, respectively.

Table 16.7 Effect of study drug on PCWP from 'Last Value Carried Forward' analysis for hour 6.

Hour	Treatment	PCWP, Change from Baseline ^a	p Value for Tx Difference (Change in PCWP)	% Change from Baseline in PCWP ^a	p Value for Tx Difference (% Change in PCWP)
1.5	Placebo	-0.08	0.0001	-0.44	0.0001
	0.015	-3.13		-12.13	
	0.030	-6.92		-26.08	
3	Placebo	+0.29	0.0001	NA ^b	NA ^b
	0.015	-5.35			
	0.030	-9.09			
4.5	Placebo	+1.17	0.0001	+4.76	0.0001
	0.015	-6.18		-21.43	
	0.030	-10.50		-38.44	
6	Placebo	+1.96	0.0001	+7.87	0.0001
	0.015	-5.92		-20.86	
	0.030	-9.96		-36.72	

a. Least square mean estimate

b. Presence of treatment-by-baseline interaction (LVCF analysis).

Table 16.8 gives the results of pairwise comparisons for change in PCWP between a dosed group and placebo using LVCF imputation, indicating a statistically significant treatment difference in change from baseline in PCWP between each pair of groups under the comparison.

Table 16.8 Pairwise comparisons for change in PCWP between nesiritide dose groups and placebo at hour 6.

Hour	Treatment Comparison	p Value for Tx Differences (Change in PCWP ^a)
1.5	0.015 vs. Placebo	0.0065
	0.030 vs. Placebo	0.0001
3	0.015 vs. Placebo	0.0001
	0.030 vs. Placebo	0.0001
4.5	0.015 vs. Placebo	0.0001
	0.030 vs. Placebo	0.0001
6	0.015 vs. Placebo	0.0001
	0.030 vs. Placebo	0.0001

a. ANCOVA with treatment, center and baseline PCWP as factors and covariate respectively

Noting that there was a slight imbalance among the treatment groups with respect to gender, a worst case analysis was performed within each gender group at Hour 6. Significant treatment differences were found in both gender groups.

Table 16.9 Analysis of change in PCWP between a dosed group and placebo using LVCF imputation, grouped according to gender.

Sex	Treatment Group, # of Subjects	p Value for Tx Difference (Change in PCWP ^a)	p Value for Tx Difference (% Change in PCWP ^a)
Female	Placebo / 9, 0.015 / 8, 0.30 / 17	0.0029	0.0033
Male	Placebo / 33, 0.015 / 35, 0.030 / 25	0.0003	0.0001

a. Kruskal-Wallis test (worst case analysis)

The numerical trend of treatment effect, measured as mean change from baseline in PCWP, appears consistent across all investigators (data not shown).

Global assessment of clinical status

The results of global assessment of clinical status by patients and investigators at Hour 6 are summarized in the following table. A statistically significant difference in global assessment of clinical status at Hour 6 by investigators or by patients was found. The p Values for the overall difference are 0.0001 in the two assessments. Pairwise comparison between a Natrecor treated group and placebo showed a higher percentage of improvement in clinical status for Natrecor as compared to placebo.

Table 16.10 Global assessment of clinical status / Hour 6 in trial 704.325.

Treatment	Assessment / n (%)					Total n	p Value
	Much worse	Worse	No change	Better	Much better		
Investigator's Assessment							
Placebo	3 (7.1%)	9 (21.4%)	28 (66.8%)	2 (4.7%)	0 (0.0%)	42	0.0001a
Nesiritide 0.015	4 (10%)	4 (10%)	10 (25%)	17 (42.5%)	5 (12.5%)		
Nesiritide 0.030	2 (5.1%)	1 (2.5%)	6 (15.4%)	26 (66.7%)	4 (10.3%)		
Patient's Assessment							
Placebo	3 (7.1%)	2 (4.8%)	31 (73.8%)	6 (14.3%)	0 (0.0%)	42	0.0001a
Nesiritide 0.015	4 (10.0%)	2 (5.0%)	10 (25.0%)	19 (47.5%)	5 (12.5%)		
Nesiritide 0.030	2 (5.1%)	2 (5.1%)	9 (23.1%)	23 (59.0%)	3 (7.7%)		

a. Overall difference (Kruskal-Wallis test)

b. Difference between a dose and placebo groups (two-sample Wilcoxon test)

Numerically, the investigator and patient's assessments agreed well. The percentage of the exact agreements between the two assessments is 71.1% (73.8%, 67.5%, 71.8% for placebo, 0.03, and 0.06 Natrecor groups, respectively). If allow at most one category difference, overall agreement rate of the assessments is 98.3% (100.0% for placebo, 97.5% and 97.4% for 0.03 and 0.06 Natrecor groups). The percentage of patients who had Hour 6 assessment scores by patient or investigator indicating an improvement (better or much better) is much higher for the Natrecor treated group as compared to placebo. The difference is statistically significant.

Table 16.11 Improvement in global assessment of clinical status at hour 6 in trial 704.325.

Treatment	Assessment n (%)		Total	p Value
	Not improved	Improved		
Investigator Assessment				
Placebo	40 (95.2%)	2 (4.8)	42	0.001 a
Nesiritide 0.015	18 (45%)	22 (55.0)		
Nesiritide 0.030	9 (23.1%)	30 (76.9)		
Patient Assessment				
Placebo	36 (85.7%)	6 (14.3)	42	0.001a
Nesiritide 0.015	16 (40%)	24 (60.0)		
Nesiritide 0.030	13 (33.3%)	26 (66.7)		

a. Overall difference, two-sided chi²-test

According to the sponsor's analyses, there was a numerical relationship between improvement in PCWP and an improvement in global assessment at the end of 6 hours. These figures are reproduced in appendix seven, section 17.0.

The results of global assessment of clinical status by patients and investigators at Hour 24 are given in the following table. No significant difference was found.

Table 16.12 Global assessment of clinical status at hour 24 in trial 704.325.

Treatment	Assessment / n (%)					Total	p Value
	Much worse	Worse	No change	Better	Much better		
Investigator's Assessment							
Control	0 (0.0)	1 (2.6)	9 (23.7)	23 (60.5)	5 (13.2)	38	0.4398a
Nesiritide 0.015	0 (0.0)	2 (5.0)	6 (15.0)	25 (62.5)	7 (17.5)		
Nesiritide 0.030	1 (2.4)	3 (7.1)	2 (4.8)	27 (64.3)	9 (21.4)		
Patient's Assessment							
Control	0 (0.0)	1 (2.6)	9 (23.7)	22 (57.9)	6 (15.8)	38	0.3372a
Nesiritide 0.015	0 (0.0)	3 (7.5)	5 (12.5)	23 (57.5)	9 (22.5)		
Nesiritide 0.030	0 (0.0)	2 (4.9)	3 (7.3)	26 (63.4)	10 (24.4)		

a. Overall difference (Kruskal-Wallis test).

b. Difference between a dose and placebo (two-sample Wilcoxon test).

Numerically, slightly higher percentage of nesiritide patients had improvement in clinical status at Hour 24 (with a score better or much better) for both investigator evaluation and patient evaluation. Since placebo patients were treated with the standard therapy after Hour 6, such a numerical difference is small and not statistically significant. The percentages of patients with improvement for both investigator assessment and patient assessment at Hour 24 seem comparable to those at Hour 6.

Table 16.13 Improvement in global assessment of clinical status at Hour 24 in trial 704.325.

Treatment	Assessment n (%)		Total	p Value
	Not improved	Improved		
Investigator Assessment				
Control ^b	10 (26.3%)	28 (73.7)	38	0.406 ^a
Nesiritide 0.015	8 (20%)	32 (80.0)	40	
Nesiritide 0.030	6 (14.3%)	36 (85.7)	42	
Patient Assessment				
Control ^b	10 (26.3%)	28 (73.7)	38	0.281 ^a
Nesiritide 0.015	8 (20%)	32 (80.0)	40	
Nesiritide 0.030	5 (12.2%)	36 (87.8)	41	

a. overall difference, two-sided χ^2 -test.

b. Placebo-controlled for hours 0-6 and active-controlled from hours 6-24.

The agreement between the investigator's and patient's assessments was also examined. The percentage of the exact agreements between the two assessments is 79% (84.2%, 72.5%, 80.5% for placebo, 0.03, and 0.06 Natrecor groups, respectively). If a difference of one category is allowed, overall agreement rate of the assessments is 97.3% (97.3% for placebo, 100% and 100% for 0.030 and 0.060 Natrecor groups). The overall degree of agreement in this case was 99%.

Although the data showed an apparent dose response global assessment of clinical status, and a very good agreement between the assessments by patients and by investigators, the interpretation of the results may not be so straight forward. The reasons for this are: 1) the investigators participated in 'patient's assessment' of clinical status, and 2) the investigators knew patient's PCWP at the time when the assessments were made. The good agreement between the assessments by investigators and patients may just be a consequence of the investigator's involvement in the patient assessments. The higher percentage of improvement in the treated group might be related to investigator's knowledge of the change in PCWP. It is difficult to conclude that Natrecor treatment can improve patient's symptoms based on this study.

16.0.3 Trial 704.326 Statistics Review

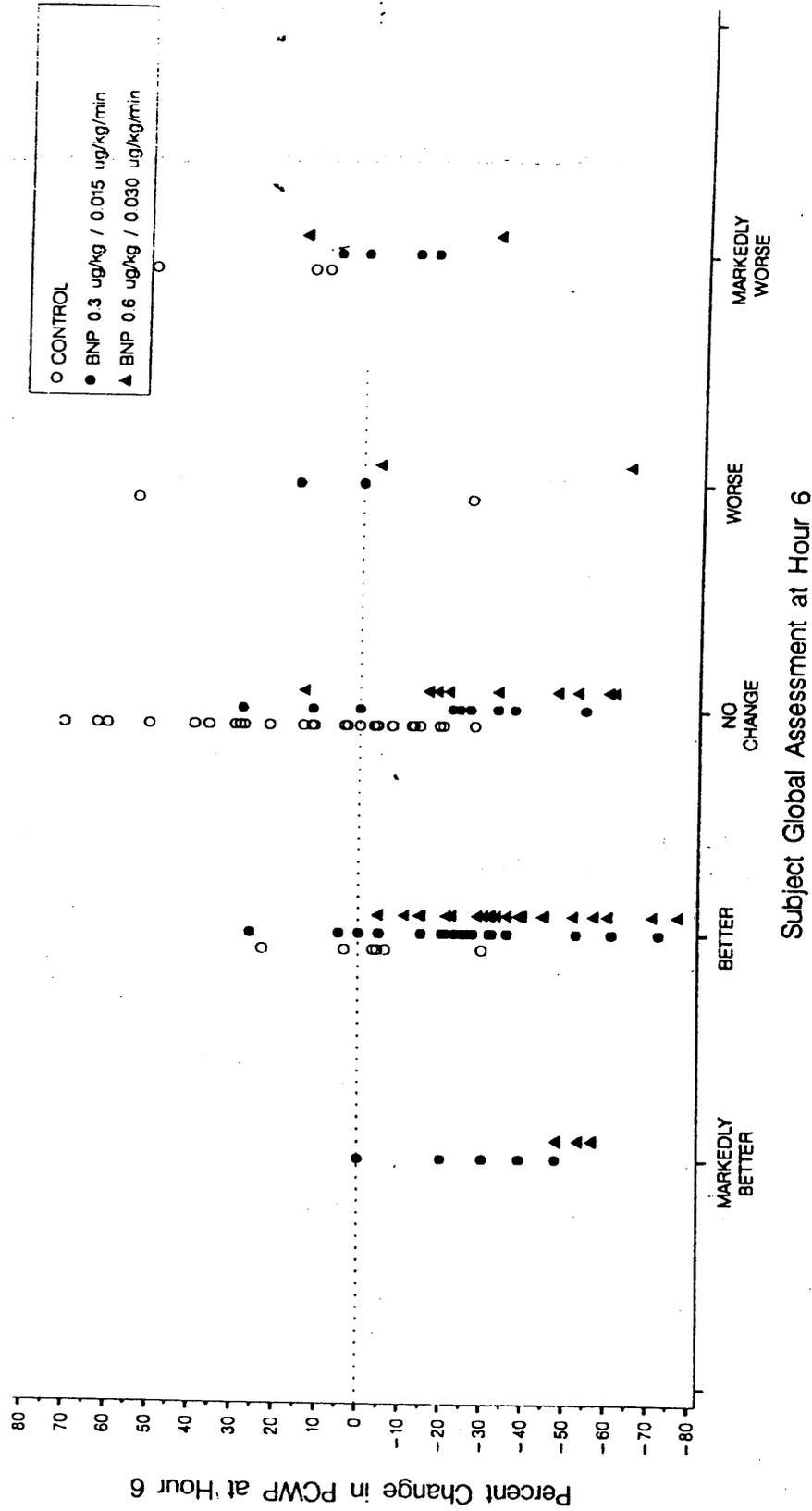
This trial focused on the collection of safety information regarding the use of nesiritide, and no formal statistical analysis of these results was performed.

17.0 Appendix 7: Relationship Between PCWP and Changes in CHF Signs and Symptoms.

In the tables reproduced here, the sponsor graphed the association between a change in PCWP and change in the subject and investigator-derived global assessment at the end of Hour 6 in study 704.325.

FIGURE 6
SUBJECT GLOBAL ASSESSMENT VS PCWP AT HOUR 6
(INTENT-TO-TREAT RESULTS)

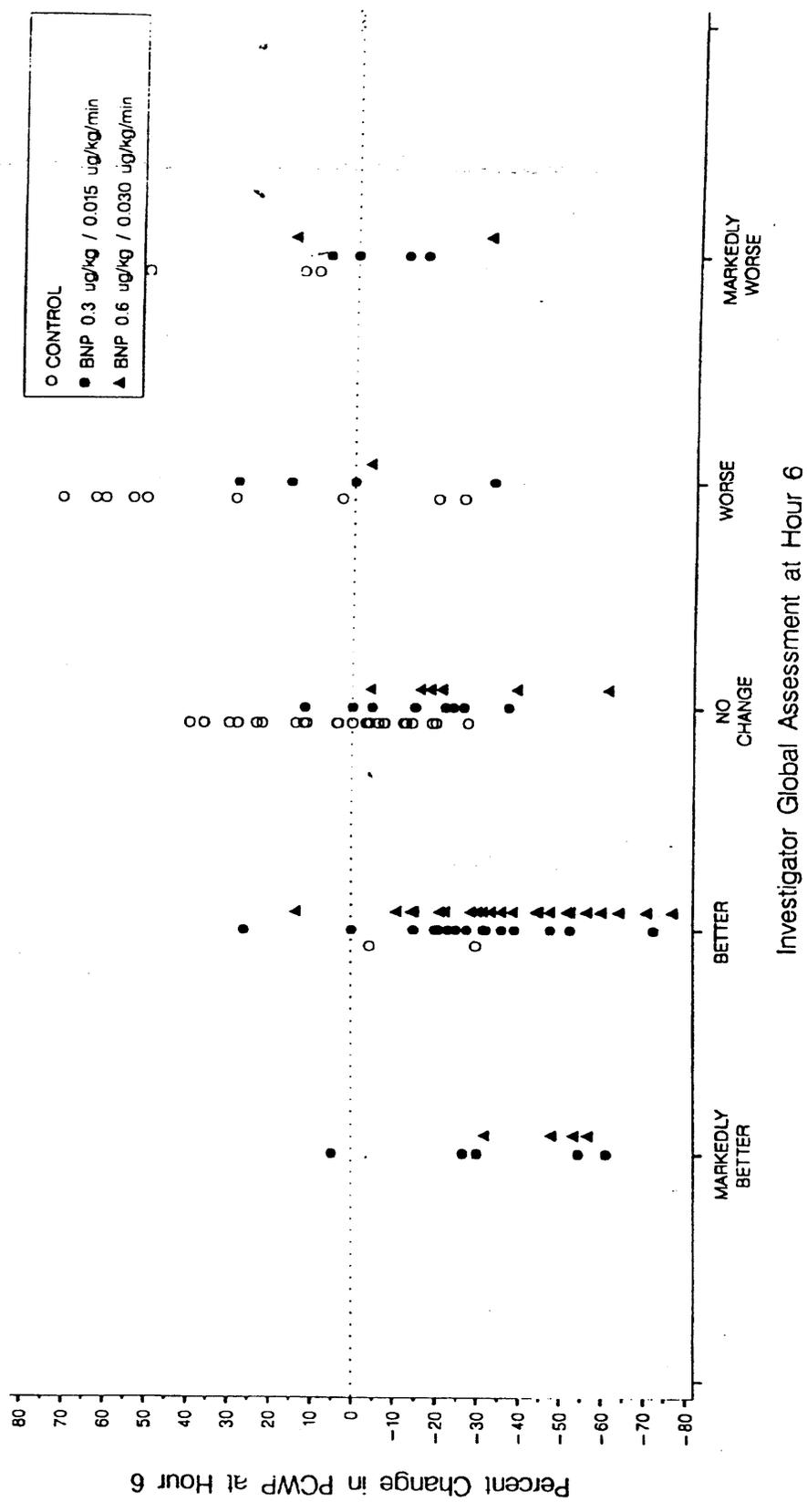
STUDY 704.325
FINAL ANALYSIS



NOTE: PCWPS ARE BASED ON THE CARRY FORWARD ANALYSIS DATA SET.
SOURCE: LA (16MAR98 14:47) BNP\$DISK:(S704_325.FINAL.PROG)GSCAT_CPCWP_ASSPT_6H.SAS

STUDY 704.325
FINAL ANALYSIS

FIGURE 7
INVESTIGATOR GLOBAL ASSESSMENT VS PCWP AT HOUR 6
(INTENT-TO-TREAT RESULTS)



NOTE: PCWPS ARE BASED ON THE CARRY FORWARD ANALYSIS DATA SET.
SOURCE: LA (16MAR98 14:46) RNP\$DISK:(S704_325.FINAL.PROG)GSCAT_CPCWP_ASSINV_6H.SAS

18.0 Appendix 8: Individual Case Report Form Reviews of Subjects With Severe and Symptomatic Hypotension

The sponsor submitted a list of all subjects in studies 704.311, 704.325, and 704.326 who had the following clinical consequences:

1. Where the greatest severity of hypotension (symptomatic and asymptomatic) was 'severe.'
Trials 704.311, 704.325, and 704.326
2. Where the greatest impact of hypotension (symptomatic and asymptomatic) on drug dosing was 'discontinued.'
Trials 704.311, 704.325, and 704.326
3. Where the lowest recorded BP was : <80, <70 and <60 mm Hg.
Trials 704.311, 704.325, and 704.326

A summary of the outcomes for each of the patients can be found in the tables below, along with information regarding the timing of the hypotension relative to study drug use, other medications administered.

Table 18.0.1 Subjects with hypotension in the first 24 hours where the greatest severity was 'severe'^a.

Treatment Group/ Patient ID #	While on Study Drug?	Outcome/ AEs	Duration of Hypotension	Notes
Control 535003	Y/ Dobutamine 1 hr	EMD with Seizure BP 140/- to 0	<5 mins	Study Drug D/C'd No renal failure
Nesiritide 0.030 356002	Y 3 hrs	BP to 86/52	30 mins	Drug D/C'd
357001	Y 23 hrs	135/78 to 58/48 'Hypotensive Crisis'	9 hrs, 55 mins	Tx'd O ₂ , IV fluids Tx'd intubation, levophed, dopamine, IV fluids, Intra-aortic balloon pump
493011	Y/ 7 hrs	BP 150/80 to 90/60 with diaphoresis, LOC	3 hours	IV NS, Trendelenburg, Study Drug D/C'd No renal failure
508004	N	HR from 80-88 to 53 BPM BP 140/70 to 50/30	N/A	Made DNR after OR, Support withdrawn NQWMI
519002	Yes, 40 mins and 4.5 hrs	BP 170/77 to 73/43, then later to 79/32	2 episodes, each <1 hr	
562001	Y 20 mins	BP 152/64 to 80/39 with Junctional rhythm	3 hrs 45 min	Tx'd with IV D5W, Trendelenburg position
579002	Y 7 hrs 45 mins	Symptomatic: vomited BP 108/61 to 88/61 Symptomatic: dizzy	2.5 hrs	Nesiritide discontinued, later developed VTach and Coagulopathy
Nesiritide 0.060 017008	Y 1 hr	BP 98/64 to 62/-	30 minutes	AEs unknown, no lab F/U Pt tx'd with Trendelenburg position
369005	Y 35 mins	BP 98/40 to 70/-, pulse 71	3 hrs	Tx'd Trendelenburg, Atropine, IV NS
369014	Y 1 hr	BP 140/82 to 60/-- Pulse 73 to 61 Symptomatic: light-headed	20 minutes	No Lab F/U Tx'd Dopamine, IV NS No lab F/U

Table 18.0.2 Subjects with hypotension in the first 24 hours where the greatest impact on dosing was discontinuation^a.

Treatment Group/ Patient ID #
Control
541005
Nesiritide 0.015
352001
360001
493013
519008
533002
554002
554037
564001
564002
571002
588004
605002
Nesiritide 0.030
356002
357001
382008
389006
493011
493015
504002
508004
519002
520007
521006
538001
543001
547004
554050
559001
562001
571003
575001
Nesiritide 0.060
017008
369014
376021

Table 18.0.3 Subjects with hypotension in the first 24 hours where the lowest recorded value was <80 mm Hg from study 704.326^a.

Treatment Group/ Patient ID #
Control
493003
535003
549003
551001
Nesiritide 0.015
352001
504003
524004
533002
536002
554013
554017
560002
564002
570003
571002
575002
580003
Nesiritide 0.030
377003
493011
493015
504002
508002
508004
519002
520001
520007
521003
543001
554010
554029
554039
556002
558001
559001
570008
571003
572001
585003
587005

Table 18.0.3 Subjects with hypotension in the first 24 hours where the lowest recorded value was <70 mm Hg from study 704.326^a.

Treatment Group/ Patient ID #
Control
535003
Nesiritide 0.015
570083
Nesiritide 0.030
508002
520001
520007
521003
554029
558001
559001

Table 18.0.3 Subjects with hypotension in the first 24 hours where the lowest recorded value was <60 mm Hg from study 704.326^a.

Treatment Group/ Patient ID #
Control
535003
Nesiritide 0.030
508002
554029