

**STATISTICAL REVIEW AND EVALUATION
(ADDENDUM #3)**

NDA #: 20-920 Major Amendment

Applicant: Scios Inc.

Drug Name: Natrecor (nesiritide)

Indication: decompensated congestive heart failure

This addendum reports the results of dyspnea evaluation at 3 hours, 6 hours, and 24 hours after infusion. Recall that at 3 hours the Natrecor group had a statistically significantly greater improvement on dyspnea score compared to the placebo group (see Table 4B-0 in the Appendix of this addendum, also Table 4 of statistical review, dated 04/18/01). The 3-hour dyspnea results observed in the study appeared to be mainly driven by the results of the catheterized patients (Table 4B-1 in the Appendix of this addendum and in the statistical review, Addendum #1). In the non-catheterized patients, the Natrecor group seemed to have little advantage over the placebo group (Table 4B-2 in the appendix of this review and in the statistical review, Addendum #2).

After 3 hours, the placebo patients were divided to receive either Natrecor or nitroglycerin according to the original randomization assignments. There was no statistically significant difference in dyspnea score between Natrecor and nitroglycerin. Numerically, as compared to nitroglycerin, the Natrecor group appeared to have a greater improvement on dyspnea score (in terms of mean score and percent of patients who felt better) at 3 hours, 6 hours and 24 hours (Table 4B-0 in the appendix and Table 4C-0). This numerical trend was seen in both non-catheterized patients and catheterized patients (Tables 4B-1 and 4B-2 in the appendix and Tables 4C-1 and 4C-2). More patients in both treatment groups seemed to feel better based on the dyspnea score profile over time in 24 hours. The numerically greater improvement associated with Natrecor seemed to be more apparent (nominal p-value < 0.03 at 24 hours) in non-catheterized patients. Since a significant difference in dyspnea score was not shown in all treated patients, it is very difficult to interpret the $p < 0.03$ in the non-catheterized patients. In my view, the comparison of Natrecor with nitroglycerin in dyspnea assessment remains inconclusive, though the study suggests that Natrecor might improve dyspnea score to a greater extent than nitroglycerin.

Table 4C-0. All treated subject's 6-hour and 24-hour dyspnea evaluation (as randomized)

	6 hours		24 hours	
	Nitroglycerin (N=216)	Natrecor (N=273)	Nitroglycerin (N=216)	Natrecor (N=273)
# of subjects analyzed	214	265	215	266
Mean \pm se	1.4 \pm 1.1	1.5 \pm 1.1	1.8 \pm 1.0	2.0 \pm 1.1
p-value ¹	----	0.43	-----	0.10
Markedly better	38 (18%)	57 (22%)	67 (31%)	100 (38%)
Moderately better	67 (31%)	77 (29%)	76 (35%)	84 (32%)
Minimally better	54 (25%)	71 (27%)	39 (18%)	53 (20%)
No change	52 (24%)	56 (21%)	29 (13%)	28 (11%)
Minimally worse	3 (1%)	2 (1%)	2 (1%)	0 (0%)
Moderately worse	0 (0%)	1 (0%)	2 (1%)	1 (0%)
Markedly worse	0 (0%)	1 (0%)	0 (0%)	0 (0%)
p-value ²	----	0.37	-----	0.13

Reviewer's analysis

¹ versus nitroglycerin (ANOVA)² versus nitroglycerin (Wilcoxon)

Table 4C-1. Catheterized subject's 6-hour and 24-hour dyspnea evaluation (as randomized)

	6 hours		24 hours	
	Nitroglycerin (N=92)	Natrecor (N=148)	Nitroglycerin (N=92)	Natrecor (N=148)
# of subjects analyzed	92	147	92	148
Mean \pm se	1.3 \pm 1.1	1.4 \pm 1.1	1.9 \pm 1.1	1.9 \pm 1.1
p-value ¹	----	0.55	-----	1.0
Markedly better	14 (15%)	29 (20%)	33 (36%)	51 (34%)
Moderately better	28 (30%)	43 (29%)	28 (30%)	47 (32%)
Minimally better	28 (30%)	44 (30%)	18 (20%)	30 (20%)
No change	20 (22%)	28 (19%)	11 (12%)	19 (12%)
Minimally worse	2 (2%)	1 (1%)	2 (2%)	0 (0%)
Moderately worse	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Markedly worse	0 (0%)	1 (1%)	0 (0%)	0 (0%)
p-value ²	-----	0.45	-----	0.94

Reviewer's analysis

¹ versus nitroglycerin (ANOVA)² versus nitroglycerin (Wilcoxon)

Table 4C-2. Non-catheterized subject's 6-hour and 24-hour dyspnea evaluation (as randomized)

	6 hours		24 hours	
	Nitroglycerin (N=124)	Natrecor (N=119)	Nitroglycerin (N=124)	Natrecor (N=119)
# of subjects analyzed	122	118	123	118
Mean \pm se	1.4 \pm 1.1	1.5 \pm 1.1	1.71 \pm 1.1	2.1 \pm 1.0
p-value ¹	-----	0.61	-----	0.018
Markedly better	24 (20%)	28 (24%)	34 (28%)	49 (42%)
Moderately better	39 (32%)	34 (29%)	48 (39%)	37 (31%)
Minimally better	26 (21%)	27 (23%)	21 (17%)	23 (19%)
No change	32 (26%)	28 (24%)	18 (15%)	9 (8%)
Minimally worse	1 (1%)	1 (1%)	0 (0%)	0 (0%)
Moderately worse	0 (0%)	0 (0%)	2 (2%)	0 (0%)
Markedly worse	0 (0%)	0 (0%)	0 (0%)	0 (0%)
p-value ¹		0.60		0.027

Reviewer's analysis

¹ versus nitroglycerin (ANOVA)² versus nitroglycerin (Wilcoxon)

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This review consists of 5 pages of text.

cc: NDA 20-920 Major Amendment (Addendum #2)
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Appendix

Table 4B-0. All treated subject's 3-hour dyspnea evaluation (as randomized)

	Nitroglycerin (N=143)	Natrecor (N=204)	Placebo (N=142)
# of subjects analyzed	143	203	142
Mean \pm se	1.3 \pm 1.1	1.3 \pm 1.1	1.1 \pm 1.2
p-value ¹ compared to placebo	0.41	0.050	----
p-value ¹ Natrecor vs. NTG		0.29	
Markedly better	17 (12%)	34 (17%)	25 (18%)
Moderately better	50 (35%)	54 (27%)	24 (17%)
Minimally better	37 (26%)	64 (32%)	41 (29%)
No change	33 (23%)	45 (22%)	46 (32%)
Minimally worse	5 (3%)	5 (2%)	6 (32%)
Moderately worse	0 (0%)	1 (0.5%)	0 (0%)
Markedly worse	1 (1%)	0 (0%)	0 (0%)
p-value ² compared to placebo	0.19	0.034	----
p-value ² Natrecor vs. NTG		0.57	

¹ based on ANOVA analysis ² based on van Elteren's test
Reviewer's analysis

Table 4B-1. Catheterized Subject's 3-hour dyspnea evaluation (as randomized)

	Nitroglycerin (N=60)	Natrecor (N=124)	Placebo (N=62)
# of subjects analyzed	60	123	62
Mean \pm se	1.1 \pm 1.3	1.3 \pm 1.1	0.9 \pm 1.2
p-value ¹ for comparison to placebo	0.43	0.052	----
p-value ¹ for Natrecor vs. NTG		0.31	
Markedly better	8 (13%)	18 (15%)	9 (15%)
Moderately better	17 (28%)	33 (27%)	8 (13%)
Minimally better	14 (23%)	40 (33%)	18 (29%)
No change	16 (27%)	28 (23%)	23 (37%)
Minimally worse	4 (7%)	4 (3%)	4 (6%)
Moderately worse	0 (0%)	0 (0%)	0 (0%)
Markedly worse	1 (2%)	0 (0%)	0 (0%)
p-value ² for comparison to placebo	0.31	0.030	----
p-value ² for Natrecor vs. NTG		0.44	

Reviewer's analysis ¹ based on ANOVA analysis ² based on Wilcoxon test

Table 4B-2. Non-Catheterized Subject's 3-hour dyspnea evaluation (as randomized)

	Nitroglycerin (N=83)	Natrecor (N=80)	Placebo (N=80)
# of subjects analyzed	83	80	80
Mean \pm se	1.4 \pm 1.0	1.4 \pm 1.1	1.3 \pm 1.2
p-value ¹ for comparison to placebo	0.47	0.47	----
p-value ¹ for Natrecor vs. NTG		0.99	
Markedly better	9 (11%)	16 (20%)	16 (20%)
Moderately better	33 (40%)	21 (26%)	16 (20%)
Minimally better	23 (28%)	24 (30%)	23 (29%)
No change	17 (20%)	17 (21%)	23 (29%)
Minimally worse	1 (1%)	1 (1%)	2 (3%)
Moderately worse	0 (0%)	1 (1%)	0 (0%)
Markedly worse	0 (0%)	0 (0%)	0 (0%)
p-value ² for comparison to placebo	0.40	0.41	----
p-value ² for Natrecor vs. NTG		0.96	

Reviewer's analysis ¹ based on ANOVA analysis ² based on Wilcoxon test

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/s/

James Hung
4/26/01 05:35:41 PM
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Need sign off by April 27 [last day for going out to AC member]

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5/7/01 11:04:50 AM
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