SYNOPSIS

NAME OF SPONSOR/COMPANY: Scios Inc.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Natrecor® NAME OF ACTIVE INGREDIENT: Nesiritide	Volume: Page:	

Protocol No.: A014, IND 43,998 CR003352

Title of Study: A Pilot, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Nesiritide Infusion, Initiated Post-Induction of Anesthesia, in the Management of Coronary Artery Bypass Graft (CABG) Patients Requiring Cardiopulmonary Bypass (CPB).

Lead Investigator: Mehmet C. Oz, M.D., MBA, Director of the Heart Institute, College of Physicians and Surgeons, Columbia University, New York, New York, US.

Study Centers: 54 enrolling centers in the US, as listed in Appendix 1.4.1

Study Initiation/Completion Dates: First informed consent: 25 March 2004; Last follow-up with subject contact for Day-180 data: 28 February 2006.	**Phase of Development:** 2

Objectives: To assess the effects of nesiritide in the perioperative setting for patients undergoing CABG requiring CPB. Objectives of particular interest were effect on renal function, effect on hemodynamics, need for intravenous (IV) interventions (inotropes, vasopressors, vasodilators), and clinical outcomes (durations of ICU/CCU stay, hospital stay, CPB, and intubation).

Methodology

Study Design: This multicenter, randomized, double-blind, and placebo-controlled trial compared renal, hemodynamic, and safety effects of the addition of nesiritide or placebo to standard care for the treatment of CHF patients undergoing CABG surgery with CPB. Standard-care medical therapies may have included vasopressor/inotropic agents, vasodilators, or antiarrhythmic agents, as needed.

Dose/Route/Regimen: Study drug administration was initiated after induction of anesthesia and measurement of qualifying baseline hemodynamics and prior to chest incision. Nesiritide or placebo was administered as a continuous IV infusion at a fixed rate of 0.01 µg/kg/min (with no bolus) for at least 24 and up to 96 hours; infusion duration was based on subject clinical status and at the discretion of the investigator. Study assessments took place during five sequential time periods: (1) before surgery, (2) during surgery, (3) in the ICU/CCU, (4) in the hospital medical/surgical unit, and (5) follow-up after hospital discharge 14, 21, 30, and 180 days after start of study medication.

Number of Subjects: Planned enrollment was 300 subjects to obtain 250 subjects evaluable for efficacy, prospectively defined as subjects who received study drug and underwent CABG surgery with CPB.

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Entry Criteria

Inclusion Criteria:

1. Age ≥ 18 years.
2. NYHA class II–IV congestive heart failure (CHF).
3. Presented for CABG surgery with or without mitral valve repair/replacement.
4. Planned utilization of CPB.
5. Documented left ventricular ejection fraction ≤ 40% measured by nuclear scan, echocardiogram, or ventriculogram, within 90 days before surgery.

Exclusion Criteria:

1. Planned aortic valve repair/replacement.
2. Ongoing or chronic dialysis (either hemodialysis or continuous ambulatory peritoneal dialysis).
3. Restrictive or obstructive cardiomyopathy, constrictive pericarditis, pericardial tamponade, or other conditions in which cardiac output is dependent on venous return.
4. Documented or suspected low cardiac filling pressures.
5. Any known congenital heart disease.
6. Known allergic reaction or sensitivity to nesiritide or excipients.
7. Females of childbearing potential with a positive serum pregnancy test, and nursing mothers.
8. Treated with investigational drug or device within last 30 days, unless approval for inclusion was obtained from sponsor.
9. Documented fever (> 101°F) within 72 hours of surgery.
10. White blood cell count ≥ 15,000/mm^3 within 72 hours of surgery.
11. Documented bacterial/fungal/viral infection requiring administration of IV antibiotics within 7 days before surgery.
12. Pulmonary disease (chronic obstructive pulmonary disease, asthma, or other condition) that required inpatient medical or surgical treatment within 60 days before surgery.
13. Treatment Exclusion Criteria—obtained after anesthesia induction and before chest incision prior to the start of study drug.
    a. Mean pulmonary artery pressure consistently ≤ 15 mmHg.
    b. Central venous pressure consistently < 6 mmHg.
    c. Systolic blood pressure consistently < 90 mmHg.
14. Use of open-label nesiritide within 48 hours of study drug administration

Test Product, Dose, and Mode of Administration: In agreement with Natrecor® Package Insert, study drug was reconstituted with IV diluent to a final concentration of 6 µg/mL in a 250-mL IV diluent bag containing 0.9% sodium chloride, 5% dextrose in water or other known compatible diluents. Study drug was administered as a fixed-rate infusion of 0.01µg/kg/min with no bolus, based on preoperative body weight, 24 to 96 hours.

Natrecor® Finished Lot Numbers including placebo and study drug dispensed: CQ0051A, CR0057A CR0064A, and CR0065A. Drug Lot Numbers of Natrecor® were P0002A1 for 95 subjects and Q0015A1 for the remainder.

Reference Therapy, Dose, and Mode of Administration, Batch No.: Placebo Lot Number P0007A (reconstituted and added to a 250 mL diluent IV bag) was administered as a fixed rate infusion, at a volume equivalent to 0.01 µg/kg/min of nesiritide infusion based on preoperative body weight, for 24 to 96 hours.

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Efficacy Evaluation

Endpoints of primary interest included the following:

- Change from baseline serum creatinine (measured within 24 hours before initiation of study drug infusion) to the highest serum creatinine measured up to hospital discharge or up to Study Day 14, whichever came first. If discharge was after Study Day 14, the highest serum creatinine measued up to Study Day 14 was used.
- Change from baseline GFR (measured within 24 hours before initiation of study drug infusion) to the lowest GFR up to hospital discharge or up to Study Day 14, whichever came first. If discharge was after Study Day 14, the lowest GFR prior to Study Day 14 was used.
- Change from baseline in mean pulmonary artery pressure for first 24 hours after study drug initiation or after removal of Swan-Ganz catheter, whichever came first.
- IV inotrope/vasopressor drug utilization during the 30-day study.
- IV vasodilator drug utilization during the 30-day study.
- Urine output for first 24 hours after admission to ICU/CCU or until discharge from ICU/CCU, whichever came first. If the collection duration was less than 24 hours, this variable was standardized as the total collected urine output divided by the duration (in hours), multiplied by 24. Because urine output was collected and measured in four 6-hour consecutive time periods, the duration was calculated as the sum of each individual time period. This standardization algorithm also applied to individual 6-hour urine output calculations.

Endpoints of secondary interest included the following:

- Duration of ICU/CCU stay, in days, from unit admission to unit discharge.
- Duration of hospital stay, in days, from date of study drug initiation to date of hospital discharge.
- Duration of CPB, in minutes, from start to stop.
- Duration of intubation, in hours, from intubation to extubation.
- Change from baseline in hemodynamic parameters other than mean pulmonary artery pressure.
- In addition to duration of the above hospital events, duration of two other hospital events, (1) time on the aortic cross-clamp, in minutes, and (2) time on ultrafiltration, in hours, were analyzed post-hoc.

Safety Evaluation: Adverse events, mortality, laboratory assessments, and vital signs. A follow-up communication 180 days after the start of study drug was implemented to collect mortality data.

Statistical Methods

This was an exploratory study. Formal adjustments for multiplicity of the prespecified endpoints of primary or secondary interest were not made any conclusions recognize the limitations due to multiple hypotheses being tested.

Efficacy Analyses: Efficacy analyses were based on evaluable subjects, defined as randomized and treated subjects who underwent CABG surgery with CPB. Differences were considered significant at $p < 0.05$, two-sided.

Change from baseline to postoperative peak serum creatinine was analyzed with a one-way analysis of covariance (ANCOVA), with treatment group as a qualitative factor and baseline serum creatinine value as a covariate. The difference of least squares means of the change and the 95% confidence interval of the difference were presented.

Similar analyses were performed for GFR values, mean pulmonary artery pressure, and other hemodynamic parameters. Time profiles for serum creatinine and GFR were plotted.

Time to the peak serum creatinine value was summarized. Change from baseline serum creatinine was presented at each scheduled time point. Proportion of subjects who met criteria for a clinically meaningful serum creatinine increase ($\geq 50\%$ and to ≥ 2.0 mg/dL) was also assessed using Fisher's exact test. Proportion of subjects having IV inotrope/vasopressor support and proportion of subjects requiring high-dose IV inotrope/vasopressor support were analyzed using the chi-square test. IV vasodilator drug use was analyzed in a similar manner.

Urine output was analyzed with a one-way analysis of variance (ANOVA).

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Statistical Methods (Cont'd)

Durations of ICU/CCU stay, CPB, intubation, and aortic cross-clamp were evaluated using a two-sample Wilcoxon rank-sum test. Ultrafiltration duration was evaluated using ANOVA.

Safety Analyses: All randomized subjects who received study drug were included in the safety analysis. Adverse events were summarized descriptively by treatment group and were mapped using the Medical Dictionary for Regulatory Activities (MedDRA), Version 6.0. Overall incidence of treatment-emergent adverse events was summarized by treatment group and classified by system organ class and preferred term. Adverse events were summarized with respect to time period: during the first 24 hours after initiation of study drug infusion, during surgery, after surgery, during treatment, 14 days after initiation of study drug, and during the 30-day study period. Incidence rates of hypotension, serious adverse events, adverse events leading to study withdrawal, and adverse events leading to discontinuation of study drug were determined. Frequency of adverse events by maximum severity and by relationship to study medication was summarized. Summaries of adverse event profiles were presented for subgroups of subjects, based on age, sex, race, and baseline serum creatinine.

Mortality rates at Days 7, 14, 30, and 180 were analyzed using a log-rank test with treatment included in the model. Kaplan-Meier survival curves were estimated. If a subject expired after a specified time point, this subject was considered a 'survivor' up to that time point. Similar analyses were performed by subgroup variables age, baseline GFR, and baseline NT-pro BNP.

Hospital re-admission rate to Study Day 30 was analyzed using Fisher's exact test.

Use of prospectively selected IV and non-IV medications, which were coded and classified according to the World Health Organization (WHO) Drug dictionary (1Q04) were summarized for each treatment group.

Findings were summarized for changes from baseline in laboratory analytes (serum chemistry, hematology, BNP, NT-pro BNP, hsCRP, IL-6, cystatin-C, troponin T, and endothelin-1), systolic blood pressure and heart rate, number and volume of blood transfusions, and ECG data.

Results

Efficacy: Nesiritide significantly improved postoperative renal function, as indicated by a smaller maximal increase in peak serum creatinine, better preservation of GFR, and greater urine output in the immediate postoperative period. Lower postoperative increases (absolute and percent change) in serum creatinine were experienced by nesiritide-treated subjects (0.15 mg/dL, 17.1%) compared with placebo-treated subjects (0.34 mg/dL, 33.4%, $p < 0.001$) and this effect was amplified among subjects with baseline serum creatinine levels > 1.2 mg/dL (placebo, 0.48 mg/dL, 29.3%; nesiritide, 0.02 mg/dL, 2.7%, $p = 0.001$). This therapeutic benefit on renal function also was reflected by better GFR preservation (MDRD calculation) among nesiritide-treated subjects. Driven by an early rise in urine output during the first six hours after ICU/CCU admission, 24-hour urine output also was statistically better for the nesiritide group (2,926 mL) when compared with the placebo group (2,350 mL, $p < 0.001$). No statistically significant differences were evident between treatment groups with respect to hemodynamic parameters and vasoactive drug use. The many vasodilators, vasopressors, and inotropes permitted and administered during the study may have masked the documented nesiritide effect of lowering preload, thus reducing pulmonary capillary wedge pressure and pulmonary artery pressure.

Vasoactive drug use was extensive in both treatment groups; vasopressor, inotropic, and/or inodilating agents were administered to approximately 96% of subjects and vasodilators were given to approximately 76% of subjects. Use of individual agents, including milrinone (placebo, 47%; nesiritide, 44%) was similar for the two treatment groups except for dobutamine (placebo, 37%; nesiritide, 28%).

Nesiritide shortened length of hospital stay; mean duration of hospital stay was 11.5 (± 9.84) and 9.1 (± 6.08) days for placebo and nesiritide groups, respectively ($p = 0.043$). Durations of intubation, CPB, and aortic cross-clamp were similar for the two treatment groups.

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Results (Cont'd)

Safety: Nesiritide was generally well tolerated and the results of this study might be expected to represent what would be observed in CHF patients undergoing CABG that would be treated with the drug. The fixed and continuous infusion dose (0.01 µg/kg/min) was well tolerated, even among severely ill patients with multiple comorbidities and among those receiving many other vasoactive therapies. Smaller proportions of nesiritide-treated subjects discontinued study medication because of adverse or serious adverse events and encountered fewer serious adverse events, most notably atrial fibrillation, respiratory failure, and acute renal failure.

During the course of the study, nearly all subjects experienced at least one adverse event and 33.7% of subjects experienced serious adverse events. Adverse events and serious adverse events possibly or probably related to study medication were reported by 21.1% and 2.9% of subjects, respectively. Adverse events leading to study drug discontinuation or premature study withdrawal were reported by 8.6% and 3.6% of subjects, respectively. Nesiritide was associated with a trend toward decreased mortality by the 30-day assessment, a benefit preserved at the 180-day assessment ($p = 0.046$), which included mortality status of 69% of subjects in each treatment group.

Conclusions

This study of patients undergoing CABG with CPB indicates that nesiritide, administered after anesthesia induction, exerted beneficial postoperative effects on renal function, evidenced by lower peak serum creatinine, better-preserved GFR, and increased urine output. The salutary effect on renal function was more pronounced in high-risk subjects with poorer baseline renal function (baseline serum creatinine > 1.2 mg/dL). Nesiritide was relatively well tolerated with similar adverse event profiles in the two treatment groups. These results warrant a large-scale trial with prespecified endpoints.

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