2. Synopsis

MERCK RESEARCH LABORATORIES
MK-7418
rolofylline, Injectable Emulsion
Heart Failure

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Hemodynamic Effects of Rolofylline Injectable Emulsion in the Treatment of Patients With Heart Failure #503

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter study involving 14 centers: four in Germany, three in Poland, two in the United States, two in Israel, one in the Czech Republic, one in Italy and one in Serbia.

PUBLICATION(S): Not applicable

PRIMARY THERAPY PERIOD: 6 November 2008 to 4 March 2009 | **CLINICAL PHASE:** 2

DURATION OF TREATMENT: Patients received a single dose of rolofylline 30 mg or placebo as a 4-hour infusion following randomization, at least 4 hours following insertion of the balloon thermodilution catheter that was to be used for hemodynamic measurements. Ongoing treatment with oral or IV loop diuretics was resumed at the end of the 4-hour infusion with study drug in all patients.

OBJECTIVE(S): The objectives of the study were to estimate the effects of rolofylline, alone and in addition to loop diuretic therapy, on various hemodynamic parameters, renal function and safety in patients with heart failure and renal impairment.

STUDY DESIGN: Multicenter, randomized, double-blind, parallel-group, placebo-controlled. Following a screening period and a baseline period occurring at least 3 hours following insertion of the balloon thermodilution catheter, eligible patients were randomized to receive rolofylline or placebo by infusion. Hemodynamic measurements and other efficacy assessments were performed up to 8 hours post-dosing. Clinical follow-up and assessments of patients' general medical condition continued through to 24 hours after the start of the study drug infusion. Adverse events were recorded through Day 7, and serious adverse events through Day 14.

SUBJECT/PATIENT DISPOSITION:

	Placebo	**Rolofylline 30 mg**	**Total**
ENROLLED AND RANDOMIZED	30	29	59
Male (age range)	25 (25 – 87)	24 (25 – 86)	49 (25 – 87)
Female (age range)	5 (73 – 82)	5 (48 – 84)	10 (48 – 84)
COMPLETED THROUGH TO DAY 7:	30	29	59
DISCONTINUED PRIOR to DAY 7:	0	0	0
Withdrawn	0	0	0
Death	0	0	0
Unable to contact	0	0	0
COMPLETED THROUGH TO DAY 14:	29	28	57
DISCONTINUED BETWEEN DAY 7 and DAY 14:	1	1	2
Withdrawn	0	0	0
Death	1	1	2
Unable to contact	0	0	0
TREATED			
Received the full 4-hour treatment	30	29	59

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-2-

DOSAGE/FORMULATION NOS.: Rolofylline (CCI [redacted]) 30 mg or placebo (CCI [redacted]) was given by continuous infusion over a 4-hour period.

DIAGNOSIS/INCLUSION CRITERIA: Male and female patients 18 years of age or older with heart failure and renal impairment (creatinine clearance between 20-80 mL/min calculated as per the Cockcroft-Gault equation) who required oral furosemide ≥80 mg/day or IV furosemide ≥40 mg/day (or equivalent dose of oral/IV loop diuretic) therapy and at least 12 hours of hemodynamic monitoring in the period after screening, demonstrating stable heart failure therapy (excluding diuretics) for ≥24 hours prior to screening, BNP >500 pg/mL OR NT-pro-BNP > 2000 pg/mL, and a systolic BP ≥95 mmHg.

EVALUATION CRITERIA:

Efficacy measurements: The primary endpoint of this study was the change in pulmonary capillary wedge pressure (PCWP) 4 and 8 hours after initiation of study drug.

Secondary endpoints consisted of change in cardiac output (CO), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), pulmonary artery pressure (PAP) and right atrial pressure (RAP) at 4 and 8 hours after initiation of study drug, as well as change in urine output, fractional excretion of sodium, potassium, urea, uric acid, creatinine, FiO_2, blood pressure (BP), and heart rate (HR) during and after study drug administration, up to 8 hours after initiation of study drug.

Safety measurements: The safety assessments performed during this study included adverse events (AEs), laboratory measurements, physical examination and vital signs. Non-serious AEs were reported from the time informed consent was obtained through Day 7; serious AEs were captured through to Day 14. Neurological AEs including seizures or seizure-like activity were carefully evaluated within the framework of the study by the Neurological Event Team (NET).

STATISTICAL PLANNING AND ANALYSIS:

All statistical tables, listings and analyses were produced using SAS® release 9.1.3.

Efficacy analyses:

All efficacy analyses were conducted using the efficacy evaluable set, defined as all patients treated with study drug for the full 4 hours and with PCWP and CO measures at baseline and Hour 4. Patients were analyzed on the basis of treatment received.

Primary efficacy analysis: The effect of rolofylline alone and in addition to loop diuretic therapy on the changes in wedge pressure was quantified by the least-square (LS) mean of differences between treatment groups and associated two-sided 95% confidence intervals in the changes from study drug initiation to 4 and 8 hours after initiation, respectively. The primary endpoint was analyzed using a longitudinal data analysis (LDA) method proposed by Liang and Zeger (9). The LS mean and associated 95% CI of within or between treatment groups was estimated by the repeated measures model that included terms for treatment, time (baseline, Hour 4, Hour 8), and the interaction of time by treatment.

Secondary efficacy analyses: A similar approach was used to estimate mean changes from baseline and 95% CIs for each treatment group, along with estimates of the differences between treatment groups with associated 95% confidence intervals. No adjustment for multiple comparisons was made to the significance level.

Safety analyses:

All safety analyses were conducted using the safety analysis set, defined as all patients receiving any amount of study drug. Patients were analyzed on the basis of treatment received.

Adverse events: The analyses were limited to those events with a reported onset after the initiation of study drug. Differences between the proportions and associated 95% confidence intervals comparing active treatment with placebo were calculated for those events which occurred in four or more patients within at least one of the treatment groups using the method of Miettinen and Nurminen (12).

Laboratory data: For each parameter analyzed, mean differences between treatment groups with 95% CIs were calculated for each time point using an ANCOVA model including baseline value as a covariate.

RESULTS:

On March 4, 2009, a recommendation was received from the DMC chair to stop the study early, due to

the observation of a small cluster of neurological events in the rolofylline group. As a result, enrollment was halted at 59 patients.

Demographic and baseline characteristics:

The majority of the patients were white, and male. Mean age was 65.3 years, ranging from 25 to 87, with 55.9% of the patients more than 65 years of age. There were no clinically meaningful differences between treatment groups in this regard, nor with regard to other baseline characteristics.

Efficacy:

Primary: As expected in this patient population, pulmonary capillary wedge pressure was elevated at baseline (25.7 mmHg in the rolofylline group and 23.9 mmHg in the placebo group). Small decreases from baseline were observed at four and eight hours following initiation of study drug in both treatment groups, including placebo. The changes from baseline were consistently more pronounced in the rolofylline group, both before and after addition of the IV loop diuretic.

Secondary:

1. Cardiac output: There was no evidence of significant changes within or between treatment groups over the eight hour hemodynamic observation period.
2. Systemic and pulmonary vascular resistance: Changes relative to baseline were small and not clinically relevant. There was little evidence of treatment differences with regard to these parameters during the eight hours hemodynamic observation period.
3. Pulmonary artery pressure (systolic, diastolic and mean): small decreases relative to baseline were observed in all measures at four and eight hours following initiation of study drug in both treatment groups, including placebo. The changes from baseline were consistently more pronounced in the rolofylline group, both before and after addition of the IV loop diuretic.
4. Right atrial pressure: no substantial changes were observed within or between treatment groups.
5. Blood pressure and heart rate: changes relative to baseline were small in both treatment groups, and there was no evidence for any treatment difference during the eight hour hemodynamic observation period.
6. Oxygen saturation: there were no differences observed within or between treatment groups.
7. Urine flow rate increased substantially relative to baseline in the rolofylline group prior to and after addition of loop diuretic, and in the placebo group after addition of the loop diuretic. Differences between treatment groups were observed at both time points (68.2 mL/hr [95% CI: 20.0 to 116.4] at Hour 2 to Hour 4, and 103.0 mL/hr [95%CI: 20.5 to 185.4] Hour 4 to Hour 8).
8. Fractional excretion of sodium and potassium increased from baseline in both treatment groups. A small increase in fractional excretion of uric acid and a small decrease in plasma BUN were observed for the rolofylline group. There was little evidence of any change in plasma creatinine in either group.

Safety:

Exposure to study drug was similar in both treatment groups, with treatment duration and dose close to target (60 mL in 4.0 hours) for the majority of the patients.

Adverse events: Similar proportions of patients experienced one or more adverse events during the study period. Cardiac disorders (mostly congestive heart failure), vascular disorders (mostly hypotension), as well as infections and infestations were the most frequent events, affecting a minimum of four patients in either of the two treatment groups, cardiac and vascular disorders being regarded as disease-related events within the framework of this study. There was no difference between treatment groups in this regard. Seven patients experienced nervous system disorders, mostly in the rolofylline group (five patients) where two patients experienced seizure and two patients a cerebrovascular accident. Seizure was defined as an adverse event (AE) of special interest within the framework of the study. Two patients in the rolofylline group experienced seizure during treatment with study drug. In both cases these events were severe, considered related to study drug, and reported as serious adverse events. Study-drug related events were reported in five patients only: one patient in the placebo group and four patients in the rolofylline group. There was no statistical difference between treatment groups in this regard. Three patients died during the course of the study: two in the placebo group and one in the rolofylline group. In none of these cases was death considered related to study drug. The timing of the deaths ranged from 12 to 30 days after drug treatment. One patient in the rolofylline group discontinued study drug as a result

of an adverse event (SAE).

In summary: the adverse event profile of rolofylline-treated patients was similar to that of patients treated with placebo, except for seizure, which was experienced by two patients in the rolofylline group.

Laboratory parameters

1. Clinical chemistry: changes from baseline in clinical chemistry following initiation of study drug were small and not clinically relevant. Clinical chemistry parameters most frequently exhibiting shift from normal were potassium, magnesium and calcium. There were no notable differences between treatment groups in this regard.
2. Urinalysis: For most parameters, changes from baseline were small and not clinically relevant, with no clear evidence of differences between treatment groups. Changes in sodium appeared to be treatment dependent, increasing by 25.64 mmol/L in the rolofylline group by Hour 8, with a statistically significant treatment difference of 18.60 mmol/L (95% CI: 4.66, 32.55). Treatment difference at Hour 4 was also statistically significant, with a mean difference of 15.47 mmol/L (95% CI: 1.18, 29.76).

In summary: there were no notable differences between groups with regard to changes in clinical chemistry. The small changes in urinalysis that were observed were compatible with an increase in natriuresis, as anticipated based on the postulated mechanism of rolofylline.

CONCLUSIONS:

- Rolofylline appeared to show a trend toward lowering of PCWP
- Rolofylline appeared to be generally well tolerated; however, there were two patients treated with rolofylline who experienced seizure compared to none in the placebo group, which resulted in the study being terminated.

AUTHORS

(Clinical)	(Statistician)	(Clin. Monitor)
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