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**Formulations:**

Dobutamine was taken from the hospital formulary.

Natrecor (Lot # H0007A2) was produced by recombinant DNA Technology.

**Dates of Study:**

The protocol date: 9 April 1998

First subject was randomized: 15 August 1998

Last subject Randomized: 30 December 1998

Statistical protocol not dated.

**Oversight Committees:** There were no planned oversight committees.

**Protocol:** This study was divided into several phases:

- A screening phase
- Randomization
- A pre-treatment baseline Holter phase
- A on-treatment 24-hour infusion
- Post-treatment that extends from the end of the 24-hour period to 14 days.
- A 14-day mortality and hospitalization record.

**Primary Analysis:** The primary statistical analysis of this study is to compare the two Natrecor regimens to dobutamine with respect to heart rate and cardiac ectopy. The primary measures of interest are average heart rate and ventricular premature beats as well as average repetitive beats. Repetitive beats are defined as the sum of the number of beats contained in doublets, triplets and runs of VT. In addition the sponsor will tabulate the number of subjects who meet the criteria for defining a subject as having a proarrhythmic event as defined by Velebit<sup>1</sup>, Morganroth<sup>2</sup> and CAPS<sup>3</sup>.

<sup>1</sup> Velebit V, Podrid P, Lown B et al. "Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs" *Circulation*, 1982; 65 (5) 886-94

<sup>2</sup> Morganroth J, Michelson EL, Horowitz LN et al, "Limitation of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency" *Circulation*, 1978; 58 9e0 408-14

<sup>3</sup> The CAPS Investigators. "The Cardiac Arrhythmic Pilot Study". *Am J Cardiol*, 1986; 57: 01-5.

The initial analysis will include all subjects receiving study drug and having both baseline and treatment Holter data. All data from the entire baseline and entire treatment period while the subject is receiving study drug as a single IV vasoactive agent and while on stable antiarrhythmic therapy will be included. The analysis is therefore bounded on the duration side by the 24-hour period of Holter observation but the treatment duration could be shortened if drug is discontinued or if antiarrhythmic treatment is initiated or the regimen changed.

A supplemental analysis will consider only the last 6 hours of baseline data as well as the first six-hour of treatment.

A subgroup analyses for heart rate will be those subjects whose predominant cardiac rhythm during the treatment Holter period is (or is not) an atrial rhythm.

If a between-group inferential strategy at an  $\alpha=0.05$  demonstrates a difference, then the individual groups will be compared at a level of  $\alpha=0.05$ . If the global test is not significant at a  $\alpha=0.05$  level, then the treatments will be compared by the step-down method of Benjamini and Hochberg<sup>4</sup> will be used to compare treatment groups.

Quantitative endpoints will be normalized to unit time (minute or hour where appropriate). Variables will be evaluated as a change from baseline. These variables will be analyzed by a non-parametric Kruskal-Wallis test, followed by pairwise 2-sample Wilcoxon test.

Proarrhythmia by the criteria of Velebit, Morganroth or CAPS are binary (yes, no) outcomes. These will be analyzed by the generalized Fisher's exact test followed by pair-wise Fisher's Exact test. The incidence (presence/absence) of various arrhythmias will be evaluated within each treatment group using McNemar's test and between groups using the generalized Fisher's Exact test followed by pairwise Fisher's exact test.

*Other statistical issues:* There were no planned interim analyses, although the protocol allowed for the sponsor to perform analysis for corporate planning or regulatory review. One could conclude that the sponsor was not blinded to the treatments (i.e. dose of Natrecor) if such analyses were possible.

The omnibus F-test had a 74% -86% power to detect a 4 BPM difference with a SD of 8 BPM between groups. The range of power is dependent on the value of the intermediate treatment. For pairwise comparisons of ectopy, 100 premature ventricular beat (PVB) difference and a SD of 200 PVB/Hour, pairwise contrasts have an 83% power to detect differences.

#### Randomization and Blinding:

The study was open-labeled with respect to Dobutamine and Natrecor. The two doses of Natrecor were however blinded. Only subjects who successfully complete the 24-hour baseline Holter are to be randomized. At this point subjects will be randomized with the randomization stratified based on the baseline history of VT in a 1:1:1 ratio to dobutamine: Natrecor 0.015 ug/kg : Natrecor 0.03 ug/kg. Randomization is to occur as late as possible during the 24-hour Holter

<sup>4</sup> Benjamini Y and Hochberg Y. "Controlling the false discovery rate: a practical and powerful approach o multiple testing". J Royal Stat Soc, Series B, 1995; 57:289-300.

Abraham M. Karkowsky, MD, Ph.D.: reviewer Natrecor® (nesiritide)

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monitoring period. Aside from the on-site pharmacist, others at the study site are to remain blinded to the treatment assignment until the infusion is about to begin. The study drug is to be delivered to the bedside in a sealed, tamper-proof envelope. In the event that drug is not administered the sealed, unopened envelope is to be returned to the pharmacist.

The results of the Holter data are not to be disclosed either to the subject or investigator during the course of the study.

#### Inclusion Criteria: Subjects

- Are 18 years old
- Have a history of worse than or equal to NYHA Class III CHF
- Present with symptomatic, decompensated CHF for which in-subject therapy with either dobutamine or Natrecor administered with or without diuretics is deemed appropriate
- Are on stable doses of antiarrhythmics (>48 hours).

#### Exclusion criteria: Subjects are excluded if the subject:

- Is unable to tolerate either the washout period or the 24 hour Holter monitoring period without IV vasoactive medication support. Dobutamine, nitroprusside, nitroglycerin and dopamine must be withheld at least for 30 minutes prior to the baseline Holter.
- Has evidence of vascular instability or hypotension (e.g., SBP < 85 mm Hg, cardiogenic shock or evidence of hemodynamic instability requiring immediate inotropic support).
- Requires more than one vasoactive drug.
- Received more than 4 hours of treatment with dobutamine, milrinone, nitroprusside or IV NTG during this hospitalization.
- Required IV antiarrhythmic drug within during 48 hours before starting study drug.
- Serum K < 3.5 meq/L not corrected.
- Had a MI within 48-hours of initiation of study drug, unstable angina or ongoing cardiac ischemia.
- Had other cardiovascular disease (valvular stenosis, obstructive cardiomyopathy, constrictive pericarditis that might adversely respond to potent dilating agents.
- Sustained an arrhythmia i.e., VT or VF or cardiac arrest within seven days before study drug
- Had second or third degree heart block or whose AICD whose back up pacing is set at > 50 BPM.
- Had previous hypersensitivity to drugs that are to be used in this study.
- Participated in another investigational drug protocol.
- Is unlikely to survive the 14-day observation period due to other medical condition.
- Cannot give informed consent or for whom compliance with follow-up procedures a likely to be a problem.

#### Doses:

Dobutamine: The dobutamine dose should begin with 5 ug/kg/min or may be titrated to this dose rapidly (within 1 hour). The dose may be increased but should not be decreased below 5 ug/kg/min during the first 24 hours, except as dictated by adverse events. The dobutamine, once stopped may be re-initiated, with the minimum dose set for 5 ug/kg/min

**Natrecor:** The two Natrecor regimens are constant infusions of either 0.015 ug/kg/min or 0.03 ug/kg/min. There is no bolus. The dose of Natrecor may be decreased or stopped due to symptomatic hypotension or if the systolic blood pressure falls to < 80 mm Hg. If Natrecor is stopped, the infusion may be restarted once the hypotension has resolved at an infusion rate of ½ that previously administered. The dose may be increased at intervals of no greater than every three hours and the dose precipitating the hypotensive episode should not be exceeded.

For subjects on Natrecor whose status worsens, the dose may be increased as appropriate but no more frequently than every three hours.

**Concomitant therapy:** IV and oral diuretics are not restricted. Morphine and non-intravenous cardiac medications are allowed.

There are no restrictions to medications post 24-hour Holter.

**Procedures timing:** The procedures and timing during the study are shown in Table 51.

Table 51. Timing of procedures in study 704.329

	Before Enrollment								Study days			
		0	15 min	30 min	3 Hr	8 Hr	16 Hr	24 Hr	2-7	8-9	10-14	
Informed consent, Med History, Randomization	X											
Phys Ex, Height, Weight	X <sup>5</sup>											
CBC General chemistry	X <sup>5</sup>							X <sup>6</sup>				
Discontinue IV Meds <sup>7</sup>	X	X	→	→	→	→	→	X				
Holter	X <sup>8</sup>	X	→	→	→	→	→	X				
Clinical Signs and symptoms of CHF	X <sup>9</sup>				X			X				
Global Clinical Assessment					X			X				
BP and heart rate	X	X	X	X	X	X	X	X	X <sup>10</sup>			
Study drug administration		X	→	→	→	→	→	X <sup>11 12 13</sup>	X <sup>12 13</sup>	X <sup>13</sup>		
Na, K, CO <sub>2</sub> , Cl, Cr, BUN								X <sup>14</sup>				X
Na, K, Ca, Mg		X <sup>15</sup>										
Humoral factors (at selected sites)	X <sup>16</sup>				X			X				X
Adverse Events, deaths, re-admissions		X	→	→	→	→	→	→	→	→	X <sup>17</sup>	

<sup>5</sup> Obtain within 36 hours of study drug.

<sup>6</sup> Obtain within 24-hour study drug termination or day 7 whichever occurs earlier.

<sup>7</sup> As per protocol

<sup>8</sup> Obtain baseline Holter of 24 hours with recording to stop no earlier than 30 minutes before study drug infusion is started.

<sup>9</sup> Obtain within six ours of study dug

<sup>10</sup> Monitor per usual at this point

<sup>11</sup> Administer as a single IV agent

<sup>12</sup> Can continue Natrecor through day 7

<sup>13</sup> Dobutamine infusion is to be determined by the principal investigator

<sup>14</sup> I f study drug is used more than 24 hours obtain 24 hours during the start of the study drug

<sup>15</sup> Record any additional values during the 24 hour treatment period.

<sup>16</sup> Obtain within 1 hour of study drug

<sup>17</sup> Record all such events through day 14/

**Results:**

**Demographics:** A total of 255 subjects were enrolled into this study. The demographic characteristics of those are shown in Table 52.

Table 52 Demographics of patients enrolled into study 704.329

	Dobutamine (n=86)	NAT 0.015 ug/kg/min (N=85)	NAT (0.03 ug/kg/min) (N=84)	p-value
Age (mean ± SD)	62 ± 14	60 ± 14	61 ± 14	0.9
Ethnicity				0.9
White	48 (56%)	47 (55%)	41 (49%)	
Black	25 (29%)	23 (27%)	23 (27%)	
Hispanic	11 (13%)	13 (15%)	16 (19%)	
Asian	2 (2%)	0 (0%)	2 (2%)	
Missing		2 (3%)		
Gender M/F (% M)	54/32 (63%)	58/27 (68%)	58/26 (69%)	0.6
NYHA III/IV (% IV)	55/31 (36%)	68/17 (20%)	65/19 (23%)	0.04
Treated subjects as random	N=83	N=84	N=79	
CHF History				0.3
Ischemia	42 (49%)	44 (52%)	44 (52%)	
Idiopath dilated cardiomy	22 (26%)	13 (15%)	24 (29%)	
Hypertensive	10 (12%)	14 (16%)	6 (7%)	
# not included	10 (12%)	13 (14%)	5 (6%)	
Cardiovascular history:				
Previous MI	37 (45%)	43 (51%)	46 (58%)	0.2
Hypertension	54 (65%)	56 (67%)	51 (65%)	0.96
Arrhythmia History				
AF or AF/Fl	29 (35%)	18 (21%)	21 (27%)	0.1
NSVT	25 (30%)	22 (26%)	19 (24%)	0.7
Sustained VT	7 (8%)	7 (8%)	5 (6%)	0.9

The groups overall were balanced. The dobutamine group, however, had a greater fraction of those enrolled having NYHA Class IV heart failure than either of the two Natrecor groups. The most common cause of disease was ischemic heart disease.

**Dose:** The study was carried out as planned. The duration of infusions is shown below.

Table 53 Duration of infusion study 704.329

	Dobutamine (n=83)		Natrecor	
			0.015 ug/kg/min (n=84)	0.03 ug/kg/min (n=79)
# terminated at < 22 Hrs	6 (7%)		4 (5%)	11 (14%)
# whose dose ≥ planned	3 (4%)		2 (2%)	6 (8%)
# whose dose < planned	3 (4%)		2 (2%)	5 (6%)
# dosed ≥ 22 Hrs.	77 (93%)		80 (95%)	68 (86%)
# whose dose ≥ planned	63 (76%)		61 (73%)	48 (61%)
# whose dose < planned	14 (17%)		19 (23%)	20 (25%)
AE as reason for premature termination	6 (7%)		4 (5%)	11 (14%)
Reason dose decreased to < minimum				
AE	14 (17%)		21 (25%)	23 (29%)
Other	6 (7%)		10 (12%)	13 (16%)
# Subjects with dose > minimum			2 (2%)	3 (4%)

Duration of Natrecor Infusion excluding interruptions is shown in Table 54. The time at each dose level are shown in Table 55.

Table 54 Duration of infusions excluding interruptions.

	Dobutamine (n=83)	Natrecor 0.15 ug/kg/min (n=84)	0.03 ug/kg/min (n=79)
Time of infusion mean ± SD (Hrs)	52.0 ± 40	38.7 ± 28	36.7 ± 33
Median (25-75%) (Hrs)	33 (24-71)	24.1 (24-44)	24.1 (24-44)
< 1 Hr	0	0	0
1 to <3	1 (1%)	0	1 (1%)
3 to <6	3 (4%)	2 (2%)	4 (5%)
6 to <22	2 (2%)	5 (6%)	10 (13%)
22 to < 26	31(37%)	51 (61%)	38 (48%)
26 to < 48	14(17%)	7 (8%)	9 (11%)
48 to < 72	13(16%)	9 (11%)	9 (11%)
> 72	19(23%)	10 (12%)	8 (10%)

Table 55 Through 22 hours, the number of hours at each dose level. (Mean ± SD)

Dose Range (ug/kg/min)	Dobutamine	Dose Range (ug/kg/min)	Natrecor	
			0.015 ug/kg/min	0.03 ug/kg/min
0 (study drug interrupted/stopped)	0.1 ± 0.5	0 (study drug interrupted/stopped)	0.3 ± 1.2	0.9 ± 2.8
>0 to <4.0	1.6 ± 4.9	>0 to 0.01125	2.1 ± 5.0	0 + 0
>4.0 to 6.0	17.8 ± 7.7	>0.01125 to 0.0225	19.2 ± 6.0	2.3 ± 5.25
> 6.0	1.0 ± 4.1	0.0225 to 0.0375	0.0 ± 0.1	16.9 ± 7.6
		>0.0375	0	0.1 ± 0.7

For the dobutamine group, 1.7 of the 22 hours the infusions were at doses < 80% the proposed target dose. For the Natrecor 0.015 ug/kg/min dose, subjects spent 2.4 hours of the 22 hours examined at < 75% of the targeted dose. With respect to the Natrecor 0.03 ug/kg/min dose subjects spent 3.2 hours at < 75% of the targeted dose.

**Concomitant medications:** The percent of subjects in each group taking medication are shown in Table 56. The medication lists consists of the % subjects taking medication chronically (CHRNC) and during the 24 hour baseline Holter phase (B'LINE) and during the active infusion phase (INFUS). There were no great differences either between groups or during the three phases of the study.

With respect to types of medications commonly used for heart failure, the vast majority of subjects were on some form of diuretics, but there is no description as to whether the diuretics were oral or intravenous. ACE-inhibitors were taken by approximately 60-70% of the subject population and AII blockers in 7-16% of the population. Beta-blockers were less frequently used (10-25% of those enrolled). 20-29 % of those enrolled was treated with Statins. There was no line listing for spironolactone. The medication profile among those who had a history of VT at baseline did not substantially differ from the group as a whole. Class III antiarrhythmic drugs were used slightly higher frequency 25% for those with VT at baseline versus 7-16% for the population as a whole.

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Table 56 Percent subjects taking class of medication (CHRNC)= chronic use of class before study; (B'LINE)= Baseline Holter pre-infusion period; (INF) infusion period.

	Dobutamine (% pts)			Natrecor 0.015 ug/kg/min			Natrecor 0.03 ug/kg/min		
	CHRNC	B'LINE	INFUS	CHR	BL	INF	CHR	BL	INF
Dobutamine	0	0	0	0	0	0	0	0	1
PDE inhibitors	0	0	0	0	0	0	0	0	0
Nitrates	42	51	52	38	35	35	49	47	43
IV NTG	0	0	0	0	0	0	0	0	0
Nitroprusside	0	0	0	0	0	0	0	0	0
Dopamine	0	0	0	0	0	1	0	0	0
Pressors	0	0	0	0	0	0	0	0	0
Diuretics	93	92	87	90	92	92	96	95	91
Digoxin	75	73	80	73	73	75	75	76	75
ACE inhibitors	70	70	71	71	74	70	70	68	63
Hydralazine	8	10	12	8	8	8	10	10	9
Class III antiarrhythmics	16	16	14	8	6	7	14	11	14
Beta blockers	25	22	22	25	23	20	18	10	11
Ca Channel blockers	14	11	8	15	8	10	14	9	9
Other antiarrhythmics	2	5	4	1	4	1	1	5	5
Other antihypertensives	2	4	5	7	7	6	6	6	6
ATI receptor blocker	16	14	12	11	10	7	13	11	9
Warfarin	34	22	29	19	20	21	33	16	20
Low Mol Wt Heparin	1	5	5	6	5	6	0	3	3
Heparin	0	10	12	0	14	17	3	10	11
Aspirin	41	42	43	58	61	60	46	49	52
IIb/IIIa inhibitors	0	0	0	1	2	2	0	0	0
Stains	29	29	29	21	20	23	28	20	20

Interventions of note during the 24-hour infusion:

**Dobutamine:**

- one dobutamine subject had a new antiarrhythmic added.

**NAT 0.015 ug/kg/min**

- one subject had new antiarrhythmic medication added and
- one subject required dopamine.

**NAT 0.03 ug/kg/min**

- one subject was placed on IV vasoactive medication and
- one subject had their antiarrhythmic drug-dosing regimen altered.

Efficacy end points:

Quality of data: The quality of the data in general appears good. The vast majority of subjects had Holters of duration of > 22 hours with > 90% of the Holters interpretable both at baseline and during treatment. Where data is missing there did not appear to be a bias for missing data in any treatment.

The baseline values for heart rate and ectopy (PVBs and average repetitive beats) are shown in Table 57. The groups are reasonably well matched at baseline. The distribution of ectopy is however skewed with marked differences between mean and median values.

Table 57 Baseline measurements of heart rate and ectopy

	Dobutamine (N=83)	Natrecor ug/kg/min		Nominal p-value (stratified Van Elteren procedure controlled for VT status)
		0.015 (N=84)	0.03 (N=79)	
Average heart rate				
Mean ± SD	83 ± 17	82 ± 15	85 ± 14	0.6
Median (25-75%)	82 (73-96)	81 (72-91)	84 (76-93)	
Average PVBs				
Mean ± SD	192 ± 338	110 ± 170	165 ± 265	0.3
Median (25-75%)	39 (13-338)	35 (5-145)	50 (8-200)	
Average hourly repetitive beats				
Mean ± SD	30 ± 102	14 ± 36	23 ± 58	0.3
Median (25-75%)	1 (0-8)	1 (0-5)	1 (0-12)	

The effect of treatment on baseline is shown in Table 58. Dobutamine increases average heart rate as well as hourly PVBs and hourly repetitive beats.

Table 58 Changes in values from baseline

	Dobutamine (N=83)	Natrecor ug/kg/min		Nominal p-value (stratified Wilcoxon procedure controlled for VT status)
		0.015 (N=84)	0.03 (N=79)	
Average Heart Rate (Holter)				
Mean ± SD	5 ± 8	-1 ± 6	1 ± 7	<0.001
Median (25-75%)	4 (-2- + 10)	-1 (-5 -+3)	1 (-3 -+ 5)	
p-value versus dobutamine		<0.001	0.002	
Average hourly PVBs				
Mean ± SD	69 ± 214	-13 ± 83	-5 ± 96	0.001
Median (25-75%)	4 (-7- +107)	-1 (-24- +3)	-1 (-29 -+5)	
p-value versus dobutamine		0.001		
Average hourly repetitive beats				
Mean ± SD	15 ± 53	-5 ± 19	3 ± 34	<0.001
Median (25-75%)	0 (0-+7)	0 (-2-0)	0 (-2-0)	
p-value versus dobutamine		<0.001	0.001	

**Heart rate:** Based on the Holter tapes there was a average increase from baseline in heart rate of 5 BPM in the dobutamine group and essentially no change among those treated with Natrecor. This difference was highly significant. Not surprisingly, the time in tachycardia (HR > 100) was substantially longer for dobutamine then either of the Natrecor doses. The time in bradycardia was substantially reduced by dobutamine to a greater extent than was reduced by either of the two Natrecor doses (this was a secondary end point).

Table 59 Holter time in tachycardia and bradycardia

	Dobutamine (N=83)	Natrecor (ug/kg/min)		p-value
		0.015 (N=83)	0.03 (N=79)	
Baseline time in tachycardia (Hrs)	4.0 ± 6.3	3.7 ± 6.8	3.2 ± 5.6	0.8
Baseline time in bradycardia	2.3 ± 5.4	2.0 ± 4.8	1.7 ± 4.9	0.6
Change in Time in Tachycardia (Hrs)				
Mean ± SD	1.7 ± 5.3	0 ± 4.2	0.8 ± 3.5	0.044
Median (25-75%)	0 (0- + 2.3)	0 (-0.4 -+0.1)	0 (-0.2 -+1.1)	
p-value versus dobutamine		0.02	0.4	
Change in time in bradycardia (Hrs)				
Mean ± SD	-1.3 ± 3.4	0.3 ± 2.8	-0.2 ± 2.6	<0.001
Median (25-75%)	0 (-0.6-0)	0 (0- +0.1)	-0 (0-0)	
p-value versus dobutamine		<0.001	0.02	

**Premature Ventricular Beats:** There was a substantial increase in the mean and a smaller increase in median PVB relative to baseline for those receiving dobutamine. There was essentially no change or perhaps a small decrease among those treated with Natrecor See Table 58, above).

**Changes in Average Hourly repetitive beats.** Mean baseline values show modest differences between the three treatment groups, with the dobutamine having numerically more repetitive beats/hour than the two Natrecor groups (table 58). The change from baseline shows a significant increase in repetitive beats/hour for the dobutamine group relative to either of the two Natrecor regimens.

With respect to specific ventricular ectopy i.e., couplets, triplets and VT beats, there was an increase in all measurements of ectopy in the dobutamine treated group relative to the Natrecor groups.

Table 60 Ectopy and change in ectopy from baseline Holter measurements

	Dobutamine (N=83)	Natrecor (ug/kg/min)		p-values (overall)
		0.015 (N=84)	0.03 (N=79)	
<b>Couplets (events/24 Hr)</b>				<b>Baseline</b>
Mean ± SD (Baseline)	310 ± 1008	139 ± 372	228 ± 561	0.3
Median (25-75%)	12 (2- +83)	5 (1-59)	9 (1- +133)	
<b>Change from baseline</b>				<b>Change</b>
Mean ± SD	+68 ± 427	-52 ± 200	38 ± 317	0.001
Median (25-75%)	+ 2 (-3 - + 41)	-1 (-17 - + 1)	0 (-7- + 4)	
p-value relative to dobutamine		<0.001	0.0080	
<b>Triplets (events/24 Hr)</b>				<b>Baseline</b>
Mean ± SD (Baseline)	27 ± 129	10 ± 33	20 ± 61	0.3
Median (25-75%)	0 (0-+3)	0 (0-+2)	1 (1-133)	
<b>Change from baseline</b>				<b>Change</b>
Mean ± SD	+22 ± 86	-5 ± 15	3 ± 38	<0.001
Median (25-75%)	+ 0 (0 - + 2)	0 (-1 - + 0)	+0 (-1- + 0)	
p-value relative to dobutamine		<0.001	0.0080	
<b>VT (events/24 Hr)</b>				<b>Baseline</b>
Mean ± SD (Baseline)	30 ± 144	13 ± 39	27 ± 89	0.2
Median (25-75%)	0 (0-+5)	1 (0-+3)	1(0-+8)	
<b>Change from baseline</b>				<b>Change</b>
Mean ± SD	+48 ± 205	-6 ± 17	2 ± 60	<0.001
Median (25-75%)	+ 0(+0- +3)	+0 (-2 - + 0)	0 (-1- + 0)	
p-value relative to dobutamine		<0.001	<0.001	

The number of subjects with no VT events at baseline who developed VT and the number of subjects with VT at baseline whose VT events were not evident during on-treatment Holters are shown in Table 61.

Table 61 New onset or disappearance of VT events on treatment.

	Dobutamine (N=83)	Natrecor (ug/kg/min)			Dobutamine (N=83)	Natrecor (ug/kg/min)	
		0.05 (N=84)	0.3 (N=79)			0.05 (N=84)	0.3 (N=79)
<b>VT absent on baseline tape</b>				<b>VT present on baseline tape</b>			
Absent → Present	11 (15%)	7 (9%)	6 (8%)	Present → Absent	4 (5%)	12 (15%)	8 (11%)
Absent → Absent	24 (33%)	28 (35%)	22 (31%)	Present → Present	34 (47%)	33 (41%)	36 (50%)

(Comment: the number of subjects does not sum to those enrolled. For dobutamine only 73/83 subjects are accounted for in this table. For Natrecor 0.015 ug/kg/min the number 80/84 have data, for Natrecor 0.03 ug/kg/min 72/79 have data. The reason for the discrepancy is not stated).

The overall p-value (based on a CMH general association statistic controlling over baseline VT (present or absent) of Natrecor relative to dobutamine showed a nominal p-value for the 0.015 ug/kg/min regimen of 0.039 and for the 0.03 ug/kg/min the nominal p-value was 0.191. (Comment: The p-values were not corrected for multiple comparisons).

**Proarrhythmia:** Several criteria have been used that define a subject as having a pro-arrhythmic episode.

The sponsor only analyzes the criteria based on the Velebit and The CAPS criteria.

Table 62 Proarrhythmia events based on criteria of Velebit and CAPS

	Dobutamine	Natrecor (ug/kg/min)		Overall p-values
		0.015	0.03	
<b>Velebit Criteria:</b>				
Proarrhythmia: yes	17 (23%)	3(4%)	0	<0.001
No	56 (77%)	77 (96%)	72 (100%)	
p-value versus dobutamine		<0.001	<0.001	
<b>CAPS Criteria:</b>				
Proarrhythmia: yes	7 (10%)	0(0%)	0	0.001
No	66 (90%)	80 (100%)	72 (100%)	
p-value versus dobutamine		0.005	0.013	

[Comment: The numbers also don't add up to those enrolled.]

**Global assessment of clinical status:** At 3 and 24 hours, both the subject and the investigator were asked to evaluate their clinical symptom change relative to baseline. A five-point scale was used: Markedly better, better, no change, worse and markedly worse. There was no difference in evaluations in considering either the subject or investigator's responses (both are listed in Table 63).

Table 63 Assessment of symptom score

	Subject				Investigator			
	Dobut	Natrecor (ug/kg/min)		p-value nominal K-W	Dobut	Natrecor (ug/kg/min)		p-value nominal K-W
		0.015	0.03			0.015	0.03	
<b>3 Hours</b>								
Markedly Better	3 (4%)	1 (1%)	0	0.5	1(1)	0	0	0.7
Better	23 (29%)	30 (38%)	26 (34%)		25(31%)	25 (32%)	21 (27%)	
No change	49 (61%)	45 (58%)	48 (62%)		53 (66%)	51 (65%)	54 (70%)	
Worse	5 (6%)	2 (3%)	2 (3%)		1 (1%)	2 (3%)	1 (1%)	
Markedly worse	0	0	1 (1%)		0	0	1 (1%)	
p-value Vs. DOB		0.3	0.9			0.8	0.4	
p-value Vs. NAT low dose			0.4				0.5	
<b>24 Hours</b>								
Markedly Better	12 (15%)	13 (16%)	8 (11%)	0.2	5 (6%)	8 (10%)	4 (5%)	0.1
Better	56 (68%)	55 (66%)	47 (63%)		63 (77%)	61 (73%)	48 (66%)	
No change	13 (16%)	13 (16%)	14 (19%)		12 (15%)	14 (17%)	16 (22%)	
Worse	1 (1%)	2 (2%)	6 (8%)		2 (2%)	1 (1%)	5 (7%)	
Markedly worse	0	0	0		0	0	0	
p-value Vs. DOB		0.98	0.1			0.7	0.1	
p-value Vs. NAT low dose			0.1				0.1	

Subject's status improved over time as judged either by the subject or the investigator's assessment. There did not appear to be a benefit of either treatment or either dose of Natrecor.

### Safety:

**Exposure:** The median duration of exposure for dobutamine and the two Natrecor doses are shown in Table 54. The number of subject\*days for the three treatment groups were 180 for the dobutamine cohort, and 135 for the Natrecor 0.015 and 121 for the Natrecor 0.03 ug/kg/min infusion regimens.

**Deaths/Dropouts/ Discontinuations:** The protocol prespecified a 14-day follow-up. There were a total of 7 deaths during the initial 14-day follow up, period; 2 in the dobutamine and NAT 0.015 groups and 3 in the NAT 0.03 group. In addition the sponsor collected the number of subjects who died during the one-month and six months following treatment. The results for the 1 and 6-month follow up are shown in Table 64. There were some differences in baseline with more dobutamine classified as Class IV subjects than either of the two Natrecor cohorts.

Capsular summaries for those who died during the pre-specified 14-day follow-up are supplied by the sponsor and are summarized below.

Table 64 Deaths at one and 6 months

	Dobutamine (n=83)	Natrecor 0.015 ug/kg/min (n=84)	Natrecor 0.03 ug/kg/min (n=79)
<b>1 month</b>			
Deaths	5	3	3
Mortality rate	6.1%	3.6%	3.8%
95% C.I. (Peto's)	2.2 to 12.6%	1.0 to 9.3 %	1.0 to 9.8%
p-Value (versus dobutamine)		0.5	0.5
p-Value Nat low versus NAT high		-----	0.94
Censored before 1 month (%)	1 (1%)	2 (2%)	1 (1%)
<b>6 month</b>			
Deaths	18	13	13
Mortality rate	22.2%	15.9%	16.7%
95% C.I. (Peto's)	13.8 to 31.8%	8.9 to 9.3 %	1.0 to 9.8%
p-Value (versus dobutamine)		0.3	0.4
p-Value Nat low versus NAT high		-----	0.9
Censored before 1 month (%)	3 (4%)	3 (4%)	2 (3%)

There were numerically more deaths on dobutamine than on either of the Natrecor doses at both 1 and 6 months. Capsular summaries of those who died within 14-days of the infusion are summarized below.

### Dobutamine

Subject # 502-215: This was a 93-y/o male with NYHA Class IV CHF as a consequence of ischemia. He was treated for 3.5 hours with dobutamine but was discontinued due to symptomatic hypotension. The event resolved but the subject remained hospitalized and died on day 8.

Subject # 536-214: This was a 78-y/o female with NYHA Class IV CHF. She was treated for approximately 4 hours with dobutamine that was stopped because the subject experienced multiple arrhythmias, not seen during baseline. The subject's ectopy resolved after approximately 30 minutes. She was discharged on day 2 but died on day 7 of a cardiopulmonary arrest.

### NATRECOR (0.015 ug/kg/min).

Subject # 554-211: This was a 60-y/o male with NYHA Class III CHF who was treated for 22 hours with Natrecor (0.015 ug/kg/min) with the infusion stopped due to symptomatic (dizziness) hypotension (BP 68/38). His creatinine increased from 1.4 at baseline to 1.9 at day 2. He had an episode of AV block that lasted 60 seconds but resolved spontaneously. His K<sup>+</sup> level rose to 7.5 mg/dL on day

6. No follow-up creatinine values were supplied. He was found unresponsive while still hospitalized (day 8). He had new onset atrial fibrillation and a junctional rhythm. He was intubated but arrested and died.

Subject # 618-206: This was a 59-y/o male NYHA Class III who was treated for 24 hours with study drug, with the infusion stopped because of clinical improvement. Nine hours after the start of study drug infusion, the subject experienced an episode of asymptomatic NSVT. The subject was discharged on day 2 but arrested and died on day 14.

#### NATRECOR (0.03 ug/kg/min)

Subject # 498-203 was a 44-y/o male with NYHA Class III. He was treated for 7.5 hours with NAT (0.03 ug/kg/min) with the infusion discontinued due to symptomatic hypotension (SBP decreased from 98 mm Hg at baseline to 74 mm Hg at 6 hours 53 minutes). The subject was discontinued from the infusion. A Swan-Ganz catheter was inserted demonstrating elevated right and left filling pressures and marked hypo-perfusion. He was treated with Nipride and improved. He was discharged on day 13 but died that evening at home. An autopsy was performed but the results were not included in the summary.

Subject # 551-205 is a 67-y/o male with NYHA Class IV CHF. On admission the subject had severe edema, paroxysmal nocturnal dyspnea and SOB. The subject was treated for 4.5 days with Natrecor, with the infusion discontinued because the physician believed the subject had received maximum benefit. The subject had originally been admitted for hip surgery and after the completion of the infusion the subject was taken to the operating room. The subject had two short episodes of bradycardia during the NAT infusion. On day 6 post-op, he was found unresponsive and died despite resuscitative efforts.

Subject # 352-203 was a 54-y/o male NYHA class III CHF who was admitted with volume overload and underwent diuresis. His BUN/Cr on admission were 71/2.4 mg/dL respectively. The dose of Natrecor was increased to 1.5 times the initial dose. IV diuretics were also administered but any diuresis was not sustained. Natrecor was discontinued and dobutamine and later dopamine was started. On day 10, chronic continuous dialysis was started. On day 12 he developed symptomatic bradycardia and hypotension and arrested. He was resuscitated with bradycardia and hypotension persisting on day 14. He died on day 19.

Serious adverse events: Excluding those who died, serious adverse events are summarized below:

#### Dobutamine:

Subject # 356-201 was a 61-y/o male with NYHA class II status due to ischemic cardiomyopathy. He was treated with dobutamine for 5 days. He was electively admitted for the placement of a LVAD on day 13 and is awaiting a heart transplant.

Subject # 413-201 was a 62-y/o female with NYHA class II CHF with a history of paroxysmal VT. She was treated for 24 hours and then discharged. On day 10 she was readmitted with worsening CHF and treated with milrinone, Lasix and oxygen for 24 hours and then discharged. She was again admitted on day 14 for worsening shortness of breath and was treated with milrinone and oxygen for 10 hours before discharge.

Subject # 502-206 was a 61-y/o female NYHA class III CHF due to ischemia, She was treated for 36 hours with dobutamine which was discontinued due to clinical improvement. She was readmitted for substernal chest pain on study day #7, treated with NTG and observation.

Subject # 536-213 was an 87-y/o female with NYHA Class IV was treated for 24 hours with dobutamine. The infusion was discontinued due to clinical improvement. She was discharged on day 3 but readmitted on day 5 for worsening CHF and was discharged on day 7.

Subject # 551-206 was a 74-y/o male with NYHA class III he was treated for 2 days with dobutamine and discharged from the hospital on day 7. On day 10 the subject was readmitted for increased shortness of breath. He was treated with Bumex and was discharged on study day 12. He had an elective lung biopsy that confirmed the diagnosis of lung cancer. He was readmitted for placement of a chest tube to treat the pneumothorax. He was discharged on day 21.

Subject # 560-213 was a 59-y/o male with idiopathic dilated cardiomyopathy and NYHA Class III who was treated for 24 hours with dobutamine. The subject's hospitalization was prolonged due to hyperglycemia and hyperkalemia. He was treated with insulin and Kayexalate and discharged on study day # 4.

Subject # 585-201 was a 55-y/o male with NYHA Class III CHF who was treated for 24 hours with dobutamine. He was discharged on day 3 but readmitted on day 4 for worsening CHF.

**NATRECOR 0.015 ug/kg/min**

Subject # 369-205 was a 60-y/o male NYHA Class III and a history of ischemic cardiomyopathy that was treated for approximately 24 hours. The infusion was discontinued because the patient had low cardiac output. Dobutamine was started. The subject was discharged on day 4 but readmitted on day 8 for low cardiac output. He was treated with dobutamine and discharged on day 11.

Subject # 498-202 was an 82-y/o female with a history of ischemic cardiomyopathy, NYHA class III was treated with 24 hours with Natrecor that was stopped due to clinical improvement. On day 5 she was noted to have a UTI. She was transferred to a cardiac rehabilitation facility on day 6. Her creatinine and BUN began to rise and she was readmitted. By study day 14, her creatinine and BUN were improving and she was discharged. Renal function parameters re-approached those measurements of baseline.

Subject # 502-202 was an 83-y/o female with NYHA class III status due to severe mitral regurgitation. She was treated for 4 days with Natrecor that was discontinued due to clinical improvement. On day 6, due to shortness of breath and pulmonary edema she was treated with dobutamine with no response. A mitral valve replacement was scheduled (the subject had a history of mitral regurgitation). On day 9, she required dialysis for worsening renal insufficiency. Mitral valve replacement was performed on day 10.

Subject # 502-210 was a 68-y/o male with NYHA class IV CHF who was treated for 24 hours with Natrecor. The infusion was discontinued due to clinical improvement. He was discharged on day 2. Over the next 12 days the subject had worsening symptoms and was admitted on day 14 for exacerbation of CHF and was treated with dobutamine. On day 15, he experienced a cardiac arrest after an episode of VT. He was resuscitated and discharged on day 18 in stable condition.

Subject # 538-203 was a 69-y/o female with NYHA class III CHF and a past history of cerebrovascular accident. Four hours during the infusion, the subject developed aphasia and facial droop. Her blood pressure had decreased from 135/65 to 99/54 (not defined as hypotension). The subject was started on heparin and shortly thereafter, the subject developed symptomatic hypotension (BP-74/43). Dopamine was started and the Natrecor infusion interrupted. The SBP rose slightly to 91/38. Natrecor was restarted at half the infusion regimen. The aphasia resolved. A CT scan done on day 7 demonstrated a right occipital CVA.

Subject # 605-207 was a 73-y/o female who was treated for 24 hours with Natrecor and discharged on day 3 but readmitted on day 10 with exacerbation of CHF. During this admission she had intractable hypertension. A renal ultrasound revealed bilateral renal artery stenosis. She subsequently underwent bilateral renal artery angioplasty and stent placement. She was hospitalized for 2 weeks before discharge.

Subject # 370-202 was a 70-y/o male with NYHA class IV CHF due to ischemic cardiomyopathy. He was treated for 8 days with Natrecor and discharged. He was readmitted on day 13 due to shortness of breath. He was treated with Lasix and discharged the following day.

Subject # 382-201 was an 81-y/o female with NYHA class III who was treated with infusion for 24 hours with Natrecor. She was admitted on day 13 for increasing disorientation, weakness and dizziness associated with her baseline condition of anemia and also attributed to CHF. She was treated with IV Lasix and two units of packed red blood cells. She was discharged on day 17.

Subject # 536-219 was a 37-y/o male with NYHA class III due to alcohol-induced cardiomyopathy and also a history of NSVT. He was discharged on day 3 but readmitted on day 7 with worsening of shortness of breath. He was discharged on day 9.

Subject # 536-220 was a 62-y/o male with NYHA class III due to amyloidosis that was treated for 24 hours with clinical improvement. During the course of the infusion the dose of Natrecor was decreased because of symptomatic hypotension (BP 72/50). He was discharged on day 3. When seen on day 11 in clinic he had an increase in shortness of breath and also elevations of his BUN /Cr (90/3.2, respectively). He was admitted on day 14 for scheduled inotropic therapy. [Comment: Patient with restrictive cardiac disease tolerated infusion.]

Subject # 560-209 was a 67-y/o female NYHA class III was treated for 24 hours with Natrecor with the infusion discontinued due to clinical improvement. On day 8 she was readmitted for worsening CHF. A mitral valve repair was unsuccessful on day 16 so valve replacement was performed. The subject was discharged from the hospital on study day 28.

Subject # 620-204 was a 78-y/o male with NYHA class III CHF who was treated with study drugs for 3 days with the infusion stopped because of clinical improvement. He was discharged on day 7 but was readmitted on day 11 due to worsening anemia. He was treated with several transfusions of packed red blood cells and discharged on day 19.

***Adverse Events with Intensity Listed as "severe"***. Adverse events with intensity labeled as "severe". The events labeled as "severe" in intensity are shown in Table 61. More subjects treated with Natrecor 0.03 ug/kg/min had such events than the lower dose Natrecor or the dobutamine group.

***Premature terminations:*** 21 subjects prematurely terminated (before 22 hours of infusion). These subjects consisted of 6 dobutamine, 4 NAT 0.015 ug/kg/min and 11 NAT 0.03 ug/kg/min subjects. The sponsor tabulates specifics of the early termination that are reproduced in Table 66. The most common causes of premature for those treated with dobutamine were related to ectopy. The most common causes for those treated with Natrecor were episodes of hypotension.

Table 65 Events "severe" in intensity (through day 14).

Pt #	Tx	Demographics: Age/Race/Gender/NYHA	Event
369-206	DOB	35/B/F/IV	Fever
502-215	DOB	93/C/M/IV	Symptomatic hypotension, bilateral tibial edema, Cheyne-Stokes respiration, agitation, severe bradycardia.
536-214	DOB	78/B/F/IV	Cardiopulmonary arrest
551-206	DOB	74/C/M/III	Increased shortness of breath
560-213	DOB	59/B/M/III	Worsening hyperkalemia, hyperglycemia
560-216	DOB	43/B/F/IV	Worsening renal function, abdominal pain
561-201	DOB	69/C/M/III	Chest pain, angina
369-205	NAT 0.015	60/H/M/III	Worsening CHF
502-202	NAT 0.015	83/C/F/IV	Increasing creatinine, BUN, symptomatic hypotension, pulmonary edema
502-205	NAT 0.015	77/C/M/III	Headache, anxiety
502-210	NAT 0.015	68/Pac Is/M/IV	Worsening CHF
502-211	NAT 0.015	63/C/M/III	Cold sweat, non-symptomatic hypotension
524-201	NAT 0.015	57/C/M/III	Symptomatic hypotension
540-201	NAT 0.015	64/C/M/IV	Fatigue
554-211	NAT 0.015	60/H/M/III	Worsening CHF, asystole, cardiac arrest
605-207	NAT 0.015	73/B/F/III	Renal artery stenosis
618-206	NAT 0.015	59/B/M/III	Acute MI
306-203	NAT 0.030	76/C/F/IV	Hyperkalemia, dehydration
352-203	NAT 0.030	53/C/M/III	Worsening CHF, worsening renal failure, symptomatic hypotension, symptomatic sinus bradycardia, sepsis
622-201	NAT 0.030	44/A/F/III	Fatigue
387-201	NAT 0.030	49/H/F/IV	Claustrophobia
488-201	NAT 0.030	61/C/M/III	Dizziness, , Asymptomatic hypotension
498-203	NAT 0.030	64/H/M/III	Death
502-208	NAT 0.030	54/C/M/III	Anxiety, dizziness, visual hallucinations, symptomatic hypotension., anginal chest pain
502-209	NAT 0.030	77/C/F/IV	Anginal chest pain
536-220	NAT 0.030	62/B/M/III	Exacerbation of CHF
551-205	NAT 0.030	67/C/M/IV	Bradycardia, cardiac arrest
554-213	NAT 0.030	43/C/F/III	Asymptomatic hypotension
560-209	NAT 0.030	67/H/F/III	Worsening CHF
560-210	NAT 0.030	46/H/F/III	Headache
567-203	NAT 0.030	51/C/M/III	Symptomatic hypotension
620-204	NAT 0.030	78/C/M/III	Worsening anemia

Abbreviations C=Caucasian B=Black A= Asian H= Hispanic Pac is= Pacific islander M= male F= female

Table 66 Early terminations.

Subject #	Tx	Time of infusion till termination	Reason	14-day status
<b>Dobutamine</b>				
498-204	DOB	3.5 hr	Increased heart rate and increased ectopy	Alive
502-215	DOB	3.35	Symptomatic hypotension	Alive
536-214	DOB	3.5	Multifocal PVCs	Died
554-201	DOB	2.5	Palpitations	Alive
625-202	DOB	17.5	SVT	Alive
627-209	DOB	19.15	IV infiltration	Alive
<b>Natrecor 0.015</b>				
352-202	0/015	21.75	Symptomatic hypotension	Alive
554-202	0.015	21.55	Symptomatic hypotension, blurred vision	Alive
554-220	0.015	4.14	Symptomatic hypotension, diaphoresis, warmth	Alive
624-201	0.015	3.14	Abdominal pain, decreased cardiac output, left hand numbness, right shoulder pain, elbow pain, non-productive cough, headache	Alive
<b>Natrecor 0.030</b>				
488-201	0.030	5.0	Asymptomatic hypotension	Alive
498-203	0.030	7.38	Symptomatic hypotension, eye pressure	Died
538-202	0.030	2.25	Symptomatic hypotension	Alive
549-203	0.030	15.26	Symptomatic hypotension	Alive
550-204	0.030	9.0	Asymptomatic hypotension	Alive
556-210	0.030	4.14	Sweating, anxiety, shortness of breath	Alive
580-206	0.030	5.36	Hot flashes and diaphoresis	Alive
622-201	0.030	5.17	Bitter taste in mouth, sweating, fatigue, headache and nausea	Alive
627-204	0.030	8.15	Symptomatic hypotension	Alive
635-201	0.030	6.57	Symptomatic hypotension	Alive
530-206	0.030	16.59	Symptomatic hypotension	Alive

**Hospitalizations:** One hundred ninety eight of the 246 treated subjects were admitted to the hospital on the day of or the day before the start of the baseline Holter. The mean duration of hospitalization approximated five days. Re-admissions, within 30 days were similar across groups.

Table 67 Description of the index hospitalization and additional hospitalizations.

	Dobutamine (n=83)	Natrecor (ug/kg/min)		P-value nominal
		0.015 (n=84)	0.03 (n=79)	
Total Days of Hospitalization through Day 14.				
Mean $\pm$ SD	5.7 $\pm$ 3.9	5.7 $\pm$ 3.7	5.8 $\pm$ 4.0	0.9
Median (range)				
2-3 days	28 (34%)	29 (35%)	32 (41%)	
4-5 days	24 (29%)	22 (26%)	16 (20%)	
6-7 days	13 (16%)	16 (19%)	9 (11%)	
8-14 days	10 (12%)	10 (12%)	14 (18%)	
Not Discharged by day 14	8 (10%)	7 (8%)	8 (10%)	
Number Discharged who were readmitted	7/75 (9%)	5/77 (6%)	9/71 (13%)	0.5
1 readmission	5	5	9	
2 readmission	2	0	0	
Reason for readmission				
CHF (acute)	6	3	4	
CHF (elective)	0	0	0	
Other (acute)	2	2	2	
Other Elective)	1	0	3	

**Adverse Events:** Adverse events during the first 24-hours of the infusion are shown in table 68.

Table 68 Adverse events during the 24-hour infusion

	Dobutamine	Natrecor (ug/kg/min)		p-value (nominal)
		0.015	0.03	
Cardiovascular	34 (41%)	33 (39%)	45 (57%)	0.048
Hypotension	5 (6%)	23 (27%)	35 (44%)	<0.001
Symptomatic Hypotension	2 (2%)	14 (17%)	19 (24%)	<0.001
Asymptomatic hypotension	4 (5%)	9 (11%)	17 (22%)	0.005
Ventricular tachycardia	11 (13%)	5 (6%)	5 (6%)	>0.1
Sustained ventricular tachycardia	0	0	1 (1%)	>0.1
Non-sustained ventricular tachycardia	11 (13%)	5 (6%)	4 (5%)	>0.1
Ventricular extrasystoles	9 (11%)	3 (4%)	5 (6%)	>0.1
Tachycardia	11 (13%)	1 (1%)	2 (3%)	0.001
Bradycardia Events	1 (1%)	2 (2%)	4 (5%)	>0.1
Bradycardia	0	1 (1%)	0	>0.1
Sinus bradycardia	1 (1%)	0	4 (5%)	0.03
Nodal arrhythmia	0	1 (1%)	0	>0.1
Angina pectoris	3 (4%)	2 (2%)	1 (1%)	>0.1
Bigeminy	3 (4%)	1 (1%)	1 (1%)	>0.1
Body as a whole	13 (16%)	14 (17%)	14 (18%)	>0.1
Headache	2 (2%)	7 (8%)	8 (10%)	>0.1
Injection site reaction	6 (7%)	1 (1%)	2 (3%)	>0.1
Abdominal pain	1 (1%)	2 (2%)	3 (4%)	>0.1
Nervous	6 (7%)	16 (19%)	13 (16%)	0.061
Dizziness	3 (4%)	9 (11%)	9 (11%)	>0.1
Anxiety	1 (1%)	2 (2%)	3 (4%)	>0.1
Insomnia	1 (1%)	2 (2%)	3 (4%)	>0.1
Digestive	5 (6%)	12 (14%)	15 (19%)	0.037
Nausea	3 (4%)	7 (8%)	14 (18%)	0.011
Vomiting	0	4 (5%)	3 (4%)	>0.1
Metabolic and nutritional disorders	6 (7%)	5 (6%)	2 (3%)	>0.1
Hypokalemia	2 (2%)	3 (4%)	1 (1%)	>0.1
Skin and appendages	2 (2%)	5 (6%)	5 (5%)	>0.1
Sweating	1 (1%)	2 (2%)	3 (4%)	>0.1
Respiratory	0	3 (4%)	6 (8%)	0.02
Cough increased	0	2 (2%)	3 (4%)	>0.1
Dyspnea	0	1 (1%)	2 (3%)	>0.1
Musculoskeletal	3 (4%)	3 (4%)	0	0.07
Leg cramps	3 (4%)	0	0	0.07

Hypotension both symptomatic and asymptomatic is increased among those taking Natrecor. On the other hand, tachycardia and other measurements of ectopy are increase in the dobutamine-treated subjects. Adverse events reflected "nervous system" trend higher in the Natrecor treatments and reflect largely the increase in dizziness among those treated with Natrecor. There were more adverse events in the "digestive" system among those treated with Natrecor, reflecting an in crease in nausea and vomiting. "Respiratory" adverse events were also increased among those treated with Natrecor.

Hypotension: Specifics of hypotension are shown in Table 69.

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Table 69 Description of All Hypotensive events

	Dobutamine	Natrecor (ug/kg/min)		P-value
		0.015	0.03	
<b>Greatest Severity</b>				0.000
No hypotension reported	78 (94%)	61 (73%)	44 (56%)	
Mild	1(1%)	9(11%)	14(18%)	
Moderate	2(2%)	14(17%)	17(22%)	
Severe	2(2%)	0	4(5%)	
<b>Greatest effect on study drug</b>				0.000
None/increased	1(1%)	4(5%)	10(13%)	
Dose decreased/interrupted	3(4%)	15(18%)	16(20%)	
Discontinued	1(1%)	4(5%)	9(11%)	
<b>Onset of hypotension</b>	?	?	?	
<b>Duration of hypotension</b>	?	?	?	

? = no data submitted

### Laboratory:

**Chemistries:** Laboratory values were collected at baseline and within 24 hours of the discontinuation of the infusion. Na, K, CO<sub>2</sub>, Cl, creatinine and Bun were also to be collected between 10-14 days post enrollment. The results are shown below.

Table 70 Laboratory values at baseline and change from baseline mean + SD.

		Dobutamine			Natrecor					
		B'Line	Day 2	Day 14	0.015 ug/kg/min			0.03 ug/kg/min		
					B'Line	Day 2	Day 14	B'Line	Day 2	Day 14
BUN	N=/(missing)	83 (0)	76 (7)	72 (11)	84 (0)	79 (5)	74 (10)	78 (1)	70 (9)	64 (15)
	Value	32.9 + 17	-0.8 + 7.0	6.4 + 16.7	35.4 + 27.2	2.1 + 9.1*	2.8 + 14.5	33.1 + 21.9	2.6 + 8.3*	2.3 + 23.0
Creat.	N=/(missing)	83 (0)	77 (6)	72 (11)	84 (0)	79 (5)	74 (10)	78 (1)	74 (5)	64 (15)
	Value	1.5 + 0.7	0.0 + 0.3	0.1 + 0.4	1.6 + 0.8	0.1 + 0.4	0.1 + 0.4	1.5 + 0.9	0.1 + 0.3*	0.1 + 0.6
CO <sub>2</sub>	N=/(missing)	78 (3)	40 (41)	NA	78 (3)	53 (30)	NA	76 (3)	48 (31)	NA
	Value	28.9 + 4.6	-0.2 + 2.5	NA	28.0 + 3.4	-0.6 + 3.1	NA	27.9 + 4.7	0.3 + 3.7	NA
Ca	N=/(missing)	79 (3)	48 (34)	NA	81 (1)	63 (19)	NA	71 (6)	50 (27)	NA
	Value	8.9 + 0.5	-0.2 + 0.4	NA	9.0 + 0.7	-0.1 + 0.4	NA	8.9 + 0.5	-0.3 + 0.5	NA
Mg	N=/(missing)	82 (1)	55 (28)	NA	83 (1)	70 (14)	NA	71 (6)	57 (20)	NA
	Value	2.1 ± 0.3	0.1 ± 0.29	NA	2.1 ± 0.3	0.0 ± 0.2	NA	2.1 ± 0.3	-0.0 ± 0.3	NA
Na <sup>±</sup>	N=/(missing)	83 (0)	80 (3)	72 (11)	84 (0)	82 (2)	75 (9)	78 (1)	74 (5)	64 (15)
	Value	138 + 4.6	-1.4 + 2.7	-0.5 + 4.2	138 + 4.2	-1.6 + 3.1	-0.6 + 3.5	138 + 4.8	-1.8 + 4.1	-0.8 + 4.2
K <sup>±</sup>	N=/(missing)	83 (0)	81 (2)	72 (11)	84 (0)	82 (2)	75 (9)	78 (1)	76 (3)	65 (14)
	Value	4.2 + 0.5	0.1 + 0.5	0.4 ± 0.7	4.2 + 0.4	0.2 + 0.6	0.3 + 0.6	4.3 + 0.5	0.1 + 0.7	0.1 + 0.8
Cl <sup>-</sup>	N=/(missing)	83 (0)	44 (39)	NA	84 (0)	56 (28)	NA	78 (1)	52 (27)	NA
	Value	99.6 + 6.2	-1.3 + 2.8	NA	100.3 + 5.1	-1.3 + 3.0	NA	100.0 + 5.8	-1.3 + 4.6	NA

\*Nominal p-value < 0.05.

There was a nominally significant increase in BUN for both Natrecor doses relative to dobutamine at day 2. There was also an increase in creatinine in the high dose Natrecor dose group relative to dobutamine on day 2.

This reviewer considered those subjects whose creatinine increased by > 0.5 mg/dL during any of the measurements. There were a total of 38 subjects whose creatinine increased by this value at some time during the study period. Of these subjects, 14 were in the Natrecor 0.015 g/kg/min group and 15 were in the 0.03 ug/kg/min Natrecor subjects. There were a total of 9 subjects in the dobutamine group that had increases in creatinine values of > 0.5 mg/dL. The median baseline value among those whose creatinine increased during the study was approximately equivalent to the

value of those at baseline. There did not appear to be an increased risk of a 0.5mg/dl increase among those with higher baseline creatinine values.

Among those treated with Natrecor, substantial increases in creatinine occurred earlier than among dobutamine-treated subjects. The first abnormal value occurred more frequently during the first week among Natrecor treated subjects than in the dobutamine treated subjects (Nat 0.015= 7; Nat 0.03 =7, Dobutamine =2). The number with abnormal values at the last measurement were Natrecor 0.015 ug/kg/min =8; Nat 0.03 ug/kg/min = 9; Dobutamine=7.

Table 71 Subjects with increase in creatinine of 0.5 mg/dl (Bold still > 0.5 above baseline at last visit). A √ reflects those whose value was abnormal within the first week.

pt#	Tx	baseline Value	first value inc > 0.5 mg/dl (day)	worst creatinine (day)	last creatinine (day)	pt#	Tx	baseline Value	first value inc > 0.5 mg/dl (day)	worst creatinine (day)	last creatinine (day)
554-202	0.015	0.9	1.9 (2) √	1.9 (2)	0.8 (12)	357-202	0.03	1	1.7 (7)	1.7 (7)	0.8 (13)
488-205	0.015	1	1.6 (6) √	1.6 (6)	1.0 (12)	<b>306-203</b>	<b>0.03</b>	<b>1.1</b>	<b>2.2 (11)</b>	<b>2.2 (11)</b>	<b>2.2 (11)</b>
<b>560-205</b>	<b>0.015</b>	<b>1.1</b>	<b>2.1 (14)</b>	<b>2.1 (14)</b>	<b>2.1 (14)</b>	554-213	0.03	1.2	2.0 (3) √	2.0 (3)	1.0 (10)
554-220	0.015	1.3	2.0 (2) √	2.0 (2)	1.0 (10)	535-202	0.03	1.3	1.9 (5) √	1.9 (5)	1.1 (13)
539-211	0.015	1.4	2.2 (2) √	2.2 (2)	1.6 (10)	549-203	0.03	1.3	2.0 (3) √	2.0 (3)	1.8 (15)
387-202	0.015	1.5	2.7 (2) √	2.7 (2)	1.4 (14)	<b>605-205</b>	<b>0.03</b>	<b>1.4</b>	<b>2.0 (2) √</b>	<b>2.0 (2)</b>	<b>2.0 (2)</b>
<b>626-203</b>	<b>0.015</b>	<b>1.6</b>	<b>2.2 (34)</b>	<b>2.2 (34)</b>	<b>2.2 (34)</b>	560-206	0.03	1.4	2.3 (2) √	2.3 (2)	1.6 (14)
<b>498-202</b>	<b>0.015</b>	<b>1.6</b>	<b>2.5 (15)</b>	<b>2.5 (15)</b>	<b>2.5 (15)</b>	<b>487-201</b>	<b>0.03</b>	<b>1.5</b>	<b>2.4 (14)</b>	<b>2.4 (14)</b>	<b>2.4 (14)</b>
<b>352-202</b>	<b>0.015</b>	<b>2.1</b>	<b>3.7 (2) √</b>	<b>3.7 (2)</b>	<b>2.9 (31)</b>	<b>538-202</b>	<b>0.03</b>	<b>1.6</b>	<b>2.3 (14)</b>	<b>2.4 (14)</b>	<b>2.3 (14)</b>
<b>626-204</b>	<b>0.015</b>	<b>2.2</b>	<b>3.3 (5) √</b>	<b>3.3 (5)</b>	<b>3.3 (13)</b>	<b>635-202</b>	<b>0.03</b>	<b>1.7</b>	<b>2.5 (11)</b>	<b>2.5 (11)</b>	<b>2.5 (11)</b>
<b>369-210</b>	<b>0.015</b>	<b>4.1</b>	<b>5.0 (16)</b>	<b>5.0 (16)</b>	<b>5.0 (16)</b>	<b>352-203</b>	<b>0.03</b>	<b>2.4</b>	<b>4.6 (11)</b>	<b>4.6 (11)</b>	<b>4.6 (11)</b>
<b>355-202</b>	<b>0.015</b>	<b>4.3</b>	<b>5.4 (13)</b>	<b>5.4 (13)</b>	<b>5.4 (13)</b>	<b>536-220</b>	<b>0.03</b>	<b>2.5</b>	<b>3.1 (11)</b>	<b>3.1 (11)</b>	<b>3.1 (11)</b>
<b>627-210</b>	<b>0.015</b>	<b>5.4</b>	<b>6.2 (18)</b>	<b>6.2 (18)</b>	<b>6.2 (18)</b>	<b>370-202</b>	<b>0.03</b>	<b>2.8</b>	<b>3.4 (13)</b>	<b>3.4 (13)</b>	<b>3.4 (13)</b>
						<b>554-203</b>	<b>0.03</b>	<b>5.4</b>	<b>6.8 (3) √</b>	<b>6.8 (3)</b>	<b>6.6 (11)</b>
						360-201	0.03	6.9	7.8 (2) √	7.8 (2)	3.9 (9)
						<b>620-203</b>	<b>DOB</b>	<b>1.1</b>	<b>1.7 (7)</b>	<b>1.7 (7)</b>	<b>1.7 (14)</b>
						<b>627-209</b>	<b>DOB</b>	<b>1.1</b>	<b>2.3 (15)</b>	<b>2.3 (15)</b>	<b>2.3 (15)</b>
						<b>580-202</b>	<b>DOB</b>	<b>1.2</b>	<b>2.8 (14)</b>	<b>2.8 (14)</b>	<b>2.8 (14)</b>
						<b>620-202</b>	<b>DOB</b>	<b>1.3</b>	<b>2.1 (7)</b>	<b>2.4 (15)</b>	<b>2.4 (15)</b>
						<b>580-201</b>	<b>DOB</b>	<b>1.3</b>	<b>2.7 (13)</b>	<b>2.7 (13)</b>	<b>2.7 (13)</b>
						<b>516-202</b>	<b>DOB</b>	<b>1.4</b>	<b>2.4 (4) √</b>	<b>2.4 (4)</b>	<b>2.4 (4)</b>
						369-206	DOB	1.4	2.5 (7)	2.5 (7)	1.0 (13)
						<b>580-216</b>	<b>DOB</b>	<b>2.6</b>	<b>3.8 (2) √</b>	<b>3.9 (15)</b>	<b>3.9 (15)</b>
						<b>627-208</b>	<b>DOB</b>	<b>3.6</b>	<b>4.5 (14)</b>	<b>4.5 (15)</b>	<b>4.5 (15)</b>

Hematology: values were collected at baseline and day 2. No results were submitted.

Urinalyses: were neither collected nor analyzed.

Vital signs: Vital signs were measured at baseline 15 and 30 minutes and 3, 8, 16, 24 hours and within 24 hours of discontinuation of study drug. The sponsor tabulated only systolic blood pressure and heart rate. The results of the two parameters are shown below. There is a substantial drop in systolic blood pressure that appears to stabilize at between the 3 and 8-hour time point for the two Natrecor doses. For dobutamine, the blood pressure increased slightly initially but re-

approached baseline between ½ to 3 hours after the start of the infusion. Both Natrecor doses differed in the extent of blood pressure reduction relative to dobutamine (nominal p-values < 0.001) but did not differ from each other.

With respect to heart rate, for dobutamine there was an initial increase in heart rate relative to baseline, which diminishes over time. For the Natrecor doses, despite the large drop in blood pressure heart rate either minimally changed or perhaps decreased. The two Natrecor doses differed (with a nominal p-value of < 0.05) only at the 3-hour time point.

Figure 18

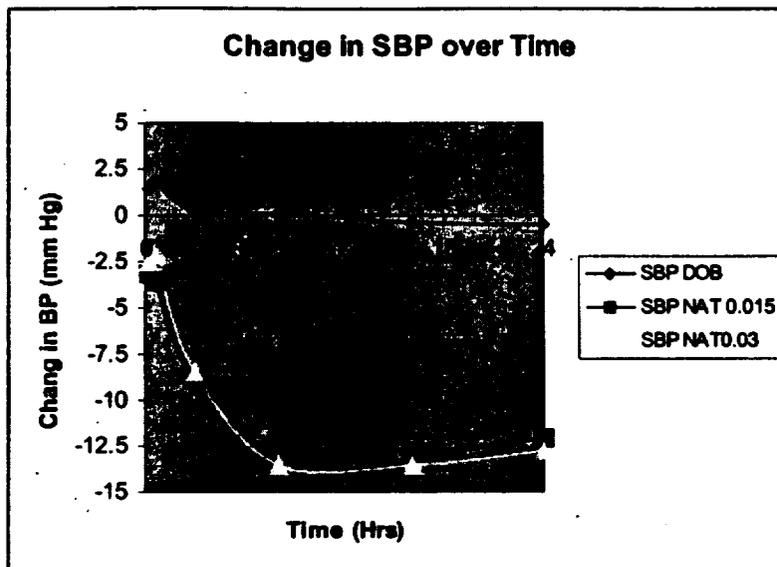
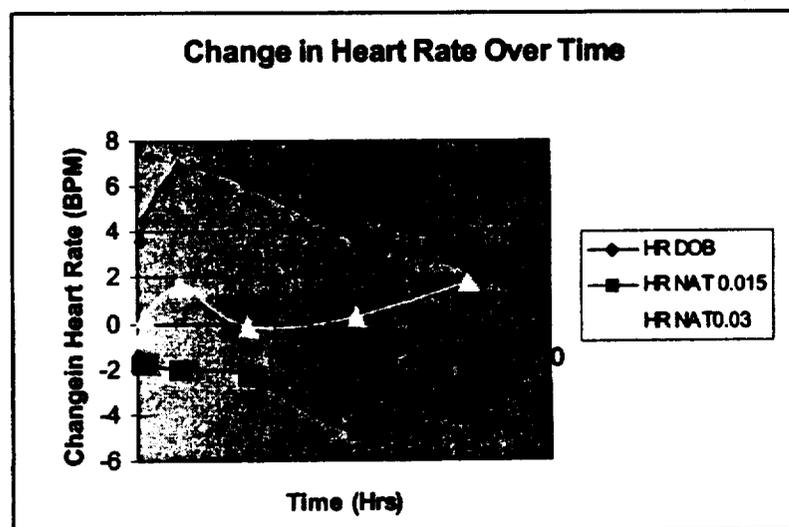


Figure 19



[Comment: It is unclear to this reviewer if the hypotension produced by Natrecor was the stimulus for worsening renal function. In particular, the substantial hypotension produced by Natrecor in conjunction with the lack of reflexive tachycardia may provoke the renal dysfunction. I've asked the sponsor to analyze whether those patients particularly with symptomatic or asymptomatic hypotensive episodes were more prone to renal dysfunction. I've also asked the sponsor to analyze the heart rate response among those who were hypotensive. Did these subjects demonstrate an increase in heart rate in response to the hypotensive episode?]

**Study Summary:** The PRECEDENT trial was a large multicenter study that explored the effect of dobutamine (at a goal dose of > 5 ug/min) and Natrecor at 2 doses, 0.015 and 0.030 ug/kg/min with respect to heart rate and ectopy as captured by Holter monitoring. The study was open-labeled between Natrecor and dobutamine but blinded between the two Natrecor doses. The Natrecor regimen differs from those used in other studies in that no bolus was administered.

A total of 255 subjects were enrolled. Those enrolled were to have symptomatic, decompensated CHF for which in-patient therapy was deemed appropriate. Treatment, however, could be delayed for 24 hours to collect baseline Holter data, so the degree of acute decompensation was not so severe to require immediate intervention. Most subjects enrolled were class III NYHA with a sizable proportion of class IV subjects (20-36%). Between (9-25%) of those enrolled had breathing difficulty at rest at baseline. The overall mortality at 6-months was between 16-22%, so the underlying disease was clearly severe. There was some imbalance in that a larger number of symptomatic subjects were allocated to the dobutamine group. None of those enrolled required intravenous inotropes or after-load reducers at the time of enrollment.

Dobutamine increases heart rate and increases ectopy relative to either of the Natrecor doses. The time in tachycardia over the 24-hour Holter period increased while on dobutamine, but did not substantially change while on either Natrecor dose. Ectopy as assessed, either by the number of premature ventricular beats, couplets, triplets or VT events or using the binary criteria of either the CAPS study or those of Velebit, was more frequent on dobutamine treatment than on Natrecor treatment.

Relative to baseline, symptoms improved both at 3 and 24 hours of infusion for all treatments. The treatments did not differ from each other.

With respect to safety, there were relatively few deaths at either 1- or 6- months of treatment. Numerically, the trends favored Natrecor.

There were no differences in duration of index hospitalization or in the number of hospitalization in the 14 days post infusion.

Hypotension was a prominent adverse event among those treated with Natrecor in a dose dependent manner. Hypotensive events (both symptomatic and asymptomatic) were classified as adverse events in 27% and 44% of those treated with Natrecor 0.015 and 0.03 ug/kg/min, respectively. The corresponding rate among those treated with dobutamine was 6%. Hypotension was the reason for early termination in 3, 8 and 1 patient in the Natrecor 0.015, Natrecor 0.03 and

dobutamine groups, respectively. This reviewer is awaiting the specifics of the hypotension from the sponsor. Means SBP changes (the DBP were not analyzed) decreased from baseline by 12-14 mm Hg in the Natrecor treated groups and were essentially unchanged in the dobutamine group. There was no reflex tachycardia.

Renal function was adversely altered by Natrecor treatment. Group-mean values for creatinine were significantly increased for the Natrecor 0.03 ug/kg/min dose, and trended to higher values for the low dose Natrecor group compared to dobutamine. Numerically, more Natrecor subjects had substantial (> 0.5 mg/dL) increases in creatinine at one or more measurements.

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Division of Cardio-Renal Drug Products  
 Medical Officer Review  
 Addendum #1

NDA 20-920

Name of Drug: Natrecor® (nesiritide)

Date of Review May 10, 2001

This addendum attempts to address the following issues:

- 1) A fuller description of the hypotensive episodes in study # 703.329
- 2) To ascertain whether there is a relationship of between hypotension and alterations of renal function (as defined as an increase in creatinine values of 0.5 mg/dL relative to baseline measurements). Since there were more hypotensive events among those treated with the higher doses of Natrecor, the analysis was limited to the outcomes of study 703.329.
- 3) To ascertain whether the hypotension associated with Natrecor treatment was unaccompanied by a reflex tachycardia in Study 703.329.

The information included in this addendum was submitted on 20 April 2001.

- 1) Description of the hypotensive episodes.

Table Addendum-1 includes information with respect to the onset and duration of both symptomatic and asymptomatic episodes of hypotension.

Table Addendum-1. Description of All Hypotensive events study 703.329

	Dobutamine (n=83)	Natrecor (ug/kg/min)		P-value
		0.015 (n=84)	0.03 (n=79)	
Number with at least one episode (symptomatic)	2 (2%)	14 (17%)	19 (24%)	0.000 Fisher
Number of episodes	2	16	19	
Onset of hypotension (symptomatic)				0.6
< 1 hour	0	1 (1%)	0	
1- 3 hours	1 (2%)	0	3 (4%)	
> 3 hours- 6 hours	0	3 (4%)	4 (5%)	
>6- 24 hours	1 (2%)	12 (14%)	12 (15%)	
Duration of hypotension (symptomatic)				0.7
< 30 minutes	1 (1%)	2 (2%)	2 (3%)	
31-< 60 minutes	0	3 (4%)	2 (3%)	
61-120 minutes	0	4 (5%)	5 (6%)	
121-180 minutes	0	2 (2%)	2 (3%)	
3 hours -7 hours	0	3 (4%)	2 (3%)	
> 7 hours	1 (1%)	2 (2%)	6 (8%)	
Number with at least one episode (asymptomatic)	4 (5%)	9 (11%)	17 (22%)	0.000 Fisher
Number of episodes	4	11	17	
Onset of hypotension (asymptomatic)				0.5
< 1 hour	1 (1%)	1 (1%)	1 (6%)	
1- 3 hours	1 (1%)	0	2 (3%)	
> 3 hours- 6 hours	0	2 (2%)	2 (3%)	
>6- 24 hours	2 (2%)	8 (10%)	12 (15%)	
Duration of hypotension (asymptomatic)				

< 30 minutes	1 (1%)	5 (6%)	1 (1%)	0.08
31-< 60 minutes	0	1 (1%)	3 (4%)	
61-120 minutes	0	0	1 (1%)	
121-180 minutes	0	2 (2%)	2 (3%)	
3hours -7 hours	0	1 (1%)	2 (3%)	
> 7 hours	1 (1%)	2 (2%)	7 (9%)	

The total number of hypotensive episodes was greater on Natrecor than while on dobutamine and the number of subjects with these events among those treated with Natrecor appear to be dose related. Approximately 50% of the episodes (both symptomatic and asymptomatic) among those treated with Natrecor lasted > 2 hours. The onset of such events were generally scattered throughout the infusion regimen (the > 6 – 24 hour span is substantially longer than the other time intervals).

2) There was no obvious relationship between hypotension and creatinine changes. The sponsor submitted the ID numbers of those who had hypotension. This reviewer compared this listing with those subjects whose creatinine increased by more than 0.5 mg/dL. Overall, there were 13 and 15 subject in the 0.015 and 0.03 who had increases in creatinine of > 0.5 mg/dl. There were 23 and 35 patients with hypotension (either symptomatic or asymptomatic). There were 4 (5%) and 8 (10%) subjects who had hypotension (either symptomatic or asymptomatic) and also had increases in creatinine of > 0.5 mg/dL in the Natrecor 0.015 and 0.03 ug/kg/min infusions, respectively. The fraction of subjects in the overall population who had increases in creatinine of > 0/05 was not enriched among those with hypotensive episodes.

Table Addendum-2. Relationship between hypotension and creatinine increases of > 0.5 mg/dL.

	Natrecor dose (ug/kg/min)	
	0.015	0.03
Total enrolled (A)	84	79
Total with hypotension (B) (B/A x 100%)	23 (27%)	35 (44%)
Total with increased Creatinine (C) (C/A x 100%)	13 (15%)	15 (19%)
Total with both hypotension and increase in creatinine (D)	4	8
Increased Creatinine among those with hypotension (D) (D/B x 100%)	4/23 (18%)	8/35 (23%)

With respect to the magnitude of change in creatinine among those with either symptomatic or asymptomatic events, these are shown below. There was a marked increase in creatinine among those with symptomatic hypotension at day 2 especially for the 0.015 ug/kg/min dose, but the results seem to re-approach baseline at day 14. It is, therefore, difficult to attribute chronic changes in renal function among those treated with Natrecor to hypotensive episodes. The mechanism by which changes in renal function occur among those treated with Natrecor is still obscure.

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Table Addendum -3 Time effect of the creatinine among those with hypotension

		Natrecor Dose					
		0.015 ug/kg/min			0.03 ug/kg/min		
		Baseline	Change day 2	Change day 14	Baseline	Change day 2	Change day 14
All Patients	N (missing)	84 (0)	79 (5)	74 (10)	78 (1)	74 (5)	64 (15)
	Value	1.6 + 0.8	0.1 + 0.4	0.1 + 0.4	1.5 + 0.9	0.1 + 0.3*	0.1 + 0.6
Symptomatic Hypotension	N (missing)	14 (0)	14 (0)	12(2)	19 (0)	18(1)	17(2)
	Value	1.4 + 0.5	0.5 + 0.5	-0.1 +0.2	1.3 + 0.4	0.2 +0.3	0 +0.4
Asymptomatic Hypotension	N (missing)	9 (0)	9 (0)	7 (2)	16 (0)	15 (1)	12 (4)
	Value	2.0 + 1.1	0.0 + 0.3	0.1 + 0.9	1.6 + 0.5	0.1 + 0.3	0.0 + 0.39

3) Lastly, It appears that the hypotensive episodes were not associated with tachycardia. This conclusion is subject to some caveats. First heart rates at the time of hypotension were not always available. Often blood pressure data was recorded at the time of the event, but no corresponding heart rate data was available any where near these events (i.e. within 15 minutes of hypotension). Second, there is no adequate control group for comparison. The appropriate heart rate response for a given degree of hypotension cannot accurately be assessed. The available control data is dobutamine, which on its own increase heart rate is less than optimum comparator.

Table addendum-4 lists the maximum percentage decrease in heart rate for those Natrecor-treated subjects with symptomatic and asymptomatic hypotension and those who were not hypotensive (the data was supplied by the sponsor). The table lists also the baseline heart rate and the heart rate response at the time of maximum BP drop.

Among those not categorized as having hypotensive episodes, the maximum SBP drop was 15- 17 % of their baseline values (the baseline value was approximately 120 mm Hg). The heart rate change for those not hypotensive were -3.9 to + 1.5 BPM for the two Natrecor groups.

Among those with symptomatic hypotension there was a 30 and 38% drop in SBP for the 0.015 and 0.03 ug/kg/min, respectively (the baseline SBP was between 108-110 mm Hg). The corresponding heart rate changes were modest +2.7 BPM and + 8.5 BPM, for the low and high dose group, respectively.

With respect to asymptomatic hypotensive patients the drop of blood pressure was equivalent 23-30% (the baseline blood pressure was approximately 110 mm Hg). The heart rate response was decreased for the low dose group (-5 BPM) and minimal increased for the high dose group (0.7 BPM).

Table Addendum-3 Hypotension and heart rate increases all values are Mean + SD

		Natrecor dose					
		0.015 (ug/kg/min)			0.03 (ug/kg/min)		
		Maximum SBP Drop %	Baseline Heart Rate (BPM)	Change in Heart rate at Max BP Drop (BPM)	Maximum SBP Drop (%)	Baseline Heart Rate (BPM)	Change in Heart rate at Max BP drop (BPM)
No Hypotension	N (missing)	60 (1)	60 (1)	60 (1)	44 (0)	44 (0)	44 (0)
	Value	17 + 9	84 + 16	-3.9 + 8	15 + 9.0	83 + 15	1.5 + 10
Symptomatic	N (missing)	14 (0)	14 (0)	12 (2)	19 (0)	19 (0)	14 (5)
	Value	30 + 12	82 + 13	2.7 + 10	38 + 10	84 + 11	8.5 + 10
Asymptomatic	N (missing)	9 (0)	9 (0)	9 (0)	16 (0)	16 (0)	15 (1)
	Value	33 + 7	83 + 13	-5 + 17	23 + 11	82 + 20	0.7 + 10

Some of the more extreme heart rate changes are shown in the table below. There were several subjects whose BP dipped but had minimal tachycardia or even a profound bradycardia.

Table Addendum -5: Some extremes in heart rate changes associated with hypotension.

Pt ID	Dose	Baseline SBP	SBP at Event (change)	Symptomatic or Asymptomatic'	Time of Event	Baseline HR	HR at time of Event (change)
502-213	DOB	157	72 (-85)	Asymptomatic	17:15	79	72 (-7)
352-202	NAT 0.015	111	77 (-34)	Symptomatic	18:00	75	66 (-9)
367-201	NAT 0.015	98	80 (-18)	Symptomatic	4:20	72	60 (-12)
369-201	NAT 0.015	110	70 (-40)	Asymptomatic	16:05	76	73 (-3)
369-218	NAT 0.015	100	76 (-24)	Asymptomatic	0:48	88	72 (-16)
538-203	NAT 0.015	135	74 (-61)	Symptomatic	13:11	54	50 (-4)
560-201	NAT 0.015	105	76 (-29)	Symptomatic	6:38	95	45 (-50)
560-205	NAT 0.015	122	85 (-37)	Asymptomatic	14:40	95	69 (-26)
624-205	NAT 0.015	125	78 (-47)	Asymptomatic	12:20	105	65 (-40)
627-705	NAT 0.015	124	80 (-44)	Asymptomatic	16:05	73	72 (-1)
357-202	NAT 0.030	131	108 (-23)	Symptomatic	11:05	77	71 (-6)
370-203	NAT 0.030	104	78 (-26)	Asymptomatic	8:17	76	71 (-5)
387-201	NAT 0.030	150	110 (-40)	Asymptomatic	8:10	84	72 (-12)
539-210	NAT 0.030	155	78 (-77)	Symptomatic	6:00	86	90 (+4)
554-215	NAT 0.030	117	78 (-39)	Asymptomatic	8:00	104	98 (-6)
560-210	NAT 0.030	128	80 (-48)	Symptomatic	8:58	97	96 (-1)

Although there is not an adequate control, some of those treated with Natrecor had profound drops in blood pressure but had unusually low heart rate response, the mechanism is unclear.

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Safety Update

See Dr. Karkowsky's 5-15-01 review and 5-15-01 addendum and Dr. Throckmorton's 6-21-01 review.

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## Item 9

### SAFETY UPDATE REPORT

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#### Additional Safety Information

All clinical studies included in the Natrecor® amended NDA have completed enrollment and data collection, with the exception of 6-month mortality in the VMAC trial (704.339). The Agency requested the collection of 6-month mortality several months after the initiation of the VMAC trial. The Agency agreed that Scios would provide the 6-month mortality assessment on data available to meet a December 2000 filing date. Consequently 22% of the subjects have not yet been included in the 180 day analysis at the time of this submission.

Once the 6-month data is collected on the last patient enrolled in the VMAC trial, Scios will provide the Agency with an updated assessment of 6-month mortality for the VMAC trial. The Agency and Scios agreed this updated mortality information would be provided 3 months following the filing of this amended NDA. The final 6-month mortality assessment will be provided, in March 2001, under Item 9 of this amendment.

As noted in the cover letter, the final reports for each of these studies in this amended NDA are included in both Item 8 (Volumes 7-30) and Item 10 (numbered on the Archive Volume Covers as Volumes 32-55); the clinical and statistical sections, respectively.

D. Willard

MAR 3 - 1999

**Combined Medical & Statistical Review  
Natrecor<sup>®</sup> Injection  
(Nesiritide Citrate)**

**NDA 20-920**

**Division of Cardiovascular and Renal Drugs**

**February 26, 1999**

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- a. A detailed tables of contents for this trial or section appears below.  
b. PCWP = pulmonary capillary wedge pressure.  
c. CHF = congestive heart failure.

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- a. A detailed tables of contents for this trial or section appears below.  
 b. PCWP = pulmonary capillary wedge pressure.  
 c. CHF = congestive heart failure.

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INTEGRATED MEDICAL & STATISTICAL REVIEW  
OF NEW DRUG APPLICATION 20-920

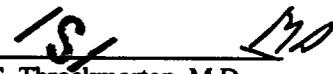
NDA: 20-920  
DRUG NAME: Nesiritide citrate  
TRADE NAME: Natrecor®  
FORMULATION: For intravenous infusion  
SPONSOR: Scios Inc.  
TYPE OF DOCUMENT: New Drug Application

MEDICAL REVIEWER: Douglas C. Throckmorton, M.D.  
Division of Cardio-Renal Drug Products (DCRDP), HFD-110  
STATISTICAL REVIEWER: Lu Cui, Ph.D.  
Division of Biometrics-I, HFD-710

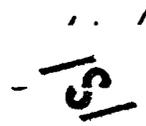
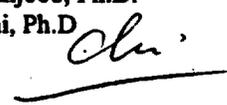
PROPOSED INDICATION: Natrecor is proposed for short-term treatment of congestive heart failure.

DATE OF NDA SUBMISSION: 4.24.98  
DATE ASSIGNED: 4.29.98  
DATE FINAL REVIEW COMPLETED: 2.26.99

REVIEWER'S SIGNATURES

  
\_\_\_\_\_  
Douglas C. Throckmorton, M.D.  
Medical Reviewer

  
\_\_\_\_\_  
Lu Cui, Ph.D.  
Statistical Reviewer

  
Concur: Kooros Mahjoob, Ph.D.  
George Chi, Ph.D.  


#### Trial 704.326

This was a trial in patients with acutely decompensated CHF, comparing the effects of standard care (i.e., dobutamine, and nitroprusside) with two doses of nesiritide. The primary goal of the trial was to collect safety information regarding the use of nesiritide in the acutely decompensated CHF population. The patients in this trial were required to be off of their other parenteral vasoactive medications for 4 hours, as in the 704.325 study. Patients were randomly assigned to receive either nesiritide or standard therapy in open-label fashion. For subjects assigned to one of the two nesiritide groups, investigators and patients were blinded to the dose of nesiritide administered.

With regard to clinical efficacy, nesiritide appeared as effective as, but not superior to, the active comparators in relieving the symptoms of CHF at the end to 6 and 24 hours. There was no tendency for the high-dose nesiritide to be more effective than the low-dose nesiritide as regards symptomatic benefit.

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

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

With regard to safety, the incidence of hypotension was again significantly greater in the nesiritide groups. The severity of the hypotension was also greater in the nesiritide groups.

#### Efficacy Summary

The data clearly demonstrate a significant hemodynamic effect of nesiritide that is dose-dependent and persists for at least 24 hours. Following discontinuation of nesiritide, hemodynamics return to baseline within 4 hours, without evidence for 'rebound.' While the magnitude of the nesiritide effect on mean hemodynamics (especially PCWP) appears to decrease by the end of 24 hours, the overall effects of nesiritide on hemodynamics compared with placebo persist through 24 hours. The pharmacodynamic half-life of nesiritide is significantly longer than the pharmacokinetic half-life, reflected in the time to maximal effect on PCWP (4-6 hours) and time to return to baseline after discontinuation of nesiritide (2-4 hours).

The link between nesiritide administration and clinical benefits is more tenuous, with a single study (704.325) supporting a greater acute effect of nesiritide than placebo on the signs and symptoms of CHF through 6 hours. These data are weakened by the fact that the investigators were aware of the PCWP values when performing their assessments. Additionally, the same investigator elicited the patient-assessments, introducing a potential bias in the symptom score data. This potential bias also undermines the observed link between the clear effects of nesiritide on PCWP and the observed improvement in signs and symptoms of CHF. The data from trial 704.326 suggests that the effects of nesiritide on CHF signs and symptoms is comparable to the active controls with regard to symptomatic relief over the first 24 hours of therapy. No other beneficial or adverse clinical effect of nesiritide (i.e., re-hospitalization rate, mortality rate) was suggested by the data.

Insufficient data are available in the NDA to comment on the following critical aspects of use:

- 1) information about the use of nesiritide in patients who are already taking other parenteral CHF therapies (especially other vasodilators),
- 2) information regarding the use of nesiritide in patients with CHF and myocardial infarction (these patients were excluded from the three pivotal trials),
- 3) information regarding the titration of nesiritide to achieve desired clinical effect,
- 4) information regarding the development of tolerance beyond 24 hours (where tolerance to nitrates develops), and
- 5) information about the effects of nesiritide at infusion doses below 0.015 µg/kg/min.

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Safety Summary

Regarding overall mortality, there was no suggestion of either an adverse or beneficial effect of nesiritide on mortality rates over the period of follow-up in the trials.

Regarding overall safety, the nesiritide administration is associated with the occurrence of adverse events that are likely to be clinically significant and lead to increased patient morbidity. Of the adverse events, hypotension was most worrisome to this reviewer. The data suggest that hypotension requiring drug discontinuation will be more common in patients treated with nesiritide, when compared with current therapies. The data also suggest that the nesiritide use is associated with both clinically severe and prolonged hypotension. Unfortunately, no risk factors to identify patients at high risk for these hypotensive episodes were found.

The clinical database suggests that patients receiving nesiritide are also at increased risk for other clinically significant adverse events related to bradycardia and abnormal renal function. While more data is needed to place the risk of these adverse events into clinical context, the NDA does suggest that some patients may suffer significant clinical consequences related to nesiritide administration. With regard to less common adverse events, further data are needed to fully assess the clinical consequences of some of the adverse events associated with nesiritide use.

Recommendations of Medical Reviewer

Nesiritide has a demonstrated hemodynamic effect that is superior to placebo and persists through at least 24 hours. There is a suggested effect of nesiritide to relieve some of the acute symptoms of CHF, similar to currently available therapies. The available data are insufficient to demonstrate superiority of nesiritide to placebo with regard to symptom relief, which appears at best to be similar to the effects of other currently available parenteral therapies. Nesiritide use is associated with several clinically relevant adverse effects, especially hypotension. The prolonged pharmacodynamic half-life of nesiritide predicts that this hypotension will be more difficult to manage than for currently available therapies that work by the same intracellular mechanism (NTG, nitroprusside). Finally, the database is inadequate to address several important questions regarding its use: the concomitant use of other parenteral vasodilators, potential dose titration, the use in patients with acute myocardial ischemia, the potential effect of nesiritide on vascular permeability, and the potential for the development of tolerance beyond 24 hours, and effective lower dose. With the availability of other therapies also working through the cGMP-dependent protein kinase to cause vasodilatation that have a shorter pharmacodynamic half-life, the presence of significant safety concerns, and the inadequate database to describe its safe and effective use, nesiritide is not approvable.

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## 1.0 Materials Utilized in Review

### 1.1 Materials from NDAs/ INDs

1. NDA 20-920 (nesiritide); volumes 1.1 through 1.89.

2. Nesiritide computer-assisted NDA (CANDA), including case report forms (CRFs). The CRFs were submitted electronically by the sponsor in the following categories:

- a. Deaths.
- b. Discontinued from therapy due to an adverse experience.
  - b1. Discontinued due to an adverse experience.
  - b2. Discontinued due to a clinical endpoint.
- c. Discontinued from therapy for any other reason.
- d. Serious adverse experiences.

3. IND (nesiritide).

4. INDs for Atrial Natriuretic Peptide: L

### 1.2 Related Reviews & Consults

No outside reviews or consultants were obtained, and no related reviews utilized as part of this NDA review.

### 1.3 Other Resources

Four outside resources were reviewed, and relevant portions included in section 5.2.:

1. The printed transcript of the FDA Cardio-Renal Advisory Committee meeting on IV therapy for CHF (1.27.98).
2. The draft guidelines for the clinical evaluation of drugs for the treatment of congestive heart failure, written by Milton Packer for the Cardio-Renal Advisory Committee (12.7.87).
3. The published literature of for all atrial- and ventricular-derived natriuretic peptides.
4. The draft guidelines for the clinical evaluation of drugs for the treatment of congestive heart failure, discussed at the Cardio-Renal Advisory Committee (10.22.98).

## 2.0 Background

Human B-type natriuretic peptide (hBNP) is a 32-amino acid peptide, which was originally discovered in the brain (hence, B-type). It is produced mainly in the cardiac ventricle, and has vasodilatory, diuretic, natriuretic, and neurohormonal actions, similar to atrial natriuretic peptide, which is found in the atria of the heart (ref. 5). These peptides were first identified in the late 70's. Natrecor (nesiritide citrate) is a preparation containing the purified hBNP peptide produced by recombinant DNA technology, with an amino acid sequence identical to that of naturally occurring hBNP. In animals, hBNP causes vasodilation, and increases urinary sodium and water excretion. Similar natriuretic effects have been reported in humans, perhaps through inhibition of proximal sodium reabsorption (refs. 5, 12).

The effects of hBNP in patients with decompensated congestive heart failure (CHF) were studied as part of this NDA submission. CHF is characterized by abnormalities in cardiac function, renal water and salt handling, and peripheral vascular resistance. The latter abnormalities reflect an attempt by the body to compensate for decreased cardiac function, to maintain cardiac output. Ultimately, these compensatory mechanisms become maladaptive, and contribute to the progression of disease in CHF. Increased sympathetic tone leads to activation of the renin-angiotensin-aldosterone axis, and increased peripheral vascular resistance and sodium/ water retention by the kidney.

Patients with CHF have a combination of poor cardiac output (with decreased stroke volume and cardiac index), increased peripheral resistance with increased cardiac filling pressures (pre-load). This leads to increases in pulmonary artery pressures (PAP), pulmonary capillary wedge pressures (PCWP), and mean right atrial pressures (MRAP). Per the sponsor, the aim of therapy for the treatment of acutely decompensated CHF, such as nesiritide, is to improve the symptoms of CHF as well as any abnormalities in the cardiac hemodynamics, blood pressure and fluid retention. Decompensated CHF is a serious problem, and accounts for approximately one million hospitalizations per year in the U.S. It is now the most common discharge diagnosis for patients >65 years old. The incidence of CHF has also been rising in the U.S., and continues to carry a poor prognosis for survival, despite advances in therapy. This prognosis is worsened by the high prevalence of concomitant diseases in patients with CHF: diabetes; atrial fibrillation; ventricular arrhythmias; coronary artery, renal, and pulmonary disease. These patients also have elevated circulating levels of both ANP and hBNP (ref. 9).

The vasodilatory and natriuretic/diuretic properties of hBNP suggested that it might have therapeutic benefit in patients with CHF (ref. 12). Based on the submitted data, the sponsor proposes the use of hBNP for the treatment of decompensated CHF.