patients are shown in the following table. The two extreme situations can be compared. For the UM patients with Css,max of 247.5 ng/mL will have a QTc of 375 msec based on the direct effect model, whereas the PM patients with Css,max of 1664.7 ng/mL will have a QTc of 379 msec. The 4 msec difference in QTc resulted from 8-fold concentration difference would not have significant clinical relevance.

Genotype	Css, max (ng/mL)	$AUC_{0-\tau}$ (μg•hr/mL)
EM	325.1	2.07
UM	247.5	1.13
PM	1664.7	18.39

Model Qualification

For the population pharmacokinetic study, parameter sensitivity analysis was conducted to identify 95% confidence intervals of the parameters in the final population pharmacokinetic model. The results of this analysis are shown in the table and figure below.

Parameter	Parameter Estimate	Calculated 95% Confidence Interval
Rate of Absorption with food (1/hour)	0.679	(0.600, 0.772)
Rate of Absorption without food (1/hour)	0.926	(0.764, 1.14)
Apparent Clearance for EM Patients (L/hour)	17.4	(16.6, 18.6)
Apparent Clearance for PM Patients (L/hour)	1.96	(1.61, 2.40)
Apparent Clearance for UM Patients (L/hour)	31.8	(23.5, 43.1)
Apparent Volume of Distribution (L)	75.8	(68.8, 83.4)
Effect of Body Weight on Clearance	0.834	(0.671, 0.997)
Effect of Body Weight on Volume	0.947	(0.731, 1.17)
Effect of albumin on Clearance	-0.942	(-1.40, -0.486)

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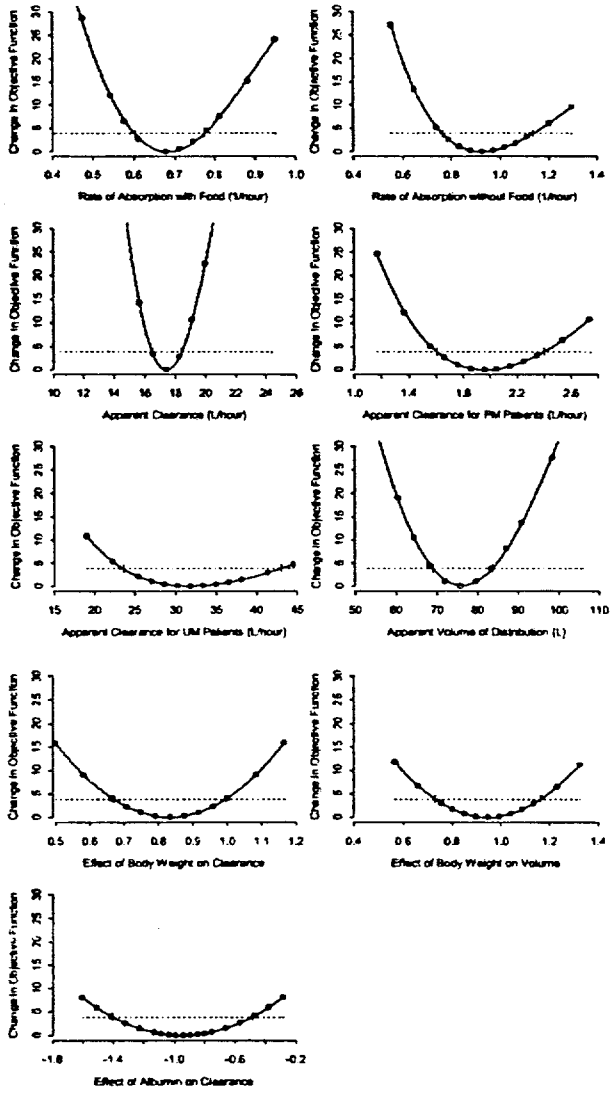

Another qualification procedure was the leverage analysis designed to evaluate the contribution or leverage of selected patients on the model. The procedure was performed twice with different subsets of the patients omitted. The parameter estimates from all runs were compared with the 95% confidence intervals calculated in the parameter sensitivity analysis. All parameter estimates were within the 95% confidence intervals. The results are summarized in the following table. The leverage analysis showed that all parameter estimates from the patient subsets were within the

Parameter	Range of Values Analysis I	Range of Values Analysis II
Rate of Absorption with food (1/hour)	(0.636, 0.702)	(0.645, 0.719)
Rate of Absorption without food (1/hour)	(0.849, 0.982)	(0.852, 0.986)
Apparent Clearance for EM Patients (L/hour)	(17.2, 17.7)	(17.1, 17.7)
Apparent Clearance for PM Patients (L/hour)	(1.88, 2.03)	(1.93, 2.03)
Apparent Clearance for UM Patients (L/hour)	(30.6, 35.4)	(30.1, 35.2)
Apparent Volume of Distribution (L)	(73.5, 78.2)	(73.8, 79.3)
Effect of Body Weight on Clearance	(0.766, 0.880)	(0.796, 0.879)
Effect of Body Weight on Volume	(0.891, 1.02)	(0.894, 0.994)
Effect of albumin on Clearance	(-1.14, -0.702)	(-1.11, -0.687)

95% confidence intervals. No subset of the patient population had an undue influence on the parameter estimates.

The final model was also evaluated using external qualification, which is the application of the developed model to a new dataset (validation dataset), from study B4Z-MC-LYAC. The final model parameters were held constant and used to predict the data for the validation dataset, and empirical Bayesian estimates of concentrations for each patient in the validation dataset were obtained. These empirical Bayesian predictions were compared to the actual observed concentrations. Agreement in the predicted and observed concentrations is shown in the following figure.

In addition, model parameters were estimated by refitting the final model to the validation dataset, and the parameter estimates compared with those obtained previously. The parameter estimates from the LYAC analysis were compared with the parameter estimates and 95% confidence intervals obtained previously in the combined analysis of HFBC/D/E/F/K and are shown in the table below. The %SE for the estimates in the LYAC analysis are greater due to fewer patients and observations than the combined analysis. It was also noted the inter-patient variability

Parameter	Study LYAC Parameter Estimate	Studies HFBC/D/E/F/K Parameter Estimate	95% Confidence Interval
Ka for fed patients	0.595	0.679	(0.600, 0.772)
Ka for fasted patients	0.572	0.926	(0.764, 1.14)
Clearance for EM patients	18.3	17.4	(16.6, 18.6)
Clearance for PM patients	2.51	1.96	(1.61, 2.40)
Clearance for UM patients	35.6	31.8	(23.5, 43.1)
Effect of Weight on Clearance	0.823	0.834	(0.671, 0.997)
Effect of Albumin on Clearance	-0.240	-0.942	(-1.40, -0.486)
Volume of Distribution	79.0	75.8	(68.8, 83.4)
Effect of Weight on Volume	0.814	0.947	(0.731, 1.17)

estimates for CL/F and V/F are higher for this analysis compared to the combined analysis. Most of the parameter estimates from the LYAC dataset are within the 95% confidence intervals of the combined analysis except for 4 parameters: Ka for fed patients, Ka for fasted patients, clearance for PM patients, and effect of albumin on clearance.

To further evaluate the differences in these parameters, 4 additional models were evaluated. In each of the 4 models, the parameter of interest was estimated while all of the other parameters remained fixed at the values obtained from the combined analysis. Comparison using the objective function of these 4 models to the model in which all parameters were fixed indicated

that Ka for fasted patients in LYAC was significantly different (MOF decrease of 12.205; p-value=0.0005) from the combined analysis estimate. The Ka for fed patients (MOF decrease of 0.391; p-value=0.53), the clearance for PM patients (MOF decrease of 1.228; p-value=0.27), and the effect of albumin on clearance (MOF decrease of 1.872; p-value=0.17) were not different from the combined analysis estimates.

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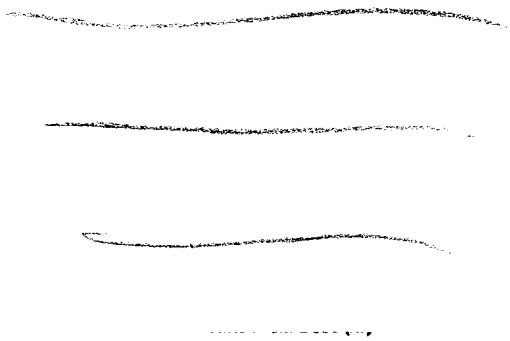
Discussion

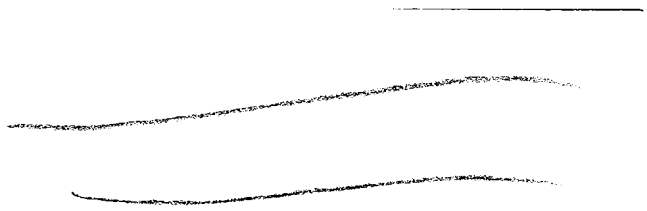
The validity of the results

For the population pharmacokinetic analysis, the model appeared to underpredict the observed values at higher plasma concentrations. The serial sampling data (samples at 0, 1, 2, 4, 8, 12, and 24 hours after dosing) from Study HFBC were used to evaluate the model fit of the overall plasma concentration-time profile within an individual patient.

The following figure shows a representative individual patient plots from Study HFBC. This evaluation suggested there was a bias in the model fit around the Cmax value and the Cmax was generally underpredicted (note the logrithemic scale of y-axis).



Because the population pharmacokinetic analysis was the basis for further PK/PD analysis and therefore was of importance, the reviewer attempted to improve the fit by using zero order absorption and by using combination of zero and first order absroption instead of first order. The control streams are listed in the Appendix. The agreement of the observed and predicted values of the models is shown in the following figues (left panel for zero order absorption and right panel for combination of the first and zero order).



As can be seen, not much improvement was achived. The reasons for this underprediction is not obvious.

The observed Cmax is underpredicted by about 44% on average. Therefore, if this model is used to simulate Cmax at a given dose, the simulated Cmax should be corrected for this bias. The geometric mean of the CL/F values predicted from the population model was compared to the mean clearance from the previous noncompartmental analysis of Study HFBC. Agreement between the means indicated that the model has predictive ability for CL/F. Since the PK/PD analysis for study LYAC

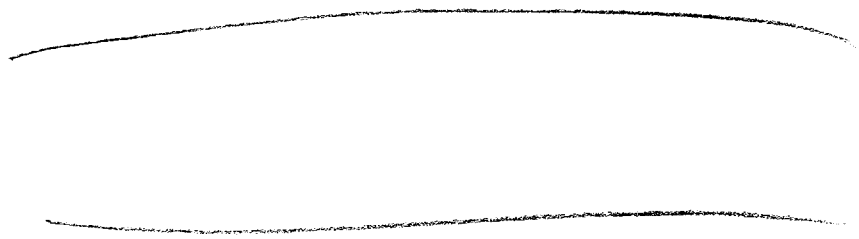
The significance of the results

The PK/PD analysis showed that the drug concentrations and the ADHDRS-IV-Parent:Inv total score are related. At the observed median AUCs for the atomoxetine 0.5 mg/kg/day, 1.2 mg/kg/day and 1.8 mg/kg/day groups, 62%, 78%, and 85% of the maximum improvement over baseline would be expected, respectively. Therefore, there appears to be a relationship between the concentrations and responses. As a concequence of this result, the factors significantly affecting drug concentrations should be considered for dose adjustments. For example, the body weight had a significant effect on atomoxetine disposition. The predicted effect of body weight on CL/F and V/F illustrated in the figure below indicates that as body weight increases, CL/F and V/F both increases nearly proportionally. Therefore, the weight based dosing is adopted.

On the other hand, poor metabolizer status had the largest effect on atomoxetine disposition of all the covariates evaluated. The final population model predicts CL/F is 9-fold lower in PMs compared to EMs resulting in increased exposure to atomoxetine at similar doses. The predicted mean concentrationn are shown in the following figure (right panel) for a 1 mg/kg twice daily dosing regimen.

However, the proposed label does not suggest adjustment of dosing regimen due to differences of CYP2D6 although the weight based dosing is recommended.

We can compare the two situations. The left panel of the following figure shows the predicted effect of body weight on atomoxetine plasma concentrations when a fixed 40-mg dosing regimen is used in children and adolescents. The right panel shows the predicted steady-state atomoxetine plasma concentrations over a 12-hour dosing interval in EM, PM, and UM after a 1 mg/kg twice daily dosing regimen. The profiles were notably different between patients of different body weights when the fixed dosing regimen was used. Therefore, it is demonstrated that weight-based dosing of atomoxetine is more appropriate than a fixed mg dosing regimen in child and adolescent patients, since weight-based dosing provides comparable exposures between patients of different body weights. By the same concept, the difference between EM and PM (the right panel) should be considered.



Based on this consideration, we recommend dose adjustment according to the CYP2D6 genotype of the patients.

Conclusions and Recommendations

Conclusions

The answers for each of the questions raised are provided below:

1. Is there a concentration to response relationship?

Yes. The modeling showed that the expected maximum improvement of ADHDRS-IV-Parent:Inv total scores from baseline would be –17.4 (compared to –6.2 for 8 weeks of placebo dosing). This

suggested an overall maximum benefit over placebo of –11.2. At the observed median AUCs for the atomoxetine 0.5 mg/kg/day, 1.2 mg/kg/day and 1.8 mg/kg/day groups, 62%, 78%, and 85% of the maximum improvement over baseline would be expected. Therefore, there appears to be a relationship between systemic exposure and effectiveness.

2. Is there a concentration– QTc prolongation relationship?

Yes. The direct model (using plasma concentrations as the coviarate) showed a significant improvement compared to the model without the coviarate. However, the correlation between the plasma concentrations and QTc prolongation is rather shallow.

3. Is there a necessity to adjust the dose based on the above relationships?

Dose adjustment needs consideration of both effectiveness and safety. The PK/PD analysis showed the relationship between the drug concentrations and effectiveness as measured by the primary variable the ADHDRS-IV-Parent:Inv total score. On the other hand, from a safety point of view, the concentration-QTc relationship is shallow. The current proposed labeling suggests weight-based dosing (0.5 to 1.2 mg/kg). The typical clearance for a 25 kg, 50 kg and 100 kg child according to the population pharamcokinetic model are listed in the following table.

Weight (kg)	Clearance (L/hr)	Fold increase compared to CL for 25 kg	Fold increase compared to AUC for 25 kg*
25	13.2	1	1
50	23	1.7	0.6
100	40	3	0.3

*the fold increase of AUC is calculated by taking the reciprical of fold increase compared to CL for 25 kg.

As can be seen, when the body weight is doubled, the AUC is decreased to 60% compared to the value for 25 kg, as the clearance is increased to about 1.7-fold. When the body weight is 4-fold higher (100 kg compared to 25 kg), the AUC is decreased to 33% as clearance is increased to about 3-fold. This indicates that a 1.7- to 3-fold difference, due to body weight, in clearance warranted a dose adjustment. Now, the final population model predicts CL/F is 9-fold lower in PM patients compared to EM patients resulting in increased exposure to atomoxetine at similar doses. Based on the same analogy as used for the body weight based dosing, the 9-fold lower clearance in PMs (i.e. 9-fold higher AUC) compared to EMs calls for dose adjustment. It is also noted that QT prolongation per se may not be of great safety concern, within the concentration range observed in PM patients. Hence we suggest the medical reviewers to take into consideration other dose related safety variables in order to recommend a more rational dosing regimen. It might be necessary to ensure that the dosing adjustment is consistent across prognostic factors (e.g. 40% drop in AUC for doubling the body weight versus 800% increase in AUC for PM patients over EM patients). Considering that the population predicted steady state C_{max} in PM patients is 5-fold higher than that in EM patients, we recommend a 5-fold dose reduction for PM pateints.

Labeling Recommendations

1. Adding a heading under **CLINICAL PHARMACOLOGY**, which reads:

2. Eliminating a paragraph under subheading Metabolism, which reads:

Comments to Medical Officers

Dose adjustment needs consideration of both effectiveness and safety. The PK/PD analysis showed the relationship between the drug concentrations and effectiveness as measured by the primary variable the ADHDRS-IV-Parent:Inv total score. On the other hand, from a safety point of view, the concentration-QTc relationship is shallow. The current proposed labeling suggests weight-based dosing (0.5 to 1.2 mg/kg). The typical clearance for a 25 kg, 50 kg and 100 kg child according to the population pharamcokinetic model are listed in the following table.

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Appendix

Population Pharmacokinetics Base Model Control Stream

```
$PROBLEM Tomoxetine CDEFK 1cmpt RUN=104
$INPUT PROJ,INV=DROP,ID,IP=DROP,VST=DROP,VSTP=DROP,
       VDTE=DROP,SMDT=DROP,SMTM=DROP,DSDT=DROP,DSTM=DROP,TMDY=DROP,
       TIME,TFDS,DV,CDV=DROP,NMDV=DROP,LNDV=DROP,
       DSMG=DROP,NDOS=DROP,AMT,DDI,II,ADDL,
       MDV,EVID,CMT,GEN,ORIG,AGEE,
       HTE=DROP,WTV,BSAV=DROP,BMI,SMOK=DROP,ALCO=DROP,
       CAFF=DROP,CMPL=DROP,AGEv=DROP,SUMV=DROP,GENO,GEN2=DROP,
       ALLE=DROP,ALL2,FOOD=DROP,CGCe=DROP,CGCL=DROP,TBI=DROP,
       ALBM=DROP,ALT=DROP,CREA=DROP,FPAT=DROP

$DATA cdefk13_V2.csv IGNORE=C
$SUBROUTINES ADVAN2 TRANS2
;Analyst: Mike Heathman
;Notes: eta on CL&V, prop_err, cond_inter, PM on CL, WTV(power) on CL,V

$PK
   PM=0
   IF (GENO.EQ.2) PM=1

   WVAL=WTV/35.3
   IF(WTV .EQ. 0) WVAL=1.0

   TVKA = THETA(1)
   KA   = TVKA

   TVCL1=  (1-PM)*THETA(2) + PM*THETA(3)
   TVCL =  TVCL1*(WVAL**THETA(5))
   CL   =  TVCL*EXP(ETA(1))

   TVV  =  THETA(4)*(WVAL**THETA(6))
   V    =  TVV*EXP(ETA(2))
   S2   =  V

$ERROR
 IPRED = F + 0.000001
 IRES = DV - IPRED
 IWRES = IRES/IPRED
 Y = F*EXP(EPS(1))

;INITIAL ESTIMATES
$THETA (0.1,0.7,2) ;ka(hr-1)
$THETA (1,20,100)  ;CL_EM(L/hr)
$THETA (1,5,100)   ;CL_PM
$THETA (10,75,300) ;V(L)
$THETA (0,0.1)       ;wtv_CL
$THETA (0,0.1)       ;wtv_V
$OMEGA 0.2         ;eta_CL
$OMEGA 0.2         ;eta_V
$SIGMA 0.5         ;err

$EST MAXEVAL=9000 PRINT=5 METH=1 INTER NOABORT
```

```
$COVARIANCE
$TABLE ID TIME TFDS IPRED IWRES WTV GENO CL V FILE=cdefk_base.tb
       NOPRINT ONEHEADER
```

Population Pharmacokinetics Final Model Control Stream

```
$PROBLEM Tomoxetine CDEFK 1cmpt RUN=601
$INPUT PROJ,INV=DROP,ID,IP=DROP,VST=DROP,VSTP=DROP,
       VDTE=DROP,SMDT=DROP,SMTM=DROP,DSDT=DROP,DSTM=DROP,TMDY=DROP,
       TIME,TFDS,DV,CDV=DROP,NMDV=DROP,LNDV=DROP,
       DSMG=DROP,NDOS=DROP,AMT,DDI,II,ADDL,
       MDV,EVID,CMT,GEN,ORIG=DROP,AGEE=DROP,
       HTE=DROP,WTV,BSAV=DROP,BMI=DROP,SMOK=DROP,ALCO=DROP,
       CAFF=DROP,CMPL=DROP,AGEv=DROP,SUMV=DROP,GENO,GEN2=DROP,
       ALLE=DROP,ALL2=DROP,FOOD,CGCe=DROP,CGCL=DROP,TBI=DROP,
       ALBM,ALT=DROP,CREA=DROP,FPAT=DROP

$DATA cdefk13_V2.csv IGNORE=C
$SUBROUTINES ADVAN2 TRANS2
;Analyst: Mike Heathman
;Notes: ALBM(power),WTV(power),PM,UM on CL; WTV(power) on V; FOOD on KA
;;Remove DDI,ORIG on CL; GEN on KA; CAFF,UM on V
;;Full Model: ALBM(power),UM,ORIG(=6),DDI(power) on CL,
;;             FOOD,GEN on KA, CAFF(=1),UM on V
;;       MOF: 22478.078
;;Base model: ETA on CL&V, prop_err, cond_inter, PM on CL, WTV(power)
on CL,V
;;       MOF: 22546.646

$PK
   PM=0
   IF (GENO.EQ.2) PM=1

   UM=0
   IF (GENO.EQ.3) UM=1

   I1=0
   IF(FOOD .EQ. 1) I1=1

   WVAL=WTV/35.3
   IF(WTV .EQ. 0) WVAL=1.0

   AVAL=ALBM/43.0
   IF(ALBM .EQ. 0) AVAL=1.0

   TVKA =  (1-I1)*THETA(1) + I1*THETA(9)
   KA   =  TVKA

   TVCL1   =   (1-UM)*(1-PM)*THETA(2)   +   (1-UM)*PM*THETA(3)   +   UM*(1-
PM)*THETA(4)
   TVCL2 = TVCL1*(WVAL**THETA(6))
   TVCL  = TVCL2*(AVAL**THETA(8))
   CL    = TVCL*EXP(ETA(1))

   TVV   = THETA(5)*(WVAL**THETA(7))
   V     = TVV*EXP(ETA(2))
```

```
   S2     = V

$ERROR
 IPRED = F + 0.000001
 IRES = DV - IPRED
 IWRES = IRES/IPRED
 Y = F*EXP(EPS(1))

;INITIAL ESTIMATES
$THETA (0.1,0.7,2) ;ka(hr-1)
$THETA (1,20,100)  ;CL_EM(L/hr)
$THETA (1,10,100)   ;CL_PM
$THETA (1,30,100)  ;CL_UM(L/hr)
$THETA (10,100,200) ;V(L)
$THETA (0,1,3)       ;wtv_CL
$THETA (0,1,3)       ;wtv_V
$THETA (-5,-1,0)      ;albm_CL
$THETA (0,1,5)       ;food_KA
$OMEGA 0.1          ;eta_CL
$OMEGA 0.1          ;eta_V
$SIGMA 0.5          ;err

$EST MAXEVAL=9000 PRINT=5 METH=1 INTER NOABORT
$COVARIANCE
$TABLE ID TIME TFDS IPRED IWRES GEN WTV GENO ALBM CL V FOOD
       FILE=cdefk_reduce.tb NOPRINT ONEHEADER
```

Study LYAC Pharmacokinetics Final Model Control Stream

```
$PROBLEM Tomoxetine LYAC final model RUN=001
$INPUT PROJ=DROP,GINV=DROP,INV=DROP,ID,IP=DROP,VST,VSTP=DROP,VDTE=DROP,
       SMDT=DROP,SMTM=DROP,TMDY=DROP,TIME,TFDS=DROP,

DV,CDV=DROP,NDV=DROP,LNDV=DROP,THER,DSMG=DROP,NDOS=DROP,NTDS=DROP,AMT,

DDI,II,ADDL,MDV,EVID,CMT=DROP,SSII=DROP,ASSY=DROP,LAB=DROP,REQN=DROP,

GEN,GEOC=DROP,ORIG=DROP,BRDT=DROP,AGEE=DROP,HTE=DROP,WTV,CRTN=DROP,ALBM
,

SYBP=DROP,DSBP=DROP,HRTR=DROP,GENO,ALLE=DROP,GEN2=DROP,ALL2=DROP,
       SIGN=DROP,NEUR=DROP,ATOT,AINA,AHYP,ACOU=DROP,

CSEV,CANX=DROP,CDEP=DROP,CREV=DROP,C_RT=DROP,C_EI=DROP,CTOT=DROP,COPP=D
ROP,
       CCOG=DROP,CHYP=DROP,CIND=DROP,FOOD

$DATA lyac_nm_19FEB01_v2.csv IGNORE=C
$SUBROUTINES ADVAN2 TRANS2
;Analyst: Darcie Kurtz
;Notes: Final Pop PK Model, Estimate parameters for LYAC

$PK
   PM=0
   IF (GENO.EQ.2) PM=1
```

```
   UM=0
   IF (GENO.EQ.3) UM=1

   I1=0
   IF(FOOD .EQ. 1) I1=1

   WVAL=WTV/36.7
   IF(WTV .EQ. 0) WVAL=1.0

   AVAL=ALBM/43.0
   IF(ALBM .EQ. 0) AVAL=1.0

   TVKA =  (1-I1)*THETA(1) + I1*THETA(9)
   KA   =  TVKA

   TVCL1   =   (1-UM)*(1-PM)*THETA(2)   +   (1-UM)*PM*THETA(3)   +   UM*(1-
PM)*THETA(4)
   TVCL2 = TVCL1*(WVAL**THETA(6))
   TVCL  = TVCL2*(AVAL**THETA(8))
   CL    = TVCL*EXP(ETA(1))

   TVV   = THETA(5)*(WVAL**THETA(7))
   V     = TVV*EXP(ETA(2))
   S2    = V

   AUC   = 1000*DDI/CL

$ERROR
 IPRED = F + 0.000001
 IRES = DV - IPRED
 IWRES = IRES/IPRED
 Y = F*EXP(EPS(1))

;INITIAL ESTIMATES
$THETA (0.1,0.7,2) ;ka(hr-1)
$THETA (1,20,100) ;CL_EM(L/hr)
$THETA (1,10,100)  ;CL_PM
$THETA (1,30,100)  ;CL_UM(L/hr)
$THETA (10,100,200) ;V(L)
$THETA (0,1,3) ;wtv_CL
$THETA (0,1,3) ;wtv_V
$THETA (-5,-1,0)   ;albm_CL
$THETA (0,1,5) ;food_KA
$OMEGA 0.1          ;eta_CL
$OMEGA 0.1          ;eta_V
$SIGMA 0.5         ;err

$EST MAXEVAL=9000 PRINT=5 METH=1 SIGD=2 INTER NOABORT
$COVARIANCE
$TABLE ID VST AUC IPRED IWRES ATOT AINA AHYP CSEV
       FILE=lyac_est_001.tb NOPRINT ONEHEADER
```

Combined Population Pharmacokinetics Study Model (using zero order absorption) Control Stream

```
$PROB XEVOENE PHARMACOKINETICS 1CM WITH ZERO ORDER ABSORPTION MODEL

$INPUT ID TIME AMT MDV EVID XCMT WTV GENO ALBM DV=CP II ADDL FOOD RATE
PROJ

$DATA ..\NOMEMzero.PRN IGNORE=#

$SUBROUTINES  ADVAN1 TRANS2

$PK
   PM=0
   IF (GENO.EQ.2) PM=1
   UM=0
   IF (GENO.EQ.3) UM=1
   I1=0
   IF (FOOD .EQ. 1) I1=1
   WVAL=WTV/35.3
   IF(WTV .EQ. 0) WVAL=1.0
   AVAL=ALBM/43.0
   IF(ALBM .EQ. 0) AVAL=1.0

   TVD1  = (1-I1)*THETA(1) + I1*THETA(9)
   D1    = TVD1*ETA(3)

   TVCL1 =(1-UM)*(1-PM)*THETA(2)+(1-UM)*PM*THETA(3)+UM*(1-PM)*THETA(4)
   TVCL2 = TVCL1*(WVAL**THETA(6))
   TVCL  = TVCL2*(AVAL**THETA(8))
   CL    = TVCL*EXP(ETA(1))

   TVV   = THETA(5)*(WVAL**THETA(7))
   V     = TVV*EXP(ETA(2))

   S1    = V

$ERROR

   Y = F*EXP(ERR(1))
   IPRE = F + 0.000001
   IRES = DV - IPRE
   IWRES = IRES/IPRE

$THETA (0,22,200)                ;1 D1
$THETA (1,17,100)               ;2 CL
$THETA (1,2,100)              ;3 CL
$THETA (0,50,100)               ;4 V2
$THETA (10,100,200)               ;5 V2
$THETA (0,1,3)              ;6 V2
$THETA (0,1,3)              ;7 WT ON V
$THETA (-5,-1,0)              ;8 V2
$THETA (0,1,5)              ;9 D1 WITH FOOD

$OMEGA
   0.2
   0.2
```

```
   0.2
$SIGMA
   0.5


$EST MAXEVAL=9999 PRINT=5 POSTHOC METH=1 INTER

$COV

$TABLE ID TIME D1 CL V Y AMT ETA(1) ETA(2)
IPRE IRES NOPRINT ONEHEADER FILE=1cmtbase.fit
```

Combined Population Pharmacokinetics Study Model (using the combination of zero order and first order absorption) Control Stream 1

```
$PROB XEVOENE PHARMACOKINETICS 1CM WITH ZERO FIRST COMBINATION ORDER
ABSORPTION MODEL

$INPUT ID TIME AMT xMDV xEVI CMT WTV GENO ALBM DV=CP II ADDL FOOD RATE
PROJ

$DATA ..\NOMEMcombine1.prn IGNORE=#

$SUBROUTINES  ADVAN2 TRANS2

$PK
   PM=0
   IF (GENO.EQ.2) PM=1
   UM=0
   IF (GENO.EQ.3) UM=1
   I1=0
   IF (FOOD .EQ. 1) I1=1
   WVAL=WTV/35.3
   IF(WTV .EQ. 0) WVAL=1.0
   AVAL=ALBM/43.0
   IF(ALBM .EQ. 0) AVAL=1.0

   TVKA  = (1-I1)*THETA(1) + I1*THETA(9)
   KA    = TVKA

   TVCL1 = (1-UM)*(1-PM)*THETA(2)+(1-UM)*PM*THETA(3)+UM*(1-PM)*THETA(4)
   TVCL2 = TVCL1*(WVAL**THETA(6))
   TVCL  = TVCL2*(AVAL**THETA(8))
   CL    = TVCL*EXP(ETA(1))

   TVV   = THETA(5)*(WVAL**THETA(7))
   V     = TVV*EXP(ETA(2))

   TVD2  = THETA(10)
   D2    = TVD2;*EXP(ETA(3))

   S2    = V

   F2    = THETA(11)
   F1    = 1-F2
```

```
$ERROR

   Y = F*EXP(ERR(1))
   IPRE = F + 0.000001
   IRES = DV - IPRE
   IWRES = IRES/IPRE

$THETA (0.5 FIX)                    ;1 KA
$THETA (1,20,100)                   ;2 CL EM
$THETA (1,2,100)                   ;3 CL PM
$THETA (0,50,100)                   ;4 CL UM
$THETA (10,100,200)                   ;5 V2
$THETA (0,1,3)                    ;6 WT ON CL
$THETA (0,1,3)                    ;7 WT ON V
$THETA (-5,-1,0)                    ;8 ALB ON CL
$THETA (0,1,5)                    ;9 KA WITH FOOD
$THETA (0,2.2,5)                    ;10 D2
$THETA (0,0.8,1)                    ;11 F2

$OMEGA
   0.1
   0.1
;    0.1

$SIGMA
   0.5

$EST MAXEVAL=9999 PRINT=5 POSTHOC METH=1 INTER

$COV

$TABLE ID TIME KA D2 CL V F1 F2 Y AMT ETA(1) ETA(2)
IPRE IRES NOPRINT ONEHEADER FILE=1cmtbase.fit
```

5.1.1 Combined Population Pharmacokinetics Study Model (using the combination of zero order and first order absorption) Control Stream 2

```
$PROB XEVOENE PHARMACOKINETICS 1CM WITH ZERO FIRST COMBINATION ORDER
ABSORPTION MODEL

$INPUT ID TIME AMT xMDV xEVI CMT WTV GENO ALBM DV=CP II ADDL FOOD RATE
PROJ

$DATA ..\NOMEMcombine1.prn IGNORE=#

$SUBROUTINES  ADVAN2 TRANS2

$PK
   PM=0
   IF (GENO.EQ.2) PM=1
   UM=0
   IF (GENO.EQ.3) UM=1
   I1=0
   IF (FOOD .EQ. 1) I1=1
   WVAL=WTV/35.3
```

```
   IF(WTV .EQ. 0) WVAL=1.0
   AVAL=ALBM/43.0
   IF(ALBM .EQ. 0) AVAL=1.0

   TVKA  = (1-I1)*THETA(1) + I1*THETA(9)
   KA    = TVKA

   TVCL1 = (1-UM)*(1-PM)*THETA(2)+(1-UM)*PM*THETA(3)+UM*(1-PM)*THETA(4)
   TVCL2 = TVCL1*(WVAL**THETA(6))
   TVCL  = TVCL2*(AVAL**THETA(8))
   CL    = TVCL*EXP(ETA(1))

   TVV   = THETA(5)*(WVAL**THETA(7))
   V     = TVV*EXP(ETA(2))

   TVD2  = THETA(10)
   D2    = TVD2;*EXP(ETA(3))

   S2    = V

   F2    = THETA(11)
   F1    = 1-F2

$ERROR

   Y = F*EXP(ERR(1))
   IPRE = F + 0.000001
   IRES = DV - IPRE
   IWRES = IRES/IPRE

$THETA (0,0.5,20)                ;1 KA
$THETA (1,20,100)               ;2 CL EM
$THETA (1,2,100)               ;3 CL PM
$THETA (0,50,100)               ;4 CL UM
$THETA (10,100,200)               ;5 V2
$THETA (0,1,3)                ;6 WT ON CL
$THETA (0,1,3)                ;7 WT ON V
$THETA (-5,-1,0)               ;8 ALB ON CL
$THETA (0,1,5)                ;9 KA WITH FOOD
$THETA (2.2 FIXED);,3)                ;10 D2
$THETA (0,0.8,1)               ;11 F2

$OMEGA
   0.1
   0.1
;   0.1

$SIGMA
   0.5

$EST MAXEVAL=9999 PRINT=5 POSTHOC METH=1 INTER

$COV

$TABLE ID TIME KA D2 CL V F1 F2 Y AMT ETA(1) ETA(2)
IPRE IRES NOPRINT ONEHEADER FILE=1cmtbase.fit
```

Study LYAE Pharmacokinetics Final Model Control Stream

```
$PROB XEVOENE LYAE PHARMACOKINETICS 1CM WITH ABSORPTION MODEL

$INPUT ID WTV AMT DOSE XTIM DROP=DATE TIME GEND GENO DV MDV

$DATA lyaepk3.prn IGNORE=#

$SUBROUTINES  ADVAN2 TRANS2

$PK
   PM=0
   IF (GENO .EQ.2) PM=1

   WVAL=WTV/70
   IF(WTV .EQ. 0) WVAL=1.0

   TVKA  = THETA(1)
   KA    = TVKA*EXP(ETA(1))

   TVCL1 = (1-PM)*THETA(2)+PM*THETA(3)
   TVCL  = TVCL1*(WVAL**THETA(4))
   CL    = TVCL*EXP(ETA(2))

   TVV   = THETA(5)*(WVAL**THETA(6))
   V     = TVV*EXP(ETA(3))

   S2    = V

$ERROR

   Y = F*EXP(ERR(1))
   IPRE = F + 0.000001
   IRES = DV - IPRE
   IWRES = IRES/IPRE

$THETA (0.1,0.7,5)                ;1 KA
$THETA (1,30,100)                 ;2 CL
$THETA (1,20,100)                 ;3 CL
$THETA (0,0.8,5)                  ;4 WT ON CL
$THETA (10,100,200)               ;5 V2
$THETA (0,0.7,5)                  ;6 WT ON V2


$OMEGA
   0.1
   0.1
   0.1

$SIGMA
   0.5


$EST MAXEVAL=9999 PRINT=5 POSTHOC METH=1 INTER

$COV
```

```
$TABLE ID TIME KA CL V Y AMT ETA(1) ETA(2)
ETA(3) IPRE IRES NOPRINT ONEHEADER FILE=1cmtlyaedate.fit
```

5.1.2 Study LYAE Alpha and Beta Estimation of QTc Model Control Stream

```
$PROB XEVOENE ECG MODEL WITH 1CM PHARMACOKINETICS WITH ABSORPTION

$INPUT ID AMT DATE=DROP TIME CONC SS II ADDL RR DV=QT IKA ICL IV MDV

$DATA ..\lyaeecg.prn IGNORE=#

$SUBROUTINES  ADVAN5

$MODEL ;NCOMP=3
       COMP=(DEPOT)
       COMP=(CENTRAL)
       ;COMP=(EFFECT)

$PK

   K12 = IKA
   CL  = ICL
   V2  = IV
   K20 = CL/V2
;   K23 = 0.01*K20

;   K30 = THETA(3)*EXP(ETA(3))
   S2  = V2
;   S3  = S2*K20/K30

$ERROR

;   CP=A(2)/S2
;   CE=A(3)/S3

   ALPH=THETA(1)*EXP(ETA(1))
   BETA=THETA(2)*EXP(ETA(2))
   Q=ALPH*RR**BETA

   Y = Q*EXP(ERR(1))

$THETA
   (0,350,2000)     ;ALPHA
   (0,0.186,10)     ;BETA
;   (0,0.1,10)       ; K30

$OMEGA
   0.09 0.09 ;0.09

$SIGMA
   0.0702

$EST MAXEVAL=9999 PRINT=5 POSTHOC METH=1 INTER

$COV
```

```
$TABLE ID TIME IKA ICL IV DV RR Y ALPH BETA
NOPRINT ONEHEADER FILE=lyaeecg1.fit
```

5.1.3 Study LYAE: Direct Effect Model Control Stream

```
$PROB XEVOENE ECG MODEL WITH 1CM PHARMACOKINETICS WITH ABSORPTION

$INPUT ID AMT DATE=DROP TIME CONC SS II ADDL RR DV=QT IKA ICL IV MDV

$DATA ..\lyaeecg.prn IGNORE=#

$SUBROUTINES  ADVAN5

$MODEL ;NCOMP=3
       COMP=(DEPOT)
       COMP=(CENTRAL)
       ;COMP=(EFFECT)

$PK

   K12 = IKA
   CL  = ICL
   V2  = IV
   K20 = CL/V2
   ;K23 = 0.01*K20

   ;K30 = THETA(3)*EXP(ETA(3))
   S2  = V2
   ;S3  = S2*K20/K30

$ERROR

   CP=A(2)/S2
   ;CE=A(3)/S3

   SLOP=THETA(3)*EXP(ETA(3))
   ALPH=THETA(1)*EXP(ETA(1))
   BETA=THETA(2)*EXP(ETA(2))
   Q=ALPH*RR**BETA+CP*SLOP

   Y = Q*EXP(ERR(1))

$THETA
   (0,350,2000)     ;ALPHA
   (0,0.186,10)     ;BETA
;   (0,0.1,10)      ; K30
   (0,0.1,2)       ; SLOP

$OMEGA
   0.09 0.09 0.09 0.09

$SIGMA
   0.0702

$EST MAXEVAL=9999 PRINT=5 POSTHOC METH=1 INTER

$COV
```

```
$TABLE ID TIME IKA ICL IV DV CP RR Y ALPH BETA SLOP
NOPRINT ONEHEADER FILE=lyaeecgcp1.fit
```

Study LYAE: Link Model Control Stream

```
$PROB XEVOENE ECG MODEL WITH 1CM PHARMACOKINETICS WITH ABSORPTION

$INPUT ID AMT DATE=DROP TIME CONC SS II ADDL RR DV=QT IKA ICL IV MDV

$DATA ..\lyaeecg.prn IGNORE=#

$SUBROUTINES  ADVAN5

$MODEL NCOMP=3
       COMP=(DEPOT)
       COMP=(CENTRAL)
       COMP=(EFFECT)

$PK

   K12 = IKA
   CL  = ICL
   V2  = IV
   K20 = CL/V2
   K23 = 0.01*K20

   K30 = THETA(3)*EXP(ETA(3))
   S2  = V2
   S3  = S2*K20/K30

$ERROR

   CP=A(2)/S2
   CE=A(3)/S3

   SLOP=THETA(4)*EXP(ETA(4))
   ALPH=THETA(1)*EXP(ETA(1))
   BETA=THETA(2)*EXP(ETA(2))
   Q=ALPH*RR**BETA+CE*SLOP

   Y = Q*EXP(ERR(1))

$THETA
   (0,350,1000)     ;ALPHA
   (0,0.286,10)     ;BETA
   (0,0.8,15)      ; K30
   (0,0.1,2)       ; SLOP

$OMEGA
   0.09 0.09 0.09 0.09

$SIGMA
   0.0702

$EST MAXEVAL=9999 PRINT=5 POSTHOC METH=1 INTER
```

```
$COV

$TABLE ID TIME IKA ICL IV DV RR Y ALPH BETA SLOP
NOPRINT ONEHEADER FILE=lyaeecgce1.fit
```

Bioavailability and Bioequivalence Studies

Study B4Z-LC-LYAM (Vol. 56): ***Absolute Bioavailability and the Effect of Maalox and Omeprazole Treatments on Relative Bioavailability***

Twenty healthy subjects (9 men and 11 women, 14 Caucasians, 5 Blacks, 1 Asian and 1 E/South E) aged 20 to 55 years, inclusive, who were extensive metabolizers of CYP2D6 participated in this study. Randomization and dosing schedule are shown below:

Group	Subject #	Period 1	Period 2	Period 3	Period 4
1	4, 8, 12, 15, 19	A	D	B	C
2	1, 2, 9, 14, 17	B	C	D	A
3	5, 6, 10, 11, 20	C	B	A	D
4	3, 7, 13, 16, 18	D	A	C	B

Treatment A: oral 1x40-mg atomoxetine capsule (Lot CT16543) under fasting condition
Treatment B: intravenous 20-mg dose atomoxetine (Lot CT16544, 10 mg/ml) infused over 20 minutes
Treatment C: oral 1x40-mg atomoxetine capsule (Lot CT16543) under fasting condition, administered approximately 24 hours after omeprazole (80 mg, MFG Lot # K4876) and 2 hours after a second dose of omeprazole (80 mg)
Treatment D: oral 1x40-mg atomoxetine capsule (Lot CT16543) under fasting condition, administered within approximately 10 minutes after 20 ml of Maalox antacid suspension (MFG Lot # 306648)

There was a minimum washout of at least 96 hours between each dose. Blood samples for the measurement of atomoxetine, 4-hydroxytomoxetine, and *N*-desmethylatomoxetine were collected after each of the treatments with atomoxetine prior to dosing, at the end of infusion (for iv only), then at 0.17, 0.34, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20, and 24 hours postdose. The samples were analyzed at [redacted] over the concentration ranges 0.25 to 2000 ng/ml for LY404363 (atomoxetine) and 1.0-800 ng/ml for 4-hydroxytomoxetine and *N*-desmethylatomoxetine.

Table 1. Values of Pharmacokinetic Parameters (Arithmetic Mean with %CV)

Parameter	C_{max} (ng/ml)	AUC_{inf} (μg.hr/ml)	CL/F (L/hr/kg)	V_z/F (L/kg)	T_{max} (h)	$t_{1/2}$ (h)
N=20			***Atomoxetine***			
40 mg Oral	326 (30)	1.80 (54)	0.36 (39)	1.82 (37)	1.0 (0.5-4.0)	3.7 (2.7-6.2)
20 mg IV	663 (22)	1.37(42)	0.22 (24)	1.09 (20)	0.3 (0.3-0.4)	3.6 (2.8-6.1)
40 mg + Omep	364 (29)	2.00 (59)	0.33 (38)	1.73 (32)	1.0 (0.5-4.0)	3.9 (3.0-7.9)
40 mg + Maalox	306 (31)	1.80 (50)	0.36 (40)	1.78 (33)	1.0 (0.5-4.0)	3.6 (2.7-5.4)
		AUC_{0-t}	***4-Hydroxyatomoxetine***			
40 mg Oral	3.1 (34)	0.018 (43)			2.0 (1.0-8.0)	N=18
20 mg IV	1.7 (25)	0.005 (75)			1.3 (0.5-4.3)	N=13
40 mg + Omep	3.2 (45)	0.017 (52)			1.8 (1.0-8.0)	N=20
40 mg + Maalox	3.6 (76)	0.018 (48)			2.0 (1.0-8.0)	N=20
N=20		AUC_{0-t}	***N-Desmethylatomoxetine***			
40 mg Oral	9.7 (52)	0.10 (78)			2.0 (1.0-12.0)	5.6 (2.6-17.0)
20 mg IV (N=18)	3.9 (81)	0.04 (122)			4.3 (0.7-8.3)	8.3 (4.7-17.0)
40 mg + Omep	4.3 (33)	0.04 (87)			1.7 (1.0-12.0)	6.3 (3.0-13.3)
40 mg + Maalox	9.9 (54)	0.10 (72)			4.0 (1.0-6.0)	6.8 (3.0-19.5)

Median with range for T_{max}, and mean with range for $t_{1/2}$.

Table 2. Atomoxetine Geometric Mean, Ratio of Geometric Mean (90% CI)

	C_{max}	AUC_{0-t}	AUC_{inf}
	(ng/ml)	(μg.hr/ml)	(μg.hr/ml)
40 mg Oral, A	312	1.60	1.63
(A/2xB)		**0.63 (0.59, 0.67)**	**0.63 (0.59, 0.67)**
20 mg IV, B	647	1.28	1.29
40 mg + Omep, C	346	1.75	1.79
(C/A)	**1.11 (0.99, 1.25)**	**1.09 (1.03, 1.16)**	**1.10 (1.03, 1.17)**
40 mg + Maalox, D	294	1.62	1.64
(D/A)	**0.94 (0.84, 1.06)**	**1.01 (0.95, 1.07)**	**1.01 (0.94, 1.07)**

Summary

- Absolute bioavailability of atomoxetine 40 mg capsule formulation was 63% compared with the 20 mg IV dose.
- Atomoxetine bioavailability (BA) was not affected by the coadministration of Maalox or omeprazole, the relative BA of atomoxetine in the presence of Maalox or omeprazole was 100% compared to atomoxetine administered alone.
- Measured metabolite concentrations in plasma were a low percentage (<5%) of atomoxetine.
- All doses of atomoxetine were well tolerated and no clinical relevant prolongation in the Fridericia QT_c intervals of the ECGs were seen.

B4Z-LC-LYAK (Vol. 58)*: *Atomoxetine Hydrochloride: Pilot Bioavailability Study in Poor Metabolizer Subjects

Eight healthy subjects (5 men and 3 women, all Caucasians) aged 20 to 55 years, inclusive, who were poor metabolizers of CYP2D6 participated in this study. Randomization and dosing schedule are shown below:

Group	Subject #	Period 1	Period 2	Period 3
1	1003, 1004, 1008	B	A	C
2	1001, 1006	C	B	A
3	1002, 1005, 1007	A	C	B

Treatment A: oral 1x40-mg atomoxetine market-image capsule (CT16530) under fasting condition
Treatment B: oral 2x20-mg atomoxetine capsule (CT16528) under fasting condition
Treatment C: intravenous 20-mg dose atomoxetine (CT16533, 10 mg/ml) infused over 20 minutes

There was a minimum washout of at least 13 days between each dose. Blood samples for the measurement of atomoxetine, 4-hydroxytomoxetine, and *N*-desmethylatomoxetine were collected after each of the treatments with atomoxetine prior to dosing, at the end of infusion (for iv only), then at 0.17, 0.34, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours postdose. The samples were analyzed at over the concentration ranges 0.25 to 2000 ng/ml for atomoxetine and 1.0-800 ng/ml for both 4-hydroxytomoxetine, and *N*-desmethylatomoxetine.

Table 1. Values of Pharmacokinetic Parameters (Arithmetic Means with %CV)

Parameter	C_{max} (ng/ml)	AUC_{inf} (µg.hr/ml)	CL/F (L/hr/kg)	V_z/F (L/kg)	T_{max} (h)	$t_{1/2}$ (h)
N=8			*Atomoxetine*			
40 mg Oral	564 (23)	14.5 (19)	0.035 (17)	1.02 (33)	6.0 (1.5-6.0)	20.2 (13.9-27.1)
2x20 mg Oral	533 (12)	15.0 (23)	0.035 (22)	1.04 (29)	4.0 (1.0-6.0)	21.2 (14.5-28.9)
20 mg IV	555 (21)	7.6 (21)	0.034 (19)	1.02 (28)	0.3 (0.3-0.4)	21.2 (14.8-30.6)
N=8		AUC_{0-t}	*N-Desmethylatomoxetine*			
40 mg Oral	83.4 (30)	6.06 (26)			24 (12-71)	78 (27-197)
2x20 mg Oral)	84.8 (31)	6.12 (29)			24 (12-72)	70.(28-168)
20 mg IV	40.2 (34)	2.97 (32)			36 (12-72)	47 (29-76)

Median with range for T_{max}, and mean with range for $t_{1/2}$. The extrapolated AUC for the metabolite was above 20% (40-50%).

Table 2. Atomoxetine Geometric Mean, Ratio of Geometric Mean (90% CI)

	C_{max} (ng/ml)	AUC_{0-t} (µg.hr/ml)	AUC_{inf} (µg.hr/ml)
40 mg Capsule, A	548,	13.3,	13.8
A/2xC			**0.94 (0.88, 0.99)**
2x20 mg Capsules, B	535	13.9	14.5
B/A	**0.98 (0.84, 1.13)**	**1.04 (0.99, 1.10)**	**1.05 (0.99, 1.11)**
20 mg IV, C			7.36,
B/2xC			**0.99 (0.93, 1.04)**

Summary

- Absolute bioavailability of atomoxetine 40 mg capsule formulation was 94% compared with the 20 mg IV dose in CYP2D6 poor metabolizers (PM).
- The 20 mg and 40 mg capsule formulations are bioequivalent in CYP2D6 PM subjects at equivalent doses.
- Plasma concentration values for 4-hydroxyatomoxetine were all below the limit of quantitation. Measured *N*-desmethylatomoxetine metabolite concentrations in plasma were a low percentage of atomoxetine in CYP2D6 PM subjects. However, the exposure to the metabolite is not low compared to the parent drug (C_{max} ~15% and AUC ~40%).
- All doses of atomoxetine were well tolerated and no clinical relevant prolongation in the Fridericia QT_c intervals of the ECGs were seen.

B4Z-LC-HFBG (Vol.58-60): Atomoxetine Hydrochloride Relative Bioavailability Study

Twenty-five healthy subjects (14 men and 11 women, 23 Caucasians, 1 Black, and 1 Hispanic) aged 20 to 55 years, inclusive, who were extensive metabolizers of CYP2D6 participated in this study. Randomization and dosing schedule are shown below:

Group	Period 1	Period 2	Period 3	Period 4	Period 5
1	B	E	D	C	A
2	B	E	D	A	C
3	E	D	B	C	A
4	E	D	B	A	C

Group	Period 1	Period 2	Period 3	Period 4	Period 5
5	D	B	E	C	A
6	D	B	E	A	C

Atomoxetine hydrochloride single dose under fasting condition:
Treatment A - 1x5 mg capsule (CT14743)
Treatment B - 2x20 mg capsules (CT14744)
Treatment C - 2x2.5 tablets (CT14745)
Treatment D - 1x40-mg tablet (CT14750)
Treatment E - 40 mg aqueous solution (powder CT14744 to prepare solution in 20 ml of water)

Each subject was randomly assigned to one of six sequences to receive a single dose of atomoxetine on five separate occasions. There was a minimum washout of at least 96 hours between each dose. Blood samples for the measurement of atomoxetine, 4-hydroxytomoxetine, and *N*-desmethylatomoxetine were collected after each of the treatments with atomoxetine prior to dosing, then at 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 15, 18, 21, and 24 hours postdose. The samples were analyzed at _____ over the concentration ranges 0.25 to 2000 ng/ml for atomoxetine and 1.0-800 ng/ml for both 4-hydroxytomoxetine, and *N*-desmethylatomoxetine. Lower ranges (0.25-25 ng/ml for atomoxetine, 1.0-100 ng/ml for both metabolites) were also used.

Table 1. Values of Pharmacokinetic Parameters (Arithmetic Means with %CV)

Parameter	C_{max} (ng/ml)	AUC_{inf} (µg.hr/ml)	CL/F (L/hr/kg)	V_z/F (L/kg)	T_{max} (h)	$t_{1/2}$ (h)
N=20			***Atomoxetine***			
40 mg Solution	325 (30)	1.61 (64)	0.46 (42)	2.44 (40)	0.5 (0.5-6.0)	4.0 (2.6-9.1)
2x20 mg capsule	323 (25)	1.62 (63)	0.46 (42)	2.44 (36)	1.0 (0.5-4.0)	4.0 (2.7-9.0)
40 mg Tablet	286 (45)	1.52 (60)	0.49 (45)	2.59 (37)	1.0 (0.5-4.0)	4.0 (2.2-8.0)
5 mg capsule	42 (41)	0.19 (66)	0.49 (39)	2.50 (38)	1.0 (0.5-2.0)	4.0 (1.5-12.4)
2x2.5 mg tablet	36 (29)	0.17 (67)	0.53 (41)	2.72 (44)	1.0 (0.5-1.5)	3.9 (1.7-7.2)
			4-Hydroxyatomoxetine			
40 mg Solution	3.69 (52)	0.033 (30)			1.8 (1.0-6.0)	5.9 (2.2-16.2)
2x20 mg capsule	3.65 (34)	0.033 (28)			2.0 (1.0-6.0)	6.1 (3.1-14.6)
40 mg Tablet	3.19 (40)	0.032 (24)			2.0 (0.5-6.0)	6.4 (3.0-13.8)
			N-Desmethylatomoxetine			
40 mg Solution	10.8 (81)	0.161 (176)			1.5 (0.5-10.0)	6.3 (2.4-25.6)
2x20 mg capsule	10.5 (74)	0.145 (170)			1.5 (1.0-6.0)	5.9 (2.4-27.3)
40 mg tablet	10.1 (93)	0.133 (145)			1.5 (1.0-6.0)	6.2 (2.4-15.4)

Median with range for T_{max} and Mean with range for $t_{1/2}$.

Table 2. Atomoxetine Geometric Mean, Ratio of Geometric Mean (90% CI)

	C_{max} (ng/ml)	AUC_{0-t} (µg.hr/ml)	AUC_{inf} (µg.hr/ml)
40 mg solution, E	308	1.37	1.40
2x20 mg capsule, B	308	1.38	1.40
(Cap/Sol)	**1.00 (0.90, 1.12)**	**1.01 (0.93, 1.08)**	**1.01 (0.93, 1.08)**
40 mg Tablet, D	259	1.29	1.31
(Tab/Sol)	**0.84 (*0.75*, 0.94)**	**0.94 (0.87, 1.01)**	**0.94 (0.87, 1.01)**
(Tab/Cap)	**0.84 (*0.75*, 0.94)**	**0.93 (0.87-1.01)**	**0.93 (0.87-1.00)**
2x2.5 mg Tablet, C	35.6	0.15	0.16
5 mg Capsule, A	39.6	0.16	0.17
(Tab/Cap)	**0.90 (0.82, 0.98)**	**0.94 (0.90, 0.98)**	**0.93 (0.90, 0.97)**

Table 3. Inter- and Intrasubject Coefficient of Variation (CV) Estimates of Atomoxetine

Parameter	p-Value for Hypothesis of Equal Variances and Equal Correlations	Intersubject CV (%)	Intrasubject CV (%)
C_{max}	0.15	25.4	20.6
AUC_{0-t}	0.12	46.0	13.9
AUC_{inf}	0.054	48.3	13.8

Summary

- The relative bioavailability of the atomoxetine capsule formulation was 100% compared with the oral solution.
- Atomoxetine 40 mg tablet formulation had a slower rate, but a similar extent of bioavailability, compared with the capsule and oral solution formulations.
- Atomoxetine 2x2.5 mg tablets had similar bioavailability compared with 5 mg capsules.
- Measured metabolite concentrations in plasma were a low percentage of atomoxetine.
- Atomoxetine plasma concentration increased proportionally with dose between 5 and 40 mg doses.
- Moderate intersubject variability (48%) and low intrasubject variability (14% was observed for AUC_{inf} parameter.
- The 40 mg doses of atomoxetine were associated with orthostatic blood pressure decreases and a corresponding heart rate increase.

B4Z-LC-LYAL (Vol. 60-61): Atomoxetine Hydrochloride: Pivotal Bioequivalence and Food Effects Study

Primary objectives were (1) to evaluate the bioequivalence of the market-image 40 mg capsule formulation and the phase II 20 mg capsule formulation, and (2) to evaluate the effect of a standardized high-fat meal on the bioavailability of the 40 mg capsule formulation.

Twenty-five healthy subjects (17 men and 8 women, 23 Caucasians, 2 Blacks) aged 18 to 55 years, inclusive, who were extensive metabolizers of CYP2D6 participated in this study. Randomization and dosing schedule are shown below:

Group	Subject #	Period 1	Period 2	Period 3
1 (n=8)	6, 8, 11, 12, 16, 20, 21, 23	A	B	C
2 (n=8)	4, 7, 9, 10, 14, 15, 19, 24	B	C	A
3 (n=8)	1, 2, 3, 5, 13, 17, 18[a], 22	C	A	B

[a] This subject discontinued after the first treatment period and was placed by Subject 25.

Atomoxetine hydrochloride single dose:
Treatment A - 1x40 mg market-image capsule (CT16527) under fasting condition
Treatment B - 2x20 mg Phase II capsules (CT16526) under fasting condition
Treatment C - 1x40 mg market-image capsule (CT16527) immediately after the ingestion of a standardized high-fat meal.

There was a minimum washout of at least 96 hours between each dose. Blood samples for the measurement of atomoxetine, 4-hydroxytomoxetine, and *N*-desmethylatomoxetine were collected after each of the treatments with atomoxetine prior to dosing, then at 0.17, 0.34, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20, and 24 hours postdose. The samples were analyzed at [redacted] over the concentration ranges 2.5 to 2000 ng/ml and 0.25 to 25 ng/ml for atomoxetine.

Table 1. Values of Atomoxetine Pharmacokinetic Parameters (Arithmetic Means with %CV)

Parameter	C_{max} (ng/ml)	AUC_{inf} (µg.hr/ml)	CL/F (L/hr/kg)	V_z/F (L/kg)	T_{max} (h)	$t_{1/2}$ (h)
N=24						
40 mg (fasted)	333 (39)	2.11 (90)	0.35 (42)	1.77 (27)	1.0 (0.5-4.0)	4.2 (2.3-13.2)
2x20 mg (fasted)	367 (37)	2.20 (89)	0.33 (440	1.70 (31)	1.0 (0.5-4.0)	4.1 (2.4-10.8)
40 mg (fed)	210 (40)	2.05 (85)	0.35 (42)	1.95 (33)	4.0 (0.5-12.0)	4.4 (2.6-12.5)

Median with range for T_{max} and Mean with range for $t_{1/2}$.

Table 2. Atomoxetine Geometric Mean, Ratio of Geometric Mean (90% CI)

		C_{max} (ng/ml)	AUC_{0-t} (µg.hr/ml)	AUC_{inf} (µg.hr/ml)
40 mg (fasted), A		313	1.67	1.73
2x20 mg (fasted), B		346	1.76	1.81
	A/B	**0.91 (0.80, 1.02)**	**0.95 (0.91, 0.99)**	**0.95 (0.92, 0.99)**
40 mg (fed), C		199	1.62	1.70
	C/A	**0.63 (0.56, 0.71)**	**0.97 (0.93, 1.02)**	**0.98 (0.94, 1.03)**

Summary

- The 20 mg (Phase II) and 40 mg (market image) capsule formulations are bioequivalent when administered under fasting conditions at the same 40 mg dose.
- Food affects the absorption rate (T_{max} prolonged 3 hours, C_{max} decreased 37%), but not the extent, of atomoxetine bioavailability.
- The frequency of adverse events, except dizziness, was reduced during the administration of atomoxetine with food.
- Atomoxetine single dose treatments of 40 mg were safe and well-tolerated. A few individuals showed an increased QT_c interval >30 msec (one had a change >60 msec). All QT_c intervals were ≤450 msec.

B4Z-LC-LYAZ (Vol. 61-62): Atomoxetine Hydrochloride: 60-mg Bioequivalence and Food Effects Study

Primary objectives were to evaluate (1) the bioequivalence of the market-image 40 mg capsule formulation and the Phase III capsule formulation, (2) the effect of a standardized high-fat meal on the bioavailability of the 60 mg capsule formulation and, (3) the safety of 60 mg single dose of atomoxetine in healthy men and women.

Fifty-eight healthy subjects (26 men and 32 women, 54 Caucasians, 4 Blacks) aged 18 to 55 years, inclusive, who were extensive metabolizers of CYP2D6 participated in this study. Randomization and dosing schedule are shown below:

Group	Period 1	Period 2	Period 3
1 (n=20)	A	B	C
2 (n=20)	B	C	A
3 (n=20)	C	A	B

Atomoxetine hydrochloride single dose:
Treatment A - 1x60 mg market-image capsule (CT18408) under fasting condition
Treatment B - 1x20 mg (CT18808) +1x40 mg (CT18807) Phase III capsules under fasting condition
Treatment C - 1x60 mg market-image capsule (CT18408) immediately after the ingestion of a standardized high-fat meal.

There was a minimum washout of at least 96 hours between each dose. Blood samples for the measurement of atomoxetine, 4-hydroxytomoxetine, and *N*-desmethylatomoxetine were collected after each of the treatments with atomoxetine prior to dosing, then at 0.34, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours postdose. The samples were analyzed at [redacted] over the concentration ranges 2.5 to 2000 ng/ml and 0.25 to 25 ng/ml for atomoxetine.

Table 1. Values of Atomoxetine Pharmacokinetic Parameters (Arithmetic Means with %CV)

Parameter	C_{max} (ng/ml)	AUC_{inf} (µg.hr/ml)	CL/F (L/hr/kg)	V_z/F (L/kg)	T_{max} (h)	$t_{1/2}$ (h)
N=58						
60 mg (fasted)	529 (34)	3.02 (81)	0.39 (49)	1.87 (37)	0.9 (0.5-6.0)	3.8 (1.7-9.6)
20+40 mg (fasted)	550 (44)	2.84 (93)	0.46 (79)	2.42 (88)	1.0 (0.5-6.0)	4.0 (2.1-16.1)
60 mg (fed)	347 (54)	2.79 (75)	0.41 (47)	2.12 (52)	4.0 (0.5-16.0)	4.1 (2.0-16.6)

Median with range for T_{max} and mean with range for $t_{1/2}$.

Table 2. Atomoxetine Geometric Mean, Ratio of Geometric Mean (90% CI)

		C_{max} (ng/ml)	AUC_{0-t} (µg.hr/ml)	AUC_{inf} (µg.hr/ml)
60 mg (fasted), A		500	2.38	2.44
20+40 mg (fasted), B		488	2.13	2.18
	A/B	**1.02 (0.93, 1.13)**	**1.12 (1.03, 1.22)**	**1.12 (1.03, 1.21)**
60 mg (fed), C		311	2.24	2.35
	C/A	**0.62 (0.57, 0.68)**	**0.94 (0.90, 0.99)**	**0.96 (0.92, 1.01)**

Summary

- The 1x20 mg plus 1x40 mg (Phase III) and 60 mg (market image) capsule formulations are bioequivalent when administered under fasting conditions at the same 60 mg dose.
- Food affects the absorption rate (T_{max} prolonged 3 hours, Cmax decreased by 38%), but not the extent, of atomoxetine bioavailability.
- The frequency of adverse events was reduced during the administration of atomoxetine with food.
- There were brief syncopal episodes experienced by 2 subjects (1 fasted and 1 fed).
- There were no clinically relevant changes pre- and postdose in $QT_{c\ (F)}$ intervals and no subjects had a $QTC_{(F)}$ greater than or equal to 450 msec.

and binding was determined using
The concentration ranges evaluated were 150 to 3000 ng/ml for ^{12}C-atomoxetine and ^{14}C-*N*-desmethylatomoxetine and 15 to 1500 ng/ml for 4-hydroxyatomoxetine.

Table 1. Percent Plasma Protein Bound (Mean±SEM)

Species	Human	Beagle Dog			Fischer 344 Rat			B6C3F1 Mouse
Age		Adult	12-Week	8-Week	Adult	28-Day	10-Day	
Atomoxetine	98.3±0.3	97.0±0.1,	96.0±0.2,	96.6±0.4	88.5±0.2,	82.6±1.0,	76.0±0.9	79.7±1.0
N-Desmethyl-	99.1±0.1	98.2±0.2,	97.5±0.4,	97.5±0.2	89.5±0.7,	86.2±0.2,	NA	83.6±0.9
4-Hydroxy-	66.6±0.3	60.0±3.6,	59.2±0.7,	58.3±1.4	55.3±1.0,	47.6±0.8,	47.1±0.6	62.6±0.2

Table 2. Recovery of Radioactivity from Krebs-Ringer Solution (Mean±SEM, N=4)

	% Recovery				
Concentration	15 ng/ml	150 ng/ml	500 ng/ml	1500 ng/ml	3000 ng/ml
N-Desmethyl-	NA	91.8±0.3	95.9±1.6	96.2±1.4	95.2±0.3
4-Hydroxy-	93.5±0.8	95.0±2.2	99.4±2.9	101.8±4.2	NA

Summary

- Human plasma protein binding are approximately 98% for atomoxetine, 99% for *N*-desmethylatomoxetine and 67% for 4-hydroxyatomoxetine.
- Although the extent of plasma protein binding varied among species, the relative binding rank order of atomoxetine and its two metabolites was similar across species: *N*-desmethylatomoxetine>atomoxetine>4-hydroxyatomoxetine.
- Differences (10 to 15%) in plasma protein binding were observed between adult and young rat plasma with atomoxetine and its two metabolites. Maturity appeared to have little effect on plasma protein binding in the dog.

ADME Report 50: ***In Vitro Protein Binding of ^{14}C-Atomoxetine to Purified Human Plasma and Interaction Studies with ^{14}C-Warfarin, ^{14}C-Acetylsalicylic Acid, ^{14}C-Phenytoin, ^{3}H-Desipramine, ^{14}C-Diazepam, ^{3}H-Paroxetine, and Midazolam in Human Plasma***

The objectives of this study were to identify the protein primarily responsible for the binding of atomoxetine in plasma, and to evaluate the potential for atomoxetine to interact with other drugs that are highly bound to plasma protein.

Table 1. Atomoxetine Percent Protein Binding (Mean±SEM, n=3) to Albumin, α_1-Acid Glycoprotein and Immunoglobulin G (IgG)

	Fraction of ^{14}C-Atomoxetine Bound to Protein		
^{14}C-Atomoxetine (ng/ml)	Albumin (417 mg)	α_1-Acid Glycoprotein (9.93 mg)	IgG (116.4 mg)
	Dissolved in 10 mL Krebs-Ringer Buffer, pH 7.4 to provide physiological levels		
3000	97.3±0.24	64.9±0.12	13.2±0.28
1500	97.4±0.03	78.2±0.30	16.3±3.15
500	97.8±0.15	83.2±0.30	14.3±0.27
150	97.3±0.17	82.7±0.60	14.3±1.36
Mean±SEM	**97.5±0.09**	**76.7±2.11**	**14.5±0.81**

Table 2. Percent Protein Binding (Mean±SEM, n=3) in the Presence of Interacting Drugs

Therapeutic Drug Level	Interacting Drug		^{14}C-Atomoxetine[b]
	Without Atomoxetine	with Atomoxetine	3000-3500 ng/ml
Control			97.7±0.14
^{14}C-ASA[a] (20 µg/ml)	89.6±0.17	89.4±0.15	98.0±0.01
^{3}H-Desipramine (100 ng/ml)	67.9±6.70	68.8±6.46	97.7±0.26
^{14}C-Diazepam (384 ng/ml)	97.5±0.46	96.0±0.10	97.6±0.39
Midazolam (50 ng/ml)	ND[C]	ND	98.2±0.08
^{3}H-Paroxetine (75 ng/ml)	89.3±0.97	87.3±0.66	97.2±0.28
^{14}C-Phenytoin (12 µg/ml)	83.8±0.47	82.0±0.63	98.0±0.12
^{14}C-Warfarin (2.2 µg/ml)	97.8±0.49	98.4±0.10	97.9±0.49

[a]. ^{14}C-Acetylsalicylic Acid, [b]Interacting drugs were not radiolabeled, [C]Not determined.

Table 3. Percent Protein Binding (Mean±SEM, n=3) at Different ASA Concentrations

ASA (µg/ml)	10	20	100	300	500
Atomoxetine % Bound	97.6±0.08	97.9±0.04	97.5±0.35	96.1±0.35	93.4±1.19

ASA-Acetylsalicylic Acid

Summary

- Atomoxetine was most highly bound to albumin (97.5%) and, to a lesser extent, bound to α_1--acid glycoprotein (76.7%) and IgG (14.5%).
- At therapeutic concentrations, acetylsalicylic acid, desipramine, diazepam, midazolam, paroxetine, phenytoin, and warfarin have no effect on the plasma protein binding of atomoxetine.
- Atomoxetine, at therapeutic concentrations, does not affect the plasma protein binding of acetylsalicylic acid, desipramine, diazepam, paroxetine, phenytoin, and warfarin.
- Acetylsalicylic acid at toxic concentrations (>300 µg/ml) can reduce the plasma protein binding of atomoxetine resulting in an approximately 3-fold increase in the fraction of unbound atomoxetine.

Metabolism Study Reports Using Hepatocytes and Microsomes (Vol. 62-63)

ADME Report 08: *In Vitro Metabolism of Atomoxetine by Rat, Mouse, Dog, Monkey and Human Liver Microsomes*

The present study was conducted to determine the *in vitro* metabolism of atomoxetine by Fischer 344 rat, CD-1 mouse, beagle dog, cynomolgus monkey and human liver microsomes. Also, the *in vitro* metabolism with human microsomes that were partially or totally deficient in CYP2D6 was studied. Liver microsomes were prepared by differential centrifugation. Protein concentrations of the microsomes were determined by Lowry method:

Procedure - 100 mM sodium phosphate (pH 7.4), 2 mM final concentration NADPH and 1 mg/ml final concentration of microsomal protein were added on ice to a volume of 0.495 ml. The mixture was pre-incubated for 3 minutes at 37°C in a shaking water bath. The reaction was

initiated by adding 0.005 ml of substrate (5 mM ^{14}C-LY139603, atomoxetine hydrochloride as free-base); final concentration of the substrate was 0.05 mM. The reaction was allowed to proceed in the shaking water bath for 1 hour at 37°C. The reaction was terminated by the addition of 0.5 ml of cold acetonitrile. Controls included samples without NADPH and samples without substrate.

Atomoxetine and several metabolites were observed in the ——— profile of the microsomal extract from each species. Structure elucidation was performed using ——— as well as proton and carbon-13 NMR analysis.

Table 1. Metabolites Identified in Hepatic Microsomal Incubations with ^{14}C-Atomoxetine

Metabolite	Rat	Monkey	Mouse	Dog	Human
Putative *N*-desmethyl-hydroxy-A				—	—
4'-Hydroxy-Atomoxetine	*	*	*	*	*
2'-Hydroxymethyl-Atomoxetine					
N-Desmethyl-Atomoxetine					
Total (% of dose)	95.4	78.3	68.9	60.3	63.6

* -indicates major metabolite.

Summary

- Radioprofiling of the microsomal incubations showed that atomoxetine was extensively metabolized by Fischer rat and cynomolgus monkey liver microsomes, while only moderately metabolized by CD-1 mouse, human and beagle dog liver microsomes.
- The metabolism of atomoxetine by the liver microsomes of five species was very similar. The major metabolite produced by hepatic microsomes of all five species was identified as 4-hydroxyatomoxetine (LY424478).
- All five species produced minor amount of *N*-desmethylatomoxetine (LY137877) and 2'-hydroxymethylatomoxetine (LY415973). The only metabolic difference observed between the five species was that dog and human liver microsomes did not produce any detectable quantities of the putative *N*-desmethyl-hydroxyatomoxetine metabolite.
- Based on the structures of the identified metabolites, three metabolic pathways were identified for atomoxetine: aromatic hydroxylation, alkyl hydroxylation, and *N*-demethylation.
- The formation of 4-hydroxyatomoxetine (aromatic hydroxylation) was substantially reduced in microsomes with low levels of CYP2D6 and completely absent in microsomes deficient of CYP2D6. Thus, CYP2D6 plays a central role in aromatic hydroxylation of atomoxetine.

ADME Report 22: *In Vitro Metabolism of Atomoxetine by Cultured Human Precision-Cut Liver Slices*

Viable human liver tissue was obtained from two donors free of liver pathology or other disease. The liver tissue was transported on ice in the ——— organ preservation solution and slices were prepared within approximately 50 and 28 hours of cold-perfusion for donors HH553 and HH584, respectively.

Procedure - Upon arrival of the donor liver tissue, cylindrical tissue cores were made (8 mm diameter). Then they were sliced to a thickness of approximately 200 to 250 µm, and the slices (two per vial) were floated onto titanium screen inserts inside Teflon rollers. The rollers were blotted and placed in 20 ml scintillation vials containing 1.7 ml media with or without ^{14}C-atomoxetine. The vials were sealed with a cap having a hole of approximately 2 mm in diameter to allow gas exchange and were placed in a dynamic roller culture incubator at 37°C, under an atmosphere of 95% O_2/5% CO_2 at a flow rate of 0.5 L/min. Metabolism was determined at 6 hours and 24 hours. At these times, vials were removed from the dynamic roller culture incubator. The slices were weighed and sonicated in their medium and were quick frozen on dry ice. Homogenates were maintained at –70°C prior analysis.

7-Ethoxycoumarin metabolism was used as a positive control to demonstrate the metabolic capacity of the human liver slice preparations. 7-Ethoxycoumarin is metabolized by cytochromes P450 to 7-hydroxycoumarin, which is then available for conjugation via *O*-glucuronidation or *O*-sulfation reactions.

Table 1. Metabolism of 7-Ethoxycoumarin by Human Precision-Cut Liver Slice (Mean±SE)

	Metabolite Formation (nmol/g liver)*			
Donor	7-HC**	7-HC-glucuronide	7-HC-sulfate	Total
HH553 (male, 66 yrs)	ND	62.6±6.7	61.5±4.5	124.1±6.9
HH584 (female, 56 yrs)	6.7±2.9	103.9±14.1	111.6±19.8	222.2±31.6

*Single slices (n=3) were incubated with 50 µM 7-ethoxycoumarin for 3 hours at 37°C. **7-HC = 7-hydroxycoumarin.

Table 2. Estimation of the Amount of Atomoxetine and Its Metabolites Present in Liver Slice Preparation

Metabolite	50 µM		250 µM		50 µM		250 µM	
	6 hr	24 hr	6 hr	24 hr	6 hr	24 hr	6 hr	24 hr
% of Total Radioactivity	Adult Male Liver				Adult Female Liver			
4-hydroxy-Atomoxetine	10.5	13.2	4.8	7.4	3.3	10.6	2.4	1.9
N-desmethyl-Atomoxetine	1.6	1.3	0.6	2.0	1.0	1.5	1.9	1.9
4-hydroxy-*N*-desmethyl-A-*O*-glucuronide	1.3	1.7	1.7	2.2	2.6	3.0	2.9	9.2
4-hydroxy-A-*O*-glucuronide	25.1	55.5	3.4	7.1	23.6	54.3	5.9	9.6
Atomoxetine	71.8	23.4	86.4	67.3	46.7	27.8	66.5	77.9

Summary

- The metabolic profiles with the human liver slices confirmed that the Phase I and Phase II metabolic capacities were well-maintained in the slice preparations from both liver donors.
- In these preparations, six atomoxetine-related metabolites were identified.
- The predominant metabolite produced by human liver slices, as well as slices from each of the other species evaluated, was identified as 4-hydroxyatomoxetine-*O*-glucuronide. Minor metabolites included 4-hydroxyatomoxetine, 2-hydroxymethylatomoxetine, *N*-desmethylatomoxetine, 4-hydroxy-*N*-desmethyl atomoxetine (LY440035), and 4-hydroxy-*N*-desmethylatomoxetine-*O*-glucuronide.
- Based on the structures of the identified metabolites, three oxidative (phase I) metabolic pathways are proposed for the biotransformation of atomoxetine in human liver slices: aromatic ring-hydroxylation, benzylic/aliphatic oxidation, and *N*-demethylation.

- Subsequent O-glucuronidation of the hydroxylated metabolites was the only conjugation (phase II) pathway to participate in the formation of atomoxetine-related metabolites in human liver slices.

ADME Report 01: ***In Vitro Interaction of Atomoxetine (LY139603) with Human Cytochrome P450 CYP3A, CYP2D6, CYP2C9, and CYP1A2***

Human liver samples designated HLB, HLH, HLM, and HLP were obtained and microsomes were prepared by differential centrifugation. A mixture of equal protein concentrations of microsomes from these liver samples was prepared and used in the study. The ability of atomoxetine (LY139603) to inhibit the metabolism of marker catalytic activities for the cytochromes P450 CYP3A, CYP2D6, CYP2C9, and CYP1A2 was examined.

Table 1. Incubation Conditions

Metabolism Type	Incubation Mixture	Incubation Time
1'Hydroxylation of Midazolam (CYP3A) (Formation linear with respect to time)	200 µl: HLM (0.1 mg protein) in 100 mM sodium phosphate buffer (pH 7.4), 1 mM NADPH	1 min
1'-Hydroxylation of Bufuralol (CYP2D6) (Formation linear for at least 50 min)	150 µl: HLM (15 ug protein) in in 100 mM sodium phosphate buffer (pH 7.4),1 mM NADPH	30 min
4'-Hydroxylation of Diclofenac (CYP2C9) (Formation linear for 30 min)	200 µl: HLM (0.05 mg protein) in 100 mM sodium phosphate buffer (pH 7.4), 1 mM NADPH	15 min
O-Deethylation of Phenacetin (CYP1A2) Acetaminophen Formation linear for 50 min)	200 µl: HLM (0.1 mg protein) in 100 mM sodium phosphate buffer (pH 7.4), 1 mM NADPH	30 min

Table 2. Inhibition of CYP3A and CYP2D6 Form-Selective Catalytic Activities by Atomoxetine

Form-Selective Catalytic Activity	Type of Inhibition	Atomoxetine	Apparent Ki
CYP3A			
Midazolam 1'-Hydroxylation 5, 10, 25, 50 or 100 µM	Mixed competitive/ competitive	25, 50, 75, or 100 µM	34.3±8.6µM
CYP2D6			
Bufuralol 1'-hydroxylation 5, 10, 25, 50, 100 µM	competitive	5.75, 7.5, 15 or 25 µM	3.6±0.3 µM

All incubations were performed in duplicate. K_i values represent parameter estimate±standard error.

Table 3. Effect of Atomoxetine in Vitro on the CYP2C9 and CYP1A2 Mediated Metabolism

	Atomoxetine Concentrations (µM)					
CYP2C9 Mediated Metabolism (Diclofenac, 2.5 µM)	0	10	100	200	500	800
4'-Hydroxy Diclofenac (pmol/min/mg)	269	238	242	256	200	171
Percent of Control (%)	100	88	90	95	74	64
CYP1A2 Mediated Metabolism (Phenacetin, 12.5 µM)						
Acetaminophen Formation (pmol/min/mg)	111	113	NA	114	84	78
Percent of Control (%)	100	102	NA	103	76	70

Summary

- The formation of 1'-hydroxy midazolam catalyzed by CYP3A followed simple Michaelis-Menten kinetics in microsomal mixture, yielding an apparent K_m of 3.0±0.5 µM, V_{max} of 915.3±29.7 pmol/min/mg protein. The best fit model describing

the inhibition by atomoxetine was found to be mixed competitive/non competitive yielding an apparent K_i value of 34.3±8.6 μM and α of 6.1±2.6. This large K_i value suggests that the circulating levels of atomoxetine need to approach 34.3 μM (8.8 μg/ml) before significant inhibition of the metabolism of a co-administered CYP3A substrate would be predicted.

- The formation of 1'-hydroxy bufuralol catalyzed by CYP2D6 followed simple Michaelis-Menten kinetics in microsomal mixture, yielding an apparent K_m of 6.3±0.4 μM, V_{max} of 119.1±2.3 pmol/min/mg protein. The best fit model describing the inhibition by atomoxetine was found to be competitive yielding an apparent K_i value of 3.6±0.3 μM. The projected *in vivo* inhibition of CYP2D6 mediated metabolism was determined to be 57% by atomoxetine under the studied conditions.
- The maximum plasma concentration of atomoxetine after a dose of 90 mg has been shown to be 4.8 μM. Assuming a conservative concentration of 4.8 μM at the active site of the enzyme, the projected *in vivo* inhibition of CYP2D6 mediated metabolism was determined to be 57% by atomoxetine.
- Atomoxetine at concentrations of 500 and 800 μM with a 2.5 μM concentration of diclofenac inhibited the 4-hydroxylation (catalyzed by CYP2C9) of diclofenac by 26% and 36%, respectively.
- Acetaminophen formation from 12.5μM phenacetin (catalyzed by CYP1A2) was inhibited by <30% using the following concentrations of Atomoxetine: 10, 200, 500, or 800 μM.
- The marker catalytic activities for CYP2C9 and CYP1A2 were only minimally inhibited by atomoxetine at concentrations up to 800 μM.
- Overall, atomoxetine is not a potent inhibitor for CYP3A, CYP2C9 and CYP1A2.

ADME Report 36: ***In Vitro Interaction of N-Desmethylatomoxetine (137877) and 4-Hydroxyatomoxetine (424478) with Human Cytochrome P450 CYP3A, CYP2D6, CYP2C9, and CYP1A2***

Table 1. Inhibition of CYP3A, CYP2D6, CYP2C9, and CYP1A2 Form-Selective Catalytic Activities *in Vitro* by 137877 and 424478

Form-Selective Catalytic Activity	Compound	Type of Inhibition	Apparent K_i (Estimate±SE)
CYP3A:			
Midazolam 1'-Hydroxylation	137877 (1, 10, 25, 50 μM)	Mixed comp/noncom	15.9±1.0 μM
5, 10, 25, 50 or 100 μM	424478 (25, 75, 250, 500 μM)	Competitive	461±32 μM
CYP2D6:			
Bufuralol 1'-hydroxylation	137877 (1, 5, 10, 20 μM)	Competitive	5.3±0.2 μM
5, 10, 25, 50, 100 μM	424478 (5, 10, 25, 50 μM)	Competitive	17.3±0.9 μM
CYP2C9:			
Diclofenac 4'-Hydroxylation	137877 (25, 50, 100, 250 μM)	Competitive	53.2±3.3 μM
2.5, 5, 10, 25, 50 μM	424478	N/A	N/A
CYP1A2:			
Phenacetin O-Deethylation	137877 (50, 100, 250, 500 μM)	Mixed Com/noncom	271±26 μM
(12.5, 50, 75, 100 μM)	424478	N/A	N/A

N/A: Not applicable; <34% inhibition. All incubations were performed in duplicate.

Table 2. Effect of 4-Hydroxyatomaxetine on CYP2C9 and CYP1A2 Mediated Metabolism

	Atomoxetine (LY139603) Concentrations (μM)								
CYP2C9	0	0.5	1.0	10	25	50	100	250	500
4'-Hydroxy Diclofenac (pmol/min/mg)	450	436	452	448	413	409	367	326	296
Percent of Control	100	97	100	100	92	91	82	72	66
CYP1A2									
Acetaminophen Formation (pmol/min/mg)	199	199	198	202	207	198	199	190	180
Percent of Control	100	100	99	102	104	99	100	95	90

Diclofenac, 2.5μM , Phenacetin, 12.5 μM

Table 3. Circulating or Estimated Concentrations of Atomoxetine and Its Metabolites

Compound	Atomoxetine		N-Desmethylatomoxetine		4-Hydroxyatomoxetine	
Circulating	EM	PM	EM	PM	EM	PM
C (ng/ml)	1221	4700	85.5	2350	21.8	21.8
C (μM)	4.8	18.4	0.4	9.8	0.08	0.08

Table 4. Predicted Inhibition by Atomoxetine and Its Two Metabolites in CYP2D6 Extensive and Poor Metabolizer Populations

	CYP3A		CYP2D6		CYP2C9		CYP1A2	
	EM	PM	EM	PM	EM	PM	EM	PM
Parent	12%	35%	57%	N/A	*	*	*	*
N-Des-	2.5%	38%	7.1	N/A	0.7%	16%	0.1%	3.5%
4-hydro-	0.02%	0.02	0.5	N/A	*	*	*	*
Total	15%	73%	65%	N/A	0.7%	16%	0.1%	3.5%

N-Des: *N*-desmethylatomoxetine, 4-Hydro-: 4Hydroxyatomoxetine.

Summary

The K_I values generated in this study for the major phase I metabolites of atomoxetine (*N*-desmethylatomoxetine-137877 and 4-hydroxyatomoxetine-424478) in conjugation with the K_I values generated in a previous study for atomoxetine and the estimated in vivo plasma concentrations of atomoxetine and its metabolites have been used to predict potential drug-drug interactions with co-administration of atomoxetine:

- Inhibition of CYP2D6 mediated metabolism by 137877, 424478, and atomoxetine (total predicted inhibition of 65%) suggested there may be an effect of these compounds on the metabolic clearance of co-administered agents metabolized by CYP2D6 in the EM population.
- Due to lack of CYP2D6 in a PM population, inhibition of CYP2D6 mediated metabolism could not occur in this population.
- Little effect of atomoxetine administration is predicted on CYP3A metabolism in the EM population (15%).
- In the PM population in which atomoxetine and 137877 accumulate to levels that are higher than EM population, CYP3A mediated metabolism was predicted to be inhibited by a total of 73%.
- Little inhibition of CYP1A2 and CYP2C9 mediated metabolism was predicted in either the PM or EM populations based on the studies reported.

- A prediction concerning the amount of inhibition expected in vivo from in vitro results cannot be definitely modeled without information as to the concentrations of atomoxetine, 137877, and 424478 at the active site of the enzymes.

ADME Report 34: *Identification of the Human Cytochrome P450 Responsible for the Formation of 424478, the 4-Hydroxy Metabolite of LY139603 (Atomoxetine HCL)*

Studies were performed to determine the human enzymes responsible for the biotransformation of LY 139603 (atomoxetine) to 424478 (4-hydroxyatomoxetine).

Table 1. Kinetic Analyses of the Formation of 4-Hydroxyatomoxetine by Microsomes from Human Liver Samples (Parameter Estimate ±SE)

Containing a full complement	Microsomal Sample	K_M (μM)	V_{max} (pmol/min/mg)	CL_{int} (μL/min/mg)
of P450 enzymes:	HLM	2.2±0.1	340±6	155
	HLC	2.3±0.1	115±2	50
Deficient in CYP2D6:	HLK	153±13	17.4±1.0	0.1
	HLN	144±9	37.2±1.1	0.3

Atomoxetine concentrations were 0.0625, 0.25, 1.0, 5.0, 10, 20, 40, 80, 160, 240, 360, and 500 μM. All incubations were performed in duplicate.

The rate of formation of 4-hydroxyatomoxetine was examined in a bank of human liver microsomes previously characterized for activities/levels of nine CYPs at concentrations of 1 μM and 100 μM atomoxetine. The ability of nine cDNA expressed CYP enzymes to form 4-hydroxyatomoxetine was examined. Inhibitors of the CYP mediated reactions were examined for their ability to effect the formation of 4-hydroxyatomoxetine in microsomes known to be CYP2D6 deficient. Enzyme kinetics of 4-hydroxyatomoxetine formation were examined in cDNA expressed enzymes.

Summary

- An average K_M value of 2.3 μM for the formation of 4-hydroxyatomoxetine was obtained using microsomal samples containing a full complement of drug metabolizing enzymes.
- An average apparent K_M value of 149 μM for 4-hydroxyatomoxetine formation was obtained for microsomal samples known to be deficient in CYP2D6.
- When the rate of formation of 4-hydroxyatomoxetine was examined in a bank of human liver microsomes previously characterized for activities/levels of nine CYPs at a low concentration of atomoxetine (1 μM), only CYP2D6 showed as a significant regressor, while at higher concentration (100 μM) in the presence of the CYP2D6 inhibitor quinidine (10 μM), CYP2C8, CYP2C19, CYP2D6, and CYP3A were all identified as significant univariate regressors.
- Detectable levels of 4-hydroxyatomoxetine were formed by CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. However, the formation rate by CYP2D6 was >400-fold greater than the rate of formation observed for the other enzymes.

- In CYP2D6 deficient microsomes, the inhibitors of CYP2D6 (quinidine, 10 μM) and CYP2C9 (sulfaphenazole, 10 μM) had no significant effect on the formation rates of 4-hydroxyatomoxetine. Inhibition from 20% to 67% of 4-hydroxyatomoxetine formation was observed following incubations with inhibitors of CYP2C19 (S-mephenytoin, 250 μM), CYP3A (ketoconazole, 2 μM), CYP1A2 (furafylline, 10 μM), CYP2A6 (coumarin, 500 μM), and CYP2E1 (DDC, 300 μM).
- Enzyme kinetic study of 4-hydroxyatomoxetine formation yielding K_M values of 29.4, 96.0, 5.0, and 399 μM for CYP2B6, CYP2C19, CYP2E1, and CYP1A2, respectively.

Conclusions

- These data in total show that CYP2D6 is the enzyme primarily responsible for the formation of 4-hydroxyatomoxetine. Therefore, alterations in the catalytic activity of CYP2D6 due to drug-drug interactions or genetic polymorphism may have the potential to effect atomoxetine clearance.
- In patients exhibiting the poor metabolizer CYP2D6 phenotype, multiple enzymes are capable of forming 4-hydroxyatomoxetine. Therefore, should one of these multiple routes of metabolism to 4-hydroxyatomoxetine be affected due to drug-drug interactions or due to inter-individual differences in the levels of CYP enzymes, formation of 4-hydroxyatomoxetine should be relatively unaffected in CYP2D6 deficient patients.

ADME Report 42: ***Identification of the Human Enzyme(s) Responsible for the Formation of 137877, the N-Desmethyl metabolite of Atomoxetine Hydrochloride (LY139603)***

Studies were performed to determine the human enzyme(s) responsible for the biotransformation of atomoxetine hydrochloride to the *N*-desmethylated metabolite.

Table 1. Kinetic Analyses of the Formation of N-desmethylatomoxetine by Microsomes from Human Liver Samples (Parameter Estimate ±SE)

Containing a full complement	Microsomal Sample	K_M (μM)	V_{max} (pmol/min/mg)	CL_{int} (μL/min/mg)
of P450 enzymes:	HLC	91±4	68±1	0.75
	HLM	45±8	36±2	0.80
Deficient in CYP2D6:	HLK	113±11	97±5	0.86

Atomoxetine concentrations were 5.0, 10, 25, 50, 75, 100, 150, 200, 250, 350, and 500 μM. All incubations were performed in duplicate.

The rate of formation of *N*-desmethylatomoxetine following incubations with 10 μM and 75 μM atomoxetine was examined in a bank of human liver microsomes (n=20) previously characterized for catalytic activities associated with CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, and flavin-containing monooxygenase. The ability of cDNA expressed CYPs to form N-desmethylatomoxetine was examined following incubations with 10 μM and 75 μM

atomoxetine. Monoclonal antibodies to CYP2D6, CYP3A4/5, CYP2B6, and the CYP2C subfamily of enzymes were examined for their ability to inhibit N-desmethylatomoxetine formation by human liver microsomes in the presence of 10 μM atomoxetine. Chemical inhibitors of several CYPs were also examined for their ability to inhibit *N*-desmethylatomoxetine formation at atomoxetine concentrations of 10 μM and/or 75 μM.

Summary

- Numerous CYPs were able to form *N*-desmethylatomoxetine after incubations with 10 μM and/or 75 μM atomoxetine, with formation by CYP2C19 the greatest at both concentrations examined.
- At an atomoxetine concentration of 10 μM, the only inhibitor able to decrease *N*-desmethylatomoxetine formation were the inhibitors of CYP2C19 (omeprazole and S-mephenytoin) and CYP1A2 (furafylline). A number of the inhibitors exhibited the ability to inhibit the formation of N-desmethylatomoxetine at atomoxetine concentrations of 75 μM.

Conclusions

- These data in total indicate that CYP2C19 is the primary enzyme responsible for the metabolism of atomoxetine to *N*-desmethylatomoxetine. At a higher substrate concentration (75 μM), multiple enzymes appear to be capable of metabolizing atomoxetine to *N*-desmethylatomoxetine.
- Alterations in CYP2C19 catalytic activity due to drug-drug interactions or individual differences in expression of CYP2C19 may have the potential to effect the overall level of *N*-desmethylatomoxetine formation. However, this is likely to have little effect on the overall clearance of atomoxetine, as the metabolic elimination of atomoxetine by *N*-desmethylation appears secondary to 4-hydroxyatomoxetine formation.

ADME Report 52: ***Examination of CYP1A2 and CYP3A Induction by LY139603 in Primary Cultures of Human Hepatocytes***

The ability of atomoxetine to induce the catalytic activities associated with CYP1A2 and CYP3A was examined in primary cultures of human hepatocytes from three separate donors. Primary cultures of human hepatocytes were treated for 48 hours with atomoxetine at concentrations of 0.01, 0.1, 1, 10, and 100 μM, and the effects of treatment on catalytic activities associated with CYP1A2 mediated 7-ethoxyresorufin O-deethylase (EROD) and CYP3A mediated midazolam 1'-hydroxylase (MZD-1OH) were compared with those activities in vehicle-treated (0.1% DMSO) cultures (Control) and in cultures exposed to known inducers of CYP1A2 (3-methylcholanthrene, 3-MCLT) and CYP3A (rifampicin).

Table 1. Effects of Treatment on Catalytic Activities Associated with CYP1A2 and CYP3A

	CYP1A2			CYP3A		
Hepatocyte	Control (pmol/min/mg)	3-MCLT	Atomoxetine	Control (pmol/min/mg)	Rifampicin	Atomoxetine
HH868	0.170	116-fold	NS	100.6	3.6-fold	NS
HH870	0.067	196-fold	NS	15.9	10.1-fold	NS
HH914	0.109	61-fold	<2-fold	33.5	2.4-fold	NS

Atomoxetine concentrations were 0.01, 0.1, 1, 10, and 100 µM. NS-not significant different.

Samples from donor HH914 had EROD activities that were not significantly different than control values at 0.01, 0.1 and 10 µM atomoxetine, however, 1.0 µM atomoxetine had a significant increase in EROD activity (<2-fold). This change was not considered an important effect due to its small magnitude relative to the effect of the positive control, and the lack of a dose-response.

Summary

- The known inducers 3-methylcholanthrene and rifampicin, which served as positive controls for CYP1A and CYP3A induction, respectively, produced significant induction (>2-fold).
- Atomoxetine was not an inducer of CYP1A2 or CYP3A in the three human hepatocyte preparations examined.

Human Pharmacokinetics (PK) Studies

In Vivo Human Metabolism (Vol. 63-64): B4Z-LC-HFBH - *Metabolism and Disposition of ^{14}C-LY139603 in Healthy CYP2D6 EM and PM Men and Women*

In the early 1980's during the initial development of atomoxetine, its excretion and metabolism were evaluated in four healthy adult male subjects (CSR.HFAR). Although the excretion of atomoxetine was well characterized in Study B4Z-LC-HFAR, the metabolism of atomoxetine was not completely defined and the differences between CYP2D6 extensive metabolizers (EM) and poor metabolizers (PM) were not well understood. Therefore, an additional excretion and metabolism study was conducted with atomoxetine in healthy subjects of known CYP2D6 status (CSR.HFBH). Although slightly different study designs were applied, both studies demonstrate a similar disposition profile for atomoxetine in humans.

As the primary routes of excretion for the metabolites of atomoxetine were well understood, the design of this study was optimized for the elucidation of the metabolites of atomoxetine. This study was an open-label study in healthy adult men (all Caucasians) with either EM (4 subjects) or PM (3 subjects) genotype. Multiple 20-mg doses of atomoxetine were administered twice daily over a 5-day period followed by a single 20-mg dose of ^{14}C-atomoxetine on the morning of the 6th day.

Table 1. Values of Pharmacokinetic Parameters (Arithmetic Mean with %CV)

Parameter		^{14}C-Equivalents	Atomoxetine	4-Hydroxy-A	*N*-Desmethyl-A	4-Hydroxy-A-*O*-Glucuronide
C^{ss}_{max}	EM	515.4 (22.9)	159.7 (51.9)	2.03 (17.5)	7.02 (71.5)	413.9 (35.5)
(ng/ml)	PM	427.8 (30.5)	914.7 (30.5)		259.2 (39.6)	88.0 (16.9)
C^{ss}_{min}	EM		36.1 (115.8)	0.52 (115.6)	3.12 (113.6)	104.4 (19.3)
(ng/ml)	PM		502.8 (29.2)		193.1 (40.6)	69.3 (16.4)
C^{ss}_{avg}	EM		89.6 (64.3)		5.15 (86.4)	228.7 (13.6)
(ng/ml)	PM		703.6 (26.9)		234.9 (31.2)	77.9 (17.0)
T_{max}	EM	2.0 (2.0-4.0)	2.0 (1.0-3.0)	2.5 (2.0-4.0)	3.5 (2.0-6.0)	2.0 (2.0-4.0)
(hr)	PM	2.0 (2.0-6.0)	2.0 (2.0-3.0)		6.0 (3.0-6.0)	4.0 (2.0-6.0)
$t_{1/2}$	EM	17.7 (15.1-19.3)	5.3 (3.7-9.1)		9.0 (2.1-21.9)	6.7 (5.9-8.3)
(hr)	PM	62.4 (61.9-63.3)	20.0 (16.8-25.2)		33.3 (27.7-42.7)	19.0 (15.2-22.8)
AUCτ	EM	4.54 (16.8)	1.08 (64.3)		0.06 (86.4)	2.74 (13.6)
(μg.hr/ml)	PM	18.4 (13.5)	8.44 (26.9)		2.82 (41.2)	0.94 (17.0)
CL^{ss}/F	EM	0.061 (26.2)	0.37 (75.1)			
(L/hr/kg)	PM	0.016 (22.6)	0.036 (26.2)			
Vz/F	EM	1.56 (32.7)	2.33 (51.0)			
(L/kg)	PM	1.41 (22.6)	1.06 (42.9)			

Medians with ranges for T_{max} and Means with ranges for $t_{1/2}$.

Table 2. Estimation of Atomoxetine and Its Metabolites in Urine (% Dose)

Analyte	PM			EM			
	P1	P2	P3	E1	E2	E3	E4
4-Hydroxyatomoxetine	8.7	5.8	3.8	1.1	2.9	2.0	3.9
4-Hydroxyatomoxetine-*O*-glucuronide	28.0	32.6	32.4	88.7	82.1	79.6	85.5
N-Desmethylatomoxetine	0.6	0.5	0.6	ND	ND	ND	ND
4-Hydroxy-*N*-Desmethylatomoxetine	4.3	2.1	2.9	ND	ND	ND	ND
4-Hydroxy-*N*-Desmethylatomoxetine-*O*-glucuronide	1.9	1.0	3.2	1.4	2.5	2.8	4.6
2-Hydroxymethylatomoxetine-*O*-glucuronide	2.4	1.1	3.5	ND	ND	ND	ND
4-hydroxy-2-carboxyatomoxetine-*O*-glucuronide	6.3	7.2	6.0	ND	ND	ND	ND
Dihydroxyatomoxetine-*O*-glucuronide	2.3	3.8	1.4	ND	ND	ND	ND
Hydroxy carboxyatomoxetine-*O*-glucuronide	4.2	2.9	4.0	ND	ND	ND	ND
Atomoxetine	2.9	2.2	2.3	0.3	0.1	0.9	0.7
Total	**61.5**	**59.2**	**60.1**	**91.5**	**87.6**	**85.3**	**94.7**

Based on the amount of radioactivity recovered in urine for 0-168 hr for EM subjects and 0-120 hr for PM subjects.

Table 3. Estimation of Atomoxetine Metabolites in Feces (% Dose)

Analyte	PM			EM			
	P1	P2	P3	E1	E2	E3	E4
4-Hydroxyatomoxetine	3.6	Low	ND	ND	ND	ND	ND

The 1-minute fractions of . ' column effluent showed that although radioactivity was present in most fractions, the largest amount was that corresponded to elution time of 4-hydroxyatomoxetine.

Table 4. Excretion of Radioactivity in Urine and Feces (% of Dose)

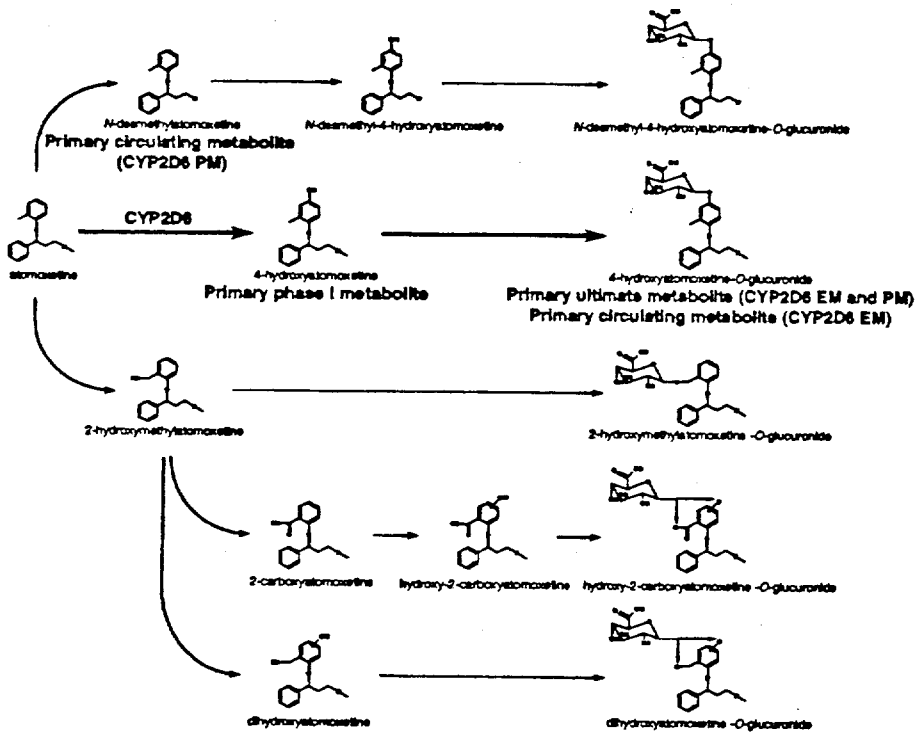
Genotype	Total	Urine	Feces
EMs in 24 hours		89.7-99.9%	1.1-2.4%
PMs in 72 hours		76.7-84.5%	13.1-21.6%
EMs (168 hrs)+PMs (up to 312 hrs)	97.2±1.1%	89.0±3.5%	8.2±3.2%

Table 5. Plasma Protein Binding (% Binding of Total Radioactivity, Mean±SEM)

EMs	53.8%±4.9%	PMs	96.7%±0.5%

— radio-profiles of the 2-hour plasma and ultracentrifuged protein free plasma samples from all 4 EM subjects showed only one radiolabeled component and this was identified by selective reaction monitoring-MS as 4-hydroxyatomoxetine-*O*-glucuronide, The 2-hour plasma from 3 PM subjects showed only a single radioactive peak having the same — retention time as atomoxetine. No detectable peaks were present in radio-profiles of protein free plasma from any PM subjects.

Figure 1. Proposed Scheme for the Metabolism of Atomoxetine in Humans



Summary

- In both EM and PM subjects, atomoxetine was well absorbed from the gastrointestinal tract and primarily cleared from the body by oxidative metabolism with nearly all its metabolites being eliminated by excretion into the urine.
- Atomoxetine and 4-hydroxyatomoxetine-*O*-glucuronide are the principle circulating species in the plasma of EM subjects, while atomoxetine and *N*-desmethylatomoxetine (6%) are the principle circulating species in PM subjects.
- In EM subjects, the majority of the radioactive dose was excreted within the first 24 hours. Excretion was much slower in PM subjects with the majority of the radioactive dose being excreted within 72 hours. The total recovery was similar in all subjects, independent of their CYP2D6 metabolic status.

- It appears that the major radioactive component in feces for both EM and PM subjects is 4-hydroxyatomoxetine. However, it is not known whether this metabolite is directly eliminated into the feces or if it results from the deconjugation of 4-hydroxyatomoxetine-*O*-glucuronide by bacterial metabolism in the feces.
- None of the subjects had any evidence of ^{14}C-carbon dioxide released in breath samples.
- The primary phase I metabolite of atomoxetine produced by both EM and PM subjects is 4-hydroxyatomoxetine, which is subsequently conjugated forming the primary ultimate metabolite of atomoxetine, 4-hydroxyatomoxetine-*O*-glucuronide. However, the amount of the dose excreted as 4-hydroxyatomoxetine-derived metabolites was greater in the EM subjects (85%) compared to PM subjects (45%).
- In PM subjects the mean half-life of atomoxetine was 20 hours, while in EM subjects the mean half-life of atomoxetine was only approximately 5 hours.
- Although the same major metabolites of atomoxetine are produced regardless of CYP2D6 metabolic status, the rate of metabolic elimination for atomoxetine is substantially (10-fold) slower in PM subjects (mean CLss/F=0.0357 L/hr/kg) as compared to EM subjects (mean CL^{ss}/F=0.373 L/hr/kg). However, the relative amount of metabolites derived from secondary routes of biotransformation, such as *N*-desmethylatomoxetine- and 2-hydroxymethylatomoxetine-derived metabolites, was greater in the PM subjects (55%) as compared to EM subjects (15%).
- Differences in atomoxetine concentrations between EM and PM subjects are due to a decrease in the rate of formation of 4-hydroxyatomoxetine (and subsequently 4-hydroxyatomoxetine-*O*-glucuronide), which results in a reduction in the rate of elimination of atomoxetine in PM subjects.
- Regardless of CYP2D6 metabolic status, very little atomoxetine was excreted into the urine unchanged, indicating a relatively minor role for renal clearance (<3%).
- The difference in percentage of plasma protein binding of total radioactivity between EM and PM subjects is likely due to the relative amount of atomoxetine and its metabolites present in the plasma. Although atomoxetine and many of its metabolites are observed in the plasma of EM subjects, the plasma radio-profile is dominated by 4-hydroxyatomoxetine-*O*-glucuronide. In the plasma of the majority of PM subjects, unchanged atomoxetine was the only detectable radioactive component.
- Atomoxetine 20-mg twice daily dosing was well-tolerated by 4 EM and 3 PM adult male subjects.

Pharmacological Activity of Atomoxetine Derived Metabolites

The pharmacological selectivity and potency of the primary phase I metabolites of atomoxetine, 4-hydroxyatomoxetine and *N*-desmethylatomoxetine, were evaluated *in vitro* for the inhibition of the monoamine reuptake transporters, as well as several receptor systems and it was concluded as follows:

- The primary metabolites of atomoxetine, 4-hydroxyatomoxetine and *N*-desmethylatomoxetine, are also pharmacologically active as norepinephrine reuptake inhibitors.

- While 4-hydroxyatomoxetine (K_i=3.0 nM) possesses similar inhibitory activity at the norepinephrine transporter to that of atomoxetine, *N*-desmethylatomoxetine (K_i=92 nM) is approximately 20-fold less active than atomoxetine.
- 4-hydroxyatomoxetine also has potent pharmacological activity as a serotonin reuptake inhibitor (K_i=43 nM); however, both *N*-desmethylatomoxetine and 4-hydroxyatomoxetine, like atomoxetine, show very little relative affinity for other receptor systems.

Baseline (Initial Safety and Tolerability) PK Studies

In Healthy Volunteers

B4L-LC-HFBJ (Vol. 64-66): ***Single and Multiple Dose Studies in Adults of Known CYP2D6 Status***

The objectives of this study were to evaluate
(1) the safety of atomoxetine administered as single oral doses (ranging from 10 mg to 120 mg) and multiple doses of 40 mg twice a day in healthy adults,
(2) the effect of CYP2D6 status (EM and PM) on safety,
(3) dose proportionality of atomoxetine in healthy adults of known CYP2D6 status, and
(4) the effect of single and multiple oral doses of atomoxetine on orthostatic blood pressure and pulse changes.

Part A Single Oral Dose Schedule for EM Subjects

Subject #	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
EM: 01, 07, 13 PM 101, 107	Placebo	10 mg*	30 mg	60 mg	90 mg*	120 mg*	Placebo
EM: 02, 08, 14 PM: 102, 108, 113	Placebo	10 mg*	30 mg	60 mg	90 mg*	Placebo	120 mg*
03, 09, 15 PM: 103, 109, 114	Placebo	10 mg*	30 mg	60- mg	Placebo	90 mg*	120 mg*
EM: 04, 10, 16 PM: 104, 110	Placebo	10 mg*	30 mg	Placebo	60 mg	90 mg*	120 mg*
EM: 05, 11 PM: 105, 111	Placebo	10 mg*	Placebo	30 mg	60 mg	90 mg*	120 mg*
EM: 06, 12 PM: 106, 112	Placebo	Placebo	30 mg*	30 mg	60 mg	90 mg*	120 mg*

Washout period was at least 4 days for EM subjects and at least 14 days for PM subjects. *Indicating PK profile was obtained.

Part B Multiple Dose Randomization for EM Subjects

Subject #	N	Treatment
01, 05, 06, 10, 11, 16	6	Placebo
02, 03, 04, 07, 09, 12, 13, 14	8	Atomoxetine 40 mg, twice daily

All Caucasians with one native American, 4 males and 4 females.

Blood samples were collected for the 10-, 90-, and 120-mg doses. In the EM group, samples were drawn prior to dosing, then at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48, 60, and 72 hours post dose (15 samples). In the PM group, samples were drawn prior to

dosing, then at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48, 60, 72, 96, 120, 144, 168, 216, 264, and 312 hours post a single dose (22 samples). Urine samples were collected from both EM and PM subjects after the 90-mg dose over the intervals of 0-1, 1-2, 2-4, 4-6, and 6-24 hours post a single dose.

Pharmacokinetic Results are shown in Table1 to Table 9:

Table 1. Values of Single-Dose Atomoxetine Pharmacokinetic Parameters (Arithmetic Mean with %CV)

Parameter	C_{max} (ng/ml)	$AUC_{0\text{-}inf}$ (μg.hr/ml)	CL/F (L/hr/kg)	V_z/F (L/kg)	T_{max} (h)	$t_{1/2}$ (h)
10 mg (n=16)-EM	84.5 (37)	0.512 (70)	0.356 (47)	1.92 (52)	1.5 (1.0-2.0)	4.2 (2.2-7.5)
(n=11)-PM	171.4 (20)	4.21 (20)	0.0345 (22)	0.965 (11)	2.0 (1.0-4.0)	19.9 (15.6-24.5)
90 mg (n=15)-EM	812.6 (30)	5.47 (72)	0.289 (42)	2.22 (44)	1.0 (0.5-4.0)	5.6 (3.8-8.6)
(n=11)-PM	1518 (22)	36.7 (21)	0.0352 (23)	1.06 (19)	4.0 (1.0-6.0)	21.4 (15.2-27.0)
120mg (n=15)-EM	1053 (31)	7.42 (66)	0.278 (40)	1.99 (45)	1.5 (0.5-4.0)	5.2 (3.7-7.5)
(n=10)-PM	2233 (36)	51.6 (19)	0.0332 (19)	1.01 (11)	2.0 (1.0-8.0)	21.6 (14.1-26.8)

Medians with ranges for T_{max} and means with ranges for $t_{1/2}$.

Table 2. Dose Proportionality Assessment from Power Model for Atomoxetine

	EM		PM	
Variable	C_{max} (ng/ml)	$AUC_{0\text{-}inf}$ (μg.hr/ml)	C_{max} (ng/ml)	$AUC_{0\text{-}inf}$ (μg.hr/ml)
Power Model Eqn.	$630*D^{1.02}$	$4*D^{1.07}$	$1226*D^{1.01}$	$29*D^{0.99}$
Dose (mg/kg)	0.134 (10-mg) 1.63 (120-mg)	0.134 (10-mg) 1.63 (120-mg)	0.142 (10-mg) 1.69 (120-mg)	0.142 (10-mg) 1.63 (120-mg)
Geometric M	79.6 1011	0.43 6.16	167.8 2048	4.11 48.6
Ratio (90% CI)	1.06 (0.94, 1.20)	1.20 (1.11, 1.29)	1.02 (0.94, 1.10)	0.99 (0.95, 1.02)
Conclusion	Dose proportional	Unclear	Dose Proportional	Dose Proportional
DP[a]	22.0	8.6	429	122862

Dose proportionality (DP) could be theoretically concluded for any dose ratio less than this value.

Table 3. Multiple-Dose Atomoxetine Pharmacokinetic Parameters (40 mg BID)

	First Dose			Steady-State		
(N=6-8)	C_{max} (ng/ml)	$AUC_{0\text{-}t}$ (μg.hr/ml)	T_{max} (hr)	C^{ss}_{max} (ng/ml)	$AUC^{ss}_{0\text{-}\tau}$ (μg.hr/ml)	T_{max} (hr)
EM	340 (31)	1.82 (53)	2.0 (0.5-2.0)	527 (67)	2.59 (78)	0.7 (0.5-2.0)
PM	723 (22)	5.98 (25)	2.0 (1.5-8.0)	1949 (20)	18.6 (21)	1.5 (1.0-4.0)
	C^{ss}_{min} (ng/ml)	C^{ss}_{avg} (ng/ml)	Flux (%)	$t_{1/2}$ (hr)	CL^{ss}/F (L/hr/kg)	V_z/F (L/kg)
EM	69.5 (134)	215.5 (78)	248 (31)	5.2 (3.0-7.8)	0.298 (53)	2.06 (58)
PM	1117 (22)	1554 (21)	53.8 (21.3)	24.4 (19.4-31.1)	0.032 (14)	1.13 (13)
Accumulation Index		EM 1.27 (14)	PM 3.47 (16)			
Accumulation Ratio		EM 1.30 (24)	PM 3.01 (22)			

Table 4. Comparison of Clearance between Single Dose and Multiple Doses of Atomoxetine

Metabolizer	Part of Study	Geometric mean	Ratio of	90% CI	P-value

Status		(L/hr/kg)	Geometric Mean		
EM	Multiple-Dose	0.254	0.916	(0.82, 1.02)	0.1922
	Single-Dose	0.277			
PM	Multiple-Dose	0.031	0.906	(0.86, 0.96)	0.0058
	Single –Dose	0.034			

Table 5. Values of Single-Dose *N*-Desmethylatomoxetine Pharmacokinetic Parameters

Parameter	C_{max} (ng/ml)	AUC_{0-t} (μg.hr/ml)	AUC_{inf} (μg.hr/ml)	T_{max} (h)	$t_{1/2}$ (h)
10 mg (n=15-EM	3.3 (76)	0.05 (175)	0.078 (132)	2.0 (1.5-8.0)	8.3 (3.9-16.5)
(n=11)-PM	26.9 (38)	2.48 (38)	2.56 (37)	36(12-60)	38.4 (28.9-49.4)
90 mg (n=15)-EM	28.1 (96)	0.48 (189)	0.51 (188)	2.0 (1.0-8.0)	7.1 (3.0-16.1)
(n=11)-PM	216.8 (43)	21.3 (430	21.5 (43)	36.0 (18-48)	39.0 (27.5-51.1)
120mg (n=15)-EM	39.9 (108)	0.65 (170)	0.68 (167)	4.0 (1.0-12.0)	6.8 (3.3-12.9)
(n=10)-PM	277.1 (40)	29.0 (41)	29.4 (41)	36 (12-60)	40.2 (27.4-56.2)

Table 6. Values of Multiple Dose *N*-Desmethylatomoxetine Pharmacokinetic Parameters (40 mg BID)

	First Dose			Steady-State	
	C_{max}	AUC_{0-t}	T_{max}	C^{ss}_{max}	$AUC^{ss}_{0-\tau}$
(N=6-8)	(ng/ml)	(μg.hr/ml)	(hr)	(ng/ml)	(μg.hr/ml)
EM	10.7 (61)	0.084 (79)	2.0 (2.0-8.0)	25.6 (108)	0.199 (115)
PM	84.3 (45)	0.621 (51)	11.9 (8.0-11.9)	914.8 (32)	9.73 (34)
Steady State	C^{ss}_{min} (ng/ml)	C^{ss}_{avg} (ng/ml)	Flux (%)	$t_{1/2}$ (hr)	T_{max} (hr)
EM	9.7 (140)	16.6 (115)	131 (36)	6.6 (2.4-12.0)	2.0(1.5-6.0)
PM	658 (30)	811 (34)	30.8 (66)	34.0 (26.5-40.6)	3.1 (1.0-12)

Table 7. Values of Single-Dose 4-Hydroxyatomoxetine Pharmacokinetic Parameters

Parameter	C_{max} (ng/ml)	AUC_{0-t} (μg.hr/ml)	AUC_{inf} (μg.hr/ml)	T_{max} (h)	$t_{1/2}$ (h)
10 mg (n=15-EM	All values were below quantifiable limit.				
10 mg (n=11)-PM	All values were below quantifiable limit.				
90 mg (n=15)-EM	7.7 (51)	0.0663 (55)	0.0797 (47)	2.0 (1.0-8.0)	5.6 (4.1-10.1)
90 mg (n=11)-PM	1.3 (19)	0.0078 (108)		1.8 (0.9-6.0)	
120mg (n=15)-EM	9.7 (49)	0.094 (49)	0.108 (39)	4.0 (1.5-6.0)	6.4 (3.7-12.8)
120mg (n=10)-PM	1.5 (16)	0.0209 (39)		8.0 (1.0-12.0)	

Table 8. Values of Multiple-Dose 4-Hydroxyatomoxetine Pharmacokinetic Parameters (40 mg BID)

	First Dose			Steady-State	
	C_{max}	AUC_{0-t}	T_{max}	C^{ss}_{max}	$AUC^{ss}_{0-\tau}$
(N=6-8)	(ng/ml)	(μg.hr/ml)	(hr)	(ng/ml)	(μg.hr/ml)
EM	3.4 (51)	0.0199 (68)	2.0 (1.5-4.0)	4.9 (40)	0.033 (37)
PM				1.8 (22)	0.019 (12)
Steady State	C^{ss}_{min} (ng/ml)	C^{ss}_{avg} (ng/ml)	Flux (%)	$t_{1/2}$ (hr)	T_{max} (hr)
EM	0.98 (69)	2.77 (37)	141 (27)	6.2 (3.3-10.8)	1.5 (1.0-2.0)
PM	1.02 (50)	1.59 (12)	41.0 (40)	—	3.0 (1.5-6.0)

Table 9. Cumulative Amounts of Atomoxetine and Metabolites Excreted in Urine from 0-24 Hour following a 90-mg Dose

Compound	Atomoxetine	*N*-Desmethyl-A	4-Hydroxy-A	4-Hydroxy-A-*O*-Glu
EM Subjects	151 µg (74)	30.0 µg (98)	1150 µg (34)	56500 µg (27)
(% of dose)	0.168 (74)	0.0352 (98)	1.20 (34)	59.0 (27)
PM Subjects	816 (78)	342 (90)	346 (42)	8680 (54)
(% of dose)	0.907 (78)	0.402 (90)	0.361 (42)	9.08 (54)

Pharmacodynamic results are shown in Table 10 to Table 14:

Table 10. Effect of Single Doses Atomoxetine on $QT_{c(F)}$ Intervals

	Least Square Mean (msec) (Difference from Placebo)					
Dose	0	10	30	60	90	120
2 hours Postdose						
EM	376.6	375.4 (-1.2)	382.4 (5.8)	377.8 (1.2)	380.0 (3.4)	378.2 (1.5)
PM	382.8	383.3 (0.5)	389.4 (6.5)	387.8 (5.0)	390.7 (7.9)	388.8 (6.0)
24 hours Postdose						
EM	378.0	372.9 (-5.2)	373.7 (-4.3)	373.8 (-4.3)	374.2 (-3.9)	374.1 (-4.0)
PM	383.9	382.2 (-1.8)	385.6 (1.6)	390.9 (7.0)	390.7 (6.8)	384.9 (1.0)

Table 11. Effect of Multiple Dose Atomoxetine on $QT_{C(F)}$ Intervals

CYP2D6 Status	Dose	Days	Least Square Mean (msec)	Difference from Placebo	p-Value	95% Confidence Interval
EM	Placebo	1-7	369.0			
EM	40 mg BID		374.5	5.5	0.43	(-8.9, 19.9)
PM	40 mg BID		376.9	7.9	0.28	(-6.9-22.8)

Table 12. Effects of Atomoxetine on Blood Pressure and Heart rates after Single Doses

Dose (mg)	10	30	60	90	120
		Standing Heart Rate (bpm)			
EM Subjects	87.8	91.4	94.4	100.3	101.7
PM Subjects	87.6	90.7	99.2	100.0	104.7
		Orthostatic Heart Rate Change (bpm)			
EM Subjects	19.0	23.1	25.4	28.6	29.7
PM Subjects	17.4	20.2	28.9	23.6	29.3
		Orthostatic Systolic Blood Pressure Change (mm Hg)			
EM Subjects	5.8	5.8	-0.7	2.1	2.3
PM Subjects	2.8	3.6	-0.4	-0.03	-0.3

Table 13. Effects of Atomoxetine on Standing Heart rate after 40-mg Multiple Doses (at Day 7 morning)

Time (hr)	-0.5	0	0.5	1	1.5	2	2.5	3
Placebo	79.0	79.0	73.7	71.7	84.8	85.3	88.8	90.2
EM Subjects	94.9	92.2	90.9	95.6	97.4	109.2	115.5	115.7
PM Subjects	113.6	114.9	109.0	110.8	112.7	124.5	122.3	123.6

Table 14. Mean Hemodynamic Measures on Day 7 after 40-mg Multiple doses

	EM Subjects	PM Subjects
Standing Heart Rate (bpm)	101.4	116.4
Orthostatic Change in Heart Rate (bpm)	28.0	37.7
Orthostatic Change in Systolic Blood Pressure (mm Hg)	3.0	-5.5

The atomoxetine capsules used in this study were 10-mg (Lot CT12231), 20-mg (Lot CT12232, Lot CT10709) and placebo (Lot CT12515, Lot CT12231).

Summary

- Atomoxetine pharmacokinetics are linear in both CYP2D6 PM and EM subjects with generally proportional increases in Cmax and AUC with increasing dose.
- Steady state pharmacokinetic parameters of atomoxetine are linear with respect to time.
- At equivalent doses, plasma concentrations of atomoxetine and *N*-desmethylatomoxetine are higher in PM subjects than EM subjects, with 4-hydroxyatomoxetine concentrations substantially lower in the PM subjects due to a reduction in CYP2D6 catalyzed hydroxylation.
- Following a 90-mg dose of atomoxetine, there was a clear delineation in urinary ratios of atomoxetine to 4-hydroxyatomoxetine between PM and EM subjects resulting in an expected bimodal distribution of subjects that corresponded to the genotype of the subject.
- Single doses of atomoxetine between 10 and 120 mg resulted in increases in standing heart rate of similar magnitude in CYP2D6 PM and EM subjects. The magnitude of heart rate increase was not proportional to the atomoxetine dose increase.
- Multiple doses of 40-mg of atomoxetine, taken twice daily for 7 days, resulted in similar mean standing heart rate increases in CYP2D6 PM and EM subjects with PM subjects reaching maximum heart rates about 10 bpm higher than EM subjects.
- CYP2D6 PM and EM subjects reached a plateau to the increases in standing heart rate during atomoxetine twice daily dosing.
- Orthostatic changes in systolic blood pressure and heart rate were not clinically significant in CYP2D6 PM and EM subjects.
- QT_c interval changes appeared to be statistically different in the CYP2D6 PM subjects at some single doses and some times during the multiple dose regimen compared to EM subjects. There was no evidence, however, of a concentration by QT_c relationship for PM subjects. No such differences were noted among the mean QT_c intervals of the EM subjects.
- Individual changes in QT_c interval >30 msec were equally represented in the CYP2D6 PM and EM populations and were nearly equally represented by placebo and drug administration.

B4Z-LC-LYAE (Vol. 67-68): ***Tolerance and Safety of Multiple Dose Regimens of Atomoxetine Hydrochloride in Healthy Adults***

The objectives of this study was to evaluate the safety and tolerance of gradually increasing multiple-dose regimens of atomoxetine in healthy CYP2D6 extensive

metabolizer (EM) and poor metabolizer (PM) adults. A total of 16 healthy subjects (11 males and 5 females, of which 6 PMs and 10 EMs, 13 Caucasians, 2 Blacks and 1 Asian) participated in this single-blinded, placebo-controlled, multiple-dose escalation study. Placebo or atomoxetine capsules 60 to 150 mg/day were given as twice daily doses of 30 mg, 45 mg, 60 mg, and 75 mg for 5 days of each dose level. Atomoxetine capsules used in this study were 5-mg (Lot CT15501), 10-mg (Lot CT16039), 20-mg (Lot CT16038) and placebo (Lot CT15500).

The following blood samples were taken with respect to the morning dose of atomoxetine on Study Day 5 of Study Period 1 through 5: 0, 0.5, 1, 2, 4, 6, 9, and 12 hours postdose. A "trough" sample was taken immediately prior to the morning and evening doses of atomoxetine on Study Day 4 of Study Period 1 through 5. Plasma concentrations of atomoxetine and its two metabolites were analyzed using validated

Table 1. Values of Atomoxetine Pharmacokinetic Parameters after 5 Days of BID Dosing

Parameter		30 mg BID	PM/EM	45 mg BID	60 mg BID	75 mg BID	PM/EM
C^{ss}_{max} (ng/ml)	EM	320.4 (30)		490.3 (31)	645.5 (34)	821.0 (26)	
	PM	1264 (12)	**3.9**	1868 (17)	2919 (21)	3999 (27)	**4.8**
C^{ss}_{min} (ng/ml)	EM	14.4 (78)		23.2 (66)	33.6 (75)	57.0 (83)	
	PM	670.5 (19)	**46.6**	1017 (26)	1076 (53)	2277 (40)	**39.9**
C^{ss}_{avg} (ng/ml)	EM	101.7 (31)		164.1 (33)	222.1 (39)	308.6 (42)	
	PM	992.7 (13)	**9.8**	1504 (18)	2226 (24)	3119 (29)	**10.1**
T_{max} (hr)	EM	1.0 (0.5-2.0)		1.0 (0.5-2.0)	1.0 (0.5-2.0)	1.5 (1.0-4.0)	
	PM	1.5 (1.0-6.0)		4.0 (2.0-6.0)	3.0 (1.0-4.0)	3.0 (2.0-4.0)	
$AUC_{0-\tau}$ (µg.hr/ml)	EM	1.22 (31)		1.97 (33)	2.67 (39)	3.70 (42)	
	PM	11.9 (13)	**10.0**	18.0 (18)	26.7 (24)	37.4 (29)	**10.3**
CL^{ss}/F (L/hr/kg)	EM	0.374 (30)		0.353 (32)	0.355 (32)	0.322 (31)	
	PM	0.0364 (10)		0.0358 (16)	0.0331 (25)	0.0299 (24)	
Vz/F (L/kg)	EM	1.30 (25)		1.32 (31)	1.28 (34)	1.17 (30)	
	PM	Not estimated because half-life could not be determined.					

N=10 for EM subjects, N=6 for PM subjects.

Table 2. Values of *N*-Desmethylatomoxetine Pharmacokinetic Parameters after 5 Days of BID Dosing

Parameter		30 mg BID	PM/EM	45 mg BID	60 mg BID	75 mg BID	PM/EM
C^{ss}_{max} (ng/ml)	EM	8.9 (48)		15.5 (57)	21.7 (710	26.5 (69)	
	PM	488.5 (59)	**54.9**	914.8 (56)	1308 (60)	1646 (57)	**62.1**
C^{ss}_{min} (ng/ml)	EM	1.8 (77)		3.4 (83)	5.3 (117)	7.6 (104)	
	PM	318.6 (66)	**177**	564.0 (65)	732.3 (93)	1127 (58)	**148**
C^{ss}_{avg} (ng/ml)	EM	5.5 (47)		9.1 (71)	12.8 (85)	16.6 (84)	
	PM	482.5 (45)	**87.7**	749.8 (55)	1087 (65)	1405 (57)	**84.6**
T_{max} (hr)	EM	1.0 (1.0-2.0)		2.0 (1.0-6.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	
	PM	4.0 (4.0-9.0)		5.0 (4.0-9.0)	4.0 (1.0-9.0)	4.0 (4.0-12.0)	
$AUC_{0-\tau}$ (µg.hr/ml)	EM	0.066 (47)		0.110 (71)	0.154 (85)	0.199 (84)	
	PM	5.79 (45)	**87.7**	9.00 (55)	13.0 (65)	16.9(57)	**84.9**

N=10 for EM subjects, N=6 for PM subjects.

Table 3. 4-Hydroxyatomoxetine Pharmacokinetic Parameters after 5 Days of BID Dosing

Parameter		30 mg BID	PM/EM	45 mg BID	60 mg BID	75 mg BID	PM/EM
C^{ss}_{max} (ng/ml)	EM	9.8 (149)		21.6 (132)	29.4 (122)	24.8 (153)	
	PM	1.4 (18)	**0.14**	2.4 (23)	12.4 (179)	4.6 (230	**0.18**
C^{ss}_{min} (ng/ml)	EM	3.5 (235)		2.3 (71)	2.7 (32)	12.4 (226)	
	PM	0.5 (110)	**0.14**	1.4 (22)	1.9 (26)	2.9 (25)	**0.23**
C^{ss}_{avg} (ng/ml)	EM	6.6 (181)		10.4 (145)	13.4 (141)	19.1 (188)	
	PM	1.3[a] (2)	**0.37**	1.9 (18)	4.7 (101)	3.9 (20)	**0.20**
T_{max} (hr)	EM	2.0 (1.0-2.0)		2.0 (1.0-4.0)	2.0 (0.5-9.0)	2.0 (1.0-4.0)	
	PM	6.0 (2.0-9.0)		4.0 (2.0-6.0)	5.0 (2.0-9.0)	6.0 (1.0-12.0)	
$AUC_{0-\tau}$ (µg.hr/ml)	EM	0.079 (181)		0.124 (145)	0.161 (141)	0.229 (188)	
	PM	0.016[a] (2)	**0.20**	0.023 (18)	0.056 (101)	0.047(20)	**0.21**

N=10 for EM subjects, N=6 for PM subjects. [a] N=3.

Table 4. Comparison of C^{ss}_{min} Values of Atomoxetine for All Treatments

Time of Dose	Morning	Evening	Morning	Evening
	EM Subjects		PM Subjects	
Geometric C^{ss}_{min} (ng/ml)	42.0	25.9	1149	1279
Ratio (Morning/Evening)	1.62		0.898	
90% CI	1.39, 1.90		0.82, 0.985	

The approximate 62% difference in the EM subjects' morning and evening C^{ss}_{min} values tested statistically significant. None of the metabolite nadirs nor any of the PM nadirs had differences as large or that tested significant. This data will have to be compared with other C^{ss}_{min} values from different twice daily dosage regimens to determine if there is any clinical significance.

Table 5. Effects of Atomoxetine on Vital Signs

		EM		PM	
	Reference[a]	Naïve to drug	Exposure to Drug	Naïve to drug	Exposure to Drug
Standing HR (bpm)	92.5	76.5	93.3	71.7	86.9
Change in Orthostatic					
HR (bpm)	12.3	12.1	26.1	10.2	20.9
SBP (mm Hg)	-6.5	-1.5	-6.0	-0.8	-18.0

Naïve to Drug – Averaged over all observations in which subjects were not exposed to atomoxetine.
[a]Reference population as noted in Streeten, 1987.

In spite of the difference in atomoxetine concentrations of EM and PM groups, post atomoxetine standing (93.3 vs. 86.9 bpm) and orthostatic change in heart rates (26.1 vs. 20.9 bpm) are similar but numerically greater in the EM than the PM group. This is the opposite of what would be expected if a relationship between HR increase and atomoxetine concentrations existed. The major difference in HR is between placebo and the first dose of atomoxetine.

EM and PM metabolizer experiences do differ, however, for orthostatic systolic blood pressure change. The mean fall recorded for the PM group (-18 mm Hg) is much larger than the mean fall for the EM group (-6 mm Hg), which is within the normal expected change in healthy people.

The statistical analysis of the SBP and HR change from Day 1 compared to Days 4 and 5 were performed to look at accommodation to atomoxetine cardiovascular effects over time. Mean measurements taken at doses greater than 30 mg were combined. The orthostatic HR increase is significantly less following atomoxetine doses of 45 mg and above in EM and PM groups. The orthostatic SBP drop is larger in PM subjects than EM subjects and attenuates with continued atomoxetine dosing.

Summary

- Plasma concentrations of atomoxetine were much higher than 4-hydroxyatomoxetine (equipotent active metabolite) and *N*-desmethylatomoxetine in both EM and PM subjects.
- Atomoxetine and *N*-desmethylatomoxetine plasma concentrations were much higher in PM than EM subjects at the same dose. The 4-hydroxyatomoxetine plasma concentrations were lower in PM subjects.
- When LYAE data were combined with other study data, atomoxetine concentrations increased proportionally with dose over the 10- to 75-mg dose range studied.
- The heart rate responses of EM and PM subjects to identical doses of atomoxetine are similar. Both groups experienced orthostatic tachycardia, most of it asymptomatic. PM subjects experienced mostly asymptomatic orthostatic hypotension with atomoxetine doses above 30 mg BID.
- EM and PM subjects experienced attenuation of the cardiovascular stimulating effects of atomoxetine over each 5-day dosing regimen, suggesting tolerance develops to these effects. With continued 5-day atomoxetine dosing, the amount the HR increases becomes smaller over time. This may be evidence of physiologic accommodation or tolerance.
- Maximum tolerated concentration of 5596 ng/ml was identified following symptoms in 1 PM subject on the fifth day of 75 mg BID.
- QT_c interval prolongation was unrelated to atomoxetine concentration in EM subjects over the dose range of 60 to 150 mg/day in divided dose and the atomoxetine concentration range of up to 1200 ng/ml.
- QT_c interval changes were time dependent in PM subjects. The largest QT_c interval change (approximately 30 msec after 75 mg BID) were at the highest predose (trough) concentrations in PM subjects. No statistically significant changes in QT_c were noted 1 hour postdose.
- EM and PM subjects experienced a similar frequency and severity of adverse events over the dosing range of this study (0.7 to 2.8 mg/kg). The most common events were headache, nausea, dizziness, dry mouth, insomnia, and taste prevention in descending order.
- Orthostatic drops in SBP following atomoxetine doses of 30 mg BID or greater is a feature of PM subjects' cardiovascular response, but not EM subjects' response. These changes in SBP are more than would be expected in the Naïve State. The fall in diastolic BP with standing is also a finding in PM and not EM subjects.

In Patients

B4Z-MC-HFBC (Vol. 68-70): ***Safety and Pharmacokinetic study of Atomoxetine Hydrochloride in Pediatric Patients with ADHD***

The objective of this study was to evaluate the safety, effectiveness, and pharmacokinetics of atomoxetine hydrochloride in pediatric patients, ages 7 through 13 at the time of entry into the study, who met DSM-IV criteria for ADHD. A total of 7 patients (5 male and 2 female) participated in the single dose part and 16 patients (13 male and 3 female) participated in the steady-state discontinuation part of this PK study. All patients were CYP2D6 extensive metabolizers (EM). Atomoxetine 10 to 90 mg/day as oral 5-mg, 10-mg, or 20-mg capsules (CT08681) twice daily.

Blood samples were collected at 0, 1, 2, 4, 8, 12, and 24 hours post single dose as well as at steady state discontinuation. Plasma samples were analyzed for atomoxetine and its two metabolites using a validated ——— method at Eli Lilly Lab.

Table 1. Mean Single-Dose and Steady-State Pharmacokinetic Parameters after Atomoxetine Administration (Mean±SD)

Dose (mg)	Body Weight (kg)	C_{max} (ng/ml)/(mg/kg)	T_{max} (hr)	$t_{1/2}$ (hr)	CL/F (L/hr) (L/hr/kg)	V_z/F (L) (L/kg)
Single 10 mg	39±11 (N=16)	533±173	2.15±1.36	3.12±0.60	17.3±6.2 0.455±0.159	74.4±18.5 1.96±0.47
Steady state 20-45 mg BID	44±16 (N=16)	584±268	1.54±0.50	3.28±0.44	20.3±8.0 0.477±0.195	95.9±41.2 2.25±1.00

Table 2. Values of Single-Dose and Multiple-Dose Atomoxetine Pharmacokinetic Parameters

	Age (yr)	Dose (mg/kg)	C_{max} (ng /ml)	$AUC_{0-\infty(\tau)}$ (ng.hr/ml)	T_{max} (hr)
Single-Dose	10.9±1.6	0.272±0.067	144±53	645±220	2.2±1.4
Multiple-Dose	10.5±2.0	0.951±0.337	537±306	2251±1132	1.5±0.5
	C^{ss}_{min} (ng/ml)	C^{ss}_{avg} (ng/ml)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	V_z/F (L/kg)
Single-Dose			3.1±0.6	0.455±0.159	1.96±0.47
Multiple-Dose	18.9±17.0	188±94	3.3±0.4	0.477±0.195	2.25±1.00

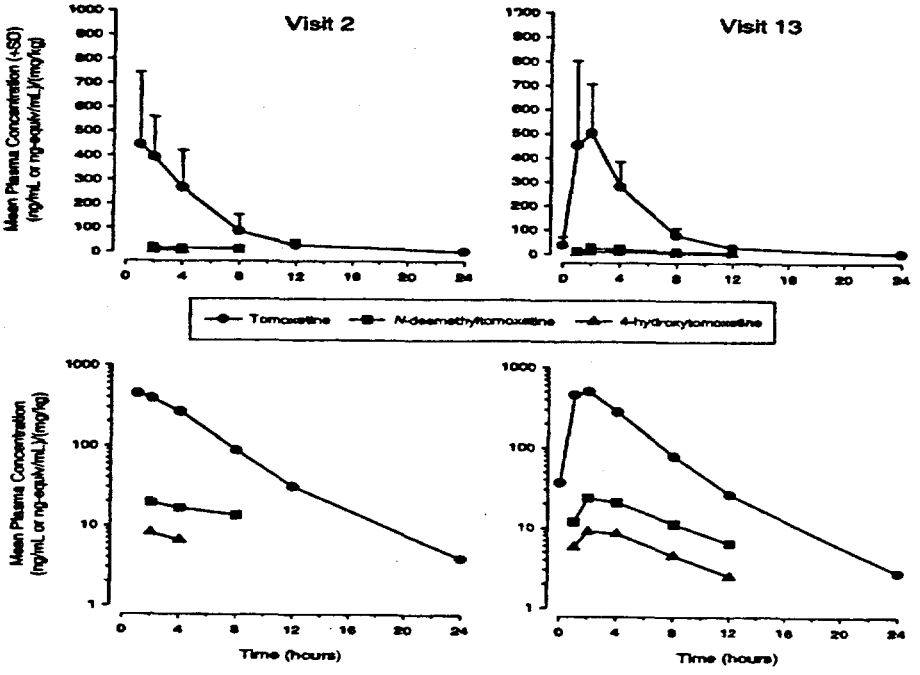
Single dose N=7, multiple dose N=16. Flux=273%±52%, Accumulation index=1.09±0.03.

Table 3. Single-Dose and Multiple-Dose Metabolites Pharmacokinetic Parameters

	C_{max} (ng-equiv/ml)	$AUC_{0-t(\tau)}$ (ng-equiv.hr/ml)	$AUC_{0-\infty}$	T_{max} (hr)	MR Parent/Metabolite
***N*-Desmethylatomoxetine**					
Single-Dose	5.4±3.2	39.3±27.1	54.7±35.8	3.0±2.4	16.2±7.4
Multiple-Dose	24.0±23.6	167.6±190.5		2.5±1.1	23.0±16.0
4-Hydroxyatomoxetine					
Single-Dose	2.4±0.9	15.5±5.7	25.8±3.2	3.0±2.4	27.9±8.1
Multiple-Dose	9.4±4.6	67.4±31.3		2.9±1.8	36.7±12.3

The mean atomoxetine plasma concentration profiles, after normalizing to a 1 mg/kg dose, for Visit 2 and Visit 13 are shown in Figure 1.

Figure 1. Mean Plasma Concentrations-Time Plot (Normalized to 1 mg/kg Dose)



Summary

- After oral administration, absorption was rapid with peak concentrations observed at approximately 1 to 2 hours after dosing. The atomoxetine C_{max} observed ranged from 80 to 1221 ng/ml. The mean profile after multiple twice daily dosing at Visit 13 was very similar to the mean single-dose profile, indicating little accumulation at steady-state in EM patients. The accumulation observed averaged 9%, which was predictable based on single-dose PK. The minimal accumulation observed in the EM pediatric patients was similar to that seen in EM adults in previous PK studies.

- The figure also shows the mean plasma concentration profiles, after converting to ng-equiv/ml and normalizing to a 1 mg/kg dose for 4-hydroxyatomoxetine and *N*-desmethylatomoxetine metabolites. The plasma concentrations and AUC values of these metabolites were much lower than atomoxetine. The mean parent to metabolite ratio (±SD) of AUC was 27.9±8.1 after single dose and 36.7±12.3 at steady state for 4-hydroxyatomoxetine; 16.2±7.4 after single dose and 23.0±16.0 at steady-state for *N*-desmethylatomoxetine. Although the active metabolite, 4-hydroxyatomoxetine, was measurable in plasma, the exposure of atomoxetine was approximately 20 to 30 times greater.

Effectiveness

The primary efficacy outcome instrument was the ADHDRS-IV-P: Inv. Analysis of baseline to endpoint change (last observation carried forward) with this measure revealed a statistically significant decrease in the ADHDRS-IV-P: Inv total score beginning with Visit 3 (1 week after beginning treatment with atomoxetine) and continuing through the final visit. The mean reduction at endpoint was 15.2 (95% CI [–20.3, -10.21]), which represented a mean percentage decrease of 37% from baseline. More than 50% of the reduction occurred during the first 3 weeks of treatment. Statistically significant decreases were also seen in both the Inattention and Hyperactivity-Impulsivity subscales of the ADHDRS-IV-P: Inv.

Analyses of secondary efficacy measures (CGI-ADHD-S and the Cognitive Problems, Hyperactivity, and ADHD Index subscales of the CORS-R:S) also revealed statistically significant reductions in severity ratings from baseline to endpoint. Sixteen patients (59.2%) met CGI-ADHD-I criteria (a score of 2 or less at endpoint) as treatment responders using an intent-to-treat analysis. In addition, 16 patients (59.2%) had endpoint scores on the CGI-EI indicating moderate or marked improvement with minimal or no adverse events. Too few teacher ratings were available for analyses of teacher rated instruments.

In this open-label study, atomoxetine was found to be effective in reducing the severity of ADHD symptoms in a pediatric population.

Evaluation of Effects of Intrinsic Factors

B4Z-LC-HFBM (Vol. 70): ***Single Dose Pharmacokinetics of Atomoxetine Hydrochloride in Subjects with End Stage Renal Disease***

The objectives of this study were to evaluate

(1) the influence of severe renal impairment on the plasma PK of atomoxetine and 4-hydroxyatomoxetine,
(2) the safety of a 20-mg single oral dose of atomoxetine in subjects with ESRD,
(3) plasma protein binding of atomoxetine in healthy control subjects and subjects with end-stage renal disease (ESRD), and
(4) the influence of severe renal impairment on the plasma PK of *N*-desmethylatomoxetine and the glucuronide conjugates of 4-hydroxyatomoxetine and *N*-desmethylatomoxetine.

Six ESRD subjects in Group 1 (requiring hemodialysis for at least 3 months, 5 Blacks, 1 Hispanic) and six healthy subjects (5 Caucasians and 1 Black) with normal renal function ($CL_{cr} \geq 90$ ml/min) received a single dose of 20 mg atomoxetine capsule (Lot CT14744).

The atomoxetine dose was administered in the afternoon after a 3-hour fast, except for water. After the dose, a 1-hour period of fasting was observed followed by a meal. Blood samples were taken with respect to each dose of atomoxetine: prior to dosing, then 1, 2, 4, 6, 8, 14, 20, 28 and 40 hours postdose. The 40-hour sample was taken prior to the next

dialysis treatment, and therefore the collection times vary. An additional 5 ml sample was drawn prior to the atomoxetine dose for an atomoxetine plasma protein binding evaluation. The samples were analyzed using .

Table 1. Individual Mean Atomoxetine Plasma Protein Binding Results

Subject #	Age	Gender	Origin	% Protein Binding (SEM)	Albumin (mg/dl)
			Healthy Contr		
0005-2785	36	M	Caucasian		
0006-3518	49	F	Caucasian		
0007-2773	40	F	Caucasian		
0009-3634	50	F	Caucasian		
0010-3721	46	F	Black		
0013-3512	35	F	Caucasian		
Group Mean±SD				**98.0±1.5**	**3.8±0.3**
			ESRD		
0001-3474	42	F	Black		
0002-2619	37	M	Black		
0003-2642	40	F	Black		
0004-3475	37	F	Black		
0008-3633	44	F	Hispanic		
0011-3691	44	M	Black		
Group Mean±SD				**94.8±6.9**	**3.6±0.3**

Table 2. Values of Atomoxetine Pharmacokinetic Parameters

Group	Cmax (ng/ml)	AUC_{0-t} (µg.hr/ml)	AUC_{0-inf} (µg.hr/ml)	CL/F (L/hr/kg)	V_z/F (L/kg)
Healthy (n=6)	92.3 (40)	0.496 (38)	0.507 (39)	0.470 (40)	2.25 (29)
ESRD (n=6)	105 4 (52)	1.00 (68)	1.02 (68)	0.422 (59)	2.82 (48)
	T_{max} (hr)	$t_{1/2}$ (hr)			
Healthy	1.0 (1.0-2.0)	3.5 (2.6-4.9)			
ESRD	3.0 (1.0-6.0)	5.1 (3.5-6.7)			

Table 3. Values of Pharmacokinetic Parameters for Metabolites of Atomoxetine

	4-Hydroxyatomoxetine		*N*-Desmethylatomoxetine		4-Hydroxyatomoxetine-*O*-G	
Parameter	Healthy	ESRD	Healthy	ESRD	Healthy	SERD
C_{max} (ng/ml)	1.9 (27)	1.5 (21)	2.3 (59)	7.6 (66)	313.7 (21)	681.5 (33)
AUC_{0-t} (µg.hr/ml)	0.0083 (58)	0.0294 (78)	0.0131 (116)	0.147 (98)	2.34 (15)	21.3 (34)
$AUC_{0-\infty}$ (µg.hr/ml)	–	–	–	0.181 (89)	2.41 (16)	–
T_{max} (hr)	4.0 (1-4)	4.0 (2-8)	3.0 (2-4)	6.0 (4-8)	2.0 (2-4)	20 (14-28)
$t_{1/2}$ (hr)	–	–	5.0-5.7	10.6 (5.7-17.6)	4.8 (4.1-5.2)	–