Table 11.1.4.1.2 (from table 6.2.12.4.2) Summary of changes in blood pressure using 'last value carried forward' population from study 704.325)[a].

Blood Pressure changes in study 704.325	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	Nominal p Value[b]
Mean Systemic Arterial BP (MAP), mm Hg				
MAP at baseline and 6 hours				
At baseline	[illegible]	[illegible]	[illegible]	[illegible]
At 6 hours	[illegible]	[illegible]	[illegible]	[illegible]
Nominal p Value (compared to control)	---	<0.001	<0.001	
Change in MAP from baseline at 6 hrs (mm Hg)				
Mean±SD	[illegible]	[illegible]	[illegible]	[illegible]
Median	-1.3	-4.5	-8.7	
Range	-17 to +19	-44 to +20	-24 to +11	
Nominal p Value (change from baseline)[c]	---	0.005	<0.001	
Nominal p Value (comp. to control)[c]	---	0.008	<0.001	

a. Data from NDA volume 1.59, Appendix 1, Table 26a to 40a and electronic data sets.
b. p Value using Omnibus F test.
c. p Value compares the 6 hour value for each group individually with the control baseline using T-test or 1-sample Wilcoxon.

Table 11.1.4.1.2 (from table 6.3.12.3.1) Changes in blood pressure from baseline to 3 hours in study 326[a].

Blood Pressure changes in study 704.326	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal p Value
Systolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	120.7±20	127±25	124±26	0.197
Change from Baseline to 3 hours	[illegible]	[illegible]	[illegible]	[illegible]
Nominal p Value (Chg from Base)[b]	0.183	<0.001	<0.001	
Nominal p Value (Compared to Standard Care)[c]	--	0.003	<0.001	
Nominal p Value (Compared to Low-dose BNP)[c]	--	--	0.426	
Diastolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	70±13	71±15	68±15	0.477
Change from Baseline to 3 hours	[illegible]	[illegible]	[illegible]	[illegible]
Nominal p Value (Chg from Base)[b]	<0.001	<0.001	<0.001	
Nominal p Value (Compared to Standard Care)[c]	--	0.376	0.125	
Nominal p Value (Compared to Low-dose BNP)[c]	--	--	0.016	

a. Data from NDA volume 1.66, table 21.
b. Comparison by T test.
c. Comparison by ANOVA contrast.

Heart Rate

The acute effect of nesiritide on heart rate was also compared with control in the three infusion trials. Overall, no clear pattern of effect was discernable, perhaps related to the different controls used in each of the trials (placebo in 311, active control in 326).

Table 11.1.4.1.1 (from table 6.1.12.4.1) Mean change in heart rate from baseline to 3 hours in trial 704.311[a].

Heart Rate in study 704.311	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	Nominal p Value[b]
Heart Rate (BPM)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

a. Data from NDA 20-998, vol. 54, Table 2. Data are expressed as absolute and (%) change from baseline for ITT population.
b. p Value comparing arithmetic means from baseline using ANOVA.

Table 11.1.4.1.2 (from table 6.2.12.4.2) Summary of changes in heart rate using 'last value carried forward' population from study 704.325)[a].

Heart Rate in study 704.325	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.0305 n=42	Nominal p Value[b]
HR at baseline and 6 hours				
At baseline	89.5±12.8	90.3±14.6	87.4±16.7	0.640
At 6 hours	90.9±15.4	88.8±14.5	87.5±16.0	0.576
Nominal p Value (compared to control)	---	0.516	0.300	
Change in HR from baseline at 6 hrs (mm Hg)				
Mean±SD	1.4 ±7	-1.6±7	0.0±9	0.218
Median	0.5	-3.0	0.0	
Range	-16 to +24	-16 to +14	-28 to +28	
Nominal p Value (change from baseline)[c]	0.240	0.149	0.972	
Nominal p Value (comp. to control)[c]	---	0.082	0.435	

a. Data from NDA volume 1.59, Appendix 1, Table 26a to 40a and electronic data sets.
b. p Value using Omnibus F test.
c. p Value compares the 6 hour value for each group individually with the control baseline using T-test or 1-sample Wilcoxon.

Table 11.1.4.1.2 (from table 6.3.12.3.1) Changes in vital signs from baseline to 3 hours in 704.326[a].

Heart Rate in study 704.326	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal p Value
Baseline (mean±sd)	85±15	83±18	84±15	0.823
Change from Baseline to 3 hours	+3.5±15	-0.6±9	+0.6±10	0.053
Nominal p Value (Chg from Base)[b]	0.029	0.501	0.569	
Nominal p Value (Compared to Standard Care)[c]	--	0.018	0.107	
Nominal p Value (Compared to Low-dose BNP)[c]	--	--	0.469	

a. Data from NDA volume 1.66, table 21.
b. Comparison by T test.
c. Comparison by ANOVA contrast.

11.1.4.5 Adverse Events Related to Special Examinations

ECGs

No formal analysis of the ECGs was performed by the sponsor beyond the Holter Monitors evaluated as described below.

Holter Monitors

Per the sponsor, 15 of the 46 clinical sites in study 704.326 performed pilot Holter monitoring on 45 subjects (15 standard care subjects, and 16 and 14 subjects receiving the 0.015 and 0.030 mg/kg/min nesiritide doses, respectively). No formal analysis of the effects of study drug on arrhythmias was performed, as subjects did not have adequate baseline Holter information to permit a comparative analysis of pre- and on-drug Holter data. The sponsor reported that 'a descriptive review of on-drug Holter information was qualitatively consistent with the investigators' reports of arrhythmic adverse events in that ventricular ectopy (PVCs, couplets, NSVT) was observed less frequently in the nesiritide subjects than in standard care subjects while the reverse trend was found for bradycardia.'

Urinalyses

Urinalyses were not performed as part of either study 704.325 and 704.326. In study 704.311, the only recorded urinalyses come from the screening period. In the absence of urinalysis data from the long infusion trials, the effect of nesiritide on urinary abnormalities cannot be determined, including: proteinuria, hematuria, pyuria, and glycosuria.

11.1.4.5 Discontinuations

The reasons for discontinuation from the three long infusion trials are summarized in the first three tables below, which are drawn from the individual trial reviews. Note that the time used to calculate 'completion' is short in all three trials (3 to6 hours).

Table 6.1.12.2.1 Disposition of subjects randomized in the trial 311[a].

Patient Disposition	Placebo	Nesiritide 0.25/ 0.015	Nesiritide 0.5/ 0.030	Nesiritide 1.0/ 0.060
Randomized	29	22	26	26
Completed up to 3 hours	29 (100%)	22 (100%)	25 (96%)	23 (88%)
Discontinued within 24 hours (Total)	5 (17%)	0 (0%)	2 (8%)	6 (23%)
D/C'd due to an AE prior to hour 3	0 (0%)	0 (0%)	1 (4%)	3 (12%)
D/C'd due to an AE between hours 3 & 24	5 (17%)	0 (0%)	1 (4%)	3 (12%)
D/C'd due to hypotension	0 (0%)	0 (0%)	2 (8%)	6 (23%)
D/C'd due to worsened CHF	5 (17%)	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 54, page 108.

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

Patient Disposition	Placebo	Nesiritide 0.3/ 0.015	Nesiritide 0.6/ 0.030
Randomized	42	43	42
Completed up to 5.5 hours	41	42	39
Discontinued	1 (2%)	1 (1%)	3 (7%)
D/C'd prior to 5.5 hrs after start of infusion	1 (2%)	1 (1%)	3 (7%)
D/C due to AE	1 (2%)	1 (1%)	3 (7%)
D/C'd due to hypotension[b]	0 (0%)	0 (0%)	2 (5%)
D/C'd due to worsening CHF	0 (0%)	1 (1%)	0 (0%)
D/C'd with other AEs	1 (2%)	0 (0%)	1 (2%)

a. Data from NDA volume 1.59, section 4.2 and electronic data sets.
b. Includes one individual with hypotension and one with PCWP = 6 mm Hg.

Table 6.3.12.2.1 Disposition of subjects randomized in the study 326 at the end of 21 days[a].

Patient Disposition	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100
Randomized	102	103	100
Completed to 6 hours	100 (98%)	101 (98%)	94 (94%)
Discontinued			
D/C prior to 6 hours[b]	2 (2%)	2 (2%)	5 (5%)
D/C due to hypotension	0 (0%)	2 (2%)	5 (5%)
D/C due to arrhythmia	2 (2%)	0 (0%)	1 (1%)
Alive at day 21	96 (94%)	94 (91%)	94 (94%)
Dead	5 (5%)	6 (6%)	6 (6%)
Lost to F/U	1 (1%)	3 (3%)	0 (0%)

a. Data from NDA volume 66, appendix table 11.
b. 6 hour time point represents the end of the blinded analysis in the earlier trial 704.325.

The sponsor also summarized the reasons for study drug withdrawal for the 'CHF trials' population and for the 'long infusion studies' population, as shown below. A higher % of the control group (either placebo or active control) was discontinued per protocol, and a higher % of the nesiritide groups was discontinued for adverse events. The increased % of withdrawals in the nesiritide group in the 'long infusion study' population was dose-related.

Table 11.1.4.3.1.2 Reasons for termination of study drug in the 'all CHF' studies[a].

Reasons for study drug termination	Control n=235	Nesiritide n=505	Nominal p Value[a]
Per Protocol	[illegible]	[illegible]	[illegible]
Adverse Events	[illegible]	[illegible]	[illegible]
Inadequate Therapeutic Response	20 (9%)	41 (8%)	0.886
Other	9 (4%)	17 (3%)	0.831

a. Data from table 6A per the sponsor. p Values by 's Exact test.

Table 11.1.4.3.1.2 Reasons for termination of study drug in the long-infusion studies[a].

Reasons for study drug termination	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value[a]
Per Protocol	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Adverse Events	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Inadequate Therapeutic Response	14 (8%)	17 (10%)	18 (11%)	0 (0%)	0.322
Other	9 (5%)	9 (5%)	8 (5%)	0 (0%)	0.875

a. Data from supplemental table 6D per the sponsor.

11.1.5.2 Discontinuations associated with Serious Adverse Events (SAEs)

Discontinuations associated with SAEs are included in the tables below, summarizing all known withdrawals for adverse events, including SAEs.

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11.1.5.3 Discontinuations associated with Adverse Events (AEs)

The table below summarizes the discontinuations due to AEs in the CHF trials. The shading indicates a nominally significant difference between the control and nesiritide groups.

Table 11.1.5.3.1 Discontinuations prior to day 14 due to AEs in the 'CHF trials' population[a].

Body System/ AE	Control n=235	Nesiritide n=505	Nominal p Value[a]
Cardiovascular System	15 (6%)	78 (15%)	<0.0001
Hypotension	[illegible]	[illegible]	[illegible]
Symptomatic Hypotension	[illegible]	[illegible]	[illegible]
Congestive Heart Failure	7 (3%)	14 (3%)	0.817
Bradycardic Event	0 (0%)	7 (1%)	0.104
Bradycardia	0 (0%)	6 (1%)	0.184
Nodal Arrhythmias	0 (0%)	1 (0%)	1.000
Decreased Pulmonary Pressure	0 (0%)	5 (1%)	0.185
Elevated PCWP	2 (1%)	2 (0%)	0.595
Ventricular Tachycardia	[illegible]	[illegible]	[illegible]
Digestive System	1 (0%)	12 (2%)	0.072
Nausea	1 (0%)	10 (2%)	0.188
Vomiting	0 (0%)	3 (1%)	0.555
Nausea and Vomiting	0 (0%)	1 (0%)	1.000
Nervous System: None			
Urogenital System	[illegible]	[illegible]	[illegible]
Oliguria	0 (0%)	5 (1%)	0.185
Creatinine Increased	0 (0%)	4 (1%)	0.313
Acute Kidney Failure	0 (0%)	1 (0%)	1.000
Metabolic & Nutritional System	0 (0%)	5 (1%)	0.185
BUN Increased	0 (0%)	4 (1%)	0.313
Hypovolemia	0 (0%)	1 (0%)	1.000
Respiratory System: None			
Body as a Whole: None			
Skin & Extremities: None			
Special Senses: None			
Amblyopia	0 (0%)	1 (<1%)	1.000

a. Data from NDA appendix 8.4, table 28A.

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Next, the discontinuations associated with AEs in the long infusion studies are summarized.

Table 11.1.5.3.1 Discontinuations due to AEs in the long infusion trials[a].

AE	Placebo (n=29)	Nesiritide 0.015 (n=22)	Nesiritide 0.030 (n=26)	Nesiritide 0.060 (n=26)	Nominal p Value[b]
Cardiovascular	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hypotension	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Symptomatic Hypotension	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Congestive Heart Failure	4 (2%)	5 (3%)	5 (3%)	0 (0%)	0.946
Bradycardic Events	0 (0%)	2 (1%)	4 (2%)	0 (0%)	0.170
Bradycardia	0 (0%)	2 (1%)	3 (2%)	0 (0%)	0.325
Nodal Arrhythmia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Decreased Arterial Pressure	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Ventricular Tachycardia	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0.234
Sustained VT	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0.395
Non-sustained VT	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1.000
Tachycardia	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1.000
Digestive System	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Nausea	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Vomiting	0 (0%)	1 (1%)	2 (1%)	0 (0%)	0.326
Nausea and Vomiting	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Urogenital	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Oliguria	0 (0%)	1 (1%)	4 (2%)	0 (0%)	0.125
Creatinine Increased	0 (0%)	1 (1%)	3 (2%)	0 (0%)	0.249
Acute Kidney Failure	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Body As A Whole	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Abdominal Pain	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Headache	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0.291
Central & Peripheral Nervous System	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dizziness	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Nervousness	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Stupor	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Vertigo	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.677
Metabolic & Endocrine	0 (0%)	2 (1%)	3 (2%)	0 (0%)	0.325
BUN Increased	0 (0%)	2 (1%)	2 (1%)	0 (0%)	0.510
Hypovolemia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Respiratory System: None					
Special Sense					
Amblyopia	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.677
Skin and Appendages: None					

a. Data from supplemental table 28D.

11.1.5.4 Discontinuations associated with Laboratory Adverse Events

Discontinuations for laboratory AEs are included in the tables above.

11.1.6 Special Studies

In this section, problems germane to all NDA submissions are reviewed: These include: tolerance, withdrawal/ rebound, abuse potential, human reproductive toxicity, and overdose.

11.1.6.1 Special Studies: Tolerance/ Withdrawal

Tolerance

The potential for tolerance or tachyphylaxis to the vasodilatory effects of nesiritide was discussed in section 7.0.1c (Durability of the Effect of Nesiritide on PCWP and Other Hemodynamic Measures). The reader is referred there for the discussion, which concluded the following: the data are inadequate to fully assess the development of tachyphylaxis following long nesiritide infusion. Based on the decrease in the magnitude of the hemodynamic effect of nesiritide in trial 704.311, a degree of tolerance to the hemodynamic effects of nesiritide is possible. This decrease, however, did not reverse the overall significant effects of nesiritide on hemodynamics, when compared with placebo through 24 hours The clinical significance of the decreases in mean hemodynamic changes through 24 hours.

Withdrawal

The potential for a withdrawal phenomenon was discussed in section 7.0.1a.4 (Changes in PCWP Following Withdrawal of Nesiritide), with the following conclusion: no evidence was detected of a 'rebound' phenomenon with regard to PCWP. Following withdrawal of nesiritide, the PCWP returned to within 10% of baseline by the end of 4 hours. After 2 hours, the PCWP for the high-dose nesiritide (1.0/ 0.060) group was still approximately 20% below baseline.

11.1.6.2 Special Studies: Abuse Potential

The anticipated abuse potential for nesiritide is low. First, it is administered intravenously in an intensive care unit-setting. Second, it has no known mood-altering properties. There are, however, receptors for nesiritide in the brain. A related compound, atrial natriuretic peptide, has been proposed as a therapy for 'flashbacks' related to Post-Traumatic Stress Syndrome, suggesting some activity on personality and behavior.

11.1.6.3 Special Studies: Human Reproduction Data

Per the sponsor, no pregnant individuals are known to have been exposed to nesiritide during the product development.

11.1.6.4 Special Studies: Overdose

In the three infusion studies, patients were dose on the basis of body weight. Per the sponsor, there have been no observed instances of overdosage during the clinical program and no studies related to overdosage have been conducted.

Sponsor's Comments

The sponsor pointed out that while the proposed nesiritide dose range is 0.015 to0.03 μg/kg/min, it has been administered to subjects with CHF at doses as high as 0.1 μg/kg/min as a continuous infusion. At this higher dose, symptomatic hypotension was frequent and limited drug tolerance. While the hypotension and accompanying symptoms usually resolved soon after dose reduction or discontinuation of nesiritide infusion, one subject had prolonged symptomatic hypotension and junctional bradycardia following infusion at the 0.1 μg/kg/min dose with labile blood pressure for approximately 5.5 hours. During this time he required IV fluids, dopamine and atropine. Nesiritide has been administered as a bolus at doses up to 32 μg/kg, which likely achieves quite high plasma hBNP levels for a short period of time. For these patients,. decreases in blood pressure were the only adverse events that accompanied the bolus administration.

Finally, in preclinical studies, nesiritide has been administered to monkeys for 2 weeks at doses as high as 20 μg/kg/min (approximately 1000-foldhigher than the current clinical dose). A decrease in blood pressure was observed, but there was no evidence of acute adverse effects on clinical status or electrocardiography.

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11.1.6.5 Special Studies: Allergic Reactions/ Antibody Formation

In that nesiritide is identical in structure to a naturally-occurring molecule, allergic reactions to it are unlikely. Nesiritide is produced using *E. coli*, which could induce an allergic reaction, despite the extensive process used to both remove and screen for any components of *E. coli* in the finished drug substance. The sponsor reports that there were no reported allergic reactions to either nesiritide or any of the other components of the drug substance. As an indirect marker for allergic reactions, the occurrence of pruritus and urticaria are summarized below.

Table 11.1.6.5.1 Pruritus, rash and urticaria in the long-infusion studies through day 14[a].

	Control n=173	Nesiritide n=0.015 n=169	Nesiritide n=0.030 n=167	Nesiritide n=0.060 n=26	Nominal p Value
Pruritus	4 (2%)	6 (4%)	6 (4%)	0 (0%)	0.844
Urticaria	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0.593
Rash	5 (3%)	2 (1%)	9 (5%)	0 (0%)	0.150

a. Data from supplemental table 11D per the sponsor.

Antibody Formation

Because of the concerns about the potential formation of antibodies against nesiritide, the sponsor collected baseline and day 21 titers of anti-nesiritide antibodies in trial 704.325. A total of 61 subjects who received nesiritide had baseline and follow-up antibody titers measured, and none of the subjects had an increase at day 21, relative to baseline.

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12.0 Appendix Two: Narratives of subject deaths in NDA 20-920

Narratives for the 34 deaths known to have occurred in subjects who enrolled in one of the trials in NDA 20-920 are summarized below.

Study 704.306

1. Subject 324-010 (Placebo): Subject was a 57-year-old white man with a history of NYHA Class III CHF due to ischemic cardiomyopathy, mitral and tricuspid valve regurgitation, dobutamine dependence, and pulmonary hypertension; he died on study day 15. This subject was already hospitalized at the time of entry into the study awaiting cardiac transplantation. He tolerated all study procedures well. On study day 15, he underwent a heart transplant after which he was not able to wean from cardiopulmonary bypass and died.

Study 704.309

1. Subject 381-001 (Placebo): Subject was a 53-year-old white man with a history of NYHA Class IV CHF due to alcoholic cardiomyopathy, diabetes mellitus, chronic renal insufficiency, and chronic obstructive lung disease; the subject died on study day 6. This subject tolerated all study procedures well and was considered stable upon completion of study drug dosing. Four days following the termination of study drug dosing, he experienced ventricular fibrillation and cardiac arrest resulting in death despite efforts at cardiopulmonary resuscitation. This death was not considered study related.

2. Subject 315-005 (Nesiritide, 5 μg/kg q4h) Subject was a 65-year-old white man with NYHA Class IV CHF, hypertension, bifascicular heart block, and a history of previous episodes of supraventricular arrhythmias. He tolerated the 24-hour dosing period well but subsequently had a complicated hospital course with numerous arrhythmias requiring defibrillation and respiratory distress requiring intubation. He subsequently died of refractory CHF on day 30.

Study 704.310

No deaths occurred in this study during the 14-day study follow-up period. Two deaths on days 19 and 30 were later reported to Scios.

1. Subject 356-103 (Placebo) Subject was a 73-year-old white man with a history of NYHA Class IV CHF, coronary artery disease and hypertension. He tolerated all study procedures without incident. He died on day 19 due to ventricular fibrillation and electromechanical dissociation.

2. Subject 373-301 (Nesiritide, 10 μg/kg) Subject was a 47-year-old black man with a history of NYHA Class III CHF, hypertension, and sick sinus syndrome requiring a permanent pacemaker. He experienced mild dyspnea, sweating, insomnia, and dizziness during the study drug treatment period, possibly because of problems with capture by his pacemaker. The subject was discharged following the study and was seen in follow-up in clinic a month later without complaints of adverse events. He died two days later (on day 30) at home of sudden cardiac death.

Study 704.311

Three deaths occurred during the 15-day study follow-up period, one in each of the three treatment groups. Two additional deaths were reported after day 15, both in the placebo group.

1. Subject 376-016 (Placebo): Subject was a 60-year-old white man with a history of NYHA Class III CHF, coronary artery disease, ventricular arrhythmias, hypertension, diabetes, and chronic obstructive pulmonary disease (COPD). He presented to clinic with dyspnea and peripheral edema and was enrolled in the study. He tolerated study drug infusion well and had no reported adverse events during his hospital stay. He was discharged to home and was found dead at home on day 6; cause of death.
was reported as sudden death.

2. Subject 376-022 (Placebo) Subject was a 60-year-old white woman with a history of NYHA Class III CHF (with an ejection fraction of 9%), rheumatic heart disease requiring mitral valve replacement, and chronic atrial fibrillation. She tolerated study drug infusion well. The day after study drug infusion, the subject underwent an elective atrio-ventricular (AV) nodal ablation and placement of a pacemaker without complications and was discharged from the hospital soon thereafter. No adverse events were reported during the 15-day study reporting period. The subject was found dead at home on day 21; cause of death was reported as sudden death.

3. Subject 370-006 (Placebo) Subject was a 50-year-old man from India with a history of NYHA Class IV CHF, coronary artery disease, a previous ventricular aneurysmectomy and marked cachexia at admission for worsening CHF. He was enrolled in the study but terminated study drug (placebo) infusion prematurely due to worsening CHF after 3 hours 25 minutes of infusion. The subject was then treated with IV dobutamine and furosemide. An episode of supraventricular tachycardia accompanied by chest pain was also reported on day 6. The subject was discharged to home, but was readmitted to another hospital on approximately day 18 with dyspnea and end-stage CHF; he was reported to have died during this hospitalization on approximately day 46, although information on the precise date and cause of death was not available.

4. Subject 017-007 (0.03 μg/kg/min nesiritide) Subject was an 85-year-old white man with NYHA Class IV CHF, coronary artery disease, a pacemaker, and atrial fibrillation. He was admitted with a four day history of worsening dyspnea. The subject received the full study drug infusion (0.03 μg/kg/min nesiritide), which was well tolerated. On day 4, the subject underwent elective cardiac catheterization with coronary stent placement. His renal function deteriorated in the days following this procedure, presumably due to contrast administration during the procedure; the adverse events of worsening CHF and acute renal failure were reported on day 8 (with a rise in serum creatinine from 2.4 mg/dL before enrollment to 3.6 mg/dL on day 8), requiring acute dialysis. The subject also required emergent intubation for worsening cardiac and respiratory failure. Due to the subject's generally poor prognosis, the subject and family chose not to pursue further resuscitative measures.

5. Subject 382-004 (0.06 μg/kg/min nesiritide) Subject was a 70-year-old white woman with NYHA Class IV CHF and a complex medical history including previous mitral and tricuspid valve replacements for rheumatic heart disease, ventricular pacemaker placement, chronic atrial fibrillation, and renal insufficiency. She was admitted for worsening CHF and enrolled in the study. She tolerated the full 24-hour study drug infusion well. Hypokalemia was reported on day 4, attributed to aggressive diuresis over the few days following study drug. After some improvement in her overall condition, she was discharged but was found dead at home on day 8. Death was attributed to a presumed ventricular arrhythmia and end-stage CHF.

Study 704.325

During the 21-day study reporting period, 6 deaths occurred, two in each of the three treatment groups.

1. Subject 368-001 (Placebo) Subject was a 63-year-old white man with NYHA Class IV CHF due to ischemic heart disease and severe mitral and tricuspid valvular disease. After the placebo period, he received dobutamine. On day 3, the subject underwent a surgical cardiac ventricular reduction procedure, coronary artery bypass graft surgery, and mitral and tricuspid valve repair. The subject's postoperative course was complicated by worsening CHF and acute renal failure ultimately requiring dialysis. On day 15, the subject died due to ventricular fibrillation while awaiting cardiac transplantation.

2. Subject 503-001 (Placebo) Subject was a 24-year-old white man with NYHA Class IV CHF due to idiopathic dilated cardiomyopathy. After the placebo period, he was treated with dobutamine, dopamine, and milrinone. On day 17, he developed ventricular fibrillation during milrinone infusion. Resuscitation was attempted (including intubation) but was not successful. The cause of death was reported to be endstage CHF and acute bronchopneumonia.

3. Subject 374-001 (nesiritide, 0.015 μg/kg/min) Subject was a 64-year-old white man with NYHA Class IV CHF due to ischemic cardiomyopathy, diabetes, and chronic renal insufficiency. He responded well to a 24-hour infusion of nesiritide; thereafter, dobutamine was added for inotropic support. The subject's digoxin had been discontinued 1 month earlier due to renal insufficiency. On study day 2, digoxin was reinstituted. After receiving his second dose, he developed hypotensive bradycardia (Wenckebach type atrioventricular node block) while sleeping. Atropine was administered, a ventricular pacing wire was placed, and nesiritide was discontinued. Although the heart rate improved with pacing, hypotension persisted due to AV dyssynchrony. Digoxin toxicity was suspected (although digoxin level was 1.1 ng/mL 2 hours earlier) and Digibind was given. Forty minutes later, sinus tachycardia resumed; BP improved within 2 hours. The subject later revealed that he had had a similar event with digoxin in the past and, therefore, had previously been prescribed a low dose of digoxin. His subsequent hospital course included worsening CHF leading to inotrope dependence and a cardiopulmonary arrest. On day 4, after requesting that all medications be discontinued, the subject died due to endstage heart failure from severe coronary artery disease.

4. Subject 387-013 (nesiritide, 0.015 μg/kg/min) Subject was an 80-year-old white man with NYHA Class IV CHF due to ischemic cardiomyopathy and progressive renal insufficiency. He had not responded to 7 days of dobutamine therapy before he was enrolled into the study. After 6 hours of nesiritide therapy, his hemodynamics were only minimally improved and dobutamine was restarted. Nesiritide was discontinued on study day 3 due to hypotension and nausea. After a short trial of milrinone added to the dobutamine, it was decided that the subject was refractory to vasoactive medications. The subject was made "Do Not Resuscitate." On day 5, the subject expired due to endstage CHF and progressive renal insufficiency.

5. Subject 357-002 (Nesiritide, 0.03 μg/kg/min) Subject was a 54-year-old white man with a history of NYHA Class III CHF due to ischemic cardiomyopathy and chronic angina. Nesiritide was discontinued after 4.5 hours because his PCWP had decreased to 6 mm Hg. However, the subject was symptomatically improved, so no additional parenteral agents for CHF were started and he was discharged on day 2. On day 15, he died in the emergency room from a myocardial infarction after an unsuccessful resuscitation (including acute intubation).

6. Subject 370-002 (Nesiritide, 0.03 μg/kg/min) Subject was a 66-year-old white man with NYHA Class IV CHF and chronic atrial fibrillation. He responded well to 5 days of nesiritide therapy (the maximum allowed infusion duration per protocol). On day 6 (during nesiritide infusion), he developed bilateral femoral artery thromboses (presumably due to the discontinuation of warfarin 8 days earlier) requiring urgent surgical revascularization. On day 20, the subject experienced an acute episode of cardiopulmonary decompensation requiring emergency intubation and pressor support leading to the subject's death later that day.

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Seventeen subjects in this study died by day 21. Five (5%), 6 (6%), and 6 (6%) subjects in the standard care, the 0.015 and 0.03 nesiritide groups, respectively. One additional death in the 0.03 μg/kg/min nesiritide group occurred on day 22.

1. Subject 493-019 (Standard care: dobutamine) Subject was a 70-year-old white man with NYHA Class IV endstage ischemic cardiomyopathy. He received dobutamine for 90 hours, which was discontinued due to an inadequate therapeutic response. On day 3, he suffered a cardiopulmonary arrest (requiring acute intubation and defibrillation). On day 5, due to his poor prognosis, support was withdrawn, and he expired.

2. Subject 493-021 (Standard care: dobutamine) Subject was a 77-year-old white man with NYHA Class IV CHF and coronary artery disease. He received dobutamine for approximately 13 days and expired on day 18 from endstage cardiomyopathy.

3. Subject 509–001 (Standard care: dobutamine) Subject was a 61-year-old white man with a history of NYHA Class III CHF, a previous myocardial infarction, chronic renal insufficiency, Non-sustained VT, and bradycardia. During the study, he was treated with dobutamine for 1 day with no improvement and was discharged to home at his request. On day 10, he was readmitted with bullous cellulitis. On study day 13, he developed worsening renal function and received hemodialysis beginning on day 19. On day 21, he died following a cardiac arrest, presumably associated with a myocardial infarction.

4. Subject 538-011 (Standard care: dobutamine) Subject was a 78-year-old white man with a history of NYHA Class IV CHF, atrial fibrillation, ventricular ectopy, and chronic renal insufficiency. Dobutamine was administered for 8 days. On day 3, he developed acute renal failure. On day 4, he experienced bradycardia and a respiratory arrest requiring intubation and mechanical ventilation. He died on day 9 of severe left ventricular heart failure.

5. Subject 585-002 (Standard care: dobutamine) Subject was a 72-year-old white man with a history of NYHA Class IV CHF and coronary artery disease. For almost 3 days, he received dobutamine that was then discontinued because of an inadequate therapeutic response. His CHF continued to worsen, resulting in his death on day 21.

6. Subject 369-003 (Nesiritide, 0.015 μg/kg/min) Subject was a 88-year-old white woman with NYHA Class III CHF due to ischemic cardiomyopathy. For 31 hours, she received nesiritide that was discontinued due to inadequate clinical response, acute shortness of breath, and sinus tachycardia. On day 2, nesiritide was replaced with milrinone and dobutamine, which were infused for 4 days. After progressive worsening of her heart failure on these agents, she was made "do not resuscitate" and all medications were discontinued on day 6. She died on day 8 due to endstage CHF.

7. Subject 493-008 (Nesiritide, 0.015 μg/kg/min) Subject was an 81-year-old white man with NYHA Class IV CHF and ischemic cardiomyopathy. He was admitted 9 days before study entry with a junctional bradycardia. Nesiritide was administered for 3 days and then discontinued by subject request. Dobutamine was initiated on day 3, but all parenteral therapy was discontinued on day 11 by subject request. On day 14, he died of endstage cardiomyopathy.

8. Subject 504-003 (Nesiritide, 0.015 μg/kg/min) Subject was a 70-year-old white man with NYHA Class IV CHF, ischemic cardiomyopathy, and ventricular arrhythmias requiring an AICD. He received nesiritide for the 7-day maximum permitted by the protocol; on day 5, dobutamine was added for inotropic support. On day 10 (2 days after nesiritide was discontinued), he experienced a cardiopulmonary arrest for which he was intubated and resuscitated. On day 11, he died due to a recurrent cardiac arrest and endstage cardiomyopathy.

9. Subject 538-010 (Nesiritide, 0.015 μg/kg/min) Subject was an 89-year-old white woman with NYHA Class III CHF, coronary artery disease, mitral regurgitation, and chronic atrial fibrillation. Nesiritide was administered for 65 hours, then discontinued because of clinical improvement. On day 4, dobutamine was initiated in response to worsening oliguria. The subject's general condition worsened over the ensuing days. Sepsis was suspected and broad spectrum antibiotics were initiated. Comfort measures only were initiated, and the subject died from a cardiopulmonary arrest on day 9.

10. Subject 550-002 (Nesiritide, 0.015 μg/kg/min) Subject was a 73-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy and a history of atrial and ventricular arrhythmias. He was treated with nesiritide for 3 days which was then discontinued because of clinical improvement. On day 14, he developed worsening CHF unresponsive to dobutamine and dopamine. He died on day 14 due to CHF.

11. Subject 559-005 (Nesiritide, 0.015 μg/kg/min) Subject was a 58-year-old black man with NYHA Class II CHF due to aortic insufficiency and tricuspid endocarditis. He was treated for 5 days with nesiritide, which was discontinued due to clinical improvement. On day 7, he died after an unsuccessful attempt to resuscitate him during a cardiac arrest. The cause of death was severe cardiomyopathy and tricuspid endocarditis.

12. Subject 382-002 (Nesiritide, 0.03 μg/kg/min) Subject was a 73-year-old white woman with NYHA Class IV CHF, ischemic cardiomyopathy and active lung disease at the time of entry into the study. She received nesiritide followed by dobutamine. During placement of a Swan-Ganz catheter, 6 hours after nesiritide was discontinued, she experienced hypotension and respiratory failure requiring intubation and mechanical ventilation. Given the subject's underlying poor prognosis, her status was made "Do Not Resuscitate" on day 2. On day 3, she died due to endstage heart failure and respiratory failure.

13. Subject 508-004 (Nesiritide, 0.03 μg/kg/min) Subject was a 69-year-old white man with a history of Class IV CHF, severe ischemic cardiomyopathy, and multiple vascular surgeries. Before entering the study, he underwent cardiac catheterization that revealed that his coronary grafts were occluded and that he was not a candidate for angioplasty or CABG. He initially received nesiritide for 1 day. On day 2, he developed a left femoral thrombosis, due to catheterization of that vessel the day before, requiring emergent thrombectomy. Postoperatively, the nesiritide infusion was restarted at half the original infusion dose and his blood pressure remained stable. Postoperatively, the subject never regained his baseline level of consciousness. Throughout day 2, he developed more difficulty breathing, was made "do not resuscitate", and the nesiritide infusion was discontinued. He expired 2.5 hours later. The cause of death was endstage heart failure.

14. Subject 509-002 (Nesiritide, 0.03 μg/kg/min) Subject was a 61-year-old white man with NYHA Class IV CHF due to idiopathic, dilated cardiomyopathy, and a history of Non-sustained VT. He received nesiritide for 5 days. For the first few days of the infusion, he responded very well with excellent diuresis and improvement in his congestive symptoms. On day 5, his condition deteriorated with worsening respiratory symptoms and decreased urine output. Nesiritide was discontinued and replaced with dobutamine and dopamine. Later on day 6, the subject died due to worsening CHF.

15. Subject 524-005 (Nesiritide, 0.03 μg/kg/min) Subject was a 61-year-old white man with NYHA Class IV CHF of unknown etiology and a ventricular aneurysm. On day 1, coumadin therapy was begun due to the presence of a left ventricular mural thrombus. He was treated for 3 days with nesiritide that was discontinued because of clinical improvement. The subject was intended to be discharged to home the following day when, 13 hours after discontinuation of nesiritide (day 5), he died due to ventricular fibrillation.

16. Subject 528-001 (Nesiritide, 0.03 μg/kg/min) Subject was a 71-year-old white man with a history of NYHA Class III CHF, ischemic cardiomyopathy, atrial fibrillation, bronchiolitis obliterans, and diabetes. He received nesiritide for 3 days to which he responded very well with diuresis and improvement in CHF symptoms. On day 5, he was noted to have hyperkalemia (K+ = 7.6) and an elevated serum creatinine (Crt = 3.9 mg/dL). He was diagnosed as having nonoliguric acute renal failure which improved by day 8 (K+ = 4.3, Crt = 1.5) after the administration of dobutamine, dopamine, and IV furosemide. He died on day 22 due to cardiac arrest when his pacemaker failed to capture; resuscitation was not attempted due to the wishes of the family.

17. Subject 572-001 (Nesiritide, 0.03 μg/kg/min) Subject was a 71-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy. He received nesiritide for 1 day with a good hemodynamic response, but was switched to dobutamine therapy on day 2. His subsequent hospital course was complicated by multifocal atrial tachycardia and hypotension, oliguric acute renal failure, intermittent chest pain, and elevated cardiac enzymes indicative of a myocardial infarction, worsening hyponatremia, gastrointestinal bleed and progressively worsening cardiac and renal function. The subject died on day 20 because of endstage heart failure.

18. Subject 585-003 (Nesiritide, 0.03 μg/kg/min) Subject was a 77-year-old white man with NYHA Class IV CHF due to ischemic cardiomyopathy admitted from a nursing home for treatment of decompensated CHF. The subject received nesiritide for 2 days with little improvement. On day 3, he was switched to dobutamine, which he received for 2 days, again with little improvement overall in his clinical condition. On day 5, he was transferred back to the nursing home. During the several subsequent days, the subject developed worsening shortness of breath and a loss of appetite. On day 13, he died due to endstage heart failure.

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13.0 Appendix 3: Narratives for Serious Adverse Events

Study 704.311

1. Subject 369-009 (0.015 μg/kg/min Nesiritide) Subject 369-009 is a 60-year-old black man with NYHA Class IV CHF, second degree AV block, and hypertension. He received the full 24-hour study drug infusion (0.015 μg/kg/min Nesiritide) with one dose reduction in response to an excessive decrease in PCWP. He subsequently was treated with IV dobutamine and discharged on day 11. On day 13, he was readmitted with decompensated CHF and again was treated with IV dobutamine and diuretics. He was then transferred to another hospital for cardiac transplantation evaluation.

2. Subject 369-004 (0.03 μg/kg/min Nesiritide) Subject 369-004 is a 51-year-old black man with NYHA Class III CHF. He received the full 24-hour study drug infusion (0.03 μg/kg/min nesiritide) with one dose reduction in response to an excessive decrease in PCWP, then received therapy with IV milrinone prior to discharge. He presented to the Emergency Department on day 11 with complaints of shortness of breath and fatigue and was readmitted with the diagnosis of decompensated CHF. He was treated with IV inotropes and responded well.

3. Subject 376-008 (0.03 μg/kg/min Nesiritide) Subject 376-008 is a 57-year-old white man with a history of NYHA Class III CHF, idiopathic cardiomyopathy, atrial fibrillation, and ventricular arrhythmias. He received the full 24-hour study drug infusion (0.03 μg/kg/min nesiritide) without incident and was discharged. He was readmitted on day 9 with recurrent decompensated CHF and treated with IV dobutamine and furosemide. He was discharged again on day 12.

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

5. Subject 367-003 (0.06 μg/kg/min Nesiritide) Subject 367-003 is a 56-year-old black man with NYHA Class IV CHF, idiopathic dilated cardiomyopathy, a pacemaker, and hyponatremia. He received the full 24-hour study drug infusion (0.06 μg/kg/min Nesiritide) with one reduction in dose in response to a decreased PCWP. He was discharged home but presented to the Emergency Department on day 7 with complaints of shortness of breath, nausea, and vomiting; he was readmitted with the diagnosis of CHF and dehydration. His symptoms resolved with hydration and withholding of his digoxin.

Study 704.325

1. Subject 502-001 (Placebo) Subject 502-001 is 68-year-old white man with NYHA Class III CHF, chronic atrial fibrillation, hypertension, and peripheral vascular disease who was admitted for treatment of decompensated CHF, with a pre-scheduled femoral-popliteal bypass surgery to follow. His chronic warfarin therapy was discontinued on day 1 in anticipation of the surgery. After the 6-hour placebo infusion, he was treated with dobutamine. On day 2, he underwent femoral-popliteal bypass surgery. On day 3, he sustained a cerebrovascular accident. Cardiac echocardiogram revealed a left ventricular apical thrombosis. He was discharged to home on day 11.

2. Subject 369-018 (Placebo) Subject 369-018 is 73-year-old black man with a history of NYHA Class III CHF, dilated cardiomyopathy, chronic atrial fibrillation, and sustained ventricular tachycardia requiring an automatic implantable cardiac defibrillator (AICD). Placebo was discontinued after 25 minutes, when the subject developed sustained ventricular tachycardia (triggering AICD discharge) and loss of consciousness. Two hours later, he experienced a second episode of sustained VT that again resolved after the AICD discharge. He received 5 days of dobutamine therapy and was discharged to home on day 6 with no sequelae from these events.

3. Subject 352-009 (Nesiritide, 0.015 μg/kg/min) Subject 352-009 is a 49-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy. After 3 hours of nesiritide therapy, nesiritide was discontinued because of worsening CHF. He was subsequently treated with dobutamine and milrinone for 6 days and was discharged to home on day 12. On day 15, he was rehospitalized for decompensated CHF.

4. Subject 369-006 (Nesiritide, 0.015 μg/kg/min) Subject 369-006 is a 73-year-old white woman with NYHA Class III CHF and emphysema. After 6.5 hours, nesiritide was discontinued due to a lack of improvement. She was treated with dobutamine for 5 days, and the subject was discharged on day 12. On day 20, she was readmitted to the hospital for worsening emphysema.

5. Subject 373-002 (Nesiritide, 0.015 μg/kg/min) Subject 373-002 is a 68-year-old black man with NYHA Class III CHF due to idiopathic, dilated cardiomyopathy. He responded well to therapy with nesiritide and dobutamine, and was discharged to home on day 3. The following day, he was readmitted for IV antibiotic therapy in response to a bacteremia (presumably due to the indwelling Swan-Ganz catheter used during the study).

*6. Subject 523-003 (Nesiritide, 0.015 μg/kg/min)*Subject 523-003 is a 75-year-old white man with a history of NYHA Class III CHF, ischemic cardiomyopathy, chronic atrial fibrillation, ventricular ectopy, and diabetes. Nesiritide was discontinued after 6.5 hours due to clinical improvement. He was discharged to home on day 6. On day 7, he was rehospitalized for 2 days for management of hyperglycemia due to his underlying diabetes and poor home medication management. On day 14, he was again hospitalized for syncope and bradycardia due to his underlying atrial fibrillation with a slow junctional response. He also developed intermittent episodes of sustained ventricular tachycardia requiring acute intubation, electrical cardioversion, and amiodarone therapy. His dysrhythmias persisted, and, on day 27, a permanent pacemaker was placed. On day 56, he was discharged to a rehabilitation facility.

7. Subject 324-001 (Nesiritide, 0.03 μg/kg/min) Subject 324-001 is a 47-year-old white man with NYHA Class III CHF, ischemic cardiomyopathy, obesity, and severe sleep apnea hospitalized for worsening sleep apnea and decompensated CHF. He responded well to therapy with nesiritide, dobutamine, and dopamine. After 60 hours of nesiritide therapy, he experienced a cardiopulmonary arrest precipitated by apnea, hypoxia, and third degree heart block. The subject's physicians believed that this event was due to his underlying sleep apnea. Nesiritide was discontinued, and he was successfully resuscitated. However, he remained intubated and ultimately required a tracheostomy. He was discharged for home ventilatory support on day 25. At follow-up 5 months later, the subject was still requiring respiratory support for apnea.

8. Subject 352-007 (Nesiritide, 0.03 μg/kg/min) Subject 352-007 is a 61-year-old white man with a history of NYHA Class IV CHF, ischemic cardiomyopathy, and a previous deep venous thrombosis. After 6 hours of nesiritide therapy, dobutamine was added for inotropic support. On day 3, both infusions were discontinued due to clinical improvement, and the subject was discharged to home. Later that day, he was rehospitalized for anticoagulation therapy for a deep venous thrombosis of the subclavian vein felt to be due to the indwelling Swan-Ganz catheter used during the study. He was discharged to home on day 8.

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

10. Subject 368-003 (Nesiritide, 0.03 μg/kg/min) Subject 368-003 was a 69-year-old white woman with NYHA Class IV CHF due to ischemic cardiomyopathy who was admitted for a pre-scheduled coronary bypass graft (CABG) surgery but required parenteral therapy for CHF before the procedure. She responded well to a 24-hour infusion of nesiritide and subsequently received dobutamine for inotropic support prior to the CABG procedure. Six days after nesiritide was discontinued, the CABG procedure was performed. Postoperatively she required an intra-aortic balloon pump due to her underlying poor ventricular function. Several hours later, she developed an occlusion of the femoral artery due to the intra-aortic balloon pump, requiring urgent surgical revascularization. On day 29, after a postoperative course complicated by respiratory failure, infections, and renal insufficiency, the subject died due to septic shock.

11. Subject 369-009 (Nesiritide, 0.03 μg/kg/min) Subject 369-009 was a 67-year-old Hispanic man with NYHA Class IV CHF due to alcohol-induced cardiomyopathy, chronic renal insufficiency, carotid occlusions, and emphysema. Before entry into the study, he was being treated with dobutamine, which was discontinued before study drug administration. After 6 hours of nesiritide therapy, the infusion was discontinued due to worsening CHF and dobutamine was restarted for 6 days. He was discharged to home on study day 8. On day 11, he was readmitted for treatment of cardiogenic shock, sepsis, and renal failure (serum creatinine = 6.3 mg/dL) due to his underlying endstage CHF. By day 25, his physicians felt that he was dobutamine-dependent; however, he refused home dobutamine therapy and was discharged to home. On day 28, he was readmitted with endstage heart failure. The subject's family refused further treatment and he died on day 30.

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

13. Subject 382-001 (Nesiritide, 0.03 μg/kg/min) Subject 382-001 is a 72-year-old white woman with NYHA Class IV CHF due to rheumatic heart disease. Before entry into the study, she underwent an aortic valve replacement that was complicated by postoperative respiratory failure. At study entry, she was mechanically ventilated. She received nesiritide for five days (the maximum allowed by the protocol) with clinical improvement. On day 13 (7 days after nesiritide was discontinued), she developed significant renal failure requiring dialysis. Due to hypotension, dialysis was not tolerated well and pressors (phenylephrine, norepinephrine) were required to maintain adequate blood pressure. Since the subject had previously responded so well to nesiritide, the investigator's request to Scios to re-administer nesiritide was approved on day 19, under an Emergency Use protocol and a physician-sponsored IND. After approximately 15 hours of nesiritide administration, the patient developed atrial fibrillation and the patient's oliguric renal failure had not improved, so nesiritide was discontinued. By day 25, she was hemodynamically more stable and had weaned from the pressors. By day 33, a tracheostomy was performed and the subject was receiving long-term dialysis therapy. She was discharged to home with a tracheostomy on day 40.

14. Subject 523-004 (Nesiritide, 0.03 μg/kg/min) Subject 523-004 is a 71-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy. Nesiritide was discontinued after approximately 6 hours and dobutamine was administered for 2 days. The following day he was started on antibiotics for bacteremia, and the Swan-Ganz catheter was removed. He was discharged on day 14 with no sequelae.

15. Subject 532-001 (Nesiritide, 0.03 μg/kg/min) Subject 532-001 is a 78-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy, and a history of atrial fibrillation, hypertension, diabetes, chronic renal failure of a solitary kidney (status post nephrectomy due to renal cell carcinoma). He was treated with nesiritide for two days with clinical improvement and was discharged to home on day 7. On day 10, a home health nurse noticed the subject having mental status changes for which he was rehospitalized. A cerebral meningioma was diagnosed by head CT scan. The subject refused treatment for this problem, his mental status changes resolved spontaneously, and he was discharged on day 15.

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1. Subject 519-006 (Standard care: dopamine) Subject 519-006 is a 64-year-old white man with NYHA Class III CHF, idiopathic, dilated cardiomyopathy, and acutely decompensated CHF due to subacute myocarditis. He had significant respiratory failure and bilateral pleural effusions at the time of entry into the study. Dopamine (3 μg/kg/min) was administered as the standard care vasoactive agent. A few hours after the dopamine infusion was started, he experienced significant respiratory distress and acute pulmonary edema that required intubation, mechanical ventilation, and additional IV vasoactive medications.

2. Subject 535-003 (Standard care: dobutamine) Subject 535-003 is a 23-year-old black man with NYHA Class IV CHF due to idiopathic, dilated cardiomyopathy, and a history of electromechanical dissociation and arrhythmias who was admitted for treatment of decompensated CHF due to an arrhythmia exacerbation. One hour after initiation of dobutamine, he experienced seizure activity and electromechanical dissociation. He was successfully resuscitated and subsequently treated with dobutamine, milrinone, and dopamine. On day 3, he developed hypoxia and acute respiratory failure requiring bronchoscopy and antibiotics. This resolved with treatment and he was discharged to home on day 14.

3. Subject 536-009 (Standard care: dobutamine) Subject 536-009 is a 71-year-old white man with NYHA Class IV CHF due to ischemic cardiomyopathy, atrial fibrillation, and pacemaker-dependent bradycardia. He received dobutamine for 6 days. On day 1, he developed severe hemorrhage after a transurethral resection of the prostate that prolonged hospitalization due to the need for colloids, blood and surgical repair. Ultimately, he was discharged to an extended care facility.

4. Subject 538-008 (Standard care: dobutamine) Subject 538-008 was an 82-year-old white woman with a history of NYHA Class II CHF, idiopathic, dilated cardiomyopathy, chronic atrial fibrillation, supraventricular tachycardia, and Non-sustained VT who was admitted with shortness of breath and abdominal pain. She was randomized to nesiritide; however, dobutamine was administered instead because of a nursing error. On day 6, during an invasive gastrointestinal procedure, she developed sustained VT and had a respiratory arrest, requiring defibrillation and intubation. On day 9, she was extubated and discharged to a skilled nursing facility on day 26. On day 38 (after the 21-day study reporting period), she died due to progressive heart failure.

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

6. Subject 533-005 (Nesiritide, 0.03 μg/kg/min) Subject 533-005 is a 78-year-old white man with NYHA Class IV CHF and a history of Non-sustained VT. He received nesiritide for 4 days and responded favorably. On day 4, the subject developed urosepsis (believed to be caused by an indwelling urinary catheter) which was treated successfully with antibiotics. Also, on day 4, during and after placement of a left subclavian central venous line, he experienced multiple episodes of sustained VT which were successfully treated with electrical cardioversion. These events were considered caused by placement of the central venous line and to the subject's underlying ventricular ectopy due to endstage heart failure.

7. Subject 561-009 (Nesiritide, 0.03 μg/kg/min) Subject 561-009 is a 63-year-old white woman with NYHA Class II CHF due to mitral valve dysfunction requiring mitral valve replacement and severe COPD. After 25 hours of nesiritide infusion, she experienced hemoptysis accompanied by hypotension due to blood loss. Nesiritide was discontinued, neosynephrine was added for pressor support, and the subject received a blood transfusion. A bronchoscopy was performed which located the source of the bleeding. Relevant concomitant medication included coumadin.

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14.0 Appendix 4: Narratives of patient discontinuations

Study 704.311

1. Subject 017-010 (Placebo) Subject 017-010 is a 55-year-old black man with a history of NYHA Class IV CHF, adriamycin-induced dilated cardiomyopathy, a previous myocardial infarction. He terminated study drug (placebo) infusion after 22 hours due to worsening CHF (i.e., worsening dyspnea, increase in PCWP to 32 mm Hg from 28 mm Hg pretreatment). He was subsequently treated with IV dobutamine and dopamine. No other adverse events were reported.

2. Subject 369-006 (Placebo) Subject 369-006 is a 66-year-old Hispanic man with a history of NYHA Class IV CHF, peripheral vascular disease, and hypertension. He terminated study drug (placebo) administration after approximately 9 hours of infusion due to worsening CHF (i.e., worsening dyspnea and increase in PCWP to 30 mm Hg from 24 mm Hg pretreatment). He was subsequently treated with IV dobutamine and furosemide. No other adverse events were subsequently reported.

3. Subject 370-005 (Placebo) Subject 370-005 is a 49-year-old Hispanic man with a history of NYHA Class IV CHF, coronary artery disease, diabetes, and ventricular arrhythmias (premature ventricular contractions and bigeminy) at study enrollment. He terminated study drug (placebo) administration after 12 hours, 20 minutes of infusion due to worsening CHF (with an increase in PCWP to 25 mm Hg from 23 mm Hg pretreatment). He was subsequently treated with IV dobutamine and furosemide. His serum creatinine increased from 1.4 mg/dL at baseline to a peak of 4.1 mg/dL on day 10. He also experienced an episode of severe symptomatic hypotension requiring cardiopulmonary resuscitation on day 8. He was subsequently followed through day 27 with no further complications.

4. Subject 370-006 (Placebo) Subject 370-006 was a 50-year-old man from India with a history of NYHA Class IV CHF, coronary artery disease, a previous ventricular aneurysmectomy, and marked cachexia at admission for worsening CHF. He was enrolled in the study but terminated study drug (placebo) infusion prematurely after 3 hours, 25 minutes of infusion due to worsening CHF (with an increase in PCWP to 27 mm Hg from 24 mm Hg pretreatment). The subject was then treated with IV dobutamine and furosemide. An episode of supraventricular tachycardia accompanied by chest pain was also reported on day 6. The subject was discharged to home, but was readmitted to another hospital on approximately day 18 with dyspnea and end-stage CHF; he was reported to have died during this hospitalization on approximately day 46, although information on the precise date and cause of death was not available.

5. Subject 373-006 (Placebo) Subject 373-006 is a 58-year-old black woman with a history of NYHA Class III CHF, coronary artery disease, supraventricular arrhythmias (treated with electrophysiological ablation), and hypertension. She terminated study drug (placebo) administration after 4 hours, 30 minutes of infusion due to worsening CHF (with an increase in PCWP to 34 mm Hg from 32 mm Hg pretreatment). She was subsequently treated with IV dobutamine and milrinone. No other significant adverse events were reported.

6. Subject 380-004 (0.03 μg/kg/min Nesiritide) Subject 380-004 is a 60-year-old Asian man with a history of NYHA Class III CHF, an ejection fraction of 10%, and hypertension. He terminated study drug (0.03 μg/kg/min Nesiritide) administration after 2 hours, 12 minutes of infusion due to worsening CHF (with an increase in PCWP to 28 mm Hg from 25 mm Hg pretreatment). He was subsequently treated with IV diuretics and the resumption of his oral regimen of ACE inhibitors. No other adverse events were reported.

7. Subject 389-006 (0.03 μg/kg/min Nesiritide) Subject 389-006 is a 45-year-old Hispanic man with a history of NYHA Class III CHF and hypertension. At baseline, his PCWP was 12 mm Hg, his PAD was 12 mm Hg, and his blood pressure was 120/80 mm Hg. After 90 minutes of study drug (0.03 μg/kg/min Nesiritide) infusion, his PCWP had decreased to 13 mm Hg and his PAD had decreased to 5 mm Hg. The dose of study drug was reduced. At this time, his blood pressure was stable at 120/70 mm Hg with a heart rate of 58 beats/min. After a total of 120 minutes of infusion, the subject developed symptomatic hypotension (systolic blood pressure of 80 mm Hg) accompanied by bradycardia (heart rate of 39 beats/min). Study drug was discontinued. Within 30 minutes, his blood pressure returned to 99/66 mm Hg with a heart rate of 58 beats/min without pharmacological intervention. There were no long-term sequelae of this event.

8. Subject 373-007 (0.03 μg/kg/min Nesiritide) Subject 373-007 is a 53-year-old Hispanic woman with a history of NYHA Class II CHF. She was enrolled in the study and had a baseline PCWP of 24 mm Hg and blood pressure of 120/76 mm Hg. After 65 minutes of study drug infusion (0.03 μg/kg/min Nesiritide), her PCWP had decreased to 8 mm Hg (with a blood pressure of 113/71 mm Hg) and the study drug infusion rate was decreased. After 8 hours, 55 minutes of infusion, her PCWP was noted to be 6 mm Hg (with a blood pressure of 103/62 mm Hg); study drug was discontinued, as required by the protocol. No other adverse events were reported during the 14-day study follow-up period.

9. Subject 017-008 (0.06 µg/kg/min Nesiritide) Subject 017-008 is a 61-year-old white man with a history of NYHA Class IV CHF and coronary artery disease. At baseline, his blood pressure was 103/58 mm Hg and his PCWP was 30 mm Hg. After 68 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), he developed symptomatic hypotension (dizziness and a systolic blood pressure as low as 62 mm Hg). Study drug infusion was reduced and then discontinued minutes later. He was placed in Trendelenberg position, and IV dopamine was initiated. His blood pressure had returned to 104/89 by the next recorded measurement 20 minutes later. On day 8, the subject developed recurrent asymptomatic hypotension that was attributed to oral vasodilator therapy. The investigator noted that this subject appeared in general to have unexpectedly large changes in blood pressure to small changes in medication doses.

10. Subject 369-005 (0.06 g/kg/min Nesiritide) Subject 369-005 is a 44-year-old black man with a history of NYHA Class III CHF, hypertension, and Non-sustained ventricular tachycardia. At baseline, his PCWP was 18 mm Hg and his blood pressure was 150/104 mm Hg. After 30 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), his PCWP had dropped to 10 mm Hg (with a blood pressure of 120/100 mm Hg), and study drug infusion was reduced. After 1 hour, 45 minutes of infusion, his PCWP was noted to be 6 mm Hg (with a blood pressure of 98/70), and study drug was discontinued per protocol guidelines. Thirty-five minutes later, he developed symptomatic hypotension (systolic blood pressure of 70 mm Hg, heart rate 71 beats/min). He was treated with IV fluids and atropine. Within 20 minutes, his systolic blood pressure had returned to 100 mm Hg. There were no long-term sequelae of this event.

11. Subject 369-014 (0.06 µg/kg/min Nesiritide) Subject 369-014 is an 84-year-old black woman with NYHA Class IV CHF, chronic atrial fibrillation, and a pacemaker. At baseline, her blood pressure was 138/78 mm Hg and her PCWP was 22 mm Hg. After 65 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), she developed symptomatic hypotension (systolic blood pressure of 82 mm Hg). Study drug was discontinued, but her blood pressure continued to drop to a low of 58 mm Hg. She was treated with IV dopamine, and her blood pressure returned to baseline levels within minutes. There were no long-term sequelae of this event.

12. Subject 373-003 (0.06 µg/kg/min Nesiritide) Subject 373-003 is a 40-year-old black man with NYHA Class II CHF and hypertension. At baseline, his PCWP was 26 mm Hg, MRAP was 10 mm Hg, and blood pressure was 166/105 mm Hg. After 3 hours, 45 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), his PCWP was 6 mm Hg, MRAP was 0 mm Hg, and his blood pressure was 127/68 mm Hg; an episode of nausea and vomiting was reported. Study drug infusion was reduced per protocol dosing guidelines. After 6 hours, 35 minutes of infusion, his PCWP remained low at 5 mm Hg with a MRAP of 1 mm Hg (and blood pressure of 114/76 mm Hg). Study drug infusion was terminated. No subsequent adverse events occurred.

13. Subject 376-021 (0.06 µg/kg/min Nesiritide) Subject 376-021 is a 48-year-old white man with NYHA Class III CHF and coronary artery disease. At baseline, his PCWP was 35 mm Hg, MRAP was 10 mm Hg, and blood pressure was 112/70 mm Hg. After 2 hours, 5 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), his PCWP was 10 mm Hg and his blood pressure was 81/46 mm Hg. Study drug infusion rate was reduced. After 5 hours of infusion, his PCWP was 15 mm Hg, but his blood pressure was 67/38 mm Hg. Study drug was discontinued. No other adverse events were reported.

14. Subject 388-001 (0.06 µg/kg/min Nesiritide) Subject 388-001 is a 52-year-old white man with NYHA Class III CHF, coronary artery disease, and hypertension. At baseline, his PCWP was 34 mm Hg, MRAP was 11 mm Hg, and blood pressure was 103/74 mm Hg. After 2 hours, 19 minutes of study drug infusion (0.06 µg/kg/min Nesiritide), his PCWP was 4 mm Hg with an MRAP of 0 mm Hg (and a blood pressure of 106/62 mm Hg). Study drug infusion rate was reduced. After 4 hours, 4 minutes of infusion, his PCWP was noted to be 2 mm Hg (with a blood pressure of 114/63). The subject also complained of abdominal cramping and nausea. Study drug infusion was terminated. No other adverse events were reported.

Study 704.325

Five subjects terminated study drug prematurely, i.e., prior to completing 5.5 hours of infusion. Narrative summaries for each of these subjects are included below. Note that some of these subjects were also described in the Appendix 3, SAEs.

1. Subject 369-018 (Placebo) As Appendix 3, subject 369-018 is a 73-year-old black man with a history of NYHA Class III CHF, dilated cardiomyopathy, chronic atrial fibrillation, and sustained ventricular tachycardia requiring an automatic implantable cardiac defibrillator (AICD). The placebo infusion was discontinued after 25 minutes, when the subject developed sustained ventricular tachycardia (VT) and loss of consciousness that terminated after an AICD discharge. He received 5 days of dobutamine therapy and was discharged to home on day 6.

2. Subject 352-009 (Nesiritide, 0.015 µg/kg/min) As described in Appendix 3, subject 352-009 is a 49-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy. After 3 hours of nesiritide therapy, nesiritide was discontinued because of worsening CHF. He was subsequently treated with dobutamine and milrinone for 6 days and was discharged to home on day 12. On day 15, he was rehospitalized for decompensated CHF.

3. Subject 356-002 (Nesiritide, 0.03 µg/kg/min) Subject 356-002 is a 54-year-old black woman with NYHA Class IV CHF and idiopathic, dilated cardiomyopathy who was hospitalized for a cardiac transplant evaluation. Before entry into the study, she was being treated with milrinone and nitroprusside, which were discontinued. Nesiritide was administered for 4.5 hours, then discontinued due to symptomatic hypotension and nausea that was treated with IV fluids. Fourteen hours later, milrinone was started and was continued beyond day 6. She remained hospitalized through day 21 awaiting cardiac transplant.

4. Subject 357-002 (Nesiritide, 0.03 µg/kg/min) Subject 357-002 was a 54-year-old white man with NYHA Class III CHF due to ischemic cardiomyopathy. Nesiritide was discontinued after 4.5 hours because his PCWP had decreased to 6 mm Hg. The subject was symptomatically improved, so no additional therapy for CHF was instituted. He was discharged on day 2. On day 15, he presented to the emergency room with a myocardial infarction and died.

5. Subject 498-003 (Nesiritide, 0.03 µg/kg/min) Subject 498-003 is a 69-year-old black woman with NYHA Class III CHF and chronic renal insufficiency. Before entry into the study, she was being treated for oliguria and CHF with dobutamine, which was discontinued before study drug administration. After 4 hours, the nesiritide infusion was discontinued due to worsening oliguria. Dobutamine was restarted, and dopamine was added 7 hours later. Three days later nitroprusside was added. All parenteral vasoactive therapy was discontinued on day 7, and she was discharged on day 14.

Study 704.326

Nine patients discontinued therapy prior to 6 hours in trial 326: two in the standard care, two in the 0.015µg/kg/min group, and five in the 0.03 µg/kg/min group. Narrative prepared by the sponsor for these discontinuations are below.

1. Subject 535-001 (Standard Care: dopamine) Subject 535-001 is a 45-year-old white woman with NYHA Class IV CHF. Dopamine was discontinued after 30 minutes because of sinus tachycardia.

2. Subject 550-005 (Standard Care: milrinone) Subject 550-005 is a 72-year-old white woman with NYHA Class III CHF. Milrinone was terminated after 3 hours because of Non-sustained ventricular tachycardia.

3. Subject 352-001 (nesiritide, 0.015 µg/kg/min) Subject 325-001 is a 64-year-old black man with NYHA Class IV CHF. Nesiritide was discontinued after 2 hours, 15 minutes of infusion because of hypotension (reduction in SBP from 100 mm Hg at baseline to 84 mm Hg). Dopamine was initiated.

4. Subject 519-008 (nesiritide, 0.015 µg/kg/min) Subject 519-008 is a 71-year-old white man with NYHA Class III CHF. Nesiritide infusion was interrupted after 3 hours, 15 minutes because of asymptomatic hypotension (decrease in SBP from 99 mm Hg at baseline to 85 mm Hg). Study drug infusion was restarted at half of the original dose but at 5 hours, 45 minutes, infusion was terminated because of recurrent asymptomatic hypotension.

5. Subject 504-002 (nesiritide, 0.03 µg/kg/min) Subject 504-002 is a 68-year-old white man with NYHA Class IV CHF. Nesiritide infusion was interrupted after 45 minutes because of asymptomatic hypotension (decrease in SBP from 102 mm Hg at baseline to 70 mm Hg). Study drug infusion was restarted at half of the original dose but at 4 hours, 30 minutes, infusion was terminated because of recurrent asymptomatic hypotension.

6. Subject 519-002 (nesiritide, 0.03 µg/kg/min) Subject 519-002 is a 77-year-old black woman with NYHA Class III CHF. Nesiritide infusion was interrupted after 41 minutes because of asymptomatic hypotension (decrease in SBP from 170 mm Hg at baseline to 73 mm Hg). Study drug infusion was restarted at half of the original dose but at 4 hours, 30 minutes, infusion was terminated because of recurrent asymptomatic hypotension. Approximately 30 minutes later, the subject was noted to have sinus bradycardia (heart rate = 48 beats/min) which resolved spontaneously. On day 2, it was discovered that this subject had had elevated cardiac enzymes (myoglobin, with a normal CPK) at enrollment and was diagnosed by the investigator as having had a non-Q wave myocardial infarction (before study drug infusion).

7. Subject 521-006 (nesiritide, 0.03 µg/kg/min) Subject 521-006 is a 92-year-old white woman with NYHA Class II CHF. Nesiritide infusion was terminated after 3 hours, 30 minutes because of symptomatic hypotension (decrease in SBP from 138 mm Hg at baseline to 92 mm Hg accompanied by pallor and diaphoresis).

8. Subject 562-001 (nesiritide, 0.03 μg/kg/min) Subject 562-001 is a 72-year-old black man with a history of NYHA Class IV CHF due to ischemic cardiomyopathy, first degree heart block, and left bundle branch block. After 3 hours and 45 minutes of the nesiritide infusion, the subject developed symptomatic hypotension (BP = 80/39 mm Hg) accompanied soon thereafter by junctional bradycardia (heart rate of 36 beats/min). nesiritide was discontinued, and fluids and atropine were administered with improvement of the heart rate to a sinus rate of 66 beats per minute. Blood pressure increased to 114/43 mm Hg within approximately 30 minutes. The investigator felt that the event was due to a vagally mediated bradycardia secondary to the hypotension caused by the nesiritide infusion. Nesiritide was not restarted and dobutamine was initiated instead. After the event, the subject was feeling well and there were no sequelae.

9. Subject 571-003 (nesiritide, 0.03 μg/kg/min) Subject 571-003 is a 76-year-old white woman with NYHA Class III CHF. nesiritide infusion was interrupted after 25 minutes because of asymptomatic hypotension (decrease in SBP from 93 mm Hg at baseline to 77 mm Hg). Study drug infusion was restarted at a lower dose but at 3 hours, 50 minutes, infusion was terminated because of recurrent asymptomatic hypotension.

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15.0 Appendix 5 Analysis Strategies in Study 704.325

The primary endpoint in study 704.235 was of 6-hour PCWP analyzed using a "worst outcome" nonparametric analysis. This strategy was applied to the endpoints PCWP, MRAP, SVR, and CI, through the nominal 6-hour assessment. Two additional analyses were employed, in part, to evaluate the robustness of the "worst outcome" hemodynamic results: (1) a "carry forward" parametric analysis, and (2) a "data as available" parametric analysis. A slightly different "data as available" analysis was applied to the 24-hour data. The four analysis strategies are outlined below.

Worst Outcome Strategy

The endpoints PCWP, MRAP, SVR, and CI were analyzed with a "worst outcome" analysis strategy through the nominal 6-hour assessment. Gould discusses this general approach to the analysis of clinical trials with non-completers.

The 6-hour analysis value was determined as follows: For subjects who were not classified as worst outcome, the set of all hemodynamic observations with non-missing PCWP Values, recorded between 5 1/2 (inclusive) and 7 hours (exclusive) after start of study drug, before cardiovascular intervention and before unblinding, was considered. Assuming that the set was not empty, the observation closest to 6 hours was selected for analysis. If the set was empty, then the set of hemodynamic observations with non-missing PCWP Values, recorded between 2 hours (inclusive) and 5 1/2 hours (exclusive) after start of study drug, before cardiovascular intervention and before unblinding, was considered. Assuming that this set was not empty, the latest observation, i.e., closest to 6 hours, was selected for use in analysis. Subjects classified as worst outcome (who by definition have no blinded, pre-intervention hemodynamic observation after 5 1/2 hours [except for any subjects classified as worst outcome due to death]) were assigned an arbitrarily poor analysis value for all hemodynamic endpoints at all nominal assessments through 6 hours. For example, an appropriate worst outcome value for percent change in PCWP would be +999%, and for percent change in CI, –999%. Because analysis is by rank-based nonparametric methods, the "worst outcome" value is arbitrary except that (1) it must be the same for all worst outcome subjects, and (2) it must be worse than any value actually observed across all subjects in the study. The 1 1/2-, 3-, and 4 1/2-hour analysis values were determined by similar algorithm. Subjects were assigned a worst outcome value if the precipitating event (intervention, unblinding, or death) occurred on or before 1 1/2, 3, and 4 1/2 hours after start of study drug, respectively. Otherwise, a blinded, pre-intervention hemodynamic observations was selected from within the respective windows of (30 min, 2 h 15 min), (1 h, 3 h 45 min), and (2 h, 5 h 15 min); windows were inclusive. The three treatment groups were tested for non-specific differences with a Kruskal-Wallis test, and for dose-related differences with the Jonckheere-Terpstra test. Each nesiritidetreatment group was compared to the placebo treatment group with a 2 sample Wilcoxon test. When the endpoint was represented as change or percent change from baseline, the hypothesis of a non-zero change from baseline was tested with a 1-sample Wilcoxon test. The protocol stated that exact, as opposed to asymptotic, inferential methods would be employed. Exact calculations were found to be computationally infeasible for SAS, the analysis software used by the sponsor, and so asymptotic results are reported.

Carry Forward Strategy

All hemodynamic endpoints were analyzed by a "carry forward" analysis strategy, as described below, through the nominal 6-hour assessment. To be eligible for "carry forward" analysis, observations were required to have been recorded prior to both cardiovascular intervention and treatment unblinding. The observation recorded closest to the nominal assessment time being summarized was selected for analysis. If a blinded, pre-intervention observation did not exist in the temporal vicinity of the nominal assessment time, then the last eligible observation, possibly the baseline observation, was extrapolated (i.e., "carried forward") to the nominal assessment time for analysis. In contrast to the "worst outcome" analysis, all "carry forward" analysis values are *bona fide* hemodynamic measurements. To be considered for "carry forward" analysis at the nominal 1.5, 3-, 4.5-, and 6-hour nominal assessments, observations had to have been observed on or before 2 hours 15 minutes, 3 hours 45 minutes, 5 hours 15 minutes, and 7 hours, respectively. The effect of treatment group was analyzed within the framework of one-way analysis of variance (ANOVA). The three treatment groups were tested for non-specific differences with the omnibus F test, and for dose-related differences with a linear contrast using equally spaced scores. Each nesiritide treatment group was compared to the placebo treatment group with a pairwise contrast. When an endpoint was represented as the change or percent change from baseline, a one-sample *t* test was run within each treatment group to test for a non-zero mean change from baseline. This test used the within-group estimate of variance, not the pooled estimate from the ANOVA model.

Data as Available Strategy

Through 6 Hours the endpoints PCWP, MRAP, SVR, CI, and SBP were also analyzed with a "data as available" analysis strategy, as described below. The resulting summary tables are presented later in this appendix. To be eligible for "data as available" analysis, observations were required to have been recorded prior to both cardiovascular intervention and treatment unblinding. In particular, if a blinded, pre-intervention hemodynamic observation did not exist within a predefined time window around the nominal assessment time being summarized, then that value was considered missing and the subject was effectively excluded from the analysis of that time point. In contrast to the "worst outcome" and "carry forward" analyses, all "data as available" analysis values were required to have been made while the subject was still receiving study drug or within 10 minutes after termination study drug. All "data as available" analysis values are *bona fide* hemodynamic measurements. The effect of treatment group was analyzed within the framework of one-way analysis of variance (ANOVA), as previously described for the "carry forward" analyses.

Data as Available Strategy, through 24 Hours

The selected endpoints of PCWP, MRAP, and SVR were analyzed by a "data as available" strategy, as described below, through the nominal 24-hour assessment. The analysis was restricted to the subset of nesiritide subjects who had a 24-hour hemodynamic observation recorded between 21 and 27 hours (inclusive) after start of study drug. In contrast to the summarizations through the initial 6-hour study period, observations were not required to have been recorded prior to cardiovascular intervention or treatment unblinding. Summaries were prepared of baseline values, change from baseline at 6 hours, change from baseline at 24 hours, and change from 6 hours to 24 hours. Within the restrictions of the above-specified subset, summary tables were prepared on two subject populations: (1) all nesiritide subjects, without regard to dose modification or drug termination, and (2) subjects who received nesiritide, though possibly modifying dose, through (or terminated no earlier than 10 minutes before) the 24-hour hemodynamic observation and received no additional parenteral medication through the 24-hour observation. The effect of treatment group was analyzed within the framework of one-way analysis of variance (ANOVA), as previously described for the "carry forward" analyses.

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16.0 Appendix 6: FDA Statistical Comments

16.0.1 Trial 704.311 Statistics Review

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

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

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

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

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

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

Interim analysis, requiring unblinding of the data, was planned before starting the trial. In the protocol, the sponsor states that the interim was to be purely for administrative purposes, but also states that the efficacy would be declared if the p Value from an interim analysis was <0.0027. The planned final analysis would be tested at alpha = 0.05. The difference in mean PCWP change was to be explored by ANOVA (analysis of variance). The dose response was to be explored by testing of a linear contrast. The effect of each dose at hour 24 was to be compared with placebo using Donnett's test. The protocol specified that the evaluable patient population would be used for the primary analysis even though the intent to treat (ITT) analysis would also be done.

The efficacy results based on the sponsor's analyses are shown in the table below.

Table 16.1 Mean change in PCWP (mm Hg) at hours 3 and 24 in the 'evaluable' and ITT populations of 704.311.

Analysis	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	p Value (Global Diff)	p Value (Linear Trend)
Evaluable at 3 hours	-1.8 (n=29)	-10.0 (n=16)	-6.8 (n=17)	-9.9 (n=18)	0.001	0.004
Evaluable at 24 hours	-1.8 (n=25)	-8.8 (n=17)	-3.8 (n=19)	-8.4 (n=19)	0.001	0.025
ITT at 3 hours	-1.8 (n=29)	-8.9 (n=21)	-6.0 (n=23)	-10.8 (n=24)	<0.001	<0.001
ITT at 24 hours	-1.8 (n=25)	-8.3 (n=21)	-3.7 (n=21)	-8.4 (n=19)	0.001	0.017

The sponsor did two interim analyses, as per above, with the first 55 and 92 patients. The sponsor's results, based on the evaluable and ITT populations, show a significant reduction in mean change in PCWP at hours 3 and 24 after a conservative adjustment of the p Value, for the two primary endpoints at both interim analyses. The first adjustment of the significance level for the multiple endpoints was based on Bonferroni's procedure. The resulting p Value also incorporated the adjustment for the interim analyses (described above). The resulting significance level is 0.05-(2 times 0.0027) = 0.0446. With this adjustment, a significant increasing trend of reduction in mean PCWP was found at both hour 3 and 24 for the ITT population and at hour 3 for the evaluable patient population. The reductions in mean PCWP in the low and high-dose nesiritide groups were statistically significant as compared to placebo. The reduction is numerically larger for the intermediate (0.030) nesiritide dose as compared to placebo, but was not statistically significant.

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

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

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

a. Kruskall-Wallis using worst rank.

Several subgroup analyses on PCWP at 3 hours were performed with respect to patient's gender, age, race, and baseline ejection fraction. The analyses used all 103 evaluable patients and LVCF imputation for the missing observations. The results are shown below.

Table 16.4 Mean change in PCWP from baseline to 3 hours grouped by demographics in study 704.311.

Analysis	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	p Value (ANOVA)
Gender					
Male	-2.3 (n=21)	-8.0 (n=18)	-6.8 (n=19)	-11.4 (n=23)	0.0006
Female	-2.6 (n=8)	-6.4 (n=4)	-7.3 (n=5)	-2.1 (n=3)	0.3349
Age					
≥65	-3.2 (n=2)	-5.5 (n=4)	-3.5 (n=6)	-5.5 (n=9)	0.8865
<65	-2.2 (n=27)	-8.6 (n=18)	-7.9 (n=20)	-12.7 (n=17)	<0.001
Race					
White	-4.4 (n=10)	-7.0 (n=15)	-7.9 (n=20)	-12.5 (n=17)	0.0222
Non-White	-0.6 (n=19)	-8.3 (n=7)	-6.6 (n=12)	-7.5 (n=9)	0.0079
Baseline LVEF					
>20%	-1.4 (n=9)	-10.1 (n=12)	-6.5 (n=9)	-6.2 (n=15)	0.0587
≤20%	-2.9 (n=20)	-8.7 (n=10)	-7.8 (n=15)	-10.3 (n=11)	0.0108

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16.0.2 Trial 704.325 Statistics Review

Based on the analysis as presented below, the FDA statistical reviewer made the following conclusions:

1. Statistically significance treatment difference among the treatment groups exists with regard to changes in PCWP starting at 1.5 hours and persisting through 6 hours.
2. Both dose regimens effectively lower PCWP as compared to the control.
3. The numerical trend of treatment effect appears consistent across all investigators.
4. PCWP was lowered significantly in both women and men at hour 6.

Analysis of Primary Endpoint

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

Analyses for change and percentage change from baseline in PCWP were performed for ITT population using worst-score imputation and LVCF imputation. The results, based on worst-score analysis, showed a statistically significant treatment difference in change from baseline in PCWP among the three treatment groups starting at Hour 1.5 (Table 16.5). The number of subjects in all three treatment groups was 42 (total of 126 subjects).

Table 16.5 Significance of changes in PCWP from baseline for ITT population in 704.325.

Hour	Treatment	Nominal p Value for Absolute Change in PCWP[a]	p Value for % Change in PCWP
1.5	Placebo 0.015 0.030	0.0001	0.0001
3	Placebo 0.015 0.030	0.0001	0.0001
4.5	Placebo 0.015 0.030	0.0001	0.0001
6	Placebo 0.015 0.030	0.0001	0.0001

a Kruskall-Wallis test (worst case analysis)

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

Table 16.6 Comparison of effect of two nesiritide doses with placebo for change in PCWP from baseline to 6 hours, from ITT population.

Hour	Treatment	Nominal p Value for Absolute Change in PCWP[a]	p Value for Percent Change in PCWP[a]
1.5	0.015 vs. Placebo 0.030 vs. Placebo	0.0021 0.0001	0.0020 0.0001
3	0.015 vs. Placebo 0.030 vs. Placebo	0.0004 0.0001	0.0002 0.0001
4.5	0.015 vs. Placebo 0.030 vs. Placebo	0.0001 0.0001	0.0001 0.0001
6	0.015 vs. Placebo 0.030 vs. Placebo	0.0019 0.0001	0.0009 0.0001

a. Wilcoxon 2-sample test

Similar results (Table 16.7) were seen based on LVCF method. In this case, the estimated change or percentage change from baseline was obtained for each treatment group. Since there was a significant baseline effect in most cases, the analyses were done using an Analysis of Covariance (ANCOVA) model with treatment, investigator, and baseline PCWP as factors and covariate respectively. In the analyses, centers missing at least one treatment group were combined. No baseline-by-treatment or investigator-by-treatment were found except for the percentage change at Hour 3 for which a significant baseline-by-treatment interaction was seen. The baseline PCWP readings (means) for the placebo, nesiritide 0.015, and nesiritide 0.030 were 28.45, 28.09, and 27.55 mm Hg, respectively.

Table 16.7 Effect of study drug on PCWP from 'Last Value Carried Forward' analysis for hour 6.

Hour	Treatment	PCWP, Change from Baseline[a]	p Value for Tx Difference (Change in PCWP)	% Change from Baseline in PCWP[a]	p Value for Tx Difference (% Change in PCWP)
1.5	Placebo 0.015 0.030	-0.08 -3.13 -6.92	0.0001	-0.44 -12.13 -26.08	0.0001
3	Placebo 0.015 0.030	+0.29 -5.35 -9.09	0.0001	NA[b]	NA[b]
4.5	Placebo 0.015 0.030	+1.17 -6.18 -10.50	0.0001	+4.76 -21.43 -38.44	0.0001
6	Placebo 0.015 0.030	+1.96 -5.92 -9.96	0.0001	+7.87 -20.86 -36.72	0.0001

a. Least square mean estimate
b. Presence of treatment-by-baseline interaction (LVCF analysis).

Table 16.8 gives the results of pairwise comparisons for change in PCWP between a dosed group and placebo using LVCF imputation, indicating a statistically significant treatment difference in change from baseline in PCWP between each pair of groups under the comparison.

Table 16.8 Pairwise comparisons for change in PCWP between nesiritide dose groups and placebo at hour 6.

Hour	Treatment Comparison	p Value for Tx Differences (Change in PCWP[a])
1.5	0.015 vs. Placebo 0.030 vs. Placebo	0.0065 0.0001
3	0.015 vs. Placebo 0.030 vs. Placebo	0.0001 0.0001
4.5	0.015 vs. Placebo 0.030 vs. Placebo	0.0001 0.0001
6	0.015 vs. Placebo 0.030 vs. Placebo	0.0001 0.0001

a. ANCOVA with treatment, center and baseline PCWP as factors and covariate respectively

Noting that there was a slight imbalance among the treatment groups with respect to gender, a worst case analysis was performed within each gender group at Hour 6. Significant treatment differences were found in both gender groups.

Table 16.9 Analysis of change in PCWP between a dosed group and placebo using LVCF imputation, grouped according to gender.

Sex	Treatment Group, # of Subjects	p Value for Tx Difference (Change in PCWP[a])	p Value for Tx Difference (% Change in PCWP[a])
Female	Placebo / 9, 0.015 / 8, 0.30 / 17	0.0029	0.0033
Male	Placebo /33, 0.015 / 35, 0.030 / 25	0.0003	0.0001

a. Kruskal-Wallis test (worst case analysis)

The numerical trend of treatment effect, measured as mean change from baseline in PCWP, appears consistent across all investigators (data not shown).

Global assessment of clinical status

The results of global assessment of clinical status by patients and investigators at Hour 6 are summarized in the following table. A statistically significant difference in global assessment of clinical status at Hour 6 by investigators or by patients was found. The p Values for the overall difference are 0.0001 in the two assessments. Pairwise comparison between a Natrecor treated group and placebo showed a higher percentage of improvement in clinical status for Natrecor as compared to placebo.

Table 16.10 Global assessment of clinical status / Hour 6 in trial 704.325.

Treatment	Assessment / n (%)					Total n	p Value
	Much worse	Worse	No change	Better	Much better		
Investigator's Assessment							
Placebo	3 (7.1%)	9 (21.4%)	28 (66.8%)	2 (4.7%)	0 (0.0%)	42	0.0001[a]
Nesiritide 0.015	4 (10%)	4 (10%)	10 (25%)	17 (42.5%)	5 (12.5%)	40	0.0003[b]
Nesiritide 0.030	2 (5.1%)	1 (2.5%)	6 (15.4%)	26 (66.7%)	4 (10.3%)	39	0.0001[b]
Patient's Assessment							
Placebo	3 (7.1%)	2 (4.8%)	31 (73.8%)	6 (14.3%)	0 (0.0%)	42	0.0001[a]
Nesiritide 0.015	4 (10.0%)	2 (5.0%)	10 (25.0%)	19 (47.5%)	5 (12.5%)	40	0.0009[b]
Nesiritide 0.030	2 (5.1%)	2 (5.1%)	9 (23.1%)	23 (59.0%)	3 (7.7%)	39	0.0001[b]

a. Overall difference (Kruskal-Wallis test)
b. Difference between a dose and placebo groups (two-sample Wilcoxon test)

Numerically, the investigator and patient's assessments agreed well. The percentage of the exact agreements between the two assessments is 71.1% (73.8%, 67.5%, 71.8% for placebo, 0.03, and 0.06 Natrecor groups, respectively). If allow at most one category difference, overall agreement rate of the assessments is 98.3% (100.0% for placebo, 97.5% and 97.4% for 0.03 and 0.06 Natrecor groups). The percentage of patients who had Hour 6 assessment scores by patient or investigator indicating an improvement (better or much better) is much higher for the Natrecor treated group as compared to placebo. The difference is statistically significant.

Table 16.11 Improvement in global assessment of clinical status at hour 6 in trial 704.325.

Treatment	Assessment n (%)		Total	p Value
	Not improved	Improved		
Investigator Assessment				
Placebo	40 (95.2%)	2 (4.8)	42	0.001 [a]
Nesiritide 0.015	18 (45%)	22 (55.0)	40	
Nesiritide 0.030	9 (23.1%)	30 (76.9)	39	
Patient Assessment				
Placebo	36 (85.7%)	6 (14.3)	42	0.001[a]
Nesiritide 0.015	16 (40%)	24 (60.0)	40	
Nesiritide 0.030	13 (33.3%)	26 (66.7)	39	

a. Overall difference, two-sided chi^2-test

According to the sponsor's analyses, there was a numerical relationship between improvement in PCWP and an improvement in global assessment at the end of 6 hours. These figures are reproduced in appendix seven, section 17.0.

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The results of global assessment of clinical status by patients and investigators at Hour 24 are given in the following table. No significant difference was found.

Table 16.12 Global assessment of clinical status at hour 24 in trial 704.325.

Treatment	Assessment / n (%)					Total	p Value
	Much worse	Worse	No change	Better	Much better		
Investigator's Assessment							
Control	0 (0.0)	1 (2.6)	9 (23.7)	23 (60.5)	5 (13.2)	38	0.4398[a]
Nesiritide 0.015	0 (0.0)	2 (5.0)	6 (15.0)	25 (62.5)	7 (17.5)	40	0.4940[b]
Nesiritide 0.030	1 (2.4)	3 (7.1)	2 (4.8)	27 (64.3)	9 (21.4)	42	0.2041[b]
Patient's Assessment							
Control	0 (0.0)	1 (2.6)	9 (23.7)	22 (57.9)	6 (15.8)	38	0.3372[a]
Nesiritide 0.015	0 (0.0)	3 (7.5)	5 (12.5)	23 (57.5)	9 (22.5)	40	0.4559[b]
Nesiritide 0.030	0 (0.0)	2 (4.9)	3 (7.3)	26 (63.4)	10 (24.4)	41	0.1325[b]

a. Overall difference (Kruskal-Wallis test).
b. Difference between a dose and placebo (two-sample Wilcoxon test).

Numerically, slightly higher percentage of nesiritide patients had improvement in clinical status at Hour 24 (with a score better or much better) for both investigator evaluation and patient evaluation. Since placebo patients were treated with the standard therapy after Hour 6, such a numerical difference is small and not statistically significant. The percentages of patients with improvement for both investigator assessment and patient assessment at Hour 24 seem comparable to those at Hour 6.

Table 16.13 Improvement in global assessment of clinical status at Hour 24 in trial 704.325.

Treatment	Assessment n (%)		Total	p Value
	Not improved	Improved		
Investigator Assessment				
Control[b]	10 (26.3%)	28 (73.7)	38	0.406[a]
Nesiritide 0.015	8 (20%)	32 (80.0)	40	
Nesiritide 0.030	6 (14.3%)	36 (85.7)	42	
Patient Assessment				
Control[b]	10 (26.3%)	28 (73.7)	38	0.281[a]
Nesiritide 0.015	8 (20%)	32 (80.0)	40	
Nesiritide 0.030	5 (12.2%)	36 (87.8)	41	

a. overall difference, two-sided c^2-test.
b. Placebo-controlled for hours 0-6 and active-controlled from hours 6-24.

The agreement between the investigator's and patient's assessments was also examined. The percentage of the exact agreements between the two assessments is 79% (84.2%, 72.5%, 80.5% for placebo, 0.03, and 0.06 Natrecor groups, respectively). If a difference of one category is allowed, overall agreement rate of the assessments is 97.3% (97.3% for placebo, 100% and 100% for 0.030 and 0.060 Natrecor groups). The overall degree of agreement in this case was 99%.

Although the data showed an apparent dose response global assessment of clinical status, and a very good agreement between the assessments by patients and by investigators, the interpretation of the results may not be so straight forward. The reasons for this are: 1) the investigators participated in 'patient's assessment' of clinical status, and 2) the investigators knew patient's PCWP at the time when the assessments were made. The good agreement between the assessments by investigators and patients may just be a consequence of the investigator's involvement in the patient assessments. The higher percentage of improvement in the treated group might be related to investigator's knowledge of the change in PCWP. It is difficult to conclude that Natrecor treatment can improve patient's symptoms based on this study.

16.0.3 Trial 704.326 Statistics Review

This trial focused on the collection of safety information regarding the use of nesiritide, and no formal statistical analysis of these results was performed.

17.0 Appendix 7: Relationship Between PCWP and Changes in CHF Signs and Symptoms.

In the tables reproduced here, the sponsor graphed the association between a change in PCWP and change in the subject and investigator-derived global assessment at the end of Hour 6 in study 704.325.

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18.0 Appendix 8: Individual Case Report Form Reviews of Subjects With Severe and Symptomatic Hypotension

The sponsor submitted a list of all subjects in studies 704.311, 704.325, and 704.326 who had the following clinical consequences:

1. Where the greatest severity of hypotension (symptomatic and asymptomatic) was 'severe.' Trials 704.311, 704.325, and 704.326
2. Where the greatest impact of hypotension (symptomatic and asymptomatic) on drug dosing was 'discontinued.' Trials 704.311, 704.325, and 704.326
3. Where the lowest recorded BP was : <80, <70 and <60 mm Hg. Trials 704.311, 704.325, and 704.326

A summary of the outcomes for each of the patients can be found in the tables below, along with information regarding the timing of the hypotension relative to study drug use, other medications administered.

Table 18.0.1 Subjects with hypotension in the first 24 hours where the greatest severity was 'severe'[a].

Treatment Group/ Patient ID #	While on Study Drug?	Outcome/ AEs	Duration of Hypotension	Notes
Control				
535003	Y/ Dobutamine 1 hr	EMD with Seizure BP 140/- to 0	<5 mins	Study Drug D/C'd No renal failure
Nesiritide 0.030				
356002	Y 3 hrs	BP to 86/52	30 mins	Drug D/C'd Tx'd O_2, IV fluids
357001	Y 23 hrs	135/78 to 58/48 'Hypotensive Crisis'	9 hrs, 55 mins	Tx'd intubation, levophed, dopamine, IV fluids, Intra-aortic balloon pump
493011	Y/ 7 hrs	BP 150/80 to 90/60 with diaphoresis, LOC HR from 80-88 to 53 BPM	3 hours	IV NS, Trendelenburg, Study Drug D/C'd No renal failure
508004	N	BP 140/70 to 50/30	N/A	Made DNR after OR, Support withdrawn
519002	Yes, 40 mins and 4.5 hrs	BP 170/77 to 73/43, then later to 79/32	2 episodes, each <1 hr	NQWMI
562001	Y 20 mins	BP 152/64 to 80/39 with Junctional rhythm Symptomatic: vomited	3 hrs 45 min	Tx'd with IV D5W, Trendeleburg position
579002	Y 7 hrs 45 mins	BP 108/61 to 88/61 Symptomatic: dizzy	2.5 hrs	Nesiritide discontinued, later developed VTach and Coagulopathy
Nesiritide 0.060				
017008	Y 1 hr	BP 98/64 to 62/-	30 minutes	AEs unknown, no lab F/U Pt tx'd with Trendelenberg position
369005	Y 35 mins	BP 98/40 to 70/-, pulse 71	3 hrs	Tx'd Trendelenberg, Atropine, IV NS No Lab F/U
369014	Y 1 hr	BP 140/82 to 60/-- Pulse 73 to 61 Symptomatic: light-headed	20 minutes	Tx'd Dopamine, IV NS No lab F/U

Table 18.0.2 Subjects with hypotension in the first 24 hours where the greatest impact on dosing was discontinuation[a].

Treatment Group/ Patient ID #
Control
541005
Nesiritide 0.015
352001
360001
493013
519008
533002
554002
554037
564001
564002
571002
588004
605002
Nesiritide 0.030
356002
357001
382008
389006
493011
493015
504002
508004
519002
520007
521006
538001
543001
547004
554050
559001
562001
571003
575001
Nesiritide 0.060
017008
369014
376021

Table 18.0.3 Subjects with hypotension in the first 24 hours where the lowest recorded value was <80 mm Hg from study 704.326[a].

Treatment Group/ Patient ID #
Control
493003
535003
549003
551001
Nesiritide 0.015
352001
504003
524004
533002
536002
554013
554017
560002
564002
570003
571002
575002
580003
Nesiritide 0.030
377003
493011
493015
504002
508002
508004
519002
520001
520007
521003
543001
554010
554029
554039
556002
558001
559001
570008
571003
572001
585003
587005

Table 18.0.3 Subjects with hypotension in the first 24 hours where the lowest recorded value was <70 mm Hg from study 704.326[a].

Treatment Group/ Patient ID #
Control
535003
Nesiritide 0.015
570003
Nesiritide 0.030
508002
520001
520007
521003
554029
558001
559001

Table 18.0.3 Subjects with hypotension in the first 24 hours where the lowest recorded value was <60 mm Hg from study 704.326[a].

Treatment Group/ Patient ID #
Control
535003
Nesiritide 0.030
508002
554029

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