CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-272

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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) -				
Healthy Volunteers-				
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:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:	x	1	1	
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:	X	2	2	
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	11	11	

Filability and QBR comments

	"X" if yes	***Comments***
Application filable ?	x	Reasons if the application is not 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.

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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, SvO_2 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 EC_{50} 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 Cmax, respectively, and 3x and 5x higher $AUC_{0\text{-inf}}$

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 ½ of UT-15 is between 2-4 hours, however in the radiolabeled study, the radioactive T ½ was 65 hours. A plausible reason for this long T ½ 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

Jogarao 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 Cmax, respectively, and 3x and 5x higher $AUC_{0\text{-}inf}$ 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 EC_{50} 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 [redacted] 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.

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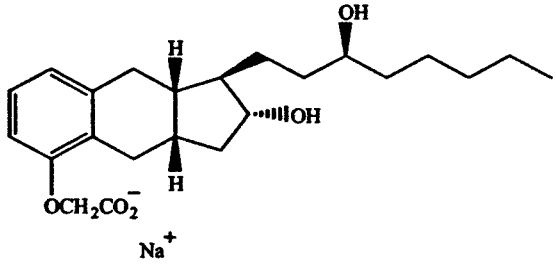
QUESTION BASED REVIEW

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: $C_{23}H_{33}NaO_5$
molecular weight: 412.49

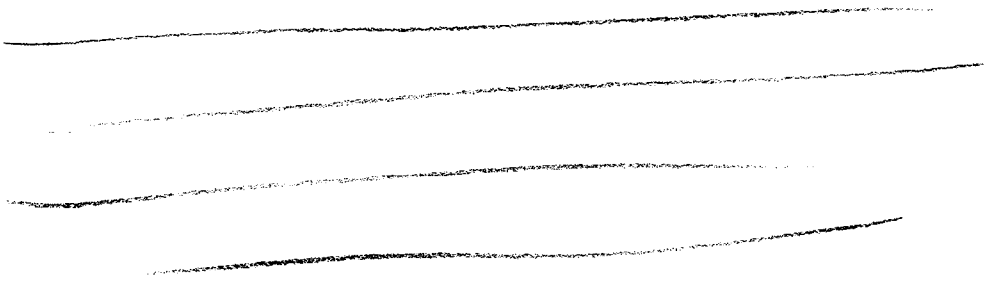
FORMULATION AND MANUFACTURING

UT-15 for injection contains the active ingredient treprostinol sodium. It is a white to cream colored powder. It will be packaged in [redacted], 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)	[redacted]			
Metacresol, USP	3.0	3.0	3.0	3.0
Sodium hydroxide, NF/BP	[redacted]			
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 [redacted] NDA demonstration batches and Phase 3 clinical batches were manufactured by [redacted] UT-15 is manufactured by [redacted].



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 ( ) 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)

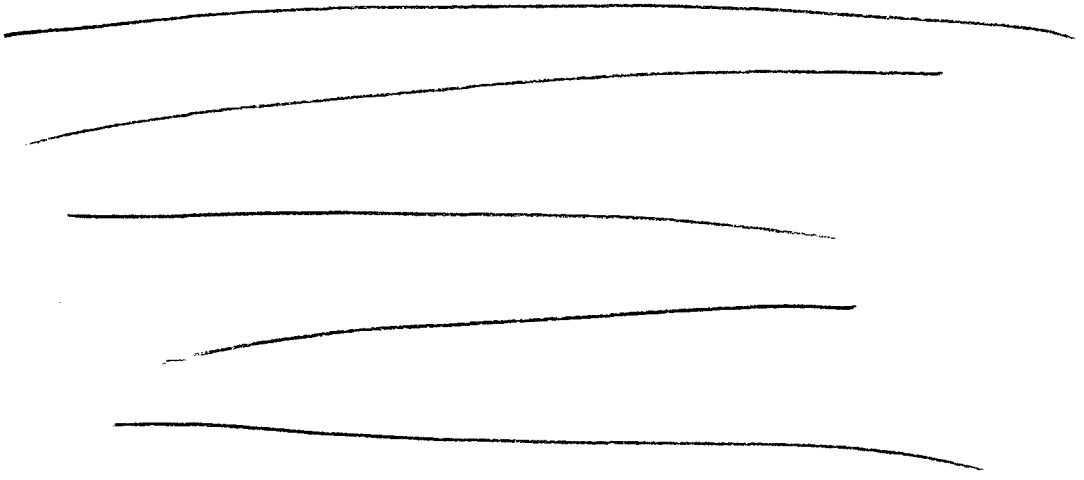
mean right arterial pressure (RAPm)
pulmonary vascular resistance index (PVRI)
cardiac index (CI)
mixed venous saturation (SvO_2)
BORG dyspnea score

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



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, SvO_2 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.

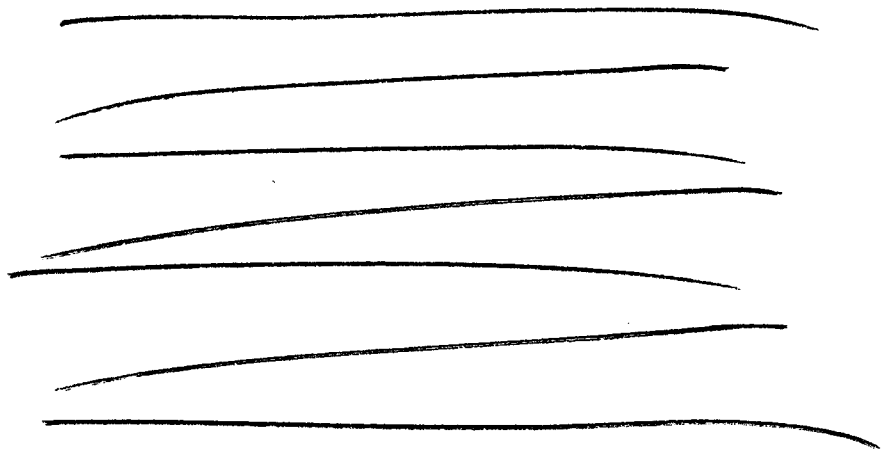
- ***HOW LONG TO OFFSET?***

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.

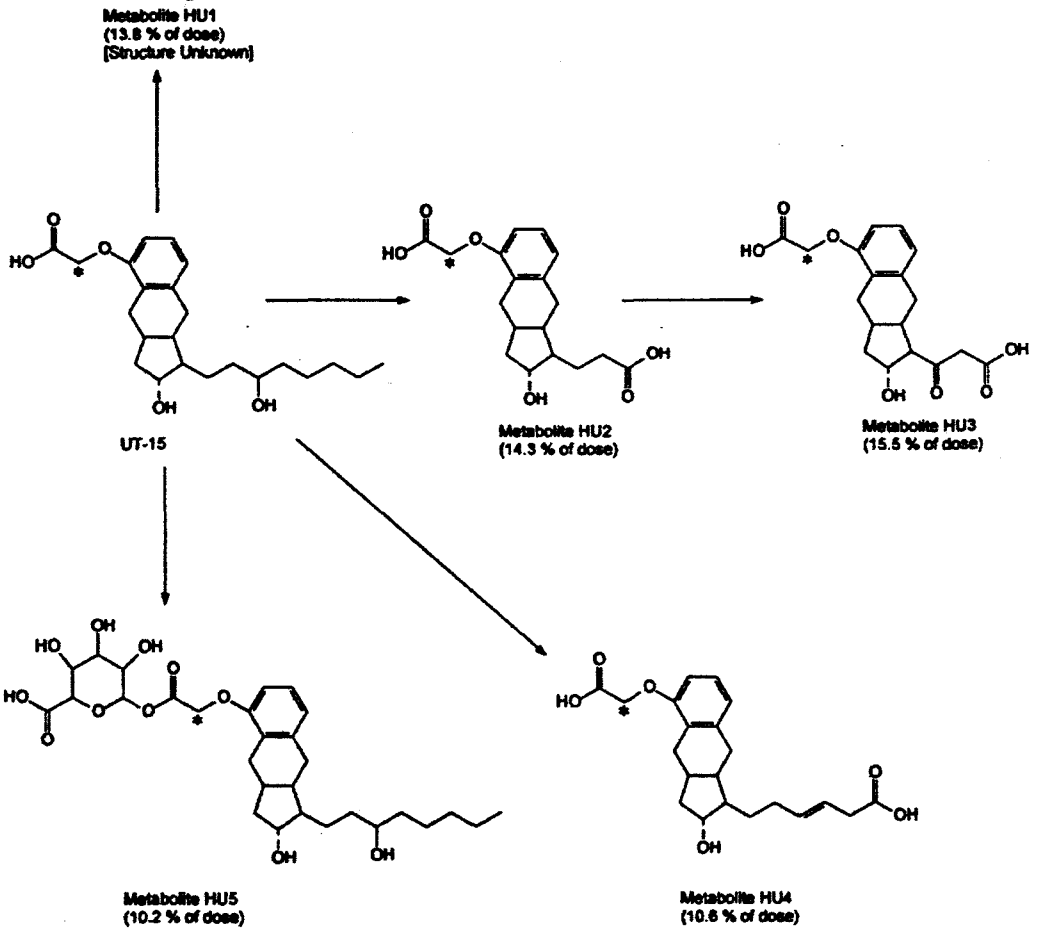


DISTRIBUTION
The volume of distribution of the central compartment is small, ~ 14 L/70 kg ideal body weight person. *In-vitro* studies indicate that UT-15 is ~ 91% bound to human plasma protein over the

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.



* Position of ^{14}C label.

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 Cmax and 3x higher AUC $_{0\text{-inf}}$ compared to healthy subjects. Patients with moderate HI have 4x higher Cmax and 5x higher AUC $_{0\text{-inf}}$ 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 Cmax 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.

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3 page(s) of revised draft labeling has been redacted from this portion of the review.

APPENDIX I

14 page(s) of revised draft labeling has been redacted from this portion of the review.

APPENDIX II

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

STUDY NO: [redacted] 7049-106 **VOLUME:** 2.14 **PAGES:** 3956 to 3995

PRINCIPAL INVESTIGATOR: Sheela PaiBir, PhD
CLINICAL LABORATORY: [redacted]

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 [redacted] Pooled female human plasma was fortified with [^{14}C] UT-15 (0.33 and 10 µg/mL) and filtered in triplicate. An aliquot of the remaining plasma in the reservoir portion of the [redacted] device was analyzed by [redacted] 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 ug/L) and at a single concentration of the ligand, [^{3}H] digoxin 2 ug/L and [^{14}C] 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
[^{14}C] 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 [^{14}C] UT-15-derived radioactivity following [redacted] 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 ug/L did not significantly affect the *in-vitro* protein binding of [^{3}H] digoxin and [^{14}C] 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 [^{14}C] UT-15. Radiopurity of [^{14}C] 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 [^{14}C] UT-15 was stable during the study, but the impurities will contribute to the free fraction of [^{14}C] UT-15.

The radiopurity of [^{3}H] digoxin and [^{14}C] 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 [^{14}C] UT-15, [^{3}H] digoxin, and [^{14}C] warfarin because the non-specific binding to the ~~~~ device was minimal. The mean percent bound to the ~~~~ 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 [^{14}C] 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 [^{14}C] 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 [^{14}C]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 [redacted] Thus, the lowest concentration of [^{14}C]UT-15 was [redacted] fold higher than most measured concentrations of UT-15.

It should also be noted that the radiopurity of [^{14}C] UT-15 was less than 90%. Thus, the impurities will contribute to the free fraction of [^{14}C] 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 [redacted] A single dose of warfarin 25 mg produces concentrations between [redacted] 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.

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

STUDY NO: [redacted] 7049-100 **VOLUME:** 2.14 **PAGES:** 3801 to 3845

PRINCIPAL INVESTIGATOR: Sanjeev Thohan, PhD
CLINICAL LABORATORY: [redacted]

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 (IC_{50}) 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 (Km) 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 tranylcypromine
dextromethorphan O-demethylase	CYP2D6	0.75 M quinidine
p-nitrophenol hydroxlyase	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 IC_{50} 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 IC_{50} 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
6β-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, [redacted] Thus the range of the UT-15 concentrations studied was quite wide [redacted] 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.

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STUDY TITLE: A single center, open-label, mass balance, urinary metabolite profiling, and safety study of [^{14}C] 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: [redacted] Medical Director, [redacted]

STUDY SITE: [redacted]

CITATION: not applicable

STUDY STARTED: January 6, 2000
STUDY COMPLETED: January 16, 2000

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

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

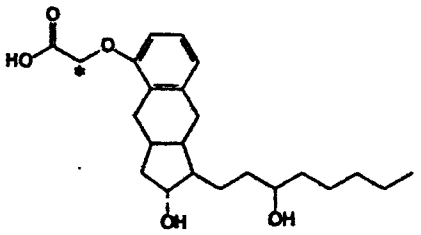
POPULATION: Six normal healthy male subjects between the ages of 18 to 50 years and a body weight within –10 to +20% of ideal body weight.

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 [^{14}C] 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 [^{14}C] 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 ^{14}C was attached to UT-15.



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 [^{14}C] 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}, $AUC_{0-\infty}$, 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 ≥ 5% of the nominal time.

Pharmacodynamics Descriptive statistics were calculated on the safety parameters.

FORMULATION: UT Corp provided UT-15 and [^{14}C] UT-15. UT-15 was from lot UT15-98K001, [redacted] No. LRR-0003) and was to be stored in refrigeration. radiolabeled UT-15 was provided to UT Corp by [redacted] 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 [^{14}C] 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	[redacted]		
Sodium hydroxide, NF	R9709017			
Sodium chloride	R9903095			
Hydrochloric acid, NF	R9901064			

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 ± 53,877 ng and 83.6 µCi [^{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.

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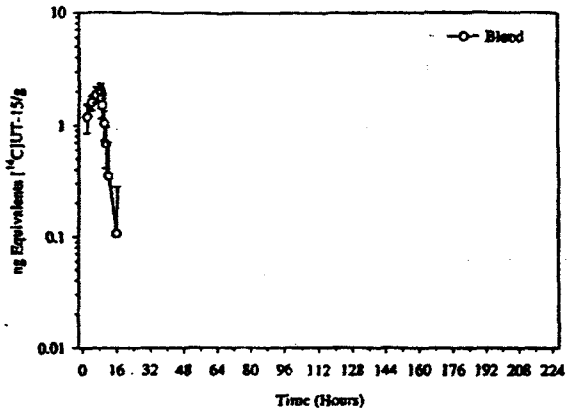

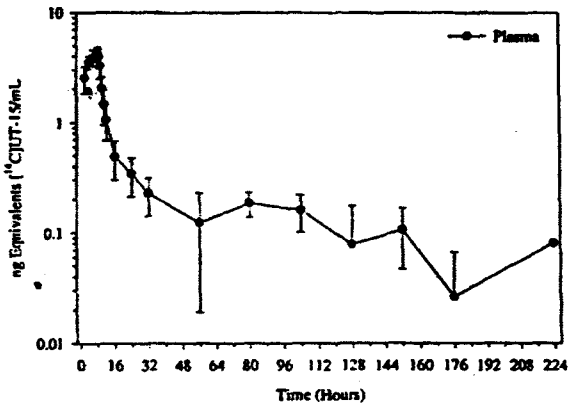

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Figure 16.3-1. Mean concentrations of radioactivity in blood and plasma at specified times after administration of a single subcutaneous infusion of [^{14}C]UT-15 (15 ng/kg/min) to healthy male subjects.

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

Table 16.3-9. Mean Blood:Plasma Concentration Ratios 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)	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.

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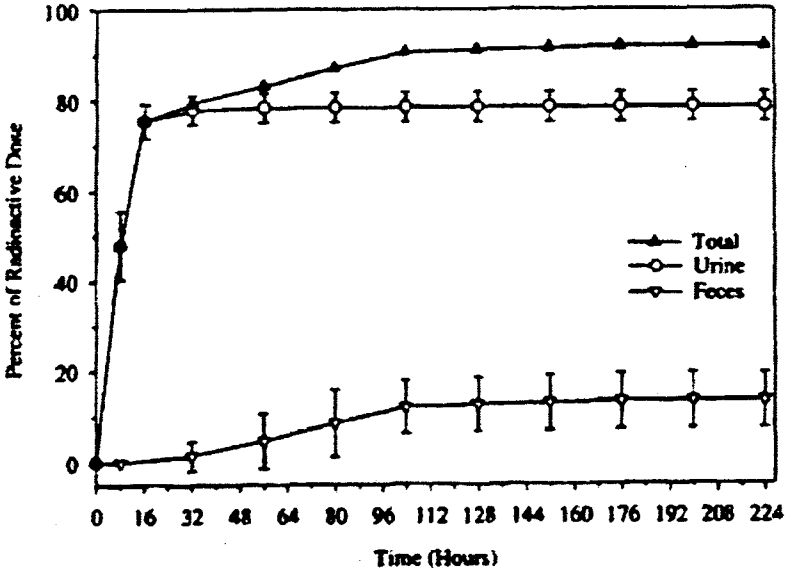
The pharmacokinetic parameters of radioactivity in blood and plasma are summarized in the table below.

[^{14}C]UT-15-derived radioactivity	Blood	[^{14}C]UT-15-derived radioactivity	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-t} (ng Equivalents-hr/g)	16.4 ± 2.02	AUC_{0-t} (ng Equivalents-hr/mL)	63.1 ± 11.86
$AUC_{0-\infty}$ (ng Equivalents-hr/g)	17.5 ± 2.56	$AUC_{0-\infty}$ (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 ½ of the radioactivity in blood varied from approximately 1 to 4 hours. The T ½ 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 ½ 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.



profiling of urine showed that 3.7% of the [^{14}C] 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.

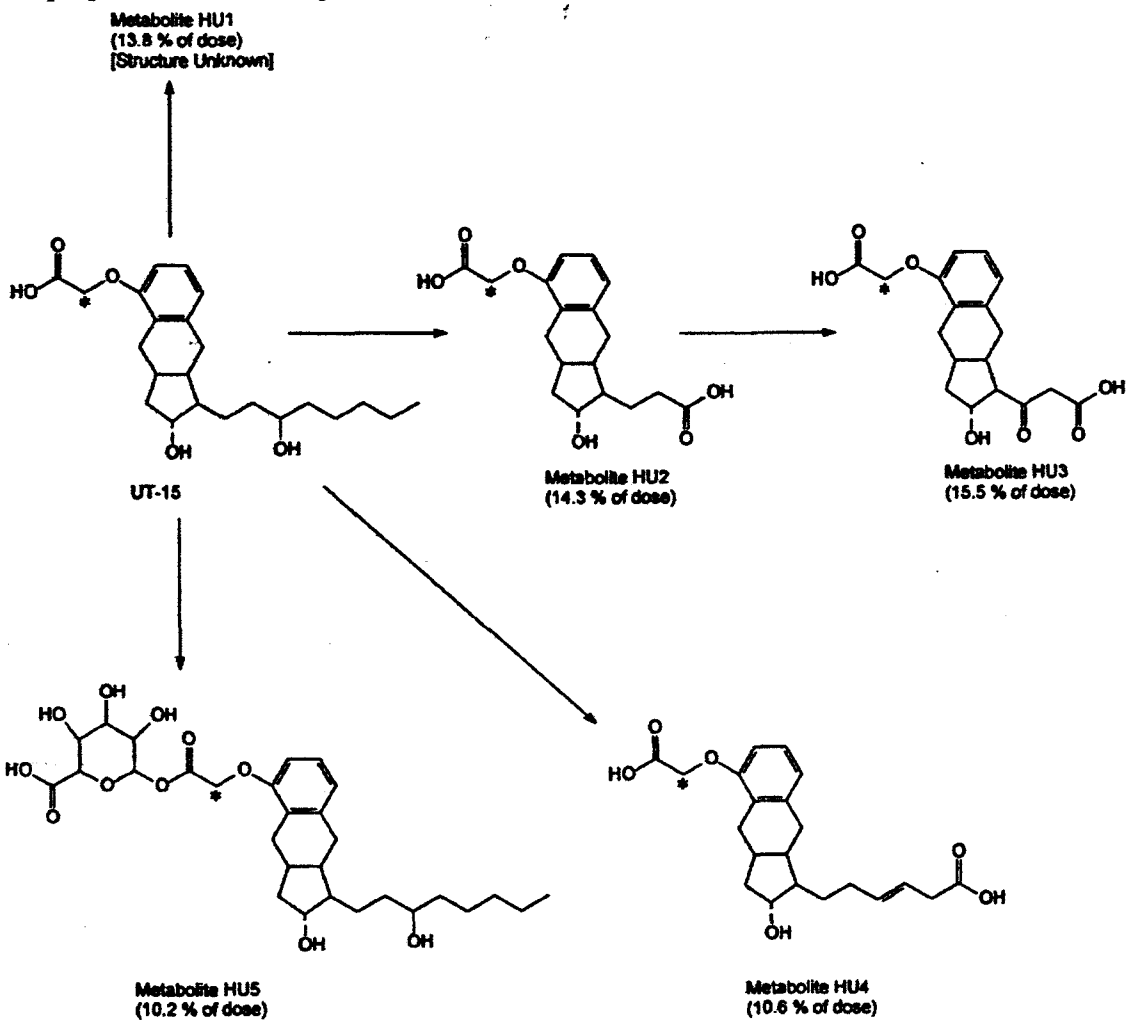
Table 16.3-8. Percentage of Sample Radioactivity and Percent of Dose Excreted as [^{14}C]UT-15 or Metabolites of [^{14}C]UT-15 in Urine from Humans Following a Subcutaneous Infusion to Six Healthy Males

		Percent of Sample Radioactivity in Metabolite and Parent Peaks (Percent of Dose)							
	Retention Time Range (Minutes)	Subject Number 1	2	3	4	5	6	Mean	SD
Percent of Dose in Urine		72.6	80.9	77.0	72.2	78.3	72.4		
Component									
HU1	10.8 to 10.9							18.1 (13.8)	8.78 (6.96)
HU2	11.4							19.0 (14.3)	3.86 (3.02)
HU3	12.7							20.5 (15.5)	4.68 (3.80)
HU4	14.0 to 14.1							14.1 (10.6)	4.64 (3.15)
HU5	15.6							13.6 (10.2)	3.75 (2.40)
[^{14}C]UT-15	19.6							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.

[redacted] 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 [redacted] results.

The proposed structure of parent and metabolites are shown below.



* Position of ^{14}C 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 ½ of radioactivity in blood, 2 hours, is consistent with the reported mean T ½ from pharmacokinetic studies. Of note is the T ½ of radioactivity in plasma of 65 hours. It is possible that this represents the T ½ 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 [redacted]. At the end of the SC infusion, the catheter along with the [redacted] 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 (D_5W) 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 [redacted]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 [redacted]
The extracts were analyzed for UT-15 using a validated [redacted] assay over a standard curve range of [redacted]

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 [redacted]

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

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.

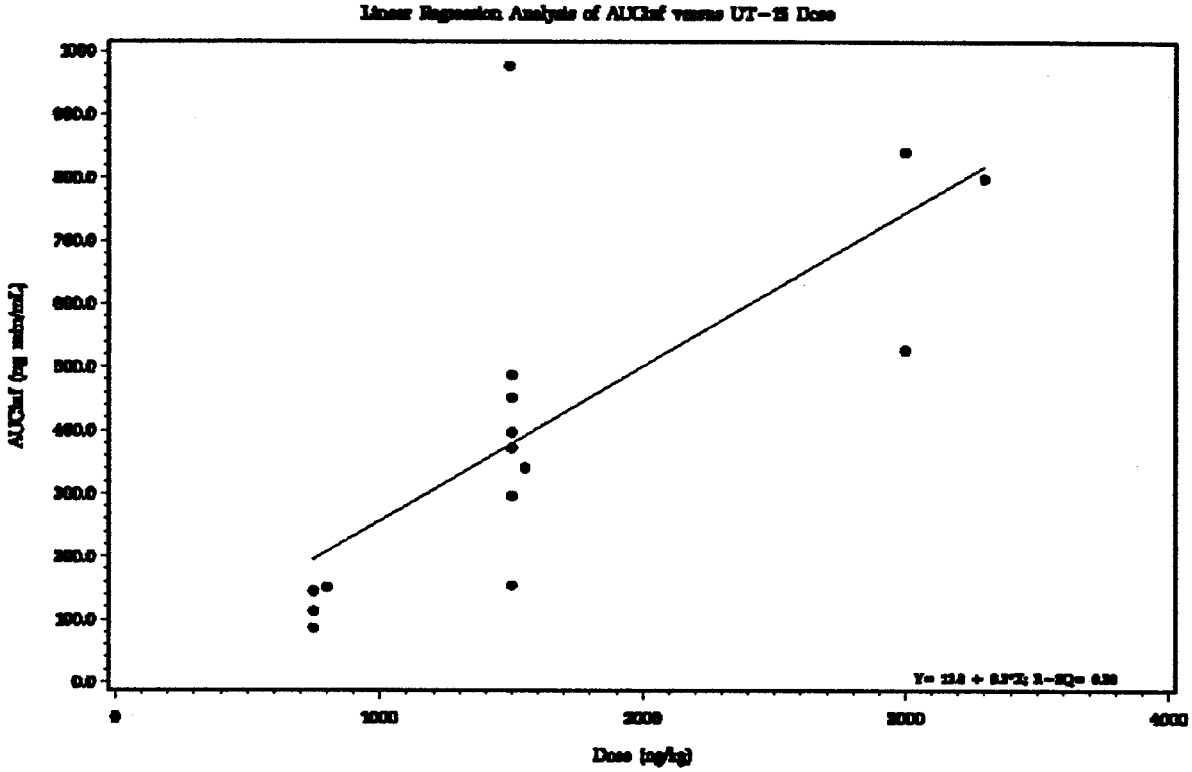
RESULTS: Twenty-five patients (20 female and 5 male) were enrolled. There were 18 Caucasians, 3 Hispanics, 2 Asians and 2 Blacks. Their ages ranged from 22 to 71 years with a median age of 41 years. Weight ranged from 45 kg to 123 kg with a median weight of 76 kg.

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 %
IV dosing	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 (%)						
Minimum						
Maximum						
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 (%)						

Minimum						
Maximum						

* 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 %
IV Dosing - 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 (%)						
Minimum						
Maximum						
SC dosing - 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 (%)						
Minimum						
Maximum						

* 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.

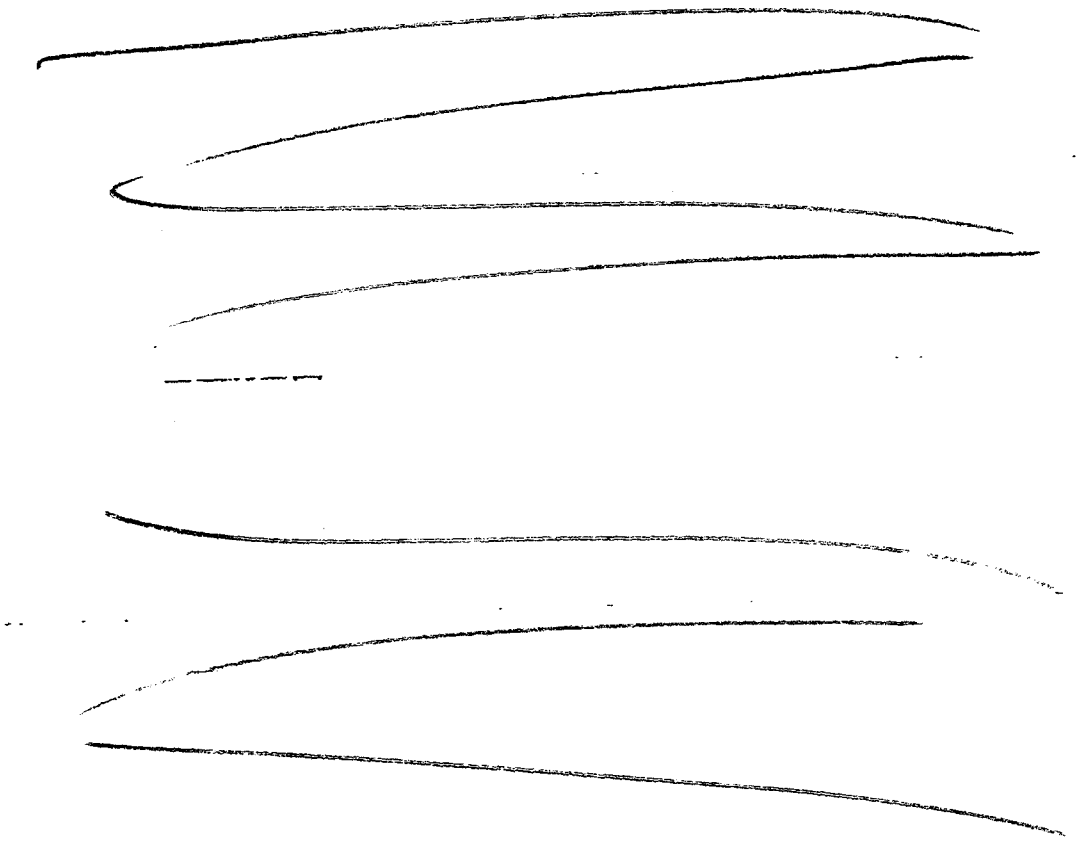
Cohort III (n = 3)*

	C_{max} ug/L	T_{max} min	$T_{1/2}$ min	AUC_{inf} ng-min/mL	CL/F mL/min/kg	Abs F %
IV Dosing - 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 (%)						-
Minimum						
Maximum						
SC dosing - 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 (%)						
Minimum						
Maximum						

* 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 Cmax was biphasic. Below is a representative patient's concentration vs. time profile on a linear and log scale.



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 assay used in this study (with a LOQ of) 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 ½ for SC and IV UT-15 are not very different. The mean T ½ (CV%) for the IV dose was 41.7 (146%), 35.4 (90%), and 25.6 (47%) minutes. The mean T ½ 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 ½ from the SC data is the one obtained with the highest dose. Thus, after considering the variability in the data, the T ½ 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 —— 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 —— whereas other studies have had sensitivities as low as ——. 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.

APPEARS THIS WAY
ON ORIGINAL

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 [redacted] pump, or intravenously into an arm vein with a [redacted] 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 D_5W to an appropriate strength. For SC administration, UT-15 was delivered without any dilution.

ASSAY: [redacted] analyzed the plasma samples with a validated [redacted] assay. A dimethylene homologue of UT-15 (LRXA-97J02) was used as an internal standard. Quality controls were analyzed at concentrations of [redacted]

[redacted]

Sensitivity The LOQ was [redacted] of plasma.

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

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 [redacted] 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.

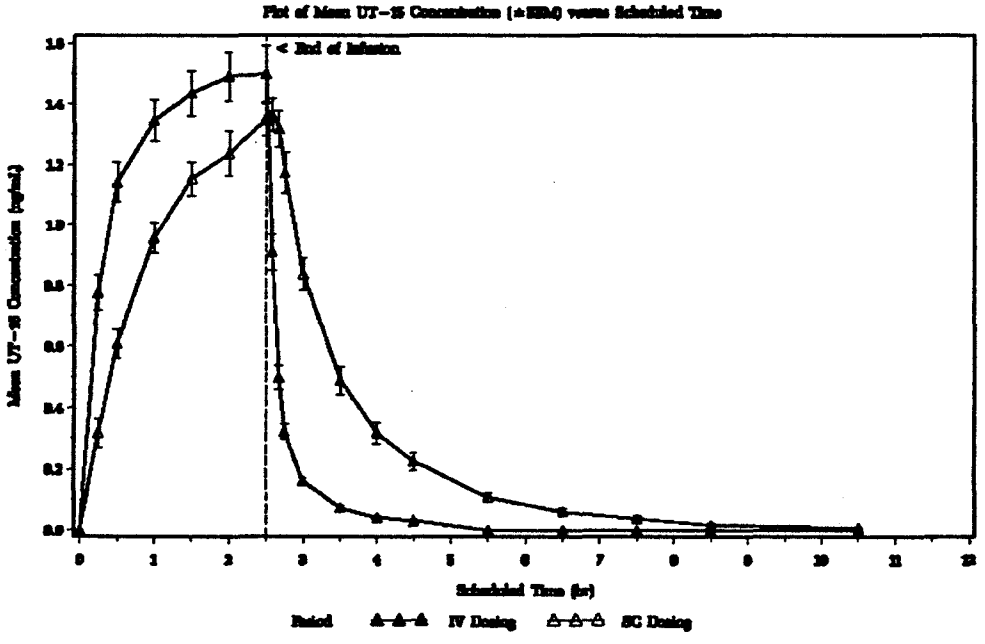
Safety A total of 30 adverse events (AEs) were reported by 11 of 15 volunteers during the study; none of the events was a serious adverse event (SAE). The majority of the AEs (67%) had an onset during the 150-minute infusion period while the remainder (33%) had an onset after the termination of the infusion. 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%.

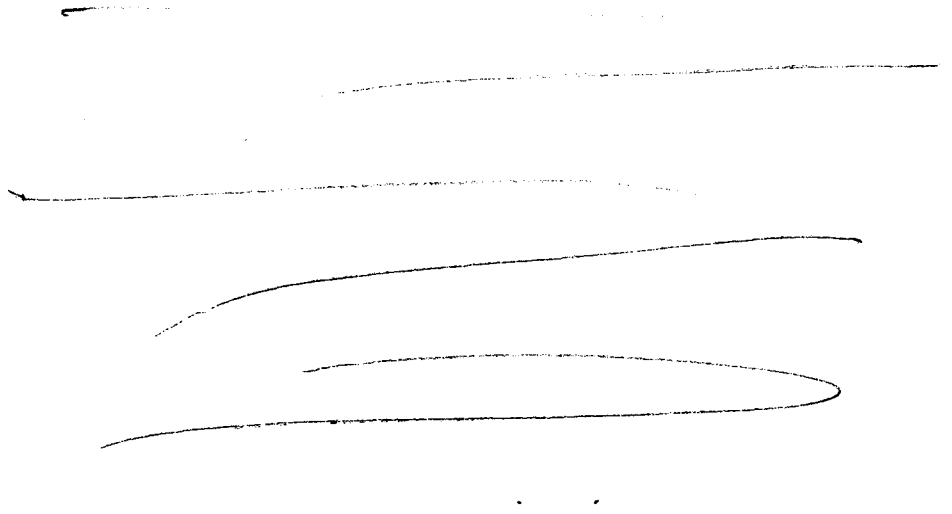
Plasma concentrations increased quickly (IV faster than SC), peaked at the end of the infusion (~ 2.5 hours) (see figure below). In some subjects Cmax for SC UT-15 occurred shortly after termination of the infusion. Plasma concentrations ranged from [redacted] for IV and SC infusions, respectively. The 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
Cmax (ug/L)	1.57	0.31	19.8		
T_{max} (hr)	2.13	0.34	16.1		
$T_{1/2}$ (hr)	0.87	0.43	49.5		
AUC_{inf} (ng hr/mL)	3.52	0.71	20.0		
CL (mL/kg/hr)	663.0	132.2	19.9		

Subcutaneous UT-15 Pharmacokinetic Parameters (n = 15)

Parameters	Mean	SD	CV (%)	Minimum	Maximum
C_{max} (ug/L)	1.47	0.20	13.6		
T_{max} (hr)	2.51	0.22	8.8		
$T_{1/2}$ (hr)	1.38	0.66	47.8		
AUC_{inf} (ng hr/mL)	3.97	0.76	19.0		
Cl (mL/kg/hr)	589.4	129.6	22.0		
Absolute F (%)	113.1	10.0	8.9		

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 ½ 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 ½.

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 ½ 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
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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 [redacted] 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: [redacted] analyzed the plasma samples with a validated [redacted] assay. A dimethylene homologue of UT-15 (LRXA-97J02) was used as an internal standard. Quality controls were analyzed at concentrations of [redacted]

Precision Intraday and interday CV was less than 15%.

Accuracy Intraday and interday accuracy was within 20%.

Sensitivity The lower LOQ was [redacted]

Linearity The assay was linear over a standard curve of seven concentrations ranging from

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 ½.

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

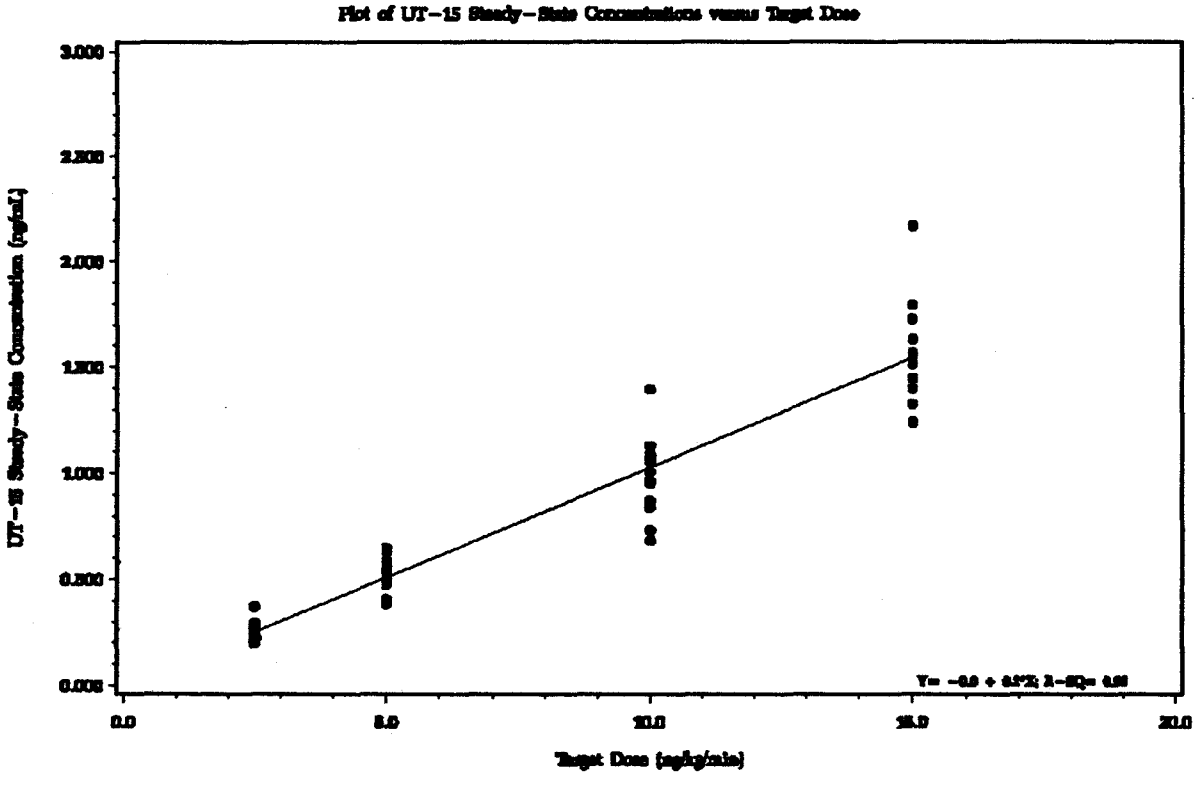
Six of these eight subjects provided steady state UT-15 plasma concentrations for at least 72 hours in all of the dosing periods.

PHARMACOKINETIC RESULTS: The sponsor determined only clearance and T ½. The following number of subjects were included in the following analysis at each dose:

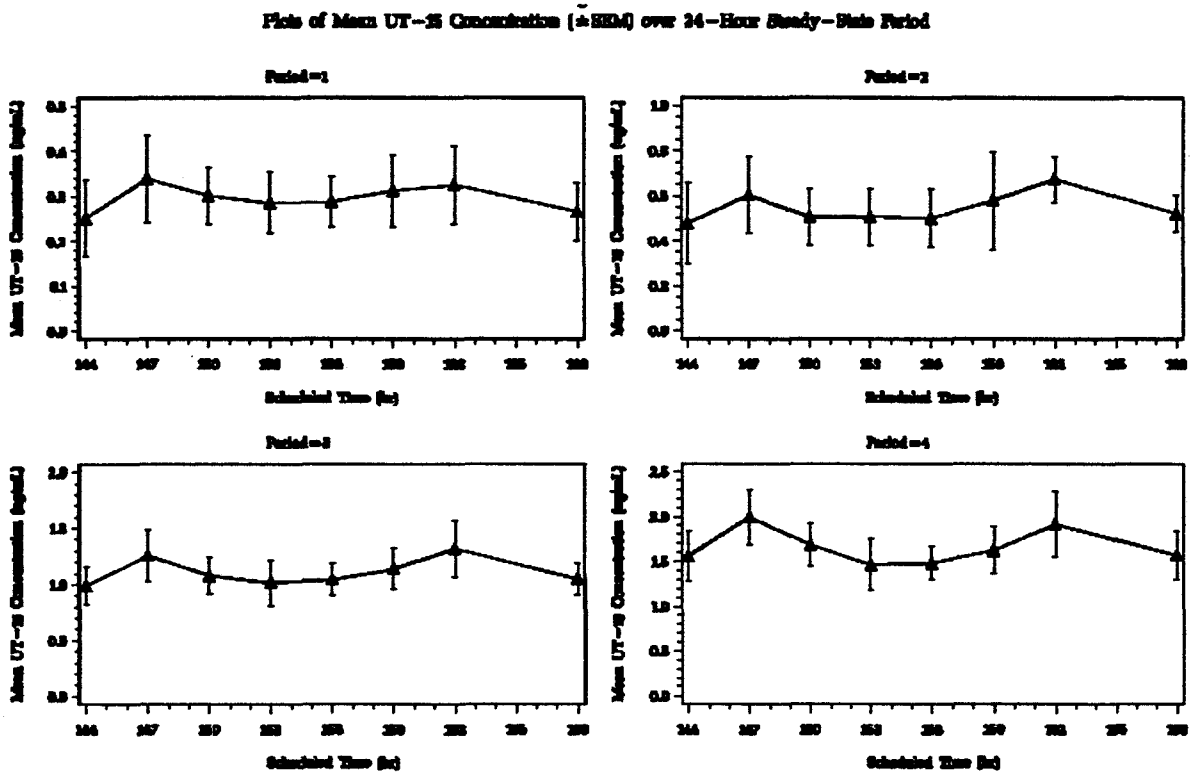
Dose (ng/kg/min)	No. subjects Dose proportionality and clearance	No. subjects Diurnal cycles
2.5	14	14
5	14	13
10	13	13
15	13	6

Fourteen subjects contributed to the determination of plasma T ½; 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 See linear regression below.



Steady state was achieved during each dosing period (see figure below). Mean Css values ranged from



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.