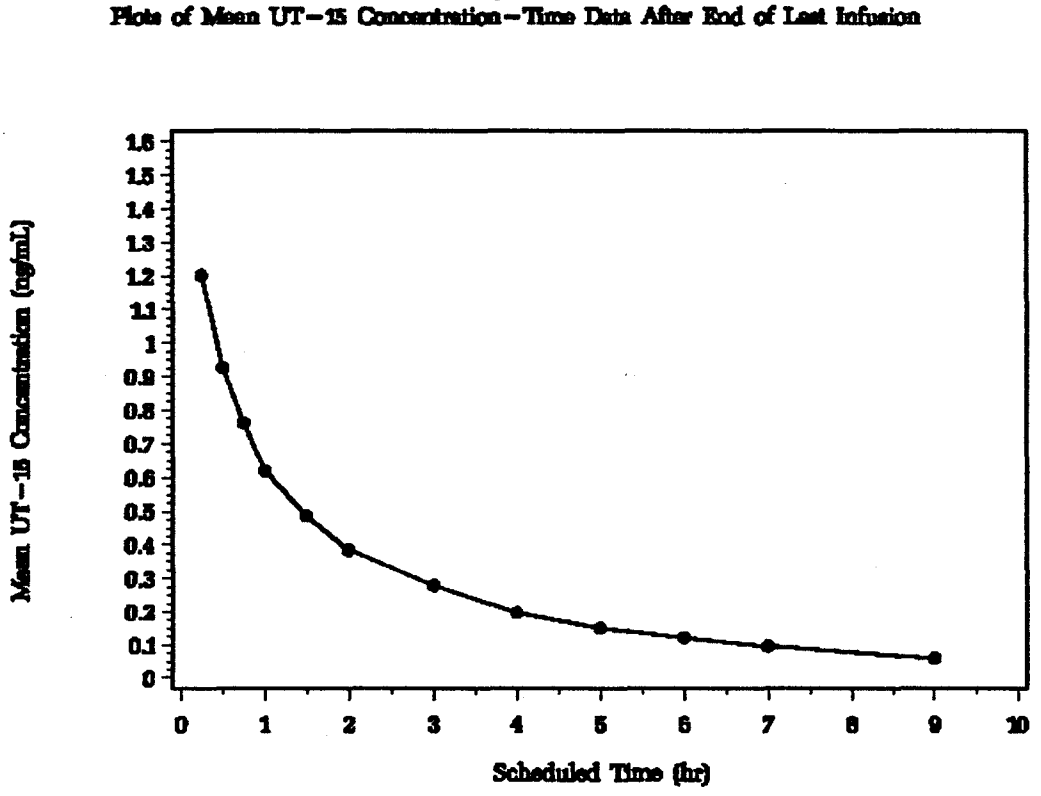
Plasma clearance values for all of the four doses ranged from [redacted], supporting the linear kinetics over the dose range used. The terminal T ½ determined after termination of the 15 ng/kg/min infusion was 2.93 hours. Inter-subject variability of Css,CL and T ½ ranged from 13.6 – 25.5%. The mean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



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 [redacted] 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]).

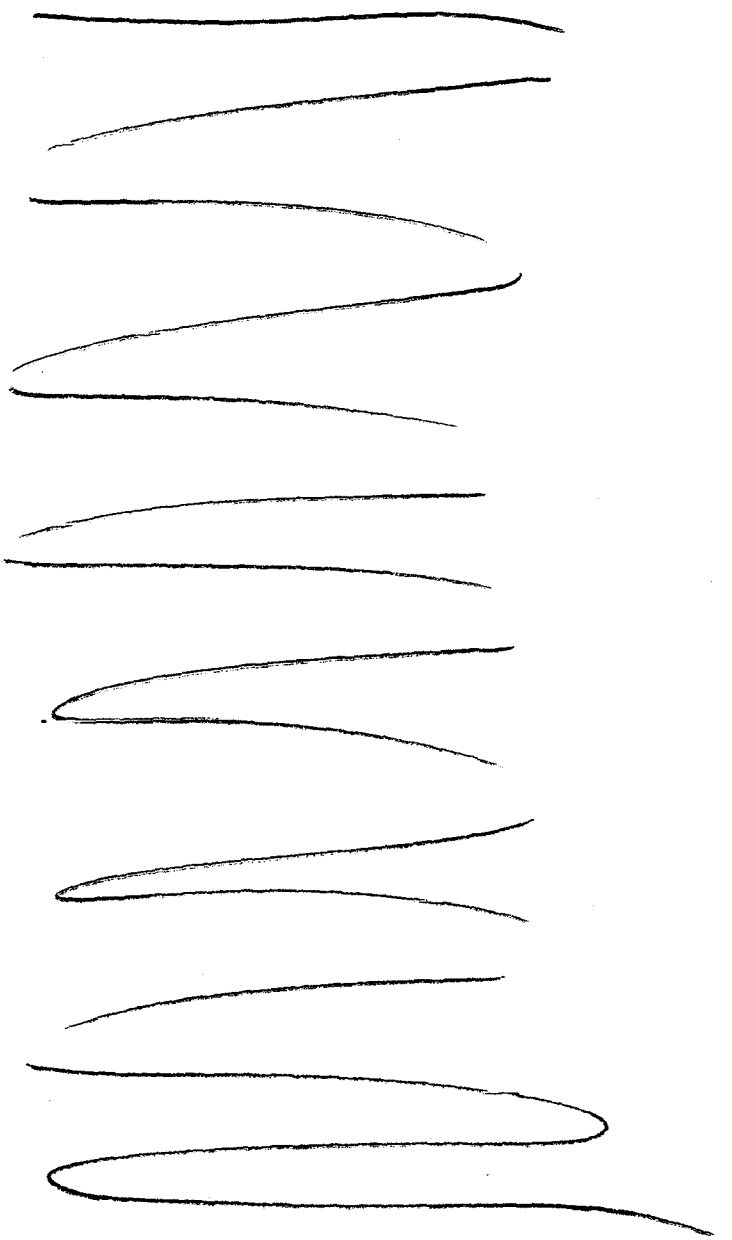
RESULTS: Seventeen patients were randomized to receive UT-15 and nine were randomized to receive placebo. Of the patients that received UT-15, only 15 completed the study in its entirety. Two patients discontinued because of adverse effects. All patients that received UT-15 were Caucasian and 14 were 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.

Data from five patients demonstrated PK linearity. The remaining patients did not have 3 or more steady state values documented over the 8 week study period.

PHARMACODYNAMIC RESULTS: Correlation analysis of Week 8 plasma UT-15 concentration versus various hemodynamic variables failed to show any meaningful relationships. The coefficient of determination ranged from [redacted] Visual inspection of the data suggests that a correlation exists with several of the hemodynamic parameters, but a better study will have to confirm these data.



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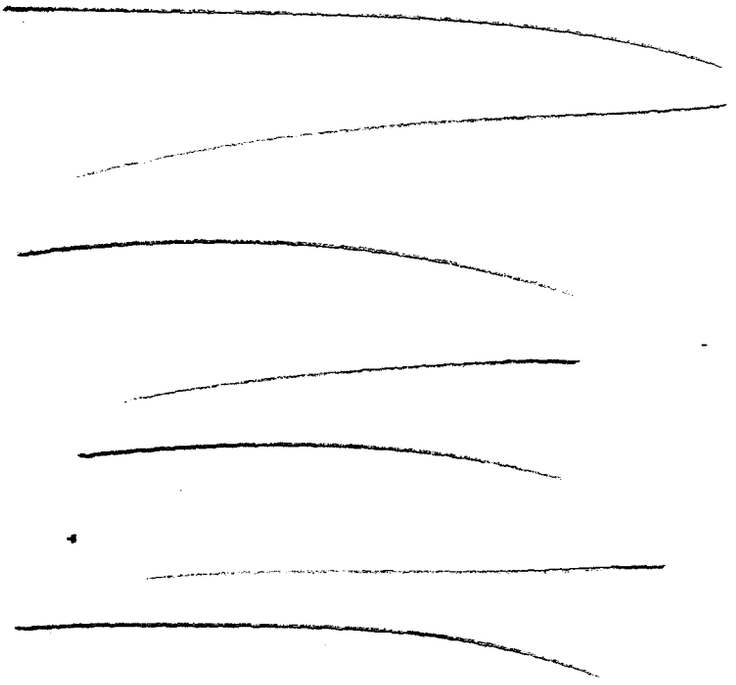


COMMENTS: Dose escalation and optimization were individualized and no two patients had exactly the same dosing regimen. From a PK perspective, non standardization of dose escalation and optimization made the summarization of PK outcome across patients an impossible task.

CONCLUSION: The pharmacokinetics of UT-15 was linear in those patients with adequate data. There was no meaningful correlation between UT-15 plasma concentration and various hemodynamic variables.

REVIEWERS COMMENTS: Because of the problems identified with the design of this study, little meaningful information can be obtained from this study. It is unclear why some of the hemodynamic paramters trended in the wrong direction with higher concentrations of UT-15 (e.g.CI, PVRI, RAP and SvO_2). Perhaps the PD data would have shown a better correlation if more data were obtained and more subjects were studied.

STUDY TITLE: An international, multicenter, double-blind, randomized, parallel placebo-controlled comparison of the safety and efficacy of chronic-subcutaneous UT-15 plus conventional therapy to conventional therapy in patients with pulmonary hypertension: a 12 week study

STUDY P01:04 and P01:05 **VOLUME:** 2.11 **PAGES:** 2942 to 3254
PRINCIPAL INVESTIGATOR: Gaine S, et al.

CLINICAL LABORATORY: Final PK report prepared by Allen Lai, Ph.D. of CPKD Solutions, PO Box 13822, Research Triangle Park, NC 27709

CITATION: not applicable

FIRST SUBJECT DOSED: November 11, 1998 (P01:04), December 15, 1998 (P01:05)
LAST SUBJECT COMPLETED: November 22, 1998 (P01:04), February 3, 2000 (P01:05)

OBJECTIVES: This study had two objectives. The primary objective was to assess the effects of chronic UT-15 SC infusions compared to placebo on exercise capacity in an out-patient environment. The effects of UT-15 on signs and symptoms of PAH, dyspnea-fatigue rating and time to discontinuation were used in this assessment. Secondary objectives included assessing the effects of quality of life, and assessing the effects of patient factors (gender, race, age and weight) on the disposition of UT-15 and to evaluate PK drug interactions.

This review will only focus on the assessment made on the effects of patient factors on the disposition of UT-15 and the evaluation of PK drug interactions.

STUDY DESIGN: multinational, multicenter, randomized, double-blind, placebo-controlled trial

DURATION: 12 weeks

POPULATION: The planned enrollment was 224 patients in each study (04 and 05) with clinically stable symptom-limited (NYHA Class II, III or IV) PAH despite use of chronic vasodilators for at least one month. These patients were also not receiving Flolan or other iv or inhaled prostaglandins or prostaglandin analogues. Patients were male and nonpregnant females between 8 and 75 years old. Study P01:04 was conducted in North America, and study P01:05 was conducted in Europe, Israel and Australia, but also enrolled patients from the US and Canada.

PROCEDURE:
Treatment The first weekly infusion was initiated at 1.25 ng/kg/min. If the initial dose was intolerable, the dose was reduced to 0.625 ng/kg/min. Patients were maintained on the first infusion during week 1. Dose changes during the next 11 weeks were based upon signs and symptoms of disease and AEs. There was no washout period between changes in UT-15 infusion rates. The infusion was increased weekly if the drug was tolerated, and symptoms of pulmonary hypertension did not improve or if the patient's clinical condition deteriorated and the patient became more symptomatic. From week 1 to week 4, doses could be increased by no

more than 1.25 ng/kg/min per week. After week 4, doses could be increased by no more than 2.5 ng/kg/min per week. Thus, the maximum allowable dose was 5 ng/kg/min by week 4 and 22.5 ng/kg/min by week 11. The infusion rate remained constant during weeks 11 and 12.

If dose reductions were required, the infusion rate was to be decreased by no more than 2.5 ng/kg/min every week until the symptom or sign precipitating the dose reduction was resolved.

UT-15 solution was infused SC into the abdominal wall via a [redacted] pump. The SC catheter was changed every 3 days. The infusion site was moved, if necessary, every 24 hours.

Pharmacokinetics Blood samples were collected from specified centers at baseline, week 1, 6 and 12. Patients in the P01:05 study did not have samples from week 1 and 6 analyzed, only samples at baseline and week 12 were reported. Blood samples collected from patients receiving placebo were not analyzed.

FORMULATION: UT-15 was provided as a sterile solution in 20 mL vials in 1 mg/mL and 2.5 mg/mL strengths. The to-be-marketed formulation was used.

Treatment	Dose	Formulation	Lot numbers
UT-15 (SC)	1.25 (or less) to 22.5 ng/kg/min	1.0 mg /mL	800412, 800504, 800506, 800557, 800559
		2.5 mg/mL	800413, 800505, 800560
Placebo (citrate buffer vehicle)			800348

UT-15 was buffered with a citric acid/sodium citrate buffer. Hydrochloric acid or sodium hydroxide was used to adjust the pH of the 1.0 and 2.5 mg/mL formulations to 6.5. Drug in vials or syringes was stored at 36°F [redacted], drug in vials could be stored at controlled room temperature for up to 3 months to facilitate shipping and handling. The drug was protected from light and not exposed to extreme cold or heat.

ASSAY: Plasma concentrations of UT-15 were determined with a validated [redacted] assay. Quantification was based on peak area ratios. The elution order was internal standard [redacted] followed by UT-15. The concentration of quality control samples was [redacted]

Precision
The intraday and interday coefficient of variations were less than 7% for the P01:04 study. The intraday and interday coefficient of variations were less than 17% for the low control and less than 12% for the other controls in the P01:05 study.

Accuracy
For the P01:04 study, intraday accuracy was within 5%. Interday accuracy was within 14, 8 and 11% for low, medium and high controls, respectively. For the P01:05 study, intraday and interday accuracy was within 14, 6, and 5% for low, medium and high controls, respectively.

Sensitivity The LOQ using a 25 µL injection volume was [redacted]

Linearity The assay was linear within the tested range of [redacted] The $r^2 \geq 0.9933$ for the P01:04 standards and ≥ 0.9939 for the P01:05 standards.

ANALYSIS:

Pharmacokinetic Data Individual patient plasma UT-15 clearance values were determined from the ratio between the infusion rate and steady state UT-15 plasma concentrations at week 12. Univariate analyses (Kruskal-Wallace rank sum test followed by simple linear regression) were first performed to assess the relationship between UT-15 plasma clearance and individual patient covariates. Only significant univariate factors ($p \leq 0.1$) that had an R square (coefficient of determination) of at least 0.05 were selected for evaluation in the final backwards-stepwise regression model. The stepwise multivariate regression analysis was performed to identify the best predictors for plasma UT-15 clearance. This procedure accounted for confounding interactions. The patient covariates used in the final model were obesity, furosemide and serum creatinine.

RESULTS: 236 patients received UT-15. Thirty-three dropped out prior to week 12. Of the remaining 203 patient, 17 patients did not have usable week 12 plasma samples (9 samples lost, 4 samples not drawn, 1 sample drawn too late, and the infusion was changed in 3 patients less than 24 hours prior to blood sampling). Thus, 186 patients (87 in the P01:04 and 99 in the P01:05) were included in the PK analysis. Demographics are listed in the table below. The mean age was 45 ± 15 years. The majority of patients were female and Caucasian. Patients mean weight were 71 ± 20 kg.

	n (%)
Age (years)	
≥ 65	17 (9.1)
≤ 18	9 (4.8)
17 to 64	160 (86.0)
Female	157 (84.4)
Race	
Caucasian	159 (85.5)
Hispanic	12 (6.5)
African American	9 (4.8)
Asian	4 (2.2)
Native American	1 (0.5)
Multiracial	1 (0.5)
Weight	
Normal	79 (42.3)
Obese	48 (25.8)
Overweight	46 (24.3)
Underweight	14 (7.5)

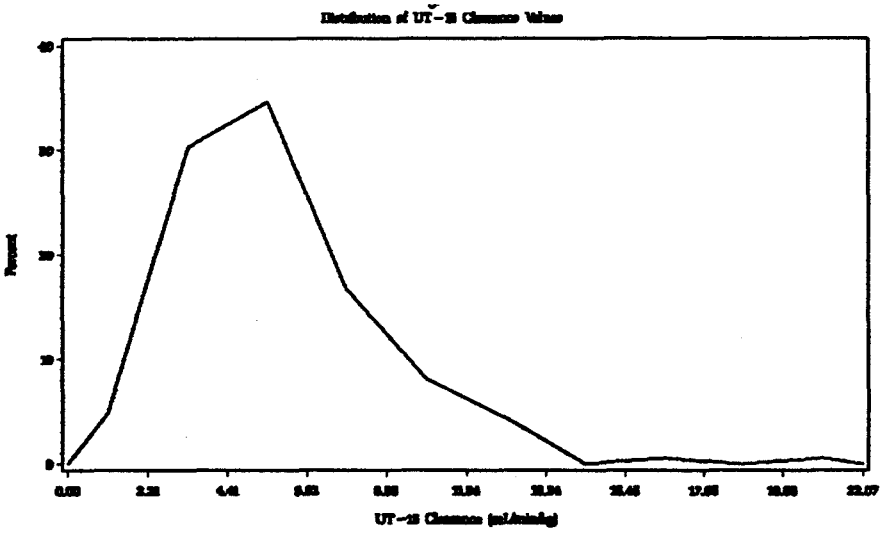
Serum creatinine was another covariate analyzed in this study. Two out of 186 patients had scr > 2.5 mg/dL. The remainder were divided into two groups: 176 with scr ≤ 1.2 mg/dL (classified as normal) 8 with 1.2 < scr ≤ 1.5 mg/dL (classified as mild renal dysfunction).

Another covariate was concomitant medicines. Ten medicines were included in this analysis: warfarin, furosemide, amlodipine, digoxin, levothyroxine, nifedipine, omeprazole, paracetamol (acetaminophen), prednisone and spironolactone. The most prevalent medication was warfarin, with 57.5% of patients taking it.

The doses at week 12 ranged from 0.62 to 22.5 ng/kg/min. The patient receiving 0.62 ng/kg/min was also on the lowest dose after adjustment for weight, 58.9 ng/min. Seven patients reached the highest allowed dose, 22.5 ng/kg/min. The highest weight adjusted dose was 1890 ng/min.

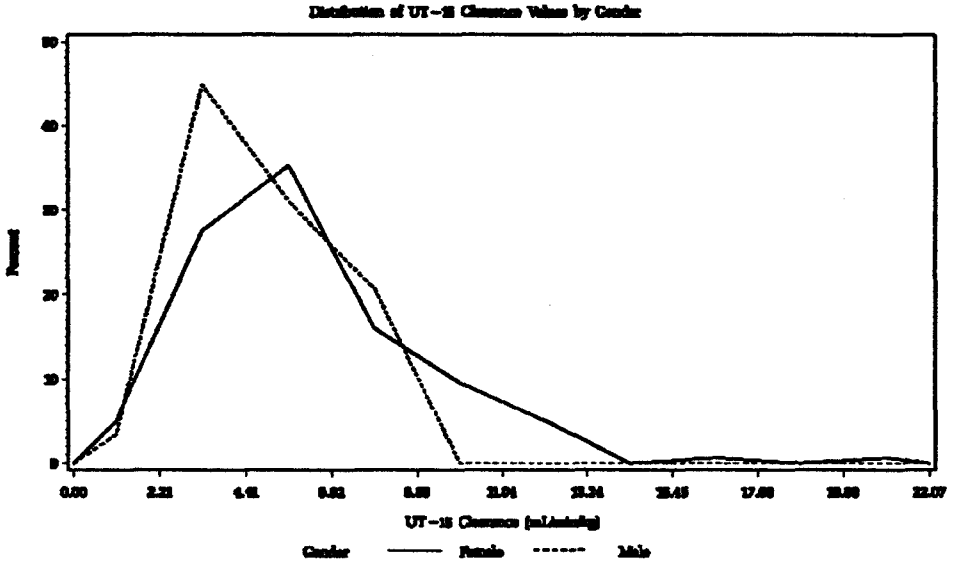
PHARMACOKINETIC RESULTS: Mean ± SD dose was 9.2 ± 5.254 ng/kg/min. Plasma concentration was 1.892 ± 1.294 ug/L (mean ± SD). The range of plasma concentrations was from

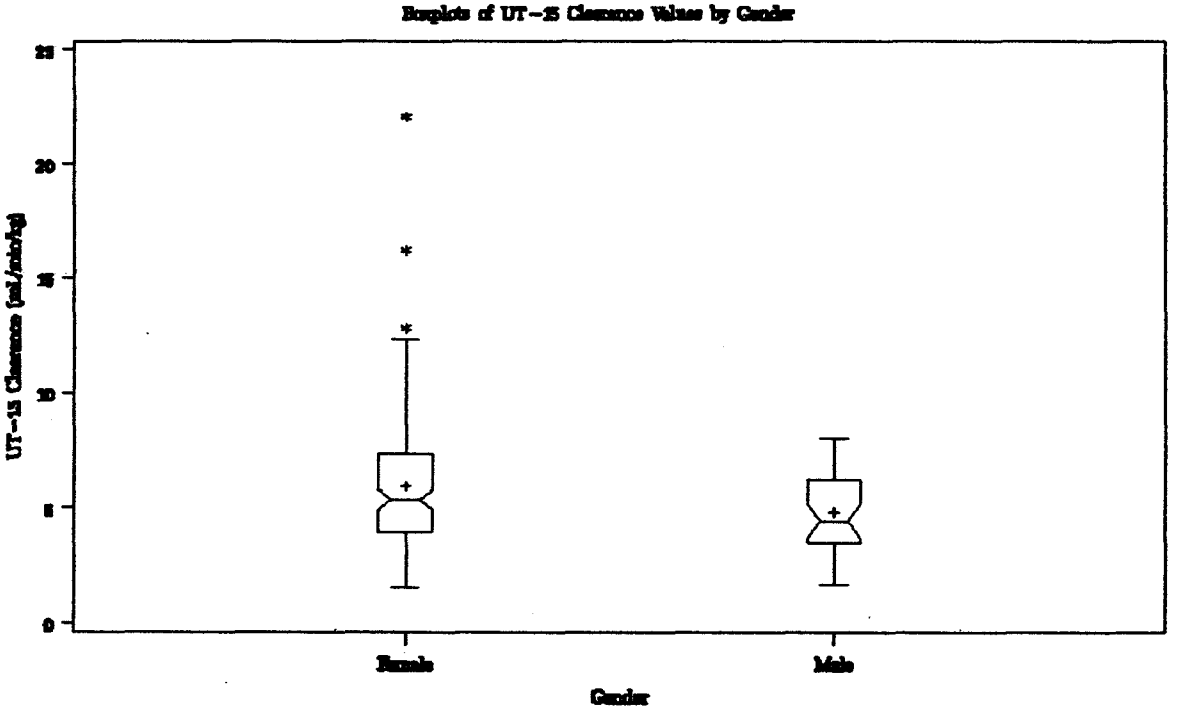
Mean ± SD clearance was 6.1 ± 5.79 mL/min/kg. The distribution of clearance is shown in the figure below. Three patients were classified as outliers. These patients had clearances > 15 ml/min/kg; 16.2, 22.1 and 74.3 mL/min/kg. These patients were dropped during all regression analyses but were included in the nonparametric analyses.



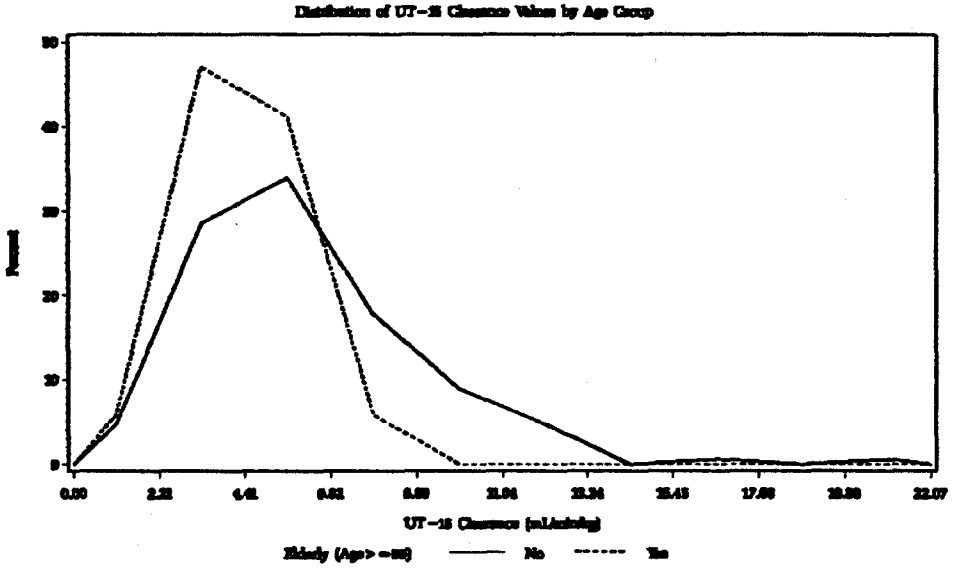
Based on descriptive statistics the following observations were made about median steady state UT-15 clearance:

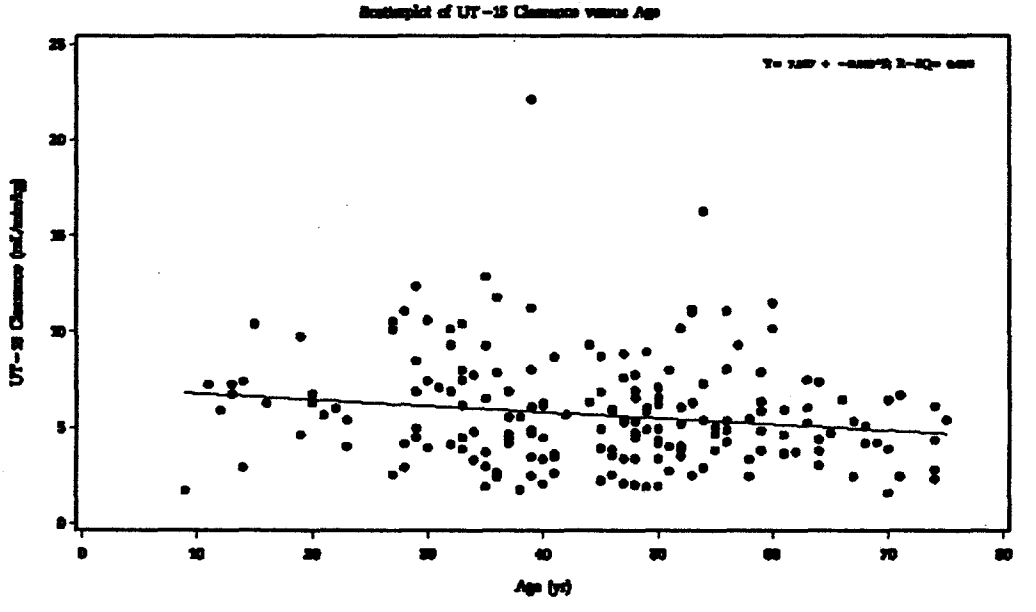
- Clearance is 17% lower in males versus females,





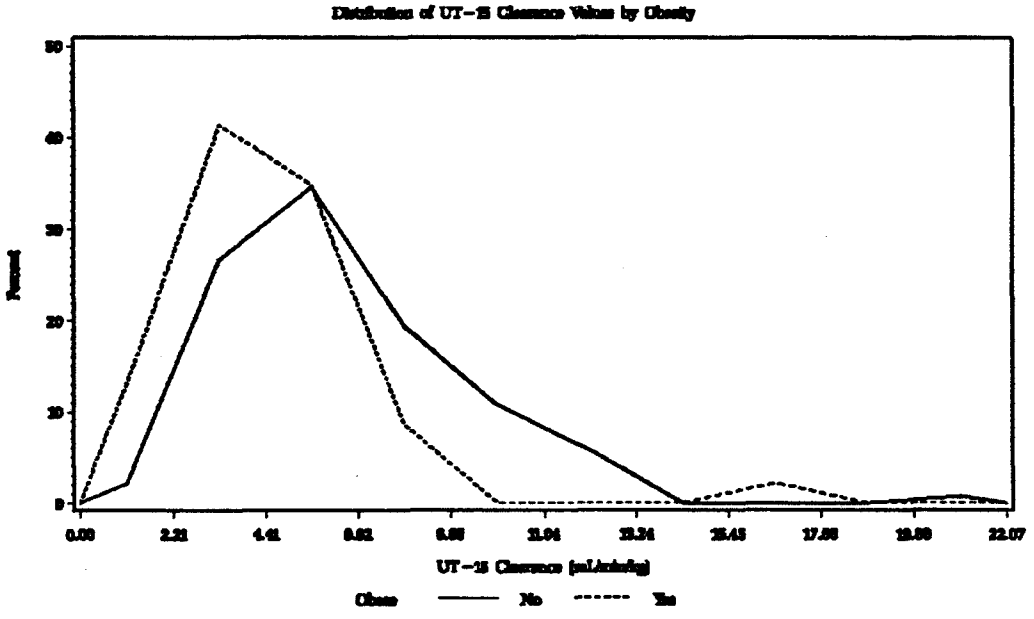
- 20% lower in patients ≥ 65 years old (elderly) versus those < 65 years old,

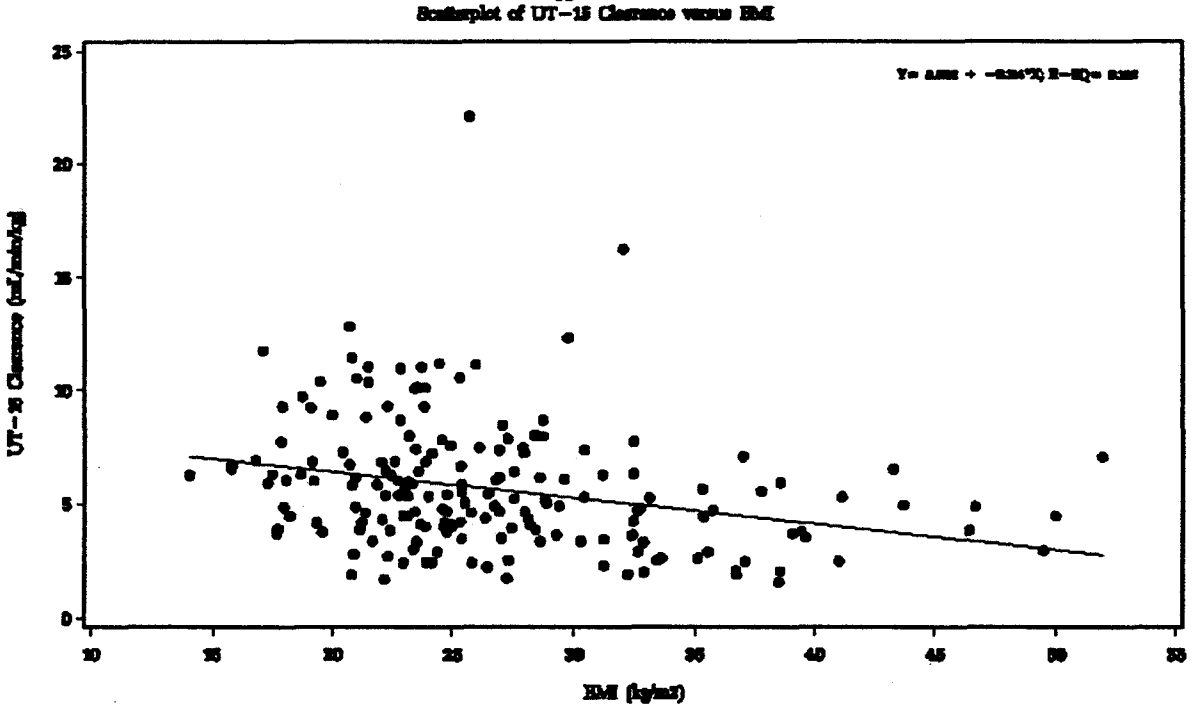




[1] Clearance > 70 not shown.
[2] Clearance > 35 not included in regression.

- 29% lower in obese than non-obese patients.

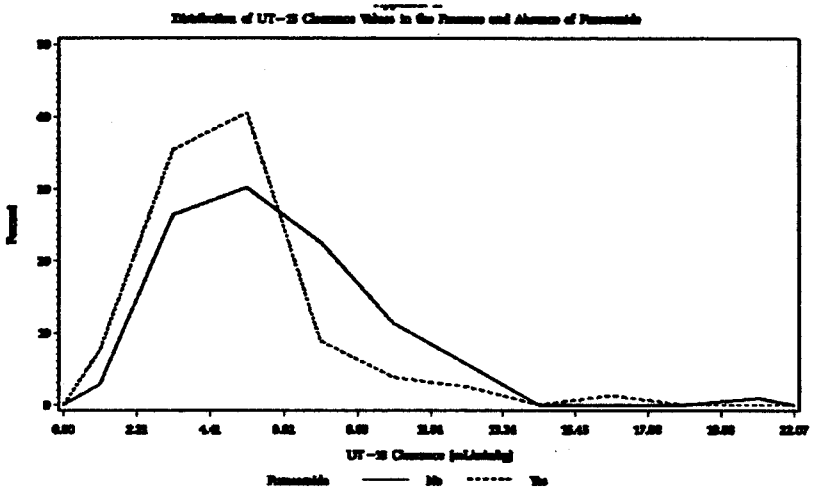


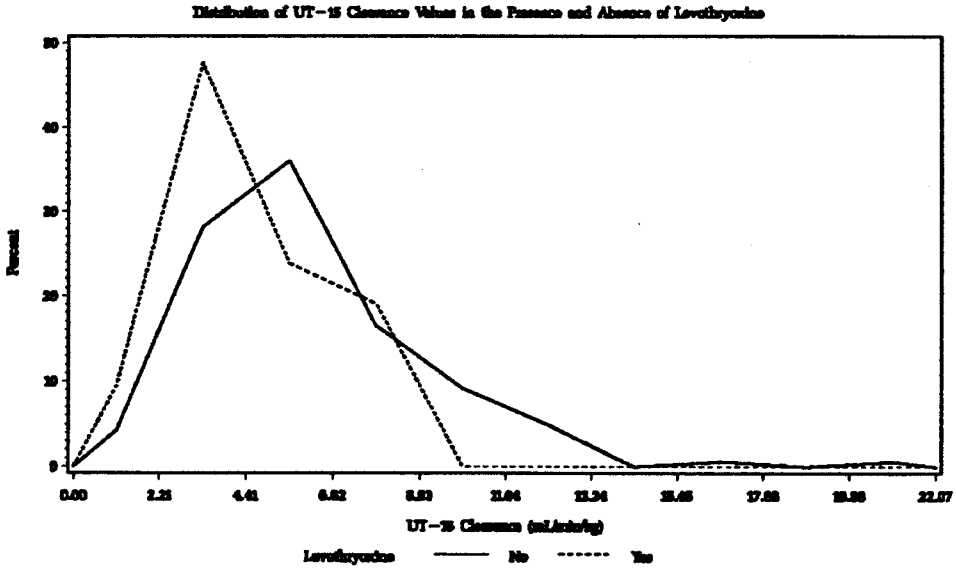


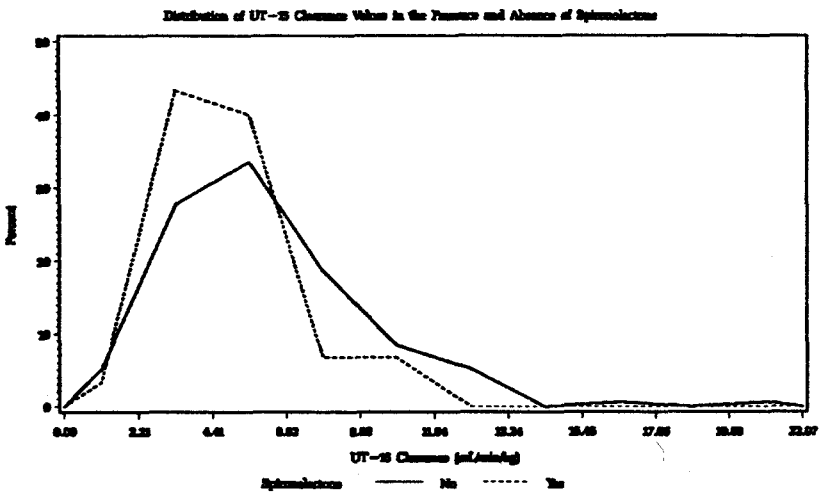
Presence or absence of most medications did not affect the distribution of clearance. Based on univariate analysis, median UT-15 clearance was affected by these three drugs:

- 22% lower in patients taking furosemide (43%) versus those not taking furosemide,
- 19% lower in patients taking levothyroxine (11%) versus those not taking levothyroxine, and
- 19% lower in patients taking spironolactone (16%) versus those not taking spironolactone.

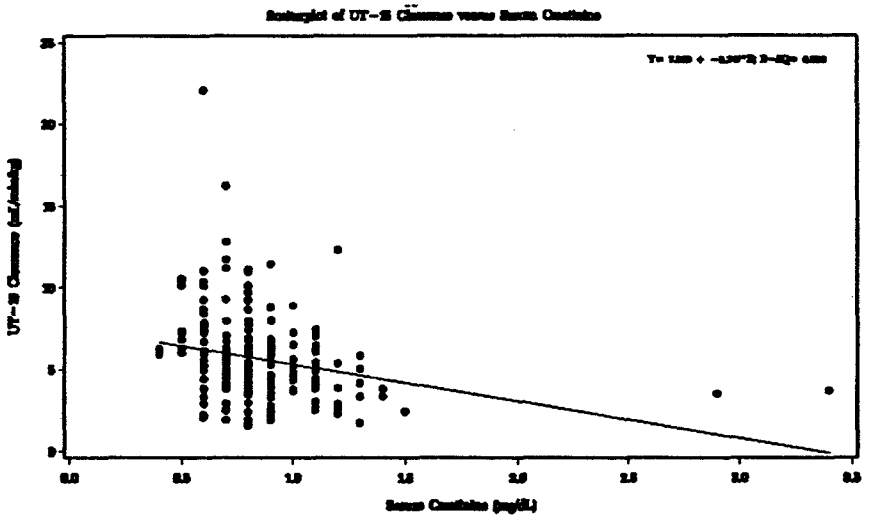
The graphs are shown below.







The results of simple linear regression analyses of covariates that were significant by univariate analysis (elderly, BMI, serum creatinine, furosemide, levothyroxine and spironolactone) showed that obesity ($r^2 = 0.119$), defined as a BMI > 30.0 kg/m^2, furosemide ($r^2 = 0.061$) and serum creatinine ($r^2 = 0.083$) were significantly associated with steady state clearance of UT-15. See scatterplot below of UT-15 clearance and serum creatinine.



Obesity, furosemide, serum creatinine and creatinine/obesity interaction jointly explained 26.2% of the variability in UT-15 clearance. Obesity was the best predictor of steady state clearance. It accounted for 12% of the observed inter-patient variability in clearance. Furosemide was also an important predictor of steady state clearance. It accounted for 6% of the variability.

SPONSOR'S COMMENTS: Furosemide accounted for 6% of the inter-subject variability in plasma UT-15 clearance values. The sponsor offers a possible mechanistic explanation for the drug interaction. The elimination of furosemide is mostly via glucuronidation of the carboxylate group. While UT-15 has two hydroxyl groups and one carboxylate group, only the carboxylate group undergoes glucuronidation. Approximately 14% of a SC dose of UT-15 is eliminated via this conjugation. It is speculated that furosemide might have prevented UT-15 from reaching the active site of the enzyme that facilitates glucuronidation.

The sponsor acknowledges that the finding that serum creatinine was also an important predictor of steady state clearance is illogical since 98.9% of patients had serum creatinine from 0.5 to 1.4 mg/dL and renal excretion of unchanged drug has a minor role in the elimination of UT-15.

SPONSOR'S CONCLUSION: The sponsor concludes that obesity was the best predictor of steady-state plasma UT-15 clearance. It accounted for ~12% of the observed inter-individual variability in plasma UT-15 clearance. Dosing of UT-15 chould be based on ideal body weight.

Furosemide was an important predictor of plasma UT-15 clearance accounting for ~6% of the variability.

Serum creatinine was also shown to be a significant predictor of plasma UT-15 clearance. The sponsor states the cause for this finding to be "happenstance".

REVIEWER'S COMMENTS: Dosing of UT-15 should be based on ideal body weight.

The increase in UT-15 concentration caused by furosemide is of little clinical significance. Additionally, it was difficult to determine the sponsor's definition of concomitant medication.

We analyzed the data using a physiologic model and found no difference in pharmacokinetics with respect to age, gender or obesity. See the pharmacometrics review for further details.

APPEARS THIS WAY
ON ORIGINAL

STUDY TITLE: A pharmacokinetic study of subcutaneous UT-15 in patients with secondary pulmonary hypertension a study in patients with portopulmonary hypertension

STUDY P02:01 **VOLUME:** 2.4 **PAGES:** 555 - 602

PRINCIPAL INVESTIGATOR:
CLINICAL LABORATORY:

CITATION: not applicable

FIRST SUBJECT SCREENED: May 19, 2000
LAST SUBJECT COMPLETED: July 26, 2000

OBJECTIVES:
Primary To characterize the pharmacokinetic profile of subcutaneous UT-15 in patients with mild to moderate hepatic dysfunction associated with portopulmonary hypertension.

STUDY DESIGN: open label, single-dose
DURATION: The study duration consisted of a 150 minute treatment phase and a 300 minute washout phase.

POPULATION: Five patients with mild hepatic dysfunction (Child Pugh Grade B) and four patients with moderate hepatic dysfunction (Child Pugh Grade A) associated with portopulmonary hypertension were studied. These patients were in NYHA Class II-III for PPH. Mean time since diagnosis of primary pulmonary hypertension was 6 months. Mean age was 49 years. Patients were within 30% of ideal body weight. There were three females. All patients were Caucasian, except for one who was Black.

PROCEDURE: Hepatic function status was determined using the Child Pugh Classification scale. During the Baseline/screening phase, all patients underwent right heart catheterization to determine baseline hemodynamic parameters. Cardioplumonary hemodynamics were also assessed every 15-30 minutes during the dose and washout periods.

Treatment The treatment phase consisted of two phases; a dosing phase and a washout phase.
Dosing phase: UT-15 10 ng/kg/min SC for 150 minutes.
Washout phase: 300 minutes

Pharmacokinetics Blood samples for determination of UT-15 were collected at Baseline and at the following times during the dosing phase: 15, 30, 60, 90, 120, and 150 minutes. During the washout phase blood samples were collected at 5, 10, 15, 30, 60, 90, 120, 180, 240, and 300 minutes. One additional sample was obtained during the post-treatment phase.

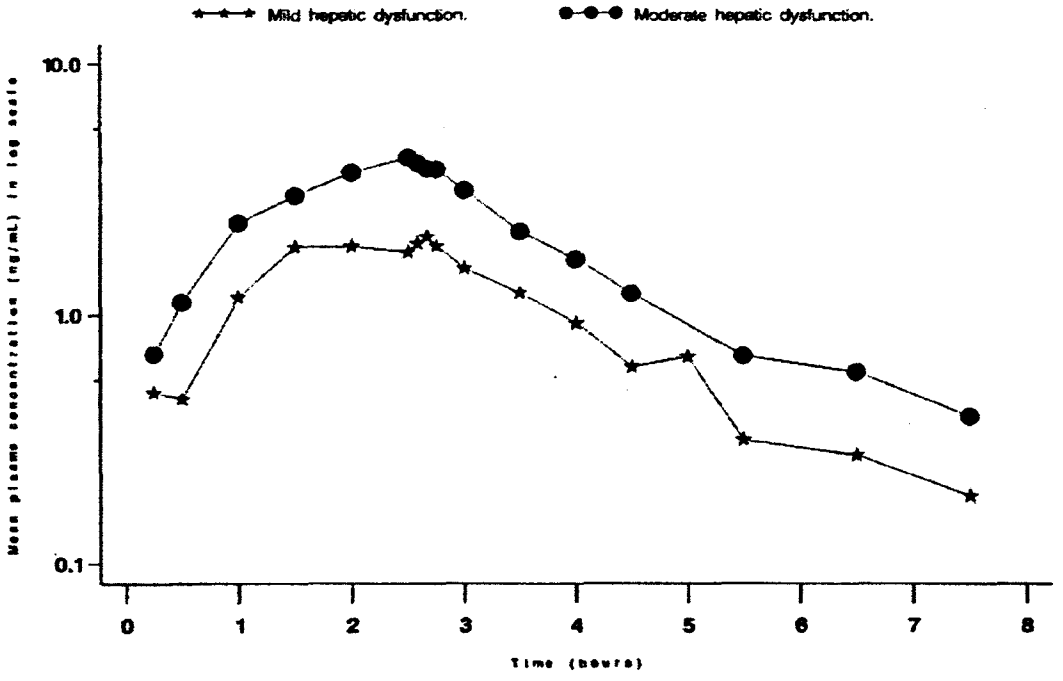
FORMULATION: UT-15 0.5 mg/mL, lot number Y7H0978A was used.

UT-15 ASSAY: The plasma samples were analyzed with a validated [redacted] assay. The lower LOQ was [redacted] and the upper LOQ was [redacted] No other details of the assay were submitted.

ANALYSIS:

Pharmacokinetic Data PK parameters from this study were compared to that obtained from healthy subject that received 15 ng/kg/min in the P01:07 study. Cmax and AUC $_{0\text{-inf}}$ in healthy subjects were dose normalized for a 10 ng/kg/min dose. The PK parameters were compared using descriptive statistics.

PHARMACOKINETIC RESULTS: The concentration versus time profile are shown in the figure below for the patients with mild and moderate hepatic insufficiency.



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Mean ± SD PK parameters for the healthy subjects and hepatically impaired patients are shown in the table below.

Parameter	Healthy subjects [a] (n=15)	Mild hepatic dysfunction (n=5)	Moderate hepatic dysfunction (n=4)
Cmax (ug/L)	0.98 [b]	2.22 ± 0.43	4.32 ± 1.48
Tmax (hr) [c]	———	2.58 ———	2.50 ———
AUC $_{0-t}$ (ng*hr/mL)	NR	6.47 ± 1.59	12.73 ± 4.57
AUC $_{0-inf}$ (ng*hr/mL)	2.65 [b]	6.91 ± 1.80	13.57 ± 4.16
CL/F (mL/hr/kg) [d]	589.4 ± 129.6	228.2 ± 54.39	118.75 ± 36.22
Vz/F (mL/kg) [d]	1113.6 ± 453.0	451.6 ± 141.80	225.00 ± 164.21
T ½ (hr) [d]	1.38 ±0.66	1.42 ± 0.48	1.32 ± 0.83

NR = not reported
[a] The results for healthy subjects from study P01:07 which gave a SC dose of 15 ng/kg/min for 150 minutes.
[b] Cmax and AUC $_{0-inf}$ mean values listed in this table are dose-normalized for a 10 ng/kg/min dose and assume that UT-15 PK parameters are linear with respect to dose and not dose dependent. No SD values are reported for Cmax and AUC $_{0-inf}$ since mean values are reported after dose normalization.
[c] Median (min, max) are shown for Tmax of patients with hepatic dysfunction however, only (min, max) is shown for Tmax of healthy subjects.
[d] Comparison of CL/F, Vz/F and T ½ assumes that these parameter are dose independent.

Observation shows that patients with hepatic insufficiency have higher concentrations of UT-15 than normal subjects. Concentrations were highest at the end of the 150 minute infusion in moderately impaired patients and 10 minutes post infusion in mildly impaired patients. Cmax and AUC $_{0-inf}$ for patients with mild hepatic dysfunction were higher by ~ 127% and 161%, respectively compared to the healthy subjects. The corresponding values for patients with moderate hepatic dysfunction were higher by ~ 340% and 412%, respectively.

Apparent total clearance and volume of distribution was lower in patients with mild and moderate hepatic dysfunction compared to healthy subjects. Apparent clearance was lower by ~ 62 % and 80% in mild and moderate hepatic dysfunction, respectively.

SPONSOR'S COMMENTS: Inter-individual variability for most of the PK parameters from this study and study p01:07 was within ~40%.

There were no differences in mean T ½ among the different groups. Thus, it appears that lower CL/F values in patient with mild/moderate hepatic dysfunction were principally caused by lower Vz/F values. The reasons for lower Vz/F values are not evident. Differences in protein binding for UT-15, either in plasma or tissue, are likely the cause for the lower Vz/F values in patients with mild/moderate hepatic dysfunction.

CONCLUSION: This observational study shows that mild to moderate hepatic dysfunction results in higher concentrations and lower clearance of UT-15 compared to healthy subjects. Patients with portopulmonary hypertension and mild/moderate hepatic dysfunction should be administered appropriate lower doses of UT-15 and closely monitored for signs and symptoms as well as emergence of adverse experiences.

REVIEWER'S COMMENTS: There are PK differences between patients with hepatic insufficiency and healthy subjects. Patients with mild hepatic insufficiency had 2x higher Cmax and 3x higher AUC_{0-inf} than healthy subjects. Patients with moderate hepatic insufficiency had 4x higher Cmax and 5x higher AUC_{0-inf} than healthy subjects. Apparent clearance was lower by ~ 62 % and 80% in mild and moderate hepatic dysfunction, respectively.

Observation of the data does not reveal similar half-lives. The half-life in patients with hepatic insufficiency is ~3 hours.

The Vz/F values were calculated from the CL/F and terminal slope, thus Vz/F will change with CL/F and terminal slope. The sponsor's speculation about Vz/F are invalid.

Concentrations were not detectable or not quantifiable by 4 hours post infusion in 2 patients and by 5 hours in 1 patient.

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STUDY TITLE: A study to evaluate the effects of acetaminophen on the pharmacokinetics of UT-15 in healthy volunteers

STUDY P01:08 **VOLUME:** 2.7 – 2.8 **PAGES:** 1199 - 2097

PRINCIPAL INVESTIGATOR: Thomas Hunt, MD, PhD.
CLINICAL LABORATORY: PPD Development
706 Ben White Blvd, West
Austin, TX 78704-7016

CITATION: not applicable

FIRST PATIENT ENROLLED: August 3, 1999
LAST PATIENT COMPLETED: September 20, 1999

OBJECTIVES: To evaluate the effect of oral acetaminophen on the pharmacokinetic and safety characteristics of UT-15 administered subcutaneously in healthy volunteers.

NOTE: This review will discuss the pharmacokinetic aspect of the study.

STUDY DESIGN: single center, randomized, two-period, cross-over

DURATION: The total duration of the study ranged from two to five weeks. Subjects were screened within 3 weeks of the first dosing period. The actual dosing period consisted of two days with a washout of five to seven days between the two dosing periods.

POPULATION: Twenty-nine healthy adult subjects were enrolled and 26 completed the study. Female volunteers were of non-childbearing potential or had a negative serum pregnancy test. Subjects weighed from 40 to 90 kg and were within 10% of ideal body weight.

PROCEDURE: Subjects remained in the clinic during dosing periods 1 and 2. A standard low fat breakfast was consumed 1 hour prior to the first oral dose of acetaminophen or placebo. UT-15 and acetaminophen were dosed and plasma samples were collected as described below. Subjects were monitored during the study for adverse events. Subjects were discharged after completion of the last pharmacokinetic sample in period 2.

Treatment Subjects were randomized to receive acetaminophen or placebo. Acetaminophen/placebo was given on Day 1, approximately 25 hours prior to the UT-15 dose. The last dose was taken 7 hours after termination of UT-15. The acetaminophen dose was 1000 mg (two 500 mg tablets) every 6 hours for 7 doses. Placebo was given every 6 hours for 7 doses also. A five to seven day washout period separated placebo and acetaminophen doses.

All subjects received 15 ng/kg/min of SC UT-15 for 6 hours via an abdominal site while supine during periods 1 and 2. The infusion of UT-15 started 1 hour after the first acetaminophen or placebo dose on Day 2.

Pharmacokinetics Blood samples for PK analysis of UT-15 were collected before the infusion, at 0.25, 0.5, 1, 1.5, 2, 2.5, 4 and 6 hours after the start of the infusion, and at 5, 10, 15 minutes and 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours after termination of the infusion.

OTHER MEDICATIONS: Subjects were not allowed to use any prescription medications (excluding oral and non-oral contraceptives approved by the sponsor) within 14 days or OTC medications within 72 hours of dosing and during the study. Tobacco products were not allowed within 90 days prior to dosing and during the study.

FORMULATION: UT-15 was provided as a sterile, pyrogen-free, isotonic solution in 20 mL multidose vials (lot no. 800559). The to-be-marketed formulation was used. UT-15 solution (undiluted) was administered subcutaneously using a [redacted] pump designed for continuous SC drug delivery.

Tylenol® Extra Strength 500 mg tablets, lot number 0045-0499-60. Matching placebo tablets, lot number 0223-1469-02 were used. Both products were manufactured by McNeil.

ASSAY: [redacted] analyzed the plasma samples with a validated [redacted] assay. A dimethylene homologue of UT-15 (LRXA-97302) was used as an internal standard. Quality controls were analyzed at concentrations of [redacted]

[redacted]

Sensitivity The lower LOQ was [redacted]

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

ANALYSIS: ***Pharmacokinetic Data*** Acetaminophen was considered to not have clinically significant effects on the pharmacokinetics of UT-15 when the 90% confidence intervals for the log-transformed UT-15 Cmax ratio and the AUC_{inf} ratio for the test and reference treatments fall within 80 – 120%. All PK parameters were determined with actual blood sampling time.

Statistical analysis Twenty-two subjects were needed to complete the study in order to attain 80% power, assuming a variance of 19% from study p01:07. Descriptive statistics were computed for pertinent UT-15 pharmacokinetic parameters in addition to the analysis above.

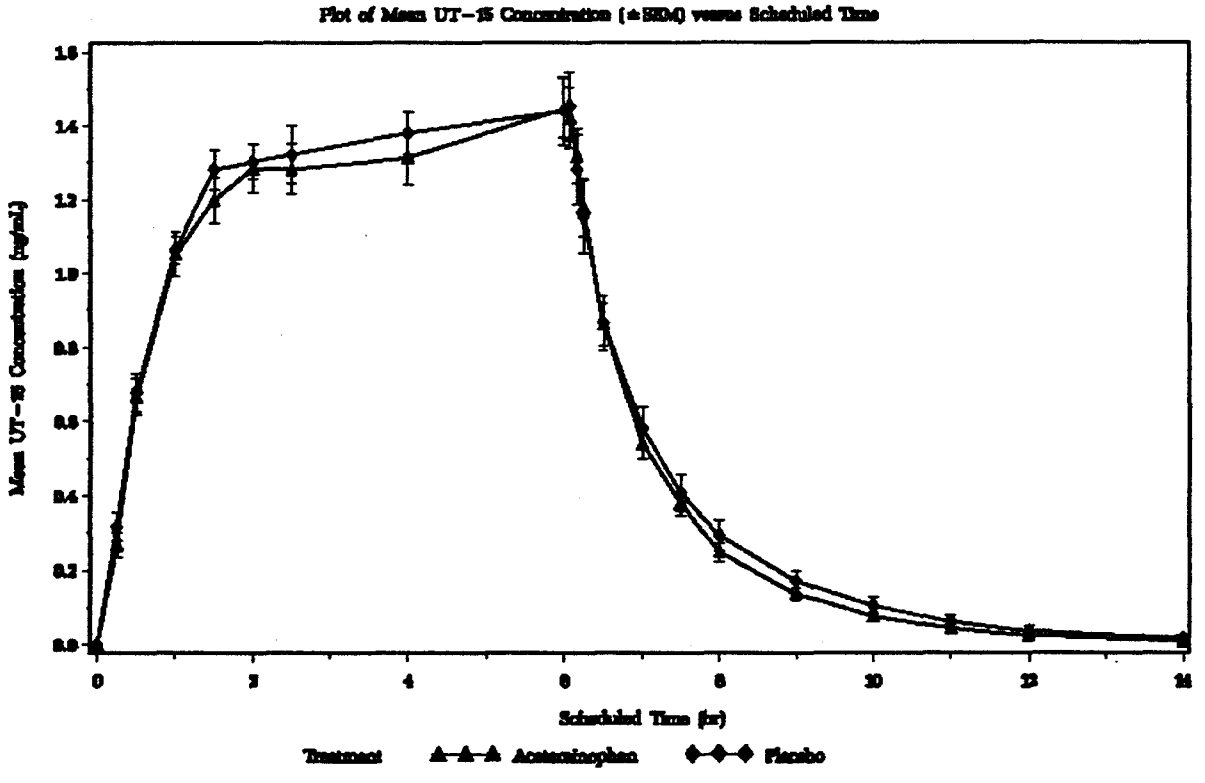
RESULTS: Twenty-six out of 29 subjects completed the entire study. The results reported include all 29 subjects, except for the PK results which only includes the 26 subjects that completed the study. The mean ± SD age was 29 ± 9 years and the mean ± SD body weight was 70.5 ± 9.8 kg. The study population was mostly Caucasian (72% Caucasian, 24% Hispanic and 3% other race). There were more females than males (59% vs. 41%).

Most adverse effects were related to the vasodilatory affects of UT-15, and consisted of headaches (reported by 17 subjects), nausea (n=11), vomiting (n=6), jaw pain (n=5), injection site pain (n=3) and dizziness (n=3).

There were few protocol deviations. Two subjects were above their ideal body weight by 1.6 kg and 0.8 kg, respectively. Treatment administration deviations occurred in two subjects, and both were dropped from the study. A few vital sign measurements and PK samples were not obtained in some subjects because of technical difficulties. One subject ingested acetaminophen 4 days before starting period 2.

Dropouts Three subjects dropped out of the study. One subject withdrew consent midway through the study. One subject was discharged because of pump failure and another was discharged because she vomited an acetaminophen dose during the SC UT-15 infusion.

PHARMACOKINETIC RESULTS: Acetaminophen does not effect the pharmacokinetics of UT-15. The 90% confidence interval for the UT-15 Cmax ratio and AUC ratio in the presence and absence of acetaminophen was within the 80 – 125% equivalence interval, 92.7 – 105.7% and 88.7 – 101.7%, respectively. The concentration versus time profile on acetaminophen and on placebo were similar (see graph below). For both Cmax and AUC_{inf} comparisons, treatment by sequence interaction and treatment by period interaction were not statistically significant.



UT-15 PK parameters were similar with acetaminophen and with placebo, although there was a lot of variability (see tables below).

Subcutaneous UT-15 PK with acetaminophen

Parameter	Mean	SD	CV %	Minimum	Maximum
Cmax (ug/L	1.56	0.40	25.5		
Tmax (hr)	4.03	1.92	47.6		
T ½ (hr)	1.38	0.59	42.4		
AUC_{inf} (ng*hr/mL)	8.93	2.35	26.3		
CL/F (L/kg/hr)	0.65	0.19	28.7		

Subcutaneous UT-15 PK without acetaminophen

Parameter	Mean	SD	CV %	Minimum	Maximum
Cmax (ug/L	1.57	0.42	26.7		
Tmax (hr)	4.53	1.80	39.7		
T ½ (hr)	1.53	0.65	42.7		
AUC_{inf} (ng*hr/mL)	9.37	2.41	25.7		
CL/F (L/kg/hr)	0.61	0.15	24.7		

COMMENTS: United Therapeutics conducted this interaction study because of the common concomitant use of acetaminophen with UT-15 and the presence of similar functional groups. Acetaminophen is often used concurrently with UT-15 to minimize the most common side effects, headache and infusion site pain. Additionally, acetaminophen possesses a hydroxyl group that undergoes glucuronidation and sulfation in the liver, and UT-15 possesses two hydroxyl groups and one carboxyl group. Thus, UT-15 might also undergo conjugation.

CONCLUSION: Analgesic doses of acetaminophen do not affect the pharmacokinetics of UT-15.

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STUDY TITLE: A study to assess the effects of continuous subcutaneous infusion of UT-15 therapy on single-dose warfarin pharmacodynamics and pharmacokinetics in healthy volunteers

STUDY P01:12 **SUBMITTED:** January 25, 2001 under amendment N-BB

PRINCIPAL INVESTIGATOR: Thomas Hunt, MD, PhD.
CLINICAL LABORATORY:

CITATION: not applicable

FIRST SUBJECT SCREENED: May 19, 2000
LAST SUBJECT COMPLETED: July 26, 2000

OBJECTIVES:
Primary To assess the pharmacodynamic effect (INR) of single-dose warfarin in healthy volunteers receiving continuous subcutaneous UT-15 infusion.
Secondary To assess the pharmacokinetic effects of single-dose warfarin in healthy volunteers receiving continuous subcutaneous UT-15 infusion and to assess the safety of concomitant warfarin and UT-15.

STUDY DESIGN: single-center, single-blind, vehicle-controlled, two-period crossover study
DURATION: The study duration consisted of two treatment periods, each lasting 10 days and containing 9 days of dosing. A 13 day washout period separated the two treatments so that Study Day 1 for both periods was on the same day of the week.

POPULATION: Healthy subjects between the ages of 18 to 45 years, weighing within 15 % of their ideal body weight and free of clinically significant abnormal findings were enrolled. Abnormal findings were determined by medical history, a baseline physical examination, vital signs measurements, clinical laboratory tests and ECG measurements. Enrollment of 16 subjects was planned to ensure completion of 12 subjects.

Female subjects were not pregnant or lactating. Female subjects of reproductive potential were practicing adequate contraception (intrauterine or double-barrier device) for at least 3 months prior to and for the duration of their study participation. Additionally, females of reproductive potential had a negative pregnancy test at screening and at check-in to the clinic. Females did not use oral contraceptives for at least 2 months prior to entering the study.

PROCEDURE: Subjects were confined to the clinic for all study procedures and evaluations. Each subject was randomized to receive UT-15 infusion or vehicle during Period 1 and the alternate treatment during Period 2 in a two-way crossover design.

Safety evaluations included screening for adverse events, performing physical examinations, measuring vital signs, recording 12-lead EKGs and performing clinical laboratory tests.

Administration of the dose relative to meals was as follows. Subjects received a low fat breakfast 1 hour prior to the start and increase of the infusion. Warfarin was administered 2 hours prior to breakfast.

Treatment Treatment A consisted of continuous SC UT-15 plus oral warfarin 25 mg. Treatment B consisted of vehicle infusion plus oral warfarin 25 mg.
Day 1: 5 ng/kg/min of study drug
Day 2-9: 10 ng/kg/min of study drug
Day 3: warfarin 25 mg po (one 5 mg tablet plus two 10 mg tablets)

Pharmacokinetics Blood samples to measure R- and S- warfarin were collected at 0 hour (pre-warfarin dose) and 1, 2, 3, 6, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours post-warfarin dose during each treatment period. Blood samples to measure UT-15 concentrations were collected at 0 hour (pre-warfarin dose), 24 and 48 hours after warfarin dosing.

Pharmacodynamics Blood samples to measure warfarin pharmacodynamics (INR) were collected at -48, -24 and 0 hour (pre-warfarin dose) and 6, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-warfarin dose during each treatment period.

OTHER MEDICATIONS: Subjects were not allowed to use investigational medication within 30 days, prescription medications within 14 days, or OTC medications within 7 days prior to entering the study. Tobacco products were not allowed within 90 days prior to dosing and during the study. Use of medications known to alter blood coagulation variables were prohibited.

Subjects with a history of alcohol or drug abuse within the 2 years preceding the study were also excluded. Subjects had to pass a urine drug screen.

FORMULATION:
- UT-15 was provided as a sterile, pyrogen-free, isotonic solution in 20 mL multidose vials, 1 mg/mL (lot no. 801013).
- Placebo to match UT-15 (vehicle) was provided in a 20 mL vial (lot no. 800860)
- Warfarin 5 mg and 10 mg tablets (lot no. ENC127A and ENB084A, respectively)

UT-15 ASSAY: [redacted] analyzed the plasma samples with a validated [redacted] assay with a quantitation range of [redacted] Details of the assay were not submitted.

WARFARIN ASSAY: [redacted] analyzed the samples for R- and S-warfarin and for INR. The assay had a quantitation range of [redacted] Details of the assay for R- and S-warfarin were not submitted.

ANALYSIS: ***Pharmacokinetic Data*** Plasma concentration-time data for R- and S- enantiomers of warfarin were used to calculate the following PK parameters: AUC_{0-t}, AUC_{0-inf}, Cmax, Tmax, K_{el}, T ½, apparent oral clearance (CL/F), and apparent volume of distribution (Vd/F).

Summary statistics were generated for the PK parameters. Subjects completing both periods with sufficient plasma samples to determine the plasma concentration time curve were included in the summary statistics. The PK parameters were logarithmically transformed and evaluated using ANOVA. The 90% confidence intervals for the treatment differences for AUC and Cmax were calculated using the estimate and standard error of the estimate. If the test to reference ratio for AUC and Cmax fell within the 0.80 to 1.25 confidence interval then there was no effect on warfarin PKs from co-administration with UT-15.

Pharmacodynamic Data PD measures were determined from warfarin INR values that were both uncorrected and corrected for baseline. Corrected INR was determined by dividing each INR with the mean INR determined from the three predose values.

The following INR PD parameters were calculated: area under the pharmacodynamic effect time curve (AUEC $_{0\text{-}t}$), time to maximum PD effect (Tmax), and the maximum PD effect over the entire sampling phase (sponsor called Emax). Logarithmic transformation of the PD parameters were statistically evaluated using an ANOVA model examining mean differences. The subject within the sequence was used as the error term to evaluate the sequence effect of the α=0.10 level of significance. The mean square error of the model was used to evaluate the treatment and period terms at an α=0.05 level of significance. The 90% confidence intervals for the treatment differences for AUEC $_{0\text{-}t}$ and Emax were calculated using the estimate (test least-squares mean (LSM) minus reference LSM) and standard error of the estimate provided by the ANOVA. These intervals were exponentiated to give the 90% confidence intervals for the ratios between test and reference treatments. The test treatment was the PD effect of warfarin in the presence of UT-15 and the reference treatment was the PD effect in the absence of UT-15. Confidence intervals for the primary parameters that fell within 0.80 and 1.25 translated to no effect of UT-15 on warfarin PD.

RESULTS: Of the 46 subjects screened, 16 subjects were planned to be studied. A second cohort (Cohort 2) was formed that consisted of replacement subjects.

There were no significant protocol deviations.

Dropouts Three subjects (ID 005, 013 and 014) discontinued prior to dosing and one subject (ID 004) discontinued from the study on Day 2 of Period 1 prior to warfarin dosing because of intolerable emesis (attributed to UT-15). It is not known from the submission the reason for the other three dropouts. Thus, four subjects (IDs 017-020) were recruited for Cohort 2 and were sequentially assigned the treatment indicated for those subjects who discontinued. Subject 18 discontinued prior to receiving study medication. Subject 19 discontinued due to intolerable infusion site pain from UT-15 after data were collected. Thus, only 14 subjects completed the study.

Safety Overall, a higher incidence of adverse events occurred during UT-15 dosing (94% compared to 38% with vehicle). Over 80% were considered treatment related. No serious adverse events were reported during the study. There were no clinically significant changes in clinical laboratory results, vital signs, or EKGs.

Demographics Of the 16 subjects in Cohort 1 and 2, there were 10 males and 6 females. Subjects were between 19 – 43 years (mean ± SD, 27 ± 8 years). Subjects were primarily Caucasian (n=11). There were two Blacks, two Hispanics and one Other.

PHARMACODYNAMIC RESULTS: Continuous SC UT-15 did not affect INR in healthy subjects taking warfarin. The table below shows that test to reference ratio for AUEC $_{0\text{-}t}$ and for the maximum INR effect over the sampling phase fell within the 0.80 to 1.25 confidence interval.

Uncorrected for Baseline				
Parameter	UT-15 (n=15)	Vehicle (n=15)	Ratio	90% Confidence interval of ratio
AUEC $_{0\text{-}t}$ (hr)				
Mean	218.24	217.99	0.989	(0.955, 1.025)
Median	201.19	202.31		
Range				
INR				
Mean	2.07	2.035	0.958	(0.913, 1.005)
Median	1.88	2.060		
Range				
Corrected for Baseline				
AUEC $_{0\text{-}t}$ (hr)				
Mean	219.58	218.93	0.993	(0.949, 1.039)
Median	203.25	216.90		
Range				
INR				
Mean	2.07	2.04	0.961	(0.916, 1.009)
Median	1.85	1.95		
Range				

PHARMACOKINETIC RESULTS: UT-15 did not affect warfarin PK. The PK parameters for R- and S- warfarin and the respective test to reference ratios are shown in the table below.

PK parameters and treatment comparisons for R-warfarin				
Parameter	UT-15 (n=15)	Vehicle (n=15)	Ratio	90% Confidence interval of ratio
AUC $_{0\text{-}inf}$ (hr*ug/L)				
Mean ± SD	93,573 ± 19,918	94, 659 ± 22,893	1.001	(0.964, 1.040)
Range				
Cmax (ug/L)				
Mean ± SD	1781 ± 273	1807 ± 256	0.986	(0.918, 1.059)
Range				
PK parameters and treatment comparisons for S-warfarin				
AUC $_{0\text{-}inf}$ (hr*ug/L)				
Mean ± SD	65,482 ± 21,989	66,806 ± 20,240	0.981	(0.927, 1.038)
Range				
Cmax (ug/L)				
Mean ± SD	1,793 ± 305	1,854 ± 232	0.962	(0.888, 1.042)
Range				

Warfarin PK did not differ significantly between coadministration with vehicle and with UT-15. Mean R-warfarin Tmax was 1.5 and 1.9 hours when administered with vehicle and UT-15, respectively. Mean R-warfarin T ½ was ~ 52 hours with vehicle and with UT-15. R-warfarin elimination rate was also similar between vehicle and UT-15 (mean k_{el} of 0.0137/hr). S-warfarin results were similar to R-warfarin results. Mean S-warfarin Tmax was 1.1 and 1.7 hours with vehicle and with UT-15, respectively. Mean S-warfarin T ½ were similar with vehicle and with UT-15, ~42 hours. The elimination rate of S-warfarin was 0.0178/hour and 0.0173/hour when administered with vehicle and with UT-15, respectively.

CONCLUSION: Concomitant administration of UT-15 with warfarin does not significantly effect the pharmacokinetics or pharmacodynamics (INR) of warfarin.

REVIEWER'S COMMENTS: Individual data and some tables mentioned in the summary report were omitted in the submission. The sponsor will be submitting these data. The effects of warfarin on UT-15 PK were not determined.

The mean data shows that UT-15 does not effect the PK/PD of warfarin. Warfarin is a substrate for CYP1A2, and 3A4. S-warfarin is a substrate for CYP2C9 and R-warfarin is a substrate for CYP2C19. This *in-vivo* study shows that UT-15 does not significantly inhibit or induce these four isozymes consistent with the results of the *in-vitro* study (—— report 7049-100).

ADDENDUM: The sponsor submitted these data. The conclusion remains the same.

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APPENDIX III

Office of Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-272
Volume: 1 – 69 volumes
Compound: Uniprost (treprostinol sodium, UT-15)
Submission Date: 17 Oct 2000
Sponsor: United Therapeutics Corp.
Pharmacometrics Reviewer: Joga Gobburu
Primary Reviewer: Nhi Nguyen

Aim

To develop a PK (UT-15 concentrations) – PD (PAPm, RAPm, CI, Sv02, Dyspnea-BORG, Opiate use as a surrogate for injection site pain and walk) relationship for UT-15. Specifically, the review will attempt to answer the following questions:

1. What are the prognostic factors that determine the dose – UT-15 concentration relationship? (e.g.: total body weight, obesity, ideal body weight, gender, age, etc)
2. Are the changes in the hemodynamic variables related to the UT – 15 drug concentrations?
3. Are the changes in the target pharmacological effect on PAPm related to changes in the distance walked in 6 min?
4. Is the probability of the patients receiving opiate through the duration of the trial drug related and/or dose – dependent?
5. Is there any evidence that there is tolerance to UT-15's effect on its pharmacological effects (PAPm and/or pain)?

(The answers to the above questions are provided at the end of the review)

Methods

The sparse PK samples (2 to 3 samples per patient at fixed time points) collected in studies 04 and 05 will not allow reliable estimation of the PK parameters. Hence study 09 was employed to provide rich PK information. The data from the above 3 studies were combined to develop a PK/PD relationship.

Study 09

This phase 1 study utilized a single – center, open – label, non – randomized, chronic, dose escalation design. Each of the 14 volunteers received a continuous SC infusion of UT-15 at a fixed rate of 2.5 ng/kg/min for 7 days (Period 1). Dose increases occurred at 7-day interval, with each subject receiving 5 ng/kg/min during week 2 (Period 2), 10 ng/kg/min during week 3 (Period 3), and 15 ng/kg/min during week 4 (Period 4). There were no washout periods between periods. Serial plasma samples were collected throughout the 4 periods. Additional plasma samples were collected after the last dose.

Studies 04/05

This was an international, multicenter, double-blind, randomized, 12 – week, parallel placebo-controlled comparison of the safety and efficacy of chronic subcutaneous UT-15 plus conventional therapy to conventional therapy in patients with pulmonary hypertension. The study included a total of 470 patients with 233 in the UT-15 group and 237 in the placebo group. The 12 – week treatment phase consisted of an initial 1 – week dose initiation phase and an 11 – week chronic administration period. The patients were started at a dose rate of 1.25 ng/min/kg and the dose was increased in increments of 1.25 ng/min/kg. During the 12 – week treatment phase, exercise capacity, hemodynamic variables and steady state plasma samples were collected for analysis.

A two – compartment model was fitted to the concentration – time data. Although the drug was given as a subcutaneous infusion, the absorption was rapid enough to be ignored. Ideal body weight (IBW) was used as a covariate to describe a part of the inter – individual variability (IIV) of the PK parameters. These relationships were based on the allometric equations:

$$CL = \theta_{CL} \cdot (IBW/70)^{\beta} \qquad (1)$$

$$V = \theta_{V} \cdot IBW/70 \qquad (2)$$

All the clearances and volumes of distribution were modeled using the equations 1 and 2. The value of the exponent 'β' was estimated.

The concentration – effect relationships for the PD variables pulmonary artery pressure *mean* (PAPm), cardiac index (CI), pulmonary vascular resistance index (PVRI), right atrial pressure *mean* (RAPM), mixed venous oxygenation (Sv02) and Borg dyspnea scale were developed. The effect on PAPM, which is the principal pharmacological activity marker (based on the mechanism), was correlated with the distance walked in 6 min. All the hemodynamic variables were measured once at the baseline and once towards the end of the study. Distance walked in 6 min was measured for about 4 times in each patient. Data from the placebo and active treatment groups were analyzed simultaneously. The PD models used are elaborated under the corresponding sub-sections in 'Results and Discussion'.

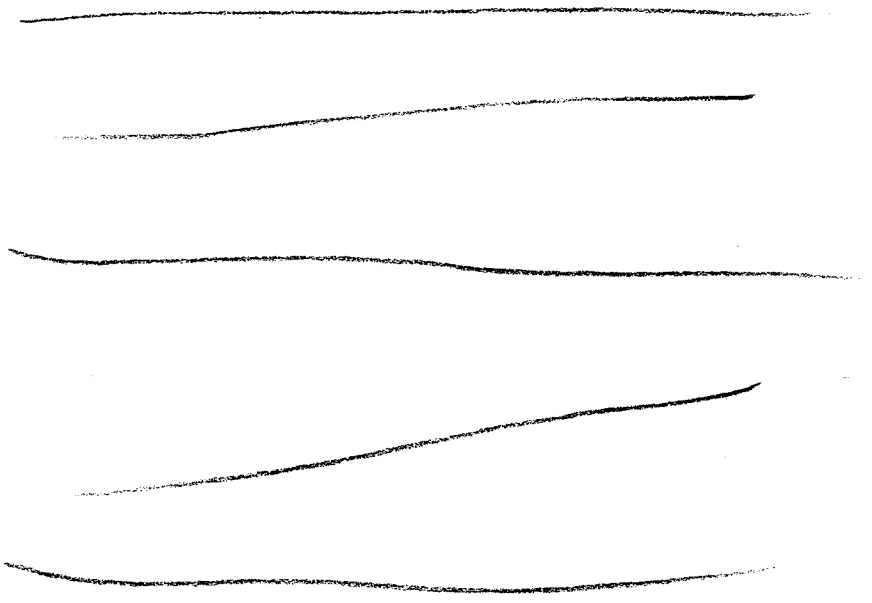
The PK/PD model was developed using NONMEM (ver 5, level 1.1). Where the data are rich (study 09) the first – order conditional estimation was used and first order estimation otherwise (studies 04 and 05). All data manipulations were performed using SAS (ver 6.12) and graphs were produced using Splus 2000.

Results and Discussion

Pharmacokinetics

Firstly, data from the study 09 were analyzed separately, to gain insights into the basic PK properties of UT-15. Figure 1 shows the PK profiles in a representative subject. The 2 – compartment model described the time course of concentrations well.

Figure 1. Observed versus fitted concentration – time profile in subject # 7 from study 09. The filled circles represent the observed concentrations, the solid line represents the population predicted concentrations and the dotted line represents the individual predicted concentrations.



The typical PK parameter estimates of UT-15 are presented in Table 1.

Table1. Population pharmacokinetic parameters of UT-15 based on the data from study#09.

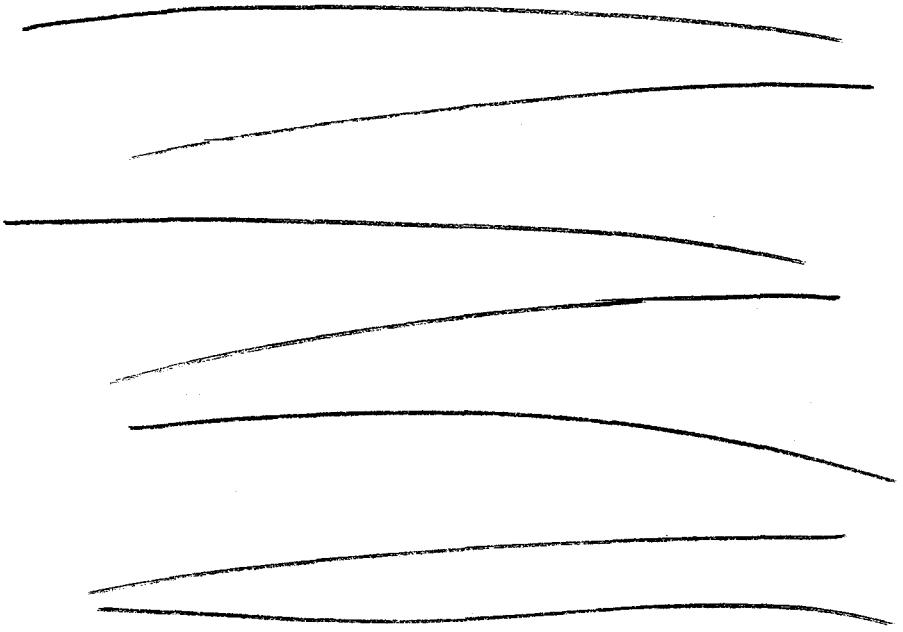
Parameter	CL, L/h/70kg	Vc L/70kg	Q L/h/70kg	Vt L/70kg
Mean	40.8	34.6	11.7	32.6
IIV (% CV)	11	33	-	39
Residual Error	22 (% CV)	0.03 (ug/L)		

IIV = inter-individual variability; Allometric equations were used to describe the body weight PK parameter relationships.

The data from the 3 studies (09, 04, 05) were now combined for estimating the individual PK parameters of the patients in the 04 and 05 studies. The observed versus predicted plot in Figure 2 shows that the predictions were reasonably close to the observed. Other time course plots do not add much to the understanding of the goodness of fit as only few samples were collected per patient.

Figure 2. Observed and predicted concentrations of the subjects in studies 09, 04 and 05. The model predicted the concentrations reasonably well. The triangles represent the population predictions, the circles represent the individual posthoc predictions and the solid line is the line

of identity. Particularly, the individual concentrations (circles) are predicted very well which will be used to drive the PD effects.



Observed concentration, ug/L

Table 2 below shows the typical estimates of the PK parameters when the data from the all the 3 studies were combined.

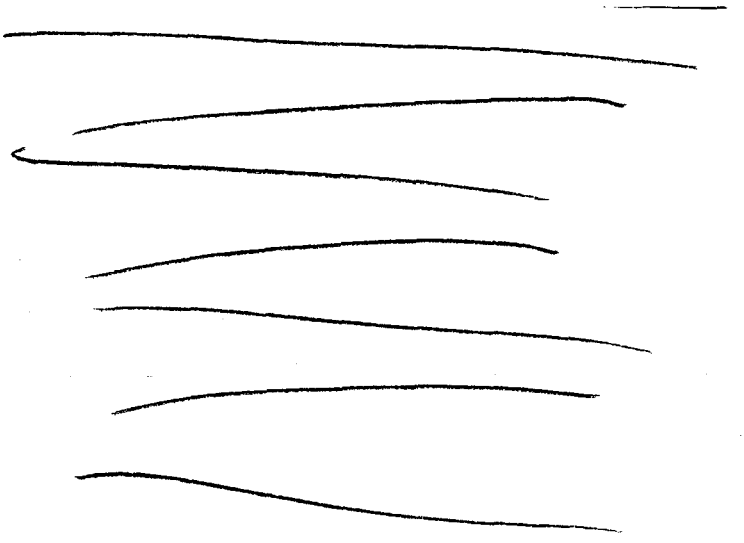
Table2. Population pharmacokinetic parameters of UT-15 based on the data from studies#09, 04 and 05.

Parameter	CL, L/h/70kg	Vc L/70kg	Q L/h/70kg	Vt L/70kg	β
Mean	29.7	13.6	25.3	37.1	1.52
IIV (% CV)	46	809	-	14	
Residual Error	13 (% CV)	0.14 (ug/L)			

IIV = inter-individual variability; Allometric equations were used to describe the ideal body weight – PK parameter relationships.

The use of ideal body weight instead of total body weight is more appropriate. 58 patients out of about 238 total patients, in which plasma concentrations were measured, are obese (BMI > 30 m^2). The drug has a volume of distribution at steady state of about 45 L for a 70kg (IBW) person. This is not a large volume of distribution and the drug may not be seeping into deeper tissues. Hence total body weight based dosing in obese patients may not be appropriate.

Figure 3. The time course of individual (model) predicted concentrations. As evident the concentrations, as a result of increasing dose rates, by and large go up over the duration of the trials. The average concentration is about 2 ug/L as determined from all concentrations beyond 1500 h.



There seem to be some minor differences in the estimates when the 09 study was analyzed alone vs. when the combined data were analyzed. The clearance estimate for the combined data is about 30 L/h/70 kg compared to a value of 40 L/h/70 kg for 09 study. The inter – individual variability is much larger for this study hence estimation could have been affected. Nevertheless, the individual concentrations are predicted quite well.

Pharmacodynamics

Mean Pulmonary Arterial Pressure (PAPm)

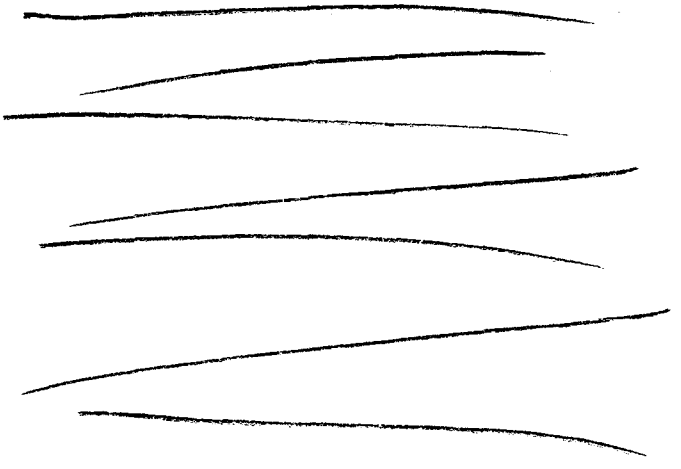
The individual predicted concentrations of UT-15 were employed to drive the change in the PAPm. The concentrations for the patients who received the vehicle were assumed to be zero. A linear model was adequate to describe this relationship. Figure 3 shows the age – baseline PAPm relationship. Table 3 shows the estimated PD parameters. No time trends or the existence of complications such as tolerance could be identified owing to limited measurements. The model that assumed that the slope of the concentration – PAPm line was zero (null hypothesis) yielded a –2 log likelihood estimate of 5194 as against 5176 for the model with the slope. Based on the chi-square distribution of the log likelihood ratios, the significance level is less than 0.001. The final model also included age as a covariate to describe inter-individual baseline PAPm differences.

Table 3. PD parameter estimates of UT – 15, for its effect on PAPm.

Parameter	PAPm0, mm Hg	Age Effect, mm Hg/yr	SLOPE, mm Hg/ug/L
Mean	58.7	-0.396 @	-1.04
SE (%)	1.1	20.2	12.4
IIV (%CV)	23		-
SE (%)	8.5		-
Residual Error	5.5 mm Hg		
SE (%)	8.4		

IIV = inter-individual variability; @Baseline PAPm0 = PAPm0 – 0.396*(AGE-50)

Figure 3. Age – baseline PAPm relationship described using a linear PD model. The observed (circles) and population predicted (solid line) baseline PAPm are shown.



Distance walked in 6 min

The relationship between the absolute change in PAPm and the distance walked in 6 min was modeled using placebo effect model and a linear drug effect model. There appeared to be a relatively abrupt increase in the distance walked in 6 min between the baseline and week 1, which gradually disappeared. This behavior was modeled using a bi-exponential equation, as follows:

$$\text{Placebo Effect} = \text{DIST}(0) + \text{GAIN} \cdot (e^{-k_{plcb} \cdot \text{time}} - e^{-k_{dis} \cdot \text{time}}) \quad (3)$$

$$\text{Drug Effect} = \gamma_{walk} \cdot \Delta\text{PAPm} \quad (4)$$

$$\text{Distance walked in 6 min} = \text{Placebo Effect} + \text{Drug Effect} \quad (5)$$

Where, DIST(0) is the baseline distance walked, GAIN is the scaling factor for the magnitude of placebo effect, k_{plcb} is the first order rate constant for the increase in the placebo effect, k_{dis} is the first order rate constant for the waning of the placebo effect and/or the time course of

disease progression, γ_{papm} is the slope of the relationship between the change in PAPm, ΔPAPm, and distance walked in 6 min. The data did not support the use of an Emax drug effect model.

The PD parameter estimates are shown in Table 4. The NYHA class (2, 3, or 4), age and etiology (PPH, CSPS or CTD) were found to be important determinants ($p < 0.01$) of baseline distance walked, DIST(0). However, the magnitude of the influence of etiology was about 1% of that of PPH and hence judged unimportant, though significant. The final model did not contain etiology as a covariate since estimation of the other parameters was not affected by the removal of etiology. Figure 4 shows the typical time – UT-15 concentration – PAPm – Distance walked in 6 min relationships using the dosing history of a random patient from the 04/05 studies.

Figure 4a. The typical time – UT-15 concentration relationship simulated using the actual dosing history of a random 50 yr old patient from the 04/05 studies.

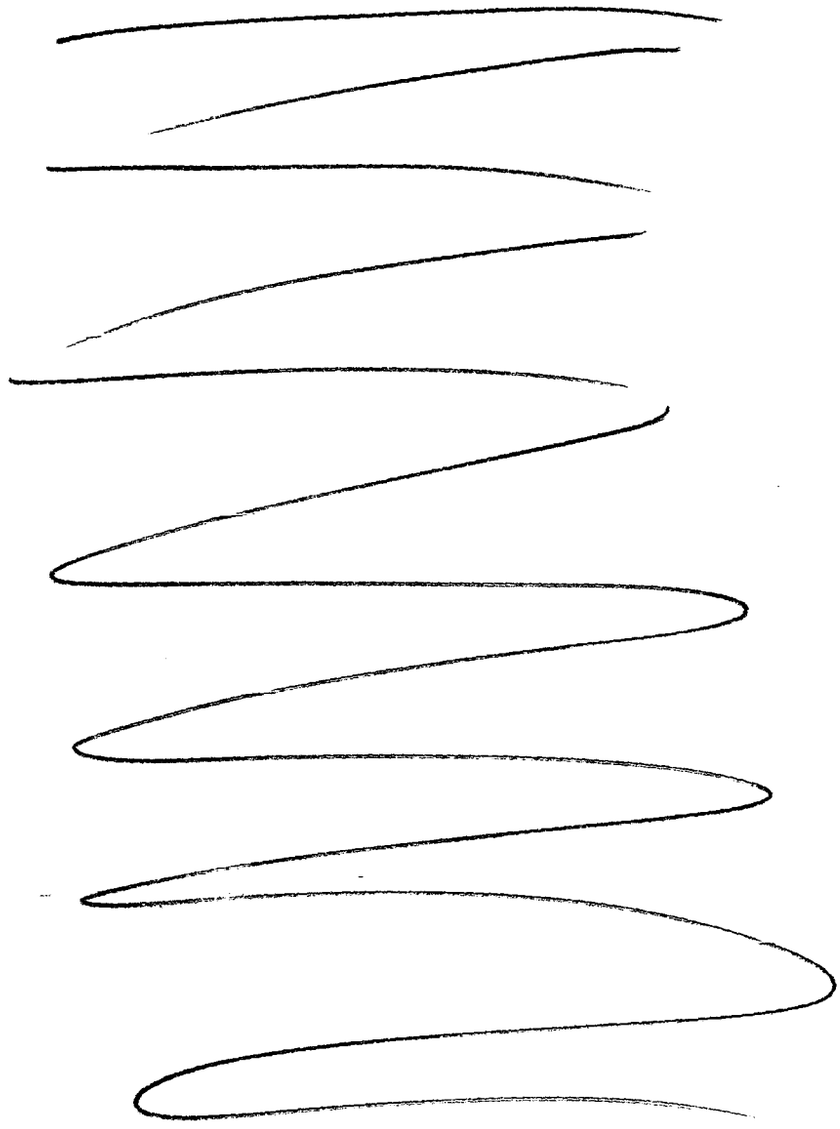


Figure 4b.

Figure 4c. The typical 'net placebo effect' on distance walked in 6 min. The placebo effect reaches a peak in about 1 week and decreases over next several weeks.

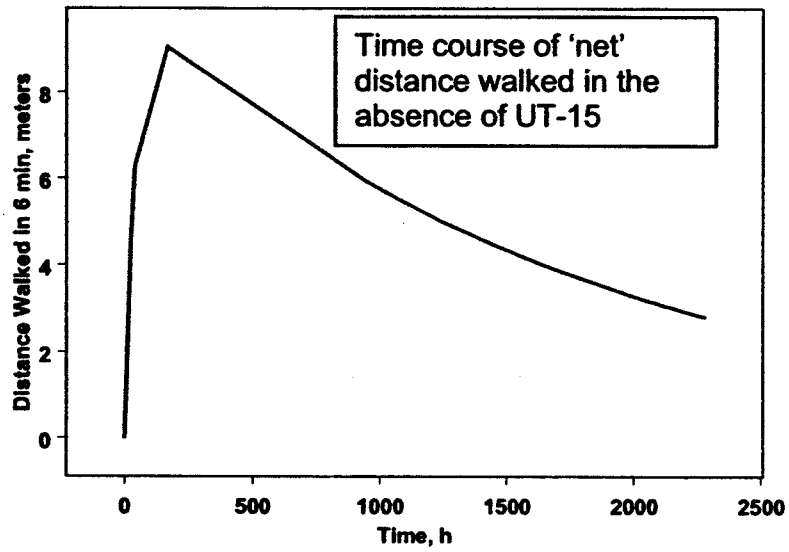


Figure 4d. The typical time course of 'gross' placebo effect for the NYHA II, III and IV patients. Essentially the curve in figure 4c is multiplied by the typical baseline distances walked by the patients.

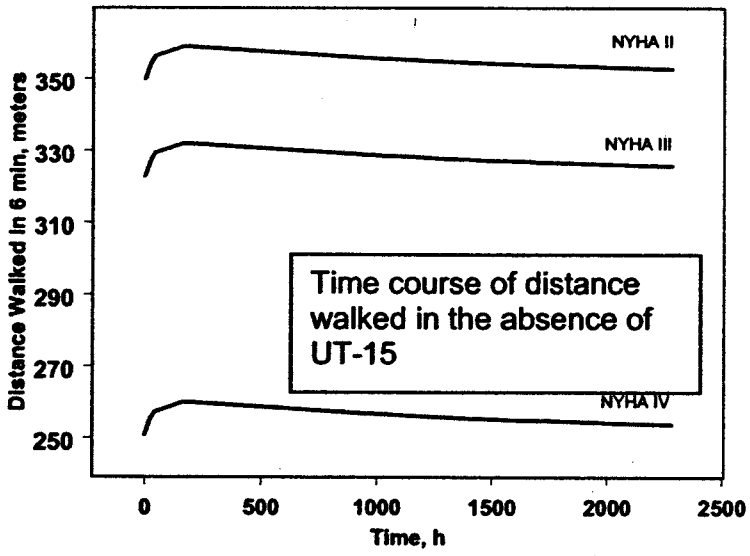


Figure 4e. The typical change in PAPm versus the distance walked in 6 min that is purely attributable to UT-15 (placebo corrected).

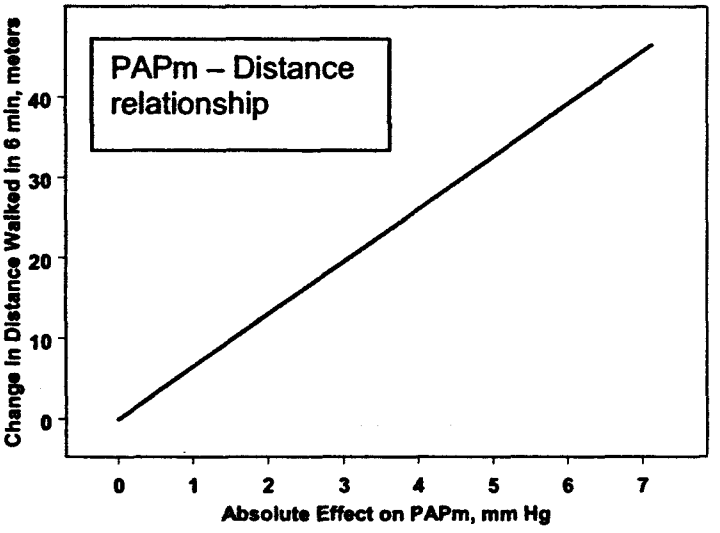


Table 4. PD parameter estimates of UT – 15, for its effect on walk.

Parameter	E0age meters/yr	γwalk meters/mm Hg	k_{plcb} h^{-1}	k_{dis} h^{-1}	GAIN	E0 NYHA II	E0 NYHA III	E0 NYHA IV
Mean	-0.946	6.53	0.000561	0.0255	10.1	350	323	251
SE(%)	28.4	28.6	18.2	42.4	23.1	2.3	1.4	4.7
IIV (%CV)	23	88	1200	700				
SE(%)	8.6	92.4	46.9	151.5				
Residual Error	33 meters							
SE(%)	9.5							

IIV = inter-individual variability

Dyspnea – BORG:

The dyspnea – BORG scale ranges are supposed to be between 0 and 10. The higher the score the worse is the anguish. However, the sponsor extended the scale to include values as high as 20. There were only 6 cases where the BORG scale was above 10 and were not converted to 10, which is the maximum. Although BORG score is an ordinal variable, the range of the scores is wide enough to be treated as a continuous scale. The dyspnea was assessed in the patients on 3 occasions (0, 6, 12 weeks). The UT-15 concentration – dyspnea relationship could be described using an exponential decline model, as follows:

$$BORG = BORG(0) \cdot e^{\gamma_{BORG} \cdot UT15Conc} \qquad (5)$$

Where, BORG(0) is the baseline BORG score, γ_{BORG} is the rate constant for the change in the BORG score with UT-15 concentrations (UT-15Conc). The reason for using the exponential model instead of a linear model is to constrain the values of BORG from being less than zero,

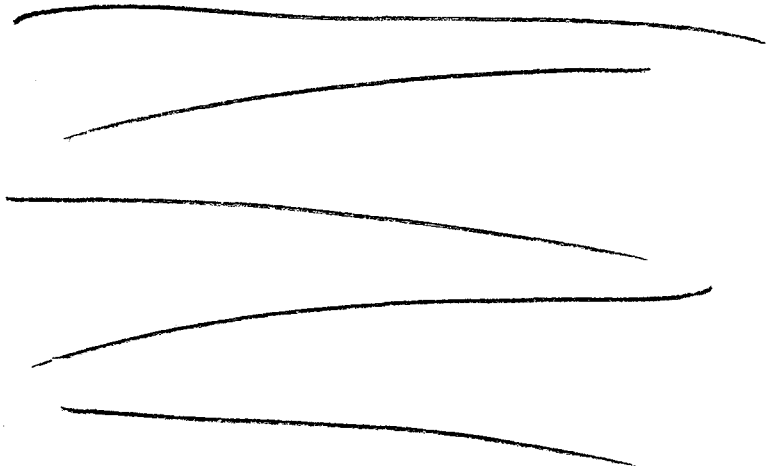
which is the lowest value possible. A linear model could produce negative values for BORG score. Small values of the rate constant in the exponential model can essentially behave like a linear model, with the added advantage of protecting the predictions from being less than zero. The PD parameter estimates are shown in Table 5 and the fittings are shown in Figure 5.

Table 5. Estimated PD parameters of UT 15 for its effect on dyspnea (BORG).

Parameter	BORG(0)	γ_{BORG}, score/ug/L
Mean	4.25	-0.11*
SE (%)	2.4	18.4
IIV (%CV)	49	11
SE (%)	9.3	71
Residual Error	1.2	
SE (%)	8	

IIV = inter-individual variability; $p < 0.001$

Figure 5. UT-15 concentration versus BORG score relationship described using an exponential decay model.



Mean Right Arterial Pressure (RAPm):

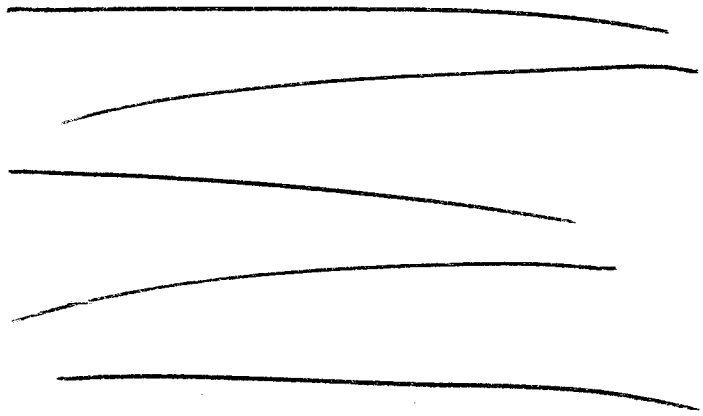
The concentration – RAPm relationship was described using a linear model, as shown in Figure 6. The estimated parameters are shown in Table 6. **The slope estimated was not significantly different from zero (p>0.05).**

Table 6. Estimated PD parameters of UT-15 for its effect on RAPm.

Parameters	Baseline RAPm, mm Hg	SLOPE mm Hg/ug/L
Mean	10.4	-0.22 (NS)
SE (%)	2.6	100
IIV (%CV)	48	-
SE (%)	7.8	-
Residual Variability	3.5 mm Hg	
SE (%)	10.2	

IIV = inter-individual variability; NS=not significant, p>0.05

Figure 6. Concentration – RAPm relationship as described using a linear model. The slope of the line was not significantly different from zero (p>0.05).



PVRI:

The concentration – PVRI relationship was described using a linear PD model, as shown in Figure 7. The estimated PD parameters are presented in Table 7.

Figure 7. Concentration – PVRI relationship as described using a linear PD model.

Table 7. Estimated PD parameters of UT-15 for its effect on PVRI.

Parameters	Baseline PVRI, mm Hg/L/min/m^2	SLOPE mm Hg/L/min/m^2/ug/L
Mean	26.2	-1.59*
SE (%)	2.4	13.7
IIV (%CV)	47	-
SE (%)	14.1	-
Residual Variability	5.7 mm Hg/L/min/m^2	
SE (%)	17.8	

IIV = inter-individual variability; * $p < 0.001$

$SV0_2$

The concentration – $SV0_2$ relationship was described using a linear PD model, as shown in Figure 8. The estimated PD parameters are presented in Table 8. The slope was found to be significantly different from zero ($p = 0.01$).

Figure 8. Concentration – SvO_2 relationship as described by a linear PD model.

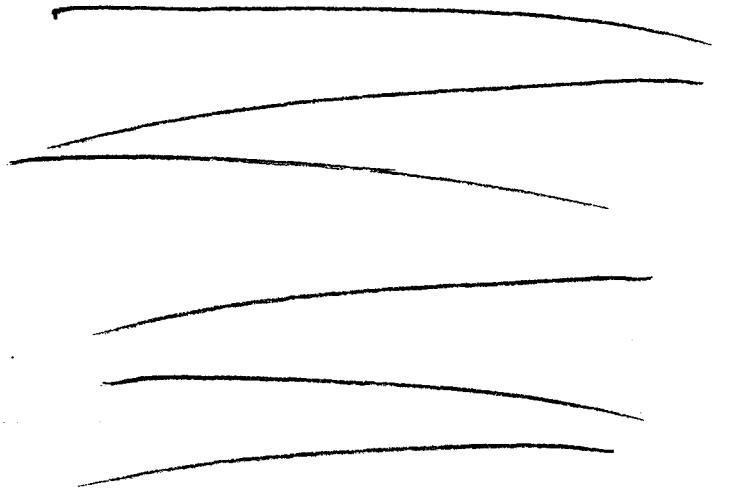


Table 8. Estimated PD parameters of UT-15 for its effect on SvO_2.

Parameters	Baseline SvO_2, %	SLOPE % / ug/L
Mean	60.8	0.756*
SE (%)	0.8	33.2
IIV (%CV)	14	-
SE (%)	9.9	-
Residual Variability	6.8 % SvO_2	
SE (%)	13.7	

IIV = inter-individual variability; * p = 0.01

Cardiac Index (CI):

The concentration – CI relationship was described using a linear PD model, as shown in Figure 9. The estimated PD parameters are presented in Table 9. The slope was found to be significantly different from zero ($p < 0.001$).

Figure 9. Concentration – Cardiac Index relationship fitted to a linear model.

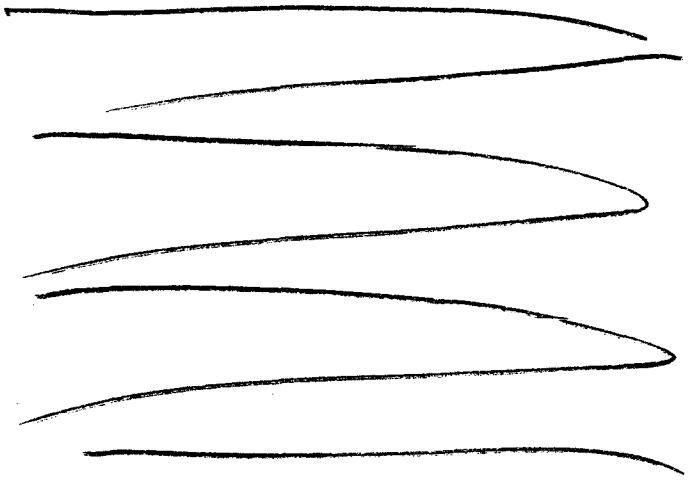


Table 9. Estimated PD parameters of UT-15 for its effect on cardiac index.

Parameters	Baseline CI L/min/m^2	SLOPE L/min/m^2 / ug/L
Mean	2.31	0.0662*
SE (%)	1.7	26.4
IIV (%CV)	34	-
SE (%)	14.4	-
Residual Variability	0.42	
SE (%)	14 L/min/m^2	

IIV = inter-individual variability; * $p < 0.001$

OPIATE MEDICATION AS SURROGATE FOR INJECTION SITE PAIN

The probability of a patient to be administered opiate was correlated with the UT-15 dose given currently. The assumption was that opiate was administered as a consequence of injection site pain. Table 10 shows the observed percentage of patients who received opiate at various dose rate intervals.

Table 10. Probability of opiate administration, as a surrogate for injection site pain at various intervals of dose rates.

Dose Rate ng/min/kg	Percentage of patients given opiate #
0	0.25
>0	10.02
>5	24.65
>10	19.78

Each patient had multiple observations over 12 weeks; percentage is calculated as the number of patients given opiate times 100 divided by the total number of patients in each of the above dose ranges (column#1).

In table 10 all observations per patient over the duration of the study are considered. There are several confounding factors in interpreting the values in table 9. The number of observations per patient varies. The time course of the need for an opiate is not captured. That is, a patient may be on an analgesic for some time before he/she is switched over to an opiate. So, as time progresses there may be more and more patients with intolerable pain and need opiate. The dose also increases as time progresses. Hence it is difficult to discern dose dependency of the effect. Although not definitive, it 'appears' as if the probability of opiate use is higher with higher dose input rate.

Conclusions:

1. What are the prognostic factors that determine the dose – UT-15 concentration relationship? (e.g.: total body weight, obesity, ideal body weight, gender, age, etc)

   UT-15 exhibits linear pharmacokinetics, implying that higher doses would produce higher concentrations, within the concentration range studied. When total body weight (TBW) was employed to describe the inter-individual variability in clearances and volumes of distribution, obesity showed up as a significant covariate. Thus ideal body weight (IBW) instead of TBW was used as a covariate. The dosing of UT-15 should be based on IBW and not on TBW. The volume of distribution is not very big to support the hypothesis that UT-15 distributes into deeper tissues. Hence dosing based on TBW will result in overestimating the required dose.

2. Are the changes in the hemodynamic variables related to the UT – 15 drug concentrations?

   All hemodynamic variables, except for RAPm, were significantly correlated with the UT – 15 concentrations. However, the slopes of the relationships seemed to be rather shallow. Table 12 below presents the average changes in the PD variables for an average UT-15 concentration of 2 ug/L (see Figure 3).

3. Are the changes in the target pharmacological effect on PAPm related to changes in the distance walked in 6 min?

The changes in PAPm correlated well with the changes in the distance walked in 6 min. There appeared to be a significant placebo effect, where the patients showed a transient increase in the distance walked in 6 min by the first week that declined gradually. Patients with different NYHA class had different baseline distances walked in 6 min, but no difference in the placebo or drug effect. Table 12 shows the average improvement in the distance walked in 6 min.

4. Is the probability of the patients receiving opiate through the duration of the trial drug related and/or dose – dependent?

Though not definitive from the crude analysis of the observed data, the probability of the patients receiving opiate appears to be UT-15 dose – dependent. Higher dose rates showed higher probabilities.

5. Is there any evidence that there is tolerance to UT-15's effect on its pharmacological effects?

Tolerance is said to have developed when the 'efficacy' (Emax) decreases and/or 'sensitivity' (EC50) increases with higher concentrations of the drug or a biological substance triggered by the drug concentrations. So, consider a simple hypothetical situation that UT-15 was given at a fixed rate for a long duration and in addition let us also assume that the disease state stays constant. Then, if tolerance develops then the effect (at pharmacodynamic steady state) would not stay at a constant value but declines as exposure continues. Physiologically this is possible as a result of a loss of the receptors or due to the initiation of a feed-back mechanism directly or indirectly by the drug and/or the pharmacological effect. An example is that of the tachycardia produced by the calcium channel blocker Nifedipine at higher rates of drug input as a feed-back effect to the anti-hypertensive effect. Tolerance, thus, if any would be reflected in the effects on the hemodynamic variables such as PAPm and/or pain. Unfortunately, there are only 2 measurements of almost all hemodynamic variables (baseline and 12 weeks), which will not permit any quantitative or qualitative assessments. Although not certain, the need for opiate therapy is dose – dependent (see Table 10).

Table 11. Model predicted average changes in the primary and secondary end points at an average UT-15 concentration of 2 ug/L (see Figure 3 for the range of UT-15 concentrations).

PD Variable	Baseline	Effect	% Effect
PAPm, mm Hg	58.7	-2.04	-3.5
Distance, meters	251[a]	12.5[b]	5.0
BORG	4.25	0.8	18.8
PVRI, mm Hg / L/min/m^2	26.2	-3.2	-12.2
SvO_2, %	60.8	1.5	2.5
CI, L/min/m^2	2.31	0.12	5.2

[a] Baseline value for NYHA IV; [b] Pure drug effect (placebo corrected)