T2416

A Fixed-Dose Combination of Olmesartan Medoxomil (OM), Amlodipine (AML), and Hydrochlorothiazide (HCTZ): Use of Modeling and Simulation to Support an Understanding of the Dose Response of Intermediate Dose Combinations not Included in the Pivotal Phase 3 Study

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Objectives

- Develop population pharmacokinetic (PopPK) models of olmesartan medoxomil (OM), amlodipine (AML), and hydrochlorothiazide (HCTZ) for application to the hypertensive patient population using relevant Phase 1 and Phase 3 datasets from the clinical development programs for CS-866 (OM+HCTZ), CS-8663 (OM+AML), and CS-8635 (OM+AML+HCTZ).
- Characterize and quantify the effects of covariates on the oral clearances of the compounds, OM, AML, and HCTZ, including demographics (age, weight, gender, creatinine clearance, alanine aminotransferase and aspartate aminotransferase) and disease status (hypertension with and without diabetes).
- Develop exposure-response models that characterize the effect of the drug on seated trough diastolic blood pressure (SeDBP) and seated trough systolic blood pressure (SeSBP) based on the data in the three relevant Phase 3 studies: CS866-318 (OM+HCTZ), CS8663-A-U301 (OM+AML), and CS8635-A-U301 (OM+AML+HCTZ).
- Characterize and quantify the effects of covariates (age, race, weight, sex, creatinine clearance, and baseline SeDBP or SeSBP) on the exposure-response models.
- Simulate the systolic and diastolic blood pressure lowering effects of clinically unevaluated market image formulations of CS8635: 20/5/12.5, 40/5/12.5, 40/10/12.5, and 40/5/25 mg (OM/AML/HCTZ) based on the population PK/PD models and the demographic and baseline characteristics of the CS8635-A-U301 population.

Primary Study for Analysis

- Study CS8635-A-U301: A randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of administration of high-dose triple-combination olmesartan, hydrochlorothiazide and amlodipine (40/10/25 mg) compared to the three respective high-dose dual combinations in patients with mild to severe hypertension.
- Fixed-dose combinations planned for marketing not part of the study: 20/5/12.5, 40/5/12.5, 40/10/12.5 and 40/5/25 mg (OM/AML/HCTZ).

Data and Methods

Table 1. Demographic Summary of PK Subjects

Study	Phase	N	M:F	Age [y] Mean (SD)	Weight [kg] Mean (SD)	CLCR* [ml/min] Mean (SD)	Race/Ethnicity† W:B:H:A:O	Diabetes (%)
All Phase I studies	I	492	349:143	30.9 (7.9)	77 (13)	127 (26)	143:199:131:9:10	0
CS8663-A-U301 (OM+AML)	III	556	283:273	54.6 (11)	94.6 (22)	99.6 (34)	351:117:69:8:11	13.7
CS8635-A-U301 (OM+AML)	III	956	517:439	55.8 (10)	95.5 (22)	117 (43)	547:223:167:14:5	16.3
Both Phase III studies	III	1512	800:712	55.4 (11)	95.2 (22)	111 (41)	898:340:236:22:16	15.3
All studies	–	2004	1149:855	49.4 (15)	90.7 (21)	115 (38)	1041:539:367:31:26	11.6

*Creatinine clearance [Cockcroft-Gault]
†White/Black/Hispanic/Asian/Other

Table 2. Demographic Summary of Exposure-Response Dataset Subjects

Study	N	Baseline SBP	Baseline DBP	M:F	Age [y] Mean (SD)	Weight [kg] Mean (SD)	Race/Ethnicity W:B:H:A:O	Diabetes (%)
All data	4873	165 (16)	102 (8.7)	2625:2248	54.8 (11)	94.9 (22)	2869:1216:654:93:41	14.1
CS866-318	495	154 (13)	104 (3.1)	278:217	53.5 (11)	88.1 (18)	369:60:48:12:6	8.9
CS8663-A-U301	1920	164 (17)	102 (5.6)	1043:877	54.6 (11)	95.2 (22)	1169:452:241:36:22	13.4
→ non-PK subjects	1365	165 (17)	102 (5.7)	761:604	54.6 (11)	95.4 (22)	819:335:172:28:11	13.3
→ PK subjects	555	163 (17)	102 (5.3)	282:273	54.6 (11)	94.6 (22)	350:117:69:8:11	13.7
CS8635-A-U301	2458	169 (14)	101 (7.8)	1304:1154	55.2 (11)	96.1 (23)	1331:704:365:45:13	15.6
→ non-PK subjects	1542	169 (14)	101 (7.9)	804:738	54.7 (11)	96.4 (24)	801:492:209:31:9	15.0
→ PK subjects	916	168 (14)	101 (7.5)	500:416	56.1 (10)	95.5 (22)	530:212:156:14:4	16.6

- Model-predicted exposures from the population PK model were used in the exposure-response analysis. (Covariate-adjusted median-predicted exposures were used for subjects without PK sampling.)
- The analysis used seated cuff blood pressure measurements taken at the per-protocol baseline and end of the primary efficacy analysis period (Week 8 in CS866-318 and CS8663-A-U301; Week 12 in CS8635-A-U301).
- Simulations of the CS-8635 blood pressure lowering effect were conducted based on the PK and exposure-response models:
  - Primary Objective: To compare the blood pressure lowering effects of clinically un-evaluated CS-8635 dose strengths (20/5/12.5, 40/5/12.5, 40/10/12.5, 40/5/25 mg OM/AML/HCTZ) to those of the clinically evaluated dose strength (40/10/25 mg OM/AML/HCTZ).
  - Patient Population used in Simulation: The CS8635-A-U301 population.
  - Dose combinations simulated: A full factorial design, i.e., all possible dose combinations, of OM (0/20/40 mg), AML (0/5/10 mg) and HCTZ (0/12.5/25 mg) for the placebo, mono, dual and triple combinations.

Population Pharmacokinetic Modeling Results

The concentrations of each drug were successfully described by a mammillary two-compartment model with first order elimination and first order absorption with time lag. A covariate analysis identified demographic relationships with drug concentrations, as follows:

- OM: Patients with lower creatinine clearances had lower clearance of the drug.
- AML: Older patients had lower clearance of the drug.
- HCTZ: Older patients, female patients, and patients with lower creatinine clearances had lower clearance of the drug.

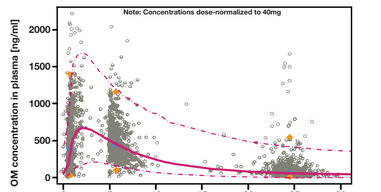
Post-predictive checks (Figures 1-6) for each drug demonstrated that the models successfully described the patient exposure profiles.

OM: $$\left(\frac{CL}{F}\right)_i [L/h] = (6.32) \times \left(\frac{CLCR_i}{111}\right)^{0.425}$$

AML: $$\left(\frac{CL}{F}\right)_i [L/h] = (23.4) \times \left(\frac{Age_i}{50.9}\right)^{-0.349}$$

HCTZ: $$\left(\frac{CL}{F}\right)_i [L/h] = (20.3) \times \exp(-0.219 \times SEX_i) \times \left(\frac{CLCR_i}{117.5}\right)^{0.499} \times \left(\frac{Age}{49.5}\right)^{-0.214}$$

Figure 1. Post-predictive Check for CS8635-A-U301 for the Olmesartan Medoxomil Pharmacokinetic Model



Raw data from studies plotted as grey dots.
Blue dots represent the mean of the data, orange dots represent the 97.5th and 2.5th quantiles of the data. For sparsely sampled studies, dots are plotted at the median observed time for the nominal sample time.
Results from model simulation drawn as red lines, with solid line representing the mean model prediction, and the dotted lines representing the 95% prediction interval of the simulation.

Figure 2. Post-predictive Check for Phase 1 Studies (AUCss) for Olmesartan Medoxomil

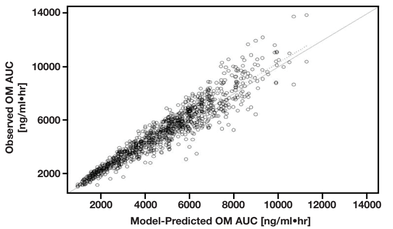
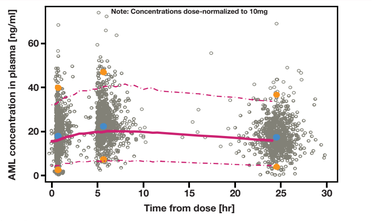


Figure 3. Post-predictive Check for CS8635-A-U301 for the Amlodipine Pharmacokinetic Model



Raw data from studies plotted as grey dots.
Blue dots represent the mean of the data, orange dots represent the 97.5th and 2.5th quantiles of the data. For sparsely sampled studies, dots are plotted at the median observed time for the nominal sample time.
Results from model simulation drawn as red lines, with solid line representing the mean model prediction, and the dotted lines representing the 95% prediction interval of the simulation.

Figure 4. Post-predictive Check for Phase 1 Studies (AUCss) for Amlodipine

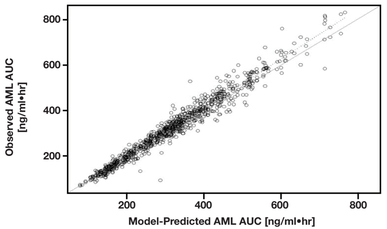
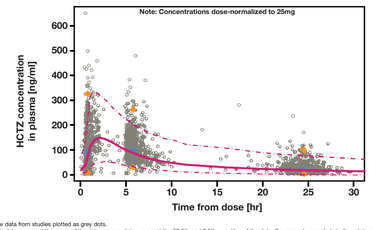
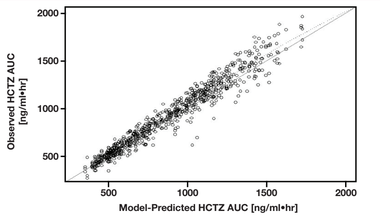


Figure 5. Post-predictive Check for CS8635-A-U301 for the Hydrochlorothiazide Pharmacokinetic Model



Raw data from studies plotted as grey dots.
Blue dots represent the mean of the data, orange dots represent the 97.5th and 2.5th quantiles of the data. For sparsely sampled studies, dots are plotted at the median observed time for the nominal sample time.
Results from model simulation drawn as red lines, with solid line representing the mean model prediction, and the dotted lines representing the 95% prediction interval of the simulation.

Figure 6. Post-predictive Check for Phase 1 Studies (AUCss) for Hydrochlorothiazide



Results from Exposure-Response Modeling of Blood Pressure

The final exposure-response model for SeDBP and SeSBP related the drug effects of olmesartan medoxomil, amlodipine, and hydrochlorothiazide to their systemic exposures, AUC-OM, AUC-AML, and AUC-HCTZ, respectively. The drug effects for olmesartan medoxomil and amlodipine were described by an Emax model, whereas the drug effect for hydrochlorothiazide was described by a linear model. The drug effect of combination therapy was greater than any of the drug effects in monotherapy, but slightly less than their additive sum. This finding was modeled via a series of interaction terms. Key covariate findings in the exposure-response modeling included:

- For both SeDBP and SeSBP, the placebo effect varied by study and was stronger for subjects with higher baseline BP.
- For OM, subjects of black race showed a weaker response than non-black subjects.
- For AML, subjects of lower weight showed a stronger response.

Exposure-Response Analysis for Seated Diastolic Blood Pressure

$$DBP_{i,j} = BaseDBP_j + PlaceboEffect_j + TreatmentEffect_j + \eta_j + \varepsilon_i$$

where,

$DBP_{i,j}$ is the i^{th} measurement within the j^{th} subject at steady-state,
η_j is additive inter-subject variability in response, and
ε_i is additive residual intra-subject variability.

$$PlaceboEffect_j = \begin{pmatrix} -3.80*(CS8635-A-U301) \\ -3.57*(1-0.607*Black)*(CS8663-A-U301) \\ -6.08*(866-318) \end{pmatrix} \times \left(\frac{age_j}{54.8}\right)^{\theta_{10}} \times \left(\frac{BaselineDBP_j}{101}\right)^{\theta_{19}}$$

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

$$ER_{OM,j} = \left(\frac{-10.5*AUC_{OM,ss,j}}{1850+AUC_{OM,ss,j}}\right) \times \left(1-0.263*Black\right)^{\theta_{18}} \times \left(\frac{age_j}{54.8}\right)^{\theta_{18}} \times \left(\frac{DBP_{base,j}}{101}\right)^{2.06}$$

$$ER_{AML,j} = \left(\frac{-19.3*AUC_{AML,ss,j}}{453+AUC_{AML,ss,j}}\right) \times \left(\frac{weight_j}{95.2}\right)^{\theta_{20}} \times \left(\frac{DBP_{base,j}}{101}\right)^{+12}$$

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

Exposure-Response Analysis for Seated Systolic Blood Pressure

$$SBP_{i,j} = BaseSBP_j + PlaceboEffect_j + TreatmentEffect_j + \eta_j + \varepsilon_i$$

where,

$SBP_{i,j}$ is the i^{th} measurement within the j^{th} subject at steady-state,
η_j is additive inter-subject variability in response, and
ε_i is additive residual intra-subject variability.

$$PlaceboEffect_j = \begin{pmatrix} -4.20*(1-0.554*Hispanic)*(CS8635-A-U301) \\ -3.45*(CS8663-A-U301) \\ -5.26*(866-318) \end{pmatrix} \times \left(\frac{age_j}{54.8}\right)^{\theta_{36}} \times \left(\frac{BaselineSBP_j}{164}\right)^{\theta_{38}}$$

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

$$ER_{OM,j} = \left(\frac{-18.8*AUC_{OM,ss,j}}{1590+AUC_{OM,ss,j}}\right) \times \left(1-0.393*Black\right)^{\theta_{36}} \times \left(\frac{SBP_{base,j}}{164}\right)^{\theta_{36}}$$

$$ER_{AML,j} = \left(\frac{-23.1*AUC_{AML,ss,j}}{309+AUC_{AML,ss,j}}\right) \times \left(\frac{weight_j}{95.2}\right)^{\theta_{36}} \times \left(1+0.301*female\right)^{\theta_{40}} \times \left(\frac{SBP_{base,j}}{164}\right)^{\theta_{40}}$$

$$ER_{HCTZ,j} = -9.38*\frac{AUC_{ss,HCTZ,j}}{1000} \times \left(\frac{SBP_{base,j}}{164}\right)^{\theta_{42}}$$

Results from Simulation Models

Table 3. Predicted and Observed BP Lowering Effects (CS8663-A-U301, CS866-318)

			CS8663-A-U301		Final model Prediction ("PRED") with individual-level variability parameter		Final model Prediction ("PRED") without individual-level variability parameter	
OM Dose [mg]	AML Dose [mg]	HCTZ Dose [mg]	observed mean ΔSBP [mm Hg]	observed mean ΔSBP [mm Hg]	predicted mean ΔSBP [mm Hg]	predicted mean ΔSBP [mm Hg]	predicted mean ΔSBP [mm Hg]	predicted mean ΔSBP [mm Hg]
0	0	0	-3.08	-2.81	-3.09	-2.88	-3.24	-3.89
0	10	0	-13.0	-20.2	-13.0	-20.1	-13.3	-20.0
0	5	0	-9.68	-15.3	-9.68	-15.3	-9.78	-15.1
10	0	0	-6.07	-11.9	-6.01	-11.9	-6.38	-12.8
10	10	0	-16.3	-25.8	-16.3	-25.8	-16.0	-25.6
10	5	0	-14.2	-24.7	-14.2	-24.6	-13.9	-23.5
20	0	0	-9.11	-13.5	-9.16	-13.7	-10.0	-15.7
20	10	0	-17.1	-29.1	-17.1	-29.1	-16.9	-28.6
20	5	0	-14.0	-23.4	-14.0	-23.5	-14.5	-24.3
40	0	0	-10.6	-17.1	-10.6	-17.1	-10.9	-17.1
40	10	0	-19.2	-30.5	-19.2	-30.6	-18.4	-31.0
40	5	0	-15.8	-26.2	-15.7	-26.2	-15.3	-25.3

			CS866-318		Final model Prediction ("PRED") with individual-level variability parameter		Final model Prediction ("PRED") without individual-level variability parameter	
OM Dose [mg]	AML Dose [mg]	HCTZ Dose [mg]	observed mean ΔSBP [mm Hg]	observed mean ΔSBP [mm Hg]	predicted mean ΔSBP [mm Hg]	predicted mean ΔSBP [mm Hg]	predicted mean ΔSBP [mm Hg]	predicted mean ΔSBP [mm Hg]
0	0	0	-7.51	-2.92	-7.43	-3.02	-6.55	-4.10
0	0	12.5	-9.28	-9.61	-9.26	-8.76	-9.03	-10.4
0	0	25	-12.9	-17.6	-12.8	-17.7	-12.2	-17.8
10	0	0	-12.7	-10.3	-12.6	-10.5	-11.6	-12.6
10	0	12.5	-15.3	-20.3	-15.2	-20.2	-14.5	-18.9
10	0	25	-18.4	-23.9	-18.3	-23.9	-17.4	-23.4
20	0	0	-12.4	-14.9	-12.5	-14.9	-13.4	-14.9
20	0	12.5	-15.8	-21.3	-15.8	-21.4	-15.0	-19.3
20	0	25	-18.9	-25.7	-18.9	-25.6	-19.0	-25.2
40	0	0	-14.4	-16.3	-14.5	-16.4	-15.0	-17.1
40	0	12.5	-18.4	-20.4	-18.3	-20.4	-17.7	-21.2
40	0	25	-21.9	-27.8	-21.7	-27.7	-20.7	-26.1

Table 4. Predicted and Observed BP Lowering Effects (CS8635-A-U301) Mean (SD)

		Δ (SeDBP)		Δ (SeSBP)	
Treatment	(mg)	Observed	Predicted	Observed	Predicted
OM/AML	40/10	-17.8 (9.9)	-17.8 (9.0)	-31.1 (16)	-31.1 (15)
OM/HCTZ	40/25	-16.5 (10)	-16.5 (10)	-31.2 (19)	-31.1 (18)
AML/HCTZ	10/25	-14.8 (9.3)	-14.8 (8.3)	-29.0 (16)	-29.0 (14)
OM/AML/HCTZ	40/10/25	-21.5 (11)	-21.5 (9.8)	-38.1 (18)	-38.1 (17)

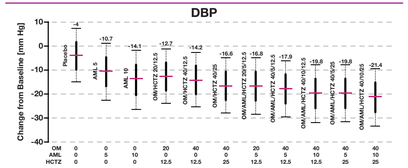
Table 5. Predicted BP Lowering Effect of CS-8635 – (Amlodipine to Benicar HCT®) Mean (SD)

	AML (mg)					
	0 m		5		10	
Benicar HCT® (mg/mg)	ΔSeDBP	ΔSeSBP	ΔSeDBP	ΔSeSBP	ΔSeDBP	ΔSeSBP
0/0	-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	-12.7 (9.4)	-22.4 (16.0)	-16.8 (9.7)	-30.4 (16.8)	-18.9 (9.9)	-33.7 (17.1)
40/12.5	-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	-16.6 (9.6)	-29.9 (16.7)	-19.8 (9.8)	-35.9 (17.0)	-21.4 (9.9)	-38.4 (17.2)

Table 6. Predicted BP Lowering Effect of CS-8635 – (HCTZ to AZOR®) Mean (SD)

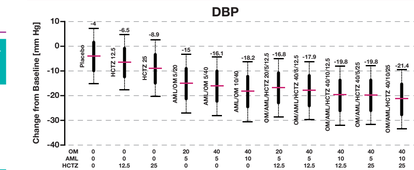
	HCTZ (mg)					
	0		12.5		25	
AZOR® (mg/mg)	ΔSeDBP	ΔSeSBP	ΔSeDBP	ΔSeSBP	ΔSeDBP	ΔSeSBP
0/0	-4.0 (9.2)	-4.7 (15.2)	-6.4 (9.3)	-12.5 (15.7)	-8.9 (9.4)	-20.3 (16.9)
5/20	-15.0 (9.7)	-26.5 (16.8)	-16.8 (9.7)	-30.4 (16.8)	-18.6 (9.7)	-34.4 (17.0)
5/40	-16.0 (9.7)	-28.2 (16.7)	-17.9 (9.7)	-32.1 (16.8)	-19.8 (9.8)	-35.9 (17.0)
10/40	-18.2 (9.9)	-32.0 (17.1)	-19.8 (9.9)	-35.2 (17.1)	-21.4 (9.9)	-38.4 (17.2)

Figure 7. Boxplots of DBP Simulation Results for "Add to Benicar HCT®" Scenario



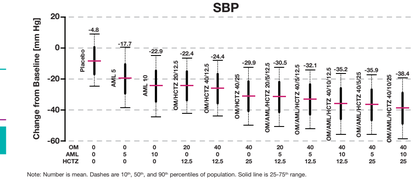
Note: Number is mean. Dashes are 10th, 50th, and 90th percentiles of population. Solid line is 25-75th range.

Figure 8. Boxplots of DBP Simulation Results for "Add to AZOR®" Scenario



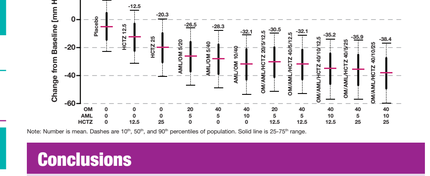
Note: Number is mean. Dashes are 10th, 50th, and 90th percentiles of population. Solid line is 25-75th range.

Figure 9. Boxplots of SBP Simulation Results for "Add to Benicar HCT®" Scenario



Note: Number is mean. Dashes are 10th, 50th, and 90th percentiles of population. Solid line is 25-75th range.

Figure 10. Boxplots of SBP Simulation Results for "Add to AZOR®" Scenario



Note: Number is mean. Dashes are 10th, 50th, and 90th percentiles of population. Solid line is 25-75th range.

Conclusions

- Olmesartan medoxomil PK was adequately characterized by a two-compartment model with first-order absorption and time lag; creatinine clearance was a significant predictor of the apparent oral clearance of olmesartan medoxomil.
- Amlodipine PK was adequately characterized by a two-compartment model with first-order absorption and a time lag; age was a significant predictor of the apparent oral clearance of amlodipine.
- Hydrochlorothiazide PK was adequately characterized by a two-compartment model with first-order absorption and a time lag; sex, age, and creatinine clearance were significant predictors of the apparent oral clearance of hydrochlorothiazide.
- The blood pressure lowering effects of olmesartan medoxomil and amlodipine exposure on seated trough DBP and SBP were described by an E_{max} model, whereas the blood pressure lowering effect of hydrochlorothiazide exposure was described by a linear model.
- The blood pressure lowering effects of olmesartan medoxomil, amlodipine, and hydrochlorothiazide in monotherapy, dual combination therapy, and triple combination therapy were well characterized by a model composed of the sum of the individual effects and interaction among the components.
- The model-predicted and simulated blood pressure lowering effects of the various tested combinations of the three compounds were in good agreement with the observed data from the three Phase 3 studies upon which the model was built.
- In the exposure-response model, black race was a covariate, decreasing the maximal possible effect on blood pressure of olmesartan medoxomil without influencing PK parameters.
- In the exposure-response model, baseline seated trough DBP and SBP were covariates, with more blood pressure lowering effect associated with higher baseline blood pressure.
- The exposure-response model predicted the blood pressure lowering effects of triple combination therapy permutations to be superior to their respective mono and dual treatments of OM, AML, and HCTZ.
- The order of the blood pressure lowering effects among the different CS-8635 dose strengths was: 20/5/12.5<40/5/12.5<[40/10/12.5~40/5/25]<40/10/25 mg [OM/AML/HCTZ].

Encore from the American Society of Hypertension Annual Meeting, New York City, May 1, 2010.