

The next tables continue the summary of nesiritide effects on individual signs and symptoms in 704.325.

Table 7.0.2b.1.4 (from 6.2.12.4.10) Assessment of individual signs and symptoms of CHF after 6 hours of study drug in study 704.325<sup>a</sup>.

Signs and Symptoms of CHF at 6 hours (compared with baseline)	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value <sup>b</sup>
<b>Peripheral Circulation: Baseline</b>				
Extremities warm and well-perfused	26 (62%)	18 (42%)	26 (62%)	0.106
Extremities cool with decreased perfusion	12 (29%)	21 (49%)	15 (36%)	
Extremities cold and vasoconstricted	4 (10%)	4 (9%)	1 (2%)	
<b>Peripheral Circulation: 6 hour time-point</b>				
Improved from baseline	2 (5%)	7 (18%)	6 (15%)	0.271
No change from baseline	40 (95%)	31 (79%)	34 (85%)	
Worse than baseline	0 (0%)	1 (3%)	0 (0%)	
<b>Fatigue: Baseline</b>				
No fatigue	2 (5%)	1 (2%)	2 (5%)	0.253
Fatigue with moderate activity	9 (21%)	7 (16%)	4 (10%)	
Fatigue with minimal activity	21 (50%)	22 (51%)	20 (48%)	
Fatigue at rest	10 (24%)	13 (30%)	16 (38%)	
<b>Fatigue: 6 hour time-point</b>				
Improved from baseline	2 (5%)	12 (32%)	15 (38%)	<0.001
No change from baseline	35 (83%)	25 (66%)	24 (60%)	
Worse than baseline	4 (12%)	1 (3%)	1 (3%)	

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

b. p Value using Kruskal-Wallis test.

Table 7.0.2b.1.5 (from 6.2.12.4.11) Assessment of individual signs and symptoms of CHF after 6 hours of study drug in study 704.325<sup>a</sup>.

Signs and Symptoms of CHF at 6 hours (compared with baseline)	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value <sup>b</sup>
<b>Lightheadedness: Baseline</b>				
No lightheadedness	32 (76%)	29 (67%)	32 (76%)	0.592
Lightheadedness with moderate activity	4 (10%)	5 (12%)	2 (5%)	
Lightheadedness with minimal activity	5 (12%)	5 (12%)	3 (7%)	
Light headedness at rest	1 (2%)	4 (9%)	5 (12%)	
<b>Lightheadedness: 6 hour results</b>				
Improved from baseline	2 (5%)	9 (24%)	4 (10%)	0.023
No change from baseline	39 (93%)	29 (76%)	34 (85%)	
Worse than baseline	1 (2%)	0 (0%)	2 (5%)	
<b>Peripheral Edema: Baseline</b>				
None	13 (31%)	13 (30%)	19 (45%)	0.382
Mild	19 (45%)	15 (35%)	13 (31%)	
Moderate	6 (14%)	12 (28%)	6 (14%)	
Severe	4 (10%)	3 (7%)	4 (10%)	
<b>Peripheral Edema: 6 hour results</b>				
Improved from baseline	3 (7%)	8 (21%)	9 (23%)	0.028
No change from baseline	36 (86%)	30 (79%)	31 (78%)	
Worse than baseline	3 (7%)	0 (0%)	0 (0%)	

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

b. p Value using Kruskal-Wallis test.

The next table completes the summary of nesiritide effects on individual signs and symptoms in 704.325.

Table 7.0.2b.1.6 (from 6.2.12.4.12) Assessment of individual signs and symptoms of CHF after 6 hours of study drug in study 704.325<sup>a</sup>.

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

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

b. p Value using Omnibus F test.

#### Change in Respiratory Rate Through 6 hours from Study 704.325

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

The table below summarizes the data from 704.325 for changes in respiratory rate between 0 and 6 hours for the nesiritide group (combining both doses) and placebo. For the entire population, as well as those patients who started with tachypnea (≥20 respirations per minute), there was a small decrease in the mean and median respiratory rates in the nesiritide group. This decrease was not seen in the placebo group. The sponsor performed a similar analysis (not shown), which agreed in general with these findings. The sponsor also pointed out that the majority of the patients were on supplemental O<sub>2</sub>, complicating interpretation of these data.

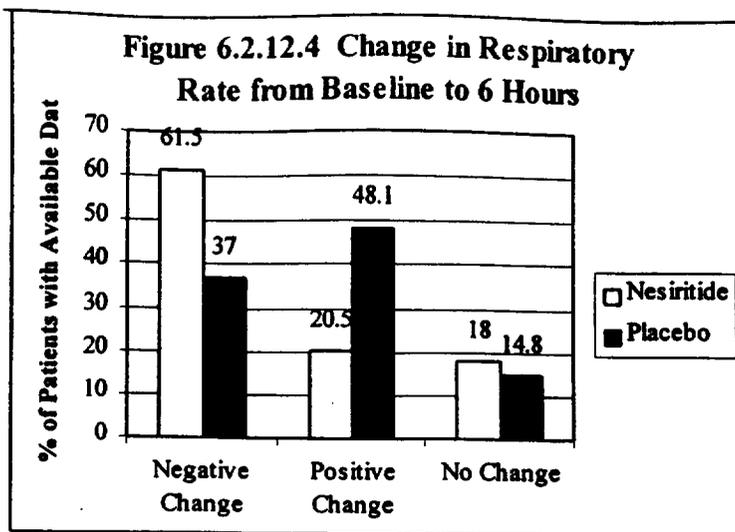
Table 6.2.12.4.4a Summary of changes in respiratory rate (RR) using 'last value carried forward' population with respiratory rate ≥20 RPM from study 704.325<sup>a</sup>.

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

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

b. p Value comparing incidence of decreased RR using Fisher's Exact test =0.08.

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

Table 6.2.12.4.b Summary of changes in respiratory rate (RR) using 'last value carried forward' population from study 704.325<sup>a</sup>.

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

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

#### 7.0.2b.2 Effect of Nesiritide on Signs and Symptoms of CHF, Compared with Active Controls

Information was also collected in open-label fashion comparing the effects of nesiritide to those of active controls in both 704.325 and 704.326. In general, these analyses suffer from the withdrawal of patients who are not improving on therapy, the absence of a placebo group, and the crossing over of patients to other therapies.

#### Trial 704.325

##### Overall Assessment of Well-Being from trial 704.325 Beyond 6 Hours

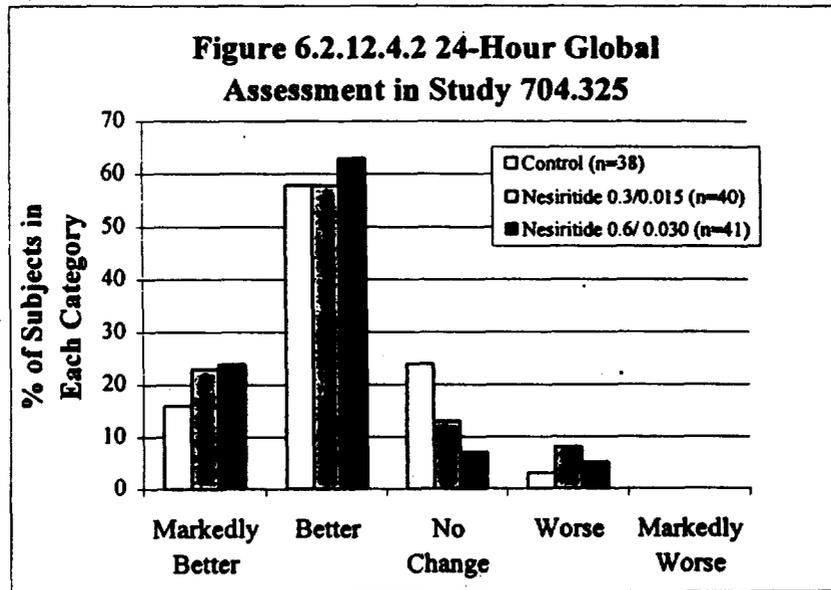
The global clinical status of all three study groups were much more similar at the 24 hour time-point, even though the average subject continued to receive nesiritide for >30 hours (see section 6.2.12.2c above). There was an increase in the % of nesiritide patients who felt 'markedly better', relative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

Finally, when the Global Assessment was performed after discontinuation of all parenteral vasoactive substances (or at day 5), no significant difference between the three groups was seen (see table 6.2.12.4.6 for details).

Table 7.0.2b-2.1 (from 6.2.12.4.8) Subject global assessments at end of parenteral vasoactive administration, from study 704.325<sup>a</sup>.

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

- a. Data from NDA volume 59, Appendix 1, Table 45a and electronic datasets.  
 b. Global assessment must be made at least 20 hours after start of study drug.  
 c. p Value using Omnibus F test.  
 d. Control comparator was placebo for first 6 hours and active control at 24 hours.



Numerically, slightly higher percentage of nesiritide patients had improvement in clinical status at Hour 24 (with a score better or markedly better) for both investigator evaluation and patient evaluation. There was good agreement between the investigator- and subject-derived scores of clinical status at 24 hours.

Table 7.0.2b.2.1 (from 6.2.12.4.7) Improvement in global clinical status at Hour 24 in trial 704.325.

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

- a. overall difference, two-sided  $\chi^2$ -test.  
 b. Includes either 'markedly improved' or 'improved'. All others are considered Not Improved.  
 c. Placebo for 0-6 hours and active control from 6-24 hours.

**Signs and Symptoms of CHF from trial 704.325 Beyond 6 Hours**

At the end of 24 hours, there were non-significant trends towards greater improvement in fatigue and lightheadedness in the nesiritide groups, but no other differences between the two treatment groups. The overall CHF total score was quite similar for all three groups at the end of 24 hours. In data shown in the study review, when the signs and symptoms were assessed after discontinuation of all parenteral vasoactive substances (or at day 5), no significant difference between the three groups was seen (see table 6.2.12.4.6 for details).

Table 7.0.2b.2.2 (from 6.2.12.4.13) Assessment of individual signs and symptoms of CHF after 24 hours of study drug in study 704.325<sup>a</sup>.

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

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

b. p Value using Omnibus F test.

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**Trial 704.326**

**Overall Assessment of Well-Being from Trial 704.326**

Global assessments at 6 and 24 hours of treatment were compared for the three study groups. While all three treatment groups improved significantly over baseline to 6 hours, there was not a significant difference between the Global Assessment Scores between the three groups. As was the case for the trial 704.325 data, there was no indication of either a superior or inferior effect of the nesiritide 0.030 group on any signs or symptoms relative to the nesiritide 0.015 group.

Table 7.0.2b.2.3 (from 6.3.12.3.3) Global assessment, by subjects, of their clinical status at 6 and 24 hours in study 704.326<sup>a</sup>.

Global Assessment	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
<b>6 Hour Assessment</b>	n=84	n=86	n=82	0.318 <sup>c</sup>
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') <sup>b</sup>	<0.001	<0.001	<0.001	
p Value (comp with standard care group) <sup>d</sup>	--	0.569	0.358	
p Value (comp. with low-dose nesiritide group) <sup>d</sup>	--	--	0.133	
<b>24 Hour Assessment</b>	n=92	n=99	n=90	0.302 <sup>c</sup>
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') <sup>b</sup>	<0.001	<0.001	<0.001	
p Value (comp with standard care group) <sup>d</sup>	--	0.370	0.515	
p Value (comp. with low-dose nesiritide group) <sup>d</sup>	--	--	0.128	
<b>Last Recorded Assessment</b>	n=98	n=101	n=93	0.628 <sup>c</sup>
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') <sup>b</sup>	<0.001	<0.001	<0.001	
p Value (comp with standard care group) <sup>d</sup>	--	0.532	0.728	
p Value (comp. with low-dose nesiritide group) <sup>d</sup>	--	--	0.354	

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

b. Comparison by 1-Sample Wilcoxon.

c. Comparison by Kruskal-Wallis.

d. Comparison using 2-Sample Wilcoxon.

Signs and Symptoms of CHF from Trial 704.326

The sponsor also looked at the effect of the study drugs on individual signs/ 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 7.0.2b.2.4 (from 6.3.12.3.4) Assessment of 'breathing difficulty', by subjects, at 6 and 24 hours in study 704.326<sup>a</sup>.

Global Assessment of Breathing Difficulty	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Value
<b>6 Hour Assessment</b>				
Improved from Baseline	52 (61%)	56 (63%)	44 (55%)	0.583 <sup>c</sup>
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') <sup>b</sup>	<0.001	<0.001	<0.001	
p Value (comp with standard care group) <sup>d</sup>	--	0.726	0.515	
p Value (comp. with low-dose nesiritide group) <sup>d</sup>	--	--	0.302	
<b>24 Hour Assessment</b>				
Improved from Baseline	77 (80%)	77 (78%)	63 (70%)	0.230 <sup>c</sup>
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') <sup>b</sup>	<0.001	<0.001	<0.001	
p Value (comp with standard care group) <sup>d</sup>	--	0.726	0.112	
p Value (comp. with low-dose nesiritide group) <sup>d</sup>	--	--	0.199	

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

b. Comparison by 1-Sample Wilcoxon.

c. Comparison by Kruskal-Wallis.

d. Comparison using 2-Sample Wilcoxon.

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

Table 7.0.2b.2.5 (from 6.3.12.3.5) Subject assessment of 'lightheadedness', at 6 and 24 hours in 704.326<sup>a</sup>.

Global Assessment of Lightheadedness	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
<b>Baseline</b>				
No lightheadedness	57 (56%)	56 (56%)	58 (59%)	0.868 <sup>c</sup>
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%)	
<b>6 Hour Assessment</b>				
Improved from Baseline	11 (13%)	17 (19%)	11 (14%)	0.369 <sup>c</sup>
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') <sup>b</sup>	0.006	0.007	0.481	
p Value (comp with standard care group) <sup>d</sup>	--	0.594	0.340	
p Value (comp. with low-dose nesiritide group) <sup>d</sup>	--	--	0.193	
<b>24 Hour Assessment</b>				
Improved from Baseline	25 (26%)	26 (27%)	18 (20%)	0.742 <sup>c</sup>
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') <sup>b</sup>	<0.001	0.001	0.001	
p Value (comp with standard care group) <sup>d</sup>	--	0.886	0.450	
p Value (comp. with low-dose nesiritide group) <sup>d</sup>	--	--	0.560	

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

b. Comparison by 1-Sample Wilcoxon.

c. Comparison by Kruskal-Wallis.

d. Comparison using 2-Sample Wilcoxon.

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

Table 7.0.2b.2.6 (from 6.3.12.3.6) Subject assessment of 'peripheral edema', at 6 and 24 hours in 704.326<sup>a</sup>.

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
<b>Baseline</b>				
None	29 (29%)	28 (28%)	29 (30%)	0.342 <sup>c</sup>
Mild	33 (33%)	23 (23%)	27 (28%)	
Moderate	32 (32%)	33 (33%)	30 (31%)	
Severe	7 (7%)	17 (17%)	12 (12%)	
<b>6 Hour Assessment</b>				
<b>Improved from Baseline</b>	68 (80%)	59 (66%)	54 (68%)	0.060 <sup>d</sup>
No Change from Baseline	1 (1%)	0 (0%)	1 (1%)	
Worse than Baseline				
p Value (test of 'No Change') <sup>b</sup>	<0.001	<0.001	<0.001	
p Value (comp with standard care group) <sup>d</sup>	--	0.021	0.076	
p Value (comp. with low-dose nesiritide group) <sup>d</sup>	--	--	0.653	
<b>24 Hour Assessment</b>				
<b>Improved from Baseline</b>	46 (48%)	43 (43%)	47 (52%)	0.147 <sup>d</sup>
No Change from Baseline	1 (1%)	0 (0%)	0 (0%)	
Worse than Baseline				
p Value (test of 'No Change') <sup>b</sup>	<0.001	<0.001	<0.001	
p Value (comp with standard care group) <sup>d</sup>	--	0.406	0.713	
p Value (comp. with low-dose nesiritide group) <sup>d</sup>	--	--	0.229	

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

b. Comparison by 1-Sample Wilcoxon.

c. Comparison by Kruskal-Wallis.

d. Comparison using 2-Sample Wilcoxon.

### **Conclusions Regarding Nesiritide Effects on Signs and Symptoms of CHF**

If the conclusion is reached that nesiritide is significantly better than either placebo or active control as regard to symptom relief, this will add another piece of data supporting efficacy. To make this argument, the sponsor has submitted data from two trials, of which one portion is 'blinded' and placebo-controlled, while the other is open-label, and compared with active control therapy.

Regarding the placebo-controlled data, it exists in one trial (704.325) from baseline to 6 hours of drug infusion, and reflects the exposure of 79 patients (in two dose groups) to nesiritide compared with 42 patients exposed to placebo. The problems with the data collection in this trial have been summarized above; these limit the strength of any interpretation of the symptom data. In this group of patients from 704.325, a significant effect of nesiritide to reduce the following components of CHF were detected at the end of 6 hours of study drug infusion:

- 1) Global assessment of well-being,
- 2) Individual signs and symptoms of CHF, including breathlessness, fatigue, appetite, fatigue, light-headedness, and peripheral edema, and
- 3) CHF Global score.

There was also a small decrease in the median respiratory rate at the end of 6 hours in the nesiritide groups (2 breathes per minute less than the placebo group).

After 6 hours, these same patients were unblinded with regard to therapy and followed. At the end of 24 hours, no significant differences between treatment groups with regard to any of these parameters were seen, although the % of subjects in the nesiritide groups who were either markedly better or better was slightly higher than the control group. This may have been due to the lag in initiation of parenteral vasoactive therapy in the control group (where none were administered until after the blind was broken). There was also no clear indication that the high-dose nesiritide group had a greater effect on the signs and symptoms of CHF than did the low-dose nesiritide group. This is in contrast to the hemodynamic data, where there was a dose-response effect for nesiritide. Whether this reflects the relative insensitivity of the symptom scales cannot be determined.

### Conclusions-Regarding Nesiritide Effects on Signs and Symptoms of CHF (cont)

With regard to the comparison between nesiritide and active control therapies, from study 704.326, none of the measured variables suggested any greater or lesser effect of nesiritide on CHF signs and symptoms at any time point. Again, there was no suggestion of a dose-dependent effect of nesiritide in this population.

In conclusion, one placebo-controlled trials supports a significant effect of nesiritide on the signs and symptoms of CHF during a 6-hour infusion period. The data comparing the efficacy of nesiritide and other active controls regarding CHF symptoms and signs suggest that the effects of the two treatment groups on CHF signs and symptoms are similar in magnitude. Again, no dose-response effect for nesiritide was found.

### 7.0.2c Effect of Nesiritide on Hospitalization Rates

#### Trial 704.325

The effect of study drug on hospitalization was examined in several ways in 704.325. First, the duration of hospitalization prior to entry into the study was similar in the treatment groups:  $3.0 \pm 2.9$ ,  $4.1 \pm 4.4$  and  $5.3 \pm 11.4$  for the subjects in the control, nesiritide 0.3/ 0.015, and 0.6/ 0.030 groups respectively ( $p > 0.05$ ). One individual in the high-dose nesiritide group accounted for most of the numerical increase in duration of hospitalization.

The number of patients discharged before day 21 was examined, as was their average duration of hospitalization, and the results summarized in the table below. Note that while 95% of the control group was discharged prior to 21 days, 19% of both nesiritide groups remained hospitalized at 21 days. There was no significant difference in the duration of hospitalization among the treatment groups.

Table 7.0.2c.1 (from 6.2.12.4.17) Hospitalization through 21 days in study 704.325<sup>a</sup>.

Volume parameter and period of measurement	Control n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value
Subjects discharged prior to day 21	40 (95%)	35 (81%)	34 (81%)	
Total days of hospitalization for subjects D/C'd prior to 21 days				
Mean±SD	7.6±4.9	7.3±3.9	7.8±4.5	0.891 <sup>b</sup>
Median	6.5	6.0	7.0	
Time to discharge				
2-3 days	10 (24%)	5 (12%)	5 (12%)	
4-5 days	8 (19%)	10 (23%)	5 (12%)	
6-7 days	5 (12%)	6 (14%)	13 (31%)	
8-14 days	11 (26%)	13 (30%)	8 (19%)	
15-21 days	6 (14%)	1 (2%)	3 (7%)	
Subjects not discharged as of day 21	2 (5%)	8 (19%)	8 (19%)	0.085 <sup>c</sup>

a. Data from NDA volume 59, Appendix 1, Tables 59 and 60. All subjects with available data are included ( $\geq 90\%$  of enrolled subjects for all points).

b. p Value using Kruskal-Wallis test.

c. p Value using Fisher's exact test.

If the subjects who were hospitalized for  $>5$  days before entering the study were excluded from the analysis, the duration of hospitalization was still similar between the three treatment groups. In data not shown, subjects hospitalized  $>5$  days when entering the trial also had similar duration of hospitalization.

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### Hospital Readmission in 704.325

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

Table 7.0.2c.2 (from 6.2.12.4.18) Hospital readmission through 21 days in study 704.325<sup>a</sup>.

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

a. Data from NDA volume 59, Appendix 1, Tables 60. Includes all subjects who were discharged before day 21.

b. p Value using Fisher's Exact test.

### Trial 704.326

The effect of study drug on hospitalization was examined in several ways in study 704.326. First, the duration of hospitalization prior to entry into the study was  $1.5 \pm 2.4$ ,  $1.5 \pm 3.5$ , and  $1.7 \pm 2.9$  for the subjects in the control, nesiritide 0.3/ 0.015, and 0.6/ 0.030 groups respectively ( $p > 0.05$ ). Note that these durations were shorter than for the 704.325 trial.

The number of patients discharged before day 21 was also examined, as was their average duration of hospitalization. The results are summarized in the table below. A small percentage of all three groups remained in the hospital at the end of 21 days. There was no significant difference in the duration of hospitalization among the treatment groups.

Table 7.0.2c.3 (from 6.3.12.3.7) Hospitalization through 21 days in study 704.326<sup>a</sup>.

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

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

**Effect of Study Drug on Hospital Readmission in 704.326**

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

Table 7.0.2c.4 (from 6.3.12.3.8) Hospital readmission through 21 days in study 704.326<sup>a</sup>.

	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	p Value
Subjects discharged prior to day 21	97	101	96	
If discharged, % of subjects readmitted by day 21	16 (16%)	13 (13%)	15 (16%)	0.1815 <sup>b</sup>
<b>If readmitted, primary reason for first readmittance</b>				
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%)	
<b>If readmitted, primary reason for all readmittance</b>				
CHF recurrence	9 (53%)	4 (44%)	6 (46%)	
Elective, unrelated to CHF	1 (6%)	0 (0%)	1 (8%)	
Medical condition other than CHF	6 (35%)	2 (22%)	6 (46%)	
Other	1 (6%)	3 (33%)	0 (0%)	

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

b. p Value using Fisher's Exact test.

**Conclusion Regarding the Effect of Nesiritide on Hospitalization**

Regardless of the measure, there was no consistent, reproducible beneficial effect of nesiritide on any aspect of hospitalization rates. For instance, in 704.325, a higher percentage of patients who were discharged from the nesiritide groups required re-hospitalization prior to 21 days. This effect was not evident in the larger trial 704.326, where the rate of re-hospitalization was non-significantly reduced in the nesiritide groups relative to the active control group.

As another example, the number of patients re-hospitalized for CHF was higher in the nesiritide groups in 704.311, but slightly lower in the 704.326 study.

In conclusion, the data regarding the effects of nesiritide on hospitalization and re-hospitalization do not demonstrate a benefit for nesiritide relative to the control groups.

**7.0.2d Effect of Nesiritide on Need for Invasive Medical Interventions**

**Trial 704.325**

The number of patients intubated at baseline and during the 21 day follow-up is shown below. Note the 5 subjects in the high-dose nesiritide group intubated before day 21. Of these, two in the nesiritide 0.030 group were intubated during or shortly after their nesiritide infusion. The other 3 were intubated >10 days after starting the trial.

Table 7.0.2d.1 (from 6.2.13.6) Requirement for intubations in study 704.325<sup>a</sup>.

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

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

The need for dialytic intervention is summarized in the table below. Note that interventions for worsening renal failure (short of dialysis) were more nominally significantly more common in the nesiritide groups.

Table 7.0.2d.2 (from 6.2.13.5) Need for intervention due to worsening renal failure in study 704.325<sup>a</sup>.

Intervention for Worsening Renal Function	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	p Value
No Intervention	41 (98%)	37 (86%)	33 (79%)	0.033
Medical Intervention Without Dialysis	0 (0%)	6 (14%)	7 (17%)	0.009
Dialysis	1 (2%)	0 (0%)	2 (5%)	—

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

#### Trial 704.326

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

Table 7.0.2d.3 (from 6.3.12.3.9) Need for selected medical interventions through 21 days in study 704.326<sup>a</sup>.

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

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

#### Conclusions Regarding the Need for Other Medical Interventions

The data are inconsistent regarding the need for other medical interventions, and do not suggest a clear benefit for nesiritide as regards any specific intervention. The suggested decrease in the rate of intubations in the 704.326 trial was not seen in the 704.325 trial (in which the number of intubations was clearly higher in the high-dose nesiritide group relative to control). There was a suggestion of an increased need for non-dialytic interventions due to renal failure in the 704.325. study, which again was not confirmed in the 704.326 study.

In conclusion, no benefit of nesiritide with regard to the need for medical interventions was demonstrated or strongly suggested.

#### **7.1 Medical Reviewer's Conclusion's Regarding Nesiritide Efficacy**

The database adequately demonstrates a significant, dose-dependent effect of nesiritide infusions to decrease PCWP relative to placebo in two trials. The time to peak hemodynamic effect also suggests that the pharmacodynamic half-life of nesiritide is significantly prolonged (2-4 hours) relative to its pharmacokinetic half-life (12-30 minutes). This hemodynamic effect on PCWP was associated significantly with the dose and plasma concentrations of nesiritide. Nesiritide also had significant, dose-dependent effects on other hemodynamics, including systolic blood pressure. The time-course for changes in PCWP and other hemodynamic measurements in study 704.311 through 24 hours suggest a decrease in the magnitude, but not the significance, of the effect of nesiritide on hemodynamics. While these data support the development of some 'tolerance' or 'tachyphylaxis' to nesiritide through 24 hours, they also suggest that nesiritide continues to have a significant hemodynamic effect.

The database demonstrates a nominally significant effect of nesiritide to improve CHF signs and symptoms at the end of 6 hours, when compared with placebo, in one trial. In contrast to the hemodynamic data, this effect was not dose-related. There is also a suggested effect of nesiritide to decrease the median respiratory rate relative to placebo. These data are also flawed by problems relating to their collection, and cannot be interpreted as independent confirmation of nesiritide efficacy, although they are suggestive of benefit. No advantage for nesiritide relative to the 'active control' group with regard to CHF signs and symptoms was demonstrated or suggested by the data from two other trials. The data suggesting a small effect of nesiritide to reduce the respiratory rate does support a beneficial effect of nesiritide on respiration. There was no indication that nesiritide was less effective at improving symptoms than the active control. No other clinical benefits of nesiritide infusion were demonstrated, when compared the active control groups, including: mortality rate, hospitalization rate, or need for other medical interventions.

## 8.0 Integrated Review of Safety

This section will summarize the critical adverse events identified by the Medical Reviewer for NDA 20-920. Within body systems, the data relating to each adverse event will be summarized, followed by an opinion regarding its association to nesiritide administration. The strength of the association between nesiritide and a given adverse event will be qualified as possible, probable, or definite, based on the conclusions of the Medical Reviewer. The primary data-tables used for this review can be found in Appendix one, section 11.0. Data will be examined in the following order:

- 1) incidence of both AEs and SAEs,
- 2) deaths associated the safety issue, and
- 3) any lab measurements, including vital signs, relevant to the safety issue.
- 4) the demographics of individual AEs and SAEs where possible.
- 5) special studies of relevance to individual AEs. Some of these were performed by the sponsor, or at the request of the FDA. Others were performed by the FDA, and will be identified as such.

The adverse events to be discussed have been included either because, in the opinion of this reviewer, their occurrence is associated with nesiritide administration (e.g., hypotension) or because they are part of a usual safety review (e.g., abnormal LFTs). Those adverse events that are not listed in this section are interpreted as either occurring too rarely to determine their association with nesiritide use or occurred with no evidence of specific association with study drug administration (either control or nesiritide). The critical safety issues where the data were considered insufficient will be identified as such.

In reviewing the database summarized above, this reviewer was careful to examine the data for evidence of events occurring more frequently in the control/placebo group relative to nesiritide, in addition to searching for events linked to nesiritide use. This is important so as to avoid the bias potentially present in any analysis that includes multiple analyses such as the safety review. It is also important to remember that the use of statistics to examine the incidence of rare and unusual events in a safety database is flawed with the same difficulties inherent to multiple looks. The intent of the following sections is to look for trends suggesting an association between a given AE (or group of AEs) and one of the treatment groups, based on multiple lines of evidence. This is, of course, the nature of a safety review.

There are two limiting factors that an NDA places on the detection of renal and cardiac adverse events (AEs): 1) the extent of patient exposure in both controlled and uncontrolled trials, and 2) the potential absence of relevant data. The patients exposed to study drug will be discussed below. Issues relating to the collection of individual data (e.g., Holter monitor data, follow-up abnormal labs) will be addressed in the discussion of each specific safety issue as relevant.

### Patient Exposure

Overall, 505 patients were exposed to nesiritide as part of the NDA. The number of patient-years of exposure puts absolute limits on detecting and characterizing the renal and cardiac safety of nesiritide. Using the number 505, and not taking into account the duration of exposure, we can estimate a 95% likelihood of detecting at least one occurrence of adverse events occurring at a rate of between 1/150 and 1/200. As part of the three large infusion trials, 362 patients received nesiritide, compared with 173 control patients (both placebo- and active-control). This smaller number of patients will limit our ability to detect significant adverse events even further. Less information, obviously, will be available regarding the relative rates for adverse events (nesiritide vs. control group). Comparative rates between nesiritide and placebo will be limited by the use of active, open-label controls after short periods of exposure to nesiritide in the infusion trials.

The comparative rates of adverse events for the three nesiritide dose groups also needs to be commented on. With only 26 subjects in the highest nesiritide dose group (0.060 µg/kg/min), adverse event rate comparisons with the other nesiritide dose groups need to be interpreted with great caution.

It is also critical to note that patients who had CHF in combination with an acute MI were not eligible for enrollment in the trial. No direct information is available regarding the safety or efficacy of nesiritide in this population.

A final note needs to be made about the conventions used for the labels in the data summary below. The long infusion trials had small differences in the doses of nesiritide used, especially with regard to the dose of the nesiritide bolus prior to the start of the infusion. These dose groups are summarized on the next page.

### Treatment groups in the long infusion trials

#### 704.311

There were four treatment groups in study 704.311:

- Group 1: Nesiritide: IV bolus of 0.25 µg/kg followed by a 0.015 µg/kg/min infusion.
- Group 2: Nesiritide: IV bolus of 0.50 µg/kg followed by a 0.030 µg/kg/min infusion.
- Group 3: Nesiritide: IV bolus of 1.0 µg/kg followed by a 0.060 µg/kg/min infusion.
- Group 4: IV bolus of placebo followed by a placebo infusion.

#### 704.325

There were three treatment groups in study 704.325:

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

#### 704.326

There were three treatment groups in study 704.326:

- Group 1: Nesiritide: IV bolus of 0.3 µg/kg followed by a 0.015 µg/kg/min infusion.
- Group 2: Nesiritide: IV bolus of 0.6 µg/kg followed by a 0.03 µg/kg/min infusion.
- Group 3: A standard care agent.

In presenting the safety data, the doses of nesiritide have been 'lumped' according to their infusion dose. These will be listed as nesiritide 0.015 or 0.015 µg/kg/min, nesiritide 0.030 or 0.30 µg/kg/min, or nesiritide 0.060/0.060 µg/kg/min. Given the small number of patients available for the safety summary, this 'lumping' was judged by the Medical Reviewer as in the interest of effective review. Where individual trial data is summarized, the bolus information will be included that is correct for the trial in question.

Another note must be made regarding the inclusion of nominal p Values in the tables below. The Medical Reviewer recognizes that few, if any, of these carry any true statistical power (pre-specified, corrected for multiple looks, etc.). Their inclusion in the review is rather to serve as a marker for differences which may (or may not) be clinically relevant, but which bear further scrutiny. As such, all of these p Values should be seen as nominal.

### 8.0.1 Occurrence of Adverse Events by Body System

First, the relative occurrence of adverse events by body system is summarized from the adverse event table above. Nesiritide administration was associated with a nominally significant increase in the rate of overall adverse events within two systems, and a decreased incidence in one, which are shaded in the table below.

Table 8.0.1.1 (from 11.1.3.2) Adverse Events (AEs) during the first 14 days in the 'long infusion' trials, summarized by body system<sup>a</sup>.

Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Cardiovascular System					
Body as a Whole					
Digestive System	52 (30%)	67 (40%)	60 (36%)	7 (27%)	0.242
Neurological System					
Metabolic & Nutritional	34 (20%)	28 (17%)	34 (20%)	5 (19%)	0.813
Respiratory System	25 (14%)	33 (20%)	36 (22%)	2 (8%)	0.179
Urogenital System	22 (13%)	28 (17%)	35 (21%)	3 (12%)	0.209
Skin & Appendages	15 (9%)	20 (12%)	23 (14%)	0 (0%)	0.114
Musculoskeletal	15 (9%)	10 (6%)	9 (5%)	1 (4%)	0.648
Hemic & Lymphatic	9 (5%)	3 (2%)	8 (5%)	1 (4%)	0.286
Special Senses	3 (2%)	4 (2%)	5 (3%)	1 (4%)	0.602

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

### 8.0.2 Adverse Events in the Cardiovascular System

The following adverse events within the cardiovascular system will be examined: hypotension, bradycardia, other ventricular and atrial arrhythmias, congestive heart failure, and decreased pulmonary pressure. Adverse events analyzed but not discussed further include hypertension, and myocardial infarct.

#### 8.0.2a Hypotension

##### AEs

The first two tables summarize the incidence of AEs related to hypotension in the 'all CHF' and the 'long infusion' databases. There was a highly significant increase in the incidence of hypotension, including symptomatic hypotension, in the nesiritide groups, which was dose-dependent in the 'long infusion' trial population.

Table 8.0.2a.1 (from 11.1.3.1) Hypotensive AEs in the 'all CHF' trials from NDA 20-920<sup>a</sup>.

Hypotension	Control n=235	Nesiritide n=505	Nominal p Value
Cardiovascular System	116 (49%)	300 (59%)	0.011
Hypotension			
Symptomatic Hypotension			

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.2a.2 (from 11.1.3.2) Hypotensive AEs in the first 14 days in the 'long infusion' trials<sup>a</sup>.

Hypotension	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Cardiovascular System	93 (54%)	110 (65%)	114 (68%)	14 (54%)	0.027
Hypotension	27 (16%)	27 (16%)			
Symptomatic Hypotension	11 (6%)	20 (12%)			
Decreased Pulmonary Pressure	0 (0%)	0 (0%)			
Syncope	2 (1%)	2 (1%)	1 (1%)	0 (0%)	

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

The sponsor also summarized the data for the first 24 hours of the long infusion trials. The incidences of selected AEs from the table above are shown. The majority of the hypotensive AEs occurred during the first 24 hours, during the study drug infusion.

Table 8.0.2a.3 (from 11.1.3.3) Hypotensive AEs during the first 24 hours in the 'long infusion' trials<sup>a</sup>.

Hypotension	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Hypotension					
Symptomatic Hypotension					
Decreased Pulmonary Pressure					

a. Data from appendix 8.4, table 12C and from company at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

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### Hypotensive SAEs

The occurrence of hypotensive SAEs in the 'all CHF' and long infusion trials is summarized below. The SAEs were uncommon.

Table 8.0.2a.4 Hypotensive SAEs through 14 days in the nesiritide NDA database from all CHF trials<sup>a</sup>.

Serious Adverse Event	Control n=235	Nesiritide n=505
Hypotension	1 (<1%)	4 (1%)
Hypotension, symptomatic	1 (<1%)	4 (1%)
Syncope	1 (<1%)	2 (<1%)

a. Data from NDA appendix 8.4, table 27A.

Table 8.0.2a.5 (from 11.1.2.2) Hypotensive SAEs through 14 days in the 'long infusion' trials<sup>a</sup>.

Serious Adverse Event	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min
Hypotension <sup>b</sup>	1 (1%)	0 (0%)	1 (1%)	0 (0%)

a. Data from appendix 8.4, table 27C and from company at request of reviewer.

b. Includes 'hypotension' and 'symptomatic hypotension.'

### Discontinuations

There were significantly more discontinuations for hypotensive adverse events in the nesiritide group, as shown below for both the 'all CHF' and 'long infusion' groups. Dizziness is included as a sign of hypotension that can be misinterpreted, and also leads to discontinuation.

Table 8.0.2a.6 (from 11.1.5.3.1) Discontinuations prior to day 14 for hypotensive AEs in the 'all CHF' population<sup>a</sup>.

Hypotension/ Dizziness	Control n=235	Nesiritide n=505	Nominal p Value <sup>a</sup>
Cardiovascular System	15 (6%)	78 (15%)	<0.001
Hypotension Symptomatic			
Decreased Pulmonary Pressure	0 (0%)	5 (1%)	0.185
Nervous System			
Dizziness	0 (0%)	6 (1%)	0.184

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

Table 8.0.2a.7 (from 11.1.5.3.1) Discontinuations for hypotensive AEs in the long infusion trials<sup>a</sup>.

Hypotension/ Dizziness	Control	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value <sup>b</sup>
Cardiovascular	9 (5%)	23 (14%)	33 (20%)	6 (23%)	<0.001
Hypotension Symptomatic					
Decreased Pulmonary Pressure					
Dizziness					

a. Data from supplemental table 28D, with p Value per sponsor.

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### Hypotensive Deaths

After reviewing both the sponsor's summaries and the case report forms for individual patients, the following deaths were associated with hypotensive episodes. For both patients listed below, there is no apparent association between nesiritide administration and the death.

Table 8.0.2a.8 (from 11.1.1.2) Known deaths associated with hypotension in NDA 20-920<sup>a</sup>.

Treatment Group/ Patient #	# of Days After Study Entry	Cause of Death
<u>Placebo</u> None	--	--
<u>Active Control<sup>b</sup></u> None	--	--
<u>Nesiritide Bolus</u> None	--	--
<u>Nesiritide 0.015 µg/kg/min infusion</u> 382013	5	Progressive Renal Insufficiency CHF
<u>Nesiritide 0.030 µg/kg/min infusion</u> 357002	15	MI

a. Data from NDA volume 1.81, listing 7, and examination of individual case report forms.

1. *Subject 382-013 (nesiritide, 0.015 µg/kg/min)* Subject was an 80-year-old white man with NYHA Class IV CHF due to ischemic cardiomyopathy and progressive renal insufficiency. He had not responded to 7 days of dobutamine therapy before he was enrolled into the study. After 6 hours of nesiritide therapy, his hemodynamics were only minimally improved and dobutamine was restarted. Nesiritide was discontinued on study day 3 due to hypotension and nausea. After a short trial of milrinone added to the dobutamine, it was decided that the subject was refractory to vasoactive medications. The subject was made "Do Not Resuscitate." On day 5, the subject expired due to endstage CHF and progressive renal insufficiency.

### Deaths (cont)

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

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**Special Studies: Changes in Measured Blood Pressure**

In all three long infusion trials there was an association between nesiritide dose and the frequency of hypotension. This reflected an acute effect of nesiritide to lower blood pressure, as shown in the tables below, which come from the individual study reviews.

Table 8.0.2a.9 (from table 6.1.12.4.1) Effect of 3 hour infusion of nesiritide on blood pressure in trial 704.311<sup>a</sup>.

Blood Pressure Changes in Study 704.311	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	Nominal p Value <sup>b</sup>
Systolic BP (mm Hg)	+1.2 (+1%)	-7.4 (-6%)	-4.3 (-3%)	-10.0 (-8%)	0.006

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

Table 8.0.2a.10 (from table 6.2.12.4.2) Summary of changes in blood pressure using 'last value carried forward' population from study 704.325<sup>a</sup>.

Blood Pressure Changes in Study 704.325	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.0305 n=42	Nominal p Value <sup>b</sup>
Mean Systemic Arterial BP (MAP), mm Hg				
MAP at baseline				
MAP at 6 hours				
Nominal p Value (compared to control)	---	<0.001	<0.001	
Change in MAP from baseline at 6 hrs (mm Hg)				
Mean±SD				
Median	-1.3	-4.5	-8.7	
Range				
Nominal p Value (change from baseline) <sup>c</sup>	---	0.005	<0.001	
Nominal p Value (comp. to control) <sup>c</sup>	---	0.008	<0.001	

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

Table 8.0.2a.11 (from table 6.3.12.3.1) Changes in blood pressure from baseline to 3 hours in 704.326<sup>a</sup>.

Blood Pressure Changes in Study 704.326	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal p Value
Systolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	120.7±20	127±25	124±26	0.197
Change from Baseline				
Nominal p Value (Chg from Base) <sup>b</sup>	0.183	0.0001	<0.001	
Nominal p Value (Compared to Standard Care) <sup>c</sup>	--	0.003	<0.001	
Nominal p Value (Compared to Low-dose BNP) <sup>c</sup>	--	--	0.426	
Diastolic Blood Pressure (mm Hg)				
Baseline (mean±sd)	70±13	71±15	68±15	0.477
Change from Baseline				
Nominal p Value (Chg from Base) <sup>b</sup>	<0.001	<0.001	<0.001	
Nominal p Value (Compared to Standard Care)	--	0.376	0.125	
Nominal p Value (Compared to Low-dose BNP)	--	--	0.016	

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

**Special Studies: Timing and Severity of Hypotension**

The majority of the hypotensive events occurred during the first 24 hours of study drug administration. The sponsor performed further analyses of hypotension.

First, the frequency and severity of all hypotension was summarized. Both the severity of the hypotension and the effect on study drug administration were greatest in the nesiritide group. The effects also tended to be dose-related, with the highest incidence of severe hypotension resulting in drug discontinuation occurring in the nesiritide 0.060 dose group.

Table 8.0.2a.12 (from 11.1.3.2a.1) Severity and effect of all reported hypotension as an AE during the first 24 hours in the 'long infusion' trials in NDA 20-920<sup>a</sup>.

Hypotension	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
<b>Greatest Severity</b>					
No hypotension reported	158 (91%)	136 (80%)	115 (69%)	19 (73%)	<0.001
Mild	7 (4%)	14 (8%)	20 (12%)	2 (8%)	
Severe	1 (1%)	1 (1%)	1 (1%)	1 (4%)	
<b>Greatest Effect on Study Drug Administration<sup>b</sup></b>					
None	10 (6%)	9 (5%)	12 (7%)	2 (8%)	<0.001
Dose Decreased	4 (2%)	12 (7%)	21 (13%)	2 (8%)	
Dose Discontinued	1 (1%)	1 (1%)	1 (1%)	1 (4%)	

a. Data from supplemental data table 23D.2 at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

b. p Value for 'Greatest Effect on Drug Administration' performed including data for patients without hypotension.

Next, the sponsor analyzed the incidence of symptomatic hypotension in the long infusion trials. Once again, the severity of the hypotension and the effect on study drug administration were greatest in the nesiritide group. The severity of the hypotension also tended to be dose-related in the three nesiritide doses examined.

Table 8.0.2a.13 (from 11.1.3.2a.1) Severity and effect of symptomatic hypotension as an AE during the first 24 hours in the 'long infusion' trials in NDA 20-920<sup>a</sup>.

Symptomatic Hypotension	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
<b>Greatest Severity</b>					
No hypotension reported	167 (97%)	155 (92%)	144 (86%)	22 (85%)	0.004
Mild	2 (1%)	4 (2%)	4 (2%)	1 (4%)	
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
<b>Greatest Effect on Study Drug Administration<sup>b</sup></b>					
None	3 (2%)	3 (2%)	2 (1%)	2 (8%)	0.004
Dose Decreased	2 (1%)	5 (3%)	9 (5%)	0 (0%)	
Dose Discontinued	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

a. Data from supplemental data table 23D.2 at request of reviewer. Reflects trials 311, 325, and 326 data.

b. p Value for 'Greatest Effect on Drug Administration' performed including data for patients without hypotension.

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**Special Studies: Timing and Severity of Hypotension (cont)**

The sponsor analyzed the severity of the hypotension during the first 24 hours in the 704.326 study. There was a higher incidence of hypotension in the nesiritide groups for any SBP <100 mm Hg. Very few patients had extreme hypotension in any group (<60 mm Hg). In data not shown, the time to minimum SBP following start of study drug ranged widely, from 15 minutes to >1400 minutes in all three treatment groups.

Table 8.0.2a.14 (from 11.1.3.2a.2) Severity of hypotension during the first 24 hrs in 704.326<sup>a</sup>.

Changes in systolic BP (SBP)	Control n=173	Nesiritide 0.3/0.015 µg/kg/min n=169	Nesiritide 0.6/0.030 µg/kg/min n=167	Nominal p Value
Mean Minimum SBP (mm Hg)	100±17.50	97.9±18	91.0±16	0.001
Median	100.0	94.0	90.0	
Minimum SBP <100				
Minimum SBP <90				
Minimum SBP <80				
Minimum SBP <70				
Minimum SBP <60	1 (1%)	0 (0%)	2 (2%)	

a. Data from NDA appendix 8.4, table 25.

The mean and median decreases in systolic BP were also greater in the nesiritide groups in 704.326, even though the SBP was similar in all three groups at baseline..

Table 11.1.3.2a.15 Severity of hypotension during the first 24 hours in 704.326<sup>a</sup>.

Changes in systolic BP (SBP)	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nominal p Value
SBP at Baseline	121±20	127±25	123±26	0.197
Absolute Decrease in SBP (mm Hg)	21.2±16	29.4±16	33.1±19	<0.001
Median Decrease in SBP (mm Hg)	19.0	26.0	29.0	

a. Data from NDA appendix 8.4, table 25.

Finally, the duration of hypotension was examined by the sponsor in the three long infusion studies. Since only one patient in the control or placebo arms was discontinued for hypotension, only those patients in the nesiritide 0.015 and 0.30 groups were included in the analysis. Note that the onset of hypotension was frequently after several hours of nesiritide therapy, that prolonged hypotension was common in both nesiritide dose groups, and that a large majority of the symptomatic hypotension necessitated discontinuation of nesiritide.

Table 11.1.3.2a.16 Clinical features of first onset of symptomatic hypotension within first 24 hours<sup>a</sup>.

Symptomatic Hypotension	Nesiritide 0.015 n=14 (of 169 total)	Nesiritide 0.030 n=23 (of 167 total)
<b>Time of Onset (hrs)</b>		
<1 hrs	0	1
1 to <3 hrs	4	3
3 to <6 hrs	3	7
6 to 24 hrs	7	11
Unknown	0	1
<b>Severity</b>		
Mild	5	4
Moderate	9	12
Severe	0	7
<b>Duration</b>		
≤0.5 hrs	5	5
0.5 to <1 hrs	2	5
1 to 2 hrs	2	2
>2 to 7 hrs	4	8
>7 hrs	8	14
<b>Greatest Effect on Drug Dosing</b>		
No Effect	3	1
Dose Decreased	3	8
Nesiritide Discontinued	8	14

a. Data from sponsor at request of Medical Reviewer. A listing of the individual patients with hypotension to varying systolic BPs is found in appendix 18.0.

### Demographics of Hypotension

#### 1. Age

Hypotension occurred equally in both the elderly subjects (>65), and for those <65, as shown below for the long infusion trial population. Symptomatic hypotension occurred with equal frequency in the two groups (not shown). Note that in both age groups, hypotension was significantly more common in the nesiritide groups.

Table 8.0.2a.17 Hypotension an AE in the 'long infusion' population according to age<sup>a</sup>.

Hypotension	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
>65 Years Old	11/70 (16%)	20/69 (29%)	36/77 (47%)	2/9 (22%)	0.001
<65 Years Old	16/103 (10%)	27/100 (27%)	31/90 (34%)	6/17 (35%)	0.013

a. Data from supplemental data table 13D at request of reviewer. Reflects trials 311, 325, and 326 data.

#### 2. Gender

Symptomatic hypotension occurred more commonly in females.

Table 8.0.2a.18 Hypotension an AE in the 'long population according to gender'.

Hypotension	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
<b>Male</b>	n=127	n=120	n=113	n=23	
Hypotension	15 (12%)	35 (29%)	44 (39%)	7 (30%)	0.0001
Symptomatic Hypotension	8 (6%)	14 (12%)	16 (14%)	3 (13%)	0.190
<b>Female</b>	n=46	n=49	n=54	n=3	
Hypotension	12 (26%)	12 (24%)	23 (43%)	1 (33%)	0.166
Symptomatic Hypotension	3 (7%)	6 (12%)	16 (30%)	1 (33%)	0.009

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data.

#### 3. Other Medications

There was no detected relationship between nesiritide and the use of ACE inhibitors, digoxin, or beta blockers with respect to the occurrence of hypotension or symptomatic hypotension.

Table 8.0.2a.19 Hypotensive AEs by use of other medications in addition to nesiritide from study 704.326.

Occurrence of Hypotensive AEs <sup>b</sup>	Nesiritide 0.3/0.015 and 0.6/0.030 µg/kg/min
<b>ACE Inhibitor Use</b>	
Yes	42/124 (34%)
No	15/49 (31%)
<b>Digoxin Use</b>	
Yes	38/117 (32%)
No	11/45 (24%)
<b>Beta Blockers</b>	
Yes	6/18 (33%)
No	57/183 (31%)

a. Data from ISS table 8-39, reflecting trial 704.326 data.

b. Includes symptomatic and asymptomatic hypotension.

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#### 4. NYHA Class III or IV

Hypotensive AEs occurred with equal frequency in Class III and IV NYHA patients. The pattern, with a greater frequency of hypotension in the nesiritide groups, was also evident in both NYHA classes.

Table 8.0.2a.20 Hypotensive AEs in the 'long infusion' population<sup>a</sup> according to NYHA Class<sup>b</sup>.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
<b>Class III</b>	n=107	n=97	n=81	n=15	
Hypotension	12 (11%)	30 (31%)	28 (35%)	5 (38%)	<0.001
Symptomatic Hypotension	6 (6%)	12 (12%)	14 (17%)	1 (7%)	0.067
<b>Class IV</b>	n=58	n=64	n=71	n=9	
Hypotension	11 (19%)	16 (25%)	31 (44%)	2 (22%)	0.014
Symptomatic Hypotension	3 (5%)	7 (11%)	15 (21%)	2 (22%)	0.032

a. Data from supplemental data table 17D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes hypotension and symptomatic hypotension.

#### 5. Etiology of CHF

The sponsor also analyzed the occurrence of AEs by the original etiology of their CHF. With the exception of hypotension due to hypertensive CHF, there was an association between nesiritide and hypotension (both total and symptomatic).

Table 8.0.2b.21 Hypotensive AEs in the 'long infusion' population<sup>a</sup> according to etiology of CHF<sup>b</sup>.

Hypotension <sup>b</sup>	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
<b>Hypertensive CHF</b>	N=13	N=14	N=12	N=3	
Hypotension	3 (23%)	4 (29%)	4 (33%)	2 (67%)	0.582
Symptomatic Hypotension	2 (15%)	2 (14%)	3 (25%)	2 (67%)	0.228
<b>Ischemic CHF</b>	N=89	N=88	N=87	N=16	
Hypotension	10 (11%)	27 (31%)	36 (41%)	5 (31%)	<0.001
Symptomatic Hypotension	5 (6%)	13 (15%)	14 (16%)	2 (13%)	0.102
<b>Idiopathic/Dilated CHF</b>	N=38	N=40	N=11	N=5	
Hypotension	7 (18%)	11 (28%)	19 (54%)	1 (20%)	0.008
Symptomatic Hypotension	3 (8%)	5 (13%)	11 (31%)	0 (0%)	0.038

a. Data from supplemental tables provided at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

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**Special Studies: Individual Cases**

The tables in Appendix 18.0 list all the patients who had severe hypotension by a series of markers during the infusion trials.

The table below summarizes the clinical events for patients who had 'severe' hypotension (as defined by investigators) during the first 24 hours of the long infusion trials. As can be seen, several of the patients had prolonged hypotension, requiring additional medical interventions, including intubation, pressor medications, and IV fluids. The time to onset of the hypotension was also quite variable, ranging from 30 minutes (potentially related to the bolus infusion) to almost 10 hours. Finally, inadequate follow-up labs exist for some patients so determine whether there was renal injury following the hypotension.

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

Table 8.0.2b.22 (from 18.0.1) Subjects with hypotension in the first 24 hours where the greatest severity was 'severe'.

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

A list of all subjects with discontinuation or severe AEs related to hypotension can be found in appendix 18.0 below. Below are two notable patients from that list, who had hypotension during nesiritide infusion.

**Special Studies: Individual Cases (cont)**

One patient developed hypotension with a 'hypotensive crisis' requiring intubation while on nesiritide. This necessitated nesiritide discontinuation, and was associated with renal failure.

1. *Subject 357001 (Nesiritide 0.030 µg/kg/min)*, was a 63 y/o WM with CHF who received nesiritide 0.030 µg/kg/min for 2 days, until 30 minutes prior to cardiopulmonary arrest with electromechanical dissociation for 'hypotensive crisis' (recorded BP 68/42 mm Hg). His blood pressures recorded 2 hours prior to the cardiac arrest showed a decline in his systolic BP from a baseline of approximately 130 to 88 mm Hg. The reason recorded for discontinuation of study drug was 'hypotension.' During nesiritide infusion the patient also developed a worsening of his tachycardia (118 at baseline to 144 BPM at the end of 6 hours). After the hypotensive arrest, patient was treated with levophed and dopamine and intubated, but his blood pressure remained <70 systolic for approximately 2 hours. His creatinine rose from a baseline of 1.5 to 3.4, for which he received renal dose dopamine. His last recorded BUN/creatinine were 106/3.0 mg/dl.

Another patient, who the sponsor believes enrolled in the trial despite having a NQWMI, had marked decrease in blood pressure on two occasions associated with bradycardia, ultimately requiring nesiritide discontinuation. Whether this lability of BP/hypotension would occur in other patients with acute MIs treated with nesiritide is unknown.

2. *Subject 519-002 (nesiritide, 0.03 µg/kg/min)* Subject 519-002 is a 77-year-old black woman with NYHA Class III CHF. Nesiritide infusion was interrupted after 41 minutes because of asymptomatic hypotension (decrease in SBP from 170 mm Hg at baseline to 73 mm Hg). Nesiritide infusion was restarted at half of the original dose but at 4 hours, 30 minutes, infusion was terminated because of recurrent asymptomatic hypotension (to SBP of 79 mm Hg). Approximately 30 minutes later, the subject was noted to have sinus bradycardia (heart rate = 48 beats/min) which resolved spontaneously. On day 2, it was discovered that this subject had had elevated cardiac enzymes (myoglobin, with a normal CPK) at enrollment and was diagnosed by the investigator/sponsor as having had a non-Q wave myocardial infarction (before study drug infusion). No follow-up labs are available regarding the development of renal failure, although this is not listed as an adverse event.

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### Sponsor's Comments Regarding Hypotension

The sponsor felt that while hypotension is the most frequent adverse event associated with nesiritide administration, that this AE is an extension of the pharmacological effect as a vasodilator. They argued that... 'it is therefore unlikely that the benefits of vasodilators (such as preload and afterload reduction) could be derived without exposing some patients to a greater than desired reduction in blood pressure.' They also pointed out that there was no pre-specified definition for hypotension, such that there might be some investigator variability regarding the reporting of hypotension as an AE.

The sponsor sought to determine those demographics that might predict patients who are more likely to develop hypotension. Per the sponsor, 'no single factor assessed emerged as a reliable predictor of the development of symptomatic hypotension, although small sample sizes in many of the subgroups may have confounded this analysis.'

The sponsor concluded that 'no long term or significant adverse sequelae have been clearly associated with nesiritide -induced hypotension to date. The majority of subjects tolerate moderate dose-related decreases in blood pressure well and experience an overall beneficial clinical response to nesiritide therapy. Nesiritide should be administered in a clinical setting in which blood pressure can be adequately monitored and dose adjustment instituted as clinically indicated.'

### Reviewer's Conclusions Regarding Hypotension

There is a definite, dose-dependent association between nesiritide administration and the occurrence of hypotension (tables 8.0.2a 9 through 8.0 2a.11). This hypotension was clinically significant, as assessed by the following:

- 1) the greater incidence of symptomatic hypotension in the nesiritide groups (tables 8.0.2a.1 8.0.2a.2, and 8.0.2a.3).
- 2) the increased incidence of discontinuations for decreased BP (tables 8.0.2a.6 and 8.0.2a.7).
- 3) the greater severity of the hypotension in the nesiritide groups (tables 8.0.2a.12, 8.0.2a.13, and 8.0.2a.14).
- 4) the presence of individuals who developed hypotension during nesiritide infusion who had clearly adverse clinical outcomes (table 8.0.2a.22).
- 5) data from trial 704.326, comparing nesiritide with current therapy, which shows that the incidence of hypotension leading to discontinuation of drug within 6 hours of initiation was significantly higher with nesiritide than with the compounds currently being used to treat CHF. These data are of particular interest, since they suggest that the use of nesiritide in practice will lead to significantly more hypotension than is caused by the drugs in current use. This statement is limited by the fact that 704.326 enrolled very few patients who received pure vasodilators (18 patients got IV NTG, none IV nitroprusside). There is, then, no way to know the frequency of these same adverse events for the other pure vasodilators. Given that the pharmacodynamic half-life of these agents is shorter than nesiritide, it is possible that fewer episodes of severe hypotension or renal failure would be seen with these agents.

Further, the time of onset, and duration of hypotension in association with nesiritide is quite variable. Some individuals, however, clearly have sustained hypotension (table 11.1.3.2a.16)

Finally, the sub-group analyses did not reveal any sub-group definitely at increased risk for hypotension, although women had a higher incidence of symptomatic hypotension.

In conclusion, there is a definite association between nesiritide use and a dose-dependent increase in clinically significant hypotension.

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### 8.0.2b Bradycardia

#### AEs

The first two tables summarize the incidence of AEs related to bradycardia in the 'all CHF' and the 'long infusion' databases. An increase in bradycardic AEs was seen in both sets of trials.

Table 8.0.2b.1 (from 11.1.3.1) Bradycardic AEs in the 'all CHF' trials from NDA 20-920<sup>a</sup>.

Bradycardic AEs	Control n=235	Nesiritide n=505
<b>Bradycardic Events<sup>b</sup></b>	2 (1%)	26 (5%)
Bradycardia	2 (1%)	22 (4%)
Sinus Bradycardia	0 (0%)	1 (<1.0%)
<b>AV Node Conduction Abnormalities</b>	4 (2%)	9 (2%)
AV Block, Complete	1 (<1.0%)	0 (0%)
AV Block, First Degree	3 (1%)	5 (1%)
AV Block, Second Degree	1 (<1.0%)	4 (1%)

a. Data from NDA appendix 8.4, table 11A.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

Table 8.0.2b.2 (from 11.1.3.2) Bradycardic AEs in the first 14 days in the 'long infusion' population<sup>a</sup>.

Bradycardic AEs	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
<b>Bradycardic Events</b>	11 (6%)	19 (11%)	11 (6%)	11 (42%)	
Bradycardia	1 (1%)	9 (5%)	10 (6%)	11 (42%)	
Sinus Bradycardia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Nodal Bradycardia	0 (0%)	0 (0%)	3 (2%)	0 (0%)	0.169
<b>AV Node Conduction Abnormalities</b>	3 (2%)	5 (3%)	4 (2%)	0 (0%)	0.846
AV Block, First Degree	3 (2%)	3 (2%)	2 (1%)	0 (0%)	1.000
AV Block, Second Degree	1 (1%)	2 (1%)	2 (1%)	0 (0%)	0.804

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

The sponsor also summarized the data for the first 24 hours of the long infusion trials. The incidences of selected AEs from the table above are shown. Overall, similar trends in the incidence of AEs were seen in both sets.

Table 8.0.2b.3 (from 11.1.3.3) Bradycardic AEs during the first 24 hours in the 'long infusion' population<sup>a</sup>.

Bradycardic AEs	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
<b>Bradycardic Events</b>	11 (6%)	19 (11%)	11 (6%)	11 (42%)	
Bradycardia	1 (1%)	9 (5%)	10 (6%)	11 (42%)	

a. Data from appendix 8.4, table 12C and from company at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal bradycardia, and sinus bradycardia.

#### Bradycardic SAEs

The sponsor also summarized the occurrence of bradycardia as a reported SAE. These events were rarely reported.

Table 8.0.2b.4 (from 11.1.2.1) Bradycardic SAEs through 14 days from 'all CHF' population<sup>a</sup>.

Bradycardic SAEs	Control n=235	Nesiritide n=505
<b>Bradycardic events</b>	1 (<1%)	3 (1%)
Bradycardia	1 (<1%)	3 (1%)

a. Data from NDA appendix 8.4, table 27A.

### Bradycardic SAEs (cont)

Examination of the list of SAEs identified in the infusion studies found no significant differences between nesiritide and the control group with regard to bradycardic SAEs.

Table 8.0.2b.5 (from 11.1.2.2) The occurrence of bradycardic SAEs through 14 days in the 'long infusion' population<sup>a</sup>.

Bradycardic SAEs	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=31	Nominal p Value
Bradycardia <sup>b</sup>	1 (1%)	0 (0%)	2 (1%)	0 (0%)	0.795

a. Data from appendix 8.4, table 27C and from company at request of reviewer.

b. Included 'bradycardic events' and bradycardia.

### Discontinuation

Discontinuations for bradycardia were infrequent, and only occurred in the nesiritide groups.

Table 8.0.2b.6 (from 11.1.5.3.1) Discontinuations prior to day 14 due to bradycardic AEs in the 'all CHF' population<sup>a</sup>.

Body System/ AE	Control n=235	Nesiritide n=505	Nominal p Value <sup>a</sup>
Cardiovascular System	15 (6%)	78 (15%)	<0.001
Bradycardic Event <sup>b</sup>	0 (0%)	7 (1%)	0.104
Bradycardia	0 (0%)	6 (1%)	0.184
Nodal Arrhythmias	0 (0%)	1 (0%)	1.000

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

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

Next, the discontinuations associated with AEs in the long infusion studies are summarized. The rate of discontinuations associated with bradycardia was quite low, and similar in all treatment groups.

Table 8.0.2b.7 (from 11.1.5.3.1) Discontinuations due to bradycardic AEs in the 'long infusion' population<sup>a</sup>.

D/Cs with Bradycardia	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
Bradycardic Events <sup>b</sup>	0 (0%)	2 (1%)	4 (2%)	0 (0%)	0.170
Bradycardia	0 (0%)	2 (1%)	3 (2%)	0 (0%)	0.325
Nodal Arrhythmia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361

a. Data from supplemental table 28D, with p Value per sponsor.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

### Bradycardic Deaths

No deaths were attributable to bradycardia induced by study drugs. One death was associated with digoxin toxicity and bradycardia. The narrative of this patient appears below.

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

Another subject receiving nesiritide developed marked bradycardia associated with hypotension.

2. Subject 360-101 (nesiritide, 0.030 µg/kg/min) became acutely diaphoretic with bradycardia (ECG, Junctional Bradycardia, rate 34/ min) and hypotension (85/61) during nesiritide administration. Just prior to the event he had received his usual medications: isordil and enalapril, with a BP of 134/76. He recovered with atropine and fluids following discontinuation of nesiritide. He had another episode of bradycardia two weeks later during infusion of IV NTG, which the sponsor suggests may have contributed to the episode.

**Special Studies: Heart Rate**

The acute effect of nesiritide on heart rate was also compared with control in the three infusion trials. Overall, no clear pattern of effect was discernable, perhaps related to the different controls used in each of the trials (placebo in 704.311, active control in 704.326). Note that the placebo group in 704.311 had an increase in their mean heart rate.

Table 8.0.2b.8 (from table 6.1.12.4.1) Mean change in heart rate from baseline to 3 hours in trial 704.311<sup>a</sup>.

Heart Rate in Study 704.311	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	Nominal p Value <sup>b</sup>
Heart Rate (BPM)	80.8	80.7	80.7	80.7	0.921

a. Data from NDA 20-998, vol. 54, Table 2 for ITT population.

b. p Value comparing arithmetic means from baseline using ANOVA.

Table 8.0.2b.9 (from table 6.2.12.4.2) Summary of changes in heart rate using 'last value carried forward' population from study 704.325<sup>a</sup>.

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

a. Data from NDA volume 1.59, Appendix 1, Table 26a to 40a and electronic data sets.

b. p Value using Omnibus F test.

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

Table 8.0.2b.10 (from table 6.3.12.3.1) Changes in heart rate from baseline to 3 hours in study 704.326<sup>a</sup>.

Heart Rate in Study 704.326	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal p Value
Baseline Heart Rate (mean±sd)	85±15	83±18	84±15	0.823
<b>Change in Heart Rate (mm Hg)</b>				
Nominal p Value (Chg from Base) <sup>b</sup>	0.029	0.501	0.569	
Nominal p Value (Compared to Standard Care) <sup>c</sup>	---	0.018	0.107	
Nominal p Value (Compared to Low-dose BNP) <sup>c</sup>	---	---	0.469	

a. Data from NDA volume 1.66, table 21.

b. Comparison by T test.

c. Comparison by ANOVA.

## Demographics of Bradycardia

### 1. Age

No effect of age on the incidence of bradycardic events was detected.

Table 8.0.2b.11 Bradycardic AEs in the 'long infusion' population according to age<sup>a</sup>.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
<b>&gt;65 Years Old</b>	n=70	n=69	n=77	n=9	
<b>Bradycardic Events<sup>b</sup></b>	1 (1%)	6 (9%)	8 (10%)	0 (0%)	0.102
<b>Bradycardia</b>	1 (1%)	0 (0%)	5 (6%)	0 (0%)	0.233
<b>Sinus Bradycardia</b>	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1.000
<b>&lt;65 Years Old</b>	n=103	n=100	n=90	n=17	
<b>Bradycardic Events<sup>b</sup></b>	0 (0%)	3 (3%)	6 (7%)	0 (0%)	0.041
<b>Bradycardia</b>	0 (0%)	3 (3%)	5 (6%)	0 (0%)	0.079

a. Data from supplemental data table 13D at request of reviewer. Reflects trials 311, 325, and 326 data. p Value per sponsor.

b. Includes bradycardia, sinus bradycardia, and nodal arrhythmia.

### 2. Gender

Bradycardic AEs occurred rarely, and there was no apparent influence of gender on their incidence.

Table 8.0.2b.12 Bradycardic AEs in the 'long infusion' population according to gender<sup>a</sup>.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
<b>Male</b>	n=127	n=120	n=113	n=23	
<b>Bradycardic Events<sup>b</sup></b>	1 (1%)	5 (4%)	10 (9%)	0 (0%)	0.016
<b>Bradycardia</b>	1 (1%)	5 (4%)	8 (7%)	0 (0%)	0.054
<b>Female</b>	n=46	n=49	n=54	n=3	
<b>Bradycardic Events<sup>b</sup></b>	0 (0%)	4 (8%)	4 (7%)	0 (0%)	0.221
<b>Bradycardia</b>	0 (0%)	4 (8%)	2 (4%)	0 (0%)	0.238

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

### 3. Other Medications

In study 704.326, the incidence of bradycardia was more frequent in patients taking nesiritide and ACE inhibitors, digoxin, but not beta blockers. The numbers of such patients were quite small, however. The table shows incidences for the 0.015 and 0.030 groups combined (there was no 0.060 group in this study).

Table 8.0.2b.13 Bradycardic AEs arranged by use of other medications in addition to nesiritide from study 704.326<sup>a</sup>.

Occurrence of Bradycardic AEs <sup>b</sup>	Nesiritide 0.015 µg/kg/min
<b>ACE Inhibitor Use</b>	
Yes	10/124 (8%)
No	1/49 (2%)
<b>Digoxin Use</b>	
Yes	9/117 (8%)
No	1/45 (2%)
<b>Beta Blockers</b>	
Yes	2/18 (11%)
No	10/183 (5%)

a. Data from ISS VOL. 79, table 8-39, reflecting trial 704.326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

#### 4. NYHA Class III or IV

Bradycardic AEs occurred with equal frequency in Class III and IV NYHA patients.

Table 8.0.2b.14 Bradycardic AEs in the 'long infusion' population\* according to NYHA Class<sup>a</sup>.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
NYHA III Bradycardic Events <sup>b</sup>	n=107 7 (7%)	n=97 13 (13%)	n=81 3 (4%)	n=15 0 (0%)	0.094
NYHA IV Bradycardic Events <sup>b</sup>	n=58 0 (0%)	n=64 3 (5%)	n=71 4 (6%)	n=9 0 (0%)	0.413

a. Data from supplemental data table 17D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

#### 5. Etiology of CHF

Bradycardic events occurred with equal frequency regardless of the original etiology of the CHF (with small numbers for analysis).

Table 8.0.2b.15 Bradycardic AEs in the 'long infusion' population\* according to etiology of CHF<sup>a</sup>.

Bradycardic Events <sup>b</sup>	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Hypertensive	0/13 (0%)	0/14 (0%)	3/12 (25%)	0/3 (0%)	0.047
Ischemic	0/89 (0%)	5/88 (6%)	8/87 (9%)	0/16 (0%)	0.013
Idiopathic/Dilated	0/38 (0%)	3/40 (8%)	1/35 (3%)	0/5 (0%)	0.383

a. Data from supplemental tables provided at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

#### Sponsor's Comments

The sponsor argued that the increased incidence of bradycardia in patients who received nesiritide might be due to an effect by nesiritide to both decrease sympathetic and increase parasympathetic tone. Additionally, while bradycardia has accompanied nesiritide -induced hypotension, these events were self-limited following nesiritide discontinuation or have responded to atropine.

The sponsor also argued that nesiritide use was not associated with increases in either ventricular arrhythmias or AV-nodal conduction abnormalities. They pointed out that increases in heart rate are often seen with inotropes such as dopamine and dobutamine.

The sponsor concluded that the association between nesiritide and bradyarrhythmias but not ventricular or nodal arrhythmias, 'is an interesting and important observation for a new drug for this indication and bears further investigation.'

#### Reviewer's Conclusions Regarding Bradycardia

There is a definite association between nesiritide administration and the development of bradycardia as an adverse event. While the incidence of SAEs related to decreased heart rate is rare, bradycardia caused discontinuation of a higher percentage of nesiritide patients. No sub-groups of patients were identified who were at higher risk of bradycardia. A bradycardic effect of nesiritide has been reported in the literature, where it was associated with profound hypotension leading to loss of consciousness and required atropine and fluids for treatment (ref. 2). For the drug-drug interaction analysis, there was some suggestion that patients on ACE inhibitors, digoxin or beta-blockers were at higher risk, but the patient numbers are simply too small for any firm conclusion.

In conclusion, there is a definite association between nesiritide administration and the development of bradycardia.

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8.0.2c Other Ventricular and Atrial Arrhythmias

**AEs and SAEs**

The occurrence of AEs related to arrhythmias in the two trial populations are summarized below.

Table 8.0.2c.1 (from 11.1.3.1) Arrhythmic AEs in the 'all CHF' population<sup>a</sup>.

Arrhythmic AEs	Control n=235	Nesiritide n=505
Ventricular Tachycardia	36 (15%)	75 (15%)
Sustained Ventricular Tachycardia	6 (3%)	9 (2%)
Ventricular Extrasystoles	13 (6%)	22 (4%)
Tachycardia	10 (4%)	12 (2%)
Atrial Fibrillation	5 (2%)	14 (3%)
Supraventricular Tachycardia	5 (2%)	12 (2%)
Bigeminy	3 (1%)	8 (2%)
Syncope	2 (1%)	4 (1%)
Palpitations	1 (0%)	8 (2%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.2c.2 (from 11.1.3.2) Arrhythmic AEs in the first 14 days in the 'long infusion' group<sup>a</sup>.

Arrhythmias	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Values
Ventricular Extrasystoles	13 (8%)	11 (7%)	8 (5%)	0 (0%)	0.477
Ventricular Tachycardia					
Sustained VT	6 (3%)	5 (3%)	3 (2%)	0 (0%)	0.791
Non-sustained VT					
Atrial Fibrillation	5 (3%)	2 (1%)	8 (5%)	1 (4%)	0.188
Tachycardia	9 (5%)	5 (3%)	5 (3%)	1 (4%)	0.644
SVT	3 (2%)	4 (2%)	7 (4%)	0 (0%)	0.490
Supraventricular Extrasystoles	2 (1%)	3 (2%)	1 (1%)	0 (0%)	0.781

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

The sponsor also summarized the data for the first 24 hours of the long infusion trials. Of note, less than 50% of the ventricular tachycardias reported took place during the first 24 hours of study drug infusion.

Table 8.0.2c.3 (from 11.1.3.3) Ventricular tachycardia during the first 24 hours in the 'long infusion' trials.

Ventricular Tachycardia	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Ventricular Tachycardia					

**SAEs Due to Ventricular Arrhythmias**

The reported SAEs related to arrhythmias other than bradycardia are summarized below. These events were reported infrequently, at similar rates in both groups.

Table 8.0.2c.4 (from 11.1.2.1) The occurrence of arrhythmic SAEs through 14 days in the nesiritide NDA database from 'all CHF' trials<sup>a</sup>.

SAEs related to Arrhythmias	Control n=235	Nesiritide n=505
Heart Arrest	4 (2%)	7 (1%)
Ventricular Tachycardia	2 (1%)	4 (1%)
Sustained Ventricular Tachycardia	2 (1%)	4 (1%)

a. Data from NDA appendix 8.4, table 27A.

Table 8.0.2c.5 (from 11.1.2.2) Occurrence of arrhythmic SAEs through 14 days in the 'long infusion' trials\*.

Serious Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min
Cardiovascular				
Ventricular Tachycardia	2 (1%)	2 (1%)	2 (1%)	0 (0%)
Sustained VT	2 (1%)	2 (1%)	2 (1%)	0 (0%)

a. Data from appendix 8.4, table 27C and from company at request of reviewer.

### Discontinuations

Discontinuations prior to day 14 for ventricular tachycardia were rare, and occurred only in the control group in the 'CHF trials' population\*.

Table 8.0.2c.6 (from 11.1.5.3.1) Discontinuations prior to day 14 for ventricular tachycardia in the 'CHF trials' population\*.

Body System/ AE	Control n=235	Nesiritide n=505	Nominal p Value <sup>a</sup>
Ventricular Tachycardia	3 (1%)	0 (0%)	0.032

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

Next, the discontinuations associated with AEs in the long infusion studies are summarized. Again, the only discontinuations for ventricular tachycardia occurred in the control group.

Table 8.0.2c.7 (from 11.1.5.3.1) Discontinuations due to arrhythmic AEs in the long infusion trials\*.

Arrhythmic AEs associated with Discontinuation	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value <sup>b</sup>
Ventricular Tachycardia	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0.234
Sustained VT	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0.395
Non sustained VT	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1.000
Tachycardia	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1.000

a. Data from supplemental table 28D.

### Deaths

Several deaths were associated with arrhythmias, as might be expected in this patient population. The narrative for these patients can be found in Appendix two.

Table 8.0.2c 8 (from 11.1.1.2) Known deaths associated with arrhythmias (non-bradycardic)\*.

Treatment Group/ Patient #	# of Days After Study Entry	Cause of Death
<b>Placebo</b>		
381001	6	Ventricular arrhythmia Dilated cardiomyopathy
356103	19	Ventricular Fibrillation, EMD
376016	6	Sudden Death, CHF
376022	21	Sudden Death, CHF
368001	16	Ventricular Fibrillation, CHF
<b>Nesiritide Bolus</b>		
315005	30	CHF
373301	30	Sudden Cardiac Death Dilated cardiomyopathy
<b>Nesiritide 0.015 µg/kg/min infusion</b>		
538010	9	Mitral regurgitation Chronic atrial flutter
<b>Nesiritide 0.030 µg/kg/min infusion</b>		
524005	5	Ventricular fibrillation
<b>Nesiritide 0.060 µg/kg/min infusion</b>		
3282004	8	Ventricular Arrhythmia Congestive Cardiomyopathy

a. Data from NDA vol. 1.81, listing 7, and examination of individual case report forms.

b. In study 326 subjects were randomized to receive other IV cardiovascular meds.

## Demographics of Ventricular Arrhythmias

### 1. Age

The pattern of non-bradycardic arrhythmias was similar in both > and <65 year olds with the exception of the nesiritide 0.015 dose group, where the incidence of ventricular tachycardia was somewhat higher in the <65 age group. In both groups, the rate of VT was lower in the nesiritide 0.030 group than in control. For rarer AEs, such as atrial fibrillation, the number of cases is too few to justify comparisons (data not shown).

Table 8.0.2c.9 Arrhythmic AEs in the 'long infusion' population according to age<sup>a</sup>.

Arrhythmic AEs by Age	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
<b>&gt;65 Years Old</b>	n=70	n=69	n=77	n=9	
Ventricular Tachycardia	15 (21%)	12 (17%)	9 (12%)	0 (0%)	0.249
Sustained VT	4 (6%)	2 (3%)	1 (1%)	0 (0%)	0.481
Non-sustained VT	12 (17%)	11 (16%)	8 (10%)	0 (0%)	0.441
<b>&lt;65 Years Old</b>	n=103	n=100	n=90	n=17	
Ventricular Tachycardia	19 (18%)	30 (30%)	13 (14%)	0 (0%)	0.005
Sustained VT	2 (2%)	3 (3%)	2 (2%)	0 (0%)	0.931
Non-sustained VT	17 (17%)	29 (29%)	12 (13%)	0 (0%)	0.005

a. Data from supplemental data table 13D at request of reviewer. Reflects trials 311, 325, and 326 data. p Value per sponsor.

### 2. Gender

Arrhythmic AEs occurred in all groups at a higher rate in males, but the pattern of occurrence was similar in both males and females, with a trend towards less non-sustained VT in the high-dose nesiritide groups.

Table 8.0.2c.10 Arrhythmic AEs in the 'long infusion' population according to gender<sup>a</sup>.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
<b>Male</b>	n=127	n=120	n=113	n=23	
Ventricular Tachycardia	29 (23%)	36 (30%)	16 (14%)	0 (0%)	0.001
Sustained VT	5 (4%)	5 (4%)	2 (2%)	0 (0%)	0.684
Non-sustained VT	24 (19%)	34 (28%)	14 (12%)	0 (0%)	0.001
<b>Female</b>	n=46	n=49	n=54	n=3	
Ventricular Tachycardia	5 (11%)	6 (12%)	6 (11%)	0 (0%)	1.000
Sustained VT	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0.769
Non-sustained VT	5 (11%)	6 (12%)	6 (11%)	0 (0%)	1.000

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data. p Values per the sponsor.

### 3. NYHA Class III or IV

Ventricular arrhythmias occurred with equal frequency in Class III and IV NYHA patients.

Table 8.0.2c.11 Arrhythmic AEs in the 'long infusion' population<sup>a</sup> according to NYHA Class<sup>a</sup>.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
<b>NYHA III</b>	n=107	n=97	n=81	n=0	
Ventricular Tachycardia	17 (16%)	27 (28%)	8 (10%)	0 (0%)	0.003
Sustained VT	4 (4%)	4 (4%)	0 (0%)	0 (0%)	0.257
Non-sustained VT	13 (12%)	25 (26%)	8 (10%)	0 (0%)	0.005
<b>NYHA IV</b>	n=58	n=64	n=71	n=0	
Ventricular Tachycardia	15 (20%)	13 (20%)	14 (20%)	0 (0%)	0.394
Sustained VT	1 (2%)	1 (2%)	3 (4%)	0 (0%)	0.704
Non-sustained VT	14 (24%)	13 (20%)	12 (17%)	0 (0%)	0.394

a. Data from supplemental data table 18D at request of reviewer. Reflects trials 311, 325, and 326 data. p Values per the sponsor.

#### 4. Etiology of CHF

Ventricular arrhythmias occurred with equal frequency regardless of the original etiology of CHF. Note the predominance of ischemic etiologies for CHF.

Table 8.0.2b.12 Ventricular tachyarrhythmias as AEs in the 'long infusion' population according to etiology of CHF<sup>a</sup>.

Ventricular Tachycardia <sup>b</sup>	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Hypertensive	2/13 (15%)	2/14 (14%)	3/12 (25%)	0/3 (0%)	0.867
Ischemic	16/89 (18%)	19/88 (22%)	12/87 (14%)	0/16 (0%)	0.135
Idiopathic/Dilated	11/38 (29%)	13/40 (33%)	3/35 (9%)	0/5 (0%)	0.034

a. Data from supplemental tables provided at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes sustained and non-sustained VT.

#### Special Studies: Holter Monitors

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

#### Reviewer's Conclusions Regarding Non-Bradycardic Arrhythmias

The available data support the conclusion that an adverse effect of nesiritide on the incidence of non-bradycardic arrhythmias, especially ventricular arrhythmias, is unlikely. There is, instead, a possible effect of nesiritide to decrease the incidence of non-sustained ventricular tachycardias relative to placebo. This observation is based on the nominally significant decrease in ventricular tachycardia (especially non-sustained VT) in the nesiritide group. Whether this possible effect is related to the bradycardic effects of nesiritide or to other factors is unknown.

In conclusion, an adverse association between nesiritide infusion and ventricular arrhythmias is unlikely.

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**8.0.2d Congestive Heart Failure**

**AEs**

The incidence of CHF identified as an AE in the two trial populations is summarized below.

Table 8.0.2d.1 (from 11.1.3.1) CHF as an AE in the CHF trials from NDA 20-920<sup>a</sup>.

CHF	Control n=235	Nesiritide n=505
Congestive Heart Failure	20 (9%)	48 (10%)

a. Data from NDA appendix 8.4, table 11A.

Examination of the list of AEs identified in the infusion studies (through day 14) found the following.

Table 8.0.2d.2 (from 11.1.3.2) CHF as an AE reported during the first 14 days in the 'long infusion' group<sup>a</sup>.

CHF	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Congestive Heart Failure	11 (6%)	18 (11%)	20 (12%)	3 (12%)	0.274

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

Examination of the list of AEs identified in the infusion studies (through 24 hours) found that the majority of the CHF reported occurred after the first 24 hours in the study.

Table 8.0.2d.3 CHF as an AE reported during the first 24 hours in the 'long infusion' group<sup>a</sup>.

CHF	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Congestive Heart Failure	4 (2%)	5 (3%)	6 (4%)	0 (%)

a. Data from company at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

**SAEs**

The occurrence of CHF as an SAE was also collected, and is summarized below. No significant differences were detected between the treatment groups.

Table 8.0.2d.4 (from 11.1.2.1) CHF as an SAE through 14 days from 'all CHF' population<sup>a</sup>.

CHF	Control n=235	Nesiritide n=505
Congestive Heart Failure	4 (2%)	11 (2%)

a. Data from NDA appendix 8.4, table 27A.

CHF as an SAE was also collected in the 'long infusion' studies.

Table 8.0.2d.5 (from 11.1.2.2) The occurrence of CHF SAEs through 14 days in the 'long infusion' trials<sup>a</sup>.

Serious Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Congestive Heart Failure	3 (2%)	3 (2%)	7 (4%)	1 (4%)

a. Data from appendix 8.4, table 27D and from company at request of reviewer.

**Discontinuations**

CHF associated with discontinuation is summarized below, again showing no difference between treatment groups with small numbers of subjects.

Table 8.0.2d.6 (from 11.1.5.3.1) Discontinuations for CHF prior to day 14 in the 'all CHF' population<sup>a</sup>.

CHF leading to discontinuation	Control n=235	Nesiritide n=505	Nominal p Value
Congestive Heart Failure	7 (3%)	14 (3%)	0.817

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

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

Table 8.0.2d.7 (from 11.1.5.3.1) Discontinuations due to CHF AEs in the long infusion trials<sup>a</sup>.

AE	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
Congestive Heart Failure	4 (2%)	5 (3%)	5 (3%)	0 (0%)	0.946

a. Data from supplemental table 28D.

#### Rehospitalizations for CHF

The sponsor collected information about the re-admission through 21 days in trials 704.325 and 704.326. In both, there were more re-admissions for CHF in the nesiritide groups. The data for 704.326 are shown below, and show that there was no difference in the rate of re-hospitalization for CHF between the study groups. Similar data (not shown) was found in 704.325.

Table 8.0.2d.8 (from 6.2.12.2e.7) Hospital readmission through 21 days in study 704.326<sup>a</sup>.

Volume parameter and period of measurement	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal p Value
Subjects discharged prior to day 21				
If discharged, # of subjects readmitted by day 21	16 (16%)	8 (8%)	11 (11%)	0.181
If readmitted, primary reason for first readmittance				
CHF recurrence	8 (50%)	4 (50%)	4 (36%)	
Elective, unrelated to CHF	1 (6%)	0 (0%)	1 (9%)	
Medical condition other than CHF	6 (38%)	2 (25%)	6 (55%)	
Other	1 (6%)	2 (25%)	0 (0%)	
If readmitted, primary reason for all readmittance				
CHF recurrence	9 (53%)	4 (44%)	6 (46%)	
Elective, unrelated to CHF	1 (6%)	0 (0%)	1 (8%)	
Medical condition other than CHF	6 (35%)	2 (22%)	6 (46%)	
Other	1 (6%)	3 (33%)	0 (0%)	

a. Data from NDA volume 1.66, Appendix 1, Table 34, and electronic data sets. Includes all subjects discharged before day 21.

#### Deaths

Several deaths were associated with worsening congestive heart failure, as would be expected for this patient population. None were clearly associated with nesiritide administration. The narrative for these patients can be found in Appendix two.

#### Demographics

The small number of subjects who had CHF reported as an AE make subset analysis fruitless.

#### Reviewer's Conclusions Regarding CHF as an AE

The meaning of an adverse event for 'CHF' in trials enrolling only patients with CHF is hard to interpret exactly, but may reflect worsening CHF on therapy. If this is the case, one might expect to see an increase in re-hospitalizations for CHF. This was not seen.

In conclusion, the data suggest an effect of nesiritide on the incidence of 'CHF' as an adverse event is unlikely. The meaning of this AE in the context of the larger trial is unclear, and the data are inadequate to fully resolve this issue. This absence of an effect on 'CHF' as an AE cannot be taken as an indicator of efficacy for the overall trials.

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