CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200175

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA (Biopharmaceutics) Review

NDA: 200-175 (000)
Submission Date: 09/30/2009, 07/01/2010
Product: CS-8635 ([redacted] (b) (4))
Dosage Form: Immediate Release Tablets containing Olmesartan Medoxomil (OM)/Amlodipine (AML) /Hydrochlorothiazide (HCTZ)
Strength(s): 40/10/25; 40/10/12.5; 40/5/25; 40/5/12.5 mg
Type of Submission: Response to FDA Request for Information
Sponsor: Daiichi Sankyo Pharma Development
Reviewer: Tapash K. Ghosh, Ph.D.

Background:

The sponsor, Daiichi Sankyo Pharma Development (DS) submitted this 505(b) (2) New Drug Application (NDA) 200-175 on June 30, 2009, for CS-8635 [[redacted] (b) (4) (initially proposed name)] for fixed dose triple combination tablets containing Olmesartan Medoxomil (OM), Amlodipine (AML) and Hydrochlorothiazide (HCTZ). [redacted] (b) (4) Tablets are intended for the treatment of hypertension. The original Biopharmaceutics review was placed in DARRT on 5/18/2010 recommending modification of the dissolution specification as follows:

- ***Dissolution Method:***

  The sponsor's proposed dissolution methodology as described below is acceptable.

Medium:	0.05 M Phosphate buffer solution pH 6.8
Volume:	900 ml
Temperature:	37^0C
Apparatus:	USP 2
Paddle speed:	50 RPM

- ***Dissolution Specifications:***

  Based on the dissolution data from the pilot and production batches, the Agency recommends the following dissolution specifications:

  - ***Olmesartan medoxomil (OM): Q-value of [redacted] (b) (4) at 30 minutes (all tablets have achieved [redacted] (b) (4) dissolution at S_1 level)***

  - ***Amlodipine (AML): Q-value of [redacted] (b) (4) at 30 minutes (all tablets have achieved [redacted] (b) (4) dissolution at S_1 level)***

- ***Hydrochlorothiazide (HCTZ): Q-value of (b) (4) at 15 minutes (all tablets have achieved (b) (4) dissolution at S_1 level)***

The recommendation was forwarded to the sponsor via an information request (IR) letter dated June 7, 2010. Following that, there was a teleconference between the sponsor's representatives and the Division of New Drug Quality Assessment and the Biopharmaceutics representatives on June 24, 2010, where finalization of the dissolution acceptance criteria was mutually agreed upon:

Recommendation:

The dissolution specifications and the biowaiver requests as outlined below and mutually agreed upon are acceptable to the Agency:

- ***Dissolution*:**

Test	Acceptance Criteria						Method
	20/5/12.5 mg	20/10/12.5 mg[1]	40/5/12.5 mg	40/5/25 mg	40/10/12.5 mg	40/10/25 mg	
Dissolution in 0.05 M phosphate buffer pH 6.8 30 minutes	Release 50 rpm: Q = (b) (4) of label claim for olmesartan medoxomil Q = (b) (4) of label claim for amlodipine Q = (b) (4) of label claim for hydrochlorothiazide			Shelf-life 50 rpm: Q = (b) (4) of label claim for olmesartan medoxomil Q = (b) (4) of label claim for amlodipine Q = (b) (4) of label claim for hydrochlorothiazide			UV-VIS multicomponent analysis [J-G000225] alternatively: HPLC [J-A000315] K-MZ OLME/ AMLO/ HCTZ_E

- ***Biowaiver***: Based on the referenced June 24 teleconference with the Division, the sentence in the FDA's IR Letter of June 7 is revised to read "…a *biowaiver* is granted for the three intermediate strengths; OM/AML/HCTZ 40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg.

Tapash K. Ghosh, Ph. D.
Biopharmaceutics Primary Reviewer
Office of New Drugs Quality Assessment

FT Initialed by Patrick Marroum, Ph. D. _____

FDA Request #1 (via IR letter dated June 7, 2010)

P.5.1 Specification

1. *Based on the dissolution data from the pilot and production batches, the Agency recommends the following dissolution acceptance criteria:*

    - *Olmesartan medoxomil (OM): Q - value of* (b) (4) *at 30 minutes (all tablets have achieved* (b) (4) *dissolution at S_1 level)*
    - *Amlodipine (AML): Q - value of* (b) (4) *at 30 minutes (all tablets have achieved* (b) (4) *dissolution at S_1 level)*
    - *Hydrochlorothiazide (HCTZ): Q - value of* (b) (4) *at 15 minutes (all tablets have achieved* (b) (4) *dissolution at S_1 level)*

Provide the revised acceptance criteria sheet.

Response:

Based on agreements reached with the Division in the June 24, 2010 teleconference, the revised acceptance criteria sheet for dissolution are provided in the drug product release and shelf life specification (Table 1), and replaces Table 1 in section 3.2.P.5.1 in Sequence 0012 and Tables 1 and 2 in section 2.3.P.5.1 in Sequence 0000.

1. SPECIFICATIONS [CS-8635, TABLETS]

The release and stability specifications for CS-8635 Tablets (20/5/12.5 mg, 20/10/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, and 40/10/25 mg) are presented in Table 1.

Table 1: Release and Shelf-Life Specifications for CS-8635 Tablets

Test	Acceptance Criteria						Method
	20/5/12.5 mg	20/10/12.5 mg[1]	40/5/12.5 mg	40/5/25 mg	40/10/12.5 mg	40/10/25 mg	
Appearance	Round film-coated tablets	Round film-coated tablets	Round film-coated tablets	Oval film-coated tablets	Round film-coated tablets	Oval film-coated tablets	Visual [J-A000164] K-MZ OLME/AMLO/ HCTZ_E
Diameter (approx.)	8 mm	9.5 mm	9.5 mm	15 x 7 mm	9.5 mm	15 x 7 mm	
Color	Orange white	Orange white	Light yellow	Light yellow	Greyish red	Greyish red	
Debossed Code[2]	C51	C52	C53	C54	C55	C57	
Identification for Olmesartan Medoxomil, Amlodipine and Hydrochlorothiazide: only for Release							
1. Retention Time (RT) 2. UV-Spectrum	1. Chromatogram of sample solution exhibits major peak for olmesartan medoxomil amlodipine and hydrochlorothiazide, the RT of which corresponds to that exhibited in the chromatogram of the standard solution. 2. UV-spectrum of sample solution corresponds to spectrum of reference solution						HPLC [J-A000313] alternatively: UPLC [J-A000373] K-MZ OLME/AMLO/ HCTZ_E
Uniformity of Dosage Units: only for Release	Corresponding to EP monograph 2.9.40 and USP <905> criteria						HPLC [J-A000313] alternatively : UPLC [J-A000373] K-MZ OLME/ AMLO/ HCTZ_E
Dissolution in 0.05 M phosphate buffer pH 6.8 30 minutes	Release 50 rpm: Q = (b) (4) of label claim for olmesartan medoxomil Q = (b) (4) of label claim for amlodipine Q = (b) (4) of label claim for hydrochlorothiazide			Shelf-life 50 rpm: Q = (b) (4) of label claim for olmesartan medoxomil Q = (b) (4) of label claim for amlodipine Q = (b) (4) of label claim for hydrochlorothiazide			UV-VIS multicomponent analysis [J-G000225] alternatively: HPLC [J-A000315] K-MZ OLME/ AMLO/ HCTZ_E

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Biowaiver: There was an omission in the original review regarding biowaiver. That has been corrected as follows:

FDA Comment #2

Based on acceptable BE data for the lowest and the highest strengths and the similarity of the dissolution profiles, the Agency considers that your waiver request is acceptable and a biowaiver is granted for the two intermediate strengths; OM/AML/HCTZ 40/10/12.5 mg and 40/5/25 mg.

Response:

Based on the referenced June 24 teleconference with the Division, the sentence in the FDA's IR Letter of June 7 is revised to read "…a biowaiver is granted for the three intermediate strengths; OM/AML/HCTZ 40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg.

Discussion:

The dissolution specifications and the biowaiver requests as outlined below and mutually agreed upon are acceptable by the Agency:

- *Dissolution*:

Test	Acceptance Criteria						Method
	20/5/12.5 mg	20/10/12.5 mg[1]	40/5/12.5 mg	40/5/25 mg	40/10/12.5 mg	40/10/25 mg	
Dissolution in 0.05 M phosphate buffer pH 6.8 30 minutes	Release 50 rpm: Q = (b) (4) of label claim for olmesartan medoxomil Q = (b) (4) of label claim for amlodipine Q = (b) (4) of label claim for hydrochlorothiazide			Shelf-life 50 rpm: Q = (b) (4) of label claim for olmesartan medoxomil Q = (b) (4) of label claim for amlodipine Q = (b) (4) of label claim for hydrochlorothiazide			UV-VIS multicomponent analysis [J-G000225] alternatively: HPLC [J-A000315] K-MZ OLME/ AMLO/ HCTZ_E

- Based on the referenced June 24 teleconference with the Division, the sentence in the FDA's IR Letter of June 7 is revised to read "…a *biowaiver* is granted for the three intermediate strengths; OM/AML/HCTZ 40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide

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/s/

TAPASH K GHOSH
07/08/2010

PATRICK J MARROUM
07/08/2010

CLINICAL PHARMACOLOGY REVIEW

Application Number	NDA 200175
Submission Type	S
Submission Number (Date)	30 Sep 2009
Brand Name	Tribenzor ™ (proposed)
Generic Name	Olmesartan, Amlodipine, HCTZ in fixed dose combination
Proposed Indication	Treatment of hypertension
Primary CP Reviewer	Rajanikanth Madabushi, Ph.D.
Primary PM Reviewer	Jiang Liu, Ph.D.
Secondary CP Reviewer	Mehul U. Mehta, Ph.D.
Secondary PM Reviewer	Pravin Jadhav, Ph.D.
Sponsor	Daiichi Sankyo

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1.0 Executive Summary

On September 30, 2009 Daiichi Sankyo Pharma Development (DS) submitted a New Drug Application (NDA) 200175, TRIBENZOR™ (proposed name) for fixed dose triple combination tablets containing olmesartan medoxomil, amlodipine and hydrochlorothiazide. Tribenzor is intended for the treatment of hypertension. However, Tribenzor is not proposed for initial therapy, rather it is intended for substitution of its individual components or as add-on/switch therapy to provide additional blood pressure lowering for patients not adequately controlled on any two of the following antihypertensive classes: angiotensin receptor blockers, calcium channel blockers, and diuretics.

The clinical program for this NDA comprises one pivotal safety/efficacy study with a long term safety component as well as the following clinical pharmacology/ biopharmaceutics studies: one bioequivalence study, one food effect study and two drug-drug interaction studies. In addition exposure-response analyses were conducted.

This clinical pharmacology review focuses on the clinical pharmacology studies and exposure-response analyses.

1.1 Recommendation

- The Office of Clinical Pharmacology (OCP) finds the clinical pharmacology and biopharmaceutics information submitted to NDA 200175 acceptable pending the inspection findings by the Division of Scientific Investigations (DSI).
- Additionally, agreement must be reached between OCP and the applicant regarding labeling.
- The (b) (4) dose-response prediction (b) (4) is not acceptable (b) (4) . A statement indicating the dose-dependent increase in the blood pressure lowering effect of the triple combination products is more appropriate:

"All of the dose strengths of the triple combination are expected to provide superior blood pressure lowering effects compared to their respective mono and dual combination components. The order of the blood pressure lowering effects among the different dose strengths of the triple combination is expected to be 20/5/12.5<40/5/12.5<(40/10/12.5≈40/5/25)<40/10/25 [OM/AML/HCTZ]."

<u>Comment to Division of Cardiovascular and Renal Products regarding Amlodipine Bioanalytical Assay</u>

In two of the four clinical pharmacology/biopharmaceutic studies reviewed there was a relatively high failure rate for the amlodipine assay (about 30 %). This finding suggests that the amlodipine assay in those studies was not optimal. There is currently no clear FDA guideline that specifies the number of runs that can be conducted during sample analyses. However, a relatively high failure rate may be indicative of a potential systematic problem with the assay.

It should be noted that DSI was asked to carry out a Bioequivalence (BE) Inspection shortly after NDA filing for the pivotal BE study, but inspections were not requested for the two studies that had relatively low pass rates (67 % and 72 %). <u>These findings do not impact the final approval or label for this submission</u>, but is of importance if the sponsor considers future development.

1.2 Phase 4 Study Commitment

No Phase 4 Commitments have been identified.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Bioequivalence: Bioequivalence (BE) was established between the market image formulations (highest dose strength and lowest dose strength) and the reference clinical trial formulations used in the pivotal efficacy trial. The BE study results
are summarized in Table 1.

Table 1: Bioequivalence Assessment [Point Estimate (90 % Confidence Interval)] - Market Image Formulations vs. Clinical Trial Formulations

	Component		
	Olmesartan	Amlodipine	Hydrochlorothiazide
Measure	High Dose Comparisons (Cohort 1)		
AUCinf			
A vs. C	112.97	104.38	101.57
	(106.00, 120.40)	(98.52, 110.58)	(96.86, 106.51)
A vs. E	103.81	98.82	96.58
	(97.28, 110.79)	(93.18, 104.81)	(92.02, 101.37)
Cmax			
A vs. C	113.77	103.02	103.11
	(104.03, 124.42)	(96.62, 109.84)	(94.13, 112.95)
A vs. E	107.93	101.42	103.25
	(98.44, 118.34)	(94.94, 108.34)	(94.01, 113.39)
	Low Dose Comparisons (Cohort 2)		
AUCinf			
B vs. D	102.70	104.82	97.89
	(96.99, 108.75)	(100.48, 109.36)	(94.11, 101.84)
B vs. F	100.82	105.64	100.75
	(95.21, 106.76)	(101.31, 110.16)	(96.89, 104.76)
Cmax			
B vs. D	107.76	104.67	106.32
	(100.74, 115.28)	(97.09, 112.85)	(97.33, 116.14)
B vs. F	100.78	99.61	113.53
	(94.28, 107.73)	(92.46, 107.31)	(104.03, 123.91)

Treatment A: 40 mg OM/ 10 mg AML/ 25 mg HCT (HD-MIF) Treatment C: 40/25 mg Benicar HCT® + 10 mg Antacal® (HD-RFI) Treatment E: 40/10 mg Azor™ + 25 mg HCT (HD-RFII)
Treatment B: 20 mg OM/ 5 mg AML/ 12.5 mg HCT (LD-MIF) Treatment D: 20/12.5 mg Benicar HCT® + 5 mg Antacal® (LD-RFI) Treatment E: 20/5 mg Azor™ + 12.5 mg HCT (LD-RFII)

Food Effect: Food does not have a clinically significant effect on the disposition of the components (olmesartan, amlodipine and hydrochlorothiazide) of the triple combination product (Table 2).

Drug-Drug Interactions: There is no anticipated clinically significant interaction between any of the components of the proposed fixed dose combination product.

Exposure-Response: The exposure-response relationship of the three compounds for blood pressure reduction was adequately explored. The blood pressure lowering effects of olmesartan medoxomil and amlodipine were described by an E_{max} model, whereas the drug effect for hydrochlorothiazide was

described by a linear model. The interaction terms of dual and triple combinations were added to the respective response. Mean placebo effect was a scalar value that varied by study. The effect was larger in subjects with higher baseline. The systemic exposures, AUC_{OM}, AUC_{AML}, and AUC_{HCTZ}, were used in the analysis. The parameters of the final PK/PD model were estimated with good precision (see Pharmacometrics Review).The model was robust across the studies and analyzed populations, once the study-specific placebo effect was accounted for.

Dosage Form: Tribenzor tablets are an immediate release, fixed-dose combination film-coated drug product for oral use. The product is a combination of three FDA approved active pharmaceutical ingredients, olmesartan medoxomil, amlodipine besylate and hydrochlorothiazide.

Dosage: Tribenzor is titrated to effect (blood pressure control) with a maximum dose of 40/10/25 mg (OM/AML/HCT) given once daily; upward titration should occur at biweekly intervals.

Primary Reviewer, Rajanikanth Madabushi, Ph.D.
Clinical Pharmacology
(Note: The review of the Pivotal BE, Food-Effect and Drug Interaction studies were performed by Dr. Robert Kumi Ph.D.)

Primary Reviewer, Jiang Liu, Ph.D.
Pharmacometrics

Concurrence
Team Leader, Pravin Jadhav, Ph.D.
Pharmacometrics

Team Leader, Mehul U. Mehta, Ph.D.
Clinical Pharmacology

2.0 Question Based Review

This clinical pharmacology and biopharmaceutics review employs an abridged version of the question based review (QBR) since critical QBR elements were addressed in previous NDAs [see Table 3, General Attributes of the Component Drugs]. Relevant QBR elements are addressed in some detail in this Clinical Pharmacology Review. Apart from two studies utilizing pilot formulations, all clinical pharmacology studies submitted in NDA 200175 were reviewed.

2.1 General Attributes of the Component Drugs

Regulatory Background

NDA 200175 is a 505(b) (2) application that relies on the FDA's previous finding of safety and efficacy for the following listed products (Table 3); all of these products were also developed by Daiichi Sankyo.

Table 2: Reference listed drugs and products supporting 505(b) (2) application

Product	Approval Date	NDA	Components	Tablet Strengths (mg)
Benicar®	04/2002	21- 286	Olmesartan medoxomil (OM)	5, 20 and 40
Benicar HCT®	06/2003	21-532	OM/Hydrochlorothiazide	20/12.5, 40/12.5 and 40/25
Azor®	09/2007	22-100	Amlodipine/OM	5/20, 10/20, 5/40, and 10/40

The following table highlights some key meetings/submissions and outcomes involving FDA and the applicant.

Table 3: Meetings/Submission and Agreements (Outcomes) between FDA and Daiichi Sankyo

Meeting (Submission) Description / Objective	Agreement
Type C Guidance Meeting (07/24/2007) / Discussed requirements of development program to support NDA approval for the treatment of hypertension	- one phase III study (CS8635-A-U301) that should demonstrate superiority of highest strength combination vs. highest dose combination of lower strengths - clinical pharmacology and non-clinical program appeared adequate - lower dose triple combinations could be further supported by Modeling and Simulation (M&S) data.
Special Protocol Assessment (SPA) for the Clinical Study Protocol CS8635-A-U301 on December 7, 2007 (IND 77,651, serial No. 007). / Reach agreement on protocol design	Agreement reached on protocol
SPA for Primary Stability Studies submitted on 01/31/2008 (serial No. 010).	Agreement reached on protocol
Type B CMC- Specific End of Phase 2 Meeting (April 3, 2009) / Discussed Chemistry, Manufacturing and Controls (CMC) development strategy needed to support the NDA approval.	Agreement reached on CMC requirements
Type B Pre-NDA Meeting (scheduled for July 16, 2009)/ Reach agreement on format and content of the NDA, non-clinical and clinical development programs.	- Type B pre-NDA meeting was cancelled as the Agency agreed on all of the pre-NDA meeting questions -FDA agreed with Daiichi Sankyo's request to include the MS data in the NDA and in the proposed label

Mechanisms of Action and Proposed Indication

The three components in the proposed product belong to three distinctive classes of compounds; each compound affects hypertension via a different mechanism of action:

- Olmesartan is an angiotensin II receptor blocker
- Amlodipine is a calcium channel blocker
- Hydrochlorothiazide is a diuretic

The applicant is proposing the following indication for the fixed dose combination: TRIBENZOR™ is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy.

Proposed Dosage

Tribenzor is proposed for once daily administration and can be substituted for its individual components for patients on olmesartan medoxomil, amlodipine, and hydrochlorothiazide. Two additional features of the proposed Tribenzor dosage are:

- use as add-on/switch therapy to provide additional blood pressure lowering for patients not adequately controlled on any two of the following antihypertensive classes: angiotensin receptor blockers, calcium channel blockers, and diuretics.
- dosage may be increased after 2 weeks to a maximum dose of 40/10/25 mg once daily, usually by increasing one component at a time but any component can be raised to achieve more rapid control.

2.2 General Clinical Pharmacology

Design features of the clinical pharmacology and clinical studies used to support dosing or claims

Table 4: Study design features in clinical studies conducted for NDA 200175

Study	Objective	Population	Study Design/Endpoint
Pivotal Efficacy	Evaluate superiority of triple combination vs. dual combination at highest dose strengths	Subjects with hypertension (n ~ 2500)	Randomized, double-blind, parallel-group study / change in seated diastolic blood pressure
Bioequivalence Dose Proportionality	Determine if market image formulation (MIF) is bioequivalent to clinical trial formulations (CTF)	Healthy subjects (n = 72)	Randomized, open-label, single dose, 4-period crossover study/ 90 % confidence interval of point estimate (MIF/CTF)
Drug Interaction	Determine if addition of third component affects kinetics of components in dual combination and vice versa	Healthy subjects (n = 36)	Randomized, open-label, single dose, 3-way crossover study/ 90 % confidence interval of point estimate (dual + single vs. single; dual + single vs. dual)
Food Effect	Evaluate the impact of food on MIF exposure	Healthy subjects (n = 34)	Randomized, open-label, single dose, randomized, 2-way crossover design.

Dose Proportionality Assessment

Dose proportionality was demonstrated for all components over the lowest and highest dosage strength of the fixed dose combination product: 20 – 40 mg olmesartan medoximil; 5 to 10 mg amlodipine and 12.5 to 25 mg hydrochlorothiazide. This finding is consistent with the linearity observed with the respective components over the studied dose range.

Table 5: Dose proportionality assessment [Geometric Mean Ratio for dose normalized PK measures (90 % confidence interval)] – Highest strength MIF vs. lowest strength MIF

Parameters	Geometric LSM		Ratio of Geometric LSM (A/B) and 90% CI (%)
	Treatment A HD-MIF (Test)	Treatment B LD-MIF (Reference)	
Olmesartan			
AUC_{last} (ng·h/mL/mg)	151.2	165.4	91.43 (87.27, 95.79)
$AUC_{0\text{-}inf}$ (ng·h/mL/mg)	154.5	167.6	92.19 (88.50, 96.04)
C_{max} (ng/mL/mg)	22.49	25.85	86.99 (81.78, 92.54)
Amlodipine			
AUC_{last} (ng·h/mL/mg)	33.34	32.02	104.12 (101.02, 107.31)
$AUC_{0\text{-}inf}$ (ng·h/mL/mg)	36.51	34.99	104.33 (101.11, 107.64)
C_{max} (ng/mL/mg)	0.7671	0.7265	105.58 (102.26, 109.00)
HCT			
AUC_{last} (ng·h/mL/mg)	46.63	45.58	102.30 (99.47, 105.21)
$AUC_{0\text{-}inf}$ (ng·h/mL/mg)	47.60	47.30	100.65 (97.97, 103.40)
C_{max} (ng/mL/mg)	7.204	7.333	98.24 (91.95, 104.97)

Dose proportionality between the highest and lowest dosage strength was determined by administering the high and low dose strength tablets to individuals in a crossover manner. Dose proportionality was concluded if the dose normalized 90 % confidence interval for the GMR (high dose vs. low dose) was within the 80 -125 % range (no difference).

Exposure-Response Analysis (Pharmacometrics Review by Dr. Jiang Liu)

The pivotal Phase 3 study (CS8635-A-U301) demonstrated superiority of the triple fixed-dose combination of olmesartan (OM), amlodipine (AML), and hydrochlorothiazide (HCTZ) compared to the highest dosage dual combinations of OM, AML, and HCTZ in lowing blood pressure. Figure 1 shows that: 1) the responder rate in the triple therapy is higher than the dual therapies at the clinically relevant diastolic blood pressure target and 2) the median diastolic blood pressure reduction after triple therapy is clearly better than the dual therapies. Similar inference can be obtained for the SBP (see Pharmacometrics Review for details). The final population PK models and exposure-response models for blood pressure reduction are generally acceptable based on the following (see Pharmacometrics Review):

- goodness of fits, precision of parameter estimates
- good agreement between the observed data and the model-predicted blood pressure lowering effects of the various tested combinations of the three compounds
- knowledge of the primary elimination pathways of the three compounds, and
- consistency of predictions with the results of the previous studies.

The model is robust across the studies and analyzed populations, once the study-specific placebo effect was accounted for. As shown in Table 6, the predicted placebo-adjusted blood pressure lowering effects of the tested combinations are in good agreement with the observed data from different studies and are

also consistent with the previous labels. The demographic characteristics of the population in the current study (CS8635-A-U301) are similar to those in previous studies. Hence, the model-predicted blood pressure responses for the clinically unevaluated to-be-marketed triple combination dosages as initial therapy are reasonable.

Figure 1. The cumulative percent of diastolic blood pressure change from baseline for the triple and dual combination therapies

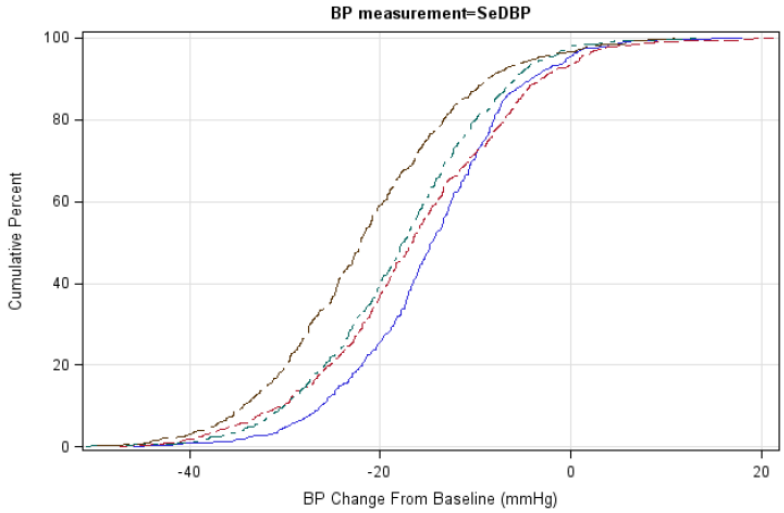


Table 6. Comparison among the predicted placebo-adjusted blood pressure lowering effects of CS-8635, the observed data and the previous labels

(a) Based on adding HCTZ to Azor

Placebo-Adjusted Changes in Sitting Systolic/Diastolic Blood Pressure (mmHg)

Azor (AML/OM)	HCTZ								
	0 mg			12.5 mg			25 mg		
	Simulated	Observed	Azor Label	Simulated	Observed	Benicar HCT Label	Simulated	Observed	Benicar HCT Label
0 mg	-/-	-/-	-/-	-7.8/-2.4	-5.7/-1.8	-5/-1	-15.6/-4.9	-14.7/-5.4	-14/-5
5/20 mg	-21.8/-11	-20.6/-10.9	-20/-11	-25.7/-12.8			N/A	N/A	N/A
5/40 mg	-23.5/-12	-23.4/-12.7	-22/-13	-27.4/-13.9			-31.2/-15.8		
10/40 mg	27.3/-14.2	-27.7/16.1 -26.9/-14*	-26/-16	-30.5/-15.8			-33.7/-17.4	-33.9/-17.7*	

N/A: not applicable; * adjusted with the model estimated placebo effect in Study CS8635-A-U301

(b) Based on adding amlodipine to Benicar HCT

Placebo-Adjusted Changes in Sitting Systolic/Diastolic Blood Pressure (mmHg)

Benicar HCT (OM/HCTZ)	AML								
	0 mg			5 mg			10 mg		
	Simulated	Observed	Benicar HCT Label	Simulated	Observed	Azor Label	Simulated	Observed	Azor Label
0 mg	-/-	-/-	-/-	-13.6/-6.7	-12.5/-6.6	-12/-7	-18.2/-10.1	-17.4/-9.9	-16/-10
20/12.5 mg	-17.7/-8.7	-18.4/-8.3	-17/-8	-26.4/-12.8			N/A	N/A	N/A
40/12.5 mg	-19.7/-10.1	-17.5/-10.9	-16/-10	-27.4/-13.9			-30.5/-15.8		
40/25 mg	-25.2/-12.6	-24.9/-14.4 -27/-12.7*	-24/-14	-31.2/-15.8			-33.7/-17.4	-33.9/-17.7*	

N/A: not applicable; * adjusted with the model estimated placebo effect in Study CS8635-A-U301

2.3 Intrinsic Factors: Not applicable

2.4 Extrinsic Factors (Drug Interactions)

Drug Interactions

No clinically relevant drug-drug interactions occurred between the individual components of the proposed triple combination product when a dual combination product was administered with or without a third single component. Collectively, the drug interaction studies suggest that no drug-drug interactions are expected to occur among the components of the MFI (OM + AML + HCT).

Two drug-drug interaction studies were conducted with components of the triple combination to determine if addition of a third component to a dual combination product would alter the disposition of any individual component. Standard drug-drug interaction approaches were followed, and a lack of a drug interaction was concluded if the 90 % confidence interval of the GMR (Test vs. Reference) was between 80 and 125 %. The findings from the drug interaction studies in NDA 200175 and previous NDAs are summarized in the following table.

Table 7: Possible Dual/Triple Combination Products

	Components	Studied	Finding (PK Effects primarily)
Dual^	HCT + AML	No	No specific PK study has been conducted, but the agents are concomitantly administered clinically without reported safety issues.
	HCT + OM	Yes	No effect on either component
	AML + OM	Yes	No effect on either component
Triple*	HCT + (AML + OM)	Yes	No effect of dual combination on HCT and no effect of HCT on components of the dual combination product
	(HCT + OM) + AML	Yes	No effect of dual combination on AML and no effect of AML on components of Dual combination product

^ Studied in previously approved product/NDAs, where applicable; * Studied in current NDA
HCT + OM → Benicar HCT; OM + AML → Azor (CS-8663)

As shown in Table 7, the drug interaction potential for two of the three possible dual combination products have been evaluated previously. There is no common elimination pathway [HCT – not metabolized; OM- esterase hydrolysis with negligible further metabolism; AML- extensive hepatic metabolism] among the three components. Thus, there is no *a priori* expectation of an interaction between compounds in these three drug classes* and none was observed.

*It is noted that no interactions were observed when a triple combination product, ExforgeHCT, containing amlodipine, hydrochlorothiazide and valsartan (belongs to same class as olmesartan, but has a different elimination pathway) was evaluated for potential drug interactions.

2.5 General Biopharmaceutics

Formulation Composition

The composition of TRIBENZOR tablets is tabulated below.

Table 8: Composition of MIF

Component	Quality Std.	Function	20/5/12.5 mg	40/5/12.5 mg	40/5/25 mg	40/10/12.5 mg	40/10/25 mg
(b) (4)							
Olmesartan medoxomil	DMF (b) (4)	Drug substance	20.000	40.000	40.000	40.000	40.000
Amlodipine besylate	EP/USP DMF (b) (4) DMF (b) (4)	Drug substance	6.944[1]	6.944[1]	6.944[1]	13.888[1]	13.888[1]
Hydrochlorothiazide	EP/USP DMF (b) (4) DMF (b) (4)	Drug substance	12.500	12.500	25.000	12.500	25.000
Starch, pregelatinized	EP	(b) (4)					
Silicified microcrystalline cellulose[2]	DMF (b) (4)						
Croscarmellose sodium	EP						
Magnesium stearate (b) (4)	EP						
(b) (4)							
(b) (4)							
Total Tablet Weight (mg)			208	310	412	310	412

[1] Equivalent to 5 mg (6.944 mg) and 10 mg (13.888 mg) amlodipine

(b) (4)

The Applicant does not intend to market the 20/5/12.5 strength in the US.

Amlodipine Formulation Comparisons (European vs. US manufactured products)*

The relative bioavailability (RBA) of amlodipine administered as Antacal^{EU} appeared comparable to that when administered as Azor^{US} (same study); similarly, amlodipine RBA was comparable when administered as Antacal vs. Norvasc^{US} (cross-study) comparison.

Table 9: Amlodipine PK measures for US and European amlodipine containing products (Mean ± SD)

Measure	Product Administered at Olmesartan/Amlodipine/Hydrochlorothiazide (10/40/25 mg) Dose				
	Norvasc[US]	Antacal + Benicar HCT[US]	Norvasc[US] + Benicar HCT[US]	Azor + HCT[US]	MIF
AUClast	335 ± 95	328 ± 99	339 ± 89	338 ± 81	339 ± 89
Cmax	7.0 ± 2.0	7.6 ± 2.1	7.5 ± 2.0	7.9 ± 3.5	7.7 ± 1.8
T1/2	44 ± 13	40 ± 8	45 ± 13	42 ± 9	41 ± 8

[EU] manufactured in Europe; [US] manufactured in US

The sponsor did not provide any comparison of these amlodipine formulations; these data were extracted from the submitted studies

Bioequivalence

Bioequivalence (BE) was established between the following:

a) the highest dose strength MIF and the high dose CTF (reference)
b) the lowest dose strength MIF and the low dose clinical trial CTF (reference)

One BE study was conducted: MIF vs. CTF that mimicked administration of the proposed triple combination tablet. BE was concluded if the 90 % confidence interval for the point estimate (MIF vs. CTF) was in the 80 – 125 % range for each of the components. The BE statistical results for the high and low dose MIFs are tabulated below.

Table 10: Bioequivalence Assessment [Point Estimate (90 % Confidence Interval)] - Market Image Formulations vs. Clinical Trial Formulations

Measure	OM	AML	HCT	Conclusion
	High Dose Comparisons (Cohort 1)			
AUCinf				
A vs. C	112.97 (106.00, 120.40)	104.38 (98.52, 110.58)	101.57 (96.86, 106.51)	Bioequivalence established between high dose MIF and reference CTF
A vs. E	103.81 (97.28, 110.79)	98.82 (93.18, 104.81)	96.58 (92.02, 101.37)	
Cmax				
A vs. C	113.77 (104.03, 124.42)	103.02 (96.62, 109.84)	103.11 (94.13, 112.95)	
A vs. E	107.93 (98.44, 118.34)	101.42 (94.94, 108.34)	103.25 (94.01, 113.39)	
	Low Dose Comparisons (Cohort 2)			
AUCinf				
B vs. D	102.70 (96.99, 108.75)	104.82 (100.48, 109.36)	97.89 (94.11, 101.84)	Bioequivalence established between low dose MIF and reference CTF
B vs. F	100.82 (95.21, 106.76)	105.64 (101.31, 110.16)	100.75 (96.89, 104.76)	
Cmax				
B vs. D	107.76 (100.74, 115.28)	104.67 (97.09, 112.85)	106.32 (97.33, 116.14)	
B vs. F	100.78 (94.28, 107.73)	99.61 (92.46, 107.31)	113.53 (104.03, 123.91)	

Treatment A: 40 mg OM/ 10 mg AML/ 25 mg HCT (HD-MIF) Treatment C: 40/25 mg Benicar HCT® + 10 mg Antacal® (HD-RFI) Treatment E: 40/10 mg Azor™ + 25 mg HCT (HD-RFII)

Treatment B: 20 mg OM/ 5 mg AML/ 12.5 mg HCT (LD-MIF) Treatment D: 20/12.5 mg Benicar HCT® + 5 mg Antacal® (LD-RFI) Treatment E: 20/5 mg Azor™ + 12.5 mg HCT (LD-RFII)

Biowaiver for Intermediate Dosage Strengths

Four MIF strengths have been proposed, but BE studies were not conducted for the intermediate strengths. The sponsor has provided information in support of a biowaiver for these intermediate strengths. Per the MOU between the Office of Clinical Pharmacology (OCP) and the Office of New Drug Quality Assessment (ONDQA), ONDQA and OCP will jointly evaluate the biowaiver. At the time of completion of this document, the biowaiver evaluation is not complete.

Food Effect

Food did not alter the exposure (AUC or Cmax) of olmesartan or amlodipine. However, food caused a statistically significant reduction (about 23 %) in HCT Cmax with no statistically significant effect on AUC. The change in HCT Cmax is not considered clinically significant.

A standard food effect study was conducted using the highest strength fixed dose combination tablet (40 mg olmesratan/10 mg amlodipine/25 mg hydrochlorothiazide) and a high fat meal. A lack of a food effect was concluded if the 90 % confidence interval for the point estimate (MIF vs. CTF) was in the 80 – 125 % range for each of the components. The results from the food effect study are summarized in the following table.

Table 11: Food Effect Assessment [Point Estimate (90 % confidence intervals)] - Fed vs. Fasted

	Component		
Measure	OM	AML	HCT
AUC_{last}	92.52 (86.95 – 98.46)	104.52 (101.20 – 107.96)	92.17 (88.39 – 96.12)
Cmax	97.83 (90.60 – 105.63)	97.63 (92.55 – 102.99)	77.24 (71.03 – 84.00)

The food effect findings are consistent with those observed for amlodipine, olmesartan and hydrochlorothiazide formulations (per respective product labels and literature). Based on the food effect findings, Tribenzor can be administered without regard for meals.

2.6 Analytical section

Analytical methods

The following moieties were measured and identified in plasma for the clinical pharmacology (biopharmaceutics) studies:

- olmesartan
- amlodipine
- hydrochlorothiazide

A validated Turbo Ion Spray LC/MS/MS method was used in these studies; overall the assay performance in these studies was generally acceptable as shown in Table 12. However several of the amlodipine runs did not pass; this finding is of some concern for routine analysis.

Table 12: Summary of bioanalytical studies in four reviewed clinical pharmacology studies

Analytes	Method	Calibration Range[1] (ng/mL) all studies	Precision (CV %) all studies	Accuracy * (Bias %) all studies	Runs passed (%) in each study
Olmesartan	Turbo Ion Spray	1 – 1000	< 3 to < 16	< | 6 |	98.6; 83.3; 95.2; 88

Amlodipine	LC/MS/MS	0.05 – 50	< 5 to < 17	< | 21 |	100; **66.7**; 89.4; **72**
Hydrochlorothiazide		1 – 1000	< 3 to < 20	< | 6 |	100; 84.2; 100; 86

| x| absolute value of x

Per the Bioanalytical study reports, the main reasons for the inability to pass the run were:

- QC (quality control) sample failed to meet acceptance criteria
- contamination issues
- incorrect preparation of standards
- poor chromatography
- incorrect programming of auto sampler

Per the FDA Guidance to Industry on Bioanalytical Method Validation, QC failure is the only reason to reject a run; thus rejection of a run based on contamination is not acceptable. In contrast, sample reanalysis is acceptable for all of the listed reasons, if it complies with a Standard Operating Procedure. Per the study report, the contamination issue appears to be associated with (b) (4) , although the sponsor claims that the contamination is sporadic and difficult to isolate. It is important that the issue of contamination be addressed and may require a change in the equipment and overall method.

Reviewer Comment on Amlodipine Assay

Although the applicant's explanation for amlodipine assay failure has merit and suggests the assay performance is acceptable, further action by FDA may be warranted after OCP reviews the DSI inspection findings for the pivotal bioequivalence study.

4.0 APPENDICES

4.1 Recommended Changes to proposed Package Insert (Draft)

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

- The following proposed language describing the exposure-response relationship of Tribenzor is not acceptable. Although the language is supported by the sponsor's comprehensive population exposure-response analysis, similar limitations apply as noted below. The predictions are mostly applicable for initial therapy of Tribenzor and do not represent the clinical scenario under which Tribenzor will be used. Therefore, the utility of model predictions for labeling purposes cannot be justified. The team recommends including the observed data in this section.

12 Clinical Pharmacology
12.2 Pharmacodynamics

(b) (4)

(b) (4)

- The population PK and exposure-response analyses for blood pressure reduction as initial therapy are generally reasonable. However, the (b) (4) dose-response prediction (b) (4) is not acceptable (b) (4)

  The simulations designed to predict the add-on blood pressure lowering effect from a dual combination to a triple combination or the titration-effect from an existing triple combination to a higher dose of triple combination were not able to predict the results from the open-label study, which is the closet empirical data we have for qualifying the simulations (See Pharmacometrics Review for details). Hence, the following modifications are suggested for the proposed text in Section 14 of the label:

14 Clinical Studies
14.1 Tradename

(b) (4)

(b) (4)

All of the dose strengths of the triple combination are expected to provide superior blood pressure lowering effects compared to their respective mono and dual combination components. The order of the blood pressure lowering effects among the different dose strengths of the triple combination is expected to be 20/5/12.5<40/5/12.5<(40/10/12.5≈40/5/25)<40/10/25 [OM/AML/HCTZ].

4.2 Individual Study Review

Introduction to Individual Study Reviews

The following sections are common in the following four studies, thus are mentioned only in the first study (4.2.1) and not repeated in the following studies.

1. Statistical Analysis for the assessment of bioequivalence, food-effect and drug interaction.
2. Plasma-Concentration Time profiles for each of the components were reasonably similar when compared to the respective control arms unless specifically presented.
3. All tables and figures in the Individual Study Reviews are derived from respective applicant's study reports, unless specifically stated.

4.2.1 An open label, phase 1, four-period crossover study in healthy subjects to assess the bioequivalence of the highest and lowest dose CS-8635 market image formulations (MIF) to reference clinical trial formulations and dose proportionality of CS-8635 MIF

PROTOCOL #	CS8635-A-E105
Link to Report	\\cdsesub1\EVSPROD\NDA200175\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\cs8635-a-e105\cs8635-a-e105-body.pdf
INVESTIGATOR	A. J. Stewart MB, MFPM
STUDY SITE	MDS Pharma Services, Belfast, Northern Ireland, BT9 6AD
STUDY PERIOD	September 2008 – March, 2009

Reviewer Note on Inspection Status

A Division of Scientific Investigations Inspection was requested at the time of NDA filing. There was no status update at the time this review was drafted. However, it is expected that the inspection will be completed prior to the user fee goal date (07/31/2010).

Objectives (per applicant):

- Primary: to compare the pharmacokinetics of olmesartan medoxomil (OM), amlodipine besylate (AML) and hydrochlorothiazide (HCT) when administered as the MIF versus the two reference clinical formulations at the dose strengths of 40/10/25 mg (OM/AML/HCT) and 20/5/12.5 mg (OM/AML/HCT).
- Secondary:
    - To determine the dose proportionality of two dose levels of CS-8635 MIF
    - To compare the PK of HCT when administered as a component in Reference Clinical Formulation I (Benicar HCT®) and Reference Clinical Formulation II (HCT);
    - To evaluate the safety and tolerability of the CS-8635 MIF at its highest and lowest strength dose combinations.

Study Design

This was an open-label, 4-period crossover study where a total of 72 healthy subjects (53 males and 19 females) were randomized to one of twelve sequences. Six sequences comprised Cohort 1 and six sequences comprised Cohort 2, for a total of 36 subjects per cohort. Each cohort was designated as "High Dose – (HD)" or "Low Dose – (LD)" as follows:

- Cohort 1 - HD: ACEB, CEAB, EACB, AECB, CAEB and ECAB;
- Cohort 2 – LD: BDFA, DFBA, FBDA, BFDA, DBFA and FDBA

The following treatments were administered:

A- 40 mg olmesartan medoximil/10mg amlodipine/25 mg hydrochlorothiazide (HD)
B- 20 mg olmesartan medoximil/5mg amlodipine/12.5 mg hydrochlorothiazide (LD)
C- Benicar-HCT (olmesartan/HCT; 40/25 mg) + Antacal (10 mg) [HD]
D- Benicar-HCT (olmesartan/HCT; 20/12.5 mg) + Antacal (5 mg) [LD]
E- Azor (olmesartan/amlodipine; 40/10 mg) + HCT (25 mg) [HD]
F- Azor (olmesartan/amlodipine; 20/5 mg) + HCT (12.5 mg) [LD]

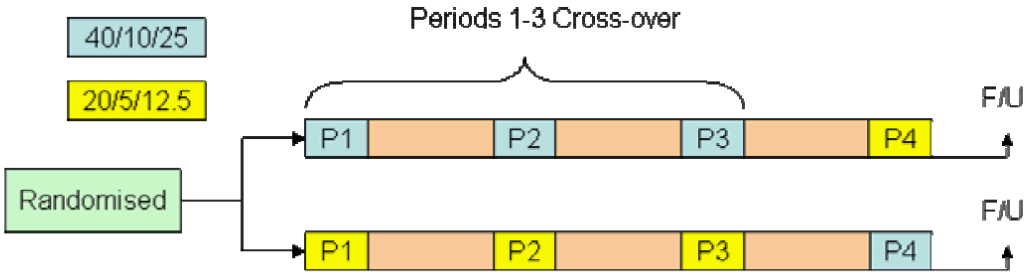
This study had two sections:

(1) Section 1: bioequivalence of each analyte (OM, AML and HCT) when administered as the CS-8635 MIF compared to two reference formulations

(2) Section 2: dose proportionality between the two dose levels of CS-8635 MIF during period 4

The trial design is depicted schematically in the following figure.

Figure 2: Trial Design schematic for study^



^Note: All subjects in Cohort 1 received the LD strength formulation in the last period; similarly all subjects in Cohort 2 received the HD strength formulation in the last period. This approach eliminated complete randomization that does not allow for the evaluation of period effects related to the dose proportionality assessment.

Formulation

- Test investigational products:
  - High Dose CS-8635 (olmesartan medoxomil 40 mg /amlodipine besylate10 mg /hydrochlorothiazide 25 mg) Market Image Formulation; Manufactured by: Daiichi Sankyo Lot No.: 3265V07006 Expiration date: 05/2009. Batch size (b) (4) tablets.
  - Low Dose CS-8635 (olmesartan medoxomil 20 mg /amlodipine besylate 5 mg /hydrochlorothiazide 12.5 mg) Market Image Formulation. Manufactured by: Daiichi Sankyo Lot No.: 3260V07002 Expiration date: 05/2009. Batch size (b) (4) tablets.
- Reference Products
  - Benicar HCT (olmesartan medoxomil-hydrochlorothiazide) 40/25 mg Manufactured by: Daiichi Sankyo Lot No.: 455001A Expiration date: May/2010
  - Benicar HCT (olmesartan medoxomil-hydrochlorothiazide) 20/12.5 mg Manufactured by: Daiichi Sankyo Lot No.: 454973A Expiration date: May/2010
  - Antacal* (amlodipine mesylate) 5 mg; Manufactured by (b) (4); Lot No.: 610149930I Expiration date: 05/2011
  - Antacal* (amlodipine mesylate) 10 mg; Manufactured by (b) (4); Lot No.: 610076530I Expiration date: 03/2011
  - Azor (amlodipine besylate and olmesartan medoxomil) 40/10 mg Manufactured by: Daiichi Sankyo Lot No.: 455581A Expiration date: Jul/2009
  - Azor (amlodipine besylate and olmesartan medoxomil) 20/5 mg Manufactured by Daiichi Sankyo; Lot No.: 455563A Expiration date: Jun/2009
  - Hydrochlorothiazide 25 mg Manufactured by (b) (4); Lot No.: 8B8918 Expiration date: Jan/2010
  - Hydrochlorothiazide 12.5 mg Manufactured by (b) (4); Lot No.: 8M9739 Expiration date: 12/2010

* Antacal is sold in Europe

Pharmacokinetic Measures and Sampling Times

Plasma pharmacokinetics were calculated for olmesartan, amlodipine and hydrochlorothiazide using non-compartmental analyses. The following pharmacokinetic measures for olmesartan, amlodipine, and hydrochlorothiazide were estimated: Cmax, tmax, AUClast, AUCinf, AUCext, tmax, t1/2, and CL/F.

Pharmacokinetic sampling times were as follows:
Predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, 9, 12, 16, 24, 36, 48, 60, 72, 96, 120 and 144 hours post-dose.

Statistical Methods (Bioequivalence, Dose Proportionality, and Tmax):

Bioequivalence and dose proportionality were assessed via standard pharmaco-statistical approaches.

Bioequivalence: The data were subset by cohort. For each of the two cohorts, an analysis of variance (ANOVA) was based on a model with Sequence, Treatment, Period as fixed effects and Subject nested within Sequence as a random effect. The ANOVA was performed on the ln-transformed AUClast, AUC0-inf and Cmax for each analyte obtained from each treatment in the first three periods. The geometric mean ratios and associated 90 % confidence intervals (CIs) were calculated by exponentiation of the differences of the least-square-means (LSM) between formulations from the analyses on the ln-transformed AUClast, AUC0-inf and Cmax, for each analyte. If the resulting 90% CIs of the PK parameters for each of the three analytes of the treatments being compared were entirely contained within 80-125% interval, the formulations were considered bioequivalent. The comparisons of interest for Cohort 1 (HD) were: A versus C and A versus E and the comparisons of interest for Cohort 2 (LD) were: B versus D and B versus F

Dose proportionality: The assessment used the same ANOVA model (included treatment and cohort as fixed effects and subject within cohort as a random effect) and subsequent data manipulation described for bioequivalence. If the resulting 90% CIs for the analytes of the two CS-8635 doses being compared were entirely contained within 80-125% interval, the PK of the analytes were considered dose proportional.

Tmax: Nonparametric statistical analysis was used to construct the 90% CI for tmax. The Hodges Lehmann estimator of the median of the differences in tmax values and the CIs generated with the Moses method were presented for each comparison.

Reviewer Note on Tmax
The Tmax evaluation does not play a significant role in the exposure or pharmacokinetic comparisons.

Results

Bioanalytical Methods

A validated Turbo Ion Spray LC/MS/MS method was used to determine the concentrations of olmesartan, amlodipine and hydrochlorothiazide. The performance of the assay for each analytes was acceptable as summarized in the following table.

Table 13: Performance* of OM, AML and HCT in Pivotal BE Study

Parameter	Measure	Reviewer Comment
	Olmesartan (RNH-6270)	
Linearity	The assay was linear over the 1 to 1000 ng/mL range; $R^2 > 0.997$	Satisfactory
Between day Precision	CV was < 3 %	Satisfactory
Accuracy	QC samples were between -3.3 and -1.7 % of nominal concentration	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
	Amlodipine	

Linearity	The assay was linear over the 0.05 to 50.0 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CV was < 5 %	Satisfactory
Accuracy	QC samples were between 0 and 2 % of nominal concentration	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
	Hydrochlorothiazide	
Linearity	The assay was linear over the 1.0 to 1000 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CV was < 3 %	Satisfactory
Accuracy	QC samples were between -2.8 and -0.8 % of nominal concentration	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

* one out of 68 runs were rejected for amlodipine (98.6 % runs passed; all OM and HCT runs passed.

Subject Disposition

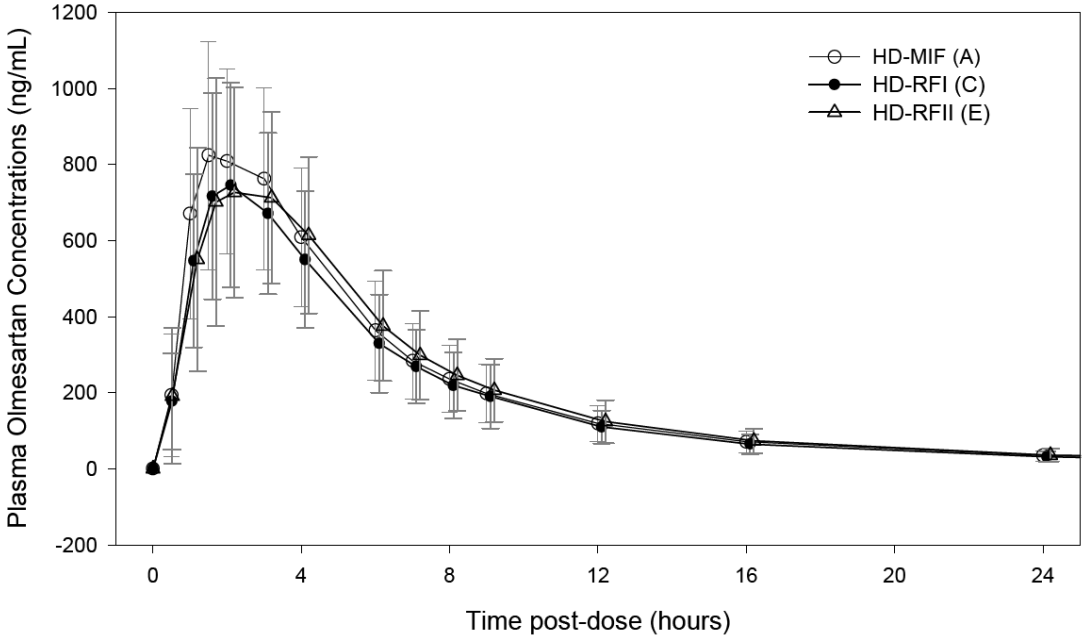
Seventy two subjects received study drug however 52 subjects completed the study. Of the fifteen who withdrew only three did so because of adverse events. The other withdrawals were due to protocol violations, consent withdrawal and other reasons. The reasons provided appear reasonable. However, it should be noted that data from Subject 0024* were excluded from PK analysis. It appeared that the subject was not compliant regarding amlodipine administration; therefore exclusion of this subject's data is reasonable in this reviewer's opinion. Additionally, one to two subjects were excluded in some analyses for different reasons (Please see notes associated with PK tables for additional information)

Olmesartan Pharmacokinetics

High Dose

The mean olmesartan plasma concentration-time profiles following Treatments A, C and E were similar with overlapping standard deviations; these profiles are depicted in the following figure.

Figure 3: Mean ± SD concentration-time profiles following administration of Treatments A, C and E (High Dose Formulations- Cohort 1



The olmesartan PK measures and associated statistical analysis (exposure comparisons) for the various treatments are presented in the following two tables.

Table 14: Olmesartan statistical exposure comparisons for high dose formulations – Cohort 1

Parameters	Geometric LSM			Ratio of Geometric LSM and 90% CI (%)	
	Treatment A Test	Treatment C Reference I	Treatment E Reference II	A/C	A/E
AUC_{last} (ng·h/mL)	5826	5251	5718	110.94 (103.75, 118.64)	101.88 (95.15, 109.07)
$AUC_{0\text{-}inf}$ (ng·h/mL)	5980	5294	5761	112.97 (106.00, 120.40)	103.81 (97.28, 110.79)
C_{max} (ng/mL)	864.8	760.2	801.3	113.77 (104.03, 124.42)	107.93 (98.44, 118.34)

Source: Table 15.4.1.1.7
Treatment A: 40 mg OM/ 10 mg AML/ 25 mg HCT (HD-MIF)
Treatment C: 40/25 mg Benicar HCT® + 10 mg Antacal® (HD-RFI)
Treatment E: 40/10 mg Azor™ + 25 mg HCT (HD-RFII)

The 90 % CIs fell within the equivalence range [80 – 125 %] indicating that olmesartan administered as the high dose CS-8635 MIF was bioequivalent to the high dose reference formulations of Benicar

HCT® co administered with Antacal® (HD-RFI) and Azor™ co administered with hydrochlorothiazide (HD-RFII).

Table 15: Olmesartan PK measures for high dose formulations – Cohort 1

Olmesartan Parameter	Treatment A Test (N=34)	Treatment C Reference I (N=34)	Treatment E Reference II (N=32)
AUC_{last} (ng·h/mL)			
Arithmetic Mean ± SD	6142.7 ± 1827.29	5395.1 ± 1412.68	5973.4 ± 1840.08
Geometric Mean (CV%)	5891.8 (30.0%)	5222.1 (26.4%)	5703.1 (32.1%)
$AUC_{0\text{-}inf}$ (ng·h/mL)			
Arithmetic Mean ± SD	6277.0 ± 1794.89	5435.8 ± 1412.22	6024.0 ± 1840.40
Geometric Mean (CV%)	6042.5 (28.6%)	5263.9 (26.2%)	5756.6 (31.8%)
AUC_{extr} (%)			
Arithmetic Mean ± SD	0.8342 ± 0.51773	0.7934 ± 0.48683	0.9267 ± 0.64386
Median (Min, Max)	0.6634 (0.179, 2.10)	0.7159 (0.252, 2.35)	0.7276 (0.264, 3.23)
C_{max} (ng/mL)			
Arithmetic Mean ± SD	907.5 ± 263.14	801.2 ± 241.26	840.1 ± 269.88
Geometric Mean (CV%)	867.8 (32.2%)	766.7 (31.0%)	796.3 (35.5%)
t_{max} (h)			
Median (Min, Max)	1.5000 (0.983, 4.00)	1.983 (1.00, 8.98)	1.983 (1.48, 4.00)
$t_{½}$ (h)			
Arithmetic Mean ± SD	17.429 ± 8.4227	15.945 ± 7.1013	16.160 ± 6.6043
Median (Min, Max)	14.514 (8.48, 46.3)	14.341 (7.45, 43.2)	15.481 (8.78, 34.4)
CL/F (L/h)			
Arithmetic Mean ± SD	6.878 ± 1.9873	7.848 ± 2.0498	7.288 ± 2.3969

Source: Tables 15.4.1.1.4.1, 15.4.1.1.5.1 and 15.4.1.1.6.1
Treatment A: 40 mg OM/ 10 mg AML/ 25 mg HCT (HD-MIF)
Treatment C: 40/25 mg Benicar HCT® + 10 mg Antacal® (HD-RFI)
Treatment E: 40/10 mg Azor™ + 25 mg HCT (HD-RFII)
Note1: $AUC_{0\text{-}inf}$, AUC_{extr}, $t_{1/2}$ and CL/F could not be estimated for Subject 0051 in Treatment A and for Subject 0029 in Treatment C.
Note2: Subject 0029 was withdrawn on Day 2 of Period 3 (Treatment C), therefore, AUC_{last} was excluded from the summary statistics and PK analyses.

The statistical analysis for olmesartan Tmax is shown in the following below.

Table 16: Tmax statistical comparison for olmesartan high dose

Parameters	Medians			Hodges-Lehmann Estimator and 90% CI (%)	
	Treatment A Test	Treatment C Reference I	Treatment E Reference II	A-C	A-E
t_{max} (h)	1.500	1.983	1.983	-0.0210 (-0.492, 0.225)	-0.2333 (-0.492, 0.017)

Source: Table 15.4.1.1.8

The statistical analysis indicated that the tmax values of olmesartan were similar between the high dose CS-8635 MIF and the reference formulations.

Low Dose

As seen with the High-Dose, the mean plasma concentration time profiles and the pharmacokinetics of olmesartan following Treatments B, D and F (Low-Dose) were similar; these profiles and PK parameters are depicted in the following figure and tables, respectively.

Figure 4: Mean olmesartan plasma concentration-time profiles for LD cohort

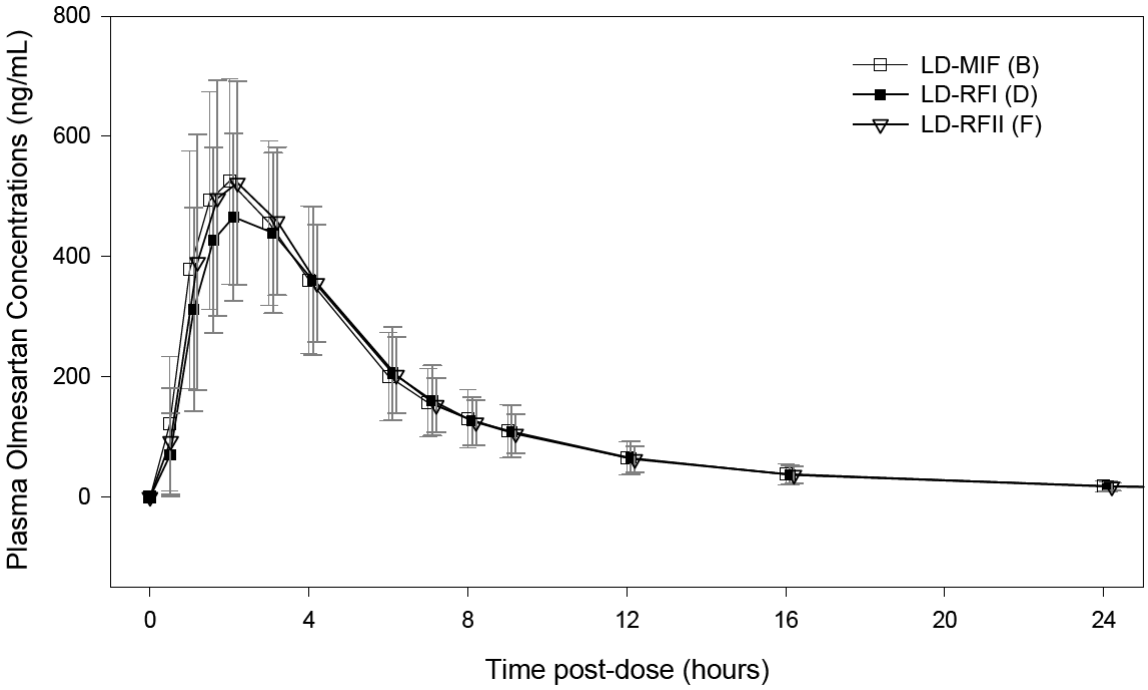


Table 17: Olmesartan statistical exposure comparisons for low dose formulations – Cohort 2*

Parameters	Geometric LSM			Ratio of Geometric LSM and 90% CI (%)	
	Treatment B Test	Treatment D Reference I	Treatment F Reference II	B/D	B/F
AUC_{last} (ng·h/mL)	3351	3263	3329	102.72 (97.01, 108.76)	100.68 (95.14, 106.54)
$AUC_{0\text{-}inf}$ (ng·h/mL)	3391	3302	3363	102.70 (96.99, 108.75)	100.82 (95.21, 106.76)
C_{max} (ng/mL)	548.9	509.4	544.7	107.76 (100.74, 115.28)	100.78 (94.28, 107.73)

* Subject 0027 was withdrawn while on Treatment B, therefore AUClast for this subject excluded. Also, AUCinf could not be estimated for Subjects OO27 and 0028.

The relevant 90% CIs fell within the equivalence range [80 – 125 %] indicating olmesartan administered as the low dose CS-8635 MIF was bioequivalent to the low dose reference formulations.

Table 18: Olmesartan PK measures for low dose formulations – Cohort 2

Olmesartan Parameter	Treatment B Test (N=34)	Treatment D LD-RF1 (N=33)	Treatment F LD-RFII (N=34)
AUC_{last} (ng·h/mL)			
Arithmetic Mean ± SD	3525.0 ± 1111.55	3375.3 ± 1025.07	3460.1 ± 980.30
Geometric Mean (CV%)	3366.7 (31.3%)	3233.8 (30.2%)	3331.7 (28.3%)
$AUC_{0\text{-}inf}$ (ng·h/mL)			
Arithmetic Mean ± SD	3565.9 ± 1120.79	3411.8 ± 1028.85	3508.7 ± 996.93
Geometric Mean (CV%)	3406.5 (31.2%)	3270.6 (30.0%)	3376.8 (28.6%)
AUC_{extr} (%)			
Arithmetic Mean ± SD	1.1640 ± 1.11269	1.1225 ± 0.53765	1.1787 ± 0.63412
Median (Min, Max)	0.8235 (0.321, 6.17)	1.1157 (0.400, 3.32)	0.9871 (0.429, 3.31)
C_{max} (ng/mL)			
Arithmetic Mean ± SD	569.9 ± 163.34	515.5 ± 133.36	565.2 ± 173.23
Geometric Mean (CV%)	546.1 (31.0%)	498.4 (27.2%)	540.1 (31.5%)
t_{max} (h)			
Median (Min, Max)	1.9830 (0.983, 4.03)	2.000 (1.00, 4.00)	2.000 (1.00, 4.00)
$t_{½}$ (h)			
Arithmetic Mean ± SD	15.548 ± 6.9242	16.071 ± 7.5553	16.513 ± 7.2283
Median (Min, Max)	13.603 (7.79, 40.8)	14.203 (8.40, 39.0)	13.538 (9.08, 33.8)
CL/F (L/h)			
Arithmetic Mean ± SD	6.135 ± 1.8262	6.371 ± 1.8319	6.148 ± 1.6793

Source: Tables 15.4.1.1.12.1, 15.4.1.1.13.1 and 15.4.1.1.14.1
Treatment B: 20 mg OM/ 5 mg AML/ 12.5 mg HCT (LD-MIF)
Treatment D: 20/12.5 mg Benicar HCT® + 5 mg Antacal® (LD-RFI)
Treatment F: 20/5 mg Azor™ + 12.5 mg HCT (LD-RFII)

The statistical analysis for olmesartan Tmax is shown in the following table.

Table 19: Nonparametric Statistical comparisons of tmax for olmesartan (Cohort 2)

Parameters	Medians			Hodges-Lehmann Estimator and 90% CI (%)	
	Treatment B Test	Treatment D Reference I	Treatment F Reference II	B-D	B-F
t_{max} (h)	1.983	2.000	2.000	-0.3667 (-0.750, 0.000)	-0.0170 (-0.259, 0.233)

Source: Table 15.4.1.1.16

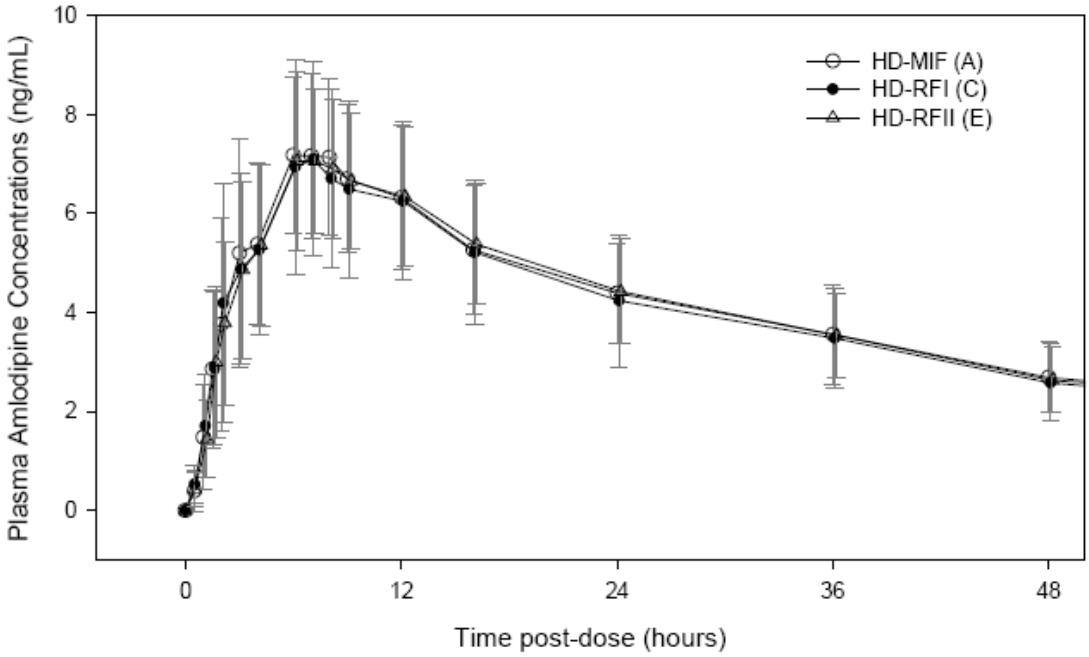
The statistical analysis indicated that olmesartan Tmax were similar between low dose CS-8635 and the reference clinical trial formulations.

Amlodipine Pharmacokinetics

High Dose

The mean amlodipine plasma concentration-time profiles following Treatments A, C and E were similar with overlapping standard deviations; these profiles are depicted in the following figure.

Figure 5: Mean amlodipine plasma concentration-time profiles for HD cohort



The amlodipine PK measures and statistical analysis (exposure comparisons) for the high dose cohort are summarized in the following two tables.

Table 20: Amlodipine statistical exposure comparisons for low dose formulations – Cohort 1

Parameters	Geometric LSM			Ratio of Geometric LSM and 90% CI (%)	
	Treatment A Test	Treatment C Reference I	Treatment E Reference II	A/C	A/E
AUC_{last} (ng·h/mL)	324.3	312.0	327.6	103.96 (98.30, 109.94)	98.99 (93.51, 104.80)
$AUC_{0\text{-}inf}$ (ng·h/mL)	354.3	339.4	358.5	104.38 (98.52, 110.58)	98.82 (93.18, 104.81)
C_{max} (ng/mL)	7.452	7.233	7.348	103.02 (96.62, 109.84)	101.42 (94.94, 108.34)

Source: Table 15.4.1.2.7

The relevant 90 % CIs fall within the equivalence range [80 – 125 %] indicating that amlodipine administered as the high dose CS-8635 MIF was bioequivalent to the high dose reference formulations.

Table 21: Amlodipine PK measures for high dose formulations – Cohort 1

Amlodipine Parameter	Treatment A Test (N=34)	Treatment C Reference I (N=34)	Treatment E Reference II (N=32)
AUC_{last} (ng·h/mL)			
Arithmetic Mean ± SD	339.1 ± 88.80	327.76 ± 99.388	338.2 ± 80.80
Geometric Mean (CV%)	328.8 (25.6%)	311.49 (35.5%)	329.1 (24.2%)
$AUC_{0\text{-}inf}$ (ng·h/mL)			
Arithmetic Mean ± SD	372.1 ± 103.28	357.45 ± 110.626	371.6 ± 95.20
Geometric Mean (CV%)	359.1 (27.6%)	338.52 (37.0%)	359.9 (26.3%)
AUC_{extr} (%)			
Arithmetic Mean ± SD	8.365 ± 3.5981	7.923 ± 3.4514 7.325	8.493 ± 3.9778
Median (Min, Max)	8.370 (2.17, 16.8)	(2.34, 18.6)	7.924 (2.78, 18.4)
C_{max} (ng/mL)			
Arithmetic Mean ± SD	7.747 ± 1.8317	7.598 ± 2.1380	7.558 ± 1.6820
Geometric Mean (CV%)	7.563 (22.0%)	7.271 (33.2%)	7.391 (21.5%)
t_{max} (h)			
Median (Min, Max)	6.992 (2.00, 12.0)	6.542 (1.98, 12.0)	7.000 (3.98, 12.0)
$t_{½}$ (h)			
Arithmetic Mean ± SD	41.46 ± 8.287	40.22 ± 7.773	41.66 ± 8.689
Median (Min, Max)	40.73 (26.4, 58.0)	39.88 (27.6, 64.2)	38.72 (29.6, 61.6)
CL/F (L/h)			
Arithmetic Mean ± SD	28.87 ± 8.219	31.79 ± 15.474	28.72 ± 7.837

Source: Tables 15.4.1.2.4.1, 15.4.1.2.5.1 and 15.4.1.2.6.1

Treatment A: 40 mg OM/ 10 mg AML/ 25 mg HCT (HD-MIF)
Treatment C: 40/25 mg Benicar HCT® + 10 mg Antacal® (HD-RFI)
Treatment E: 40/10 mg Azor™ + 25 mg HCT (HD-RFII)
Note1: $AUC_{0\text{-}inf}$, AUC_{extr}, $t_{1/2}$ and CL/F could not be estimated for Subject 0029 in Treatment C.
Note2: Subject 0029 was withdrawn on Day 2 of Period 3 (Treatment C), therefore, AUC_{last} was excluded from the summary statistics and PK analyses.

The statistical analysis for amlodipine tmax is presented below.

Table 22: Nonparametric Statistical comparisons of tmax for amlodipine (Cohort 1)

Parameters	Medians			Hodges-Lehmann Estimator and 90% CI (%)	
	Treatment A Test	Treatment C Reference I	Treatment E Reference II	A-C	A-E
t_{max} (h)	6.992	6.542	7.000	-0.0080 (-0.508, 0.517)	-0.5210 (-1.025, -0.033)

The statistical analysis indicates that the amlodipine Tmax for the HD MIF is:

- is not different when compared to the Benicar HCT + Antacal reference clinical trial formulation
- shorter compared to the Azor + hydrochlorothiazide reference clinical trial formulation

Low Dose

As seen with the High-Dose, the mean plasma concentration time profiles and the pharmacokinetics of amlodipine following Treatments B, D and F (Low-Dose) were similar; these profiles and PK measures are depicted in the following figure and tables, respectively.

Figure 6: Mean amlodipine plasma concentration-time profiles for LD cohort

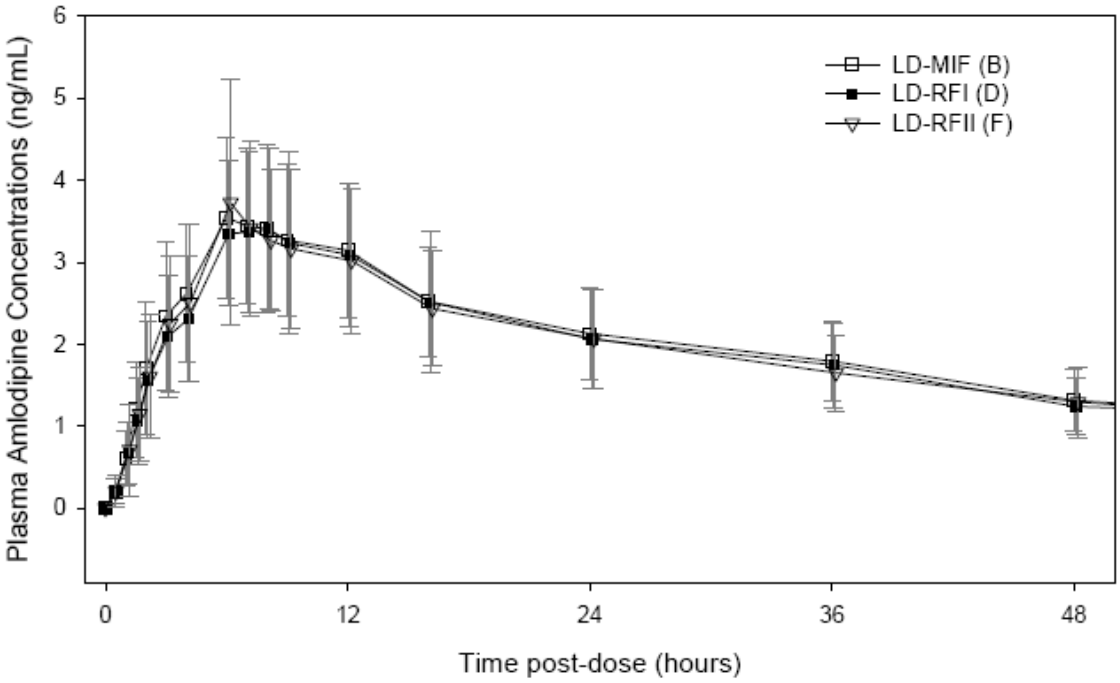


Table 23: Amlodipine statistical exposure comparisons for low dose formulations – Cohort 2

Parameters	Geometric LSM			Ratio of Geometric LSM and 90% CI (%)	
	Treatment B Test	Treatment D Reference I	Treatment F Reference II	B/D	B/F
AUC_{last} (ng·h/mL)	164.7	155.5	155.0	105.93 (101.76, 110.28)	106.27 (102.12, 110.58)
$AUC_{0\text{-}inf}$ (ng·h/mL)	180.2	171.9	170.6	104.82 (100.48, 109.36)	105.64 (101.31, 110.16)
C_{max} (ng/mL)	3.690	3.525	3.704	104.67 (97.09, 112.85)	99.61 (92.46, 107.31)

Source: Table 15.4.1.2.15

The relevant 90 % confidence intervals fell within the equivalence region [80 – 125], indicating that amlodipine administered as low dose MIF formulation was BE to the clinical trial reference formulations.

Table 24: Amlodipine PK measures for high dose formulations – Cohort 2

Amlodipine Parameter	Treatment B Test (N=34)	Treatment D Reference I (N=33)	Treatment F Reference II (N=34)
AUC_{last} (ng·h/mL)			
Arithmetic Mean ± SD	166.07 ± 42.790	162.51 ± 46.682	161.80 ± 45.940
Geometric Mean (CV%)	160.79 (26.4%)	156.63 (27.7%)	155.66 (28.9%)
$AUC_{0\text{-}inf}$ (ng·h/mL)			
Arithmetic Mean ± SD	182.7 ± 49.10	180.48 ± 54.562	179.07 ± 53.310
Geometric Mean (CV%)	176.2 (28.2%)	173.24 (29.3%)	171.47 (30.8%)
AUC_{extr} (%)			
Arithmetic Mean ± SD	8.212 ± 3.4706	9.501 ± 4.0678	9.147 ± 3.7291
Median (Min, Max)	7.580 (3.19, 15.6)	9.340 (2.86, 17.3)	9.531 (3.37, 15.4)
C_{max} (ng/mL)			
Arithmetic Mean ± SD	3.732 ± 0.9397	3.659 ± 1.0674	3.907 ± 1.5038
Geometric Mean (CV%)	3.630 (23.8%)	3.536 (26.0%)	3.704 (32.1%)
t_{max} (h)			
Median (Min, Max)	7.000 (5.98, 12.0)	7.983 (5.98, 12.1)	6.034 (5.97, 16.0)
$t_{½}$ (h)			
Arithmetic Mean ± SD	40.91 ± 7.566	43.73 ± 8.606	42.88 ± 7.925
Median (Min, Max)	40.60 (29.7, 56.7)	46.00 (28.6, 58.8)	44.16 (30.9, 57.8)
CL/F (L/h)			
Arithmetic Mean ± SD	29.45 ± 8.314	30.00 ± 8.312	30.48 ± 9.321

The statistical analysis for amlodipine tmax is presented in the following table.

Table 25: Nonparametric Statistical comparisons of tmax for amlodipine (Cohort 2)

Parameters	Medians			Hodges-Lehmann Estimator and 90% CI (%)	
	Treatment B Test	Treatment D Reference I	Treatment F Reference II	B-D	B-F
t_{max} (h)	7.000	7.983	6.034	-0.4873 (-0.992, 0.467)	0.4915 (-0.475, 1.000)

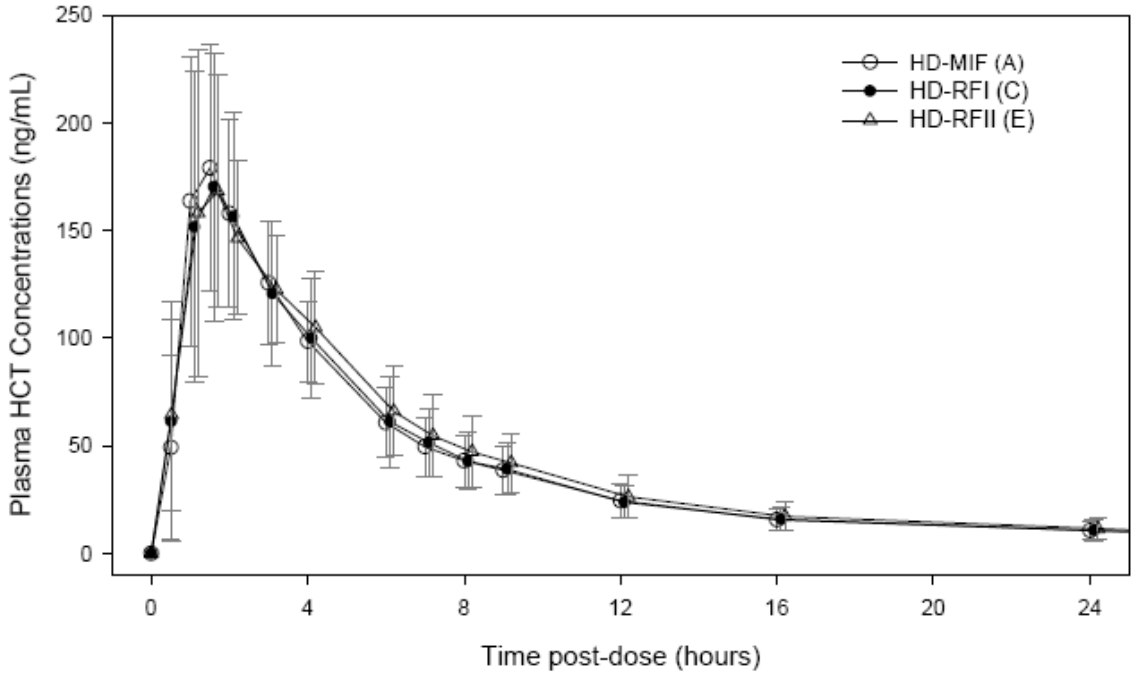
The statistical analysis indicates that the amlodipine Tmax is comparable for the MIF and clinical trial formulations in the low dose cohort.

Hydrochlorothiazide Pharmacokinetics

High Dose

The mean hydrochlorothiazide (HCT) plasma concentration-time profiles following Treatments A, C and E were similar with overlapping standard deviations; these profiles are depicted in the following figure.

Figure 7: Mean HCT plasma concentration-time profiles for HD cohort



The HCT PK measures and associated statistical analysis (exposure comparisons) for the high dose cohort are summarized in the following two tables.

Table 26: HCT statistical exposure comparisons for high dose formulations – Cohort 1

Parameters	Geometric LSM			Ratio of Geometric LSM and 90% CI (%)	
	Treatment A Test	Treatment C Reference I	Treatment E Reference II	A/C	A/E
AUC_{last} (ng·h/mL)	1152	1133	1194	101.66 (96.83, 106.73)	96.50 (91.83, 101.40)
$AUC_{0\text{-}inf}$ (ng·h/mL)	1177	1159	1219	101.57 (96.86, 106.51)	96.58 (92.02, 101.37)
C_{max} (ng/mL)	183.6	178.1	177.9	103.11 (94.13, 112.95)	103.25 (94.01, 113.39)

Source: Table 15.4.1.3.7

The relevant 90 % confidence intervals fell within the equivalence range [80 – 125], indicating that HCT administered as HD MIF formulation was bioequivalent to the clinical trial reference formulations.

Table 27: HCT PK measures for high dose formulations – Cohort 1

HCT Parameter	Treatment A Test (N=34)	Treatment C Reference I (N=34)	Treatment E Reference II (N=32)
AUC_{last} (ng·h/mL)			
Arithmetic Mean ± SD	1198.3 ± 269.73	1179.2 ± 303.93	1243.3 ± 304.83
Geometric Mean (CV%)	1169.1 (22.9%)	1140.6 (27.0%)	1207.2 (25.2%)
$AUC_{0\text{-}inf}$ (ng·h/mL)			
Arithmetic Mean ± SD	1222.7 ± 270.24	1203.7 ± 305.24	1267.1 ± 303.13
Geometric Mean (CV%)	1193.9 (22.5%)	1165.8 (26.4%)	1232.2 (24.5%)
AUC_{extr} (%)			
Arithmetic Mean ± SD	2.0741 ± 0.77337	2.149 ± 1.0737 2.011	2.0254 ± 0.96007
Median (Min, Max)	1.9302 (0.753, 3.83)	(1.03, 6.92)	1.8588 (0.872, 4.86)
C_{max} (ng/mL)			
Arithmetic Mean ± SD	192.9 ± 56.74	188.86 ± 54.637	186.9 ± 58.91
Geometric Mean (CV%)	184.8 (30.5%)	180.85 (31.4%)	178.5 (31.4%)
t_{max} (h)			
Median (Min, Max)	1.5000 (0.500, 4.00)	1.4830 (0.983, 5.98)	1.4830 (0.983, 4.00)
$t_{½}$ (h)			
Arithmetic Mean ± SD	10.204 ± 1.8683	10.037 ± 1.6590 9.920	9.626 ± 1.2620 9.703
Median (Min, Max)	10.218 (6.36, 16.2)	(6.81, 15.9)	(7.18, 12.9)
CL/F (L/h)			
Arithmetic Mean ± SD	21.45 ± 4.814	22.17 ± 5.963	20.87 ± 5.100

Source: Tables 15.4.1.3.4.1, 15.4.1.3.5.1 and 15.4.1.3.6.1

The statistical analysis for HCT tmax is presented in the following table.

Table 28: Nonparametric Statistical comparisons of tmax for HCT (Cohort 1)

Parameters	Medians			Hodges-Lehmann Estimator and 90% CI (%)	
	Treatment A Test	Treatment C Reference I	Treatment E Reference II	A-C	A-E
t_{max} (h)	1.500	1.483	1.483	0.0085 (-0.242, 0.259)	0.2330 (0.000, 0.259)

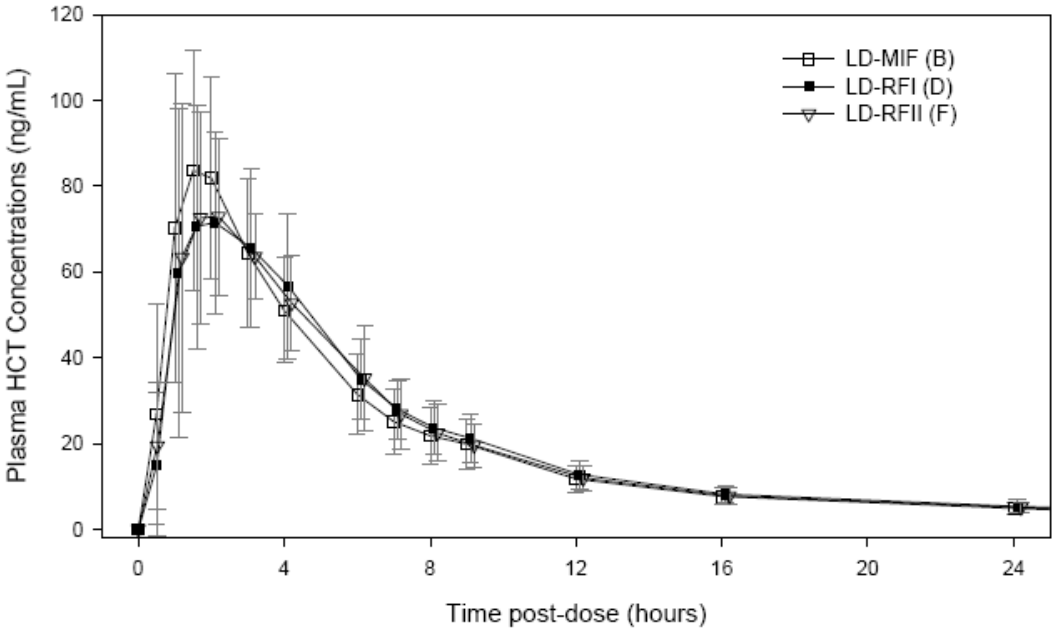
Source: Table 15.4.1.3.8

The statistical analysis indicates that the HCT Tmax is comparable for HD MIF and reference clinical trial formulations.

Low Dose

As seen with the High-Dose, the mean plasma concentration time profiles and the pharmacokinetics of HCT following Treatments B, D and F (Low-Dose) were similar; these profiles and PK measures are depicted in the following figure and tables, respectively.

Figure 8: Mean HCT plasma concentration-time profiles for LD cohort



The HCT PK measures and associated statistical analysis (exposure comparisons) for the low dose cohort are summarized in the following two tables.

Table 29: HCT statistical exposure comparisons for high dose formulations – Cohort 1*

Parameters	Geometric LSM			Ratio of Geometric LSM and 90% CI (%)	
	Treatment B Test	Treatment D Reference I	Treatment F Reference II	B/D	B/F
AUC_{last} (ng·h/mL)	562.6	576.8	560.5	97.53 (93.53, 101.69)	100.37 (96.30, 104.61)
$AUC_{0\text{-}inf}$ (ng·h/mL)	584.8	597.4	580.5	97.89 (94.11, 101.84)	100.75 (96.89, 104.76)
C_{max} (ng/mL)	91.90	86.44	80.94	106.32 (97.33, 116.14)	113.53 (104.03, 123.91)

Source: Table 15.4.1.3.15

Table 30: HCT PK measures for high dose formulations – Cohort 1

HCT Parameter	Treatment B Test (N=34)	Treatment D LD-RF1 (N=33)	Treatment F LD-RFII (N=34)
AUC_{last} (ng·h/mL)			
Arithmetic Mean ± SD	574.3 ± 124.21	589.8 ± 128.28	573.1 ± 114.66
Geometric Mean (CV%)	561.4 (21.9%)	576.4 (22.1%)	562.0 (20.3%)
$AUC_{0\text{-}inf}$ (ng·h/mL)			
Arithmetic Mean ± SD	595.7 ± 123.25	610.0 ± 128.24	592.9 ± 115.27 582.1
Geometric Mean (CV%)	583.6 (20.8%)	597.0 (21.3%)	(19.7%)
AUC_{extr} (%)			
Arithmetic Mean ± SD	3.802 ± 1.4873	3.453 ± 1.2524	3.448 ± 1.0548
Median (Min, Max)	3.487 (1.72, 9.67)	3.241 (1.67, 6.98)	3.491 (1.48, 5.94)
C_{max} (ng/mL)			
Arithmetic Mean ± SD	94.64 ± 26.416	88.12 ± 25.736	84.11 ± 28.408 80.47
Geometric Mean (CV%)	90.55 (32.3%)	84.99 (27.1%)	(29.6%)
t_{max} (h)			
Median (Min, Max)	1.5000 (0.983, 4.03)	1.9830 (0.983, 4.00)	1.9915 (0.983, 5.97)
$t_{½}$ (h)			
Arithmetic Mean ± SD	9.912 ± 2.2392	9.380 ± 1.3951	9.757 ± 1.8929
Median (Min, Max)	9.832 (7.01, 19.0)	9.568 (6.88, 13.0)	10.077 (6.46, 15.9)
CL/F (L/h)			
Arithmetic Mean ± SD	21.86 ± 4.459	21.39 ± 4.500	21.87 ± 4.255

Source: Tables 15.4.1.3.12.1, 15.4.1.3.13.1 and 15.4.1.3.14.1

Treatment B: 20 mg OM/ 5 mg AML/ 12.5 mg HCT (LD-MIF)

Treatment D: 20/12.5 mg Benicar HCT® + 5 mg Antacal® (LD-RFI)

Treatment F: 20/5 mg Azor™ + 12.5 mg HCT (LD-RFII)

Note1: $AUC_{0\text{-}inf}$, AUC_{extr}, $t_{1/2}$ and CL/F could not be estimated for Subjects 0027 in Treatment B.

Note2: Subject 0027 was withdrawn on Day 2 of Period 1 (Treatment B), therefore, AUC_{last} was excluded from the summary statistics and PK analyses.

The statistical analysis for HCT tmax is presented in the following table.

Table 31: Nonparametric Statistical comparisons of tmax for HCT (Cohort 2)

Parameters	Medians			Hodges-Lehmann Estimator and 90% CI (%)	
	Treatment B Test	Treatment D LD-RFI	Treatment F LD-RFII	B-D	B-F
t_{max} (h)	1.500	1.983	1.992	-0.2585 (-0.742, 0.017)	-0.2500 (-0.500, 0.000)

Source: Table 15.4.1.3.16

The statistical analysis indicates that HCT Tmax is comparable for the MIF and clinical trial formulations in the low dose cohort.

Reviewer Note on Applicant's Supplemental Bioequivalence Analysis (Re: Study Objectives)
The applicant conducted a secondary analysis to compare HCT bioequivalence among the clinical trial reference formulations. Although this analysis provides supportive evidence of HCT bioequivalence, it is not critical to the assessment of BE of the to-be-marketed formulations (MIF). Consequently, this reviewer decided not to review this information and this information is not included in this review.

Dose Proportionality Assessment
The following table summarizes the statistical comparisons used to assess dose proportionality.

Table 32: Statistical comparisons of dose normalized PK measures between the high dose and low dose MIFs (Treatment A vs. Treatment B).

Parameters	Geometric LSM		Ratio of Geometric LSM (A/B) and 90% CI (%)
	Treatment A HD-MIF (Test)	Treatment B LD-MIF (Reference)	
Olmesartan			
AUC_{last} (ng·h/mL/mg)	151.2	165.4	91.43 (87.27, 95.79)
$AUC_{0\text{-}inf}$ (ng·h/mL/mg)	154.5	167.6	92.19 (88.50, 96.04)
C_{max} (ng/mL/mg)	22.49	25.85	86.99 (81.78, 92.54)
Amlodipine			
AUC_{last} (ng·h/mL/mg)	33.34	32.02	104.12 (101.02, 107.31)
$AUC_{0\text{-}inf}$ (ng·h/mL/mg)	36.51	34.99	104.33 (101.11, 107.64)
C_{max} (ng/mL/mg)	0.7671	0.7265	105.58 (102.26, 109.00)
HCT			
AUC_{last} (ng·h/mL/mg)	46.63	45.58	102.30 (99.47, 105.21)
$AUC_{0\text{-}inf}$ (ng·h/mL/mg)	47.60	47.30	100.65 (97.97, 103.40)
C_{max} (ng/mL/mg)	7.204	7.333	98.24 (91.95, 104.97)

Source: Table 15.4.2.1.7, 15.4.2.2.7 and 15.4.2.3.7
Treatment A: 40 mg OM/ 10 mg AML/ 25 mg HCT (HD-MIF)
Treatment B: 20 mg OM/ 5 mg AML/ 12.5 mg HCT (LD-MIF)

The relevant geometric mean ratios and 90% CIs for the dose-normalized PK measures were entirely contained within the 80 – 125 % interval for all three analytes. This finding indicates that the CS-8635 MIFs showed dose proportional increases in exposure for olmesartan, amlodipine and HCT between the low dose of 20/5/12.5 mg (OM/AML/HCT) and high dose of 40/10/25 mg (OM/AML/HCT). It is noted that the kinetics of all three components are linear in the studied dose range, thus the dose-proportional observation is consistent with the PK linearity.

Applicant's Safety Highlights

There were no deaths or serious adverse events (SAEs) during this study. Three subjects (Subjects 0014, 0037 and 0069) in Cohort 1 were discontinued early and Subject 0057 did not receive Treatment E in Period 3 due to adverse events. The most frequently reported treatment emergent adverse events (TEAEs) were headache (37.5% of subjects), followed by dizziness (33.3% of subjects), oropharyngeal pain (20.8% of subjects), nausea (16.7% of subjects), cough (15.3% of subjects) and nasal congestion (12.5% of subjects). There were no AEs judged definitely treatment-related in this study. All mean and

most individual values for laboratory parameters (hematology, serum chemistry, and urinalysis) were within normal ranges, and no abnormal result was deemed clinically significant except ALT, creatine kinase and creatinine for Subject 0057, and Subject 0036's repeat test for uric acid. There were no clear differences in mean vital signs measurements between the high and low dose treatments. Slight decreases from baseline were apparent for systolic and diastolic blood pressure measurements for up to 24 hours following treatment, but blood pressures remained within normal physiological ranges. All mean and most individual post-dose ECG results were within normal limits and no ECG abnormality was deemed clinically significant. ECG results were comparable across high and low dose treatments. All individual QTc intervals remained below 450 msec.

Conclusions

- The high dose CS-8635 MIF (40 mg olmesartan, 10 mg amlodipine and 25 mg HCT) was bioequivalent to the reference clinical trial formulations of 40/25 mg Benicar HCT® co administered with 10 mg Antacal® and 40/10 mg AzorTM co administered with 25 mg HCT.
- The low dose CS-8635 MIF (20 mg olmesartan, 5 mg amlodipine and 12.5 mg HCT) was bioequivalent to the reference formulations of 20/12.5 mg Benicar HCT® co administered with 5 mg Antacal® and 20/5 mg AzorTM co administered with 12.5 mg HCT.
- The CS-8635 MIFs showed dose proportional pharmacokinetics for olmesartan, amlodipine and HCT between the low dose of 20/5/12.5 mg (OM/AML/HCT) and high dose of 40/10/25 mg (OM/AML/HCT).

4.2.2 An open label, phase 1, two-way crossover food effect study of CS-8635 market image formulation in healthy subjects

PROTOCOL #	CS8635-A-U106
Link to Report	\\cdsesub1\EVSPROD\NDA200175\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\cs8635-a-u106\cs8635-a-u106-body.pdf
INVESTIGATOR	Frank Lee, MD
STUDY SITE	MDS Pharma Services, Neptune, New Jersey 07753
STUDY PERIOD	October – November, 2009

Objectives (per applicant)

- Primary: to compare the pharmacokinetics of olmesartan, amlodipine and hydrochlorothiazide when administered as the highest strength dose combination of the CS-8635 MIF* [40/10/25 mg (olmesartan medoxomil/ amlodipine besylate/ hydrochlorothiazide)] under fed and fasting conditions.
- Secondary: to evaluate the safety and tolerability of the CS-8635 MIF at its highest strength dose combination under fed and fasting conditions.

*MIF- market image formulation

Study Design

This was an open-label, randomized, 2- way crossover study in 34* healthy subjects (26 males and 8 females). The following two treatments were administered on two occasions and were separated by a washout period of at least 21 days:

- Treatment A (Reference): single oral dose of the highest dose strength of CS-8635 MIF under fasting conditions
- Treatment B (Test): single oral dose of the highest dose strength of CS-8635 MIF under fed conditions.

* Subject 0004 was dropped by the principal investigator (PI) due to high AST and ALT at Period 2 check-in. The lab values were not considered to be clinically significant by the PI.

Formulation

CS-8635 MIF: olmesartan medoxomil/ amlodipine besylate/ hydrochlorothiazide (40 mg/10 mg/25 mg Tablet) manufactured by Daiichi Sankyo; Lot No.: 3265V07006 Expiration Date: 05/2009

Pharmacokinetic Measures and Sampling Times

Plasma pharmacokinetics were calculated for olmesartan, amlodipine and hydrochlorothiazide using non-compartmental analyses. The following pharmacokinetic (PK) measures of hydrochlorothiazide (HCT), olmesartan (OM), and amlodipine (AML) were estimated: Cmax, tmax, AUClast, AUCinf, AUCext, tmax, t1/2, and CL/F.

Pharmacokinetic sampling times were as follows:
Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, 9, 12, 16, 24, 36, 48, 60, 72, 96, 120, and 144 h post dose.

Statistical Methods

The food effect was evaluated using standard pharmaco-statistical approaches. See Introduction to ISRs and refer to Pivotal Bioequivalence study for details on the approaches.

Results

Bioanalytical Methods

A validated Turbo Ion Spray LC/MS/MS method was used to determine the concentrations of olmesartan, amlodipine and hydrochlorothiazide. The performance of the assay for each analyte was acceptable as summarized in the following table.

Table 33: Performance of Analyte Assays in Food Effect Study

Parameter	Measure	Reviewer Comment
	Olmesartan (RNH-6270)	
Linearity	The assay was linear over the 1 to 1000 ng/mL range; $R^2 > 0.997$	Satisfactory
Between day Precision	CV was < 16 %	Satisfactory
Accuracy	QC samples were between -2.5 and 5 % of nominal concentration	Satisfactory
Specificity	Chromatograms were provided and demonstrated specificity	Satisfactory
Pass Rate	83.3 % (20 out of 24 were not rejected)	Satisfactory
	Amlodipine	
Linearity	The assay was linear over the 0.05 to 50.0 ng/mL range; $R^2 > 0.991$	Satisfactory
Between day Precision	CV was < 13 %	Satisfactory
Accuracy	QC samples were between 1 and 4 % of nominal concentration	Satisfactory
Specificity	Chromatograms were provided and demonstrated specificity	Satisfactory
Pass Rate	*66.7 % (16 out of 24 were not rejected)	Satisfactory
	Hydrochlorothiazide	
Linearity	The assay was linear over the 1.0 to 1000 ng/mL range; $R^2 > 0.994$	Satisfactory
Between day Precision	CV was < 20 %	Satisfactory
Accuracy	QC samples were between -3 and 2.3 % of nominal concentration	Satisfactory
Specificity	Chromatograms were provided and demonstrated specificity	Satisfactory
Pass Rate	84.2 % (16 out of 19 were not rejected)	Satisfactory

Reviewer Comment on Amlodipine Assay

The pass rate for amlodipine was rather low suggesting that assay may not be suitable for routine measurement of amlodipine. The two main reasons for the rejections (pass rate) are documented as follows (b) (4) Bioanalytical Report; Page 22 of 1766).

- QC sample failed to meet acceptance criteria
- Contamination issues

Per the study report, the investigation^ into the reasons for the amlodipine run rejections revealed that the issues were due to a random bias from run to run and was not a systematic problem. Thus, the report concludes that the integrity of the data was not compromised.

^Findings from the investigation:

- Acceptable reproducibility for amlodipine during reassays of runs and repeat analyses of samples throughout the study; also acceptable for additional incurred sample reanalysis (from runs with isolated contamination)
- Three runs, Runs 10, 16 and 17, show a gross contamination issue that is common to all three analytes. (b) (4)

Reviewer Recommendation on Amlodipine Assay

Overall the applicant's explanation appears reasonable, thus the assay is acceptable. However, further investigation by FDA may be useful. It is noted that an inspection has been requested for the pivotal bioequivalence study that uses the same validated assay.

Olmesartan Pharmacokinetics

The mean olmesartan plasma concentration-time profiles following the fed and fasted treatments were similar and overlapping standard deviations (figure not shown) and PK measures were comparable. The olmesartan PK measures and associated statistical analysis (exposure comparisons) are presented in the following two tables.

Table 34: Olmesartan PK measures in food effect study

Parameter Olmesartan	Treatment A, Reference (N=34)	Treatment B, Test (N=33)
AUC_{last} (ng·h/mL) Arithmetic Mean ± SD Geometric Mean (CV%)	 7097.5 ± 1794.16 6872.9 (26.5%)	 6519.4 ± 1644.63 6326.8 (25.3%)
$AUC_{0\text{-}inf}$ (ng·h/mL) Arithmetic Mean ± SD Geometric Mean (CV%)	 7144.1 ± 1800.23 6921.5 (26.3%)	 6394.2 ± 1497.58 6227.2 (23.9%)
AUC_{extr} (%) Arithmetic Mean ± SD Median (Min, Max)	 0.9 ± 1.4 0.5 (0.2, 7.6)	 1.0 ± 1.5 0.4 (0.2, 7.9)
C_{max} (ng/mL) Arithmetic Mean ± SD Geometric Mean (CV%)	 1121.1 ± 316.34 1079.2 (28.6%)	 1094.4 ± 261.95 1060.9 (26.8%)
t_{max} (h) Median (Min, Max)	 2.000 (1.00, 3.00)	 3.000 (1.50, 6.00)
$t_{½}$ (h) Arithmetic Mean ± SD Median (Min, Max)	 16.802 ± 13.3622 12.294 (6.69, 64.4)	 16.679 ± 14.8158 11.617 (6.15, 83.2)
CL/F (L/h) Arithmetic Mean ± SD	 5.973 ± 1.6095	 6.603 ± 1.6461

Source: Tables 15.4.1.1.3 and 15.4.1.1.5
Treatment A: Single Dose of CS-8635 MIF under Fasting Conditions
Treatment B: Single Dose of CS-8635 MIF under Fed Conditions
Note: $AUC_{0\text{-}inf}$, AUC_{extr}, $t_{1/2}$ and CL/F could not be estimated for Subjects 0016, 0019, 0025 in Treatment A and Subjects 0014, 0019 and 0021 in Treatment B.

The 90% CIs fell within the equivalence range [80-125] indicating that food does not alter olmesartan PK.

Table 35: Olmesartan statistical exposure comparisons in food effect study

Parameter Olmesartan	Geometric LSM		Ratio B/A (%)	90% CI (%)
	Treatment A Reference	Treatment B Test		
AUC_{last}	6873	6359	92.52	(86.95, 98.46)
$AUC_{0\text{-}inf}$	6940	6314	90.98	(85.52, 96.78)
C_{max}	1079	1056	97.83	(90.60, 105.63)

Source: Table 15.4.1.1.7
Treatment A: Single Dose of CS-8635 MIF under Fasting Conditions
Treatment B: Single Dose of CS-8635 MIF under Fed Conditions

The nonparametric statistical analysis for olmesartan Tmax is presented in the following table.

Table 36: Tmax statistical comparison for Olmesartan

Parameter Olmesartan	Medians		Hodges-Lehmann Estimator for B-A	90% CIs
	Treatment A Reference	Treatment B Test		
t_{max} (h)	2.000	3.000	0.5125	(0.500, 0.759)

Source: Table 15.4.1.1.8
Treatment A: Single Dose of CS-8635 MIF under Fasting Conditions
Treatment B: Single Dose of CS-8635 MIF under Fed Conditions

The statistical analysis indicates that tmax under fed conditions was longer than under fasted conditions. However, this difference is unlikely to be clinically significant based on the exposure comparisons. It is noted that Tmax is not the primary determinant in the food effect assessment.

Amlodipine Pharmacokinetics

The mean amlodipine plasma concentration-time profiles following the fed and fasted treatments were similar and overlapping standard deviations (figure not shown) and PK measures were comparable. The amlodipine PK measures and associated statistical analysis (exposure comparisons) are presented in the following two tables.

Table 37: Amlodipine PK measures in food effect study

Parameter Amlodipine	Treatment A, Reference (N=33)	Treatment B, Test (N=32)
AUC_{last} (ng·h/mL)		
Arithmetic Mean ± SD	395.0 ± 91.10	415.2 ± 110.12
Geometric Mean (CV%)	385.1 (23.1%)	402.3 (25.5%)
$AUC_{0\text{-}inf}$ (ng·h/mL)		
Arithmetic Mean ± SD	427.0 ± 101.34	464.9 ± 144.31
Geometric Mean (CV%)	415.7 (23.7%)	446.1 (29.1%)
AUC_{extr} (%)		
Arithmetic Mean ± SD	9.4 ± 3.5	9.7 ± 4.1
Median (Min, Max)	9.3 (2.3, 17.5)	9.1 (2.6, 18.7)
C_{max} (ng/mL)		
Arithmetic Mean ± SD	9.018 ± 2.4023	8.723 ± 1.8149
Geometric Mean (CV%)	8.728 (26.4%)	8.545 (20.9%)
t_{max} (h)		
Median (Min, Max)	8.000 (3.98, 12.0)	8.209 (5.98, 16.0)
$t_{½}$ (h)		
Arithmetic Mean ± SD	43.09 ± 8.022	43.58 ± 9.349
Median (Min, Max)	42.67 (26.3, 65.7)	43.18 (28.6, 64.0)
CL/F (L/h)		
Arithmetic Mean ± SD	24.69 ± 5.677	23.27 ± 6.133

Source: Tables 15.4.1.2.3 and 15.4.1.2.5
Treatment A: Single Dose of CS-8635 MIF under Fasting Conditions
Treatment B: Single Dose of CS-8635 MIF under Fed Conditions
Note: $AUC_{0\text{-}inf}$, AUC_{extr}, $t_{1/2}$ and CL/F could not be estimated for Subjects 0010 and 0033 in Treatment A

The 90% CIs fell within the equivalence range [80-125] indicating that food does not alter amlodipine PK.

Table 38: Amlodipine statistical exposure comparisons in food effect study.

Parameter Amlodipine	Geometric LSM		Ratio B/A (%)	90% CI (%)
	Treatment A Reference	Treatment B Test		
AUC_{last}	385.1	402.5	104.52	(101.20, 107.96)
$AUC_{0\text{-}inf}$	430.5	446.6	103.73	(99.93, 107.66)
C_{max}	8.708	8.501	97.63	(92.55, 102.99)

Source: Table 15.4.1.2.7
Treatment A: Single Dose of CS-8635 MIF under Fasting Conditions
Treatment B: Single Dose of CS-8635 MIF under Fed Conditions

The nonparametric statistical analysis for amlodipine Tmax is presented in the following table.

Table 39: Tmax statistical comparison for Amlodipine

Parameter Amlodipine	Medians		Hodges-Lehmann Estimator for B-A	90% CIs
	Treatment A Reference	Treatment B Test		
t_{max} (h)	8.000	8.209	0.4915	(-0.483, 1.017)

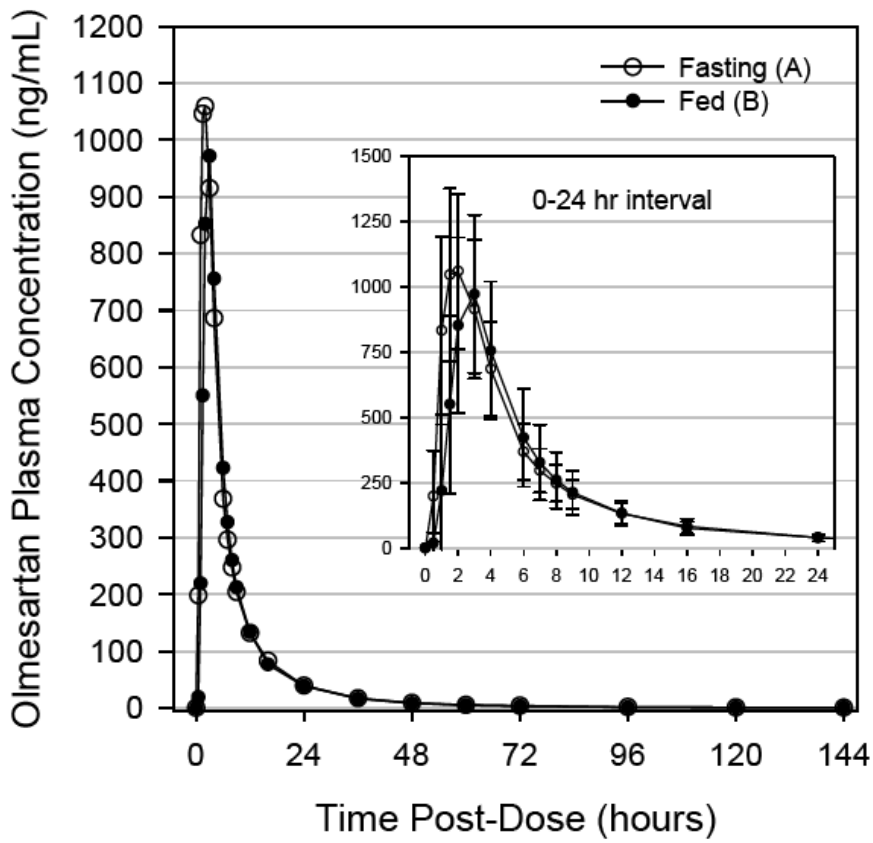
Source: Table 15.4.1.2.8
Treatment A: Single Dose of CS-8635 MIF under Fasting Conditions
Treatment B: Single Dose of CS-8635 MIF under Fed Conditions

The tmax comparison indicated that the tmax values for Treatments A and B were comparable.

Hydrochlorothiazide (HCT) Pharmacokinetics

The mean HCT plasma concentration-time profiles following the fed and fasted treatments are depicted in the following figure.

Figure 9: Mean hydrochlorothiazide plasma concentration-time profiles in food effect study



The HCT PK measures and the associated statistical analysis (exposure comparisons) are presented in the following two tables.

Table 40: HCT PK measures in food effect study

Parameter Hydrochlorothiazide	Treatment A, Reference (N=34)	Treatment B, Test (N=33)
AUC_{last} (ng·h/mL) Arithmetic Mean ± SD Geometric Mean (CV%)	 1154.0 ± 253.25 1126.4 (22.8%)	 1056.0 ± 233.65 1029.7 (23.6%)
$AUC_{0\text{-}inf}$ (ng·h/mL) Arithmetic Mean ± SD Geometric Mean (CV%)	 1174.4 ± 255.12 1147.3 (22.4%)	 1080.7 ± 231.75 1055.4 (22.8%)
AUC_{extr} (%) Arithmetic Mean ± SD Median (Min, Max)	 2.3 ± 0.9 2.2 (0.8, 4.4)	 2.4 ± 0.9 2.5 (1.1, 4.4)
C_{max} (ng/mL) Arithmetic Mean ± SD Geometric Mean (CV%)	 192.09 ± 59.573 183.54 (31.4%)	 147.47 ± 40.664 142.37 (27.3%)
t_{max} (h) Median (Min, Max)	 1.500 (1.00, 3.00)	 2.000 (1.00, 4.00)
$t_{½}$ (h) Arithmetic Mean ± SD Median (Min, Max)	 10.578 ± 1.8362 10.179 (7.16, 14.8)	 10.195 ± 1.4139 10.302 (7.33, 14.9)
CL/F (L/h) Arithmetic Mean ± SD	 22.32 ± 5.009	 24.30 ± 5.888

Source: Tables 15.4.1.3.3 and 15.4.1.3.5
Treatment A: Single Dose of CS-8635 MIF under Fasting Conditions
Treatment B: Single Dose of CS-8635 MIF under Fed Conditions
Note: $AUC_{0\text{-}inf}$, AUC_{extr}, $t_{1/2}$ and CL/F could not be estimated for Subject 0019 in Treatment A

Table 41: HCT PK statistical exposure comparisons in food effect study

Parameter Hydrochlorothiazide	Geometric LSM		Ratio B/A (%)	90% CI (%)
	Treatment A Reference	Treatment B Test		
AUC_{last}	1126	1038	92.17	(88.39, 96.12)
$AUC_{0\text{-}inf}$	1147	1065	92.78	(89.02, 96.70)
C_{max}	183.5	141.8	77.24	(71.03, 84.00)

Source: Table 15.4.1.3.7
Treatment A: Single Dose of CS-8635 MIF under Fasting Conditions
Treatment B: Single Dose of CS-8635 MIF under Fed Conditions

The statistical results indicate that overall food decreased HCT exposure; specifically,

- Cmax of HCT decreased by about 23 %
- AUC of HCT decreased by about 12 %

The Cmax decrease was outside of the equivalence region whereas the decrease in AUC was not. The reason for the statistically significant decrease in Cmax is unclear; however some HCT-containing formulations exhibit a food effect [Ref: Fosinopril and HCT label refers to findings of inconclusive food effects; HCT capsule by Unichem Pharmaceuticals] This reviewer conducted a brief literature search to determine which of the exposure measures (dose, AUC or Cmax), was the primary driver for HCT effectiveness. Generally, HCT exhibits a relatively flat dose response (anti-hypertensive effect) given as monotherapy or in combination with other agents (Hypertension 2004, Carter et al.). Additionally,

exposure increases are approximately dose-proportional. These two observations suggest a relatively minor change in Cmax (< 25 %) is unlikely to alter the exposure-response relationship. Consequently, the observed HCT Cmax decrease with food is not likely to be clinically significant.

The statistical analysis for HCT Tmax is presented in the following table.

Table 42: Tmax statistical comparison for hydrochlorothiazide

Parameter Hydrochlorothiazide	Medians		Hodges-Lehmann Estimator for B-A	90% CIs
	Treatment A Reference	Treatment B Test		
t_{max} (h)	1.500	2.000	0.7750	(0.500, 1.250)

Source: Table 15.4.1.3.8
Treatment A: Single Dose of CS-8635 MIF under Fasting Conditions
Treatment B: Single Dose of CS-8635 MIF under Fed Conditions

The tmax comparison indicated that the median tmax value in the fed state is longer than that in the fasted state. This prolongation in the fed state does not appear clinically significant in light of the primary comparison.

Applicant's Safety Highlights

No serious or severe adverse event (AE) occurred during this study, and no subject was withdrawn from the study due to an AE. A similar number of subjects reported treatment emergent adverse events in Treatments A and B, although the incidence of reported AEs was greater under fasting conditions than fed conditions. The most frequently reported AE in this study was headache by 11 subjects (32.4% of total subjects). All mean and most individual values for laboratory parameters (hematology, serum chemistry, and urinalysis) were within normal ranges, and no abnormal result was deemed to be clinically significant. Consistent with the pharmacological action of olmesartan, hydrochlorothiazide and amlodipine, slight decreases from baseline were apparent for systolic and diastolic blood pressure measurements for up to 24 hours following treatment. Nevertheless, blood pressures remained within normal physiological ranges, and there were no clear differences between fed and fasting conditions.

Conclusions

The administration of CS-8635 MIF [40/10/25 mg (olmesartan medoxomil/ amlodipine besylate/ hydrochlorothiazide)] with food did not have a significant effect on the bioavailability of olmesartan and amlodipine. However, the administration of CS-8635 MIF with food decreased (23%) the peak exposure (Cmax) of hydrochlorothiazide, without affecting the total extent of exposure (AUC). The change in HCT exposure does not appear clinically significant.

Recommendation

The triple combination fixed dose combination tablet may be given without regard for meals.

4.2.3 A randomized, open-label, single-dose cross-over study to determine the bioavailability of olmesartan, amlodipine, and hydrochlorothiazide when administered as CS-8663 plus hydrochlorothiazide together versus separately in healthy subjects

PROTOCOL #	CS8635-A-U102
Link to Study Report	\\cdsesub1\EVSPROD\NDA200175\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\cs8635-a-u102\cs8635-a-u102-body.pdf
INVESTIGATOR	Robert J. Noveck, MD, PhD, FCP
STUDY SITE	MDS Pharma Services, Neptune, New Jersey 07753
STUDY PERIOD	June – August, 2007

Objectives (per applicant)

- To determine the bioavailability of olmesartan, amlodipine and hydrochlorothiazide (HCT) when administered together as CS-8663 (olmesartan medoxomil plus amlodipine besylate) and hydrochlorothiazide and when administered alone.
- To evaluate the safety and tolerability when CS-8663 is co administered with HCT.

Methodology

This was an open-label, randomized, single dose 3-way crossover study. Thirty-six healthy subjects (30 males and 6 females) were enrolled. The subjects were randomized to receive each of the following three treatments according to the randomization schedule:

- Treatment A: a single fixed dose combination CS-8663 (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) co administered with hydrochlorothiazide 25 mg
- Treatment B: single fixed dose combination of CS-8663
- Treatment C: a single dose of hydrochlorothiazide 25 mg alone

Each treatment was administered with 240 mL of water after a minimal 10 hour fast and subjects remained in a fasted state for 4 hours following dosing on Day 1 of each period. Each treatment dose was separated by a 21-day washout.

Formulations

The formulations used in the study are tabulated below.

Products	Tablet	Lot Number
CS-8663 (Olmesartan medoxomil and amlodipine besylate equivalent to 10 mg amlodipine base) Tablet	40 mg/ 10 mg	3223V07001
Hydrochlorothiazide	25 mg	BCR17AA

Pharmacokinetic Measures and Sampling

Plasma pharmacokinetics were calculated for olmesartan, amlodipine and hydrochlorothiazide using non-compartmental analyses. The following PK parameters of olmesartan, amlodipine and hydrochlorothiazide were estimated: AUC0-t, AUC0-inf, AUC%extr, Cmax, Tmax, Lambda z, t1/2 and CL/F.

Pharmacokinetic blood sampling times were as follows:
Predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, 9, 12, 16, 24, 36, 48, 60, and 72 hours.

Additionally, for amlodipine, samples were collected at 96, 120 and 144 hours post-dose.

Statistical Methods

Drug-drug interaction was assessed using standard pharmaco-statistical approaches as described for previous studies in this NDA. The test was Treatment A [(olmesartan and amlodipine) + hydrochlorothiazide)] and the references were Treatment B (olmesartan and amlodipine) and C (hydrochlorothiazide).

Results

Bioanalytical Methods

A validated Turbo Ion Spray LC/MS/MS method was used to determine the concentrations of olmesartan, amlodipine and hydrochlorothiazide. The performance of the assay for each analytes was acceptable as summarized in the following table.

Table 43: Performance* of Assay in Food Effect Study

Parameter	Measure	Reviewer Comment
	Olmesartan (RNH-6270)	
Linearity	The assay was linear over the 1 to 1000 ng/mL range; $R^2 > 0.989$	Satisfactory
Between day Precision	CV was < 6 %	Satisfactory
Accuracy	QC samples were between -5.0 and -3.0 % of nominal concentration	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
	Amlodipine	
Linearity	The assay was linear over the 0.05 to 50.0 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV was < 7 %	Satisfactory
Accuracy	QC samples were between -2.0 and 0.5 % of nominal concentration	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
	Hydrochlorothiazide	
Linearity	The assay was linear over the 1.0 to 1000 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CV was < 5 3 %	Satisfactory
Accuracy	QC samples were between -5.2 and -2.6 % of nominal concentration	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

* one out of 21 runs rejected for olmesartan; two out of 19 runs rejected for amlodipine; all HCT runs passed

*Subject Disposition**

Thirty-six subjects enrolled and 29 subjects completed. The subjects who discontinued did so for the following reasons:

- Misadministration (mis-dosing): Subject 009, randomized to BAC treatment sequence and dosed as BAB sequence, had missing hydrochlorothiazide reference and incomplete sampling of third period
- Discontinued due to Adverse events (AEs): Two Subjects were dropped by the principal investigator
- Subject 019 between Period 2 and 3 due to abnormal lab work (elevated blood creatine phosphokinase and aspartate aminotransferase)
- Subject 024 on Day –1 of Period 3 due to low hemoglobin.
- Protocol Deviation: three subjects (010, 017 and 018) were on prohibited drugs
- Did not return to clinic after receiving some treatments (Subject 034)

* Subject 025 was included in the safety analyses, but not in PK analysis: left the clinic in the middle of treatment but returned to complete study

<u>Olmesartan Pharmacokinetics</u>

The mean olmesartan plasma concentration-time profiles in the drug interaction study treatments were similar with overlapping standard deviations (figure not shown), and PK measures were comparable. The olmesartan PK measures and associated statistical analysis (exposure comparisons) are presented in the following two tables.

Table 44: Olmesartan PK measures in drug interaction study

Olmesartan	Treatment A N = 33*	Treatment B N = 30
AUC_{0-t} (ng.h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	 6976.9 ± 1709.89 6759.8 (26.8%)	 6776.1 ± 1503.53 6617.3 (22.5%)
AUC_{0-inf} (ng.h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	 7113.4 ± 1748.65 6896.2 (26.3%)	 6879.1 ± 1506.23 6721.5 (22.3%)
C_{max} (ng/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	 1070.1 ± 304.01 1028.6 (29.6%)	 1055.1 ± 306.40 1013.6 (29.6%)
T_{max} (h) Median (Min, Max)	 1.9830 (0.983, 3.98)	 2.000 (1.00, 4.00)
$t_{½}$ (h) Arithmetic Mean ±SD	 15.835 ± 6.1931	 15.560 ± 6.1679
CL/F (L/h) Arithmetic Mean ±SD	 6.001 ± 1.6977	 6.093 ± 1.3700

Source: Tables 14.2.1.1.3 and 14.2.1.1.5
Treatment A: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet Co-administered with 25 mg Hydrochlorothiazide Tablet
Treatment B: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet
*N = 32 for the AUC_{0-inf}, $t_{½}$ and CL/F variables (Lambda z could not be reliably characterized)

Table 45: Olmesartan PK statistical comparisons* in drug interaction study

	Geometric LSMEANS			
PK Parameter	**Treatment A (Test)**	**Treatment B (Reference)**	**Ratio of LSMEANS (%) (A/B)**	**90% C.I. for Ratio (%)**
AUC_{0-inf}	6912	6537	105.74	(99.15, 112.77)
AUC_{0-t}	6763	6395	105.76	(99.01, 112.97)
C_{max}	1020	975.8	104.56	(96.84, 112.90)

Source: Table 14.2.1.1.7.
LSMEANS are the least squares means from ANOVA
Treatment A: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet Co-administered with 25 mg Hydrochlorothiazide Tablet
Treatment B: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet

*This analysis (primary analysis) excludes data from Subject 009 in the third period (mis-dosed). The applicant conducted additional analyses that 1) excluded all Subject 009 data and 2) included all Subject 009 data. These additional analyses had similar results as the primary analysis (reported in this review)

The relevant 90% confidence intervals were within the equivalence region [80.0 – 125.0 %] indicating the pharmacokinetics of olmesartan in the fixed dose combination (CS8663) is not affected by the co administration of hydrochlorothiazide.

The statistical analysis of olmesartan Tmax values (including all data from Subject No. 009) are presented in the following table.

Table 46: Olmesartan Tmax statistical comparisons

Olmesartan	Median		Difference (A – B)	90% CI (Lower , Upper)
	Treatment A	Treatment B		
T_{max} (h)	1.983	2.000	-0.0165	(-0.459 , 0.259)

Source: Table 14.2.1.1.8
Treatment A: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet Co-administered with 25 mg Hydrochlorothiazide Tablet
Treatment B: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet

The statistical analysis indicates that olmesartan Tmax is comparable for both treatments.

Amlodipine Pharmacokinetics

The mean amlodipine plasma concentration-time profiles in the drug interaction study treatments were similar with overlapping standard deviations (figure not shown), and PK measures were comparable. The amlodipine PK measures and associated statistical analysis (exposure comparisons) are presented in the following two tables.

Table 47: Amlodipine PK measures in drug interaction study

Amlodipine	Treatment A N = 33	Treatment B N = 30
AUC_{0-t} (ng.h/mL)		
Arithmetic Mean ±SD	359.4 ± 127.09	364.7 ± 110.24
Geometric Mean (CV%)	338.0 (37.0%)	347.2 (33.9%)
AUC_{0-inf} (ng.h/mL)		
Arithmetic Mean ±SD	410.0 ± 170.89	416.0 ± 139.30
Geometric Mean (CV%)	378.7 (42.0%)	392.1 (37.2%)
C_{max} (ng/mL)		
Arithmetic Mean ±SD	7.301 ± 2.0067	7.782 ± 2.4615
Geometric Mean (CV%)	7.027 (29.1%)	7.426 (31.9%)
T_{max} (h)		
Median (Min, Max)	7.017 (5.98, 16.0)	7.983 (5.98, 12.0)
$t_{½}$ (h)		
Arithmetic Mean ±SD	44.36 ± 10.765	46.36 ± 11.213
CL/F (L/h)		
Arithmetic Mean ±SD	28.51 ± 11.213	27.23 ± 10.559

Source: Tables 14.2.1.2.3 and 14.2.1.2.5
Treatment A: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet Co-administered with 25 mg Hydrochlorothiazide Tablet
Treatment B: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet

Table 48: Amlodipine PK measures in drug interaction study

	Geometric LSMEANS			
PK Parameter	**Treatment A (Test)**	**Treatment B (Reference)**	**Ratio of LSMEANS (%) (A/B)**	**90% C.I. for Ratio (%)**
$AUC_{0\text{-}inf}$	383.3	386.4	99.18	(95.50, 103.00)
$AUC_{0\text{-}t}$	343.7	341.4	100.68	(97.37, 104.11)
C_{max}	7.269	7.399	98.25	(93.62, 103.11)

The relevant 90% confidence intervals fell within the equivalence range [80.0 – 125.0 %] indicating that the pharmacokinetics of amlodipine, in the fixed dose combination (CS-8663) is not affected by the co-administration of hydrochlorothiazide.

The statistical analysis of amlodipine Tmax is presented in the following table.

Table 49: Tmax statistical comparisons for amlodipine

Amlodipine	**Median**		**Difference (A – B)**	**90% CI (Lower , Upper)**
	Treatment A	**Treatment B**		
T_{max} (h)	7.017	7.983	0.0170	(-0.491 , 0.983)

Source: Table 14.2.1.2.8
Treatment A: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet Co-administered with 25 mg Hydrochlorothiazide Tablet
Treatment B: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet

The statistical analysis indicates that Tmax is comparable for both treatments.

Hydrochlorothiazide (HCT) Pharmacokinetics

The mean HCT plasma concentration-time profiles in the drug interaction study treatments were similar with overlapping standard deviations (figure not shown), and PK measures were comparable. The HCT PK measures and associated statistical analysis (exposure comparisons) are presented in the following two tables.

Table 50: HCT PK measures in drug interaction study

Hydrochlorothiazide	Treatment A N = 32	Treatment C N = 33
AUC_{0-t} (ng.h/mL)		
Arithmetic Mean ±SD	1054.7 ± 202.82	1127.8 ± 251.41
Geometric Mean (CV%)	1036.4 (19.1%)	1102.0 (21.9%)
AUC_{0-inf} (ng.h/mL)		
Arithmetic Mean ±SD	1081.4 ± 202.63	1153.5 ± 249.21
Geometric Mean (CV%)	1063.5 (18.7%)	1128.7 (21.3%)
C_{max} (ng/mL)		
Arithmetic Mean ±SD	158.46 ± 50.355	162.92 ± 45.449
Geometric Mean (CV%)	150.38 (34.9%)	156.92 (28.3%)
T_{max} (h)		
Median (Min, Max)	1.742 (1.00, 8.97)	1.9830 (0.983, 4.03)
$t_{½}$ (h)		
Arithmetic Mean ±SD	11.151 ± 1.6693	10.839 ± 1.4503
CL/F (L/h)		
Arithmetic Mean ±SD	23.90 ± 4.426	22.62 ± 4.718

Source: Tables 14.2.1.3.3 and 14.2.1.3.5
Treatment A: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet Co-administered with 25 mg Hydrochlorothiazide Tablet
Treatment C: 25 mg Hydrochlorothiazide Tablet

Table 51: HCT PK measures in drug interaction study

	Geometric LSMEANS			
PK Parameter	**Treatment A (Test)**	**Treatment C (Reference)**	**Ratio of LSMEANS (%) (A/C)**	**90% C.I. for Ratio (%)**
AUC_{0-inf}	1083	1131	95.74	(92.79, 98.79)
AUC_{0-t}	1056	1104	95.64	(92.64, 98.74)
C_{max}	152.7	158.7	96.24	(88.85, 104.24)

Source: Table 14.2.1.3.7
LSMEANS are the least squares means from ANOVA
Treatment A: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet Co-administered with 25 mg Hydrochlorothiazide Tablet
Treatment C: 25 mg Hydrochlorothiazide Tablet

The relevant 90% confidence intervals fell within the equivalence range [80.0 – 125.0 %] indicating that the pharmacokinetics of HCT are not affected when HCT is co administered with CS-8663.

The statistical analysis of HCT Tmax is presented in the following table.

Table 52: Tmax statistical comparisons

Hydrochlorothiazide	Median		Difference (A – C)	90% CI (Lower , Upper)
	Treatment A	Treatment C		
T_{max} (h)	1.742	1.983	0.0085	(-0.483 , 0.250)

Source: Table 14.2.1.3.8
Treatment A: CS-8663 (40 mg Olmesartan Medoxomil and 10 mg Amlodipine Besylate Combination) Tablet Co-administered with 25 mg Hydrochlorothiazide Tablet
Treatment C: 25 mg Hydrochlorothiazide Tablet

The statistical analysis indicates that HCT Tmax is comparable for both treatments.

Applicant's Safety Highlights

No serious adverse events (AEs) or deaths occurred during this study. One subject was withdrawn from the study due to two severe adverse AEs that were considered unlikely related to treatment. Overall, 20 subjects (55.6%) reported 60 treatment-emergent adverse events (TEAEs). Fifty-three (53) of the TEAEs were mild (88.3%), 5 were moderate (8.3%), and 2 were severe (3.3%). The most frequently observed TEAE was headache, with 18 episodes experienced by 13 subjects. There were some out of range laboratory results that were classified as Grade 1 and 2 toxicities according to the Common Technology Criteria for Adverse Events v3.0, the majority of results were not considered clinically significant. Clinically significant decreases in hemoglobin were apparent only for Subject 024 at check-in of period 3

Conclusions

- The pharmacokinetics of olmesartan administered as the fixed dose combination (CS-8663) are not affected by the co-administration of hydrochlorothiazide.
- The pharmacokinetics of amlodipine administered as the fixed dose combination (CS-8663) are not affected by the co-administration of hydrochlorothiazide
- The pharmacokinetics of hydrochlorothiazide are not affected by the co-administration of the fixed dose combination of olmesartan medoxomil and amlodipine besylate (CS-8663).

Recommendation

The labeling should reflect the findings form the drug-drug interaction study as outlined in the conclusions above.

4.2.4 A randomized, open-label, single-dose crossover study of olmesartan, amlodipine, and hydrochlorothiazide, to determine the bioavailability when administered as Benicar HCT® plus Norvasc® together versus separately in healthy subjects

PROTOCOL #	CS8635-A-U101
Link to Study Report	\\cdsesub1\EVSPROD\NDA200175\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\cs8635-a-u101\cs8635-a-u101-body.pdf
INVESTIGATOR	Robert J. Noveck, MD, PhD, FCP
STUDY SITE	MDS Pharma Services, Neptune, New Jersey 07753
STUDY PERIOD	June – September, 2007

Objectives per Applicant

- To determine the bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered together as Benicar HCT® (Olmesartan medoxomil plus hydrochlorothiazide) and Norvasc® (amlodipine besylate) and when administered alone.
- To evaluate the safety and tolerability when Benicar HCT® is co-administered with Norvasc®.

Study Design

This was an open-label, randomized, single dose 3-way crossover study in 36 healthy subjects (28 males and 8 females were enrolled). The subjects were randomized to receive each of three following treatments according to the randomization schedule:

- Treatment A: A single fixed dose combination of Benicar HCT® (40 mg olmesartan medoxomil and 25 mg hydrochlorothiazide) co administered with Norvasc® (amlodipine besylate 10 mg)
- Treatment B: A single fixed dose combination of Benicar HCT®
- Treatment C: A single dose of Norvasc®

Each treatment was administered with 240 mL of water after a minimal 10 hour fast and subjects remained in a fasted state for 4 hours following dosing on Day 1 of each period. Each treatment was separated by a 21-day washout.

Formulations

The formulations used in the study are tabulated below.

Products	Tablet	Lot Number	Expiration
Benicar HCT® (olmesartan medoxomil/hydrochlorothiazide)	40 mg/ 25 mg	451968	09/08
Norvasc® (amlodipine besylate)	10 mg	6QL349A	01-November-2011

Pharmacokinetic Measures and Sampling

Standard non-compartmental PK parameters for olmesartan, amlodipine, and hydrochlorothiazide were determined from the plasma concentration time profiles. The following PK parameters were estimated: AUC0-t, AUC0-inf, AUC%extr, Cmax, Tmax, Lambda z, t1/2 and CL/F.

Blood samples for pharmacokinetic analysis were collected at the following time points: prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, 9, 12, 16, 24, 36, 48, 60 and 72 hours post dose. Blood samples were also drawn at 96, 120 and 144 hours for the determination of plasma concentrations for amlodipine only (Treatments A and C).

Statistical Methods

Drug-drug interaction was assessed using standard pharmaco-statistical approaches as described for previous studies in this NDA. The test was Treatment A [(olmesartan/hydrochlorothiazide + and amlodipine)] and the references were Treatment B (olmesartan/hydrochlorothiazide) or C (amlodipine).

Results

Bioanalytical Methods

A validated Turbo Ion Spray LC/MS/MS method was used to determine the concentrations of olmesartan, amlodipine and hydrochlorothiazide. The performance of the assay for each analytes was acceptable as summarized in the following table.

Table 53: Performance* of Assay in Food Effect Study

Parameter	Measure	Reviewer Comment
	Olmesartan (RNH-6270)	
Linearity	The assay was linear over the 1 to 1000 ng/mL range; $R^2 > 0.997$	Satisfactory
Between day Precision	CV was < 8 %	Satisfactory
Accuracy	QC samples were between -5.3 and -0.9 % of nominal concentration	Satisfactory
Specificity	Chromatograms were not provided	Satisfactory
Pass rate	88 % (22 out of 25 runs passed)	Satisfactory
	Amlodipine	
Linearity	The assay was linear over the 0.05 to 50.0 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CV was < 17 %	Satisfactory
Accuracy	QC samples were between -6.7 and 21% of nominal concentration	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
Pass rate	72 % (18 out of 25 runs passed) *	Satisfactory
	Hydrochlorothiazide	
Linearity	The assay was linear over the 1.0 to 1000 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CV was < 6 %	Satisfactory
Accuracy	QC samples were between -5.0 and 1 % of nominal concentration	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
Pass rate	86 % (19 out of 22 runs passed)	Satisfactory

* (b) (4)

Subject Disposition

Four subjects did not complete the study per protocol: three subjects discontinued for personal reasons and one subject for a protocol violation (tested positive for alcohol and amphetamines).

<u>Olmesartan Pharmacokinetics</u>

The mean olmesartan plasma concentration-time profiles in the drug interaction study treatments were similar with overlapping standard deviations (figure not shown), and PK measures were comparable. The olmesartan PK measures and associated statistical analysis (exposure comparisons) are presented in the following two tables.

Table 54: Olmesartan PK measures in drug interaction study

Olmesartan	Treatment A N = 34	Treatment B N = 35
AUC_{0-t} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	6134.4 ± 1676.74 5938.7 (25.8%)	6399.5 ± 1816.81 6068.9 (38.3%)
AUC_{0-inf} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	6249.8 ± 1678.98 6055.8 (25.5%)	6501.9 ± 1837.56 6189.9 (35.8%)
C_{max} (ng/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	912.5 ± 305.57 871.2 (30.7%)	1016.3 ± 317.94 957.4 (40.2%)
T_{max} (h) Median (Min, Max)	1.983 (1.00, 4.00)	1.983 (1.00, 3.00)
$t_{½}$ (h) Arithmetic Mean ±SD	17.394 ± 7.8206	16.257 ± 8.6458
CL/F (L/h) Arithmetic Mean ±SD	6.804 ± 1.6651	6.958 ± 3.6439

Table 55: Olmesartan PK statistical comparisons in drug interaction study

	Geometric LSMEANS				
PK Parameter	**Treatment A (Test)**	**Treatment B (Reference)**	**Ratio of LSMEANS (%) (A/B)**	**90% C.I. for Ratio (%)**	**Intra-Subject CV (%)**
AUC_{0-inf}	5989	6184	96.84	(89.14, 105.20)	20.2
AUC_{0-t}	5876	6068	96.83	(88.49, 105.96)	22.0
C_{max}	866.2	954.1	90.79	(83.24, 99.01)	21.1

Source: Table 14.2.1.1.7
LSMEANS are the least squares means from ANOVA
Treatment A: Benicar HCT 40 mg/25mg (Olmesartan 40 mg and Hydrochlorothiazide 25 mg Combination) Tablet Plus Norvasc 10 mg (Oral Amlodipine Besylate) Tablet
Treatment B: Benicar HCT 40 mg/25 mg (Olmesartan 40 mg and Hydrochlorothiazide 25 mg Combination) Tablet

The relevant 90% confidence intervals were within the equivalence region [80.0 – 125.0 %] indicating that olmesartan PK in the fixed dose combination (Benicar HCT®) is not affected by the co-administration of amlodipine.

The statistical analysis of olmesartan Tmax is presented in the following table.

Table 56: Olmesartan Tmax comparisons in drug interaction study

Olmesartan	Median		Difference (A – B)	90% CI (Lower , Upper)
	Treatment A	Treatment B		
T_{max} (h)	1.983	1.983	0.008	(-0.250 , 0.259)

The statistical analysis indicated that olmesartan Tmax values were comparable for both treatments.

Amlodipine Pharmacokinetics

The mean amlodipine plasma concentration-time profiles in the drug interaction study treatments were similar with overlapping standard deviations (figure not shown), and PK measures were comparable. The amlodipine PK measures and associated statistical analysis (exposure comparisons) are presented in the following two tables.

Table 57: Amlodipine PK measures in drug interaction study

Amlodipine	Treatment A N = 33*	Treatment C N = 34
AUC_{0-t} (ng.h/mL)		
Arithmetic Mean ±SD	339.1 ± 89.12	334.7 ± 95.38
Geometric Mean (CV%)	327.7 (27.5%)	321.3 (30.1%)
AUC_{0-inf} (ng.h/mL)		
Arithmetic Mean ±SD	381.9 ±112.01	378.3 ± 126.45
Geometric Mean (CV%)	365.8 (31.0%)	358.6 (34.2%)
C_{max} (ng/mL)		
Arithmetic Mean ±SD	7.456 ±1.9622	7.013 ± 2.0320
Geometric Mean (CV%)	7.224 (25.7%)	6.747 (28.7%)
T_{max} (h)		
Median (Min, Max)	7.017 (5.98, 12.0)	7.000 (5.97, 12.0)
$t_{½}$ (h)		
Arithmetic Mean ±SD	45.18 ±12.802	44.11 ± 12.909
CL/F (L/h)		
Arithmetic Mean ±SD	28.63 ± 9.356	29.43 ± 10.022

Source: Tables 14.2.1.2.3 and 14.2.1.2.5

Treatment A: Benicar HCT 40 mg/25 mg (Olmesartan 40 mg and Hydrochlorothiazide 25 mg Combination) Tablet Plus Norvasc 10 mg (Oral Amlodipine Besylate) Tablet

Treatment C: Norvasc 10 mg (Oral Amlodipine Besylate) Tablet

*N = 32 for the AUC_{0-inf}, $t_{½}$ and CL/F variables

Table 58: Amlodipine PK statistical exposure comparisons in drug interaction study

	Geometric LSMEANS			
PK Parameter	**Treatment A (Test)**	**Treatment C (Reference)**	**Ratio of LSMEANS (%) (A/C)**	**90% C.I. for Ratio (%)**
$AUC_{0\text{-}inf}$	365.6	361.8	101.05	(95.89, 106.49)
$AUC_{0\text{-}t}$	328.4	324.6	101.19	(96.71, 105.87)
C_{max}	7.186	6.768	106.18	(101.97, 110.56)

Source: Table 14.2.1.2.7
LSMEANS are the least squares means from ANOVA
Treatment A: Benicar HCT 40 mg/25mg (Olmesartan 40 mg and Hydrochlorothiazide 25 mg Combination) Tablet Plus Norvasc 10 mg (Oral Amlodipine Besylate) Tablet
Treatment C: Norvasc 10 mg (Oral Amlodipine Besylate) Tablet

The relevant 90% confidence intervals were within the equivalence region [80.0 – 125.0 %] indicating that the pharmacokinetics of amlodipine are not affected by the fixed dose combination (Benicar HCT®).

The statistical analysis of amlodipine Tmax values are presented in the following table.

Table 59: Amlodipine Tmax comparisons in drug interaction study

Amlodipine	**Median**		**Difference (A – C)**	**90% CI (Lower , Upper)**
	Treatment A	**Treatment C**		
T_{max} (h)	7.017	7.000	0.008	(-0.483, 0.508)

Source: Table 14.2.1.2.8
Treatment A: Benicar HCT 40 mg/25 mg (Olmesartan 40 mg and Hydrochlorothiazide 25 mg Combination) Tablet Plus Norvasc 10 mg (Oral Amlodipine Besylate) Tablet
Treatment C: Norvasc 10 mg (Oral Amlodipine Besylate) Tablet

The statistical analysis indicates that amlodipine Tmax values are comparable for both treatments.

Hydrochlorothiazide Pharmacokinetics

The mean HCT plasma concentration-time profiles in the drug interaction study treatments were similar with overlapping standard deviations (figure not shown), and PK measures were comparable. The HCT PK measures and associated statistical analysis (exposure comparisons) are presented in the following two tables.

Table 60: HCT PK measures in drug interaction study

Hydrochlorothiazide	Treatment A N = 34	Treatment B N = 35
AUC_{0-t} (ng.h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	 1043.4 ± 224.90 1020.7 (21.6%)	 1052.7 ± 231.13 1021.8 (27.4%)
AUC_{0-inf} (ng.h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	 1069.3 ± 224.78 1047.1 (21.0%)	 1079.8 ± 229.12 1050.9 (25.8%)
C_{max} (ng/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	 161.51 ± 53.714 153.90 (31.8%)	 164.78 ± 57.837 155.34 (37.0%)
T_{max} (h) Median (Min, Max)	 1.5000 (0.983, 4.00)	 1.5000 (0.983, 4.00)
$t_{½}$ (h) Arithmetic Mean ±SD	 10.800 ± 1.4435	 10.866 ± 2.0647
CL/F (L/h) Arithmetic Mean ±SD	 24.38 ± 5.164	 24.70 ± 8.513

Source: Tables 14.2.1.3.3 and 14.2.1.3.5
Treatment A: Benicar HCT 40 mg/25 mg (Olmesartan 40 mg and Hydrochlorothiazide 25 mg Combination) Tablet Plus Norvasc 10 mg (Oral Amlodipine Besylate) Tablet
Treatment B: Benicar HCT 40 mg/25 mg (Olmesartan 40 mg and hydrochlorothiazide 25 mg Combination) Tablet

Table 61: HCT PK statistical exposure comparisons in drug interaction study

	Geometric LSMEANS			
PK Parameter	**Treatment A (Test)**	**Treatment B (Reference)**	**Ratio of LSMEANS (%) (A/B)**	**90% C.I. for Ratio (%)**
AUC_{0-inf}	1051	1050	100.06	(95.01, 105.39)
AUC_{0-t}	1025	1021	100.33	(94.93, 106.05)
C_{max}	154.9	155.1	99.89	(91.97, 108.48)

Source: Table 14.2.1.3.7
LSMEANS are the least squares means from ANOVA
Treatment A: Benicar HCT 40 mg/25mg (Olmesartan 40 mg and Hydrochlorothiazide 25 mg Combination) Tablet Plus Norvasc 10 mg (Oral Amlodipine Besylate) Tablet
Treatment B: Benicar HCT 40 mg/25 mg (Olmesartan 40 mg and Hydrochlorothiazide 25 mg Combination) Tablet

The relevant 90 % CIs fell within the equivalence region [80 – 125] indicating that HCT PK are not affected by co-administration of amlodipine, when HCT is administered as Benicar HCT.

The statistical analysis for HCT Tmax is presented in the following table.

Table 62: HCT Tmax comparisons in drug interaction study

Hydrochlorothiazide	Median		Difference (A – B)	90% CI (Lower , Upper)
	Treatment A	Treatment B		
T_{max} (h)	1.500	1.500	-0.242	(-0.492, 0.008)

Source: Table 14.2.1.3.8
Treatment A: Benicar HCT 40 mg/25 mg (Olmesartan 40 mg and Hydrochlorothiazide 25 mg Combination) Tablet Plus Norvasc 10 mg (Oral Amlodipine Besylate) Tablet
Treatment B: Benicar HCT 40 mg/25 mg (Olmesartan 40 mg and Hydrochlorothiazide 25 mg Combination) Tablet

The statistical analysis indicates that the HCT Tmax values were comparable for both treatments.

Applicant's Safety Highlights:

No serious or severe adverse event (AE) occurred during this study, and no subject was withdrawn from the study due to an AE. Overall, 16 subjects (44.4%) reported 62 treatment-emergent AEs (TEAEs). Fifty-seven (57) of the TEAEs were mild (91.9%) and 5 were moderate (8.1%). No TEAEs were considered definitely or probably drug-related. Twenty-nine (46.8%) were considered possibly treatment-related, 11 (17.7%) were considered unlikely related, while the remaining 22 (35.5%) were considered unrelated to the study medication.

Conclusions

- The pharmacokinetics of olmesartan in the fixed dose combination (Benicar HCT®) are not affected by the co-administration of amlodipine.
- The pharmacokinetics of amlodipine are not affected by the fixed dose combination (Benicar HCT®).
- The pharmacokinetics of hydrochlorothiazide in the fixed dose combination (Benicar HCT®) are not affected by the co-administration of amlodipine.

Recommendation

The labeling should reflect the findings form the drug-drug interaction study as outlined in the conclusions above.

4.3 Pharmacometrics Review

APPEARS THIS WAY ON ORIGINAL

Office of Clinical Pharmacology: Pharmacometric review

Application Number	NDA 200175
Submission Number (Date)	30 Sep 2009
Drug Name	Olmesartan, Amlodipine, HCTZ (Tribenzor)
Proposed Indication	Treatment of hypertension
Clinical Division	Division of Cardiovascular and Renal Products
Primary CP Reviewer	Robert O Kumi, Ph.D.
Primary PM Reviewer	Jiang Liu, Ph.D.
Secondary CP Reviewer	Rajanikanth Madabushi, Ph.D.
Secondary PM Reviewer	Pravin Jadhav, Ph.D.
Sponsor	Daiichi Sankyo

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions.

Are the dose-response (blood pressure) predictions in the proposed label reasonable?

No. Although the original tables illustrating predicted placebo-adjusted blood pressure lowering effects of the various combinations were considered reasonable, the predictions correspond to the use of Olmesartan+Amlodipine+Hydrochlorthiazide (Olm+Alm+HCTZ) as initial therapy (Table 63). Olm+Alm+HCTZ is indicated to be used as an add-on therapy to existing double combination therapy or modifying the existing triple combination therapy for patients without adequate reduction in blood pressure. The revised tables (requested by the reviewer) reflected the proposed clinical scenario. However, the observed data from the open-label study, which is closest to the desired clinical scenario, did not support the predicted titration effects (Table 64). Also, the model used for predictions was not sensitive to different clinical indications reflected in table 63 (initial therapy) and table 64 (add on therapy). The predictions were identical for both scenarios.

Table 63. Comparison among the predicted placebo-adjusted blood pressure lowering effects of CS-8635, the observed data and the previous labels

(a) Based on adding HCTZ to Azor

Placebo-Adjusted Changes in Sitting Systolic/Diastolic Blood Pressure (mmHg)

Azor (AML/OM)	HCTZ								
	0 mg			12.5 mg			25 mg		
	Simulated	Observed	Azor Label	Simulated	Observed	Benicar HCT Label	Simulated	Observed	Benicar HCT Label
0 mg	-/-	-/-	-/-	-7.8/-2.4	-5.7/-1.8	-5/-1	-15.6/-4.9	-14.7/-5.4	-14/-5
5/20 mg	-21.8/-11	-20.6/-10.9	-20/-11	-25.7/-12.8			N/A	N/A	N/A
5/40 mg	-23.5/-12	-23.4/-12.7	-22/-13	-27.4/-13.9			-31.2/-15.8		
10/40 mg	27.3/-14.2	-27.7/16.1 -26.9/-14*	-26/-16	-30.5/-15.8			-33.7/-17.4	-33.9/-17.7*	

N/A: not applicable; * adjusted with the model estimated placebo effect in Study CS8635-A-U301

(b) Based on adding amlodipine to Benicar HCT

Placebo-Adjusted Changes in Sitting Systolic/Diastolic Blood Pressure (mmHg)

Benicar HCT (OM/HCTZ)	AML								
	0 mg			5 mg			10 mg		
	Simulated	Observed	Benicar HCT Label	Simulated	Observed	Azor Label	Simulated	Observed	Azor Label
0 mg	-/-	-/-	-/-	-13.6/-6.7	-12.5/-6.6	-12/-7	-18.2/-10.1	-17.4/-9.9	-16/-10
20/12.5 mg	-17.7/-8.7	-18.4/-8.3	-17/-8	-26.4/-12.8			N/A	N/A	N/A
40/12.5 mg	-19.7/-10.1	-17.5/-10.9	-16/-10	-27.4/-13.9			-30.5/-15.8		
40/25 mg	-25.2/-12.6	-24.9/-14.4 -27/-12.7*	-24/-14	-31.2/-15.8			-33.7/-17.4	-33.9/-17.7*	

N/A: not applicable; * adjusted with the model estimated placebo effect in Study CS8635-A-U301

Table 64. Comparison of the titration effect in change in blood pressure (mmHg) between the prediction based on the model and the observation based on the open label study

Parameter	OM40/AML5/HCTZ12.5 To OM40/AML5/HCTZ25		OM40/AML5/HCTZ12.5 To OM40/AML10/HCTZ12.5		OM40/AML5/HCTZ25 To OM40/AML10/HCTZ25		OM40/AML10/HCTZ12.5 To OM40/AML10/HCTZ25	
	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted
Change in Diastolic Blood Pressure								
n [1]	604		639		360		383	
Mean (SD)	-2.9 (8.32)	-1.81	-4.4 (8.67)	-1.93	-5.7 (9.41)	-1.68	-5.0 (9.06)	-1.58
Change in Systolic Blood Pressure								
n [1]	604		639		360		383	
Mean (SD)	-5.9 (13.62)	-3.85	-6.8 (13.25)	-3.29	-9.9 (14.99)	-2.58	-10.2 (13.78)	-3.15

Observed titration effect was calculated as blood pressure at last visit on new dose regimen minus blood pressure at last visit of previous regimen in the current open label study.

The approval is based on a successful pivotal Phase 3 study (CS8635-A-U301) that demonstrated superiority of the triple fixed-dose combination of olmesartan (OM), amlodipine (AML), and hydrochlorothiazide (HCTZ) compared to the highest strengths of the dual combinations in lowering blood pressure as initial therapy. Figure 10 shows that: 1) at any targeted clinical relevant blood pressure reduction the responder rate in the triple therapy is higher than the dual therapies and 2) the median blood pressure reduction in the triple therapy is clearly better than the dual therapies. The final population PK models and exposure-response models for blood pressure reduction as initial therapy are generally reasonable based on:

- the goodness of fits, precision of parameter estimates (Table 67-

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Table 71),

- good agreement between the observed data and the model-predicted blood pressure lowering effects of the various tested combinations of the three compounds (

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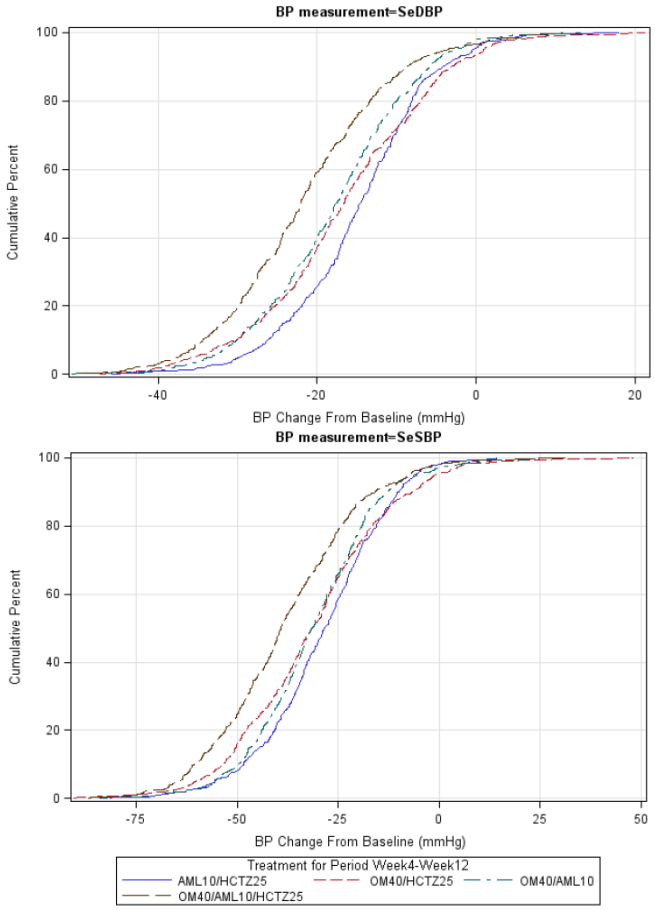
Table 72-Table 73),

- knowledge of the primary elimination pathways of three compounds, and
- consistency of predictions with the results of the previous studies.

Figure 10. The cumulative percent of diastolic (top) and systolic (bottom) blood pressure change from baseline for the triple and dual combination therapies



Recommendations

The population PK and exposure-response analyses for blood pressure reduction as initial therapy are generally reasonable. However, the (b) (4) dose-response prediction (b) (4) is not acceptable (b) (4) A statement indicating the dose-dependent increase in the blood pressure lowering effect of the triple combination products is more appropriate:

"All of the dose strengths of the triple combination are expected to provide superior blood pressure lowering effects compared to their respective mono and dual combination components. The order of the blood pressure lowering effects among the different dose strengths of the triple combination is expected to be 20/5/12.5<40/5/12.5<(40/10/12.5≈40/5/25)<40/10/25 [OM/AML/HCTZ]."

Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

Pertinent regulatory background

Olmesartan (OM), amlodipine (AML), and hydrochlorothiazide (HCTZ) are approved for the treatment of hypertension. The dual combination tablets Benicar HCTZ (OM and HCTZ) and Azor (OM and AML) are also approved.

In this application, the sponsor submitted a pivotal study to support the registration of fixed-dose triple combinations of OM, AML, and HCTZ. Population exposure-response analysis was conducted to establish relationship between the mono, dual, and triple combination doses and change from baseline in blood pressure. The analysis used data from three clinical development programs: CS-8635 (OM 40 mg + AML 10 mg + HCTZ 25 mg), CS-866 (OM+HCTZ), and CS-8663 (OM+AML). The model was used to predict change from baseline in blood pressure. The sponsor intends to include predicted values in the proposed label to interpolate information for the clinically unevaluated to-be-marketed triple combination dosages (OM 20 mg + AML 5 mg + HCTZ 12.5 mg, OM 40 mg + AML 5 mg + HCTZ 12.5 mg, OM 40 mg + AML 10 mg + HCTZ 12.5 mg, and OM 40 mg + AML 5 mg + HCTZ 25 mg) (see RESULTS OF SPONSOR'S ANALYSIS and APPENDIX for the details of studied doses and observed versus predicted response values).

Results of Sponsor's Analysis

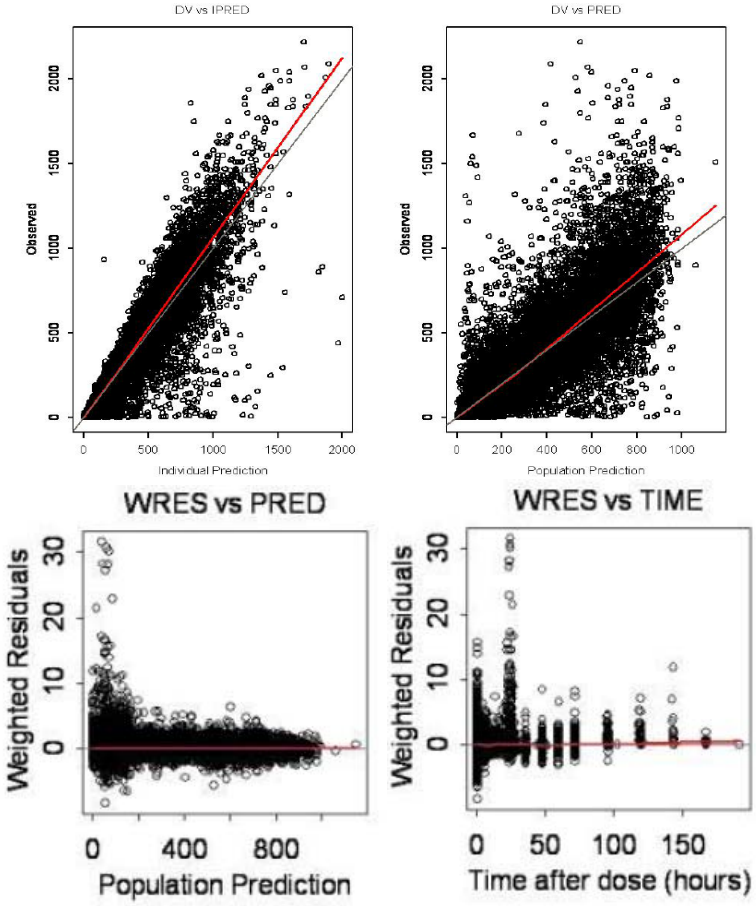
Population exposure-response analysis

Population PK analysis used data from three clinical development programs: CS-866 (OM+HCTZ), CS-8663 (OM+AML), and CS-8635 (OM+AML+HCTZ). The dataset contained a total of thirteen Phase 1 studies: three studies from the CS-866 program (866-126, 866-127, 866-134), four studies from the CS-8663 program (CS8663-AU101, CS8663-A-U110, CS8663-A-U111, CS8663-A-U112), and six studies from the CS8635 program (CS8635-A-U101, CS8635-A-U102, CS8635-A-U103, CS8635-A-U104, CS8635-A-E105, and CS8635-A-U106). The dataset also contained two Phase 3 studies (CS8663-A-U301 and CS8635-A-U301). The modeling population included 492 healthy volunteers (349 male, 143 female) from Phase 1 trials and 1512 patients (800 male, 712 female) with mild to severe hypertension from the Phase 3 trials.

- The final OM PK model was a two-compartment model with an absorption time lag. For clearance, renal function as measured by creatinine clearance (mL/min) was a clinically significant covariate. Body weight is significant covariate for central and peripheral volumes of the distributions.
- The final AML PK model was a two-compartment model with an absorption time lag. For clearance, age was a covariate. Body weight is significant covariate for central and peripheral volumes of the distributions.
- The final HCTZ PK model was a two-compartment model with an absorption time lag. Clearance was affected by sex, renal function as measured by creatinine clearance, and age. Body weight is significant covariate for central and peripheral volumes of the distributions.

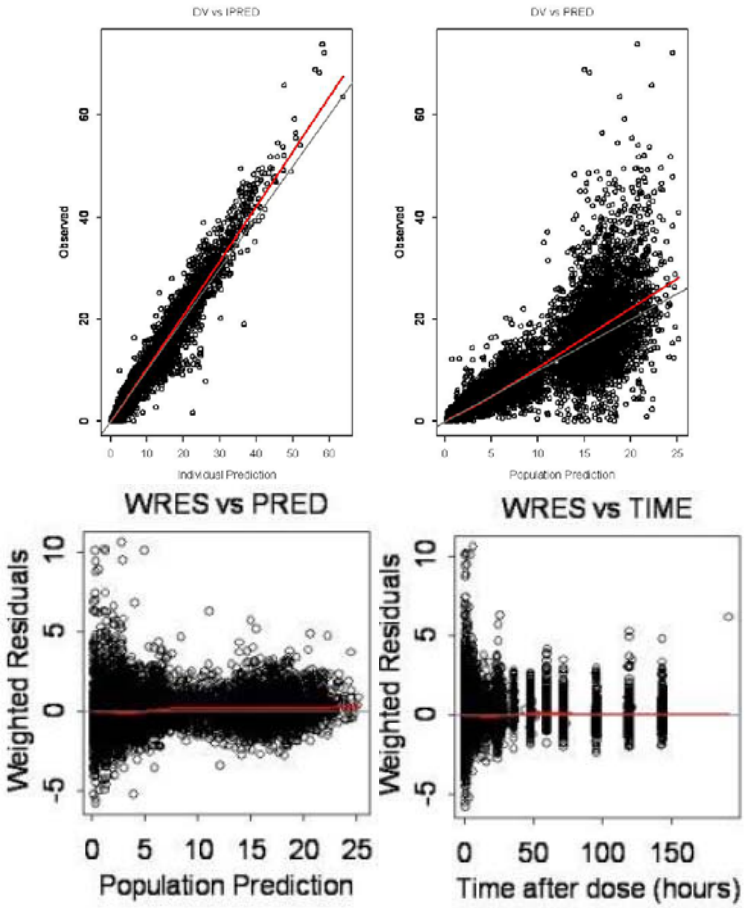
The goodness-of-fit plots for the final popPK model are displayed in Figure 11 to Figure 13.

Figure 11. Goodness-of-fit plots for the final olmesartan medoximil population pharmacokinetic model [line of unity (grey line) and trend line (red line)]



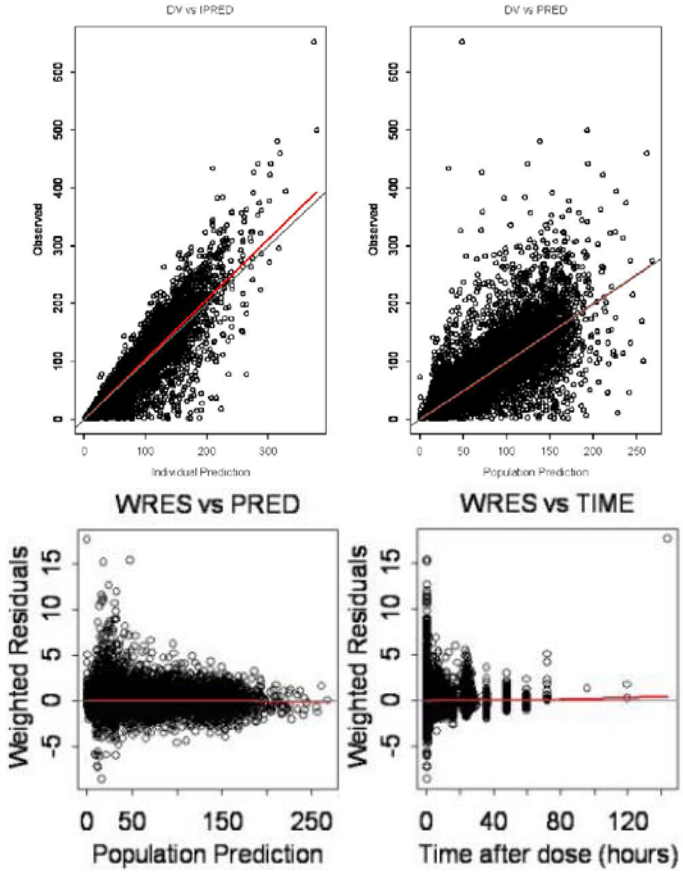
Source: Sponsor's Population PK Analysis Report: Figure 8-9, page 87, 88

Figure 12. Goodness-of-fit plots for the final amlodipine population pharmacokinetic model [line of unity (grey line) and trend line (red line)]



Source: Sponsor's Population PK Analysis Report: Figure 15-16, page 94, 95

Figure 13. Goodness-of-fit plots for the final hydrochlorothiazide population pharmacokinetic model [line of unity (grey line) and trend line (red line)]



Source: Sponsor's Population PK Analysis Report: Figure 22-23, page 101, 102

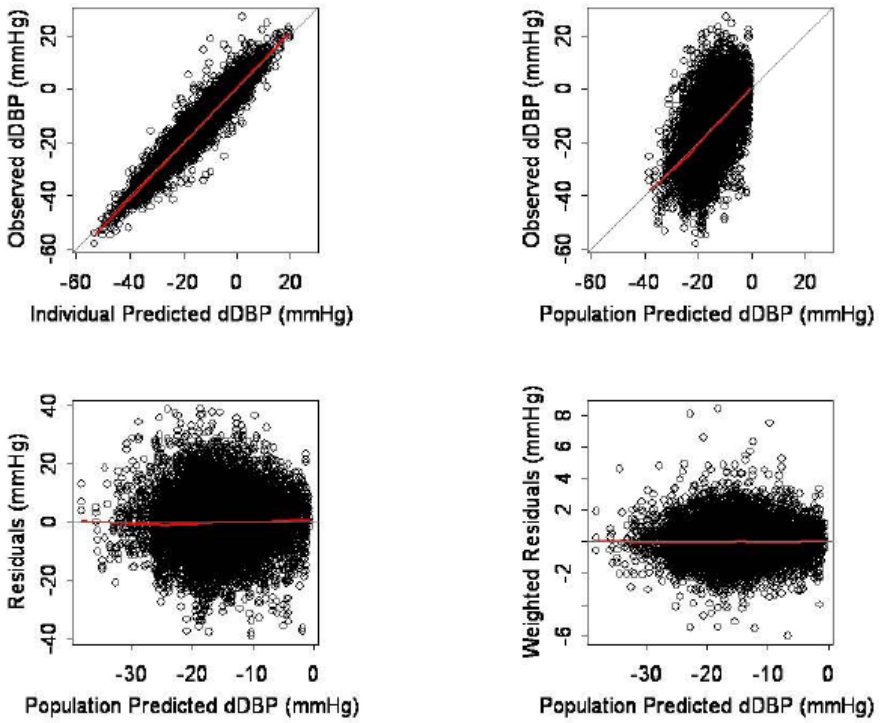
The exposure-response analysis for change from baseline in blood pressure used data from the pivotal Phase 3 studies from the three clinical development programs: 866-318 (OM+HCTZ), CS8663-A-U301 (OM+AML), and CS8635-A-U301 (OM+AML+HCTZ) (see APPENDIX for the dose details). In Study CS8635-A-U301 and CS8663-A-U301, PK samples were taken for approximately one-third of the patients. In Study 866-318, no PK samples were taken for the patients. The exposure-response population included 4873 subjects (2625 male, 2248 female) with mild to severe hypertension. For subjects in CS8663-A-U301 and CS8635-A-U301 who had PK sampling, model predicted individual-specific exposures from the population pharmacokinetic model were utilized in the exposure-response analysis. For subjects in CS8663-A-U301 and CS8635-AU301 who did not have PK sampling, and for all patients in 866-318, none of whom had PK sampling, model-predicted covariate-adjusted median exposures from the population pharmacokinetic model were used. The systemic exposures, AUC_{OM}, AUC_{AML}, and AUC_{HCTZ}, were used in the analysis (see APPENDIX for the modeling details).

- The BP lowering effects of olmesartan medoxomil and amlodipine were described by an E_{max} model [MonoResponse=E_{max}*Predictor/(Predictor+EC_{50})], whereas the drug effect for hydrochlorothiazide was described by a linear model [MonoResponse = slope*Predictor].
- The interaction terms of dual and triple combinations were added to the respective response equations: Response = Placebo + MonoResponse + Interaction

- Mean placebo effect was a scalar value that varied by study. The effect was larger in subjects with higher baseline. For diastolic BP change, Placebo effect was larger in subjects of more advanced age, and smaller in subjects of Black Race within study CS8663-A-U301. For systolic BP change, Placebo effect was smaller in subjects of more advanced age, and smaller in subjects of Hispanic ethnicity within study CS8635-AU301.
- For diastolic blood pressure, black population showed smaller blood pressure lowering effects compared to the other population. Patients with higher baseline blood pressure showed stronger exposure response for OM and AML. For OM, elderly population showed less exposure-response. For AML, heavier population showed less exposure-response.
- For systolic blood pressure, black population showed smaller blood pressure lowering effects compared to the other population. Patient with higher baseline blood pressure showed stronger exposure response for all of the three drugs. For AML, heavier population showed weaker exposure-response and female population showed stronger exposure response.

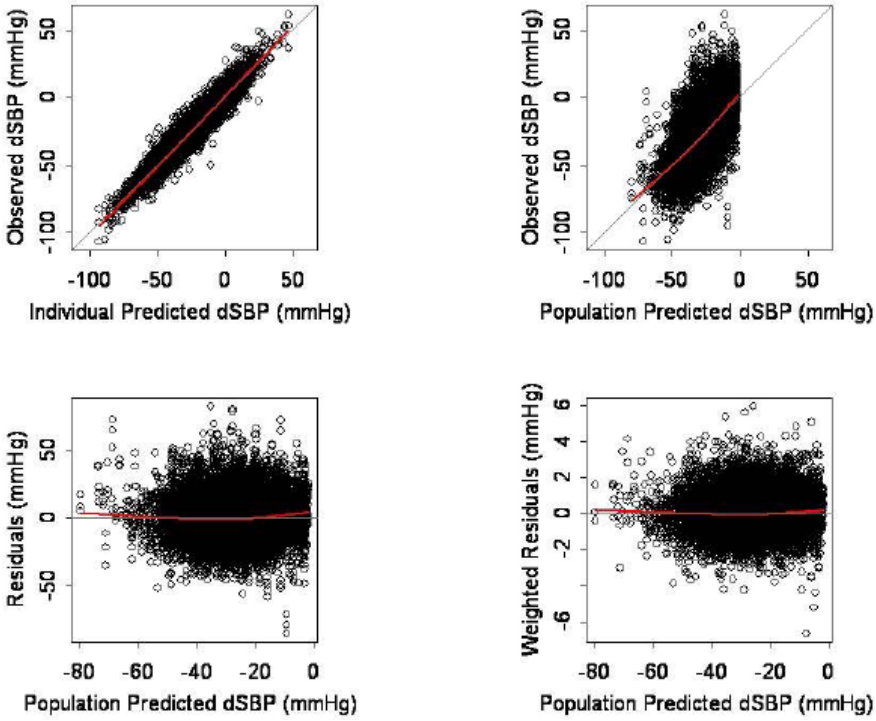
The goodness-of-fit plots for the final population exposure-response model are displayed in Figure 14 and Figure 15.

Figure 14. Goodness-of-fit plots for the final population DBP model [line of unity (grey line) and trend line (red line)]



Source: Sponsor's Population PK Analysis Report: Figure 29b, page 110

Figure 15. Goodness-of-fit plots for the final population SBP model [line of unity (grey line) and trend line (red line)]



Source: Sponsor's Population PK Analysis Report: Figure 35b, page 123

Reviewer's Comments:

The sponsor conducted a comprehensive population exposure-response analysis. The final population PK models and exposure-response models for blood pressure reduction are generally reasonable based on

- *the goodness of fits, precision of parameter estimates (Table 67-*

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Table 71),

- *good agreement between the observed data and the model-predicted blood pressure lowering effects of the various tested combinations of the three compounds (*

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Table 72-Table 73),

- *knowledge of the primary elimination pathways of three compounds, and*
- *consistency of predictions with the results of the previous studies.*

The model is robust across the studies and analyzed populations, once the study-specific placebo effect was accounted for.

Model based simulation of the to-be-marketed dose strengths of CS-8635

The model was used to simulate all possible combinations of dosages in mono-, dual combo-, and triple combo-therapy. All subjects (N=2458) from CS8635-A-U301 were used in the simulation for each study arm, with particular attention on triple combinations intended to be marketed but not tested in the Phase 3 study. The predicted changes from baseline in blood pressure for Azor + HCTZ and Benicar HCT + Aml are shown in Table 65 with clinically unevaluated triple combinations highlighted in yellow. The order of the model predicted change from baseline in diastolic and systolic blood pressures for to-be-marketed CS-8635 formulations was 20/5/12.5 < 40/5/12.5 < (40/10/12.5 ≈ 40/5/25) < 40/10/25 [OM/AML/HCTZ mg].

Table 65. Predicted blood pressure lowering effects of Olm + Aml + HCTZ with particular attention on triple combinations not tested in the Phase 3 study (highlighted in yellow)

(a) Azor + HCTZ

Azor (AML/OM)	HCTZ 0 mg dSeDBP Mean (SD)	HCTZ 0 mg dSeSBP Mean (SD)	HCTZ 12.5 mg dSeDBP Mean (SD)	HCTZ 12.5 mg dSeSBP Mean (SD)	HCTZ 25 mg dSeDBP Mean (SD)	HCTZ 25 mg dSeSBP Mean (SD)
0 mg	-4.0 (9.2)	-4.7 (15.2)	-6.4 (9.3)	-12.5 (15.7)	-8.9 (9.4)	-20.3 (16.9)
5/20 mg	-15.0 (9.7)	-26.5 (16.6)	-16.8 (9.7)	-30.4 (16.8)	N/A	N/A
5/40 mg	-16.0 (9.7)	-28.2 (16.7)	-17.9 (9.7)	-32.1 (16.8)	-19.8 (9.8)	-35.9 (17.0)
10/40 mg	-18.2 (9.9)	-32.0 (17.1)	-19.8 (9.9)	-35.2 (17.1)	-21.4 (9.9)	-38.4 (17.2)

N/A = not applicable; SD = standard deviation.

(b) Benicar HCT + Aml

Benicar HCT (OM/HCTZ)	AML 0 mg dSeDBP Mean (SD)	AML 0 mg dSeSBP Mean (SD)	AML 5 mg dSeDBP Mean (SD)	AML 5 mg dSeSBP Mean (SD)	AML 10 mg dSeDBP Mean (SD)	AML 10 mg dSeSBP Mean (SD)
0 mg	-4.0 (9.2)	-4.7 (15.2)	-10.7 (9.8)	-17.6 (16.5)	-14.1 (10.2)	-22.9 (17.4)
20/12.5 mg	-12.7 (9.4)	-22.4 (16.0)	-16.8 (9.7)	-30.4 (16.8)	N/A	N/A
40/12.5 mg	-14.1 (9.5)	-24.4 (16.1)	-17.9 (9.7)	-32.1 (16.8)	-19.8 (9.9)	-35.2 (17.1)
40/25 mg	-16.6 (9.6)	-29.9 (16.7)	-19.8 (9.8)	-35.9 (17.0)	-21.4 (9.9)	-38.4 (17.2)

N/A = not applicable; SD = standard deviation.

Source: Sponsor's Annotated Label: Section 14 CLINICAL STUDIES, page 32-33

Reviewer's comments:

The predicted changes in blood pressure at the clinically unevaluated to-be-marketed triple combination dosages as initial therapy, as highlighted in the Table 65, are reasonable. As discussed in the population exposure-response analysis section, the sponsor's population exposure-response model is reasonable. The model-predicted changes in blood pressure (from baseline) at various tested combinations of the three compounds are in the good agreement with the observed data across studies (

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Table 72-Table 73). The model is robust across the studies and analyzed populations, once the study-specific placebo effect was accounted for. As shown in Table 63, the predicted placebo-adjusted blood pressure lowering effects of the tested combinations are in good agreement with the observed data from different studies and are also consistent with the previous labels. The demographic characteristics of the population in the current study (CS8635-A-U301) are similar as those in previous studies (Table 66).
However, the current clinical trial was only designed to demonstrate superiority of the triple combination to the highest strengths of dual combinations by using the drugs as the first therapy. The triple combinations are not indicated for initial therapy. Therefore, as recommended by the reviewer, the sponsor calculated the add-on blood pressure lowering effect from a dual combination to a triple combination or the titration-effect from an existing triple combination to a higher dose of triple combination only for patients without adequate reduction in blood pressure under the current treatment:

1. *find the mean BP value for non-responders on AZOR treatment from the current simulation. Report the number of non-responders (N_{AZOR}) and the mean BP value; DBP=A (Step one).*
2. *find the mean BP value in the current simulation for the same N_{AZOR} non-responder on AZOR treatment when they are using AZOR+ HCTZ 12.5 (Step two: mean DBP=$B_{AZOR+HCTZ12.5}$) or AZOR+ HCTZ 25 (mean DBP= $B_{AZOR+HCTZ25}$) and report the additional effect as the difference from A for each dose level ($B_{AZOR+HCTZ12.5}$-A and $B_{AZOR+HCTZ25}$-A);*
3. *record the number of non-responders ($N_{AZOR+HCTZ12.5}$) on AZOR+ HCTZ 12.5 and the number of non-responders ($N_{AZOR+HCTZ25}$) on AZOR+ HCTZ 25 from N_{AZOR} non-responders on AZOR treatment ($N_{AZOR+HCTZ12.5}$ and $N_{AZOR+HCTZ25}$ will be subsets of N_{AZOR});*
4. *find the mean BP value in the current simulation for the same $N_{AZOR+HCTZ12.5}$ non-responders on AZOR+ HCTZ 12.5 (mean DBP=$C_{AZOR+HCTZ12.5}$) and the corresponding value when they are using AZOR+ HCTZ 25 (Step three: mean DBP= $C_{AZOR+HCTZ25}$) and record the additional effect as the difference between these two values ($C_{AZOR+HCTZ25}$- $C_{AZOR+HCTZ12.5}$). Report the number of non-responders on AZOR+ HCTZ 25 ($N_{AZOR+HCTZ25}$") through two-step up-titration.*

However, the observed data from the open-label study, which is closest to the desired clinical scenario, did not support the predicted titration effects (Table 64). Also, the model used for predictions was not sensitive to different clinical indications reflected in table 63 (initial therapy) and table 64 (add on therapy). The predictions were identical for both scenarios. Therefore, a generic statement indicating the dose-dependent increase in the blood pressure lowering effect of the triple combination products is more appropriate:
"All of the dose strengths of the triple combination are expected to provide superior blood pressure lowering effects compared to their respective mono and dual combination components. The order of the blood pressure lowering effects among the different dose strengths of the triple combination is expected to be 20/5/12.5<40/5/12.5<(40/10/12.5≈40/5/25)<40/10/25 [OM/AML/HCTZ]."

Table 66. The demographic characteristics of the exposure-response dataset

Study	N	Base SBP [mmHg] Mean (sd)	Base DBP [mmHg] Mean (sd)	M:F	Age [y] Mean (sd)	Weight [kg] Mean (sd)	Race/Ethnicity W:B:H:A:O	Diabetic (%)
All data	4873	165 (16)	102 (6.7)	54:46	54.8 (11)	94.9 (22)	59:25:13:2:1	14.1 %

CS866-318 (OM+HCTZ)	495	154 (13)	104 (3.1)	56:44	53.5 (11)	88.1 (18)	75:12:10:2:1	8.9 %
CS8663-A-U301 (OM+AML)	1920	164 (17)	102 (5.6)	54:46	54.6 (11)	95.2 (22)	61:23:13:2:1	13.4 %
CS8635-A-U301 (OM+AML+HCTZ)	2458	169 (14)	101 (7.8)	53:47	55.2 (11)	96.1 (23)	54:29:14:2:1	15.6 %

Appendix

Table 67. Population pharmacokinetic parameter estimates for olmesartan medoxomil

Parameter	*Population Mean*		*Intersubject variability*	
	Estimate	*SE*[a] *(% CV)*	*Estimate*[b] *(%CV)*	*SE*[c] *(%)*
CL_{TYP} (L/h)	6.32	1.1	39	25
Vc (L)	36.8	1.4	26	34
Vp (L)	29.0	3.0	51	30
Ka (per h)	1.25	3.3	109	26
ALAG1 (h)	0.406	0.5	-	-
Q (L/h)	1.64	2.3	39	33
CL_{CLCR}	0.425	7.4	-	-
$Vc_{,WTKG}$	0.681	8.3	-	-
$Vp_{,WTKG}$	0.405	34	-	-
σ^2_1 (multiplicative)	0.0839	17[c]	-	-
σ^2_2 (additive) $(ng/mL)^2$	0.0627	63[c]	-	
σ^2_3 (additive CS8635-A-U301) $(ng/mL)^2$	298	49[c]	-	-

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

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

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

Source: Sponsor's Population PK Analysis Report: Table 4, page 64

Table 68. Population pharmacokinetic parameter estimates for amlodipine

Parameter	*Population Mean*		*Intersubject variability*	
	Estimate	*SE*[a] *(% CV)*	*Estimate*[b] *(%CV)*	*SE*[c] *(%)*
CL_{TYP} (L/h)	23.4	1.1	39	26
Vc (L)	1060	1.7	30	31
Vp (L)	465	2.8	17	46
Ka (per h)	0.215	2.6	38	28
ALAG1 (h)	0.315	1.7	-	-
Q (L/h)	26.6	4.1	-	-
CL_{AGE}	-0.349	7.2	-	-
$Vc_{,WTKG}$	0.285	18	-	-
σ^2_1 (multiplicative)	0.045	18[c]	-	-
σ^2_3 (additive CS8635-A-U301) $(ng/mL)^2$	1.6	44[c]	-	-

a Coefficient of variation of the estimates (100×SEestimate/estimate).

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

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

Source: Sponsor's Population PK Analysis Report: Table 6, page 67

Table 69. Population pharmacokinetic parameter estimates for hydrochlorothiazide

Parameter	*Population Mean*		*Intersubject variability*	
	Estimate	*SE*[a] *(% CV)*	*Estimate*[b] *(%CV)*	*SE*[c] *(%)*
CL_{TYP} (L/h)	20.3	1.4	30	40
V2 (L)	27.7	5.5	88	38
V3 (L)	174	1.7	24	40
Ka (per h)	0.364	2.0	18	39
ALAG1 (h)	0.419	1.6	-	-
Q (L/h)	18.3	2.0	22	43
CL_{CLCR}	0.499	9.5	-	-
CL_{SEX}	-0.219	11	-	-
CL_{AGE}	-0.214	13	-	-
$Vc_{,WTKG}$	1.92	8.8		
$Vp_{,WTKG}$	0.846	10	-	-
σ^2_1 (multiplicative Ph I)	0.0595	20	-	
σ^2_2 (multiplicative Ph III)	0.0819	43	-	-

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

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

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

Source: Sponsor's Population PK Analysis Report: Table 8, page 69

The population exposure-response model for both diastolic and systolic blood pressure

$$BP_{i,j} = BaseBP_j + PlaceboEffect_j + TreatmentEffect_j + \eta_j + \varepsilon_i$$

where,

$BP_{i,j}$ is the ith measurement within the jth subject at steady-state,

$BaseBP_j$ is the mean baseline for subject j,

$PlaceboEffect_j$ is a function of subject demographics and study,

$TreatmentEffect_j$ is a function of subject demographics and steady state exposure(s),

η_j is inter-subject variability in response, and

ε_i is residual intra-subject variability.

$$\begin{aligned} TreatmentEffect_j = {} & ER_{OM,j} + ER_{AML,j} + ER_{HCTZ,j} + \left(IOA * ER_{OM,j} * ER_{AML,j}\right) \\ & + \left(IAH * ER_{AML,j} * ER_{HCTZ,j}\right) + \left(IOH * ER_{OM,j} * ER_{HCTZ,j}\right) \\ & + \left(IOAH * ER_{OM,j} * ER_{AML,j} * ER_{HCTZ,j}\right) \end{aligned}$$

where,

$ER_{OM,j}$ is the olmesartan monotherapy model, a function of steady-state olmesartan exposure and subject demographics,

$ER_{AML,j}$ is the amlodipine monotherapy model, a function of steady-state amlodipine exposure and subject demographics,

$ER_{HCTZ,j}$ is the hydrochlorothiazide monotherapy, a function of steady-state hydrochlorothiazide exposure and subject demographics,

IOA is a scalar parameter for modeling the interaction in olmesartan and amlodipine combination therapy,

IAH is a scalar parameter for modeling the interaction in amlodipine and hydrochlorothiazide combination therapy,

IOH is a scalar parameter for modeling the interaction in olmesartan and hydrochlorothiazide combination therapy, and

IOAH is a scalar parameter for modeling the interaction in triple combination therapy.

For seated diastolic blood pressure:

$$PlaceboEffect_j =$$

$$\begin{Bmatrix} -3.80*(StudyCS8635\_A\_U301) \\ -3.57*(1-0.607*Black)*(StudyCS8663\_A\_U301) \\ -6.08*(Study866\_318) \end{Bmatrix} * \left(\frac{age}{54.8}\right)^{1.37} * \left(\frac{BaselineDBP_j}{101}\right)^{3.19}$$

$$TreatmentEffect_j = ER_{OM,j} + ER_{AML,j} + ER_{HCTZ,j} + \left(0.0430*ER_{OM,j}*ER_{AML,j}\right)$$
$$+\left(0.0747*ER_{AML,j}*ER_{HCTZ,j}\right) + \left(0.00512*ER_{OM,j}*ER_{AML,j}*ER_{HCTZ,j}\right)$$

$$ER_{OM,j} = \left(\frac{-10.5*AUC_{ss,OM,j}}{1850+AUC_{ss,OM,j}}\right)*(1-0.263*Black)*\left(\frac{age_j}{54.8}\right)^{-0.818} * \left(\frac{DBP_{Base,j}}{101}\right)^{2.46}$$

$$ER_{AML,j} = \left(\frac{-19.3*AUC_{ss,AML,j}}{453+AUC_{ss,AML,j}}\right)*\left(\frac{weight_j}{95.2}\right)^{-0.830} * \left(\frac{DBP_{Base,j}}{101}\right)^{4.12}$$

$$ER_{HCTZ,j} = -3.3*\frac{AUC_{ss,HCTZ,j}}{1000}$$

For seated systolic blood pressure:

$$PlaceboEffect_j =$$

$$\begin{Bmatrix} -4.20*(1-0.554*Hispanic)*(StudyCS8635\_A\_U301) \\ -3.45*(StudyCS8663\_A\_U301) \\ -5.26*(Study866\_318) \end{Bmatrix} * \left(\frac{age}{54.8}\right)^{-0.746} * \left(\frac{BaselineSBP_j}{164}\right)^{4.08}$$

$$TreatmentEffect_j = ER_{OM,j} + ER_{AML,j} + ER_{HCTZ,j} + \left(0.0182*ER_{OM,j}*ER_{AML,j}\right)$$
$$+\left(0.0263*ER_{AML,j}*ER_{HCTZ,j}\right) + \left(0.0195*ER_{OM,j}*ER_{HCTZ,j}\right)$$
$$+\left(0.000736*ER_{OM,j}*ER_{AML,j}*ER_{HCTZ,j}\right)$$

$$ER_{OM,j} = \left(\frac{-18.8*AUC_{ss,OM,j}}{1590+AUC_{ss,OM,j}}\right)*(1-0.393*Black)*\left(\frac{SBP_{Base,j}}{164}\right)^{1.96}$$

$$ER_{AML,j} = \left(\frac{-23.1*AUC_{ss,AML,j}}{309+AUC_{ss,AML,j}}\right)*\left(\frac{weight_j}{95.2}\right)^{-0.586} *(1+0.301*female)*\left(\frac{SBP_{Base,j}}{164}\right)^{3.65}$$

$$ER_{HCTZ,j} = -9.38*\frac{AUC_{ss,HCTZ,j}}{1000}*\left(\frac{SBP_{Base,j}}{164}\right)^{2.82}$$

Table 70. Parameter estimates for the Final DBP model

Parameter		
	Estimate	*SE*[a] *(% CV)*
Placebo Effect (Study CS8635-A-U301) [mmHg]	-3.80	13%
Placebo Effect (Study CS8663-A-U301) [mmHg]	-3.57	13%
Placebo Effect (Study SE866-318) [mmHg]	-6.08	10%
Emax, OM [mmHg]	-10.5	11%
$EAUC_{50}$, OM [ng/mL*h]	1850	31%
Emax, AML [mmHg]	-19.3	21%
$EAUC_{50}$, AML [ng/mL*h]	453	40%
Slope HCTZ [mm Hg / (1000 ng/mL*h)]	-3.3	9%
Interaction OM*AML [1/mmHg]	0.043	10%
Interaction HCTZ*AML [1/mmHg]	0.0747	13%
Interaction OM*HCTZ [1/mmHg]	n.s.	-
Interaction OM*HCTZ*AML [1/(mmHg)^2]	0.00512	29%
Effect of baseline on Drug Effect of AML	4.12	13%
Effect of baseline on Drug Effect of OM	2.46	18%
Effect of Black Race on Placebo Effect in study CS8663-A-U301	-0.607	23%
Effect of weight on Drug Effect of AML	-0.830	15%
Effect of Black Race on Drug Effect of OM	-0.263	24%
Effect of age on Drug Effect of OM	-0.818	17%
Effect of baseline on Placebo Effect	3.19	24%
Effect of age on Placebo Effect	1.37	21%
Additive Inter-subject Variability [mmHg]	8.56[b]	16%[c]
Residual Intra-subject Variability [mmHg]	3.62[d]	18%[c]

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

[b] Square root of $ETA_{estimate}$

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

[d] Residual intra-subject variability, expressed as square root of EPS

Source: Sponsor's Population PK Analysis Report: Table 9, page 70

Table 71. Parameter estimates for the Final SBP model

Parameter		
	Estimate	*SE[a] (% CV)*
Placebo Effect (Study CS8635-A-U301) [mmHg]	-4.20	23%
Placebo Effect (Study CS8663-A-U301) [mmHg]	-3.45	25%
Placebo Effect (Study SE866-318) [mmHg]	-5.26	19%
Emax, OM [mmHg]	-18.8	12%
$EAUC_{50}$, OM [ng/mL*h]	1590	35%
Emax, AML [mmHg]	-23.1	17%
$EAUC_{50}$, AML [ng/mL*h]	309	37%
Slope HCTZ [mm Hg / (1000 ng/mL*h)]	-9.38	11%
Interaction OM*AML [1/mmHg]	0.0182	18%
Interaction HCTZ*AML [1/mmHg]	0.0263	9%
Interaction OM*HCTZ [1/mmHg]	0.0195	31%
Interaction OM*HCTZ*AML [$1/(mmHg)^2$]	0.000736	22%
Effect of baseline on Drug Effect of AML	3.65	9%
Effect of baseline on Drug Effect of OM	1.96	19%
Effect of weight on Drug Effect of AML	-0.586	18%
Effect of Black Race on Drug Effect of OM	-0.393	15%
Effect of baseline on Drug Effect of HCTZ	2.82	30%
Effect of baseline on Placebo Effect	4.08	13%
Effect of age on Placebo Effect	-0.746	28%
Effect of sex on Drug Effect of AML	0.301	20%
Effect of Hispanic Ethnicity on Placebo Effect in study CS8635-A-U301	-0.554	40%
Additive Inter-subject Variability [mmHg]	14.0[b]	16%[c]
Residual Intra-subject Variability [mmHg]	6.02[d]	15%[c]

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

[b] Square root of $ETA_{estimate}$

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

[d] Residual intra-subject variability, expressed as square root of EPS

Source: Sponsor's Population PK Analysis Report: Table 11, page 73

Table 72. The concordance of the observed data and the model predictions in DBP change from baseline, by arm within study

(a) Study CS8635-A-U301

			CS8635-A-U301	Final model	
OM Dose [mg]	**AML Dose [mg]**	**HCTZ Dose [mg]**	observed **mean (sd) dDBP [mmHg]**	Prediction ("IPRED") with individual-level variability parameter **mean (sd) dDBP [mmHg]**	Prediction ("PRED") without individual-level variability parameter **mean (sd) dDBP [mmHg]**
0	10	25	-14.8 (9.3)	-14.8 (8.3)	-15.1 (3.2)
40	0	25	-16.5 (11)	-16.5 (10)	-16.4 (3.1)
40	10	0	-17.8 (9.9)	-17.8 (9.0)	-18.1 (4.0)
40	10	25	-21.5 (11)	-21.5 (9.8)	-21.4 (3.8)

(b) Study CS8663-A-U301

			CS8663-A-U301	Final model	
OM Dose [mg]	**AML Dose [mg]**	**HCTZ Dose [mg]**	observed **mean (sd) dDBP [mmHg]**	Prediction ("IPRED") with individual-level variability parameter **mean (sd) dDBP [mmHg]**	Prediction ("PRED") without individual-level variability parameter **mean (sd) dDBP [mmHg]**
0	0	0	-3.08 (10)	-3.09 (9.1)	-3.24 (1.5)
0	10	0	-13.0 (8.6)	-13.0 (7.8)	-13.3 (4.0)
0	5	0	-9.68 (8.3)	-9.68 (7.5)	-9.78 (2.8)
10	0	0	-8.07 (10)	-8.01 (8.8)	-8.38 (2.3)
10	10	0	-16.3 (9.3)	-16.3 (8.4)	-16.0 (3.6)
10	5	0	-14.2 (7.7)	-14.2 (7.0)	-13.9 (2.9)
20	0	0	-9.11 (10)	-9.16 (9.4)	-10.0 (2.2)
20	10	0	-17.1 (8.9)	-17.1 (8.0)	-16.9 (3.4)
20	5	0	-14.0 (10)	-14.0 (9.0)	-14.5 (2.8)
40	0	0	-10.6 (11)	-10.6 (10)	-10.9 (2.3)
40	10	0	-19.2 (9.4)	-19.2 (8.4)	-18.4 (3.5)
40	5	0	-15.8 (9.0)	-15.7 (7.8)	-15.3 (2.6)

(c) Study 866-318

			866-318	Final model	
OM Dose [mg]	**AML Dose [mg]**	**HCTZ Dose [mg]**	observed **mean (sd) dDBP [mmHg]**	Prediction ("IPRED") with individual-level variability parameter **mean (sd) dDBP [mmHg]**	Prediction ("PRED") without individual-level variability parameter **mean (sd) dDBP [mmHg]**
0	0	0	-7.51 (7.8)	-7.43 (6.8)	-6.59 (1.7)
0	0	12.5	-9.28 (8.1)	-9.26 (7.2)	-9.03 (2.1)
0	0	25	-12.9 (8.5)	-12.8 (7.8)	-12.2 (2.3)
10	0	0	-12.7 (8.7)	-12.6 (7.8)	-11.6 (1.3)
10	0	12.5	-15.3 (8.3)	-15.2 (7.5)	-14.5 (1.8)
10	0	25	-18.4 (7.6)	-18.3 (6.9)	-17.4 (2.4)
20	0	0	-12.4 (8.5)	-12.5 (7.6)	-13.4 (1.5)
20	0	12.5	-15.8 (8.6)	-15.8 (7.8)	-15.9 (1.7)
20	0	25	-18.9 (7.8)	-18.9 (7.0)	-19.0 (2.4)
40	0	0	-14.4 (9.3)	-14.5 (8.3)	-15.0 (1.2)
40	0	12.5	-18.4 (8.8)	-18.3 (7.8)	-17.7 (1.4)
40	0	25	-21.9 (9.6)	-21.7 (8.7)	-20.2 (2.1)

Source: Sponsor's Population PK Analysis Report: Table 10, page 70-71

Table 73. The concordance of the observed data and the model predictions in SBP change from baseline, by arm within study

(a) Study CS8635-A-U301

			CS8635-A-U301	Final model	
OM Dose [mg]	**AML Dose [mg]**	**HCTZ Dose [mg]**	observed **mean (sd) dSBP [mmHg]**	Prediction ("IPRED") with individual-level variability parameter **mean (sd) dSBP [mmHg]**	Prediction ("PRED") without individual-level variability parameter **mean (sd) dSBP [mmHg]**
0	10	25	-29.0 (16)	-29.0 (14)	-29.7 (7.5)
40	0	25	-31.2 (19)	-31.1 (18)	-30.0 (7.6)
40	10	0	-31.1 (16)	-31.1 (15)	-31.8 (7.9)
40	10	25	-38.1 (18)	-38.1 (17)	-38.1 (8.2)

(b) Study CS8663-A-U301

			CS8663-A-U301	Final model	
OM Dose [mg]	**AML Dose [mg]**	**HCTZ Dose [mg]**	observed **mean (sd) dSBP [mmHg]**	Prediction ("IPRED") with individual-level variability parameter **mean (sd) dSBP [mmHg]**	Prediction ("PRED") without individual-level variability parameter **mean (sd) dSBP [mmHg]**
0	0	0	-2.81 (18)	-2.88 (16)	-3.89 (1.7)
0	10	0	-20.2 (17)	-20.1 (16)	-20.0 (11)
0	5	0	-15.3 (16)	-15.3 (14)	-15.1 (7.6)
10	0	0	-11.9 (17)	-11.9 (15)	-12.8 (4.3)
10	10	0	-25.8 (17)	-25.8 (16)	-25.6 (9.6)
10	5	0	-24.7 (16)	-24.6 (14)	-23.5 (8.5)
20	0	0	-13.5 (19)	-13.7 (17)	-15.7 (4.9)
20	10	0	-29.1 (18)	-29.1 (17)	-28.6 (9.2)
20	5	0	-23.4 (17)	-23.5 (16)	-24.3 (8.4)
40	0	0	-17.1 (17)	-17.1 (15)	-17.1 (4.7)
40	10	0	-30.5 (17)	-30.6 (16)	-31.0 (10)
40	5	0	-26.2 (16)	-26.2 (15)	-25.3 (7.5)

(c) Study 866-318

			866-318	Final model	
OM Dose [mg]	**AML Dose [mg]**	**HCTZ Dose [mg]**	observed **mean (sd) dSBP [mmHg]**	Prediction ("IPRED") with individual-level variability parameter **mean (sd) dSBP [mmHg]**	Prediction ("PRED") without individual-level variability parameter **mean (sd) dSBP [mmHg]**
0	0	0	-2.92 (12)	-3.02 (11)	-4.10 (1.4)
0	0	12.5	-8.61 (14)	-8.76 (12)	-10.4 (3.3)
0	0	25	-17.6 (13)	-17.7 (12)	-17.8 (4.8)
10	0	0	-10.3 (12)	-10.5 (10)	-12.6 (2.7)
10	0	12.5	-20.3 (13)	-20.2 (12)	-18.9 (5.2)
10	0	25	-22.9 (14)	-22.9 (13)	-23.4 (6.4)
20	0	0	-14.9 (16)	-14.9 (14)	-14.9 (3.2)
20	0	12.5	-21.3 (17)	-21.2 (16)	-19.3 (5.4)
20	0	25	-25.7 (13)	-25.6 (12)	-25.2 (6.9)
40	0	0	-16.3 (14)	-16.4 (13)	-17.1 (3.6)
40	0	12.5	-20.4 (16)	-20.4 (14)	-21.2 (4.9)
40	0	25	-27.8 (16)	-27.7 (14)	-26.1 (6.2)

Source: Sponsor's Population PK Analysis Report: Table 12, page 73-74

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide

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/s/

RAJANIKANTH MADABUSHI
06/27/2010
(Note: The primary reviews for the Pivotal BE, Food-Effect and DDI studies were performed by Dr. Robert Kumi, Ph.D.)

PRAVIN R JADHAV
06/27/2010

JIANG LIU
06/28/2010

MEHUL U MEHTA
06/28/2010

ONDQA (Biopharmaceutics) Review

NDA: 200-175 (000)
Submission Date: 09/30/2009
Product: CS-8635 (b) (4)
Dosage Form: Immediate Release Tablets containing Olmesartan Medoxomil (OM)/Amlodipine (AML) /Hydrochlorothiazide (HCTZ)
Strength(s): 40/10/25; 40/10/12.5; 40/5/25; 40/5/12.5 mg
Type of Submission: Original 505(b) (2) Submission
Sponsor: Daiichi Sankyo Pharma Development
Reviewer: Tapash K. Ghosh, Ph.D.

Background:

The sponsor, Daiichi Sankyo Pharma Development (DS) submitted this 505(b) (2) New Drug Application (NDA) 200-175 for CS-8635 [(b) (4) (b) (4)] for fixed dose triple combination tablets containing Olmesartan Medoxomil (OM), Amlodipine (AML) and Hydrochlorothiazide (HCTZ). (b) (4) Tablets are intended for the treatment of hypertension. This NDA relies on the FDA's previous finding of safety and efficacy for the following listed products (Table 1) which are also developed by Daiichi Sankyo.

Table 1: Reference listed drugs and products supporting 505(b) (2) application

Product	Approval Date	NDA	Components	Tablet Strengths (mg)
Benicar®	04/2002	21- 286	Olmesartan medoxomil (OM)	5, 20 and 40
Benicar HCT®	06/2003	21-532	OM/Hydrochlorothiazide	20/12.5, 40/12.5 and 40/25
Azor®	09/2007	22-100	Amlodipine/OM	5/20, 10/20, 5/40, and 10/40

Five (5) different fixed dose combinations of (b) (4) as mentioned in Table 2 were developed and four strengths are the subject of this NDA application. The Applicant does not intend to market the 20/5/12.5 strength in the US.

The application contains BA/BE information on the lowest (OM/AML/ HCTZ : 20/5/12.5) and the highest (OM/AML/HCTZ: 40/10/25) strengths but not on the intermediate strengths. The sponsor has provided dissolution information in support of a biowaiver request for the intermediate strengths OM/AML/HCTZ 40/10/12.5 mg and 40/5/25 mg.

This review will focus on the dissolution methodology, dissolution specifications and the biowaiver request.

RECOMMENDATIONS:

- ***Dissolution Method:***

  The sponsor's proposed dissolution methodology as described below is acceptable.

Medium:	0.05 M Phosphate buffer solution pH 6.8
Volume:	900 ml
Temperature:	37^0C
Apparatus:	USP 2
Paddle speed:	50 RPM

- ***Dissolution Specifications:***

  Based on the dissolution data from the pilot and production batches, the Agency recommends the following dissolution specifications:

  - ***Olmesartan medoxomil (OM): Q-value of (b) (4) at 30 minutes (all tablets have achieved (b) (4) dissolution at S_1 level)***

  - ***Amlodipine (AML): Q-value of (b) (4) at 30 minutes (all tablets have achieved (b) (4) dissolution at S_1 level)***

  - ***Hydrochlorothiazide (HCTZ): Q-value of (b) (4) at 15 minutes (all tablets have achieved (b) (4) dissolution at S_1 level)***

- ***Biowaiver Request***

  Based on the acceptable BA/BE data for the lowest and the highest strengths and the similarity of the dissolution profiles (even though the formulations are not compositionally proportional), the Agency considers that the waiver request is acceptable and a biowaiver can be granted for the intermediate OM/AML/HCTZ 40/10/12.5 mg and 40/5/25 mg strengths.

Tapash K. Ghosh, Ph. D.
Biopharmaceutics Primary Reviewer
Office of New Drugs Quality Assessment

FT Initialed by Patrick Marroum, Ph. D. _____

Formulation Composition:

The composition of five (5) different fixed dose combinations of (b) (4) market image formulations (MIF) tablets is tabulated below.

Table 2: Composition of MIF

Component	Quality Std.	Function	20/5/12.5 mg	40/5/12.5 mg	40/5/25 mg	40/10/12.5 mg	40/10/25 mg
(b) (4)							
Olmesartan medoxomil	DMF (b) (4)	Drug substance	20.000	40.000	40.000	40.000	40.000
Amlodipine besylate	EP/USP DMF (b) (4) DMF (b) (4)	Drug substance	6.944[1]	6.944[1]	6.944[1]	13.888[1]	13.888[1]
Hydrochlorothiazide	EP/USP DMF (b) (4) DMF (b) (4)	Drug substance	12.500	12.500	25.000	12.500	25.000
Starch, pregelatinized	EP	(b) (4)					
Silicified microcrystalline cellulose[2]	DMF (b) (4)						
Croscarmellose sodium	EP						
Magnesium stearate (b) (4)	EP						
(b) (4)							
(b) (4)							
(b) (4)							
Total Tablet Weight (mg)			208	310	412	310	412
(b) (4)							

Dissolution Testing

A dissolution test method was developed by selecting a discriminatory dissolution test conditions appropriate for monitoring all three active substances simultaneously. Previous experiences from the approved OM monotherapy product Benicar® Tablets and the two fixed-dose combination products Benicar HCT® Tablets and Azor® Tablets, as well as the experience gained during CS-8635 Tablet formulation development, the *in vivo* and *in vitro* performance of the test batches were used to optimize the test method.

Media pH: The pH-dependent solubility profiles of OM, AML and HCTZ are provided in Figure 1.

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(b) (4)

[redacted]

Dissolution Method: Based on the previous discussion, for *in vitro* dissolution testing, the following key parameters were chosen:

Medium:	0.05 M Phosphate buffer solution pH 6.8; [redacted] (b) (4)
Volume:	900 mL
Temperature:	37°C
Bath type:	USP Apparatus 2
Paddle speed:	50 rpm [redacted] (b) (4)

Dissolution testing of CS-8635 Tablets will be carried out using a Sotax AT7 Smart dissolution tester equipped with isocratic reverse-phase HPLC using C8 column and acidic mobile phase (22.5% acetonitrile in 0.25% phosphoric acid) with UV detection at 250 nm suitable for Multi-Component-Analysis.

Dissolution Profiles of Registration and Bioequivalence Batches:

Dissolution profile investigations of the CS-8635 Tablets (n=12) using 20/5/12.5 mg (lot

3260V07002 used in the Pivotal BE study), 20/10/12.5 mg (lot 3261V07005), 40/5/12.5 mg (lot 3262V07002), 40/10/12.5 mg (lot 3263V07003), 40/5/25 mg (lot 3264V07003) and 40/10/25 mg lot (3265V07006 used in the Pivotal BE study) were carried out with USP Apparatus 2 (paddle speed 50 rpm) using either 900 mL of 1st fluid pH 1.2 (JP), 900 mL of 0.05 M acetate buffer pH 4.5 (USP) or 900 mL of 0.05 M phosphate buffer pH 6.8. Data tables and plots for only 0.05 M phosphate buffer pH 6.8 are provided in Figures 9, 12, 15, 18, 21 and 24, respectively.

In order to show that the 20/5/12.5 mg (lot 3260V07002) and 40/10/25 mg (lot 3265V07006) tablets utilized in the pivotal BE study CS-8635-A-E105 have similar dissolution profiles as the intermediate strengths, a similarity assessment was performed by comparison of the dissolution profiles and calculations of the similarity factor f_2. According to the f_2 similarity testing, all dissolution profiles at pH 1.2, pH 4.5, and pH 6.8 for the intermediate strengths (40/5/12.5 mg, 40/10/12.5 mg and 40/5/12 mg) are assessed as similar to the reference profiles of the 20/5/12.5 mg and 40/10/25 mg strength tablets utilized in the pivotal BE study. The f_2 calculations are provided in Table 22, Table 23 and Table 24.

Dissolution Profiles of Full Production-Scale Batches:

(b) (4)

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(b) (4)

Reviewer's Comments:

- *The sponsor's final dissolution methodology as described below is acceptable.*

Medium:	0.05 M Phosphate buffer solution pH 6.8
Volume:	900 ml
Temperature:	37^0C
Apparatus:	USP 2
Paddle speed:	50 RPM

- *Based on the dissolution data from the pilot and production batches, the Agency recommends the following dissolution specifications:*
  - ***Olmesartan medoxomil (OM): Q-value of (b) (4) at 30 minutes (all tablets have achieved (b) (4) dissolution at S_1 level)***
  - ***Amlodipine (AML): Q-value of (b) (4) at 30 minutes (all tablets have achieved (b) (4) dissolution at S_1 level)***

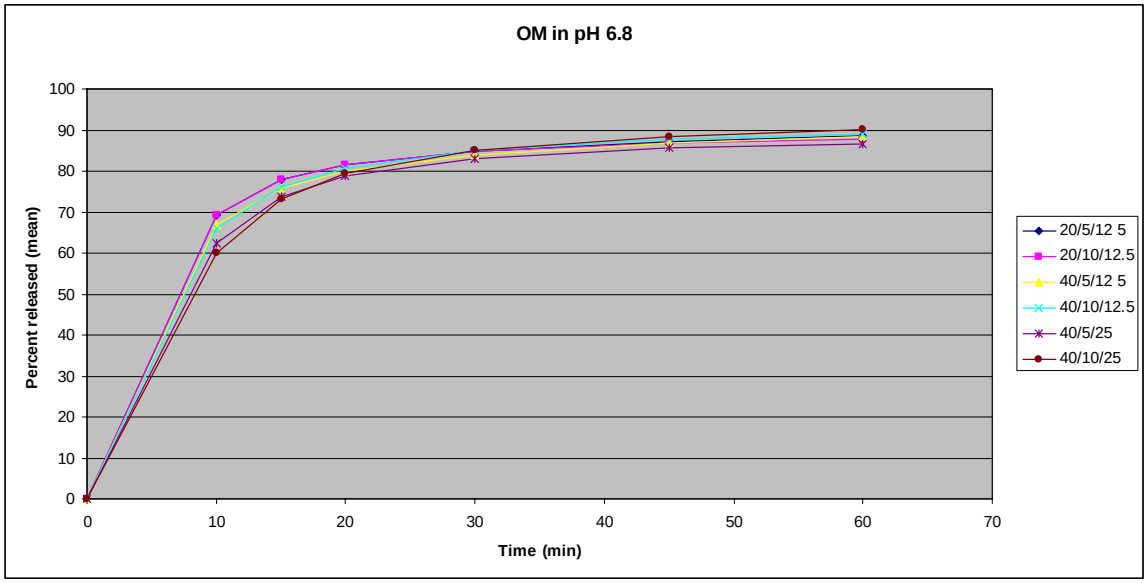
- ***Hydrochlorothiazide (HCTZ): Q-value of*** (b) (4) ***at 15 minutes (all tablets have achieved*** (b) (4) ***dissolution at S1 level)***

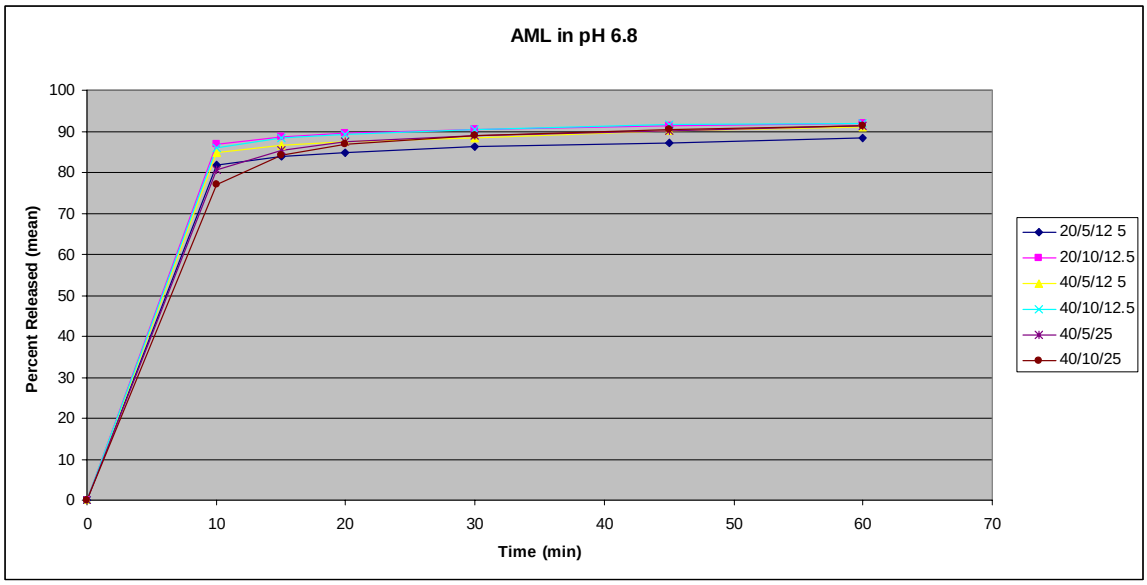
Biowaivers for Intermediate Dosage Strengths:

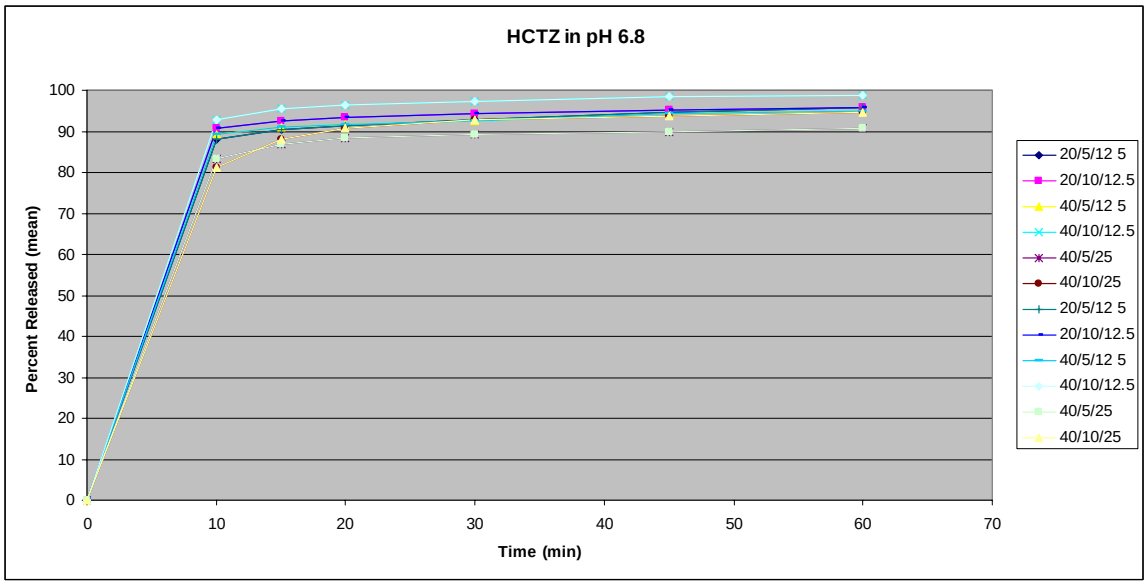
Five (5) different fixed dose combinations of (b) (4) were developed and four strengths are the subject of this NDA application. The Applicant does not intend to market the 20/5/12.5 strength in the US.

An open label, phase 1, four-period crossover study in healthy subjects to assess the bioequivalence of the highest and lowest dose CS-8635 market image formulations (MIF) to reference clinical trial formulations and dose proportionality of CS-8635 MIF was conducted (CS8635-A-E105). The primary objective of the study was to compare the pharmacokinetics of olmesartan medoxomil (OM), amlodipine besylate (AML) and hydrochlorothiazide (HCTZ) when administered as the MIF versus the two reference clinical formulations at the dose strengths of highest 40/10/25 mg (OM/AML/HCTZ) and lowest 20/5/12.5 mg (OM/AML/HCTZ). One of the secondary objectives was to determine the dose proportionality of two dose levels of CS-8635 MIF. The conclusion of interest for this review is that the CS-8635 MIFs showed dose proportional pharmacokinetics for olmesartan, amlodipine and HCT between the low dose of 20/5/12.5 mg (OM/AML/HCTZ) and high dose of 40/10/25 mg (OM/AML/HCTZ) (see Clinical Pharmacology review for detail).

In terms of calculating the similarity factors (f2), the sponsor has rightfully calculated f2 factors for the intermediate strengths with respect to the lowest strength and the highest strengths as references separately in 3 mediums [pHs 1.2 (Table 22), 4.5 (Table 23) and 6.8 (Table 24)]. Representative profiles comparison of OM, AML and HCTZ at pH 6.8 are presented in the following Figures:







Reviewer's Comments:

The following information was provided to support the biowaiver request for the intermediate strengths:

- *Acceptable BA/BE data for the lowest (OM/AML/HCTZ : 20/5/12.5) and the highest (OM/AML/HCTZ: 40/10/25) strengths.*

- *Dissolution comparison profile data and f2 values. In terms of calculating the similarity factors (f2), the sponsor has rightfully calculated the f2 factors for the intermediate strengths with respect to the lowest strength*

and the highest strengths as references separately in 3 mediums (pHs 1.2, 4.5 and 6.8).

Therefore, the Agency considers that the waiver request is acceptable and a biowaiver can be granted for the intermediate OM/AML/HCTZ 40/10/12.5 mg and 40/5/25 mg strengths.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide

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/s/

TAPASH K GHOSH
05/18/2010

PATRICK J MARROUM
05/18/2010