SYNOPSIS

Name of Sponsor/Company: Xian-Janssen Pharmaceutical, Ltd. Name of Finished Product: Nesiritide Name of Active Ingredient(s): Nesiritide	

Protocol No.: A073

Title of Study: An Open-label, Single Arm, Multi-centered Clinical Trial on the Hemodynamics and Safety of Nesiritide in the Treatment of Patients with Acute Decompensate Heart Failure

Principal Investigator: Yishi Li, Institution for Clinical Trial, Chinese Academy of Medical Sciences & Peking Union Medical College, Cardiovascular Institute & Fuwai Hospital, Beijing, China

Publication (Reference):

1.Gu Dongfeng, Huang Guangyong, et al. Investigation of prevalence and distributing feature of chronic heart failure in Chinese adult population. Chin J Cardiol, 2003; 31: 3-6

2.Modern Diagnosis and Treatment of Heart Failure. Hu Dayi, etc. 2002

Study Period: 28 Nov 2006 to 16 May 2007	**Phase of development:** 3

Objectives: The main objective of this clinical trial was to evaluate the change of pulmonary capillary wedge pressure (PCWP) compared with baseline value and the safety of Nesiritide in the treatment of patients with acute decompensate heart failure. Pharmacokinetic study was also performed. The clinical data will be used for registration of Nesiritide in China.

Methodology: The present study was an open-label, uncontrolled, and multi-centered phase III clinical trial for evaluation of the efficacy (clinical efficacy and hemodynamics) and safety of nesiritide. The total duration was 180 days, including a screening phase, an open treatment phase (24 hours in all) and a safety follow-up phase (day 30 and day 180).

Number of Subjects (planned and analyzed): 40

Diagnosis and Main Criteria for Inclusion: All subjects must be at least 18 years old, who present dyspnoea under resting condition due to heart failure and its severity met the requirement of hospitalization and intravenous administration. The systolic blood pressure (SBP) must exceed 90 mmHg. There must be clinical manifestation of increased cardiac perfusion pressure. In addition, PCWP at screening phase and the baseline value must be ≥20 mmHg. Subjects who suffered from known or suspected acute coronary syndrome or cardiac shock within 2 weeks before drug administration, and those who were not tolerant to floating catheter or baseline evaluation because of serious disease condition were excluded.

Test Product, Dose and Mode of Administration, Batch No.: 1.5mg/vial. The investigational drug was administered via infusion pump. Infusion rate was adjusted according to body weight. Batch No. is R0023A.

Reference Therapy, Dose and Mode of Administration, Batch No.: [text]

Duration of Treatment: Step 1: The drug was administered directly via venous cannula or the nearest injection port to the venous cannula for 60 sec. The dosage of nesiritide was 2 μg/kg. Step 2**:** The infusion rate of nesiritide was adjusted to 0.01 μg/kg/min (can not exceed 0.01 μg/kg/min) immediately after nesiritide injection. The duration of nesiritide was 24 h.

Criteria for Evaluation: *(order & subheadings may vary cross-J&J pharma, based on report body content)*

Pharmacokinetics: [if applicable] [text]

Efficacy: The primary endpoint of this study was to evaluate the change of PCWP at 3h compared with baseline value.

Safety: Abnormal cases before and after treatment and its percentage were described in terms of all subjects as well as two subgroups. Averse events were described by case time, case and incidence rate. In addition, inter-group significance test was performed on incidence rate. Meanwhile, manifestation, degree and relationship with the drug of all adverse events were described in details.

SYNOPSIS (CONTINUED)

Pharmacodynamics: [if applicable] [text]

Pharmacokinetic/Pharmacodynamic Relationships: [if applicable] [text]

Pharmacogenomics: [if applicable] [text]

Statistical Methods: Efficacy analysis population: It was consisted of intention-to-treat population and per-protocol population. **Full analysis set (FAS):** Statistical analysis was performed according to intention-to-treat (ITT) principle. The data set was consisted of all included ITT population with evaluation on baseline efficacy. LOCF (Last observation carry forward) principle was applied in subjects who were unable to be followed-up on day 180 for data conversion. **Per-protocol set (PPS):** meant treatment subgroup in which subjects seriously against the protocol were excluded (against the inclusion criteria or exclusion criteria). Efficacy analysis was based on full analysis set and per-protocol set. All baseline demographic data analysis was performed on full analysis set, while safety evaluation was performed on safety set.

SUMMARY - CONCLUSIONS [Cite any study limitations]
(order & subheadings may vary cross-J&J pharma, based on report body content)

Causes of heart failure in 40 patients: 12 cases (30%) of ischemic heart disease, 18 cases (45%) of dilated cardiomyopathy, 4 cases (10%) of hypertension, 5 cases (12.5%) of cardiomyopathy and 1 case (2.5%) of peripartum cardiomyopathy.Among 10 female patients, 9 were of non child-bearing age, so pregnancy test was not performed for them. 1 woman of child-bearing age showed negative results in pregnancy test.NYHA grading: 11 cases were identified as grade III (28%), and 29 cases were identified as grade IV (73%). Cardiac rhythm of the patients: 25 cases (62.5%) of sinus rhythm, 14 cases (35%) of atrial fibrillation, and 1 case (2.5%) of atrial flutter.

PHARMACOKINETICS: [if applicable] [text & table]

EFFICACY RESULTS: PCWP was decreased in 40 patients at all time points after administration of nesiritide (decreased by 18.8%~24.8%), and there was significant difference compared with baseline value ($P<0.001$). The decrease in PCWP was present as early as 15 min after drug administration. It was most significant at 3 h after drug administration (decreased by 7.9 ± 6.5 mmHg) and lasted until 24 h after drug administration (decreased by 8.2 ± 7.5 mmHg). Cardiac index (CI) was increased (by 11%~17.8%), and there was significant difference compared with baseline value ($P<0.01$). The increase was most significant at 15 min (increased by 0.35 ± 0.62 L/min/m^2) and 1 h (increased by 0.29 ± 0.44 L/min/m^2) after drug administration. Both right atrial pressure(RAP) including systolic pressure and diastolic pressure were decreased, and there was significant difference compared with baseline value ($P<0.01$). The decrease was most significant at 24 h after drug administration. Both pulmonary arterial systolic pressure and diastolic pressure were decreased, and there was significant difference compared with baseline value ($P<0.01$). The decrease was most significant at 24 h after drug administration.

SAFETY RESULTS: All adverse events were unrelated with the investigational drug. No hypotension with clinical symptom was observed during the treatment, and there was no death. There were 4 severe adverse events, which were all unrelated with the investigational drug.

PHARMACODYNAMICS: [if applicable] [text]

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: [if applicable] [text]

PHARMACOGENOMICS: [if applicable] [text]

SYNOPSIS (CONTINUED)

CONCLUSION: Intravenous administration of nesiritide for the treatment of acute heart failure can improve hemodynamics, decrease pulmonary wedged pressure, pulmonary arterial systolic pressure and diastolic pressure, increase cardiac index, attenuate dyspnoea, and improve peripheral edema, clinical symptoms and overall clinical efficacy. Meanwhile, it did not cause any severe adverse events in this study.

Date of the report: 6 October 2008

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