2. Synopsis

MERCK RESEARCH LABORATORIES MK-7418 rolofylline, IV Congestive 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 and Renal Function in Subjects with Acute Heart Failure Syndrome and Renal Impairment who are Hospitalized for Volume Overload and Require Intravenous Diuretic Therapy. #301-302

PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. For study audit information see [16.1.8].

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter 239 sites Worldwide, 18 countries [16.1.3.1; 16.1.4.1]

PUBLICATION(S):

PRIMARY THERAPY PERIOD: 02May2007 to 23JAN2009. Day 60 Follow-Up completed 23MAR2009; Day 180 Follow-up completed 30JUL2009.	**CLINICAL PHASE:** III

DURATION OF TREATMENT: All patients were treated with active drug or exact match placebo given as a 4-hour intravenous infusion for up to 3 days or until discharge, whichever occurred first.

OBJECTIVE(S): The objectives of this study were to evaluate the effect of rolofylline in addition to intravenous (IV) loop diuretic therapy on heart failure signs and symptoms, persistent renal dysfunction, morbidity and mortality, and safety in subjects hospitalized with acute heart failure syndrome (AHFS), volume overload, and renal impairment, and to estimate and compare within-trial medical resource utilization and direct medical costs between patients treated with rolofylline and placebo.

STUDY DESIGN: Two identical multicenter, randomized, double-blind, placebo-controlled Phase III protocols (301 and 302) were combined to evaluate the effect of rolofylline on acute heart failure syndrome and volume overload. Patients were randomized within 24 hours of presentation to the hospital (including time spent in the emergency department). Patients included those who needed to be hospitalized for AHFS with volume overload and renal impairment and required IV diuretic therapy. Patients were randomized in a 2:1 ratio to either rolofylline 30 mg or placebo through an Interactive Voice Response System (IVRS) stratified by investigative site. The allocation schedule by site can be found in [16.1.7.1] Patients were dosed as soon as possible following randomization, preferably in the morning hours and the study drug was to be given as a 4 hour infusion at approximately the same time each day. Patients were to receive study drug for 3 days or until discharge, whichever occurred sooner, and the study drug was to be administered with at least 15 hours between the conclusion of the previous dose and the start of the next dose. Furosemide IV at a dose of at least 40 mg/day or equivalent was to be given for at least 24 hours after the start of study drug. The dosing and administration of furosemide or equivalent was up to the investigator's discretion. Patients were evaluated daily through Day 6 or discharge and at Days 7 and 14 for signs and symptoms of heart failure, e.g., dyspnea, and renal function. Patients were also evaluated up to Day 7 for adverse events and to Day 14 for serious adverse events. A telephone call was made at Day 60 (for mortality or rehospitalizations) and at Day 180 for mortality.

The studies were overseen by an independent Steering Committee and Data Monitoring Committee (DMC) and regular meetings were held to assess unblinded data. The full details of the membership for both committees can be found in [16.1.4.2; 16.1.4.3] and the operational methodology for the DMC can be found in the charter [16.1.4.4] In general the study would not be stopped for efficacy unless the DMC assessed the mortality data combined from the 301 and 302 protocols showed an overwhelming
benefit, or harm. An independent Clinical Events Committee (CEC) adjudicated all deaths and rehospitalizations to Day 60. The CEC members and the charter can be found in [16.1.4.5; 16.1.4.6]. Two neurologists along with the CEC Chair also classified stroke events in the study after the DMC requested this in October 2008. [16.1.4.7; 16.1.4.8] In addition, a Neurological Event Team (NET) evaluated all seizure and seizure-like events. The flowchart that was provided to sites to determine if an event was to be captured on a NET form can be found in [16.1.4.9]

Audits that were done throughout the course of the study can be found in [16.1.8.1].

SUBJECT/PATIENT DISPOSITION:

	Placebo	Rolofylline 30 mg	Total
Male	452 (66.8%)	912 (67.3%)	1364 (67.1%)
Female	225 (33.2%)	444 (32.7%)	669 (32.9%)
Completed Day 60* Follow Up	610 (90.1%)	1225 (90.3%)	1835 (90.3%)
Died Prior to Day 60	64 (9.5%)	120 (8.8%)	184 (9.1%)
Contacted Prior to Contact Window (Day 55)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Withdrew Prior to Day 60	3 (0.4%)	9 (0.7%)	12 (0.6%)
Lost To Follow Up Prior to Day 60	0 (0.0%)	1 (0.1%)	1 (0.0%)
Completed Day 180 Follow-Up	554 (81.8%)	1101 (81.2%)	1655 (81.4%)
Died Prior to Day 180	117 (17.3%)	241 (17.8%)	358 (17.6%)
Contacted Prior to Contact Window (Day 175)	0 (0.0%)	3 (0.2%)	3 (0.1%)
Withdrew Prior to Day 180	3 (0.4%)	9 (0.7%)	12 (0.6%)
Lost To Follow Up Prior to Day 180	3 (0.4%)	2 (0.1%)	5 (0.2%)

* Phone call made between Day 55 to Day 65 and all events during that period captured.

Data Source: [16.2.7.4]

DOSAGE/FORMULATION NOS.:

Rolofylline 30 mg I.V.

lot #	Merck lot #	manufacturer	manufacture date	expiration date	updated expiration
CCI					

Placebo for Rolofylline I.V.

lot #	Merck lot #	manufacturer	manufacture date	expiration date	updated expiration
CCI					

DIAGNOSIS/INCLUSION CRITERIA: Patients were at least 18 years of age, male or female, with a history of heart failure of at least 14 days in duration for which previous diuretic therapy had been prescribed, and hospitalized for AHFS requiring IV diuretic therapy. Patients had to have at least one of the following at the time of randomization: JVP > 8 cm or pulmonary rales ≥ 1/3 up the lung fields, not clearing with cough or ≥ 2+ peripheral edema or sacral edema. Patients had to be eligible for randomization within 24-hours of presentation to the hospital. In order to be enrolled, there had to be an anticipated need for ≥ 40 mg/day IV furosemide or equivalent for at least 24-hours after the start of study drug. Patients needed to have a systolic blood pressure (SBP) 95 to less than 160 mmHg at randomization, serum potassium >greater than 3.5 mEq/L, BNP of at least 500 pg/mL or NT-pro-BNP of 2000 pg/mL or higher. Patients needed to have estimated creatinine clearance on admission between 20 and 80 ml/min as determined by the Cockcroft-Gault equation.

Patients could not be enrolled if renal impairment was due to contrast nephropathy, or the patient had an oral temperature of 38^{o}C or greater. Patients that had planned or ongoing IV therapy with positive inotropic agents, vasopressors, vasodilators (nitrates were allowed) or mechanical support or dialytic therapies were excluded. The presence of severe pulmonary disease ascertained by use of oral steroids, current use of IV steroids, prior history of carbon dioxide retention or intubation was a reason for exclusion. Patients with acute coronary syndromes within 2 weeks and those with arrhythmias as the cause of the heart failure were also not eligible. Patients treated with potent CYP3A4 inhibitors such as ketoconazole were excluded.

Due to the concern that adenosine A1 antagonists lower the seizure threshold and the observation of seizures in Phase 2 studies, an approach was taken to exclude patients at high risk for seizures and to treat those with an intermediate risk with a benzodiazepine. Reasons for exclusion due to high risk for seizures were: history of seizures (except febrile seizures), stroke within 2 years, history of or current brain tumor, brain surgery within 2 years, encephalitis or meningitis within 2 years, any history of penetrating head trauma, a closed head injury with loss of consciousness (LOC) over 30 minutes within 2 years, history of drug or alcohol abuse, advanced Alzheimer's disease or multiple sclerosis. Patients with the following clinical conditions were considered at intermediate risk and were treated with 1 mg lorazepam (or clonazepam if lorazepam not available) 30 minutes prior to the start of each dose of blinded study medication: history of stroke greater than 2 years, brain surgery, meningitis or encephalitis ≥ 2 years; closed head injury with LOC < 30 minutes or LOC greater than 30 minutes if ≥ 2 years and serum sodium < 128 mM within 24 hours prior to randomization. In addition, patients taking medications known to lower the seizure threshold such as neuroleptics, antidepressants, and antihistamines were also treated with lorazepam (see protocol for more details [16.1.1]) prophylatically.

If a subject required administration of lorazepam or clonazepam, then it was given with all subsequent doses of study drug. The investigator could reduce the dose to 0.5 mg if an unacceptable level of sedation was seen with the 1 mg dose.

EVALUATION CRITERIA:

EFFICACY:

PRIMARY ENDPOINT: The primary endpoint was a three category, ordered outcome of treatment success, patient unchanged, or treatment failure based on the following definitions:

- Treatment Success: (determined at 24 and 48 hours after the start of study drug [Days 2 and 3] or the day of discharge if earlier):
  - Dyspnea reported by the patient using the 7 point Likert scale as moderately or markedly better compared to study start, AND
  - Not a treatment failure
- Patient Unchanged: Neither treatment success or treatment failure
- Treatment Failure (includes any of the following criteria):

  - Death or Readmission for heart failure any time through Day 7; OR

  - Worsening symptoms and/or signs of heart failure occurring greater than 24 hrs after the start of study drug to Day 7 or discharge, whichever occurs first, such that there is a need for any one of the following types of "rescue therapy":
    - An increase in the dose or reinstitution of IV loop diuretic therapy, or initiation of oral metalazone or IV chlorothiazide as accompanying therapy to loop diuretic, or
    - Initiation of ultrafiltration, or
    - Initiation of IV positive inotropes, vasopressors, or IV vasodilators, or
    - Initiation of mechanical ventilatory (including BiPAP or CPAP) or circulatory support), or

  - Persistent renal impairment as defined as serum creatinine (SCr) increase of 0.3 mg/dL or greater from randomization to both Day 7, and Day 14, or the initiation of hemofiltration or dialysis through Day 7

SECONDARY ENDPOINT: The secondary endpoints were:

(1) Time to death or rehospitalization for cardiovascular or renal causes through Day 60

(2) The proportion of patients with persistent renal impairment as defined by a SCr increase of at least 0.3 mg/dL from randomization to both Day 7 and Day 14, or the initiation of hemofiltration or dialysis through Day 7, or death through Day 7.

SAFETY:

Monitoring and reporting of adverse events (AEs) that occurred during the study treatment period were used to assess patient safety. AEs were recorded through Day 7. Serious adverse events (SAEs) were recorded through Day 14. Disease related events (DRE) were pre-specified adverse events that were expected for the condition. These events adhered to all for the characteristics and reporting procedures that applied to AEs/SAEs. However, if an SAE was also a DRE, then narratives were not created unless the DRE was considered to be drug related by the investigator or resulted in death. With the exception of the narrative in cases of non-drug related, non-fatal DREs, all other DRE information was captured on the CRFs in the same manner as AEs and SAEs. Further safety assessments included physical examinations and laboratory data. Patients were evaluated for re-hospitalization and mortality after discharge by telephone at Day 60 and mortality at Day 180 after randomization. AEs of seizure or similar terms were closely monitored as adenosine A1 receptor antagonists like rolofylline are known to lower the seizure threshold, so a seizure mitigation plan was implemented for patients deemed at risk. This plan required prophylactic lorazepam (or clonazepam) 1.0 mg given orally approximately 30 minutes prior to each dose of study drug initiation. For a complete list of medical conditions that require lorazepam co-administration, refer to the Protocol [16.1.1]. Sites were to obtain detailed neurological assessment in cases where seizure was suspected. This could include neurological consultation and imaging or other testing of patients with suspected seizures. If a patients was suspected to have a seizure, sites would complete a detailed questionnaire related to seizures and this would then be sent to an independent neurologist who reviewed the data and made an assessment of whether the reported event was a seizure or not.

STATISTICAL PLANNING AND ANALYSIS: The two individual studies, protocol 301 and protocol 302 were pre-planned to be combined for the purposes of the analysis in the main study phase as discussed in this report.

EFFICACY:

All efficacy endpoints were evaluated in the intent-to-treat population. The effectiveness of rolofylline on the primary clinical composite endpoint was evaluated in the combined studies at a two-sided 0.00125 significance level. The planned sample size of 2,000 patients provided approximately 90% power at the two-sided 0.00125 significance to detect a difference between a distribution of 25% failure, 34% unchanged and 41% success in the rolofylline group vs. 33% failure, 35% unchanged and 32% success in the placebo group. Additionally, to declare significance 2-sided P-values for each study $\leq$0.20 were required. If the primary endpoint was achieved, the two secondary endpoints were to be tested and declared statistically significant at a nominal two-sided 0.05 level. The study design provided approximately 95% power at the two-sided 0.05 significance level to detect a hazard ratio of 0.74. The study had approximately 95% power at the two-sided 0.05 significance level to detect a 33% relative reduction in the rate of persistent renal impairment.

The treatment groups were compared on the primary endpoint using the van Elteren extension of the Wilcoxon test, stratified by study and region (Region 1: North America, Western Europe, Israel; Region 2: Central and Eastern Europe and Argentina). The odds ratio and 95% confidence interval for the treatment effect were determined from an ordered logistic regression (proportional odds) model that included terms for the effects of treatment, study, and region. Given the parameterization (-1=failure, 0=unchanged, 1=success), an odds ratio <1.0 would favor active treatment.

For the secondary endpoint of time to death from any cause or rehospitalization for cardiovascular or renal causes through day 60, the treatment groups were compared using a Cox regression model that included treatment as an explanatory variable and study-by-region as strata. The relative risk was expressed as a hazard ratio (HR) with a 95% confidence interval and was calculated using the Cox model. Cumulative event rates were calculated using the Kaplan-Meier method. The proportion of subjects with persistent renal impairment was analyzed using a Cochran-Mantel-Haenszel test stratified by study and region.

SAFETY:

Safety and tolerability were assessed by statistical and/or clinical review of all safety parameters, including adverse experiences and changes in laboratory values. Differences between treatment groups in the proportion of patients with adverse experiences were assessed by 95% confidence intervals using the Miettenen and Nurminen method for AEs that occurred in 5 or more patients combined across treatment groups. Changes from baseline in laboratory values were analyzed using analysis of variance models with treatment as a factor.

Detailed statistical approaches to efficacy and safety analyses are described in the protocol and the statistical considerations memo. [16.1.9.1]

RESULTS: PATIENT CHARACTERISTICS

- The baseline demographics of the 2 groups in the ITT population were similar with 95% of the population in each treatment group being Caucasian, approximately 2/3 of each treatment group was male, and the mean age in each treatment group was approximately 70 years old. By design, patients had elevated BNP or NT-pro-BNP values measured at the bedside or obtained through the local clinical laboratory. The majority of patients were treated with IV loop diuretics during their hospitalization with 97.8% of the placebo treatment group and 98.0% of the rolofylline treatment group receiving at least one dose of diuretic therapy. The median dose of IV diuretics given was similar in both treatment groups overall from randomization through Day 7 (or discharge if earlier). Table 10, 11, 12 in [16.2.7.4].
- Concomitant medications between presentation and randomization were similar in both treatment groups with the most common concomitant medications being: ACE inhibitors (59.3% and 59.6%) ACE inhibitors or ARB (69.8% and 70.5%), beta blockers (70.0% and 67.8%) and aldosterone inhibitors (46.1% and 46.1%) in the placebo group and rolofylline treatment groups respectively. Table 15.2 in [16.2.7.4].

RESULTS: PHARMACOKINETIC

- A subset of plasma samples from patients from PROTECT (both pilot phase and main phase) were analyzed for pharmacokinetic (PK) parameters and compared with that of normal healthy subjects. [16.1.11.2] The average area under the curve (AUC) and Cmax from these studies were moderately reduced relative to corresponding values from normal healthy subjects.
- A full PK analysis can be found in [16.1.11.1].

RESULTS: EFFICACY

- The primary hypothesis of the study, that rolofylline 30 mg will provide a favorable shift in the distribution of the composite endpoint of success, unchanged, failure compared to placebo, was not met. There were more successes, but also more failures in the rolofylline 30 mg group compared to the placebo group (p=0.348). The odds ratio (95% CI) was 0.92 (0.78, 1.09). The results are summarized in the table below (Table 2-1), and more detailed information including reasons for failure, are displayed in Table 2-2.

Table 2-1

Primary Efficacy Endpoint
ITT Population

	Success n (%)	Unchanged n (%)	Failure n (%)	Total
Rolofylline 30 mg	551 (40.6)	509 (37.5)	296 (21.8)	1356
Placebo	244 (36.0)	299 (44.2)	134 (19.8)	677

- In addition, as pre-specified in the protocol, tests of the composite endpoint of success, unchanged, and failure were performed for each protocol. For protocol 301, the odds ratio (95% CI) was 0.83 (0.65, 1.06) and the p=0.138; for protocol 302 the odds ratio (95% CI) was 1.02 (0.80, 1.30) and p=0.877.

- The primary efficacy endpoint was analyzed to assess the possible modifiers of the treatment effect, including region, gender, age (≤70, >70 years), race, ethnicity, benzodiazepine use, ejection fraction (<40%, ≥40%), serum creatinine (< median, ≥ median), NYHA class prior to hospitalization (I/II, III, IV), creatinine clearance (<30 ml/min, 30-<60 ml/min, 60-<80 ml/min, ≥80 ml/min). The results of comparing rolofylline to placebo across these pre-specified subgroup analyses were generally consistent with the results of the primary efficacy analysis. Please see Tables 19.1 to 19.10 [16.2.7.4]

- A planned sensitivity analysis of the primary endpoint which treated the dyspnea assessment as missing for patients who had the assessment form translated from English to their native language at the bedside by the medical professional administering the assessment gave a similar result to the primary analysis [16.1.9.1]

Table 2-2

Primary Efficacy Endpoint and Components
ITT Population

	Placebo	**Rolofylline 30 mg**
Number of patients in the ITT population	677	1356
Primary Endpoint		
N	677	1356
Treatment Success	244 (36.0%)	551 (40.6%)
Patient Unchanged	299 (44.2%)	509 (37.5%)
Treatment Failure	134 (19.8%)	296 (21.8%)
P-value (vs. placebo)*		0.348
Odds ratio relative to placebo (95% CI)**		0.92 (0.78, 1.09)
Treatment Failure Criteria***		
Death through Day 7	14 (10.4%)	23 (7.8%)
Heart Failure readmission through Day 7	4 (3.0%)	5 (1.7%)
Worsening HF (after Day 2) through Day 7 or Discharge	66 (49.3%)	123 (41.6%)
Persistent Renal Impairment	75 (56.0%)	172 (58.1%)
Serum Creatinine Increase from Baseline of at least 0.3 mg/dL at Day 7 and confirmed at Day 14	72 (96.0%)	167 (97.1%)
Initiation of hemofiltration or dialysis	6 (8.0%)	6 (3.5%)

Data Source [16.2.7.4]

* Analysis performed using the van Elteren extension of the Wilcoxon test with stratification by study and region (North American/Western Europe [UK, Sweden, Germany, France, Belgium, Netherlands, and Italy]/Israel versus Russia/ Central & Eastern Europe/ Argentina)

** From the proportional odds model that included terms for the effect of treatment, study and region. Parameterization of outcome: -1, 0, +1 for failure, unchanged, success, respectively.

*** Percentages for each treatment failure criteria are based on patients who are treatment failures, except for reasons for persistent renal impairment where percentages are based on the number of patients with persistent renal impairment. Also, patients could be counted twice as failures if they met more than one failure criteria.

Secondary endpoint – Death or cardiovascular or renal rehospitalization

- The secondary hypothesis of the study, that rolofylline 30 mg will reduce the risk of death or cardiovascular or renal rehospitalization through Day 60 compared to placebo, was not met. Three hundred and eighty-six of 1356 (Kaplan-Meier (KM) rate=30.7) patients in the rolofylline 30 mg group and 195 of 677 (KM rate=31.9) patients in the placebo group had at least one event by Day 60 (hazard ratio=0.98, 95% CI=0.83 to 1.17, p=0.861). The results are displayed in Table 2-3.

Secondary endpoint – Persistent renal impairment

- The secondary hypothesis of the study, that rolofylline 30 mg will reduce the incidence of persistent renal impairment compared to placebo, was not met. Fifteen percent (15.0%, 195/1297) of patients in the rolofylline 30 mg group and 13.7% (88/644) of patients in the placebo group had persistent renal impairment (odds ratio relative to placebo= 1.11, 95% CI= 0.85, 1.46, p=0.441). The results are displayed in Table 2-4.

Analyses of full analysis set population for the primary and secondary endpoints were consistent with those described above.

Additional Analyses

There were several other pre-planned analyses as listed below. See the protocol for full definitions [16.1.1]:

- Proportion of Successes Based on Subject-Reported Dyspnea through Day 7
- Time to Treatment Success through Day 7
- Time to Death from any Cause or Rehospitalization for Heart Failure through Day 60
- Time to Death from any cause or Rehospitalization for any Reason through Day 60
- Proportion of failures through Day 7
- Time to Achieving Treatment Success Defined by Subject Reported Dyspnea and Treatment Success determined by the investigator through Day 7
- Proportion of Subjects with Worsening Heart Failure through Day 7
- Time to Worsening Heart Failure
- Time to the First serum creatinine increase of 0.3 mg/dL or higher above baseline through baseline

- Time to the First Serum Creatinine increase of 25% or higher above baseline through Day 7
- Proportion of Subjects with Increases in Serum Creatinine of 0.2, 0.3, 0.4, and 0.5 mg/dL or higher at any time from Randomization through Day 14
- Proportion of Subjects with Increases in Serum Creatinine of 20, 30, 40 and 50% at any Time from Randomization through Day 14
- Changes from baseline in Heart Failure Signs and Symptoms on Day 2 through Day 7
- Total Dose if IV Loop Diuretics from Randomization through Day 7 or Discharge if Earlier
- Change in Serum Creatinine and BUN from Randomization to Days 2 through 6 or Discharge, whichever comes first, and to Day 7 and Day 14
- Length of Hospital Stay (hours) from start of first study drug dose
- Time to Death through Day 180
- Days Alive and Out of Hospital through Day 60

Results of the pre-planned additional analyses were generally consistent with that of the primary and secondary endpoints with no significant differences observed between placebo and rolofylline.

Summary of Key Safety Results

The number of subjects with at least one adverse experience (AE), serious AE (SAE), cardiac disorder, and nervous system disorder and the associated MedDRA preferred terms for cardiac and nervous system disorders are provided. Within the nervous system disorder class, the number of subjects with at least one seizure AE and the number of subjects with at least one stroke/cerebrovascular accident AE are provided.

Adverse Event Summary

- Sixty-three percent (62.9%, 840/1336) of subjects in the rolofylline 30 mg group and 61.4% (409/666) of subjects in the placebo group had at least one AE (difference in percentages= 1.5%, 95% CI= –3.0% to 6.0%).
- Fourteen percent (13.8%, 185/1336) of subjects in the rolofylline 30 mg group and 14.7% (98/666) of subjects in the placebo group had at least one SAE (difference in percentages= –0.9%, 95% CI= –4.3% to 2.3%).
- Twenty percent (20.4%, 272/1336) of subjects in the rolofylline 30 mg group and 23.1% (154/666) of subjects in the placebo group had at least one Cardiac Disorder AE (difference in percentages= –2.8%, 95% CI= –6.7% to 1.0%).
- Eight percent (7.9%, 106/1336) of subjects in the rolofylline 30 mg group and 6.6% (44/666) of subjects in the placebo group had at least one Nervous System Disorder AE (difference in percentages= 1.3%, 95% CI= –1.2% to 3.6%).

- Less than one percent (0.8%, 11/1336) of subjects in the rolofylline 30 mg group and no subjects (0/666) in the placebo group had Seizure AEs (difference in percentages= 0.8%, 95% CI= 0.3% to 1.5%) as defined by the MedDRA dictionary terms of 'convulsion' and 'seizure'. Seizure events are listed in Table 2-6. The seizure mitigation plan was implemented prior to the start of the PROTECT protocols, and there were 11 total seizures in the combined studies, with all seizures occurring in patients randomized to rolofylline. Of the total seizures that occurred, 2 patients met the criteria for pre-dosing with lorazepam, and were pre-dosed. All other patients did not meet the pre-specified criteria for lorazepam dosing as defined in the Protocol [16.1.1].
- One percent (1.2%, 16/1336) of subjects in the rolofylline 30 mg group and less than one percent (0.5%, 3/666) of subjects in the placebo group had at least one stroke/cerebrovascular accident AE (difference in percentages= 0.7%, 95% CI= -0.2% to 1.6%) as defined by the MedDRA dictionary terms of 'cerebral infarction', 'cerebrovascular accident', 'hemorrhage intracranial', 'hemorrhagic stroke', 'spinal cord infarction', 'transient ischemic attack', 'cerebral hematoma', and 'embolic cerebral infarction'. The strokes were adjudicated and are classified by ischemic or hemorrhagic. The full listing of adjudicated stroke events can be found in Table 2-5. Narratives on the patients who experienced strokes and seizures, as well as serious adverse events (SAE) are found in [16.2.7].
- The summary of Cardiac Disorder and Nervous System Disorder AEs by body system and preferred term is displayed in Table 2-7. The complete AE by body system table can be found in [16.2.7.4]

Table 2-3

Secondary Efficacy Endpoint: Death or Cardiovascular or Renal Rehospitalization through Day 60
ITT Population

	Placebo	Rolofylline 30 mg
Number of patients in the ITT population	677	1356
Number of patients who died or who were rehospitalized for a cardiovascular or renal reason***	195	386
Kaplan Meier estimates of event rates (95% CI)		
By 7 Days	2.8 (1.6; 4.1)	2.4 (1.6; 3.2)
By 14 Days	7.1 (5.2; 9.1)	7.3 (5.9; 8.7)
By 30 Days	16.2 (13.4; 19.0)	16.1 (14.2; 18.1)
By 60 Days *	31.9 (27.4; 36.4)	30.7 (27.8; 33.6)
Hazard ratio through Day 60* (95% CI) relative to Placebo **		0.98 (0.83; 1.17)
P-value		0.861
Number of patients who were rehospitalized for a cardiovascular or renal reason***	146	302
Kaplan-Meier estimates of event rate (95% CI)		
By 60 Days*	25.6 (21.3; 29.8)	25.7 (22.9; 28.5)
Number of patients who died***	64	120
Kaplan Meier estimates of event rate (95% CI)		
By 60 Days)*	9.5 (7.3; 11.7)	8.9 (7.4; 10.4)

Data Source: [16.2.7.4]
Rehospitalizations classified by the Clinical Events Committee (CEC)
* The visit window around the Day 60 telephone contact was Day 60 +/- 5 days. At a subject level, the first event that occurred up to and including relative Day 65 was included in the analysis. Patients without an event were censored at the earlier of the Day 60 contact or relative Day 65.
** From Cox proportional hazards regression model with treatment effect as explanatory variable and study-by-region as strata.
***The total number of patients who died, or were rehospitalized for a cardiovascular or renal reason does not add up to the sum of the parts due to the fact that a patient could be counted twice.

Table 2-4

Secondary Efficacy Endpoint: Persistent Renal Impairment
ITT Population

	Placebo	Rolofylline 30 mg
Number of Patients in ITT population	677	1356
Number of patients with available data	644	1297
Number of patients (%) with persistent renal impairment	88 (13.7%)	195 (15.0%)
Odds Ratio relative to Placebo* (95%CI)		1.11 (0.85; 1.46)
Cochran-Mantel-Haenszel test*		
P-value		0.441

Data Source [16.2.7.4]

Note: Persistent renal impairment is defined by a serum creatinine (SCr) increase of at least 0.3 mg/dl from randomization to Day 7 confirmed at Day 14, or the initiation of hemofiltration or dialysis through Day 7. Patients who died by Day 7 are considered as having persistent renal impairment. Percentages are based on the number of available observations.
* Stratified by study and region.

Table 2-5

Adjudicated Stroke Events Through Day 60

Placebo Treatment Group				
Patient ID	**Gender**	**Age**	**Onset Day**	**Adjudicated Term**
PPD			3	Fatal ischemic stroke, cryptogenic
			8	Non fatal neither stroke nor TIA
			4	Fatal ischemic stroke, cardioembolism
			56	Non-fatal ischemic stroke, cryptogenic
Rolofylline Treatment Group				
PPD			5	Fatal hemorrhagic stroke
			14	Non-fatal ischemic stroke cryptogenic
			34	Fatal ischemic stroke, cardioembolism
			34	Non-fatal stroke, unknown mechanism
			3	Non-fatal ischemic stroke, cardioembolism
			49	Fatal ischemic stroke, thrombotic large artery
			10	Fatal hemorrhagic stroke
			10	Non-fatal hemorrhagic stroke
			8	Fatal ischemic stroke, cryptogenic
			8	Fatal ischemic stroke, cryptogenic
			3	Non-fatal TIA
			3	Non-fatal ischemic stroke cryptogenic
			8	Non-fatal stroke, unknown mechanism
			37	Non-fatal ischemic stroke, cardioembolism
			1	Fatal ischemic stroke, cryptogenic
			4	Non-fatal hemorrhagic stroke
			33	Non-fatal ischemic stroke, thrombotic small artery
			9	Fatal hemorrhagic stroke
			4	Non-fatal ischemic stroke, cardioembolism
			40	Fatal hemorrhagic stroke
			2	Non-fatal neither stroke nor TIA
			14	Fatal ischemic stroke, cardioembolism
			5	Non-fatal ischemic stroke, cardioembolism

Data Source: [16.2.7.4]

Table 2-6

Seizure Events
Rolofylline Treatment Group

Patient ID	Gender	Age	Onset Day	Received benzodiazepine?	Seizure Confirmed by Adjudication
PPD			1	N	Yes
			5	N	No, transient cerebral hypoxia
			10	N	Yes
			8	Y	Yes
			3	N	No, TIA
			3	N	Yes
			2	N	Yes
			1	N	Yes
			6	N	Yes
			2	N	Yes
			3	N	Yes

Data Source [16.2.7.4]

Table 2-7

Adverse Events (highlighted SOC only) through Day 14 (Occurring at 1.0% or Higher in At Least One Treatment Group)
Safety Population

	Placebo	Rolofylline 30 mg	Total	Difference in Proportions (95% CI)**
Number of Patients in Safety population	666	1336	2002	
Patients with at least one AE	409 (61.4%)	840 (62.9%)	1249 (62.4%)	1.5 (-3.0; 6.0)
Total AEs	961	2089	3050	
CARDIAC DISORDERS	154 (23.1%)	272 (20.4%)	426 (21.3%)	-2.8 (-6.7; 1.0)
Atrial Fibrillation*	7 (1.1%)	15 (1.1%)	22 (1.1%)	0.1 (-1.1; 1.0)
Bradycardia*	3 (0.5%)	16 (1.2%)	19 (0.9%)	0.7 (-0.2; 1.6)
Cardiac Failure Acute*	16 (2.4%)	16 (1.2%)	32 (1.6%)	-1.2 (-2.8; -0.0)
Cardiac Failure Congestive *	71 (10.7%)	122 (9.1%)	193 (9.6%)	-1.5 (-4.5; 1.2)
Cardiac Failure*	11 (1.7%)	19 (1.4%)	30 (1.5%)	-0.2 (-1.6; 0.9)
Cardiogenic Shock	7 (1.1%)	7 (0.5%)	14 (0.7%)	-0.5 (-1.7; 0.2)
Ventricular Tachycardia*	29 (4.4%)	39 (2.9%)	68 (3.4%)	-1.4 (-3.4; 0.2)
NERVOUS SYSTEM DISORDERS	44 (6.6%)	106 (7.9%)	150 (7.5%)	1.3 (-1.2; 3.6)
Dizziness	13 (2.0%)	25 (1.9%)	38 (1.9%)	-0.1 (-1.6; 1.1)
Headache	17 (2.6%)	33 (2.5%)	50 (2.5%)	-0.1 (-1.7; 1.3)

Data Source: [16.2.7.4]
Note: Percentages are based on the number of patients in the safety population.
Only events with an onset after study drug initiation are reported. Non-serious AEs were to be reported through Day 7, and all Serious AEs (SAEs) were to be reported through Day 14.
*Disease Related Event (DRE)
**The 95% Confidence Interval (CI) is based on the Miettenen and Nurminen method.

DISCUSSION:

Rolofylline was believed to have a renal protective effect in acute heart failure because of its adenosine A1 receptor blocking actions. If this unique renal benefit could be provided to patients with acute heart failure, then it was believed likely that patients would experience improvements in subsequent outcomes. This translation of renal benefit into more general clinical benefit was based on the robust epidemiological data linking worsening renal function during hospitalization with acute heart failure to short and long term morbidity and mortality.

Efficacy:

Primary trichotomous endpoint: The overall distribution of the response to treatment with rolofylline compared to placebo was not significantly shifted in a favorable direction. Nevertheless, there was a small increase in the proportion of successes but a nearly equal relative increase in patients classified as failures. The results of comparing rolofylline to placebo across subgroup pre-specified in the protocol and the statistical considerations memo were generally consistent with the results of the primary efficacy analysis. The subgroup results of are shown in [16.2.7.4]

Components of "success" and "failure:" Rolofylline appeared to increase the chance of success, a measure driven by improvement in dyspnea as reported by the patient in the absence of any failure criteria. Dyspnea improvement compared to study start that was moderately or markedly improved was observed in more patients on rolofylline. Rolofylline treated patients tended to have less heart failure-related failure criteria during the first 7 days after hospitalization (worsening heart failure, heart failure readmissions, and death), though there were a small number of events to compare. However, other measures of renal dysfunction (persistent renal impairment and serum creatinine increases at Days 7 and 14) occurred more frequently on rolofylline.
Despite a similar rate of success in the PROTECT main study compared to the Pilot, fewer patients in the main study on placebo experienced failure. Also, unlike the pilot study, the mean changes in creatinine from baseline to day 7 and 14 were similar in rolofylline and placebo groups in the larger PROTECT study. It is unclear why fewer patients would experience failure in the main study.

Secondary endpoints

Time to death or cardiovascular or renal rehospitalization: Rolofylline compared to placebo did not reduce the risk of death or cardiovascular or renal rehospitalization through Day 60 compared to placebo. Analyses of this endpoint for pre-specified subgroups were generally consistent with the effect observed in the full analysis. The fact that rolofylline did not prevent worsening of renal function in patients with acute decompensated heart failure may have contributed to the lack of an effect of rolofylline on the risk of death and rehospitalization at 60 days.
Proportion of patients with persistent renal impairment: Rolofylline compared to placebo did not reduce the incidence of persistent renal impairment. However, there was evidence of a diuretic effect in the group of patients treated with rolofylline. On average, patients receiving rolofylline experienced more weight loss over the first 4 days compared to placebo. This difference occurred despite the rolofylline group receiving an average dose of total IV loop diuretic to Day 7 or discharge that was similar to that for patients on Placebo.

That rolofylline had no effect to reduce the risk of renal function deterioration was surprising in view of the strong pre-clinical, data in healthy humans and 3 studies in populations that were very similar to the PROTECT main population.

Pre-clinical data: Mechanistic studies in small and large animal species showed that rolofylline could provide advantages for renal function through the inhibition of tubulo-glomerular feedback and renal vasodilation.

Phase 2 studies:

Protocol 203: Additional data was obtained in a study of ambulatory patients with heart failure. In this protocol [16.1.12.2], 32 patients with estimated GFR of 30-80 mls/min were randomized to receive a single dose rolofylline 30 mg iv or placebo over 2 hours in a cross over design. All subjects received furosemide 80 mg IV 30 minutes into the infusion. Renal function and blood flow were carefully measured with iothalamate and para-amino-hippurate. Rolofylline caused a marked increase in both GFR and renal blood flow (32 and 48% respectively) compared to placebo. In this study there was also a suggestion that the single dose of rolofylline had a clinical effect well beyond its PK as patients who initially received rolofylline and who returned on average 6 days later for the placebo had about a 9 mls/min higher GFR than baseline.

These results were also consistent with data from the diuretic resistant protocol and the dose ranging phase 2 studies. In the diuretic resistant protocol, 35 patients with advanced heart failure with impaired renal function who were deemed diuretic resistant were randomized to a single infusion of placebo or rolofylline 10 mg, 30 mg or 60 mg. While those receiving placebo experienced reductions in urine output, those receiving rolofylline experienced increased urine flow and also estimate creatinine clearance. Protocol 202 [16.1.12.1]

In the Phase 2 study of 146 patients with acute heart failure, volume overload and renal impairment (creatinine clearance 20-80 mls/min), patients were randomize d to receive rolofylline at doses of 2.5 mg to 60 mg or placebo infused over 2 h for up to 3 days. Rolofylline monotherapy resulted in statistically significant increases in urine output during the first 6 hours compared to placebo. This effect was most marked at the 30 mg dose. Protocol 203 [16.1.12.2]

Lastly, in the pilot phase of the Phase 3 PROTECT trial, there were important confirmatory evidence of these potential beneficial effects on renal function, clinical status and 60 day outcomes. [16.1.12.3]

Despite this initial set of studies, rolofylline did not have the expected benefit in the larger Phase 3 trial. The possible factors that could have resulted in lack of an effect of rolofylline on renal function include 1) the changes in renal hemodynamics seen in prior human studies are transient and do not confer renal protection out to Day 14, 2) the renal hemodynamic changes were not of the magnitude (either too high or too low) that would provide renal protection, and 3) the lack of importance of adenosine in maintaining renal function when there is intense renin-angiotensin system blockade.

Demographics in this population were fairly similar to other large heart failure studies and similar to the Pilot study. It is unclear why fewer patients experienced persistent renal impairment in the main study and why the mean change from baseline in creatinine at Day 7 and Day 14 were much less compared to the Pilot. A suggested factor in the development of persistent renal impairment is the dose of IV loop diuretics, as well as the intensity of diuresis, but the dose of IV loop diuretics to Day 7 or discharge was similar in the 2 groups.

SAFETY:
Rolofylline given via a 4 hour infusion per dose for 3 days was overall well tolerated with similar incidences of adverse events in the 2 arms of the study for the majority of system organ classes.
Overall AEs: Slightly more patients in the placebo arm experienced adverse events compared to those receiving rolofylline. The proportion of placebo patients experiencing cardiac events was slightly greater than that of the rolofylline group. Given the theoretical concerns that adenosine is cardio-protective in ischemia and an adenosine antagonist could be potentially harmful, this result was reassuring. Slightly more rolofylline patients had neurological AEs. When examining types of neurological AEs, there was a numerically higher proportion of patients on rolofylline who experienced a stroke event. This imbalance was seen across all types of strokes (ischemic and hemorrhagic) with no clear explanation especially since the imbalance was seen in etiologically different strokes. [16.2.7.3; 16.2.7.2]

As expected, the frequency of seizures in the rolofylline group was higher than in the placebo group with all seizures actually being in patients on rolofylline. However, in general, the patients who experienced seizure were found after the event to have had underlying disorders that predisposed them to seizure and if recognized, would have resulted in either exclusion or pretreatment with benzodiazepine. All but one of these patients had not received prophylaxis. In summary, the seizure mitigation approach was generally successful. [16.1.11.3]
SAEs: A slightly greater proportion of placebo patients experienced serious adverse events. [16.2.7.1]

Conclusion: The study demonstrated that rolofylline infused over 4 hours for up to 3 days in patients hospitalized with AHFS with concomitant renal dysfunction did not significantly alter the distribution of patients classified by a 3 category ordered endpoint of the response to treatment as a success, failure or unchanged. Rolofylline also did not improve the likelihood of death or cardiovascular or renal rehospitalization to Day 60 and rolofylline did not prevent worsening renal function. The risk of seizure was confirmed but effectively mitigated by pre-treatment with benzodiazepine. A slightly higher incidence of strokes of all types in the rolofylline treated group was noted and remains unexplained.

The primary authors signature page can be found in [16.1.5.1]

AUTHORS

PPD