

Yook-Hwan Noh, Namyi Gu, Mi Jo Kim, Yo Han Kim, Hee Youn Choi, Kyun-Seop Bae, Hyeong-Seok Lim

Department of Clinical Pharmacology and Therapeutics,
Asan Medical Center and College of Medicine, University of Ulsan, Seoul, Korea

ABSTRACT

OBJECTIVES In general bioequivalence (BE) study is conducted in healthy volunteers with serial dense blood sampling for pharmacokinetics (PK). However, some drugs are inadequate to administer to healthy volunteers mainly for the toxicity. In this case, population modeling analysis with sparse concentration data in each patient could be an alternative option. The study was designed to explore the possible implementation of modeling method for BE test especially for drugs, the BE study of which can't be conducted in healthy volunteers for ethical reason such as cytotoxic anti-cancer agents with anastrozole as a model drug, BE study in healthy volunteers was done recently.

METHODS We evaluated the bioequivalency with AUC, and C_{max} as metrics using the same concentration data sets. The plasma concentration data was obtained from a BE study conducted in the Clinical Trial Center at the Asan Medical Center (Seoul, Korea). A total of 24 healthy male Korean volunteers were enrolled and evaluated for PK analysis. Participants were randomized to receive 1 mg of the test or reference formulation, and PK parameters were calculated by noncompartmental analysis using Phoenix WinNonlin® 6.1 (Pharsight Corporation, MO, USA). The formulations were considered bioequivalent if the 90% confidence intervals of the geometric mean ratios of test to reference formulations for AUC and Cmax were within the BE limits of 0.8 to 1.25. Nonlinear mixed-effect modeling for both formulations were also conducted using NONMEM® (ICON development solutions, Dublin, Ireland) and the results were used to characterize and compare the PK. In addition, Individual AUC and Cmax were calculated using NONMEM®, which were used for the BE test for both formulations.

RESULTS In noncompartmental analysis, the 90% confidence intervals of the geometric mean ratios of test formulation to reference formulation were 0.96–1.08 for C_{max} and 0.93–1.0 for AUC. In modeling analysis both formulations could be best described by a two-compartmental disposition model with lag phase in absorption and the 90% confidence intervals of the geometric mean ratios of test formulation to reference formulation were 0.96–1.04 for C_{max} and 0.92–0.99 for AUC_{last}.

METHODS

Clinical study design

•A single-center, open-label, 2x2 crossover, bioequivalence study

Volunteers

•A total of 24 healthy male Korean volunteers with no clinical abnormalities were enrolled.

RESULTS

Table 1. Baseline patient characteristics

Characteristics	Number of patients	Age (years)	Height (cm)	Weight (kg)
Median (Range)	24	26 (19 – 49)	175 (163 – 183)	68.2 (57 – 84.5)

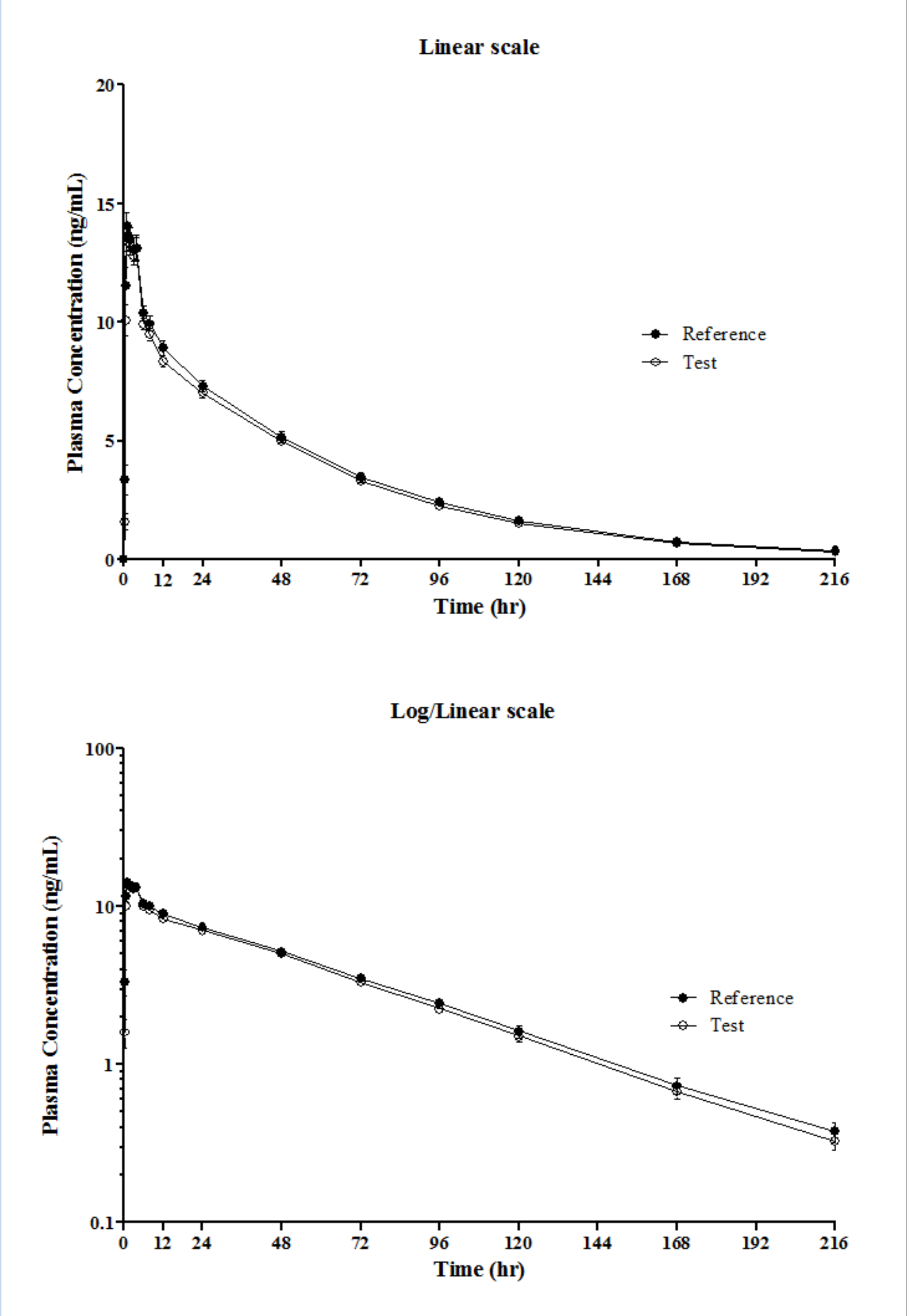


Figure 1. Mean plasma concentration-time profiles of anastrozole after oral administration of anastrozole. Bars represent standard errors. (upper: linear scale, lower; log-linear scale)

RESULTS (continued)

Table 2. Major Pharmacokinetic parameters of anastrozole

Method	Treatment	Variable	Number of patients	Mean	SD	CV%
Phoenix WinNonlin®	Reference drug	AUC _{last}	24	681.52	160.54	23.56
		C _{max}	24	14.83	2.58	17.37
	Test drug	AUC _{last}	24	647.79	118.02	18.22
		C _{max}	24	15.0	2.26	15.08
NONMEM®	Reference drug	AUC _{inf}	24	695.68	174.93	25.14
		C _{max}	24	14.25	2.27	15.94
	Test drug	AUC _{inf}	24	654.76	125.26	19.13
		C _{max}	24	14.19	1.88	14.06

Table 3. Geometric mean ratio of Pharmacokinetic parameters of anastrozole between test and reference drug

Method	Variable	Test vs Reference ratio (%)	90% Confidence Interval
Phoenix WinNonlin®	AUC _{last}	96.13	92.79 – 99.59
	C _{max}	101.50	95.75 – 107.58
NONMEM®	AUC _{inf}	95.36	92.06 – 98.77
	C _{max}	99.97	95.89 – 104.22

Abbreviations:
C_{max}: maximum concentration after oral administration, AUC_{last}: area under the curve from the administration time to the last drug concentration observable sampling time, AUC_{inf}: area under the curve from the administration time to infinity.

<pre>\$PROBLEM ARIMIDEX P:211 F:Test_PK \$INPUT ID TAD=TIME TAFD AMT RATE=DROP DV TRT PRD MDV AGE WT HT \$DATA ANA1C.CSV IGNORE=@ ; ACCEPT (TRTEQ,1) ; Test DRUG ONLY ; AMT(mg), DV(microg/l) \$\$SUBROUTINES ADVAN6 TOL=6 \$ABB COMRES=2 \$MODEL COMP=(DEPOT) COMP=(CENTRAL) COMP=(PERI) \$PK IF(NEWIND.LE.1) THEN COM(1) = -1 COM(2) = -1 ENDIF TVCL = THETA(1) TVV2 = THETA(2) TVQ = THETA(3) TVV3 = THETA(4) TVKA = THETA(5) CL = TVCL * EXP(ETA(1)) V2 = TVV2 * EXP(ETA(2)) Q = TVQ V3 = TVV3 * EXP(ETA(4)) KA = TVKA * EXP(ETA(3)) ALAG1 = THETA(8) * EXP(ETA(5)) S2 = V2 / 1000 K = CL / V2 K23 = Q / V2 K32 = Q / V3 \$DES DADT(1) = -A(1)*KA DADT(2) = A(1)*KA - (K+K23)*A(2) + A(3)*K32 DADT(3) = K23*A(2) - A(3)*K32 CONT = A(2)/S2 IF(CONT.GT.COM(1)) THEN COM(1) = CONT COM(2) = T ENDIF \$ERROR IPRED = F W = SQRT(THETA(6)**2 + THETA(7)**2 * IPRED**2) IRES = DV - IPRED IWRES = IRES / W Y = IPRED + W * EPS(1) IPRE = IPRED CMAX = COM(1) TMAX = COM(2) AUC = 1000/CL \$THETA (0, 1.2) ; TVCL (0, 4) ; TVV2 (0, 16) ; TVQ (0, 79) ; TVV3 (0, 0.28) ; TVKA 0.000001 FIX ; Additive Residual Variability (0, 0.1) ; Proportional Residual Variability (0, 0.32) ; lag time \$OMEGA BLOCK(4) 0.5 0.2 1 0.1 0.3 0.5 0.01 0.1 0.1 0.3 \$SIGMA 1 FIX \$EST MAXEVAL=9999 PRINT=2 METHOD = COND INTER SLOW MSFO=212.MSF \$COVARIANCE PRINT=E</pre>	<pre>\$PROBLEM ARIMIDEX P:201 F:Ref_PK \$INPUT ID TAD=TIME TAFD AMT RATE=DROP DV TRT PRD MDV AGE WT HT \$DATA ANA1C.CSV IGNORE=@ ; ACCEPT (TRTEQ,0) ; Reference DRUG ONLY ; AMT(mg), DV(microg/l) \$\$SUBROUTINES ADVAN4 \$ABB COMRES=2 \$PK IF(NEWIND.LE.1) THEN COM(1) = -1 COM(2) = -1 ENDIF TVCL = THETA(1) TVV2 = THETA(2) TVQ = THETA(3) TVV3 = THETA(4) TVKA = THETA(5) CL = TVCL * EXP(ETA(1)) V2 = TVV2 * EXP(ETA(2)) Q = TVQ V3 = TVV3 * EXP(ETA(4)) KA = TVKA * EXP(ETA(3)) ALAG1 = THETA(8) * EXP(ETA(5)) S2 = V2 / 1000 K = CL / V2 K23 = Q / V2 K32 = Q / V3 \$ERROR IPRED = F W = SQRT(THETA(6)**2 + THETA(7)**2 * IPRED**2) IRES = DV - IPRED IWRES = IRES / W Y = IPRED + W * EPS(1) IPRE = IPRED IF(F.GT.COM(1)) THEN COM(1) = F COM(2) = TIME ENDIF CMAX = COM(1) TMAX = COM(2) AUC = 1000/CL \$THETA (0, 1.2) ; TVCL (0, 6) ; TVV2 (0, 16) ; TVQ (0, 79) ; TVV3 (0, 0.29) ; TVKA 0.000001 FIX ; Additive Residual Variability (0, 0.1) ; Proportional Residual Variability (0, 0.29) \$OMEGA BLOCK(3) 0.2 0.1 0.8 0.05 0.1 0.2 \$SIGMA 1 FIX \$EST MAXEVAL=9999 PRINT=2 METHOD = COND INTER MSFO=202.MSF NOABORT NOTBT NOOBT NOSBT SIGDIGITS=3 \$COV PRINT=E</pre>
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Figure 2. NONMEM® codes for each test and reference drug modeling (two-compartment disposition model with lag time in absorption) after oral administration of anastrozole. (left: test drug, right: reference drug)

CONCLUSION

The BE test of both test and reference formulations had similar results for PK parameters such as AUC and C_{max} in both noncompartmental and modeling analysis, which suggest the possible use of modeling analysis in BE test with sparse concentration data. Through modeling and extensive simulation analysis, we expect that we could figure out the number of sampling point and subject number needed to obtain an accurate pharmacokinetic parameters. The simulation study to find out the least sampling points and subject numbers needed to estimate the equivalent results with true AUC and C_{max} is undergoing.