

**STATISTICAL REVIEW AND EVALUATION
(ADDENDUM #1)**

NDA #: 20-920 Major Amendment

Applicant: Scios Inc.

Drug Name: Natrecor (nesiritide)

Indication: decompensated congestive heart failure

This addendum pertains to the issue raised by Dr. Karkowsky. In a number of patients, the baseline dyspnea assessment was done more than one hour prior to drug infusion. Was there any substantial difference in such a gap time? If yes, did such a difference have an impact on the results of the 3-hour dyspnea assessment? Based on the data sets provided, 20 (9.8%) patients in the Natrecor group, 15 (10.5%) in the nitroglycerin group, and 13 (9.2%) in the placebo group had baseline dyspnea assessment more than 1 hour before infusion. The average times between baseline dyspnea assessment and infusion were 1.5, 1.8 and 1.5 hours, in the three treatment groups, respectively. The analyses adjusting for this gap time gave the results very similar to those of the analyses without adjustment (Table 4A compared to Table 4 of statistical review of 04/18/01).

Table 4A. Subject's 3-hour dyspnea evaluation
(All treated subjects 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 for comparison to placebo	0.37	0.043	----
p-value ¹ for 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 for comparison to placebo	0.19	0.036	----
p-value ² for Natrecor vs. NTG		0.60	

Reviewer's analysis

¹ based on ANCOVA analysis

² based on van Elteran's test stratified by cathetered or not and time between baseline dyspnea assessment and infusion greater than one hour or not

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Acting Team Leader

This review consists of 2 pages of text.

cc: NDA 20-920 Major Amendment (Addendum #1)
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/s/

James Hung
4/20/01 04:17:42 PM
BIOMETRICS

Also need your prompt attention by 4/23/01

George Chi
4/20/01 05:22:58 PM
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