SYNOPSIS OF CLINICAL STUDY REPORT — PROTOCOL 704.351

TITLE OF THE STUDY/DATE OF REPORT	Evaluation of Synergy Between Natrecor® (nesiritide) and Furosemide on Renal and Neurohormone Responses in Chronic Heart Failure: A Phase IV Study
INVESTIGATORS/CENTERS AND COUNTRIES	Nine investigators at 9 centers in the U.S.
PERIOD OF TRIAL	20 April 2003 to 6 February 2004
CLINICAL PHASE	IV
OBJECTIVES	The objectives of this study were to compare the effects on renal function of treatment with Natrecor® (nesiritide) in combination with furosemide versus furosemide alone and nesiritide alone, and to assess the effect of 3 treatment regimens on neurohormone levels.
STUDY DESIGN/STUDY DRUG DOSE/REGIMEN	This trial was a randomized, open-label, three-way crossover design study with 3 treatment groups: TREATMENT A: Furosemide administered as a 40 mg intravenous (IV) bolus over 2 minutes TREATMENT B: Nesiritide administered as a 2 µg/kg IV bolus, followed by an infusion of 0.01 µg/kg/min for 6 hours TREATMENT C: Treatment B for at least 15 minutes, then administration of treatment A All sequences involving both furosemide and nesiritide had the nesiritide infusion started first, at least 15 minutes before furosemide was administered. Each treatment was administered according to 1 of 6 sequences to which subjects were randomized. Subjects remained in the Clinical Research Unit (CRU) for 7 days, with treatments administered on Days 2, 4, and 6, with equilibrium (rest) days on Days 1, 3, and 5. All subjects were followed for safety throughout the treatment phase, and by telephone between 7 and 14 days after they were discharged from the CRU.
NUMBER OF SUBJECTS	42 randomized with intent to treat; 40 treated; 35 completed the full 3-treatment sequence; 28 evaluable

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	This study enrolled subjects who had chronic congestive heart failure (CHF) and were at risk for "diuretic resistance" as defined by their daily maintenance dose of furosemide. Listed below are the inclusion and exclusion criteria, which describe the subject/subject population for this study. To be included in the study, each subject was to have met all the following entry requirements: 1. Men and women aged ≥ 18 years. 2. Chronic symptomatic NYHA Class II or III CHF for at least 90 days before the study. 3. Left ventricular systolic dysfunction as evidenced by left ventricular ejection fraction < 40%, measured using contrast or radionuclide ventriculography or by echocardiography, within 180 days of the study start. 4. Serum potassium > 3.5 mEq/L. 5. Chronic oral daily requirement of 80–240 mg of furosemide for at least 7 days before the study start. 6. Receiving a stable medical regimen for CHF for at least 60 days before the study start, including angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), and/or beta-blockers. 7. Able to sign and fully understand elements of Informed Consent before the initiation of protocol-specific procedures.
EXCLUSION CRITERIA	Subjects were excluded from the study if they met any of the following criteria: 1. Clinical instability such that withholding diuretic therapy would be unsafe. 2. Significant renal impairment (e.g., creatinine clearance < 45 mL/min by the Cockcroft-Gault formula), or changing renal function during the 7 days before study start, or intrinsic renal disease. 3. Systolic blood pressure (SBP) consistently < 90 mm Hg. 4. Myocardial infarction within 90 days of study start, unstable angina within 14 days of study start, or any clinical evidence of active myocardial ischemia. 5. Percutaneous coronary intervention or cardiac surgery within 90 days of study start. 6. Any other surgery requiring general anesthesia within 14 days of study start. 7. Restrictive or obstructive cardiomyopathy, constrictive pericarditis, pericardial tamponade, other conditions in which cardiac output was dependent on venous return, or for subjects expected to have low filling pressures. 8. Prior cardiac or renal allografts. 9. Sustained ventricular tachycardia or ventricular fibrillation within 14 days of study start. 10. Second-degree (Mobitz type II block) or third-degree block, unless the subject had a permanent implanted pacemaker.

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EXCLUSION CRITERIA (CONT'D)	11. Intrinsic liver disease or serum transaminases (AST, ALT), bilirubin, or alkaline phosphatase with a value greater than 3× the upper limit of normal at screening visit. 12. Serum sodium concentration < 128 mEq/L. 13. Receiving NSAIDs or COX-2 inhibitors that could not be discontinued 72 hours before the study start. 14. Any contraindications to the use of a vasodilator, furosemide, para-amino hippuric acid (PAH), lithium carbonate, or iohexol. 15. Any contraindications to the use of nesiritide or any of the components in nesiritide. 16. Admission to the hospital for CHF or recent CHF decompensation within 30 days of study start. 17. Use of Viagra within 5 days of study start. 18. Use of spironolactone, amiloride, or eplerenone within 5 days of study start. 19. Administration of IV contrast media within 4 days of study start. 20. Therapy with an investigational drug or participation in another clinical trial within 30 days of study start. 21. Females of childbearing potential with a positive pregnancy test, pregnant, or nursing mothers, or suspected pregnancy.
TRIAL DRUG / BATCH No(s).	Nesiritide for IV infusion, Lot No. CP0002A1
REFERENCE DRUG / BATCH No(s).	Commercial IV furosemide, Lot No. 96-491-DK (Abbott Labs)
CRITERIA FOR EVALUATION EFFICACY	• Primary endpoint (refer to Section 3.1.3): – urinary excretion rate of sodium. • Secondary endpoints (refer to Section 3.1.3): – urinary flow rate – urinary excretion of potassium, calcium and magnesium – urinary excretion of cGMP and furosemide – change from baseline in plasma aldosterone – change in BNP levels – iohexol clearance (Glomerular Filtration Rate)
SAFETY	Baseline blood chemistries and hematology, daily blood chemistries, adverse events (AEs), and serious adverse events (SAEs).
STATISTICAL METHODS	All efficacy endpoints were analyzed using a three-period, three-treatment crossover analysis of covariance (ANCOVA) model. The statistical model includes parameters for sequence, subject within sequence, treatment, and study period. The sequence effect was evaluated for the presence of differential treatment carryover. When the carryover effect was not significant, analysis results were listed by treatment group, regardless of study period. Descriptive statistics were calculated for continuous endpoints. Proportions are presented for categorical and ordinal variables.

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