

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-272	Brand Name	Remodulin™
OCPB Division (I, II, III)	I	Generic Name	Treprostinol sodium, UT-15
Medical Division	Cardio-Renal Drug Products	Drug Class	Prostacyclin analogue
OCPB Reviewer	B. Nhi Nguyen & Jogarao Gobburu	Indication(s)	Pulmonary artery hypertension
OCPB Team Leader	Angelica Dorantes	Dosage Form	Injection
		Dosing Regimen	1.25 ng/kg/min x 1 wk, then increase weekly by a maximum of 1.25 ng/kg/min. After 4 wks, increase weekly by a maximum of 2.5 ng/kg/min
Date of Submission	10/16/00	Route of Administration	Continuous subcutaneous infusion
Estimated Due Date of OCPB Review	3/16//01	Sponsor	United Therapeutics Corp.
PDUFA Due Date	4/16/01	Priority Classification	1PV
Division Due Date	3/16/01		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1	1	
Isozyme characterization:				
Blood/plasma ratio:	X	1	1	
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
<u>Healthy Volunteers-</u>				
acute dose:	X	1	1	
chronic dose:	x	1	1	
Patients-				
acute dose:				
chronic dose:				
Dose proportionality -				
fasting / non-fasting acute dose:	X	1	1	
fasting / non-fasting chronic dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	
In-vivo effects of primary drug:	X	1	1	
In-vitro:	X	1	1	
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	X	1	1	

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:	x	1	1	
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	2	2	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; acute / multi dose:				
replicate design; acute / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		11	11	
<i>Filability and QBR comments</i>				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	N/A	Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	1a. Is there an exposure-response relationship? b. If yes, does tolerance develop to UT-15? 2. Has the metabolism of UT-15 been adequately characterized?			
Other comments or information not included above				
Primary reviewer Signature and Date PM reviewer Signature and Date	B. Nhi Nguyen 3/05/01 Jogarao Gobburu 3/05/01			
Secondary reviewer Signature and Date	Angelica Dorantes 3/05/01			

CC: NDA 21-272, HFD-850(Electronic Entry or Lee), HFD-110(CSO), HFD-860(Dorantesa, Mehta), CDR (B. Murphy)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-272	SUBMISSION DATES
TYPE:	1PV	Original NDA 10/16/00
BRAND NAME:	Remodulin™	Original amendment N-BB 1/25/01
GENERIC NAME:	treprostinol sodium	Original amendment N-BB 2/28/01
ALTERNATE NAMES:	UT-15, uniprost, LRX-15, 15AU81, BW A15AU, U-62,840	
DOSAGE STRENGTH:	1.0, 2.5, 5.0, 10.0 mg/mL injection	
SPONSOR:	United Therapeutics Corp.	

DIVISION OF PHARMACEUTICAL EVALUATION: I
PRIMARY REVIEWER: B. Nhi Nguyen, Pharm.D.
PHARMACOMETRICS REVIEWER: Jogarao Gobburu, Ph.D.
TEAM LEADER: Angelica Dorantes, Ph.D.

TABLE OF CONTENTS

	PAGE
RECOMMENDATION (COMMENTS TO THE SPONSOR)	4
COMMENTS TO THE MEDICAL OFFICER	4
EXECUTIVE SUMMARY	6
QUESTION BASED REVIEW	8
LABELING RECOMMENDATIONS	15
APPENDIX I: PROPOSED PACKAGE INSERT	18
APPENDIX II: REVIEW OF INDIVIDUAL STUDIES	33
<i>IN-VITRO</i> PLASMA PROTEIN BINDING STUDY	
Covance Report 7049-106 <i>In vitro</i> protein binding of [¹⁴ C]-UT-15 in human plasma	34
<i>IN-VITRO</i> METABOLISM STUDY	
Covance Report 7-49-100 Effect of UT-15 on cytochrome P450 isozymes	37
MASS BALANCE STUDY	
P01:10 Mass balance, metabolite profiling and safety study of [¹⁴ C] UT-15 following an 8-hour SQ infusion in healthy males	39
PHARMACOKINETICS	
P01:02 Bioavailability of SQ vs. IV UT-15 in NYHA Class III/IV patients with primary pulmonary hypertension (PPH)	47
P01:07 Bioavailability of SQ vs. IV UT-15 in healthy volunteers	54
P01:09 Pharmacokinetics of chronic, escalating doses of continuous SQ UT-15 in healthy volunteers	59
PHARMACOKINETICS & PHARMACODYNAMICS	
P01:03 Safety and efficacy of chronic (8 weeks) SQ UT-15 plus conventional therapy vs. conventional therapy in severe PPH	66
P01:04 and P01:05 Safety and efficacy of chronic (12 weeks) SQ UT-15 plus conventional therapy vs. conventional therapy in pulmonary artery hypertension	72
SPECIAL POPULATIONS	
P02:01 Pharmacokinetics in portopulmonary hypertension with mild and moderate hepatic insufficiency	82
DRUG INTERACTION STUDIES	
P01:08 Effects of acetaminophen on the pharmacokinetics of UT-15 in healthy volunteers	86
P01:12 Effect of UT-15 on warfarin PK/PD in healthy volunteers	90
APPENDIX III: PHARMACOMETRICS REVIEW	95

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-272 and find the clinical pharmacology and biopharmaceutics section acceptable provided the following **comments to the sponsor** are addressed:

1. The sponsor should identify the enzymes responsible for the metabolism of UT-15.
2. The sponsor should make every effort to identify the fifth metabolite (HU1).
3. The sponsor should make every effort to determine the activity of all five metabolites.
4. Labeling comments #1 - 7 should be adequately addressed if the medical officer also concurs.

COMMENTS TO THE MEDICAL OFFICER

1. Exposure-Response

The PK/PD analysis performed on the P01:04/05 data shows that UT-15 has a statistically significant effect on the hemodynamic variables PAPm, CI, SvO₂ and PVRI, and dyspnea (BORG score). Additionally, the change in PAPm correlated with the distance walked in six minutes by the patients. Although these relationships were statistically significant, the slope of the relationship was very shallow. Based on the shallow slope and the EC₅₀ derived from *in-vitro* experiments, the data are probably in the lower part of the exposure – response curve. Although uncertain, crude analysis suggests a dose-dependent opiate (surrogate for injection site pain) use.

2. Tolerance

We were unable to assess if patients develop tolerance to UT-15 with respect to its effect on PAPm. Although uncertain, crude analysis suggests a dose-dependent opiate (surrogate for injection site pain) use. Both PAPm and injection site pain are biomarkers of pulmonary and systemic vasodilation. Tolerance implies that higher exposure of the drug not necessarily produces proportionally greater effects. The fact that the PAPm was measured once at baseline and once towards the end of the study will not permit explorations of whether tolerance develops to UT-15. The frequency of patients with pain is dependent on dose rate in the P01:04/05 studies. The percentage of patients receiving opiates did not decrease at higher dose rates.

3. Dose adjustment for body size

Analysis of studies P01:04/05 and P01:09 data suggest that dosing adjusted for ideal body weight (IBW) is more appropriate than dosing based on total body weight. The volume of distribution at steady state is not very large (~50 L/kg in a 70 kg IBW person) implying that the drug is not distributed into deeper adipose tissues.

4. Hepatic insufficiency (HI)

The sponsor studied patients with mild and moderate HI. The sponsor found that patients with mild and moderate HI have 2x and 4x higher C_{max}, respectively, and 3x and 5x higher AUC_{0-inf}

than healthy subjects. Clearance is decreased by ~60% in mild HI and 80% in moderate HI compared to healthy adults. Effect of UT-15 in severe HI has not been established.

5. Renal insufficiency

UT-15 has not been studied in patients with renal insufficiency. UT-15 forms five metabolites (activity unknown), all of which are excreted in the urine. One metabolite is unidentified, and the other four are products of phase I and phase II biotransformation reactions. It may be possible for the metabolites to accumulate in severe renal insufficiency. Additionally, the T_{1/2} of UT-15 is between 2-4 hours, however in the radiolabeled study, the radioactive T_{1/2} was 65 hours. A plausible reason for this long T_{1/2} is a slowly cleared metabolite.

6. Metabolism

The sponsor has not identified the enzymes responsible for the metabolism of UT-15.

OCPB briefing held on March 9, 2001.

(Lesko, Lee P, Karkowsky, Lazor, Malinowski, Mehta, Sahajwalla, Dorantes, Gobburu, Bonapace, Fetterly, Kim J, Sobel, Chou W, Collins, Hussain were present.)

B. Nhi Nguyen, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary reviewer

Jogaroo Gobburu, Ph.D.
Division of Pharmaceutical Evaluation I
Pharmacometrics reviewer

FT Initialed by Angelica Dorantes, Ph.D. _____

CC list: HFD-110: NDA 21-272; HFD-860: (Nguyen, Gobburuj, Mehta); CDER Central Document Room

EXECUTIVE SUMMARY

United Therapeutics Corp. is seeking the approval of UT-15 for the long-term treatment of pulmonary arterial hypertension in NYHA Class II-IV patients. UT-15 for injection contains the active ingredient treprostinol sodium, a structural analogue of prostacyclin which vasodilates pulmonary and systemic vasculatures, thus reducing pulmonary and systemic pressures. It is administered as a continuous subcutaneous (SC) infusion. The proposed initial infusion is 1.25 ng/kg/min to be increased weekly by a maximum of 1.25 ng/kg/min for the first 4 weeks. Thereafter, the dose may be increased weekly by a maximum of 2.5 ng/kg/min. The usual dose studied in pharmacokinetic studies ranged from 2.5 – 15 ng/kg/min.

Section 6 of NDA 21-272 includes 12 studies. An additional warfarin drug interaction study was later submitted and is also included in this review. Of the 12 studies submitted with the original NDA, ten were reviewed. These include three pharmacokinetic studies (acute and chronic), two PK/PD studies (8 and 12 weeks duration), one mass balance study, one *in-vitro* metabolism study, one *in-vitro* plasma protein binding study, one hepatic insufficiency study and one drug interaction study. The remaining two studies not reviewed are animal studies.

UT-15 is at least 91% bound to human plasma proteins. Absorption of SC UT-15 is relatively rapid and complete with an absolute bioavailability of ~ 100%. The rate of absorption following a SC infusion is slower than the elimination rate after an IV infusion. UT-15 is largely metabolized in the liver with less than 4% excreted unchanged in the urine. Five metabolites of unknown activity are formed. Each metabolite comprises 10-16% of the dose and are excreted primarily in the urine. Approximately 78.6% of the dose is excreted in the urine and 13.4% is excreted in the feces. *In-vitro* human hepatic cytochrome P450 studies indicate that UT-15 does not inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1 or 3A. The enzymes responsible for UT-15 metabolism have not been identified.

The pharmacokinetics of SC UT-15 are linear over the dose range of 1.25 – 22.5 ng/kg/min (0.03 – 8 µg/L) and could be described by a two-compartment body model. The terminal half-life of UT-15 is ~2-4 hours. Clearance is ~ 30 L/hr/70 kg ideal body weight person. Volume of distribution of the central compartment is small, ~ 14 L/70 kg ideal body weight person. According to our population PK analysis there were no differences in pharmacokinetics with respect to gender, age or obesity. Patients with mild and moderate hepatic insufficiency have 2x and 4x higher C_{max}, respectively, and 3x and 5x higher AUC_{0-inf} than healthy subjects. Clearance is decreased ~60% and 80% in mild and moderate HI, respectively. The effect of renal insufficiency is unknown, but may be of concern since the metabolites are excreted in the urine. There is no significant drug interaction between UT-15 and warfarin or UT-15 and acetaminophen.

In support of approval for this NDA, the sponsor conducted one large clinical efficacy trial which is actually two combined trials, P01:04 and P01:05. Based on the PK/PD analysis (nonlinear mixed effects modeling) performed on the P01:04 / 05 data, UT-15 has a statistically significant effect on the hemodynamic variables mean pulmonary artery pressure (PAPm), cardiac index, mixed venous saturation, and pulmonary vascular resistance index, and dyspnea (BORG score). Further, the change in PAPm correlated with the distance walked in 6 min by the

patients. The model predicted that PAPm changes ~1% (relative to the placebo group) with one unit change in concentration or dose, and the distance walked in 6 min changes ~2% with one unit change in PAPm. These results are consistent with the conventional statistical findings. Although these relationships were statistically significant the slope of the relationship was very shallow. Based on the shallow slope and the EC₅₀ derived from *in-vitro* experiments, the data are probably in the lower part of the exposure – response curve. Although uncertain, crude analysis suggests a dose-dependent opiate (surrogate for injection site pain) use.

The assay (LC/MS/MS) used to quantify UT-15 was precise and accurate, but insensitive with respect to the lower limit of quantitation. Thus, the sponsor was unable to measure UT-15 concentrations for an adequate duration to appropriately assess the pharmacokinetics in several studies.

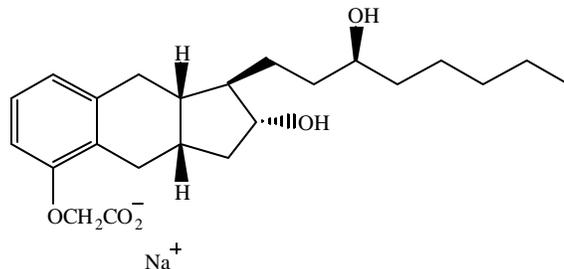
QUESTION BASED REVIEW

I. INTRODUCTION

A. WHAT ARE THE HIGHLIGHTS OF THE CHEMISTRY, FORMULATION AND PHYSICAL-CHEMICAL PROPERTIES OF THE DRUG AND DRUG PRODUCT?

STRUCTURE

UT-15 is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid monosodium salt.



molecular formula: C₂₃H₃₃NaO₅

molecular weight: 412.49

FORMULATION AND MANUFACTURING

UT-15 for injection contains the active ingredient treprostinol sodium. It is a white to cream colored powder. It will be packaged in flint glass vials, and supplied in 20 mL multi-use vials in dosage strengths of 1.0, 2.5, 5.0 and 10 mg/mL of UT-15. The to-be-marketed formulations for UT-15 (see table below) were used in all of the studies reviewed.

Ingredient	mg per mL			
Treprostinol	1.0	2.5	5.0	10.0
Sodium citrate, USP (dihydrate)	6.3	6.3	6.3	6.3
Hydrochloric acid, NF (mg, q.s. pH 6.3 to 6.5)	0.4	0.2	0.4	0.3
Metacresol, USP	3.0	3.0	3.0	3.0
Sodium hydroxide, NF/BP	0.24	0.32	0.62	1.2
Sodium chloride, USP	5.3	5.3	5.3	4.0
Water for injection, USP/EP	q.s.	q.s.	q.s.	q.s.

Sodium hydroxide and hydrochloric acid are added to obtain a target pH of 6.4 (range 6.3-6.5). It is chemically stable at room temperature and neutral pH.

UT-15 injection for commercial distribution will be manufactured, packaged, and labeled by Cook Pharmaceutical Solutions, Bloomington, IN. NDA demonstration batches and Phase 3 clinical batches were manufactured by Cook Pharmaceutical Solutions. UT-15 is manufactured by SynQuest, Inc., Chicago, IL.

SOLUBILITY AND PARTITION COEFFICIENT

UT-15 is freely soluble in methanol, ethanol, and high pH buffers. It is practically insoluble in water and low pH buffers. The apparent pKa value of UT-15 determined by aqueous titration is 4.5 with 20% ethanol as co-solvent. UT-15 distributes into the octanol layer at all pHs. The octanol/water partition coefficients for UT-15 are shown below.

	pH 2	pH 4	pH 6	pH 8	pH 10	water
Partition coefficient	1.7	2.0	1.4	0.43	0.43	1.5
Buffer	phosphate	citrate	citrate	phosphate	borate	

B. WHAT IS THE PROPOSED MECHANISM OF ACTION AND THERAPEUTIC INDICATION?

UT-15 is vasodilates pulmonary and systemic vasculatures and inhibits platelet aggregation. United Therapeutics Corporation is seeking the approval of UT-15 for the long-term treatment of pulmonary arterial hypertension (PAH) in NYHA Class II - IV patients. Thus, the sponsor is seeking approval to treat patients with primary and secondary pulmonary hypertension.

C. WHAT IS THE PROPOSED DOSAGE AND ADMINISTRATION?

The proposed initial infusion is 1.25 ng/kg/min to be given as a continuous subcutaneous (SC) infusion. If intolerable, the initial infusion can be reduced to 0.625 ng/kg/min. The infusion can be increased weekly by a maximum of 1.25 ng/kg/min for the first 4 weeks. Thereafter, the infusion can be increased weekly by a maximum of 2.5 ng/kg/min for the remaining duration of the infusion. This is the same dosing scheme used in the pivotal clinical study, P01:04/05.

A MiniMed (Model 506) positive pressure micro-infusion pump is used to infuse UT-15 subcutaneously via an abdominal site.

II. CLINICAL PHARMACOLOGY

A. WAS THERE REASONABLE BASIS FOR THE SELECTION OF THE CLINICAL ENDPOINTS, SURROGATE ENDPOINTS OR BIOMARKERS AND WERE THEY MEASURED PROPERLY TO ASSESS EFFICACY AND SAFETY IN CLINICAL PHARMACOLOGY STUDIES ?

The clinical endpoint measured was distance walked in 6 minutes. This is typically used clinically to assess exercise capacity in patients with PAH. This was assessed by standard methods (measuring the distance a patient walked in 6 minutes). The typical distances walked in 6 minutes were 350, 323 and 251 meters for NYHA Class II, III and IV patients, respectively.

The biomarkers measured are measurements used to assess improvement and deterioration in patients with PAH. They include the following:

mean pulmonary artery pressure (PAPm)

mean right arterial pressure (RAPm)
pulmonary vascular resistance index (PVRI)
cardiac index (CI)
mixed venous saturation (SvO₂)
BORG dyspnea score

Hemodynamic parameters were measured by insertion of a pulmonary artery catheter into the proximal pulmonary artery, a standard technique. The BORG dyspnea score was also assessed by standard techniques.

B. WERE THE CORRECT MOIETIES IDENTIFIED AND PROPERLY MEASURED TO ASSESS CLINICAL PHARMACOLOGY?

UT-15 was the only substance measured in plasma. None of its five metabolites (activity unknown) were measured in any of the clinical or pharmacokinetic studies.

ASSAY VALIDATION

The sponsor used a precise (CV ~ 20%), accurate and validated assay (LC/MS/MS), however it lacked the sensitivity to adequately measure the low concentrations of UT-15 obtained in many of the studies. Studies P01:02 and P01:03 used assays with a lower LOQ of 0.1 µg/L. These studies provided little reliable pharmacokinetic information because the sponsor was unable to measure plasma concentrations for an adequate duration to make an appropriate assessment of pharmacokinetics.

Subsequent studies used an improved assay, with a sensitivity of 0.025 µg/L. The standard curve consisted of seven concentrations ranging from 0.025 – 10.0 µg/L. Despite the improvement in the assay sensitivity, problems still existed with measuring plasma concentrations for an adequate duration to appropriately assess the pharmacokinetics. This assay was adequate for measuring the high concentrations in PK studies. The dose for these studies ranged from 2.5 – 15 ng/kg/min. Concentrations ranged from the lower limit of quantitation, 0.025 µg/L to ~7 µg/L. The highest dose obtained in an ongoing clinical study (p01:06) is ~80 ng/kg/min so this assay may be inadequate for some studies.

C. WHAT ARE THE EXPOSURE-RESPONSE RELATIONSHIPS FOR EFFICACY AND SAFETY?

The PK of UT-15 are linear and could be described by a two-compartment model. The PK/PD analysis performed on the P01:04/05 data shows that UT-15 concentrations have a statistically significant effect on the hemodynamic variables PAPm, CI, SvO₂ and PVRI, and dyspnea (BORG score). Additionally, the change in PAPm correlated with the distance walked in 6 minutes by the patients. Although these relationships were statistically significant, the slope of the relationship was very shallow. Although uncertain, crude analysis suggests a dose-dependent opiate (surrogate for injection site pain) use.

- **DO PK PARAMETERS CHANGE WITH TIME?**

The sponsor claims that there are indications of diurnal variation in the systemic clearance. Neither the changes in clearance over the time of the day are obvious from the concentration – time data, nor is there any *a priori* expectation for such a behavior.

- **HOW LONG TO ONSET?**

The pivotal studies (P01:04/05) are not designed to answer this question.

- **HOW LONG TO OFFSET?**

The pivotal studies (P01:04/05) are not designed to answer this question.

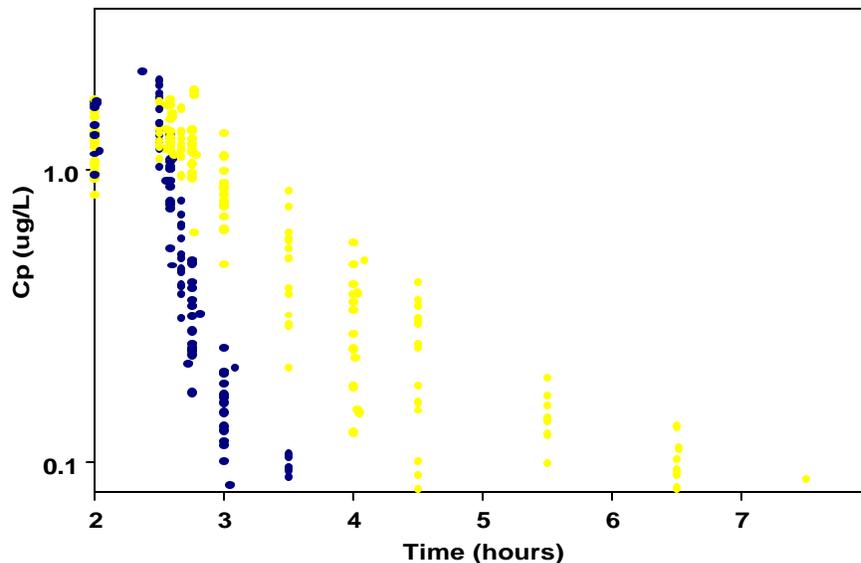
D. ARE THE PHARMACOKINETICS IN HEALTHY VOLUNTEERS SIMILAR TO THAT IN PATIENTS?

Yes, the pharmacokinetics of UT-15 in healthy subjects are similar to that in patients. The pharmacokinetics of the metabolites are unknown.

ABSORPTION

Absorption of SC UT-15 is relatively rapid and complete in healthy volunteers and in patients with primary pulmonary hypertension. Absolute bioavailability of UT-15 is ~ 100%. The pharmacokinetics are dose-proportional over the dose range of 2.5 – 15 ng/kg/min (0.025 - ~10 ug/L). Absorption of SC UT-15 is slower than the elimination after IV infusion such that a marginal flip-flop phenomenon is observed (see next figure) in the terminal slopes.

Figure. Individual plasma concentrations of IV UT-15 (darker circles) and SC UT-15 in healthy volunteers following a 2.5 hour infusion.



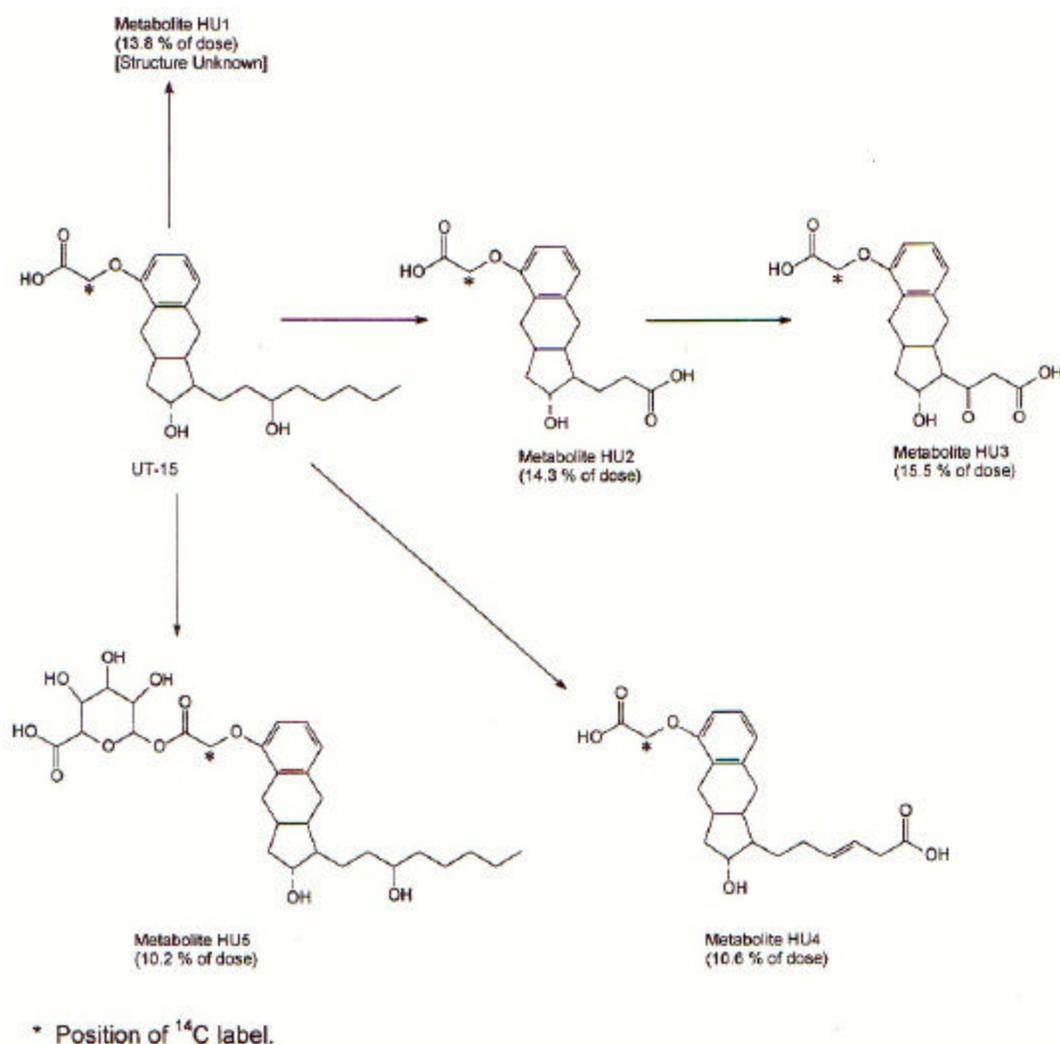
DISTRIBUTION

The volume of distribution of the central compartment is small, ~ 14 L/70 kg ideal body weight person. *In-vitro* studies indicate that UT-15 is ~ 91% bound to human plasma protein over the

concentration of 0.05 – 50 ug/L. It is expected that at physiologic concentrations, 0.025 ug/L to 7 ug/L, UT-15 will be at least 91% bound.

METABOLISM

UT-15 is primarily metabolized in the liver. The enzymes responsible for its metabolism are unknown. Five metabolites (HU1, HU2, HU3, HU4 and HU5) of unknown activity have been identified in the urine, and account for 64.4% of the dose. There is no major metabolite. Each metabolite accounts for 10-16% of the dose. HU1 is unidentified. HU2 and HU3 are products of oxidation of the 3-hydroxyloctyl side chain, HU4 is the product of oxidation of the 3-hydroxyloctyl side chain with an additional dehydration of the 3-hydroxyl group of that side chain, and HU5 is the product of glucuronidation. See figure below for proposed metabolite structures.



EXCRETION

The elimination is biphasic. The mean terminal half-life of SC UT-15 is ~2-4 hours. The primary route of elimination is renal, accounting for 78.6% of an administered dose. Mostly

metabolites are cleared in the urine since less than 4% of the dose is excreted as unchanged drug. Approximately 13.4% of an administered dose is excreted in the feces. Clearance is ~ 30 L/hr/70 kg ideal body weight person.

- **WHAT ARE THE VARIABILITIES OF PK PARAMETERS IN VOLUNTEERS AND PATIENTS?**

The inter-individual variability between volunteers and patients was similar. After adjustment for ideal body weight, the unexplained variability in clearance and volume of distribution of the central compartment was 11 and 33%, respectively.

E. WHAT ARE THE INTRINSIC FACTORS THAT INFLUENCE EXPOSURE OR RESPONSE? WHAT IS THEIR IMPACT ON EXPOSURE AND/OR RESPONSE? BASED UPON WHAT IS KNOWN ABOUT EXPOSURE-RESPONSE RELATIONSHIPS AND THEIR VARIABILITY AND THE GROUPS STUDIED, WHAT DOSAGE REGIMEN ADJUSTMENTS, IF ANY, DO YOU RECOMMEND FOR EACH OF THESE GROUPS?

- **ELDERLY**

There were no differences in pharmacokinetics in patients ≥ 65 years old according to the population PK/PD analysis.

- **PEDIATRIC PATIENTS**

This patient population was not studied.

- **GENDER**

There were no differences in pharmacokinetics between males and females according to the population PK/PD analysis.

- **RACE**

Most subjects studied were Caucasian (85% in the pivotal P01:04/05 study). Differences in PK between race were not assessed.

- **RENAL INSUFFICIENCY**

Mass balance studies suggest that renal elimination is not important for the parent drug, UT-15, since $< 4\%$ is excreted unchanged in the urine. However, all five metabolites are excreted in the urine and account for 64.4% of the dose. Of the 92.2% of the dose eliminated 224 hours after the infusion is initiated, 78.6% is in the urine and 13.4% is in the feces. Thus, the metabolites may accumulate in severe renal insufficiency. Studies in patients with renal insufficiency were not conducted.

- **HEPATIC INSUFFICIENCY (HI)**

Patients with mild and moderate HI have 2x higher C_{max} and 3x higher AUC_{0-inf} compared to healthy subjects. Patients with moderate HI have 4x higher C_{max} and 5x higher AUC_{0-inf} compared to healthy subjects. Apparent clearance was ~60% lower in mild HI and 80% lower in moderate HI compared to healthy subjects.

- **OBESITY**

According to the population PK/PD analysis, obesity does not affect the clearance of UT-15, after adjusted for ideal body weight.

E. WHAT ARE THE EXTRINSIC FACTORS THAT INFLUENCE EXPOSURE OR RESPONSE?

- ***DRUG-DRUG INTERACTIONS***

In-vitro

The enzymes responsible for the metabolism of UT-15 have not been identified. *In-vitro* human hepatic cytochrome P450 studies indicate that UT-15 does not inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1 or 3A.

In-vivo

UT-15 does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S-warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous SC UT-15, 10 ng/kg/min. The effects of warfarin on UT-15 were not determined.

Analgesic doses of acetaminophen do not affect the pharmacokinetics of UT-15. Acetaminophen 1000 mg every 6 hours for 7 doses was given to healthy volunteers receiving UT-15, 15 ng/kg/min. The pharmacokinetics of UT-15 with acetaminophen and without acetaminophen were similar. The 90% confidence intervals for UT-15 C_{max} and AUC ratio in the presence and absence of acetaminophen was within the 80 – 125% equivalence interval, 92.7 – 105.7% and 88.8 – 101.7%, respectively. The effects of UT-15 on acetaminophen pharmacokinetics were not determined.

LABELING RECOMMENDATIONS

Clinical Pharmacology

Pharmacokinetics

1. Delete “In a chronic pharmacokinetic study in normal volunteers with chronic subcutaneous Remodulin doses ranging from 2.5 to 15 ng/kg/min, steady state plasma treprostinol concentrations achieved peak levels twice (at 1 a.m. and 10 a.m., respectively) and achieved trough levels twice (at 7 a.m. and 4 p.m., respectively). The peak concentrations were ~20% to 30% higher than trough concentrations. Dose adjustments are not deemed to be necessary due to diurnal variation..”

2. The sponsor should change the other two paragraphs to reflect what is contained below:

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 1.25-22.5 ng/kg/min and can be described by a two-compartment model. These doses correspond to concentrations of 0.025 - ~8 ug/L. Dose proportionality at infusions greater than 22.5 ng/kg/min are unknown.

Absorption: Absorption of Remodulin is relatively rapid and complete with an absolute bioavailability of ~100%. Following a subcutaneous infusion of remodulin, steady-state plasma concentrations are usually achieved in about 10 hours.

Distribution: The volume of distribution of the drug in the central compartment is small, ~ 14 L/ 70 kg ideal body weight. Remodulin is ~91% bound to human plasma protein over the Remodulin concentration range of 330 – 10,000 ug/L.

Metabolism: Remodulin is heavily metabolized in the liver, however the precise enzymes responsible are unknown. Five metabolites have been described and are labeled as HU1 through 5. The biologic activity and metabolic fate of these metabolites are unknown. The chemical structure of HU1 is unknown. HU5 is the glucuronide conjugate of Remoduline. The other metabolites are formed by oxidation of the 3-hydroxyloctyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). Based on the results of *in-vitro* human hepatic cytochrome P450 studies indicate that remodulin does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1 or 3A.

Excretion: The elimination of Remodulin is biphasic with a terminal half-life of subcutaneous remodulin is ~2-4 hours. Approximately 79% of an administered dose is excreted in the urine as unchanged drug (4%) and as the identified metabolites (64%). Approximately 13% of the dose is excreted in the feces. Each of the identified metabolites was 10 – 16% of the dose in the urine. Systemic clearance is ~ 30 liters/hour in a 70 kg ideal body weight person.

3. The following changes are recommended for the **Special populations** section:

Hepatic insufficiency

This section should be changed to reflect the following: “In patients with portopulmonary hypertension and mild (n=5) or moderate (n=4) hepatic insufficiency, Remodulin at a

subcutaneous dose of 10 ng/kg/min for 150 minutes increased C_{max} 2-fold and 4-fold, respectively, and increased AUC₀₋₄ 3-fold and 5-fold, respectively compared to healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults. Remodulin has not been studied in patients with severe hepatic insufficiency. (See PRECAUTIONS.)”

Renal insufficiency

This section should be changed to reflect the following: “No studies have been performed in patients with renal insufficiency. Although less than 4% of the administered dose is excreted unchanged in the urine, the five isolated metabolites are excreted primarily in the urine. Caution should be exercised when administering Remodulin to patients with renal insufficiency. (See PRECAUTIONS.”

4. Delete “Obese Patients: Obese subjects (BMI greater than 30.0 kg/m²) clear treprostinol at a slower rate. Since doses of Remodulin are increased from very low initial doses to doses that improve disease symptoms while minimizing adverse effects, dosing to ideal body weight in obese patients should not be necessary.”

5. The following part of the **Drug interactions** section should be reworded to state the following:

Effect of Other Drugs on Remodulin

In-vitro studies

Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In-vivo studies

Acetaminophen – Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

Effect of Remodulin on Other Drugs

In-vivo studies

Warfarin - Remodulin does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S-warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous Remodulin, 10 ng/kg/min.

6. It is recommended to add a statement similar to the following to the **PRECAUTIONS** section:

Hepatic insufficiency

The clearance of Remodulin is reduced by up to 80% in patients with moderate hepatic insufficiency compared to healthy adults. In patients with mild insufficiency, the initial dose of Remodulin should be decreased to 0.625 ng/min/kg ideal body weight and should cautiously be

increased. In patients with moderate insufficiency, the initial dose of Remodulin should be decreased to 0.312 ng/min/kg ideal body weight and should cautiously be increased. There is no information in patients with severe hepatic insufficiency. Great caution should therefore be exercised during the treatment of these patients with Remodulin. (See CLINICAL PHARMACOLGY.)

Renal insufficiency

Remodulin should be used with caution in patients with renal insufficiency. Although Remodulin is not extensively renally excreted, its major metabolites are. There are no studies in patients with renal impariment. (See CLINICAL PHARMACOLGY.)

7. The following change should be reflected in the **DOSAGE AND ADMINISTRATION** section:

In the infusion rate formula, “remodulin concentration” should be changed to “remodulin dosage strength concentration”.

APPENDIX I

Sponsor proposed package insert -Revised 2/21/01
NDA 21-272

PRODUCT INFORMATION

REMODULIN[®] (treprostinol sodium)
Injection

(a) Description

Remodulin (treprostinol sodium) Injection is a sterile sodium salt formulated for subcutaneous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL or 10.0 mg/mL of treprostinol. Each mL also contains 5.3 mg sodium chloride (except for the 10.0 mg/mL strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, and 6.3 mg sodium citrate. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinol is a tricyclic benzindene analogue of epoprostenol (prostacyclin, PGI₂) with potent pulmonary and systemic vasodilatory activity. Treprostinol is a potent inhibitor of platelet aggregation *in vitro* and *in vivo*. Treprostinol is chemically stable at room temperature and neutral pH.

Treprostinol is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid monosodium salt. Treprostinol sodium has a molecular weight of 412.49 and a molecular formula of C₂₃H₃₃NaO₅.

The structural formula of treprostinol is:

(b) Clinical Pharmacology

General: The major pharmacological actions of treprostinol are direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. The effect of treprostinol on heart rate in animals varies with dose. No major effects on cardiac conduction have been observed.

(1) Pharmacokinetics:

In humans, following the initiation of subcutaneous infusion of Remodulin, steady-state plasma concentrations are usually achieved within 15 to 18 hours. Steady-state plasma concentrations of treprostinol are dose-proportional at subcutaneous infusion rates of 2.5 to 15 ng/kg/min; however, it is not known if the proportionality between dose and steady-state plasma levels is maintained at infusion rates greater than 15 ng/kg/min. REMODULIN when administered chronically as a

subcutaneous infusion is completely absorbed and has a mean apparent elimination half-life of 3 hours compared to 45 minutes when administered intravenously. The mean volume of distribution and plasma clearance for treprostinol are 1.1 L/kg and 589 mL/kg/hr, respectively.

In a [¹⁴C] treprostinol mass balance and metabolic fate study in healthy volunteers, 78.6% and 13.4% of the subcutaneous radioactive dose were recovered in the urine and feces, respectively, over a period of 224 hours. There was no single major metabolite observed. Five metabolites were detected in the urine, ranging from 10.2% to 15.5% of the dose administered. These five metabolites accounted for a combined total of 64.4%. Three are products of oxidation of the 3-hydroxyoctyl side chain, one is glucuronide conjugate (treprostinol glucuronide) and one is unidentified. Only 3.7% of the dose was recovered in the urine as unchanged parent drug.

In a chronic pharmacokinetic study in normal volunteers with chronic subcutaneous Remodulin doses ranging from 2.5 to 15 ng/kg/min, steady state plasma treprostinol concentrations achieved peak levels twice (at 1 a.m. and 10 a.m., respectively) and achieved trough levels twice (at 7 a.m. and 4 p.m., respectively). The peak concentrations were ~20% to 30% higher than trough concentrations. Dose adjustments are not deemed to be necessary due to diurnal variation.

(2) Special Populations:

Hepatic Insufficiency: An acute study of Remodulin™ administered subcutaneously at a dose of 10 ng/kg/min for 150 minutes was conducted in nine patients with portopulmonary hypertension and stable, mild or moderate hepatic dysfunction. Remodulin was well tolerated and improved cardiopulmonary hemodynamics. Hepatic dysfunction reduced plasma clearance of Remodulin by up to 80% compared to healthy adult volunteers primarily by lowering the volume of distribution without effecting plasma half-life. Remodulin should be increased more conservatively in patients with hepatic dysfunction and these patients should be closely monitored for signs and symptoms or emergence of AEs due to excess Remodulin.

Renal Insufficiency: No studies have been performed in patients with renal insufficiency. Treprostinol is not excreted to any significant degree by the kidney; however, patients with renal insufficiency may have different sensitivities (usually increased sensitivity) to agents. Based on the individual patient dose titration recommended for Remodulin, doses of Remodulin should be increased more conservatively in patients with renal insufficiency.

Obese Patients: Obese subjects (BMI greater than 30.0 kg/m²) clear treprostinol at a slower rate. Since doses of Remodulin are increased from very low initial doses to doses that improve disease symptoms while minimizing adverse effects, dosing to ideal body weight in obese patients should not be necessary.

Clinical Trials in Pulmonary Arterial Hypertension (PAH):

Hemodynamic Effects: Acute infusion of Remodulin at 10 ng/kg/min intravenously for 75 minutes followed by a 10 ng/kg/min infusion subcutaneously for 150 minutes, in patients with primary pulmonary hypertension produced increases in cardiac index (CI) and mixed venous oxygen saturation (SvO₂), and decreases in mean pulmonary arterial pressure (PAPm), mean right atrial pressure (RAPm) and pulmonary vascular resistance indexed (PVRI), with little effect on mean systemic arterial pressure (SAPm) or heart rate (HR).

Chronic continuous, subcutaneous infusion of Remodulin in NYHA Class II, III or IV patients with PAH was studied in two identical, 12-week, double-blind, placebo-controlled, multicenter, parallel-group, randomized trials comparing Remodulin plus conventional therapy to conventional

therapy alone. Dosage of Remodulin was determined as described in DOSAGE AND ADMINISTRATION and averaged 9.3 ng/kg/min at Week 12. Conventional therapy used to treat patients with PAH included some or all of the following: anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen.

As the two studies were identical in design and conducted simultaneously, results were analyzed both pooled and individually. As shown in Table 1, hemodynamic effects after chronic therapy with Remodulin™ were generally consistent with the pharmacological effects seen acutely. There were statistically significant increases in CI and SvO₂, and statistically significant decreases in PAPm, RAPm, PVRI and SVRI in patients treated with Remodulin for 12 weeks compared to patients treated with placebo. Heart rate and SAPm were unchanged. In patients with pulmonary hypertension, elevated RAPm and PAPm, and reduced CO and SvO₂ are predictive of mortality.

Table 1: Hemodynamics During Chronic Administration of Remodulin in Patients with PAH

Hemodynamic Parameter	Baseline		Mean change from baseline at Week 12	
	Remodulin (N=204-231)	Placebo (N=215-235)	Remodulin (N=163-199)	Placebo (N=182-215)
CI (L/min/m ²)	2.37 ± 0.06	2.24 ± 0.05	+0.12 ± 0.04*	-0.06 ± 0.04
PAPm (mmHg)	61.8 ± 1.16	59.9 ± 0.96	-2.3 ± 0.51*	+0.7 ± 0.58
RAP (mmHg)	10.3 ± 0.38	10.0 ± 0.39	-0.5 ± 0.36*	+1.4 ± 0.33
PVRI (mmHg/L/min/m ²)	26.51 ± 0.97	25.11 ± 0.87	-3.54 ± 0.64*	+1.20 ± 0.57
SVRI (mmHg/L/min/m ²)	37.87 ± 1.05	39.23 ± 1.02	-3.54 ± 0.96*	-0.80 ± 0.85
SvO ₂ (%)	61.5 ± 0.70	60.2 ± 0.77	+2.0 ± 0.76*	-1.4 ± 0.65
SAPm (mm Hg)	89.6 ± 0.92	90.7 ± 0.89	-1.7 ± 0.86	-1.0 ± 0.91
HR (bpm)	82.4 ± 0.83	82.1 ± 0.97	--0.5 ± 0.80	-0.8 ± 0.74

*Denotes statistically significant difference between Remodulin and placebo, p≤0.0005

CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVRI = pulmonary vascular pressure indexed; RAPm = mean right atrial pressure, SAPm = mean systemic arterial pressure; SVRI = systemic vascular resistance indexed; SvO₂ = mixed venous oxygen saturation, HR = heart rate

Clinical Effects: Exercise capacity, as measured by the six-minute walk test, improved significantly in patients receiving continuous subcutaneous Remodulin plus conventional therapy (N=232) for 12 weeks compared to those receiving conventional therapy plus placebo (N=236) (p=0.0064). Improvements were apparent as early as Week 6 of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnea and fatigue, as

measured by the Dyspnea-Fatigue Rating and Borg Scale. Signs and symptoms of PAH and Quality of Life also improved.

(c) Indications and Usage

Remodulin™ is indicated for the long-term subcutaneous treatment of Pulmonary Arterial Hypertension in NYHA Class II, III, and IV patients. (see Clinical Pharmacology: Clinical Trials).

(d) Contraindications

Remodulin is contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds

(e) Warnings

Remodulin has been administered intravenously in acute clinical trials with no unexpected adverse effects. However, no chronic controlled trials have been performed with intravenous Remodulin therefore it is indicated for subcutaneous use only.

(f) Precautions

(1) General

Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH.

Remodulin is a potent pulmonary and systemic vasodilator. Initiation of Remodulin must be performed in a setting with adequate personnel and equipment for physiologic monitoring and emergency care. Dosage adjustments in clinical trials were based on the patient's signs and symptoms of PAH and side effects of Remodulin. Dosage of Remodulin should be adjusted at the first sign of recurrence or worsening of symptoms attributable to PAH or the occurrence of intolerable adverse events associated with Remodulin. (see DOSAGE and ADMINISTRATION)

The decision to initiate therapy with Remodulin should be based on the understanding that there is a high likelihood that subcutaneous therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to administer Remodulin and care for an infusion system should be carefully considered. As with any potent vasodilator, abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms. In clinical trials, no patient death from discontinuation of Remodulin was judged attributable to the interruption of Remodulin. Only three of 55 (5%) patients with abrupt disruption of Remodulin developed increased symptoms of PAH, and no patients developed hemodynamic instability. In addition, among patients who discontinued Remodulin abruptly, no relationship has been established between abrupt discontinuation and rebound pulmonary hypertension.

(2) Information for patients

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous catheter, via an infusion pump. The decision to receive Remodulin should be based upon the understanding that therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to accept, place and care for a subcutaneous catheter and to use an infusion pump should be carefully considered. Additionally, patients should be aware that subsequent disease management may require the initiation of an intravenous therapy.

(3) Drug interactions

Additional reductions in blood pressure may occur when Remodulin™ is administered with diuretics, antihypertensive agents, or other vasodilators. When other antiplatelet agents or anticoagulants are used concomitantly, there is the potential for Remodulin to increase the risk of bleeding. However, patients receiving Remodulin in clinical trials were maintained on anticoagulants without evidence of increased bleeding. No untoward clinical manifestations have been observed in patients in whom Remodulin was used concurrently with the following classes of drugs: anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications. Chronic subcutaneous Remodulin administration required concomitant therapies to manage adverse events associated with the use of Remodulin. Adverse events associated with these concomitant therapies may occur and should be handled as medically appropriate.

Effect of Other Drugs on Treprostinol

The effect of large daily doses of acetaminophen (4g/day) on the kinetics of treprostinol was investigated in a healthy volunteer study. The results demonstrate that acetaminophen does not have any clinically important effect on the pharmacokinetics of treprostinol. Treprostinol did not significantly affect the plasma protein binding of digoxin or warfarin when evaluated in human plasma at physiologic concentrations. In a multivariate analysis of treprostinol plasma clearance values obtained in two controlled trials, 6% of the variability in treprostinol plasma clearance values could be explained by the presence of furosemide (both treprostinol and furosemide undergo glucuronidation at the carboxylate group during metabolism). Based on the modest suggestion of an interaction, a reduction in dose in patients receiving furosemide is not recommended, although patients should be monitored for excess adverse effects of Remodulin.

Effect of Treprostinol on Other Drugs

In Vitro Studies

Results from an *in vitro* study in human hepatic microsomes demonstrated that treprostinol does not significantly inhibit the following P450 isoforms - CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. In a separate study which investigated the induction effect of treprostinol on rat liver microsomal cytochrome P450 enzymes, treprostinol was found to lack any significant induction effect on (CYP1A), (CYP2B) and (CYP3A).

In Vivo Studies

Treprostinol had no effect on warfarin pharmacodynamics as measured by the effect on INR. Treprostinol also had no effect on the pharmacokinetics of either the R- or S- enantiomer of warfarin.

(4) Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies have not been performed to evaluate carcinogenic potential. *In vitro* and *in vivo* mutagenicity studies did not demonstrate any mutagenic or clastogenic effects of treprostinol. Treprostinol was not teratogenic in pregnant rats at doses up to 900 ng/kg/min. No developmental toxicity was seen in rabbits at 50 ng/kg/min. In reproductive performance studies in rats, treprostinol had no effect on male or female fertility at doses up to 450 ng/kg/min.

(5) Pregnancy

Pregnancy Category B. No developmental toxicity was seen in rats at any dose of treprostinol up to 900 ng/kg/min and in rabbits at 50 ng/kg/min. In pregnant rabbits, developmental toxicity characterized by minimal increases in fetal skeletal variations per litter was observed at doses of 150 and 300 ng/kg/min and was associated with maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Remodulin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

(6) Nursing mothers

It is not known whether treprostinol is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Remodulin™ is administered to nursing women.

(7) Pediatric use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin did not include sufficient numbers of patients aged ≤ 16 years to determine whether they respond differently from older patients. In general, dose selection should be cautious.

(8) Geriatric use

Clinical studies of Remodulin did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

(g) Adverse Reactions

Interpretation of AEs reported during clinical trials should be undertaken with an awareness of expected events attributable to the progression of the underlying disease, to Remodulin, and/or to the drug delivery system.

Interpretation of adverse events is complicated by the clinical features of PAH, which are similar to some of the pharmacological effects of Remodulin (e.g., dizziness, syncope). Adverse events probably related to the underlying disease include dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor. Several adverse events can clearly be attributed to Remodulin, the most common of which is pain at the infusion site, tolerated by a majority of patients. Other adverse events include infusion site reaction, diarrhea, jaw pain, edema, vasodilatation and nausea. Infusion site reaction was defined as any local adverse event other than infusion site pain or infusion site bleeding/bruising, such as erythema, induration, or rash.

Adverse Events During Chronic Dosing: In an effort to separate the adverse effects of Remodulin™ from those of the underlying disease, Table 2 lists adverse events that occurred at a rate at least 5% more frequently in patients treated with Remodulin than with placebo in controlled trials in PAH.

Table 2: Frequency of Adverse Events Regardless of Attribution Occurring in Patients with PAH with ≥5% Difference Between Remodulin and Placebo in Controlled Studies

Adverse Event	UT- (N=236) N (%)	Placebo (N=233) N (%)
Occurrence More Common with Remodulin		
General (Body as Whole)		
Jaw pain	31 (13.1)	11 (4.7)
Gastrointestinal (Digestive)		
Diarrhea	58 (24.6)	36 (15.5)
Metabolic and Nutritional		
Edema	21 (8.9)	6 (2.6)
Neurological/Nervous		
Vasodilatation	25 (10.6)	11 (4.7)
Skin and Appendages		
Infusion site pain	200 (84.7)	62 (26.6)
Infusion site reaction	196 (83.1)	62 (26.6)
Occurrence More Common with Placebo		
Hematologic and Lymphatic		
Ecchymosis	9 (3.8)	27 (11.6)
Respiratory		
Cough	7 (3.0)	19 (8.2)
Skin and Appendages		
Infusion site bleed/bruise	79 (33.5)	102 (43.8)

Table 3 lists all adverse events reported in controlled clinical trials of patients with PAH, that were significantly more frequently encountered in the Remodulin™ group than in the placebo group, regardless of attribution.

Table 3: AEs That Were Significantly (p<0.1) More Frequently Encountered in the Remodulin Group Than in the Placebo Group, Regardless of Attributability

AE Description, as COSTART Preferred Term	Number of events Remodulin-group / placebo group	p-value
Any AE	231 / 218	0.0173
Infusion site pain	200 / 62	<0.0001
Infusion site reaction	196 / 62	<0.0001
Diarrhea	58 / 36	0.0091
Jaw pain	31 / 11	0.0010
Vasodilatation	25 / 11	0.0127
Edema	21 / 6	0.0026
Anorexia	11 / 4	0.0592
Epistaxis	10 / 4	0.0904
Nausea and vomiting	7 / 2	0.0909
Hypokalemia	5 / 0	0.0316
Melena	5 / 0	0.0316

Adverse Events Attributable to the Drug Delivery System in PAH Controlled Trials: There were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 4 placebo) reported non-serious adverse events resulting in infusion system complications. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration, although in some cases PAH symptoms reappeared.

(h) Overdosage

Signs and symptoms of overdose with Remodulin during clinical trials are similar to expected dose-limiting pharmacological effects of Remodulin, including flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

In controlled clinical trials, seven patients received some level of overdose and in the chronic, uncontrolled trial seven additional patients received an overdose; these occurrences resulted from accidental bolus of Remodulin, errors in pump programmed rate of administration and prescription of incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope). No deaths occurred as a result of overdose.

(i) Dosage and Administration

Remodulin™ is supplied in 20 mL vials in concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL and 10.0 mg/mL.

Initial Dose:

Remodulin is administered by continuous subcutaneous infusion. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated, the infusion rate should be reduced to 0.625 ng/kg/min.

Dosage Adjustments:

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while achieving an acceptable side effect profile. The infusion rate should be adjusted based on PAH signs and symptoms and Remodulin side effects. The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first four weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion. Dose-related symptoms may necessitate a decrease in infusion rate; however, the event may resolve without dosage adjustment. Should an adverse event worsen and/or become intolerable, the infusion rate should be reduced.

Administration:

Remodulin is administered by continuous subcutaneous infusion, via a self-inserted subcutaneous catheter, using a infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient should have access to a backup infusion pump and subcutaneous infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) be able to adjust infusion rates in approximately 0.002 mL/hr, (3) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (4) have delivery accuracy of ±6% or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Infusion rates are calculated using the following formula.

$$\text{Infusion Rate (mL/hr)} = \text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times [0.00006/\text{Remodulin concentration (mg/mL)}]$$

Tables 4 through 7 provide Remodulin infusion delivery rates for doses up to 155 ng/kg/min, based on patient weight, drug delivery rate and concentration. These tables may be used to select the most appropriate concentration and infusion rate for Remodulin.

Table 4

1.0 mg/ml Concentration of UT-15
MiniMed 407C pump Infusion Rate Setting (mls/hr) for 1.0 mg/ml UT-15

Dose (ng/kg/min)	Patient Weight (kg)															
	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
1.25	0.002	0.002	0.003	0.003	0.003	0.004	0.004	0.005	0.005	0.005	0.006	0.006	0.006	0.007	0.007	0.008
2.5	0.004	0.005	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
3.75	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021	0.023
5	0.008	0.009	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
6.25	0.009	0.011	0.013	0.015	0.017	0.019	0.021	0.023	0.024	0.026	0.028	0.030	0.032	0.034	0.036	0.038
7.5	0.011	0.014	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
8.75	0.013	0.016	0.018	0.021	0.024	0.026	0.029	0.032	0.034	0.037	0.039	0.042	0.045	0.047	0.050	0.053
10	0.015	0.018	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
11.25	0.017	0.020	0.024	0.027	0.030	0.034	0.037	0.041	0.044	0.047	0.051	0.054	0.057	0.061	0.064	0.068
12.5	0.019	0.023	0.026	0.030	0.034	0.038	0.041	0.045	0.049	0.053	0.056	0.060	0.064	0.068	0.071	0.075
13.75	0.021	0.025	0.029	0.033	0.037	0.041	0.045	0.050	0.054	0.058	0.062	0.066	0.070	0.074	0.078	0.083
15	0.023	0.027	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
16.25	0.024	0.029	0.034	0.039	0.044	0.049	0.054	0.059	0.063	0.068	0.073	0.078	0.083	0.088	0.093	0.098
17.5	0.026	0.032	0.037	0.042	0.047	0.053	0.058	0.063	0.068	0.074	0.079	0.084	0.089	0.095	0.100	0.105
18.75	0.028	0.034	0.039	0.045	0.051	0.056	0.062	0.068	0.073	0.079	0.084	0.090	0.096	0.101	0.107	0.113
20	0.030	0.036	0.042	0.048	0.054	0.060	0.066	0.072	0.078	0.084	0.090	0.096	0.102	0.108	0.114	0.120
21.25	0.032	0.038	0.045	0.051	0.057	0.064	0.070	0.077	0.083	0.089	0.096	0.102	0.108	0.115	0.121	0.128
22.5	0.034	0.041	0.047	0.054	0.061	0.068	0.074	0.081	0.088	0.095	0.101	0.108	0.115	0.122	0.128	0.135
23.75	0.036	0.043	0.050	0.057	0.064	0.071	0.078	0.086	0.093	0.100	0.107	0.114	0.121	0.128	0.135	0.143
25	0.038	0.045	0.053	0.060	0.068	0.075	0.083	0.090	0.098	0.105	0.113	0.120	0.128	0.135	0.143	0.150
27.5	0.041	0.050	0.058	0.066	0.074	0.083	0.091	0.099	0.107	0.116	0.124	0.132	0.140	0.149	0.157	0.165
30	0.045	0.054	0.063	0.072	0.081	0.090	0.099	0.108	0.117	0.126	0.135	0.144	0.153	0.162	0.171	0.180
32.5	0.049	0.059	0.068	0.078	0.088	0.098	0.107	0.117	0.127	0.137	0.146	0.156	0.166	0.176	0.185	0.195
35	0.053	0.063	0.074	0.084	0.095	0.105	0.116	0.126	0.137	0.147	0.158	0.168	0.179	0.189	0.200	0.210
37.5	0.056	0.068	0.079	0.090	0.101	0.113	0.124	0.135	0.146	0.158	0.169	0.180	0.191	0.203	0.214	0.225
40	0.060	0.072	0.084	0.096	0.108	0.120	0.132	0.144	0.156	0.168	0.180	0.192	0.204	0.216	0.228	0.240
42.5	0.064	0.077	0.089	0.102	0.115	0.128	0.140	0.153	0.166	0.179	0.191	0.204	0.217	0.230	0.242	0.255

NOTE: Blank spaces indicate that this concentration of UT-15 is inappropriate for the corresponding dose

The infusion rate for 1.0 mg/ml can be calculated using the following formula: Patient weight(kg) x dose(ng/kg/min) x 0.00006.

Shaded areas indicate the highest infusion rate supported by one syringe change every three days

2.5 mg/ml Concentration of UT-15

Table 5

MiniMed 407C pump Infusion Rate Setting (mls/hr) for 2.5 mg/ml UT-15

Patient Weight (kg)

Dose (ng/kg/min)	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
5	0.003	0.004	0.004	0.005	0.005	0.006	0.007	0.007	0.008	0.008	0.009	0.010	0.010	0.011	0.011	0.012
6.25	0.004	0.005	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
7.5	0.005	0.005	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.014	0.015	0.016	0.017	0.018
8.75	0.005	0.006	0.007	0.008	0.009	0.011	0.012	0.013	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021
10	0.006	0.007	0.008	0.010	0.011	0.012	0.013	0.014	0.016	0.017	0.018	0.019	0.020	0.022	0.023	0.024
11.25	0.007	0.008	0.009	0.011	0.012	0.014	0.015	0.016	0.018	0.019	0.020	0.022	0.023	0.024	0.026	0.027
12.5	0.008	0.009	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
13.75	0.008	0.010	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
15	0.009	0.011	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
16.25	0.010	0.012	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
17.5	0.011	0.013	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
18.75	0.011	0.014	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
20	0.012	0.014	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
21.25	0.013	0.015	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
22.5	0.014	0.016	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
23.75	0.014	0.017	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
25	0.015	0.018	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
27.5	0.017	0.020	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
30	0.018	0.022	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
32.5	0.020	0.023	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
35	0.021	0.025	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
37.5	0.023	0.027	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
40	0.024	0.029	0.034	0.038	0.043	0.048	0.053	0.058	0.062	0.067	0.072	0.077	0.082	0.086	0.091	0.096
42.5	0.026	0.031	0.036	0.041	0.046	0.051	0.056	0.061	0.066	0.071	0.077	0.082	0.087	0.092	0.097	0.102

NOTE: Blank spaces indicate that this concentration of UT-15 is inappropriate for the corresponding dose
 The infusion rate for 2.5 mg/ml can be calculated using the following
 formula: Patient weight(kg) x dose(ng/kg/min) x 0.00024

Table 6 **5.0 mg/mL Concentration of UT-15**
Pump Infusion Rate Setting (mL/hr) for 5.0 mg/mL UT-15

Patient Weight (kg)

Dose (ng/kg/min)	35	40	45	50	55	60	65	70	75	80	85	90	95	100
10	0.004	0.005	0.005	0.006	0.007	0.007	0.008	0.008	0.009	0.010	0.010	0.011	0.011	0.012
12.5	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
15	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.014	0.015	0.016	0.017	0.018
17.5	0.007	0.008	0.009	0.011	0.012	0.013	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021
20	0.008	0.010	0.011	0.012	0.013	0.014	0.016	0.017	0.018	0.019	0.020	0.022	0.023	0.024
22.5	0.009	0.011	0.012	0.014	0.015	0.016	0.018	0.019	0.020	0.022	0.023	0.024	0.026	0.027
25	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
27.5	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
30	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
32.5	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
35	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
37.5	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
40	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
42.5	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
45	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
47.5	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
50	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
55	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
60	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
65	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
70	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
75	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
80	0.034	0.038	0.043	0.048	0.053	0.058	0.062	0.067	0.072	0.077	0.082	0.086	0.091	0.096

The infusion rate for 5.0 mg/mL may be calculated using the following formula: Patient Weight(kg) x dose(ng.kg/min) x 0.000012.

**10.0 mg/mL Concentration of UT-15
Pump Infusion Rate Setting (mLs/hr) for 10.0 mg/mL UT-15**

Patient Weight (kg)

	35	40	45	50	55	60	65	70	75	80	85	90	95	100
0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030	
0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033	
0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036	
0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039	
0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042	
0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045	
0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048	
0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051	
0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054	
0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057	
0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060	
0.022	0.025	0.028	0.032	0.035	0.038	0.041	0.044	0.047	0.050	0.054	0.057	0.060	0.063	
0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066	
0.024	0.028	0.031	0.035	0.038	0.041	0.045	0.048	0.052	0.055	0.059	0.062	0.066	0.069	
0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072	
0.026	0.030	0.034	0.038	0.041	0.045	0.049	0.053	0.056	0.060	0.064	0.068	0.071	0.075	
0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078	
0.028	0.032	0.036	0.041	0.045	0.049	0.053	0.057	0.061	0.065	0.069	0.073	0.077	0.081	
0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084	
0.030	0.035	0.039	0.044	0.048	0.052	0.057	0.061	0.065	0.070	0.074	0.078	0.083	0.087	
0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090	
0.033	0.037	0.042	0.047	0.051	0.056	0.060	0.065	0.070	0.074	0.079	0.084	0.088	0.093	

Note: Blank spaces indicate the this concentration of UT-15 is inappropriate for the corresponding dose. The infusion rate for the 10 mg/mL concentration can be calculated by using the following formula: Patient weight (kg) x dose (ng/kg/mL) x .000006.

Shaded areas indicate the highest infusion rate supported by one syringe change every three days

(j) How Supplied

Remodulin™ is supplied in 20 mL multi-use vials at concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL treprostinol, as sterile solutions in water for injection, individually packaged in a carton. Each mL contains treprostinol sodium equivalent to 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, or 10.0 mg/mL treprostinol. Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25°C (59 to 77°F).

During use, a single reservoir of Remodulin can be administered up to 72 hours at 37°C.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, Remodulin should not be administered.

20-mL vial containing treprostinol sodium equivalent to 1 mg treprostinol per mL, carton of 1 (NDC xxxx-xxxx-xx).

20-mL vial containing treprostinol sodium equivalent to 2.5 mg treprostinol per mL, carton of 1 (NDC xxxx-xxxx-xx).

20-mL vial containing treprostinol sodium equivalent to 5.0 mg treprostinol per mL, carton of 1 (NDC xxxx-xxxx-xx).

20-mL vial containing treprostinol sodium equivalent to 10.0 mg treprostinol per mL, carton of 1 (NDC xxxx-xxxx-xx).

US Patent No. 5,153,222 (Use Patent)

United Therapeutics Corp.
Research Triangle Park, NC 27709

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REMODULIN manufactured by

Cook Pharmaceutical Solutions

Bloomington, IN 47403

For United Therapeutics Corp.

Research Triangle Park, NC 27709

APPENDIX II

STUDY TITLE: The *in-vitro* protein binding of [¹⁴C] UT-15 in human plasma

STUDY NO: Covance 7049-106

VOLUME: 2.14

PAGES: 3956 to 3995

PRINCIPAL INVESTIGATOR: Sheela PaiBir, PhD

CLINICAL LABORATORY: Covance Laboratories Inc.

3301 Kinsman Blvd

Madison Wisconsin 53704

CITATION: not applicable

PROPOSED ANALYTICAL START DATE: February 4, 2000

PROPOSED ANALYTICAL END DATE: March 28, 2000

OBJECTIVES :

- To determine the extent of protein binding of UT-15 in female human plasma *in-vitro*;
- To evaluate the potential for protein binding interactions of UT-15 with digoxin and with warfarin in female human plasma

PROCEDURE: The *in-vitro* protein binding of UT-15 was assessed by ultrafiltration. Pooled female human plasma was fortified with [¹⁴C] UT-15 (0.33 and 10 µg/mL) and filtered in triplicate. An aliquot of the remaining plasma in the reservoir portion of the ultrafiltration device was analyzed by LSC to assess the total radioactive recovery.

The effect of UT-15 on the protein binding of digoxin and warfarin was evaluated in human plasma at four concentrations of UT-15 (0.05, 0.5, 5 and 50 µg/L) and at a single concentration of the ligand, [³H] digoxin 2 µg/L and [¹⁴C] warfarin 2.5 µg/mL.

The following test materials and lots were used:

Materials	Lots
[¹⁴ C] UT-15	CSL-99-832-83-20
UT-15	UT15 RP-98I001
[³ H] digoxin	3363-229
digoxin	98H0922
[¹⁴ C] warfarin	B60
warfarin	H-1

STATISTICAL ANALYSIS: Descriptive statistics were used where appropriate.

RESULTS: Protein binding to human plasma protein

[¹⁴C] UT-15 was highly bound to human plasma proteins in females at concentrations of 0.33 and 10 µg/mL (330 and 10,000 µg/L). Mean protein binding was 91% at both concentrations. Mean recovery of [¹⁴C] UT-15-derived radioactivity following ultrafiltration was 104% at 0.33 µg UT-15/mL and 103% at 10 µg UT-15/mL.

Protein binding of digoxin and warfarin

UT-15 over a concentration range of 0.05 to 50 µg/L did not significantly affect the *in-vitro* protein binding of [³H] digoxin and [¹⁴C] warfarin in pooled female human plasma. Binding of

digoxin averaged 33.4% and 35.7% in the presence and absence, respectively, of UT-15. Binding of warfarin was 98.9% and 99.1% in the presence and absence, respectively, of UT-15.

Radiopurity and stability

Results should be interpreted cautiously because of the impurity of [¹⁴C] UT-15. Radiopurity of [¹⁴C] UT-15 was less than 90%; 87.5% at the beginning of the study and 86.3% at the end of the study. This implies that [¹⁴C] UT-15 was stable during the study, but the impurities will contribute to the free fraction of [¹⁴C] UT-15.

The radiopurity of [³H] digoxin and [¹⁴C] warfarin were high; 98.6% and 98.9%, respectively.

Nonspecific Binding

Ultrafiltration was an acceptable method for assessing the *in-vitro* plasma protein binding of [¹⁴C] UT-15, [³H] digoxin, and [¹⁴C] warfarin because the non-specific binding to the ultrafiltration device was minimal. The mean percent bound to the ultrafiltration device and the mean percent recovered are shown in the table below.

		% of radioactivity	
		Bound	Recovered
[¹⁴ C] UT-15	0.33 µg/mL	5.95	92.8
[¹⁴ C] UT-15	10 µg/mL	8.23	98.0
[³ H] digoxin		6.14	97.9
[¹⁴ C] warfarin		3.95	97.7

SPONSOR'S COMMENTS: Because of the limit of detection due to the specific activity of [¹⁴C] UT-15, the lowest concentration was ~ 6.6 to 66 fold higher than physiologic concentrations of UT-15 (5-50 ug/L).

The plasma protein binding of [¹⁴C] UT-15 in females was independent of concentration, suggesting that binding of UT-15 to plasma proteins in females is concentration-independent at the physiologic concentrations of UT-15.

SPONSOR'S CONCLUSION: UT-15 is ~ 91% bound to human plasma protein *in-vitro*.

UT-15, over the concentration range of 0.05 to 50 ug/L, does not have a significant effect on the protein binding of digoxin or warfarin *in-vitro*.

REVIEWER'S COMMENTS: UT-15 is at least 91% bound to human plasma protein. Assuming there is saturable protein binding, then more drug is free (less bound) at high concentrations compared to low concentrations. Thus, at the lower concentrations that were measured in studies more than 91% will be bound to human plasma protein.

The percent bound to human plasma protein was constant, 91% at the high concentrations studied, 330 and 10,000 ug/L. It can be concluded that plasma protein binding is independent of concentration between these ranges, however it is unknown if binding is concentration independent at lower concentrations.

The sponsor states that the lowest concentration of [¹⁴C]UT-15, 330 ug/L, studied was 6.6 to 66 fold higher than physiologic concentrations of UT-15. This is based on the concentration range of 5 to 50 ug/L. However, in studies that measured concentrations of UT-15, these concentrations ranged from the lower LOQ 0.025 ug/L to ~ 8 ug/L. Thus, the lowest concentration of [¹⁴C]UT-15 was 47 to 13,200-fold higher than most measured concentrations of UT-15.

It should also be noted that the radiopurity of [¹⁴C] UT-15 was less than 90%. Thus, the impurities will contribute to the free fraction of [¹⁴C] UT-15.

The concentration of digoxin and warfarin used in this study was appropriate. “Therapeutic” concentrations of digoxin range from 0.8 – 2.0 ug/L. Studies that measure warfarin concentrations used assays with a range from 0.04 – 5 µg/mL. A single dose of warfarin 25 mg produces concentrations between 0.2 – 2 µg/mL, with a Cmax around 1.5 µg/mL. Thus, the conclusion that UT-15 does not have a significant effect on the protein binding of digoxin or warfarin *in-vitro* are meaningful.

It is not clear why plasma from only females were used.

STUDY TITLE: Inhibitory potential of UT-15 towards human hepatic microsomal cytochrome P450

STUDY NO: Covance 7049-100

VOLUME: 2.14

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PRINCIPAL INVESTIGATOR: Sanjeev Thohan, PhD

CLINICAL LABORATORY: Covance Laboratories Inc.
3301 Kinsman Blvd
Madison Wisconsin 53704

CITATION: not applicable

PROPOSED ANALYTICAL START DATE: June 8, 1999

PROPOSED ANALYTICAL END DATE: July 30, 1999

OBJECTIVES: To characterize the *in-vitro* inhibitory potential of UT-15 towards human hepatic cytochrome P450 (CYP450) isozymes.

PROCEDURE: The concentration of UT-15 that inhibited 50% of the control activity (IC₅₀) was evaluated for six isozyme-specific assays with pooled human liver microsomal fractions.

Substrate concentrations were fixed. The concentration that produces half the maximum reaction velocity (K_m) for human liver microsomal fractions was used. Control incubations with a single concentration of a known inhibitor of the respective isozyme were performed in duplicate or triplicate. The following were used as substrates:

Substrate	Substrate for:	Control (inhibitor)
7-ethoxyresorufin O-deethylase	CYP1A2	100nM n-naphthoflavone
tolbutamide 4-methyl hydroxylase	CYP2C9	5 M sulfaphenazole
S-mephenytoin 4'-hydroxylase	CYP2C19	60 M tranilcypromine
dextromethorphan O-demethylase	CYP2D6	0.75 M quinidine
p-nitrophenol hydroxylase	CYP2E1	100 M diethyldithiocarbamate
erythromycin N-demethylase	CYP3A	100 M troleandomycin

Assays were performed in the presence and absence of UT-15. UT-15 concentrations ranged from 0.1 to 1000 ug/L; 0.1, 1.0, 10, 100, and 1000 ug/L. The UT-15 IC₅₀ for each isozyme was estimated by evaluating the effect of various UT-15 concentrations on isozyme activity. The percent of activity remaining vs. log UT-15 was plotted. When greater than 50% inhibition of isozyme activity occurred, the IC₅₀ was calculated.

The lot number for UT-15 was 800504. Pooled, human liver microsomal fractions came from ten individuals (lot no. HHM-0257). The characterization of the microsomal pool is listed in the table below.

Parameter	Value
total protein	24 mg/mL
total P450	0.47 nmol/mg protein
cytochrome P450 reductase	62 nmol/mg/minute
7-ethoxycoumarin O-deethylase	288 pmol/mg/minute
phenacetin O-deethylase (CYP1A2)	229 pmol/mg/minute
coumarin 7-hydroxylase (CYP2A6)	1.01 nmol/mg/minute
S-mephenytoin 4'-hydroxylase (CYP2C19)	12 pmol/mg/minute

dextromethorphan O-demethylase (CYP2D6)	77 pmol/mg/minute
chlorzoxazone 6-hydroxylase (CYP2E1)	1155 pmol/mg/minute
6 β -hydroxytestosterone production (CYP3A3/4)	2.0 nmol/mg/minute
omega-hydroxy-lauric acid production (CYP4A)	1.7 nmol/mg/minute

ANALYSIS :

Statistical analysis Descriptive statistics were used where appropriate.

RESULTS: UT-15, in the concentration range of 0.1 to 1000 ug/L did not inhibit the activity of the CYP450 isozymes tested; CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A.

SPONSOR'S CONCLUSION: UT-15 does not inhibit human hepatic cytochrome P450 isozymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A *in-vitro*.

REVIEWER'S COMMENTS: Measured concentrations of UT-15 from PK studies range from the lower LOQ, 0.025 ug/L, to ~8 ug/L. Thus the range of the UT-15 concentrations studied was quite wide (0.1 – 1,000 ug/L), covering 100-fold higher concentrations. It is difficult to perceive that UT-15 concentrations will ever reach the order of magnitude that was studied, however none of the substrates demonstrated a significant amount of inhibition over the whole range of UT-15 that was studied. The sponsor did not assess UT-15 concentrations lower than 0.1 ug/L, but it is unlikely that lower concentrations will inhibit CYP450 isozymes. The concentrations of the substrates used in this study were all appropriate.

STUDY TITLE: A single center, open-label, mass balance, urinary metabolite profiling, and safety study of [¹⁴C] UT-15 following an 8-hour subcutaneous infusion in six normal healthy male subjects

STUDY 01:10 VOLUME: 2.12-2.13 **PAGES:** 3256 - 3800

INVESTIGATORS: Russell M. Dixon, MD, Medical Director, Covance CRU Inc.

STUDY SITE: Covance Clinical Research Unit Inc.
309 West Washington Ave., Suite 5
Madison, WI 53703

CITATION: not applicable

STUDY STARTED: January 6, 2000

STUDY COMPLETED: January 16, 2000

OBJECTIVES:

- To characterize whole blood and plasma radioactivity of [¹⁴C] UT-15
- To characterize the urinary and fecal excretion of radioactivity
- To evaluate the safety of [¹⁴C] UT-15
- To examine the pattern of metabolites in urine

STUDY DESIGN: This was a single center, open-label study.

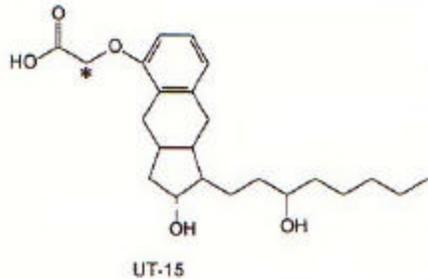
POPULATION: Six normal healthy male subjects between the ages of 18 to 50 years and a body weight within -10 to +20% of ideal body weight.

PROCEDURE: *Duration* Subjects were confined to the clinical site from the day prior to the infusion (Day -1) until approximately 168 hours (7 days) after the end of the infusion. Subjects were eligible for discharge when fecal and urine samples collected over a 24-hour period contained ≤ 1% of the radioactive dose given to that subject.

The 8-hour SC infusion was started on Day 0. Day 1 started at the end of the infusion. Blood, plasma, urine, fecal and emesis samples were collected from Day 0 until study discharge for determination of [¹⁴C] radioactivity. UT-15 concentrations were determined from plasma. Metabolite profiling was determined from urine samples collected prior to the infusion until approximately 168 hours after the infusion ended. Adverse event information was collected throughout the study.

No concomitant oral medications were used during the study. Topical medicines for infusion site pain were allowed. Topical agents containing epinephrine, other vasoconstrictors and ice were not used since they may affect absorption.

Treatment Each subject received a single 8-hour SC infusion of 15 ng/kg/min as a prepared mixture of [¹⁴C] UT-15 and non-radiolabeled UT-15 for a total of ~80 μCi for a 70 kg subject. The asterisk in the figure below shows where the ¹⁴C was attached to UT-15.



On Day 0, subjects received a light breakfast prior to the infusion. During the infusion and up to 2 hours after the end of the infusion, subject's food intake was restricted to light snacks or small, low-fat meals. Water consumption was ad libitum throughout the study.

Pharmacokinetics Blood samples were collected for [¹⁴C] activity at the following times: Day 0 – initially, after the infusion started at 2, 4, and 6 hours, after the infusion ended (named Day 1) at 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours. Unchanged UT-15 was measured post infusion at 0.25, 0.5, 1, 2, 3, 4, 8, 12 and 24 hours. No pharmacokinetic analysis was conducted on unlabeled UT-15. For each subject, the following were calculated or obtained by usual methods: C_{max} , T_{max} , AUC_{0-t} , AUC_{0-4} , α , $T_{1/2\beta}$, and $T_{1/2\alpha}$. Nominal times for sample collection were used in the calculations of the pharmacokinetic parameters, because none of the actual times deviated by $\geq 5\%$ of the nominal time.

Pharmacodynamics Descriptive statistics were calculated on the safety parameters.

FORMULATION: UT Corp provided UT-15 and [¹⁴C] UT-15. UT-15 was from lot UT15-98K001 (Magellan Ref. No. LRR-0003) and was to be stored in refrigeration. radiolabeled UT-15 was provided to UT Corp by ChemSyn and was from lot 99-832-83-20. radiolabeled UT-15 was to be stored at -70°C and protected from light, and the prepared solution was to be stored in refrigeration. The specific activity of [¹⁴C] UT-15 was 57.9 mCi/mmol. The materials in the following table were also used to prepare the dosing solution.

ID	Lot no.	Qty received weight of bottle + contents (gm)	Qty remaining	Storage conditions
Sodium citrate, dihydrate, USP	R9811025	91.3326	90.6060	ambient
Sodium hydroxide, NF	R9709017	86.4112	85.2406	ambient
Sodium chloride	R9903095	102.4247	101.9972	ambient
Hydrochloric acid, NF	R9901064	96.7069	94.8090	ambient

RESULTS: A total of 6 healthy adult males (4 Caucasian, 1 Black and 1 Asian) completed the study. (See table.)

	Range	Mean ± SD
Age (yrs)	23-45	33 ± 7
Ht (cm)	166-190	174 ± 7
Wt (kg)	69-90	79 ± 8

Duration Four subjects were discharged in seven days, one in eight days, and one in nine days due to radioactivity levels.

Dose The mean dose of UT-15 received in 8 hours was $517,150 \pm 53,877$ ng and $83.6 \mu\text{Ci}$ [^{14}C]UT-15 (dose range: 463,300 – 592,200 ng and 72.5 – 95.7 μCi [^{14}C] UT-15). Subject 3 (white male) had 3 dose interruptions during the infusion for 10, 10 and 3 minutes, respectively.

Dosimetry The extrapolated radiation dose equivalent for tissues in humans following a 100 mCi SC dose ranged from 0.00200 mrem (brain) to 36.9 mrem (small intestine). These dose equivalents were at least 81 times lower than the allowable limit of 3,000 mrem. The extrapolated dose equivalent for whole body was 169 mrem.

Pharmacokinetics Concentrations of radioactivity in blood and plasma steadily declined with time (see table and figure below). Radioactive concentrations peaked at the end of the infusion (8 hours) in blood and plasma. Radioactivity in blood was not detected 16 hours after the infusion was started (8 hours after the infusion was stopped). There is a lot of variance in the measured radioactivity in plasma after 56 hours (48 hours after the infusion was stopped). No concentrations were detected in plasma 200 hours after the infusion was started, but measurable concentrations were obtained at 224 hours.

Table 16.3-2. Mean Concentrations of Radioactivity in Blood and Plasma at Specified Times After Administration of a Single Subcutaneous Infusion of [^{14}C]UT-15 (15 ng/kg/min) to Healthy Male Subjects

Collection Time (Hours) ^a	ng Equivalents [^{14}C]UT-15/g Blood			ng Equivalents [^{14}C]UT-15/mL Plasma		
	Mean	SD	%CV	Mean	SD	%CV
2	1.19	0.340	28.6	2.55	0.703	27.5
4	1.59	0.241	15.3	3.54	0.492	13.9
6	1.86	0.292	15.7	3.92	0.657	16.7
8	2.04	0.294	14.5	4.22	0.627	14.8
8.25	1.94	0.222	11.5	4.14	0.583	14.0
8.5	1.74	0.324	18.6	3.91	0.694	17.7
9	1.50	0.353	23.6	3.29	0.769	23.4
10	1.03	0.303	29.4	2.06	0.551	26.7
11	0.680	0.272	40.0	1.47	0.517	35.1
12	0.351	0.351	100	1.06	0.375	35.5
16	0.107	0.175	164	0.492	0.190	38.5
24	0.000	0.000	0.000	0.345	0.133	38.5
32	0.000	0.000	0.000	0.227	0.0856	37.7
56	0.000	0.000	0.000	0.124	0.105	84.9
80	0.000	0.000	0.000	0.187	0.0467	25.1
104	0.000	0.000	0.000	0.161	0.0599	37.3
128	0.000	0.000	0.000	0.0785	0.0966	123
152	0.000	0.000	0.000	0.107	0.0602	56.5
176	0.000	0.000	0.000	0.0262	0.0406	155
200	0.000	NA	NA	0.000	NA	NA
224	0.000	NA	NA	0.0815	NA	NA

a After the start of infusion.
 NA Not applicable.
 SD Standard deviation.
 %CV Coefficient of variation.

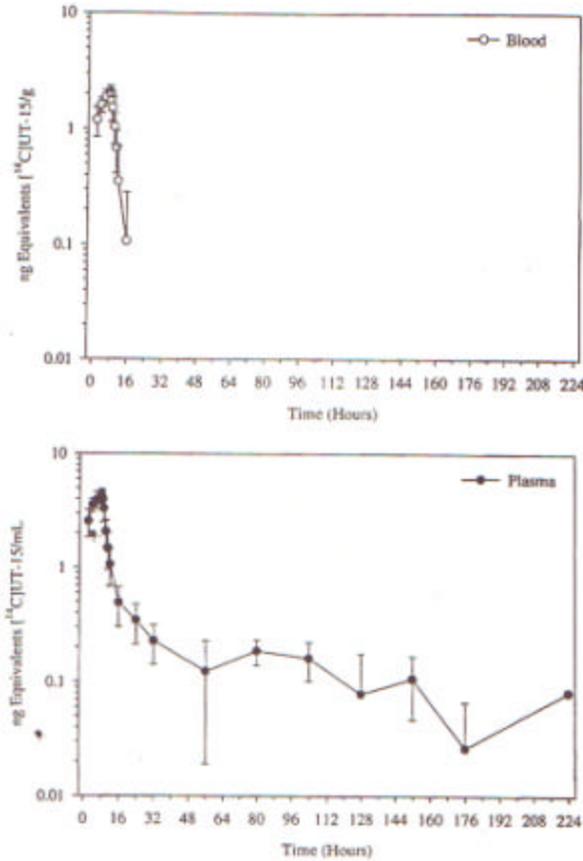


Figure 16.3-1. Mean concentrations of radioactivity in blood and plasma at specified times after administration of a single subcutaneous infusion of [¹⁴C]UT-15 (15 ng/kg/min) to healthy male subjects.

The blood:plasma concentration ratio was around 0.47 ± 0.02 . See table below.

Table 16.3-3. Mean Blood:Plasma Concentration Ratios at Specified Times After Administration of a Single Subcutaneous Infusion of [¹⁴C]UT-15 (15 ng/kg/min) to Healthy Male Subjects

Collection Time (Hours)	Blood:Plasma Concentration Ratio	
	Mean	SD
2	0.467	0.060
4	0.448	0.014
6	0.476	0.021
8	0.483	0.033
8.25	0.471	0.017
8.5	0.445	0.022
9	0.457	0.011
10	0.498	0.022
11	0.457	0.104
12	0.294	0.250
16	0.152	0.257
24	NA	NA
32	NA	NA
56	NA	NA
80	NA	NA
104	NA	NA
128	NA	NA
152	NA	NA
176	NA	NA
200	NA	NA
224	NA	NA

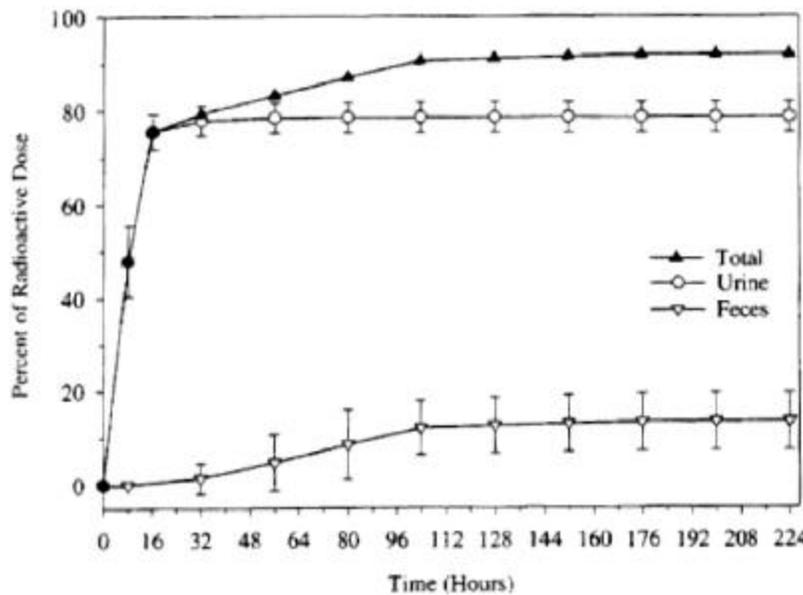
NA Not applicable.
 SD Standard deviation.

The pharmacokinetic parameters of radioactivity in blood and plasma are summarized in the table below.

[¹⁴ C]UT-15-derived radioactivity	[¹⁴ C]UT-15-derived radioactivity	
	Blood	Plasma
C _{max} (ng Equivalents/g)	2.11 ± 0.282	C _{max} (ng Equivalents/mL) 4.47 ± 0.627
T _{max} (Hour)	7.71 ± 0.843	T _{max} (Hour) 7.79 ± 0.900
AUC _{0-∞} (ng Equivalents-hr/g)	16.4 ± 2.02	AUC _{0-∞} (ng Equivalents-hr/mL) 63.1 ± 11.86
AUC _{0-∞} (ng Equivalents-hr/g)	17.5 ± 2.56	AUC _{0-∞} (ng Equivalents-hr/mL) 79.6 ± 3.91
β (Hour ⁻¹)	0.4208 ± 0.19765	β (Hour ⁻¹) 0.0125 ± 0.00565
t _{1/2} (β) (Hour)	2.03 ± 1.083	t _{1/2} (β) (Hour) 64.6 ± 32.0
		α (Hour ⁻¹) 0.3838 ± 0.12344
		t _{1/2} (α) (Hour) 1.97 ± 0.807

The T_{1/2} of the radioactivity in blood varied from approximately 1 to 4 hours. The T_{1/2} of the radioactivity in plasma was measurable only in 3 subjects. These half-lives were 38.1, 55.5 and 100 hours for a mean plasma T_{1/2} of 65 hours.

Excretion and Mass Balance The sponsor was able to recover 92.2% of the radioactive dose (see figure below). By 224 hours after dose initiation, the cumulative percent of radioactive dose was 78.6% in the urine, 13.4% in the feces and 0.05% in fecal wipes for a total of 92.2%. Most of the dose excreted is rapidly eliminated, 75.6% recovered in the urine within 16 hours and 13.3% recovered in the feces by 176 hours after dose initiation. Two subjects vomited during the infusion and 48% of the radioactive dose was found in the vomitus. The remaining uncharacterized radioactivity was composed of minor metabolites and background radioactivity.



HPLC profiling of urine showed that 3.7% of the [¹⁴C] UT-15 dose was excreted unchanged. Additionally, five prominent peaks were observed. These metabolites were arbitrarily named, HU1-5 and comprised 64.4% of the dose. (See table below.)

	% of dose	Product of:
[¹⁴ C] UT-15	3.7	---
HU1	13.8	Unidentified
HU2	14.3	Oxidation of the 3-hydroxyloctyl side chain
HU3	15.5	Oxidation of the 3-hydroxyloctyl side chain
HU4	10.6	Oxidation of the 3-hydroxyloctyl side chain with an additional dehydration of the 3-hydroxyl group of that side chain
HU5	10.2	glucuronidation of the parent

The percentage of radioactivity (and percent of dose) are shown in the table below for UT-15 and its five metabolites. No major metabolite could be discerned from the data. However, in four out of six subjects, HU3 was the most abundant.

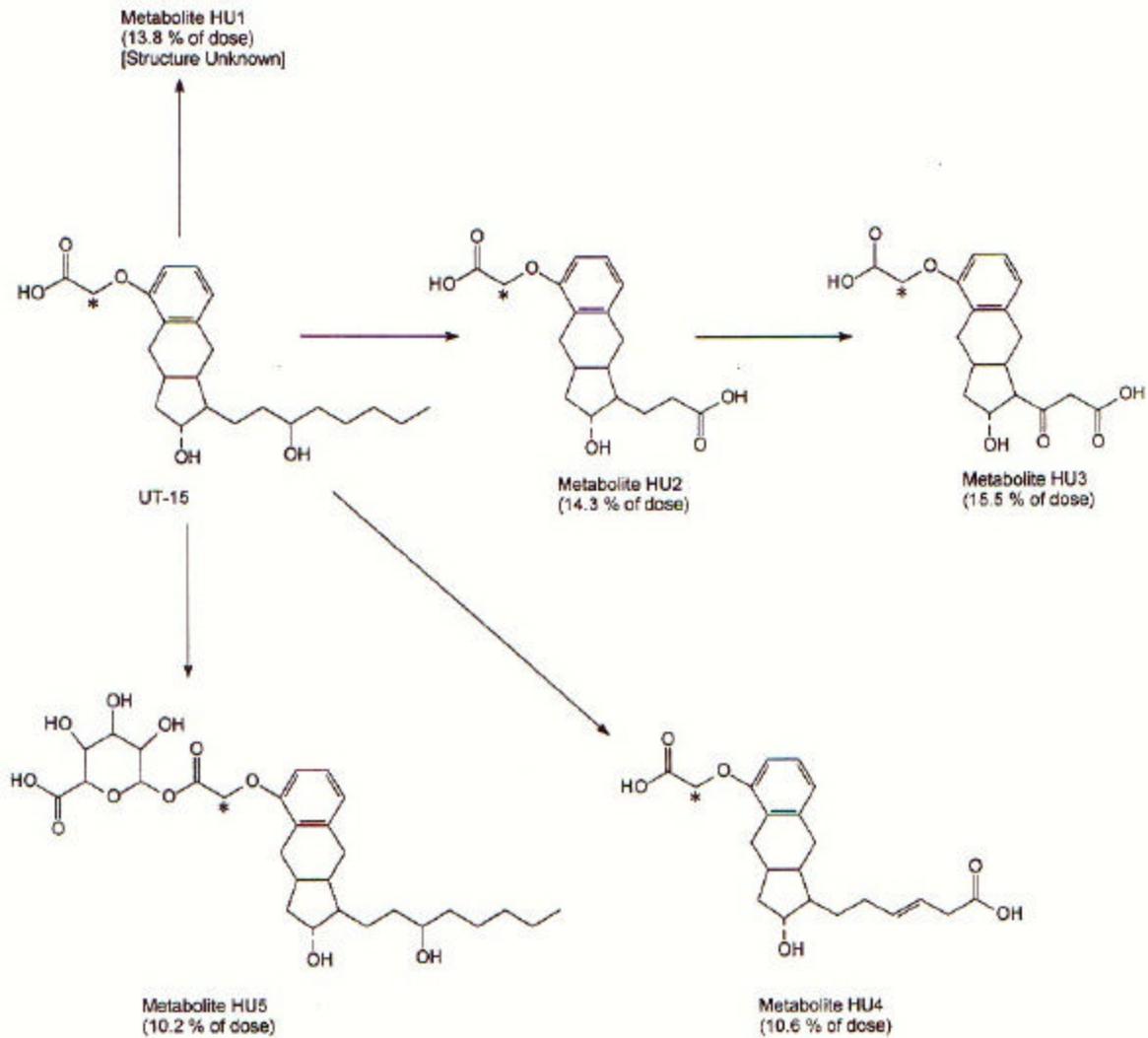
Table 16.3-8. Percentage of Sample Radioactivity and Percent of Dose Excreted as [¹⁴C]UT-15 or Metabolites of [¹⁴C]UT-15 in Urine from Humans Following a Subcutaneous Infusion to Six Healthy Males

Retention Time Range (Minutes)	Percent of Sample Radioactivity in Metabolite and Parent Peaks (Percent of Dose)						Mean	SD	
	Subject Number								
	1	2	3	4	5	6			
Percent of Dose in Urine	72.6	80.9	77.0	72.2	78.3	72.4			
Component									
HU1	10.8 to 10.9	10.3 (7.48)	18.1 (14.6)	34.6 (26.6)	16.0 (11.6)	18.3 (14.3)	11.2 (8.11)	18.1 (13.8)	8.78 (6.96)
HU2	11.4	24.1 (17.5)	22.8 (18.4)	13.7 (10.5)	18.3 (13.2)	17.0 (13.3)	17.8 (12.9)	19.0 (14.3)	3.86 (3.02)
HU3	12.7	17.9 (13.0)	23.4 (18.9)	12.4 (9.55)	23.1 (16.7)	25.1 (19.7)	21.3 (15.4)	20.5 (15.5)	4.68 (3.80)
HU4	14.0 to 14.1	23.2 (16.8)	11.5 (9.30)	10.8 (8.32)	12.0 (8.66)	12.5 (9.79)	14.7 (10.6)	14.1 (10.6)	4.64 (3.15)
HU5	15.6	13.2 (9.58)	8.58 (6.94)	12.1 (9.32)	18.3 (13.2)	11.9 (9.32)	17.8 (12.9)	13.6 (10.2)	3.75 (2.40)
[¹⁴ C]UT-15	19.6	1.57 (1.14)	4.14 (3.35)	7.52 (5.79)	5.43 (3.92)	4.75 (3.72)	6.00 (4.34)	4.90 (3.71)	2.00 (1.52)

SD Standard deviation
 a Approximately 1 to 2% by volume of each sample collection interval from Day 0, 8 hour and Day 1, 8 hour for each subject was combined.

LC/MS/MS results showed that 4.9% of the administered dose was excreted as UT-15 and 10.4% was excreted as the glucuronide of UT-15. These results are similar to the HPLC results.

The proposed structure of parent and metabolites are shown below.



* Position of ¹⁴C label.

PHARMACODYNAMIC RESULTS: The medical officer will review these.

CONCLUSION: UT-15 is heavily metabolized in the liver. Less than 5% of a dose is excreted unchanged and 10% is excreted as the glucuronide in the urine. There are no major metabolites, but five are identified, all of which are primarily excreted in the urine. The structure of the HU1 metabolite is unknown. HU2 and HU3 are products of oxidation of the 3-hydroxyloctyl side chain. HU4 is formed from oxidation followed by dehydration of the 3-hydroxyl group. HU5 is a product of glucuronidation. These five metabolites and the parent drug comprise 68.1% of the administered dose in the urine.

By 224 hours after dose initiation, 92.2% of the dose is recovered; 78.6% in the urine, 13.4% in the feces, and 0.05% in fecal wipes. Most of the dose is excreted in the urine rapidly; 75.6% is recovered within 16 hours.

REVIEWER'S COMMENTS: The sponsor was able to recover a substantial (92.2%) amount of the dose. Five metabolites and the parent drug comprised 68.1% of the administered dose in urine. If the sponsor had analyzed feces for parent and metabolites, they might have been able to account for more of the parent and metabolites since 13.4% of the dose was recovered in the feces.

The mean $T_{1/2}$ of radioactivity in blood, 2 hours, is consistent with the reported mean $T_{1/2}$ from pharmacokinetic studies. Of note is the $T_{1/2}$ of radioactivity in plasma of 65 hours. It is possible that this represents the $T_{1/2}$ of radioactivity of a slowly cleared metabolite.

The content of parts of this report is inconsistent, which made the report confusing and the information harder to decipher. For example, page 3260 states that the lower range of [^{14}C]UT-15 was 463,300 ng, whereas on page 3294 (and table 14-3, page 3328) this number is 448,300 ng. The corresponding amount of [^{14}C]UT-15 is stated as 72.5 μCi on both pages. Nevertheless, the minimum amount of radioactivity received was not harmful. Another example is that the sponsor confused the data for metabolite HU1 and HU5 in the section 6 summary. After looking at the analytical report, it is concluded that HU1 is the unidentified metabolite and HU5 is the glucuronide metabolite.

There is large variance in the measured radioactivity in plasma after 56 hours (48 hours after the infusion was stopped). Concentrations were undetected in plasma 200 hours after the infusion was started, but measurable concentrations were obtained at 224 hours.

STUDY TITLE: A dose range finding study comparing intravenous and subcutaneous 15AU81 (UT-15) in NYHA Class III/IV patients with primary pulmonary hypertension

STUDY P01:02 VOLUME: 2.3 **PAGES:** 47 - 349
PRINCIPAL INVESTIGATOR: Gaine S, MD et al.

CLINICAL LABORATORY: multicenter

CITATION: not applicable

FIRST PATIENT ENROLLED: September 4, 1997

LAST PATIENT COMPLETED: January 27, 1998

OBJECTIVES:

- To describe the safety, dose-response and acute hemodynamic effects of SC UT-15 in patients with severe primary pulmonary hypertension (PPH)
- To determine the maximum tolerated dose
- To characterize the PK profile of SC UT-15 in patients with PPH

NOTE: This review will focus on the PK part of the study.

STUDY DESIGN: multicenter, parallel, sequential, dose-escalation design.

DURATION: The PK part of the study took one day.

POPULATION: Thirty people with severe PPH (NYHA Class III or IV) aged > 12 years were planned to be enrolled. Females were physiologically incapable of childbearing or practicing an acceptable method of birth control.

PROCEDURE: During the screening/baseline phase all patients underwent right heart catheterization and had baseline hemodynamic parameters determined. Patients were then assigned sequentially to one of three cohorts of at least 6 patients each.

Treatment There were three cohorts that received the treatment outlined below. The IV dose for all cohorts was 10 ng/kg/min. The SC dose was 5 ng/kg/min in Cohort I, 10 ng/kg/min in Cohort II, and 20 ng/kg/min in Cohort III. A Cohort IV (30 ng/kg/min) and Cohort V (40 ng/kg/min) were planned, but 20 ng/kg/min was the maximally tolerated dose, thus, dose escalation was stopped.

The treatment phase consisted of four segments: (a) an IV UT-15 75-minute dosing segment, (b) an IV UT-15 150 minute washout segment, (c) a SC UT-15 150-minute dosing segment, and (d) a SC UT-15 150-minute washout segment.

Hemodynamics, vital signs, and blood samples were taken during the treatment phase. Patients were observed for clinical signs and symptoms and queried for occurrence of adverse events throughout the study. The infusion was stopped if the patient showed intolerability.

The IV infusion was delivered by a positive-pressure infusion pump provided by the clinical site via a catheter in the peripheral or central vein. SC UT-15 solution was infused into the abdominal wall via a MiniMed (Model 506) positive pressure micro-infusion pump. At the end of the SC infusion, the catheter along with the MiniMed pump was removed and the 150-minute SC washout segment commenced immediately.

The primary endpoints were safety parameters, and changes from baseline in clinical laboratory values, vital signs, physical examination findings and EKGs. The surrogate efficacy endpoints were hemodynamics.

Pharmacokinetics Five milliliter plasma samples were collected at baseline, 15, 30, 60 and 75 minutes during the intravenous infusion, and at 5, 10, 15, 30, 60, 90, and 120 minutes post infusion. During the subcutaneous administration of UT-15, plasma samples were collected at baseline, 15, 30, 60, 90, 120 and 150 minutes, and at 5, 10, 15, 30, 60, 90, 120 and 150 minutes post infusion.

OTHER MEDICATIONS: Patients must not be taking any medications for PPH other than anticoagulants.

FORMULATION: UT-15, 0.5 mg/mL was supplied as a sterile solution in 2 mL vials. The UT-15 lot used in this trial was #Y7H0978A. Each mL contained 0.5 mg UT-15, 5.0 mg sodium citrate, 0.5 mg citric acid, and 0.2 mg sodium hydroxide. The pH of the UT-15 injection was 5.5 to 7.5. A placebo (citrate buffer vehicle) was also supplied as a sterile solution in 2 mL vials (Lot #Y7H0977A) to be used as a diluent where necessary. Each mL contained 5.0 mg sodium citrate, 0.5 mg citrate acid, and 0.2 mg sodium hydroxide (pH 5.5 – 7.5).

For both routes of administration, the infusion solution was made up of UT-15 injection and the citrate buffer to achieve the correct UT-15 concentration. IV UT-15 for injection was diluted in dextrose 5% in water (D₅W) to a final concentration of 7500 ug/L (7.5 µg/mL).

For the 5 ng/kg/min SC infusion (Cohort I), UT-15 Injection at a concentration of 0.5 mg/mL was mixed with sterile diluent solution on a 1:1 ratio to achieve a final concentration of 0.25 mg/mL. For the 10 and 20 ng/kg/min SC infusion, no dilution was necessary prior to placement into the infusion pump.

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 to 46°F, 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, not exposed to extreme cold or heat.

ASSAY: Plasma samples were analyzed by Alta Analytical Laboratory, El Dorado Hills, CA. The extracts were analyzed for UT-15 using a validated LC/MS/MS assay over a standard curve range of 0.10 to 50.0 ug/L .

Precision

The intraday and interday CV was less than 13%.

Accuracy

Interday accuracy was within 9.3% and intraday accuracy was within 8%.

Sensitivity

The LLOQ was 100 pg/mL (0.10 ug/L) for a 40 µL aliquot of plasma.

Linearity

The standard curve was linear over a range of 0.100 ug/L to 50.00 ug/L ($r^2 \geq 0.9965$).

ANALYSIS: *Pharmacokinetic Data* Pertinent pharmacokinetic parameters including C_{max} , T_{max} , AUC_{inf} , apparent CL, $T_{1/2}$, V_z and F were determined via non-compartmental methods using WinNonlin ver 1.1. All PK parameters were determined from UT-15 concentration values based on actual blood sampling times. PK variables were determined by usual methods and summarized with descriptive statistics.

Additionally, PVRI, was plotted against plasma UT-15 concentration values to determine whether a pharmacokinetic-pharmacodynamic relationship existed following acute iv and SC administration of UT-15.

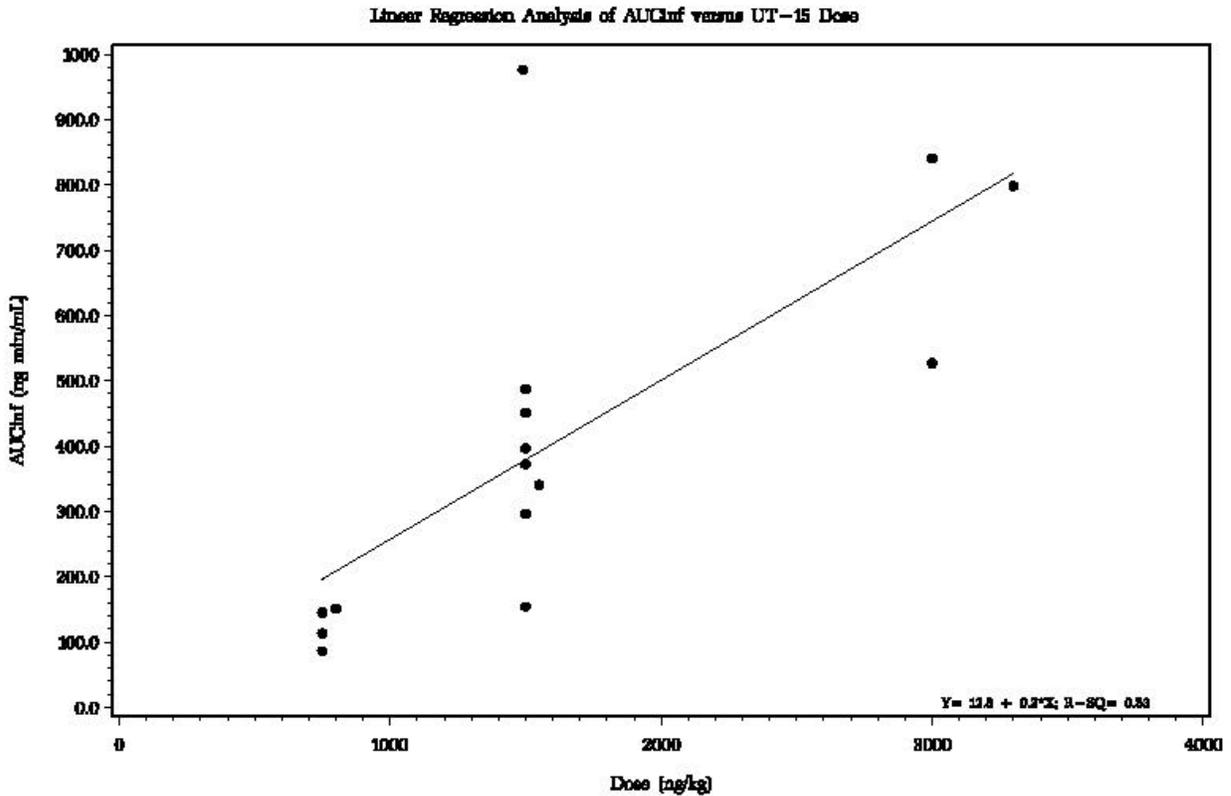
RESULTS: Twenty-five patients (20 female and 5 male) were enrolled. There were 18 Caucasians, 3 Hispanics, 2 Asians and 2 Blacks. Their ages ranged from 22 to 71 years with a median age of 41 years. Weight ranged from 45 kg to 123 kg with a median weight of 76 kg.

Six (6) patients were assigned to the 5 ng/kg/min SC cohort, 13 patients were assigned to the 10 ng/kg/min SC cohort, and 6 patients were assigned to the 20 ng/kg/min SC cohort. A protocol amendment in December 1997 allowed the enrollment of at least 6 additional patients to Cohort II (10 ng/kg/min) following the completion of Cohort III, since 20 ng/kg/min was deemed the maximally tolerated acute dose.

The plots of PVRI vs. plasma UT-15 concentration were uninterpretable.

PHARMACOKINETIC RESULTS: Only patients completing both IV and SC phase were included in the descriptive statistics. These 15 patients were comprised of 4 from Cohort I, 8 from Cohort II and 3 from Cohort III. Two patients had non-zero plasma concentrations prior to the start of the SC infusion due to the short IV washout segment. The SC AUC_{inf} values for these two patients were corrected for residual UT-15 concentrations. Approximately 30% of the patients

had delays in PK sampling time. These delays ranged from one to 30 minutes. Linear regression analysis of AUC_{inf} versus dose data yielded a coefficient of determination, r^2 , of 0.53. The figure below shows that SC UT-15 infused for 150 minutes has dose-proportional kinetics over the dose range of 5 – 20 ng/kg/min (concentrations of 0.10 – 5.03 ug/L).



The PK parameters for each cohort are shown in the following tables.

Cohort I (n = 4)*

	Cmax ug/L	Tmax min	T _{1/2} min	AUC _{inf} ng-min/mL	CL/F mL/min/kg	Abs F %
<u>IV dosing</u>	targeted infusion rate: 10 ng/kg/min for 90 minutes (see reviewer's comments)					
Mean	4.05	73	41.7	173.2	5.37	-
Median	2.19	75	13.4	145.6	5.79	-
SD	4.02	9	60.8	91.1	2.42	-
CV (%)	99.27	12	145.9	52.6	45.07	-
Minimum	1.75	60	7.3	101.3	2.50	-
Maximum	10.06	80	132.6	300.6	7.41	-

SC dosing - targeted infusion rate: 5 ng/kg/min for 150 min

Mean	1.02	119	65.1	123.7	6.46	90.2
Median	0.78	158	44.8	129.1	5.97	96.9
SD	0.64	79	48.0	30.2	1.65	47.1
CV (%)	62.91	67	73.7	24.4	25.60	52.2

Minimum	0.57	0	34.1	85.9	5.17	28.6
Maximum	1.94	160	136.7	150.9	8.73	138.6

* Two subjects were excluded in the computation of descriptive statistics. Subject 02001's IV infusion pump likely malfunctioned and Subject's 07001's SC infusion was substantially shorter than the protocol specified duration of 150 min.

Cohort II (n = 8)*

	C _{max} ug/L	T _{max} min	T _{1/2} min	AUC _{inf} ng-min/mL	CL/F mL/min/kg	Abs F %
<u>IV Dosing</u> - targeted infusion rate: 10 ng/kg/min for 90 min (see reviewer's comments)						
Mean	2.16	70	35.4	172.7	6.03	-
Median	1.91	75	20.4	142.7	5.26	-
SD	0.93	9	31.7	115.2	3.39	-
CV (%)	43.10	12	89.6	66.7	56.30	-
Minimum	0.87	60	7.7	59.2	2.11	-
Maximum	3.59	80	86.2	427.0	12.66	-

<u>SC dosing</u> - targeted infusion rate: 10 ng/kg/min for 150 min						
Mean	2.00	151	117.2	434.1	4.39	144.1
Median	1.95	155	104.1	384.3	3.91	134.1
SD	0.78	13	89.4	241.4	2.41	55.2
CV (%)	39.20	9	76.3	55.6	54.88	38.3
Minimum	0.89	120	27.1	154.1	1.53	68.5
Maximum	3.49	160	319.3	975.9	9.73	228.3

* Five subjects were excluded from the computation of descriptive statistics. Subject 01002's SC infusion was substantially shorter than the protocol specified duration; Subject's 02003's SC profile was not analyzable; Subject 04001's IV profile also was not analyzable; Subject 04003's IV infusion was interrupted because of a technical problem with the pump; and Subject #04004's IV concentration values were not detectable.

Cohort III (n = 3)*

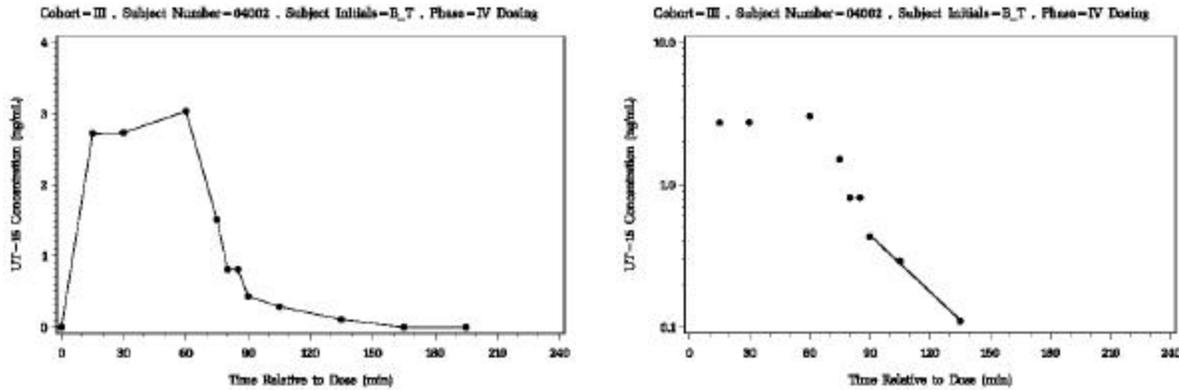
	C _{max} ug/L	T _{max} min	T _{1/2} min	AUC _{inf} ng-min/mL	CL/F mL/min/kg	Abs F %
<u>IV Dosing</u> - targeted infusion rate: 10 ng/kg/min for 90 min (see reviewer's comments)						
Mean	2.10	75	25.6	143.8	5.36	-
Median	2.13	75	22.9	138.5	5.42	-
SD	0.11	0	12.1	15.6	0.37	-
CV (%)	5.15	0	47.4	10.8	6.98	-
Minimum	1.98	75	15.0	131.6	4.96	-
Maximum	2.19	75	38.8	161.4	5.70	-

<u>SC dosing</u> - targeted infusion rate: 20 ng/kg/min for 150 min						
Mean	4.06	153	55.1	721.8	4.47	123.9
Median	3.75	160	63.4	798.1	4.13	119.9

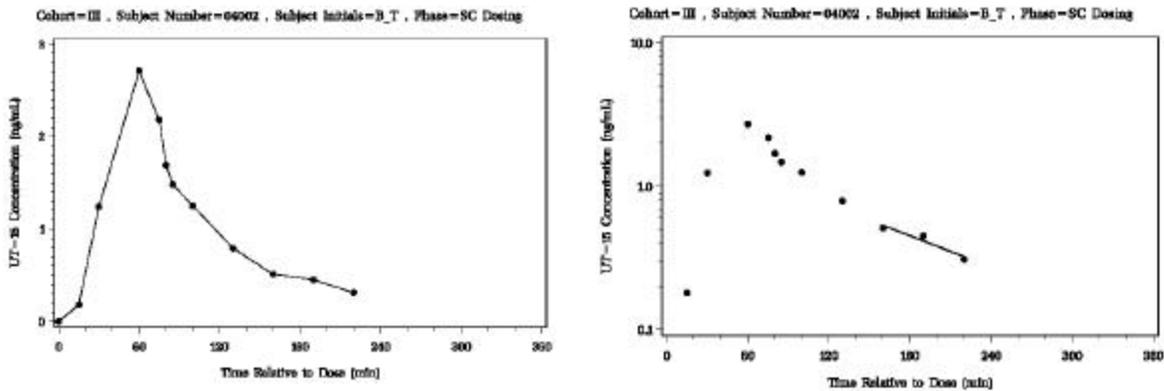
SD	0.86	31	20.1	170.1	1.10	26.0
CV (%)	21.25	20	36.5	23.6	24.63	21.0
Minimum	3.39	120	32.2	526.9	3.57	100.1
Maximum	5.03	180	69.7	840.3	5.69	151.7

* Three subjects (02004, 02005 and 04002) were excluded from the computation of descriptive statistics because their SC infusions were substantially shorter than the protocol specified duration.

IV UT-15 follows a two-compartment body model since the concentration decline after C_{max} was biphasic. Below is a representative patient's concentration vs. time profile on a linear and log scale.



The same patient's concentration vs. time profile for SC UT-15 is shown below.



SPONSOR'S CONCLUSIONS:

- The inter-subject variability of the pharmacokinetic parameters (including C_{max}, AUC_{inf}, and T_{1/2}) following acute IV or SC administration was large with coefficients of variation (CV) ranging up to 145.9%.
- The UT-15 elimination T_{1/2} following acute SC infusion was 1 to 2 hrs, however the LC/MS/MS assay used in this study (with a LOQ of 100 pg/mL) lacked the sensitivity for tracking the terminal elimination phase for five half-lives.
- The absorption of UT-15 administered by SC infusion into the systemic circulation was

complete.

- Acute SC UT-15 seems to exhibit dose-proportional pharmacokinetics over the dose range of 5-20 ng/kg/min.

REVIEWER'S COMMENTS: Absorption is complete. Acute SC UT-15 exhibits dose-proportional pharmacokinetics over the concentration range of 0.10 – 5.03 ug/L (dose range, 5 – 20 ng/kg/min).

The T_{1/2} for SC and IV UT-15 are not very different. The mean T_{1/2} (CV%) for the IV dose was 41.7 (146%), 35.4 (90%), and 25.6 (47%) minutes. The mean T_{1/2} for the SC dose was 65.1 (74%), 117 (76%), and 55 (37%) minutes for the 5, 10 and 20 ng/kg/min dose, respectively. The most reliable measurement of T_{1/2} from the SC data is the one obtained with the highest dose. Thus, after considering the variability in the data, the T_{1/2} of 55 minutes after the SC dose is comparable to the one obtained from the IV dose.

Assay insensitivity and the wide subject weight range (45-123 kg) contributed to the large inter-individual variability (IIV) in the PK parameters. The IIV of clearance ranged from 7-56%, however the sponsor's calculation was not adjusted for weight. The assay used in this study was not as sensitive as that used in other studies. The lower LOQ was 0.1 ug/L, whereas other studies have had sensitivities as low as 0.025 ug/L. Most concentrations were not quantifiable 30 – 60 minutes after the end of the IV infusion and 60 minutes after the end of the SC infusion. The inability to measure these lower concentrations would result in under or over estimation of PK parameters.

The sponsor reports that the IV infusion was to be administered for 75 minutes, yet review of the patient data shows many subjects received the IV infusion for up to 90 minutes.

STUDY TITLE: A bioavailability study of UT-15 administered subcutaneously versus intravenously in healthy volunteers

STUDY P01:07 VOLUME: 2.5 to 2.6 **PAGES:** 603 to 1198
PRINCIPAL INVESTIGATOR: Thomas L. Hunt, MD, Ph.D.

STUDY SITE: PPD Development
706 Ben White Blvd, West
Austin, TX 78704-7016

CITATION: not applicable

FIRST PATIENT ENROLLED: June 4, 1999
LAST PATIENT COMPLETED: July 28, 1999

OBJECTIVES:

- To compare the safety and tolerability of UT-15 administered as a continuous short-term IV and SC infusion in healthy volunteers.
- To determine the absolute bioavailability of UT-15 administered SC in healthy volunteers

Safety was monitored because this was the first time healthy subjects received SC and IV UT-15. This review will discuss the PK part of the study.

STUDY DESIGN: single center, open-label, two-period, single-dose, non-randomized design

POPULATION: Fifteen healthy adult subjects enrolled and completed the study. Female subjects were of non-childbearing potential or had a negative serum pregnancy test during screening and prior to receiving UT-15 in Period 2. Subjects were between the ages of 18 to 50 years and weighed from 40 to 90 kg (within 10% of the desired body weight).

PROCEDURE:

Dose After qualifying for study entry, subjects received 15 ng/kg/min of IV UT-15 for 150 minutes or 2.5 hours in the morning (Period 1). This was followed by a 5-7 day washout. Subjects then received 15 ng/kg/min of SC UT-15 for 150 minutes in the morning (Period 2).

Delivery device While supine, subjects received UT-15 subcutaneously via a catheter placed in the abdominal wall with a Minimed (Model 506) microinfusion pump, or intravenously into an arm vein with a Baxter Syringe Pump (Model AS-4A0). Both systems are positive pressure infusion pumps.

Blood and urine were collected as described below. Subjects were discharged after completion of the 48 hour urine collection, provided there were no clinically relevant abnormalities.

PHARMACOKINETICS: During Periods 1 and 2, urine and blood were collected for PK calculations. A single urine void was collected predose, and urine was collected from 0-48 hours post dose. Urine volume was recorded, and an aliquot was stored for analysis. Blood was

collected predose, after the infusion began at 0.25, 0.5, 1, 1.5, 2 and 2.5 hours, after the infusion stopped at 5, 10 and 15 minutes, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours.

OTHER MEDICATIONS: Subjects did not take prescription medications (except for approved oral contraceptives) within 14 days of dosing or OTC medications within 72 hours of dosing. Subjects also abstained from tobacco products within 90 days prior to receiving UT-15.

FORMULATION: UT-15 was provided as a sterile solution in 20 mL multidose vials (lot number 800506). The to-be-marketed formulation was used.

When administered by IV infusion, UT-15 injection (1 mg/mL sterile solution) was first diluted in D₅W to an appropriate strength. For SC administration, UT-15 was delivered without any dilution.

ASSAY: Alta Analytical Laboratory analyzed the plasma samples with a validated LC/MS/MS assay. A dimethylene homologue of UT-15 (LRXA-97J02) was used as an internal standard. Quality controls were analyzed at concentrations of 0.0750, 4.0000, and 8.0000 ug/L.

Precision Intraday and interday CV was less than 14%.

Accuracy Intraday and interday accuracy was within 12%.

Sensitivity The LOQ was 0.025 ug/L (25 pg/mL) for a 1 mL aliquot of plasma.

Linearity The assay was linear over a standard curve range of 0.025 – 10.0000 ug/L ($r^2 \geq 0.9946$).

ANALYSIS:

Pharmacokinetic Data Non-compartmental methods were used to determine the usual PK parameters: peak concentration (C_{max}), corresponding peak time (T_{max}), area under the curve (AUC_{inf}), volume of distribution (V_z), plasma clearance (CL), elimination half-life ($T_{1/2}$), and absolute bioavailability (F).

Statistical analysis Descriptive statistics were used where appropriate.

RESULTS: Fifteen healthy subjects (8 males and 7 females) ages 18 to 49 years (mean age 31) were enrolled and completed the study. There were 8 Caucasians, 4 Hispanics and 3 Blacks. Subjects weighed between 51-87 kg (mean weight 71 kg). Two subjects were above the prespecified weight by 0.5 and 0.2 kg, respectively.

Dose All subjects received 15 ng/kg/min. Total subcutaneous dose ranged from 114.75 – 195.75 mg per person (mean 159.9 mg).

Concomitant medications Two females were preapproved to take oral contraceptives. A third subject ingested naproxen 7 days prior to dosing period 1. These factors are not expected to significantly affect the pharmacokinetics.

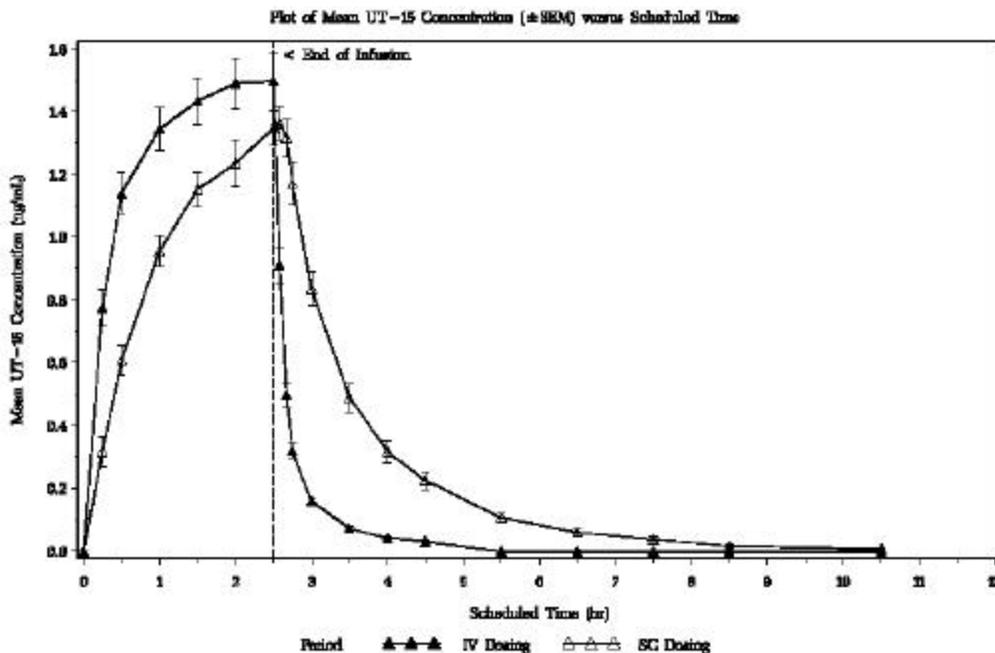
Safety A total of 30 adverse events (AEs) were reported by 11 of 15 volunteers during the study; none of the events was a serious adverse event (SAE). The majority of the AEs (67%) had an onset during the 150-minute infusion period while the remainder (33%) had an onset after the termination of the infusion. The most common systematic adverse events were headaches, dizziness and nausea and occurred more frequently during iv than SC administration (53% vs. 27%; 27% vs. 0%, and 20% vs. 7%, respectively). Acute intravenous dosing elicited a slightly higher frequency of AEs typical of vasodilators. Acute subcutaneous dosing elicited an additional AE, namely injection site pain, which was not reported by the same subjects during intravenous dosing.

Urine 10.4% (range: 2.5-15.6%) of SC UT-15 was excreted as the glucuronide. 4.9% (range 0-8.6%) was excreted unchanged. No UT-15 sulfates was found in urine aliquots.

PHARMACOKINETIC RESULTS: Absolute bioavailability was over 100%. Mean AUC_{inf} for IV and SC dosing were 3.52 and 3.97 ug/L, resulting in a mean absolute bioavailability of 113%.

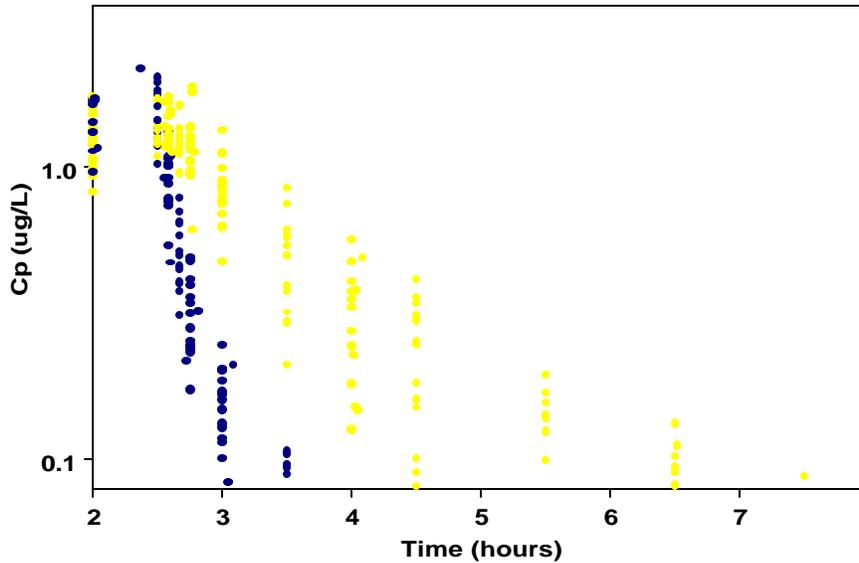
Plasma concentrations increased quickly (IV faster than SC), peaked at the end of the infusion (~2.5 hours) (see figure below). In some subjects C_{max} for SC UT-15 occurred shortly after termination of the infusion. Plasma concentrations ranged from 0.03 – 2.18 and 0.03 – 1.88 ug/L for IV and SC infusions, respectively. The mean concentration was ~0.7 ug/L.

Mean ± SE concentration vs. time profile for IV and SC UT-15



Concentrations declined in a biphasic manner. This was more evident with the IV dose (darker circles in the figure below). Concentrations were below the limit of quantification 3 hours after termination of the infusion in most subjects.

Individual plasma concentrations of UT-15



PK parameters are summarized in the tables below.

Intravenous UT-15 Pharmacokinetic Parameters (n = 15)

Parameters	Mean	SD	CV (%)	Minimum	Maximum
C _{max} (ug/L)	1.57	0.31	19.8	1.14	2.18
T _{max} (hr)	2.13	0.34	16.1	1.50	2.50
T _{1/2} (hr)	0.87	0.43	49.5	0.27	2.04
AUC _{inf} (ng hr/mL)	3.52	0.71	20.0	2.48	4.81
CL (mL/kg/hr)	663.0	132.2	19.9	467.4	907.6

Subcutaneous UT-15 Pharmacokinetic Parameters (n = 15)

Parameters	Mean	SD	CV (%)	Minimum	Maximum
C _{max} (ug/L)	1.47	0.20	13.6	1.18	1.88
T _{max} (hr)	2.51	0.22	8.8	2.00	2.77
T _{1/2} (hr)	1.38	0.66	47.8	0.63	2.52
AUC _{inf} (ng hr/mL)	3.97	0.76	19.0	2.37	5.46
Cl (mL/kg/hr)	589.4	129.6	22.0	412.2	947.8
Absolute F (%)	113.1	10.0	8.9	95.8	131.8

SPONSOR’S COMMENTS: Mean absolute bioavailability of acute subcutaneous administration of UT-15 was determined to be 113%. Possible reasons for an absolute bioavailability greater than 100% include the underestimation of intravenous dose AUC_{inf} and/or overestimation of the subcutaneous dose AUC_{inf}. The intravenous dose AUC_{inf} could have been underestimated

because most of the terminal elimination phase could not be documented due to LOQ of the assay.

According to the sponsor, the AUC_{inf} following the subcutaneous dose could have been overestimated because of enterohepatic recirculation. UT-15 has two hydroxyl groups and one carboxylate group; and it has been reported in non-clinical studies that these functional groups formed sulfate and glucuronide conjugates. Following excretion into the bile, it was possible that some of the conjugates were hydrolyzed back into the parent drug, which was reabsorbed resulting in slightly higher AUC_{inf} for the subcutaneous administration.

SPONSOR'S CONCLUSION: Absolute bioavailability of SC UT-15 is 113%.

Acute administration of UT-15 administered by IV and subcutaneous infusion at a rate of 15 ng/kg/min for 150 minutes (an acute maximum tolerated dose) achieved similar mean C_{max} , 1.57 and 1.47 ug/L, respectively.

Renal excretion was a minor elimination pathway for UT-15 since less than 5% of the dose was recovered in the urine as unchanged drug. A glucuronide metabolite of UT-15 accounted for ~10% of the dose.

REVIEWER'S COMMENTS: Absolute bioavailability of UT-15 is ~100%. It is difficult to believe that absolute bioavailability is greater than 100% from this study because of the inability to measure plasma concentrations for an adequate duration and the lack of evidence of enterohepatic recirculation from the plasma-concentration time curve. Additionally, if there was enterohepatic recirculation, it would occur with both routes of administration. Thus, both the IV and SC dose would be overestimated.

AUC_{inf} and $T_{1/2}$ were under or overestimated since concentrations were undetectable in all subjects two hours after the IV dose, and only three subjects had quantifiable concentrations for eight hours after the SC dose. (After SC administration, plasma concentrations were not quantifiable in 4 subjects after 3 hours post dose, 6 subjects after 4 hours, 10 subjects after 5 hours and 12 subjects after 6 hours post dose.) Thus, the duration of sampling was inadequate to appropriately assess AUC_{inf} and $T_{1/2}$.

There appears to be a difference in terminal IV and SC slopes. A more prominent 2-compartment model is seen with the IV dose versus the SC dose. One explanation is that the SC rate of input (absorption) is slower than the elimination rate (flip-flop phenomenon).

The $T_{1/2}$ range was 0.9 ± 0.4 hours for IV and 1.4 ± 0.66 hours for SC. It should be noted that the CV was ~50% and assay error was ~15%. The variability in weight (51-87 kg) contributed to the high CV.

Renal excretion results are similar to results from the mass balance study.

STUDY TITLE: A chronic dose escalation study of the pharmacokinetics of UT-15 administered by continuous subcutaneous infusion in healthy human volunteers

STUDY P01:09 **VOLUME:** 2.9 – 2.10 **PAGES:** 2098 - 2941

PRINCIPAL INVESTIGATOR: Thomas Hunt, MD, Ph.D.

CLINICAL LABORATORY: PPD Development
706 Ben White Blvd, West
Austin, TX 78704-7016

CITATION: not applicable

FIRST PATIENT ENROLLED: July 15, 1999

LAST PATIENT COMPLETED: August 28, 1999

OBJECTIVES:

Primary To assess the pharmacokinetics of continuous SC UT-15 (28 days) utilizing increasing doses of 2.5, 5, 10, and 15 ng/kg/min in healthy volunteers

Secondary To assess the safety and tolerability of chronic SC UT-15 in healthy volunteers

NOTE: This review will focus on the primary objective.

STUDY DESIGN: single-center, open-label, non-randomized, chronic, dose escalation design

DURATION: The treatment period lasted four weeks. Subjects were discharged after collection of the last pharmacokinetic blood sample and completion of exit procedures.

POPULATION: Fourteen healthy subjects (8 females, 6 males) between the ages of 18 to 50 years and weighing within 10% of their ideal body weight were enrolled. Female subjects either could not become pregnant or used an approved birth control method and had a negative serum pregnancy test.

PROCEDURE: Subjects checked into the clinic the evening prior to receiving the first dose. Subjects remained in the clinic during the four-week treatment phase. UT-15 was dosed as described in the treatment section below.

Blood samples were collected from an arm vein for clinical assessments and for pharmacokinetics. A saline lock was used to keep the catheter patent during frequent blood sampling on days 1 and 7 of each dosing period. Venipuncture was used at other times.

Meals were standardized and provided at prespecified times. One hour before the first infusion, a standard low fat breakfast was consumed. Each subject was provided lunch after the PK sample at 2 hours was drawn. Subsequent meals were served at fixed times.

Hemodynamics were measured throughout the study. Supine heart rate and blood pressure were measured pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5 and 6 hours relative to the start of a new

infusion. Respiration rate and temperature were measured pre-dose and 2.5 hours post-dose (relative to the start of the new infusion).

Safety was monitored throughout the study. Each subject was asked a non-leading question such as “How are you feeling?” at the start of the infusion, 6 hours following initiation of the infusion and every 24 hours. At the end of dosing period 2, all subjects had a physical examination and a 12-lead ECG performed. Exit procedures at the end of the study included a 12-lead ECG, a complete physical exam, vital sign measurements (after sitting still for 5 minutes), clinical laboratory tests and an assessment of any adverse events.

Treatment Undiluted UT-15 solution was continuously infused into the abdominal wall or another injection site as deemed appropriate by the PI. The infusion site was moved every 24 hours. Dose increases were initiated at the new infusion site. A MiniMed (Model 506) positive pressure micro-infusion pump was used to infuse UT-15 subcutaneously. The following treatment schedule was used:

Week 1 - 2.5 ng/kg/min for 7 days (168 hours)

Week 2 - 5 ng/kg/min for 7 days

Week 3 - 10 ng/kg/min for 7 days

Week 4 - 15 ng/kg/min for 7 days

Subjects were supine during the first two hours of the first infusion. There were no washout periods between doses.

Pharmacokinetics Blood samples for each week were collected pre-dose and at the following times relative to the start of the infusion: 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 24, 48, 72, 96, 120, 144, 147, 150, 153, 156, 159, 162 and 168 hours. Blood samples were collected more frequently during day 7 to determine if there is a diurnal cycle in steady state UT-15 concentrations. Samples were also collected after the infusion was terminated at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 9 hours post-infusion.

OTHER MEDICATIONS: Subjects were not allowed to use prescription medication (excluding contraceptives approved by the sponsor) within 14 days or OTC medication 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.

ASSAY: Alta Analytical Laboratory analyzed the plasma samples with a validated LC/MS/MS assay. A dimethylene homologue of UT-15 (LRXA-97J02) was used as an internal standard. Quality controls were analyzed at concentrations of 0.0750, 4.0000, and 8.0000 ug/L.

Precision Intraday and interday CV was less than 15%.

Accuracy Intraday and interday accuracy was within 20%.

Sensitivity The lower LOQ was 0.025 ug/L.

Linearity The assay was linear over a standard curve of seven concentrations ranging from 0.025 – 10.0000 ug/L ($r^2 \geq 0.9820$).

ANALYSIS: Pharmacokinetic Data Non-compartmental analysis was used to determine the pharmacokinetics of UT-15. Pharmacokinetic evaluation included determining the relationship between steady state plasma concentration vs. UT-15 infusion doses, the presence or absence of a diurnal cycle of plasma UT-15 concentrations over a 24-hour steady state infusion interval, clearance (determined from the ratio of infusion rate and steady state concentration for each UT-15 dose), and elimination $T_{1/2}$.

There were several criteria for the inclusion of subjects in the PK analysis. Subjects that achieved steady state plasma concentrations for at least 24 hours in a dosing period were included in the analysis for dose proportionality and apparent plasma clearance. Subjects that had at least 7 samples on day 7 of that dosing period were included in the analysis of diurnal cycles.

Statistical analysis Descriptive statistics were computed for PK parameters. Mean steady state plasma concentrations vs. UT-15 dose were tested for dose proportionality by linear regression.

RESULTS: Of the fourteen subjects enrolled, there were 8 females and 6 males, ages 23 to 49 (mean age, 36) years old. Their weight ranged from 52.2 – 86.9 kg. Most were Caucasian (10). There were two Blacks, one Asian and one Hispanic. Only six subjects completed the study, however most of the subjects enrolled were included in the PK analysis because sufficient blood samples were obtained.

There were few protocol deviations. Two subjects (#1 and #7) participated in a previous study within 30 days of starting this study. Subject #1 completed an investigational new drug study 29 days prior to participating in this study. Subject #7 received his last dose in an investigational study 45 days prior to starting this study, but did not complete the exit procedures until 30 days later (15 days prior to starting this study). Additionally, due to some technical difficulties, some vital sign measurements and/or PK blood samples were either late or not performed.

Safety The most common adverse events were attributed to UT-15. These consisted of injection site pain/reaction/hemorrhage (reported by 13 subjects), headaches (11 subjects), nausea (7 subjects), and dizziness (7 subjects). Injection site pain ranged from mild to severe and generally has an onset within 1 to 2 days from the start of the infusion or the start of period 2. In most instances, the infusion site pain was mild or moderate and generally persisted until UT-15 was discontinued.

Dropouts Eight subjects withdrew because of injection/infusion site pain; most of these occurred with the highest dose of 15 ng/kg/min.

- Subject ID # 8 withdrew during period 2 after 72 hours
- Subject ID # 5 period 4 after 24 hours
- Subject IDs # 2, 3, 6, 7, and 9 period 4 after 72 hours
- Subject ID # 4 period 4 after 96 hours

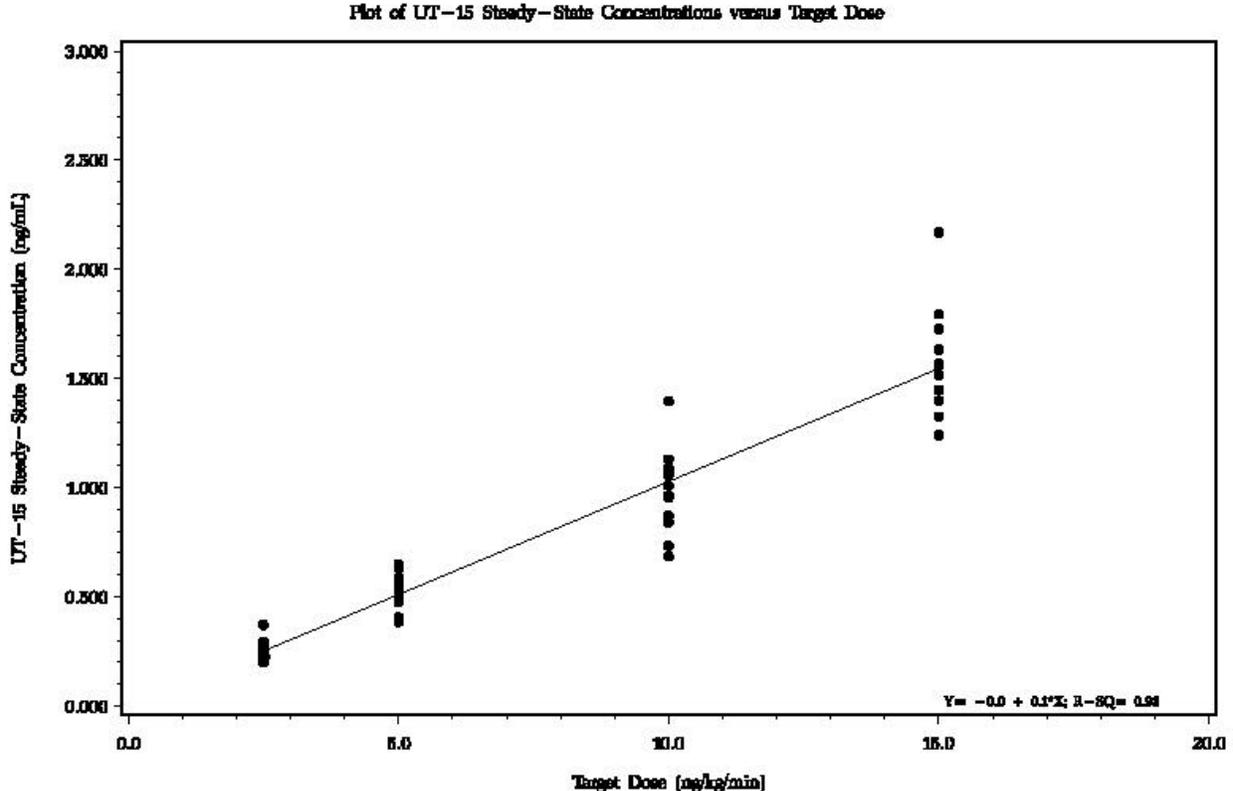
Six of these eight subjects provided steady state UT-15 plasma concentrations for at least 72 hours in all of the dosing periods.

PHARMACOKINETIC RESULTS: The sponsor determined only clearance and T_{1/2}. The following number of subjects were included in the following analysis at each dose:

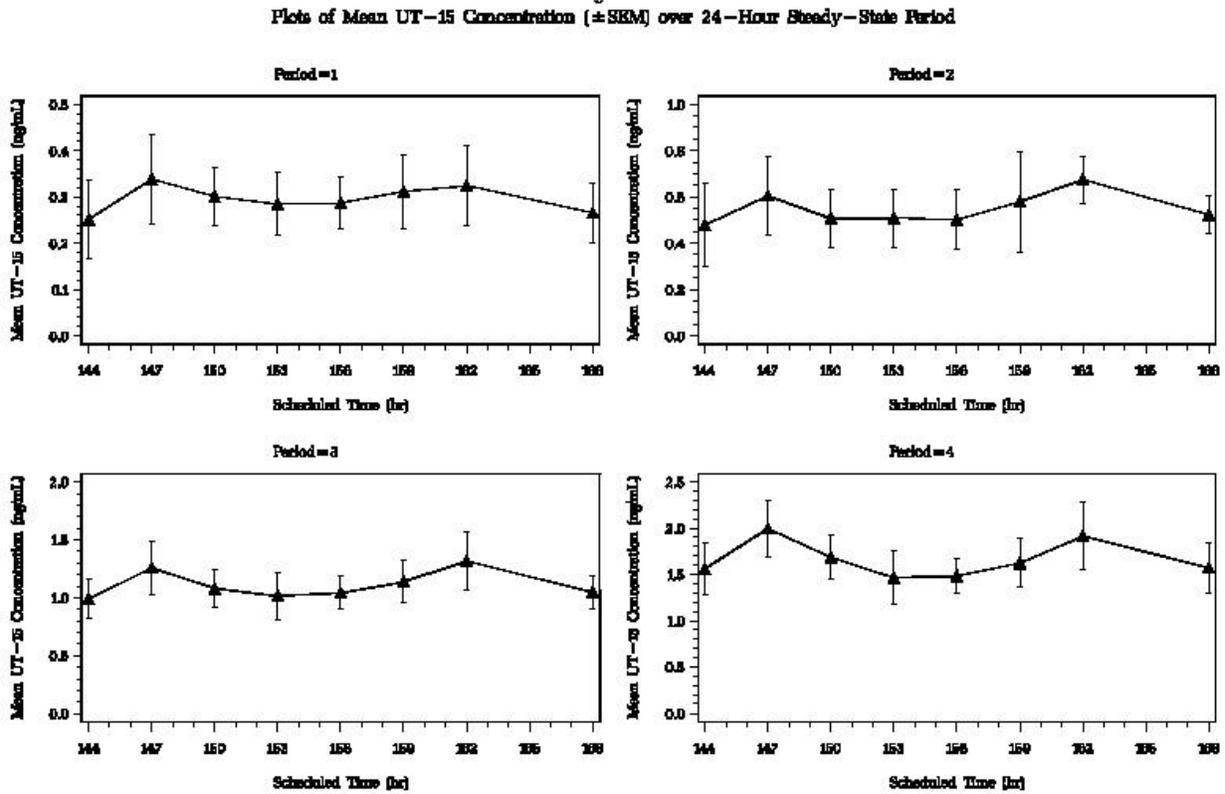
Dose (ng/kg/min)	No. subjects	
	Dose proportionality and clearance	Diurnal cycles
2.5	14	14
5	14	13
10	13	13
15	13	6

Fourteen subjects contributed to the determination of plasma T_{1/2}; the data for one subject came from dosing period 2.

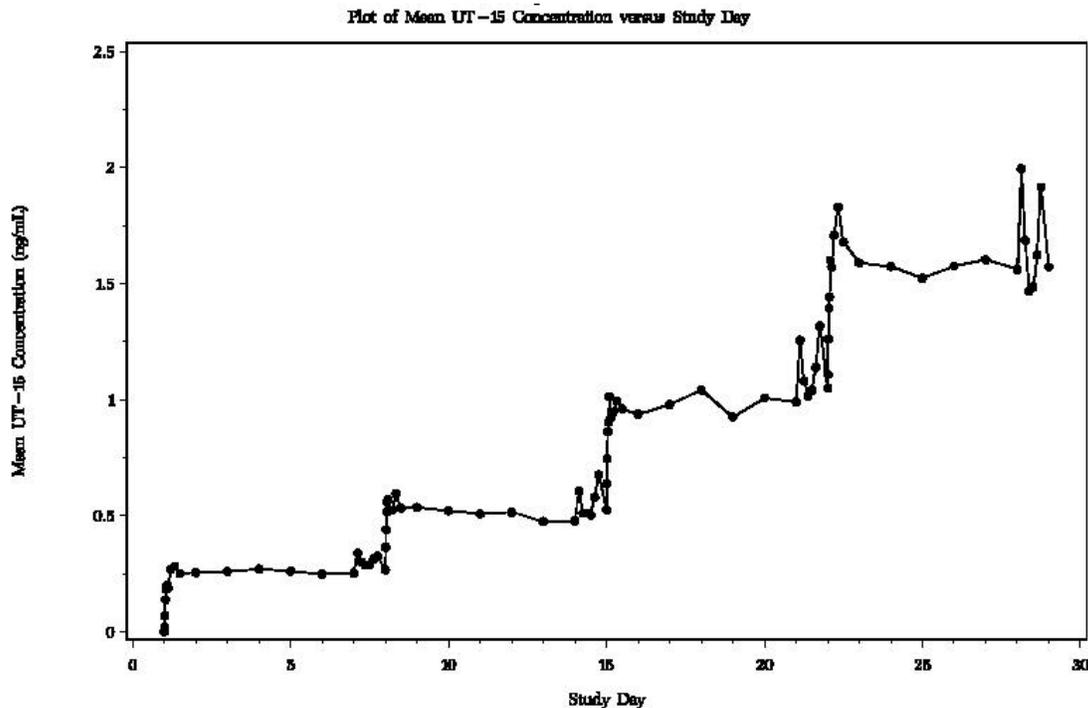
Chronic (28 day) SC UT-15 exhibits linearity ($r^2 = 0.92$) over the dose range of 2.5 – 15 ng/kg/min (concentration range, 0.03 – 2.57 ug/L). See linear regression below.



Steady state was achieved during each dosing period (see figure below). Mean C_{ss} values ranged from 0.259 ug/L to 1.564 ug/L.

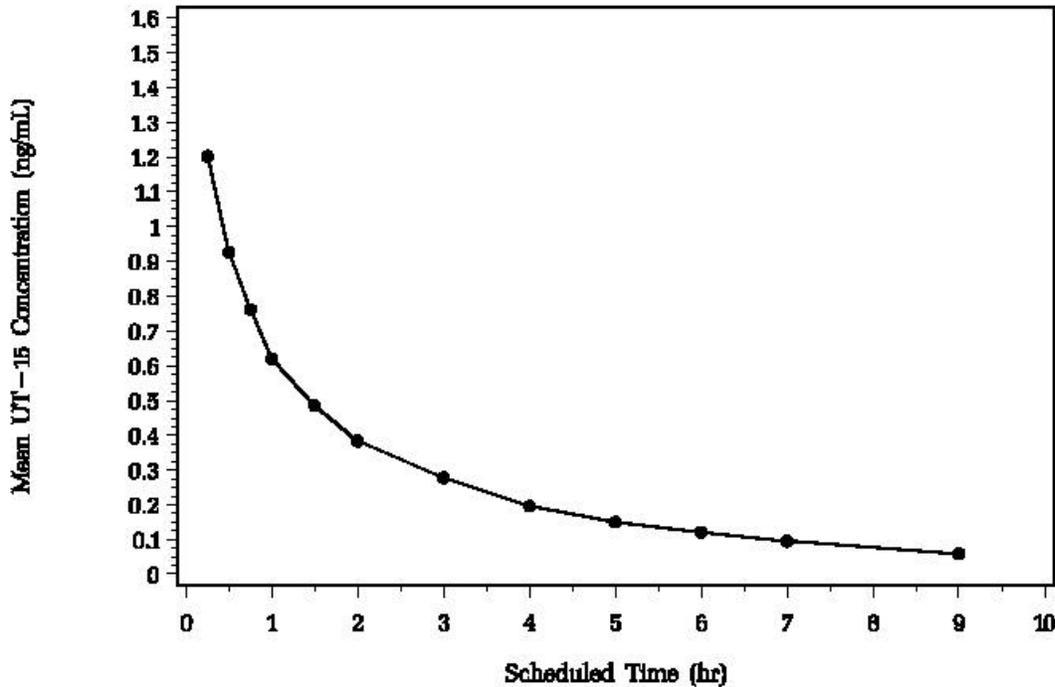


Serial plasma samples collected on day 7 of each dosing period showed a diurnal cycle of UT-15 concentrations over a 24-hour period. Peak steady state concentrations occurred at 10 a.m. and 1 a.m. while trough concentrations occurred at 4 p.m. and 7 a.m. The peak levels were generally 20 to 30% higher than the trough levels.



Plasma clearance values for all of the four doses ranged from 9.77 mL/kg/min to 10.4 mL/kg/min (~0.6 L/kg/hr), supporting the linear kinetics over the dose range used. The terminal $T_{1/2}$ determined after termination of the 15 ng/kg/min infusion was 2.93 hours. Inter-subject variability of C_{ss} , CL and $T_{1/2}$ 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 $T_{1/2}$ 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 (concentration range, 0.03 – 2.57 ug/L). 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.

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 dose was determined in a patient, the infusion rate of the study drug was to be decreased to a maximum tolerated dose.

A MiniMed (Model 506) positive pressure micro-infusion 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	0.0	6.26	6.35	6.5
Metacresol	0.0	3.0	3.0	3.0
Sodium Citrate, Dihydrate	5.0	5.26	5.65	6.3
Citric Acid	0.5	1.44	0.9	0.0
Sodium Hydroxide	0.2	0.99	0.85	0.62
Container	2 mL vial	3 mL syringe	3 mL syringe	3 mL syringe or 20 mL vial
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 at 2-8°C.

ASSAY: Alta Analytical Laboratory analyzed the plasma samples with a validated LC/MS/MS assay. Quality controls were analyzed at concentrations of 0.30, 5.00, and 37.50 ug/L.

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 0.1 ug/L (100 pg/mL) for a 1 mL aliquot of plasma.

Linearity The assay was linear over a standard curve range of 0.10 – 50.00 ug/L ($r^2 \geq 0.9981$).

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 [SvO₂]).

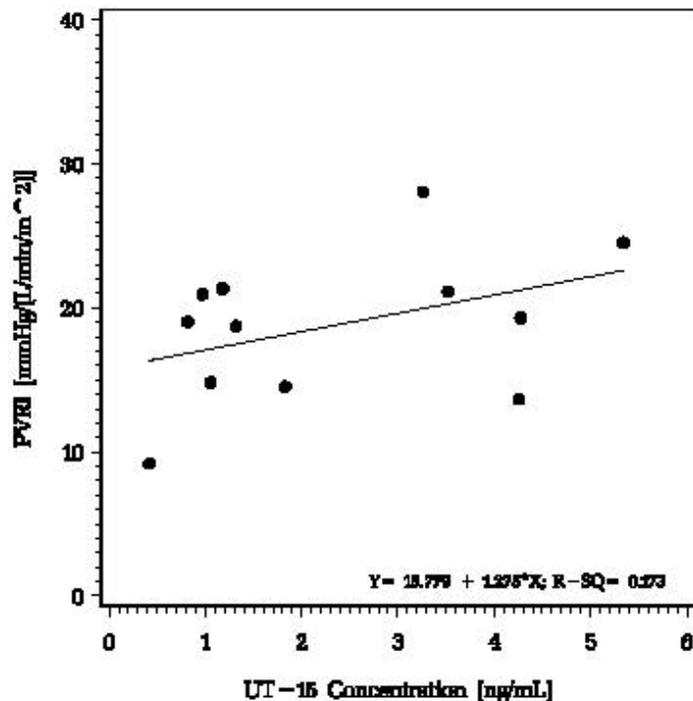
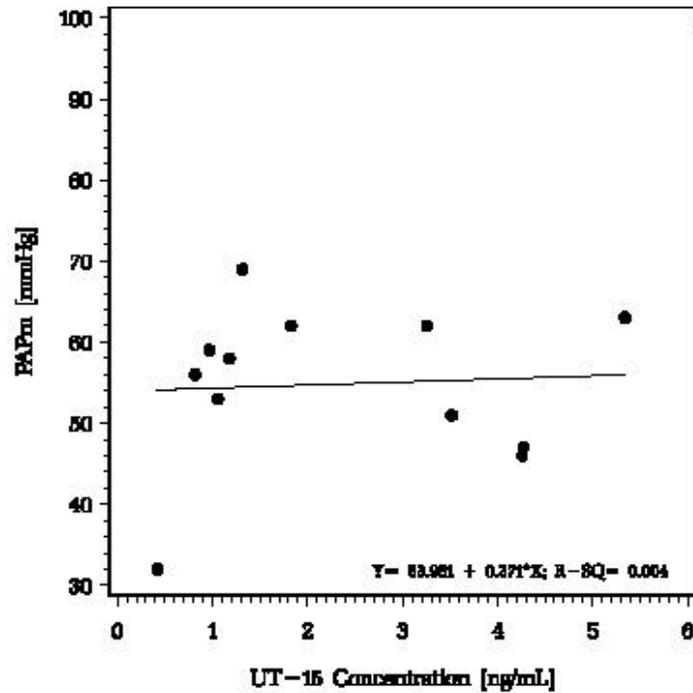
RESULTS: Seventeen patients were randomized to receive UT-15 and nine were randomized to receive placebo. Of the patients that received UT-15, only 15 completed the study in its entirety. Two patients discontinued because of adverse effects. All patients that received UT-15 were Caucasian and 14 were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

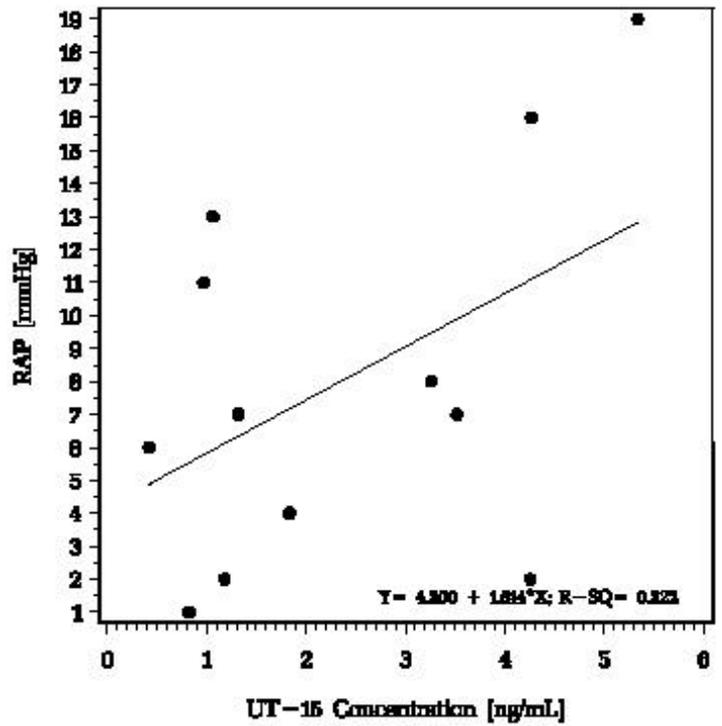
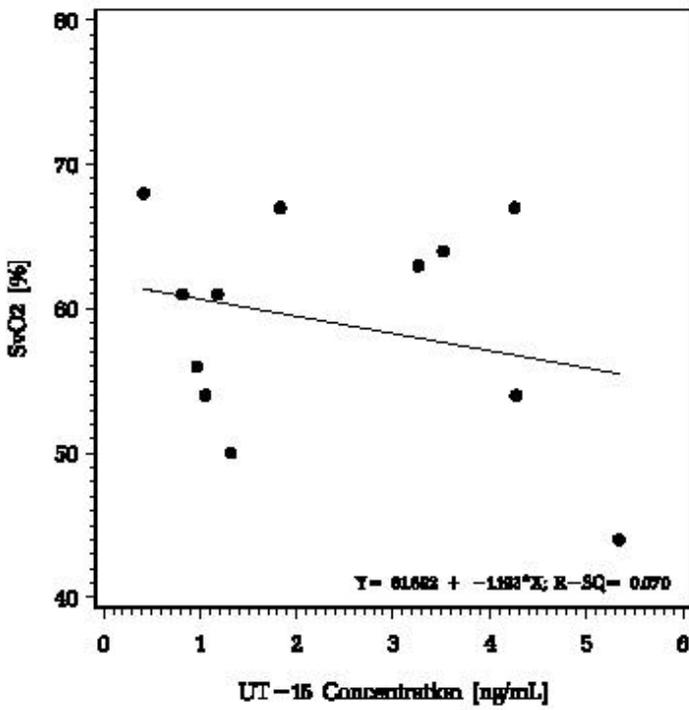
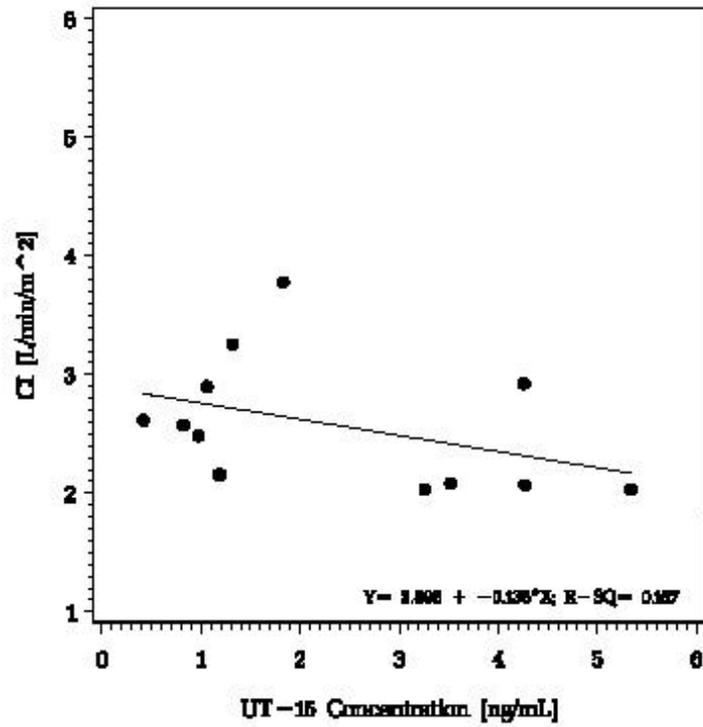
UT-15 dosing was not standardized. The initial UT-15 infusion rate was 1.25 ng/kg/min in one patient, 2.5 ng/kg/min in 15 patients and 5 ng/kg/min in one patient.

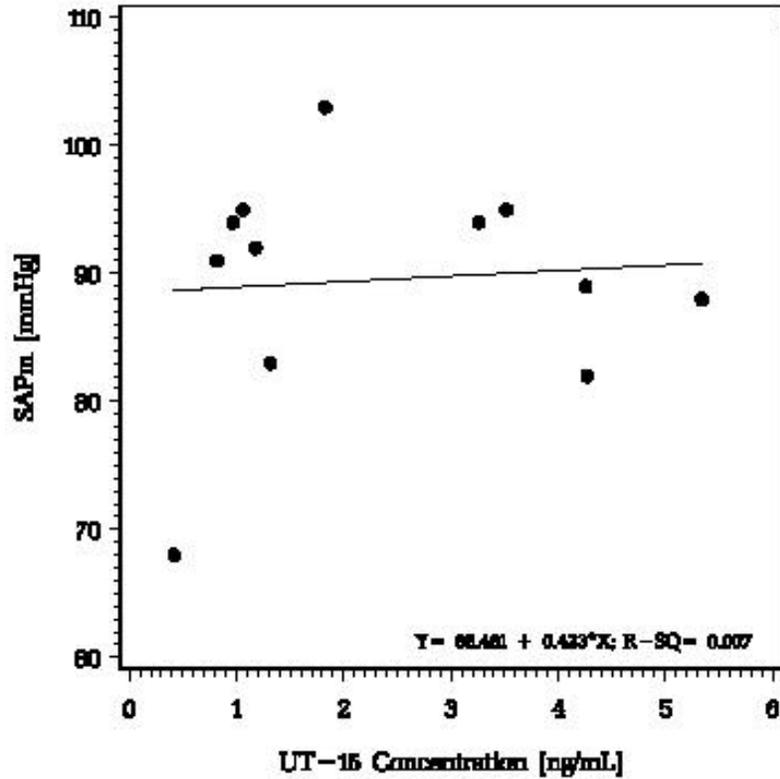
PHARMACOKINETIC RESULTS: The PK results are based on data from 17 patients. The blood sample collections were reduced to four samples to be collected on study days 2 through 5, instead of 8 samples on study days 2 through 9. There were also some unscheduled plasma samples collected from selected patients. 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 0.004 to 0.4. 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.







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 parameters trended in the wrong direction with higher concentrations of UT-15 (e.g. CI, PVRI, RAP and SvO₂). 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 MiniMed (Model 506) positive pressure micro-infusion 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 to 46°F, 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 LC/MS/MS assay. Quantification was based on peak area ratios. The elution order was internal standard (LRX-Homologue) followed by UT-15. The concentration of quality control samples was 0.075, 4.000 and 8.000 ug/L.

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 0.025 ug/L (25 pg/mL).

Linearity The assay was linear within the tested range of 0.025 – 10.000 ug/L. 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-Wallis 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)

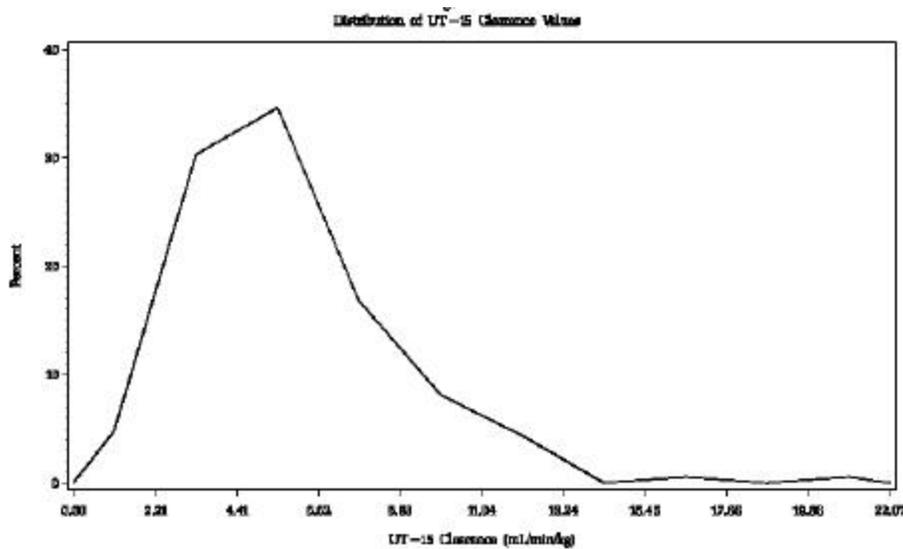
Serum creatinine was another covariate analyzed in this study. Two out of 186 patients had scr > 2.5 mg/dL. The remainder were divided into two groups: 176 with scr ≤ 1.2 mg/dL (classified as normal) 8 with 1.2 < scr ≤ 1.5 mg/dL (classified as mild renal dysfunction).

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.

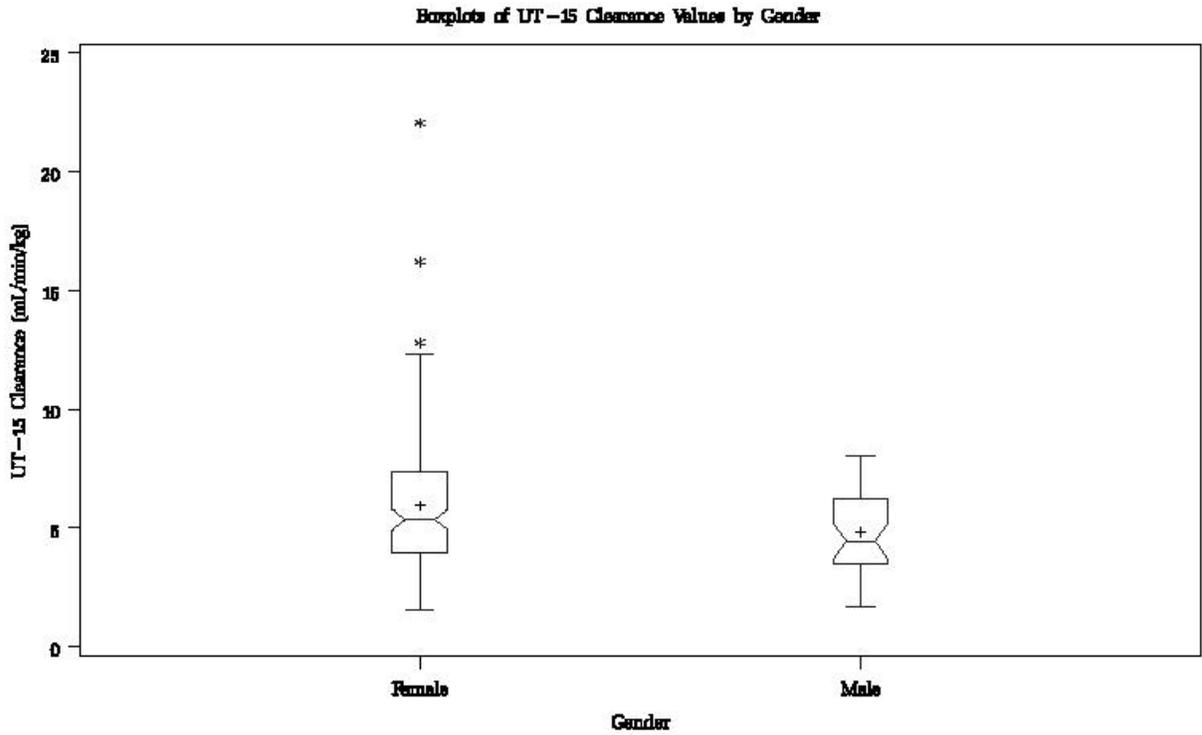
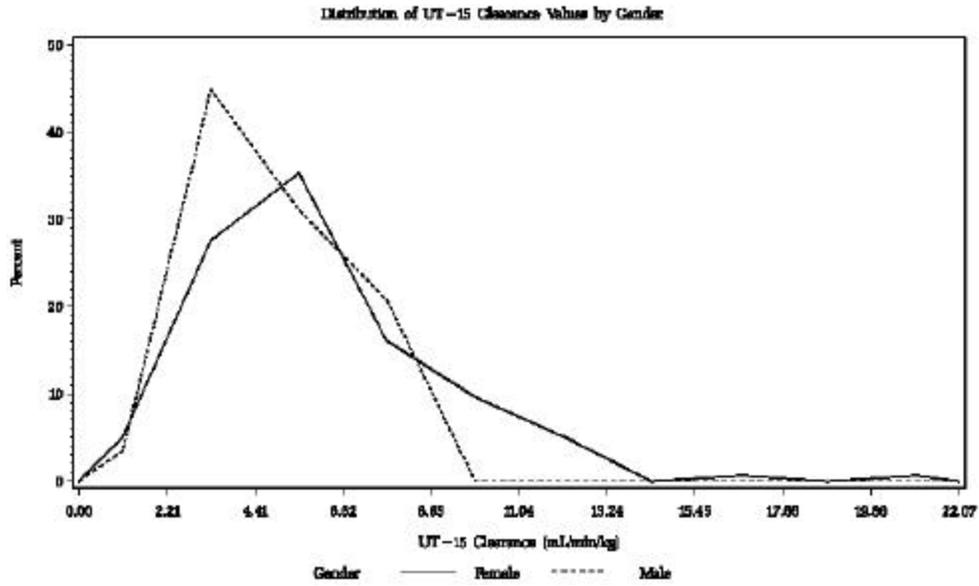
PHARMACOKINETIC RESULTS: Mean ± SD dose was 9.2 ± 5.254 ng/kg/min. Plasma concentration was 1.892 ± 1.294 ug/L (mean ± SD). The range of plasma concentrations was from 0.04 – 7.88 ug/L.

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.

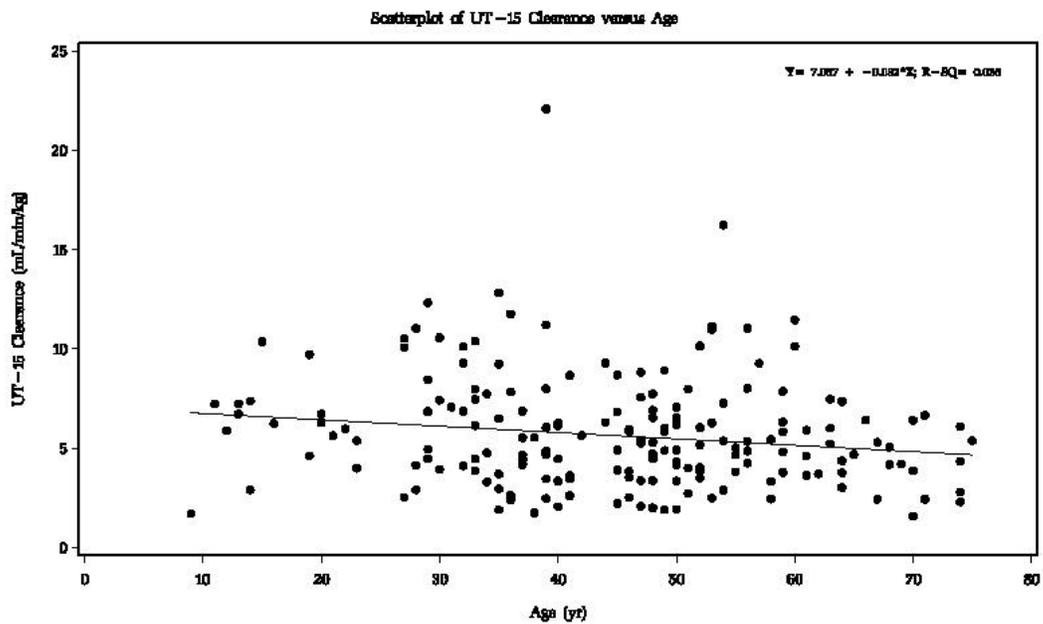
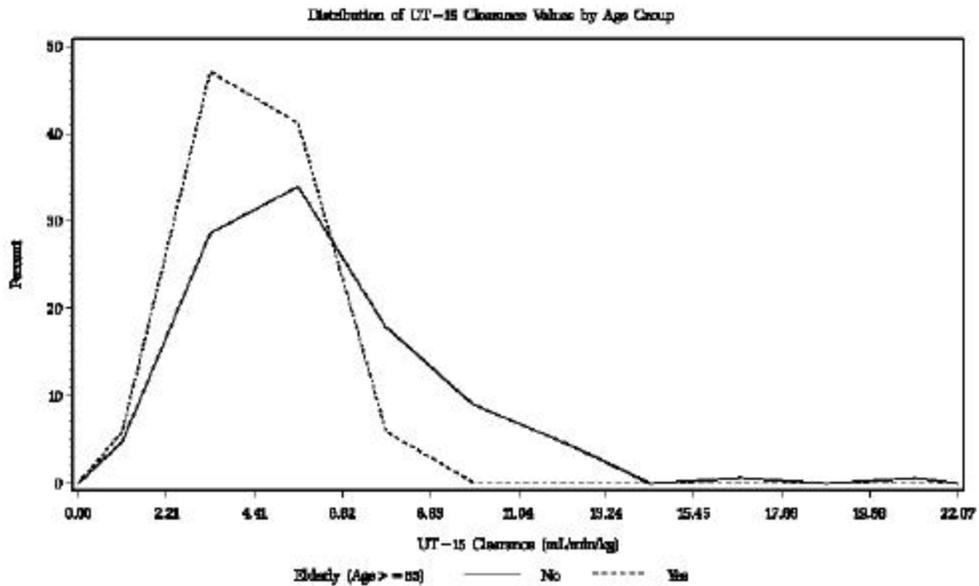


Based on descriptive statistics the following observations were made about median steady state UT-15 clearance:

- Clearance is 17% lower in males versus females,

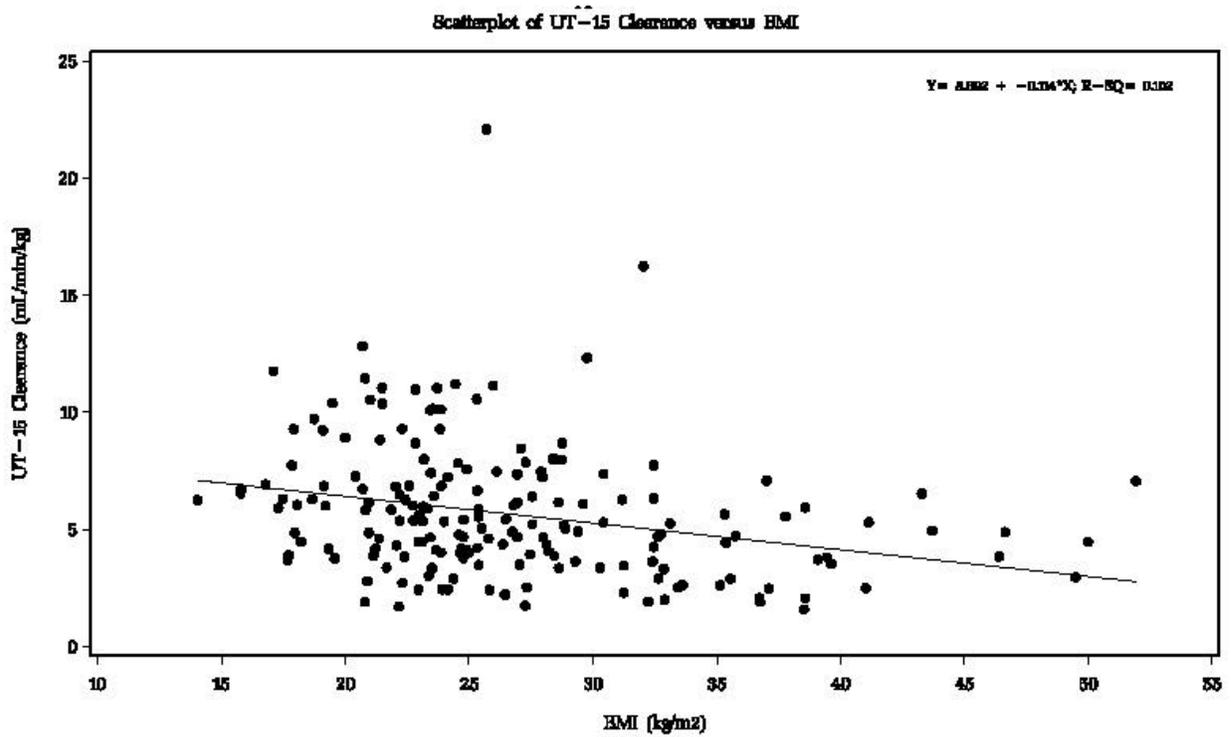
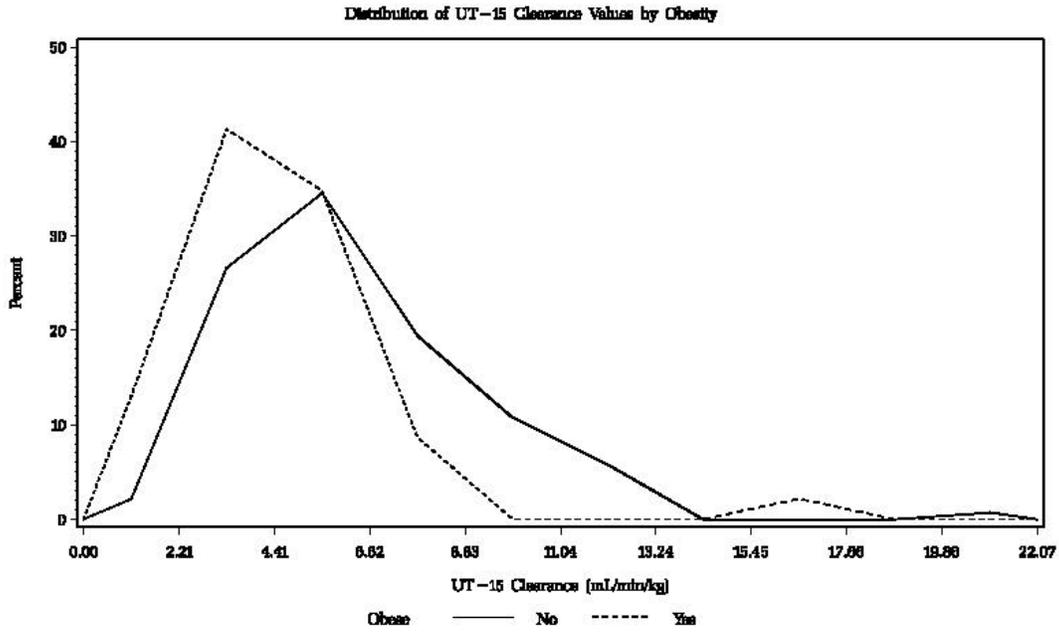


- 20% lower in patients ≥ 65 years old (elderly) versus those < 65 years old,



- [1] Clearance > 70 not shown.
- [2] Clearance > 25 not included in regression.

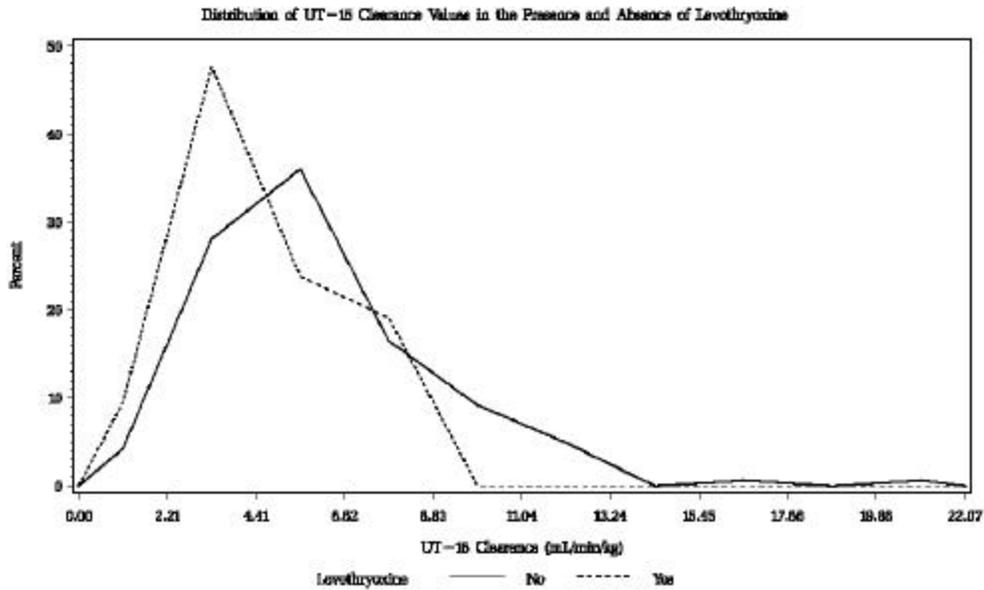
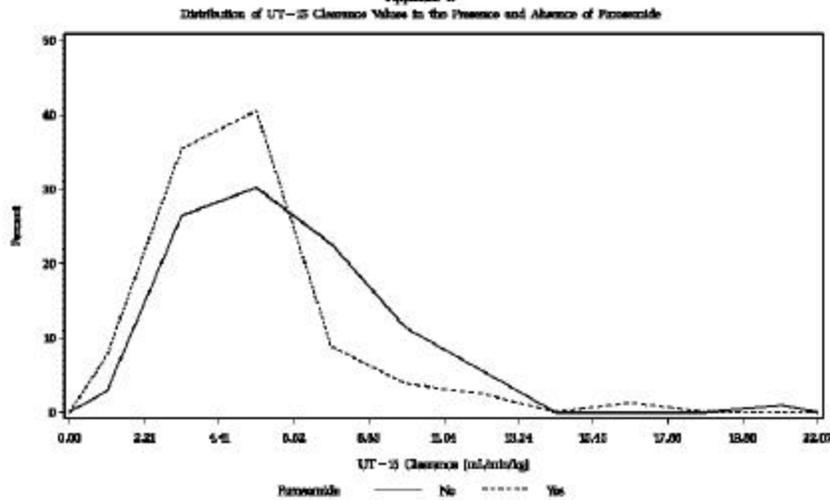
- 29% lower in obese than non-obese patients.

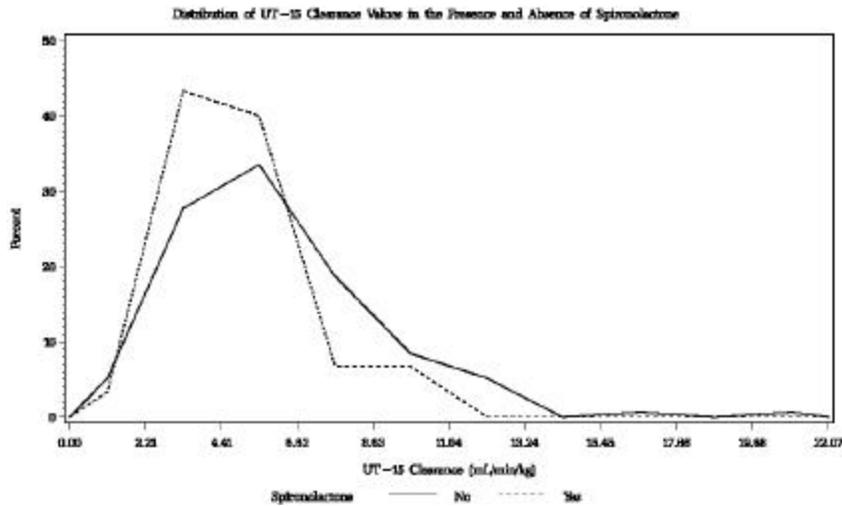


Presence or absence of most medications did not affect the distribution of clearance. Based on univariate analysis, median UT-15 clearance was affected by these three drugs:

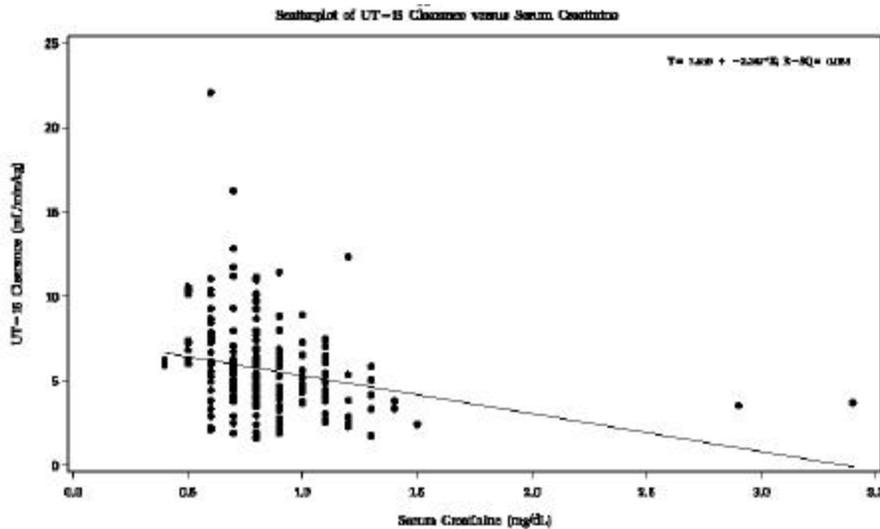
- 22% lower in patients taking furosemide (43%) versus those not taking furosemide,
- 19% lower in patients taking levothyroxine (11%) versus those not taking levothyroxine, and
- 19% lower in patients taking spironolactone (16%) versus those not taking spironolactone.

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 $> 30.0 \text{ kg/m}^2$, 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 should 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.

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: Cindy Krenger, CCRC, Manager

CLINICAL LABORATORY: Covance Clinical Research Unit
309 W. Washington Ave, #4E
Madison, WI 53703

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. Cardiopulmonary 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.

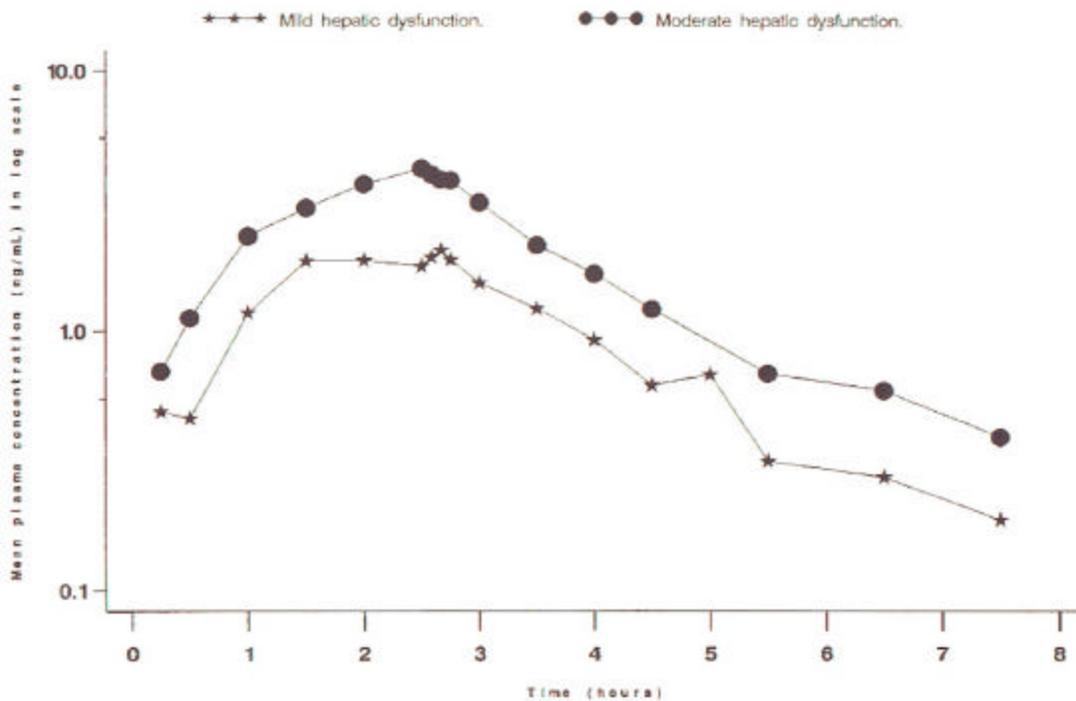
FORMULATION: UT-15 0.5 mg/mL, lot number Y7H0978A was used.

UT-15 ASSAY: The plasma samples were analyzed with a validated LC/MS/MS assay. The lower LOQ was 0.1 ug/L, and the upper LOQ was 50 ug/L. 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. C_{max} and AUC_{0-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.



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)
C _{max} (ug/L)	0.98 ^b	2.22 ± 0.43	4.32 ± 1.48
T _{max} (hr) ^c	(2.00, 2.77)	2.58 (1.42, 2.67)	2.50 (2.00, 2.75)
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
V _z /F (mL/kg) ^d	1113.6 ± 453.0	451.6 ± 141.80	225.00 ± 164.21
T _{1/2} (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 C_{max} 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 C_{max} and AUC_{0-inf} since mean values are reported after dose normalization.

^c Median (min, max) are shown for T_{max} of patients with hepatic dysfunction however, only (min, max) is shown for T_{max} of healthy subjects.

^d Comparison of CL/F, V_z/F and T_{1/2} 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. C_{max} 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_{1/2} among the different groups. Thus, it appears that lower CL/F values in patient with mild/moderate hepatic dysfunction were principally caused by lower V_z/F values. The reasons for lower V_z/F values are not evident. Differences in protein binding for UT-15, either in plasma or tissue, are likely the cause for the lower V_z/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 C_{max} and 3x higher AUC_{0-inf} than healthy subjects. Patients with moderate hepatic insufficiency had 4x higher C_{max} 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 V_z/F values were calculated from the CL/F and terminal slope, thus V_z/F will change with CL/F and terminal slope. The sponsor's speculation about V_z/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.

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 MiniMed (Model 506) positive-pressure microinfusion 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: Alta Analytical Laboratory analyzed the plasma samples with a validated LC/MS/MS assay. A dimethylene homologue of UT-15 (LRXA-97J02) was used as an internal standard. Quality controls were analyzed at concentrations of 0.0750, 4.0000, and 8.0000 ug/L.

Precision Intraday CV was less than 10% and interday CV was less than 17%.

Accuracy Intraday and interday accuracy was within 15%.

Sensitivity The lower LOQ was 0.025 ug/L.

Linearity The assay was linear over a standard curve range of 0.025 – 10.0000 ug/L ($r^2 \geq 0.9875$).

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 C_{max} 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.

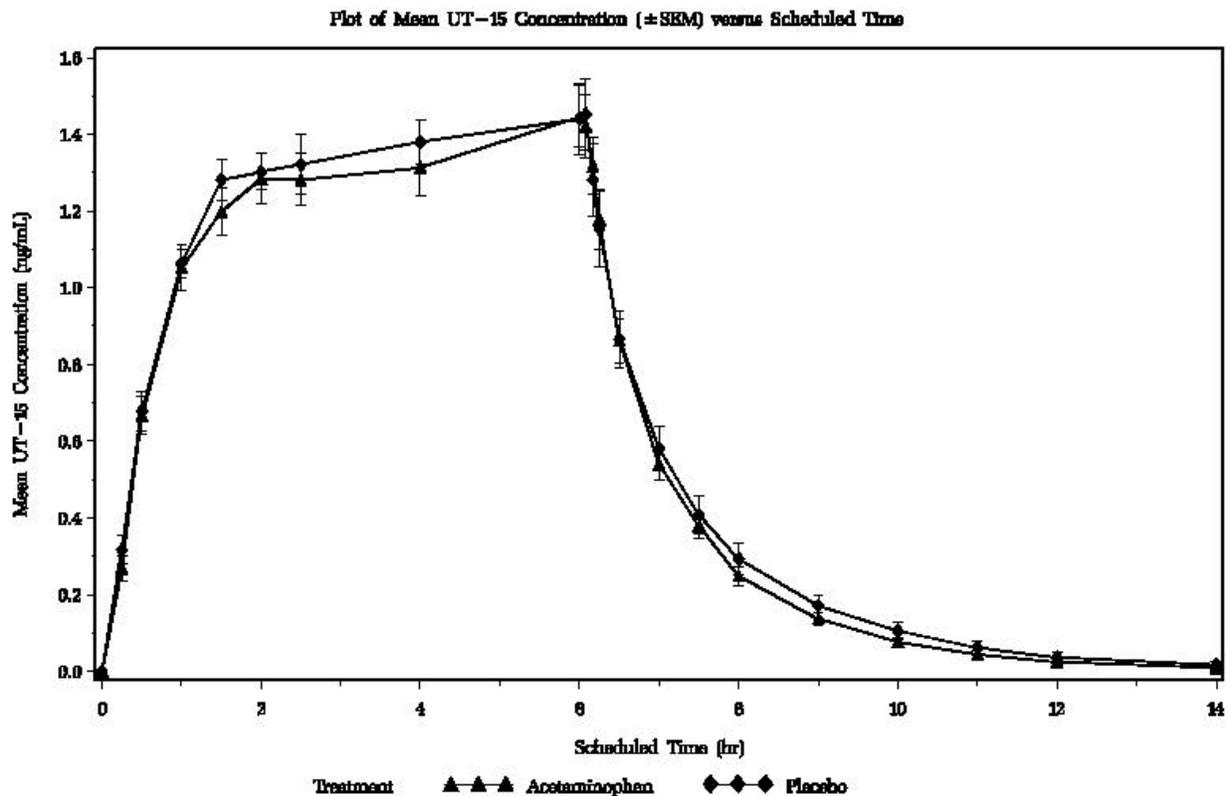
RESULTS: Twenty-six out of 29 subjects completed the entire study. The results reported include all 29 subjects, except for the PK results which only includes the 26 subjects that completed the study. The mean ± SD age was 29 ± 9 years and the mean ± SD body weight was 70.5 ± 9.8 kg. The study population 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 effects 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 C_{max} 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 C_{max} 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
C _{max} (ug/L)	1.56	0.40	25.5	0.88	2.66
T _{max} (hr)	4.03	1.92	47.6	1.00	6.17
T _{1/2} (hr)	1.38	0.59	42.4	0.74	2.99
AUC _{inf} (ng*hr/mL)	8.93	2.35	26.3	4.15	16.29
CL/F (L/kg/hr)	0.65	0.19	28.7	0.33	1.30

Subcutaneous UT-15 PK without acetaminophen

Parameter	Mean	SD	CV %	Minimum	Maximum
C _{max} (ug/L)	1.57	0.42	26.7	1.10	3.20
T _{max} (hr)	4.53	1.80	39.7	1.50	6.17
T _{1/2} (hr)	1.53	0.65	42.7	0.78	3.39
AUC _{inf} (ng*hr/mL)	9.37	2.41	25.7	5.01	17.61
CL/F (L/kg/hr)	0.61	0.15	24.7	0.31	1.11

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.

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

STUDYP01:12 **SUBMITTED:** January 25, 2001 under amendment N-BB

PRINCIPAL INVESTIGATOR: Thomas Hunt, MD, PhD.

CLINICAL LABORATORY: PPD Development
706 Ben White Blvd, West
Austin, TX 78704-7016

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: Alta Analytical Laboratory analyzed the plasma samples with a validated LC/MS/MS assay with a quantitation range of 0.025 – 10.0000 ug/L. Details of the assay were not submitted.

WARFARIN ASSAY: PPD Development analyzed the samples for R- and S-warfarin and for INR. The assay had a quantitation range of 5.00 – 1000 ug/L. 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} , C_{max} , T_{max} , K_{e1} , $T_{1/2}$, 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-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 $\alpha=0.10$ level of significance. The mean square error of the model was used to evaluate the treatment and period terms at an $\alpha=0.05$ level of significance. The 90% confidence intervals for the treatment differences for AUEC_{0-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-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-t} (hr)				
Mean	218.24	217.99	0.989	(0.955, 1.025)
Median	201.19	202.31		
Range	179.94 – 314.18	172.17 – 278.50		
INR				
Mean	2.07	2.035	0.958	(0.913, 1.005)
Median	1.88	2.060		
Range	1.20 – 4.03	1.19 – 2.94		
Corrected for Baseline				
AUEC _{0-t} (hr)				
Mean	219.58	218.93	0.993	(0.949, 1.039)
Median	203.25	216.90		
Range	187.98 – 332.09	176.40 – 268.29		
INR				
Mean	2.07	2.04	0.961	(0.916, 1.009)
Median	1.85	1.95		
Range	1.25 – 4.26	1.25 – 3.03		

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-inf} (hr*ug/L)				
Mean ± SD	93,573 ± 19,918	94,659 ± 22,893	1.001	(0.964, 1.040)
Range	66,662 – 135,630	59,288 – 138,011		
Cmax (ug/L)				
Mean ± SD	1781 ± 273	1807 ± 256	0.986	(0.918, 1.059)
Range	1,210 – 2,150	1,370 – 2,460		
PK parameters and treatment comparisons for S-warfarin				
AUC _{0-inf} (hr*ug/L)				
Mean ± SD	65,482 ± 21,989	66,806 ± 20,240	0.981	(0.927, 1.038)
Range	41,969 – 132,643	44,846 – 117,829		
Cmax (ug/L)				
Mean ± SD	1,793 ± 305	1,854 ± 232	0.962	(0.888, 1.042)
Range	1,170 – 2,330	1,410 – 2,430		

Warfarin PK did not differ significantly between coadministration with vehicle and with UT-15. Mean R-warfarin T_{max} was 1.5 and 1.9 hours when administered with vehicle and UT-15, respectively. Mean R-warfarin T_{1/2} was ~ 52 hours with vehicle and with UT-15. R-warfarin elimination rate was also similar between vehicle and UT-15 (mean k_{e1} of 0.0137/hr). S-warfarin results were similar to R-warfarin results. Mean S-warfarin T_{max} was 1.1 and 1.7 hours with vehicle and with UT-15, respectively. Mean S-warfarin T_{1/2} 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 (Covance report 7049-100).

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

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, SvO₂, 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:

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

$$V = \theta_V \cdot IBW/70 \quad (2)$$

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 (SvO₂) 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’.

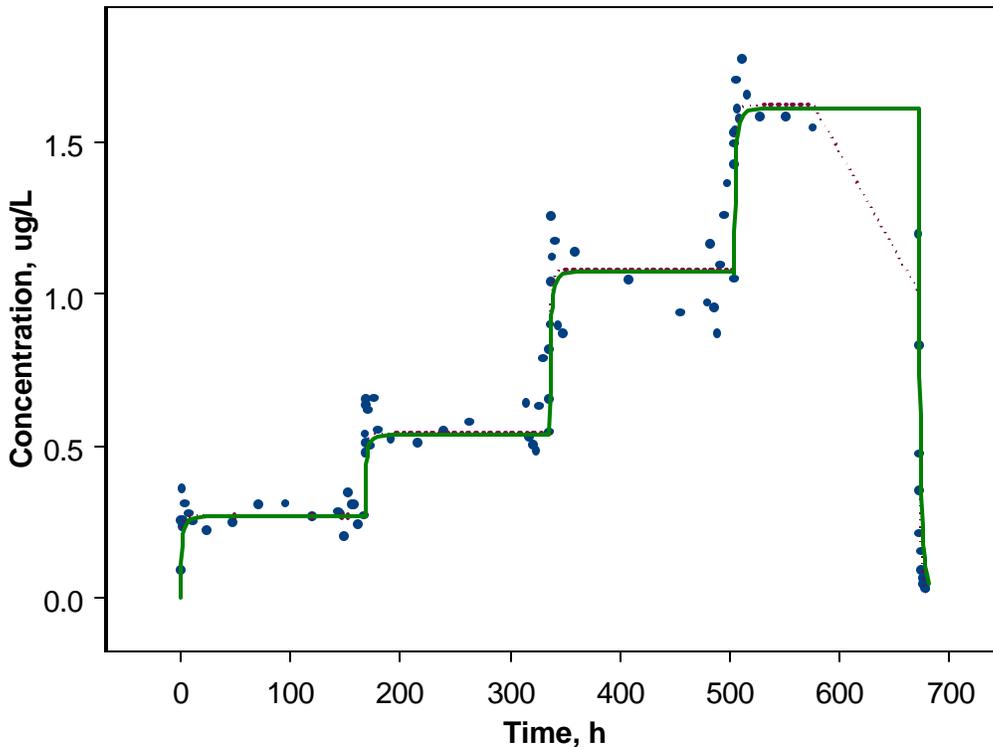
The PK/PD model was developed using NONMEM (ver 5, level 1.1). Where the data are rich (study 09) the first – order conditional estimation was used and first order estimation otherwise (studies 04 and 05). All data manipulations were performed using SAS (ver 6.12) and graphs were produced using Splus 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	22	0.03		
Error	(% CV)	(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.

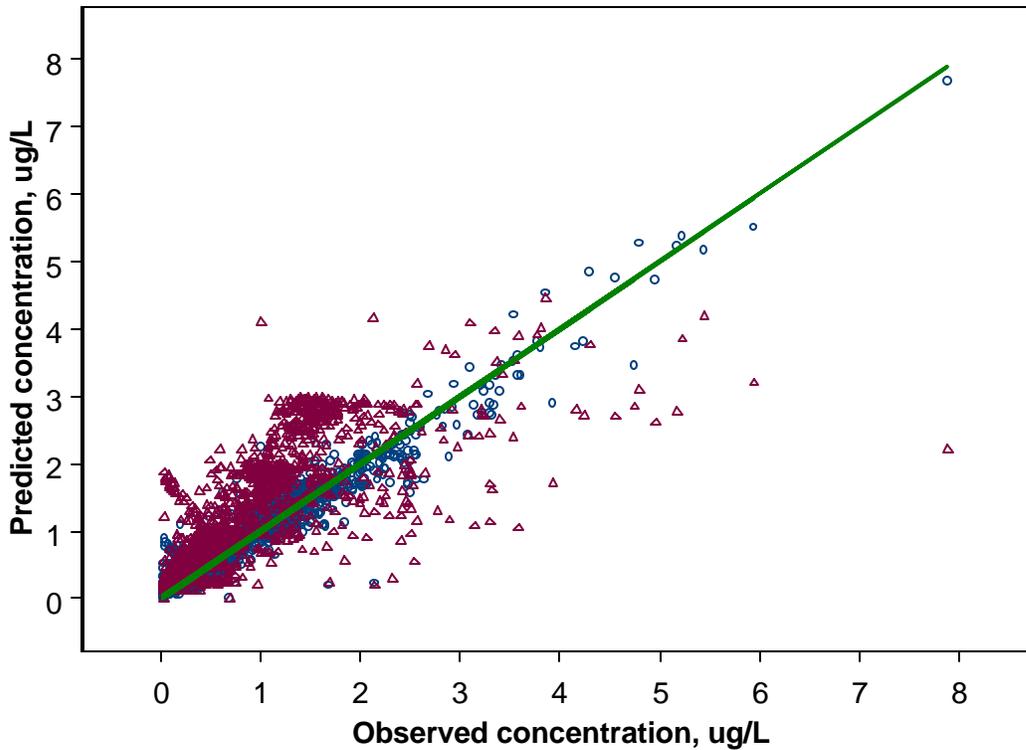


Table 2 below shows the typical estimates of the PK parameters when the data from the all the 3 studies were combined.

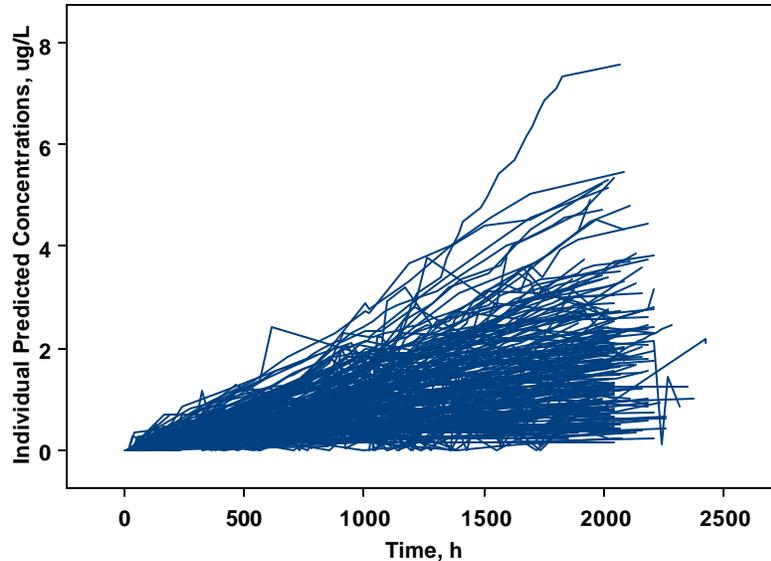
Table2. Population pharmacokinetic parameters of UT-15 based on the data from studies#09, 04 and 05.

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 m²). 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)

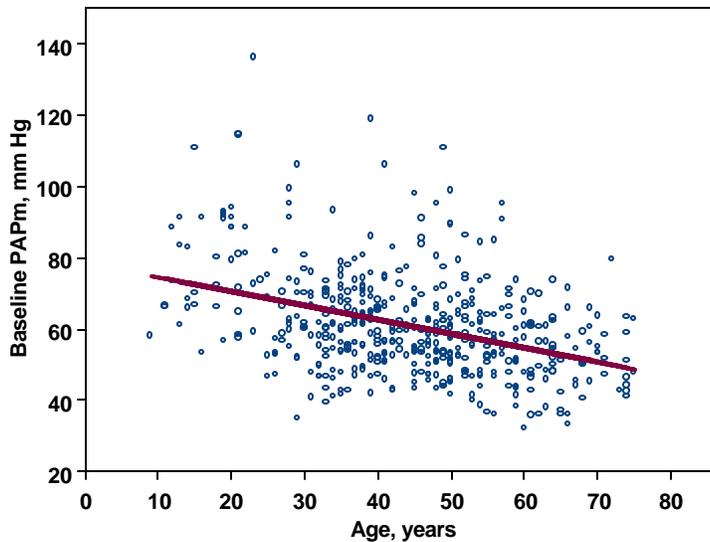
The individual predicted concentrations of UT-15 were employed to drive the change in the PAPm. The concentrations for the patients who received the vehicle were assumed to be zero. A linear model was adequate to describe this relationship. Figure 3 shows the age – baseline PAPm relationship. Table 3 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:

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

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

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

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, $\text{DIST}(0)$. 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.

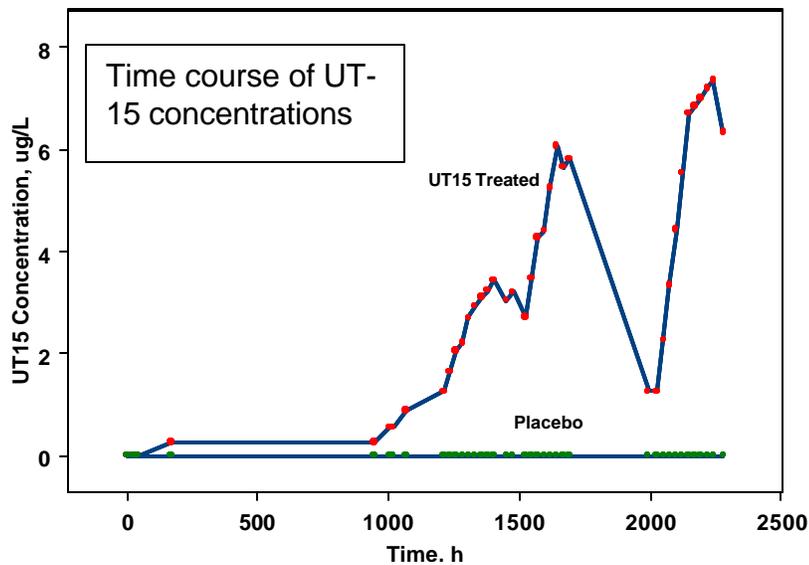


Figure 4b. The typical UT-15 concentration versus absolute change in PAPm.

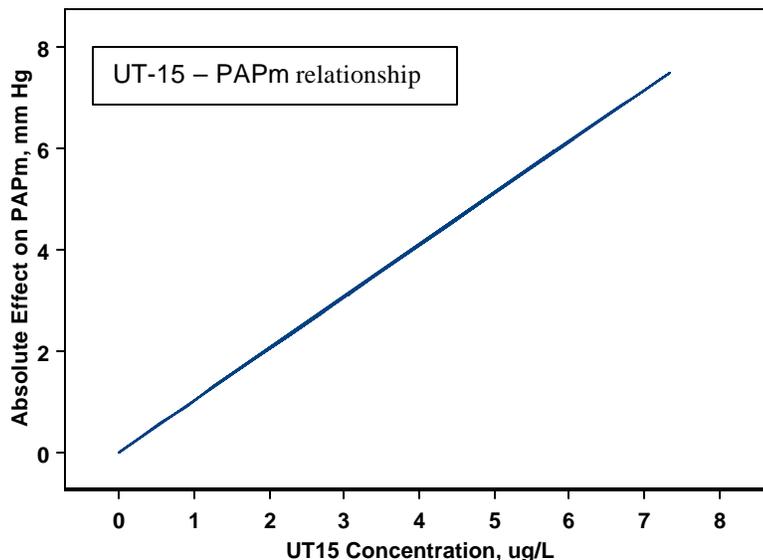


Figure 4c. The typical 'net placebo effect' on distance walked in 6 min. The placebo effect reaches a peak in about 1 week and decreases over next several weeks.

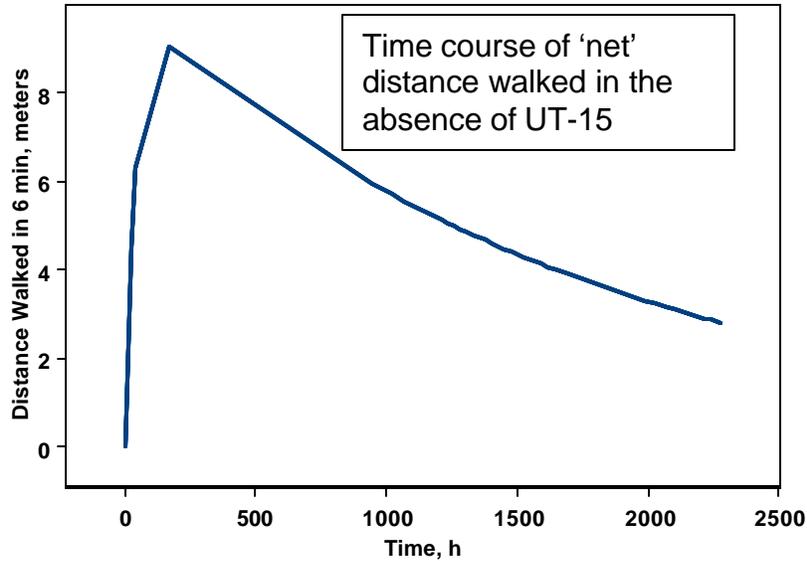


Figure 4d. The typical time course of 'gross' placebo effect for the NYHA II, III and IV patients. Essentially the curve in figure 4c is multiplied by the typical baseline distances walked by the patients.

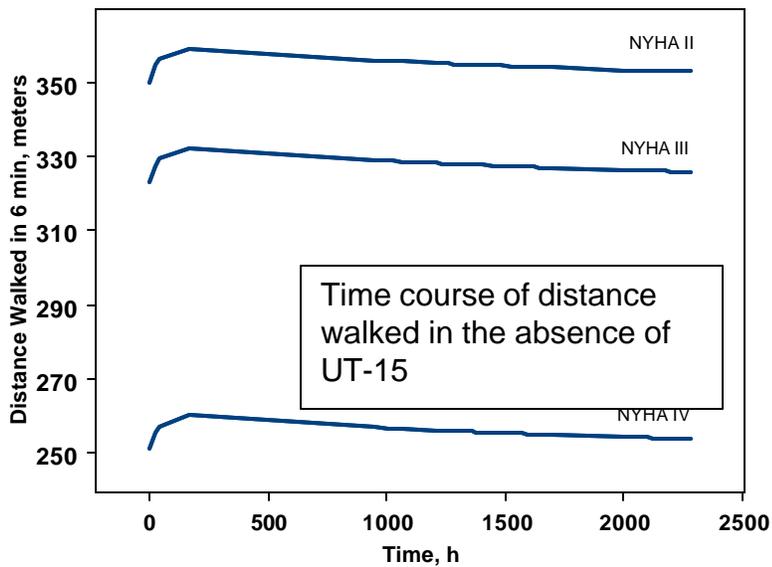


Figure 4e. The typical change in PAPm versus the distance walked in 6 min that is purely attributable to UT-15 (placebo corrected).

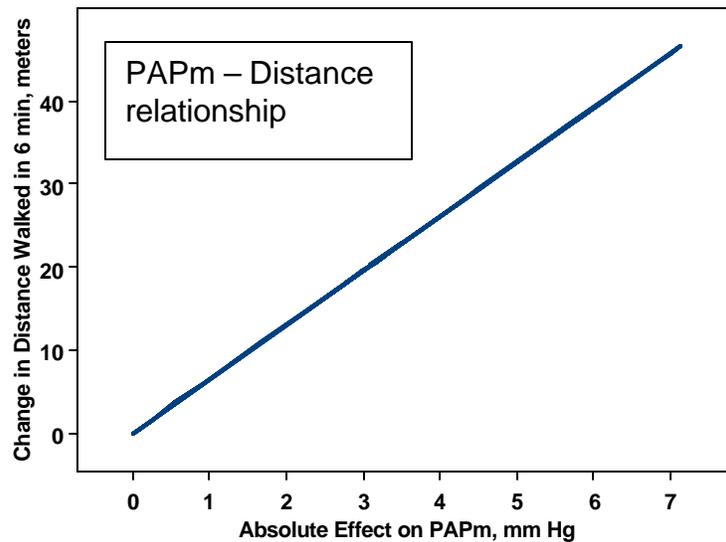


Table 4. PD parameter estimates of UT – 15, for its effect on walk.

Parameter	E0age meters/y r	γ_{walk} 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	0.00056	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	33							
Error	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:

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

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,

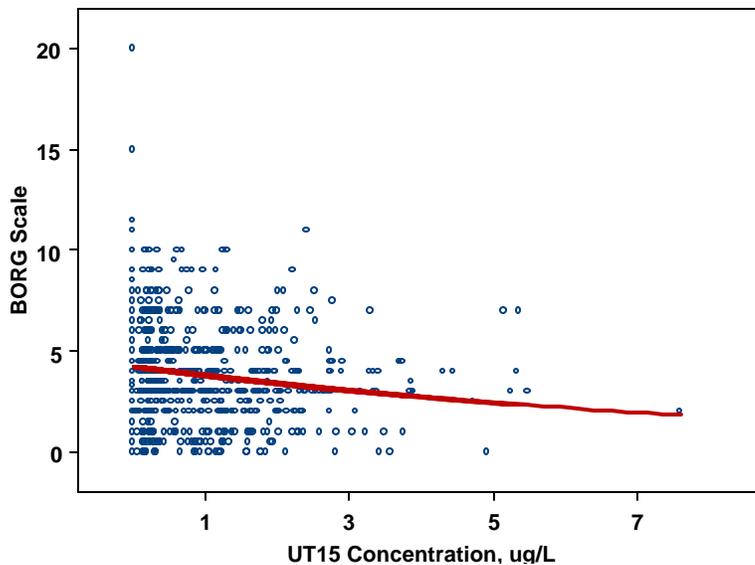
which is the lowest value possible. A linear model could produce negative values for BORG score. Small values of the rate constant in the exponential model can essentially behave like a linear model, with the added advantage of protecting the predictions from being less than zero. The PD parameter estimates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

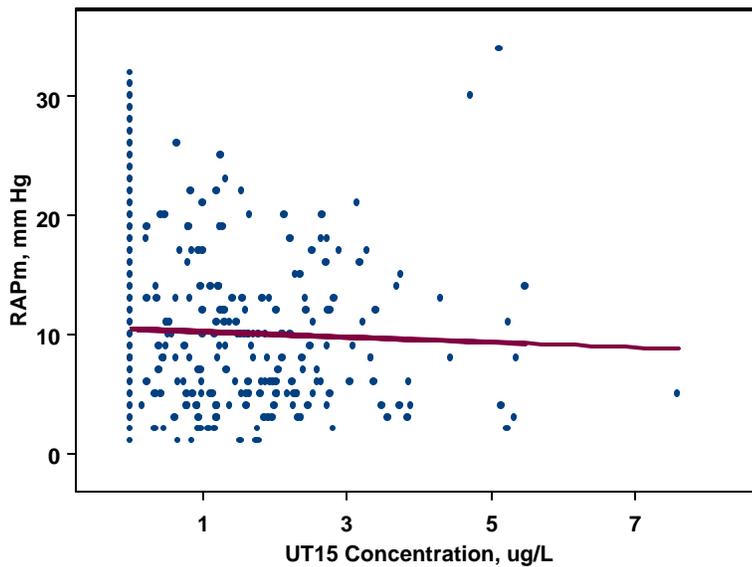
The concentration – RAPm relationship was described using a linear model, as shown in Figure 6. The estimated parameters are shown in Table 6. **The slope estimated was not significantly different from zero ($p > 0.05$).**

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.

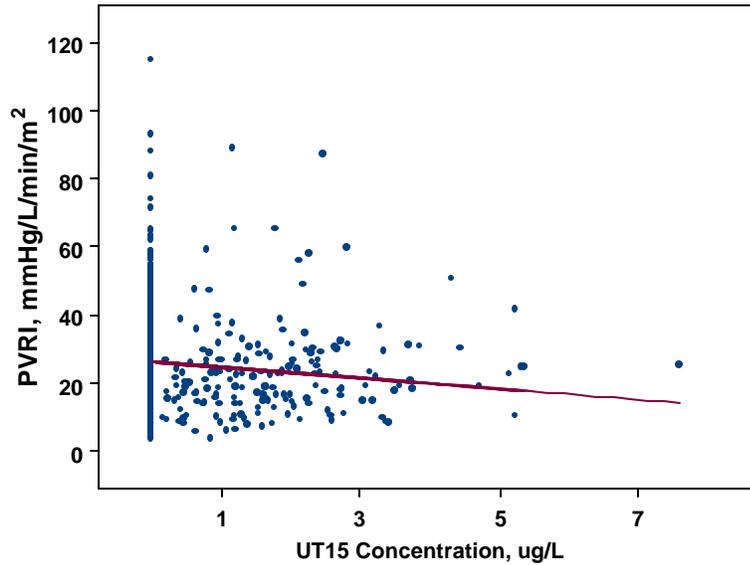


Table 7. Estimated PD parameters of UT-15 for its effect on PVRI.

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

SV₀₂

The concentration – SV₀₂ 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 – SvO₂ relationship as described by a linear PD model.

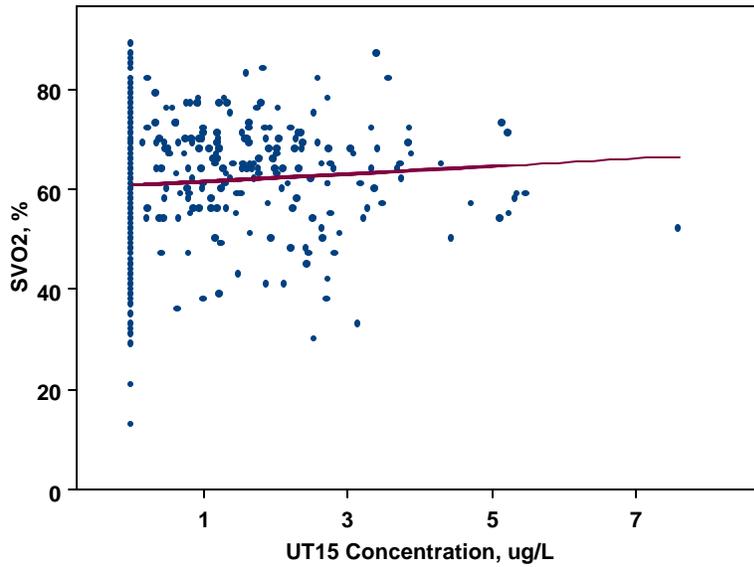


Table 8. Estimated PD parameters of UT-15 for its effect on SvO₂.

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.

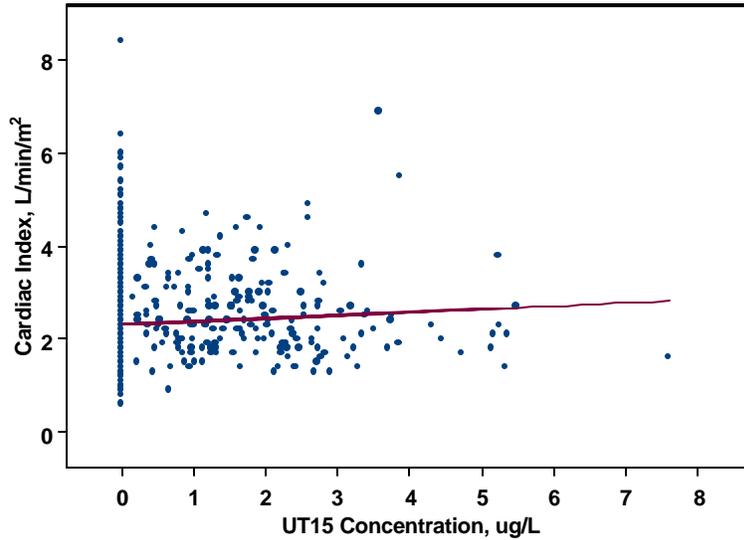


Table 9. Estimated PD parameters of UT-15 for its effect on cardiac index.

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)