SYNOPSIS

Company: Scios, Inc. **Investigational Product:** Natrecor® **Active ingredient:** Nesiritide		
Title: Follow-Up Serial Infusions of Natrecor® (nesiritide) for the Management of Patients with Heart Failure — FUSION II		
Investigator(s)/Study Centers: List of Investigators in Appendix 12.1.4/187 centers		
Publication (reference): None		
Study period: 26 April 2004 - 5 December 2006 First subject treated: 26 April 2004 Last subject completed: 5 December 2006	**Phase of Development:** IIb	
Objectives: To evaluate the efficacy and safety of nesiritide administered as serial infusions to heart failure (HF) subjects in the outpatient setting.		
Study design: This was an international, prospective, randomized, parallel, multicenter, double-blind, placebo-controlled study in HF subjects.		
Methodology: Subjects who had at least 2 qualifying hospitalizations or hospitalization equivalents in the past year (+ 30 days), with the most recent hospitalization or hospitalization equivalent within the previous 60 days (+ 14 days), but who had been out of the hospital at least 5 days, were recruited into the study if they met the following criteria: 1. Left ventricular ejection fraction (LVEF) < 40% (measured within the 24 weeks [+ 14 days] before randomization). **AND** 2. One of the following, consistently for the previous 60 days before randomization: • New York Heart Association (NYHA) Class IV. • NYHA Class III with highest calculated creatinine clearance < 60 mL/min in the previous 30 days. Subjects received study treatment for 12 weeks, subsequently followed by a 12-week follow-up period consisting of a 4-week weaning period and an 8-week assessment period. All subjects continued to receive their usual long-term cardiac medications (excluding outpatient IV inotropes [e.g., dobutamine, milrinone, dopamine, or levosimendan (in countries where the agent is approved)], vasodilators, and open-label nesiritide). During the study, the sites continued their usual disease management and/or subject education programs. Subjects in this trial were seen by their physician more frequently than would be typical due to their partipation in this study. Subjects were expected to come to the clinic once or twice a week, as defined by their randomized treatment assignment, for infusion of study drug. Subjects were randomized to one of four treatment groups in a 2:1:2:1 (nesiritide once weekly:placebo once weekly:nesiritide twice weekly:placebo once weekly) ratio.		
Number of Subjects (planned and analyzed): 900 planned; 920 randomized; 911 treated and included in the modified intention-to-treat (MITT) analysis that was used for the primary analysis of efficacy.		

Company: Scios, Inc. **Investigational Product:** Natrecor® **Active ingredient:** Nesiritide		

Diagnosis and main criteria for inclusion: Acute decompensated HF

Key inclusion criteria:

Subjects were eligible for the study if they satisfied the inclusion criteria. Key inclusion criteria include the following:

1. Were ≥ 18 years old.
2. Had at least 2 qualifying hospitalizations.
3. Had documentation indicating that the subject was consistently NYHA Class III or IV during the 60 days (+14 days) before randomization.
4. Had a LVEF < 40% (measured within 24 weeks before randomization).
5. Were (1) NYHA Class IV or (2) NYHA Class III with highest calculated creatinine clearance (CrCl) < 60 mL/min within the previous 30 days.
6. Were receiving optimal treatment with long-term oral medications (e.g., diuretics, angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], and beta blockers, unless these were documented to be contraindicated or not tolerated).

Key exclusion criteria:

Subjects were not eligible for study participation if they met any of the following criteria:

1. Systolic blood pressure (BP) consistently < 90 mm Hg.
2. Unable/unwilling to discontinue intermittent/continuous infusions of dopamine, dobutamine, milrinone, nitroglycerin, levosimendan, or open-label Natrecor® (nesiritide).
3. Recent outpatient IV vasoactive medications (e.g., milrinone, dobutamine, dopamine, nitroglycerin or levosimendan).
4. Had, or anticipated to have, any organ transplantation (heart, liver, lung, kidney, or bone marrow).
5. Biventricular pacemaker placed within the 45 days before randomization or a single or dual chamber pacemaker or an automatic implantable cardiac defibrillator placed within the 15 days before randomization.
6. Cardiogenic shock, volume depletion, or other clinical condition that contraindicated the administration of nesiritide.
7. Currently receiving chronic dialysis or expectation that dialysis would be required during the next 12 months.
8. History of an allergic reaction or sensitivity to nesiritide or any of its components.

Company: Scios, Inc. **Investigational Product:** Natrecor® **Active ingredient:** Nesiritide		

Test product, dose and mode of administration, batch number:
Nesiritide (1.5 mg for injection, reconstituted to a final concentration of 6 mcg/mL in a 250 mL diluent IV bag) administered as a 2 mcg/kg bolus followed by a fixed-rate infusion of 0.01 mcg/kg/min for 4 to 6 hours once or twice weekly. The dose was based on body weight measured just before administration at each study visit. Batch #'s: Q0017A1, Q0015A1, R0023A, Q0015A, Q00017A1, S0018A

Duration of trial: Active or placebo treatment period for 12 weeks, with a 12-week follow-up period consisting of a 4-week weaning period and an 8-week assessment period. Subjects were followed for death and all serious adverse events (SAEs) through Week 24. Mortality was followed in all subjects until 24 weeks after accrual of the last subject.

Reference therapy: Placebo (reconstituted and added to a 250 mL diluent IV bag) administered as a bolus (equivalent to 2 mcg/kg nesiritide bolus) followed by a fixed-rate infusion (equivalent to 0.01 mcg/kg/min nesiritide infusion) for 4 to 6 hours once or twice weekly. The dose was based on body weight measured just before administration at each study visit. Batch #'s: P0007A, R0024A, S0001A.

Criteria for Evaluation:

Efficacy

Primary Endpoint

- Time to all-cause mortality or the first occurrence of hospitalization for cardiovascular and/or renal causes from the day of randomization through Week 12.

Secondary Endpoints

The secondary efficacy endpoints are listed in the order prespecified for statistical testing:

- Number of cardiovascular and/or renal hospital admissions adjusted for duration of observation period through the end of Week 12.
- Days alive and out of the hospital from the day of randomization through the end of Week 12.
- Change in the overall summary score of the Kansas City Cardiomyopathy Questionnaire (KCCQ) from Baseline to Week 13.
- Time to cardiovascular death from the day of randomization through the end of Week 12.

Safety:

Safety measures included deaths, adverse events (AEs), clinical laboratory evaluations, physical examinations and vital signs.

Company: Scios, Inc. **Investigational Product:** Natrecor® **Active ingredient:** Nesiritide		

Statistical methods:

Efficacy: All key efficacy analyses were conducted on the modified intention-to-treat (MITT) population, which consists of subjects who received at least one dose of study drug after randomization at any time during the study. The primary efficacy parameter was time to all-cause mortality or the first occurrence of hospitalization for cardiovascular and/or renal causes through Week 12 from day of randomization. A blinded Adjudication Committee adjudicated the cause of each hospitalization and death.

The efficacy population was based upon subjects who were randomized and the safety population was based on subjects treated; these groups were identical. Of 920 randomized subjects, 911 were treated and included in the efficacy and safety populations (placebo 1x/wk, 153; nesiritide1x/wk, 302; placebo 2x/wk, 153; nesiritide 2x/wk, 303).

The primary analysis, based on adjudicated events, estimated the overall effect of nesiritide relative to placebo, both administered in addition to standard care. Between-group differences in the Kaplan-Meier survival curves for the primary endpoint were tested for significance by using the log-rank statistic, stratified by randomized dose frequency (once per week or twice per week) at the level of two-sided $\alpha = 0.05$ for the following null hypothesis (H_0).

- H_0: There was no overall difference between the pooled nesiritide groups and pooled placebo groups with respect to the combined risk of all-cause mortality and/or hospitalization for cardiovascular and/or renal causes through Week 12.

Secondary and additional endpoints were analyzed at each specified time point. For the other continuous variables, descriptive statistics were calculated at each study visit. Proportions were presented for categorical and ordinal variables.

The Kaplan-Meier estimates of the survival curves were presented for all time-to-event data. Between-group differences in the Kaplan-Meier survival curves for these endpoints were analyzed and tested for significance level at $\alpha = 0.05$ by the stratified log-rank statistic, stratified on the dosing frequency (once per week or twice per week). Analyses of subject clinical outcomes at the 12-, 16-, and 24-week period were provided for each treatment group. Other efficacy endpoints and additional measures were analyzed using 2-way analysis of variance (ANOVA) with treatment and dose frequency as the main effects or stratified Cochran-Mantel-Haenszel (CMH) tests. The KCCQ was analyzed at each assessment time with respect to total score and the score for each domain and tested for statistical significance using 2-way ANOVA with the same model as above.

Company: Scios, Inc. **Investigational Product:** Natrecor® **Active ingredient:** Nesiritide		

Safety: All subjects who received at least one dose of study drug, whether withdrawn prematurely or not, were included in the safety analysis. Comparisons were made according to treatment administered. Demographic and baseline characteristics were compared. The duration and dose of the study drug infusion was described. Concomitant medications given during a study visit were coded and summarized. Treatment-emergent adverse events were summarized and listed by treatment group, body system, and preferred term using the MedDRA dictionary (Version 9.0) for the following: all AEs, serious AEs, AEs leading to study termination, and AEs leading to discontinuation of study medication. Summaries of all AEs by severity and all AEs by relationship to study drug were provided. Vital signs and outpatient laboratory data were summarized and listed for changes from pretreatment, change over time, and for differences between treatment groups, in terms of absolute changes. For some outpatient laboratory data, changes relative to normal or clinically significant ranges were also summarized by treatment groups.

In addition to outpatient serum creatinine determinations, renal safety was evaluated by four composite measures that combined mortality and hospitalization for renal causes with clinical laboratory data.

Efficacy Results Summary:
There were no statistically significant efficacy findings for any of the efficacy endpoints.

The primary endpoint was time to all-cause mortality or the first occurrence of hospitalization for cardiovascular and/or renal causes from the day of randomization through Week 12. The KM event rates at the end of Week 12, estimated from the Kaplan-Meier (KM) survival distribution functions, were as follows: 36.8% for the placebo group and 36.7% for the nesiritide group, respectively. The estimated 12-week KM event rates for treatment regimens were as follows: 37.5%, 38.4%, 35.9% and 35.0% for placebo 1x/weekly, nesiritide 1x/weekly, placebo 2x/weekly and nesiritide 2x/weekly, respectively.

Company: Scios, Inc. **Investigational Product:** Natrecor® **Active ingredient:** Nesiritide		

Efficacy Results Summary (cont.):

No differences were observed between treatments with respect to the number of cardiovascular and/or renal hospital admissions, adjusted for duration of observation period, through Weeks 12, 16 or 24. For the number of cardiovascular and/or renal hospital admissions, adjusted for duration of observation period, at Week 12, the nesiritide group had a mean (SD) of 1.0 (4.02) and placebo had 0.8 (1.87). For treatment regimens, these means ranged from 0.7-0.9 for the placebo group as compared to 0.9-1.2 for the nesiritide group.

The mean number of days alive and out of the hospital through Week 12 were similar across treatment regimens (ranged from 72 to 76 days).

The overall summary scores of the KCCQ at baseline across treatment regimens were similar and ranged from 38-41. The mean change in KCCQ from baseline to Week 13 ranged from 12-15 across treatment regimens.

The KM event rates for cardiovascular deaths at the end of Week 12 were 8.7%, 9.5%, 9.7% and 6.7% for placebo 1x/weekly, nesiritide 1x/weekly, placebo 2x/weekly and nesiritide 2x/weekly, respectively.

Efficacy Conclusions: For subjects with CDHF participating in an intensive outpatient management program, serial administration of nesiritide did not offer an incremental benefit in the prevention of the composite of all-cause mortality and cardio-renal hospitalization as compared to placebo. There were no statistically significant efficacy results for the primary or any of the secondary efficacy endpoints.

Company: Scios, Inc. **Investigational Product:** Natrecor® **Active ingredient:** Nesiritide		

Safety Results Summary: A total of 920 subjects were randomized of which 911 were treated with the regimen to which they were randomized. During the course of the study, more than 85% of subjects experienced at least one adverse event (comparable rates across all treatment regimens). Treatment-emergent adverse events possibly or probably related to study medication were reported by 28.1% and 26.8% of subjects randomized to placebo 1x/weekly and 2x/weekly, respectively, compared with 39.4% and 44.2% of subjects, treated with nesiritide 1x/weekly and 2x/weekly, respectively. The disparity was due primarily to higher rates of hypotension in nesiritide-treated subjects. Treatment-emergent SAEs were experienced by 54.9% and 58.2% of subjects treated with placebo 1x/weekly and 2x/weekly, respectively, compared with 61.9% and 58.4% of subjects treated with nesiritide 1x/weekly and 2x/weekly, respectively. The primary reason for the apparent imbalance in 1x/weekly nesiritide vs. 1x/weekly placebo was 'cardiac failure congestive'. Treatment-emergent SAEs possibly or probably related to study medication were reported by 7.8% and 8.5% of subjects randomized to placebo 1x/weekly and 2x/weekly, respectively, compared with 7.9% of subjects treated with nesiritide 1x/weekly and 2x/weekly. The most common treatment-emergent SAE across all treatment groups was 'cardiac failure congestive', which occurred in 24.8%-31.4% of placebo subjects as compared to 29.4%-31.1% of nesiritide subjects. Other common SAEs were 'cardiac failure', 'pneumonia', 'renal failure acute' and 'renal failure'.

Three serious and unexpected AEs (SUAs) occurred that were considered possibly or probably related to study drug treatment. The subjects experiencing a SUA were as follows: 1084-001 (subcortical posterior circulation stroke; possibly related) subject 1122-001 (fever, chills, facial erythema; probably related), and subject 1147-003 (worsening cardiomyopathy resulting in death; possibly related). These SUAs were expedited to the FDA and sent to the Adjudication Committee. The subject blind was broken for these subjects and it was determined that these subjects were administered nesiritide.

Adverse events leading to study drug discontinuation or premature study withdrawal were reported by 26.1% and 24.8% of subjects randomized to placebo 1x/weekly and 2x/weekly, respectively, compared with 25.8% and 28.1% of subjects treated with nesiritide 1x/weekly and 2x/weekly, respectively. There were no statistically significant differences across any treatment regimen or group, with the exception of the number of treatment-related AEs (due almost exclusively to an increased incidence of hypotension) experienced by nesiritide-treated subjects (41.8% vs. 27.5%, $p<0.001$). There was a statistically significant difference in the number of subjects that experienced a related treatment-emergent AE with once weekly nesiritide and once weekly placebo (39.4% vs. 28.1%, respectively; $p=0.018$) as well as in twice-weekly administrations of nesiritide and placebo (44.2% vs. 26.8%, respectively; $p<0.001$). The most common reasons for early discontinuation due to an AE were 'cardiac failure congestive' and 'cardiac failure'.

The adverse events (by preferred terms) reported by the highest proportion of subjects across once and twice weekly treatment groups were as follows: cardiac failure congestive (30.7%-32.7%, placebo; 31.0%-34.8%, nesiritide), hypotension (12.4%-23.5%, placebo; 28.1%-36.6%, nesiritide; predominantly asymptomatic in nesiritide groups), cardiac failure (9.8%-15.0%, placebo; 11.6%-14.6%, nesiritide), blood creatinine increased (15.7% for both placebo groups; 9.9%-16.2%, nesiritide), and blood urea increased (13.1%-15.0%, placebo; 9.9%-16.8%, nesiritide).

Company: Scios, Inc. **Investigational Product:** Natrecor® **Active ingredient:** Nesiritide		

Safety Results Summary (cont.):

The incidence for the majority of AEs was similar across treatment regimens, with only a few instances of statistically significant ($p<0.05$) differences observed. The only AE reported that was statistically significant and considered clinically significant was hypotension. This outcome was expected due to the known effects of nesiritide administration. Hypotension was reported in approximately 12.4% and 28.1% of placebo- and nesiritide-treated subjects (once weekly; $p<0.001$) compared with 23.5% and 36.6% of twice weekly placebo- and nesiritide-treated subjects ($p=0.006$). Hypotension reported by subjects was predominately asymptomatic in presentation, although the between treatment differences were significantly higher for asymptomatic ($p=0.004$ and $p=0.005$ for once and twice weekly nesiritide, respectively) and symptomatic hypotension in the nesiritide-treated subjects.

A total of 283 subjects died by the end of the study (92 placebo [30.1%]; 191 nesiritide [31.6%]). The longest observation of any subject was 963 days. Over the course of the entire study, the estimated event rates for all-cause mortality were similar for placebo and nesiritide treatment groups and were 47.7% and 45.0%, respectively.

Serum chemistry and hematology demonstrated similar results across treatment regimens and groups. Although there were a few statistically significant differences at different time points in serum chemistry values, they usually normalized by the end of the study.

Concomitant medications, vital signs and physical findings were similar across treatment groups over the course of the study.

Safety Conclusions:

Common Adverse Events

- The observed pattern of adverse events observed with repeated treatment is consistent with the known safety profile of nesiritide.
- Hypotension, a labeled adverse event associated with nesiritide, was significantly more common among subjects who received nesiritide as compared to placebo.
- Approximately 75% of hypotensive episodes were asymptomatic.
- Serious episodes of hypotension were uncommon and were observed more often in subjects in the placebo group.

Mortality

The FUSION II study was not powered to assess the effect of nesiritide on mortality.

- Mortality was observed to be similar between the pooled nesiritide and pooled placebo treatment groups at the conclusion of active treatment (the pre-specified primary analysis time point of 12 weeks).

Renal Function

- The maintenance of baseline levels of serum creatinine throughout the 12-week treatment period suggests that nesiritide can be administered on a repeated basis to subjects with CDHF without the risk of compromise in renal function.

Company: Scios, Inc. **Investigational Product:** Natrecor® **Active ingredient:** Nesiritide		
Overall Conclusions: This study was designed to expand upon the favorable results demonstrated in subjects treated with outpatient infusions of nesiritide in FUSION I. In the FUSION II trial, a 12-week regimen of once or twice weekly, serial, outpatient infusions of nesiritide was well tolerated over the treatment course, but was not effective as measured by a treatment benefit in the composite endpoint of all-cause mortality and cardiovascular/renal hospitalization. Subjects receiving nesiritide experienced a higher incidence of non-serious episodes of hypotension as compared to placebo subjects. Renal function remained stable over the 12-week treatment period in both treatment groups.		
Date of the report: 26 October 2007		

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.