

## 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<sup>a</sup>.

Demographic	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value
<b>Gender</b>				
Female	9 (21%)	8 (19%)	17 (40%)	0.055 <sup>b</sup>
Male	33 (79%)	35 (79%)	25 (60%)	
<b>Race</b>				0.469 <sup>b</sup>
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%)	
<b>Age (Mean±SD)</b>	59.0±14	56.6±14	60.8±12	0.357 <sup>c</sup>
<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.

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<sup>a</sup>.

Demographic	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	All Subjects n=127	p Value
<b>Etiology of CHF</b>					
Ischemic	15 (36%)	24 (56%)	19 (45%)	58 (46%)	0.377 <sup>b</sup>
Idiopathic	16 (38%)	7 (16%)	12 (29%)	35 (28%)	
Hypertensive	1 (2%)	0 (0%)	2 (5%)	3 (2%)	
Other <sup>c</sup>	10 (24%)	12 (28%)	9 (21%)	31 (24%)	
<b>NYHA Class Prior to Hospitalization</b>					
I	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.196 <sup>d</sup>
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%)	
<b>Reason for Current Decompensation</b>					
Medication Noncompliance	5 (12%)	4 (9%)	5 (12%)	14 (11%)	0.882 <sup>b</sup>
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
<b>Pre-study systolic BP (mm Hg)</b>	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<sup>a</sup>.

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

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<sup>a</sup>.

Patient Disposition <sup>b</sup>	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	4.5±1	17.5±4

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/m<sup>2</sup>.

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<sup>a</sup>.

Treatment Group And Subject ID #	Reason and Time of Worst Case Classification <sup>b</sup>	Comments
<b><i>Placebo</i></b>		
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.
<b><i>Nesiritide 0.3/ 0.015 µg/kg/min</i></b>		
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 demdex.
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. Subject had (ineligible) PCWP reading at 6:00.
487-002	CV intervention (3:05)	Subject received 60 mg lasix by IV bolus.
<b><i>Nesiritide 0.6/ 0.03 µg/kg/min</i></b>		
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.

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Table 6.2.12.2.4 Study drug infusion in study 704.325<sup>a</sup>.

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%)	1 (2%)	1 (2%)
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<sup>a</sup>.

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	92.7	109.2
Range			

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.

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Table 6.2.12.2.6 Infusion of nesiritide and other parenteral cardiovascular meds in study 704.325<sup>a</sup>.

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.

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Worst-Outcome Population

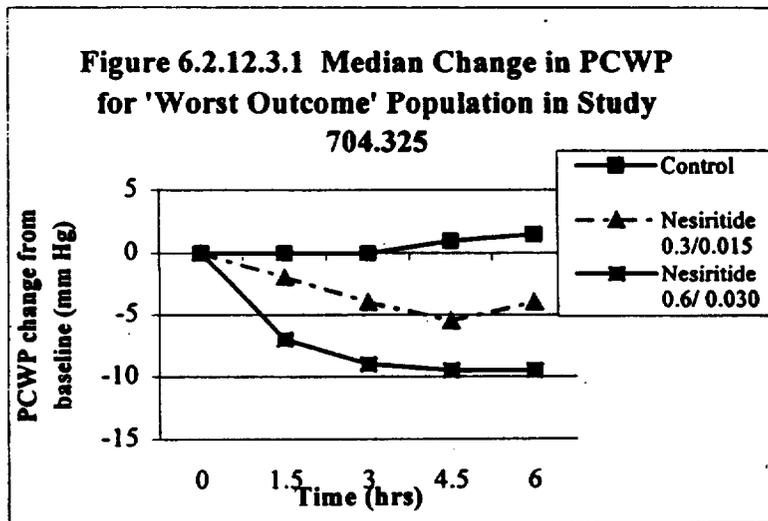
For this population, the difference between placebo and either of the two nesiritide dose-groups was highly statistically significant at the 6 hour time-point. This result was true for the pre-specified primary endpoint analysis (% change from baseline at 6 hours, shaded in the table below), or for the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

Table 6.2.12.3.1 Primary endpoint analysis for study 704.325<sup>a</sup>.

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 <sup>b</sup>
<b>PCWP at baseline and 6 hours (mm Hg)</b>				
At baseline (mm Hg)	28	27	28	0.76
At 6 hours (mm Hg)	30	23	18.5	<0.001
<b>Median Change from Baseline (mm Hg)</b>	1.5	-4.0	-9.5	<0.001
<b>p Value (change from baseline)<sup>c</sup></b>	0.011	0.222	<0.001	
<b>p Value (compared with control baseline)<sup>d</sup></b>	---	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.



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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<sup>a</sup>.

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 <sup>b</sup>
<b>PCWP at baseline and 6 hours (mm Hg)</b>				
At baseline, mean $\pm$ sd (mm Hg)	28.5 $\pm$ 7	28.1 $\pm$ 6	27.5 $\pm$ 6	0.818
At 6 hours, mean $\pm$ sd (mm Hg)	30.4 $\pm$ 8	22.1 $\pm$ 6	18.0 $\pm$ 8	<0.001
<b>Range at 6 hours</b>	13 to 52	7 to 44	6 to 38	
<b>p Value at 6 hours (compared with control baseline)<sup>c</sup></b>	---	<0.001	<0.001	
<b>Mean<math>\pm</math>SD (% Change from Baseline-6 hrs)</b>				
p Value (change from baseline) <sup>c</sup>	+8.8 $\pm$ 26%	-20.6 $\pm$ 23%	-35.2 $\pm$ 22%	<0.001
p Value (compared with control baseline) <sup>d</sup>	---	<0.001	<0.001	

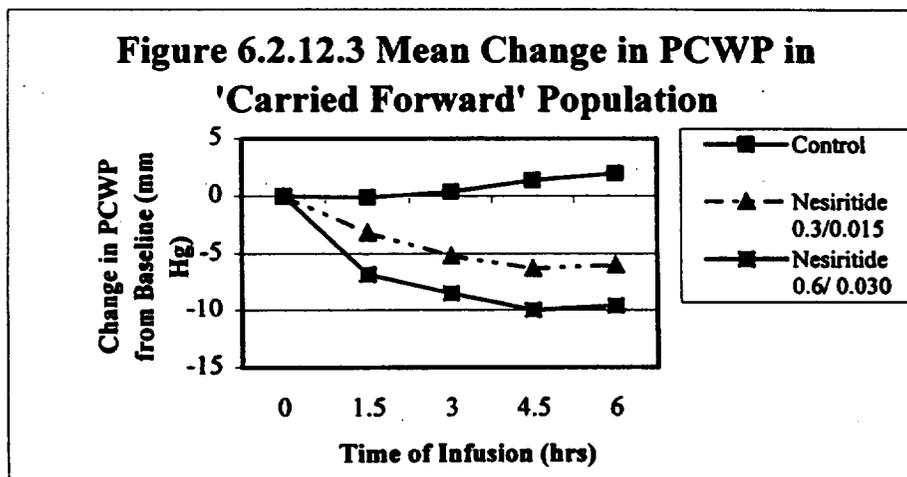
a. Data from NDA volume 59, Appendix 1, Table 26A and 26C.

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<sup>a</sup>.

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 <sup>b</sup>
<b>PCWP at baseline and 6 hours (mm Hg)</b>				
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
<b>% Change from baseline Mean±SD</b>	7.8±26	-21.9±24	-35.5±22	<0.001
Median	0	-24.6	-33.3	
Range				
p Value (change from baseline) <sup>c</sup>	0.061	<0.001	<0.001	
<b>Change from Baseline (mm Hg) Mean±SD</b>	1.8±7	-6.3±7	-9.8±6	<0.001
Median	0	-6	-10	
p Value (change from baseline) <sup>c</sup>	0.126	<0.001	<0.001	
p Value (compared with control) <sup>d</sup>	—	<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.

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#### 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<sup>a</sup>.

Hemodynamic Parameter	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value <sup>b</sup>
<b><u>Right Atrial Pressure (RAP), mm Hg</u></b>				
<b>RAP at baseline and 6 hours (mm Hg)</b>				
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) <sup>d</sup>	---	0.076	<0.001	
<b>% Change in RAP from baseline at 6 hrs (%)</b>				
Mean±SD	+8.1±29	-12.0±42	-39.4±31	<0.001
Median	0	-20	-40	
Range				
p Value (change from baseline) <sup>c</sup>	0.076	0.081	<0.001	
p Value (comp. to control) <sup>d</sup>	---	0.010	<0.001	
<b><u>Systemic Vascular Resistance (SVR) dynes/sec/cm<sup>2</sup></u></b>				
<b>SVR at baseline and 6 hours</b>				
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) <sup>d</sup>	---	0.014	0.005	
<b>% Change in SVR from baseline at 6 hrs (%)</b>				
Mean±SD	+12.8±30	-12.6±25	-17.7±26	<0.001
Median	11.2	-9.2	-20.2	
Range				
p Value (change from baseline) <sup>c</sup>	0.010	0.004	<0.001	
p Value (comp. to control) <sup>d</sup>	---	<0.001	<0.001	
<b><u>Cardiac Index (CI), L/min/m<sup>2</sup></u></b>				
<b>CI at baseline and 6 hours</b>				
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) <sup>d</sup>	---	0.165	<0.0001	
<b>% Change in CI from baseline at 6 hrs (%)</b>				
Mean±SD	-4.4±26	16.2±33	27.5±40	<0.001
Median	-2.6	12.1	21.4	
Range				
p Value (change from baseline) <sup>c</sup>	0.269	0.004	<0.001	
p Value (comp. to control) <sup>d</sup>	---	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)<sup>a</sup>.

Hemodynamic Parameter	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value <sup>b</sup>
<b><u>Pulmonary Vascular Resistance</u></b> <i>(PVR), dynes/sec/cm<sup>2</sup></i>				
<b>PVR at baseline and 6 hours</b>				
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) <sup>d</sup>	---	0.116	0.163	
<b>Change in PVR from baseline at 6 hrs (mm Hg)</b>				
Mean±SD	+26.3±197	-62.2±100	-2.0±142	0.033
Median	10.3	-53.2	-8.3	
Range				
p Value (change from baseline) <sup>d</sup>	0.392	<0.001	0.928	
<b><u>Mean Pulmonary Artery Pressure (MPAP) mm Hg</u></b>				
<b>MPAP at baseline and 6 hours</b>				
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) <sup>d</sup>	---	<0.001	<0.001	
<b>Change in MPAP from baseline at 6 hrs (mm Hg)</b>				
Mean±SD	+2.0±5.8	-7.0±6.9	-7.7±7.6	<0.001
Median	2.5	-5.0	-8.8	
Range				
p Value (change from baseline) <sup>d</sup>	0.031	<0.001	<0.001	
<b><u>Mean Systemic Arterial BP (MAP), mm Hg</u></b>				
<b>MAP at baseline and 6 hours</b>				
At baseline	86.2±12.6	81.2±10.0	85.4±11.3	0.103
At 6 hours				
p Value (compared to control) <sup>d</sup>	---	<0.001	<0.001	
<b>Change in MAP from baseline at 6 hrs (mm Hg)</b>				
Mean±SD				
Median	-1.3	-4.5	-8.7	
Range				
p Value (change from baseline) <sup>c</sup>	---	0.005	<0.001	
p Value (comp. to control) <sup>d</sup>	---	0.008	<0.001	
<b><u>Heart Rate (HR), BPM</u></b>				
<b>HR at baseline and 6 hours</b>				
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) <sup>d</sup>	---	0.516	0.300	
<b>Change in HR from baseline at 6 hrs (mm Hg)</b>				
Mean±SD	1.4 ±7	-1.6±7	0.0±9	0.218
Median	0.5	-3.0	0.0	
Range				
p Value (change from baseline) <sup>c</sup>	0.240	0.149	0.972	
p Value (comp. to control) <sup>d</sup>	---	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

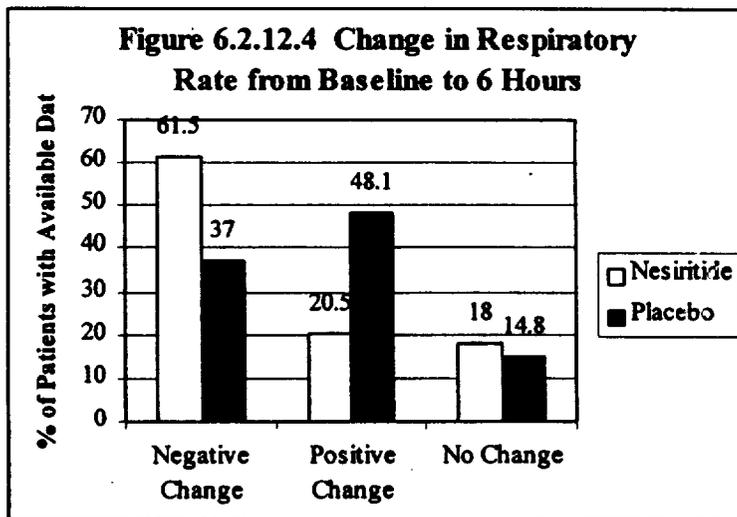
One of the symptoms of CHF, which tends to improve with successful treatment, is 'breathlessness', which often results in an increase in respiratory rate. While there are obviously many other causes of tachypnea, if a drug is successful at lowering the respiratory rate in patients with decompensated 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 ( $\geq 20$  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  $\geq 20$  RPM from study 704.325<sup>a</sup>.

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%) <sup>b</sup>
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<sup>a</sup>.

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<sup>a</sup>.

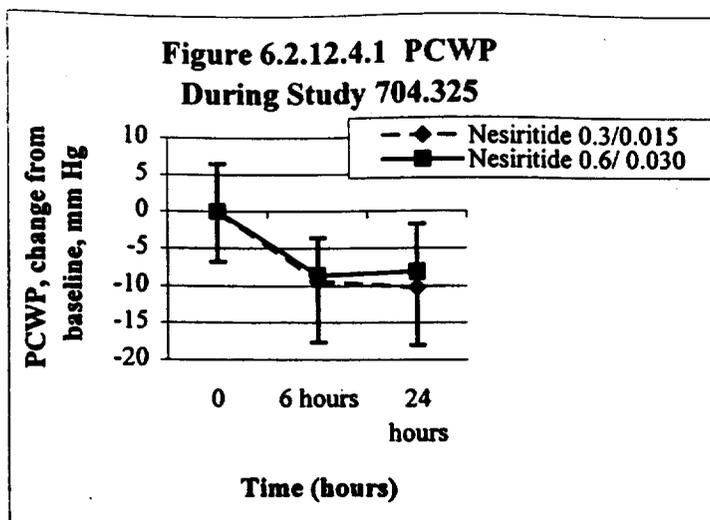
Hemodynamic Parameter	Nesiritide 0.3/ 0.015 n=37	Nesiritide 0.6/ 0.030 n=38
<b><u>Pulmonary Capillary Wedge Pressure (mm Hg)</u></b>		
Baseline	28.7±6.5	27.4±6.5
Change in PCWP from 0 to 6 hours		
Mean±SD	-6.8±7.7	-9.5±5.4
Range		
Change in PCWP from 6 to 24 hours		
Mean±SD	-0.6±7	-0.3±5.8
Range		
Change in PCWP from 0 to 24 hours		
Mean±SD	-7.0±9	-9.9±6
Range		
<b><u>Systemic Vascular Resistance (SVR)</u></b>		
Change in SVR from 0 to 6 hours		
Mean±SD	-318.4±513	-279.8±481
Range		
Change in SVR from 6 to 24 hours		
Mean±SD	-229.1±474	-1.2±404
Range		
Change in SVR from 0 to 24 hours		
Mean±SD	-489.5±630	-345.0±372
Range		
<b><u>Cardiac Index (CI), L/min/m<sup>2</sup></u></b>		
Change in CI from 0 to 6 hours		
Mean±SD	0.3±0.6	0.4±0.7
Range		
Change in CI from 6 to 24 hours		
Mean±SD	0.2±0.7	0.1±0.7
Range		
Change in CI from 0 to 24 hours		
Mean±SD	0.5±0.6	0.5±0.7
Range		

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.



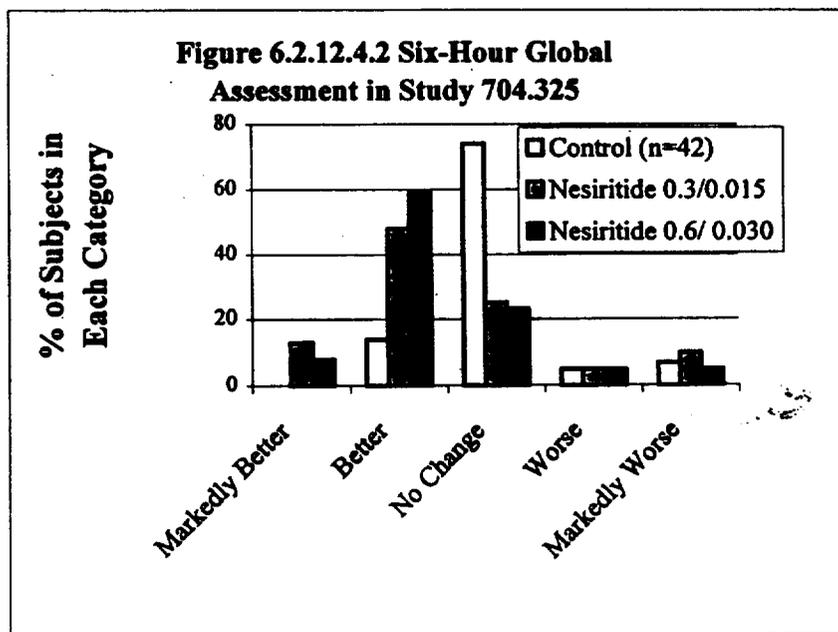
**Global Assessment of Clinical Status (Intent-to-Treat Population)**

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.

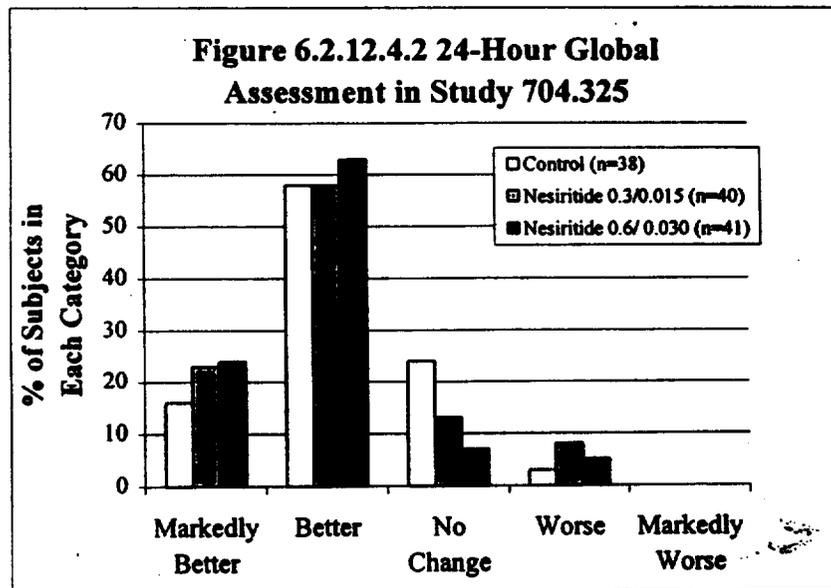
Table 6.2.12.4.6 Improvement in global assessment of clinical status at hour 6 in trial 704.325.

Treatment	Assessment n (%)		Total	p Value
	Not improved	Improved		
<b><i>Investigator Assessment</i></b>				
Placebo	40 (95.8%)	2 (4.8)	42	0.001 <sup>a</sup>
Nesiritide 0.3/ 0.015	18 (45%)	22 (55.0)	40	
Nesiritide 0.6/ 0.030	9 (23.1%)	30 (76.9)	39	
<b><i>Patient Assessment</i></b>				
Placebo	36 (85.7%)	6 (14.3)	42	0.001 <sup>a</sup>
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 <sup>b</sup>		
<b>Investigator Assessment</b>				
Control <sup>c</sup>	10 (26.3%)	28 (73.7%)	38	0.406 <sup>a</sup>
hBNP 0.3/ 0.015	8 (20%)	32 (80.0%)	40	
hBNP 0.6/ 0.030	6 (14.3%)	36 (85.7%)	42	
<b>Patient Assessment</b>				
Control <sup>c</sup>	10 (26.3%)	28 (73.7%)	38	0.281 <sup>a</sup>
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 chi<sup>2</sup>-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<sup>a</sup>.

Hemodynamic Parameter	Control <sup>d</sup>	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030	p Value <sup>c</sup>
<b>6 Hour Global Assessment</b>				
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%)	
<b>24 Hour Global Assessment</b>				
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%)	
<b>Last Recorded Global Assessment<sup>b</sup></b>				
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<sup>a</sup>.

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 <sup>b</sup>
<b><u>Breathing Difficulty: Baseline</u></b>				
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%)	
<b><u>Breathing Difficulty: 6 hour results</u></b>				
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%)	
<b><u>Appetite: Baseline</u></b>				
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%)	
<b><u>Appetite: 6 hour results</u></b>				
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.

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Table 6.2.12.4.10 Assessment of individual signs and symptoms of CHF after 6 hours of study drug in study 704.325<sup>a</sup>.

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 <sup>b</sup>
<b>Peripheral Circulation: Baseline</b>				
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%)	
<b>Peripheral Circulation: 6 hour time-point</b>				
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%)	
<b>Fatigue: Baseline</b>				
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%)	
<b>Fatigue: 6 hour time-point</b>				
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<sup>a</sup>.

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 <sup>b</sup>
<b>Lightheadedness: Baseline</b>				
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%)	
<b>Lightheadedness: 6 hour results</b>				
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%)	
<b>Peripheral Edema: Baseline</b>				
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%)	
<b>Peripheral Edema: 6 hour results</b>				
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<sup>a</sup>.

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 <sup>b</sup>
<b>CHF Total Score: Baseline</b>				
Mean ±SD	12.4±2.6	13.2±2.7	12.5±2.8	0.315
Median	12.0	13.3	12.0	
Range				
<b>CHF Total Score: 6 hour time-point</b>				
Mean ±SD	12.1±1.1	10.3±1.9	10.8±1.6	<0.001
Median	12.0	10.0	11.0	
Range				

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

b. p Value using Omnibus F test.

## 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<sup>a</sup>.

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 <sup>c</sup>
<b>Breathing Difficulty: 24 hour results</b>				
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%)	
<b>Appetite: 24 hour results</b>				
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%)	
<b>Peripheral Circulation: 24 hour time-point</b>				
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%)	
<b>Fatigue: 24 hour time-point</b>				
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%)	
<b>Lightheadedness: 24 hour results</b>				
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%)	
<b>Peripheral Edema: 24 hour results</b>				
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%)	
<b>CHF Total Score: 24 hour time-point</b>				
Mean ±SD	10.0±2.0	9.8±2.0	9.6±1.8	0.493
Median	10.0	10.0	10.0	
Range				

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

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<sup>a</sup>.

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 <sup>b</sup>
<b><u>Breathing Difficulty: last recorded assessment</u></b>				
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%)	
<b><u>Appetite: last recorded assessment</u></b>				
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%)	
<b><u>Peripheral Circulation: last recorded assessment</u></b>				
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%)	
<b><u>Fatigue: last recorded assessment</u></b>				
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%)	
<b><u>Lightheadedness: last recorded assessment</u></b>				
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%)	
<b><u>Peripheral Edema: last recorded assessment</u></b>				
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%)	
<b><u>CHF Total Score: last recorded assessment</u></b>				
Mean ±SD	8.9±1.8	9.0±2.3	9.1±1.7	0.796
Median	9.0	9.0	9.0	
Range				

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

b. p Value using 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<sup>a</sup>.

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 <sup>c</sup>
<b>0 to 6 Hour Data</b>				
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)				0.039
<b>0 to 24 Hour Data</b>				
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)				<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<sup>a</sup>.

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 <sup>c</sup>
<b>0 to 6 Hour Data</b>				
Fluid Intake (Mean ±SD)	96.2±53	98.3±41	94.1±58	0.936
Urine Output (ml/hr)				
Output minus Intake (ml/hr)				

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.

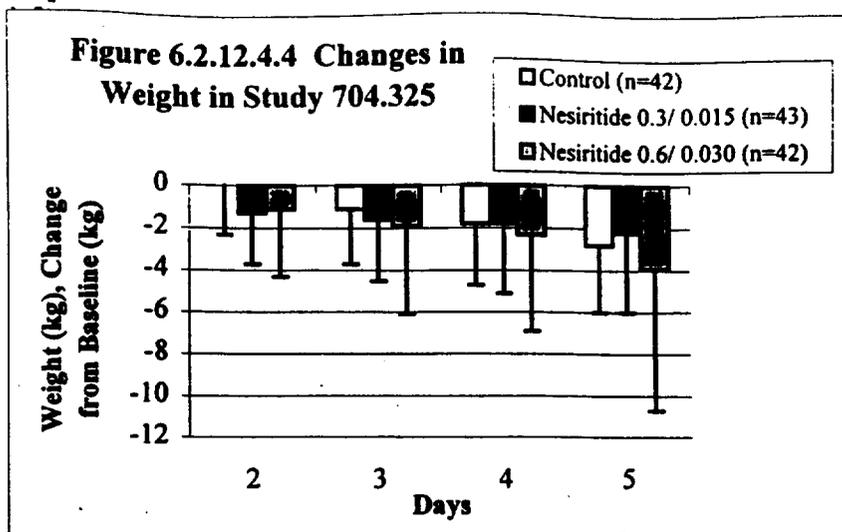
#### Plasma aldosterone and norepinephrine levels

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).

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#### 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  $3.0 \pm 2.9$ ,  $4.1 \pm 4.4$  and  $5.3 \pm 11.4$  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<sup>a</sup>.

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				0.891 <sup>b</sup>
Mean $\pm$ SD	7.6 $\pm$ 4.9	7.3 $\pm$ 3.9	7.8 $\pm$ 4.5	
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 <sup>c</sup>

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.

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<sup>a</sup>.

	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 <sup>b</sup>
If discharged, # of subjects readmitted by day 21	1 (3%)	4 (11%)	4 (12%)	0.229 <sup>b</sup>
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.

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### 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<sup>a</sup>.

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) <sup>b</sup>	2 (5%)	4 (10%)	9 (21%)
Discontinued due to an AEC <sup>c</sup>	1 (2%)	1 (2%)	3 (7%)
Lost to Follow-up	0 (0%)	1 (2%)	0 (0%)
Deaths <sup>b</sup>	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<sup>a</sup>.

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).

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Table 6.2.13.3 Serious Adverse Events in study 704.325<sup>a</sup>.

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

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<sup>a</sup>.

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 Nausea	Later died (see above)
357-002	"	1 (4.5 hrs)	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<sup>a</sup>.

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<sup>a</sup>.

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).

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#### 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<sup>a</sup>.

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%)
<b>TOTAL</b>	<b>305</b>

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.

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### 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<sup>a</sup>.

Procedure	Pre-infusion	Study Drug Infusion						Post-Infusion	Day 14	Day 21
		0	1	2	4	6	6+ <sup>e</sup>			
Informed Consent	X							X		
Medical History/ PE	X									
ECG	X									
Holter Monitors <sup>f</sup>	See Note									
CXR	X									
D/C Parenteral Cardiac Meds	X <sup>b</sup>									
Vital Signs	X	X	X	X	X	X	X <sup>c</sup>			
CBC, Chemistries <sup>d</sup>								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 <sub>2</sub> , Cl, Crt, and BUN							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.

### 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<sup>a</sup>.

Demographic	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
<b>Gender</b>				
Female	29 (28%)	36 (35%)	33 (33%)	0.610
Male	73 (72%)	67 (65%)	67 (67%)	
<b>Race</b>				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%)	
<b>Age (Mean±SD)</b>	63±14	63±14	65±12	0.453
<b>NYHA Class (prior to hospitalization)</b>				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<sup>a</sup>.

Demographic	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value <sup>b</sup>
<b>Etiology of CHF</b>				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%)	
<b>Etiology for Current Decompensation</b>				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%)	

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.

### 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<sup>a</sup>.

Demographic	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value <sup>b</sup>
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<sup>a</sup>.

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 <sup>b</sup>	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<sup>a</sup>.

Study Drug	Standard Care	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030
	n=102	n=103	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<sup>a</sup>.

Study Drug	Standard Care	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030	p Value
	n=102	n=103	n=100	
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<sup>a</sup>.

Study Drug Infusion	Standard Care	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030	p Value
	n=102	n=103	n=100	
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<sup>a</sup>.

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%)	77 (77%)	<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.

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