

**STATISTICAL REVIEW AND EVALUATION
(ADDENDUM #4)**

NDA #: 20-920 Major Amendment

Applicant: Scios Inc.

Drug Name: Natreacor (nesiritide)

Indication: decompensated congestive heart failure

This addendum reports the results of global clinical status evaluation at 3 hours, 6 hours, and 24 hours after infusion. As illustrated in the following tables, global clinical status seemed to show a similar numerical pattern as dyspnea assessment. No statistically significant difference was found between the treatment groups at 3 hours or at 6 hours. Numerically, the Natreacor group seemed to see a greater global status improvement than the nitroglycerin group at 24 hours. However, eight patients in the Natreacor group and two patients in the nitroglycerin group did not have global assessment; thus, it is difficult to interpret $p=0.044$ (Table 4E-0) which may be influenced by the values of the missing assessment. In my view, the comparisons of Natreacor with nitroglycerin and placebo in global status assessment remain inconclusive.

Table 4D-0. All treated subject's 3-hour global clinical status evaluation (s randomized)

| | Nitroglycerin (N=143) | Natreacor (N=204) | Placebo (N=142) |
|---|--------------------------|----------------------|--------------------|
| # of subjects analyzed | 143 | 203 | 142 |
| Mean \pm se | 1.1 \pm 1.2 | 1.3 \pm 1.1 | 1.1 \pm 1.2 |
| p-value ¹ compared to placebo | 0.69 | 0.11 | ----- |
| p-value ¹ Natreacor vs. NTG | | 0.23 | |
| | | | |
| Markedly better | 16 (11%) | 28 (14%) | 21 (15%) |
| Moderately better | 48 (34%) | 55 (27%) | 26 (18%) |
| Minimally better | 30 (21%) | 69 (34%) | 45 (32%) |
| No change | 41 (29%) | 44 (22%) | 45 (32%) |
| Minimally worse | 6 (4%) | 7 (3%) | 5 (4%) |
| Moderately worse | 2 (1%) | 0 (0%) | 0 (0%) |
| Markedly worse | 0 (0%) | 0 (0%) | 0 (0%) |
| p-value ² compared to placebo | 0.55 | 0.068 | ----- |
| p-value ² Natreacor vs. NTG | | 0.33 | |

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

Table 4D-1. Catheterized Subject's 3-hour global clinical status evaluation (as randomized)

| | Nitroglycerin (N=60) | Natrecor (N=124) | Placebo (N=62) |
|--|-------------------------|---------------------|-------------------|
| # of subjects analyzed | 60 | 123 | 62 |
| Mean \pm se | 1.0 \pm 1.2 | 1.2 \pm 1.1 | 1.0 \pm 1.1 |
| p-value ¹ for comparison to placebo | 0.81 | 0.19 | ---- |
| p-value ¹ for Natrecor vs. NTG | --- | 0.32 | --- |
| Markedly better | 9 (15%) | 18 (15%) | 8 (13%) |
| Moderately better | 13 (22%) | 28 (23%) | 9 (15%) |
| Minimally better | 15 (25%) | 44 (36%) | 21 (34%) |
| No change | 18 (30%) | 28 (23%) | 22 (35%) |
| Minimally worse | 4 (7%) | 5 (4%) | 2 (3%) |
| Moderately worse | 1 (2%) | 0 (0%) | 0 (0%) |
| Markedly worse | 0 (0%) | 0 (0%) | 0 (0%) |
| p-value ² for comparison to placebo | 0.75 | 0.13 | ---- |
| p-value ² for Natrecor vs. NTG | --- | 0.35 | --- |

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

Table 4D-2. Non-Catheterized Subject's 3-hour global clinical status evaluation (as randomized)

| | Nitroglycerin (N=83) | Natrecor (N=80) | Placebo (N=80) |
|--|-------------------------|--------------------|-------------------|
| # of subjects analyzed | 83 | 80 | 80 |
| Mean \pm se | 1.2 \pm 1.1 | 1.3 \pm 1.0 | 1.2 \pm 1.1 |
| p-value ¹ for comparison to placebo | 0.75 | 0.34 | ---- |
| p-value ¹ for Natrecor vs. NTG | --- | 0.52 | --- |
| Markedly better | 7 (8%) | 10 (13%) | 13 (16%) |
| Moderately better | 35 (42%) | 27 (34%) | 17 (21%) |
| Minimally better | 15 (18%) | 25 (31%) | 24 (30%) |
| No change | 23 (28%) | 16 (20%) | 23 (29%) |
| Minimally worse | 2 (2%) | 2 (3%) | 3 (4%) |
| Moderately worse | 1 (1%) | 0 (0%) | 0 (0%) |
| Markedly worse | 0 (0%) | 0 (0%) | 0 (0%) |
| p-value ² for comparison to placebo | 0.61 | 0.29 | ---- |
| p-value ² for Natrecor vs. NTG | --- | 0.66 | --- |

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

Table 4E-0. All treated subject's 6- and 24-hour global clinical status evaluation (as randomized)

| | 6 hours | | 24 hours | |
|------------------------|--------------------------|---------------------|--------------------------|---------------------|
| | Nitroglycerin (N=216) | Natrecor (N=273) | Nitroglycerin (N=216) | Natrecor (N=273) |
| # of subjects analyzed | 215 | 264 | 214 | 265 |
| Mean \pm se | 1.3 \pm 1.1 | 1.5 \pm 1.1 | 1.7 \pm 1.2 | 1.9 \pm 1.0 |
| p-value ¹ | ---- | 0.12 | ----- | 0.044 |
| Markedly better | 35 (16%) | 54 (20%) | 60 (28%) | 89 (34%) |
| Moderately better | 61 (28%) | 84 (32%) | 77 (36%) | 91 (34%) |
| Minimally better | 63 (29%) | 65 (25%) | 37 (17%) | 55 (21%) |
| No change | 51 (24%) | 56 (21%) | 34 (16%) | 27 (10%) |
| Minimally worse | 4 (2%) | 5 (2%) | 3 (1%) | 1 (0%) |
| Moderately worse | 1 (0.5%) | 0 (0%) | 3 (1%) | 2 (1%) |
| Markedly worse | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| p-value ² | ----- | 0.12 | ----- | 0.075 |

Reviewer's analysis

¹ versus nitroglycerin (ANOVA)

² versus nitroglycerin (Wilcoxon)

Table 4E-1. Catheterized subject's 6-hour and 24-hour global clinical status (as randomized)

| | 6 hours | | 24 hours | |
|------------------------|-------------------------|---------------------|-------------------------|---------------------|
| | Nitroglycerin (N=92) | Natrecor (N=154) | Nitroglycerin (N=92) | Natrecor (N=154) |
| # of subjects analyzed | 92 | 146 | 92 | 147 |
| Mean \pm se | 1.4 \pm 1.1 | 1.4 \pm 1.1 | 1.7 \pm 1.2 | 1.8 \pm 1.1 |
| p-value ¹ | ---- | 0.57 | ----- | 0.79 |
| Markedly better | 15 (16%) | 26 (18%) | 29 (32%) | 44 (30%) |
| Moderately better | 26 (28%) | 47 (32%) | 31 (34%) | 49 (33%) |
| Minimally better | 30 (33%) | 41 (28%) | 15 (16%) | 34 (23%) |
| No change | 19 (21%) | 29 (20%) | 13 (14%) | 18 (12%) |
| Minimally worse | 2 (2%) | 3 (2%) | 3 (3%) | 0 (0%) |
| Moderately worse | 0 (0%) | 0 (0%) | 1 (1%) | 2 (1%) |
| Markedly worse | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| p-value ² | ----- | 0.55 | ----- | 0.99 |

Reviewer's analysis

¹ versus nitroglycerin (ANOVA)

² versus nitroglycerin (Wilcoxon)

Table 4E-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 | 123 | 118 | 122 | 118 |
| Mean \pm se | 1.3 \pm 1.1 | 1.5 \pm 1.1 | 1.7 \pm 1.1 | 2.0 \pm 1.0 |
| p-value ¹ | ----- | 0.11 | ----- | 0.009 |
| Markedly better | 20 (16%) | 28 (24%) | 31 (25%) | 45 (38%) |
| Moderately better | 35 (28%) | 37 (31%) | 46 (38%) | 42 (36%) |
| Minimally better | 33 (27%) | 24 (20%) | 22 (18%) | 21 (18%) |
| No change | 32 (26%) | 27 (23%) | 21 (17%) | 9 (8%) |
| Minimally worse | 2 (2%) | 2 (2%) | 0 (0%) | 1 (1%) |
| Moderately worse | 1 (1%) | 0 (0%) | 2 (2%) | 0 (0%) |
| Markedly worse | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| p-value ² | | 0.12 | | 0.013 |

Reviewer's analysis

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

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 Acting Team Leader

This review consists of 4 pages of text.

cc: NDA 20-920 Major Amendment (Addendum #4)
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