

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-100**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

9/5/07

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**  
**DIVISION OF CLINICAL PHARMACOLOGY I**

**NDA 22-100/0012**

**SUBMISSION DATE** August 15, 2007

**TYPE:** FDA REQUEST FOR INFORMATION – BIOWAIVER DATA

**BRAND NAME:** Azor® combination tablets

**GENERIC NAME:** Amlodipine Bezylate/Olmesartan Medoxomil

**DOSAGE STRENGTH:** 5/20, 10/20, and 5/40, and 10/40 mg oral immediate-release tablets

**INDICATION:** Essential Hypertension

**SPONSOR:** Daiichi Sankyo Inc.  
Eddison, NJ

**PRIMARY REVIEWER:** Lydia Velazquez, Pharm.D.

**TEAM LEADER:** Patrick Marroum, Ph.D.

**SUBMISSION**

On April 9, 2007 the Agency's Clinical Pharmacology reviewer requested additional biowaiver information, specific to similarity testing (f<sub>2</sub>) of the intermediate strengths (5/20, 10/20, and 5/40 mg AML/OLM, respectively) in order to assess if granting a biowaiver of a bioequivalence study was possible. This submission has been submitted by the sponsor, Daiichi Sankyo Inc. in order to satisfy the requirement for the additional data required for assessment. This review is focused on the review and assessment of whether a biowaiver can be granted for thre intermediate strength.

**RECOMMENDATION**

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 22-100 submitted on August 15, 2007 for Azor® Tablets and finds that a waiver for performing additional bioequivalence studies with the intermediate strengths is granted.

Please forward the above recommendation to the sponsor.

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Lydia Velazquez, Pharm.D.  
Division of Pharmaceutical Evaluation I  
Primary Reviewer

FT Initialed by Patrick Marroum, Ph.D. \_\_\_\_\_  
CC list: HFD-110: NDA 22-100; HFD-860: (VelazquezL, MarroumP, MehtaM, UppoorR);  
CDER Central Document Room

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Azor® combination tablets are to be marketed as 5/20, 10/20, 5/40, and 10/40 mg immediate release tablets for oral administration. The sponsor also developed a 5/10 and 10/10 mg combination tablet; but does not intend to market them. These strengths were developed for the purposes of establishing bioequivalence and obtaining a biowaiver for the intermediate strengths. Below is a table summarizing the composition of all strengths to be marketed with the OLM strength displayed first followed by AML:

Component	Function	10/5 mg	10/10 mg	20/5 mg	20/10 mg	40/5 mg	40/10 mg
<b>Cere Tablet (mg/tablet)</b>							
Olmesartan medoxomil	Drug substance	10.000	10.000	20.000	20.000	40.000	40.000
Amlodipine besylate	Drug substance	6.944 <sup>a</sup>	13.888 <sup>a</sup>	6.944 <sup>a</sup>	13.888 <sup>a</sup>	6.944 <sup>a</sup>	13.888 <sup>a</sup>
Starch, pregelatinized							
Silicified microcrystalline cellulose <sup>b</sup>							b(4)
Croscarmellose sodium							
Magnesium stearate							

Total Tablet Weight (mg)		105	105	105	208	208	208
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<sup>a</sup>Equivalent to 5 mg (6.944 mg) and 10 mg (13.888 mg) amlodipine base

<sup>b</sup>Silicified microcrystalline cellulose is comprised of 98% microcrystalline cellulose (NF/ EP/JP) and 2% colloidal silicon dioxide (NF). Colloidal silicon dioxide is also referred to as Silica, Colloidal Anhydrous in the EP and Light Anhydrous Silicic Acid in the IP.

<sup>c</sup>The qualitative and quantitative composition statement are incorporated by reference from Refer to Section 3.2.P.4.1.2.2

The sponsor did use the lot numbers from the biobatches administered in the bioequivalence study AE102 for the generation of  $f_2$  calculations for the reference strength of 10/40 mg AML/OLM.

#### F<sub>2</sub> SIMILARITY COMPARISON:

**pH 1.2** – both AML and OLM dissolved  $\geq 85\%$  within 10 minutes for all strengths utilizing Apparatus II paddle speed 50 and 75 rpms. As a result,  $f_2$  calculations are not required.

**pH 4.5** – AML dissolved  $\geq 85\%$  within 5 minutes for all strengths utilizing Apparatus II paddle speed 50 and 75 rpms. As a result,  $f_2$  calculations are not required for AML.

OLM  $f_2$  calculations for all strengths are depicted below. OLM does not seem to be readily soluble in pH 4.5. In addition, the sponsor only sampled out to 60 minutes when

performing their dissolution test for all strengths and both paddle speeds. As a result, the reviewer is unable to establish f2 similarity with pH 4.5 (see below):

**F<sub>2</sub> Calculation for CS-8663 Tablets using 900 mL 0.05M Acetic Buffer (pH 4.5) Media and 50 rpm Paddle Speed using six time points**

Dosage Strength	Lot no.	Table Ref.	AML Mean % Dissolved (n=12 tablets)						AML f2 (n=6 TP)	OM Mean % Dissolved (n=12 tablets)						OM f2 (n=6 TP)
			5 min.	10 min.	20 min.	30 min.	45 min.	60 min.		5 min.	10 min.	20 min.	30 min.	45 min.	60 min.	
5/20 mg	3220V05002	33	89.7	-	-	-	-	-	NR	7.0	11.2	14.9	17.0	18.6	19.6	65
10/20 mg	3221V05001	35	86.0	-	-	-	-	-	NR	7.5	12.3	16.2	18.0	19.5	20.4	61
5/40 mg	3223V05002	37	89.5	-	-	-	-	-	NR	5.7	8.6	10.5	11.4	12.1	12.5	100
10/40 mg	3223V05008	39	92.3	-	-	-	-	-	REF	6.0	8.8	10.6	11.5	12.1	12.5	REF
Reference																

Legend: TP = time points REF = Reference NR = Not required

**F<sub>2</sub> Calculation for CS-8663 Tablets using 900 mL 0.05M Acetic Buffer (pH 4.5) Media and 75 rpm Paddle Speed using six time points**

Dosage Strength	Lot no.	Table Ref.	AML Mean % Dissolved (n=12 tablets)						AML f2 (n=6 TP)	OM Mean % Dissolved (n=12 tablets)						OM f2 (n=6 TP)
			5 min.	10 min.	20 min.	30 min.	45 min.	60 min.		5 min.	10 min.	20 min.	30 min.	45 min.	60 min.	
5/20 mg	3220V05002	34	99.8	-	-	-	-	-	NR	8.5	12.8	16.5	18.2	19.7	20.6	61
10/20 mg	3221V05001	36	98.3	-	-	-	-	-	NR	9.6	14.5	17.9	19.4	20.7	21.5	58
5/40 mg	3222V05002	38	96.2	-	-	-	-	-	NR	6.6	9.2	11.0	11.7	12.4	12.8	100
10/40 mg	3223V05008	40	99.3	-	-	-	-	-	REF	6.7	9.3	11.0	11.7	12.4	12.7	REF
Reference																

Legend: TP = time points REF = Reference NR = Not required

According to the "Guidance for Industry – Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation":

Multi-point dissolution profiles performed in water, 0.1N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.

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pH 6.8 AML dissolved within 5 minutes for all strengths utilizing Apparatus II paddle speed 50 and 75 rpms. As a result,  $f_2$  calculations are not required for AML.

b(4)

OLM  $f_2$  calculations for all strengths is depicted below. The sponsor sampled beyond  $\geq$  dissolved and incorporated the data into their  $f_2$  calculations. As a result, all calculations for pH 6.8 for OLM were recalculated by the Clinical Pharmacology reviewer. Below are the new results for OLM:

**F2 calculation using 900 mL JP 2<sup>nd</sup> fluid (pH6.8) media and 50 rpm Paddle speed:**

Dosage Strength	5 min	10 min	20 min	30 min	F <sub>2</sub>
5/20 mg	53.0	72.8	85.9	90.5	65.9
10/20 mg	44.4	69.4	82.9	87.3	90
5/40 mg	48.8	71.4	85.0	90.2	73.4
10/40 mg	44.2	67.4	80.9	85.7	REF
Reference					

**F2 calculation using 900 mL JP 2<sup>nd</sup> fluid (pH6.8) media and 75 rpm Paddle speed:**

Dosage Strength	5 min	10 min	20 min	F <sub>2</sub>
5/20 mg	57.7	79.8	93.3	59.5
10/20 mg	54.2	77.2	90.7	72.1
5/40 mg	54.8	77.7	90.4	70.4
10/40 mg	50.8	73.4	87.5	REF
Reference				

For pH 6.8 all strengths passed the  $F_2$  similarity comparisons calculations.

**REVIEWER'S COMMENTS:**

Even though the sponsor did not perform a correct  $F_2$  calculation in pH 4.5, the likelihood of not passing a  $F_2$  similarity comparison is unlikely since up to the 60 minute time point all strengths had passed in relation to the reference.

Since the dissolution method and specifications for Azor are with a media pH of 6.8, the  $F_2$  similarity calculation in pH 4.5 is not as critical.

As a result, the requirement for biostudies for the intermediate strengths is not required and a biowaiver is granted.

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/s/

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Lydia Velazquez  
9/5/2007 01:37:53 PM  
BIOPHARMACEUTICS

Biowaiver

Patrick Marroum  
9/5/2007 04:30:55 PM  
BIOPHARMACEUTICS

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**  
**DIVISION OF CLINICAL PHARMACOLOGY I**

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<b>NDA 22-100/N000</b>	<b>SUBMISSION DATE</b>	November 27, 2006
BB000		December 8, 2006
BZ000		February 12, 2007
SU000		March 27, 2007
BL000		April 9, 2007
BB000		June 8, 2007

**TYPE:** ORIGINAL NEW DRUG APPLICATION

**BRAND NAME:** Azor® combination tablets

**GENERIC NAME:** Amlodipine Bezylate/Olmesartan Medoxomil

**DOSAGE STRENGTH:** 5/20, 10/20, and 5/40, and 10/40 mg oral immediate-release tablets

**INDICATION:** Essential Hypertension

**SPONSOR:** Daiichi Sankyo Inc.  
Eddison, NJ

**PRIMARY REVIEWER:** Lydia Velazquez, Pharm.D.

**TEAM LEADER:** Patrick Marroum, Ph.D.

**PM Reviewer:** Rajnikanth Madabushi, Ph.D.

**PM Team Leader:** Yaning Wang, Ph.D.

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## EXECUTIVE SUMMARY

Daiichi Sankyo Inc. is seeking approval of Azor® combination Tablets for the treatment of hypertension. Azor® contains the active ingredients Amlodipine Besylate and Olmesartan Medoxomil. Amlodipine Besylate is a 1, 4-dihydropyridine derivative calcium channel blocker and Olmesartan Medoxomil is an antagonist of angiotensin II (type AT1). The submitted NDA application is for an immediate release tablet formulation that is to be taken once daily orally designed to deliver 5/20, 10/20, 5/40, and 10/40 mg of amlodipine besylate and Olmesartan medoxomil, respectively.

Section 5 of NDA 22-100 includes 13 studies. However, 7 studies conducted were with earlier formulations and are of no relevance to the final market image formulation chosen. The remaining 6 studies deal with a dose-proportionality (study U112), bioequivalence (study U111), drug interaction between amlodipine and olmesartan (study U101), bioavailability of 3 amlodipine formulations (study E102) used in their phase III trial (study 301), pharmacometrics report from their phase III study U301, and food effect (study U110) study conducted in healthy volunteers. A biowaiver has been requested for the intermediate strengths of Azor. As a result, F2 similarity dissolution data has been submitted.

### Studies submitted:

Study U112 was a dose proportionality study demonstrating that Amlodipine is more than dose-proportional and Olmesartan seems to be slightly less than dose-proportional. Results for Olmesartan are not clinically significant.

Study U111 was a bioequivalence study of the clinical trial formulations and the final market image formulation which resulted in bioequivalence being established.

Drug interaction study U101 between amlodipine and olmesartan was successful in demonstrating that no drug interaction exists between the two drugs.

In study E102, three amlodipine besylate formulations were tested for bioequivalence: Istin® from the UK, Antacal® from Italy and Norvasc® from the US. Demonstration of bioequivalence between the three formulations was performed successfully.

Food effect study U110 determined that no food effect was observed with the new fixed dose combination of Azor®.

Study 301 is a Phase III study in the targeted population that was used to generate pharmacometrics data as well as data from studies U101, U110, U111, and U112. The data analyzed found that no geriatric or gender related changes were detected with the use of the combination therapy. The drug effect of olmesartan exposure on  $\Delta$ SeDBP was described by an Emax model, whereas the drug effect of amlodipine exposure on  $\Delta$ SeDBP was described by a linear model. In the exposure-response model, black race was the most important covariate, decreasing the maximal possible effect of olmesartan on blood pressure while increasing the effect of amlodipine, without influencing pharmacokinetic parameters. The drug effect for combination therapy was defined on the basis of exposures to both compounds, and it was greater than either of the monotherapy arms alone.

The request for a biowaiver for the intermediate strengths can not be granted since the sponsor has not provided sufficient data to verify the calculations made and no data in three different media was provided. The sponsor will be required to provide data in 3 media and to include raw data with detailed information for the confirmation that an F2 similarity comparison between the reference strengths (10/40 mg and 5/10 mg) and the intermediate strengths (5/40, 10/20, 5/20, 5/40 mg of AML/OLM) have been performed in order for us to be able to grant a biowaiver.

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## RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 22-100 submission dates November 27, December 8, 2006 and February 12, March 27, April 9, June 8, 2007 for Azor® Combination Tablets (amlodipine besylate/olmesartan medoxomil) and finds the clinical pharmacology and biopharmaceutics section acceptable. The request for a biowaiver for the intermediate strengths can not be granted. The following recommendations should be addressed by the sponsor:

### REVIEWER COMMENTS TO THE SPONSOR:

#### 1. Labeling

Please refer to the attached label in Appendix I for editorial changes made to the labeling (recommendations in red).

#### 2. Biowaiver of the Intermediate strengths

The request for a biowaiver for the intermediate strengths can not be granted since the sponsor has not provided sufficient data to verify the calculations made and no data in three different media was provided. The sponsor will be required to provide data in 3 media and to include raw data with detailed information for the confirmation that an F2 similarity comparison between the reference strengths (10/40 mg and 5/10 mg) and the intermediate strengths (5/40, 10/20, 5/20, 5/40 mg of AML/OLM) have been performed in order for us to be able to grant a biowaiver.

Lydia Velazquez, Pharm.D.  
Division of Pharmaceutical Evaluation I  
Primary Reviewer

FT      Initialed by Patrick Marroum, Ph.D. \_\_\_\_\_

OCPB Briefing was held on July 25<sup>th</sup>, 2007. Attendees: Lydia Velazquez, Mehul Mehta, Patrick Marroum, Rajnikanth Madabushi, Akinwale Williams, Denise Hinton, Elena Mishina, Atul Bhattaram, Christoffer Tornoe, Ting Eng C. Ong, and Lei K Zhang.

CC list: HFD-110: NDA 22-100; HFD-860: (VelazquezL, MarroumP, MehtaM, UppoorR, StockbridgeN); CDER Central Document Room

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## Summary of Important CPB Findings

**Exposure-Response Relationship in terms of Efficacy:** Changes in sitting diastolic blood pressure ( $\Delta$ SeDBP) were found to be related to the exposures of olmesartan and amlodipine as represented by steady-state AUC. The drug effect of olmesartan exposure on  $\Delta$ SeDBP was described by an Emax model, whereas the drug effect of amlodipine exposure on  $\Delta$ SeDBP was described by a linear model. The drug effect for combination therapy was defined on the basis of exposures to both compounds, and it was greater than either of the monotherapy arms alone.

**Age Related Differences:** Based on the results of the population pharmacokinetic analysis, age was not found to be a significant predictor of the apparent oral clearance of olmesartan. However, the oral clearance of amlodipine decreased with increasing age and this relationship was found to be statistically significant. This is consistent with the literature for amlodipine. This effect of age on the clearance of amlodipine is not clinically significant enough to warrant dose adjustment in geriatrics for the proposed indications.

**Gender Based Differences:** Population pharmacokinetic analysis indicated that female patients had approximately 15% smaller clearances of olmesartan than male patients. The resulting increase in exposure does not warrant any dose adjustment in females. Gender had no effect on the clearance of amlodipine.

**Dose Proportionality:** Amlodipine is slightly more than dose-proportional and olmesartan is slightly less than dose-proportional.

Pharmacokinetic parameters for Amlodipine following 5 and 10 mg administration:

PK Parameters	Treatments A, C, E (10 mg) (n=87)	Treatments B, D, F (5 mg) (n=87)
<b>AUC<sub>0-t</sub> (pg.h/mL)</b>		
Arithmetic Mean $\pm$ SD	385781.6 $\pm$ 92061.31*	172521.5 $\pm$ 47681.79
Geometric Mean (CV%)	374920.0 (24.6%)*	166322.8 (27.6%)
<b>AUC<sub>0-inf</sub> (pg.h/mL)</b>		
Arithmetic Mean $\pm$ SD	455031.4 $\pm$ 137254.8*	200276.3 $\pm$ 69445.50
Geometric Mean (CV%)	435742.6 (30.2%)*	189816.2 (33.2%)
<b>AUC<sub>0-t</sub> / AUC<sub>0-inf</sub></b>		
Arithmetic Mean $\pm$ SD	0.8630 $\pm$ 0.06469*	0.8787 $\pm$ 0.06387
<b>C<sub>max</sub> (pg/mL)</b>		
Arithmetic Mean $\pm$ SD	7699.77 $\pm$ 1436.986	3621.0 $\pm$ 806.16
Geometric Mean (CV%)	7555.96 (20.3%)*	3527.8 (23.8%)
<b>T<sub>max</sub> (h)</b>		
Median (Min – Max)	8.000 (6.00 – 12.00)	8.000 (5.98 – 12.00)
<b>T<sub>1/2</sub> (h)</b>		
Arithmetic Mean $\pm$ SD	51.64 $\pm$ 14.094*	48.41 $\pm$ 13.104

Treatment A = Olmesartan medoxomil 40 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment B = Olmesartan medoxomil 20 mg/ Amlodipine besylate 5 mg fixed combination oral tablet  
 Treatment C = Olmesartan medoxomil 10 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment D = Olmesartan medoxomil 40 mg/ Amlodipine besylate 5 mg fixed combination oral tablet  
 Treatment E = Olmesartan medoxomil 20 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment F = Olmesartan medoxomil 10 mg/ Amlodipine besylate 5 mg fixed combination oral tablet  
 \*n=86; Cohort 1 = Treatments A,B,C; Cohort 2 = Treatments D,E,F

Source: Tables 14.2.1.28 and 14.2.1.29.

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Corresponding 90% confidence interval for Amlodipine:

PK Parameters	Geometric Mean		Ratio (90% CI) (5 mg, 10 mg)	90% CI (Lower, Upper) (%)
	5 mg amlodipine (B, D and E pooled)	10 mg amlodipine (A, C and F pooled)		
AUC <sub>0-t</sub>	33864.4	36747.3	92.2	(90.2, 94.2)
AUC <sub>0-inf</sub> *	39148.0	42589.2	91.9	(89.7, 94.2)
C <sub>max</sub>	706.5	753.5	93.8	(91.7, 95.9)

\* treatment\*cohort term kept in model

Pharmacokinetic parameters for Olmesartan following 10, 20 and 40 mg administration:

PK Parameters	Treatments A and D (40 mg) (n=59)	Treatments B and E (20 mg) (n=57)	Treatments C and F (10 mg) (n=58)
	<b>AUC<sub>0-t</sub> (ng.h/mL)</b>		
Arithmetic Mean ±SD	6006.4 ± 1715.33	3512.39 ± 983.589**	1885.0 ± 527.01
Geometric Mean (CV%)	5756.3 (30.8%)	3369.51 (30.6%)**	1809.0 (30.3%)
<b>AUC<sub>0-inf</sub> (ng.h/mL)</b>			
Arithmetic Mean ±SD	6096.2 ± 1769.47*	3573.84 ± 1013.276***	1921.0 ± 533.62
Geometric Mean (CV%)	5833.8 (31.4%)*	3424.02 (31.1%)***	1845.4 (29.8%)
<b>AUC<sub>0-t</sub> / AUC<sub>0-inf</sub></b>			
Arithmetic Mean ±SD	0.9848 ± 0.01591*	0.9865 ± 0.01151***	0.9803 ± 0.01358
<b>C<sub>max</sub> (ng/mL)</b>			
Arithmetic Mean ±SD	928.2 ± 260.90	574.877 ± 159.8304	337.2 ± 123.06
Geometric Mean (CV%)	889.8 (31.0%)	552.528 (29.7%)	319.2 (33.7%)
<b>T<sub>max</sub> (h)</b>			
Median (Min – Max)	2.000 (1.00 – 6.02)	2.000 (1.00 – 4.00)	1.767 (1.00 – 4.02)
<b>T<sub>1/2</sub> (h)</b>			
Arithmetic Mean ±SD	15.054 ± 6.6240*	14.021 ± 6.2096***	14.243 ± 5.6226

Treatment A = Olmesartan medoxonil 40 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment B = Olmesartan medoxonil 20 mg/ Amlodipine besylate 5 mg fixed combination oral tablet  
 Treatment C = Olmesartan medoxonil 10 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment D = Olmesartan medoxonil 40 mg/ Amlodipine besylate 5 mg fixed combination oral tablet  
 Treatment E = Olmesartan medoxonil 20 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment F = Olmesartan medoxonil 10 mg/ Amlodipine besylate 5 mg fixed combination oral tablet  
 Cohort 1 = Treatments A,B,C; Cohort 2 = Treatments D,E,F

\*n=58; \*\*n=56; \*\*\*n=54  
 Source : Tables 14.2.1.10-12

Corresponding 95% confidence interval of the slope estimates for each pharmacokinetic parameter from the two cohorts pooled together for Olmesartan:

PK Parameters	Slope Estimates	95% CI (Lower, Upper)
ln AUC <sub>0-t</sub>	0.84	(0.79, 0.88)
ln AUC <sub>0-inf</sub>	0.83	(0.79, 0.87)
ln C <sub>max</sub>	0.74	(0.69, 0.80)

**Evidence of a Drug Interaction between Amlodipine and Olmesartan:** Twenty-four subjects were enrolled in this study in order to determine the pharmacokinetic impact each drug had on the other under steady state conditions. Neither drug impacted the pharmacokinetics of the other when tested:

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Bioequivalence was assessed between the two treatment regimens using an ANOVA model. Results are presented below.

Amlodipine	Geometric LSM		Ratio of LSM (C/B) (%)	90% CI (%)
	Treatment C	Treatment B		
AUC <sub>t</sub>	360.2	334.3	107.7	(100.1, 115.9)
C <sub>ss,max</sub>	18.7	18.5	100.7	(91.3, 111.1)

\* Values for Treatments B and C are the least-squares means (LSMEANS) from the ANOVA back-transformed to the original scale  
Source: Table 14.2.8.

The ratio of geometric LSM and 90% confidence intervals for AUC<sub>t</sub> and C<sub>ss,max</sub> of amlodipine were all within the 80.0 to 125.0% limit. Therefore, the concomitant administration of olmesartan (Benicar® 40 mg tablet) did not affect the rate and extent of exposure of amlodipine besylate (Norvasc® 10 mg tablet) under fasting conditions.

Steady state plasma concentration levels of amlodipine were reached by Day 9 for Treatments B and C. This confirms that the PK assessment on Day 10 was performed under steady state conditions, and further demonstrated that co-administration with olmesartan had no effect on the half-life of amlodipine.

Bioequivalence assessment between the two treatments with Olmesartan (C = combined therapy, A = olmesartan alone) using an ANOVA model:

Parameters	Geometric LSM*		Ratio of LSM (C/A) (%)	90% CI (%)
	Treatment C	Treatment A		
AUC <sub>t</sub>	6640.8	6567.9	101.1	(91.5, 109.4)
C <sub>ss,max</sub>	996.1	1046.1	95.2	(87.2, 103.9)

Treatment A = 40 mg Olmesartan Medoxonal Tablet QD for 10 Days  
Treatment C = 40 mg Olmesartan Medoxonal Tablet and 10 mg Amlodipine Besylate Tablet QD for 10 Days  
\*Values for Treatments A and C are the least-squares means (LSMEANS) from the ANOVA back-transformed to the original scale  
Source: Table 14.2.7

The ratio of geometric LSM and 90% confidence intervals for AUC<sub>t</sub> and C<sub>ss,max</sub> of olmesartan were all within the 80.0 to 125.0% limit. Therefore, the concomitant administration of amlodipine besylate (Norvasc® 10 mg tablet) did not affect the rate and extent of exposure of olmesartan (Benicar® 40 mg tablet) under fasting conditions.

Steady state levels of olmesartan were reached by Day 9 for Treatments A and C. This confirms that the PK assessment on Day 10 was performed under steady state conditions, and further demonstrated that co-administration with amlodipine had no effect on the elimination half-life of olmesartan.

**Demonstration of Bioequivalence:** The sponsor conducted two bioequivalence studies. The first study was conducted to establish bioequivalence between three amlodipine besylate formulations (Treatment A = *Istin®* from the UK, Treatment B = *Norvasc®* from the US and Treatment C = *Antacal®* from Italy) and the second bioequivalence study was conducted to establish bioequivalence between the final market image and the monotherapies utilized in the clinical trials.

The first bioequivalence study demonstrated that there were no pharmacokinetic differences between the three amlodipine besylate formulations utilized throughout some of the clinical studies (*Istin®* from the UK, *Antacal®* from Italy and *Norvasc®* from the US):

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Bioequivalence of amlodipine between the three tablet formulations was assessed using an ANOVA model. Results are presented below:

Parameter	Comparison	Ratio of LSM (%)	90% CI (%) (Lower - Upper)
AUC <sub>0-t</sub> [ng.h/mL]	Treatment A <sup>1</sup> vs. B <sup>2</sup>	99.2	(94.1, 104.7)
	Treatment A <sup>1</sup> vs. C <sup>3</sup>	98.8	(93.6, 104.2)
	Treatment B <sup>2</sup> vs. C <sup>3</sup>	99.5	(94.3, 105.0)
AUC <sub>0-inf</sub> [ng.h/mL]	Treatment A <sup>1</sup> vs. B <sup>2</sup>	98.9	(94.0, 104.2)
	Treatment A <sup>1</sup> vs. C <sup>3</sup>	98.1	(93.2, 103.3)
	Treatment B <sup>2</sup> vs. C <sup>3</sup>	99.2	(94.2, 104.4)
C <sub>max</sub> [ng/mL]	Treatment A <sup>1</sup> vs. B <sup>2</sup>	108.6	(100.9, 116.8)
	Treatment A <sup>1</sup> vs. C <sup>3</sup>	98.0	(90.8, 105.7)
	Treatment B <sup>2</sup> vs. C <sup>3</sup>	90.3	(83.7, 97.3)

<sup>1</sup> Istia<sup>®</sup> 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (UK formulation)

<sup>2</sup> Norvasc<sup>®</sup> 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (US formulation)

<sup>3</sup> Antacal<sup>®</sup> 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (Italian formulation)

Source: Table 14.2.1.4.2

The second bioequivalence study also successfully demonstrated no differences between the monotherapies of Olmetec and Antacal versus Azor fixed dose combination. The highest (AML 10/OLM 40 mg) and lowest dose (AML 5/OLM 10 mg) of the formulation were tested:

Cohort 1:

Amlodipine	Geometric LSM		Ratio (A/B) of LSM (%)	90% CI (Lower - Upper) (%)	Intra-Subject CV (%)
	Treatment A (n = 30)	Treatment B (n = 30)			
AUC <sub>0-t</sub> (pg.h/mL)	146500.5	144154.0	101.63	(99.13, 104.2)	5.7
AUC <sub>0-inf</sub> (pg.h/mL)	160308.7	157724.4	101.64	(99.04, 104.3)	5.9
C <sub>max</sub> (pg/mL)	3074.2	3104.8	99.01	(95.65, 102.5)	7.9

Treatment A: CS-8663 tablet (olmesartan medoxomil 10 mg and amlodipine besylate 5 mg)

Treatment B: Olmesartan medoxomil 10 mg (Olmetec<sup>®</sup>) tablet coadministered with amlodipine besylate 5 mg (Antacal<sup>®</sup>) tablet

Source: Table 14.2.1.21.

Cohort 2:

Amlodipine	Geometric LSM		Ratio (C/D) of LSM (%)	90% CI (Lower - Upper) (%)	Intra-Subject CV (%)
	Treatment C (n = 29)	Treatment D (n = 29)			
AUC <sub>0-t</sub> (pg.h/mL)	307935.3	303067.1	101.61	(97.25, 106.2)	9.7
AUC <sub>0-inf</sub> (pg.h/mL)	336543.6	332572.6	101.19	(96.58, 106.0)	10.3
C <sub>max</sub> (pg/mL)	6625.3	6118.6	108.28	(103.2, 113.6)	10.5

Treatment C: CS-8663 tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)

Treatment D: Olmesartan medoxomil 40 mg (Olmetec<sup>®</sup>) tablet coadministered with amlodipine besylate 10 mg (Antacal<sup>®</sup>) tablet

Source: Table 14.2.1.22

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Cohort 1:

Parameters	Geometric LSM		Ratio (A/B) of LSM (%)	90% CI (Lower, Upper) (%)	Intra-Subject CV (%)
	Treatment A (n = 30)	Treatment B (n = 30)			
AUC <sub>0-t</sub> (ng·h/mL)	1824.7	1696.3	107.57	(99.67, 116.1)	17.5
AUC <sub>0-inf</sub> (ng·h/mL)	1857.1	1729.4*	107.39	(99.42, 116.0)	17.4
C <sub>max</sub> (ng/mL)	338.0	295.7	114.30	(106.6, 122.5)	15.9

Treatment A: CS-8663 tablet (olmesartan medoxomil 10 mg and amlodipine besylate 5 mg)  
 Treatment B: Olmesartan medoxomil 10 mg (Olmotec<sup>®</sup>) tablet coadministered with amlodipine besylate 5 mg (Antacal<sup>®</sup>) tablet  
 \* n = 29 (value could not be estimated for one subject)  
 Source: Table 14.2.1.9

Cohort 2:

Olmesartan	Geometric LSM		Ratio (C/D) of LSM (%)	90% CI (Lower, Upper) (%)	Intra-Subject CV (%)
	Treatment C (n = 29)	Treatment D (n = 29)			
AUC <sub>0-t</sub> (ng·h/mL)	5790.3	5164.8	112.11	(103.3, 121.6)	18.1
AUC <sub>0-inf</sub> (ng·h/mL)	5976.7*	5265.7	113.50	(104.7, 123.0)	17.4
C <sub>max</sub> (ng/mL)	911.9	831.0	109.73	(101.8, 118.3)	16.8

Treatment C: CS-8663 tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)  
 Treatment D: Olmesartan medoxomil 40 mg (Olmotec<sup>®</sup>) tablet coadministered with amlodipine besylate 10 mg (Antacal<sup>®</sup>) tablet  
 \* n = 27 (value could not be estimated for two subjects)  
 Source: Table 14.2.1.10.

**Food Effect:** Food had no impact on the pharmacokinetics of Azor when administered at the highest dose:

The rate and extent of bioavailability of amlodipine was similar when CS-8663 was administered with or without food. The mean terminal elimination half-life of amlodipine was approximately 40 hours for both treatments.

Parameters	Geometric LSM		Ratio (A/B) of LSM (%)	90% CI (Lower, Upper) (%)
	Treatment A (n = 28)	Treatment B (n = 27)		
AUC <sub>(0-t)</sub> (pg·h/mL)	306975.4	299179.0	102.61	(99.59, 105.7)
AUC <sub>(0-inf)</sub> (pg·h/mL)	334343.7	326058.9	102.54	(99.20, 106.0)
C <sub>max</sub> (pg/mL)	6354.2	6400.8	99.27	(95.98, 102.7)

Treatment A: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) with a high-fat breakfast  
 Treatment B: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) after an overnight fast  
 Source: Table 14.2.1.11.

The effect of food on the bioavailability of olmesartan was assessed using an ANOVA model. Results are presented below.

Parameters	Geometric LSM		Ratio (A/B) of LSM (%)	90% CI (Lower, Upper) (%)
	Treatment A (n = 28)	Treatment B (n = 27)		
AUC <sub>0-t</sub> (ng·h/mL)	5259.6	6034.3	87.16	(82.50, 92.09)
AUC <sub>0-inf</sub> (ng·h/mL)	5366.5*	6111.7	87.81	(82.97, 92.92)
C <sub>max</sub> (ng/mL)	881.9	939.5	93.87	(87.41, 100.8)

Treatment A: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) with a high-fat breakfast  
 Treatment B: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) after an overnight fast  
 n = 27  
 Source: Table 14.2.1.5.

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**Assay Validation:** For most studies.

Amlodipine concentrations were analyzed by a validated LC-MS/MS with an LLOQ of 0.050 to 0.5 ng/mL (depending on study) and  $r^2$  of at least 0.9919. Precision was in the range of 2.6 to 5.7%. Accuracy was  $\geq 94.8\%$ .

Olmesartan plasma concentrations were determined by a validated LC-MS/MS method. The LLOQ was 1.00 ng/mL with a coefficient of determination  $r^2$  of  $\geq 0.9908$ . Precision was  $\leq 7.5\%$  and the range in accuracy was -2.1 to 8.5%.

In the dose-proportionality study (U112), both amlodipine and olmesartan were assayed differently:

Amlodipine: assessed by a validated HPLC with mass spectrometric detection with an LLOQ of 50.0 pg/mL. The coefficient of determination was  $\geq 0.9975$ . The accuracy ranged from -6.7 to -6.9% and the precision was  $\leq 4.5\%$

Olmesartan medoxomil: assessed by a validated HPLC with mass spectrometric detection with an LLOQ of 1.00 ng/mL. The coefficient of determination was  $\geq 0.9910$ . The accuracy ranged from 1.3 to 3.0% and the precision was  $\leq 5.4\%$ .

**Biowaiver:** The request for a biowaiver for the intermediate strengths can not be granted since the sponsor has not provided sufficient data to verify the calculations made and no data in three different media was provided.

**Labeling:** Recommendations that should be addressed by the sponsor are illustrated in the proposed package insert in Appendix I in red.

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# QUESTION BASED REVIEW

## I. INTRODUCTION

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

#### FORMULATION AND MANUFACTURING

Azor® combination tablets are to be marketed as 5/20, 10/20, 5/40, and 10/40 mg immediate release tablets for oral administration. The sponsor is also developing a 5/10 and 10/10 mg combination tablet; but does not intend to market them. These strengths were developed for the purposes of establishing bioequivalence and obtaining a biowaiver for the intermediate strengths. This new formulation is a tablet composed of both drug substances blended together and then made into a tablet that is film coated. Below is a table summarizing the composition of all strengths to be marketed:

Component	Function	10/5 mg	10/10 mg	20/5 mg	20/10 mg	40/5 mg	40/10 mg
<b>Core Tablet (mg/tablet)</b>							
Olmesartan medoxomil	Drug substance	10.000	10.000	20.000	20.000	40.000	40.000
Amlodipine besylate	Drug substance	6.944 <sup>a</sup>	13.888 <sup>a</sup>	6.944 <sup>a</sup>	13.888 <sup>a</sup>	6.944 <sup>a</sup>	13.888 <sup>a</sup>
Starch, pregelatinized							
Silicified microcrystalline cellulose <sup>b</sup>							
Croscarmellose sodium							
Magnesium stearate (vegetable origin)							

b(4)

Total Tablet Weight (mg)		105	105	105	208	208	208
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<sup>a</sup> Equivalent to 5 mg (6.944 mg) and 10 mg (13.888 mg) amlodipine base

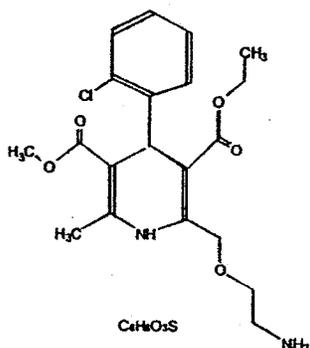
<sup>b</sup> Silicified microcrystalline cellulose is comprised of 98% microcrystalline cellulose (NF/ EP/JP) and 2% colloidal silicon dioxide (NF). Colloidal silicon dioxide is also referred to as Silica, Colloidal Anhydrous in the EP and Light Anhydrous Silicic Acid in the JP.

<sup>c</sup> The qualitative and quantitative composition statement are incorporated by reference. Refer to Section 3.2.P.4.1.2.2

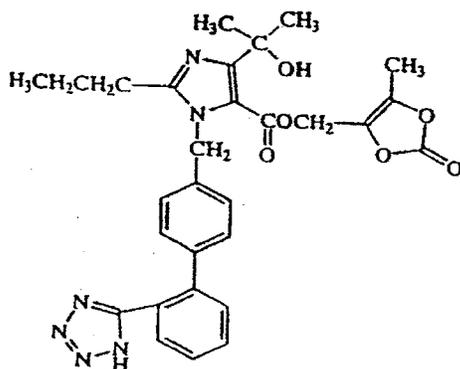
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The structural formula for amlodipine besylate is:



The structural formula for olmesartan medoxomil is:



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

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound ( $pK_a=8.6$ ), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Olmesartan - Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation

of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis. An AT<sub>2</sub> receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor.

### C. WHAT IS THE PROPOSED DOSAGE AND ADMINISTRATION?

#### *Replacement Therapy*

Azor may be substituted for its individually titrated components. Patients may be given the equivalent dose of Azor a dose of Azor with increased amounts of amlodipine, olmesartan, or both for additional blood pressure lowering effect. The dose of Azor may be increased after 2 weeks in patients requiring further reduction in blood pressure to achieve goal, to a maximum dose of 10/40 mg once daily.

#### *Add-on Therapy for Patients with Hypertension Not Adequately Controlled on Amlodipine or Olmesartan Alone*

It is usually appropriate to begin therapy after a patient has either (a) failed to achieve the desired antihypertensive effect with amlodipine or olmesartan alone, or (b) demonstrated inability to achieve adequate antihypertensive effect with amlodipine therapy without developing unacceptable edema. In these patients, therapy with Azor may achieve blood pressure control without unacceptable edema. It may be used to provide additional blood pressure lowering for patients not adequately controlled on amlodipine (or another dihydropyridine) alone or with olmesartan (or another angiotensin receptor blocker) alone. The starting dose should be selected based on the dose of the component already in use. The dose of Azor may be increased after 2 weeks in patients requiring further reduction in blood pressure to goal, to a maximum dose of 10/40 mg once daily.

#### *Initial Therapy in Patients Requiring Blood Pressure Reduction of $\geq 20/10$ mmHg*

Initial therapy with Azor should be reserved for selected hypertensive patients who require a blood pressure reduction of  $\geq 20/10$  mmHg, or where the physician considers it unlikely that blood pressure goal will be achieved with one agent, and the benefit of fast blood pressure reduction outweighs the risks. The recommended starting dose is 5/20 mg once daily. Dosage should be guided by clinical response. The dose may be increased after 2 weeks in patients requiring further reduction in blood pressure to goal, to a maximum dose of 10/40 mg once daily.

## II. CLINICAL PHARMACOLOGY

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

Amlodipine maleate was quantified in plasma. No metabolites or separate enantiomers were quantified in this submission.

Olmesartan medoxomil is a prodrug. As a result, the sponsor assayed olmesartan and was quantified in plasma as well.

### **ASSAY VALIDATION**

For most studies:

Amlodipine concentrations were analyzed by a validated LC-MS/MS with an LLOQ of 0.050 to 0.5 ng/mL (depending on study) and  $r^2$  of at least 0.9919. Precision was in the range of 2.6 to 5.7%. Accuracy was  $\geq 94.8\%$ .

Olmesartan plasma concentrations were determined by a validated LC-MS/MS method. The LLOQ was 1.00 ng/mL with a coefficient of determination  $r^2$  of  $\geq 0.9908$ . Precision was  $\leq 7.5\%$  and the range in accuracy was -2.1 to 8.5%.

In the dose-proportionality study (U112), both amlodipine and olmesartan were assayed differently:

Amlodipine: assessed by a validated HPLC with mass spectrometric detection with an LLOQ of 50.0 pg/mL. The coefficient of determination was  $\geq 0.9975$ . The accuracy ranged from -6.7 to -6.9% and the precision was  $\leq 4.5\%$

Olmesartan medoxomil: assessed by a validated HPLC with mass spectrometric detection with an LLOQ of 1.00 ng/mL. The coefficient of determination was  $\geq 0.9910$ . The accuracy ranged from 1.3 to 3.0% and the precision was  $\leq 5.4\%$ .

### **B. WERE EXPOSURE-RESPONSE RELATIONSHIPS ESTABLISHED WITH AZOR IN TERMS OF EFFICACY?**

Changes in sitting diastolic blood pressure ( $\Delta$ SeDBP) were found to be related to the exposures of olmesartan and amlodipine as represented by steady-state AUC. The drug effect of olmesartan exposure on  $\Delta$ SeDBP was described by an Emax model, whereas the drug effect of amlodipine exposure on  $\Delta$ SeDBP was described by a linear model. The drug effect for combination therapy was defined on the basis of exposures to both compounds, and it was greater than either of the monotherapy arms alone.

### **C. ARE BOTH COMPONENTS OF AZOR DOSE-PROPORTIONAL?**

A parallel-group, randomized, open-label, single-dose, 3-period crossover study was conducted to determine dose proportionality of olmesartan and amlodipine from different strengths of olmesartan medoxomil and amlodipine fixed dose combination tablets when given to 60 healthy subjects. Amlodipine is slightly more than dose-proportional and olmesartan is less than dose-proportional, as illustrated below:

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## Amlodipine

PK Parameters	Treatments A, C, E (10 mg) (n=37)	Treatments B, D, F (5 mg) (n=37)
<b>AUC<sub>0-4</sub> (pg.h/mL)</b>		
Arithmetic Mean ±SD	385781.6 ± 92061.31*	172521.5 ± 47681.79
Geometric Mean (CV%)	374920.0 (24.6%)*	166322.8 (27.6%)
<b>AUC<sub>0-inf</sub> (pg.h/mL)</b>		
Arithmetic Mean ±SD	455031.4 ± 137254.8*	200276.3 ± 69445.50
Geometric Mean (CV%)	435742.6 (30.2%)*	189816.2 (33.2%)
<b>AUC<sub>0-4</sub> / AUC<sub>0-inf</sub></b>		
Arithmetic Mean ±SD	0.8630 ± 0.06469*	0.8787 ± 0.06387
<b>C<sub>max</sub> (pg/mL)</b>		
Arithmetic Mean ±SD	7699.77 ± 1436.986	3621.0 ± 806.16
Geometric Mean (CV%)	7555.96 (20.3%)	3527.8 (23.8%)
<b>T<sub>max</sub> (h)</b>		
Median (Min - Max)	8.000 (6.00 - 12.00)	8.000 (5.98 - 12.00)
<b>T<sub>1/2</sub> (h)</b>		
Arithmetic Mean ±SD	51.64 ± 14.094*	48.41 ± 13.104

Treatment A = Olmesartan medoxomil 40 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment B = Olmesartan medoxomil 20 mg/ Amlodipine besylate 5 mg fixed combination oral tablet  
 Treatment C = Olmesartan medoxomil 10 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment D = Olmesartan medoxomil 40 mg/ Amlodipine besylate 5 mg fixed combination oral tablet  
 Treatment E = Olmesartan medoxomil 20 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment F = Olmesartan medoxomil 10 mg/ Amlodipine besylate 5 mg fixed combination oral tablet

\*n=86; Cohort 1 = Treatments A,B,C; Cohort 2 = Treatments D,E,F

Source: Tables 14.2.1.28 and 14.2.1.29.

Dose Adjusted Parameters	Geometric LSM		Ratio of LSM (%) (5 mg / 10 mg)	90% CI (Lower, Upper) (%)
	5 mg amlodipine (B, D, and F pooled)	10 mg amlodipine (A, C, and E pooled)		
AUC <sub>0-4</sub>	33864.4	36747.3	92.2	(90.2, 94.2)
AUC <sub>0-inf</sub>	39148.0	42589.2	91.9	(89.7, 94.2)
C <sub>max</sub>	706.5	753.5	93.8	(91.7, 95.9)

\* treatment\*cohort term kept in model

## Olmesartan

PK Parameters	Treatments A and D (40 mg) (n=59)	Treatments B and E (20 mg) (n=57)	Treatments C and F (10 mg) (n=58)
<b>AUC<sub>0-4</sub> (ng.h/mL)</b>			
Arithmetic Mean ±SD	6006.4 ± 1715.33	3512.39 ± 983.589**	1885.0 ± 527.01
Geometric Mean (CV%)	5756.3 (30.8%)	3369.51 (30.6%)**	1809.0 (30.3%)
<b>AUC<sub>0-inf</sub> (ng.h/mL)</b>			
Arithmetic Mean ±SD	6096.2 ± 1769.47*	3573.84 ± 1013.276***	1921.0 ± 533.62
Geometric Mean (CV%)	5833.8 (31.4%)*	3424.02 (31.1%)*	1845.4 (29.8%)
<b>AUC<sub>0-4</sub> / AUC<sub>0-inf</sub></b>			
Arithmetic Mean ±SD	0.9848 ± 0.01591*	0.9865 ± 0.01151***	0.9803 ± 0.01358
<b>C<sub>max</sub> (ng/mL)</b>			
Arithmetic Mean ±SD	928.2 ± 260.90	574.877 ± 159.8304	337.2 ± 123.06
Geometric Mean (CV%)	889.8 (31.0%)	552.528 (29.7%)	319.2 (33.7%)
<b>T<sub>max</sub> (h)</b>			
Median (Min - Max)	2.000 (1.00 - 6.02)	2.000 (1.00 - 4.00)	1.767 (1.00 - 4.02)
<b>T<sub>1/2</sub> (h)</b>			
Arithmetic Mean ±SD	15.054 ± 6.6240*	14.021 ± 6.2096***	14.243 ± 5.6226

Treatment A = Olmesartan medoxomil 40 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment B = Olmesartan medoxomil 20 mg/ Amlodipine besylate 5 mg fixed combination oral tablet  
 Treatment C = Olmesartan medoxomil 10 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment D = Olmesartan medoxomil 40 mg/ Amlodipine besylate 5 mg fixed combination oral tablet  
 Treatment E = Olmesartan medoxomil 20 mg/ Amlodipine besylate 10 mg fixed combination oral tablet  
 Treatment F = Olmesartan medoxomil 10 mg/ Amlodipine besylate 5 mg fixed combination oral tablet

Cohort 1 = Treatments A,B,C; Cohort 2 = Treatments D,E,F

\*n=58; \*\*n=56; \*\*\*n=54

Source: Tables 14.2.1.10-12

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PK Parameters	Slope Estimate	95% CI (Lower, Upper)
$\ln AUC_{0-t}$	0.84	(0.79, 0.88)
$\ln AUC_{0-inf}$	0.83	(0.79, 0.87)
$\ln C_{max}$	0.74	(0.69, 0.80)

The CI around the slope estimate of  $C_{max}$  was not entirely within the pre-specified 0.75 - 1.25 limit. A less than proportional increase in  $C_{max}$  was observed for olmesartan following oral administration of 10, 20 and 40 mg dose levels when administered in a fixed-dose combination with either 5 or 10 mg of amlodipine.

**D. WHAT ARE THE EXTRINSIC FACTORS ASSOCIATED WITH AZOR AND IS DOSAGE ADJUSTMENT NECESSARY?**

**Drug Interaction:** A randomized, open-label, multiple-dose, 3-way crossover drug interaction study was conducted in healthy subjects to determine the pharmacokinetics effects of either drug on each other at a Benicar® (Olmesartan medoxomil) dose of 40 mg and a Norvasc® (Amlodipine besylate) dose of 10 mg in 24 males (16) and females (8). No drug interaction was observed between amlodipine and olmesartan.

**Food Effect of the new formulation:** A randomized, single-dose, open-label, 2-way crossover food effect study was conducted with fixed-dose combination formulation in 28 healthy subjects (8 F and 21 M) at the highest dose of 10/40 mg amlodipine/olmesartan resulting in no food effect observed with either moiety.

**E. WHAT ARE THE INTRINSIC FACTORS ASSOCIATED WITH AZOR AND IS DOSAGE ADJUSTMENT RECOMMENDED?**

**Age Related Differences:** Based on the results of the population pharmacokinetic analysis, age was not found to be a significant predictor of the apparent oral clearance of olmesartan. However, the oral clearance of amlodipine decreased with increasing age and this relationship was found to be statistically significant. This is consistent in the literature for amlodipine. This effect of age on the clearance of amlodipine is not clinically significant enough to warrant dose adjustment in geriatrics for the proposed indications.

**Gender Based Differences:** Population pharmacokinetic analysis indicated that female patients had approximately 15% smaller clearances of olmesartan than male patients. The resulting increase in exposure does not warrant any dose adjustment in females. Gender had no effect on the clearance of amlodipine.

**III. BIOPHARMACEUTICS**

**A. WAS A BIOEQUIVALENCE STUDY CONDUCTED ESTABLISHING A CONNECTION BETWEEN THE CLINICAL FORMULATIONS AND THE TO BE MARKETED FORMULATION?**

Two bioequivalence studies were conducted:

1) --- The first study (E102) conducted was a randomized, open-label, single-dose, 3-way crossover study to determine the bioequivalence of 10 mg of amlodipine besylate known as Istin® from the UK versus 10 mg of Norvasc® from the US versus from Italy, Antacal®. All three formulations had been used in clinical trials and all three tablets were bioequivalent to one another.

2) — The second bioequivalence study conducted (U111) was a parallel-group, open-label, randomized, crossover study to determine the bioequivalence between the fixed-dose combination formulation (Azor® or also known as CS8663) to Olmetec® and Antacal® in healthy subjects since both Olmetec® and Antacal® had been administered in clinical trials. This study was conducted at the highest dose (10/40 mg amlodipine besylate/olmesartan medoxomil, respectively) and the lowest dose (5/10 mg amlodipine besylate/olmesartan medoxomil, respectively) of the fixed-dose combinations developed.

### Cohort 1: Olmesartan

Olmesartan	Geometric LSM		Ratio (A/B) of LSM (%)	90% CI (Lower, Upper) (%)	Intra-Subject CV (%)
	Treatment A (n = 30)	Treatment B (n = 30)			
AUC <sub>0-t</sub> (ng·h/mL)	1824.7	1696.3	107.57	(99.67, 116.1)	17.5
AUC <sub>0-inf</sub> (ng·h/mL)	1857.1	1729.4*	107.39	(99.42, 116.0)	17.4
C <sub>max</sub> (ng/mL)	338.0	295.7	114.30	(106.6, 122.5)	15.9

Treatment A: CS-8663 tablet (olmesartan medoxomil 10 mg and amlodipine besylate 5 mg)

Treatment B: Olmesartan medoxomil 10 mg (Olmetec<sup>®</sup>) tablet coadministered with amlodipine besylate 5 mg (Antacal<sup>®</sup>) tablet

\* n = 29 (value could not be estimated for one subject)

Source: Table 14.2.1.9

### Cohort 2: Olmesartan

Olmesartan	Geometric LSM		Ratio (C/D) of LSM (%)	90% CI (Lower, Upper) (%)	Intra-Subject CV (%)
	Treatment C (n = 29)	Treatment D (n = 29)			
AUC <sub>0-t</sub> (ng·h/mL)	5790.3	5164.8	112.11	(103.3, 121.6)	18.1
AUC <sub>0-inf</sub> (ng·h/mL)	5976.7*	5265.7	113.50	(104.7, 123.0)	17.4
C <sub>max</sub> (ng/mL)	911.9	831.0	109.73	(101.8, 118.3)	16.8

Treatment C: CS-8663 tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)

Treatment D: Olmesartan medoxomil 40 mg (Olmetec<sup>®</sup>) tablet coadministered with amlodipine besylate 10 mg (Antacal<sup>®</sup>) tablet

\* n = 27 (value could not be estimated for two subjects)

Source: Table 14.2.1.10.

### Cohort 1: Amlodipine

Amlodipine	Geometric LSM		Ratio (A/B) of LSM (%)	90% CI (Lower, Upper) (%)	Intra-Subject CV (%)
	Treatment A (n = 30)	Treatment B (n = 30)			
AUC <sub>0-t</sub> (pg·h/mL)	146500.5	144154.0	101.63	(99.13, 104.2)	5.7
AUC <sub>0-inf</sub> (pg·h/mL)	160308.7	157724.4	101.64	(99.04, 104.3)	5.9
C <sub>max</sub> (pg/mL)	3074.2	3104.8	99.01	(95.65, 102.5)	7.9

Treatment A: CS-8663 tablet (olmesartan medoxomil 10 mg and amlodipine besylate 5 mg)

Treatment B: Olmesartan medoxomil 10 mg (Olmetec<sup>®</sup>) tablet coadministered with amlodipine besylate 5 mg (Antacal<sup>®</sup>) tablet

Source: Table 14.2.1.21.

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## Cohort 2: Amlodipine

Parameter	Treatment C (n = 23)	Treatment D (n = 23)	Ratio (C/D) of LSML (%)	90% CI (Lower, Upper) (%)	95% CI (Lower, Upper) (%)
AUC <sub>0-12</sub> (pg-h/mL)	307935.3	303067.1	101.61	(97.25, 106.2)	9.7
AUC <sub>0-∞</sub> (pg-h/mL)	336543.6	332572.6	101.19	(96.58, 106.0)	10.3
C <sub>max</sub> (pg/mL)	6625.3	6118.6	108.28	(103.2, 113.6)	10.5

Treatment C: CS-8663 tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg).

Treatment D: Olmesartan medoxomil 40 mg (Olmotec<sup>®</sup>) tablet coadministered with amlodipine besylate 10 mg (Antacal<sup>®</sup>) tablet

Source: Table 14.2.1.22

Bioequivalence was demonstrated between the clinical formulations and the highest and lowest strengths of the CS8663 formulation (Azor<sup>®</sup>).

### B. WAS A BIOWAIVER GRANTED FOR THE INTERMEDIATE STRENGTHS?

The request for a biowaiver for the intermediate strengths can not be granted since the sponsor has not provided sufficient data to verify the calculations made and no data was provided in three different media.

### III. IS THE PROPOSED LABELING FOR AZOR COMBINATION TABLETS<sup>®</sup> ACCEPTABLE?

The proposed labeling is acceptable provided the Reviewer Labeling Comments as demonstrated in Appendix I in red are addressed by the sponsor. A copy of the proposed package insert for Azor combination tablets is included in Appendix I.

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## **DETAILED LABELING RECOMMENDATIONS**

**The Labeling Recommendations that should be addressed by the sponsor are illustrated in the proposed package insert in Appendix I (highlighted in red):**

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**Appendix I:  
Proposed Package Insert**

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           Trade Secret / Confidential

  b   Draft Labeling

           Deliberative Process

**Appendix II:  
Individual Review of Studies**

**Study CS8663-A-U112 – Dose Proportionality**

**Title of Trial:** A Parallel-Group, Randomized, Open-Label, Single-Dose, 3-Period Crossover Study to Determine the Dose Proportionality of Olmesartan and Amlodipine from Different Strengths of an Olmesartan Medoxomil and Amlodipine Besylate Fixed Dose Combination Tablet When Administered to Healthy Subjects

**Investigator:** Dennis Swearingen, MD

**Trial Center(s):** MDS Pharma Services, 4747 East Beautiful Lane, Phoenix, Arizona 85044

**Publication (reference):** None

**Trial Period:**

Initiation date: January 27, 2006

Completion date: April 1, 2006

**Phase of Development:**

1

**Trial Objective:** The objective of this study was to determine the dose proportionality of olmesartan and amlodipine from different strengths of olmesartan medoxomil and amlodipine besylate fixed-dose combination tablet intended for commercialization.

Dose proportionality will be determined for the following 6 tablet strengths:

- olmesartan medoxomil 40 mg and amlodipine besylate 10 mg
- olmesartan medoxomil 20 mg and amlodipine besylate 5 mg
- olmesartan medoxomil 10 mg and amlodipine besylate 10 mg
- olmesartan medoxomil 40 mg and amlodipine besylate 5 mg
- olmesartan medoxomil 20 mg and amlodipine besylate 10 mg
- olmesartan medoxomil 10 mg and amlodipine besylate 5 mg

**Trial Hypothesis:** The fixed-dose combination tablets are dose proportional for olmesartan and amlodipine.

**Investigational Product and Comparator Information:**

Treatment A

CS-8663 DCR 40 mg/10 mg tablets (olmesartan medoxomil 40 mg/amlodipine besylate 10 mg)

Manufactured by Sankyo Pharma GmbH

Lot No.: 3223V05008

Expiration date: 20 Feb 2006

Updated expiration date: 20 Apr 2006

Treatment B

CS-8663 DCR 20 mg/5 mg tablets (olmesartan medoxomil 20 mg/amlodipine besylate 5mg)

Manufactured by Sankyo Pharma GmbH

Lot No.: 3220V05002

Expiration date: 27 Feb 2006

Updated expiration date: 27 Apr 2006

Treatment C

CS-8663 DCR 10 mg/10 mg tablets (olmesartan medoxomil 10 mg/amlodipine besylate 10 mg)

Manufactured by Sankyo Pharma GmbH

Lot No.: 3219V05001

Expiration date: 24 Mar 2006

Updated expiration date: 24 May 2006

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#### Treatment D

CS-8663 DCR 40 mg/5 mg tablets (olmesartan medoxomil 40 mg/amlodipine besylate 5 mg)  
Manufactured by Sankyo Pharma GmbH  
Lot No.: 3222V05002  
Expiration date: 09 Mar 2006  
Updated expiration date: 09 May 2006

#### Treatment E

CS-8663 DCR 20 mg/10 mg tablets (olmesartan medoxomil 20 mg/amlodipine besylate 10 mg)  
Manufactured by Sankyo Pharma GmbH  
Lot No.: 3221V05001  
Expiration date: 15 Mar 2006  
Updated expiration date: 15 May 2006

#### Treatment F

CS-8663 DCR 10 mg/5 mg tablet (olmesartan medoxomil 10 mg/amlodipine besylate 5 mg)  
Manufactured by Sankyo Pharma GmbH  
Lot No.: 3218V05004  
Expiration date: 23 Mar 2006  
Updated expiration date: 23 May 2006

**Methodology:** As it is logistically difficult to conduct a 6-period study, a 3-period crossover was performed in 2 cohorts and 30 subjects were enrolled in each cohort sequentially in this study for a total of 60 subjects. For each cohort, the study was performed as a randomized, single-dose, open-label, three-way crossover trial. Subjects were confined to the Clinical Pharmacology Unit (CPU) from approximately 13 hours prior to dosing through completion of the 144-hour postdose procedures on the morning of Day 7. A 21-day washout period followed the dosing in Period 1 and Period 2. Subjects were randomized to the following treatments:

Cohort	Treatment	Olmesartan Medoxomil (mg)	Amlodipine Besylate (mg)
1	A	40	10
	B	20	5
	C	10	10
2	D	40	5
	E	20	10
	F	10	5

**Duration of Treatment:** The total duration of participation (excluding the screening period) for each subject was approximately 7 weeks.

#### **Number of Subjects:**

Planned: Two cohorts of 30 healthy adult males and females, to ensure completion of 50 subjects.

Screened: 191 male and female subjects (115 in Cohort 1 and 76 in Cohort 2).

Enrolled/Randomized: 60 male and female subjects (30 subjects per cohort).

Completed: 57 subjects (29 subjects in Cohort 1 and 28 subjects in Cohort 2).

#### **Assay Methodology:**

Amlodipine concentrations were assessed by a validated HPLC with mass spectrometric detection with an LLOQ of 50.0 pg/mL. The coefficient of determination was  $\geq 0.9975$ . The accuracy ranged from -6.7 to -6.9% and the precision was  $\leq 4.5\%$

Olmesartan medoxomil concentrations were assessed by a validated HPLC with mass spectrometric detection with an LLOQ of 1.00 ng/mL. The coefficient of determination was  $\geq 0.9910$ . The accuracy ranged from 1.3 to 3.0% and the precision was  $\leq 5.4\%$ .

**Pharmacokinetics:** Pharmacokinetic parameters were calculated from the individual plasma concentrations of olmesartan and amlodipine using noncompartmental methods. The following PK parameters were calculated:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $k_{el}$  and  $T_{1/2}$ .

**Statistical Methods:**

**Pharmacokinetics:**

Since there were three dose levels of olmesartan, an Analysis of Covariance (ANCOVA) was performed on the ln-transformed pharmacokinetic parameters  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$  using a Power Model approach. Dose proportionality was to be declared if the 95% CI of the regression coefficient (i.e., slope estimate) for ln-transformed  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$  on ln(dose) fell within an acceptable range of 0.75 to 1.25.

Since there were only 2 dose levels of amlodipine, original sequences needed to be re-coded to allow pooling of amlodipine data (i.e. dose levels). Pooling of the data was allowed if no drug interaction was shown. Analysis of Variance was performed on the ln-transformed dose-normalized pharmacokinetic parameters  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$ . Dose proportionality was to be declared if the 90% CI of the ratio of the geometric means (using the appropriate contrast for the 10 mg vs. 5 mg comparison) for dose-normalized  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$  fell within the equivalent range of 80.0% to 125.0%.

**Results:**

**Pharmacokinetics:** Descriptive statistics of the pharmacokinetic parameters for olmesartan following oral administration of the treatments (pooled data) are presented in the following tables:

PK Parameters	Treatments A and D (40 mg) (n=59)	Treatments B and E (20 mg) (n=57)	Treatments C and F (10 mg) (n=58)
<b><math>AUC_{0-t}</math> (ng.h/mL)</b>			
Arithmetic Mean $\pm$ SD	6006.4 $\pm$ 1715.33	3512.39 $\pm$ 983.589**	1885.0 $\pm$ 527.01
Geometric Mean (CV%)	5756.3 (30.8%)	3369.51 (30.6%)**	1809.0 (30.3%)
<b><math>AUC_{0-inf}</math> (ng.h/mL)</b>			
Arithmetic Mean $\pm$ SD	6096.2 $\pm$ 1769.47*	3573.84 $\pm$ 1013.276***	1921.0 $\pm$ 533.62
Geometric Mean (CV%)	5833.8 (31.4%)*	3424.02 (31.1%)***	1845.4 (29.8%)
<b><math>AUC_{0-t} / AUC_{0-inf}</math></b>			
Arithmetic Mean $\pm$ SD	0.9848 $\pm$ 0.01591*	0.9865 $\pm$ 0.01151***	0.9803 $\pm$ 0.01358
<b><math>C_{max}</math> (ng/mL)</b>			
Arithmetic Mean $\pm$ SD	928.2 $\pm$ 260.90	574.877 $\pm$ 159.8304	337.2 $\pm$ 123.06
Geometric Mean (CV%)	889.8 (31.0%)	552.528 (29.7%)	319.2 (33.7%)
<b><math>T_{max}</math> (h)</b>			
Median (Min - Max)	2.000 (1.00 - 6.02)	2.000 (1.00 - 4.00)	1.767 (1.00 - 4.02)
<b><math>T_{1/2}</math> (h)</b>			
Arithmetic Mean $\pm$ SD	15.054 $\pm$ 6.6240*	14.021 $\pm$ 6.2096***	14.243 $\pm$ 5.6226

Treatment A = Olmesartan medoxonil 40 mg/ Amlodipine besylate 10 mg fixed combination oral tablet

Treatment B = Olmesartan medoxonil 20 mg/ Amlodipine besylate 5 mg fixed combination oral tablet

Treatment C = Olmesartan medoxonil 10 mg/ Amlodipine besylate 10 mg fixed combination oral tablet

Treatment D = Olmesartan medoxonil 40 mg/ Amlodipine besylate 5 mg fixed combination oral tablet

Treatment E = Olmesartan medoxonil 20 mg/ Amlodipine besylate 10 mg fixed combination oral tablet

Treatment F = Olmesartan medoxonil 10 mg/ Amlodipine besylate 5 mg fixed combination oral tablet

Cohort 1 = Treatments A,B,C; Cohort 2 = Treatments D,E,F

\*n = 58; \*\*n=56; \*\*\*n=54

Source : Tables 14.2.1.10-12

Results of the slopes estimates for each PK parameter along with their respective 95% confidence intervals from the two Cohorts pooled together (excluding the term cohort\*ln(dose) from the model) are presented below.

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PK Parameter	Slope Estimate	90% CI (Lower - Upper)
ln AUC <sub>0-t</sub>	0.84	(0.79, 0.88)
ln AUC <sub>0-inf</sub>	0.83	(0.79, 0.87)
ln C <sub>max</sub>	0.74	(0.69, 0.80)

The CI around the slope estimate of C<sub>max</sub> was not entirely within the pre-specified 0.75 - 1.25 limit. A less than proportional increase in C<sub>max</sub> was observed for olmesartan following oral administration of 10, 20 and 40 mg dose levels when administered in a fixed-dose combination with either 5 or 10 mg of amlodipine.

Descriptive statistics of the pharmacokinetic parameters for amlodipine following oral administration of the treatments (pooled data) are presented below:

PK Parameters	Treatments A, C, E (10 mg) (n = 37)	Treatments B, D, F (5 mg) (n = 37)
<b>AUC<sub>0-t</sub> (pg.h/mL)</b>		
Arithmetic Mean ±SD	385781.6 ± 92061.31*	172521.5 ± 47681.79
Geometric Mean (CV%)	374920.0 (24.6%)*	166322.8 (27.6%)
<b>AUC<sub>0-inf</sub> (pg.h/mL)</b>		
Arithmetic Mean ±SD	455031.4 ± 137254.8*	200276.3 ± 69445.50
Geometric Mean (CV%)	435742.6 (30.2%)*	189816.2 (33.2%)
<b>AUC<sub>0-t</sub> / AUC<sub>0-inf</sub></b>		
Arithmetic Mean ±SD	0.8630 ± 0.06469*	0.8787 ± 0.06387
<b>C<sub>max</sub> (pg/mL)</b>		
Arithmetic Mean ±SD	7699.77 ± 1436.986	3621.0 ± 806.16
Geometric Mean (CV%)	7555.96 (20.3%)	3527.8 (23.8%)
<b>T<sub>max</sub> (h)</b>		
Median (Min - Max)	8.000 (6.00 - 12.00)	8.000 (5.98 - 12.00)
<b>T<sub>1/2</sub> (h)</b>		
Arithmetic Mean ±SD	51.64 ± 14.094*	48.41 ± 13.104

Treatment A = Olmesartan medoxomil 40 mg/ Amlodipine besylate 10 mg fixed combination oral tablet

Treatment B = Olmesartan medoxomil 20 mg/ Amlodipine besylate 5 mg fixed combination oral tablet

Treatment C = Olmesartan medoxomil 10 mg/ Amlodipine besylate 10 mg fixed combination oral tablet

Treatment D = Olmesartan medoxomil 40 mg/ Amlodipine besylate 5 mg fixed combination oral tablet

Treatment E = Olmesartan medoxomil 20 mg/ Amlodipine besylate 10 mg fixed combination oral tablet

Treatment F = Olmesartan medoxomil 10 mg/ Amlodipine besylate 5 mg fixed combination oral tablet

\*n=86; Cohort 1 = Treatments A,B,C; Cohort 2 = Treatments D,E,F

Source: Tables 14.2.1.28 and 14.2.1.29.

The mean terminal elimination half-life was 51.64 and 48.41 hours, respectively, for the 10 mg and 5 mg amlodipine dose levels.

Prior to pooling the data for the dose proportionality assessment, the possibility of drug interaction was assessed using the bioequivalence approach. Treatments were deemed bioequivalent and no interaction was assumed since the 90% CI of the ratio of the geometric LSMs fell within 80.0% to 125.0%.

Following the bioequivalence analysis, pooling of amlodipine data and recoding of the original sequences was performed. Analyses of Variance were performed on the ln-transformed dose-normalized pharmacokinetic parameters AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub>. The interaction term "treatment\*cohort" was statistically significant at a 5% level for the AUC<sub>0-inf</sub> parameter only. As a result, the interaction term was removed from the model for the analysis of AUC<sub>0-t</sub> and C<sub>max</sub> and 90% CIs of the ratio of the geometric LSMs were calculated for each parameter.

Dose-Adjusted Parameters	Geometric LSM		Ratio of LSM (%) (5 mg / 10 mg)	90% CI (Lower - Upper) (%)
	5 mg amlodipine (B, D, and F pooled)	10 mg amlodipine (A, C, and E pooled)		
AUC <sub>0-t</sub>	33864.4	36747.3	92.2	(90.2, 94.2)
AUC <sub>0-inf</sub>	39148.0	42589.2	91.9	(89.7, 94.2)
C <sub>max</sub>	706.5	753.5	93.8	(91.7, 95.9)

\* treatment\*cohort term kept in model

According to the sponsor:

Confidence intervals around the ratio of LSM for  $AUC_{0-4}$ ,  $AUC_{0-inf}$  and  $C_{max}$  for amlodipine were within the 80.0 – 125.0% limit.

Overall, the  $AUC_{0-4}$ ,  $AUC_{0-inf}$  and  $C_{max}$  of amlodipine following oral administration of a 5 and 10 mg dose level increased in a dose-proportional manner when administered in a fixed-dose combination with 10, 20 or 40 mg of olmesartan.

**Safety Results:**

No serious or severe AEs occurred in this study. Of the 164 TEAEs reported, 159 were mild, and 5 were moderate. No subjects were withdrawn due to TEAEs. No TEAEs were considered definitely related to the study treatments. Twenty-three (38.3%) subjects presented with TEAEs that were probably or possibly related to the study treatments and 37 (61.7%) had TEAEs that were unlikely or unrelated to the study treatments.

A total of 43 subjects (71.7%) presented with 164 TEAEs in this study. Twenty-one subjects (70.0%) had 81 TEAEs in Cohort 1, and 22 subjects (73.3%) had 83 TEAEs in Cohort 2. Consistent with results in the literature, headache was by far the most frequently reported TEAE. Twenty-two of the 60 subjects enrolled (36.7%) presented with headache, 11 subjects (36.7%) in each cohort. Headaches were mild or moderate in severity, and were either probably or possibly treatment-related. Clinical laboratory TEAEs occurred in 6 subjects (10.0%), but only one laboratory TEAE (hepatic enzymes increased in Treatment D (40 mg olmesartan medoxomil and 5 mg amlodipine besylate)) was considered related to the study treatment.

All QTcB and QTcF results were within normal limits. Seven subjects presented with QTcB and/or QTcF increases from screening greater than 30 msec. The ECGs of all subjects with QTcB and/or QTcF increases from screening greater than 30 msec were normal.

According to the Sponsor:

**Conclusions:**

The total systemic exposure of olmesartan (AUC), following oral administration of 10, 20 and 40 mg dose levels increased in a dose-proportional manner when administered in a fixed-dose combination with either 5 or 10 mg of amlodipine.

The  $C_{max}$  values of olmesartan following oral administration of 10, 20 and 40 mg dose levels increased in slightly less than dose-proportional manner when administered in a fixed-dose combination with either 5 or 10 mg of amlodipine. This observation was not considered to be of clinical significance.

The systemic exposure (AUC and  $C_{max}$ ) of amlodipine following oral administration of a 5 and 10 mg dose level increased in a dose-proportional manner when administered in a fixed-dose combination with 10, 20 or 40 mg of olmesartan.

Olmesartan medoxomil (40 mg, 20 mg, and 10 mg) in combination with amlodipine besylate (10 mg, 5 mg and 10 mg) and olmesartan medoxomil (40 mg, 20 mg, and 10 mg) in combination with amlodipine besylate (5 mg, 10 mg and 5 mg) appeared to be safe and well tolerated by the healthy male and female subjects in this study.

**Reviewer's Comments:**

1. Another DDI analysis was performed in this study, probably due to the linearity results observed. However, a DDI can not be performed this way since you have no control. Not a valid way of establishing that no DDI took place.
2. Amlodipine is more than dose-proportional. Since a BE study was performed with the highest and lowest dose, there are no issues.
3. Olmesartan is slightly less than dose-proportional; which is not of clinical significance.

### Study CS8663-A-U101 - Drug-drug Interaction

<b>Title of Trial:</b> A Randomized, Open-Label, 3-Way Crossover Multiple Dose Study to Determine the Pharmacokinetic Interaction of Olmesartan Medoxomil and Amlodipine Besylate in Healthy Subjects	
<b>Investigator:</b> Magdy L. Shenouda, MD	
<b>Trial Center(s):</b> MDS Pharma Services, 1930 Heck Avenue, Building 2, Neptune, NJ 07753	
<b>Publication (reference):</b> None	
<b>Trial Period:</b> Initiation date: October 26, 2004 Completion date: February 20, 2005	<b>Phase of Development:</b> 1
<b>Trial Objective:</b> The primary objective of this study was to investigate the pharmacokinetic interaction between olmesartan and amlodipine when administered concomitantly in healthy subjects. The secondary objective was to evaluate the safety and tolerability when the two compounds are administered concomitantly.	
<b>Trial Hypothesis:</b> The hypothesis of this study was that there would be no significant changes in the PK of either olmesartan or amlodipine when olmesartan medoxomil and amlodipine besylate are concomitantly administered.	
<b>Investigational Product and Comparator Information:</b>	
<u>Treatment A:</u> Dosage Form: Tablet. Route of Administration: Oral. Benicar® (olmesartan medoxomil), 40 mg tablets: Lot No. 442299. Packaging Information: Benicar® (olmesartan medoxomil 40 mg strength) were supplied in commercially labelled containers. Expiration date: 31-MAY-2006	
<u>Treatment B:</u> Dosage Form: Tablet. Route of Administration: Oral. Norvasc® (amlodipine besylate) 10 mg tablets: Lot No.: 4QL171A. Packaging Information: Norvasc® (amlodipine besylate 10 mg strength) was supplied in commercially labelled containers. Expiration date: 01-JUL-2008	
<u>Treatment C:</u> Dosage Form: Tablet Route of Administration: Oral. Benicar® (olmesartan medoxomil), 40 mg tablets: Lot No. 442299. Expiration date: May 31, 2006 Norvasc® (amlodipine besylate) 10 mg tablets: Lot No.: 4QL171A. Expiration date: July 01, 2008 Packaging Information: Benicar® (olmesartan medoxomil 40 mg strength) and Norvasc® (amlodipine besylate 10 mg strength) were supplied in commercially labelled containers.	

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**Methodology:** This was a randomized, open-label, multiple-dose, 3-way crossover study to determine the pharmacokinetic interaction between olmesartan medoxomil and amlodipine besylate when administered concomitantly in healthy subjects under fasting conditions. During each dosing period, subjects were confined to the clinical pharmacology unit (CPU) from approximately 24-hours prior to the first dose in each period up to the last blood draw on Day 12 for Treatment A, and Day 14 for Treatments B and C. Each treatment period was separated by a washout period of at least 21 days from the last dose. Subjects were assigned randomly to receive one of the following treatments on three separate occasions:

- Treatment A: olmesartan medoxomil tablets (Benicar<sup>®</sup>, 1 × 40 mg tablet) administered orally QD for 10 days with 240 mL of water
- Treatment B: amlodipine besylate tablets (Norvasc<sup>®</sup>, 1 × 10 mg tablet) administered orally QD for 10 days with 240 mL of water
- Treatment C: olmesartan medoxomil 40-mg tablets and amlodipine besylate 10-mg tablets administered orally QD for 10 days with 240 mL of water.

Safety monitoring included complete physical examination, vital signs, 12-lead ECG, laboratory (hematology, serum chemistry, urinalysis), and adverse events evaluation at designated times during the study.

**Duration of Treatment:** The total duration of the study beginning from check-in Period 1 for enrolled subjects was approximately 82 days.

**Number of Subjects:**

Planned: Twenty-four (24) healthy adult males or females, to ensure completion of 18 subjects.

Screened: 70 male and female subjects.

Enrolled/Randomized: 24 subjects - 16 males and 8 females.

Completed: 23 subjects - 15 males and 8 females.

Discontinued: One male subject. The Investigator dropped Subject 013 from the study on Day -1 of Period 2 due to a positive urine drug screen.

Breakfast, lunch, dinner and an evening snack were served at the same times each day, with the exception of Day 1 and Days 8 to 10, when no breakfast was served. On Day 1, and Days 8 to 10, subjects fasted for at least 10-hours prior to dosing. In each period, the same menu was followed for lunch, dinner and the evening snack. Meal times are listed in Appendix 16.2.5.5.

**Criteria for Evaluation:**

**Pharmacokinetics:** Pharmacokinetic parameters were calculated from the individual plasma concentrations of olmesartan and amlodipine using noncompartmental methods. The following PK parameters were calculated after the last dose on Day 10 of each period:  $AUC_{0-\infty}$ ,  $C_{55,max}$ ,  $C_{55,min}$ ,  $T_{55,max}$ ,  $t_{1/2}$ , Flux1 and Flux2.

As appropriate to the treatment administered in each period, blood samples (approximately 5 mL each) for the analysis of olmesartan and amlodipine in plasma were collected by venipuncture on the subject's forearm at the following times:

*Olmesartan*

Prior to dosing (0 h) on Days 1, 8, 9 and 10. On Day 10, blood samples were also collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-dose.

*Amlodipine*

Prior to dosing (0 h) on Days 1, 8, 9 and 10. On Day 10, blood samples were also collected at 1, 2.5, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 24, 48, 72 and 96-hours post-dose.

**Statistical Methods:**

**Pharmacokinetics:** The treatment contrast was constructed from the Analysis of Variance to obtain the least-squares mean difference, and the 90% confidence interval (CI) for the natural log-transformed treatment difference. The anti-logs of the least-squares mean difference and its 90% CI constitutes the ratio of sample geometric means and the 90% CI for the true treatment mean ratio. For each treatment comparison, no significant drug-drug interaction was concluded if the 90% CI for the mean ratio is within the acceptable range (80.0 to 125.0%) for  $AUC_{\tau}$  and  $C_{ss, max}$ .

**Analytical Methods:**

Samples were collected into \_\_\_\_\_ tubes. Plasma was separated and placed in labeled \_\_\_\_\_ tubes, and then frozen at -20°C pending the assay. Concentrations of olmesartan in plasma were determined using a validated analytical method, with a LLOQ of 1 ng/mL. Concentrations of amlodipine in plasma were determined using a validated analytical method, with a LLOQ of 0.5 ng/mL.

b(4)

**Linear Range**

1 – 1000 ng/mL (Olmesartan)  
0.5 – 50 ng/mL (Amlodipine)

**Limit of Quantitation**

1 ng/mL (Olmesartan)  
0.5 ng/mL (Amlodipine)

**Intra-Day Accuracy**

-2.1 to 8.5% (Olmesartan)  
-7.25 to 3.00% (Amlodipine)

**Inter-Day Accuracy**

1.2 to 14.8% (Olmesartan)  
-5.5 to 3.80% (Amlodipine)

**Intra-Day Precision**

4.8 to 10.2% (Olmesartan)  
2.48 to 3.53% (Amlodipine)

**Inter-Day Precision**

4.6 to 8.8% (Olmesartan)  
4.84 to 7.50% (Amlodipine)

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**Results:**

**Pharmacokinetics:** Descriptive statistics of olmesartan pharmacokinetic parameters for Treatment A (40 mg olmesartan medoxomil) and Treatment C (40 mg olmesartan medoxomil and 10 mg amlodipine besylate) on Day 10 are presented below.

Olmesartan	Treatment A (n=24) 40 mg Olmesartan Medoxomil Tablet OD for 10 Days	Treatment C (n=24) 40 mg Olmesartan Medoxomil Tablet and 10 mg Amlodipine Besylate Tablet OD for 10 Days
<b>AUC<sub>t</sub> (ng.h/mL)</b>		
Arithmetic Mean ±SD	6793.9 ± 1706.72	6890.9 ± 1918.03
Geometric Mean (CV%)	6586.4 (26.1%)	6640.8 (28.4%)
<b>C<sub>ss,max</sub> (ng/mL)</b>		
Arithmetic Mean ±SD	1083.8 ± 283.30	1038.1 ± 311.88
Geometric Mean (CV%)	1048.6 (26.9%)	996.1 (29.8%)
<b>C<sub>ss,min</sub> (ng/mL)</b>		
Arithmetic Mean ±SD	67.80 ± 27.588	65.57 ± 22.982
<b>T<sub>max</sub> (h)</b>		
Median (Min, Max)	1.500 (1.00, 2.52)	2.000 (1.02, 2.98)
<b>T<sub>1/2</sub> (h)</b>		
Arithmetic Mean ±SD	13.683 ± 5.5802	13.479 ± 5.3634
<b>Flux1 (%)</b>		
Arithmetic Mean ±SD	364.5 ± 61.51	341.5 ± 61.34
<b>Flux2 (%)</b>		
Arithmetic Mean ±SD	1790.8 ± 1052.78	1608.5 ± 575.06

Source: Tables 14.2.4 and 14.2.6.1.

An ANOVA model was used to determine the bioequivalence of olmesartan between the two treatment regimens. Results are presented below.

Olmesartan	Geometric LSM*		Ratio of LSM(C/A) (%)	90% CI (%)
	Treatment C	Treatment A		
AUC <sub>t</sub>	6640.8	6567.9	101.1	(93.5, 109.4)
C <sub>ss,max</sub>	996.1	1046.1	95.2	(87.2, 103.9)

\* Values for Treatments A and C are the least-squares means (LSMEANS) from the ANOVA back-transformed to the original scale  
Source: Table 14.2.7

The ratio of geometric LSM and 90% confidence intervals for AUC<sub>t</sub> and C<sub>ss,max</sub> of olmesartan were all within the 80.0 to 125.0% limit. Therefore, the concomitant administration of amlodipine besylate (Norvasc® 10 mg tablet) did not affect the rate and extent of exposure of olmesartan (Benicar® 40 mg tablet) under fasting conditions.

Steady state levels of olmesartan were reached by Day 9 for Treatments A and C. This confirms that the PK assessment on Day 10 was performed under steady state conditions, and further demonstrated that co-administration with amlodipine had no effect on the elimination half-life of olmesartan.

Descriptive statistics of amlodipine pharmacokinetic parameters for Treatment B (10 mg amlodipine besylate) and Treatment C (40 mg olmesartan medoxomil and 10 mg amlodipine besylate) are presented below.

Amlodipine	Treatment B (n=23) 10 mg Amlodipine Besylate Tablet OD for 10 Days	Treatment C (n=24) 40 mg Olmesartan Medoxomil Tablet and 10 mg Amlodipine Besylate Tablet OD for 10 Days
<b>AUC<sub>t</sub> (ng.h/mL)</b>		
Arithmetic Mean ±SD	359.2 ± 129.48	388.7 ± 155.21
Geometric Mean (CV%)	336.6 (39.0%)	360.2 (41.7%)
<b>C<sub>ss,max</sub> (ng/mL)</b>		
Arithmetic Mean ±SD	19.761 ± 6.6584	20.075 ± 7.7230
Geometric Mean (CV%)	18.610 (38.0%)	18.669 (40.9%)
<b>C<sub>ss,min</sub> (ng/mL)</b>		
Arithmetic Mean ±SD	12.443 ± 4.2244	13.463 ± 5.3101
<b>T<sub>max</sub> (h)</b>		
Median (Min, Max)	8.000 (5.00, 14.00)	8.000 (0.00, 16.1)
<b>T<sub>1/2</sub> (h)</b>		
Arithmetic Mean ±SD	51.24 ± 10.929 <sup>a</sup>	50.63 ± 11.731
<b>Flux1 (%)</b>		
Arithmetic Mean ±SD	57.50 ± 22.897	47.13 ± 14.590
<b>Flux2 (%)</b>		
Arithmetic Mean ±SD	61.63 ± 34.656	51.46 ± 20.097

<sup>a</sup> N = 22 for T<sub>1/2</sub>

Source: Tables 14.2.5 and 14.2.6.2.

Bioequivalence was assessed between the two treatment regimens using an ANOVA model. Results are presented below.

Parameter	Treatment B (n=12)		Treatment C (n=12)	
	LSMEANS	90% CI	LSMEANS	90% CI
AUC <sub>t</sub>	340.2	(334.3, 346.1)	334.3	(328.4, 340.2)
C <sub>ss,max</sub>	18.7	(18.5, 18.9)	18.5	(18.3, 18.7)

\* Values for Treatments B and C are the least-squares means (LSMEANS) from the ANOVA back-transformed to the original scale

Source: Table 14.2.8.

The ratio of geometric LSM and 90% confidence intervals for AUC<sub>t</sub> and C<sub>ss,max</sub> of amlodipine were all within the 80.0 to 125.0% limit. Therefore, the concomitant administration of olmesartan (Benicar® 40 mg tablet) did not affect the rate and extent of exposure of amlodipine besylate (Norvasc® 10 mg tablet) under fasting conditions.

Steady state plasma concentration levels of amlodipine were reached by Day 9 for Treatments B and C. This confirms that the PK assessment on Day 10 was performed under steady state conditions, and further demonstrated that co-administration with olmesartan had no effect on the half-life of amlodipine.

**Safety Results:**

No serious AEs occurred in this study and none of the subjects discontinued the study due to an AE.

No other clinically notable trends were observed in the laboratory, vital sign, physical examination, or ECG findings. Specifically, no clinically notable effects on vital signs were observed following administration of the olmesartan medoxomil monotherapy, the amlodipine besylate monotherapy, or the combination therapy.

**Conclusions:**

The pharmacokinetics parameters, AUC<sub>t</sub> and C<sub>ss,max</sub>, for olmesartan and amlodipine met the criteria considered for bioequivalence, indicating the lack of a pharmacokinetic interaction for the co-administered treatment.

The concomitant administration of olmesartan medoxomil 40 mg (Benicar® 40 mg tablet) and amlodipine besylate 10 mg (Norvasc® 10 mg tablet) appeared to be safe and well tolerated by the healthy male and female subjects in this study.

**Reviewer's Comments:**

1. Reviewer concurs.

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## Study CS8663-A-U110 - Food Effect

**Title of Trial:** A Randomized, Single-Dose, Open-Label 2-Way Crossover Study to Determine the Effect of Food on the Bioavailability of Olmesartan and Amlodipine from a Fixed-Dose Combination Tablet When Administered In Healthy Subjects

**Investigator:** Robert Noveck, MD

**Trial Center(s):** MDS Pharma Services, 1930 Heck Avenue – Building 2, Neptune, New Jersey 07753

**Publication (reference):** None

**Trial Period:**

Initiation date: February 8, 2006

Completion date: March 9, 2006

**Phase of Development:**

1

**Trial Objective:** The objective of this study was to determine the effect of food on the bioavailability of olmesartan and amlodipine from a fixed-dose combination tablet.

**Trial Hypothesis:** Administration of food would have no effect on the bioavailability of the fixed-dose combination tablet of olmesartan medoxomil and amlodipine besylate.

**Investigational Product Information:**

**Treatments A and B:**

CS-8663 DCR 40/10 (olmesartan medoxomil 40 mg/amlodipine besylate equivalent to 10 mg amlodipine base) tablets  
Lot No.: 3223V05008  
Manufactured by Sankyo Pharma GmbH  
Manufacture date: Not available  
Expiration date: Not available

**Methodology:** This was a single-center, single-dose, randomized, open-label, 2-way crossover study to determine the effect of food on the bioavailability of olmesartan medoxomil and amlodipine besylate of a fixed combination formulation in healthy adult subjects. During each dosing period, subjects were confined to the clinical pharmacology unit (CPU) on Day -2 through completion of the 144-hour post-dose procedures on Day 7. There was a 21-day washout between treatment periods. Subjects were randomized to the following treatments:

- **Test:** (Treatment A) CS-8663 oral tablet [fixed dose-combination of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg] administered orally within 30 minutes following the start of a high-fat breakfast. An approximate 10-hour overnight fast preceded the high-fat breakfast.
- **Reference** (Treatment B) CS-8663 oral tablet [fixed dose-combination of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg] administered orally with 240 mL of water, following a minimum 10-hour overnight fast.

Amlodipine besylate doses are usually expressed in terms of the base (i.e. amlodipine besylate 6.9 mg is approximately equivalent to 5 mg of amlodipine).

Safety monitoring included complete physical examination, vital signs, 12-lead ECG, laboratory measurements (hematology, serum chemistry, urinalysis), and adverse events evaluation at designated times during the study.

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**Duration of Treatment:** The total duration of the study for enrolled subjects was approximately 28 days.

**Number of Subjects:**

**Planned:** Twenty-eight (28) healthy adult males and females, to ensure completion of 22 subjects.

**Screened:** 85 male and female subjects.

**Enrolled/Randomized:** 28 male and female subjects.

**Completed:** 27 subjects.

Seven females and 21 males were enrolled in the study between the ages of 20 to 43 years. Subjects were excluded due to not qualifying as per inclusion/exclusion criteria (57), did not check-in on day of study (4), Study full (6), and found an alternate (4).

### **Exclusion Criteria**

**Use of any prescription drug within 14 days prior to the first dose of the study (with the exception of hormonal contraceptives for females of child-bearing potential).**

**Use of any non-prescription drug (including herbal supplements) within 7 days prior to the first dose of the study.**

**Treatment with any drugs known to inhibit or induce liver enzymes involved in drug metabolism (CYP P450) within the 30 days prior to the first dose of the study.**

**Consumption of any food or beverages containing grapefruit from 7 days prior to the first dose of the study through study completion.**

**Consumption of foods or beverages containing alcohol from 48 hours prior to the first dose through study completion.**

**Consumption of foods or beverages containing caffeine/xanthine from 48 hours prior to the dose of each period through release from confinement each period.**

**Use of tobacco products or nicotine-containing products (including smoking cessation aids, such as gums or patches) within the 12 months prior to the first dose of the study.**

In each treatment period, a single dose of olmesartan medoxomil and amlodipine besylate was administered. Doses were given in the morning, starting between approximately 8:00 to 9:00. The CS-8663 fixed combination tablets were administered with approximately 240 mL of water.

Breakfast, lunch, dinner and an evening snack were served at the same times each day, with the exception of one of the periods on Day 1 when no breakfast was served (according to the randomization). On the other period of Day 1, a designated breakfast consisting of two eggs fried in butter, two strips of bacon, two slices of buttered toast, four ounces of hash brown potatoes, and eight ounces of whole milk was served prior to dosing. Subjects fasted for at least 10 hours prior to dosing or prior to a high-fat breakfast on Day 1. Water was allowed as desired during the study except 1 hour before through 1 hour after each dose (with the exception of the water with dosing). No foods or beverages containing alcohol, caffeine/xanthine, or grapefruit were served during study confinement. In each period, the same menu was followed for lunch, dinner and the evening snack. Meal times are listed in Appendix 16.2.5.5.

### **Analytical Methods:**

Amlodipine concentrations in plasma were assessed by LC-MS/MS methods with an LLOQ of 0.5 ng/mL and an  $r^2 \geq 0.9980$ . Between batch precision and accuracy was less than 4.7% and from -4 to -3.7%, respectively.

Olmesartan concentrations in plasma were assessed by LC-MS/MS methods with a LLOQ of 1 ng/mL and an  $r^2 \geq 0.9941$ . Between batch precision and accuracy was less than 4.7% and from -0.3 to 2.8%, respectively.

**Criteria for Evaluation:**

**Pharmacokinetics:** Pharmacokinetic parameters were calculated from the individual plasma concentrations of olmesartan and amlodipine using noncompartmental methods. The following PK parameters were calculated:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $k_{el}$  and  $T_{1/2}$ .

In each dosing period, blood samples (approximately 5 mL each) for the analysis of olmesartan and amlodipine in plasma were collected by venipuncture at the following time points:

**Olmesartan:** Prior to dosing (0 h), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post dose.

**Amlodipine:** Prior to dosing (0 h), and at 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours post dose.

**Pharmacokinetics:** Ninety percent (90%) CIs for the difference between treatment LSMs were derived from the Analyses of Variance on the ln-transformed PK parameters  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  for olmesartan and amlodipine. The 90% CI was obtained from the antilogs of the lower and upper bounds of the 90% CI for the difference in the LSM of the ln-transformed data. Ratios of geometric LSMs (Test/Reference) and 90% CIs for the PK parameters were expressed as a percentage of the geometric LSM for the test to reference formulations (Test/Reference). Absence of food effect was concluded if the 90% CIs of the ratios for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  fell within 80.0% to 125.0%.

A non-parametric approach<sup>11</sup> was used to construct 90% CI for  $T_{max}$  values of olmesartan and amlodipine. The Hodges-Lehmann estimator between the Test and Reference formulations (Test - Reference) was presented and the CIs were generated using the Moses method.

**Results:**

**Pharmacokinetics:** Descriptive statistics of olmesartan pharmacokinetic parameters following oral administration of CS-8663 under fed and fasting conditions are presented below:

Olmesartan	Treatment A (n = 28)	Treatment B (n = 27)
<b><math>AUC_{0-t}</math> (ng·h/mL)</b>		
Arithmetic Mean ±SD	5402.2 ± 1267.27	6317.1 ± 2055.55
Geometric Mean (CV%)	5259.6 (24.1%)	6065.1 (28.3%)
<b><math>AUC_{0-inf}</math> (ng·h/mL)</b>		
Arithmetic Mean ±SD	5541.5 ± 1267.98	6395.6 ± 2065.16
Geometric Mean (CV%)	5401.5 (23.6%)*	6143.9 (28.1%)
<b><math>AUC_{0-t} / AUC_{0-inf}</math></b>		
Arithmetic Mean ±SD	0.9867 ± 0.01050*	0.9872 ± 0.00923
<b><math>C_{max}</math> (ng/mL)</b>		
Arithmetic Mean ±SD	898.3 ± 180.15	995.0 ± 312.56
Geometric Mean (CV%)	881.9 (19.5%)	947.6 (33.0%)
<b><math>T_{max}</math> (h)</b>		
Median (Min - Max)	2.509 (1.50 - 6.00)	2.000 (1.00 - 4.00)
<b><math>T_{1/2}</math> (h)</b>		
Arithmetic Mean ±SD	14.189 ± 4.1121*	14.170 ± 4.0564

Treatment A: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) with a high-fat breakfast  
 Treatment B: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) after an overnight fast  
 n = 27

Source: Tables 14.2.1.3 and 14.2.1.4.

The overall extent of bioavailability ( $AUC_{0-inf}$ ) of olmesartan was slightly lower (12.1%) when CS-8663 was administered with a high-fat breakfast than after a minimum 10 hour overnight fast (geometric means of 5401.5 versus 6143.9 ng·h/mL, respectively). Similarly, the rate of bioavailability ( $C_{max}$ ) was slightly lower by about 6.93% and the median time to reach peak plasma concentrations appeared to be delayed by approximately 30 minutes. The mean terminal elimination half-life of olmesartan was similar when administered under fed and fasting conditions (approximately 14.2 hours).

The effect of food on the bioavailability of olmesartan was assessed using an ANOVA model. Results are presented below.

Parameters	Geometric LSM		Ratio (A/B) of LSM (%)	90% CI (Lower - Upper) (%)
	Treatment A (n = 28)	Treatment B (n = 27)		
AUC <sub>0-4</sub> (ng·h/mL)	5259.6	6034.3	87.16	(82.50, 92.09)
AUC <sub>0-inf</sub> (ng·h/mL)	5366.5*	6111.7	87.81	(82.97, 92.92)
C <sub>max</sub> (ng/mL)	881.9	939.5	93.87	(87.41, 100.8)

Treatment A: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) with a high-fat breakfast  
 Treatment B: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) after an overnight fast  
 n = 27

Source: Table 142.1.5.

The ratio of LSM and 90% CIs for AUC<sub>0-4</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> of olmesartan were within the bioequivalence range of 80.0 to 125.0%. Therefore, the rate and extent of bioavailability of olmesartan were bioequivalent after oral administration of CS-8663 under fed and fasting conditions.

Descriptive statistics of amlodipine pharmacokinetic parameters following oral administration of CS-8663 under fed and fasting conditions are presented below.

Amlodipine	Treatment A (n = 28)	Treatment B (n = 27)
<b>AUC<sub>0-4</sub> (pg·h/mL)</b>		
Arithmetic Mean ±SD	312599.8 ± 59414.19	308615.5 ± 67203.76
Geometric Mean (CV%)	306975.4 (19.9%)	300720.4 (24.4%)
<b>AUC<sub>0-inf</sub> (pg·h/mL)</b>		
Arithmetic Mean ±SD	341569.2 ± 70935.32	337944.7 ± 78895.13
Geometric Mean (CV%)	334343.7 (21.5%)	328109.3 (26.1%)
<b>AUC<sub>0-4</sub> / AUC<sub>0-inf</sub></b>		
Arithmetic Mean ±SD	0.9189 ± 0.03670	0.9174 ± 0.04064
<b>C<sub>max</sub> (pg/mL)</b>		
Arithmetic Mean ±SD	6497.5 ± 1371.25	6618.1 ± 1534.04
Geometric Mean	6354.2 (22.1%)	6437.1 (24.9%)
<b>T<sub>max</sub> (h)</b>		
Median (Min - Max)	8.000 (6.00 - 12.0)	8.000 (6.00 - 12.0)
<b>T<sub>1/2</sub> (h)</b>		
Arithmetic Mean ±SD	39.96 ± 7.614	40.20 ± 8.145

Treatment A: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) with a high-fat breakfast  
 Treatment B: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) after an overnight fast

Source: Tables 142.1.9 and 142.1.10.

The rate and extent of bioavailability of amlodipine was similar when CS-8663 was administered with or without food. The mean terminal elimination half-life of amlodipine was approximately 40 hours for both treatments.

Parameters	Geometric LSM		Ratio (A/B) of LSM (%)	90% CI (Lower - Upper) (%)
	Treatment A (n = 28)	Treatment B (n = 27)		
AUC <sub>(0-4)</sub> (pg·h/mL)	306975.4	299179.0	102.61	(99.59, 105.7)
AUC <sub>(0-inf)</sub> (pg·h/mL)	334343.7	326058.9	102.54	(99.20, 106.0)
C <sub>max</sub> (pg/mL)	6354.2	6400.8	99.27	(95.98, 102.7)

Treatment A: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) with a high-fat breakfast  
 Treatment B: CS-8663 Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) after an overnight fast  
 Source: Table 142.1.11.

The ratio of LSM and 90% CIs for  $AUC_{0-4}$ ,  $AUC_{0-inf}$  and  $C_{max}$  of amlodipine were within the bioequivalence range of 80.0 to 125.0%. Therefore, the rate and extent of bioavailability of amlodipine after oral administration of CS-8663 were bioequivalent under fed and fasting conditions.

**Safety Results:**

A total of 5 subjects (17.9%) presented with 8 TEAEs in this study. Of these, 2 subjects (7.1%) had 2 TEAEs after receiving Treatment A, and 4 subjects (14.3%) had 6 TEAEs after receiving Treatment B.

The only treatment-related TEAE was headache, which occurred in 2 subjects. Headaches were mild and moderate, and both were judged possibly related to Treatment A. All remaining TEAEs were mild, and were unrelated to the study treatments. No concomitant medication was required to treat any TEAE.

There were no other clinically notable trends or clinically significant observations in the laboratory, vital sign, physical examination, or ECG findings with respect to subject safety.

**Conclusions:**

The bioavailability of olmesartan and amlodipine after oral administration of a fixed-dose combination tablet were equivalent under fed and fasting conditions.

The fixed-dose combination of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg oral CS-8663 tablet administered as a single oral dose appeared to be safe and well tolerated by the healthy male and female subjects in this study.

**Reviewer's Comment:**

The reviewer concurs.

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### Study CS8663-A-U111 – Bioequivalence Study

<b>Title of Trial:</b> A Parallel-Group, Open-Label, Randomized, Crossover Study to Determine the Bioavailability of a Fixed- Dose Combination Tablet of Olmesartan Medoxomil and Amlodipine Besylate Relative To Olmetec® And Antacal® In Healthy Subjects	
<b>Investigator:</b> Robert Noveck, MD	
<b>Trial Center(s):</b> MDS Pharma Services, 1930 Heck Avenue – Building 2, Neptune, New Jersey 07753	
<b>Publication (reference):</b> None	
<b>Trial Period:</b> Initiation date: January 23, 2006 Completion date: March 22, 2006	<b>Phase of Development:</b> 1
<b>Trial Objective:</b> The objective of this study was to determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination formulation intended for commercial use relative to coadministration of the separate entities as their marketed formulations. The bioavailability was determined for the following 2 tablet strengths: <ul style="list-style-type: none"><li>• olmesartan 10 mg and amlodipine 5 mg</li><li>• olmesartan 40 mg and amlodipine 10 mg</li></ul>	
<b>Trial Hypothesis:</b> Each test treatment will be bioequivalent to the corresponding reference treatment.	
<b>Investigational Product and Comparator Information:</b>	
<u>Treatment A</u>  CS-8663 DCR 10/5 (Olmesartan Medoxomil 10 mg/ Amlodipine besylate equivalent to 5 mg amlodipine base) tablet Lot No.: 3218V05004 Manufacturer: Sankyo GmbH Germany Expiration Date: 23 Mar 06 Manufacture Date: 23 Nov 05	
<u>Treatment B</u>  Olmetec® (Olmesartan Medoxomil) 10 mg tablet Lot No.: 447866 Manufacturer: Sankyo GmbH Germany Expiration Date: 09-2008 Manufacture Date: Sep 05  Antacal® (Amlodipine besylate equivalent to 5 mg amlodipine base) 5 mg tablet Lot No.: 410295431 Manufacturer: Heinrich Mack Nachf GmbH and Co. Germany Expiration Date: 06-2009 Manufacture Date: Not available	
<u>Treatment C</u>  CS-8663 DCR 40/10 (Olmesartan Medoxomil 40mg/ Amlodipine Besylate equivalent to 10 mg amlodipine base) tablet Lot No.: 3223V05008 Expiration Date: 20 Apr 06 Manufacture Date: 20 Oct 05	

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**Treatment D**

**Olmotec® (Olmesartan Medoxomil) 40 mg tablet**  
 Lot No.: 337610  
 Manufacturer: Sankyo Pharma GmbH Germany  
 Expiration Date: Oct 07  
 Manufacture Date: Oct 04

**Antacal® (Amlodipine besylate equivalent to 10 mg amlodipine base) 10 mg tablet**  
 Lot No.: 41019013  
 Manufacturer: Heinrich Mack Nachf GmbH and Co. Germany  
 Expiration Date: 03-2009  
 Manufacture Date: Not available

**Note:** Lot number size information for both the highest and lowest strength fixed combination tablets (CS8663) are below:

40/10 mg		30 kg	1,500,000	WT148	P40619 (C)	3228703008
10/5 mg	b(4)	30 kg	300,000	WT148	15 (M)	3218703004

**Methodology:** Two cohorts of 30 healthy adult subjects were enrolled in this study for a total of 60 subjects. For each cohort, the study was a single-center, single-dose, randomized, open-label, 2-way crossover study to determine the bioequivalence of a fixed combination formulation of olmesartan medoxomil and amlodipine besylate, versus the coadministration of the separate entities as their marketed formulations under fasting conditions. During each dosing period, subjects were confined to the clinical pharmacology unit (CPU) from Day -2 through completion of the 144-hour post-dose procedures. There was a 21-day washout between treatment periods. Subjects were randomized to the following treatments:

**Cohort 1:**

- Treatment A (Test): CS-8663 oral tablet [fixed dose-combination of olmesartan medoxomil 10 mg and amlodipine besylate 5 mg] administered orally with 240 mL of water.
- Treatment B (Reference): Olmesartan medoxomil 10 mg (Olmotec®) in combination with amlodipine besylate 5 mg (Antacal®). A single oral dose of Olmetec® tablet (1 x 10 mg olmesartan medoxomil – Sankyo, Germany) and Antacal® tablet (1 x 5 mg amlodipine besylate – manufactured by Heinrich Mack Nachf GmbH& Co., Germany, and marketed by Errekappa Euroterapici S.p.A, Italy under the license of Pfizer Italia S.r.l.) administered orally with 240 mL of water.

**Cohort 2:**

- Treatment C (Test): CS-8663 oral tablet [fixed dose-combination of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg] administered orally with 240 mL of water.

- Treatment D (Reference): Olmesartan medoxomil 40 mg (Olmotec®) in combination with amlodipine besylate 10 mg (Antacal®). A single oral dose of Olmetec® tablet (1 x 40 mg olmesartan medoxomil – Sankyo, Germany) and Antacal® tablet (1 x 10 mg amlodipine besylate – manufactured by Heinrich Mack Nachf GmbH& Co., Germany, and marketed by Errekappa Euroterapici S.p.A, Italy under the license of Pfizer Italia S.r.l.) administered orally with 240 mL of water.

Safety monitoring included complete physical examination, vital signs, 12-lead ECG, laboratory measurements (hematology, serum chemistry, urinalysis), and adverse events evaluation at designated times during the study.

**Duration of Treatment:** The total duration of the study for enrolled subjects was approximately 28 days.

**Number of Subjects:**

**Planned:** Two cohorts of 30 healthy adult males and females, to ensure completion of 22 subjects per cohort.

**Screened:** 173 male and female subjects (91 in Cohort 1 and 82 in Cohort 2).

**Enrolled/Randomized:** 60 male and female subjects (30 subjects per cohort).

**Completed:** 58 subjects (30 subjects in Cohort 1 and 28 subjects in Cohort 2).

**Analytical Methods:**

Amlodipine plasma concentrations were determined by a validated LC-MS/MS method. The LLOQ was 0.050 ng/mL with a coefficient of determination  $r^2$  of  $\geq 0.9919$ . Precision was  $\leq 5.4\%$  and the range in accuracy was  $-5.2$  to  $-4.0\%$ .

Olmesartan plasma concentrations were determined by a validated LC-MS/MS method. The LLOQ was 1.00 ng/mL with a coefficient of determination  $r^2$  of  $\geq 0.9908$ . Precision was  $\leq 7.5\%$  and the range in accuracy was  $0.7$  to  $3.3\%$ .

**Pharmacokinetics:** Pharmacokinetic parameters were calculated from the individual plasma concentrations of olmesartan and amlodipine using noncompartmental methods. The following PK parameters were calculated:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $k_{el}$  and  $T_{1/2}$ .

In each dosing period, blood samples (approximately 5 mL each) for the analysis of olmesartan and amlodipine in plasma were collected by venipuncture at the following time points:

**Olmesartan:** Prior to dosing (0 h), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post dose.

**Amlodipine:** Prior to dosing (0 h), and at 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours post dose.

**Pharmacokinetics:** Ninety percent (90%) CIs for the difference between treatment LSMs were derived from the Analyses of Variance on the ln-transformed PK parameters  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  for olmesartan and amlodipine for each cohort. The 90% CI was obtained from the antilogs of the lower and upper bounds of the 90% CI for the difference in the LSM of the ln-transformed data. Ratios of geometric LSMs (Test/Reference) and 90% CIs for the PK parameters were expressed as a percentage of the geometric LSM for the test to reference treatments (Test/Reference). Bioequivalence was concluded if the 90% CIs of the ratios for the comparison of Treatment A/Treatment B and Treatment C/Treatment D for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  fell within 80.0% to 125.0%.

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**Results:**

**Pharmacokinetics:** Descriptive statistics of olmesartan pharmacokinetic parameters following oral administration of the Test and Reference treatments for Cohort 1 are presented below:

Olmesartan	Cohort 1	
	Treatment A (n = 30)	Treatment B (n = 30)
<b>AUC<sub>0-t</sub> (ng-h/mL)</b>		
Arithmetic Mean ±SD	1871.5 ± 407.38	1738.6 ± 391.02
Geometric Mean (CV%)	1824.7 (23.9%)	1696.3 (23.0%)
<b>AUC<sub>0-inf</sub> (ng-h/mL)</b>		
Arithmetic Mean ±SD	1901.9 ± 403.11	1778.3 ± 403.09*
Geometric Mean (CV%)	1857.1 (23.1%)	1734.5 (23.2%)*
<b>AUC<sub>0-t</sub> / AUC<sub>0-inf</sub></b>		
Arithmetic Mean ±SD	0.9827 ± 0.01704	0.9835 ± 0.00916*
<b>C<sub>max</sub> (ng/mL)</b>		
Arithmetic Mean ±SD	347.5 ± 80.00	306.0 ± 80.55
Geometric Mean (CV%)	338.0 (24.8%)	295.7 (27.3%)
<b>T<sub>max</sub> (h)</b>		
Median (Min – Max)	1.559 (1.00 – 4.02)	2.000 (1.00 – 4.02)
<b>T<sub>1/2</sub> (h)</b>		
Arithmetic Mean ±SD	14.328 ± 7.5439	13.639 ± 5.6033*

Treatment A: CS-8663 tablet (olmesartan medoxomil 10 mg and amlodipine besylate 5 mg)

Treatment B: Olmesartan medoxomil 10 mg (Olmotec<sup>®</sup>) tablet coadministered with amlodipine besylate 5 mg (Antacal<sup>®</sup>) tablet

\* n = 29 (value could not be estimated for one subject)

Source: Tables 14.2.1.5 and 14.2.1.6.

When olmesartan medoxomil was administered in a fixed-dose combination with amlodipine besylate (10 and 5 mg, respectively), the rate and extent of bioavailability of olmesartan was similar to that observed when Olmetec<sup>®</sup> 10 mg was coadministered with Antacal<sup>®</sup> 5 mg as separate tablets. The mean terminal elimination half-life of olmesartan for the Test and Reference treatments were similar 14.328 and 13.639 hours, respectively.

Bioequivalence of olmesartan between the Test and Reference products was assessed using an ANOVA model. Results for Cohort 1 are presented in the next table:

Olmesartan	Geometric LSM		Ratio (A/B) of LSM (%)	90% CI (Lower, Upper) (%)	Intra-Subject CV (%)
	Treatment A (n = 30)	Treatment B (n = 30)			
AUC <sub>0-t</sub> (ng-h/mL)	1824.7	1696.3	107.57	(99.67, 116.1)	17.5
AUC <sub>0-inf</sub> (ng-h/mL)	1857.1	1729.4*	107.39	(99.42, 116.0)	17.4
C <sub>max</sub> (ng/mL)	338.0	295.7	114.30	(106.6, 122.5)	15.9

Treatment A: CS-8663 tablet (olmesartan medoxomil 10 mg and amlodipine besylate 5 mg)

Treatment B: Olmesartan medoxomil 10 mg (Olmotec<sup>®</sup>) tablet coadministered with amlodipine besylate 5 mg (Antacal<sup>®</sup>) tablet

\* n = 29 (value could not be estimated for one subject)

Source: Table 14.2.1.9

The ratio of LSM and 90% CIs for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> of olmesartan were within the bioequivalence range of 80.0 to 125.0%. Therefore, the rate and extent of bioavailability of olmesartan from the fixed-dose combination tablet is bioequivalent to Olmetec<sup>®</sup> 10 mg tablets when coadministered with Antacal<sup>®</sup> 5 mg tablets under fasting conditions. The intra-subject CV% for all three parameters ranged from 15.9 to 17.5%.

Descriptive statistics of olmesartan pharmacokinetic parameters following oral administration of the Test and Reference treatments for Cohort 2 are presented below:

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Olmесartan	Cohort 2	
	Treatment C (n = 29)	Treatment D (n = 29)
<b>AUC<sub>0-t</sub> (ng·h/mL)</b>		
Arithmetic Mean ±SD	5994.9 ± 1782.10	5383.2 ± 1297.31
Geometric Mean (CV%)	5760.8 (29.2%)	5223.1 (26.0%)
<b>AUC<sub>0-inf</sub> (ng·h/mL)</b>		
Arithmetic Mean ±SD	6168.7 ± 1789.50*	5491.5 ± 1327.74
Geometric Mean (CV%)	5942.1 (28.2%)*	5325.7 (26.3%)
<b>AUC<sub>0-t</sub> / AUC<sub>0-inf</sub></b>		
Arithmetic Mean ±SD	0.9849 ± 0.01552*	0.9809 ± 0.01646
<b>C<sub>max</sub> (ng/mL)</b>		
Arithmetic Mean ±SD	938.7 ± 240.44	859.1 ± 182.23
Geometric Mean (CV%)	907.3 (27.7%)	839.3 (22.7%)
<b>T<sub>max</sub> (h)</b>		
Median (Min – Max)	2.000 (1.00 – 4.02)	1.517 (1.00 – 3.10)
<b>T<sub>1/2</sub> (h)</b>		
Arithmetic Mean ±SD	15.630 ± 7.0027*	17.273 ± 8.1291

Treatment C: CS-8663 tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)

Treatment D: Olmesartan medoxomil 40 mg (Olmecet<sup>®</sup>) tablet coadministered with amlodipine besylate 10 mg (Antacal<sup>®</sup>) tablet

\* n = 27 (value could not be estimated for two subjects)

Source: Tables 14.2.1.7 and 14.2.1.8.

When olmesartan medoxomil was administered in a fixed-dose combination with amlodipine besylate (40 and 10 mg, respectively), the rate and extent of bioavailability of olmesartan were similar to those observed when Olmecet<sup>®</sup> 40 mg was coadministered with Antacal<sup>®</sup> 10 mg as separate tablets. The mean terminal elimination half-life of olmesartan for the Test and Reference treatments were similar 15.630 and 17.273 hours, respectively.

Bioequivalence of olmesartan between the Test and Reference products was assessed using an ANOVA model. Results for Cohort 2 are presented below.

Olmесartan	Geometric LSM		Ratio (C/D) of LSM (%)	90% CI (Lower, Upper) (%)	Intra-Subject CV (%)
	Treatment C (n = 29)	Treatment D (n = 29)			
AUC <sub>0-t</sub> (ng·h/mL)	5790.3	5164.8	112.11	(103.3, 121.6)	18.1
AUC <sub>0-inf</sub> (ng·h/mL)	5976.7*	5265.7	113.50	(104.7, 123.0)	17.4
C <sub>max</sub> (ng/mL)	911.9	831.0	109.73	(101.8, 118.3)	16.8

Treatment C: CS-8663 tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)

Treatment D: Olmesartan medoxomil 40 mg (Olmecet<sup>®</sup>) tablet coadministered with amlodipine besylate 10 mg (Antacal<sup>®</sup>) tablet

\* n = 27 (value could not be estimated for two subjects)

Source: Table 14.2.1.10.

The ratio of LSM and 90% CIs for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> of olmesartan were within the bioequivalence range of 80.0 to 125.0%. Therefore, the rate and extent of bioavailability of olmesartan from the fixed-dose combination tablet is bioequivalent to Olmecet<sup>®</sup> 40 mg tablets when coadministered with Antacal<sup>®</sup> 10 mg tablets under fasting conditions. The intra-subject CV% for all three parameters ranged from 16.8 to 18.1%.

Descriptive statistics of amlodipine pharmacokinetic parameters following oral administration of the Test and Reference treatments for Cohort 1 are presented below:

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Amlodipine	Cohort 1	
	Treatment A (n = 30)	Treatment B (n = 30)
<b>AUC<sub>0-t</sub> (pg·h/mL)</b>		
Arithmetic Mean ±SD	152301.8 ± 42443.62	149952.8 ± 43336.46
Geometric Mean (CV%)	146500.5 (29.3%)	144154.0 (29.3%)
<b>AUC<sub>0-inf</sub> (pg·h/mL)</b>		
Arithmetic Mean ±SD	168328.2 ± 54018.97	165875.9 ± 56421.90
Geometric Mean (CV%)	160308.7 (32.8%)	157724.4 (32.8%)
<b>AUC<sub>0-t</sub> / AUC<sub>0-inf</sub></b>		
Arithmetic Mean ±SD	0.9150 ± 0.04480	0.9150 ± 0.04209
<b>C<sub>max</sub> (pg/mL)</b>		
Arithmetic Mean ±SD	3168.7 ± 806.56	3188.0 ± 764.42
Geometric Mean	3074.2 (25.3%)	3104.8 (23.5%)
<b>T<sub>max</sub> (h)</b>		
Median (Min – Max)	8.017 (6.00 – 12.1)	8.000 (6.00 – 12.0)
<b>T½ (h)</b>		
Arithmetic Mean ±SD	40.74 ± 9.692	40.46 ± 9.168

Treatment A: CS-8663 tablet (olmesartan medoxomil 10 mg and amlodipine besylate 5 mg)

Treatment B: Olmesartan medoxomil 10 mg (Olmotec<sup>®</sup>) tablet coadministered with amlodipine besylate 5 mg (Antacal<sup>®</sup>) tablet

Source: Tables 14.2.1.17 and 14.2.1.18.

When amlodipine besylate was administered in a fixed-dose combination with olmesartan medoxomil (5 and 10 mg, respectively), the rate and extent of bioavailability of amlodipine were similar to those observed when Antacal<sup>®</sup> 5 mg was coadministered with Olmetec<sup>®</sup> 10 mg as separate tablets. The mean terminal elimination half-life of amlodipine for the Test and Reference treatments were similar 40.74 and 40.46 hours, respectively.

Bioequivalence of amlodipine between the Test and Reference products was assessed using an ANOVA model. Results for Cohort 1 are presented below:

Amlodipine	Geometric LSM		Ratio (A/B) of LSM (%)	90% CI (Lower, Upper) (%)	Intra-Subject CV (%)
	Treatment A (n = 30)	Treatment B (n = 30)			
AUC <sub>0-t</sub> (pg·h/mL)	146500.5	144154.0	101.63	(99.13, 104.2)	5.7
AUC <sub>0-inf</sub> (pg·h/mL)	160308.7	157724.4	101.64	(99.04, 104.3)	5.9
C <sub>max</sub> (pg/mL)	3074.2	3104.8	99.01	(95.65, 102.5)	7.9

Treatment A: CS-8663 tablet (olmesartan medoxomil 10 mg and amlodipine besylate 5 mg)

Treatment B: Olmesartan medoxomil 10 mg (Olmotec<sup>®</sup>) tablet coadministered with amlodipine besylate 5 mg (Antacal<sup>®</sup>) tablet

Source: Table 14.2.1.21.

The ratio of LSM and 90% CIs for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> of amlodipine were within the bioequivalence range of 80.0 to 125.0%. Therefore, the rate and extent of bioavailability of amlodipine from the fixed-dose combination tablet were bioequivalent to Antacal<sup>®</sup> 10 mg tablets when coadministered with Olmetec<sup>®</sup> 40 mg tablets under fasting conditions. The intra-subject CV% for all three parameters ranged from 5.7 to 7.9%.

Descriptive statistics of amlodipine pharmacokinetic parameters following oral administration of the Test and Reference treatments for Cohort 2 are presented below:

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Cohort 2		
Amlodipine	Treatment C (n = 29)	Treatment D (n = 29)
<b>AUC<sub>0-t</sub> (pg·h/mL)</b>		
Arithmetic Mean ±SD	318909.8 ± 79462.16	309796.6 ± 69009.20
Geometric Mean (CV%)	309233.5 (26.1%)	301708.0 (24.5%)
<b>AUC<sub>0-inf</sub> (pg·h/mL)</b>		
Arithmetic Mean ±SD	350212.2 ± 91655.26	341976.5 ± 84607.54
Geometric Mean (CV%)	338307.8 (27.8%)	331203.5 (27.0%)
<b>AUC<sub>0-t</sub> / AUC<sub>0-inf</sub></b>		
Arithmetic Mean ±SD	0.9147 ± 0.03393	0.9117 ± 0.03650
<b>C<sub>max</sub> (pg/mL)</b>		
Arithmetic Mean ±SD	6824.1 ± 1546.74	6238.3 ± 1391.8
Geometric Mean	6643.1 (24.6%)	6084.9 (23.3%)
<b>T<sub>max</sub> (h)</b>		
Median (Min – Max)	6.100 (6.00 – 12.0)	7.983 (5.98 – 12.0)
<b>T<sub>1/2</sub> (h)</b>		
Arithmetic Mean ±SD	40.24 ± 7.534	40.79 ± 7.114

Treatment C: CS-3663 tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)

Treatment D: Olmesartan medoxomil 40 mg (Olmotec<sup>®</sup>) tablet coadministered with amlodipine besylate 10 mg (Antacal<sup>®</sup>) tablet

Source: Tables 14.2.1.19 and 14.2.1.20.

When amlodipine besylate was administered in a fixed-dose combination with olmesartan medoxomil (10 and 40 mg, respectively), the rate and extent of bioavailability of amlodipine were similar to those observed when Antacal<sup>®</sup> 10 mg was coadministered with Olmetec<sup>®</sup> 40 mg as separate tablets. The mean terminal elimination half-life of amlodipine for the Test and Reference treatments were similar, 40.24 and 40.79 hours, respectively.

Bioequivalence of amlodipine between the Test and Reference products was assessed using an ANOVA model. Results for Cohort 2 are presented below.

Amlodipine	Geometric LSM		Ratio (C/D) of LSM (%)	90% CI (Lower, Upper) (%)	Intra-Subject CV (%)
	Treatment C (n = 29)	Treatment D (n = 29)			
AUC <sub>0-t</sub> (pg·h/mL)	307935.3	303067.1	101.61	(97.25, 106.2)	9.7
AUC <sub>0-inf</sub> (pg·h/mL)	336543.6	332572.6	101.19	(96.58, 106.0)	10.3
C <sub>max</sub> (pg/mL)	6625.3	6118.6	108.28	(103.2, 113.6)	10.5

Treatment C: CS-3663 tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)

Treatment D: Olmesartan medoxomil 40 mg (Olmotec<sup>®</sup>) tablet coadministered with amlodipine besylate 10 mg (Antacal<sup>®</sup>) tablet

Source: Table 14.2.1.22

The ratio of LSM and 90% CIs for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> of amlodipine were within the bioequivalence range of 80.0 to 125.0%. Therefore, the rate and extent of bioavailability of amlodipine from the fixed-dose combination tablet were bioequivalent to Antacal<sup>®</sup> 10 mg tablets when coadministered with Olmetec<sup>®</sup> 40 mg tablets under fasting conditions. The intra-subject CV% for all three parameters ranged from 9.7 to 10.5%.

#### Safety Results:

No serious or severe AEs occurred in this study. Most TEAEs were mild, and no moderate TEAEs were related to the study treatments. One subject was withdrawn due to TEAEs (mild local swelling [swelling to left lower jaw/parotitis] and moderate eosinophilia) occurring after administration of Treatment D; these TEAEs were considered unrelated to Treatment D. TEAEs were possibly, unlikely or unrelated to the study treatments. No TEAEs were considered definitely or probably related to the study treatments.

Consistent with results in the literature<sup>12,13</sup> the most common TEAE was headache. Headaches judged possibly treatment-related occurred in 4 subjects who received Treatments A or C. Due to the small sample size however, no statistical analysis was done.

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All postdose QTcB and QTcF measurements were less than 480 msec. One subject presented with a QTcB increase from screening greater than 60 msec, and 6 subjects had QTcB and/or QTcF increases from screening greater than 30 msec.

**Subjects with QTcB and/or QTcF Increases from Screening greater than 30 and 60 msec**

Subject Number	Cohort	Treatment	Visit	Ventricular Rate (bpm)	QTcB (msec)	ΔQTcB (msec)	QTcF (msec)	ΔQTcF (msec)
001	1	A	EOS	87	414	47	389	25
002		A	P1/V7	65	420	31	414	12
010		A	P1/V7	89	404	33	378	15
039	2	D	EOS	78	401	42	384	22
040		D	P1/V7	83	405	31	384	20
046		C	P1/V7	83	401	34	379	14
056		C	P1/V7	82	421	62	400	41

Treatment A: CS-8663 tablet (olmesartan medoxomil 10 mg and amlodipine besylate 5 mg)

Treatment B: Olmesartan medoxomil 10 mg (Olmotec®) tablet coadministered with amlodipine besylate 5 mg (Antacal®) tablet

Treatment C: CS-8663 tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)

Treatment D: Olmesartan medoxomil 40 mg (Olmotec®) tablet coadministered with amlodipine besylate 10 mg (Antacal®) tablet

P1/V1 = Period 1, Visit 1; EOS = End of study

The Investigator withdrew Subject 055 (Cohort 2) from the study at predose in Period 2 due to two TEAEs unrelated to the study medication: mild local swelling (swelling to left lower jaw/parotitis) and moderate eosinophilia. As a result, Subject 055 received Treatment D only in Period 1. Subject 057 (Cohort 2) withdrew consent for personal reasons in Period 1 and received Treatment C only. Overall, 30 subjects received Treatments A and B, and 29 subjects received Treatments C and D.

**Conclusions:**

The lower strength of CS-8663 oral tablet [fixed dose-combination of olmesartan medoxomil 10 mg and amlodipine besylate 5 mg] was bioequivalent to the coadministered Olmetec® 10 mg and Antacal® 5 mg tablets under fasting conditions.

The higher strength of CS-8663 oral tablet [fixed dose-combination of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg] was bioequivalent to the coadministered Olmetec® 40 mg and Antacal® 10 mg tablets under fasting conditions.

**Reviewer's Comments:**

1. The reviewer concurs.

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**Study CS8663-A-E102 – BE study of 3 AML formulations**

**Title of Trial:** A randomised, open-label, single-dose, three-way crossover study to determine the bioequivalence of 10 mg amlodipine besylate, Istin<sup>®</sup> (UK) vs. 10 mg amlodipine besylate, Norvasc<sup>®</sup> (US) and amlodipine besylate, Antacal<sup>®</sup> (Italy)

EudraCT Number: 2004-004032-31

**Investigator:** G. Golor, MD, PhD, PAREXEL International GmbH

**Trial Center(s):** PAREXEL International GmbH, Clinical Pharmacology Research Unit, Klinikum Westend, Haus 18, Spandauer Damm 130, 14050 Berlin, Germany

**Publication (reference):** None

**Trial Period:**

Initiation date: December 17, 2004

Completion date: February 28, 2005

**Phase of Development:**

1

**Trial Objectives:** The primary objective was to determine the bioequivalence of three marketed amlodipine besylate formulations: Istin<sup>®</sup> 10 mg (Pfizer UK) vs. Norvasc<sup>®</sup> 10 mg (Pfizer US) vs. Antacal<sup>®</sup> 10 mg (Pfizer Italy), each equivalent to 10 mg amlodipine.

The secondary objective was to assess the safety and tolerability of a single dose of amlodipine besylate equivalent to 10 mg amlodipine, Istin<sup>®</sup> 10 mg (Pfizer UK), Norvasc<sup>®</sup> 10 mg (Pfizer US) and Antacal<sup>®</sup> 10 mg (Pfizer Italy).

**Trial Hypothesis:** The three formulations of amlodipine besylate, Istin<sup>®</sup> 10 mg (Pfizer, UK) vs. Norvasc<sup>®</sup> 10 mg (Pfizer, US) vs. Antacal<sup>®</sup> 10 mg (Pfizer, Italy) are bioequivalent

**Investigational Product and Comparator Information:**

Treatment A:

- Istin<sup>®</sup> 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (UK formulation)
  - Lot No.: 0405081A 1
  - Batch No.: 3998V04009
  - Expiration Date: 05/2005
  - Manufacture Date: Not Available
  - Manufacturer: Pfizer Ltd.

Treatment B:

- Norvasc<sup>®</sup> 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (US formulation)
  - Lot No.: 4QL 166E
  - Batch No.: 3998V04010
  - Expiration Date: 05/2005
  - Manufacture Date: Not Available
  - Manufacturer: Pfizer Inc.

Treatment C:

- Antacal<sup>®</sup> 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (Italian formulation)
  - Lot No.: 410190231
  - Batch No.: 3998V04013
  - Expiration Date: 05/2005
  - Manufacture Date: Not Available
  - Manufacturer: Heinrich Mack Nachf GmbH & Co., Germany

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**Methodology:** This Phase I trial was a randomized, open-labeled, single center study with a three-way crossover design. Three amlodipine besylate formulations (each equivalent to 10 mg amlodipine, see below) were investigated in three treatment periods, separated by washout periods of at least 14 days. A total of 18 healthy male or female subjects were assigned to the following treatments:

- Treatment A, Istin® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (UK formulation).
- Treatment B, Norvasc® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (US formulation).
- Treatment C, Antacal® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (Italian formulation).

The sequence of treatment was randomly assigned. Blood samples for pharmacokinetics of amlodipine were collected until 192 hours post-dose.

**Duration of Treatment:** The total duration of the study for enrolled subjects was approximately 40 days (from Day -1 until the last day in Period 3, not including a possible Safety Follow-up).

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**Number of Subjects:**

Planned: 18 healthy adult males and females.

Screened: 62 male and female subjects.

Enrolled/Randomized: 18 subjects (10 males and 8 females).

Completed: 18 subjects.

Discontinued: None.

**Analytical Methods:**

Amlodipine plasma concentrations were determined by a validated LC-MS/MS with an LLOQ of 0.1 ng/mL and  $r^2$  of 0.9955. Precision was in the range of 2.6 to 5.7% and Accuracy was 97.7 to 101.7%.

**Pharmacokinetics:** Pharmacokinetic parameters were calculated from the individual plasma concentrations of amlodipine using noncompartmental methods. The following PK parameters were calculated:  $AUC_{0-inf}$ ,  $AUC_{0-t}$ ,  $C_{max}$ ,  $T_{max}$ ,  $T_{1/2}$ ,  $CL/f$  and  $V_{ss}/f$ .

For the determination of amlodipine levels, blood samples were taken in each period pre-dose and at 1, 2.5, 4, 6, 7, 8, 9, 10, 12, 14, 16, 18, 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 144 (Day 7) and 192 (Day 9) hours post-dose. Each sample (6 mL) was collected into tubes containing dry lithium heparin. The samples were centrifuged (15 minutes at 4°C) within 30 minutes of collection and the resulting plasma was transferred into storage tubes and stored frozen at -20°C until transport to the analytical laboratory.

**Statistical Methods:**

**Pharmacokinetics:** Ninety percent (90%) CIs for the difference between treatment LSMs were derived from the Analyses of Variance (ANOVA) on the logarithmically transformed PK parameters  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  for amlodipine. The 90% CI was obtained from the antilogs of the lower and upper bounds of the 90% CI for the difference in the LSM of the logarithmically transformed data. Ratios of geometric LSMs and 90% CIs for the PK parameters were expressed as a percentage of the geometric LSM for the three formulations. Bioequivalence was concluded if the 90% CIs of the ratios for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  fell within 80% to 125%.

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**Results:**

**Pharmacokinetics:** Descriptive statistics of amlodipine pharmacokinetic parameters following oral administration of three tablet formulations containing amlodipine besylate equivalent to 10 mg amlodipine are presented below:

Amlodipine (N=18)	Treatment A (N=18)	Treatment B (N=18)	Treatment C (N=18)
<b>AUC<sub>0-t</sub> [ng.h/mL]</b>			
Arithmetic Mean ±SD	167.8 (43.3)	168.1 (44.8)	171.3 (47.5)
Geometric Mean (CV%)	162.8 (11.0)	162.4 (11.8)	164.4 (13.2)
<b>AUC<sub>0-inf</sub> [ng.h/mL]</b>			
Arithmetic Mean ±SD	177.4 (43.7)	177.5 (45.3)	182.1 (48.7)
Geometric Mean (CV%)	172.5 (10.6)	172.0 (11.3)	175.5 (12.5)
<b>C<sub>max</sub> (ng/mL)</b>			
Arithmetic Mean ±SD	3.74 (0.94)	3.47 (0.82)	3.77 (0.83)
Geometric Mean (CV%)	3.63 (10.82)	3.39 (9.69)	3.68 (10.32)
<b>T<sub>max</sub> (h)</b>			
Median (Min – Max)	8.0 (4.0; 10.1)	8.6 (4.0; 16.0)	8.6 (7.0; 14.0)
<b>T<sub>1/2</sub> (h)</b>			
Arithmetic Mean ±SD	43.6 (11.0)	41.9 (7.37)	42.4 (6.24)
<b>CL/f [mL/min]</b>			
Arithmetic Mean ±SD	993 (236.4)	1000 (262.3)	989 (302.0)
<b>V<sub>ss</sub>/f [L]</b>			
Arithmetic Mean ±SD	3702 (1170)	3536 (794)	3573 (1060)

<sup>1</sup> Istin® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (UK formulation)

<sup>2</sup> Norvasc® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (US formulation)

<sup>3</sup> Antacal® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (Italian formulation)

Source: Table 14.2.1.2

When amlodipine besylate was administered as an oral tablet in three different formulations, the rate and extent of bioavailability of amlodipine were similar to each other. The mean terminal elimination half-life of amlodipine for the UK, US and Italian formulations were approximately 44, 42 and 42 hours, respectively.

Bioequivalence of amlodipine between the three tablet formulations was assessed using an ANOVA model. Results are presented below:

Parameter	Comparison	Ratio of LSM (%)	90% CI (%) (Lower - Upper)
AUC <sub>0-t</sub> [ng.h/mL]	Treatment A <sup>1</sup> vs. B <sup>2</sup>	99.2	(94.1, 104.7)
	Treatment A <sup>1</sup> vs. C <sup>3</sup>	98.8	(93.6, 104.2)
	Treatment B <sup>2</sup> vs. C <sup>3</sup>	99.5	(94.3, 105.0)
AUC <sub>0-inf</sub> [ng.h/mL]	Treatment A <sup>1</sup> vs. B <sup>2</sup>	98.9	(94.0, 104.2)
	Treatment A <sup>1</sup> vs. C <sup>3</sup>	98.1	(93.2, 103.3)
	Treatment B <sup>2</sup> vs. C <sup>3</sup>	99.2	(94.2, 104.4)
C <sub>max</sub> [ng/mL]	Treatment A <sup>1</sup> vs. B <sup>2</sup>	108.6	(100.9, 116.8)
	Treatment A <sup>1</sup> vs. C <sup>3</sup>	98.0	(90.8, 105.7)
	Treatment B <sup>2</sup> vs. C <sup>3</sup>	90.3	(83.7, 97.3)

<sup>1</sup> Istin® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (UK formulation)

<sup>2</sup> Norvasc® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (US formulation)

<sup>3</sup> Antacal® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (Italian formulation)

Source: Table 14.2.1.4.2

The ratio of LSM and 90% CIs for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> of amlodipine were within 80% to 125% for all three formulations. Therefore, the rate and extent of bioavailability of amlodipine from the three tablet formulations is bioequivalent under fasting conditions.

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**Safety Results:**

The three amlodipine besylate formulations (equivalent to 10 mg amlodipine) were generally well tolerated in this study. Nine (50.0%) and 8 (44.4%) subjects experienced at least one TEAE after receiving the UK formulation (Istin® 10 mg) and the US formulation (Norvasc® 10 mg), respectively, and 6 subjects (33.3%) after administration of the Italian formulation (Antacal® 10 mg). TEAEs were most frequently related to the nervous system such as dizziness and headache. One subject had a TEAE (headache) classified as severe, all other AEs were of mild to moderate severity.

No clinically notable trends were observed in the laboratory, vital sign, physical examination, or ECG findings with respect to subject safety. As expected, reductions of blood pressure reflected the pharmacodynamic effect of the drug.

**Conclusions:**

The three different formulations of amlodipine besylate 10 mg (equivalent to 10 mg amlodipine) were bioequivalent.

**Reviewer's Comments:**

1. The reviewer concurs.

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**APPENDIX III**  
**F2 SIMILARITY DISSOLUTION COMPARISON**

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The sponsor submitted summary data comparing the intermediate strengths fixed dose combinations (5/20, 10/20, 5/40 mg AML/OLM) and states that they were compared to the reference 10/40 mg and 5/10 mg (AML/OLM) formulations used in the bioequivalence study. However, there is no way of verifying that it was done since no data was provided demonstrating the comparisons to the reference.

The sponsor only submitted data for pH 6.8, and apparatus 2 (paddle) speed 50 and 75 rpm. No other media pH was provided.

The sponsor is aware of these deficiencies and is providing the required data within a month. The sponsor is aware that the CPB review will be finalized shortly and an amendment to the NDA will be made upon submission of the required data.

**REVIEWER'S COMMENTS:**

The request for a biowaiver for the intermediate strengths can not be granted since the sponsor has not provided sufficient data to verify the calculations made and no data in different media was provided.

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**APPENDIX IV**  
**PHARMACOMETRICS REVIEW**

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## PHARMACOMETRICS REVIEW

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<b>sNDA</b>	22100
<b>Submission Date(s)</b>	11/27/2006
<b>PDUFA Due Date</b>	09/27/2007
<b>Brand Name</b>	Azor (fixed dose combination of Olmesartan medoxomil and Amlodipine)
<b>Generic Name</b>	Amlodipine/Olmesartan
<b>Pharmacometrics Reviewer</b>	Rajanikanth Madabushi, Ph.D.
<b>Pharmacometrics Team Leader</b>	Yaning Wang, Ph.D.
<b>Primary Reviewer</b>	Lydia Velazquez., Pharm.D.
<b>Primary Review Team Leader</b>	Patrick J Marroum, Ph.D.
<b>Sponsor</b>	Daichi-Sankyo
<b>Submission Type</b>	NDA
<b>Formulation</b>	Fixed dose combination tablet
<b>Proposed indication</b>	Hypertension

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## Executive Summary

The aim of the document is to review the sponsor's population pharmacokinetic analysis and exposure-response modeling which form the basis for labeling statements.

The key questions and findings of the present submission are:

- Is there an effect of age on the pharmacokinetics of olmesartan and amlodipine?  
Based on the results of the population pharmacokinetic analysis, age was not found to be a significant predictor of the apparent oral clearance of olmesartan. However, the oral clearance of amlodipine, derived from the population pharmacokinetic analysis, decreased with increasing age and this relationship was found to be statistically significant. This is consistent with the previous literature reports.
- Are there any gender based differences in the pharmacokinetics of olmesartan and amlodipine?  
Population pharmacokinetic analysis indicated that female patients had approximately 15% smaller clearances of olmesartan than male patients. The resulting increase in exposure does not warrant any dose adjustment in females. Gender had no effect on the clearance of amlodipine.
- Is there an exposure-response for Azor?  
Changes in sitting diastolic blood pressure ( $\Delta$ SeDBP) were found to be related to the exposures of olmesartan and amlodipine as represented by steady-state AUC.  
The drug effect of olmesartan exposure on  $\Delta$ SeDBP was described by an Emax model, whereas the drug effect of amlodipine exposure on  $\Delta$ SeDBP was described by a linear model.  
The drug effect for combination therapy was defined on the basis of exposures to both compounds, and it was greater than either of the monotherapy arms alone.

Other important findings in the current submission are:

- Olmesartan PK was adequately characterized by a two-compartmental model with first-order absorption and time lag; sex, weight, serum creatinine, and hypertensive status were predictors of the apparent oral clearance of olmesartan.
- Amlodipine PK was adequately characterized by a one-compartmental model with first-order absorption and a time lag; weight, age, and ALT were predictors of the apparent oral clearance of amlodipine.
- Neither compound had a clinically significant impact on the clearance of the other, based on the definition of clinically significant interaction as that which causes at least a 1.25-fold change in a parameter (i.e., outside of the range 80%-125%).
- The estimates of the covariate impacts on the clearances of olmesartan and amlodipine did not change between monotherapy and combination therapy.
- In the exposure-response model, black race was the most important covariate, decreasing the maximal possible effect of olmesartan on blood pressure while increasing the effect of amlodipine, without influencing PK parameters.

## Recommendation

The labeling statements proposed by the sponsor describing the pharmacokinetics in Geriatrics and Gender sections are acceptable.

Signatures:

Rajanikanth Madabushi, Ph.D.  
Pharmacometrics Reviewer  
Office of Clinical Pharmacology

Yaning Wang, Ph.D.  
Pharmacometrics Team Leader  
Office of Clinical Pharmacology

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## Labeling Statements

The labeling statements with regards to Geriatrics and Gender for olmesartan and amlodipine based on the results of population pharmacokinetics are acceptable. The following are the labeling statements proposed by the sponsor:

### 12 CLINICAL PHARMACOLOGY

#### 12.2 Pharmacokinetics

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#### *Gender*

Population pharmacokinetic analysis indicated that female patients had approximately 15% smaller clearances of olmesartan than male patients. Gender had no effect on the clearance of amlodipine.

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## Introduction

Azor is a fixed dose combination of olmesartan medoxomil (OM), an angiotensin receptor blocker (ARB), and amlodipine (AML), a channel blocker (CCB). In the current submission, the sponsor is proposing to indicate Azor either alone or in combination with other antihypertensive agents for the treatment of hypertension and to reduce the risk of cardiovascular events, primarily fatal and non-fatal strokes, and myocardial infarctions.

## Sponsor's Analysis

In the current technical report the sponsor describes the development of a population pharmacokinetic model and the effect of Azor on seated diastolic blood pressure (SeDBP).

### 6.1 Objectives

The specific objectives of the analysis were:

- Develop population pharmacokinetic (PopPK) models of olmesartan (OM) and amlodipine (AML) using the data collected in studies CS8663-A-U101, CS8663-A-U110, CS8663-A-U111, CS8663-A-U112, and CS8663-A-U301.
- Characterize and quantify the effects of covariates on the oral clearances of the compounds. For both olmesartan and amlodipine, investigate age, weight, gender, serum creatinine, race, and patient/volunteer status in the covariate analysis. For amlodipine, also investigate alanine aminotransferase, aspartate aminotransferase, and total bilirubin in the covariate analysis.
- Based on the definition of clinically significant interaction as that which causes at least a 1.25-fold change in a parameter (i.e, outside of the bioequivalence range of 80%-125%), determine whether co-administration of amlodipine modifies the clearance of olmesartan, and *vice versa*.
- For each of the covariates identified as having a statistically significant effect on the oral clearance of olmesartan, determine whether its effect is modified by the co-administration of amlodipine, and *vice versa*.
- Develop an exposure-response model that characterizes the effect of the drug on seated diastolic trough blood pressure (SeDBP) for each compound administered separately and administered as a combination.
- Characterize and quantify effects of covariates (age, race, weight, sex and baseline SeDBP) on the parameters of the exposure-response model.

### 6.2 Data

Data from four Phase I (CS8663-A-U101, CS8663-A-U110, CS8663-A-U111, CS8663-A-U112) and one Phase III study (CS8663-A-U301) were used to conduct the PK analysis. The PK population included 170 healthy volunteers (115 males, 55 females) in Phase I trials and 546 patients (276 males, 270 females) with mild to severe hypertension in the Phase III trial. The PK patients in the Study 301 trial were a subset, recruited from the overall study population, comprising about 25% of the patients in the study. Data from the Phase III trial alone was used to conduct the exposure-response analysis.

The Phase I studies had intensive PK sampling profiles that were conducted after a steady state dose in CS-8663-A-U101 and after a single dose in the other three Phase I studies. CS8663-A-U301 had PK pre-dose (trough) samples taken at the Week 6 and Week 8 visits and two post-dose samples taken at 0.5 to 2 hours and 4 to 10 hours post-dose at the Week 8 visit.

The exposure-response analysis used seated diastolic blood pressure (SeDBP) measurements taken at the start (Visit 3) and end (Visit 7, Week 8) of Period II of Study 301. In the Period II, patients who met all the inclusion criteria and none of the exclusion criteria were randomized equally to one of the following 12 treatment arms

**Table 1:**

**Table 1:** Design of the Period II of the Phase III trial (CS8663-A-U301).

Treatment	Placebo	OM 10mg	OM 20mg	OM 40mg
Placebo	160	160	159	160
AML 5mg	161	163	160	157
AML 10mg	163	161	158	161

OM – Olmesartan, AML – Amlodipine. The numbers in the table are the number of patients in each arm.

Placebo, on each occasion, three measurements, at least one minute apart, were taken prior to dosing. Any PK samples or BP measurements that were recorded as zero, below limit of quantitation, or missing were excluded from the analysis. Unless otherwise identified as an outlier, all subject data with complete dosing records was

used in the PK analysis. For the exposure-response analysis, only SeDBP data from Visit 3 and Visit 7 in Study CS8663-A-U301 were used.

The following table (Table 2) provides the details of the size, regimen, population, duration and PK sampling for these studies.

**Table 2:** Details of the studies included for population pharmacokinetic and exposure-response modeling

Study	Title	N	Treatment Regimen	Population	Duration of Treatment	PK sampling Schedule
CS8663-A-U101	A Randomized, Open-label, 3-Way Crossover Multiple Dose Study to Determine the Pharmacokinetic Interaction of Olmesartan Medoxomil and Amlodipine Besylate in Healthy Subjects.	24	A. Olmesartan medoxomil 40mg QD B. Amlodipine besylate 10mg QD C. Olmesartan medoxomil 40mg and amlodipine besylate 10 mg QD	Healthy volunteers	3 crossover periods of 10 days each, separated by at least 21 days from the last dose.	<u>For the analysis of olmesartan (treatments A and B):</u> Days 1, 8 and 9: pre-dose. Day 10: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours. <u>For the analysis of amlodipine (treatments B and C):</u> Days 1, 8 and 9: pre-dose. Day 10: pre-dose, 1, 2.5, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 24, 48, 72 and 96 hours.

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CS8663-A-U110	A Randomized Single-dose, Open-label 2-way Crossover Study to Determine the Effect of Food on the Bioavailability of Olmesartan and Amlodipine from a Fixed-Dose Combination Tablet When Administrated in Healthy Subjects.	28	<p>A. A single dose of the combination tablet formulation of olmesartan medoxomil 40mg and amlodipine besylate 10 mg in the fasted state.</p> <p>B. A single dose of the combination tablet formulation of olmesartan medoxomil 40mg and amlodipine besylate 10 mg after a high fat breakfast.</p>	Healthy volunteers	2 crossover periods, separated by at least 21 days.	<p><u>For the analysis of olmesartan</u> Samples were collected from all subjects pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post-dose.</p> <p><u>For the analysis of amlodipine</u> Samples were collected from all subjects pre-dose and at 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours post-dose.</p>
CS8663-A-U111	A Parallel-Group, open-label, Randomized, Crossover Study to Determine the Bioavailability of a Fixed-dose Combination Tablet of Olmesartan Medoxomil and Amlodipine Besylate Relative to Olmetec® and Antacal® in healthy subjects.	60	<p><u>Within cohort 1:</u> <u>Treatment A (Test)</u> A fixed-dose combination tablet formulation of olmesartan medoxomil 10 mg and amlodipine besylate 5 mg. <u>Treatment B (Reference)</u> Olmesartan medoxomil 10 mg [Olmetec®] co-administered with amlodipine besylate 5 mg [Antacal®]. <u>Within cohort 2:</u> <u>Treatment C (Test)</u> A fixed-dose combination tablet formulation of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg. <u>Treatment D (Reference)</u> Olmesartan medoxomil 40 mg [Olmetec®] co-administered with amlodipine besylate 10 mg [Antacal®].</p>	Healthy volunteers	Within each cohort, a 2 period crossover separated by a 21 day washout.	<p><u>For the analysis of olmesartan</u> Blood samples (5 mL) for plasma concentrations of RNH-6270 were collected prior to (Hour 0) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours following each dose.</p> <p><u>For the analysis of amlodipine</u> Blood samples (5 mL) for plasma concentrations of amlodipine were collected prior to (Hour 0) and at 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours following each dose.</p>
CS8663-A-U112	A Parallel-group, Randomized, Open-label, Single-dose, 3-period Crossover Study to Determine the Dose Proportionality of Olmesartan and Amlodipine from different Strengths of an Olmesartan Medoxomil and Amlodipine Besylate Fixed Dose Combination Tablet When Administrated to Healthy Subjects.	60	<p><u>Within cohort 1:</u> <u>Treatment A</u> A fixed-dose combination tablet formulation of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg. <u>Treatment B</u> A fixed-dose combination tablet formulation of olmesartan medoxomil 20 mg and amlodipine besylate 5 mg. <u>Treatment C</u> A fixed-dose combination tablet formulation of olmesartan medoxomil 10 mg and amlodipine besylate 10 mg. <u>Within cohort 2:</u> <u>Treatment D</u> A fixed-dose combination tablet formulation of olmesartan medoxomil 40 mg and amlodipine besylate 5 mg. <u>Treatment E</u> A fixed-dose combination tablet formulation of olmesartan medoxomil 20 mg and amlodipine besylate 10 mg. <u>Treatment F</u> A fixed-dose combination tablet formulation of olmesartan medoxomil 10 mg and amlodipine besylate 5 mg.</p>	Healthy volunteers	Within each cohort, a 3 period crossover, separated by 21-day washouts.	<p><u>For the analysis of olmesartan</u> Blood samples (5 mL) for plasma concentrations of RNH-6270 were collected prior to (Hour 0) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours following each dose.</p> <p><u>For the analysis of amlodipine</u> Blood samples (5 mL) for plasma concentrations of amlodipine were collected prior to (Hour 0) and at 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours following each dose.</p>

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CS8663-A-U301	A Randomized, Double-Blind, Placebo-Controlled, Factorial Study Evaluating the Efficacy and Safety of Co-Administration of Olmesartan Medoxomil plus Amlodipine Compared to Monotherapy in Patients with Mild to Severe Hypertension	1896	<p><b>Period I:</b> Washout of any antihypertensive medication for 2 weeks.</p> <p><b>Period II (used in analysis):</b> 12-arm parallel group study for 8 weeks with the following doses and corresponding placebo arms: OM 10 mg + AML 5 mg OM 10 mg + AML 10 mg OM 20 mg + AML 5 mg OM 20 mg + AML 10 mg OM 40 mg + AML 5 mg OM 40 mg + AML 10 mg</p> <p><b>Period III:</b> All patients started on OM40+AML10. If BP was not adequately controlled, dose raised to OM40+ALM10. If the BP goal was still not reached, then sequentially HCTZ 12.5 mg and HCTZ 25 mg were added to achieve BP goal.</p>	Adult patients with mild to severe HTN defined as mean sitting trough cuff SeDBP of 95-120 mmHg (inclusive) during Period I (while off anti-HTN medication or newly diagnosed).	3 period parallel study	556 patients were assessed for PK. Visit 6 – one trough blood sample (~24-hrs post dose); Visit 7 – one trough blood sample, one sample between 0.5 and 2 hours post dose, one blood sample 4-10 hours post dose.
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### 6.3 Analysis Methods

All data preparation and graphical presentation were performed using S-PLUS\* software, Version 6.2. All pharmacokinetic and exposure-response analyses were implemented within the computer program NONMEM\*, Version V, Level 1.1. The general procedure followed for the development of models for population and exposure-response analyses were as follows:

1. Exploratory analysis using graphs
2. Fitting structural models, including residual variability
3. Optimizing the inter-subject random effect matrices
4. Covariate analysis through forward selection and stepwise backward elimination
5. Evaluation and qualification of the final model

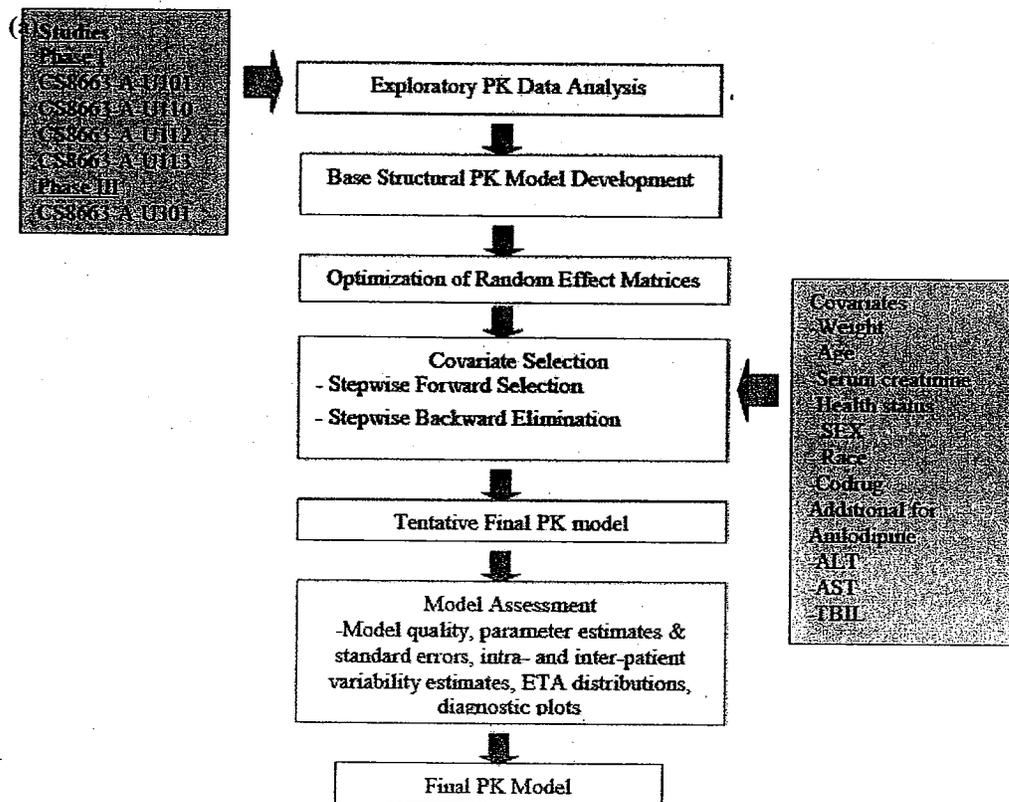
The details of the modeling approach are represented in

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**Figure 1a and 1b respectively.**

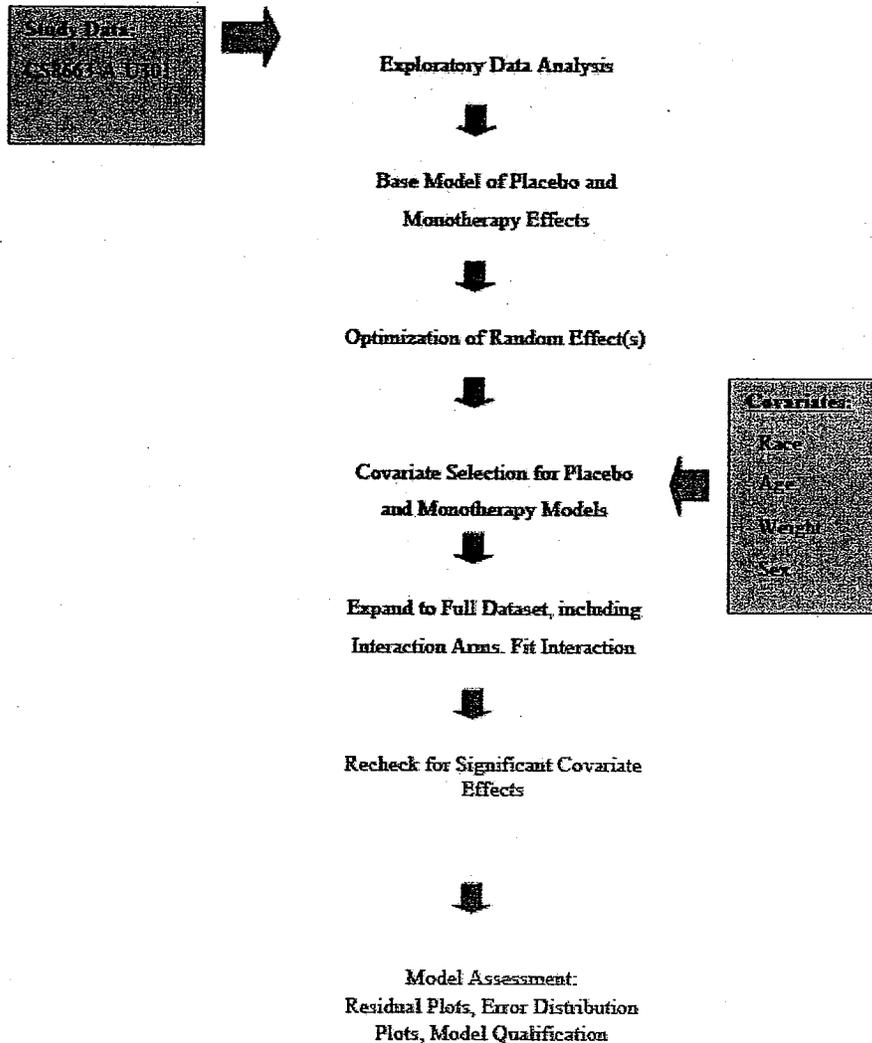
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**Figure 1:** Overview of POPPK and Exposure-Response Modeling processes. (a) POPPK modeling process (b) Exposure-Response modeling process. (Note: Left column lists the data sources, center column lists the steps in modeling processes and the right column lists the covariates tested in the analyses)



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(b)



### 6.3.1. Structural Model

Various compartmental models (one/two) and combinations of residual error models were evaluated in describing the olmesartan and amlodipine plasma concentration-time data. Inter-subject variability was modeled for all pharmacokinetic parameters as follows:

$$\theta_{ij} = \theta_{\text{typical}} e^{\eta_i}$$

where  $\theta_{ij}$  is the parameter for the  $i$ th participant on the  $j$ th occasion,  $\theta_{\text{typical}}$  is the typical value of the parameter in the population, and

$\eta_i$  is a random inter-subject effect with mean 0 and variance  $\omega^2$  ( $\eta$  is referred to as ETA hereafter).

Inter-individual variability (IIV) terms (ETAs) were added on each PK parameter except inter-compartmental clearance (in the two compartment PK model). The ETAs on  $K_a$  and lag time (if present in the model) were removed one at a time and any improvement in the model was tested.

The exposure-response modeling focused on the relationship between exposure (as measured by AUC) and change from baseline in SeDBP. AUC for each of the subjects was derived from individual clearance. Two different structural models were investigated for this purpose:

1. Linear: Response = intercept + slope\*Predictor
2. Emax: Response = intercept + Emax\*Predictor/(Predictor + E50)

Drug models for each compound in monotherapy were constructed first, using data from the respective treatment arms and the placebo arm. An additive term represented IIV in delta SeDBP. Once the best structural form for each compound was established, covariates were tested to determine their potential effects on the parameters within the structural models. After covariate relationships were established, a model incorporating the combination treatment arms data was built to determine the form of the exposure-response interaction, if any. Residual variability was modeled as either additive or proportional based on graphical exploration of different models or the change in objective function.

### 6.3.2. Covariate Analyses

Covariates explaining the IIV on pharmacokinetic and pharmacodynamic parameters were screened using the forward selection process. Continuous covariates were included in the model as follows:

$$\theta_i = \theta_{\text{Typical}} \cdot \left( \frac{\text{Cov}_i}{\text{Cov}_{\text{median}}} \right)^{\theta_{\text{eff}}}$$

where

$\theta_i$  is the value of the parameter for the  $i$ th individual,

$\theta_{\text{Typical}}$  is the typical value of the parameter in the population,

$\text{Cov}_i$  is the value of the covariate for the individual,

$\text{Cov}_{\text{median}}$  is the median value of the covariate in the study population and  $\theta_{\text{eff}}$  is the effect of the covariate on the parameter.

Categorical covariates were introduced in the model as follows:

$$\theta_i = \theta_{\text{Typical}} + \theta_{\text{eff}}(1 - K_{\text{ind}})$$

where

$K_{\text{ind}}$  is an indicator variable representing one form of the categorical variable and  $\theta_{\text{eff}}$  is the effect of the covariate on the parameter, e.g., males coded as 0 and females as 1.

Parameter-covariate relationships were included in a full tentative pharmacokinetic model if the covariate contributed at least a 3.84 change in the objective function ( $\alpha = 0.05$ , one degree of freedom chi-squared). Covariates were then excluded from the model using a simple backward elimination method if the covariate relationship did not contribute at least a 6.63 change in the objective function ( $\alpha = 0.01$ , one degree of freedom chi-squared). Covariates that had the smallest impact during forward selection were assessed first during backwards elimination.

### 6.3.3. Model Assessment

Plots of population predicted values and individual predicted values versus observed concentrations were examined. Residuals were examined to evaluate the model. Residuals versus time and residuals versus predicted concentrations were examined to determine if a model bias existed. The precision of the parameter estimation was evaluated,  $\%SEM = 100 * (\text{SE of parameter estimate} / \text{parameter estimate})$ . Relationships between structural model parameters and covariates were examined graphically, after accounting for all statistically significant covariate relationships to determine if any trends still existed.

### 6.3.4. Model Qualification

To verify that the models adequately described the central tendency and spread of the data, plots of actual data were overlaid with model predictions (mean, 95%CI) to determine the fraction of data that lay within the model prediction interval.

## **6.4 Results**

### **6.4.1. Demographics and other baseline characteristics**

Data from 630 and 590 unique subjects was available for the olmesartan PK and amlodipine PK analysis, respectively. The demographic characteristics of the combined datasets for each compound are summarized in Table below. The dataset was roughly evenly balanced between males and females, and there were at least 100 subjects in each of categories of non-Hispanic Caucasian, non-Hispanic black, and Hispanic.

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**Table 3:** Summary of Key Demographic Information of the combined pharmacokinetic datasets.

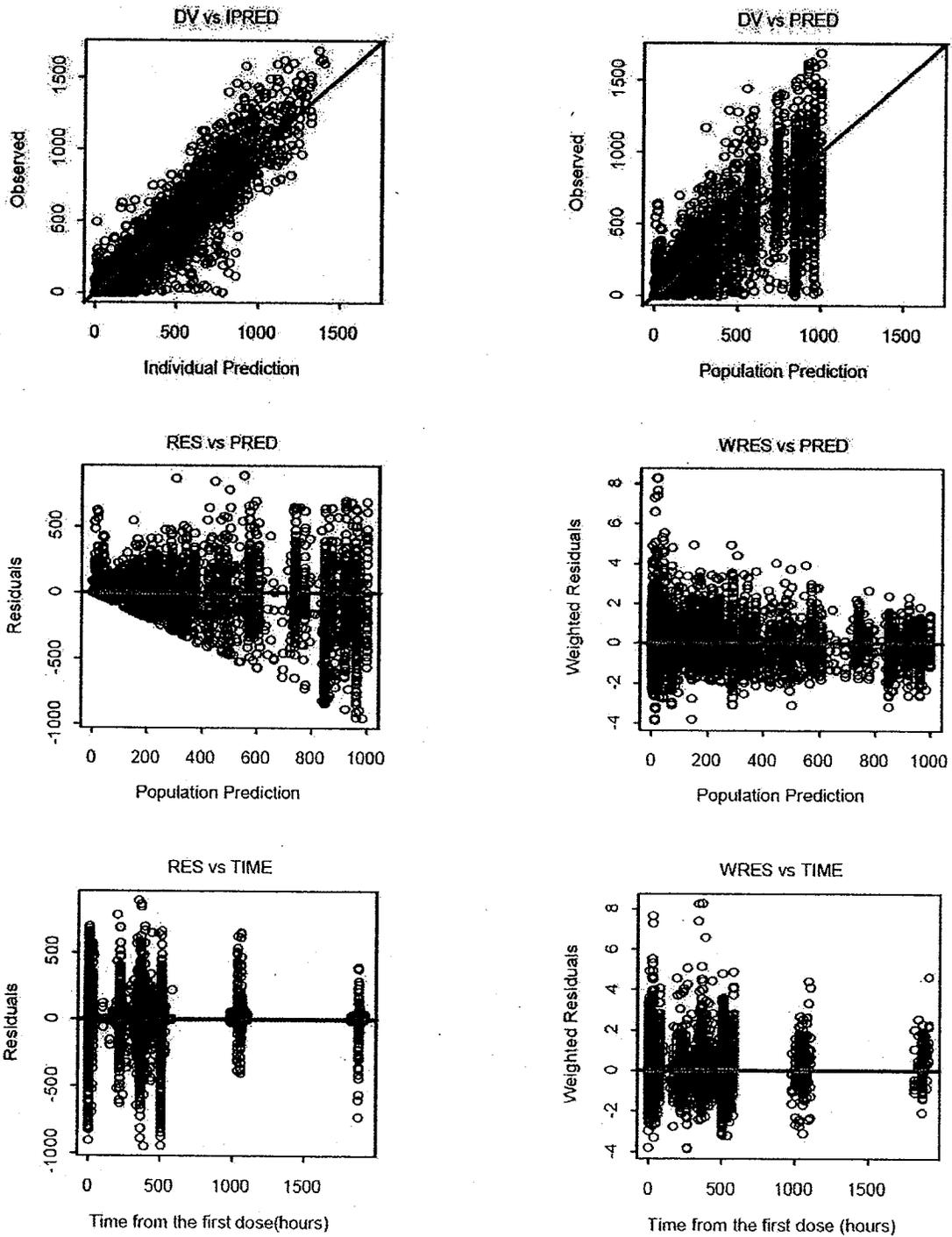
<b>Characteristic</b>	<b>Olmesartan Dataset</b>	<b>Amlodipine Dataset</b>
Age (years)	48.9 ± 14.3	48.2 ± 14.3
WT (kg)	89.4 ± 21	89.9 ± 20.6
SeCr (mg/dL)	1.03 ± 0.2	1.03 ± 0.2
SEX (Male/Female)	341/289	326/264
RACE (Caucasian/ Black/ Hispanic/Asian/other)	316/167/9/122/16	288/165/6/119/12

#### 6.4.2. Model Development for Olmesartan

A two-compartment model provided substantially better fit compared to one-compartment model. This finding was in agreement with previous POPPK analysis. IIV was estimated with an exponential error model for clearance (CL), central volume (V2), peripheral volume (V3), and absorption rate (Ka). Residual error was modeled with proportional and additive terms. Since higher residual error was associated with the Phase II study compared to the Phase I studies, a separate additive error for the Phase III study was estimated. The goodness-of-fit plots for the base model are shown in the **Figure 2**.

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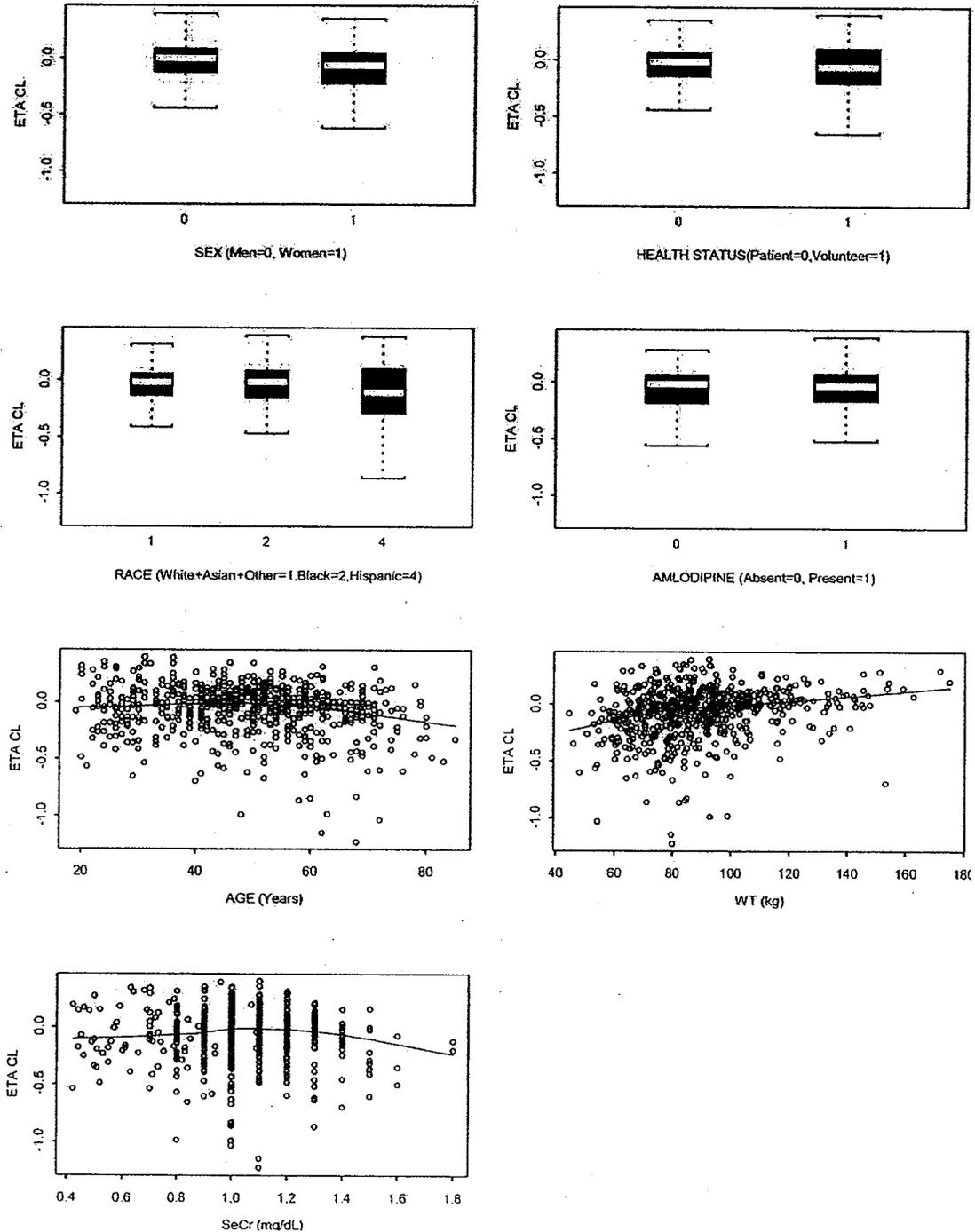
Figure 2: Goodness-of-fit plots for olmesartan base model.



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A plot of the post-hoc Etas' on clearance from the base model and the covariates (Figure 3) shows trend for increased clearance with increase in body weight.

Figure 3: Covariate plots for the base olmesartan model.



Forward selection and backward elimination process retained patient status, sex, and serum creatinine and body weight as the statistically significant covariates. The final equation for clearance was:

$$CL[L/h] = [5.9 - (0.878 * KSEX) + (1.68 * KHV)] * \left(\frac{WTKG_i}{86}\right)^{0.326} * \left(\frac{SeCR_i}{1}\right)^{-0.278}$$

Where,

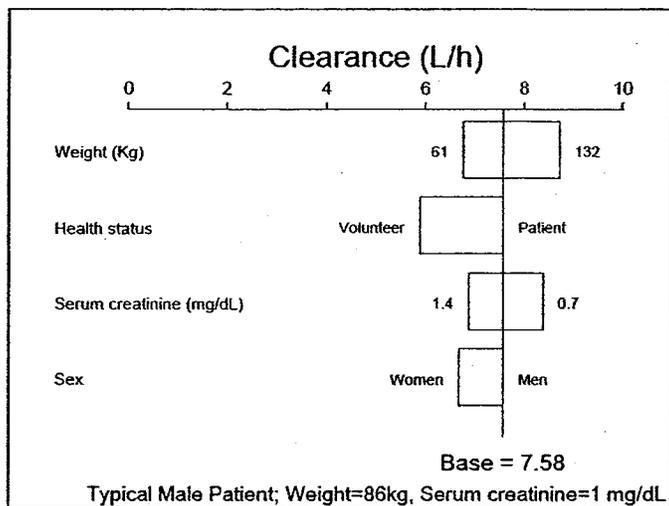
KSEX is the indicator for female, KHV is the indicator for healthy volunteer, WTKG<sub>i</sub> is the individual's weight in kg, and SeCR<sub>i</sub> is the individual's baseline serum creatinine. These covariates do not result in a clinically significant impact on the clearance as evident from the tornado plots (

**Figure 4).** The parameters for the final model are shown in the

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Table 4.

Figure 4: Tornado plot depicting the sensitivity analysis of the covariates on olmesartan clearance.



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Table 4: Olmesartan population pharmacokinetic parameters. (Note: Final Model)

<i>Parameter</i>	<i>Population Mean</i>		<i>Intersubject variability</i>	
	<i>Estimate</i>	<i>SE<sup>a</sup></i> <i>(% CV)</i>	<i>Estimate<sup>b</sup></i> <i>(%CV)</i>	<i>SE<sup>c</sup></i> <i>(%)</i>
CL <sub>TYP</sub> (L/h)	5.90	4.4	30	41
V2 (L)	32.1	2.5	32	40
V3 (L)	27.6	4.2	-	-
Ka (per h)	2.02	5.1	63	31
ALAG1 (h)	0.374	1.5	50	39
Q (L/h)	1.74	4.3	-	-
CL <sub>EV</sub>	1.68	20	-	-
CL <sub>SEX</sub>	-0.878	34	-	-
CL <sub>RTKG</sub>	0.326	31	-	-
CL <sub>SECR</sub>	-0.278	25	-	-
$\sigma^2_1$ (multiplicative) (ng/mL) <sup>2</sup>	0.091	7.7	-	-
$\sigma^2_2$ (additive Ph I) (ng/mL) <sup>2</sup>	0.515	36	-	-
$\sigma^2_3$ (additive Ph III) (ng/mL) <sup>2</sup>	3970	25	-	-

Predictive check of the model showed that 82% to 94% of the data were within the 95% confidence intervals of the model predictions.

#### 6.4.3. Model Development for Amlodipine

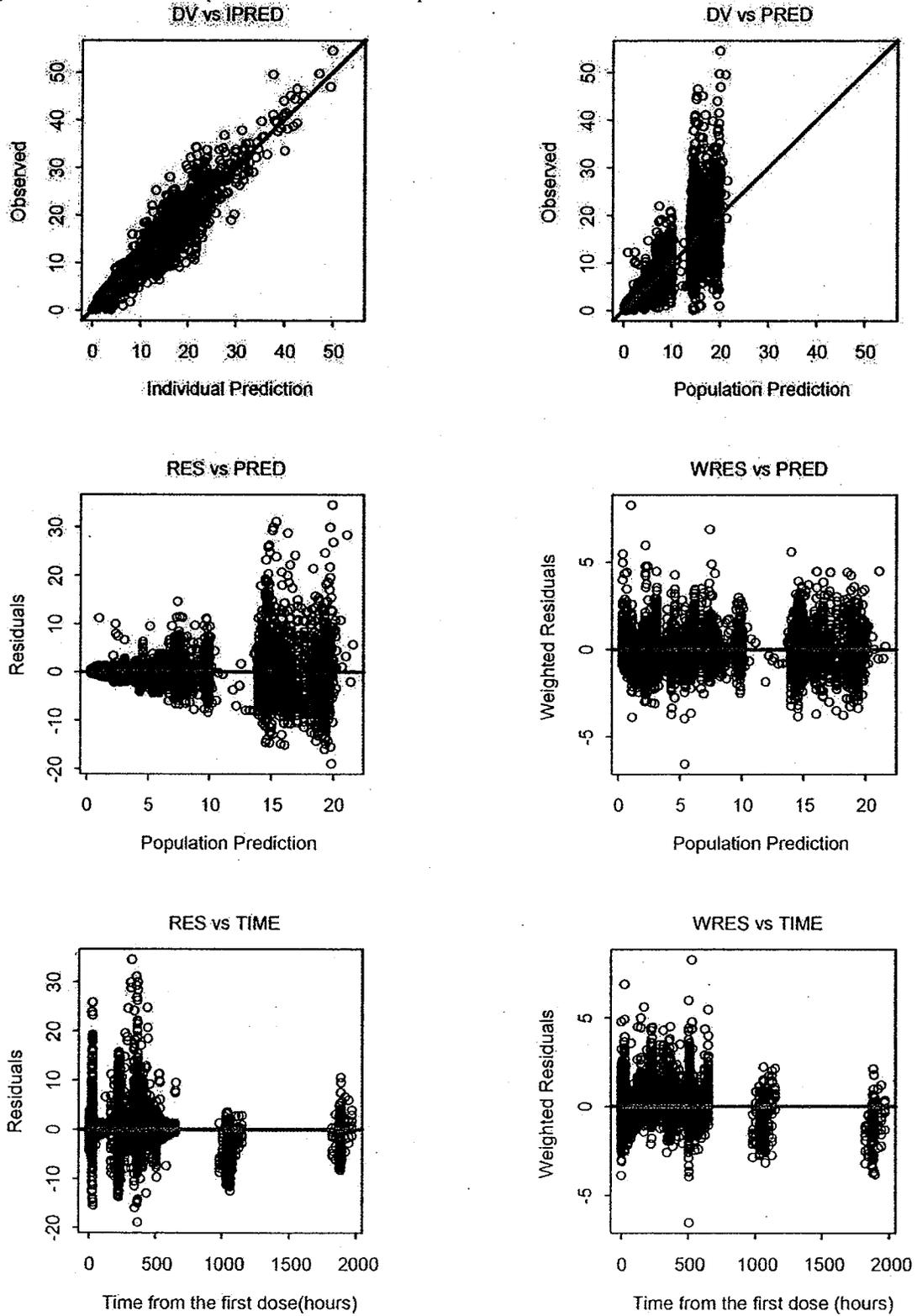
A one-compartment was found to best describe the data as shown by the goodness-of-fit plots in

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**Figure 5.** Interindividual variability was estimated with an exponential error model for clearance (CL), volume (V), absorption rate (Ka), and time lag (ALAG1). As with olmesartan, residual error was modeled with proportional and additive terms, with an additive term to account for the increased residual variability seen in the Phase III.

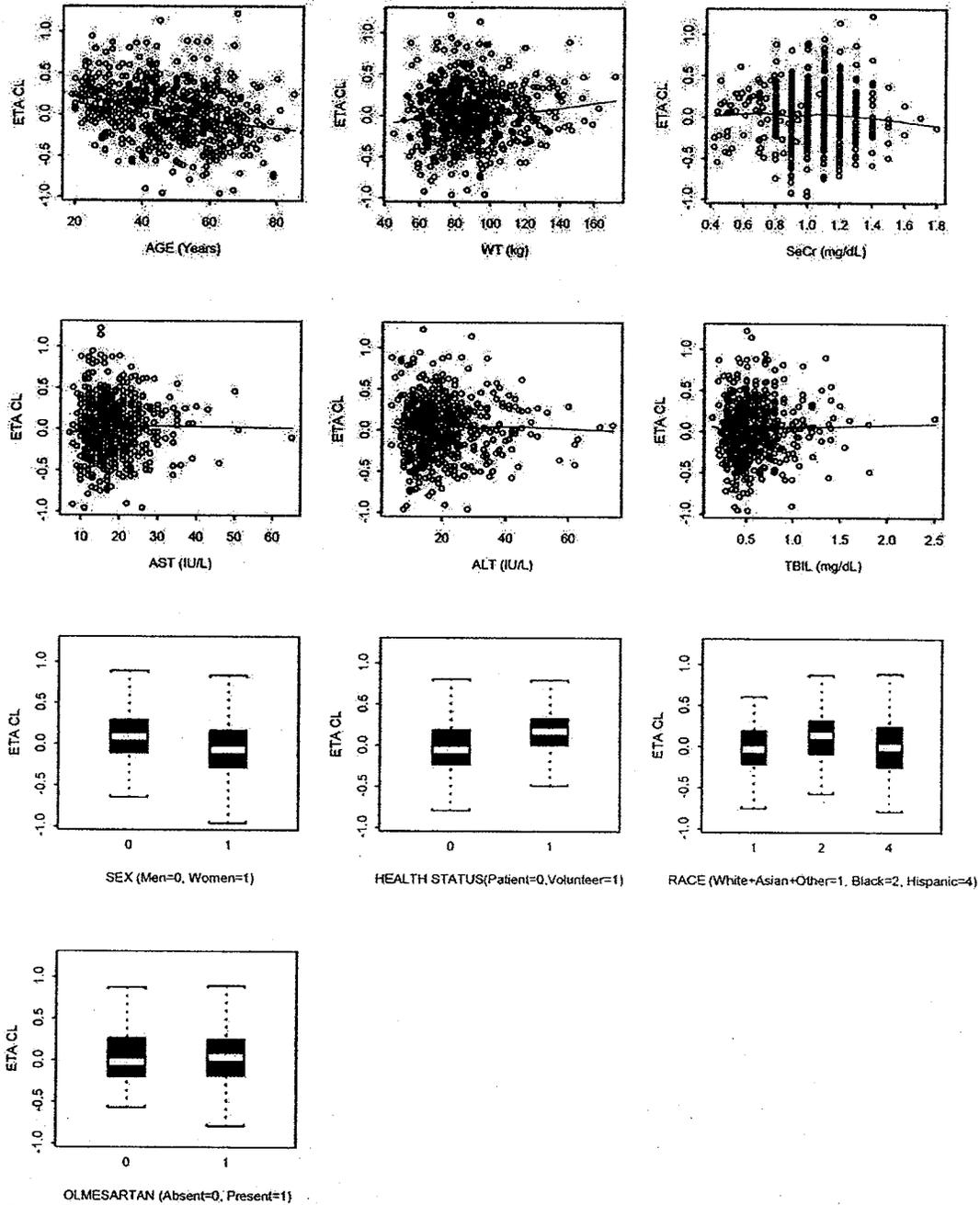
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Figure 5: Goodness-of-fit plots for the base amlodipine model.



Plots of posthoc Etas on clearance from the amlodipine base model and the covariates indicate trends of increasing clearance with increasing body weight and decreasing clearance with increasing age as shown in Figure 6.

Figure 6: Covariate plots for the base model of Amlodipine.



During forward selection, health status, sex, olmesartan, weight, age, ALT, and AST had a statistically significant impact on the model. Each of these was then tested in a backwards elimination process, beginning with the covariate that had the smallest impact on the model during forward selection. After backwards selection, weight, olmesartan, sex, ALT, and age remained statistically significant. However, the parameter representing the effect of sex was not well-estimated (i.e., the 95%CI for the parameter included 0) and was therefore removed from the final model. The final model included effects of age, weight, and ALT on the clearance of amlodipine. The final equation for clearance was as follows:

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$$CL[L/h] = 22.9 * \left( \frac{WTKG_i}{86} \right)^{0.207} * \left( \frac{AGE_i}{50} \right)^{-0.373} * \left( \frac{ALT_i}{17} \right)^{-0.138}$$

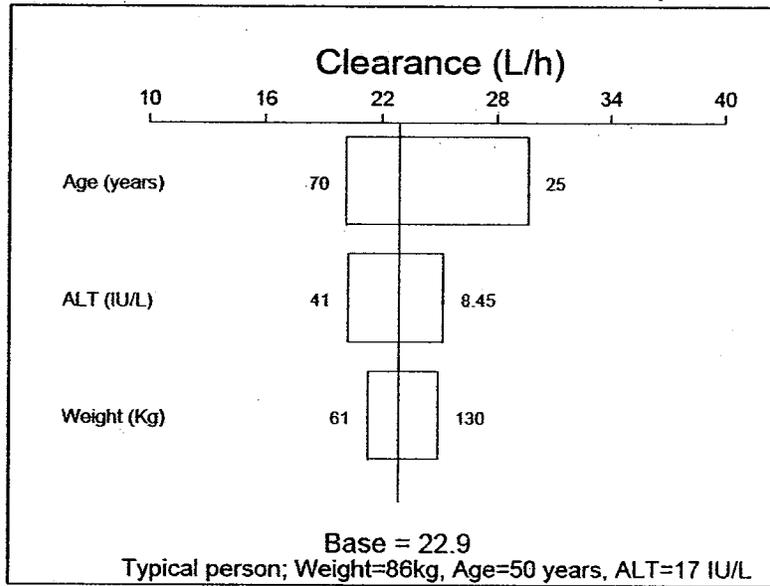
where  $WTKG_i$  is the individual's weight in kg,  $AGE_i$  is the individual's age, and  $ALT_i$  is the individual's baseline ALT in IU/L. These covariates do not result in a clinically meaningful impact of covariates on the clearance of amlodipine as evident from the tornado plots

Figure 7. The parameters for the final model are shown in.

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Table 5.

Figure 7: Tornado plots depicting the sensitivity analysis of covariates on amlodipine clearance.



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**Table 5:** Amlodipine population pharmacokinetic parameters. (Final Model)

Parameter	Population Mean		Intersubject variability	
	Estimate	SE <sup>a</sup> (% CV)	Estimate <sup>b</sup> (%CV)	SE <sup>c</sup> (%)
CL <sub>TYP</sub> (L/h)	22.9	1.66	33.8	29.0
V (L)	1530	1.97	23.2	33.2
Ka (per h)	0.640	2.28	79.2	38.0
ALAG1 (h)	0.390	10.3	26.0	106.4
CL <sub>WT</sub>	0.207	35.6	-	-
CL <sub>AGE</sub>	-0.373	13.5	-	-
CL <sub>ALT</sub>	-0.138	32.4	-	-
σ <sup>2</sup> <sub>1</sub> (multiplicative) (ng/mL) <sup>2</sup>	0.026	30.1	-	-
σ <sup>2</sup> <sub>3</sub> (additive) (ng/mL) <sup>2</sup>	1.1	69.3	-	-

a Coefficient of variation of the estimates (100SE<sub>estimate</sub>/estimate).

b Estimates of variability expressed as approximate percent coefficient of variation (%CV)  $100 \sqrt{\sigma^2}$

c Percent square root of the relative standard error of the coefficient of variation.  $100 \sqrt{\frac{SE_{Estimate}}{Estimate}}$

d Residual intra-subject variability.

Predictive check of the model showed that 92% to 94% of the data were within the 95% confidence intervals of the model predictions for all the studies indicating model qualification.

#### 6.4.4. Exposure-Response Analysis

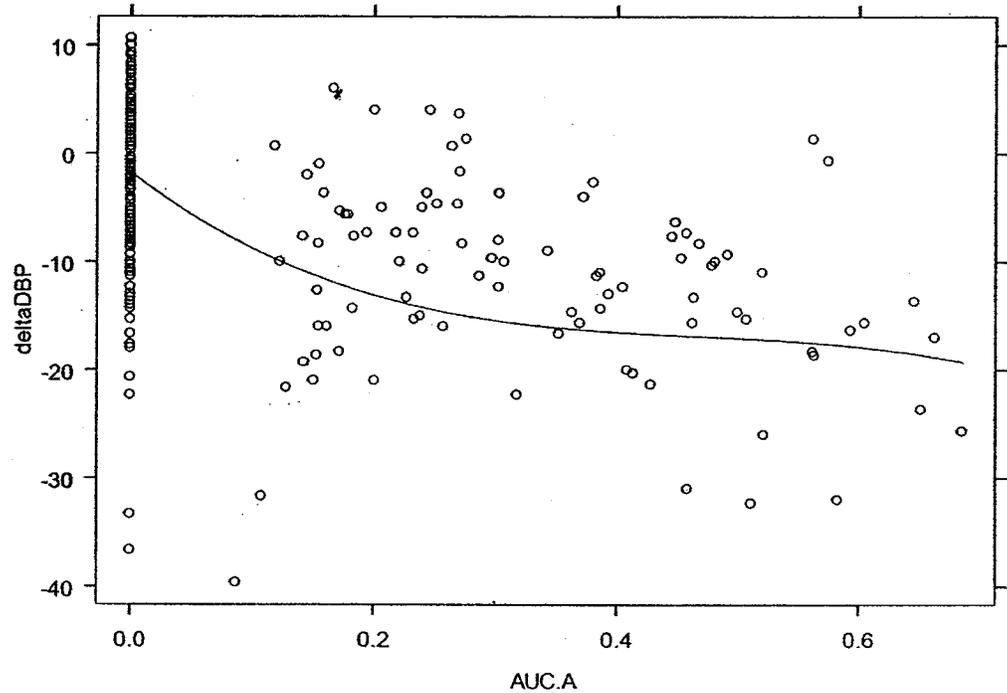
Subject-matched *post-hoc* clearances from the PopPK model were used to generate AUC values in conjunction with the subject's dose. Exploratory graphical analysis showed that the change in SeDBP (ΔSeDBP) was related to individual's AUC as shown in

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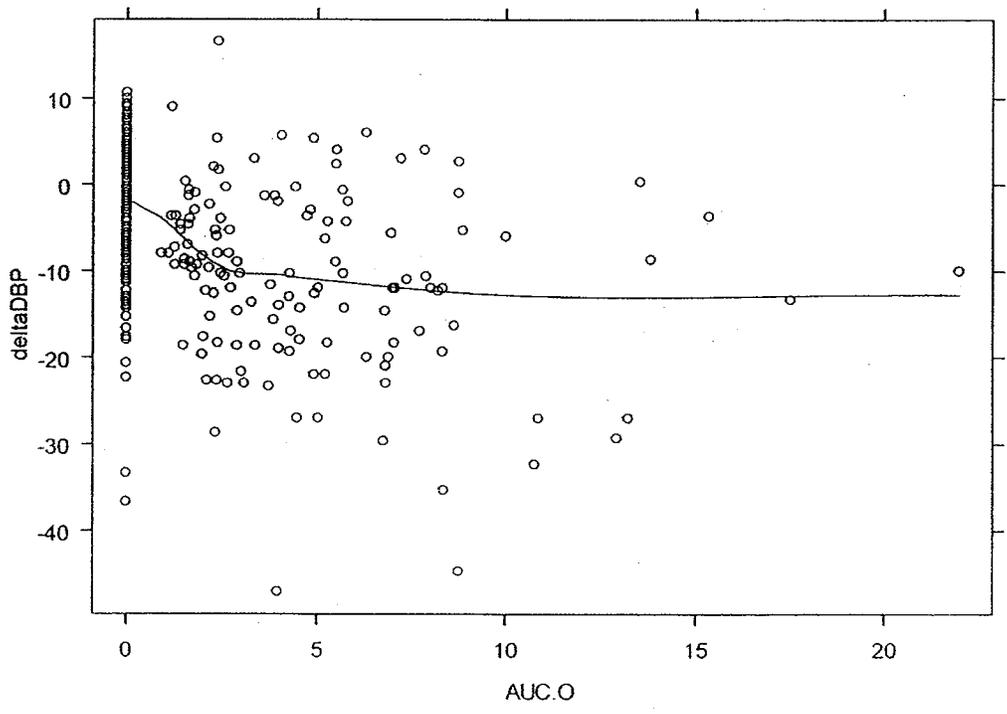
**Figure 8.**

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**Figure 8:** Exploratory plots showing the relationship between AUC and  $\Delta$ SeDBP for amlodipine and olmesartan.



Olmesartan Monotherapy and Placebo



An intercept model was fitted to the data subset from the placebo arm to determine the placebo effect and the covariates that modified it. Weight, age, sex, race, and average baseline were investigated as possible covariates on the placebo effect. Hispanic ethnicity ( $KH = 1$  in Equation below) and average baseline were both found to be significant modifiers of the placebo response. Average baseline was adjusted by the median average baseline of 100.5.

$$\text{Intercept} = \theta_{\text{Placebo}} + \theta_{\text{Hispanic}} * KH + \theta_{\text{Baseline}} * (\text{Baseline} - 100.5)$$

An Emax model was found to be appropriate for modeling the dependence of  $\Delta\text{SeDBP}$  on olmesartan exposure. A linear model was preferable for modeling the dependence of  $\Delta\text{SeDBP}$  on amlodipine exposure. Weight, age, sex, and race were investigated as possible covariates on the placebo and drug effect. In the drug effects, black race ( $KB = 1$ ) was found to be a significant modifier of both drug effect models, decreasing the  $E_{\text{max}}$  in the olmesartan model and increasing the slope in the amlodipine model. No other covariate relationships were found to be statistically significant. Equations describing the drug effects are shown below:

$$\text{DEff}_{\text{OM}} = (E_{\text{max}_{\text{OM}}} + KB * \theta_{\text{BlackonE}_{\text{max}}}) * \left( \frac{AUC_{\text{OM}}}{AUC_{\text{OM}} + EAUC50_{\text{OM}}} \right)$$

$$\text{DEff}_{\text{AML}} = (\text{Slope}_{\text{AML}} * KB + \theta_{\text{BlackonSlope}}) * AUC_{\text{AML}}$$

In modeling the full exposure-response dataset, a function of the product of the drug effects was found to yield a greater reduction in objective function than either a constant scaling term or no term at all. The final form of the model was thus:

$$\Delta\text{SeDBP} = \text{Intercept} + \text{DEff}_{\text{OM}} + \text{DEff}_{\text{AML}} + \theta_{\text{Interaction}} * \text{DEff}_{\text{OM}} * \text{DEff}_{\text{AML}} + \eta + \varepsilon$$

Where,  $\text{DEff}_{\text{OM}}$  and  $\text{DEff}_{\text{AML}}$  are the steady-state drug effects [mmHg] of olmesartan and amlodipine exposures  $AUC_{\text{OM}}$  [ng/mL\*h] and  $AUC_{\text{AML}}$  [ng/mL\*h];  $\theta_{\text{Interaction}}$  is a constant describing the interaction effect;  $\eta$  is the intersubject variability in response [mmHg]; and  $\varepsilon$  is the residual variability [mmHg].

The parameters of the final model are shown in **Table 6**. The most important covariate was black race, as it modified both drug effects, but in opposite directions. Persons of black race ( $KB = 1$ ) realized about 20% greater reduction in SeDBP at equal exposure to amlodipine than other races, but could only realize half of the maximal possible reduction in SeDBP at equal exposure to olmesartan than the other races.

The placebo effect was -3.59 mmHg, and patients of Hispanic ethnicity showed a larger placebo effect than non-Hispanics. Patients with higher baseline SeDBP experienced larger declines in SeDBP, about 3 mmHg of additional decline per 10 additional mmHg of baseline SeDBP.

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Table 6: Model parameters for the final exposure-response model.

<b>Parameter</b>		
	<b>Estimate</b>	<b>SE<sup>a</sup> (% CV)</b>
Placebo	-3.59	19
Hispanic on Placebo	-4.84	28
Baseline on Placebo	-0.33	21
Emax (OM) [mmHg]	-18.1	30
Black race on Emax	9.51	46
EAUC <sub>50</sub> (OM) [hr*ng/mL]	1630.	37
Slope (AML) [mL/(ng*hr)]	-0.0222	13
Black race on Slope	-0.00488	55
Interaction coefficient	0.05	19
IV (SD of Eta) [mmHg]	8.0 <sup>b</sup>	25 <sup>c</sup>
Sigma [mmHg] <sup>d</sup>	3.5	69.3

a Coefficient of variation of the estimates ( $100SE_{estimate}/estimate$ ).

b Square root of  $ETA_{estimate}$

c Percent square root of the relative standard error of the coefficient of variation.

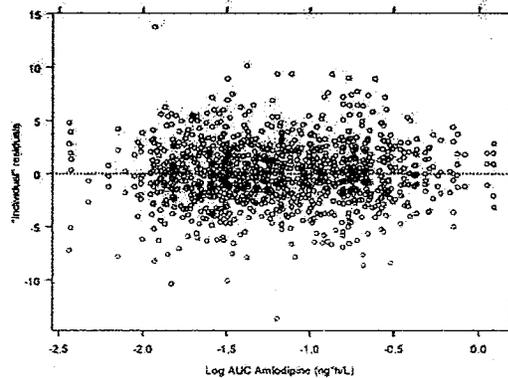
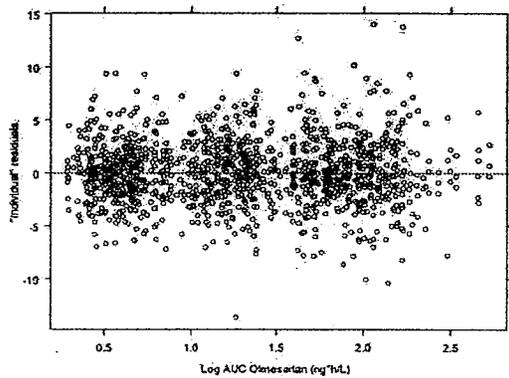
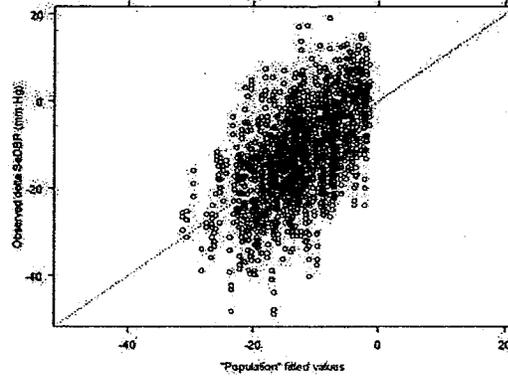
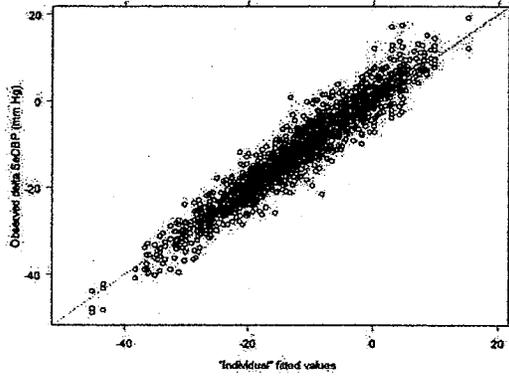
$$100 \sqrt{\frac{SE_{estimate}}{ETA_{estimate}}}$$

d Residual intra-subject variability.

The goodness-of-fit plots show that the models for olmesartan and amlodipine were appropriate (Figure 9). The residual plots versus covariates showed no remaining patterns after the final model fit. The predictive check showed that 95.5% of the data falls into the 95% confidence interval of the model predictions, a further indication of the model appropriateness. Further the E50 for AUC found here (1630 hr\*ng/mL) was comparable to the one found for Caucasians in the previous analysis (2200 hr\*ng/mL). Also, the placebo effect in this study (-3.5 mm Hg) is similar to that reported in literature (-4.7 mm Hg)<sup>1</sup>. The finding of the impact of black race on olmesartan and amlodipine effects is also expected. The impact of co-administration on exposure-response was modeled as a fraction of the product of the drug effects. The coefficient, 0.05, was well-estimated. For patients receiving the combination treatment, the effect was higher than either of the two monotherapy arms alone and roughly additive, with patients seeing from 80%-100% of the benefit calculated by adding the drug effects seen in monotherapy at each of the respective AUCs.

Figure 9: Goodness-of-fit model for the final exposure-response model.

<sup>1</sup> Gualdiero P, Niebauer J, Addison C, Clark SJ, Coats, AJ. Clinical features, anthropometric characteristics, and racial influences on the "white coat effect" in a single-centre cohort of 1553 consecutive subjects undergoing routine ambulatory blood pressure monitoring. *Blood Press Monit* 2000;5:53-57.



### Conclusion

- Olmesartan PK was adequately characterized by a two-compartmental model with first-order absorption and time lag; sex, weight, serum creatinine, and hypertensive status were predictors of the apparent oral clearance of olmesartan.
- Amlodipine PK was adequately characterized by a one-compartmental model with first-order absorption and a time lag; weight, age, and ALT were predictors of the apparent oral clearance of amlodipine.
- Neither compound had a clinically significant impact on the clearance of the other, based on the definition of clinically significant interaction as that which causes at least a 1.25-fold change in a parameter (i.e., outside of the range 80%-125%).
- The estimates of the covariate impacts on the clearances of olmesartan and amlodipine did not change between monotherapy and combination therapy.
- The drug effect of olmesartan exposure on  $\Delta$ SeDBP was described by an Emax model, whereas the drug effect of amlodipine exposure on  $\Delta$ SeDBP was described by a linear model.
- In the exposure-response model, black race was the most important covariate, decreasing the maximal possible effect of olmesartan on blood pressure while increasing the effect of amlodipine, without influencing PK parameters.
- The drug effect for combination therapy was defined on the basis of exposures to both compounds, and it was greater than either of the monotherapy arms alone.

### Reviewer's Comments

The analysis approach and the interpretation of the results of population pharmacokinetics are reasonable and acceptable.

The following are the comments regarding the exposure-response modeling:

1. The  $EAUC_{50}$  for olmesartan (1630 ng.hr/mL) reported in **Table 6** is incorrect. The  $EAUC_{50}$  is estimated as an exponential and the correct estimate upon transformation is 5104 ng.hr/mL. Further, the % RSE reported by the sponsor for  $EAUC_{50}$  (37%) is also incorrect. The %RSE reported by the sponsor is for the untransformed parameter involved in the calculation of the  $EACU_{50}$ . The correct %RSE for  $EAUC_{50}$  is 60%. The correct estimates can be verified by estimating the  $EAUC_{50}$  as such instead as an exponential.
2. The  $EAUC_{50}$  of olmesartan estimated in the current modeling exercise is not consistent with previous analysis (2200 ng.hr/mL). This discrepancy should be addressed before the sponsor can utilize the model for projecting drug effects under different scenarios.
3. The % RSEs for the IIV (25%) and Sigma (69.3%) reported by the sponsors (**Table 6**) are incorrect. The correct estimates are 3% for IIV on the placebo effect and 2.7% for the residual error. It should be noted that the sponsor correctly transformed the estimates of the IIV and Sigma.

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**APPENDIX V**  
**COVER SHEET AND OCPB FILING/REVIEW FORM**

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**Office of Clinical Pharmacology and Biopharmaceutics**  
**New Drug Application Filing and Review Form**

**General Information About the Submission**

	Information		Information
NDA Number	22-100	Brand Name	Azor
OCPB Division (I, II, III)	DPE 1	Generic Name	Amlodipine besylate/ Olmesartan medoxomil
Medical Division	HFD-110	Drug Class	CCB/ Angiotensin II (type AT1) antagonist
OCPB Reviewer	Lydia Velazquez	Indication(s)	Hypertension; in ititial therapy to be used alone or in combination with other hypertensive medications. <b>Initial Therapy:</b> in patients requiring a reduction of $\geq 20/10$ mm Hg to reach BP goal and in whom the benefit outweighs the risk.
OCPB Team Leader	Patrick Marroum	Dosage Form	Tablets – 5/20, 10/20, 5/40, and 10/40 mg
		Dosing Regimen	Increase every 2 weeks to achieve goal -- Once Daily
Date of Submission	27 November 2006	Route of Administration	Oral
Estimated Due Date of OCPB Review	15 August, 2007	Sponsor	Daiichi Sankyo, Inc.
PDUFA Due Date	15 September, 2007	Priority Classification	S
Division Due Date	15 August, 2007		

**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS INFORMATION**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	13		
HPK Summary	X			Not representative of all CPB studies in the NDA
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	13		In a separate listing.
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	11		8 BA/BE, 1 Food Effect, 1 BE, 1 Dose- proportionality
multiple dose:	X	1		1 DDI
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		Healthy volunteers
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		A and O - Multiple Dose - MD
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1		PM Analysis
pediatrics:				
geriatrics:	X	1		PM Analysis

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		1 MD, A and O, then HCTZ added on
Population Analyses -				
Data rich:				
Data sparse:	X	1		Study AU301 (phase III – 546 patients), AU101, AU110, AU111, AU112 (total of 170 healthy volunteers)
<b>II. Biopharmaceutics</b>				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	8		BA of different formulations
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:	X	1		SD
Food-drug interaction studies:	X	1		Food Effect – Healthy Volunteers - SD
Dissolution:	N/A			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
<b>III. Other CPB Studies</b>				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Permeability				
Efflux				
QT Study				
Total Number of Studies		13		13 analytical reports, 1 Dose Proportionality, 1 DDI, 8 BA (relative), 1BE, 1 Phase III efficacy trial, and 1 Food Effect. Can't find cross-reference tables of batch numbers to study and batch sizes and compositional tables.
<b>Fileability and QBR comments</b>				
		"X" IF YES	<b>COMMENTS</b>	
Application fileable ?		X	Have not been able to locate batch number table that correlates to clinical study with the batch size and compositional tables. Will request that it be submitted ASAP.	
Comments sent to firm?				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 22-100, HFD-110 (FrommE), HFD-860 (MehtaM, MarroumP, VelazquezL),  
CDR Central Document Room

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/s/

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BIOPHARMACEUTICS

CPB review of Original NDA

Yaning Wang  
7/25/2007 05:50:56 PM  
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Patrick Marroum  
7/26/2007 02:15:28 PM  
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