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

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

Medications administered	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Subjects who received only initial vasoactive agent	92 (90%)	86 (83%)	76 (76%)	0.027
Subjects who D/C'd study drug & started another agent	2 (2%)	9 (9%)	12 (12%)	0.013
First CV med added after nesiritide D/C'd				
Dobutamine	2 (2%)	7 (7%)	10 (10%)	0.041
Milrinone	0 (0%)	1 (1%)	1 (1%)	1.000
Nitroglycerin	0 (0%)	1 (1%)	0 (0%)	
Subjects who received other parenteral agent while continuing study drug	8 (8%)	8 (9%)	12 (12%)	0.511
Agent combined with study drug				
Dobutamine alone	3 (3%)	5 (5%)	11 (11%)	0.054
Milrinone	1 (1%)	1 (1%)	0 (0%)	1.000
Nitroglycerin	1 (1%)	1 (1%)	1 (1%)	1.000
Nitroprusside	1 91%)	1 (1%)	0 (0%)	1.000

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

6.3.12.3 Analyses of Study 704.326 Results

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

Effect of Study Drug on Vital Signs

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

Table 6.3.12.3.1 Changes in vital signs from baseline to 3 hours in study 704.326[a].

Vital Signs	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value[d]
Systolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	120.7±20	127±25	124±26	0.197
Change from Baseline to 3 hours	-2.5±16	-9.3±16	[illegible]	0.001
p Value (Chg from Base)[b]	0.183	0.001	0.001	
p Value (Compared to Standard Care)[c]	--	0.003	0.001	
p Value (Compared to Low-dose BNP)[c]	--	--	0.426	
Diastolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	70±13	71±15	68±15	0.477
Change from Baseline to 3 hours	-5.9±12	-4.5±12	-8.6±11	0.051
p Value (Chg from Base)[b]	0.001	0.001	0.001	
p Value (Compared to Standard Care)[c]	--	0.376	0.125	
p Value (Compared to Low-dose BNP)[c]	--	--	0.016	
Heart Rate (BPM)				
Baseline (mean±sd)	85±15	83±18	84±15	0.823
Change from Baseline to 3 hours	+3.5±15	-0.6±9	+0.6±10	0.053
p Value (Chg from Base)[b]	0.029	0.501	0.569	
p Value (Compared to Standard Care)[c]	--	0.018	0.107	
p Value (Compared to Low-dose BNP)[c]	--	--	0.469	

a. Data from NDA volume 66, table 21.
b. Comparison by T test.
c. Comparison by ANOVA, pairwise contrast.
d. Comparison by ANOVA, omnibus F-test.

Effect of Study Drug on Subject Weight

The sponsor also collected data on the changes in weight for each of the three treatment groups, which is summarized below. At all time points out to 7 days, the mean change in weight from baseline was less in the high-dose nesiritide group than in the 'standard care' group. Recall that significantly more subjects in the control group were given diuretics.

Table 6.3.12.3.2 Changes in subject weights in study 704.326[a].

Vital Signs	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value[d]
Baseline weight	79.7±21	82.9±24	79.0±19	0.401
Weight Change Day 2				
Change from Baseline	-0.9±2	-1.1±3	-0.7±2	0.453
p Value (Chg from Base)[b]	0.001	0.001	0.013	
p Value (Compared to Standard Care)[c]	--	0.496	0.551	
p Value (Compared to Low-dose BNP)[c]	--	--	0.209	
Weight Change Day 4				
Change from Baseline	-2.1±3	-2.1±4	-0.9±4	0.262
p Value (Chg from Base)[b]	0.001	0.001	0.151	
p Value (Compared to Standard Care)[c]	--	0.959	0.148	
p Value (Compared to Low-dose BNP)[c]	--	--	0.162	
Weight Change Day 6				
Change from Baseline	-2.7±6	-4.5±6	-2.6±4	0.475
p Value (Chg from Base)[b]	0.073	0.004	0.021	
p Value (Compared to Standard Care)[c]	--	0.320	0.952	
p Value (Compared to Low-dose BNP)[c]	--	--	0.277	
Weight Change Day 8				
Change from Baseline	-3.0±6	-2.8±4	-1.2±4	0.662
p Value (Chg from Base)[b]	0.182	0.085	0.289	
p Value (Compared to Standard Care)[c]	--	0.948	0.410	
p Value (Compared to Low-dose BNP)[c]	--	--	0.496	

a. Data from NDA volume 66, Appendix table 23.
b. Comparison by T test.
c. Comparison by ANOVA, pairwise contrast.
d. Comparison by ANOVA, omnibus F-test.

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Effect of Study Drug on Symptomatic Relief

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

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

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

a. Data from NDA volume 66, Appendix table 24a. Shown for 'All subjects' population.
b. Comparison by 1-Sample Wilcoxon.
c. Comparison by Kruskal-Wallis.
d. Comparison using 2-Sample Wilcoxon.

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

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

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

a. Data from NDA volume 66, Appendix table 27a. Shown for 'All subjects' population.
b. Comparison by 1-Sample Wilcoxon.
c. Comparison by Kruskal-Wallis.
d. Comparison using 2-Sample Wilcoxon.

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

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

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

a. Data from NDA volume 66, Appendix table 27a. Shown for 'All subjects' population.
b. Comparison by 1-Sample Wilcoxon.
c. Comparison by Kruskal-Wallis.
d. Comparison using 2-Sample Wilcoxon.

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

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

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

a. Data from NDA volume 66, Appendix table 31a. Shown for 'All subjects' population.
b. Comparison by 1-Sample Wilcoxon.
c. Comparison by Kruskal-Wallis.
d. Comparison using 2-Sample Wilcoxon.

Effect of Study Drug on Hospitalization

The effect of study drug on hospitalization was examined in several ways. First, the duration of hospitalization prior to entry into the study was 1.5±2.4, 1.5±3.5, and 1.7±2.9 for the subjects in the control, nesiritide 0.3/ 0.015, and 0.6/ 0.030 groups respectively ($p>0.05$). The number of patients discharged before day 21 was also examined, as was their average duration of hospitalization. The results are summarized in the table below. A small % of all three groups remained in the hospital at the end of 21 days. There was no significant difference in the duration of hospitalization among the treatment groups.

Table 6.3.12.3.7 Hospitalization through 21 days in study 704.326[a].

	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Subjects discharged prior to day 21	97 (95%)	101 (98%)	96 (96%)	0.515
Total days of hospitalization for subjects D/C'd prior to 21 days				
Mean±SD	6.4±3.7	6.2±3.5	6.6±4.2	0.914
Median	5	5	5	
Time to discharge				
2-3 days	18 (18%)	29 (28%)	25 (25%)	
4-5 days	36 (35%)	22 (21%)	26 (26%)	
6-7 days	13 (13%)	24 (23%)	9 (9%)	
8-14 days	27 (26%)	21 (20%)	26 (26%)	
15-21 days	3 (3%)	5 (5 %)	10 (10%)	
Subjects not discharged as of day 21	5 (5%)	2 (2%)	4 (4%)	

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

Effect of Study Drug on Hospital Readmission

As shown above, no difference exists between the treatment groups regarding discharge before day 21 (see table 6.2.12.2e.5). If one looks just at those subjects who were discharged, however, there was a non-significantly lower rate of re-admission through 21 days for the nesiritide groups. The reasons for these admissions, however, were mostly other medical conditions, unrelated to CHF.

Table 6.3.12.3.8 Hospital readmission through 21 days in study 704.326[a].

	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Subjects discharged prior to day 21	97	101	96	
If discharged, subjects readmitted by day 21	[illegible]	[illegible]	[illegible]	[illegible]
If readmitted, primary reason for first readmittance				
CHF recurrence	8 (50%)	4 (50%)	4 (36%)	
Elective, unrelated to CHF	1 (6%)	0 (0%)	1 (9%)	
Medical condition other than CHF	6 (38%)	2 (25%)	6 (55%)	
Other	1 (6%)	2 (25%)	0 (0%)	
If readmitted, primary reason for all readmittance				
CHF recurrence	9 (53%)	4 (44%)	6 (46%)	
Elective, unrelated to CHF	1 (6%)	0 (0%)	1 (8%)	
Medical condition other than CHF	6 (35%)	2 (22%)	6 (46%)	
Other	1 (6%)	3 (33%)	0 (0%)	

a. Data from NDA volume 66, Appendix 1, Table 34. Includes all subjects discharged before day 21.
b. p Value using Fisher's Exact test.

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

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

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

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

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

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6.3.13 Safety Outcomes

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

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

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

a. Data from NDA volume 1.42, ref. 5, table 32, and electronic datasets.
b. Another patient in this group died on day 22 of the study.

6.3.13.1 Comparisons of Defined Safety Endpoints

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

6.3.13.2 Comments on Specific Safety Parameters

Deaths

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

Table 6.3.13.2.1 Deaths in study 704.326[a].

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

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

Serious Adverse Events

SAEs during study drug administration

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

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

SAEs following study drug discontinuation

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

Table 6.3.13.2.2 Serious Adverse Events in study 704.326[a].

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

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

Table 6.3.13.2.3 Serious Adverse Events in study 704.326[a].

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

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

Table 6.3.13.2.4 Serious Adverse Events in study 704.326[a].

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

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

SAEs requiring re-hospitalization

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

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

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

a. Data from NDA volume 66.

Subject discontinuations

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

Table 6.3.13.2.6 Subject discontinuations in study 704.326[a].

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

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

6.3.14 Trial 704.326 Efficacy Summary

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

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

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

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

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

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

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

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

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

6. With regard to hospitalization:

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

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

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

6.3.15 Trial 704.326 Safety Summary

1. Almost all patients enrolled in the trial completed the first 6 hours of the trial. Discontinuations for hypotension during that period were more common in the nesiritide groups (2% and 5% for the two nesiritide groups vs. 0% in standard care, tables 6.3.13.1).

2. Deaths in the trial were balanced in the three groups: 5 (5%), 6 (6%) and 6 (6%) died in the standard care, nesiritide 0.030 and 0.060 groups respectively (table 6.3.13.2 through 6.3.13.4).

3. Serious Adverse Events (SAEs) were balanced between the three treatment groups.

4. See Section 8.0.2a in the Integrated Safety Summary for a discussion of the increased incidence of hypotension in the nesiritide treated patients in this trial.

6.3.16 Overall Summary for Trial 704.326

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

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

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

7.0 Integrated Efficacy Summary

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

7.0.1 Physiologic Efficacy of Nesiritide

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

7.0.1a Effect of Nesiritide on PCWP

7.0.1a.1 Effect of Nesiritide on PCWP Versus Placebo

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

Trial 704.311 at 3 Hours

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

Table 7.0.1a.1 (from 6.1.12.5.1) Changes in PCWP (baseline to 3 hours) in the ITT population in 704.311[a].

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

a. Data from NDA volume 54, Appendix 1, Table 17A, 17B.
b. See statistical section for statistical methods. p Value per sponsor.
c. Comparison using T-test.

FDA Review of 704.311 PCWP Data

The FDA statistical reviewer also performed several statistical analyses based on the ITT population. The first analysis used the first 80 patients enrolled (the original proposed trial size), using the last value carried forward or worst rank imputation. The reductions in mean PCWP among the treatment groups were compared using three statistical methods: 1) ANOVA, 2) 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 7.0.1a.2 (from 16.3) Mean change in PCWP from baseline for 80 and 103 subjects in study 704.311 at hours 3.

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

a. Kruskall-Wallis using worst rank.

Trial 704.311 Through 24 Hours

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

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

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

Table 7.0.1a.3 (from 6.1.12.3.2) Changes in mean PCWP from baseline to 24 hours in the 'Evaluable at 24 Hours' population[a].

Mean Measurement	Placebo n=25	Nesiritide 0.25/ 0.015 n=18	Nesiritide 0.5/ 0.030 n=21	Nesiritide 1.0/ 0.060 n=20
Baseline PCWP	28.1±6	30.5±8	27.3±4.8	30.0±6.8
24-hour PCWP	26.3±8.4	21.4±6.4	23.6±7.8	22.0±8.1
p Value (Dunnett)[b]	--	NS	<0.05	NS
p Value (P/W Con)[b]	--	0.050	0.050	0.074
Change from Baseline (0-24 hrs)	-1.8±6.4	-8.8±6.8	-3.7±6.4	-8.0±6.4
p Value (Chng from Baseline)[c]	0.169	<.001	0.024	<0.001
p Value (Dunnett)[b]	--	<0.05	NS	<0.05
p Value (P/W Con)[b]	--	0.001	0.328	0.002

a. Data from NDA volume 54, Appendix 1, Table 19A, 19B
b. See statistical section for statistical methods. p Value per sponsor.
c. Comparison using T-test.

The FDA statistical reviewer also performed several statistical analyses based on the ITT population. The first analysis used the first 80 patients enrolled (the original proposed trial size), using the last value carried forward or worst rank imputation. The reductions in mean PCWP among the treatment groups were compared using three statistical methods: 1) ANOVA, 2) 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 hour 24.

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

a. Kruskall-Wallis using worst rank.

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

Trial 704.325-from Baseline to 6 hours

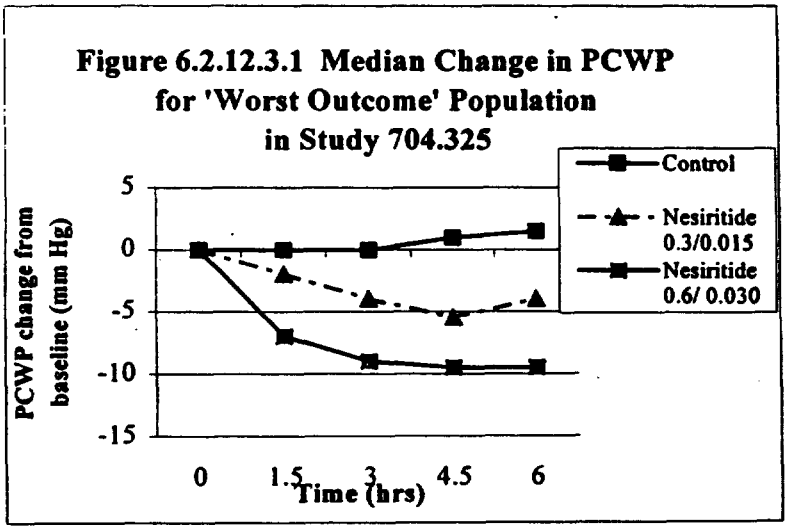
The sponsor first analyzed the 'worst-outcome' population, where the difference between placebo and either of the two nesiritide dose-groups was highly statistically significant at the 6 hour time-point. This result was true for the pre-specified primary endpoint analysis (% change from baseline at 6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

Table 7.0.1a.5 (from 6.2.12.3.1) Primary endpoint analysis for study 704.325[a].

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

a. Data from NDA volume 59, Appendix 1, Table 22A, 22B, and 22C.
b. p Value for primary endpoint by non-parametric ranked analysis (Kruskal-Wallis).
c. p Value compares the 6 hour value for each group individually with the control baseline using 2-Sample Wilcoxon.
d. p Value compares the 6 hour value for each group vs. Baseline using 1-sample Wilcoxon.

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



FDA Analysis of 0-6 Hour PCWP Data from 704.325

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

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

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

a. Kruskal-Wallis test (worst case analysis)

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

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

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

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

Conclusion Regarding Effects of Nesiritide on PCWP vs. Placebo

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

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

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

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

Trial 704.325

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

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

Pulmonary Capillary Wedge Pressure (mm Hg)	Nesiritide 0.3/ 0.015 n=37	Nesiritide 0.6/ 0.030 n=38	p Value[b]
Baseline PCWP	28.7±6.5	27.4±6.5	
Change in PCWP from Baseline to 6 hours			
Mean±SD	-6.8±7.7	-9.5±5.4	0.080
Range			
Change in PCWP from 6 to 24 hours			
Mean±SD	-0.6±7	-0.3±5.8	0.820
Range			
Change in PCWP from Baseline to 24 hours			
Mean±SD	-7.0±9	-9.9±6	0.116
Range			

a. Data from NDA volume 59, Appendix 1, Table 42A. Shown for all subjects with available 24 hour data.
b. p Value using Omnibus F test.

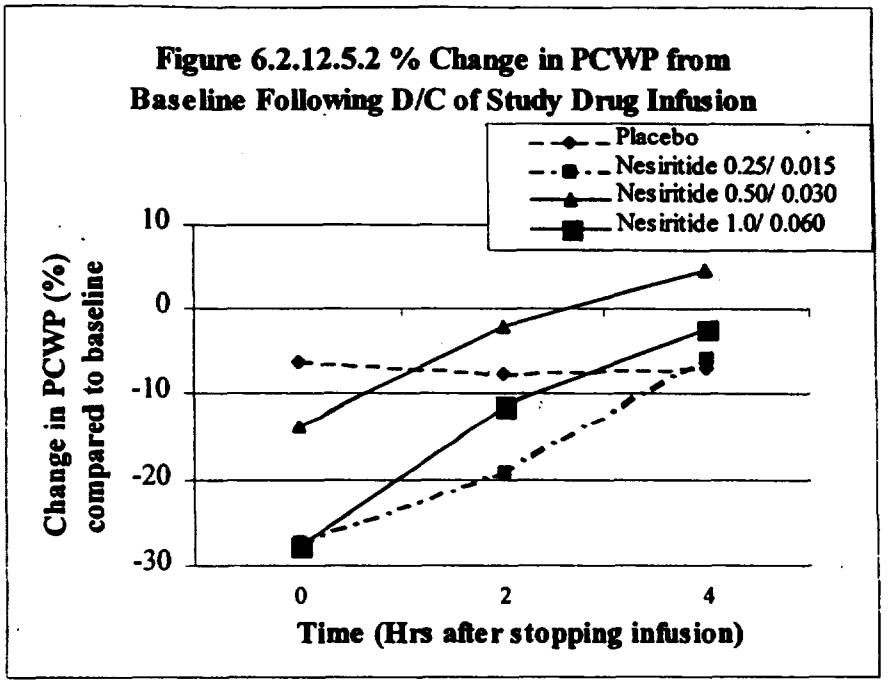
7.0.1a.3 The Demographics of the Effects of Nesiritide on PCWP

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

7.0.1a.4 Changes in PCWP Following Withdrawal of Nesiritide

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

For all study populations in study 704.311, the PCWP had returned to within 10% of the placebo levels in all nesiritide groups by 4 hours, and were intermediate between the last measurement on study drug and the 4-hour post-infusion value. The figure below shows the last recorded value on study drug for the ITT population (shown as time 0), as well as the 2- and 4-hrs post-infusion values (see NDA volume 1.54, table 17C for data).



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

Conclusion Regarding Withdrawal of Nesiritide Infusion

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

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7.0.1b Effect of Nesiritide on Other Hemodynamic Markers

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

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

Study 704.311

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

Table 7.0.1b.1 (from 6.1.12.4.1) Effect of 3 hour infusion of nesiritide on identified hemodynamic parameters[a].

Hemodynamic Parameter (Mean Change from Baseline)	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value[b]
MRAP (mm Hg)	-0.8±3.7	-3.73.5	-3.3±4.3	-4.5±6.2	0.024
SVR (Dyne-sec/cm²) %	-16.4±397	-364±863	-203±493	-500±426	0.017
Cardiac Index (L/min/M²)	+1.1±20	+28.8±50	+18.2±32	+36.6±38	0.004
Pulmonary Vascular Resistance (Dyne-sec/cm²)	+54±96	-55±251	-21±186	-47±158	0.110
Systolic BP (mm Hg)	+1.2±9	-7.4±12	-4.3±14	-10.0±14	0.011
Heart Rate (BPM)	+2.6±7.6	-3.7±6.7	-2.2±8.8	+6.2±13.8	0.002

a. Data from NDA 20-920, vol. 54, Table 20B through 30B. Data are expressed as absolute change from baseline for ITT population.
b. p Value comparing arithmetic means from baseline using ANOVA linear contrast except for heart rate, which used Omnibus F test.

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

Table 7.0.1b.1 (from 6.1.12.4.2) Effect of 24 hour infusion of nesiritide on identified hemodynamic parameters[a].

Hemodynamic Parameters (Mean Change from Baseline)	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value[b]
MRAP (mm Hg)	-1.4±5	-2.6±4	-3.6±6	-2.9±4	0.493
SVR (Dyne-sec/cm²) %	-17.6±675	-283±680	-67±776	-354±300	0.266
Cardiac Index (L/min/M²)	+4.6±18	+16.0±32	+9.7±54	+25.4±21	0.237
Pulmonary Vascular Resistance (Dyne-sec/cm²)	+3.3±113	-68.3±233	-32.8±182	-31.8±129	0.576
Systolic BP (mm Hg)	+2.1±12	-6.1±12	-3.3±13	-9.0±12	0.021
Heart Rate (BPM)	+4.5±11	-1.0±6.8	-0.2±7.6	+4.0±8.2	0.083

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

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Study 704.325-

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

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

Hemodynamic Parameter	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value[b]
Right Atrial Pressure (RAP), mm Hg				
RAP at baseline and 6 hours (mm Hg)				
At baseline (mm Hg)	14.2±6	15.1±7	14.3±7	0.817
At 6 hours (mm Hg)	14.6±6	12.1±7	9.1±6	0.001
p Value (compared to control)[d]	—	0.076	<0.001	
% Change in RAP from baseline at 6 hrs (%)				
Mean±SD	+8.1±29	-12.0±42	-39.4±31	<0.001
Median	0	-20	-40	
Range				
p Value (change from baseline)[c]	0.076	0.081	<0.001	
p Value (comp. to control)[d]	—	0.010	<0.001	
Systemic Vascular Resistance(SVR) dynes/sec/cm^2				
SVR at baseline and 6 hours				
At baseline	1524±493	1598±582	1686±589	0.407
At 6 hours	1693±633	1386±539	1340±511	0.010
p Value (compared to control)[d]	—	0.014	0.005	
% Change in SVR from baseline at 6 hrs (%)				
Mean±SD	+12.8±30	-12.6±25	-17.7±26	<0.001
Median	11.2	-9.2	-20.2	
Range				
p Value (change from baseline)[c]	0.010	0.004	<0.001	
p Value (comp. to control)[d]	—	<0.001	<0.001	
Cardiac Index (CI), L/min/m^2				
CI at baseline and 6 hours				
At baseline	2.0±0.4	1.8±0.5	1.9±0.5	0.159
At 6 hours	1.9±0.5	2.1±0.5	2.3±0.6	0.002
p Value (compared to control)[d]	—	0.165	<0.0001	
% Change in CI from baseline at 6 hrs (%)				
Mean±SD	-4.4±26	16.2±33	27.5±40	<0.001
Median	-2.6	12.1	21.4	
Range				
p Value (change from baseline)[c]	0.269	0.004	<0.001	
p Value (comp. to control)[d]	—	0.006	<0.001	

a. Data from NDA volume 59, Appendix 1, Table 27, 28, and 30 (A and C).
b. p Value using Omnibus F test.
c. p Value compares the 6 hour value for each group individually with the control baseline using 1-sample t test.
d. p Value compares the 6 hour value for each group individually with the control baseline using pairwise contrasts.

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

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

Hemodynamic Parameter	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value[b]
***Pulmonary Vascular Resistance* (PVR), dynes/sec/cm^2**				
PVR at baseline and 6 hours				
At baseline	278.8±200	293.8±183	242.2±201	0.472
At 6 hours	305.1±303	232.4±155	240.1±139	0.227
p Value (compared to control)[d]	---	0.116	0.163	
Change in PVR from baseline at 6 hrs (mm Hg)				
Mean±SD	+26.3±197	-62.2±100	-2.0±142	0.033
Median	10.3	-53.2	-8.3	
Range				
p Value (change from baseline) [d]	0.392	<0.001	0.928	
Mean Pulmonary Artery Pressure (MPAP) mm Hg				
MPAP at baseline and 6 hours				
At baseline	41.1±9	39.6±9	38.3±8	0.338
At 6 hours	43.1±11	33.0±9	30.6±10	<0.001
p Value (compared to control) [d]	---	<0.001	<0.001	
Change in MPAP from baseline at 6 hrs (mm Hg)				
Mean±SD	+2.0±5.8	-7.0±6.9	-7.7±7.6	<0.001
Median	2.5	-5.0	-8.8	
Range				
p Value (change from baseline) [d]	0.031	<0.001	<0.001	
Mean Systemic Arterial BP (MAP), mm Hg				
MAP at baseline and 6 hours				
At baseline	86.2±12.6	81.2±10.0	85.4±11.3	0.103
At 6 hours				
p Value (compared to control) [d]	---	<0.001	<0.001	
Change in MAP from baseline at 6 hrs (mm Hg)				
Mean±SD				
Median	-1.3	-4.5	-8.7	
Range				
p Value (change from baseline)[c]	---	0.005	<0.001	
p Value (comp. to control) [d]	---	0.008	<0.001	
Heart Rate (HR), BPM				
HR at baseline and 6 hours				
At baseline	89.5±12.8	90.3±14.6	87.4±16.7	0.640
At 6 hours	90.9±15.4	88.8±14.5	87.5±16.0	
p Value (compared to control) [d]	---	0.516	0.300	
Change in HR from baseline at 6 hrs (mm Hg)				
Mean±SD	1.4 ±7	-1.6±7	0.0±9	0.218
Median	0.5	-3.0	0.0	
Range				
p Value (change from baseline)[c]	0.240	0.149	0.972	
p Value (comp. to control) [d]	---	0.082	0.435	

a. Data from NDA volume 59, Appendix 1, Tables 33, 36, 39, and 40 (A and B).
b. p Value using Omnibus F test.
c. p Value compares the 6 hour value for each group individually with the control baseline using 1-sample t test.
d. p Value compares the 6 hour value for each group individually with the control baseline using pairwise contrasts.

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

Trial 704.325

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

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

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

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

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Trial 704.326-

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

Table 7.0.1b.2.2 (from 6.3.12.3.1) Changes in vital signs from baseline to 3 hours in study 326[a].

Vital Signs	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value[d]
Systolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	120.7±20	127±25	124±26	0.197
Change from Baseline to 3 hours	-2.3±16	-9.3±16	-11.2±16	<0.001
p Value (Chg from Base)[b]	0.183	0.001	0.001	
p Value (Compared to Standard Care)[c]	--	0.003	0.001	
p Value (Compared to Low-dose BNP)[c]	--	--	0.426	
Diastolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	70±13	71±15	68±15	0.477
Change from Baseline to 3 hours	-5.9±12	-4.5±12	-8.6±11	0.051
p Value (Chg from Base)[b]	0.001	0.001	0.001	
p Value (Compared to Standard Care)[c]	--	0.376	0.125	
p Value (Compared to Low-dose BNP)[c]	--	--	0.016	
Heart Rate (BPM)				
Baseline (mean±sd)	85±15	83±18	84±15	0.823
Change from Baseline to 3 hours	+3.5±15	-0.6±9	+0.6±10	0.053
p Value (Chg from Base)[b]	0.029	0.501	0.569	
p Value (Compared to Standard Care)[c]	--	0.018	0.107	
p Value (Compared to Low-dose BNP)[c]	--	--	0.469	

a. Data from NDA volume 66, table 21.
b. Comparison by T test.
c. Comparison by ANOVA, pairwise contrast.
d. Comparison by ANOVA, omnibus F-test.

Conclusions Regarding the Other Hemodynamic Effects of Nesiritide

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

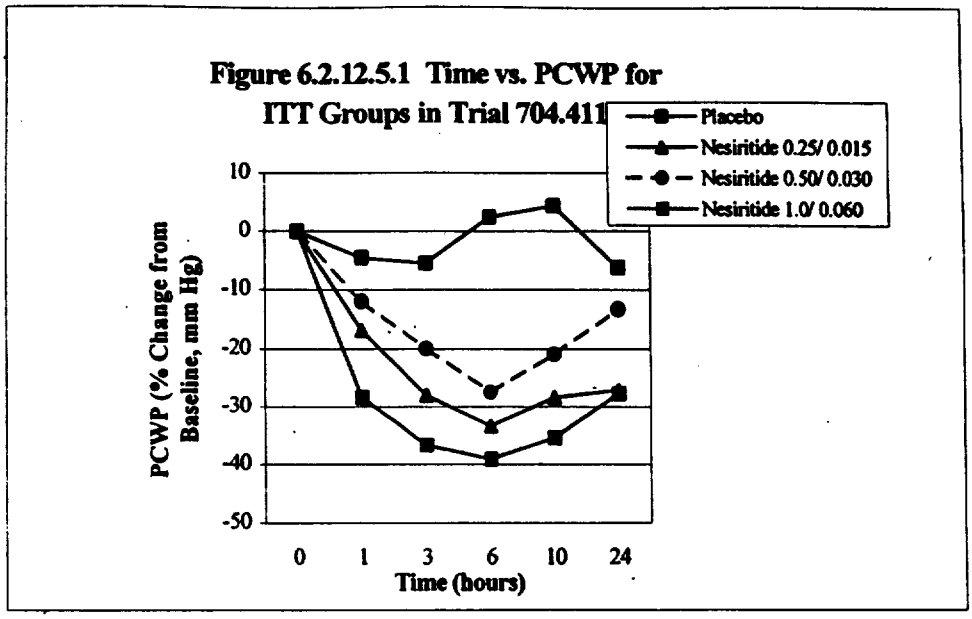
The data from both 704.311 and 704.325 demonstrate that the significant effect of nesiritide on mean and median non-PCWP hemodynamics persists through 24 hours. The data also support a dose-dependent effect on some of the hemodynamic parameters, especially measurements of systemic blood pressure. The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

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

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

7.0.1c.1 Durability of Nesiritide Effect on PCWP

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



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

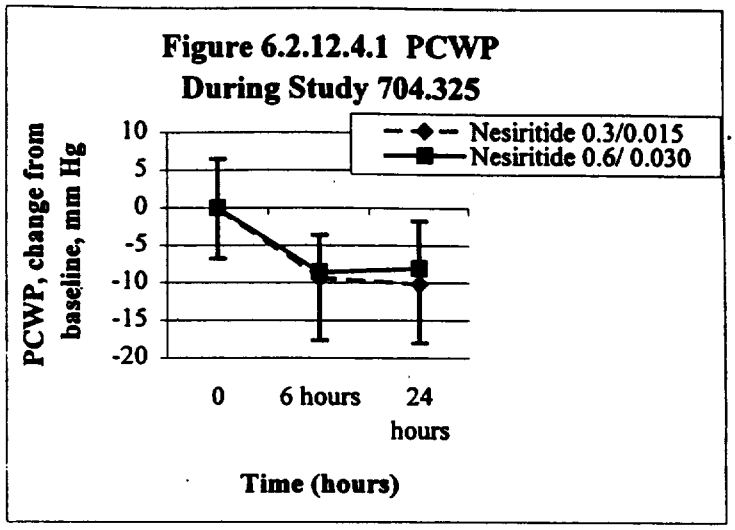
Table 7.0.1b.3 Comparison of changes in serum nesiritide levels and hemodynamic effects between 3 and 24 hours from study 704.311[a].

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

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

Trial 704.325

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



7.0.1c.2 Durability of Nesiritide Effect on Other Hemodynamics

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

Trial 704.311

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

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

Hemodynamic Parameter	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value[b]
MRAP (mm Hg)	-0.8±3.7	-3.73.5	-3.3±4.3	-4.5±6.2	0.024
SVR (Dyne-sec/cm²) %	-16.4±397	-364±863	-203±493	-500±426	0.017
Cardiac Index (L/min/M²)	+1.1±20	+28.8±50	+18.2±32	+36.6±38	0.004
PVR[c] (Dyne-sec/cm²)	+54±96	-55±251	-21±186	-47±158	0.110
Systolic BP (mm Hg)	+1.2±9	-7.4±12	-4.3±14	-10.0±14	0.011
Heart Rate (BPM)	+2.6±7.6	-3.7±6.7	-2.2±8.8	+6.2±13.8	0.002

a. Data from NDA 20-920, vol. 54, Table 20B through 30B. Data are expressed as absolute change from baseline for ITT population.
b. p Value comparing arithmetic means from baseline using ANOVA linear contrast except for heart rate, which used Omnibus F test.
c. Pulmonary Vascular Resistance.

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

Table 7.0.1c.2-2 (from 6.1.12.4.2) Effect of 24 hour infusion of nesiritide on hemodynamic parameters[a].

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

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

704.325

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

704.326

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

Conclusions Regarding the Durability of the Nesiritide Effect on Hemodynamics

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

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

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

While levels of nesiritide are known to be increased at baseline in CHF, no information exists regarding the changes in the hANP/hBNP receptor numbers or affinity following nesiritide infusion in patients with CHF (ref. 9).

In conclusion, the data are inadequate to fully assess the development of tachyphylaxis following long nesiritide infusion. Based on the decrease in the magnitude of the hemodynamic effect of nesiritide in trial 704.311, a degree of tolerance to the hemodynamic effects of nesiritide is possible. This decrease, however, did not reverse the overall significance of the effects of nesiritide on hemodynamics, when compared with placebo through 24 hours. The clinical significance of a 'lessening' of the magnitude of hemodynamic effects that nonetheless remain 'significant' compared with placebo cannot be determined. It is also important to remember that tolerance to nitrates typically develops after >24 hours of exposure to the drug, where we have no data regarding the maintenance of the hemodynamic effects of nesiritide. Finally, the patients enrolled in trial 704.311 had significantly less 'acutely' decompensated CHF relative to those in 704.325 and 704.326, raising issues of generalizability of the data to the severely decompensated CHF population for which the sponsor is seeking a claim.

7.0.1d The Relationship Between Plasma Nesiritide Concentrations and Hemodynamic Changes

In study 704.311, the sponsor performed an analysis of the steady-state pharmacokinetics of nesiritide at more than one dose level. For a full discussion of the results, please see the biopharmacologist's review.

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

There is also a relationship between the plasma nesiritide level and changes in PCWP.

Finally, and of critical importance, the sponsor analyzed the relationship between changes in PCWP and improvement in the symptoms of CHF in study 704.325. The tables for these analyses are reproduced in Appendix 17: Relationship between PCWP and changes in CHF Signs and Symptoms. In short, the greater the percentage decrease in PCWP, the greater the improvement in subject and investigator-derived 'Global Assessment of Well-Being' at hour six. Unfortunately, this analysis is severely undermined by the lack of independence of the collection of the data for hemodynamics and symptom relief.

Conclusions Regarding the Relationship between Changes in PCWP and Clinical Efficacy

Regarding the relationship between nesiritide dose and hemodynamic changes, as reflected by changes in PCWP, a significant relationship between nesiritide dose, nesiritide plasma concentrations, and changes in PCWP was seen in both the 704.311 and 704.325 trials (see study 704.325 for details).

Regarding the relationship between the hemodynamic effects of nesiritide (especially PCWP) and clinical outcomes, there is flawed data, from 704.325, linking decreases in PCWP to improvements in both the global assessment and in the degree of breathlessness. Taken in total, these data weakly support a link between the administered doses of nesiritide and an improvement in the patient's clinical state at the end of 6 hours.

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7.0.1e Other Physiologic Effects of Nesiritide

7.0.1e.1 Effects of Nesiritide on Na^+ and Water Excretion

One proposed effect of nesiritide is to promote a natriuresis and diuresis, both through direct action and through the inhibition of aldosterone production. In animals and in normal volunteers, nesiritide has been shown to cause both natriuresis and diuresis in the pre-clinical part of the NDA (see Dr. Papoian's review for details). Of note, patients with cirrhosis and ascites, who have elevated baseline hBNP levels, have a blunted diuretic response to nesiritide (ref. 15). In the clinical database, all three long infusion trials measured some aspects of Na^+ and water excretion as part of their programs. Overall, nesiritide had a small, inconsistent effect on Na+ and water excretion. Note: no information is available about the amount of IV vs. PO diuretics administered during the three trials (only total diuretic use).

Changes in Na^+ and Water Balance in Trial 704.311

The first table below summarizes the effect of nesiritide on fluid intake and urine output in the ITT population, where no significant effect of nesiritide was detected. Instead, there was a trend towards decreased urine volume in the subjects who received nesiritide, which achieved nominal statistical significance for the nesiritide 0.50/ 0.030 group. Overall, the mean and median fluid balance was positive in all of the nesiritide groups (more fluid in than out). This was a result of less urine output, and not due to differences in the amount of fluids administered to the patients. The difference between the placebo and the high-dose nesiritide groups amounted to approximately 1 liter over a 24 hour period (with more out in the placebo group). Importantly, in this trial there was no significant difference in the study groups with regard to diuretic use, although more subjects in the placebo group received diuretics during study drug administration (see table 6.1.12.2c.1).

Table 7.0.1e.1.1 (from 6.1.12.5.5) Changes in fluid intake and urinary volume during first 24 hours in the ITT population of study 704.311[a].

Measurement	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.50/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	p Value[b]
Fluid Intake (ml/ 24 hrs) Mean±sd	1935±515	1836±427	1767±545	2147±1062	0.222
p Value compared with placebo[c]	--	NS	NS	NS	
Total Urine Output (ml/24 hrs) Mean±sd	[illegible]	[illegible]			
p Value compared with placebo[c]	--	NS	<0.05	NS	
Output – Intake (ml/24 hrs) Mean ±sd	475±1094	-91±756	-287±848	-136±1872	0.113
Median	[illegible]	[illegible]			
p Value compared with placebo[c]	--	NS	NS	NS	

a. Data from NDA volume 54, Appendix 1, Table 34.
b. See statistical section for statistical methods. p Value per sponsor by ANOVA Omnibus F test.
c. Comparison using Dunnet's t-test.

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

Table 7.0.1e.1.2 (from 6.1.12.5.6) Changes in sodium and potassium excretion during first 24 hours in the ITT population of study 704.311[a].

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

a. Data from NDA volume 54, Appendix 1, Table 35.
b. See statistical section for statistical methods. p Value per sponsor by ANOVA Omnibus F test.
c. Comparison using Dunnet's t-test.

Changes in Na^+ and Water Balance in Trial 704.325

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

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

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

Table 7.0.1e.1.3 (from 6.2.12.4.13) Assessment of volume status during first 24 hours in the ITT population in study 704.325[a].

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

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

c. p Value using Omnibus F test.

In support of this possibility, if the subjects who received diuretics during the first 6 hours were removed, there remained significant differences in overall volume status at the end of 6 hours between control and nesiritide groups, except that in this case, there was more net output in the nesiritide groups relative to placebo. This increase in net fluid output, extrapolated over a 24 hour period, would result in a net loss in the nesiritide group of approximately 200 mls per day.

Table 7.0.1e.1.4 (from 6.2.12.4.14) Assessment of volume status during first 6 hours in study 704.325[a].

Volume parameter and period of measurement	Control n=39	Nesiritide 0.3/ 0.015 n=38	Nesiritide 0.6/ 0.030 n=39	p Value[c]
0 to 6 Hour Data				
Fluid Intake (Mean ±SD)	96.2±53	98.3±41	94.1±58	0.936
Urine Output [illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Output minus Intake [illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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

c. p Value using Omnibus F test.

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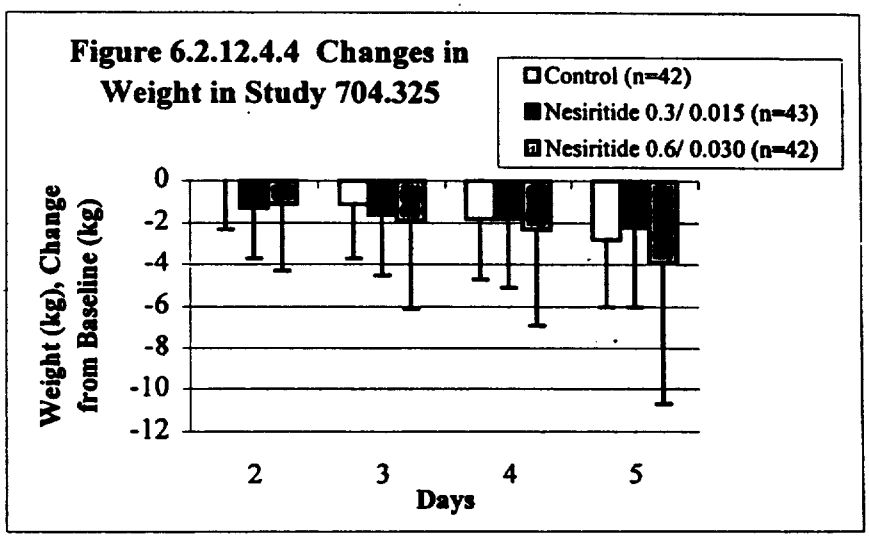
The next table summarizes the excretion of sodium and potassium during the first 24 hours of the 704.311 study. All nesiritide groups had a non-significantly lower mean sodium excretion relative to control.

Table 7.0.1e.1.5 (from 6.1.12.5.5) Changes in sodium and potassium excretion during first 24 hours in the ITT population of study 704.311[a].

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

a. Data from NDA volume 54, Appendix 1, Table 35.
b. See statistical section for statistical methods. p Value per sponsor by ANOVA Omnibus F test.
c. Comparison using Dunnet's t-test.

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



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Changes in Na^+ and Water Balance in Trial 704.326

The sponsor also collected data on the changes in weight for each of the three treatment groups in the 704.326 trial, summarized below. At all time points out to 7 days, the mean change in weight from baseline was less in the high-dose nesiritide group than in the 'standard care' group. Recall that significantly more subjects in the control group were given diuretics (97% in the control group, 82% in the nesiritide 0.015 group, and 74% in the nesiritide 0.030 group, $p<0.001$). The reasons for this difference in the amount of diuretics administered cannot be determined, given the open-label nature of the trial.

Table 7.0.1e.1.6 (from 6.3.12.3.2) Changes in subject weights in study 326[a].

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

a. Data from NDA volume 66, Appendix table 23.
b. Comparison by T test.
c. Comparison by ANOVA, pairwise contrast.
d. Comparison by ANOVA, omnibus F-test.

Conclusions Regarding Nesiritide Effects on Na^+ and Water Excretion

The data regarding the effects of nesiritide on Na^+ and water excretion are highly study-dependent. In trial (704.311) significantly less Na+ and water was lost in all of the nesiritide groups relative to placebo through 24 hours. Importantly, this is the only trial where there was not a significant imbalance with regard to diuretic use between the placebo and nesiritide groups. In the 704.325 trial, for the first 6 hours, those subjects who did not receive diuretics lost more water in the nesiritide groups relative to placebo. For the population as a whole, however, there was more fluid lost in control group than in the nesiritide group. However, because the trial was open-label, the investigators would almost certainly know of the putative natriuretic and diuretic effects of nesiritide. This prevents the use of this data to conclude, as suggested by the sponsor, that the decreased diuretic use reflects a decreased 'need' for diuretics in patients receiving nesiritide. There is also a reported blunting of the natriuretic and diuretic effect of nesiritide, seen in normal volunteers and animals, in patients who are intravascularly depleted (ref. 15).

The data on the changes in subject weights, with broad uncertainties, also suggest that any effect on diuresis and natriuresis by nesiritide has relatively little impact on overall weight change, as a surrogate for fluid loss. In trial 704.326, the high-dose nesiritide group had less weight loss at all time points relative to the active control group. In trial 704.325, there was a small increase in weight loss during the first 24 hours in the nesiritide group relative to control, which tended to diminish with time.

Finally, the literature suggests that ANP stimulates 'translocation' of fluid from the intravascular space (ref. 10). This same phenomenon was suggested by the NDA data with nesiritide (see ISS). If so, movement of salt and water to the interstitial space will prevent its excretion by the kidneys. During aggressive diuresis, the consequence may be an increased risk of renal hypoperfusion and damage. In conclusion, the data do not suggest an effect of nesiritide to increase Na^+ and water excretion, and instead suggest anti-natriuresis during the first 24 hours. Nesiritide had no clear effect on weight loss in the 'real-world' trial (704.326), and the magnitude of any effect of a 24 hour infusion of nesiritide is likely to be quite limited in this regard.

7.0.1e.2 Effects of Nesiritide on Hormone levels

Serum Aldosterone Levels

A proposed mechanism for the diuresis and natriuresis seen in animals following nesiritide infusion is the inhibition of aldosterone production. In trial 704.325, the median aldosterone concentration was decreased at the end of 6 hours in the nesiritide group, compared with placebo. For the control group, aldosterone levels rose 0.6 ng/dl (+5%), compared with a decease of 1.2 ng/dl in the nesiritide 0.015 group (-11%) and –1.6 ng/dl in the nesiritide 0.030 group (-14.5%), p=0.030. This trend was also true if the subjects who did not receive ACE inhibitors before the trial were examined. The table below shows the data, as well as the large patient-to-patient variability of the data.

Table 7.0.1e.1.7 (from 6.2.12.4.16) Changes in serum aldosterone levels from 0-6 hours in study 704.325[a].

Aldosterone (ng/dl)	Control n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value[a]
Baseline	12	11	11	0.976
Hour 6	11.5	4.6	6.2	0.137
	[illegible]	[illegible]	[illegible]	
Change from Baseline	+0.6	-2.5	-1.6	0.030
Range	[illegible]	[illegible]	[illegible]	
N (# missing data)	36 (6)	40 (3%)	38 (4)	

a. Data from NDA volume 59, table 54. p Value per sponsor.

Serum Epinephrine Levels

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

Conclusions Regarding Nesiritide Effects on Hormone Levels

In the one trial where serum aldosterone levels were measured, there was a significant decrease in the median serum aldosterone concentrations during the first 6 hours of nesiritide infusion. These data are conflicted by the increased diuretic use in the control group (which would tend to reduce intravascular volume and increase aldosterone). The patient-to-patient variability around these median values, however, was enormous, making application of this data to individual patients impossible.

7.0.2 Clinical Efficaey of Nesiritide

The next portion of the efficacy summary will concentrate on other measures of clinical benefit that are sometimes used to support the clinical efficacy of drugs.

7.0.2a Effect of Nesiritide on Mortality

The demonstration of a mortality benefit is one powerful indicator of clinical efficacy. The effects of nesiritide on mortality will also be examined in section 8.2.1 below.

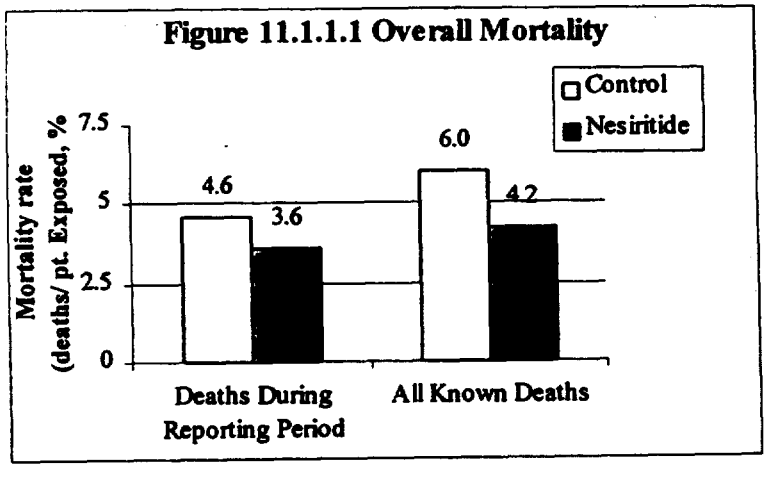
There were a total of 28 deaths occurred during the reporting periods of the CHF trials. An additional 6 deaths that occurred after the reporting period are also known to the sponsor. The first table summarizes the reported death rates for two relevant patient populations: all known deaths from all studies; and all known deaths from the nesiritide infusion studies (311, 325 and 326). The incidence of deaths during the studies is also tabulated.

Table 7.0.2a.1 (from 8.1.1.1) Reported deaths in NDA 20-920[a].

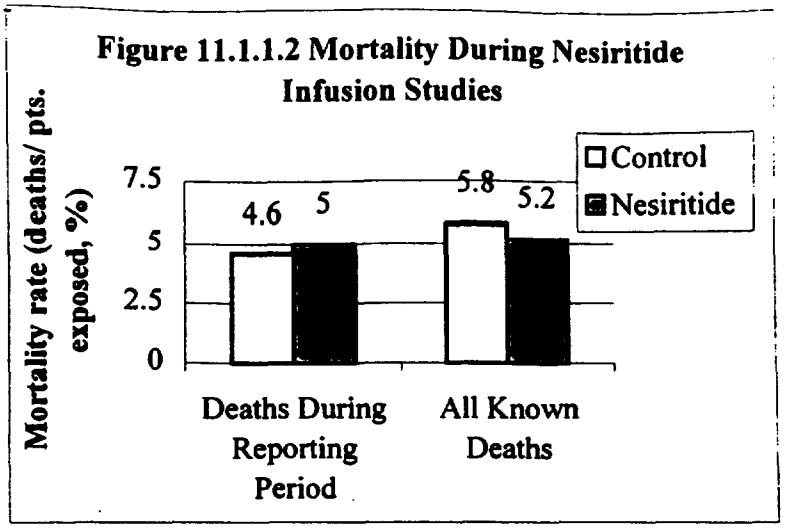
Group	Placebo	Active Control	Nesiritide Groups				Total Nesiritide
			Bolus	0.015 µg/kg/min	0.030 µg/kg/min	0.060 µg/kg/min	
	n=114	n=102	n=143	n=169	n=167	n=26	n=505
All Known Deaths	8 (7.0%)	5 (4.9%)	2 (1.4%)	8 (4.7%)	10 (6.0%)	1 (3.8%)	21 (4.2%)
Deaths During Study	5 (4.4%)	5 (4.9%)	0 (0%)	8 (4.7%)	9 (5.4%)	1 (3.8%))	18 (3.6%)
	n=71	n=102	n=N/A	n=169	n=167	n=26	n=362
All Known Deaths From Infusion Studies[b]	5 (7.0%)	5 (4.9%)	N/A	8 (4.7%)	10 (6.0%)	1 (3.8%)	19 (5.2%)
Deaths During Infusion Studies	3 (4.2%)	5 (4.9%)	N/A	8 (4.7%)	9 (5.4%)	1 (3.8%)	18 (5.0%)

a. Data from Listing 7, NDA vol. 81.
b. Studies 311, 325 and 326.

For all known deaths during the nesiritide NDA, the following graphs summarize the relative incidence of death for nesiritide and control (including both placebo and active control groups). The first graph shows the overall reported mortality for the NDA.



Similarly, the graph below shows the mortality rate during the three infusion studies, where there were 10 known deaths in the control groups (5.8%) compared with 19 deaths in the nesiritide groups (5.2%). Again, there is no evidence of a large benefit of nesiritide regarding mortality.



Finally, in the single largest trial, 704.326, there was a balanced number of deaths reported in the active control and nesiritide groups. Seventeen subjects in this study died by day 21. Five (5%), 6 (6%), and 6 (6%) subjects in the standard care and 0.015 and 0.03 nesiritide treatment groups, respectively. One additional death in the 0.03 µg/kg/min nesiritide group occurred on day 22.

Conclusion Regarding the Effect of Nesiritide on Mortality

The data are insufficient to detect a small difference in the mortality rates, but the overall trend in mortality favored nesiritide. No adverse effect of nesiritide on mortality rate is suggested.

7.0.2b Effect of Nesiritide on Signs and Symptoms of CHF

A second area of clinical benefit is relief of symptoms. In the NDA, the sponsor collected information about changes in the signs and symptoms of CHF, as well as an overall assessment of well-being (compared with baseline). The format followed in this summary will be the same as that used for the changes in hemodynamics, with an initial assessment of the blinded, placebo-controlled data, followed by open-label and active-control comparisons.

7.0.2b.1 Effect of Nesiritide on Signs and Symptoms of CHF, Compared with Placebo

The only blinded, placebo-controlled comparison of CHF symptoms took place in trial 704.325 from baseline through 6 hours of study drug infusion.

Trial 704.325

Global Assessment of Clinical Status from trial 704.325 from Baseline to 6 Hours

After six and 24 hours, and within 24 hours after discontinuation of all parenteral therapy for the episode of decompensated CHF (or on day 5, whichever occurred first)., the subject and the physician were to assess the subject's overall clinical status and rate it: markedly better, better, no change, worse, or markedly worse as compared to baseline. For the primary analysis, subjects who received a cardiovascular intervention for worsening CHF during the 6-hour blinded period, or were prematurely unblinded, were to be automatically assigned a rating of markedly worse for all subsequent assessments. The problems surrounding the independence of the symptom assessments in study 704.325 have been discussed above (section 6.2.8, Blinding in study 704.325).

6 Hours

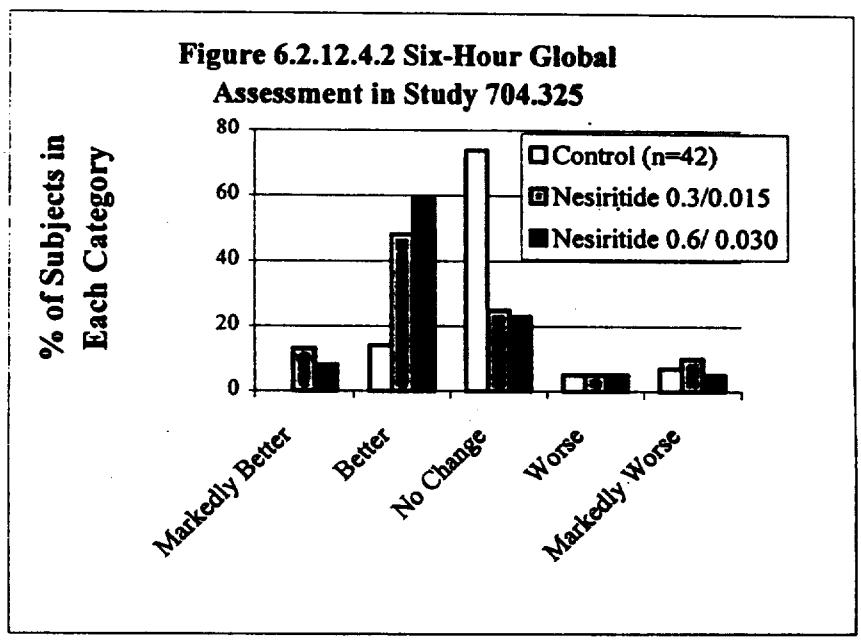
Using a non-parametric analysis, as per the primary endpoint analysis, subjects who received nesiritide felt significant improvement in symptoms relative to the control patients at the end of 6. The graph below shows the percentage of subjects in each of the assessment categories for the three dose-groups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

Numerically, the investigator and patient's assessments agreed well. The percentage of the exact agreements between the two assessments averaged 71.1% (73.8%, 67.5%, 71.8% for placebo, 0.030, and 0.060 Natrecor groups, respectively). If allow at most one category difference, overall agreement rate of the assessments is 98.8% (100.0% for placebo, 97.5% and 97.4% for 0.03 and 0.06 Natrecor groups).

Table 7.0.2b.1.1 (from 6.2.12.4.8) Subject global assessments at end of parenteral vasoactive administration, from study 704.325[a].

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

a. Data from NDA volume 59, Appendix 1, Table 45a and electronic datasets.
b. Global assessment must be made at least 20 hours after start of study drug.
c. p Value using Omnibus F test.



As shown in the table on the next page, the percentage of patients who had Hour 6 assessment scores by patient or investigator indicating an improvement (better or markedly better) was also significantly higher for the nesiritide group compared to placebo.

Table 7.0.2b.1.2 (from 6.2.12.4.4) Improvement in global clinical status at hour 6 in trial 704.325.

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

a. Overall difference, two-sided chi-squared-test

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

1. There was a statistically significant difference between placebo and both nesiritide dose groups with regard to global assessment of clinical status at Hour 6 by investigators or by patients.

2. Numerically, slightly higher percentage of nesiritide patients had improvement in clinical status at Hour 24 (with a score of 'better' or 'much better') for both investigator evaluation and patient evaluation, compared with the control group (placebo-treated 0-6 hours, active control-treated 6-24 hours).

However, Dr. Cui also concluded that, given the difficulties in the symptom data collection, it is difficult to conclude that Natrecor treatment can improve patient's symptoms based on this study.

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

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

Table 7.0.2b.1.3 (from 6.2.12.4.9) Assessment of individual signs and sxs of CHF at 6 hrs of study drug in study 704.325[a].

Signs and Symptoms of CHF at 6 hours (compared with baseline)	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value[a]
Breathing Difficulty: Baseline				
No breathing difficulty	3 (7%)	2 (5%)	4 (10%)	0.628
Breathing difficulty with moderate activity	7 (17%)	5 (12%)	4 (10%)	
Breathing difficulty with minimal activity	22 (52%)	23 (53%)	21 (50%)	
Breathing difficulty at rest	10 (24%)	13 (30%)	13 (31%)	
Breathing Difficulty: 6 hour results				
Improved from baseline	5 (12%)	22 (56%)	20 (50%)	<0.001
No change from baseline	27 64%)	16 (41%)	18 (45%)	
Worse than baseline	10 (24%)	1 (3%)	2 (5%)	
Appetite: Baseline				
Good appetite	22 (52%)	20 (47%)	24 (57%)	0.626
Decreased appetite	14 (33%)	19 (44%)	15 (36%)	
No appetite	6 (14%)	4 (9%)	3 (7%)	
Appetite: 6 hour results				
Improved from baseline	3 (7%)	11 (28%)	2 (8%)	0.017
No change from baseline	38 (90%)	27 (69%)	35 (88%)	
Worse than baseline	1 (2%)	1 (3%)	2 (5%)	

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