period. The fewest number of readmissions were among those in the Natrecor adjustable dose group. The differences, however, were small. The most common causes of rehospitalization were acute events.

Table 36 Current hospitalization and hospitalization till 30 days.

	NTG (N= 216)	NAT Fixed (N=211)	All NAT (N=273)	NAT ADJ (N= 62)
Days Hops prior to Infusion Mean ± SD	1.9 ± 3.1	1.9 ± 2.7	1.8 ± 2.8	1.7 ± 3.0
N= / Missing ( )	216 /(0)	211 / (0)	273 /(0)	62 /(0)
Days Hosp. From Start of Infusion Through Day 30 Mean ± SD	8.1 ± 7.0	10.3 ± 8.7	10.0 ± 8.4	8.8 ± 7.2
N= / Missing ( )	216 (0)	211 (0)	273 / (0)	62 (0)
# Discharged prior to 30 days				
yes	206 (95%)	194 (92%)	253 (93%)	59 (95%)
no	10 (5%)	17 (8%)	20 (7%)	3 (5%)
Of Those Discharged, Those readmitted by day 30	48 (23%)	41 (21%)	50 (20%)	9 (15%)
1 readmission	39 (19%)	38 (20%)	47 (19%)	9 (15%)
2 readmissions	9 (4%)	3 (2%)	3 (1%)	0
3 readmissions	0	0	0	0
4 readmissions	0	0	0	0
Total readmissions	57	44	53	9
Reason for Readmission				
Acute CHF	30 (14%)	18 (9%)	21 (8%)	3 (5%)
CHF elective	0	0	0	0
Other, Acute	23(11%)	23 (11%)	27 (10%)	4 (6%)
Other elective	4 (2%)	3(1%)	5 (2%)	2 (3%)

Mortality: Mortality was to be assessed at 30, 90 and 180 days after the infusion. A Kaplan-Meier representation of the mortality is shown as figure 9. Point estimates actually favor Nitroglycerine (Table 37). There was no benefit of the use of Natrecor on mortality. At one month, the worst outcome was in the Natrecor Adjustable dose (11.5% mortality rate). At six-months the mortality rate mortality rate for this cohort was 35%.

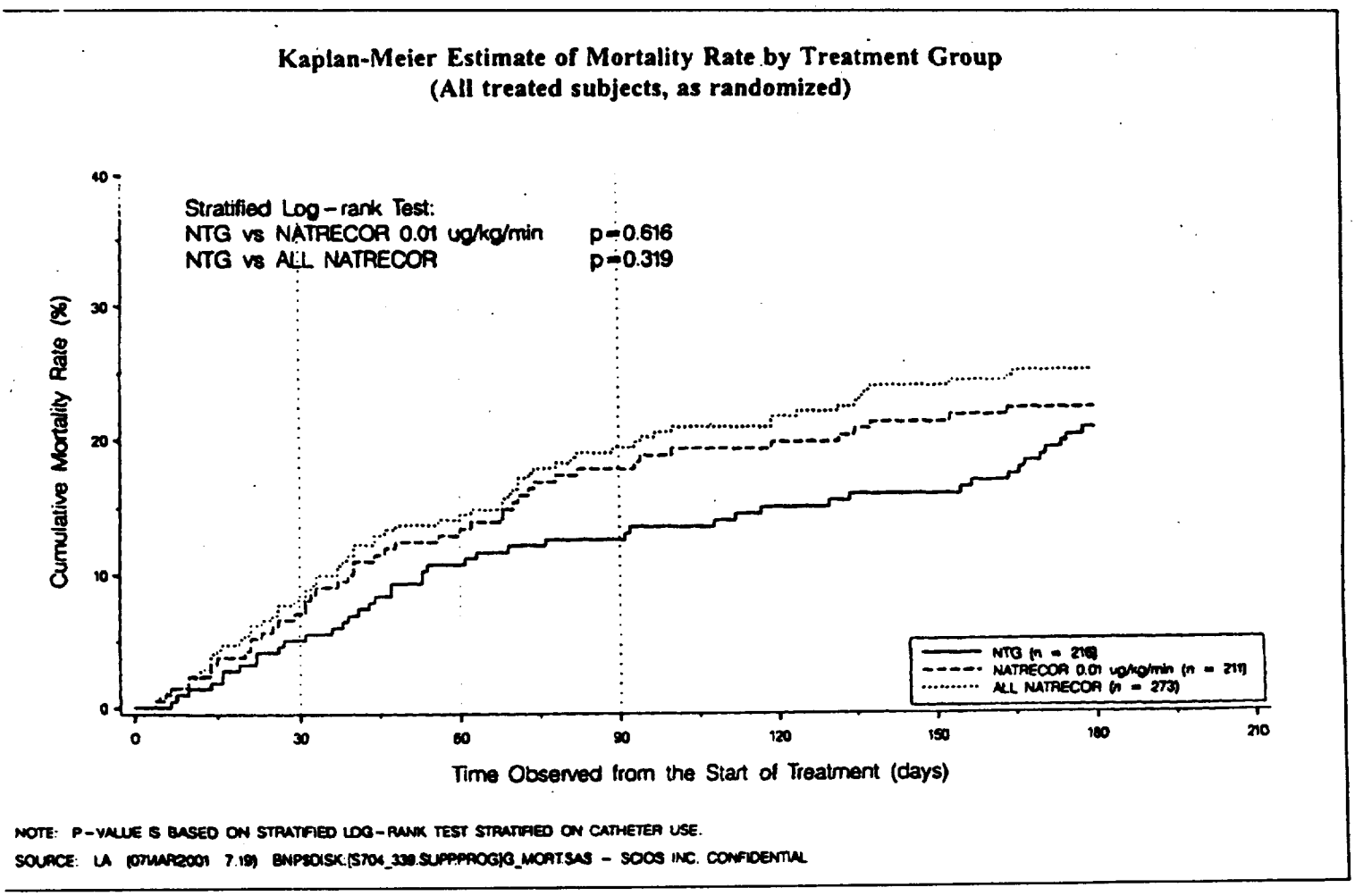
The risk ratio for death comparing the various Natrecor cohorts to the Nitroglycerin cohort ranged from 1.4 to 1.6 at 30-days. Confidence intervals were wide. At 90 days, the risk ratio comparing the cohorts off Natrecor to Nitroglycerin was between 1.4 to 1.5. At 6 months, the risk ratio again favored nitroglycerin and ranged from 1.1 to 1.2 for the Natrecor fixed and All Natrecor respectively. The risk ratio for the Natrecor adjustable dose at 6 months, compared to nitroglycerin catheterized patients was 1.6. None of these estimates of the relative hazard of death differed significantly from each other. Although the risk ratio favored nitroglycerin, the confidence intervals were large. It is unclear if the negative risk ratio is real or merely the play of chance. The sponsor attributes the differences in mortality to imbalance in the severity of disease at baseline.

Table Mortality at 30 days (1-month), 90 days (3-months) and 180 days (6-months)

	Summary			Catheterized			Not Catheterized	
	NTG	Natrecor Fixed	All Natrecor	NTG	Natrecor Fixed	Natrecor Adj	NTG	Natrecor Fixed
N=	216	211	273	92	92	62	124	119
# Deaths by 1 month	11 (5.1%)	15 (7.1%)	22 (8.1%)	7 (7.6%)	5 (5.4%)	7 (11.5%)	4 (3.2%)	10 (8.4%)
# Censored by 1 month[1]	1	2	3	0	0	1	1	2
p-value[2] compared to NTG	-----	0.4	0.2	-----	0.5	0.4	-----	0.08
Risk Ratio [3](NAT/NTG) CI	-----	1.4 0.6-3.1	1.6 0.8-3.2	-----	0.7 0.2-2.2	1.55 0.5-4.4	-----	2.7 0.8-8.6
# Deaths by 90-days	27 (13%)	37 (18%)	52 (19%)	Not analyzed				
# Censored by 90-days								
p-value[2] compared to NTG	------	0.15	0.08					
Risk Ratio [3](NAT/NTG) CI	-----	1.44 0.8-1.7	1.52 0.8-1.8					
# Deaths by 6 months	44 (21%)	46 (22%)	67 (25%)	22 (24%)	23 (25%)	21 (35%)	22 (18%)	23 (20%)7
# Censored by 6 months[4]	8	10	12	2	2	2	6	8
p-value[2] compared to NTG	------	0.6	0.3	----	0.8	0.1	----	0.6
Risk Ratio [3](NAT/NTG) CI	-----	1.11 0.7-1.7	1.22 0.8-1.8	-----	1.1 0.6-1.9	1.6 0.9-2.9	-----	1.2 0.6-2.1

[1] These were subjects lost to follow up by 30 days [2]p-value is based on stratified log rank test stratified on catheter use.
[3] Risk ratio was based on proportional hazard's model. [4] These were subjects lost to follow up by 180 days

Figure 9



Demographics and Efficacy on PCWP: Dr. Hung of the FDA analyzed these subgroups.

Table 38. Change in wedge pressure mean ± SE(?)

	Treatments		
	Nitroglycerin	Natrecor	Placebo
Gender			
Male	N=43; -3.6 ± 0.9	N=92 ; -5.9 ±0.7	N=47 ; -1.9 ± 0.6
Female	N=16; -4.5 ± 1.1	N=29 ; -5.5 ± 1.0	N=15; -2.3 ± 1.3
Race			
Caucasian	N=33; -2.6 ± 0.9	N=74; -5.4 ± 0.8	N=39; -2.2 ± 0.6
Blacks	N=17 ; -5.9 ± 1.1	N=30 –5.9 ± 0.9	N=14 ; -0.6 ± 1.2
Hispanic	N=9 ; -4.2 ±1.8	N=15; -7.0 ± 1.5	N=8; -3.4 ± 2.2
Other	N=1; -21		
Age			
< 65 years old	N=40 –4.5 ± 0.8	N=70; -6.2 ± 0.8	N=37; -1.5 ± 0.8
≥ 65 years old	N=19; -2.4 = 1.1	N=51; -5.3 ± 0.9	N=25; -2.9 ± 0.7
NYHA Class			
Class I	N=0	N=1; -5.0	-----
Class II	N=10; -4.1 ± 1.4	N=9; -5.2 ± 1.3	N=2; -7.5 ± 2.5
Class III	N=27; -4.7 ± 0.9	N=48; -7.2 ± 0.9	N=24; -2.0 ± 0.9
Class IV	N=18; -1.4 ± 1.3	N=54; -4.6 ± 1.0	N=31; -1.0 ± 0.6
No previous CHF	N=4; -8.0 ± 2.4	N=9 ; -6.8 ± 2.3	N=5; -6.8 ± 2.4

The subgroups were generally small and do not allow a definitive conclusion to be drawn.

Demographics on symptom benefit:

	Treatments		
	Nitroglycerin	Natrecor	Placebo
Gender			
Male	N=86; 1.1 ± 0.1	N=147 ; 1.3 ±0.1	N=103 ; 1.0 ± 0.1
Female	N=57; 1.4 ± 0.1	N=56 ; 1.4 ± 0.2	N=39; 1.4 ± 0.2
Race			
Caucasian	N=85; 1.1 ± 0.1	N=117; 1.1 ± 0.1	N=83; 1.0 ± 0.1
Blacks	N=35 ; 1.6 ± 0.2	.N=50 1.7 ± 0.1	N=34 ; 1.2 ± 0.2
Hispanic	N=19 ; 1.4 ±0.3	N=29; 1.3 ± 0.2	N=21; 1.4 ± 0.3
Other	N=4; 1.3 ± 0.3	N=7; 1.9 ± 0.3	N=4; 0.5 ± 0.3
Age			
< 65 years old	N=88 1.2 ± 0.1	N=118; 1.4 ± 0.1	N=73; 1.2 ± 0.1
≥ 65 years old	N=55; 1.3 = 0.1	N=85; 1.2 ± 0.1	N=69; 1.1 ± 0.1
NYHA Class			
Class I	N=; 2.0	N=1; 2.0	N=1 ; 0.0
Class II	N=18; 0.8 ± 0.2	N=13; 1.3 ± 0.1	N=7; 0.9 ± 0.5
Class III	N=57; 1.2 ± 0.1	N=88; 1.3 ± 0.1	N=59; 1.3 ± 0.1
Class IV	N=55; 1.2 ± 0.2	N=85; 1.2 ± 0.2	N=64; 0.9 ± 0.2
No previous CHF	N=12; 1.8 ± 0.3	N=16 ; 1.8 ± 0.3	N=11; 1.5 ± 0.4

The subgroups are small and no definitive conclusions are warranted.

Safety:

Duration of Exposure: The duration of exposure is shown in Table 40 (sponsors table 4.10).

Table 40 Duration of infusion

	Catheterized			Not Catheterized	
	NTG	NAT Fixed	NAT ADJ	NTG	NAT
Mean ± SD (Hours)	35.9 ± 17.5	34.4 ± 18.8	33.0 ± 16.3	35.8 ± 20.4	71.0± 350.7
Median (25%-75%)	26.6 (24-48)	24.5 (24-43)	24.5 (24-43)	24.4 (24-46)	24.4 (24-46)
Number with time of infusion (includes interruptions)					
0 hr	0	0	0	0	0
>0-3 hr	0	0	0	0	2 (2%)
>3-12 hr	4 (4%)	3 (3%)	3 (3%)	3 (2%)	3 (3%)
>12-24	13 (14%)	17 (18%)	14 (23%)	32 (26%)	25 (21%)
>24-48	57 (62%)	53 (58%)	34 (55%)	66 (53%)	67 (56%)
>48-72	15 (16%)	15 (16%)	10 (16%)	15 (12%)	10 (8%)
>72	3 (3%)	4 (4%)	1 (2%)	8 (6%)	12 (10%)

One subject in the not catheterized, NAT group received study-drug infusions for 161 days. The mean for this group is correspondingly distorted.

The mean dose for the NAT subjects was 0.01 ug/kg/min whether the subjects were or were not catheterized or were treated as a fixed or adjustable dose regimen. There were two subjects who were treated with the fixed dose regimen whose dose was increased to > 0.01 ug/kg/min. One subject's dose was between 0.1125 and 0.175 and the other subject 0.03 ug/kg/min. Among those in the adjustable dose NAT regimen, 27 subjects received doses of 0.01125 ug/kg/min or greater; 9 subjects received infusions of > 0.0225 ug/kg/min.

For those randomized to NTG groups (catheterized and not-catheterized), 87/ 216 subjects received infusions of > 20 ug/min and 33/216 received doses of > 80 ug/min. The mean doses at the various times for those catheterized and those not catheterized are shown in Figure 2.

Deaths/Dropouts/Discontinuations

There were a total of 36 subjects who were randomized who died during the 30-day observation period of the study. There were a total of four subjects who were lost to follow up and whose status at 30 days cannot be ascertained. Of the deaths, 33 received treatment and 3 died prior to the start of the infusion. There were 22 subjects that died who were treated with Natrecor (15 on the fixed dose and 7 on the adjustable dose regimens) and 11 subjects treated with nitroglycerine. No subjects died during the placebo portion or the study. The deaths are described below.

Randomized but not treated:

1) Subject # 642-501 (Natrecor Fixed Dose, not catheterized). This was a 74 y/o male with NYHA class IV CHF who was admitted shortly after sustaining a MI. his course was complicated by CHF and mitral regurgitation. The subject had a successful revascularization of the right coronary artery and obtuse marginal branch. His study drug was delayed due to hypotension. The subject arrested 2-hours later and died.

2) Subject # 687-411 (Natrecor fixed dose, catheterized). This was a 75-y/o male with NYHA Class IV CHF and a history of multiple myocardial infarctions, CABG and AICD implantation and also a history of IDDM and renal

insufficiency. He was admitted to the ICU with chest pain. A Swan Ganz catheter was inserted and he was intubated and ventilated. His troponin levels were elevated suggesting an acute MI as the etiology of his cardiac instability. The subject improved and was then randomized but suffered a cardiac arrest and died prior to the start of the infusion.

3) Subject # 540-406 (NTG, catheterized). This was a 46-y/o male with NYHA Class II CHF and idiopathic cardiomyopathy, and symptomatic bradycardia for which a DDD pacemaker was in place. The subject was randomized, but the PCWP dropped to below 14 mm Hg and study drug was not administered. The subject had a seizure with respiratory arrest and died the next morning.

Treated Subjects:

1) Subject # 369-407 (PBO/NTG, catheterized). This was a 64-y/o woman with NYHA Class III CHF due to ischemic cardiomyopathy. Concurrent conditions included peripheral vascular disease, hypertension, diabetes CAD and right ventricular failure. She completed the initial 24-hour infusion and was discharged on day 5. She was readmitted on day 11 for decompensated CHF. She was discharged on intravenous home dobutamine via a Hickman catheter. On day 25 her status decompensated. The following day she had a cardiac arrest and died.

2) Subject # 538-405 (NTG, catheterized). This was a 87-year old female with NYHA Class II CHF due to ischemic cardiomyopathy and a history of CAD, MI, atrial fibrillation, frequent PVCs a, first degree AV-nodal block and increase in cardiac enzymes. She was treated for 26 hours with study drug that was discontinued because she was feeling unwell. She was cardiac catheterized on day 4 (why???) which showed left main coronary and left anterior descending coronary artery disease. Because she did not qualify as a candidate for either angioplasty or bypass surgery she was transferred to a nursing home for hospice care and died on study day 10.

3) Subject # 618-401 (PBO/NTG, catheterized). This was a 41-y/o female with NYHA class IV CHF due to dilated cardiomyopathy and a history of ventricular septal defect with repair, paroxysmal atrial fibrillation, CVA, chronic renal insufficiency and apical thrombosis. She was treated for 44 hours with study drug that was discontinued due to lack of efficacy. She was started on dopamine but continued to deteriorate. She had an episode of VT requiring cardioversion on day 22. She arrested and died 7 hours later.

4) Subject # 627-507 (NTG, not catheterized). This was a 68-y/o male with NYHA class IV CHF due to ischemic cardiomyopathy and a history of MI, CABG, polymorphic VT requiring AICD placement, hypertension, renal insufficiency and hypothyroidism. The subject was hospitalized for fever, ascites, abdominal distention and decompensated CHF. Treatment for this subject included antibiotics, bowel rest and inotropic support. He was entered into this study and treated for 48 hours with study drug. He was discontinued due to lack of improvement. On day 5 he underwent a hemicolectomy and ileostomy for a perforated bowel. He died on day 15 due to ischemic cardiomyopathy, sepsis and ruptured bowel.

5) Subject #627-509 (NTG, not catheterized). This was a 90-y/o woman with NYHA class III CHF due to ischemic cardiomyopathy and CAD. She also had GE reflux. She was treated for 72 hours with study drug and was discontinued due to clinical improvement. She was discharged on day 7. On day 14 she arrested at home and died.

6) Subject # 636-505 (NTG, not catheterized). This was a 61-y/o male with NYHA Class IV CHF due to ischemic cardiomyopathy. Medical history included CAD, CABG, mitral valve repair, pacemaker placement, atrial fibrillation and hypertension. He was treated for 48 hours with study drug that was discontinued due to inadequate clinical response. He apparently had chronic renal failure that worsened during hospitalization. He died on day 22 due to respiratory failure, hyperthyroidism and sepsis (*enteobacter aerogens*).

7) Subject # 663-402 (NTG, catheterized). This was a 62-y/o male with NYHA class III CHF due to cardiomyopathy. He also had a history of atrial flutter, MI, chronic renal insufficiency and chronic venous stasis ulcers. He was treated for 4 days with study drug and concurrent dobutamine. The study drug was discontinued because of clinical improvement. Dobutamine was continued. On day 5 his renal function and CHF worsened. He was treated with dopamine, Diuril and Lasix. He developed pre-renal azotemia on day 6 and Lasix was held. He arrested on day 7 and died.

8) Subject # 678-403 (NTG, catheterized). This was a 44-y/o male with NYHA class III CHF due to idiopathic dilated cardiomyopathy, mitral regurgitation, CAD, previous MI and also a history of hypertension. He was treated with study drug for 67 hours and the infusion stopped because of clinical improvement. The subject was discharged on day 4. He was readmitted on day 10 due to shortness of breath and paroxysmal nocturnal dyspnea and was intubated. EKG showed sinus tachycardia. He was treated with Lasix, dopamine and milrinone, He died on day 26 due to heart failure.

9) Subject #679-402 (PBO/NTG, catheterized). This was a 73-y/o female with NYHA class IV CHF due to idiopathic dilated cardiomyopathy, a history of MI, AV nodal block (pacemaker placed) and hypertension. The infusion was discontinued due to inadequate clinical response. She was discharged to home on day 5. The subject died at home on day 8. (It is unclear if this was a witnessed demise or an unwitnessed sudden death.) The death was attributed to CHF.

10) Subject # 687-406 (PBO/NTG, catheterized). This was a 73-y/o male with NYHA Class IV CHF due to dilated ischemic cardiomyopathy and a history of left ventricular aneurysm, VT, AICD, COPD and diabetes. The subject was treated for approximately 3 days with study drug that was stopped due to inadequate clinical response. Milrinone was started when study drug was stopped. He had an episode of symptomatic hypotension that lasted 30 minutes. He was discharged home on study day 8, but was to return to the clinical to receive IV milrinone. On study day 16, the subject developed shortness of breath and overall weakness. He presented to the emergency department with pulseless electrical activity and died.

11) Subject # 687-502, (NTG, not catheterized). This was an 86-y/o male with NYHA class IV CHF due to ischemic cardiomyopathy and a history of CAD, MI, severe mitral regurgitation, atrial fibrillation and syncope. He was treated for approximately 40 hours with study drug, with the infusion stopped because of clinical improvement. The subject was discharged in day 4. He died on day 19 at home of CHF.

Natrecor subjects:

1) Subject #357-502 (Natrecor fixed dose, not catheterized) This was a 67-y/o female with NYHA class IV CHF of unknown etiology and a history of pulmonary hypertension, liver disease and Bence-Jones proteinemia. Dopamine was administered prior to the start of study drug She was treated for only 11 minutes before the infusion was stopped because of a sudden decrease in blood pressure. Her BP dropped from 94/47 to 70/25. An echocardiogram showed an ejection fraction of 20% and evidence of a restrictive cardiomyopathy (secondary to amyloidosis). On day 6 the subject had a cardio-respiratory arrest. She was intubated and transferred to CCU. She died on day 10. Autopsy confirmed amyloid heart disease.

[Comment: This is a patient with diastolic dysfunction whose blood pressure immediately bottomed post Natrecor treatment.]

2) Subject # 369-503 (Natrecor fixed dose, not catheterized). This was a 78-y/o male with NYHA class III due to non-ischemic cardiomyopathy and a history of atrial fibrillation, diabetes, hypertension and alcohol abuse. He was being treated with ongoing dopamine and dobutamine throughout the study infusion. He was treated with study drug for two days and discontinued due to inadequate clinical response. He developed sepsis on day 5, a GI bleed on day 8 acute renal failure requiring dialysis. On day 16 his CHF. He developed worsening dyspnea requiring dobutamine. He experienced a cardiac arrest on day 22 and died on day 26 with the death attributed to fulminant sepsis.

3) Subject # 538-401: (Natrecor Fixed dose, catheterized). This was a 72-y/o male with NYHA Class II CHF due to valvular heart disease and a history of tricuspid valve repair, CABG, paroxysmal atrial fibrillation, pulmonary hypertension who presented with dyspnea and pleural effusions. Wedge pressure on admission was 24 mm Hg. On day 3 his status worsened with severe shortness of breath. Bilateral plural effusions were noted on ultrasound and a thoracocentesis resulted in the removal of 500 cc of fluid. Though transiently improved, his status subsequently worsened and he required mechanical ventilation. His renal function also worsened. He died on day 15.

4) Subject # 539-502 (PBO/NAT fixed dose, not catheterized). This was a 55-y/o female with NYHA class IV CHF due to aortic insufficiency, Takayasu's arteritis, hypertension and fibromyalagia, She finished 24 hours of infusion with the infusion stopped because of clinical improvement. On day 5 she sustained a cardiac arrest and was resuscitated and ventilated. She died the next day.

5) Subject # 551-404 (PBO/NAT, fixed dose, catheterized). This was a 41-y/o female with NYHA Class IV CHF and a past history of cardiac transplantation in 1989 due to *post-partum* cardiomyopathy. She had biventricular heart failure due to accelerated graft atherosclerosis. She also had azotemia, hypertension, tachycardia and syncope. She was treated for 24-hours with study drug that was discontinued due to inadequate response. She was then started on dopamine. She was discharged for hospice care on day 8 and arrested on day 28 and died on day 29.

6) Subject 554-508 (Natrecor, fixed dose, not catheterized). This was a 55 y/o male with NYHA class IV CHF with a history of MI, CVA, hyperlipidemia and atrial fibrillation with a rapid ventricular response who was treated with study drug for 24-hours. The infusion was stopped due to clinical improvement. He had one episode of atrial fibrillation with a rapid response that was treated with metoprolol. He died on day 14 due after a cardiac arrest.

7) Subject # 572-411 (Natrecor fixed dose, catheterized). This was a 61-y/o male with NYHA class III CHF due to ischemic cardiomyopathy and a history of CAD, CABG, MI, polymorphic VT, diabetes and atrial fibrillation. He was treated for 48 hours with study drug but discontinued due to the lack of improvement in CI. Dobutamine wad added on day 2. On day 4 he was found unconscious and in agonal rhythm. The cause of death was attributed to polymorphic VT and underlying cardiomyopathy and coronary artery graft occlusion.

8) Subject #627-505 (Natrecor, fixed dose, not catheterized). This was a 71-y/o male with NYHA Class IV CHF due to idiopathic dilated cardiomyopathy and a history of CABG, pacemaker insertion for heart block, VT, renal insufficiency, pneumonia and prostatic hypertrophy. He was treated approximately 5 days with study drug that was discontinued due to clinical improvement. On day 10 he developed worsening CHF with increased SOB and worsening renal function (creatinine increased from 2.8 to 3.6 mg/dL) and decreased blood pressure. He died on day 20.

9) Subject # 627-506 (Natrecor, fixed dose, not catheterized). This was 63-y/o male with NYHA Class III CHF due to severe ischemic cardiomyopathy and a history of hypertension, left internal carotid artery stenosis, right axillary stenosis and renal artery stenosis. He was admitted for pulmonary edema associated with a non-Q wave MI. He was treated for 46 hours and discontinued due to clinical improvement. On day 7, he developed diaphoresis, sinus bradycardia and severe. He sustained an asystolic cardiac arrest and died.

10) Subject # 642-402 (Natrecor, fixed dose, catheterized). This was a 77-y/o female with NYHA Class III CHF due to ischemic cardiomyopathy, AICD placement, UTI, diabetes and esophageal dysmotility. She was treated for 24 hours with study drug and discontinued due to clinical improvement. She was readmitted on day 19 due to nausea, vomiting and UTI. On day 23, she developed hypotension and confusion leading to cardiogenic shock and death.

11) Subject # 663-413 (PBO/NAT, catheterized). This was a 72-y/o male with NYHA Class IV CHF due to ischemic cardiomyopathy and a history of CAD, CABG, AF, NSVT, sinus node disease, diabetes and hypertension. He was treated for 43 hours, with the infusion discontinued due to clinical response. He was discharged home but died on day 25 due to end-stage cardiomyopathy.

12) Subject # 666-502 (PBO/NAT, not catheterized). This was a 77-y/o male with NYHA Class IV CHF due to ischemic cardiomyopathy and a history of CAD, sick sinus syndrome, AICD placement, AF, sustained VT, diabetes and renal insufficiency. He was treated for 4 days with study drug that was discontinued due to lack of clinical response. On day 9, he developed pulmonary and renal failure and died on day 10.

13) Subject # 671-504 (Natrecor fixed dose, not catheterized). This was an 88-y/o male with NYHA class III CHF due to ischemic dilated cardiomyopathy and a history of CAD, CABG, hypertension, chronic renal disease AF, hypercholesterolemia, PVD and benign prostatic hypertrophy. He was treated for 24 hours with study drug that was discontinued due to clinical improvement. He had a single episode of asymptomatic hypotension that required a one-hour cessation of therapy. He was discharged on day 3. On day 14 he was admitted for the treatment of worsening CHF. On day 17, he underwent an angioplasty of the vein graft to the LAD. His condition deteriorated. On day 19 his creatinine level was 3.1 mg/dl (baseline was 1.8 mg/dl). On day 21 the subject died of CHF and renal failure

14) Subject # 678-515 (PBO/NAT fixed dose, not catheterized). This was a 77-y/o woman with NYHA Class IV CHF due to ischemic dilated cardiomyopathy and a history of MI, AF, sustained VT, VF with AICD placement, diabetes and hypertension. The subject was treated for 4 days and the infusion was discontinued due to inadequate clinical response.

The subject's condition continued to deteriorate. On day 19 her creatinine and BUN were 2.8 and 119 mg/dL, respectively. She died on day 21of severe left ventricular systolic function as a consequence of CAD, COPD and possibly sepsis.

15) Subject # 679-504 (PBO/NAT fixed dose, not catheterized). This was a 54-y/o male with NYHA class III CHF due to ischemic cardiomyopathy and a history of MI, CAD, VT with AICD placement, and diabetes. He was treated for 48 hours with study drug that was discontinued due to clinical improvement. He was discharged on study day 3 but was readmitted on day 15 for worsening CHF and died the same day.

16) Subject # 356-401 (Natrecor adjustable dose, catheterized). This was a 45-y/o male with NYHA class IV CHF due to idiopathic dilated cardiomyopathy and a history of sustained VT (AICD placed), CVA, hypertension and renal insufficiency. He was treated for 24 hours with study drug that was discontinued due to inadequate response. On day 8, the subject's hospitalization was prolonged for pulmonary edema. The subject extubated himself on day 14 and died 45 minutes later.

17) Subject # 369-401 (Natrecor adjustable dose, catheterized). This was a 76-y/o woman with no previous history of CHF and a history of CAD, NSVT, hypertension, diabetes and breast cancer. She presented with shortness of breath. She was treated for 19 hours with study drug. The drug was discontinued due to NSVT that lasted 6 seconds. She had an episode of asymptomatic hypotension that resolved within 10 minutes. About 12 hours she developed a second episode of NSVT. She died on day 12 due to metastatic breast cancer.

18) Subject # 642-406 (Natrecor, adjustable dose, catheterized). This was a 90-y/o male with NYHA class IV CHF due to valvular disease with progressive mitral regurgitation and a history of CAD, CABG, sick sinus syndrome requiring a pacemaker, AF, CRF, abdominal aneurysm and PAT. He was treated for 44 hours with study drug that was discontinued due to inadequate clinical response. He was receiving dobutamine throughout this active drug infusion. On study day # 4, his chest X-ray showed increased fluid retention and possibly pneumonia. His SBP was ~ 50 on day 6 and he was treated with dobutamine and saline. On study day 7 he improved. On day 16 he died due to CHF, severe mitral regurgitation and arteriosclerotic heart disease.

19) Subject # 663-412 (Natrecor, adjustable dose, catheterized). This was an 84-y/o female with NYHA class IV CHF due to ischemic cardiomyopathy and a history of MI, CABG, CAD, atrial fibrillation, VF, sustained VT and hypertension. The subject was treated with 52 hours with study drug that was discontinued due to clinical improvement. The subject was discharged to a nursing home and treated with IV dobutamine on day 8. She died on day 26.

20) Subject # #678-402 (Natrecor, adjustable dose, catheterized). This was an 80-y/o female with NYHA class III CHF due to ischemic cardiomyopathy and mitral regurgitation, CAD, MI, CABG, chronic stable angina and a pacemaker. She was treated for approximately 11 hours with study drug that was discontinued due to chest pain. At that point she withdrew consent. She was placed on a morphine drip. On day 4 the subject died of mitral regurgitation and CAD.

21) Subject # 687-425 (Natrecor adjustable dose, catheterized), This was a 62-y/o male with no previous history of CHF but a history of CAD, non-Q wave MI, CABG, AFl, SVT, hypertension, NIDDM, and treated bowel lymphoma. He was admitted secondary to hypoxia and bacterial endocarditis. The subject's creatinine was 3.6 upon entry into the study. He was treated with NTG, Betapace, digoxin, aspirin, packed RBC and antibiotics. His condition did not improve. His PCWP decreased on study drug from 40 to 24 mm Hg. He had mild bradycardia (HR=62) and severe hypoxia requiring intubation. On day 3, his condition deteriorated and he was sent for surgery. NTG was stared. He was ventilator dependent. On day 20 he died of encephalopathy secondary to the endocarditis.

22) Subject # 688-401 (Natrecor, adjustable dose, catheterized). This was a 74-y/o male with NYAH class IV CHF due to ischemic cardiomyopathy and a history of CRF, DM, CAD, CABG and atrial fibrillation, sinus bradycardia with first degree heart block and COPD. He was treated for 55 hours with study drug but was discontinued due to clinical improvement. On day 4 his creatinine worsened to 4.2 mg/dL. He died on day 12 due to end-stage CHF.

Serious Adverse Events: There were a total of 113 subjects who had serious events that did not lead to death but either led to hospitalization or prolonged an ongoing hospitalization. Fifty-one of these were in the dobutamine groups and 62 among those treated with all regimens of Natrecor.

Nitroglycerin subjects:

1) Subject # 357-506 (PBO/NTG, not catheterized). (49y/o, M, NYHA IV). This subject was readmitted on day 28 due to CHF and was found fluid overloaded. He was treated with dopamine IV Lasix and Zaroxolyn and discharged on day 31.

2) Subject # 369-501 (PBO/NTG, not catheterized) (68 y/o F, NYHA III). This subject's hospitalization was prolonged for a psoas abscess on study day 7. The abscess was drained and the subject received prolonged antibiotic treatment. Her cardiopulmonary status was also compromised, suffering worsening CHF and was treated with IV NTG, milrinone and Lasix. She underwent mitral valve repair one week later.

3) Subject # 369-505 (NTG, not catheterized) (33 y/o F, NYHA III). Hospitalized for abdominal pain from day 11-15 and was discharged on Prevacid and Maalox.

4) Subject #369-507 (PBO/NTG, catheterized) (72y/o M, NYHA III). This patient was readmitted on day 12 for worsening CHF and was treated with IV Lasix, dobutamine, Zaroxyln and Monopril. He was discharged on day 18 but readmitted on day 26. He had a GI bleed requiring transfusion and acid pump inhibitors. He was discharged on day 28.

5) Subject # 382-405 (NTG, catheterized) (79 y/o M, NYHA IV). On day 5 while in hospital and on dobutamine after study drug was discontinued he suffered a cardiac arrest. He was resuscitated. He had a second episode of VT, requiring resuscitation on day #9. He was started on Mexitil. His renal function deteriorated and he was dialyzed. He had a Perma Cath inserted and received intermittent dialysis.

6) Subject #502-403 (NTG, catheterized)(63 y/o M, NYHA II). His baseline creatinine was 4.0 mg/dL. The subject completed 48 hours of study and discontinued for clinical improvement. On day 26 the subject was readmitted for dialysis, creatinine at the time was 6.8 mg/dL. He was discharged to an outpatient hemodialysis unit.

7) Subject # 502-502 (PBO/NTG, not catheterized) (89 y/o M, NYHA IV). He was admitted on day 10 for severe weakness. He was in renal failure with a creatinine of 5.4 mg/dL (no change from baseline). He was discharged on day 22 after dialysis. He was readmitted on day 27 for shortness of breath and pulmonary edema secondary to fluid overload and insufficient dialysis. He was discharged on day 29.

8) Subject # 502-504 (NTG, not catheterized) (73y/o F, NYHA IV). She was admitted on day 21 for AF (HR=135), vomiting, dehydration and hypokalemia. She was discharged on day 29.

9) Subject # 502-507 (PBO/NTG, not catheterized) (69 y/o F, NYHA IV). This subject had an episode of hypotension during the study drug infusion. She was started on dobutamine. On day 2 she developed chest pain that was associated with elevated CK-MB (20.8 ng/ml) consistent with a diagnosis of non-Q wave MI. She was discharged on day 6.

10) Subject 502-209 (PBO/NTG, not catheterized) (77 y/o M, NYHA IV). He was discontinued for inadequate clinical response. He was readmitted to the hospital on day 19 for pneumonia. Two transbronchial lung biopsies demonstrated interstitial fibrosis. He had a GI bleed during the hospital stay. He died on day 47 (after the 30-day observation period) due to idiopathic pneumonitis.

11) Subject # 516-501 (NTG, not catheterized) (64 y/o M, NYHA III). He was treated for 48 hours with improvement. At the time of admission he had a non-Q Wave infarction. On day 6 he had pain in the left leg and fever. On day 35 post-study, he underwent an above the knee amputation due to gangrenous left foot.

12) Subject # 516-502 (NTG, not catheterized) (60 y/o M, NYHA IV). He was treated for 65 hours with discontinuation due to clinical improvement. Labile glucose control was observed during hospitalization. He was to be discharged but developed VT that caused discharge of his defibrillator. Amiodarone was started. On day 10 his renal failure worsened. (Baseline serum creatinine was 2.2 mg/dL, Bun 56 mg/dL; 19 hours post-infusion creatinine was 1.9 mg/dL and BUN was 24 mg/dL). On day 10 the creatinine the creatinine was 3.0 and the BUN was 77. He was discharged on day 26 but readmitted on day 26 for exacerbation of CHF and a UTI. The subject was treated with inotropes and IV antibiotics and discharged on day 30.

13) Subject # 516-503 (NTG, not catheterized)(62 y/o F, NYHA IV). She was successfully treated with study drug for 60 hours. She was readmitted on day 13 for exacerbation of CHF and discharged on day 16.

14) Subject # 524-503 (NTG, not catheterized) (57 y/o F, NYHA I). Successfully completed infusion for 43 hours. She was readmitted on day 16 for dehydration and renal insufficiency. Creatinine was 4.2 mg/dL, BUN was 127 mg/dL and K+ was 5.8 mmol/L. She was treated with IV fluids and Kayexalate. She was discharged on day 20 with a creatinine of 3.0 mg/dL, BUN mg/dL, and K+ 4.7 mmol/L. Baseline values were creatinine 2.4 mg/dL, BUN 68 mg/dL.

15) Subject # 538-404 (NTG, catheterized) (79 y/o F, NYHA I). She was discontinued from the original infusion due to lack of efficacy after 24 hours. She was started on open-labeled NTG. She was discharged on day 8. She was readmitted on day 30 for renal failure and dehydration. Her creatinine on admission was 4.5 mg/dl and BUN was 108 mg/dL. She was treated with IV fluids and low dose dopamine. Her creatinine and BUN upon discharge on day 35 were 1.9 and 37 mg/dL, respectively.

16) Subject # 538-407 (NTG, catheterized) (59 y/o M, NYHA III). He was successfully treated for the 76 hours of the initial infusion and discharged on day 8. He was readmitted on day 9 for cellulitis of the lower leg and was treated with IV antibiotics. He developed progressive azotemia on day 11 (with a creatinine of 5.8 mg/dL and BUN 157 mg/dL and a K+ of 7.4 mmol/L. Baseline creatinine was 2.0 mg/dl. The subject was hemodialyzed and was discharged on day 20. (did the subject need more than one dialysis?).

17) Subject # 540-401 (NTG, catheterized)(64 y/o M, NYHA II). He was treated 24 hours with study drug with minimal improvement. He had a cardiac transplant and was discharged on day 17. He was re-hospitalized on day 20 with a low-grade fever, diarrhea, rash, nausea and vomiting. A cardiac biopsy ruled out ejection. He was treated with Flagyl and IV fluids and the diarrhea resolved. He was discharged on day 23.

18) Subject # 540-501 (NTG, not catheterized) (57y/o F, NYHA II). She completed 48 hours of infusion with the infusion discontinued due to lack of efficacy. She was discharged on day 4. The subject was readmitted on day 13 for worsening heart failure and was treated with milrinone. She improved and was discharged on day 16.

19) Subject # 543-404 (NTG, not catheterized). (57 y/o M, NYHA IV). He was post open-heart surgery at the time of enrollment of the study and was on dobutamine at baseline with the inotrope continued throughout the infusion. The subject was treated for 24 hours with study infusion that was discontinued due to lack of efficacy. The subject's hospitalization was prolonged due to worsening decompensated CHF, acute renal failure and staphylococcal bacteremia. An intra-aortic balloon pump was inserted. The subject progressed to pre-renal azotemia and hyponatremia and was dialyzed. The subject's heart failure did not improve and the subject died on day 38 (post 30-day observation period).

20) Subject # 547-502 (PBO/NTG, not catheterized) (94 y/o M, NYHA II). Study drug administered for 24 hours and stopped due to improvement. He had one episode of asymptotic hypotension during the infusion. The subject's hospitalization was prolonged due to CHF exacerbation. The subject was treated with Lasix and dopamine, and discharged on study day 18.

21) Subject # 554-406 (PBO/NTG, catheterized)(58 y/o M, NYHA IV), The subject successfully completed 25 hours of infusion. He was discharged on day 7 and readmitted on day 13 for exacerbation of CHF. He was discharged on day 21.

22) Subject # 554-417 (NTG, catheterized) (44 y/o M, NYHA III). This subject successfully completed a 28-hour infusion. He was discharged on study day 9. On day 25, he was readmitted due to pulmonary edema. He was discharged on day 28.

23) Subject # 554-421 (NTG, catheterized)(62 y/o M, NYHA IV). This subject was treated successfully with study drug for 25 hours. The subject was discharged on day 5 but readmitted on day 19 due to worsening heart failure. He was treated with IV Lasix and discharged on day 24. He was re-hospitalized on day 27 for worsening heart failure. He was treated with inotropes and underwent a heart transplant. The inotropes were continued. He was discharged on day 75. The post-transplant course was complicated by right putaminal hemorrhage with subarachnoid bleeding, pulmonary hypertension, right ventricular dysfunction and acute renal failure.

24) Subject # 554-513 (NTG, not catheterized) (53 y/o F, NYHA IV). The subject was discontinued after 45 hours of study drug infusion due to clinical improvement. The subject was discharged on day 18 and was readmitted on day 23 for worsening heart failure. She was treated with IV Lasix. She developed GE reflux. She was discharged on day 51.

25) Subject # 554-527 (NTG, not catheterized) (57 y/o F, NYHA III). She was treated successfully with study drug for 24-hours. The subject was discharged on day 3 and subsequently developed a right-sided hemiparesis and was readmitted on day 10. Brain MRI revealed an old thalamic stroke. .

26) Subject # 554-528 (NTG, not catheterized) (55 y/o F, NYHA IV). She received study infusion that was discontinued due to improvement. She was discharged on day 5 but readmitted on day 8 for pneumonia. She was ventilated on day 10. Post-extubation she had vocal cord paralysis and a depressed gag reflex. She developed severe diarrhea after the initiation of tube feeding. She was discharged to a nursing home at day 54 post-infusion.

27) Subject # 554-532 (PBO/NTG, not catheterized) (41 y/o M, NYHA III). This subject was successfully treated with study drug infusion for 29 hours. He was discharged on day 3. On study day 21 he was admitted for worsening CHF and chest pain. MI was ruled out. He was discharged on day 23.

28) Subject # 561-501 (NTG, not catheterized)(66 y/o F, NYHA I). She was enrolled immediately post Q-wave MI and was stented prior to entered in the study. The attending physician stopped the infusion after the subject received 16 hours of study drug. The subject had an episode of asymptotic hypotension that lasted 1.5 hours with interruption of the infusion for 1.5 hours. On day 4 she complained of chest pain with ECG consistent with MI. A PTCA was subsequently performed. She was discharged on day 19. She was readmitted on day 20 for chest pain with a negative troponin. She was discharged on day 23

29) Subject # 572-408 (NTG, catheterized) (21 y/o M, NYHA III). This subject was treated with infusion for 48 hours with study drug discontinued due to lack of efficacy. He was discharged on day 7, but readmitted on day 14 with a 6.8-kg weight gain and shortness of breath. He was treated with IV Lasix, and discharged home on day 15.

30) Subject # 572-504 (NTG, not catheterized). (72 y/o M, NYHA III). He was initially treated for 25 hours with the infusion successfully completed. He was discharged on day 3. On study day 14 he was readmitted for worsening heart failure and was treated under Swan Ganz monitoring with IV NTG. He had AF and was cardioverted. He also had a rectus sheath hematoma. He was discharged on day 31.

31) Subject #580-402 (NTG, catheterized) (52 y/o M, NYHA IV). Treated for 24 hours with study drug that was stopped because of clinical improvement. He was discharged on day 3 and readmitted on day 7 for pneumonia. He was treated with antibiotics and discharged on day 17. He was readmitted on day 25 for decompensated CHF. He was diuresed and received inotropic support. There was some decrease in his renal function. His admission creatinine was 1.6 mg/dL; his discharge creatinine was 1.9 mg/dL. He also had a right lower extremity ulcer for which he received antibiotic treatment. He was discharged on day 37.

32) Subject # 580-411 (NTG, catheterized) (75 y/o M, NYHA IV). He was treated for 24 hours with study drug. The drug was discontinued because of clinical improvement. He was discharged on day 6 but readmitted on day 22 worsening CHF and elevated LFTs. He was treated with inotropic drug and discharged on day 32.

33) Subject # 580-504 (NTG, not catheterized) (43 y/o M, NYHA IV). He was treated with study drug for 2 days and discontinued due to clinical improvement. The subjects hospitalization was prolonged due to elevated liver enzymes (the subject had a history of hepatitis C). He was discharged on day 5 to hospice care. He was readmitted on study day 28 for recurrent hemoptysis, increased dyspnea, fatigue, malaise and edema. He was diagnosed with volume overload and treated with diuretics and antibiotics. He was discharged on day30.

34) Subject #585-502 (NTG, not catheterized) (67 y/o M, NYHA IV). He had limited response to infusion during the 24-hour infusion. On day 1 an echocardiogram showed a dehiscence of the mitral annuloplasty ring, which was the apparent cause of the CHF decompensation. On day 7 he had a mitral valve replacement. An intra-aortic balloon pump was placed. On day 8 he experienced respiratory failure and cardiogenic shock. He was mechanically ventilated. He was transfused. He also had worsening renal failure and was treated Lasix, dopamine, epinephrine, heparin and dobutamine. He had a Quinton catheter placed for continuous veno-venous hemo-filtration. These events reversed on

day 11 with veno-venous filtration continuing till day 12 and the aortic pump till day 13. He was extubated on day 14. No discharge date was supplied.

35) Subject # 627-402 (NTG, catheterized) (72 y/o M, NYHA III). He was treated for 37 hours and the infusion stopped due to clinical improvement. He was discharged on day 6 but readmitted on day 18 due to worsening renal failure. He was treated with renal dose dopamine, Kayexalate, bicarbonate, Lanoxin, albuterol and fluids and transferred to a tertiary care hospital.

36) Subject # 628-401 9NTG, catheterized) (53 y/o M, NYHA IV). He was treated for 48 hours with study drug that was discontinued due to clinical improvement. He was treated with dobutamine on day 3 (post-study drug) and started on milrinone on day 4. He was discharged on day 7. He was readmitted on day 8 for unstable angina and was treated with milrinone, IV NTG and heparin. No MI was found. He was discharged on day 13. On day 14 he was readmitted with chest pain nausea, vomiting and diarrhea. No MI was found. He was discharged on day 43.

37) Subject # 636-501 (NTG, not catheterized) (38 y/o M, NYHA IV). Treated for 3 days with study drug that was discontinued due to lack of efficacy. He was discharged on day12 and readmitted on day 30 for chest pain and shortness of breath. He was discharged the next day after receiving IV Lasix.

38) Subject # 642-204 (NTG, catheterized) (65 y/o M, NYHA III). He was treated for 24 hours with study drug that was discontinued due to clinical improvement. He was discharged on day 11 and readmitted on day 17 because of bladder outlet obstruction. He had a transurethral resection of the prostate performed. He was discharged on day 28 but readmitted on day 30 because of chest pain. An acute MI was ruled out and he was discharged on day 31.

39) Subject # 657-501 (PBO/NTG, not catheterized) (76 y/o M, NYHA I). He was admitted initially due to inferior MI and severe pulmonary edema. He received study drug for 28 hours, which was discontinued to receive open label NTG in preparation for CABG. An intra-aortic balloon pump and Swan-Ganz catheter was placed. He had 4-vessel bypass and mitral valve replacement. Post-operative complications included cardiogenic shock, respiratory insufficiency, renal insufficiency and acute pancreatitis. He was extubated on day 45 and discharged on day 54.

40) Subject # 663-45 (NTG, catheterized) (75 y/o M, NYHA II). He was admitted with an acute MI and received study drug for 24 hours. Dopamine was added after five hours of infusion. He was discharged on day 14. On study day 19, he was readmitted for CHF, AF and pleural effusion. He was treated with Lasix and discharged on day 21. He was readmitted on day 23 and treated for exacerbations of CHF and received diuretics and inotropes. He was discharged on day 30.

41) Subject # 663-406 (NTG, catheterized) (41 y/o M, NYHA I). He was admitted for an acute anterior wall MI and CHF. Post-MI, he had severe triple vessel disease and an ejection fraction of 10%. He had a quadruple vessel CABG. Acute renal failure and CHF complicated his post-operative course. He was treated with study drug 13 days after the index MI and the treated for 24 hours with clinical improvement. He was discharged 6 days later. He was readmitted on day 26 (post study drug) due to CHF exacerbation, treated with Lasix and dobutamine and discharged on day 30.

42) Subject # 663-508 (PBO/NTG, not catheterized) (83 y/o F, NYHA I). She was treated successfully for 24 hours and discharged on day 7 but readmitted on day 8 for dehydration and dyspnea. She was discharged on day 13.

43) Subject # 667-406 (PBO/NTG, catheterized) (32 y/o M, NYHA IV). He was treated 3 days with study drug that was discontinued due to clinical improvement. He had a history of CRF. On day 5, he had a CAPD catheter placed and dialysis was initiated on day 16. His creatinine was 2.8 at baseline and 2.9 mg/dL at the time of dialysis catheter placement. He was discharged on day 16 but readmitted on day 25 due to exacerbation of CHF and repair of the dialysis catheter. He was treated with IV diuretics, inotropes and after load reducers. His course was complicated by the need for a Quinton catheter. He also had cellulitis of the lower legs and 2-lumen Hickman catheter placement (for hemodialysis, the CAPD catheter was malfunctioning). He was discharged on day 38.

44) Subject # 667-412 (NTG, catheterized) (53 y/o M, NYHA III). He was treated with study drug for 24- hours that were discontinued due to clinical improvement. He was rehospitalized on day 26 for CHF exacerbation. No additional details were available.

45) Subject # 671-501 (PBO/NTG, not catheterized) (83 y/o M, NYHA IV). He was treated for 24 hours with study drug that was discontinued due to improvement. He was discharged on day 4, but readmitted on day 15 for CHF exacerbation. He was discharged on day 19.

46) Subject # 671-508 (NTG, not catheterized) (65 y/o M, NYHA IV). He was treated for 24 hours with drug that was discontinued due to lack of efficacy. He was discharged on day 5 but readmitted on day 16 for worsening CHF. He was treated and discharged on day 19.

47) Subject # 678-508 (NTG, not catheterized) (67 y/o M, NYHA III). He was treated for 24 hours with study drug that was discontinued due to clinical improvement. He was discharged on day 2 but readmitted on day 20 after a respiratory arrest post-pacemaker placement. The subject died on day 36 (after the 30-day cutoff).

48) Subject # 678-510 (NTG, not catheterized) (77 y/o NYHA IV). He was treated for 24 hours with study drug that was discontinued due to clinical improvement. He was discharged on day 3 but readmitted on day 11 for worsening CHF. He was discharged on day 15 but readmitted again on day 22 for pneumonia and worsening CHF. He was treated and discharged on day 30.

49) Subject # 681-403 (NTG, catheterized) (44 y/o F, NYHA III). She was treated with study drug for 24 hours that was discontinued due to clinical improvement. She was discharged on day 2, but readmitted on day 21 for exacerbation of CHF with fluid overload. She was treated with IV diuretics and milrinone and discharged on day 29.

50) Subject # 683-401 (NTG, catheterized) (51 y/o F, NYHA IV). She was treated for 48-hours that was discontinued due to lack of efficacy. She was subsequently given IV Lasix and dopamine. She experienced symptomatic hypotension at that time. Both study drug and dopamine were discontinued. She was discharged on study day 9 with home milrinone therapy. She was readmitted on day 27 for treatment of a left pneumothorax after Broviac placement. She had a chest tube and a Broviac placed. She was discharged on day 28.

51) Subject # 687-421 (PBO/NTG, catheterized) (79 y/o F, NYHA III). She was treated with study drug for 48 hours with the drug stopped because of lack of efficacy. She was discharged on day 6 but readmitted on day 21 for nausea, vomiting and dehydration. She was treated with fluids and her medications adjusted. She was discharged on day 25.

NATRECOR SUBJECTS:

1) Subject # 360-501 (NAT fixed dose, not catheterized) (48 y/o M, NYHA IV). He was treated for 24 hours and the infusion discontinued due to clinical improvement. He was discharged on day 4 but readmitted on day 24 for CHF exacerbation. He was diuresed and discharged on day 27.

2) Subject # 367-401 (PBO/NAT fixed dose. catheterized) (71 y/o M, NYHA IV). He was treated for 24 hours with the infusion discontinued due to inadequate clinical response. He arrested on day 22, while being evaluated for a heart transplant. He was reintubated and treated with IV fluids and discharged on day 30.

3) Subject # 369-411 (PBO/NAT, fixed dose) (68 /o M, NYHA III). He was treated for 24 hours with study drug with the infusion stopped due to clinical improvement. He was discharged on day 15. He was readmitted on day 26 for left epigastric pain. A MI was ruled out.

4) Subject # 369-416 (PBO/NAT, fixed dose, catheterized)(73y/o F, NYHA III), Treated with study drug for 24 hours with the drug discontinued due to clinical efficacy. She was discharged on day 11 but readmitted on day 12 due to shortness of breath and blisters on her BKA amputations. She was treated with oxygen and milrinone and discharged on day 32.

5) Subject # 369-420 (NA fixed dose, catheterized) (57 y/o M NYHA III). He was treated for 24 hours and discontinued due to clinical improvement. He was discharged on day 8 but readmitted on day 26 due to CHF exacerbation, hyperkalemia and renal insufficiency (he did not have renal insufficiency at baseline). He also developed short runs of VT and PVCs. He was discharged on day 35.

6) Subject # 369-514 (NAT fixed dose, not catheterized) (78 y/o M, NYHA III). He was treated with study drug for 4 days, which was discontinued due to lack of efficacy. On day 7, his renal failure worsened. Baseline creatinine and BUN were 1.1 and 52 mg/dL, respectively. Hemodialysis was initiated on day 20. He was discharged to a rehabilitation facility on day 30 with three-times a week dialysis.

7) Subject # 369-519 (NAT, fixed dose, not catheterized) (74 y/o F, NYHA III) She was treated for 24 hours with study drug, with drug discontinued due to minimal improvement. She received milrinone. Her hospitalization was prolonged due to episodes of bradycardia. A DDD pacemaker was placed. She was discharged on day 13.

8) Subject # 524-502 (PBO/NAT, fixed dose, not catheterized) (51 y/o M, NYHA III). He was treated for 43 hours with drug discontinued due to withdrawal of consent. On day 18 he was hospitalized for worsening bronchitis. He was treated with antibiotics and corticosteroids. He signed out AMA on day 23.

9) Subject # 554-522 (NAT, fixed dose, not catheterized) (70 y/o F, NYHA IV). She was treated for 24 hours with study during and discontinued due to clinical improvement. She was discharged on day 18, but readmitted on day 22 due to worsening CHF and atrial fibrillation. She was treated with digoxin and Lasix and discharged on day 27.

10) Subject # 554-524 (NAT, fixed dose, not catheterized) (63 y/o F, NYHA IV). She was treated for 24 hours and the infusion stopped due to clinical improvement. She was readmitted on day 14 with CHF exacerbation and was treated with benazapril, digoxin and Lasix. A thoracocentesis was performed and was discharged on day 22. She was readmitted on day 29, again for CHF exacerbation and was discharged on day 44.

11) Subject # 554-545 (NAT, fixed dose, not catheterized) (79 y/o F, NYHA II). She was treated with study drug infusion for 24 hours and the infusion stopped because of clinical improvement. She had baseline renal dysfunction (BUN- 63, creatinine –3.5 mg/dL). On day 5 her renal function deteriorated (BUN=98, Creatinine =6.0 mg/dL). Hemodialysis was started on day 5. She had a non-Q wave infarction on day 7. She underwent a PTCA on day 26. She was discharged on day 53 still requiring intermittent hemodialysis.

12) Subject # 560-401 (NAT, fixed dose, catheterized) (68 y/o M, NYHA IV). He was infused for 24 hours, with the infusion stopped due to clinical improvement. He was discharged on day 11 and admitted on day 26 for worsening CHF. He was treated with Lasix and milrinone and discharged on day 29.

13) Subject # 560-402 (NAT, fixed dose, catheterized) (63 y/o M, NYHA II). He was treated for 24 hours, with the infusion discontinued due to clinical improvement. On day 4, he had an episode of VT and required intubation and treatment of dopamine, amiodarone and lidocaine and an intra-aortic balloon pump was inserted. He had heart transplant surgery on day 11.

14) Subject # 561-503 (NAT, fixed dose, not catheterized) (54 y/o F, NYHA IV). She was treated with study drug for 48 hours, with the drug discontinued due to clinical improvement. She was discharged on day 6, but readmitted on day 21 for recurrent CHF and possible pyelonephritis. Her renal insufficiency worsened (creatinine peak =4.0 mg/dL; baseline =2.2 mg/dL). She was diagnosed with ATN. She was treated with IV Lasix and her CHF improved. Atrial fibrillation, a foot ulcer and a possible urinary tract infection also complicated her hospitalization. She was discharged on day 27.

15) Subject # 572-414 (NAT, fixed dose catheterized). (64 y/o M, NYHA Class III). He was treated for 49 hours with study drug with the infusion stopped due to lack of improvement. Dobutamine was added. On day 5, hospitalization was prolonged due to worsening heart failure. The subject also received milrinone for 6 weeks followed by ongoing nitroprusside and dobutamine till study day 60. As of study day 7, he was placed on a transplant list.

16) Subject # 572-420 (PBO.NAT, fixed dose, catheterized) (64 y/o F, NYHA III). He was treated with study drug for 27 hours when the infusion was discontinued due to clinical improvement. She was discharged on day 7 and readmitted on 28 due to right upper abdominal burning and pain. Renal ultrasound showed compromised blood flow to both kidneys. An HIDA scan showed chronic cholecystits. She was treated with metronidazole and ciprofloxacin and discharged on day 36.

17) Subject # 572-501 (NAT, fixed dose, not catheterized) (71 y/o M, NYHA III). He was treated with study drug for 48 clinical improvement. After 6 hours of therapy, he was treated for hyperkalemia (K=5.4, baseline 5.1 meq/L). There was no history of baseline renal dysfunction. He also had PVCs. He was discharged on day 4, and readmitted on day 22 with a K= of 6.7 meq/L. He was treated with Kayexalate and spironolactone.

18) Subject # 572-502 (NAT, fixed dose, not catheterized)(80 y/o M, NYHA IV). The study drug was infused for 27 hours and discontinued due to lack of clinical improvement. Dobutamine was added on study day 1 and switched to milrinone after study drug was discontinued. He was discharged on day 6, but readmitted on day 11 for worsening heart failure due to fluid overload and worsening renal failure (creatinine =5.1 mg/dL, baseline 2.9 mg/dL). He was treated with antibiotics and discharged on day 22 with a creatinine of 5.3 mg/dL.

19) Subject # 580-403 (PBO/NAT fixed dose, catheterized)(50 y/o M, NYHA IV). He was treated for 48 hours with drug that was discontinued due to clinical improvement. He was discharged after day 3 but readmitted on day 7 for dehydration and symptomatic hypotension. He was treated with dobutamine and fluid. Relative to baseline his renal function deteriorated (creatinine = 3.4 mg/dL; baseline 1.9 mg/dL). His renal function improved with hydration. His hospital course was complicated by fluid overload. He was diuresed and discharged on day 11.

20) Subject # 580-409 (NAT, fixed dose, catheterized) (69 y/o M, NYHA IV). He was treated with study drug for 24-hours that was stopped due to clinical improvement. He was discharged on day 3, but readmitted on day 7 with symptoms of hypotension, dehydration, abdominal pain and vomiting. Digoxin toxicity was diagnosed. His hospitalization was prolonged due to asymptomatic bradycardia. His amiodarone and digoxin were discontinued. He was discharged on study day 13.

21) Subject # 585-401 (NAT, fixed dose, catheterized) (64 y/o M, NYHA IV). This subject was treated for 24 hours of infusion with the infusion discontinued due to lack of clinical response. He was subsequently treated with dobutamine. He was discharged on day 4, but readmitted on day 25 due to dehydration, fever and hypotension (84/54 mm Hg). Carvedolol and Lasix were withheld. He subsequently was found to have a foot ulcer, a blood culture was positive. He was treated with antibiotics and discharged on day 32.

22) Subject # 605-505 (PBO/NAT, fixed dose, not catheterized). (68 y/o M, NYHA I). This subject was treated for 24 hours with study drug that was discontinued due to clinical improvement. On day 5 he was diagnosed with ARDS and was intubated. He was extubated and discharged on day 20.

23) Subject # 605-508 (NAT, fixed dose, not catheterized) (57y/o M, NYHA III). IV dobutamine was added to study drug 2 hours after the start of the infusion to increase cardiac output. Study drug was discontinued due to clinical improvement but IV dopamine was initiated. The subject had a history of chronic renal insufficiency. He had a catheter placed for dialysis and hemodialysis was initiated on day 16. He was discharged on day 18.

24) Subject # 627-502 (PBO/NAT, fixed dose, not catheterized)(74 y/o M, NYHA class I). His study drug was discontinued at day 3, due to worsening renal failure. His creatinine increased from a baseline value of 3.9 to 5.6 mg/dL. A permanent catheter was placed. Two days later he was intubated due to respiratory acidosis. He was discharged on day 40.

25) Subject # 627-510 (PBO/NAT, fixed dose, not catheterized) (78 y/o M. NYHA III) He was treated with study drug for 48 hour with the infusion discontinued due to clinical improvement. He was discharged on study day 3, but readmitted on day 7 for CHF and chest pain. He was hypertensive and tachycardic, cardiac enzymes were normal. He had a cardiac catheterization, which showed total occluded proximal left anterior descending artery and a sub-total proximal left circumflex and mid-right coronary artery. His creatinine increased from 2.0 a baseline to 2.5 mg/dL. A renal scan showed no visualization of the left kidney and poor cortical transit within the right kidney. A renal arteriogram showed an occluded left renal artery. He was discharged on study day 12 with a creatinine of 2.4 mg/dL.

26) Subject # 636-401 (NAT, fixed dose, catheterized) (46 y/o F, NYHA IV). She was treated for 56 hours and discontinued due to clinical improvement. She was discharged on day 6 and readmitted on day 9 due to dehydration and fatigue, lightheadedness, nausea and diarrhea. She was treated with IV fluids while diuretics were withheld. She was discharged on day 13.

27) Subject # 636-502(NAT, fixed dose, not catheterized)(56 y/o M, NYHA not stated). This was a subject with progressive cardiomyopathy, s/p mitral valve replacement (secondary to rheumatic heart disease) and AICD placement. He was on a cardiac transplant list with seven in subject admissions for CHF. The subject was maintained on NAT till transplanted on day 161. Post transplant he required high doses of inotropic support and an intra-aortic balloon pump was placed. Two days post transplant he developed right ventricular failure, oliguria, hyperkalemia and eventually left ventricular failure. He died of multi-organ failure 3 days later (day 164, i.e. post 30-day cut-off).

28) Subject # 636-504 (PBO/NAT fixed dose, not catheterized) (59y/o M, NYHA IV). This subject was treated for 48 hours with study drug that was discontinued due to clinical improvement. He was discharged on day 12. At that time his creatinine was 2.1 mg/dl (baseline was ???). He was readmitted on study day 15 with large-volume watery diarrhea, acute renal failure (serum creatinine 4.1 mg/dL), hyperkalemia (6.9 meq/L) and hypotension (68/43 mm Hg). He was discharged on study day 22. On study day 26 he was readmitted with CHF, increasing diarrhea, malaise, dyspnea and chest pain. His creatinine was 2.0 mg/dL. He received IV furosemide and dobutamine with minimal improvement. He was discharged to home for hospice care on study day 36. He died on day 48 (post-30 day cut-off).

29) Subject # 638-501 (NAT, fixed dose, not catheterized) (71 y/o M, NYHA III). This subject was treated for 68 hours with study drug with clinical improvement. He was discharged on day 6, but readmitted on day 11 for dehydration, CHF and hyponatremia. He had weight loss, cachexia and poor appetite. He was placed on a DO NOT RESUSCITATE status and the defibrillator was turned off. The subject was alive at day 32.

30) Subject # 638-504 (NAT, fixed dose, not catheterized) (85 y/o M, NYHA IV). He was treated with study drug that was discontinued due to clinical improvement. He was discharged on day 5, but readmitted on day 25 because of nausea, vomiting and diarrhea. He was treated with IV fluids Pepcid, Regalin and Lomotil. He was discharged on day 28.

31) Subject # 642-403 (NAT, fixed dose, catheterized) (85 y/o F, NYHA III). She was treated for 24 hours with discontinuation due to clinical improvement. She was readmitted on day 15 for a UTI, treated and discharged the next day.

32) Subject # 642-504 (NAT, fixed dose, not catheterized) (56 y/o F, NYHA I). She was treated for 45 hours with the drug discontinued due to lack of efficacy. She was readmitted on day 16 due to worsening CHF, weight gain and abdominal distention. Her CHF symptoms resolved with diuretics and she was discharged on day 19.

33) Subject #663-511 (NAT, fixed dose, not catheterized) (60 y/o M, NYHA I). He was treated for 24-hours with study drug with infusion stopped due to unwillingness to continue. He was readmitted on day 14 due to change in mental status. No diagnosis was made. The subject was discharged on day 21.

34) Subjects # 667-403 (NAT, fixed dose, catheterized) (50 y/o M NYHA IV). He was treated for 39 hours with the infusion stopped for clinical improvement. On day 10, he experienced an episode of symptomatic hypotension with SBP falling to 60 mm Hg. He was treated with dobutamine and dopamine. His symptoms resolved in 3 hours.

35) Subject # 667-425 (NAT, fixed dose, catheterized)(66 y/o M, NYHA III). He was treated for 24 hours, with the infusion stopped because of clinical improvement. His hospitalization was prolonged due to worsening renal function, with a creatinine of 3.2 mg/dL (baseline creatinine 1.4 mg/L). He was transferred to the ICU (creatinine 4.4 mg/dL). His creatinine peaked at 7.5 mg/dL on study day 18. He was treated with renal doses of dopamine. He was discharged on day 30 with a creatinine of 2.4 mg/dL.

36) Subject # 671-401 (PBO/NAT, fixed dose, catheterized) (78 y/o F, NYHA IV). She was treated with study drug for 48 hours for clinical improvement. On study day 4, she experienced symptomatic hypotension that lasted 20 minutes and a second episode on day 7 that lasted 70 minutes. She was readmitted to the hospital on day 21 due to a GI bleed. Her Hgb was 8.7 g/L. She received 2 units of PRBC. She was discharged to a nursing home on day 26.

37) Subject # 674-501 (PBO/NAT, fixed dose, not catheterized) (55 y/o F, NYHA IV). She was treated for 24 hours, with the drug discontinued due to clinical improvement. She was readmitted to the hospital on day 12 for respiratory distress and epilepsy (there was a history of seizure disorder). She was intubated and given lidocaine. She was

discharged on day 16 and readmitted on day 22 for anemia that included a bone marrow. She was discharged on study day 27.

38) Subject # 677-501 (NAT, fixed dose, not catheterized) (75 y/o F, NYHA IV). She was treated for three days with the infusion discontinued due to clinical improvement. She was discharged on day 6 but readmitted on day 8 due to worsening heart failure, She was treated with diuretics and discharged on day 12.

39) Subject # 677-503 (PBO/NAT, fixed dose, not catheterized) (80 y/o M, NYHA IV). This subject was treated for 24 hours, with the infusion stopped for clinical improvement. He developed sepsis and treated with antibiotics. He was discharged on day 11.

40) Subject # 677-504(NAT, fixed dose, not catheterized) (43 y/o M. NYHA III). He was treated for 15 days and discontinued due to clinical improvement. He was readmitted on day 25 for hyperglycemia (there was a baseline history of diabetes) and chest pain. He was discharged on day 30.

41) Subject # 678-404 (NAT, fixed dose, catheterized) (58 y/o M, NYHA III). He was treated for 4 days, with the infusion stopped due to inadequate clinical response. He had worsening heart failure on day 9 that prolonged his hospitalization. He did not respond to IV inotrope or diuretic therapy. He was placed on a cardiac transplantation list a left ventricular assist device was inserted on day 30. The subject had cardiac tamponade on day 31 and died.

42) Subject # 678-501 (NAT, fixed dose, not catheterized) (75 y/o M, NYHA IV). He was treated with study drug which was discontinued due to clinical improvement. He was discharged on day 4 but readmitted on day 6 for CHF exacerbation and AF with a rapid ventricular response. He was treated with dobutamine and Cardiazem and discharged on day 16.

43) Subject # 678-502 (PBO/NAT, fixed dose, not catheterized) (86 y/o F, NYHA IV). She was treated with study drug with clinical improvement. Dobutamine was initiated after study drug was discontinued. Hospitalization was prolonged for dialysis access. She had baseline CRF (baseline creatinine was 5.3 mg/dl). She had a Tenckhoff catheter placed and developed fever and abdominal cramping. Peritoneal dialysis was started on day 13. She was discharged with chronic dialysis.

44) Subject # 678-513 (NAT, fixed dose, not catheterized). (67 y/o M, NYHA III). The subject was treated for 42 hours with study drug that was discontinued due to clinical improvement. He was discharged on day 4 but readmitted on day 15 due to syncope attributed to atrial arrhythmia (picked up by the AICD). His amiodarone dose was increased. His creatinine worsened post treatment to 3.7 mg/dL (baseline 1.9 mg/dL). He received dobutamine and dopamine for CHF. He died on day 31 (1-day post cut-off).

45) Subject # 679-502 (NAT, fixed dose, not catheterized) (39 y/o M, NYHA III). This subject was treated for 24 hours with the infusion stopped because of clinical improvement. He was discharged on day 2 but readmitted on day 21 due to worsening CHF. A right heart catheter was placed and he was treated with IV Lasix. He was listed for cardiac transplantation.

46) Subject # 681-501 (PBO/NAT, fixed dose, not catheterized) (43 y/o M, NYHA IV). He was treated with study infusion for 24 hours, with the infusion discontinued due to clinical improvement. He was discharged on day 4 but rehospitalized on day 14 for gastroenteritis. He was treated with IV fluid for dehydration. He was hypotensive at the time. He was discharged on study day 15.

47) Subject # 681-506 (NAT, fixed dose, not catheterized) (58 y/o M, NYHA IV). He was treated for 24 hours with the infusion stopped because of clinical improvement. He was discharged on day 4 but rehospitalized on day 15 for evaluation of mental status described as catatonic. He was treated with dobutamine and Lasix (presumably because of worsened heart failure). He was discharged on day 19.

48) Subject # 681-507 (NAT, fixed dose, not catheterized) (68 y/o M, NYHA IV). He was treated for 24 hours, with study drug that was discontinued due to clinical improvement. He was discharged on day 4 but was readmitted on day 21 due to gout. He was treated with intra-articular steroids and discharged on day 25.

49) Subject # 687-401 (NAT, fixed dose, catheterized) (71 y/o M, NYHA IV). He was initially hospitalized for an exacerbation of CHF and was started on study drug thirteen days into the hospitalization. He was treated for 4 days and was discharged 6 days later but readmitted on day 29 for CHF and anemia. He was treated with Lasix, Zaroxolyn, aldactone and milrinone and discharged four days later.

50) Subject # 687-415 (PBO/NAT, fixed dose, catheterized) (69 y/o M, NYHA III). He was treated with study drug for two days. The infusion stopped due to clinical improvement. He had an episode of gastrointestinal bleeding prior to the start of the infusion that required FFP and 5 units of packed red blood cells. He was discharged on day 9 but readmitted on day 13 for rectal bleeding. He was discharged on day 22.

51) Subject # 688-402 (PBO/NAT, fixed dose, catheterized) (40 y/o M. NYHA IV). He was initially admitted for CHF and entered into the study 10 days later. He was treated with drug for 52 hours and discontinued due to lack of clinical response. He had an episode of VT during the infusion that required cardioversion. He was hypotensive with a BP of 72/25 (did this cause the VT or visa versa???). The episode lasted 45 minutes. He was discharged 2 weeks later.

52) Subject # 695-401 (NAT, fixed dose, catheterized) (58 y/o M, NYHA IV). This subject was treated with study drug for 24 hours and discontinued due to clinical response. He developed line sepsis and was treated with antibiotics for 5 days. Hemodialysis was initiated on day 9 because the subject began to hallucinate and was agitated. His psychiatric symptoms as well as leg edema resolved. He was discharged on day 16, no longer requiring dialysis.

53) Subject # 369-419 (Nat, adjustable dose, catheterized) (58 y/o F, NYHA IV). The subject was treated for 24 hours, with study drug discontinued due to clinical improvement. She was discharged on day 8 but readmitted on day 22 for decompensated CHF and evaluation for heart transplant. She was treated with Lasix and milrinone and discharged on day 28.

54) Subject # 519-401 (NAT adjustable dose, catheterized) (67 y/o F, NYHA III). She was treated for 24 hours with the infusion discontinued due to clinical improvement. Her hospitalization was prolonged due to worsening renal function that required dialysis (baseline creatinine/ BUN 2.4/ 69) on treatment creatinine/ BUN (3.3/97 mg/dL). She was discharged on hemodialysis three times a week.

55) Subject # 554-422 (NAT, adjustable dose, catheterized) (74 y/o F, NYHA III). She was treated with infusion for 24 hours and discontinued due to inadequate clinical response. She was discharged on day 4 but was readmitted on day 24 due to fluid overload. She was diuresed with Lasix and discharged on day 26.

56) Subject # 572-409 (NAT, adjustable dose, catheterized) (50 y/o F, NYHA III). She was treated for 24 hours with study drug and discontinued due to inadequate response. Milrinone was initiated after study drug discontinuation. Her hospitalization was prolonged due to episodes of VT on days 20, 23 and 24 which responded either to cardioversion plus lidocaine or amiodarone, lidocaine and adenosine. Her condition deteriorated and a LVAD was inserted as a bridge to cardiac transplant.

57) Subject # 572-417 (NAT adjustable dose, catheterized) (62 y/o M, NYHA III). This subject was treated with study drug for 48 hours and was discontinued due to clinical improvement. He was discharged on day 10 but readmitted on day 18 due to increased PVCs. .He was discharged on day 22.

58) Subject # 572-419 (NAT, adjustable dose, catheterized). (59 y/o M, NYHA IV). He was treated with study drug for 51 hours and discontinued due to clinical improvement. He was discharged on day 6 but readmitted on day 8 for confusion. His baseline creatinine was 1.9 mg/dL. On readmission his creatinine was 4.2 mg/dL. Diuretics were withheld and creatinine levels reapproached baseline. He was treated with milrinone and NTG for CHF exacerbation. He was discharged on day 35.

59) Subject # 620-401 (NAT, adjustable dose, catheterized) (60 y/o M, NYHA III). He was treated for 24 hours with the infusion stopped due to clinical improvement. He experienced a non-Q wave MI on day 6. He was discharged on day 12 but readmitted on day 21 due to increasing CHF symptoms and worsening peripheral edema and elevated creatinine (3.1 mg/dL; baseline 1.8 mg/dL). His creatinine returned to baseline and he was discharged on day 26.

60) Subject # 667-408 (NAT, adjustable dose, catheterized)(55 y/o M. NYHA III). He was treated for 18 hours with the infusion discontinued due to clinical improvement. On day 8 his CHF status worsened and he was sent back to the ICU for Swan Ganz placement and milrinone treatment. He subsequently required mechanical ventilation. His X-ray showed pulmonary edema and both nitroprusside and nitroglycerine were added to the milrinone. Sepsis, pulmonary hypertension, renal failure and pneumonia complicated his hospital course. He was discharged, milrinone dependant on day 47.

61) Subject # 675-402 (NAT adjustable dose, catheterized) (69 y/o F, Class IV). She was treated for 26 hours with study drug that was stopped due to inadequate clinical response. She was discharged on day 5 but readmitted the next day with symptoms of dyspnea. She also had renal insufficiency and diarrhea. She was treated with inotropes and discharged on day 14.

62) Subject # 678-401 (NAT, adjustable dose) (60 y/o M NYHA III). He was treated for 2 days and discontinued due to clinical improvement. He was discharged on day 3 but readmitted on day 28 for a syncopal episode attributed to phenrgan and dehydration. Diuretics and Vasotec were adjusted and carvedilol was administered. He was discharged on day 31.

Subjects whose Dose was interrupted or decreased:

There were three subjects who discontinued during the initial 3-hour infusion

1) Subject #357-502 (Natrecor fixed dose, not catheterized) This patient's course is described under deaths.

2) Subject #369-518 (NAT, fixed dose, not catheterized) (59 y/o M, NYHA III). He was initially enrolled for dobutamine therapy and was started on therapy. After approximately 1.5 hours after the start of therapy, the subject had a severe drop in blood pressures from approximately 95/59 to 60/27 mm Hg. The study drug was discontinued. The systolic blood pressure remained below 90 mm Hg for 2 hours.

3) Subject # 543-405 (PBO/NTG, catheterized) (64 y/o F, NYHA II). This subject was started on study drug despite not meeting prespecified criteria for wedge pressures. There were apparently no adverse events but the study drug was discontinued after approximately 4.5 hours. The wedge pressure at the time was 12 mm Hg. Wedge pressures were measured through 15 hours. Dyspnea assessed during the 24-hour observation period.

Adverse Events Labeled as Severe: There were a total of 152 subjects that had one or more adverse events listed as "severe" in intensity. The numbers of subjects with events listed as severe in intensity are shown in Table41. This reviewer attempted to enumerate those subjects with CHF or renal events of "severe" intensity. The inclusion by this reviewer was somewhat subjective. For example, subjects described as having respiratory failure or respiratory arrest in were treated as having worsening CHF. Subjects were counted under renal events who had events described as hyperkalemia, azotemia or uremia.

Table 41. Summary of events listed as "severe" in intensity

	Catheterized					Not Catheterized				Totals	
	NTG	FIX NAT	ADJ NAT	PBO: NTG	PBO: NAT	NTG	NAT	PBO: NTG	PBO: NAT	All NTG	All Fixed NAT
N=	60	62	62	32	30	83	80	41	39	216	211
Pts with events as severe	24 (39%)	20 (32%)	19 (30%)	10 (31%)	10 (32%)	22 (27%)	23 (28%)	11 (27%)	13 (32%)	69 (32%)	64 (30%)
CHF-related events	13 (21%)	11 (17%)	13 (21%)	3 (9%)	4 (13%)	12 (14%)	14 (17%)	8 (20%)	5 (13%)	36 (17%)	33 (16%)
Renal events	5 (8%)	5 (8%)	4 (6%)	0 (0%)	0 (0%)	2 (2%)	7 (8%)	2 (7%)	2 (5%)	9 (4%)	14 (7%)

Major Events monitored by the DSMC through day 30: Table 42 contains the number of major adverse events that were monitored by the DSMC for the first 30 days following the index infusion and include cerebrovascular accidents, myocardial infarctions, new onset dialysis and death. Deaths are summarized and tabulated above.

Table 42 Major events monitored by the DSMC through day 30

	NTG (n=216)	NAT fixed dose (N=211)	All NAT (n=273)
Cerebrovascular accident	1 (<1%)	0	0
Myocardial infarction	3 (1%)	1 (<1%)	2 (1%)
New onset dialysis	5 (2%)	7 (3%)	9 (3%)
Deaths	11 (5%)	15 (7%)	22 (8%)

Overall Adverse Events:

Adverse events during the placebo-controlled period: The adverse events during the 3-hour placebo-controlled phase are shown in Table 43. There was an increase in events in the NTG group, with nearly all the differences due to headache. Relative to placebo, headache was numerically increased in the Natrecor-treated patients.

Table 43 Events occurring in > 2 subjects in any one group 3-hour placebo controlled phase.

	NTG (N=143)	NAT (N=204)	PBO (N=142)
Any Adverse Event	39 (27%)	36 (18%)	20 (14%)
Headache	17 (12%)	11 (5%)	3 (2%)
Pain	2 (1%)	2 (1%)	2 (1%)
Hypotension	6 (4%)	5 (2%)	0
Symptomatic hypotension	2 (1%)	1 (<1%)	0
Abdominal pain	4 (3%)	0	0
Catheter pain	2 (1%)	0	0
Injection site reaction	0	2 (1%)	0
Neck pain	0	0	2 (1%)
Ventricular tachycardia	2 (1%)	2 (1%)	0
NSVT	2 (1%)	2 (1%)	0
Anxiety	0	3 (1%)	3 (2%)
Nervousness	2 (1%)	2 (1%)	0
Angina pectoris	0	2 (1%)	1 (1%)
Hyperkinesia	0	2 (1%)	0
Nausea	2 (1%)	1 (< 1 %)	1 (1%)

Adverse events through 24-hours: A tabulation of adverse events during the first 24-hours of infusion (Table 44) shows an increase in adverse events among the NTG treated subjects (68% to ~50%). The difference between the NTG and NAT groups is largely accounted for by the increased incidence of headache and nausea in the nitroglycerin group relative to the two cohorts of Natrecor

treated subjects. The event rate in the Natrecor adjustable dose group can be determined by subtracting the Nat fixed dose event rate from the all Natrecor event rate and dividing by the number of subjects treated with Natrecor, adjustable dose (N=62). There does not appear to be any large increase in adverse events in the Natrecor, adjustable dose cohort. Hypotension (both asymptomatic and symptomatic) differs minimally in comparing the three cohorts.

Table 44 Adverse events during first 24 hours > 1 ADR in any group

Adverse events	NTG (N=216)	NAT, fixed dose (N=211)	All NAT (N=273)
Any Adverse events	146 (68%)	105 (50%)	140 (51%)
Body as a whole			
Headache	44 (20%)	19 (9%)	21 (8%)
Pain	11(5%)	8 (4%)	11 (4%)
Back Pain	7 (3%)	9 (4%)	10 (4%)
Abdominal pain	11 (5%)	2 (1%)	4 (1%)
Catheter pain	11 (5%)	3 (1%)	4 (1%)
Asthenia	4 (2%)	1 (< 1%)	1 (< 1%)
Fever	5 (2%)	2 (1%)	3 (1%)
Injection site reaction	4 (2%)	3 (1%)	4 (1%)
Digestive			
Nausea	13 (6%)	7 (3%)	10 (4%)
Vomiting	4 (2%)	3 (1%)	4 (1%)
Constipation	4 (2%)	3 (1%)	3(1%)
Diarrhea	4 (2%)	2 (1%)	2 (1%)
Cardiovascular			
Asymptomatic hypotension	17 (8%)	17 (8%)	23 (8%)
Symptomatic hypotension	10 (5%)	10 (5%)	12 (4%)
Non-sustained VT	11 (5%)	6 (3%)	9 (3%)
Ventricular extrasystoles	2 (1%)	4 (2%)	7 (3 %)
Atrial fibrillation	1 (< 1%)	4 (2%)	4 (1%)
Angina pectoris	5 (2%)	4 (2%)	5 (2%)
Nervous			
Insomnia	9 (4%)	3 (1%)	6 (2%)
Anxiety	6 (3%)	6 (3%)	8 (3%)
Dizziness	4 (2%)	7 (3%)	7 (3%)
Confusion	5 (2%)	1 (< 1%)	2 (1%)
Metabolic and nutritional disorders			
Hypokalemia	1 (< 1%)	4 (2%)	6 (2%)
Hypoglycemia	4 (2%)	1 (<1%)	2(1%)
Respiratory			
Cough Increased	4 (2%)	1 (<1%)	1(< 1%)

Adverse events through day 14: Adverse events that occurred during the first fourteen days of the study, independent of the continuation of infusion, are shown in Table 45. Headache is still more common in the nitroglycerin cohort. "Kidney function abnormal" was more frequent in the "All Natrecor" cohort. The difference can be attributed to the 11% incidence (7 event in 62 subjects) of abnormal function in the adjustable Natrecor cohort.

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Table 45 Adverse events through 14 days > 3 % in any group, not corrected for duration of hospitalization or treatment.

	NTG (N=216)	Natrecor , fixed dose (N=211)	All Natrecor (N=273)
Any Event	185 (86%)	170 (81%)	219 (80%)
Body as a whole			
Headache	56 (26%)	46 (22%)	54 (20%)
Pain	32 (15%)	29 (14%)	37 (14%)
Back pain	15 (7%)	18 (9%)	23 (8%)
Abdominal pain	22 (10%)	11 (5%)	15 (5%)
Fever	11 (5%)	13 (6%)	15 (5%)
Asthenia	14 (6%)	10 (5%)	10 (4%)
Catheter pain	14 (6%)	6 (3%)	10 (4%)
Chest pain	11 (5%)	6 (3%)	11 (4%)
Injection site pain	8 (4%)	5 (2%)	8 (2%)
Cardiovascular			
Hypotension Total	51 (24%)	51 (24%)	63 (23%)
Hypotension-symptomatic	18 (8%)	24 (11%)	28 (10%)
Hypotension asymptomatic	37 (17%)	33 (16%)	42 (15%)
VT-sustained	4 (2%)	4 (2%)	5 (2%)
VT-non-sustained	28 (13%)	26 (12%)	32 (12%)
CHF	19 (9%)	16 (8%)	22 (8%)
Angina pectoris	16 (7%)	17 (8%)	20 (7%)
Ventricular extrasystoles	4 (2%)	8 (4%)	12 (4%)
Atrial fibrillation	3 (1%)	9 (4%)	9 (3%)
Bradycardia	3 (1%)	8 (4%)	9 (3%)
SVT	0	5 (2%)	6 (2%)
Heart arrest	0	5 (2%)	5 (2%)
Nervous			
Insomnia	27 (13%)	23 (11%)	31 (11%)
Dizziness	20 (9%)	21 (10%)	25 (9%)
Anxiety	12 (6%)	15 (7%)	17 (6%)
Confusion	14 (6%)	9 (4%)	12 (4%)
Nervousness	6 (3%)	7 (3%)	8 (3%)
Agitation	7 (3%)	2 (1%)	2 (1%)
Digestive			
Nausea	26 (12%)	33 (16%)	38 (14%)
Constipation	15 (7%)	15 (7%)	18 (7%)
Vomiting	13 (6%)	15 (7%)	16 (6%)
Diarrhea	9 (4%)	12 (6%)	15 (5%)
Dyspepsia	6 (3%)	8 (4%)	10 (4%)
Respiratory			
Dyspnea	12 (6%)	14 (7%)	15 (5%)
Cough increased	12 (6%)	6 (3%)	8 (3%)
Apnea	6 (3%)	4 (2%)	5 (2%)
Urogenital			
Kidney function abnormal	8 (4%)	11 (5%)	18 (7%)
Urinary tract infection	7 (3%)	8 (4%)	9 (3%)
Creatinine increased	7 (3%)	4 (2%)	5 (2%)
Metabolic and nutritional			
Hypoglycemia	9 (4%)	7 (3%)	9 (3%)
Hyperkalemia	6 (3%)	7 (3%)	8 (3%)
Hypokalemia	2 (1%)	7 (3%)	9 (3%)
BUN Increased	6 (3%)	2 (1%)	2 (1%)
Musculoskeletal			
Arthralgia	5 (2%)	8 (4%)	12 (4%)
Hemic and lymphatic			
Anemia	6 (3%)	6 (3%)	10 (4%)

[Comment: the duration of hospitalization and therefore the duration of observation among the different cohorts confound the apparent event rate listed in Table 45. Since the duration of hospitalization for Natrecor subjects is slightly longer than that for NTG subjects, any increase in event rate over the 14-day period may reflect a greater observation period than a true increase in event rate.]

Laboratory: Chemistry: No routine chemistry profiles were performed. Only serum creatinine measurements were performed at baseline, end of the 24-hour infusion, daily for two days post infusion, once somewhere between day 14-19 and once between day 30-35.

Renal function: This study did not have an enrollment requirement that excluded subjects with elevated baseline creatinine measurements. Those enrolled had large variability in their baseline renal function. Some subjects who enrolled were described as having chronic renal failure. The mean and median changes in creatinine in this study are shown in Table 46. There were small changes in serum creatinine over the course of the assessments. These differences were not statistically (nominally) different.

Table 46 Creatinine changes during and after the infusion.

	NTG (N=216)	NAT fixed dose (N=211)	Nat Adjust Dose (N=62)
Baseline			
Mean ± SD	1.6± 1.0	1.6 ± 1.1	1.7 ± 0.79
Median (25-75%)	1.3 (1.0-1.9)	1.4 (1.0-1.8)	1.5 (1.1-2.0)
N/ (missing values)	212 (4)	209 (2)	60 (2)
> 2.0 mg/dL	44 (21%)	45 (22%)	15 (25%
Day 2 (>0 -48 Hrs)			
Mean ± SD	1.5 ± 0.9	1.7 ± 1.2	1.6 ± 0.8
Median (25-75%)	1.3 (1.0-1.8)	1.4 (1.0-1.8)	1.4 (1.0-1.8)
N/ (missing values)	213 (3)	209 (2)	62 (0)
Day 5 (> 48 Hrs-7 days)			
Mean ± SD	1.6± 0.76	1.7± 1.2	1.7 ± 1.1
Median (25-75%)	1.4 (1.1-1.9)	1.5 (1.0-1.9)	1.4 (1.1-2.0)
N/ (missing values)	168 (48)	169 (42)	49 (13)
Day 14 (day 8-19)			
Mean ± SD	1.7± 1.1	1.9 ± 1.5	1.7 ± 0.7
Median (25-75%)	1.4 (1.1-2.0)	1.4 (1.1-2.1)	1.5 (1.2-1.9)
N/ (missing values)	163 (53)	166 (45)	44 (18)
Day 30 (Day 20-40)			
Mean ± SD	1.7 ± 1.1	1.8 ± 1.4	1.7 ± 1.2
Median (25-75%)	1.3 (1.1-1.8)	1.4 (1.1-2.0)	1.4 (1.2-1.9)
N/ (missing values)	173 (43)	167 (44)	51 (11)

Dialysis: The number of subjects who were newly dialyzed is listed in Table 42 above.

Extremes in creatinine:

Table 47 lists those subjects whose creatinine rose by greater than 0.5 mg/dl. The table includes the first value above this cut-off and the day post-infusion that it occurred, the worst such value (and the day it occurred) and the last available value for the subject if different than the worst value (and day). Those subjects **in bold** have their last creatinine above the 0.05 mg/dl increase above baseline at their last creatinine measurements.

Table 47 subjects whose creatinine increased greater than 0.5 from baseline. Subjects in bold are still abnormal (> 0.5 mg/dl increase above baseline) at the end of the observation period. Within each treatment, subjects are listed according to baseline value.
ANAT= Adjustable dose Natrecor, catheterized; FNAT-fixed dose Natrecor, NTG= nitroglycerin, PLA: NTG-Placebo-nitroglycerin; PLA:NAT-placebo-then Natrecor. NC=Not Catheterized, C=Catheterized. √=Abnormal within first week

	pt #	Tx	Baseline	First abnormal (day)	Worse abnormal (time)	last (time)
1	642-405	ANAT	0.6	1.4 (4) √	1.4 (4)	0.9 (30)
2	**667-408**	**ANAT**	**0.8**	**1.6 (15)**	**1.6 (15)**	**1.4 (32)**
3	**687-413**	**ANAT**	**1.2**	**1.8 (26)**	**1.8 (26)**	
4	572-402	ANAT	1.2	2.2 (3) √	2.2 (3)	1.1 (31)
5	554-412	ANAT	1.5	2.4 (3) √	2.4 (3)	1.5 (18)
6	667-414	ANAT	1.5	2.7 (15)	2.7 (15)	1.7 (32)
7	**579-401**	**ANAT**	**1.5**	**2.2 (18)**	**2.2 (18)**	**2.1 (35)**
8	**620-401**	**ANAT**	**1.5**	**3.0 (16)**	**3.0 (16)**	**2.2 (35)**
9	**642-406**	**ANAT**	**1.5**	**2.5 (15)**	**2.5 (15)**	
10	**369-419**	**ANAT**	**1.9**	**2.5 (5) √**	**2.7 (19)**	**2.6 (28)**
11	**675-402**	**ANAT**	**1.9**	**2.7 (17)**	**4.5 (33)**	
12	**688-401**	**ANAT**	**2.2**	**3.1 (3) √**	**6.0 (6)**	
13	**369-409**	**ANAT**	**2.7**	**3.8 (16)**	**3.8 (16)**	**3.6 (33)**
14	554-409	ANAT	3.6	5.5 (6) √	7.4 (9)	2.5 (25)
15	**538-403**	**ANAT**	**3.6**	**8.9 (33)**	**8.9 (33)**	
16	**667-407**	**FNAT,C**	**0.8**	**1.4 (3) √**	**2.0 (4)**	**1.6 (32)**
17	554-404	FNAT,C	0.9	2.1 (4) √	2.6 (5)	1.2 (16)
18	585-401	FNAT,C	1.0	1.6 (17)	1.6 (17)	0.9 (30)
19	636-404	FNAT,C	1.2	2.1 (19)	2.1 (19)	1.6 (29)
20	**605-401**	**FNAT,C**	**1.2**	**2.0 (28)**	**2.0 (28)**	
21	667-411	FNAT,C	1.4	2.2 (15)	2.2 (15)	1.8 (31)
22	**667-401**	**FNAT,C**	**1.4**	**2.0 (21)**	**2.0 (31)**	
23	**667-415**	**FNAT,C**	**1.5**	**6.7 (16)**	**6.7 (16)**	**2.5 (30)**
24	540-408	FNAT,C	1.6	2.2 (16)	2.2 (16)	2.0 (30)
25	**540-403**	**FNAT,C**	**1.6**	**2.7 (4) √**	**3.1(5)**	**2.4 (14)**
26	687-422	FNAT, C	1.8	2.6 (22)	2.6(22)	2.2 (29)
27	642-403	FNAT,C	1.9	3.4 (15)	3.4 (15)	1.4 (32)
28	580-401	FNAT,C	2	2.6 (4) √	2.8 (13)	2.1 (35)
29	**675-401**	**FNAT,C**	**2.1**	**5.0 (37)**	**5.0 (37)**	
30	668-401	FNAT,C	2.2	2.8 (15)	2.8 (15)	2.1 (30)
31	551-401	FNAT,C	2.3	3.8 (2) √	5.3 (4)	1.6 (30)
32	580-407	FNAT,C	2.6	3.8 (20)	3.8 (20)	2.6 (51)
33	**572-410**	**FNAT,C**	**11.1**	**11.7 (29) √**	**11.7 (29)**	**11.7 (29)**
34	681-502	FNAT,NC	0.8	1.4 (14)	1.4 (14)	0.9 (28)
35	**642-503**	**FNAT,NC**	**0.8**	**1.7 (14)**	**1.7 (14)**	**1.4 (31)**
36	**636-502**	**FNAT,NC**	**1**	**2.1 (161)**	**3.8 (163)**	**3.0 (164)**
37	**554-522**	**FNAT,NC**	**1.1**	**1.8 (3) √**	**1.8 (3)**	**1.8 (30)**
38	618-502	FNAT,NC	1.3	2.3 (3) √	2.3 (3)	1.4 (14)
39	502-501	FNAT,NC	1.4	2.1 (3) √	2.1 (3)	1.6 (30)
40	679-502	FNAT,NC	1.4	2.0 (14)	2.0 (18)	1.6 (39)
41	**369-519**	**FNAT,NC**	**1.5**	**2.2 (30)**	**2.2 (30)**	
42	560-501	FNAT,NC	1.6	3.1 (14)	3.1 (14)	1.4 (33)
43	382-504	FNAT,NC	1.6	2.4 (15)	2.4 (15)	1.5 (30)
44	**369-514**	**FNAT,NC**	**1.8**	**4.5 (14)**	**4.5 (14)**	**4.0 (30)**
45	**369-503**	**FNAT,NC**	**1.8**	**3.6 (15)**	**3.6 (15)**	
46	**678-513**	**FNAT,NC**	**1.9**	**3.7 (15)**	**3.7 (15)**	**2.6 (29)**
47	**561-503**	**FNAT,NC**	**2.2**	**3.0 (15)**	**3.0 (15)**	**2.9 (35)**

48	627-506	FNAT,NC	2.2	3.4 (5) √	3.6 (6)	
49	627-505	FNAT,NC	2.7	3.6 (6) √	3.6 (6)	3.6 (14)
50	605-508	FNAT,NC	2.7	3.7 (16)	3.7 (16)	
51	572-502	FNAT,NC	2.9	5.2 (14)	6.0 (30)	
52	554-545	FNAT,NC	3.4	4.5 (3) √	7.9 (16)	6.7 (33)
53	551-402	PLA:NAT,C	1.1	1.7 (33)	1.7 (33)	
54	369-411	PLA:NAT,C	1.2	2.8 (38)	2.8 (38)	
55	663-407	PLA:NAT,C	1.4	2.4 (33)	2.4 (33)	
56	666-408	PLA:NAT,C	1.5	2.8 (17)	2.8 (17)	1.1 (36)
57	367-403	PLA:NAT,C	1.6	2.5 (16)	2.5 (16)	1.9 (28)
58	671-401	PLA:NAT,C	1.7	2.4 (18)	2.4 (18)	1.6 (26)
59	580-403	PLA:NAT,C	1.9	2.9 (33)	2.9 (33)	
60	551-404	PLA:NAT,C	2.3	3.1 (4) √	3.1 (4)	1.3 (18)
61	687-420	PLA:NAT,C	2.4	3.7 (7)	3.7 (7)	2.4 (36)
62	687-415	PLA:NAT,C	3.6	4.7 (36)	4.7 (36)	
63	681-503	PLA:NAT,NC	1	1.6 (29)	1.6 (29)	
64	502-505	PLA:NAT,NC	1.1	4.2 (3) √	4.3 (3)	1.0 (38)
65	679-501	PLA:NAT,NC	1.2	2.0 (18)	2.0 (18)	1.1 (36)
66	605-505	PLA:NAT,NC	1.3	2.4 (3) √	2.5 (3)	1.1 (29)
67	666-510	PLA:NAT,NC	1.3	3.1 (16)	3.1 (16)	1.3 (32)
68	369-513	PLA:NAT,NC	1.8	2.5 (3) √	2.5 (3)	2.2 (33)
69	636-504	PLA:NAT,NC	1.8	3.0 (14)	3.0 (14)	2.5 (31)
70	382-501	PLA:NAT,NC	2	2.9 (30)	2.9 (30)	
71	554-515	PLA:NAT,NC	2.9	3.6 (3) √	3.6 (3)	2.3 (17)
72	627-502	PLA:NAT,NC	3.9	4.5 (2) √	9.0 (15)	6.7 (32)
73	554-523	PLA:NAT,NC	4.7	6.9 (7)	6.9 (7)	
74	678-502	PLA:NAT,NC	5.3	6.4 (32)	6.4 (32)	
75	369-512	PLA:NAT,NC	6.5	7.5 (30)	7.5 (30)	
76	554-426	NTG,C	0.8	1.4 (2) √	1.4 (2)	1.0 (27)
77	667-404	NTG,C	1	1.7 (4) √	2.0 (17)	1.8 (32)
78	580-402	NTG,C	1.1	1.9 (15)	1.9 (15)	1.9 (32)
79	687-410	NTG,C	1.3	1.9 (2)	1.9 (2)	1.6 (16)
80	667-409	NTG,C	1.9	2.6 (16)	2.6 (16)	1.3 (30)
81	687-417	NTG,C	1.9	2.6 (32)	2.6 (32)	
82	711-403	NTG,C	1.9	2.7 (4) √	2.7 (4)	1.6 (33)
83	554-417	NTG,C	2	2.7 (5) √	2.7 (5)	2.3 (39)
84	543-404	NTG,C	2.1	3. (15)	5.3 (31)	
85	627-402	NTG,C	2.5	6.1 (18)	6.1 (18)	5.5 (31)
86	538-406	NTG,C	3.3	4.9 (14)	4.9 (14)	1.6 (32)
87	382-405	NTG,C	3.4	4.1 (15)	4.1 (15)	
88	502-403	NTG,C	4	5.1 (16)	5.9 (33)	
89	554-528	NTG,C	0.9	1.5 (2) √	1.5 (2)	0.9 (31)
90	681-504	NTG,NC	1.1	1.7 (14)	1.7 (14)	
91	360-503	NTG,NC	1.2	1.9 (2) √	2.0 (3)	1.6 (36)
92	605-502	NTG,NC	1.3	2.3 (17)	2.4 (30)	
93	554-407	NTG,NC	1.5	2.4 (17)	2.4 (17)	1.8 (33)
94	516-501	NTG,NC	1.5	2.1 (30)	2.1 (30)	
95	357-503	NTG,NC	1.7	2.8 (15)	2.8(15)	
96	627-507	NTG,NC	2.1	2.7 (3) √	4.6 (16)	4.6 (1)
97	516-502	NTG,NC	2.2	3.5 (14)	3.5 (14)	2.4 (30)
98	524-503	NTG,NC	2.4	4.2 (15)	4.2 (15)	3.3 (30)

99	**636-505**	**NTG,NC**	**2.5**	**3.5 (19)**	**3.5 (19)**	
100	**580-501**	**NTG,NC**	**3.1**	**5.7 (32)**	**5.7 (32)**	
101	**678-508**	**NTG.NC**	**4.2**	**5.5 (30)**	**5.5 (30)**	
102	687-421	PLA:NTG, C	1.9	2.7 (17)	2.7 (17)	1.6 (31)
103	666-402	PLA:NTG,C	1.1	2.7 (19)	2.7 (19)	1.0 (32)
104	580-410	PLA:NTG,C	1.1	1.7 (13)	1.7 (13)	1.1 (31)
105	**369-407**	**PLA:NTG,C**	**1.2**	**2.2 (16)**	**5.5 (27)**	
106	663-404	PLA:NTG,C	1.3	2.0 (16)	2.0 (16)	1.5 (36)
107	687-405	PLA:NTG,C	1.5	2.3 (4) √	2.3 (4)	1.4 (33)
108	687-406	PLA:NTG,C	1.7	2.3 (7)	2.3 (7)	1.7 (11)
109	**618-401**	**PLA:NTG,C**	**1.9**	**3.2 (18)**	**3.2 (18)**	
110	687-424	PLA:NTG,C	0.8	1.6 (3) √	1.6 (3)	1.0 (38)
111	360-502	PLA:NTG,NC	0.5	1.3 (18)	1.3 (18)	0.9 (33)
112	666-508	PLA:NTG,NC	0.8	2.5 (3) √	2.5 (3)	1.2 (26)
113	663-510	PLA:NTG,NC	1.3	2.7 (3) √	2.7 (3)	1.5 (34)
114	642-502	PLA:NTG,NC	1.5	2.6 (14)	2.6 (14)	1.6 (31)
115	357-406	PLA:NTG,NC	1.5	2.1 (16)	2.1 (16)	1.9 (31)
116	**369-501**	**PLA:NTG,NC**	**1.5**	**2.3 (14)**	**2.8 (31)**	
117	**554-512**	**PLA:NTG,NC**	**2.2**	**2.8 (31)**	**2.8 (31)**	
118	**666-505**	**PLA:NTG,NC**	**2.2**	**2.9 (3) √**	**3.2 (4)**	
119	502-506	PLA:NTG,NC	3.2	3.9 (14)	3.9 (14)	3.7 (35)
120	554-514	PLA:NTG.NC	1.2	2.6 (4) √	2.6 (4)	1.2 (33)

Table 48 Summary of renal effects from Table 47

	Catheterized					Not Catheterized				All	
	NTG	FIX: NAT	ADJ NAT	PBO: NTG	PBO: NAT	NTG	NAT	PBO: NTG	PBO: NAT	NTG	NAT, fixed
N=	62	63	63	32	31	83	82	41	41	216	211
# with Cr increase of > 0.5 mg/dl (%)	14 (23%)	18 (29%)	15 (24%)	9 (28%)	10 (32%)	12 (14%)	19 (23%)	10 (24%)	12 (24%)	45 (21%)	59 (28%)
# abnormal within first week	5 (8%)	6 (10%)	6 (10%)	2 (6%)	1 (3%)	2 (2%)	6 (7%)	4 (10%)	5 (13%)	13 (6%)	18 (9%)
# with abnormal at last value	7 (11%)	7 (11%)	10 (14%)	2 (7%)	5 (16%)	9 (11%)	13 (16%)	3 (8%)	7 (17%)	21 (10%)	30 (14%)

Hematology: Not routinely captured on the CRFs.

Urinalysis: Urinalysis was not routinely captured on the CRFs.

ECG: ECGs were not routinely collected.

Vital Signs: The vital signs for the first three hours are shown in figures 10 and 11. There were no differences between nitroglycerine (NTG) and Natrecor (NAT). Both active treatments decreased systolic blood pressure relative to placebo at 1/2, 2 and 3 hours. NTG also significantly lowered SBP at 1 hour. With respect to diastolic blood pressures, both treatments were significantly different than placebo at ½, hour only. Heart rates did not differ (Figure 12) among treatments.

Figure 10

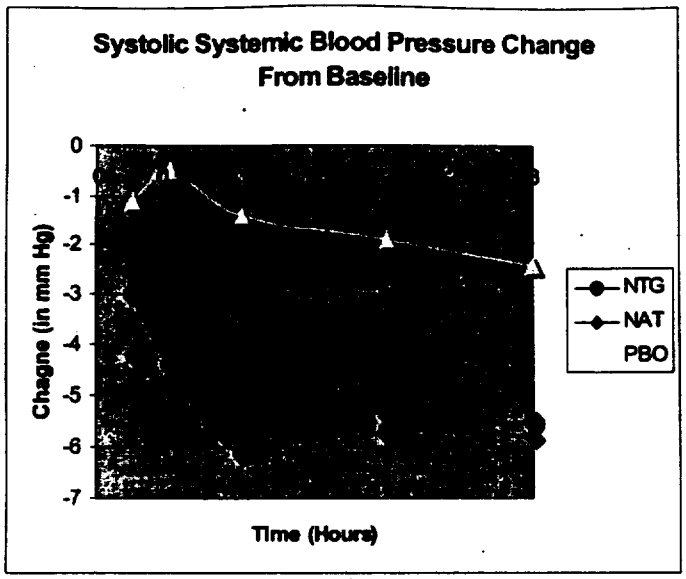


Figure 11

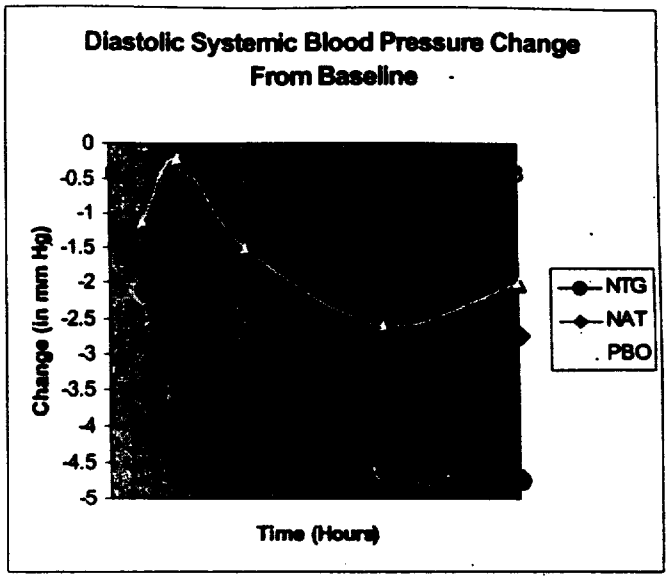
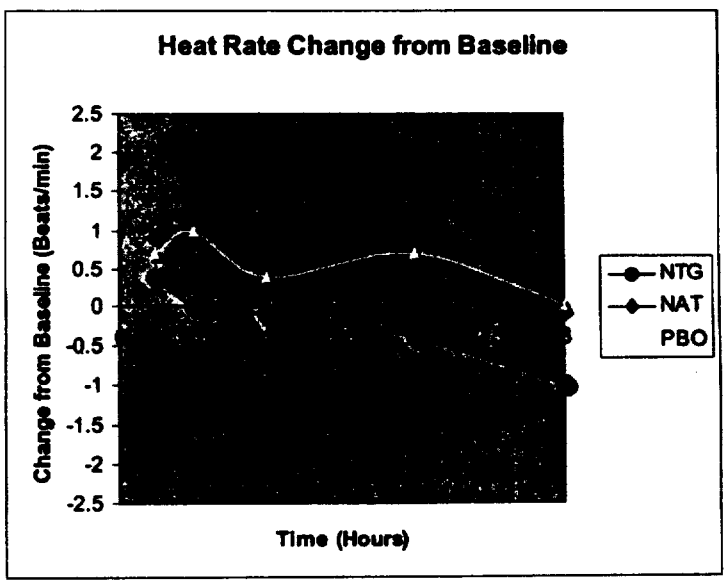


Figure 12



Vital signs after 3 hours are shown in Figure 13-15. Both the NAT fixed and NTG all include those placebo crossover subjects. The NAT fixed (ALL) excludes those in the NAT adjustable dose group. The other three groups graphed reflect those catheterized. The change reflects baseline changes. The three-hour time point for the cohorts were not available so that equivalence when the placebo subjects were reallocated is not shown. Systolic blood pressure was decreased at the 9-hour time point for the Natrecor, adjustable dose. Diastolic blood pressures show no difference between any Natrecor infusion and nitroglycerin. Heart rates show no reflexive tachycardia in response to the blood pressure decreases.

Figure 13

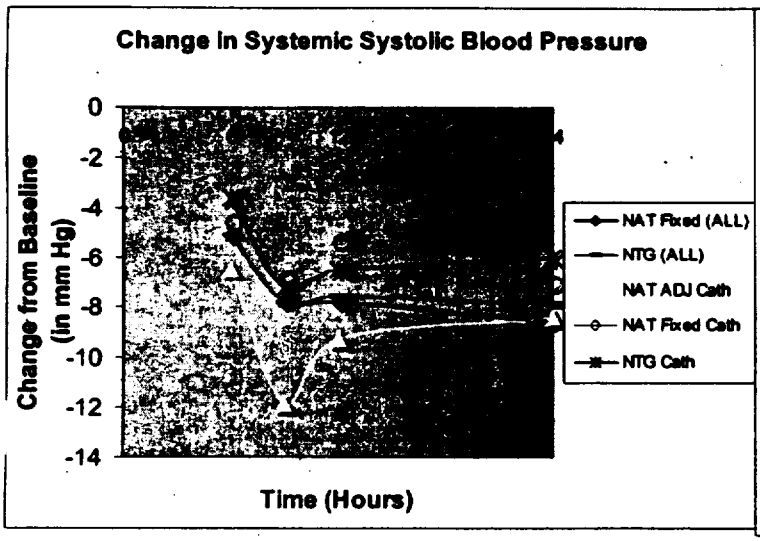


Figure 14

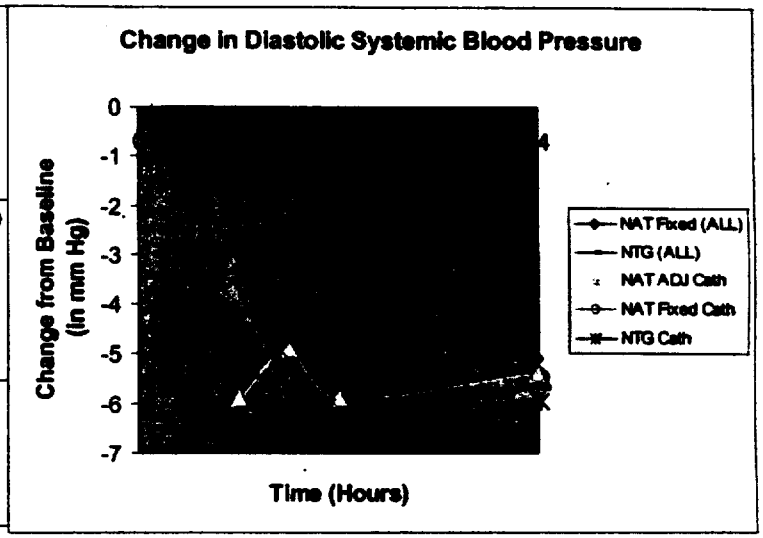
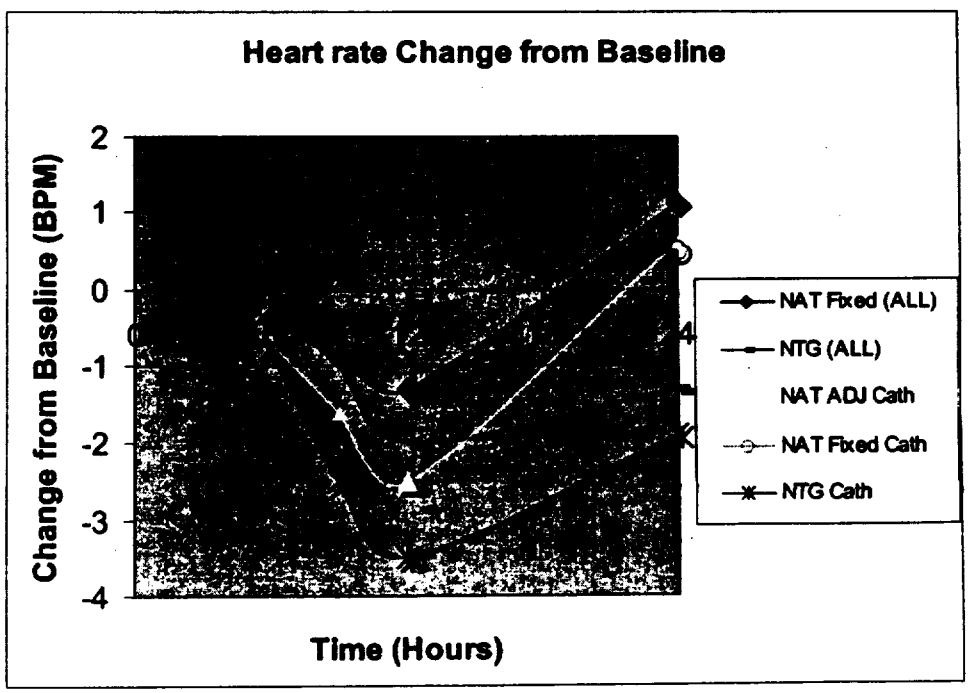


Figure 15



Episodes of Hypotension: This data is derived from Table 109.1 of the sponsor. There were several representations of the data. Table 48 reflects hypotensive events during the entire infusion period (which for many subjects was longer than 24 hours). Other tabular listings that describe the events during the first 24 hours do not significantly differ from this table. The number of episodes was approximately the same for nitroglycerin or Natrecor. The duration of the hypotensive episodes for the Natrecor treated subjects was longer.

Table 48 Description of hypotensive episodes -study 704.339.

	NTG (N=216)	Natrecor, fixed dose (N=211)	All Natrecor (N=273)	Natrecor Adjust (N=62)
Number With at ≥ 1 episode	12 (6%)	13 (6%)	15 (5%)	2 (3%)
Number of episodes	13	16	18	2
Time of onset (episode)				
< 1Hour	0	0	0	0
>1-3 Hour	1 (8%)	0	0	0
>3-6 Hour	3 (23%)	4 (25%)	4 (22%)	0
>6-24 Hour	7 (54%)	8 (50%)	10 (56%)	2 (100%)
>24 –48 Hour	2 (15%)	2 (13%)	2 (11%)	0
> 48 Hour	0	2 (13%)	2 (11%)	0
Duration of episode				
≤ 30 minutes	7 (54%)	0	0	0
31-60 minutes	2 (15%)	4 (25%)	4 (22%)	0
61-120 minutes	4 (31%)	5 (31%)	5 (28%)	0
121-180 minutes	0	4 (25%)	5 (28%)	1 (50%)
3- 7 hours	0	3 (19%)	4 (22%)	1 (50%)
> 7 hours	0	0	0	0
Severity of episode				
Mild	7 (54%)	6 (38%)	6 (33%)	0
Moderate	5 (38%)	8 (50%)	10 (56%)	2 (100%)
Severe	1 (8%)	2 (13%)	2 (11%)	0
Effect of Study Drug				
None/increased	3 (23%)	1 (6%)	1 (6%)	0
Decreased/ Interrupted	5 (38%)	6 (38%)	8 (44%)	2 (100%)
Discontinued	5 (38%)	9 (56%)	9 (50%)	0
All predominant /reported Symptoms				
Lightheadedness	4 / 7	7/11	9/13	2/2
Dizziness	4/10	7/12	7/14	0/2
Feeling Faint	1/ 2	0/3	0/3	0/0
Blurred vision	0/1	0/1	0/1	0/0
other	4/9	2/5	2/6	0/1
Additional action taken				
None	5	10	12	2
Volume challenge	4	2	2	0
Trendelenburg position	3	2	2	0
Dopamine initiated	1	0	0	0
Dopamine increased	0	0	0	0
Inotrope/pressor added	0	1	1	0
Inotrope/ pressor added	0	1	1	0
Other meds added/ increased	0	0	0	0
Other meds decreased/discontinued	0	0	0	0
Hospitalized	0	0	0	0
Other	2	1	1	0
Med decreased	1	0	0	0

With respect to the impact of catheterization, there were more hypotensive events among the NTG subjects who were catheterized versus those who were not catheterized (9% versus 3 %). In all likelihood this difference reflects the higher dose of NTG among those catheterized. Among the Natrecor subjects, there were a greater fraction of those not catheterized who had events when compared to those catheterized (4% versus 8%).

Table 49 Hypotension among those catheterized and not catheterized

	NTG subjects		NAT subjects	
	Catheterized (N=92)	Not catheterized (N=124)	Catheterized Fixed + Adjustable (N=154)	Not catheterized (N=119)
Number With at ≥ 1 episode	8	4	6	9
Number of episodes	8	5	6	12
Time of onset (episode)				
< 1Hour	0	0	0	0
>1-3 Hour	1 (13%)	0	0	0
>3-6 Hour	1 (13%)	2(40%)	0	4 (33%)
>6-24 Hour	5 (63%)	2 (40%)	5 (83%)	5(42%)
>24 –48 Hour	1 (13%)	1 (20%)	0	2 (17%)
> 48 Hour	0	0	1 (17%)	1 (8%)
Duration of episode				
≤ 30 minutes	5 (63%)	2 (40%)	0	0
31-60 minutes	1 (13%)	1 (20%)	2 (33%)	2 (17%)
61-120 minutes	2 (25%)	2 (40%)	2 (33%)	3 (25%)
121-180 minutes	0	0	1 (17%)	4 (33%)
3- 7 hours	0	0	1 (17%)	3 (25%)
> 7 hours	0	0	0	0
Severity of episode				
Mild	6 (75%)	1 (20%)	3 (50%)	3 (25%)
Moderate	1 (13%)	4 (80%)	2 (33%)	8 (67%)
Severe	1 (13%)	0	1 (17%)	1 (8%)
Effect of Study Drug				
None/increased	2 (25%)	1(20%)	0	1 (8%)
Decreased/ Interrupted	4 (50%)	1 (20%)	2 (33%)	6 (50%)
Discontinued	2 (25%)	3 (60%)	4 (67%)	5 (42%)
All reported /predominant Symptoms				
Lightheadedness	3/ 0	4/4	6/4	7/5
Dizziness	6/4	4/0	4/2	10/5
Feeling Faint	1/ 1	1/0	0/0	3/0
Blurred vision	1/1	0/0	0/0	1/0
other	6/3	3/1	2/0	4/2

Bradycardia: Bradycardia was an infrequent adverse event reported either through 24 hours or 14 days of the study. As of 48-hours of the infusion there were 3 episodes of bradycardia (1%) in the Natrecor fixed dose group and 1 (< 1%) of those treated with nitroglycerin. During the 14-day observation period 4% of those treated with Natrecor and 1% of those with nitroglycerin had bradycardia events. None of the bradycardia events among those treated with Natrecor were listed as "severe" in intensity.

Orthostatic blood pressures: No standing blood pressures were taken, no orthostatic values were available.

Tolerance: This study does not specifically address the issue of Natrecor tolerance or habituation. Nevertheless, the decrease in wedge pressures, among those treated with Natrecor over the 24 hour period for which most enrolled subjects successfully completed, was numerically better or

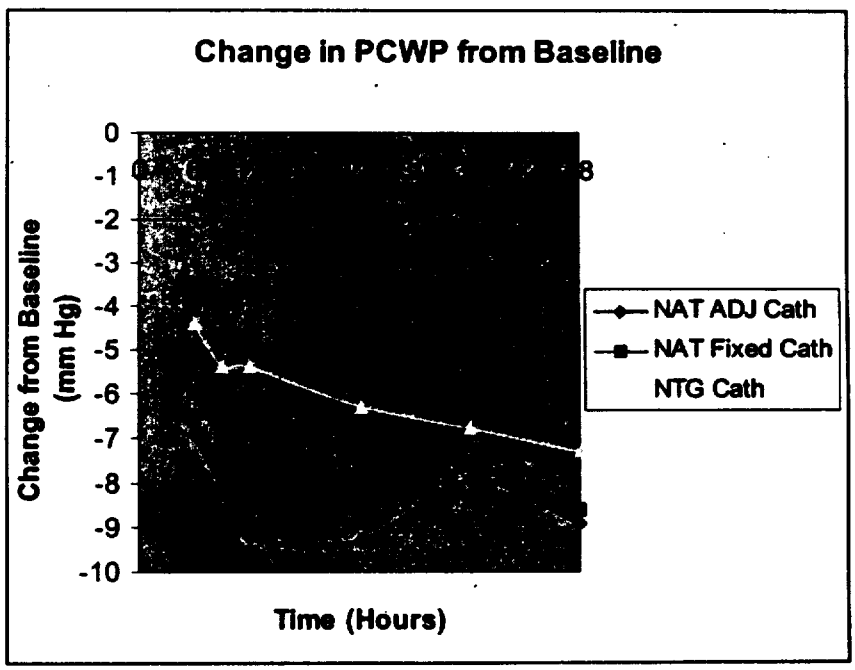
equivalent to those treated with NTG, despite an approximately 50% increase in the NTG infusion rate between 3-48 hours of the infusion. The worst that can be said is that any tolerance with Natrecor appears to be substantially less than tolerance observed with NTG.

Dose response: No dose response data can be derived from this study. The bolus dose was higher and the infusion rates lower than in previous studies of Natrecor.

Need for invasive hemodynamic monitoring: The effect on wedge pressure among those who were catheterized and those not catheterized is shown in Figure 17. The dose of Natrecor that was used among those catheterized and those Natrecor catheterized did not differ by much. The blood pressure drops paralleled the wedge pressure drops. The effect of the adjustable dose Natrecor was somewhat greater than that of the fixed dose. The safety data base among those treated with adjustable dose Natrecor was small. Only a small fraction of subjects were actually titrated to higher doses. Safety of the use of higher doses of Natrecor is better obtained from other studies, with larger databases.

It would appear that if one kept to fixed dose non-increasing doses of Natrecor, catheterization affords little benefit in either efficacy or safety.

Figure 17



Study summary: The VMAC study was a large multicenter study comparing the effects of Natrecor, nitroglycerin and placebo on both PCWP and dyspnea change in subjects with decompensated congestive heart failure. These patients on enrollment were to have dyspnea at rest, while supine or immediately upon modest activity such as eating or bathing.

Approximately 50% of those enrolled were to have the catheter inserted or if already catheterized to be allocated to the catheterized strata. The decision to place or not place a catheter was left to the discretion of the investigator. Those enrolled were to be randomized in a 1: 1: 1: 1: ratio to receive either Natrecor fixed dose: Natrecor adjustable dose : nitroglycerin : placebo. Those not catheterized were to be randomized in a 1: 1: 1 ratio of Natrecor fixed dose: Nitroglycerin: placebo. The treatment portion of the study consisted of two phases. The first three hours of the infusion were placebo-controlled. Subsequently, with the exception of placebo subjects, all subjects continued on their infusion regimen for at least a total of 24 hours. Those subjects randomized to placebo for the initial three-hours of the infusion were at the time of the initial randomized also allocated to receive either Natrecor fixed dose or nitroglycerin for the positive controlled portion of the study.

The Natrecor fixed dose consisted of a regimen of a bolus of 2 ug/kg over 60 seconds followed by a constant infusion of 0.01 ug/kg/min. This infusion regimen for Natrecor differs from that used in previous studies in that the bolus is larger and the constant infusion rates less. For the initial three-hour infusion the regimens for both the fixed and adjustable Natrecor doses were the same. After the initial placebo-controlled infusion, the dose of Natrecor among those in the adjustable dose cohort could have their dose increased. If the PCWP was > 20 mm Hg and the SBP > 90 mm Hg, the subject could receive a bolus of 1 mg/kg followed by an increase n the infusion rate of 0.005 ug/kg/min. The dose increased could be repeated but no more frequently than every three hours, predicated on the same wedge and systolic blood pressure criteria. The maximal infusion rate for the Natrecor adjustable dose was 0.03 ug/kg/min. Infusion of nitroglycerin is to be performed by the standard regimen of the investigator both through the three hour placebo-controlled and 24-hour positive –controlled phase.

The investigator was to be blinded with two infusions simultaneously administered through either different infusion sites or through a single site with "Y" connector. Each of the simultaneous infusions is to be assumed to consist of active drug.

The primary endpoints of the study were the effect of Natrecor when compared to placebo for PCWP at three hours for those catheterized and change in dyspnea symptoms at three hours for both catheterized and not catheterized patients. The prespecified plan was to pool the results of the Natrecor fixed and Natrecor adjustable dose regimens. Both PCWP and dyspnea change were to be demonstrate a statistical difference between placebo and pooled Natrecor doses (fixed and adjustable for hemodynamics and catheterized and not-catheterized for dyspnea change) at the three –hour time point, in order for the study to be considered successful.

Cardiac hemodynamics as well as change in dyspnea symptoms and the subject's global clinical status were also measured at 15 and 30 minutes and 1, 2 and 3 hours after the start of the infusion. PCWP and change in dyspnea and global score were recorded at all these time points. Other hemodynamic measurements (right atrial pressure, systemic vascular resistance, cardiac index, pulmonary vascular resistance and pulmonary artery pressure) were tabulated at baseline and 1 and 3 hours post dose.

For the positive controlled portion of the study PCWP was measured at 6, 9, 12 and 24-hours of the infusion and 36 and 48 hours of the infusion for those who were treated longer. Data

for other hemodynamics was collected at 24 hours. Symptom assessment both dyspnea change and global symptoms were collected at 6 and 24 hours and at the end of the infusion.

A total of 498 subjects were enrolled. The vast majority of subjects had their symptoms of heart failure as an exacerbation of their underlying disease. Only approximately 5% of those enrolled had their heart failure as a consequence of an acute myocardial infarction. A large portion of the population was substantially symptomatic of their CHF. Approximately 80% of those enrolled were NYHA Class III or IV at baseline. Rales and pedal edema were the most frequent symptoms and were present in approximately 70-75% of those enrolled. The protocol required patients to have dyspnea at rest for enrollment. At the time of the infusion, approximately 75% of those enrolled had symptoms either while sitting or lying flat or with one pillow.

Intravenous diuretics were used in approximately 50-70%, pressors, i.e., dobutamine, dopamine or PDE III inhibitors, were administered to 6-23%, 0-10%, and 0-6%, respectively during the 24-hours prior to the start of the infusion. After-load reducers, i.e. intravenous nitroglycerin, or nitroprusside were administered to 0-7% or 0-2%, respectively, during the same time period.

At the end of the three-hour placebo-controlled period, the placebo-subtracted effect of Natrecor (combined adjustable and fixed dose) was –3.8 mm Hg. The effect of Natrecor was highly statistically different from placebo ($p < 0.001$).

With respect to change in dyspnea Natrecor was only superior to placebo at the 3-hour measurement. The effect driven by the symptom benefit among those catheterized ($p=0.03$). There was no difference in comparing Natrecor to placebo, but the value at 3 hours was marginally in favor of Natrecor ($p=0.07$).

Wedge pressure effects of Natrecor relative to placebo was evident as early as 15 minutes (placebo-subtracted measurement was –2.3 mm Hg) after the start of the infusion. The effect remained relatively constant at –3.8 to -4.0 mm Hg after 0.5 hours.

Other hemodynamic measurements indicate an effect of Natrecor relative to placebo on right atrial pressure (decreased), systemic vascular resistance (decreased), cardiac index (increased), pulmonary vascular resistance (decreased) and mean pulmonary artery pressure at the earliest time point (1 hour). With the exception of systemic vascular resistance, all other metrics were statistically significant ($p< 0.05$) or marginally significant (cardiac index; $p=0.09$) at 3 hours.

Change in dyspnea score was assessed at the same time as the wedge pressure assessments. Patients in all treatment groups (even placebo) improved relative to baseline. Aside form the three hour time point (and largely driven by those catheterized), there was no differences between Natrecor and placebo.

During the initial three-hour infusion period, Natrecor was superior to nitroglycerin in decreasing wedge pressure at all time points with the exception of the two-hour time point. At the three-hour time point Natrecor produced a 2-mm Hg drop in wedge pressure greater than that produced by nitroglycerin. Other hemodynamic measurements were not significantly different from nitroglycerin, at three-hours, with respect to right atrial pressure, cardiac index, pulmonary vascular

resistance. Natrecor, however, did decrease mean pulmonary artery pressure when compared to nitroglycerin.

There were no differences between Natrecor and Nitroglycerin for change in dyspnea during this portion of the study.

After three hours, the placebo-treated subjects were switched to their randomized active treatment, the adjustable dose Natrecor dose could now be increased. Among those catheterized wedge pressures were measured at 6, 9, 12, 24, 36 and 48 hours. Other hemodynamic parameters were measured only at 24 hours. There were no differences between Natrecor fixed dose and nitroglycerin for any of these measurements.

On the other hand the Natrecor adjustable dose decreased wedge pressure to a greater extent than nitroglycerin at all time points through 24 hours. It also decreased right atrial pressures relative to nitroglycerin at 24 hours.

Despite the greater drop in wedge pressure of Natrecor adjustable dose relative to nitroglycerin, there was no benefit in dyspnea change.

There was no difference in urine output or weight change in comparing Natrecor adjustable or fixed to Nitroglycerin. Sodium excretion was not measured.

Natrecor's effect persists over the 24-hour infusion period and longer in a small proportion of subjects who were treated for > 24 hours, either with reference to baseline measurements or to the effect of increasing doses of nitroglycerin. These results suggest that over this duration of infusion tolerance is not a credible concern.

Hospitalization among those treated with Natrecor were approximately 2 days longer for the Natrecor treated group than the nitroglycerin group. Re-hospitalizations were equivalent between Natrecor and Nitroglycerin. Mortality at both 30 and 90 days and 6 months did not differ between the nitroglycerin and Natrecor (pooled fixed and adjustable) groups. The trend, however, favored nitroglycerin. The relative risk, comparing Natrecor to nitroglycerin at 30 and 90 days was approximately 1.5. At 6-months, the risk ratio still favored nitroglycerin but the risk ratio decreased to 1.11. There were few overall deaths at each time point and the confidence intervals for a mortality effect were therefore wide. The difference in the mortality effect is likely a s reflection of the "play-of-chance" and possibly related to the severity of disease at enrollment (i.e. need for pressors).

Several adverse events have been noted in previous studies with Natrecor. The dose employed in this study was less than those studies and consequently, the frequency and severity of such events appears to be less obvious. Hypotension was numerically more frequent but not statistically different in comparing Natrecor to nitroglycerin. The duration of these episodes was substantially longer among those treated with Natrecor than those treated with nitroglycerin.

Renal dysfunction appears to be more frequent among those treated with Natrecor. Group means of creatinine were slightly but not significantly higher among those treated with Natrecor.

The number of subjects with substantial increases in creatinine (> 0.5 mg/dL) was greater among those treated with fixed dose Natrecor (28%) than for Nitroglycerin (21%). The percent whose value was abnormal during the first week of treatment (9% versus 5%) and the percent still > 0.5 mg/dL at last measurement (14% versus 10%) was greater among those treated with fixed dose Natrecor.

Bradycardia as an adverse event was infrequently reported during this study. Through 14 days, bradycardia as an adverse event was reported in 4% of those treated with Natrecor and 1% of those treated with nitroglycerin. None of the bradycardia events among the Natrecor-treated subjects were "severe" in intensity.

This study supports the use of Natrecor at this low dose infusion rate of 0.01 ug/kg/min in subjects who are not catheterized and whose dyspnea can reliably be attributed to exacerbation of their CHF. This study by itself is insufficient to describe the effects of Natrecor as superior to that of nitroglycerine.

APPEARS THIS WAY
ON ORIGINAL

Protocol 704.329

Title of Study: Natrecor® (nesiritide) Versus Dobutamine Therapy for Symptomatic Decompensated CHF: A Safety Study Using 24-Hour Holter Monitoring

The PRECEDENT trial: Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy.

Investigator and Sites:

A total of 47 study sites enrolled subjects for this study (Table 50).

Table 50 Investigators and sites study # 704.329

Site # 546 John Boehmer, MD Milton S. Hershey Med. Center Hershey, PA	Site # 549 and # 602 D. Eric Bolster, MD Palmetto Clin Research Summerville, SC	Site # 352 Robert C. Bourge, MD U. of Alabama at Birmingham Birmingham, AL	Site # 561 Andrew Burger, MD Beth Israel Deaconess Med Cent. Boston, MA
Site # 550 James Carley, MD Cardiology Research Assoc Osmond Beach, FL	Site # 624 William Cotts, MD U of Iowa Hospitals and Clinics Iowa City, IA	Site # 620 Teresa DeMarco, MD U of California San Francisco Med Center San Francisco, CA	Site # 502 George Dennish III, MD San diego Cardiovascular Associates Encinitas, CA
Site # 618 Jay Dinerman, MD Jacksonville Heart Center PA Jacksonville Beach, Fl	Site # 379 Cra East, MD Baylor Univ Med Center Dallas, TC	Site # 554 Uri Elkayam, MD LA County-USC Med Center Los Angeles, CA	Site # 585 Lincoln Ford, MD Roudbush VA Med Center Indianapolis, IN
Site # 535 Winston Gandy, MD Saint Joseph Hospital of Atlanta Atlanta, GA	Site # 536 Jala Ghali, MD LSU Med Center Shreveport, LA	Site # 498 Michael Givertz, MD Boston Medical Center Boston, MA	Site # 538 Mitchell Greenspan, MD Lifemark Med Center Sellersville, PA
Site # 357 Joshua Hare, MD The Johns Hopkins Hosp Baltimore, MD	Site # 524 Edward Harlamert, MD Community Hosp. East Indianapolis, IN	Site # 635 and # 487 Paul J. Hauptman, MD Thomas Donohue, MD St. Louis Univ Med Center St. Louis, MO	Site # 355 Ray Hershberger, MD Oregon Health Sciences Univ Potland, OR
Site # 551 Peter Hoagland, MD Diego Cardiac Center San Diego, CA	Site # 306 Robert E. Hobbs, MD The Cleveland Clinic Foundation Cleveland, OH	Site # 382 Allen D. Johnson, MD Green Hospital of Scripps Clinic La Jolla, CA	Site # 356 Walter Kao, MD Rush-Presbyterian-St Lukes Mec Center Chicago, IL
Site # 567 Ronald Karlsberg, MD Cardiovascular Research Inst Of Southern California Beverly Hills, CA	Site # 387 Stuart D. Katz, MD Columbia Presbyterian Med Center New York, NY	Site # 627 and #493 Michael Koren, MD W. Herbert Haught, MD Jacksonville Center for Clinical Research Jacksonville, FL	Site # 367 Marrick kukin, MD Mt Sinai Medixcal Center New York, NY
Site #369 Thierry LeJemtel Albert Einstein College of Med. Bronx, NY	Site # 605 Chang-seng Liang, MD, Ph.D. U of Rochester Med Center Rochester, NY	Site # 370 Charles Lui, MD U of Arizona Health Sciences Center Tucson, AZ	Site # 540 Stephen Mallon, MD U of Miami/Jackson Memorial Medical Center Miami. FL