2. Synopsis

MERCK RESEARCH LABORATORIES
MK-7418
rolofylline, intravenous
heart failure

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Effects of KW-3902 Injectable Emulsion on Heart Failure Signs and Symptoms, Diuresis, Renal Function, and Clinical Outcomes in Subjects Hospitalized With Worsening Renal Function and Heart Failure Requiring Intravenous Therapy (Reach Up Pilot Study) #303

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (47) in the United States (17), Europe (25) and Russia (5)

PUBLICATION(S): See Appendix 16.1.1

PRIMARY THERAPY PERIOD: 22-Aug-2007 to 29-Sep-2008 (60 day), 26-Jan-2009 (180 Day)

CLINICAL PHASE: III

DURATION OF TREATMENT: The study drug was infused daily over four hours for 3 consecutive days. Study drug was continued for three days, unless the subject was discharged earlier. The last infusion of study drug was completed at least 12 hours prior to discharge.

OBJECTIVE(S): To evaluate the effect of rolofylline, in addition to standard therapy, on the proportion of patients with worsening heart failure and worsening renal function after initiation of therapy through Day 7 or discharge, whichever occurred first; to evaluate the effect of rolofylline, in addition to standard therapy, on the proportion of patients who died or were re-hospitalized for heart failure or worsening renal function over 30 days.

STUDY DESIGN: Multicenter, randomized, double-blind, parallel-group, placebo-controlled. Eligible patients were randomized on Day 1 in a 1:1 ratio to either rolofylline or placebo and infused over 4 hours for 3 consecutive days. Patients then had clinic follow-up visits at Days 7 and 14, and follow-up phone visits at Days 30, 60 and 180. The protocol was intended to enroll two separate phases, the Pilot Phase and the Main Phase. In January, 2008, Merck elected to not conduct the main phase of the study. This report describes the Pilot Phase.

SUBJECT/PATIENT DISPOSITION:

	Placebo	Rolofylline 30mg	Total
RANDOMIZED:	41	36	77
TREATED	40	36	76
Male	PPD		
Female			
Completed Day 60	34	32	66
Completed Day 180	30	27	57
Died (Day 60 Follow-up)	3	3	6
Died (Day 180 Follow-up)	7	5	12
Lost to Follow-up (Day 60 and 180 Follow-up)	0	0	0
Withdrew (Day 60 Follow-up)	1	1	2
Withdrew (Day 180 Follow-up)	1	1	2
Discontinued Due to AE	3	3	6

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-2-

DOSAGE/FORMULATION NOS: The study drug was administered as a 4-hour continuous infusion once daily for three days or until discharge, whichever occurred earlier. Rolofylline (lot number 06P0831) at a dose of 30 mg or placebo (lot number 06PL0111) was given.

DIAGNOSIS/INCLUSION CRITERIA: Male or female subjects, 18 years of age or greater, who provided written, voluntary, informed consent, were hospitalized with heart failure and volume overload, required IV therapy, had experienced worsening renal function within the past 30 days or following hospital admission, had an estimated creatinine clearance between 20-60 mL/min, a BNP >500 pg/mL or NT-pro-BNP >2000 pg/mL, and had a systolic blood pressure ≥90 mmHg at randomization.

EVALUATION CRITERIA:

Efficacy Measurements: Primary: The primary efficacy measure in this study was the proportion of treatment failures within 30 days as defined by any one of the following criteria:

- Death or readmission for heart failure or worsening renal function through 30 days after randomization,

OR

- Worsening symptoms and/or signs of heart failure occurring >24 hours after the start of study drug to Day 7 or discharge, whichever occurred first,

OR

- Worsening renal impairment as defined by an increase in SCr of ≥ 0.3 mg/dL, or the initiation of hemofiltration or dialysis, from the time of randomization to Day 7 or discharge, whichever occurred first.

Secondary: The secondary efficacy measures in this study were the number of days, during the 30 days after randomization, that the subject was alive and out of the hospital, and the change in dyspnea and general well being at Day 2 and Day 4 post-randomization.

Other: Additional exploratory analyses utilized a trichotomous endpoint which categorized the patient as a success (defined as: not a treatment failure and dyspnea reported by the patient using a 7-point Likert scale as moderately or markedly better compared to study start on both Days 2 and 3), unchanged (neither a failure nor a success), or a failure (death from any cause through Day 7, persistent renal impairment defined as either an increase in serum creatinine from Day 1 to Day 7 of ≥ 0.3mg/dL, confirmed on 14 or the initiation of hemofiltration or dialysis through Day 7), and incidence of death or re-hospitalization at 60 days after randomization.

Safety Measurements: All adverse events were monitored and reported during the study treatment period to determine safety. Adverse events were recorded through Day 7. Serious adverse events were recorded through Day 14. Physical examination and laboratory data were also evaluated. Subjects were evaluated for mortality and re-hospitalization by telephone at Days 30 and 60 and for mortality up to 180 days post-randomization.

STATISTICAL PLANNING AND ANALYSIS: The protocol was to enroll two separate phases, the Pilot Phase and the Main Phase. The Pilot Phase was pre-specified to consist of the first 80 patients (40 patients in each study drug group) enrolled into the study with the objective to check assumptions on which the sample size for the Main Phase would be based. The Pilot Phase was not designed to formally test any hypotheses nor was it powered for statistical testing. This report describes the Pilot Phase.

Efficacy: Efficacy endpoints were analyzed using an intent-to-treat (ITT) population, including all treated patients. For analysis purposes, patients were included in the treatment group to which they were randomized.

Primary: For the proportion of patients classified as a treatment failure through Day 30 as defined in the Evaluation Criteria, the treatment effect was quantified using the odds ratio with the associated asymptotic 95% confidence interval, and groups were compared using a chi-square test. The proportion of subjects meeting each of the four failure criteria (death, heart failure readmission, worsening heart failure (after Day 1) through Day 7 or discharge, and worsening renal impairment through Day 7) were described.

Secondary: For the number of days that patients were alive and out of the hospital, treatment groups were compared using the Wilcoxon rank sum test. For the change in dyspnea and general well-being, treatment groups were compared using the t-test.

Analytical methods for other efficacy endpoints are described in Section 9.7.3.

Safety: Safety analyses were conducted using an as-treated population, including patients who received any amount of active study drug and classifying patients by the study treatment they received. The frequency of reported adverse events was summarized by MedDRA preferred term grouped by system organ class. The difference between proportions and associated 95% confidence intervals comparing active treatment with placebo is presented for those events which occurred in 5 or more patients in the combined treatment groups. For laboratory analyses, mean values and mean changes from Day 1 were presented for each treatment group by study day using standard descriptive statistics.

RESULTS:

Efficacy:

Primary: Thirty-three percent (33.3%, 12/36) of patients in the rolofylline 30 mg group and 30.0% (12/40) of patients in the placebo group were treatment failures within 30 days after randomization (odds ratio relative to placebo= 1.17, 95% CI= 0.44 to 3.07).

Parameter	Placebo	Rolofylline 30 mg
Number of Patients in ITT population	40	36
Treatment failure	12 (30.0%)	12 (33.3%)
Treatment failure criteria		
Death through Day 30	3	3
Heart failure readmission through Day 30	3	2
Worsening heart failure through Day 7 or discharge	3	6
Worsening renal impairment through Day 7	6	5

Secondary: The median (interquartile range) number of days alive and out of the hospital through Day 30 was 16.0 (10.5, 21.5) days in the rolofylline 30 mg group and 15.0 (10.0, 21.0) days in the placebo group. The point estimate of the difference between groups was 0 days with a 95% CI= -3 to 4 days. At Day 2, the proportion of patients who reported markedly or moderately better dyspnea scores was 52.8% (19/36) in the rolofylline 30 mg group and 57.5% (23/40) in the placebo group, with mean dyspnea scores of 1.4 for the rolofylline 30 mg group and 1.5 for the placebo group. At Day 4, the proportion of patients who reported markedly or moderately better dyspnea scores was 77.8% (28/36) in the rolofylline 30 mg group and 70.0% (28/40) in the placebo group, with mean dyspnea scores of 1.6 for both groups.

At Day 2, the proportion of patients who reported markedly or moderately better general well-being scores was 58.3% (21/36) in the rolofylline 30 mg group and 55.0% (22/40) in the placebo group, with mean general well-being scores of 1.5 for both groups. At Day 4, the proportion of patients who reported markedly or moderately better general well-being scores was 72.2% (26/36) in the rolofylline 30 mg group and 70.0% (28/40) in the placebo group, with mean general well-being scores of 1.6 for both groups.

Safety:
Rolofylline was generally well tolerated. No seizures were observed in this study. One or more adverse experiences were reported by 15 (58.3%) patients in the rolofylline 30 mg group and 24 (60%) patients in the placebo group. A lower percentage of patients in the rolofylline treated groups (13.9%), compared to the placebo group (22.5%), experienced one or more serious adverse events during the time period from study drug initiation through Day 14. The most common adverse events occurring during the period from study drug initiation through Day 14 by SOC were cardiac disorders, metabolism and nutrition disorders, and investigations.

	Placebo	Rolofylline 30mg	Total
Number of patients in Safety population	40	36	76
Patients with at least one AE	24 (60%)	21 (58.3%)	45 (59.2%)
Patients with no AEs	16 (40.0%)	15 (41.7%)	31 (40.8%)
Patients with at least one AE that Resulted in Study Drug Discontinuation	3 (7.5%)	2 (5.6%)	5 (6.6%)
Patients with at least one SAE	9 (22.5%)	5 (13.9%)	14 (18.4%)
Number of Patients who died by Day 180 *	7 (17.9%)	5 (14.1%)	12 (15.8%)
Note: Only events with an onset after drug initiation are reported. Non-serious AEs were to be reported through Day 7, and all serious AEs through Day 14. Percentages are based on the number of subjects in Safety population * Percentages for patients who died by Day 180 are based on Kaplan-Meier estimates.			

CONCLUSIONS: In adult patients hospitalized with heart failure with volume overload and worsening renal function within the past 30 days or following hospitalization:

1. Rolofylline had no effect on the primary endpoint, treatment failure through Day 30.

2. Rolofylline had no effect on the secondary endpoints, days alive and out of the hospital through Day 30 and improvement of dyspnea and general well-being on Day 2 and Day 4.

3. Rolofylline was generally well tolerated. No seizures occurred during this study.

AUTHORS: