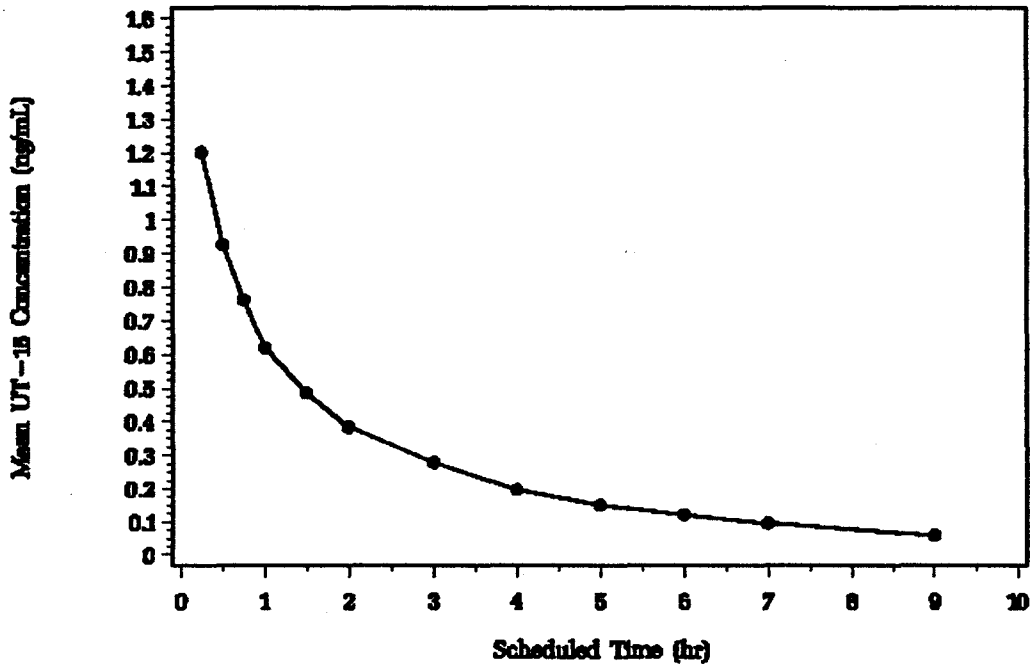
Plasma clearance values for all of the four doses ranged from , supporting the linear kinetics over the dose range used. The terminal T ½ determined after termination of the 15 ng/kg/min infusion was 2.93 hours. Inter-subject variability of Css,CL and T ½ ranged from 13.6 – 25.5%. The mean concentration-time data after the end of the infusion is shown below.

Plots of Mean UT-15 Concentration-Time Data After End of Last Infusion



SPONSOR'S CONCLUSIONS: Over a 24-hour steady state period, plasma UT-15 concentrations achieved peak levels twice (at 1 a.m. and 10 a.m., respectively) and achieved trough levels twice (at 4 p.m. and 7 a.m., respectively). The peak concentrations were approximately 20 to 30% higher than the trough concentrations.

Pharmacokinetic linearity was demonstrated over the dose range of 2.5 to 15 ng/kg/min.

The mean apparent elimination T ½ of chronic SC UT-15 was ~3 hours with a CV of 26%.

REVIEWER'S COMMENTS: PK linearity was observed in healthy volunteers over the dose range of 2.5 – 15 ng/kg/min Population PK analysis of the data produced similar clearance values (40.8 L/hr/70 kg) to those obtained by the sponsor.

It is not clearly evident that SC UT-15 produces two peaks and two troughs. The sponsor proposes that a peak occurs at 1 a.m., troughs 6 hours later at 7 a.m., peaks again 3 hours later at 10 a.m., then troughs 6 hours later at 4 p.m. Nine hours then separates the 4 p.m. trough and 1 a.m. peak. However, the sponsor did not measure concentrations at these times. Concentrations

during the 24-hour period were measured at 9 a.m., 12 noon, 3 p.m., 6 p.m., 9 p.m., midnight, 3 a.m. and 9 a.m. Since peak concentrations were generally 20-30% higher than trough concentrations, then the difference between peak and mean steady state concentration or trough and mean steady concentration is even less. Additionally, much of the fluctuations in concentrations can be explained by assay variability (CV ~20%). After all of this is considered, it seems unlikely that there is any significant fluctuation in steady state plasma concentrations of UT-15.

Chronic SC UT-15 in healthy adult volunteers elicited vasodilatory adverse events. Chronic administration of UT-15 also caused injection site pain with dose escalation every 7 days in 13 of 14 volunteers. Eight subjects discontinued from the study early because of this adverse effect. Only 6 volunteers tolerated all 4 dose levels. SC UT-15 infusion at doses up to 10 ng/kg/min was well tolerated by 13 of 14 volunteers.

The sponsor often used injection and infusion site pain interchangeably. It may be difficult to differentiate between the two. I am specifically referring to the 8 subjects that withdrew from the study. In one section it states that the subjects withdrew because of infusion site pain and in another section the sponsor states that the subjects withdrew because of injection site pain.

APPEARS THIS WAY
ON ORIGINAL

STUDY TITLE: A multicenter, double-blind, randomized, parallel comparison of the safety and efficacy of chronic subcutaneous UT-15 plus conventional therapy to conventional therapy in patients with severe primary pulmonary hypertension: an 8 week study

STUDY P01:03 **VOLUME:** 2.4 **PAGES:** 350 - 555

PRINCIPAL INVESTIGATOR: Sean Gaine, et al.
CLINICAL LABORATORY: PPD Development
706 Ben White Blvd, West
Austin, TX 78704-7016
CITATION: not applicable

FIRST SUBJECT SCREENED: April 23, 1998
LAST SUBJECT COMPLETED: October 7, 1998

OBJECTIVES: To characterize the pharmacokinetics of chronic, subcutaneous UT-15 in patients with primary pulmonary hypertension (PPH).

STUDY DESIGN: multi-center, double-blind, randomized, parallel group
DURATION: 8 weeks

POPULATION: Twenty-six patients with severe symptomatic PPH (NYHA Class III-IV) who were not receiving Flolan or other intravenous, inhaled or oral prostaglandins were enrolled.

PROCEDURE: After qualifying for the study, patients were randomized (2:1) to receive conventional therapy plus a continuous subcutaneous infusion of UT-15 or conventional therapy plus a continuous subcutaneous infusion of placebo. Blood was drawn for PK analysis and PD assessments (exercise capacity, clinical signs and symptoms of disease) were performed at weeks 1, 4, and 8. After completion of this study, patients had the option of continuing with UT-15 treatment in an open continuation study under a separate protocol (P01:06).

Treatment All patients received conventional therapy. The UT-15 dose was based on clinical signs and symptoms of PPH and the occurrence of adverse events. UT-15 was initiated at 2.5 or 5 ng/kg/min SC if tolerated. The dose was escalated in increments of 2.5 to 5 ng/kg/min at 24-hour intervals until a dose equivalent of 40 ng/kg/min was achieved. Dose escalation could be discontinued based on treatment-emergent safety signs or symptoms (e.g., hemodynamic changes, onset of nausea, emesis, or persistent headache, etc.). The maximum allowable dose at the end of weeks 1 through 8 was 20, 25, 30, 35, 40, 45, 50, and 50 ng/kg/min, respectively. Once a non-tolerated does was determined in a patient, the infusion rate of the study drug was to be decreased to a maximum tolerated dose.

A [redacted] pump was used to subcutaneously administer UT-15. The SC catheter was placed in the abdominal wall and could be moved, if needed, at the discretion of the investigator.

Pharmacokinetics Serial plasma samples were collected at baseline, and at 0.5, 1, 2, 4, and 6 hours following drug initiation and immediately before each UT-15 dose change and at 0.5, 1, 2, 4, and 6 hours after each dose change. PK samples were to be collected at the end of weeks 1, 4, and 8.

OTHER MEDICATIONS: Investigators were to maintain all patients on the same oral medications and doses as were used at baseline. However, doses of oral therapies could be adjusted and oral therapy added or discontinued based on clinical judgement. The following were not permitted: chronic (≥ 5 days) use of intravenous medications to treat PPH, chronic inhaled medications (other than oxygen), and other prostaglandins or prostaglandin analogues.

FORMULATION: UT-15 was provided as a sterile solution whose formulation is summarized in the table below. Lot number Y7H0978A had a UT-15 concentration of 0.5 mg/mL and was provided in 2 mL vials. Lot number 800003 had a UT-15 concentration of 5 mg/mL and was provided in 20 mL vials. A central pharmacy prepared prefilled 3 mL syringes at three concentrations (1, 2.5, and 5 mg/mL) from lot 800003.

Constituents	Concentration of UT-15 Solution (mg/mL)			
	0.5	**1.0**	**2.5**	**5.0**
UT-15	0.5	1.0	2.5	5.0
Sodium Chloride				
Metacresol				
Sodium Citrate, Dihydrate				
Citric Acid				
Sodium Hydroxide				
Container				
Total (mL)	1.0	1.0	1.0	1.0

The reference therapy was a placebo (citrate buffer vehicle) administered via subcutaneous infusion (Lot Number: 800001). The citrate buffer was supplied in 3 mL syringes or in 20 mL vials. Each mL of placebo contained 5.0 mg sodium citrate dihydrate, 1.8 mg citric acid, 3 mg metacresol and 6.2 mg sodium chloride.

All materials were protected from light. Vials were stored at 15-30°C, and syringes were stored

ASSAY: analyzed the plasma samples with a validated assay. Quality controls were analyzed at concentrations of

Precision Interday CV was less than 15%. Intraday precision could not be calculated because multiple samples were not analyzed in the same day.

Accuracy Interday accuracy was within 9%. Intraday accuracy could not be calculated because multiple samples were not analyzed in the same day.

Sensitivity The LOQ was [redacted] for a 1 mL aliquot of plasma.

Linearity The assay was linear over a standard curve range of [redacted]

ANALYSIS: The planned sample size was considered sufficient to provide descriptive information on the safety of UT-15, and was an initial step in the exploration of the safety, pharmacokinetics, and efficacy of UT-15.

Pharmacokinetic Data The pharmacokinetic plasma drug concentration data were listed by patient and dose. Individual patient plasma UT-15 concentration versus time data were displayed graphically. Apparent plasma clearance (CL/F) was to be determined for each infusion rate from each C_{ss}. Pharmacokinetic linearity was to be investigated based on individual patient plot of C_{ss} versus UT-15 dose.

Pharmacodynamic Data Linear correlation analysis was performed on Week 8 steady-state plasma UT-15 concentrations versus selected hemodynamic variables or percentage change in hemodynamic variables (including pulmonary vascular resistance index [PVRI], cardiac index [CI], mean pulmonary arterial pressure [PAPm], right atrial pressure [RAP], mean systemic arterial pressure [SAPm], stroke index [SI], heart rate [HR], and mixed venous oxygen saturation [SvO_2]).

RESULTS: Seventeen patients were randomized to receive UT-15 and nine were randomized to receive placebo. Of the patients that received UT-15, only 15 completed the study in its entirety. Two patients discontinued because of adverse effects. All patients that received UT-15 were Caucasian and 14 were females. Their ages ranged from 12 to 73 years with a median age of 34 years. The median body weight was 74 kg.

UT-15 dosing was not standardized. The initial UT-15 infusion rate was 1.25 ng/kg/min in one patient, 2.5 ng/kg/min in 15 patients and 5 ng/kg/min in one patient.

PHARMACOKINETIC RESULTS: The PK results are based on data from 17 patients. The blood sample collections were reduced to four samples to be collected on study days 2 through 5, instead of 8 samples on study days 2 though 9. There were also some unscheduled plasma samples collected from selected patients. The sampling times and dates were not properly documented because these collections were unanticipated. The sponsor did not calculate plasma clearance values because of concern of the accuracy of the data. Also, because the timing of dose escalation was not standardized, the PK data lacked uniformity in terms of UT-15 doses and corresponding durations of infusion. Thus, it was not possible to summarize the PK data across patients by generating descriptive statistics.

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