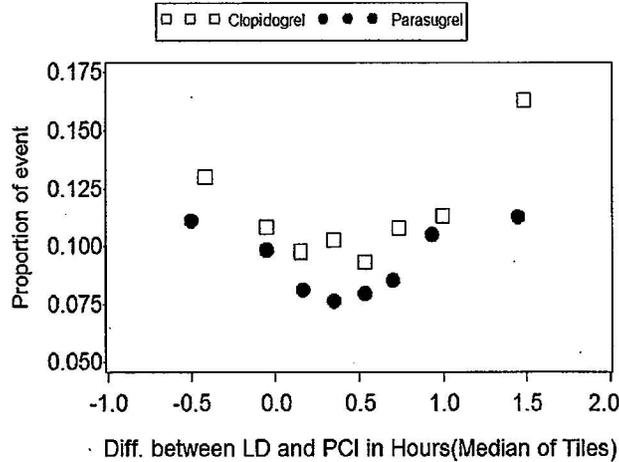


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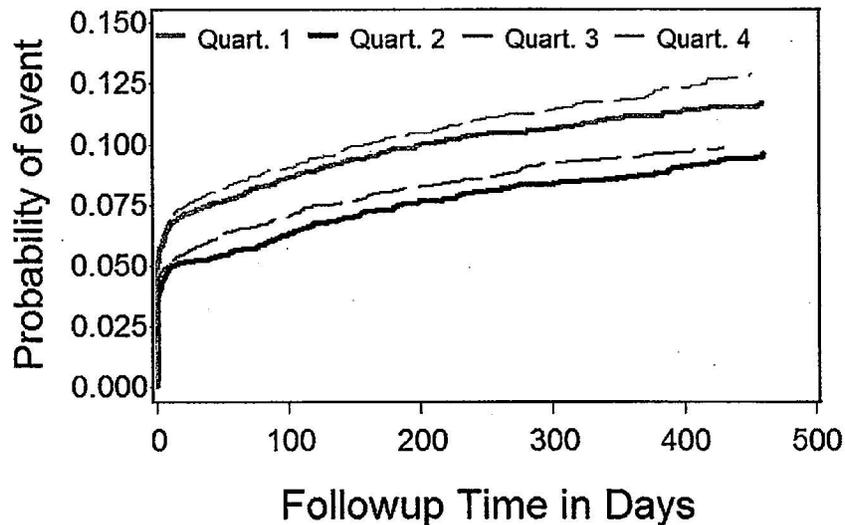
Similar relationship was seen across both the treatment arms as shown in **Figure 13**. However, it can be clearly seen that prasugrel consistently performs better than clopidogrel.

Figure 13: The effect of the timing of loading dose relative to the start of PCI is similar across prasugrel and clopidogrel



The value of administering the loading dose at the start of PCI is also evident from the Kaplan-Meier curves across the quartiles of difference between loading dose and start of PCI as shown in **Figure 14**. Similar relationship was also seen when the data was divided into octiles instead of quartiles.

Figure 14: Cumulative event rate of the cardiovascular event is lower when the loading dose is administered at the start of PCI or within 30 minutes of the start of the PCI irrespective.



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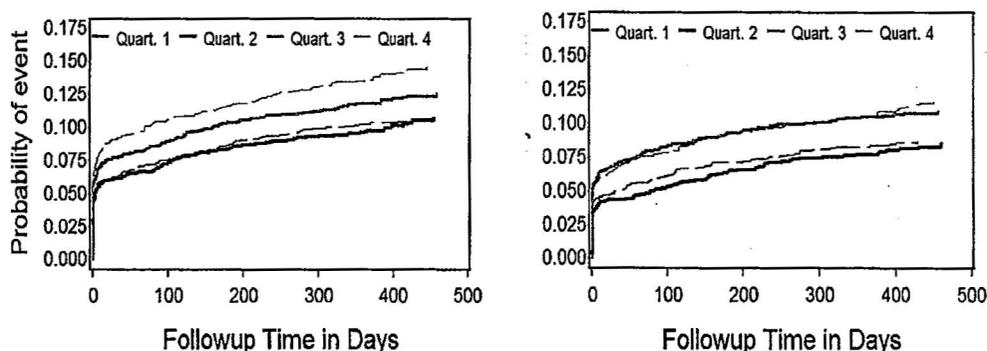
Cox Proportional regression shows that the relative risk for CVD/Non-fatal MI/Non-fatal Stroke is 28% and 24% lower for Quartiles 2 and 3 compared to Quartile 4. The details are presented in the table below:

Quartile	N	Range of Loading Dose Time – PCI Start Time (hrs)	Hazard Ratio (95% Confidence Limit)	p-value
4*	3186	0.85 – 530.13	-	-
1	3370	-234.83 - 0	0.91 (0.79 – 1.05)	0.1858
2	3274	0.02 – 0.43	0.72 (0.62 – 0.84)	<0.0001
3	3438	0.45 – 0.83	0.76 (0.66 – 0.89)	0.0004

* Quartile – 4 was used as reference to compute the relative risk for rest of the quartiles using Proc TPHREG

This relationship was consistent between prasugrel and clopidogrel as shown in Figure 15.

Figure 15: Cumulative event rate of the cardiovascular events across quartiles of difference in time of loading dose and start of PCI is similar between clopidogrel (left) and prasugrel (right).



Exploratory analyses revealed a weak but statistically significant correlation was observed with the use of GPIIb/IIIa antagonist, prior CABG and Stent use upto PCI or hospital discharge.

Further, prior CABG was found to be a statistically significant predictor (χ^2 statistic: $p < 0.0001$) of the timing of loading dose when a 2x2 contingency table was constructed between prior CABG and the timing of the loading dose (dichotomized by at least 6 hrs before PCI or not) in only those patients who received the loading dose before the start of PCI. After controlling for the prior CABG, no statistically significant association (CMH Statistics: General association $p = 0.1146$) was seen between timing of loading dose (at least 6hrs before PCI or not) and observing the efficacy endpoint. This could likely explain

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the reason for higher incidence of the primary endpoint when prasugrel or clopidogrel is dosed at least 6 hrs or before.

Hence with potent rapidly acting agents such as clopidogrel and prasugrel pre-treatment may not be necessary for achieving maximum effectiveness. However, the Loading Dose for either Prasugrel or Clopidogrel should be administered at least within 30 minutes of the start of the PCI.

Sponsor's Analysis

Study TAAD

Objectives

The objectives of the population PK/PD analyses were to:

- assess the pharmacodynamic effects (inhibition of platelet aggregation and bleeding times) of CS-747 plus aspirin compared to clopidogrel plus aspirin in patients with stable atherosclerosis
- assess pharmacokinetics of prasugrel metabolites when prasugrel is co-administered with aspirin in patients with stable atherosclerosis

Data

Study H7T-EW-TAAD was a two-centre, randomized, partially blind, parallel-group, multiple-dose study of 4 dosing regimens of prasugrel tablets (LD/MD - 40/5, 40/7.5, 60/10 and 60/15 mg) co-administered with aspirin compared with clopidogrel co-administered with aspirin, in patients with stable atherosclerosis. A LD of study drug was given on Day 1, followed by approximately 27 days of a daily MD. A total of 101 subjects entered the study. Summary of some baseline demographics are presented in Table 1.

Table 1: Summary of subject demographics
(per sponsor report H7T-EW-TAAD; Table TAAD.10.1)

Group	Mean ± SD (range)				Number
	Age (years)	Body Weight (kg)	Height (cm)	Body Mass Index (kg/m ²)	Gender
CS-747 (40 mg/5 mg) + aspirin (n = 19)	65 ± 8.7 (47-74)	84.7 ± 13.58 (61.8-118.6)	175 ± 5.2 (163-184)	27.7 ± 3.44 (22.9-36.6)	Female: 3 Male: 16
CS-747 (40 mg/7.5 mg) + aspirin (n = 19)	65 ± 7.9 (47-75)	84.2 ± 9.99 (66.4-102.2)	169 ± 9.1 (156-189)	29.5 ± 3.39 (24.1-38.3)	Female: 8 Male: 11
CS-747 (60 mg/10 mg) + aspirin (n = 19)	65 ± 6.4 (55-74)	86.6 ± 13.95 (63.3-116.0)	172 ± 7.9 (150-182)	29.0 ± 3.03 (23.9-35.8)	Female: 1 Male: 18
CS-747 (60 mg/15 mg) + aspirin (n = 21)	63 ± 7.5 (45-73)	84.7 ± 16.71 (57.3-140.0)	172 ± 7.6 (157-188)	28.5 ± 4.52 (21.8-42.7)	Female: 7 Male: 14
Clopidogrel (300 mg/75 mg) + aspirin (n = 23)	61 ± 8.0 (48-73)	86.1 ± 13.13 (67.7-120.2)	175 ± 7.7 (158-186)	28.0 ± 3.60 (22.6-36.3)	Female: 2 Male: 21
All subjects (N = 101)	64 ± 7.7 (45-75)	85.3 ± 13.45 (57.3-140.0)	173 ± 7.7 (150-189)	28.5 ± 3.63 (21.8-42.7)	Female: 21 Male: 80

CS-747 :Prasugrel, SD – Standard Deviation

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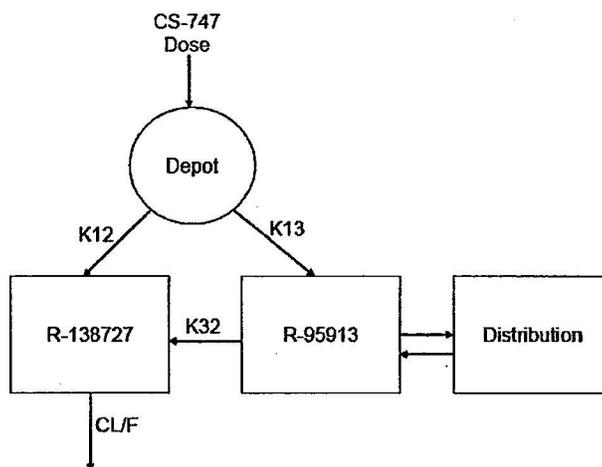
Other details of various patient characteristics can be found in detail in the sponsor report H7T-EW-TAAD-Population Pharmacokinetic report (\\Cdsesub1\evsprod\NDA022307\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\h7t-ew-taad).

Blood samples were collected for assessment of platelet aggregation response. Plasma concentrations of the precursor (R-95913), active metabolite (R-138727) and the inactive metabolites (R-119251, and R-106583) (Figure 1) for prasugrel; the inactive metabolite for clopidogrel (SR26334) were available from 78 patients.

Methods

A population pharmacokinetic model was developed utilizing the nonlinear mixed effects program (NONMEM, Version V). In this model, shown in **Figure 16**, the introduction of CS-747 into the depot compartment is modeled as a zero-order process. The formation of R-138727 occurs directly from the depot compartment (first-pass) or through the R-95913 pre-cursor. Model development was carried out using both R-95913 and R-138727 concentrations.

Figure 16: R-138727 structural model



An analysis of covariates evaluated patient specific factors listed in the table for their potential effect upon the pharmacokinetic parameters, and all significant covariates were included in the full model. After a backward reduction of the full model, only covariates that significantly reduced variability estimates of parameters were retained in the final model.

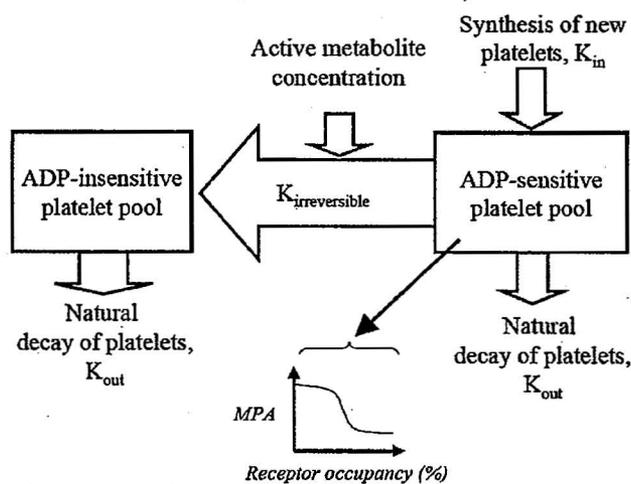
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Table 2: Patient specific factors evaluated as potential covariates
(per sponsor report H7t-EW-TAAD; Table TAAD.9.3)

Parameter	Patient Specific Factors
CL/F	Age, Weight, Cockcroft-Gault Creatinine Clearance, Gender, Smoking Status, Use of Statins, Diabetes Status
V2/F	Age, Weight, Gender
V3/F	Age, Weight, Gender
K12	Age, Dose of LY640315, Gender, Smoking Status, Use of Statins, Diabetes Status, Duration of Therapy
K32	Age, Dose of LY640315, Gender, Smoking Status, Use of Statins, Diabetes Status
F1	Dose of LY640315, Duration of Therapy, Gender

Pharmacodynamic model development incorporated the natural process of platelet turnover shown in **Figure 17**.

Figure 17: Mechanistic PK/PD model for prasugrel
(per sponsor report H7T-EW-TAAD; Table TAAD.9.4)



The rate of platelet formation (K_{in}) and platelet degradation (K_{out}) is assumed to be zero order and first-order, respectively. Without drug intervention or introduction of trauma or disease, the rates of platelet formation and degradation are relatively stable within individuals and therefore the size of the ADP-sensitive platelet pool within individuals is relatively constant.

Since the absolute size of the platelet pool is relatively stable within an individual, the active platelet pool can be expressed as a fraction of the ADP-sensitive platelet pool before drug administration. This fraction ranges from 0 to 1, with 1 representing the ADP-sensitive pool before drug administration, and 0 representing a completely decimated platelet pool. The fractional size of the platelet pool is inferred from maximum platelet aggregation (MPA), which decreases as the size of the active platelet pool decreases.

The structural model for the link between the pharmacokinetic and pharmacodynamic models was through irreversible binding of active metabolite

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to the platelet ADP-receptor. The rate constant associated with this process (irreversible) is second-order because the rate of inactivation depends on both the plasma concentration of the active metabolite and the remaining free receptors from the ADP-sensitive platelet pool.

Results

- The pharmacokinetics of R-138727 were well-described by a population pharmacokinetic model consisting of a zero-order absorption process into a depot compartment followed by fractionation of the absorbed moiety into R-138727 and R-95913. The distributions of R-138727 and R-95913 were described by a one compartment and 2-compartment model, respectively.
- The pharmacokinetics of R-138727 were not discernably affected by age, sex, prasugrel dose, Cockcroft-Gault creatinine clearance, smoking status, statin use, or presence of diabetes. The lack of dose effect suggests that R-138727 exposure is dose proportional.
- The apparent clearance of R-138727 decreased with decreasing body weight, which would produce increasing exposure as body weight decreases. Specifically, a 31% decrease in body weight from 84 kg to 58 kg produced an approximately 22% decrease in R-138727 CL/F and an increase of ≤ 10 percentage points in MPA. The clinical impact of body weight differences on safety and efficacy are unknown. The results of the final pharmacokinetic model are shown in **Table 3**.
- The PK/PD analysis described the relationship between concentration-time profiles of prasugrel active metabolites and the time-course of MPA.
- Both loading doses of 40 and 60 mg prasugrel achieved statistically significant higher mean inhibition of platelet aggregation (IPA) compared with 300 mg clopidogrel by 2 hours, 4 hours and 6 hours post loading dose.

Details of the population pharmacokinetics and the PK/PD modeling can be found in the sponsor report H7T-EW-TAAD-Population Pharmacokinetic report (<\\Cdsesub1\evsprod\NDA022307\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\h7t-ew-taad>).

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Table 3: Population pharmacokinetic parameters of the final population model
(per sponsor report H7T-EW-TAAD; Table TAAD.11.2)

Parameter Description	Population Estimate (%SEE)	Between-Patient Variability ^a (%SEE)	Inter-Occasion Variability ^b (%SEE)
Duration of Absorption	0.468	--	--
D1 (hr)	(1.84)		
Rate Constant for First-Pass	1.16	102	--
K12 (hr ⁻¹)	(14.1)	(19.5)	
Conversion of R-95913 to R-138727	0.255	18.0	--
K32 (hr ⁻¹)	(4.47)	(42.3)	
Covariance Between K12 and K32	--	32.3 (30.5)	--
Rate Constant for R-95913 Absorption	1.59	82.1	--
K13 (hr ⁻¹)	(11.8)	(22.3)	
Apparent Clearance^c			--
TVCL, base parameter for CL/F (L/hr)	115 (3.68)	24.5	
Θ_1 , parameter for effect of WT on CL/F	0.00963 (24.5)	(17.1)	
Apparent Volume of Distribution for R-138727	40.3	29.2	--
V2/F (L)	(7.49)	(63.9)	
Covariance Between CL/F and V2/F	--	23.0 (28.8)	--
Apparent Volume of Distribution for R-95913	129	37.0	--
V3/F (L)	(5.58)	(24.4)	
Rate Constant for Distribution of R-95913 from V3/F to V4/F	0.689	--	--
K34 (hr ⁻¹)	(6.69)		
Rate Constant for Distribution of R-95913 from V4/F to V3/F	0.0947	--	--
K43 (hr ⁻¹)	(5.78)		
Relative Bioavailability Across Visits^d	1 FIXED	--	14.7
TVF ₁ , base parameter for F1	-0.111 (20.8)		(52.1)
Θ_2 , parameter for effect of DT on F1			
Proportional Residual Error for R-138727^e		46.4 (6.05)	
Proportional Residual Error for R-95913^e		40.9 (4.60)	

^a Between-patient variability represented as %CV; calculated as %CV = (SQRT(EXP(OMEGA(N))-1))*100%

^b Inter-occasion variability (IOV) represented as %CV; estimated from each visit being blocked to provide estimates of IOV; calculated as %CV = (SQRT(EXP(OMEGA(N))-1))*100%

^c CL/F = TVCL*EXP(Θ_1 *WT-83.9) where 83.9 is the median body weight (WT).

^d F1 = TVF1*(1+IND* Θ_2) where IND represents Visits greater than 2.

^e Proportional residual error represented as %CV; calculated as %CV = SQRT(SIGMA(N))*100%

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Study TABR

Objectives

The objectives of the population PK/PD analyses were to:

- characterize the pharmacokinetics of the active metabolites after a LD and during daily MD of prasugrel and clopidogrel
- assess the pharmacodynamic effects (using MPA to 20 μ M ADP) after a LD and during daily MD of prasugrel and clopidogrel

Data

Study H7T-MC-TABR (TABR) was a two-center, randomized, double-blind, double dummy, 2-arm parallel group investigation to compare the pharmacodynamic effect of prasugrel 60-mg LD followed by 10 mg daily MD versus clopidogrel 600-mg LD followed by 75-mg daily MD in aspirin-treated subjects with stable atherosclerosis. Male and female (not of child-bearing potential) subjects with a history of stable coronary artery disease, 40 to 74 years old, inclusive, were eligible for enrollment.

Data for PK/PD analyses was available from 55 patients on prasugrel and 54 subjects on clopidogrel. Summary of some baseline demographics are presented in **Table 4**. Other details of various patient characteristics can be found in detail in the sponsor report H7T-MC-TABR-Population Pharmacokinetic report ([\\Cdsesub1\evsprod\NDA022307\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\h7t-mc-tabr-pop-pk](#)). This evaluation included 751 (R-138727), 763 (R-95913), and 556 (active metabolite of clopidogrel: R-130964) plasma samples from 110 subjects and 849 samples to evaluate MPA from 109 subjects.

Table 4: Patient demographics for PK/PD model development (per sponsor report H7T-MC-TABR Population Pharmacokinetics Report; Table TABR.9.1)

	Age (years)	Weight (kg)	Cockcroft-Gault Creatinine Clearance (mL/min)	Serum Creatinine (μ mol/L)
Prasugrel (n=55)				
Range	47 - 73	51.5 - 144	46.1 - 200	62.0 - 124
Mean (CV as %)	62.3 (10)	87.3 (15)	97.2 (25)	86.5 (16)
Clopidogrel (n=54)				
Range	48 - 75	65.3 - 125	40.2 - 151	70.0 - 177
Mean (CV as %)	64.6 (10)	84.2 (14)	88.4 (25)	90.9 (20)

Abbreviations: CV = coefficient of variation; n = number.

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Methods

A population pharmacokinetic model was developed utilizing the nonlinear mixed effects program (NONMEM, Version V). A 4-compartment model with zero-order absorption was selected as the base structural model for prasugrel. An analysis of covariates evaluated patient demographic, clinical history, and laboratory values for their potential effect upon the pharmacokinetic parameters, and all significant covariates were included in the full model. After a backward reduction of the full model, only covariates that significantly reduced variability estimates of parameters were retained in the final model. Similar methods were applied for the characterization of clopidogrel pharmacokinetics.

The PK/PD analysis described the relationship between concentration-time profiles of prasugrel and clopidogrel active metabolites and the time-course of MPA. To link the pharmacokinetics and pharmacodynamics, the rate constant associated with the irreversible binding of the active metabolite to the platelet ADP-receptor ($K_{\text{irreversible}}$) was reflected as a second-order process as it is dependent on both the plasma concentration of active metabolite and the remaining free receptors from the ADP-sensitive pool. The exposure-response relationship is then described with an E_{max} submodel relative to the MPA response to 20 μM ADP. Beyond those significant covariates identified in the PK analyses, no further patient specific factors were identified affecting the PD response.

For details on the methods please refer to the sponsor report H7T-MC-TABR Population Pharmacokinetics Report.

Results

- The base population pharmacokinetic model was able to adequately predict the plasma concentrations of R-138727 and R-95913.
- Analysis of covariates demonstrated that body weight, dose, and gender had a statistically significant influence on the pharmacokinetics of prasugrel. Although the mean apparent clearance of R-138727 increased by 11% as dose decreased from the 60-mg LD to the 10-mg MD, this increase in apparent clearance was contained within the 95% confidence interval (CI) limits of 1.07-1.15. The relative contribution from R-95913 in plasma and direct first-pass formation to R-138727 was higher upon administration of 10 mg compared to 60-mg; however, the total formation of R-138727 remained unchanged and there is no overall effect on R-138727 exposure. The apparent clearance of R-95913 was 26% lower in females compared to males. However, individual estimates of R-138727 area under the concentration curve (AUC) in females were entirely contained within those of males. The apparent clearance of R-138727 decreased with decreasing body weight (WT), producing increasing exposures (39% with a 37% decrease in weight). For detailed pharmacokinetic model development, diagnostics and model qualification refer the sponsor report H7T-MC-TABR Population Pharmacokinetics Report ([\\Cdsesub1\evsprod\NDA022307\0000\m5\53-clin-stud-rep\533-](#)

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rep-human-pk-stud\5335-popul-pk-stud-rep\h7t-mc-tabr-pop-pk). The final parameter estimates from the population pharmacokinetic model for prasugrel are shown in the table 5.

Table 5: Prasugrel Pharmacokinetics Parameter estimates in the final population pharmacokinetic mode
(per sponsor report H7T-MC-TABR; Table TABR.9.5)

Parameter Description	Population Estimate (%SEE)	Between-Patient Variability ^a (%SEE)
Duration of Absorption	0.473	--
D1 (hr)	(9.98)	
Rate Constant for First-Pass Formation of R-138727	6.55	327
K12 (hr ⁻¹)	(42.3)	(43.5)
Rate Constant for R-95913 Appearance ^b	3.12	317
K13 (hr ⁻¹)	(42.6)	(46.2)
Covariance Between K12 and K13	2.41	--
	(44.8)	
Rate Constant for Distribution of R-95913 to Peripheral Compartment	0.562	--
K34 (hr ⁻¹)	(5.32)	
Rate Constant for Distribution of R-95913 from Peripheral Compartment	0.218	--
K43 (hr ⁻¹)	(3.33)	
Apparent Clearance of R-138727 ^c	149	21.0
CL20/F (L/hr)	(3.98)	(22.5)
Apparent Volume of Distribution for R-138727	66.4	--
V2/F (L)	(4.62)	
Apparent Clearance of R-95913 to R-138727 ^d	36.9	31.1
CL32/F (L/hr)	(5.20)	(21.7)
Apparent Volume of Distribution for R-95913	60.5	35.7
V3/F (L)	(5.82)	(25.4)
Covariance Between CL32/F and V3/F	0.101	--
	(23.4)	
Effect of Weight on CL20/F ^c	0.0140	--
	(24.3)	
Effect of Gender (Female) on CL32/F ^d	-0.263	--
	(18.9)	
Effect of Dose (10-mg) on CL20/F ^c	0.112	--
	(20.9)	
Effect of Dose (10-mg) on K13 ^b	0.197	--
	(27.8)	
Proportional Residual Error for R-138727 ^e		33.5% (10.7)
Proportional Residual Error for R-95913 ^e		28.8% (10.3)

^a %CV = (SQRT(EXP(OMEGA(variance estimate)-1)))*100%

^b K13 = 3.12*(1+(I1*0.197)) where I1=0 for 60-mg dose and I1=1 for 10-mg dose.

^c CL20/F = 149*EXP((WT-85)*0.0140)*(1+(I1*0.112)) where I1=0 for 60-mg dose and I1=1 for 10-mg dose.

^d CL32/F = 36.9*(1+(I1*-0.263)) where I1=0 for males and I1=1 for females.

^e %CV = SQRT(SIGMA(variance estimate))*100%