

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200175

MEDICAL REVIEW(S)

CLINICAL AND STATISTICAL REVIEW

Application Type	NDA
Submission Number	200175
Submission Code	4
Letter Date	September 30, 2009
Stamp Date	September 30, 2009
PDUFA Goal Date	July 30, 2010
Reviewers' Names	Maryann Gordon, M.D. (Medical) Fanhui Kong, PhD. (Statistics)
Review Completion Date	April 19, 2010
Established Name	olmesartan medoxomil + amlodipine + hydrochlorothiazide
Proposed Trade Name	Tribenzor™
Therapeutic Class	angiotensin II antagonist + calcium ion influx inhibitor + thiazide diuretic
Applicant	Daiichi Sankyo Pharma
Priority Designation:	S
Formulation	tablets
Dosing Regimen	once daily
Indication	treatment of hypertension
Intended Population	adults

1 Executive Summary

1.1 Recommendation on Regulatory Action

The primary medical and statistical reviewers of the new drug application (NDA) #200175, pertaining to the use of the triple combination olmesartan medoxomil (OM), amlodipine besylate (AML) and hydrochlorothiazide (HCTZ) in the treatment of patients with hypertension, are recommending approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This 505(b)(2) application for the fixed-dose combination of OM, AML, and HCTZ is based on data from

- a) study CS8635-A-U301, “A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Co-Administration of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorothiazide in Subjects with Hypertension;”
- b) studies CS8663-A-U301 and CS8663-A-E303 previously submitted under the Azor®¹ NDA #22-100 program; and
- c) study SP-OLM-03-05 OLMETREAT, a non-Investigational New Drug study conducted in Europe.

In addition, there are 6 clinical pharmacology studies from the CS-8635 development program.

During the July 24, 2007 Type C Guidance Meeting, the Agency agreed that a single study (CS8635-A-U301) demonstrating that the blood pressure lowering effect of a triple combination therapy of OM + AML + HCTZ was superior to the highest dosage dual combination therapy of OM + AML, OM + HCTZ, and AML + HCTZ was sufficient, pending review, to support approval of the triple combination therapy product.

At this Type C meeting, the Agency also stated that it would be willing to consider a proposal from Daiichi Sankyo for submitting less than 24 weeks of safety data from the CS8635-A-U301 study at the time of the NDA submission. Daiichi Sankyo submitted a proposal² to include the safety data from the 12-week double-blind period of the CS8635-A-U301 study and also to

¹ Approved for use in hypertension 09/26/2007. Azor is the combination amlodipine and olmesartan medoxomil.

² Jan. 28, 2009

include safety data from the Azor NDA 22-100 program (CS8663-A-U301 and CS8663-A-E303) in support of the safety of the triple combination therapy.

The Agency agreed that the inclusion of extensive safety data from the 40-week open-label period of the CS8635-A-U301 study within the 120-Day Safety Update along with the timing of when the clinical study report (CSR) would be acceptable.

Daiichi Sankyo cross-referencing in this submission all clinical information from NDA 21-286 for Benicar, NDA 22-100 for Azor, and NDA 21-532 for Benicar HCT in support the indication of the triple combination of OM, AML, and HCTZ for the treatment of hypertension.

1.3.2 Efficacy

The efficacy of the triple combination is based on the results of the double-blind treatment period of the study CS8635-A-U301. The objective of the study was to demonstrate that the triple combination of OM 40 mg + AML 10 mg + HCTZ 25 mg is more efficacious in lowering seated diastolic blood pressure (SeDBP) than each of the corresponding dual components (OM 40 mg + AML 10 mg, OM 40 mg + HCTZ 25 mg, and AML 10 mg + HCTZ 25 mg) after 12 weeks of treatment.

Additional studies in support of efficacy for the Azor NDA (but not re-reviewed for this NDA) include:

a) CS8663-A-U30, a randomized, double-blind, placebo-controlled, factorial study. The primary objective of the study was to determine if co-administration of OM plus AML had a clinically significant benefit versus the respective monotherapy components in controlling blood pressure in subjects with mild to severe hypertension.

b) CS8663-A-E303, a randomized, double-blind, add-on study. The primary objective of the study was to demonstrate the additional antihypertensive efficacy gained by adding OM 10 mg, 20 mg, or 40 mg to the treatment regimen in subjects with moderate to severe hypertension whose blood pressure was not adequately controlled on AML 5 mg alone.

Other studies

This submission includes a Phase 1 cohort consisting of 6 individual studies, including 4 drug-drug interaction studies (CS8635-A-U101, -U102, -U103, and -U104), 1 bioequivalence study (CS8635-A-E105), and 1 food effect study (CS8635-A-U106).

-Study CS8635-A-U101 compared the triple combination (administered as dual combination therapy Benicar HCT (OM + HCTZ) and Norvasc (AML)) with the separate components.

-Study CS8635-A-U102 compared the triple combination (administered as dual combination therapy Azor (OM + AML and HCTZ) with the separate components.

-Studies CS8635-A-U103 and -U104 compared 2 formulations of the triple combination (OM 40 mg + AML 10 mg + HCTZ 25 mg) with Benicar HCT plus Antacal® (AML).

-Study CS8635-A-E105 compared a high-dose (OM 40 mg + AML 10 mg + HCTZ 25 mg) and low-dose (OM 20 mg + AML 5 mg + HCTZ 12.5 mg) formulation of the triple combination with high-dose and low-dose Azor (OM 40 mg +

AML 10 mg and OM 20 mg + AML 5 mg, respectively) plus high-dose and low-dose HCTZ (25 mg and 12.5 mg, respectively).

-Study CS8635-A-U106 assessed the food effect on the fixed-dose triple combination (OM 40 mg + AML 10 mg + HCTZ 25 mg).

Study SP-OLM-03-05 OLMETREAT was a Phase 4, non-Investigation New Drug, European, non-comparative, sequential add-on, open-label, treat-to-target study of OM and an add-on treatment algorithm consisting of HCTZ and AML in subjects with mild to moderate hypertension.

Summary of efficacy results

Study CS8635-A-U301 showed that after 12 weeks of double-blind treatment, the subjects treated with triple combination therapy (final dose OM 40 mg + AML 10 mg + HCTZ 25 mg) had significantly greater mean reductions in seated DBP and SBP measured by cuff compared to any of the component dual combination therapies.

This study also evaluated ambulatory blood pressures within a subpopulation of 440 subjects. After 12 weeks of double-blind treatment, the group treated with triple combination therapy from Week 4 to Week 12 had significantly greater mean reductions in 24-hour DBP and SBP compared to the component dual combination therapies.

1.3.3 Safety

Olmesartan medoxomil, amlodipine and HCTZ are all marketed agents. No new safety concerns were identified during the course of development of the triple combination. The reported adverse events and their incidence rates with the triple combination were similar to what is expected with the monotherapies.

The adverse event hypotension was reported more often by subjects who received the triple combination compared to the dual therapy groups. There were 11 reports of hypotension during study CS8635-A-U301 with 8 reports coming from subjects on the triple combination (1.4%) and 3 from subjects taking OM 40 mg + HCTZ 25 mg dual combination (0.5%).

Adverse events using the combined term renal impairment were more frequent with triple combination therapy compared to the dual combination therapies. The incidence of renal impairment adverse events was 2.1% in subjects treated with triple combination therapy and ranged from 0.2% to 1.3% for the dual combination therapies.

Other commonly reported adverse events with the triple combination included peripheral edema, dizziness, headache, nausea, and fatigue. The incidence rates for these adverse events reported by the subjects who received the triple combination were not dissimilar to the rates reported by those who received the dual therapies.

Additional adverse events associated with use of the components of the triple combination were also reported by subjects who received the triple combination. These events included hypokalemia, hyperkalemia, increased creatinine

1.3.4 Dosing Regimen and Administration

The following tablet (olmesartan medoxomil/amlodipine/hydrochlorothiazide) strengths will be available: 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, and 40/10/25 mg. Only the 40/10/25 mg dose was studied empirically. The triple combination can be substituted for its individual components for patients on olmesartan medoxomil, amlodipine, and hydrochlorothiazide.

The triple combination may be used 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. Maximum antihypertensive effects are attained within 2 weeks after a change in dose.

Doses not studied empirically

Treatment with triple combination therapy at doses not studied in the CS8635-A-U301 study was explored through exposure-response modeling.

2 Introduction and Background

Tribenzor™ tablets are a combination angiotensin II antagonist, calcium channel blocker, and thiazide diuretic.

Olmesartan medoxomil (an ARB), AML (a dihydropyridine CCB), and HCTZ (a diuretic), all lower blood pressure through different mechanisms of action. Their different modes of action seem to allow for an additional blood pressure lowering effect without altering the safety profiles of the individual components.

2.2 Currently Available Treatment for Indication

There are numerous choices of treatments for hypertension.

2.3 Availability of Proposed Active Ingredients in the United States

Olmesartan medoxomil, amlodipine, and hydrochlorothiazide are all currently marketed in the United States.

2.4 Important Issues with Pharmacologically Related Products

ACEs and ARBs have a Black box warning pertaining to drugs which act on the rennin-angiotensin system. These drugs can cause injury and even death to the developing fetus. When pregnancy is detected these drugs should be discontinued as soon as possible.

Many CCBs have a warning about their use in patients with heart failure especially in conjunction with beta adrenergic blockers.

Hydrochlorothiazide is contraindicated in patients with anuria and may precipitate azotemia in patients with impaired renal disease. Latent diabetes mellitus may become manifest and patients with diabetes may require adjustment of their insulin dose. Patients receiving hydro-

chlorothiazide could be at risk for developing hypokalemia, hyponatremia, hypochloremic alkalosis, hypomagnesemia, hyperuricemia, and hepatic coma (in patients with severe liver disease).

2.5 Pre-submission Regulatory Activity

- Type C guidance meeting between the FDA and Daiichi-Sankyo held July 24, 2007.
- Special protocol assessment correspondences.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor has submitted electronic submissions to the EDR dated December 29, 2009, December 17, 2009, November 17, 2009, October 9, 2009, and September 30, 2009.

4.2 List of Clinical Studies

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Tabular Listing of All Clinical Studies

Study No. (No. of Centers)	Study Design (Period)	Primary Objectives of the Study	Study Status (Completion Date)	Test Products Dose Regimen Route of Administration	Type of Patients Number Randomized (Number Completed)
CS8635-A-U301 (317)	Phase III Double-blind (Period II)	To test the hypothesis that the triple combination of OM 40 mg + AML 10 mg + HCTZ 25 mg is superior to its corresponding dual combination in terms of blood pressure reductions.	12-Week Double-Blind (Period II) Completed Open Label (Period III) Ongoing	Treatment Arms: Placebo, OM 40 mg + AML 10 mg, OM 40 mg + HCTZ 25 mg, AML 10 mg + HCTZ 25 mg, OM 40 mg + AML 10 mg + HCTZ 25 mg Dose Regimen: Once daily Route of Administration: Oral	Male and female patients with hypertension 2492 (2116)
CS8663-A-U301 (172)	Phase III Open-label Extension (Period III)	1. To gain long-term efficacy and safety experience with co-administration of OM + AML (plus the addition of HCTZ, if needed) while minimally treating patients to blood pressure goal (<140/90 mmHg, <130/80 mmHg for diabetic patients). 2. To evaluate the number (%) of patients achieving blood pressure goal (defined as blood pressure <140/90 mmHg, <130/80 mmHg for diabetic patients).	Completed (1/2007)	Test Product: OM 40 mg + AML 5 mg OM 40 mg + AML 10 mg OM 40 mg + AML 10 mg + HCTZ 12.5 mg OM 40 mg + AML 10 mg + HCTZ 25 mg Dose Regimen: Once daily Route of Administration: Oral	Male and female patients with mild to severe hypertension 1684 (1400)
CS8663-A-E303 (75)	Phase III Open-label Extension (Period IV)	To demonstrate the additional antihypertensive efficacy in lowering sitting diastolic blood pressure gained by adding OM 10 mg, 20 mg, or 40 mg to the treatment regimen in patients with moderate to severe hypertension not adequately controlled on AML 5 mg alone assessed by conventional blood pressure measurements after 8 weeks of double-blind treatment.	Completed (5/2007)	Test Product: OM 40 mg + AML 5 mg OM 40 mg + AML 10 mg OM 40 mg + AML 10 mg + HCTZ 12.5 mg OM 40 mg + AML 10 mg + HCTZ 25 mg Dose Regimen: Once daily Route of Administration: Oral	Male and female patients with moderate to severe hypertension 755 Entered Period IV: 692 (673)

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Study No. (No. of Centers)	Study Design (Period)	Primary Objectives of the Study	Study Status (Completion Date)	Test Products Dose Regimen Route of Administration	Type of Patients Number Randomized (Number Completed)
SP-OLM-03-05 (58)	Phase IV Open-label	To evaluate the rates of Subject Treated to Target overall and on each treatment combination step.	Completed (4/2008)	Test Product: Placebo, OM 20 mg, OM20/HCTZ12.5 mg, OM20/HCTZ25 mg, OM20/HCTZ25 mg + AML 5 mg, OM20/HCTZ25 mg + AML 10 mg, Dose Regimen: Once daily Route of Administration: Oral	Male and female patients with mild to moderate hypertension 694 (601)
CS8635-A-U101 (1)	3-way Cross-over, Open-label, Single-dose, Bioavailability	To determine the bioavailability of OM, AML, and HCTZ when administered together as Benicar HCT and Norvasc and when administered alone.	Completed (9/2007)	Test Product: OM40/HCTZ25 mg + AML 10 mg OM40/HCTZ25 mg AML 10 mg Dose Regimen: Once daily Route of Administration: Oral	Healthy male and female subjects 36 (32)
CS8635-A-U102 (1)	3-way Cross-over, Open-label, Single-dose, Bioavailability	To determine the bioavailability of OM, AML, and HCTZ when administered together as CS-8663 and HCTZ and when administered alone.	Completed (8/2007)	Test Product: OM40/AML10 mg + HCTZ 25 mg OM40/AML10 mg HCTZ 25 mg Dose Regimen: Once daily Route of Administration: Oral	Healthy male and female subjects 36 (29)
CS8635-A-U103 (1)	2-way Cross-over, Open-label, Single-dose, Bioavailability	To determine the relative bioavailability of OM, AML, and HCTZ when administered as a fixed dose triple component formulation and as a 2-tablet regimen.	Completed (4/2008)	Test Product: OM40/AML10/HCTZ25 mg (Formulation A) OM40/HCTZ25 mg + AML10 mg Dose Regimen: Once daily Route of Administration: Oral	Healthy male and female subjects 41 (28)

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Study No. (No. of Centers)	Study Design (Period)	Primary Objectives of the Study	Study Status (Completion Date)	Test Products Dose Regimen Route of Administration	Type of Patients Number Randomized (Number Completed)
CS8635-A-U104 (1)	2-way Cross-over, Open-label, Single-dose, Bioavailability	To determine the relative bioavailability of OM, AML, and HCTZ when administered as a fixed dose triple component formulation and as a 2-tablet regimen.	Completed (2/2008)	Test Product: OM40/AML10/HCTZ25 mg (Formulation B) OM40/HCTZ25 mg + AML10 mg Dose Regimen: Once daily Route of Administration: Oral	Healthy male and female subjects 32 (28)
CS8635-A-E105 (1)	3-way Cross-over, Open-label, Single-dose, Bioequivalence	To compare the pharmacokinetics of OM, AML, and HCTZ when administered as the Market Image Formulation versus the 2 reference clinical formulations at the dose strengths of OM40/AML10/HCTZ25 and OM20/AML5/HCTZ12.5 mg.	Completed (3/2009)	Test Product: OM40/AML10/HCTZ25 mg OM40/HCTZ25 mg + AML 10 mg OM40/AML10 mg +HCTZ 25 mg OM20/AML5/HCTZ12.5 mg OM20/HCTZ12.5 mg + AML 5 mg OM20/AML5 mg + HCTZ 12.5 mg Dose Regimen: Once daily Route of Administration: Oral	Healthy male and female subjects 72 (57)
CS8635-A-U106 (1)	2-way Cross-over, Open-label, Single-dose, Bioavailability	To compare the pharmacokinetics of OM, AML, and HCTZ when administered as the highest strength dose combination of the CS-8635 Market Image Formulation (OM40/AML10/HCTZ25) under fed and fasting conditions.	Completed (11/2008)	Test Product: OM40/AML10/HCTZ25 mg Dose Regimen: Once daily Route of Administration: Oral	Healthy male and female subjects 34 (33)

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.
Sources: CS8635-A-U301, CS8663-A-U301, CS8663-A-E303, SP-OLM-03-05, CS8635-A-U101, CS8635-A-U102, CS8635-A-U103, CS8635-A-U104, CS8635-A-E105, and CS8635-A-U106 Clinical Study Reports

4.3 Review Strategy

This review is a joint clinical-statistical review. The focus of this review is primarily the results of the double blind, randomized, placebo controlled efficacy study CS8635-A-U301.

The safety information was derived from the studies listed above as well as SP-OLM-03-05 OLMETREAT, a non IND study conducted in Europe.

4.4 Data Quality and Integrity

A routine DSI inspection was requested for study CS8635-AU301. The site inspected was found to have adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. There were minor protocol violations but DSI concluded that “the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.”

4.5 Compliance with Good Clinical Practices

Each protocol used to support this new indication stated that the study was to be conducted in compliance with Good Clinical Practices. With the exception of minor protocol violations, there is no indication that good clinical practices were not followed by any investigator.

4.6 Financial Disclosures

FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators):

The investigators listed in 1.3.4 of the original NDA submission did not, according to the sponsor, enter into any financial arrangements with Daiichi Sankyo whereby the value of compensation to the investigators could be affected by the outcome of the studies. The investigators were required to disclose to Daiichi Sankyo whether they have a proprietary interest in the product or a significant equity in Daiichi Sankyo and they did not disclose any such interests. The investigators were not recipients of significant payments of other sorts.

(b) (6) disclosed that he has received from Daiichi Sankyo (b) (6) honoraria for medical lectures and (b) (6) as a consultant. The safeguards provided within the study protocol prevented undue influence on the study results for all investigators and it was concluded by the sponsor that the participation of (b) (6) in the (b) (6) study would have no impact on the overall study results for the following reasons:

- The study was a double-blind clinical trial;
- Automated blood pressure monitoring was used to measure efficacy of the study medication;
- Monitoring of the study site was performed;
- Upon study completion there was a request for an updated financial disclosure form; and
- (b) (6) site did not randomize a significant percent of study subjects (b) (6).

4.7 Addendum to CS8635-A-U301 Week 12 Clinical Study Report (March 13, 2010)

The sponsor submitted this addendum to address discrepancies between the data presented in the CS8635-A-U301 Week 12 Clinical Study Report (CSR) dated 09 July 2009 and the final database of the complete CS8635-A-U301 study. According to the sponsor, this addendum to the CS8635-A-U301 Week 12 CSR provides the updated safety information relative to the key safety conclusions and provides a description of other minor changes to the data presented for the double-blind portion of the study (Day 1 to Week 12).

The CS8635-A-U301 Week 12 CSR was written and finalized after all subjects completed the double-blind portion of the study and while most subjects were still enrolled in the 40-week, open-label portion of the study. With the continued collection of data during the open-label portion of the CS8635-A-U301 study and through the query resolution process, several changes were made to the double-blind portion of the database, which are now incorporated as part of the database for the double-blind portion of the study and the full CS8635-A-U301 Week 54 final database. The differences between the databases for the CS8635-A-U301 Week 12 CSR and the full CS8635-A-U301 Week 54 study database included, but were not limited to: adverse events, medical history, concomitant medications, laboratory data, drug accountability, demography, dose dates, vital signs, physical examinations, and electrocardiogram data. In this addendum, key safety tables that were affected by changes in the final database from the time of the data snapshot for the CS8635-A-U301 Week 12 CSR to the time of the lock of the final database following completion of the CS8635-A-U301 study are provided, as well as a summary of the changes.

The analysis for the CS8635-A-U301 Week 12 CSR was based on a snapshot of the database that was created after all subjects completed their Week 12 visit. This interim snapshot was cleaned and a Week 12 analysis database was created where any records that occurred after each subject's Week 12 visit were removed; therefore, the analysis database only contained data up through Week 12. The same process of creating a final Week 12 analysis database was repeated following the completion of the study and

locking of the full CS8635-A-U301 Week 54 final database. The final Week 12 analysis database was created and compared to the original (interim) Week 12 analysis database to identify any changes or differences that existed between the 2. Every dataset was compared and selected adverse event, concomitant medication, medical history, and laboratory tables that were created for the CS8635-A-U301 Week 12 CSR were generated for this addendum based on the final Week 12 analysis database. Differences between the 2 analysis results were identified and used to evaluate all conclusions made in the CS8635-A-U301 Week 12 CSR.

I reviewed the addendum and the tables that were altered. I included both the original table as well as the revised table in this review as I deemed necessary. No changes were made to the efficacy portion of the review.

Overall, the changes did not alter my original conclusions about the safety of this drug.

5 CLINICAL PHARMACOLOGY

Review pending

6 REVIEW OF EFFICACY

Proof of clinical efficacy for this product relies mainly upon the results from study CS8635-A-U301, a large, double-blind, placebo controlled parallel-group trial that included nearly 2500 subjects with hypertension.

Title of Study A Randomized, Double-Blind, Parallel Group Study Evaluating the Efficacy and Safety of Co-Administration of a Triple Combination Therapy of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorothiazide in Subjects with Hypertension

Study procedures

The study was conducted at 317 sites in the United States. It consisted of 3 periods: a washout period (Period I), a 12-week, double-blind treatment period (Period II), and an open-label extension period (Period III). The efficacy review only pertains to Period II. Period III is reviewed under safety.

On Day 1, subjects were randomized to a blinded treatment sequence for the 12-week Period II. The first two weeks began with either placebo (n=36) or one of three dual combinations (n=788/treatment arm). After 2-weeks the placebo subjects were equally distributed to one of the dual combination treatments for an additional two weeks. Those subjects already on the dual combination treatments remained on their current treatment for an additional two weeks. After the 4-week adjustment, subjects were either kept to the same dosing regimen or increased to the triple combination for additional 8 weeks.

Period II						
Sequence	2 Weeks		2 Weeks		8 Weeks	n
1	OM/AML/HCTZ 0/10/25	→	OM/AML/HCTZ 0/10/25	→	OM/AML/HCTZ 0/10/25	591
2	OM/AML/HCTZ 0/10/25	→	OM/AML/HCTZ 0/10/25	→	OM/AML/HCTZ 40/10/25	197
3	OM/AML/HCTZ 40/10/0	→	OM/AML/HCTZ 40/10/0	→	OM/AML/HCTZ 40/10/0	591
4	OM/AML/HCTZ 40/10/0	→	OM/AML/HCTZ 40/10/0	→	OM/AML/HCTZ 40/10/25	197
5	OM/AML/HCTZ 40/0/25	→	OM/AML/HCTZ 40/0/25	→	OM/AML/HCTZ 40/0/25	591
6	OM/AML/HCTZ 40/0/25	→	OM/AML/HCTZ 40/0/25	→	OM/AML/HCTZ 40/10/25	197
7	OM/AML/HCTZ 0/0/0	→	OM/AML/HCTZ 0/10/25	→	OM/AML/HCTZ 0/10/25	9
8	OM/AML/HCTZ 0/0/0	→	OM/AML/HCTZ 0/10/25	→	OM/AML/HCTZ 40/10/25	3
9	OM/AML/HCTZ 0/0/0	→	OM/AML/HCTZ 40/10/0	→	OM/AML/HCTZ 40/10/0	9
10	OM/AML/HCTZ 0/0/0	→	OM/AML/HCTZ 40/10/0	→	OM/AML/HCTZ 40/10/25	3
11	OM/AML/HCTZ 0/0/0	→	OM/AML/HCTZ 40/0/25	→	OM/AML/HCTZ 40/0/25	9
12	OM/AML/HCTZ 0/0/0	→	OM/AML/HCTZ 40/0/25	→	OM/AML/HCTZ 40/10/25	3

Protocol amendments

Minor amendments to the protocol were made on January 7, 2009.

Stratifications

Subjects were stratified based on age (< 65 or ≥ 65 years), diabetes status (yes or no), and race (black or non-black). There was one subset of 36 newly diagnosed (referred to as treatment naïve) subjects who were first randomized to placebo for the first 2 weeks of treatment followed by assignment to a dual combination for 2 weeks. At Week 4, all subjects either remained on his/her dual combination therapy or began the triple combination therapy.

Inclusion criteria

A subject was included in this study if during Period I they meet all the following inclusion criteria and none of the exclusion criteria:

1. Provide informed consent for the main study.
2. Demonstrable hypertension defined as *mean sitting trough cuff* blood pressure ≥ 140/100 mmHg (SeSBP ≥ 140 mmHg and SeDBP ≥ 100 mmHg) or *mean sitting trough cuff* BP ≥ 160/90 mmHg (SeSBP ≥ 160 mmHg and SeDBP ≥ 90 mmHg). The difference in mean SeSBP/SeDBP between two consecutive visits prior to randomization had to be ≤ 20/10 mmHg. Subjects newly diagnosed or naive to hypertension medication had to meet this requirement at Visit 1 and Visit 2. Subjects washing out of hypertension medication must meet this requirement at least by Visit 2 and 2.1 or Visit 2.1 and 2.2 (if needed).
3. Male or female subjects 18 years of age or older who are of childbearing potential at the screening visit may enroll if at least four of the following criteria were met:
 - Negative urine pregnancy test at screening
 - Not lactating
 - Do not plan to become pregnant during the study

- Will practice birth control throughout the study by the following: oral or patch contraceptive, injectable or implantable contraceptive medication, intrauterine device, diaphragm or female condom plus spermicide
- Non childbearing potential must be classified by one of the following criteria
 - Had a hysterectomy or tubal ligation at least 6 months prior to consent
 - Has been postmenopausal for a least 1 year.

Exclusion Criteria

Subjects who met any of the following criteria were not to be randomized into the study:

1. *Mean sitting trough cuff DBP* <90 mmHg or *mean sitting trough cuff SBP* <140 mmHg (off antihypertensive medication).
 2. Subjects with uncontrolled hypertension taking multiple antihypertensive therapies (at the discretion of the investigator).
 3. Signs or symptoms which could exacerbate the occurrence of hypotension such as volume and salt depletion.
 4. History of hypertensive encephalopathy, stroke or transient ischemic attack (TIA).
 5. Participation in another clinical trial involving an investigational drug within one month prior to screening.
 6. History of myocardial infarction, percutaneous transluminal coronary revascularization, coronary artery bypass graft, and/or unstable angina within the past 6 months.
 7. Any history of New York Heart Association Class III or IV congestive heart failure (CHF). A history of New York Heart Association Class I or II CHF may be exclusionary at the discretion of the investigator.
 8. History of secondary hypertension including renal disease, pheochromocytoma, or Cushing's syndrome.
 9. Uncorrected coarctation of the aorta, bilateral renal artery stenosis, or unilateral renal artery stenosis in a solitary kidney.
 10. Evidence of symptomatic resting bradycardia.
 11. Evidence of hemodynamically significant cardiac valvular disease.
 12. Presence of heart block greater than first degree atrioventricular block, chronic atrial fibrillation or flutter.
 13. Uncontrolled Type I or Type II diabetes defined as HbA1c >9.0%. Diabetics must have documentation of HbA1c within 6 months of the Screening Visit. Undocumented subjects must have their HbA1c assessed prior to randomization.
- Note: Subjects with Type I or Type II diabetes controlled with insulin, diet or oral hypoglycemic agents on a stable dose for at least 30 days may be included.
14. Evidence of liver disease as indicated by ALT and AST and/or total bilirubin >3 times the upper limit of normal.
 15. Severe renal insufficiency defined as a creatinine clearance (based on the Cockcroft-Gault formula) of <30 mL/min.
 16. Clinically significant laboratory elevations at Visit 1 that compromise subject safety, based on the investigator's judgment. Consideration should take into account the potential laboratory effects of the component blinded therapies.
 17. Positive for any one of the following tests: hepatitis B surface antigen, hepatitis C antibody (confirmed by radio immunobinding assay, RIBA) or HIV antibody (confirmed by western blot assay).

18. Subjects with malignancy during the past 2 years excluding squamous cell or basal cell carcinoma of the skin.
19. Known allergy to any of the medications used in the study.
20. Subjects who require or are taking any concomitant medication, which may interfere with the objectives of the study (Refer to Section 5.2 for a listing of excluded medications).
21. Pregnant or lactating females.
22. Current history of drug or alcohol abuse.
23. A subject with any medical condition, which in the judgment of the Investigator would jeopardize the evaluation of efficacy or safety and/or constitute a significant safety risk to the subject.

Primary objective³

The primary objective of the study was to determine if the triple combination of OM 40 mg + AML 10 mg + HCTZ 25 mg is more efficacious in lowering seated diastolic blood pressure (SeDBP) compared to OM 40 mg + AML 10 mg, OM 40 mg + HCTZ 25 mg, and AML 10 mg + HCTZ 25 mg after 12 weeks of treatment.

Secondary objectives:

- To evaluate the antihypertensive efficacy for SeDBP lowering with co-administration of the triple combination OM 40 mg + AML 10 mg + HCTZ 25 mg compared to the corresponding dual components (OM 40 mg + AML 10 mg, OM 40 mg + HCTZ 25 mg, and AML 10 mg + HCTZ 25 mg) after 6, 8, and 10 weeks of treatment.
- To evaluate the antihypertensive efficacy for seated systolic blood pressure (SeSBP) lowering with co-administration of the triple combination OM 40 mg + AML 10 mg + HCTZ 25 mg compared to the corresponding dual components (OM 40 mg + AML 10 mg, OM 40 mg + HCTZ 25 mg, and AML 10 mg + HCTZ 25 mg) after 6, 8, 10, and 12 weeks of treatment.
- To evaluate the number (%) of subjects achieving blood pressure goal (defined as blood pressure <140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease [defined as creatinine clearance \geq 30 mL/min and \leq 60 mL/min], or chronic cardiovascular disease) and blood pressure targets of <140/90 mmHg, <130/85 mmHg, <130/80 mmHg and <120/80 mmHg, SeDBP <90 mmHg, and SeSBP <140 mmHg.
- To characterize the pharmacokinetic interactions and corresponding pharmacodynamic correlation (i.e., blood pressure lowering) of co-administration of OM 40 mg + AML 10 mg + HCTZ 25 mg using population pharmacokinetic sampling and modeling in a subset of subjects (n ~960 subjects, ~240 per treatment arm).
- To evaluate the change from baseline in 24-hour ambulatory blood pressure monitoring (ABPM) following 12 weeks of double-blind treatment in a subset of subjects (n ~240 subjects, 60 per treatment arm) with both baseline and end of Period II ABPM. This includes: (1) change from

³ Blood pressures were obtained at trough, i.e., 24 hours after the last dose of study drug.

baseline in mean daytime (8AM to 4PM), mean nighttime (10PM to 6AM), and mean 24-hour ABPM, (2) change from baseline in mean ABPM during the last 2, 4, and 6 hours of the dosing interval, and (3) percentage of subjects achieving mean 24-hour, daytime, nighttime, and last 2-, 4-, and 6-hour ABPM blood pressure targets:

<140/90 mmHg, <135/85 mmHg, <130/80 mmHg,
 <120/80 mmHg, SeDBP <90 mmHg, and SeSBP
 <140 mmHg after 12 weeks of treatment.

- To perform exploratory efficacy evaluations for changes in blood pressure at the end of Period II for responder and non-responder subjects to goal at Week 4 (non-responders [i.e., not at blood pressure goal] defined as having blood pressure \geq 140/90 mmHg; \geq 130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease; if either the systolic blood pressure (SBP) or diastolic blood pressure (DBP) value is greater than or equal to the given value for blood pressure goal, then the subject is considered not at goal and thus, a non-responder).
- To perform exploratory evaluations of the results of the Patient Reported Outcomes (PRO) questionnaires at baseline and Week 12.
- To perform exploratory evaluations of changes in microalbuminuria at the end of Period II.

Results

Disposition of Subjects

There were 2492 subjects randomized on Day 1. The randomization scheme is shown below.

Table 7.1: Period II Randomization Sequence

	n	Day 1 to Week 2	Week 2 to Week 4	Week 4 to Week 12
838 subjects naïve	618	OM/AML/HCTZ 40/10/0 mg		OM/AML/HCTZ 40/10/0 mg (628 subjects)
	10	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/10/0 mg	
	4	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/10/0 mg	OM/AML/HCTZ 40/10/25 mg (210 subjects)*
	206	OM/AML/HCTZ 40/10/0 mg		
846 subjects naïve	630	OM/AML/HCTZ 40/0/25 mg		OM/AML/HCTZ 40/0/25 mg (637 subjects)
	7	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/0/25 mg	
	1	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/0/25 mg	OM/AML/HCTZ 40/10/25 mg (209 subjects)*
	208	OM/AML/HCTZ 40/0/25 mg		
808 subjects naïve	592	OM/AML/HCTZ 0/10/25 mg		OM/AML/HCTZ 0/10/25 mg (600 subjects)
	8	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 0/10/25 mg	
	6	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 0/10/25 mg	OM/AML/HCTZ 40/10/25 mg (208 subjects)*
	202	OM/AML/HCTZ 0/10/25 mg		

*In total, the OM 40 mg + AML 10 mg + HCTZ 25 mg treatment group was comprised of 627 subjects, consisting of 210, 209, and 208 subjects from each of the three dual combination assignments at Week 4.

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

Source: Post-text Table 15.1.3

The numbers of subjects randomized, completed or discontinued prematurely are shown below.

Table 7.2: Subject Disposition by Randomized Treatment Group – Day 1 to Week 12 – Randomized Set

	OM40/ AML10 (N = 628) n (%)	OM40/ HCTZ25 (N = 637) n (%)	AML10/ HCTZ25 (N = 600) n (%)	OM40/ AML10/ HCTZ25 (N = 627) n (%)	Total (N = 2492) n (%)
Enrolled					6724
Randomized	628 (100.0)	637 (100.0)	600 (100.0)	627 (100.0)	2492 (100.0)
Completed	557 (88.7)	531 (83.4)	512 (85.3)	516 (82.3)	2116 (84.9)
Discontinued	71 (11.3)	106 (16.6)	88 (14.7)	111 (17.7)	376 (15.1)
Adverse event	22 (3.5)	46 (7.2)	38 (6.3)	48 (7.7)	154 (6.2)
Withdrawal by subject	20 (3.2)	21 (3.3)	19 (3.2)	23 (3.7)	83 (3.3)
Lost to follow-up	15 (2.4)	17 (2.7)	21 (3.5)	26 (4.1)	79 (3.2)
Protocol violation	11 (1.8)	13 (2.0)	9 (1.5)	8 (1.3)	41 (1.6)
Non-antihypertensive concomitant medication	0 (0.0)	2 (0.3)	1 (0.2)	2 (0.3)	5 (0.2)
Failure to comply with protocol requirements	8 (1.3)	6 (0.9)	6 (1.0)	3 (0.5)	23 (0.9)
Randomized in error	2 (0.3)	3 (0.5)	1 (0.2)	3 (0.5)	9 (0.4)
Other protocol violations	1 (0.2)	2 (0.3)	1 (0.2)	0 (0.0)	4 (0.2)
Other	3 (0.5)	9 (1.4)	1 (0.2)	6 (1.0)	19 (0.8)
Safety Set	628 (100.0)	637 (100.0)	600 (100.0)	626 (99.8)	2491 (100.0)
Safety Set 2	596 (94.9)	580 (91.1)	552 (92.0)	574 (91.5)	2302 (92.4)
Full Analysis Set	624 (99.4)	627 (98.4)	593 (98.8)	614 (97.9)	2458 (98.6)
Full Analysis Set 2	586 (93.3)	575 (90.3)	544 (90.7)	568 (90.6)	2273 (91.2)
Per-Protocol Set	528 (84.1)	513 (80.5)	494 (82.3)	490 (78.1)	2025 (81.3)
ABPM Analysis Set	112 (17.8)	116 (18.2)	95 (15.8)	117 (18.7)	440 (17.7)

For a definition of the analysis populations, see Section 7.1.

Note: 4 subjects who were simultaneously randomized at 2 different study sites are not included in any count on this table.

ABPM = ambulatory blood pressure monitoring; AML = amlodipine; HCTZ = hydrochlorothiazide;

OM = olmesartan medoxomil.

Sources: Post-text Tables 15.1.1 and 15.1.2

The number of subjects per treatment group randomized ranged from 600 to 637. The percent of subjects per treatment group completing the study ranged from 82% (OM40/AML10/HCTZ25) to 89% (OM40/AML10). The triple combination treatment group had the largest drop out rate (18%) with adverse events being the most common reason for dropping out (8%). Other reasons for dropping out were fairly uniform across treatment groups except for lost to follow up: the triple combination treatment group had the highest lost to follow up rate (4%), double the rate of the OM40/AML10 group (2%).

The table showing subject disposition from week 4 to week 12 is shown below.

Table 15.1.5
 Subject Disposition
 Week 4 to Week 12
 Randomized Set - Subjects Proceeding Past Week 4

	OM40/AML10 (N= 595)	OM40/HCTZ25 (N= 581)	AML10/HCTZ25 (N= 552)	OM40/AML10/HCTZ25 (N= 575)	Total (N=2303)
Randomized	595 (100.0)	581 (100.0)	552 (100.0)	575 (100.0)	2303 (100.0)
Completed	557 (93.6)	531 (91.4)	512 (92.8)	516 (89.7)	2116 (91.9)
Discontinued	38 (6.4)	50 (8.6)	40 (7.2)	59 (10.3)	187 (8.1)
Adverse Event	7 (1.2)	11 (1.9)	12 (2.2)	23 (4.0)	53 (2.3)
Withdrawal by Subject	15 (2.5)	15 (2.6)	7 (1.3)	14 (2.4)	51 (2.2)
Lost to Follow-up	8 (1.3)	9 (1.5)	14 (2.5)	13 (2.3)	44 (1.9)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Violation	6 (1.0)	7 (1.2)	7 (1.3)	5 (0.9)	25 (1.1)
Non-antihypertensive Concomitant Medication	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.3)	4 (0.2)
Antihypertensive Concomitant Medication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Failure to Comply with Protocol Requirements	5 (0.8)	6 (1.0)	6 (1.1)	2 (0.3)	19 (0.8)
Randomized in Error	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study Terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (0.3)	8 (1.4)	0 (0.0)	4 (0.7)	14 (0.6)

Percentage is calculated using the number of subjects in the column heading as the denominator.
 Note: 4 subjects who were randomized at more than one study site are not included in any count on this table.

When the first four weeks of the study (titration phase) are excluded, more subjects in the triple combination did not complete the study compared to the dual therapies. As expected, this was mostly the result of drop outs because of adverse events. Overall, the rate for drop outs was low (10% for subjects in the triple combination group dropping out for any reason and 4% dropping out for an adverse event).

Subject types

The subject demographics are shown below by treatment group.

Table 7.3: Demographic and Baseline Characteristics – Randomized Set

	OM40/ AML10 (N = 628)	OM40/ HCTZ25 (N = 637)	AML10/ HCTZ25 (N = 600)	OM40/ AML10/ HCTZ25 (N = 627)	P-value [6]
Age (years)					
N	628	637	600	627	0.1353
Mean (SD)	55.1 (10.93)	55.9 (10.78)	54.6 (10.82)	54.7 (11.22)	
Age Group (n, %) [1]					
<65 years	508 (80.9)	505 (79.3)	504 (84.0)	504 (80.4)	0.1793
≥65 years	120 (19.1)	132 (20.7)	96 (16.0)	123 (19.6)	
≥75 years	25 (4.0)	19 (3.0)	17 (2.8)	18 (2.9)	
Gender (n, %) [1]					
Male	325 (51.8)	339 (53.2)	334 (55.7)	320 (51.0)	0.3802
Female	303 (48.2)	298 (46.8)	266 (44.3)	307 (49.0)	
Ethnicity (n, %) [1]					
Hispanic or Latino	90 (14.3)	85 (13.3)	98 (16.3)	96 (15.3)	0.4946
Not Hispanic or Latino	538 (85.7)	551 (86.5)	502 (83.7)	531 (84.7)	
Race (n, %) [1,2]					
Caucasian/White	432 (68.8)	422 (66.2)	395 (65.8)	415 (66.2)	0.6671
Black/African or African American	181 (28.8)	200 (31.4)	192 (32.0)	184 (29.3)	0.5531
Asian	13 (2.1)	10 (1.6)	7 (1.2)	19 (3.0)	0.1011
American Indian or Alaskan Native	3 (0.5)	1 (0.2)	4 (0.7)	1 (0.2)	0.3561
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.3)	0.5736
Other	0 (0.0)	4 (0.6)	5 (0.8)	6 (1.0)	0.1289
Weight (kg)					
N	628	637	600	627	0.9982
Mean (SD)	95.9 (22.65)	96.1 (22.55)	96.1 (23.41)	96.0 (23.24)	
Height (cm)					
N	628	637	600	627	0.8804
Mean (SD)	170.1 (10.37)	170.3 (10.52)	170.4 (10.96)	170.0 (10.50)	
BMI (kg/m²) [3]					
N	628	637	600	627	0.9821
Mean (SD)	33.1 (7.27)	33.1 (7.25)	33.0 (7.05)	33.2 (6.99)	
Obesity (n, %) [1,3]					
BMI <30 kg/m ²	229 (36.5)	238 (37.4)	230 (38.3)	240 (38.3)	0.8918
BMI ≥30 kg/m ²	399 (63.5)	399 (62.6)	370 (61.7)	387 (61.7)	
Diabetic (n, %) [1]					
Yes	100 (15.9)	99 (15.5)	92 (15.3)	96 (15.3)	0.9900
No	528 (84.1)	538 (84.5)	508 (84.7)	531 (84.7)	
Smoking History (n, %) [1]					
Non-Smoker	373 (59.4)	366 (57.5)	357 (59.5)	337 (53.7)	0.2105
Ex-Smoker	126 (20.1)	143 (22.4)	110 (18.3)	140 (22.3)	
Current Smoker	129 (20.5)	128 (20.1)	132 (22.0)	150 (23.9)	
Cardiovascular Disease Status (n, %) [1]					
Yes	56 (8.9)	61 (9.6)	55 (9.2)	55 (8.8)	0.9630
No	572 (91.1)	576 (90.4)	545 (90.8)	572 (91.2)	
Chronic Renal Disease Status (n, %) [1,4]					
Yes	29 (4.6)	25 (3.9)	29 (4.8)	20 (3.2)	0.4615
No	599 (95.4)	609 (95.6)	571 (95.2)	607 (96.8)	

Table 7.3: Demographic and Baseline Characteristics – Randomized Set (Continued)

	OM40/ AML10 (N = 628)	OM40/ HCTZ25 (N = 637)	AML10/ HCTZ25 (N = 600)	OM40/ AML10/ HCTZ25 (N = 627)	P-value [6]
Antihypertensive Medication Status (n, %) [1]					
Naïve/Not Taken Within 3 Weeks of Screening	207 (33.0)	192 (30.1)	205 (34.2)	231 (36.8)	0.0869
Taken Within 3 Weeks of Screening	421 (67.0)	445 (69.9)	395 (65.8)	396 (63.2)	
Duration of Hypertension (years) [5]					
N	628	636	600	627	0.4339
Mean (SD)	10.1 (9.87)	10.3 (9.83)	9.7 (8.98)	9.5 (9.56)	
Subjects Requiring BP goal of: (n, %) [1]					
BP <140/90 mmHg	467 (74.4)	475 (74.6)	443 (73.8)	480 (76.6)	0.7048
BP <130/80 mmHg [7]	161 (25.6)	162 (25.4)	157 (26.2)	147 (23.4)	

1. Percentage is calculated using the number of subjects in the column heading as the denominator.
 2. Subjects are permitted to select more than one race.
 3. Body mass index = Weight (kg)/(Height (m))².
 4. Chronic renal disease is defined as screening creatinine clearance ≥30 mL/min and ≤60 mL/min.
 5. Duration of hypertension = (date of informed consent – date of diagnosis of hypertension + 1)/365.25.
 6. P-values tested for a significant difference among the treatment groups are obtained from a Chi-square test for categorical variables and ANOVA with treatment as the main effect for continuous variables.
 7. Subjects with diabetes, chronic renal disease, or chronic cardiovascular disease required a lower BP goal.
- AML = amlodipine; ANOVA = Analysis of Variance; BMI = body mass index; BP = blood pressure;
HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; SD = standard deviation.
Source: Post-text Table 15.1.7

Overall, the mean age was nearly 55 years and each of the treatment group had between 3% and 4% of subjects being at least 75 years old. There were more males randomized than females. Approximately 66% of subjects were white and 30% were black. The mean BMI was 33 kg/m² and 15% of subjects reported being diabetic. Around 9% of subjects reported cardiovascular disease and 4% had chronic renal disease. Approximately 33% of subjects were naïve to antihypertensive treatment at the start of the study. The mean duration of hypertension was 10 years. The treatment groups were fairly well balanced for all listed characteristics.

Baseline blood pressures

The table below shows baseline mean seated diastolic and systolic blood pressures and heart rates by treatment group.

Table 7.4: Baseline Blood Pressure and Heart Rate – Randomized Set

	OM40/ AML10 (N = 628) n (%)	OM40/ HCTZ25 (N = 637) n (%)	AML10/ HCTZ25 (N = 600) n (%)	OM40/ AML10/ HCTZ25 (N = 627) n (%)	P-value [2]
Seated Diastolic Blood Pressure (mmHg) [1]					
N	628	637	600	627	0.6224
Mean (SD)	100.9 (7.80)	100.7 (8.18)	101.3 (7.58)	100.9 (7.43)	
Seated Systolic Blood Pressure (mmHg) [1]					
N	628	637	600	627	0.3997
Mean (SD)	168.1 (13.50)	169.0 (14.94)	168.9 (14.48)	167.9 (13.40)	
Heart Rate (bpm)					
N	628	637	600	627	0.3491
Mean (SD)	76.7 (10.98)	76.9 (11.46)	75.8 (11.35)	76.8 (11.21)	

1. Baseline for blood pressure was defined as the mean of the randomization visit and the visit immediately preceding randomization.

2. P-values tested for a significant difference among the treatment groups are obtained from ANOVA.

AML = amlodipine; ANOVA = Analysis of Variance; HCTZ = hydrochlorothiazide;

OM = olmesartan medoxomil; SD = standard deviation.

Source: Post-text Table 15.1.7

The mean baseline blood pressures and heart rates were similar across treatment groups (approximately 168/101 mmHg and 77 bpm, respectively).

A section of the entry criterion required subjects to have stage 2 hypertension (defined as systolic blood pressures ≥ 160 mmHg or diastolic blood pressures ≥ 100 mmHg). The table below shows the baseline blood pressure stage and severity by treatment group.

Table 7.5: Baseline Hypertension Class – Randomized Set

	OM40/ AML10 (N = 628) n (%)	OM40/ HCTZ25 (N = 637) n (%)	AML10/ HCTZ25 (N = 600) n (%)	OM40/ AML10/ HCTZ25 (N = 627) n (%)	P-value [2]
Baseline Hypertension Class (n, %) [1]					
Stage 1	64 (10.2)	82 (12.9)	62 (10.3)	70 (11.2)	0.4053
Stage 2	552 (87.9)	540 (84.8)	521 (86.8)	542 (86.4)	
Mild	64 (10.2)	82 (12.9)	62 (10.3)	70 (11.2)	0.1379
Moderate	392 (62.4)	378 (59.3)	350 (58.3)	403 (64.3)	
Severe	160 (25.5)	162 (25.4)	171 (28.5)	139 (22.2)	
Subjects with BP below lower limit of Stage 1 or Mild classification [3]	12 (1.9)	15 (2.4)	17 (2.8)	15 (2.4)	

The Stage 1 hypertension class includes subjects with systolic blood pressures from 140 mmHg to <160 mmHg and diastolic blood pressures from 90 mmHg to <100 mmHg. The Stage 2 hypertension class includes subjects with systolic blood pressures ≥ 160 mmHg or diastolic blood pressures ≥ 100 mmHg.

The mild hypertension class includes subjects with systolic blood pressures from 140 mmHg to <160 mmHg and diastolic blood pressures from 90 mmHg to <100 mmHg. The moderate hypertension class includes subjects with systolic blood pressures from 160 mmHg to <180 mmHg and diastolic blood pressures from 100 mmHg to <110 mmHg. The severe hypertension class includes subjects with systolic blood pressure ≥ 180 or diastolic blood pressure ≥ 110 mmHg.

1. Percentage is calculated using the number of subjects in the column heading as the denominator.

2. P-values tested for a significant difference among the treatment groups are obtained from a Chi-square test.

3. These were subjects whose BPs at randomization were below the defined criteria for Stage 1 hypertension and mild hypertension (<140/90 mmHg).

AML = amlodipine; BP = blood pressure; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

Source: Post-text Table 15.1.7

Approximately 86% of subjects had the required stage 2 hypertension with the remaining 11% having stage 1. Approximately 25% of subjects reported severe hypertension. The groups were balanced for baseline mean blood pressures and severity of hypertension.

Concomitant medications

Approximately 80% of subjects were receiving concomitant medications during the study. The most common medications were 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, platelet aggregation inhibitors (excluding heparin) and propionic acid derivatives.

EFFICACY RESULTS

Data Sets Analyzed

The Full Analysis Set included 2458 (99%) randomized subjects who received at least one dose of study medication and had a baseline and at least 1 post-dose assessment of SeDBP.

The ABPM Analysis Set included 440 (18%) randomized subjects who provided consent to participate in the ABPM sub-study and provided ABPM measurements prior to and after randomization.

SeDBP at week 12

The table below displays the mean seated diastolic blood pressures at baseline, week 12 with LOCF and mean change from baseline at endpoint by treatment groups.

Table 8.1: Change in Seated Diastolic Blood Pressure (mmHg) from Baseline to Week 12 with LOCF – Full Analysis Set

Seated Diastolic Blood Pressure Statistics	OM40/ AML10 (N = 624)	OM40/ HCTZ25 (N = 627)	AML10/ HCTZ25 (N = 593)	OM40/ AML10/ HCTZ25 (N = 614)
n [1]	624	627	593	614
Baseline [2]				
Mean (SD)	101.0 (7.81)	100.6 (8.16)	101.2 (7.58)	100.9 (7.46)
Week 12 with LOCF [3]				
Mean (SD)	83.2 (9.86)	84.1 (11.70)	86.4 (9.45)	79.4 (10.57)
Change from Baseline				
Mean (SD)	-17.8 (9.47)	-16.5 (10.84)	-14.8 (8.78)	-21.5 (10.25)
LS Mean (SE)	-18.0 (0.45)	-16.9 (0.45)	-15.1 (0.46)	-21.8 (0.45)
P-value [4]	<0.0001	<0.0001	<0.0001	<0.0001
Comparisons	Between treatment comparisons [5]			
	LS Mean (SE)		P-value	
OM40/AML10/HCTZ25 vs. OM40/AML10	-3.8 (0.53)		<0.0001	
OM40/AML10/HCTZ25 vs. OM40/HCTZ25	-4.9 (0.53)		<0.0001	
OM40/AML10/HCTZ25 vs. AML10/HCTZ25	-6.7 (0.54)		<0.0001	

The Full Analysis Set included subjects who received at least 1 dose of study medication and had baseline and at least 1 post-dose assessment of seated diastolic blood pressure.

1. n was the number of subjects with values at both timepoints.
2. Baseline for blood pressure was defined as the average of the mean blood pressure measured at the randomization visit and the visit prior to the randomization visit.
3. Week 12 with LOCF was defined as the last available measurement during the double-blind treatment period.
4. Within treatment p-value testing for significant change from baseline was obtained from an ANCOVA model with baseline blood pressure as a covariate, and fixed effects of treatment, age group, race group, and diabetic status.
5. All treatment comparisons were calculated as OM40/AML10/HCTZ25 minus the respective dual combination treatment group. Least-squares mean differences, SEs, and 2-sided p-values were obtained from an ANCOVA model with baseline blood pressure as a covariate, and fixed effects of treatment, age group, race group, and diabetic status.

AML = amlodipine; ANCOVA = Analysis of Covariance; HCTZ = hydrochlorothiazide; LOCF = last observation carried forward; LS = least squares; OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.

Source: Post-text Table 15.2.1

The primary efficacy variable is the change from baseline in SeDBP at the end of Period II (Week 12) using LOCF for dropout patients before Week 12. The protocol indicated that there would be three treatment comparisons of interest: triple combination of OM40 mg + AML10 mg + HCTZ25 mg compared to each of the dual combinations OM40 mg + AML10 mg, OM40 mg + HCTZ25 mg, and AML10 mg + HCTZ25 mg and all three pair-wise comparisons must demonstrate statistically significant superiority at a two-sided 0.05 significance level, so no adjustment of multiplicity is necessary. The results in Table 8.1 show that all treatment groups had a significant decrease in blood pressure from baseline. The triple combination group of OM 40 + AML 10 + HCTZ 25 had a significantly greater decrease in SeDBP from baseline compared to each of the dual therapy groups and the mean differences in blood pressures between treatments ranged from -3.8 to -6.7 mmHg.

The above results indicate that all the three pair-wise comparisons show statistically significant superiority at a two-sided 0.05 significance level and therefore support the superiority of the triple combination of OM40 mg + AML10 mg + HCTZ25 mg over all the three dual combinations.

Statistical Evaluation and Comments

Using the Full Analysis Set provided by the sponsor, the reviewer confirmed the efficacy results of the primary endpoint at the end of Period II for LOCF data, derived the efficacy results for the

OC data for follow up time at Weeks 6, 8, 10 and 12 also derived efficacy results using the mixed model repeated measurement (MMRM) procedure. From the reviewer's findings, the statistical superiority of the triple combination over all the dual combinations was observed since Week 6 using OC analysis and the results are similar to those depicted in the Figure 8.1 which were derived using LOCF analyses. At the same time, MMRM analysis also gives the statistically significant results, supporting those of the OC and LOCF analyses. This is not surprising given the missing data are not heavy.

According to SAP, if less than 90% of the Full Analysis Set meets the per protocol definition, a per protocol analysis would be performed on the primary efficacy endpoint and the secondary endpoint of the change from baseline in SeSBP at Weeks 6, 8, 10 and 12, with and without LOCF. As indicated in Table 7.2, only 82.4% of the patients in the Full Analysis Set met the per protocol definition, the above proposed analyses for the per protocol set were not provided in the Case Study Report. Nonetheless, the statistical analyses by the statistical reviewer using the per protocol data set support the statistical superiority of the triple combination over all the dual combinations since Week 6.

In order to see how much the third therapy improves the SeDBP after the use of two therapies for 4 weeks, we compare the mean change of SeDBP from Week 4 to Week 12 under LOCF between Sequences 1 and 2, Sequences 3 and 4, and that of 5 and 6. So making such a comparison between Sequences 1 and 2 will show the improvement of adding OM 40 at the end of study after the treatment of AML 10 + HCTZ 25 for four weeks, similarly for comparison between Sequences 3 and 4, and between Sequences 5 and 6. Using the same analysis of covariance model as above, we have the following results: the mean difference of the SeDBP change from Week 4 to 12 between Sequence 2 and 1 is -4.42 (-5.92,-2.92) with p-value < 0.0001, the mean difference of the SeDBP change from Week 4 to 12 between Sequence 4 and 3 is -4.17 (-5.65,-2.70) with p-value < 0.0001, and the mean difference of the SeDBP change from Week 4 to 12 between Sequence 2 and 1 is -4.32 (-5.78,-2.85) with p-value < 0.0001. So after the therapy of AML 10 + HCTZ 25 for four weeks, the addition of therapy of OM40 improved a reduction of SeDBP of 4.42 after 8 weeks of therapy compared to the continuation of dual therapy.

The secondary endpoints

Seated systolic blood pressure (SeSBP)

As part of the secondary efficacy analyses, the table 8.2 displays the mean seated systolic blood pressures at baseline, week 12 with LOCF and mean change from baseline at endpoint by treatment groups.

Table 8.2: Change in Seated Systolic Blood Pressure (mmHg) from Baseline to Week 12 with LOCF – Full Analysis Set

Seated Systolic Blood Pressure Statistics	OM40/ AML10 (N = 624)	OM40/ HCTZ25 (N = 627)	AML10/ HCTZ25 (N = 593)	OM40/ AML10/ HCTZ25 (N = 614)
n [1]	624	627	593	614
Baseline [2]				
Mean (SD)	168.2 (13.50)	169.0 (14.88)	168.9 (14.47)	168.0 (13.40)
Week 12 with LOCF [3]				
Mean (SD)	137.0 (15.66)	137.8 (19.99)	140.0 (14.60)	129.8 (16.70)
Change from Baseline				
Mean (SD)	-31.1 (15.44)	-31.2 (18.58)	-28.9 (15.12)	-38.1 (17.40)
LS Mean (SE)	-30.0 (0.74)	-29.7 (0.73)	-27.5 (0.76)	-37.1 (0.74)
P-value [4]	<0.0001	<0.0001	<0.0001	<0.0001
Comparisons	Between treatment comparisons [5]			
	LS Mean (SE)		P-value	
OM40/AML10/HCTZ25 vs. OM40/AML10	-7.1 (0.87)		<0.0001	
OM40/AML10/HCTZ25 vs. OM40/HCTZ25	-7.4 (0.86)		<0.0001	
OM40/AML10/HCTZ25 vs. AML10/HCTZ25	-9.6 (0.88)		<0.0001	

The Full Analysis Set included subjects who received at least 1 dose of study medication and had baseline and at least 1 post-dose assessment of seated diastolic blood pressure.

1. n was the number of subjects with values at both timepoints.
2. Baseline for blood pressure was defined as the average of the mean blood pressure measured at the randomization visit and the visit prior to the randomization visit.
3. Week 12 with LOCF was defined as the last available measurement during the double-blind treatment period.
4. Within treatment p-value testing for significant change from baseline was obtained from an ANCOVA model with baseline blood pressure as a covariate, and fixed effects of treatment, age group, race group, and diabetic status.
5. All treatment comparisons were calculated as OM40/AML10/HCTZ25 minus the respective dual combination treatment group. Least-squares mean differences, SEs, and 2-sided p-values were obtained from an ANCOVA model with baseline blood pressure as a covariate, and fixed effects of treatment, age group, race group, and diabetic status.

AML = amlodipine; ANCOVA = Analysis of Covariance; HCTZ = hydrochlorothiazide; LOCF = last observation carried forward; LS = least squares; OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.

Source: Post-text Table 15.2.3

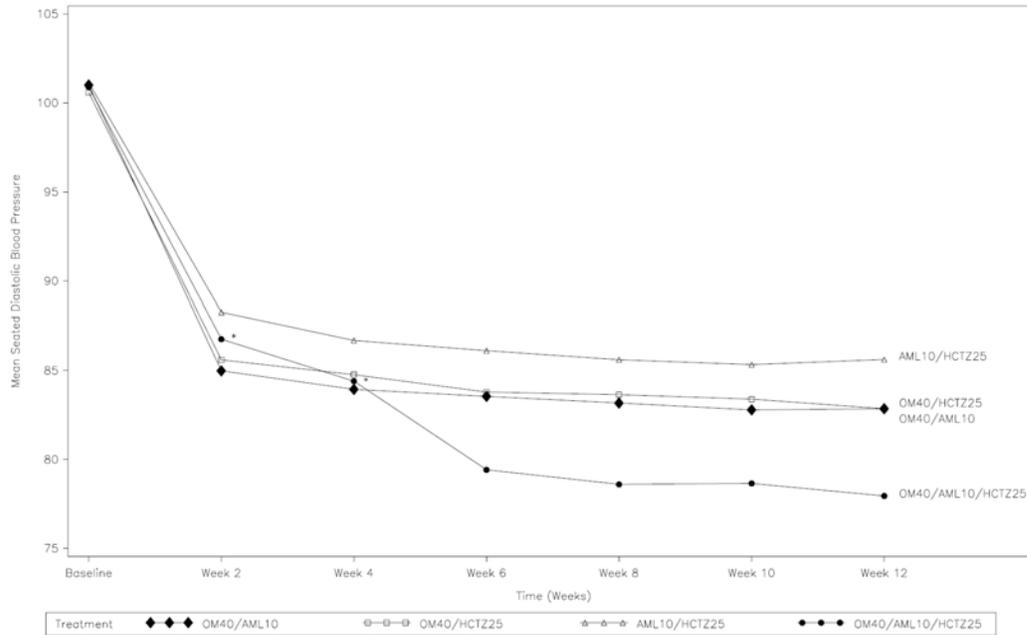
All treatment groups saw a significant drop in SeSBP from baseline to Week 12. The triple combination group had a significantly greater decrease compared to each of the dual therapy groups. The mean differences in blood pressures between treatments ranged from -7.1 to -9.6 mmHg. This is confirmed by the analysis by the reviewer.

Blood pressure at all clinic visits

N.B. Subjects who were randomized to the triple combination received either dual combination or placebo from Day 1 to Week 2; from Week 2 to Week 4, subjects who initially received placebo were switched to 1 of the dual combination treatments (as determined by their specific treatment sequence), which they received until Week 4. Triple combination therapy started at week 4.

The figures below show the mean blood pressures at the various clinic visits.

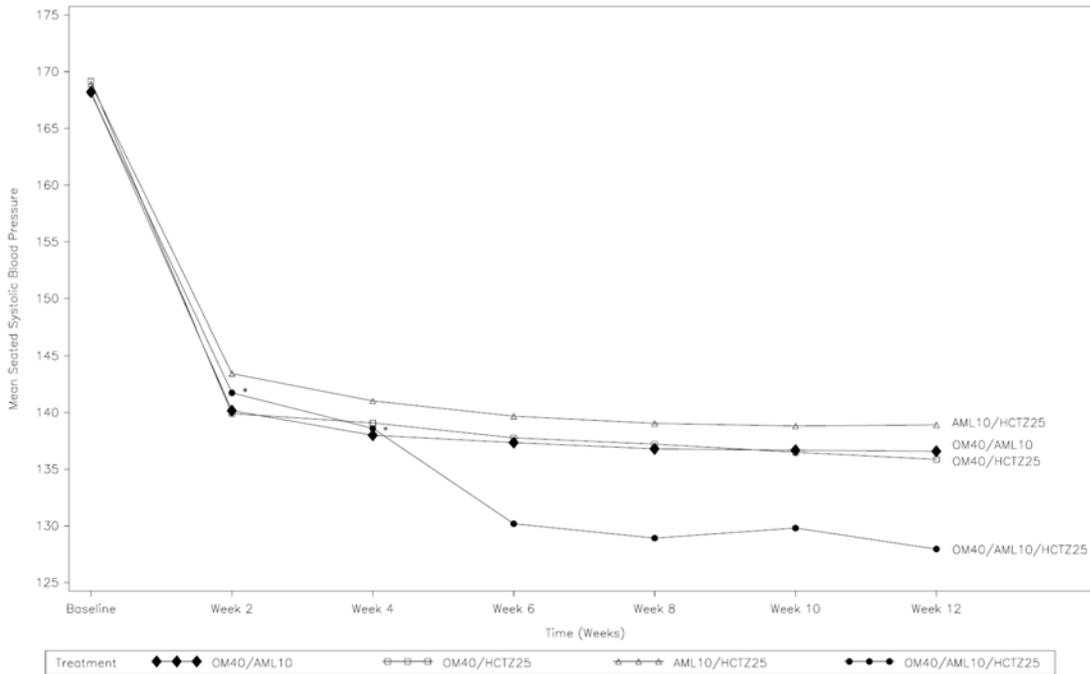
Figure 8.1: Mean Seated Diastolic Blood Pressure (mmHg) Over Time by Randomized Treatment Group – Full Analysis Set



• Prior to Week 4, subjects randomized to OM40/AML10/HCTZ25 were actually taking one of the three dual combinations.

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Figure 8.3: Mean Seated Systolic Blood Pressure (mmHg) Over Time by Randomized Treatment Group – Full Analysis Set



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* Prior to Week 4, subjects randomized to OM40/AML10/HCTZ25 were actually taking one of the three dual combinations.

Mean blood pressures at baseline, Week 2, and Week 4 were for all treatment groups. At Week 6, subjects who had been randomized to triple combination and had been taking it for 2 weeks began to experience a greater fall in blood pressure which persisted throughout the rest of the double blind treatment phase. In fact, the triple combination group started to show statistically significantly greater decrease over each of the dual therapy groups from Week 6 to Week 12 for both the primary and secondary endpoints in either the LOCF or OC data sets.

Reaching treatment goal

Table 8.3 summarizes the number of subjects reaching blood pressure goal at Week 12 with LOCF for the Full Analysis Set. Blood pressure treatment goal was defined as blood pressure <140/90 mmHg or <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease.

Table 8.3: Number (%) of Subjects Reaching Blood Pressure Treatment Goal at Week 12 with LOCF – Full Analysis Set

	OM40/ AML10 (N = 624)	OM40/ HCTZ25 (N = 627)	AML10/ HCTZ25 (N = 593)	OM40/ AML10/ HCTZ25 (N = 614)
Number achieving goal (n)	287	292	207	395
Percent achieving goal (n/N)	46.0	46.6	34.9	64.3
P-value for comparison to OM40/AML10/HCTZ25 [1]	<0.0001	<0.0001	<0.0001	

The Full Analysis Set included subjects who received at least 1 dose of study medication and had baseline and at least 1 post-dose assessment of seated diastolic blood pressure.

Blood pressure treatment goal was defined as blood pressure <140/90 mmHg (<130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease).

1. Each p-value was obtained from individual Cochran-Mantel-Haenszel tests stratified by age group, race group, and diabetic status comparing the triple combination therapy to each dual combination.

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

Source: Post-text Table 15.2.13

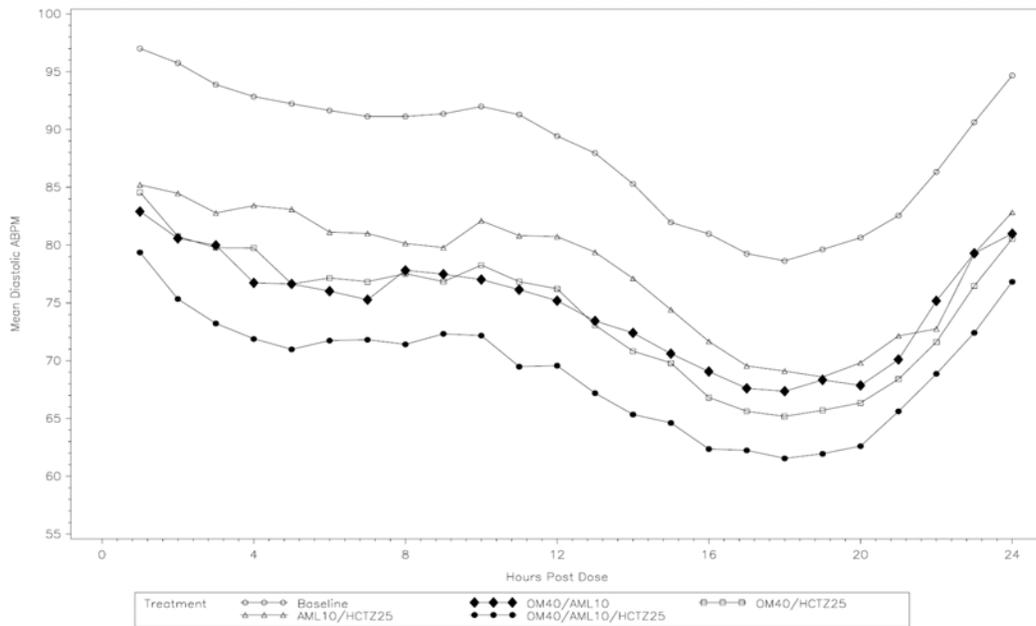
Treatment with triple combination therapy resulted in a significantly greater percentage of subjects reaching their treatment goal compared to each of the dual combination treatments. The percentage of subjects reaching blood pressure treatment goal at Week 12 with LOCF ranged from 34.9% to 46.6% for the dual combination treatment groups compared to 64.3% for the triple combination treatment group. The reviewer’s analysis confirmed the conclusions of the sponsor.

24 hour ambulatory blood pressure monitoring (24-hr ABPM)

This subgroup study involved the use of the 24 hour blood pressure device by 424 subjects to measure their 24-hour ambulatory DBP and SBP. The changes in mean 24-hour ambulatory DBP and SBP from baseline to Week 12/Early Termination for the ABPM Analysis Set are compared among the four treatment groups. Each treatment group had a statistically significant mean reduction in 24-hour DBP and SBP from baseline to Week 12/Early Termination. Triple combination therapy resulted in a significantly greater mean reduction in 24-hour SBP compared to each of its component dual therapies.

The figures below show the 24 hour blood pressure profiles for the treatment groups at baseline and at Week 12.

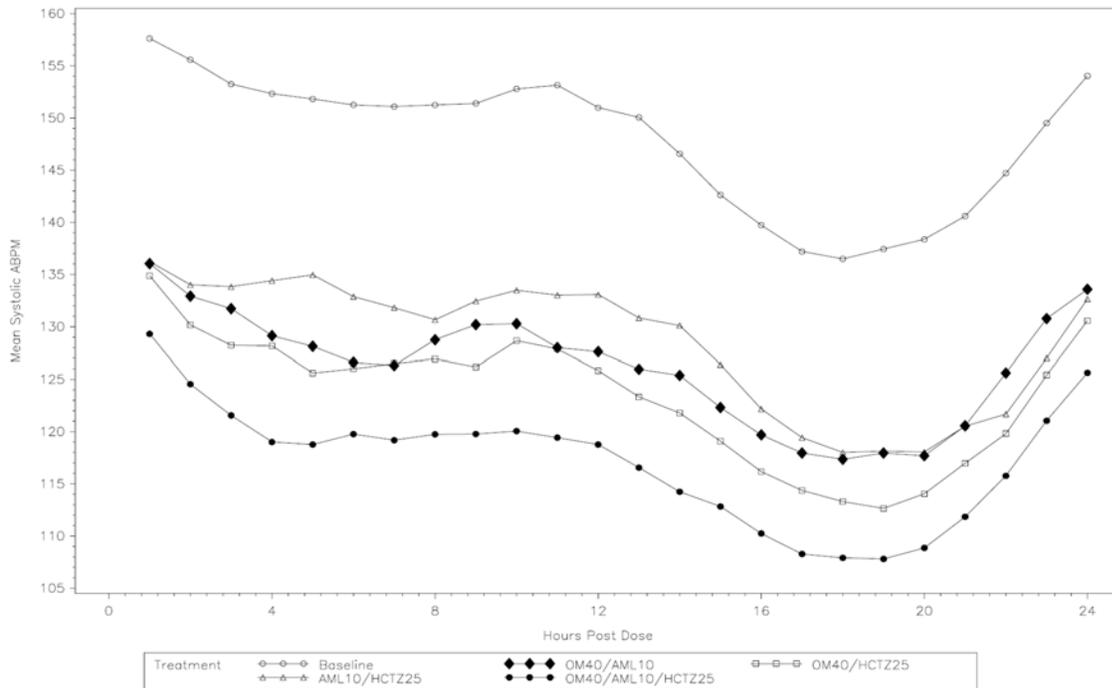
Figure 8.6: Mean Diastolic ABPM (mmHg) Over 24 Hours at Endpoint by Treatment and Hour – ABPM Analysis Set



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ABPM = ambulatory blood pressure monitoring; AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.
Source: Post-text Figure 15.2.8

Figure 8.7: Mean Systolic ABPM (mmHg) Over 24 Hours at Endpoint by Treatment and Hour – ABPM Analysis Set



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ABPM = ambulatory blood pressure monitoring; AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.
Source: Post-text Figure 15.2.9

At endpoint (week 12), the triple combination was superior to the dual combinations in lowering blood pressure throughout the 24 hour time periods.

Subgroups

The following tables show the efficacy results for selected subgroups by age, gender, race and blood pressure severity at baseline for the Full Analysis Set a Week 12 with LOCF. These results are for exploratory purposes only.

Age

Table 8.10 presents the results of the change in SeDBP from baseline to Week 12 with LOCF by age group.

Across the treatment groups, mean baseline SeDBP ranged from 101.8 mmHg to 102.1 mmHg for subjects <65 years of age, from 96.0 mmHg to 97.2 mmHg for subjects ≥65 years of age, and from 92.9 mmHg to 95.6 mmHg for subjects ≥75 years of age. Statistically significant changes in SeDBP from baseline to Week 12 with LOCF were observed in each age subgroup for all 4 treatment groups. In the subgroups of <65 years and ≥65 years of age, the triple combination therapy resulted in a significantly greater mean reduction in SeDBP from baseline to Week 12 with LOCF compared to each of the dual combination therapies. In the subgroup of ≥75 years of age, triple combination therapy resulted in a numerically greater mean reduction in SeDBP than

the dual combination therapies. There were no apparent age-related differences in terms of SeDBP reduction in any treatment group.

Table 8.10: Change in SeDBP (mmHg) from Baseline to Week 12 with LOCF – Age Subgroups – Full Analysis Set

Age Group Statistics	OM40/ AML10	OM40/ HCTZ25	AML10/ HCTZ25	OM40/ AML10/ HCTZ25
<65 Years of Age				
N [1]	504	497	497	491
Baseline [2]				
Mean (SD)	102.0 (7.66)	101.8 (7.91)	102.1 (7.52)	101.8 (7.38)
Change from Baseline				
Mean (SD)	-17.7 (9.64)	-16.8 (11.04)	-14.7 (8.80)	-21.4 (10.31)
LS Mean (SE)	-17.2 (0.42)	-16.4 (0.42)	-14.2 (0.42)	-21.0 (0.42)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
P-value for comparison to OM40/AML10/HCTZ25 [4]	<0.0001	<0.0001	<0.0001	
≥65 Years of Age				
N [1]	120	130	96	123
Baseline [2]				
Mean (SD)	96.5 (6.78)	96.0 (7.41)	96.5 (5.99)	97.2 (6.62)
Change from Baseline				
Mean (SD)	-18.1 (8.73)	-15.1 (9.99)	-15.7 (8.64)	-22.1 (10.04)
LS Mean (SE)	-20.0 (0.86)	-17.3 (0.83)	-17.6 (0.96)	-23.7 (0.85)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
P-value for comparison to OM40/AML10/HCTZ25 [4]	0.0020	<0.0001	<0.0001	
≥75 Years of Age				
N [1]	25	19	17	18
Baseline [2]				
Mean (SD)	94.9 (9.31)	95.5 (8.01)	95.6 (6.27)	92.9 (5.91)
Change from Baseline				
Mean (SD)	-20.7 (9.64)	-17.9 (11.59)	-16.2 (11.90)	-22.2 (7.49)
LS Mean (SE)	-23.3 (1.87)	-20.2 (2.15)	-18.4 (2.27)	-25.5 (2.21)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
P-value for comparison to OM40/AML10/HCTZ25 [4]	0.4323	0.0806	0.0250	

The Full Analysis Set included subjects who received at least 1 dose of study medication and had baseline and at least 1 post-dose assessment of seated diastolic blood pressure.

1. N was the number of subjects with values at both timepoints.
2. Baseline for blood pressure was defined as the average of the mean blood pressure measured at the randomization visit and the visit prior to the randomization visit.
3. Within treatment p-value testing for significant change from baseline was obtained from an ANCOVA model with baseline blood pressure as a covariate, and fixed effects of treatment, subgroup, and treatment by subgroup interaction.
4. All treatment comparisons were calculated as OM40/AML10/HCTZ25 minus the respective dual combination treatment group. The 2-sided p-values were obtained from an ANCOVA model with baseline blood pressure as a covariate, and fixed effects of treatment, subgroup, and treatment by subgroup interaction.

AML = amlodipine; ANCOVA = Analysis of Covariance; HCTZ = hydrochlorothiazide; LS = least squares; OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.

Sources: Post-text Tables 15.2.58, 15.2.59, and 15.2.60

Gender

Table 8.13 presents the results of the change in SeDBP from baseline to Week 12 with LOCF by gender. Across the treatment groups, mean baseline SeDBP ranged from 99.8 mmHg to 100.3 mmHg for females and from 101.1 mmHg to 102.1 mmHg for males. Statistically significant changes in SeDBP from baseline to Week 12 with LOCF were observed in both gender

subgroups for all 4 treatment groups. In both gender subgroups, triple combination therapy yielded a significantly greater mean reduction in SeDBP from baseline to Week 12 with LOCF compared to each of the dual combination therapies. There were no apparent gender-related differences in terms of SeDBP reduction in any treatment group.

Table 8.13: Change in SeDBP (mmHg) from Baseline to Week 12 with LOCF – Gender Subgroups – Full Analysis Set

Gender Statistics	OM40/ AML10	OM40/ HCTZ25	AML10/ HCTZ25	OM40/ AML10/ HCTZ25
Female Subjects				
N [1]	299	293	264	298
Baseline [2]				
Mean (SD)	100.3 (7.65)	100.0 (7.98)	100.1 (7.06)	99.8 (7.39)
Change from Baseline				
Mean (SD)	-18.0 (10.17)	-17.2 (10.85)	-15.3 (9.05)	-21.9 (10.25)
LS Mean (SE)	-18.3 (0.54)	-17.6 (0.55)	-15.6 (0.58)	-22.4 (0.54)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
P-value for comparison to OM40/AML10/HCTZ25 [4]	<0.0001	<0.0001	<0.0001	
Male Subjects				
N [1]	325	334	329	316
Baseline [2]				
Mean (SD)	101.6 (7.92)	101.1 (8.29)	102.1 (7.87)	102.0 (7.37)
Change from Baseline				
Mean (SD)	-17.6 (8.78)	-15.8 (10.82)	-14.5 (8.55)	-21.2 (10.26)
LS Mean (SE)	-17.3 (0.52)	-15.7 (0.51)	-14.0 (0.52)	-20.7 (0.53)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
P-value for comparison to OM40/AML10/HCTZ25 [4]	<0.0001	<0.0001	<0.0001	

The Full Analysis Set included subjects who received at least 1 dose of study medication and had baseline and at least 1 post-dose assessment of seated diastolic blood pressure.

1. N was the number of subjects with values at both timepoints.
2. Baseline for blood pressure was defined as the average of the mean blood pressure measured at the randomization visit and the visit prior to the randomization visit.
3. Within treatment p-value testing for significant change from baseline was obtained from an ANCOVA model with baseline blood pressure as a covariate, and fixed effects of treatment, subgroup, and treatment by subgroup interaction.
4. All treatment comparisons were calculated as OM40/AML10/HCTZ25 minus the respective dual combination treatment group. The 2-sided p-values were obtained from an ANCOVA model with baseline blood pressure as a covariate, and fixed effects of treatment, subgroup, and treatment by subgroup interaction.

AML = amlodipine; ANCOVA = Analysis of Covariance; HCTZ = hydrochlorothiazide; LS = least squares;

OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.

Sources: Post-text Tables 15.2.67 and 15.2.68

Race

Table 8.22 presents the results of the change in SeDBP from baseline to Week 12 with LOCF by race. Across the treatment groups, mean baseline SeDBP ranged from 102.1 mmHg to 103.5 mmHg for Black subjects and from 99.9 mmHg to 100.7 mmHg for non-Black subjects. Statistically significant changes in SeDBP from baseline to Week 12 with LOCF were observed in both race subgroups for all 4 treatment groups. In both race groups, triple combination therapy gave a significantly greater mean reduction in SeDBP from baseline to Week 12 with LOCF compared to each of the dual combination therapies. There were no apparent race-related differences in terms of SeDBP reduction in any treatment group.

Table 8.22: Change in SeDBP (mmHg) from Baseline to Week 12 with LOCF – Race Subgroups – Full Analysis Set

Race Group Statistics	OM40/ AML10	OM40/ HCTZ25	AML10/ HCTZ25	OM40/ AML10/ HCTZ25
Black				
N [1]	179	193	189	179
Baseline [2]				
Mean (SD)	103.5 (8.17)	102.1 (8.41)	102.3 (7.86)	102.6 (8.06)
Change from Baseline				
Mean (SD)	-18.1 (9.88)	-15.4 (12.45)	-15.1 (9.59)	-21.5 (11.22)
LS Mean (SE)	-17.0 (0.70)	-14.9 (0.67)	-14.5 (0.68)	-20.8 (0.70)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
P-value for comparison to OM40/AML10/HCTZ25 [4]	0.0001	<0.0001	<0.0001	
Non-Black				
N [1]	445	434	404	435
Baseline [2]				
Mean (SD)	99.9 (7.42)	99.9 (7.96)	100.7 (7.40)	100.2 (7.09)
Change from Baseline				
Mean (SD)	-17.7 (9.31)	-17.0 (10.03)	-14.7 (8.38)	-21.5 (9.84)
LS Mean (SE)	-18.1 (0.44)	-17.4 (0.45)	-14.8 (0.47)	-21.8 (0.45)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
P-value for comparison to OM40/AML10/HCTZ25 [4]	<0.0001	<0.0001	<0.0001	

The Full Analysis Set included subjects who received at least 1 dose of study medication and had baseline and at least 1 post-dose assessment of seated diastolic blood pressure.

1. N was the number of subjects with values at both timepoints.
2. Baseline for blood pressure was defined as the average of the mean blood pressure measured at the randomization visit and the visit prior to the randomization visit.
3. Within treatment p-value testing for significant change from baseline was obtained from an ANCOVA model with baseline blood pressure as a covariate, and fixed effects of treatment, subgroup, and treatment by subgroup interaction.
4. All treatment comparisons were calculated as OM40/AML10/HCTZ25 minus the respective dual combination treatment group. The 2-sided p-values were obtained from an ANCOVA model with baseline blood pressure as a covariate, and fixed effects of treatment, subgroup, and treatment by subgroup interaction.

AML = amlodipine; ANCOVA = Analysis of Covariance; HCTZ = hydrochlorothiazide; LS = least squares; OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.

Sources: Post-text Tables 15.2.85 and 15.2.86

Blood pressure severity at baseline

Table 8.19 presents the results of the change in SeDBP from baseline to Week 12 with LOCF by hypertension severity. The mild or moderate hypertension subgroup included subjects with SeSBPs from 140 mmHg to <180 mmHg and SeDBPs from 90 mmHg to <110 mmHg at baseline. The severe hypertension subgroup included subjects with SeSBPs \geq 180 mmHg or SeDBPs \geq 110 mmHg at baseline.

Across the treatment groups, mean baseline SeDBP ranged from 106.3 mmHg to 106.9 mmHg for subjects with severe hypertension and from 98.8 mmHg to 99.7 mmHg for subjects with mild or moderate hypertension.

Statistically significant changes in SeDBP from baseline to Week 12 with LOCF were observed in both hypertension severity subgroups for all 4 treatment groups. In both subgroups, the triple

combination therapy yielded a significantly greater mean reduction in SeDBP from baseline to Week 12 with LOCF compared to each of the dual combination therapies. There were no apparent hypertension severity-related differences in terms of SeDBP reduction in any treatment group.

Table 8.19: Change in SeDBP (mmHg) from Baseline to Week 12 with LOCF – Hypertension Severity Subgroups – Full Analysis Set

Hypertension Severity Group Statistics	OM40/ AML10	OM40/ HCTZ25	AML10/ HCTZ25	OM40/ AML10/ HCTZ25
Severe				
N [1]	160	160	168	136
Baseline [2]				
Mean (SD)	106.9 (9.80)	106.7 (10.07)	106.7 (9.11)	106.3 (10.20)
Change from Baseline				
Mean (SD)	-20.0 (9.42)	-17.3 (12.69)	-17.6 (9.46)	-23.6 (9.97)
LS Mean (SE)	-19.9 (0.79)	-17.3 (0.79)	-17.6 (0.77)	-23.7 (0.85)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
P-value for comparison to OM40/AML10/HCTZ25 [4]	0.0013	<0.0001	<0.0001	
Mild or Moderate				
N [1]	452	453	408	463
Baseline [2]				
Mean (SD)	99.2 (5.45)	98.8 (5.89)	99.5 (5.22)	99.7 (5.37)
Change from Baseline				
Mean (SD)	-17.2 (9.31)	-16.5 (10.00)	-14.0 (8.16)	-21.1 (10.35)
LS Mean (SE)	-17.3 (0.43)	-16.7 (0.43)	-13.9 (0.45)	-20.9 (0.43)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
P-value for comparison to OM40/AML10/HCTZ25 [4]	<0.0001	<0.0001	<0.0001	

The Full Analysis Set included subjects who received at least 1 dose of study medication and had baseline and at least 1 post-dose assessment of seated diastolic blood pressure.

The mild or moderate hypertension class included subjects with systolic blood pressures from 140 mmHg to <180 mmHg and diastolic blood pressures from 90 mmHg to <110 mmHg. The severe hypertension class includes subjects with systolic blood pressure \geq 180 or diastolic blood pressure \geq 110 mmHg.

1. N was the number of subjects with values at both timepoints.
2. Baseline for blood pressure was defined as the average of the mean blood pressure measured at the randomization visit and the visit prior to the randomization visit.
3. Within treatment p-value testing for significant change from baseline was obtained from an ANCOVA model with baseline blood pressure as a covariate and treatment as a fixed effect.
4. All treatment comparisons were calculated as OM40/AML10/HCTZ25 minus the respective dual combination treatment group. The 2-sided p-values were obtained from an ANCOVA model with baseline blood pressure as a covariate and treatment as a fixed effect.

AML = amlodipine; ANCOVA = Analysis of Covariance; HCTZ = hydrochlorothiazide; LS = least squares; OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.

Sources: Post-text Tables 15.2.79 and 15.2.80

This is a US study (at 317 sites) so there is no need to conduct a regional analysis regarding the comparison of the treatment effects on the efficacy endpoints.

In summary, statistically significant changes in SeDBP from baseline to Week 12 with LOCF were observed in all subgroups (age, gender, race, hypertension severity) for all 4 treatment groups. In all the subgroups except those who were above 75 years of age, triple combination therapy resulted in a significantly greater mean reduction in SeDBP compared to each of the dual combination therapies. There were no apparent age (except what is cited above), race, sex, hypertension severity-related differences in terms of SeDBP reduction in any treatment group.

7.0 REVIEW OF SAFETY

7.1 Overall Safety Evaluation Plan and Description of Safety Studies

This Summary of Clinical Safety presents safety results from one efficacy study (CS8635-A-U301), two additional Phase 3 studies (CS8663-A-U301 and CS8663-A-E303 from the Azor® New Drug Application [NDA] 22-100 program), six Phase 1 studies (CS8635-A-U101, -U102, -U103, -U104, -E105, and -U106), and one Phase 4 study (SP-OLM-03-05 OLMETREAT).

The agency during a series of meetings⁴ agreed to 1) a single efficacy study (CS8635-A-U301) to demonstrate blood pressure response, demonstrating that the superiority of the triple combination compared to the dual combinations in lowering blood pressure, 2) submitting less than 24 weeks of safety data from the CS8635-A-U301 study at the time of the NDA submission. 3) include the safety data from the 12-week double-blind period of the CS8635-A-U301 study and safety data from the Azor® NDA 22-100 program (studies CS8663-A-U301 and CS8663-A-E303) 4) safety data from the 40-week open-label period of the CS8635-A-U301 study would be submitted within the 120-Day Safety Update.

The safety results from study CS8635-A-U301 are described in detail below. This section is followed by safety results from the other studies.

7.2 Safety from study CS8635-A-U301

There were 2302 subjects evaluated for safety.

N.B. The addendum that was submitted by the sponsor March 13, 2010 (see section 4.7 of this review) included the following changes to the adverse events section:

“Adverse events that occurred during the double-blind period of the CS8635-A-U301 study but were reported by subjects after the Week 12 data snapshot were not included in the CS8635-A-U301 Week 12 CSR since the analyses were based on an interim database of an ongoing study. In most situations, the adverse events were reported during the open-label portion of the CS8635-A-U301 study; however, the start date for the adverse event was during the double-blind portion of the study. In other cases, with the continued monitoring of sites and subjects during the open-label portion of the study and additional information provided by subjects, the start date or stop date of the adverse event may have changed, which placed the adverse event into the double-blind period of the study. Changes in the Medical Dictionary for Regulatory Activities preferred term coding occurred in some cases as a result of additional information obtained from subjects or laboratory reports or medical review of coding across the study. Several adverse events were also removed from the analysis database due to a change in start date that reclassified the event as onset during either the screening or open-label periods, and other events were moved to medical history based on identification of the event as a preexisting condition.

⁴ 24 July 2007, 28 January 2009,

There were no newly reported discontinuations due to adverse events. There was 1 newly reported serious adverse event (SAE) in the AML 10 mg + HCTZ 25 mg group (Subject 0156-0013, hand fracture) during the double-blind portion of the study. “

Extent of exposure

The number of days subjects were exposed to a treatment arm is shown below.

Table 10.1: Summary of Extent of Exposure to Final Randomized Treatment (days) – Day 1 to Week 12 – Safety Set 2

Extent of Exposure (days)	OM40/ AML10	OM40/ HCTZ25	AML10/ HCTZ25	OM40/ AML10/ HCTZ25	Total
n	596	580	552	574	2302
Mean (SD)	82.7 (9.45)	82.5 (9.58)	83.0 (10.87)	53.9 (10.58)	75.6 (16.07)

Safety Set 2 included subjects who received at least 1 dose of double-blind study medication at or beyond the Week 4 visit.

Extent of exposure to study medication (days) = last dose date of randomized study medication – first dose date of randomized study medication + 1.

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; SD = standard deviation.

Source: Post-text Table 15.1.16

The mean extent of exposure was about 83 days except for the triple combination group which had a 2 week titration period using one of the three dual combinations.

Adverse events

Serious safety

The table below shows all reported serious safety by final randomized treatment group. This group excludes the first 4 weeks of events (no subject was receiving the triple combination prior to week 4).

Serious safety number and (percent) of randomized subjects (weeks 4-12)

event	OM40/AML10 n=596	OM40/HCTZ25 n=580	AML10/HCTZ25 n=552	OM40/AML10/HCTZ25 n=574
Deaths	0	0	0	0
Serious AE	9 (1.5)	7 (1.2)	10# (1.6)	10 (1.7)
Discontinuations for AE	7 (1.2)	12 (2.1)	11 (2.0)	23 (4.0)

From table 10.4

#Added subject 0156-0013 (fracture of bone in hand). See March 13, 2010 addendum table 1.1.

The incidence rates for reported serious adverse events were similar across treatment groups. Discontinuations because of an adverse event occurred twice as often in the triple combination (4%) compared to the dual combinations (1-2%).

For completeness, the table below shows the incidence rates for serious events reported between day 1 to week 4.

Serious safety number and (percent) of randomized subjects (Day 1-week 4)

event	OM40/AML10 n=838	OM40/HCTZ25 n=845	AML10/HCTZ25 n=807	Placebo n=36
Deaths	0	0	1+	0
Serious AE	4 (0.5)	10 (1.2)	5 (0.6)	1 (2.8)
Discontinuations for AE	25 (3.0)	45 (5.3)	32 (4.0)	0

From table 10.6

+subject 0121-0010 died on study day ^(b) from alcohol poisoning.

The results are similar across the three treatment groups.

Serious events reported for all treatment groups between week 4 and week 12 are shown in the appendices. The events reported just for the triple combination group included: uterine leiomyoma, prostate cancer, coronary artery disease, osteomyelitis, peroneal nerve palsy, diabetes mellitus, alcohol poisoning, bipolar disorder, drug dependence, dyspnea, pulmonary artery atresia obstructive airways disorder, syncope, acute pre-renal failure, prostate cancer, intervertebral disc degeneration, vertebral injury, duodenitis, gastritis, rectal hemorrhage, coronary artery disease, non-cardiac chest pain.

N.B. Some events were reported prior to week 4.

These events are not unexpected in this disease type and subject age group.

Discontinuations because of adverse events are list by individual in the appendices. There were 155 (6.2%) subjects who discontinued from the double-blind treatment period because of an adverse event (34 (4.1%) OM 40/AML 10, 57 (6.7%) OM 40/HCTZ 25, 44 (5.5%) AML 10/HCTZ 25, and 21 (3.7%) subjects on OM 40/AML 10/ HCTZ 25 mg).

Common reasons for discontinuations in the triple combination group included dizziness (12 subjects), hypotension/blood pressure decrease (6 subjects), peripheral edema (10 subjects). Subjects usually had more than one event listed as reason for drop out⁵. The list of drop outs because of adverse events is presented in the appendices.

All adverse events

The table below shows all adverse events that were reported by at least 3% in any of the treatment groups and were reported between weeks 4 and 12.

⁵ Subject 0318-0046 reported both hypotension and dizziness as reasons for dropping out.

Table 10.7: Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (≥3% in Any Treatment Group) – Day 1 to Week 12 – Safety Set 2

System Organ Class Preferred Term	OM40/ AML10 (N = 596) n (%)	OM40/ HCTZ25 (N = 580) n (%)	AML10/ HCTZ25 (N = 552) n (%)	OM40/ AML10/ HCTZ25 (N = 574) n (%)	Total (N = 2302) n (%)
Subjects with TEAEs	308 (51.7)	319 (55.0)	325 (58.9)	335 (58.4)	1287 (55.9)
Nervous system disorders	90 (15.1)	126 (21.7)	75 (13.6)	111 (19.3)	402 (17.5)
Dizziness	29 (4.9)	58 (10.0)	17 (3.1)	57 (9.9)	161 (7.0)
Headache	42 (7.0)	38 (6.6)	33 (6.0)	37 (6.4)	150 (6.5)
Infections and infestations	85 (14.3)	86 (14.8)	81 (14.7)	85 (14.8)	337 (14.6)
Upper respiratory tract infection	26 (4.4)	18 (3.1)	14 (2.5)	16 (2.8)	74 (3.2)
Nasopharyngitis	11 (1.8)	20 (3.4)	16 (2.9)	20 (3.5)	67 (2.9)
General disorders and administration site conditions	95 (15.9)	46 (7.9)	98 (17.8)	91 (15.9)	330 (14.3)
Edema peripheral	42 (7.0)	6 (1.0)	46 (8.3)	44 (7.7)	138 (6.0)
Fatigue	34 (5.7)	31 (5.3)	36 (6.5)	24 (4.2)	125 (5.4)
Musculoskeletal and connective tissue disorders	68 (11.4)	51 (8.8)	72 (13.0)	71 (12.4)	262 (11.4)
Muscle spasms	12 (2.0)	14 (2.4)	13 (2.4)	18 (3.1)	57 (2.5)
Gastrointestinal disorders	58 (9.7)	62 (10.7)	61 (11.1)	70 (12.2)	251 (10.9)
Nausea	12 (2.0)	22 (3.8)	12 (2.2)	17 (3.0)	63 (2.7)
Metabolism and nutrition disorders	15 (2.5)	21 (3.6)	39 (7.1)	20 (3.5)	95 (4.1)
Hypokalemia	2 (0.3)	3 (0.5)	25 (4.5)	4 (0.7)	34 (1.5)

Safety Set 2 included subjects who received at least 1 dose of double-blind study medication at or beyond the Week 4 visit.

Treatment-emergent adverse events were adverse events that emerged during treatment having been absent pre-treatment, or worsened relative to the pre-treatment state. Treatment-emergent adverse events were defined as having a start date on or after the first dose of double-blind medication and up to the first dose of open-label study medication for subjects continuing into the open-label period, or up to and including 14 days after the last dose of double-blind study medication for early terminated subjects. Treatment-emergent adverse events were counted under the treatment the subject received from Week 4 to Week 12.

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; TEAE = treatment-emergent adverse event.

Source: Post-text Table 15.3.1.5

N.B. The addendum submitted March 13, 2010 lists one additional episode of dizziness to the adverse events reported for the triple combination. This increases the number of dizziness reports to 58 (10.1%). There were no additional changes to the above table for the triple combination. (Table 1.2).

The percents of subjects reporting at least one adverse event were similar across treatment groups.

Events reported by subjects randomized to the triple combination arm as much as or more often than those randomized to the dual treatment groups included dizziness, nasopharyngitis, peripheral edema, and muscle spasms. Dizziness was reported equally often by the triple combination and OM40/HCTZ25 (10%); edema was reported less by the treatment group that did not receive amlodipine; and muscle spasms were reported by 1% more subjects in the triple combination group compared to the dual combination groups.

Hypokalemia was rarely reported except in the AML10/HCTZ25 group.

Adverse event reports of hypotension or suggestive of hypotension are shown below by treatment group.

No. and (percent) of reports

event	OM40/AML10 n=596	OM40/HCTZ25 n=580	AML10/HCTZ25 n=552	OM40/AML10/HCTZ25 n=574
Hypotension	0	4 (1)	1	12 (1)
Syncope	0	0	3	6 (1)
Dizziness and vertigo	33 (6)	62 (11)	19 (3)	65 (11)

From table 10.13

Subjects who were randomized to the triple combination reported slightly more events related to or suggestive of hypotension.

For completeness, adverse events reported between Day 1 and week 4 and reported by at least 3% of subjects in any treatment group are shown in the table below.

Table 10.9: Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term ($\geq 3\%$ in Any Treatment Group) – Day 1 to Week 4 – Safety Set

System Organ Class Preferred Term	OM40/ AML10 (N = 838) n (%)	OM40/ HCTZ25 (N = 845) n (%)	AML10/ HCTZ25 (N = 807) n (%)	Placebo (N = 36) n (%)	Total (N = 2491) n (%)
Subjects with TEAEs	319 (38.1)	328 (38.8)	324 (40.1)	9 (25.0)	978 (39.3)
Nervous system disorders	81 (9.7)	121 (14.3)	79 (9.8)	0 (0.0)	281 (11.3)
Dizziness	33 (3.9)	67 (7.9)	24 (3.0)	0 (0.0)	124 (5.0)
Headache	40 (4.8)	36 (4.3)	41 (5.1)	0 (0.0)	117 (4.7)
General disorders and administration site conditions	83 (9.9)	61 (7.2)	89 (11.0)	0 (0.0)	233 (9.4)
Edema peripheral	43 (5.1)	6 (0.7)	43 (5.3)	0 (0.0)	92 (3.7)
Fatigue	27 (3.2)	34 (4.0)	28 (3.5)	0 (0.0)	89 (3.6)
Gastrointestinal disorders	49 (5.8)	60 (7.1)	68 (8.4)	2 (5.6)	179 (7.2)
Nausea	14 (1.7)	25 (3.0)	19 (2.4)	0 (0.0)	58 (2.3)
Respiratory, thoracic, and mediastinal disorders	19 (2.3)	28 (3.3)	20 (2.5)	2 (5.6)	69 (2.8)
Dyspnea	5 (0.6)	5 (0.6)	5 (0.6)	2 (5.6)	17 (0.7)

The Safety Set included subjects who received at least 1 dose of study medication and had at least 1 post-dose safety assessment.

Treatment-emergent adverse events were adverse events that emerged during treatment having been absent pre-treatment, or worsened relative to the pre-treatment state. Treatment-emergent adverse events were counted under the treatment group in which the event started.

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; TEAE = treatment-emergent adverse event.

Source: Post-text Table 15.3.1.7

These events are not unexpected in subjects with this disease type.

Adverse events by subgroup

Age

The serious safety reported by subjects randomized to the triple combination and according to their age is shown below.

Subjects randomized to triple combination

reported	<65 years of age n=456	≥65 years of age n=118	≥75 years of age n=16
death	0	0	0
Any serious AE	4 (0.9)	6 (5.1)	0
Discontinuation because of AE	18 (3.9)	5 (4.2)	0

Table 10.21

While there were few subjects (n=16) who were at least 75 years of age compared to the other age groups, there is no indication that the triple combination causes serious harm to elderly subjects.

Adverse events reported by at least 5% in any treatment group were similar across age groups. Only joint swelling was substantially higher in the elderly (3, 19%) randomized to triple combination compared to the younger subjects (<1% and 8% for ages <65 and ≥ 65 but <75, respectively). Dizziness was reported less often in the elderly compared to the younger subjects. Reports of renal impairment AE were more frequent in the elderly (2, 13%) compared to the younger subjects (8, 2% and 4, 3% for ages <65 and ≥ 65 but <75, respectively). (Tables 10.22 and 10.24).

Gender

Safety was evaluated according to subject's gender.

Subjects randomized to triple combination

reported	Female n=274	Male n=300
death	0	0
Any serious AE	2 (1)	8 (3)
Discontinuation because of AE	12 (4)	11 (4)

Table 10.25

There is no indication of one gender being exposed to greater safety risks while receiving the triple combination. The one common AE of note was peripheral edema which tended to be reported by female subjects to a greater extent compared to male subjects, regardless of treatment group. (Table 10.26). Male subjects, on the other hand, had a slightly higher rate of reporting renal impairment (10, 3%) compared to their female counterparts (2, 1%). This tended to be consistent across treatment groups. (Table 10.28)

Race

Safety was evaluated according to subject's gender.

Subjects randomized to triple combination

reported	Black n=166	Non black n=408
death	0	0
Any serious AE	2 (1)	8 (2)
Discontinuation because of AE	6 (94)	17 (4)

Table 10.37

There is no indication of black subjects being exposed to greater safety risks, compared to non black subjects, while receiving the triple combination.

Compared to black subjects, non black subjects tended to report more adverse events regardless of category. Table 10.40

Clinical laboratory parameters

Marked Chemistry abnormalities⁶

The incidence rate of “marked” laboratory abnormalities, defined as “observed values exceeding the given threshold in the laboratory measurement obtained following 12 weeks of randomized double-blind treatment”, are shown below by treatment group.

Table 10.18: Number (%) of Subjects with Marked Chemistry Abnormalities at End of Double-Blind Period – Safety Set

Parameter (Threshold)	OM40/ AML10 (N = 628) n (%)	OM40/ HCTZ25 (N = 637) n (%)	AML10/ HCTZ25 (N = 600) n (%)	OM40/ AML10/ HCTZ25 (N = 626) n (%)	Total (N = 2491) n (%)
AST (>66 U/L)	7 (1.1)	12 (1.9)	14 (2.3)	8 (1.3)	41 (1.6)
ALT (>75 U/L)	14 (2.2)	17 (2.7)	22 (3.7)	17 (2.7)	70 (2.8)
GGT (>87 U/L)	54 (8.6)	51 (8.0)	66 (11.0)	42 (6.7)	213 (8.6)
Alkaline Phosphatase (>216 U/L)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.1)
Total Bilirubin (>1.65 mg/dL)	1 (0.2)	0 (0.0)	5 (0.8)	1 (0.2)	7 (0.3)
Potassium (>5.0 mmol/L)	48 (7.6)	31 (4.9)	10 (1.7)	37 (5.9)	126 (5.1)
Potassium (<3.5 mmol/L)	4 (0.6)	15 (2.4)	59 (9.8)	14 (2.2)	92 (3.7)
Creatinine (>1.4 mg/dL)	19 (3.0)	45 (7.1)	14 (2.3)	40 (6.4)	118 (4.7)
Creatinine Clearance (≤60 mL/min)	34 (5.4)	42 (6.6)	23 (3.8)	34 (5.4)	133 (5.3)

The Safety Set included subjects who received at least 1 dose of study medication and had at least 1 post-dose safety assessment.

Percentage was calculated using the number of subjects in the column heading as the denominator.

Marked laboratory abnormalities were defined as observed values exceeding the given threshold in the laboratory measurement obtained following 12 weeks of randomized double-blind treatment.

ALT = alanine transaminase; AML = amlodipine; AST = aspartate transaminase; GGT = gamma-glutamyltransferase; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

Source: Post-text Table 15.3.4.3

⁶ AST (>66 U/L), ALT (>75 U/L), GGT (>87 U/L), alkaline phosphatase (>216 U/L), total bilirubin (>1.65 mg/dL), potassium (>5 mmol/L), potassium (<3.5 mmol/L), creatinine (>1.4 mg/dL), creatinine clearance (≤60 mL/min).

The incidence rates for elevated liver enzymes are similar across treatment groups or perhaps a bit worse for the AML10/HCTZ25 group.

The incidence rates for creatinine above 1.4 mg/dL is 6.4% for the triple combination, lower than the rate for OM40/HCTZ25 (7.1%). The rates of subjects who were normal at baseline and reported a high creatinine at week 12 (or at time of study termination) are shown in the table below. The complete table is shown in the appendices.

No. and (percent) of reports of normal creatinine at baseline and high at endpoint

OM40/AML10 n=628	OM40/HCTZ25 n=637	AML10/HCTZ25 n=600	OM40/AML10/HCTZ25 n=626
5 (0.8)	30 (4.7)	8 (1.3)	26 (4.2)

The rates of subjects with missing data are similar across treatment groups
From table 15.3.4.10

The table below shows the mean changes in creatinine and creatinine clearance from baseline at endpoint by treatment group.

Changes from baseline at endpoint	OM40/AML10	OM40/HCTZ25	AML10/HCTZ25	OM40/AML10/HCTZ
Creatinine clearance (mL/min)	0	-8.2	-2.0	-7.0
Creatinine (mg/dL)	-0.025	0.067	0.007	0.063

From table 15.3.4.1.

The reports of creatinine clearance ≤ 60 mL/min are similar across treatment groups with the highest rate found again in the OM40/HCTZ25 group (6.6% compared to 5.4% in the triple combination group).

No subject taking the triple combination reported an abnormal chemistry value as a serious adverse event. One subject (0204-0015) reported acute prerenal failure but did not discontinue study medication.

There were five subjects taking the triple combination who reported abnormal chemistry values and withdrew from the study:

- Subject 0018-0019 in the OM 40 mg + AML 10 mg + HCTZ 25 mg group had increased blood creatinine phosphokinase and decreased blood potassium. The event of increased blood creatinine phosphokinase was mild in severity and unlikely related to study medication; the event of decreased blood potassium was moderate in severity and possibly related to study medication;
- Subject 0183-0021 in the OM 40 mg + AML 10 mg + HCTZ 25 mg group had increased blood creatinine and increased blood urea. Both events were moderate in severity and probably related to study medication;
- Subject 0202-0001 in the OM 40 mg + AML 10 mg + HCTZ 25 mg group had increased blood creatinine and increased blood urea. Both events were moderate in severity and possibly related to study medication;
- Subject 0228-0010 in the OM 40 mg + AML 10 mg + HCTZ 25 mg group had hyperkalemia. The event was severe and probably related to study medication; and
- Subject 0257-0020 in the OM 40 mg + AML 10 mg + HCTZ 25 mg group had increased blood creatinine and increased blood urea. Both events were mild in severity and possibly related to study medication.

Of these five subjects, three reported increased blood creatinine and urea, one increased creatinine phosphokinase and decreased potassium, and one reported hyperkalemia.

For comparison, four subjects in the double combination groups withdrew from the study:

one for increased blood creatinine and urea, one for increased glucose, and two for hypokalemia.

Marked hematology abnormalities⁷

The number and percent of subjects with marked hematology abnormalities at endpoint are shown below.

Table 10.19: Number (%) of Subjects with Marked Hematology Abnormalities at End of Double-Blind Period – Safety Set

Parameter (Threshold)	OM40/ AML10 (N = 628) n (%)	OM40/ HCTZ25 (N = 637) n (%)	AML10/ HCTZ25 (N = 600) n (%)	OM40/ AML10/ HCTZ25 (N = 626) n (%)	Total (N = 2491) n (%)
Hemoglobin (<9 g/dL for males, <8 g/dL for females)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)
Hematocrit (<30%)	1 (0.2)	0 (0.0)	2 (0.3)	2 (0.3)	5 (0.2)
RBC (<3 × 10 ⁶ /μL)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)
WBC (>20 × 10 ³ /μL)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)
Platelet Count (<100 × 10 ³ /μL)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.1)

The Safety Set included subjects who received at least 1 dose of study medication and had at least 1 post-dose safety assessment.

Percentage was calculated using the number of subjects in the column heading as the denominator.

Marked laboratory abnormalities were defined as observed values exceeding the given threshold in the laboratory measurement obtained following 12 weeks of randomized double-blind treatment.

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; RBC = red blood cells;

WBC = white blood cells.

Source: Post-text Table 15.3.4.3

There is nothing to suggest that the triple combination adversely affects any of the hematology parameter.

There were no reported discontinuations in the triple combination group because of an abnormal hematology parameter. The one report of anemia occurred while the subject (0070-0190) was receiving OM40/HCTZ25.

Vital signs

Heart rate

The following table shows the mean heart rates at baseline, week 12, and change from baseline at week 12. The numbers of subjects reflect those with both baseline and post baseline heart rate values.

⁷ hemoglobin (<9 g/dL for males, <8 g/mL for females), hematocrit (<30%), red blood cells (<3 × 10⁶/μL), white blood cells (>20 × 10³ /μL), and platelet count (<100 × 10³ /μL).

Table 15.3.5.1
Change in Heart Rate (bpm) From Baseline
Safety Set

Timepoint Statistic	OM40/AML10 (N= 628)	OM40/HCTZ25 (N= 637)	AML10/HCTZ25 (N= 600)	OM40/AML10/HCTZ25 (N= 626)
Baseline				
n [1]	557	530	512	515
Mean	76.6	76.7	75.6	76.5
Standard Deviation	11.01	11.31	11.42	11.20
Median	76.0	76.0	75.0	76.0
Minimum, Maximum	44, 114	45, 118	47, 117	48, 124
Week 12				
n [1]	557	530	512	515
Mean	76.0	76.5	76.6	77.1
Standard Deviation	10.08	11.15	11.18	10.75
Median	76.0	76.0	76.0	76.0
Minimum, Maximum	48, 109	47, 111	48, 120	50, 111
Change from Baseline to Week 12				
n [1]	557	530	512	515
Mean	-0.6	-0.1	1.0	0.7
Standard Deviation	10.06	9.72	9.53	9.52
Median	0.0	0.0	1.0	1.0
Minimum, Maximum	-43, 32	-35, 36	-32, 34	-39, 36

[1] n is the number of subjects with both baseline and post-baseline heart rate values.

The effect of these treatment groups on heart rate is negligible.

Weight

The effect of these treatment groups on weight is negligible.

7.3 Safety from other studies

Phase 1 subjects

There were six phase 1 studies (four drug-drug interaction studies (CS8635-A-U101, -U102, -U103, and -U104), one bioequivalence study (CS8635-A-E105), and one food effect study (CS8635-A-U106)).

- Study CS8635-A-U101 compared the triple combination (administered as dual combination therapy Benicar HCT® [OM + HCTZ] and Norvasc® [AML]) with the separate components.
- Study CS8635-A-U102 compared the triple combination (administered as dual combination therapy Azor [OM + AML] and HCTZ) with the separate components.
- Studies CS8635-A-U103 and -U104 compared 2 formulations of the triple combination (OM 40 mg + AML 10 mg + HCTZ 25 mg) with Benicar HCT plus Antacal® (AML).
- Study CS8635-A-E105 compared a high-dose (OM 40 mg + AML 10 mg + HCTZ 25 mg) and low-dose (OM 20 mg + AML 5 mg + HCTZ 12.5 mg) formulation of the triple combination with high-dose and low-dose Azor (OM 40 mg + AML 10 mg and OM 20 mg + AML 5 mg, respectively) plus high-dose and low-dose HCTZ (12.5 mg and 25 mg, respectively).
- Study CS8635-A-U106 assessed the food effect on the fixed-dose triple combination (OM 40 mg + AML 10 mg + HCTZ 25 mg).

The phase 1 studies are shown below along study with duration, doses, number of subjects and the mean age, percent male/female and percent white/black/other, and reports of serious safety, if any.

Study No. (No. of Centers)	Study Design	Treatments	Type and No. of Subjects Randomized (Completed)	Demographics			Key Safety Results
				Mean Age	Gender	Race	
CS8635-A-U101 (1)	3-way CO, OL, SD, BA	OM40/HCTZ25 + AML10 OM40/HCTZ25 AML 10	Healthy male and female subjects 36 (32)	30.5 years	77.8% M 22.2% F	19.4% C 72.2% B 2.8% A 5.6% AI/AN	Subjects with SAEs = 0 Discontinuations due to adverse events = 0 Subjects with drug-related SAEs = 0 Discontinuations due to drug-related adverse events = 0
CS8635-A-U102 (1)	3-way CO, OL, SD, BA	OM40/AML10 + HCTZ25 OM40/AML10 HCTZ25	Healthy male and female subjects 36 (29)	31.1 years	83.3% M 16.7% F	22.2% C 75.0% B 2.8% A	Subjects with SAEs = 0 Discontinuations due to adverse events = 2 Subjects with drug-related SAEs = 0 Discontinuations due to drug-related adverse events = 0
CS8635-A-U103 (1)	2-way CO, OL, SD, BA	OM40/AML10/HCTZ25 OM40/HCTZ25 + AML10	Healthy male and female subjects 41 (28)	32.3 years	87.8% M 12.2% F	29.3% C 63.4% B 4.9% A 2.4% AI/AN	Subjects with SAEs = 0 Discontinuations due to adverse events = 1 Subjects with drug-related SAEs = 0 Discontinuations due to drug-related adverse events = 0

A = Asian; AI/AN = American Indian/Alaskan Native; AML = amlodipine; B = Black; BA = bioavailability; BE = bioequivalence; C = Caucasian; CO = cross-over; CSR = Clinical Study Report;
DB = double-blind; F = female; HCTZ = hydrochlorothiazide; M = male; NH/PI = Native Hawaiian/Pacific Islander; O = other; OL = open-label; OM = olmesartan medoxomil;
SAE = serious adverse event; SD = single-dose.
Sources: CS8663-A-U301, CS8663-A-E303, CS8635-A-U301, CS8635-A-U101, CS8635-A-U102, CS8635-A-U103, CS8635-A-U104, CS8635-A-E105, CS8635-A-U106, and SP-OLM-03-05 CSRs

Study No. (No. of Centers)	Study Design	Treatments	Type and No. of Subjects Randomized (Completed)	Demographics			Key Safety Results
				Mean Age	Gender	Race	
CS8635-A-U104 (1)	2-way CO, OL, SD, BA	OM40/AML10/HCTZ25 OM40/HCTZ25 + AML10	Healthy male and female subjects 32 (28)	31.6 years	78.1% M 21.9% F	25.0% C 65.6% B 3.1% A 9.4% AI/AN	Subjects with SAEs = 0 Discontinuations due to adverse events = 2 Subjects with drug-related SAEs = 0 Discontinuations due to drug-related adverse events = 1
CS8635-A-E105 (1)	3-way CO, OL, SD, BE	OM40/AML10/HCTZ25 OM40/HCTZ25 + AML10 OM40/AML10 + HCTZ25 OM20/AML5/HCTZ12.5 OM20/HCTZ12.5 + AML5 OM20/AML5 + HCTZ12.5	Healthy male and female subjects 72 (57)	28.7 years	73.6% M 26.4% F	98.6% C 1.4% B	Subjects with SAEs = 0 Discontinuations due to adverse events = 3 Subjects with drug-related SAEs = 0 Discontinuations due to drug-related adverse events = 0
CS8635-A-U106 (1)	2-way CO, OL, SD, BA	OM40/AML10/HCTZ25	Healthy male and female subjects 34 (33)	32.7 years	76.5% M 23.5% F	35.3% C 61.8% B 5.9% AI/AN	Subjects with SAEs = 0 Discontinuations due to adverse events = 0 Subjects with drug-related SAEs = 0 Discontinuations due to drug-related adverse events = 0
SP-OLM-03-05 (58)	OL, 20 Weeks	Placebo OM20 OM20/HCTZ12.5 OM20/HCTZ25 OM20/HCTZ12.5 + AML5 OM20/HCTZ25 + AML10	Male and female subjects with mild to moderate hypertension 694 (601)	58.2 years	51.4% M 48.6% F	97.7% C 1.9% B 0.4% A	Subjects with SAEs = 7 Discontinuations due to adverse events = 17 Subjects with drug-related SAEs = 0 Discontinuations due to drug-related adverse events = 13

A = Asian; AI/AN = American Indian/Alaskan Native; AML = amlodipine; B = Black; BA = bioavailability; BE = bioequivalence; C = Caucasian; CO = cross-over; CSR = Clinical Study Report;
DB = double-blind; F = female; HCTZ = hydrochlorothiazide; M = male; NH/PI = Native Hawaiian/Pacific Islander; O = other; OL = open-label; OM = olmesartan medoxomil;
SAE = serious adverse event; SD = single-dose.
Sources: CS8663-A-U301, CS8663-A-E303, CS8635-A-U301, CS8635-A-U101, CS8635-A-U102, CS8635-A-U103, CS8635-A-U104, CS8635-A-E105, CS8635-A-U106, and SP-OLM-03-05 CSRs

N.B. study SP-OLM-03-05 is not discussed in this section.

A total of 251 subjects participated in one of the Phase 1 studies. Overall, there were no reports of deaths or serious adverse events. There were eight discontinuations for adverse events. (Table 2.9) and few reported adverse events (Table 2.10).

The reported adverse events leading to the withdrawal of eight subjects included abdominal pain, hypoesthesia, decreased hemoglobin, tooth abscess, cough, rash, increased CPK, increased ALT levels.

In summary, the safety review of the Phase 1 studies revealed nothing unexpected.

Phase 3 open label cohort studies

Studies CS8663-A-U301 and –E303 (from the Azor® NDA 22-100 program⁸) were open label extension studies of 44 weeks and 28 weeks in duration, respectively. There were nearly 2400 subjects enrolled for the 2 studies combined with a total of 1297 subjects receiving the triple combination.

Nearly 460 subjects received the triple combination for at least 6 months.

The table below shows the subject disposition for the two studies combined.

Table 1.7: Subject Disposition by Final Treatment Regimen – Phase 3 Open-Label Cohort

	OM40/ AML5 (N = 976) n (%)	OM40/ AML10 (N = 530) n (%)	OM40/ AML10/ HCTZ12.5 (N = 358) n (%)	OM40/ AML10/ HCTZ25 (N = 447) n (%)	Total (N = 2376) n (%)
Completed open-label periods	848 (86.9)	454 (85.7)	316 (88.3)	399 (89.3)	2073 (87.2)
Discontinued	128 (13.1)	76 (14.3)	42 (11.7)	48 (10.7)	303 (12.8)
Adverse event	34 (3.5)	22 (4.2)	11 (3.1)	14 (3.1)	86 (3.6)
Withdrawal of consent	42 (4.3)	19 (3.6)	15 (4.2)	11 (2.5)	87 (3.7)
Requirement for restricted medication	5 (0.5)	2 (0.4)	0 (0.0)	2 (0.4)	9 (0.4)
Lost to follow-up	20 (2.0)	22 (4.2)	10 (2.8)	9 (2.0)	63 (2.7)
Investigator judgment	0 (0.0)	3 (0.6)	2 (0.6)	10 (2.2)	15 (0.6)
Withdrawal criteria per protocol	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
BP and/or ABPM criteria	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Other	22 (2.3)	8 (1.5)	4 (1.1)	2 (0.4)	37 (1.6)

Includes data from CS663-A-U301 and CS8663-A-E303.
 Subjects are classified under the column that represents their final dosing regimen.
 Percentage is calculated using number of subjects in the column heading as the denominator.
 ABPM = ambulatory blood pressure monitoring; AML = amlodipine; BP = blood pressure;
 HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.
 Source: ISS Post-text Table 6

The discontinuation rates for any reason are similar across treatment groups.

The demographics for these subjects include mean age of 55 years (3% of subjects were at least 75 years), 57% were male, 80% were white, and 20% were classified as severely hypertensive.

An overview of adverse events is shown below.

⁸ AZOR is amlodipine besylate/olmesartan medoxomil; approved for the treatment of hypertension 9-26-2007.

Table 2.5: Overview of Adverse Events – Number (%) of Subjects – Phase 3 Open-Label Cohort

Category	OM40/ AML5 (N = 2370) n (%)	OM40/ AML10 (N = 1367) n (%)	OM40/ AML10/ HCTZ12.5 (N = 829) n (%)	OM40/ AML10/ HCTZ25 (N = 468) n (%)	OM/ AML/ HCTZ [1] Total (N = 865) n (%)	Total (N = 2376) n (%)
Subjects with TEAEs [2]						
Any TEAE	850 (35.9)	515 (37.7)	329 (39.7)	255 (54.5)	497 (57.5)	1461 (61.5)
Any drug-related [3] TEAE	263 (11.1)	206 (15.1)	127 (15.3)	90 (19.2)	210 (24.3)	585 (24.6)
Maximum severity of TEAEs						
Any TEAE						
Mild	466 (19.7)	270 (19.8)	174 (21.0)	140 (29.9)	241 (27.9)	671 (28.2)
Moderate	333 (14.1)	209 (15.3)	135 (16.3)	96 (20.5)	219 (25.3)	668 (28.1)
Severe	51 (2.2)	36 (2.6)	20 (2.4)	19 (4.1)	37 (4.3)	122 (5.1)
Drug-related [3] TEAEs						
Mild	172 (7.3)	132 (9.7)	85 (10.3)	68 (14.5)	144 (16.6)	365 (15.4)
Moderate	79 (3.3)	68 (5.0)	40 (4.8)	22 (4.7)	64 (7.4)	199 (8.4)
Severe	12 (0.5)	6 (0.4)	2 (0.2)	0 (0.0)	2 (0.2)	21 (0.9)
Deaths	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Subjects with SAEs						
Any treatment-emergent SAE	40 (1.7)	24 (1.8)	15 (1.8)	18 (3.8)	34 (3.9)	100 (4.2)
Any drug-related [3] SAE	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Subjects with AE leading to study discontinuation						
Any AE	35 (1.5)	19 (1.4)	11 (1.3)	11 (2.4)	22 (2.5)	79 (3.3)
Any drug-related [3] TEAE	22 (0.9)	12 (0.9)	3 (0.4)	4 (0.9)	7 (0.8)	42 (1.8)
Includes data from CS8663-A-U301 and CS8663-A-E303.						
1. OM/AML/HCTZ total includes the regimens OM40/AML10/HCTZ12.5, OM40/AML10/HCTZ25 and the following non-standard regimens: OM20/AML5/HCTZ12.5 (n=2), OM20/AML10/HCTZ12.5 (n=2), OM40/AML2.5/HCTZ12.5 (n=1), OM40/AML5/HCTZ12.5 (n=42), and OM40/AML5/HCTZ25 (n=19).						
2. Treatment-emergent adverse events were defined as having a start date on or after the first dose of open-label study medication.						
3. Drug-related was defined as definitely, probably, or possibly related to randomized study medication.						
AE = adverse event; AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; SAE = serious adverse event; TEAE = treatment-emergent adverse event.						
Source: ISS Post-text Table 9						

There was one reported death (OM40/AML10 treatment group) and the incidence rate of reporting serious adverse events was 4% for the group receiving the triple combination (OM40/AML10/HCTZ25). These events included: anemia (2), renal failure, coronary artery disease, dehydration, asthenia, dizziness, lung cancer, depression, osteoarthritis, atrial fibrillation, hernia, small intestinal obstruction, arthralgia, prostate cancer, abscess, skin necrosis, non cardiac chest pain, viral gastroenteritis, contusion, cellulitis, and TIA.

The percent of subjects discontinuing the study because of an adverse event was 2% for the triple combination. The events included hypertension (5), vasculitis, dizziness, back pain, angioneurotic edema, small intestine obstruction, increased blood creatinine.

The adverse events reported most often by the group who received the triple combination included peripheral edema (2%), and dizziness (5%). (Table 2.6).

Adverse events of special interest are shown below.

Table 2.8: Number (%) of Subjects with Treatment-Emergent Adverse Events in Adverse Event Categories of Special Interest – Phase 3 Open-Label Cohort

Adverse Event Category [1]	OM40/ AML5 (N = 2370) n (%)	OM40/ AML10 (N = 1367) n (%)	OM40/ AML10/ HCTZ12.5 (N = 829) n (%)	OM40/ AML10/ HCTZ25 (N = 468) n (%)	OM/ AML/ HCTZ Total [2] (N = 865) n (%)
Edema	162 (6.8)	164 (12.0)	95 (11.5)	64 (13.7)	161 (18.6)
Hypotension	18 (0.8)	9 (0.7)	11 (1.3)	3 (0.6)	14 (1.6)
Headache	63 (2.7)	29 (2.1)	22 (2.7)	10 (2.1)	32 (3.7)
Dizziness and vertigo	71 (3.0)	35 (2.6)	24 (2.9)	24 (5.1)	49 (5.7)
Syncope	2 (0.1)	0 (0.0)	2 (0.2)	2 (0.4)	4 (0.5)
Renal-related AEs	4 (0.2)	2 (0.1)	6 (0.7)	8 (1.7)	14 (1.6)
Hepatic-related AEs	32 (1.4)	8 (0.6)	5 (0.6)	4 (0.9)	9 (1.0)
Hyperkalemia	9 (0.4)	4 (0.3)	0 (0.0)	2 (0.4)	2 (0.2)
Hypokalemia	4 (0.2)	1 (0.1)	1 (0.1)	4 (0.9)	5 (0.6)
Glycemic control	33 (1.4)	11 (0.8)	17 (2.1)	17 (3.6)	36 (4.2)
Injury, falls, and fractures	17 (0.7)	9 (0.7)	5 (0.6)	2 (0.4)	7 (0.8)
Gout, hyperuricemia, and increased uric acid	7 (0.3)	5 (0.4)	2 (0.2)	9 (1.9)	11 (1.3)

Includes data from CS8663-A-U301 and CS8663-A-E303.
Treatment-emergent adverse events were defined as having a start date on or after the first dose of randomized study medication.
Percentage is calculated using number of subjects in column heading as denominator.
Although a subject may have had 2 or more adverse events, the subject is counted only once within a category. The same subject may appear in different categories.

- See Section 1.1.2.2.5 for the Medical Dictionary for Regulatory Activities terms included in the various adverse event categories of interest.
- OM/AML/HCTZ total includes the regimens OM40/AML10/HCTZ12.5, OM40/AML10/HCTZ25 and the following non-standard regimens: OM20/AML5/HCTZ12.5 (n=2), OM20/AML10/HCTZ12.5 (n=2), OM40/AML2.5/HCTZ12.5 (n=1), OM40/AML5/HCTZ12.5 (n=42), and OM40/AML5/HCTZ25 (n=19).

AE = adverse event; AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.
Source: ISS Post-text Table 12

There is somewhat more edema and dizziness reported by the triple combination group. Overall the incidence rates are fairly uniform across treatment groups.

The number and percent of subjects with marked laboratory abnormalities is shown below.

Table 3.7: Number (%) of Subjects with Marked Laboratory Abnormalities – Phase 3 Open-Label Cohort

Parameter (Threshold)	OM40/ AML5 (N = 2370) n (%)	OM40/ AML10 (N = 1367) n (%)	OM40/ AML10/ HCTZ12.5 (N = 829) n (%)	OM40/ AML10/ HCTZ25 (N = 468) n (%)	Total (N = 2376) n (%)
AST (>66 mU/mL)	2 (0.1)	0 (0.0)	5 (0.6)	4 (0.9)	11 (0.5)
ALT (>75 mU/mL)	13 (0.5)	3 (0.2)	3 (0.4)	7 (1.5)	24 (1.0)
GGT (>87 mU/mL)	51 (2.2)	25 (1.8)	19 (2.3)	27 (5.8)	111 (4.7)
Alkaline Phosphatase (>216 mU/mL)	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.9)	5 (0.2)
Total Bilirubin (>1.65 mg/dL)	14 (0.6)	3 (0.2)	2 (0.2)	1 (0.2)	19 (0.8)
Hemoglobin (M:<9 mg/dL, F:<8 mg/dL)	3 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	4 (0.2)
Hematocrit (<30%)	7 (0.3)	0 (0.0)	0 (0.0)	2 (0.4)	9 (0.4)
RBC (<3 × 10 ⁶ /μL)	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.1)
WBC (>20 K/mm ³)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet Count (<100 K/mm ³)	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.2)	4 (0.2)
Potassium (>5.0 mmol/L)	126 (5.3)	62 (4.5)	20 (2.4)	13 (2.8)	211 (8.9)
Potassium (<3.5 mmol/L)	13 (0.5)	8 (0.6)	7 (0.8)	35 (7.5)	59 (2.5)
Creatinine (>1.4 mg/dL)	31 (1.3)	29 (2.1)	33 (4.0)	53 (11.3)	135 (5.7)
Includes data from CS8663-A-U301 and CS8663-A-E303. Percentage was calculated using the number of subjects in the column heading as the denominator. Marked laboratory abnormalities were defined as observed values exceeding the given threshold in the laboratory measurement obtained following 12 weeks of randomized double-blind treatment. ALT = alanine transaminase; AML = amlodipine; AST = aspartate transaminase; GGT = gamma-glutamyltransferase; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; RBC = red blood cells; WBC = white blood cells. Source: ISS Post-text Table 14					

Compared to the other groups, the subjects who received the triple combination (OM40/AML10/HCTZ25) had the highest reporting rate for elevated GGT (6%), hypokalemia (8%), and elevated creatinine (11%). This, most likely, is linked to the HCTZ 25 mg component.

Phase 4

Study SP-OLM-03-05 OLMETREAT was a Phase 4, non-Investigation New Drug, European, non-comparative, sequential add-on, open-label, treat-to-target study of OM and an add-on treatment algorithm consisting of HCTZ and AML in subjects with mild to moderate hypertension. The study consisted of a 2-week placebo run-in period (Period I) followed by up to five 4-week active treatment periods. The active treatment periods consisted of the following treatments: OM 20 mg for Period II, OM 20 mg + HCTZ 12.5 mg for Period III, OM 20 mg + HCTZ 25 mg for Period IV, OM 20 mg + HCTZ 25 mg + AML 5 mg for Period V, and OM 20 mg + HCTZ 25 mg + AML 10 mg for Period VI.

Exposure and disposition

A total of 294 subjects were exposed to one of two doses⁹ of triple combination therapy for an average of 45.6 days. Of the subjects who discontinued during active treatment: 2 (0.3%) subjects did not meet entry criteria, 47 (6.8%) subjects discontinued for other reasons, 17 (2.4%) subjects had an adverse event, 15 (2.2%) subjects withdrew consent, 8 (1.2%) subjects

⁹ OM 20 mg + AML 5 mg + HCTZ 25 mg or OM 20 mg + AML 10 mg + HCTZ 25 mg

discontinued because of noncompliance or lack of cooperation, 5 (0.7%) subjects were lost to follow-up, and 2 (0.3%) subjects took a forbidden concomitant medication.

Subject type

Of the 694 subjects who entered the active treatment portion of the study, most were male (51%) subjects and white (98%) subjects were white. The mean age was 58 years, mean weight was 82 kg and mean BMI was 29 kg/m². Few (13%) subjects had diabetes.

Serious safety

There were no reported deaths. There were 14 reports of serious adverse events (cellulitis, rectal cancer, acute myocardial infarction, myocardial infarction, lung disorder, inguinal hernia, and spinal osteoarthritis) and 19 subjects who withdrew from the trial because of an adverse event (including dizziness, syncope, tinnitus, oral pain, abdominal pain, and joint swelling). No subject discontinued from the study due to a laboratory adverse event. (Table 2.11 and pages 81 and 95).

7.4 SAFETY UPDATE

This 120-Day Safety Update for CS-8635 includes safety data from the 40-week, open-label period of the CS8635-A-U301 study up to a data cutoff date of November 6, 2009.

A total of 2112 subjects entered the 40-week, open-label treatment period. All subjects participating in the CS8635-A-U301) study completed their final visits on or before December 9, 2009. The 120-Day Safety Update does not include complete data on 123 subjects who had not yet completed their study visits as of the data cutoff date. The final study report for the 40-week, open-label period of the CS8635-A-U301 is pending.

Additional studies in the safety update include

-two Phase 4 studies from the Azor clinical program (CS-8663-403 performed in the US and CS-8663-404 performed in the US and South Africa). All subjects participating in the CS-8663-403 and CS-8663-404 studies had completed their final visits at the time of the November 6, 2009 data cutoff. The database for the CS-8663-403 study was locked on July 14, 2009. The database for the CS-8663-404 study was locked on December 2, 2009. However, the CSRs for the CS-8663-403 and CS-8663-404 studies have not been finalized.

-two Phase 3 studies from the CS-8635 clinical program (CS8635-A-E302 and CS8635-A-E303), performed in Europe). Since enrollment for these two European studies is ongoing, data are blinded.

Details from all five studies are shown below.

Table 1.2: Summary of Clinical Studies

Protocol Number Number of Centers Country	Study Design	Study Status	Treatments Dose Regimen (Period)	Type and Number of Subjects Randomized (Completed)	Subjects Discontinued due to an AE	Subjects with SAEs	Demographics	
							Age Range (Mean) (years)	Sex & Race [1] M/F (%) W/B/A/O (%)
Ongoing Unblinded Studies								
CS8635-A-U301 317 US	Randomized, Double-Blind, 12-Week, Parallel Study with a 40-Week Open-Label Extension	Ongoing 40-week CSR will be submitted after the 120-Day Safety Update (30 March 2010)	Treat-to-Goal Sequence (40-Week Open-Label Period): OM/AML/HCTZ 40/5/12.5 mg Then: OM/AML/HCTZ 40/10/12.5 mg or OM/AML/HCTZ 40/5/25 mg Then: OM/AML/HCTZ 40/10/25 mg Then (subjects could be back-titrated, if needed): OM/AML/HCTZ 40/5/12.5 mg OM/AML/HCTZ 40/10/12.5 mg OM/AML/HCTZ 40/5/25 mg	Male and female subjects with hypertension 2492 Entered Period III: 2112 (1686)	114 [2,3]	103 [2,3]	22 – 88 (55.4)	53.3/46.7 67.7/29.5/1.8/1.3
CS-8663-403 33 US	Phase 4, Multicenter, Open-Label, Single-Group, Dose-Titration	All subjects completed CSR not finalized	Treatment was adjusted according to the following sequential algorithm: AML 5 mg (3 weeks), then OM/AML 20/5 mg (3 weeks), then OM/AML 40/5 mg (3 weeks), then OM/AML/HCTZ 40/10/12.5 mg (3 weeks), then OM/AML/HCTZ 40/10/25 mg (3 weeks)	Male and female subjects with type 2 diabetes and hypertension 207 (164) Exposed to OM/AML/HCTZ 146	4 [2]	3 [2]	29 – 82 59.1	58.9/41.1 78.7/16.9/3.9/1.0
CS-8663-404 140 US and South Africa	Phase 4, Multicenter, Open-Label, Single-Arm, Dose-Titration	All subjects completed CSR not finalized	Treatment was adjusted according to the following sequential algorithm: OM/AML 20/5 mg (Week 1 to Week 4), then OM/AML 40/5 mg (Week 5 to Week 8), then OM/AML 40/10 mg (Week 9 to Week 12), then OM/AML/HCTZ 40/10/12.5 mg (Week 13 to Week 16), then OM/AML/HCTZ 40/10/25 mg (Week 17 to Week 20)	Male and female subjects with hypertension in multiple subgroups 999 (736) Exposed to OM/AML/HCTZ 700	34 [2,3]	3 [2,3]	18 – 80 (55.6)	50.9/49.1 63.1/23.4/12.9/0.6

Protocol Number Number of Centers Country	Study Design	Study Status	Treatments Dose Regimen (Period)	Type and Number of Subjects Randomized (Completed)	Subjects Discontinued due to an AE	Subjects with SAEs	Demographics	
							Age Range (Mean) (Years)	Sex & Race [1] M/F (%) W/B/A/O (%)
Ongoing Blinded Studies								
CS8635-A-E302 ~230 planned Europe	Phase 3, Multicenter, Randomized, Parallel-Group with 6 Treatment Periods (4 Double-Blind, 1 Single-Blind, and 1 Open-Label)	Ongoing and blinded treatment	Period I: Placebo or OM/AML (20/5 mg, 40/5 mg, or 40/10 mg) Period II: OM/AML (20/5 mg, 40/5 mg, or 40/10 mg) or OM/AML/HCTZ (20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, or 40/10/25 mg) Period III: OM/AML/HCTZ 20/5/12.5 mg Period IV: OM/AML/HCTZ (20/5/12.5 mg or 40/5/12.5 mg) Period V: OM/AML/HCTZ (20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg) Period VI: First 4 weeks OM/AML/HCTZ (20/5/12.5 mg or 40/5/25 mg) Then (subjects could be up- or down-titrated): OM/AML/HCTZ (20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, and 40/10/25 mg)	Male and female subjects with hypertension 1641	38 [3]	5 [3]	18 – 83 (56.7)	47.6/52.4 99.8/0.0/2.0/1
CS8635-A-E303 ~190 planned Europe	Phase 3, Multicenter, Randomized, Parallel-Group with 4 Treatment Periods (2 Single-Blind and 2 Double-Blind)	Ongoing and blinded treatment	Period I: OM/AML 40/10 mg Period II: OM/AML/HCTZ (40/10/0 mg, 40/10/12.5 mg, or 40/10/25 mg) Period III: OM/AML/HCTZ 40/10/12.5 mg Period IV: OM/AML/HCTZ (40/10/12.5 mg or 40/10/25 mg)	Male and female subjects with moderate to severe hypertension 41	2 [3]	1 [3]	39 – 71 (54.7)	63.4/36.6 100.0/0.0/0

1. More than one race category could be selected.
2. Subjects on OM/AML/HCTZ triple combination therapy.
3. The counts of subjects with SAEs and subjects with adverse events leading to discontinuation from the study are based on the subject narratives and data listings.
A = Asian; AE = adverse event; AML = amlodipine; B = Black; CSR = Clinical Study Report; F = female; HCTZ = hydrochlorothiazide; M = male; O = Other; OM = olmesartan medoxomil;
SAE = serious adverse event; W = White.

Study CS8635-A-U301

As of the data cutoff date, a total of 2112 subjects entered the open label period (known as period III). Of these, 6% of the subjects are ongoing and 14% were discontinued during this period. Of the 303 subjects who discontinued, 6% discontinued because of an adverse event, 4% withdrew consent, 2% were lost to follow-up, 1% committed a protocol violation, < 1% became pregnant, and 1 % discontinued because of other reasons.

Extent of exposure

The lengths of exposure are shown below by treatment group.

Table 2.5: Extent of Exposure to Study Medications During the Open-Label Period – Period III Safety Set – Study CS8635-A-U301

	OM40/ AML5/ HCTZ 12.5 (N = 2112)	OM40/ AML5/ HCTZ25 (N = 627)	OM40/ AML10/ HCTZ12.5 (N = 655)	OM40/ AML10/ HCTZ25 (N = 790)	Total (N = 2112)
Extent of Exposure (days)					
n	2112	627	655	790	2112
Mean (SD)	116.0 (120.11)	102.3 (101.85)	104.6 (101.67)	198.2 (73.73)	252.9 (69.31)
Median	31.0	42.0	43.0	238.0	280.0
Number (%) in Specified Exposure Range					
1 day to ≤ 2 weeks	695 (32.9)	163 (26.0)	178 (27.2)	14 (1.8)	32 (1.5)
>2 weeks to ≤4 weeks	344 (16.3)	117 (18.7)	106 (16.2)	17 (2.2)	34 (1.6)
>4 weeks to ≤6 weeks	102 (4.8)	41 (6.5)	39 (6.0)	17 (2.2)	18 (0.9)
>6 weeks to ≤8 weeks	66 (3.1)	24 (3.8)	25 (3.8)	25 (3.2)	28 (1.3)
>8 weeks to ≤16 weeks	84 (4.0)	57 (9.1)	60 (9.2)	67 (8.5)	58 (2.7)
>16 weeks to ≤24 weeks	64 (3.0)	44 (7.0)	47 (7.2)	79 (10.0)	60 (2.8)
>24 weeks to ≤32 weeks	55 (2.6)	36 (5.7)	51 (7.8)	111 (14.1)	83 (3.9)
>32 weeks to ≤40 weeks	420 (19.9)	142 (22.6)	145 (22.1)	458 (58.0)	1046 (49.5)
>40 weeks	282 (13.4)	3 (0.5)	4 (0.6)	2 (0.3)	753 (35.7)

Extent of exposure to study medication (days) = last dose date – first dose date of the given study medication + 1. In case of back-titration, extent of exposure is calculated by summing all time intervals for the given study medication. AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; SD = standard deviation.

Source: Study CS8635-A-U301 Post-text Table 3

The mean exposure to the highest dose of the the triple combination was nearly 200 days. The mean exposure to all OM/AML/HCTZ triple combination therapies was 252 days.

Serious safety

The table below outlines the safety issues that were reported during the open label period.

Table 2.7: Overview of Adverse Events by Onset Dosing Regimen – Period III Safety Set – Study CS8635-A-U301

Category	OM40/ AML5/ HCTZ12.5 (N = 2112) n (%)	OM40/ AML5/ HCTZ25 (N = 627) n (%)	OM40/ AML10/ HCTZ12.5 (N = 655) n (%)	OM40/ AML10/ HCTZ25 (N = 790) n (%)	Total (N = 2112) n (%)
Subjects with AEs					
Any AE	973 (46.1)	220 (35.1)	240 (36.6)	452 (57.2)	1489 (70.5)
Any drug-related [1] AE	307 (14.5)	68 (10.8)	66 (10.1)	151 (19.1)	524 (24.8)
Maximum severity of AEs					
Any AE					
Mild	518 (24.5)	116 (18.5)	115 (17.6)	226 (28.6)	704 (33.3)
Moderate	377 (17.9)	85 (13.6)	100 (15.3)	180 (22.8)	631 (29.9)
Severe	78 (3.7)	19 (3.0)	25 (3.8)	45 (5.7)	153 (7.2)
Drug-related [1] AEs					
Mild	184 (8.7)	36 (5.7)	32 (4.9)	94 (11.9)	298 (14.1)
Moderate	105 (5.0)	24 (3.8)	30 (4.6)	49 (6.2)	189 (8.9)
Severe	18 (0.9)	8 (1.3)	4 (0.6)	8 (1.0)	37 (1.8)
Deaths	1 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	3 (0.1)
Subjects with SAEs					
Any SAE	39 (1.8)	11 (1.8)	17 (2.6)	36 (4.6)	103 (4.9)
Any drug-related [1] SAE	3 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	5 (0.2)
Discontinuation due to AEs during open-label treatment period					
Any AE [2,3]	72 (3.4)	9 (1.4)	11 (1.7)	31 (3.9)	124 (5.9)
AEs starting in Period III [3]	66 (3.1)	9 (1.4)	10 (1.5)	28 (3.5)	114 (5.4)
Drug-related [1] AEs starting in Period III	44 (2.1)	6 (1.0)	6 (0.9)	13 (1.6)	70 (3.3)

1. Drug-related was defined as definitely, probably, or possibly related to open-label study medication.
 2. Adverse events starting before Period III are counted under the final dosing regimen.
 3. Adverse events starting on non-standard open-label medication are counted under the total column only.
- AE = adverse event; AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil;
SAE = serious adverse event.
Source: Study CS8635-A-U301 Post-text Table 5

Deaths

There were three deaths (0.1%) reported during the open-label treatment period: 1 subject in the OM 40 mg + AML 5 mg + HCTZ 12.5 mg group (Subject 0171-0034 with pharyngeal abscess), 1 subject in the OM 40 mg + AML 10 mg + HCTZ 12.5 mg group (Subject 0251-0001, cause unknown¹⁰), and 1 subject in the OM 40 mg + AML 10 mg + HCTZ 25 mg group (Subject 0042-0011 with cardiac arrest).

¹⁰ This subject was a 42-year-old white male who died on study day (b)(6) dose of study medication taken. Last recorded vital signs were BP 131/81 mmHg and pulse 81 bpm. An autopsy was not completed and the death certificate is unobtainable. The subject's medical history included current tobacco use, hypercholesterolemia, and seasonal allergies. Concomitant medications included atorvastatin and albuterol. The following statement is from the case record form.

8 Narrative: (write in brief description of the event including course of the event, evaluation, assessment, and treatment)

CARC Found obituary in the newspaper AFTER being told subject died. obituary stated pt. died of NATURAL CAUSES. Subject's wife is out of the COUNTRY so will TRY TO OBTAIN DEATH CERTIFICATE.

Serious adverse events and discontinuations for adverse events

Compared to the lower doses, a higher percentage of subjects in the high dose group reported a serious adverse event (5%) and discontinued for an adverse event (4%).

Tables 2.11 in the appendices list the subjects who reported at least one serious adverse event.

The serious adverse events leading to discontinuation that were reported by subjects in the highest dose group of the triple combination included transient ischemic attack, fatal cardiac arrest, acute cholecystitis, atrial fibrillation, hypertensive crisis with ruptured cerebral aneurism and subarachnoid hemorrhage, diabetes mellitus, myocardial infarction, and pancreatitis. Table 2.12 in the appendices shows all drop outs for adverse events in the highest dose combination group.

CS-8663-403

No subjects died during the study.

Serious adverse events reported by subjects on triple combination included hyperkalemia and presyncope (Azor 10/40 mg + HCTZ 12.5 mg), presyncope and pneumonia (both subjects taking Azor 10/40 mg + HCTZ 25 mg).

There were four subjects (all receiving Azor 10/40 mg + HCTZ 12.5 mg) who discontinued study because of an adverse event. The reported events included presyncope, hypotension, musculoskeletal chest pain, dizziness.

CS-8663-404

No subjects died during the study.

The subjects who reported serious adverse events included two subjects on Azor 10/40 mg + HCTZ 12.5 mg (non-small cell lung cancer and presyncope) and one subject on Azor 10/40 mg + HCTZ 25 mg (abdominal pain).

There were 34 subjects (10 taking Azor 10/40 mg + HCTZ 12.5 mg and 24 taking Azor 10/40 mg + HCTZ 25 mg) who discontinued the study because of an adverse event. The events included mainly reports of syncope, dizziness, and hypotension. A complete list is shown in Table 2.18 in the appendices.

Ongoing blinded studies

CS8635-A-E302

Deaths

There were no reported deaths

Serious Adverse Events and discontinuations for adverse events

There were five serious adverse events reported. These included arthroscopy, extra systoles, uterine leiomyoma, torticollis, and atrial fibrillation.

There were 38 subjects who discontinued because of an adverse event. These included hypotension, edema, extrasystoles, vertigo, tachycardia, headache, GGT increase, rash, ketonuria, dizziness, asthenia, and vasculitis.

CS8635-A-E303

Deaths

There were no reported deaths.

Serious Adverse Events and discontinuations for adverse events

There was one reported serious adverse event: tonsil cancer. There were two discontinuations for adverse events: tonsil cancer and depression with headache.

Updated report for study CS8635-A-U301 dated March 12, 2010

N.B. Only deaths, serious adverse events and discontinuations for serious adverse events are discussed in this section.

This update includes safety information for 2112 subjects who entered the open-label period and received at least one dose of open-label study medication: 869 subjects received OM 40 mg + AML 5 mg + HCTZ 12.5 mg as their final dosing regimen, 246 subjects received OM 40 + AML 5 mg + HCTZ 25 mg as their final dosing regimen, 239 subjects received OM 40 mg + AML 10 mg + HCTZ 12.5 mg as their final dosing regimen, and 758 subjects received OM 40 mg + AML 10 mg + HCTZ 25 mg as their final dosing regimen.

Deaths

Three subjects died during the open-label period of the study.

- Subject 0171-0034 died of complications from a pharyngeal abscess while receiving OM 40 mg + AML 5 mg + HCTZ 12.5 mg.
- Subject 0251-0001 died of natural causes (cause of the death is unknown) while receiving OM 40 mg + AML 10 mg + HCTZ 12.5 mg. No other information was available to the investigator. The subject had a mean blood pressure of 131/81 mmHg at his last study visit.
- Subject 0042-0011 died of cardiac arrest secondary to artery obstruction syndrome while receiving OM 40 mg + AML 10 mg + HCTZ 25 mg.

Serious adverse events

In total, 106 (5.0%) subjects had a serious adverse event; 40 (1.9%) of these subjects were taking the triple combination.

In total, 127 (6.0%) subjects discontinued from the open-label period because of an adverse event: 116 subjects discontinued due to an adverse event that began on triple combination treatment during the open-label period, 10 subjects began on dual combination treatment during the double-blind period, and 1 subject began on triple combination treatment during the double-blind period.

Twenty-three (1.1%) subjects had a serious adverse event that led to discontinuation from the open-label period.

12 of these subjects were taking OM 40 mg + AML 5 mg + HCTZ 12.5 mg: Subject 0047-0009 (dehydration and pneumonia), Subject 0080-0010 (gallbladder cancer and cholelithiasis), Subject 0091-0004 (affect lability and suicidal ideation), Subject 0104-0012 (acute coronary syndrome), Subject 0112-0012 (fall and head injury), Subject 0122-0009

(multiple myeloma), Subject 0136-0012 (accidental overdose), Subject 0166-0017 (acute myocardial infarction, pneumonia aspiration, atrial fibrillation, atrioventricular block, coronary artery disease, and respiratory failure), Subject 0171-0034 (pharyngeal abscess), Subject 0208-0004 (atrial fibrillation, atrial flutter, road traffic accident, clavicle fracture, rib fracture, tibia fracture, and sternal fracture), Subject 0251-0006 (acute myocardial infarction), and Subject 0352-0002 (gastroenteritis and acute prerenal failure);

- 1 subject while taking OM 40 mg + AML 5 mg + HCTZ 25 mg: Subject 0316-0056 (hypokalemia and syncope);
- 2 subjects while taking OM 40 mg + AML 10 mg + HCTZ 12.5 mg: Subject 0251-0001 (death [cause of death unknown]) and Subject 0330-0010 (atrial fibrillation and myocardial ischemia); and
- 8 subjects while taking OM 40 mg + AML 10 mg + HCTZ 25 mg: Subject 0030-0002 (transient ischemic attack), Subject 0042-0011 (cardiac arrest), Subject 0102-0048 (cholecystitis acute), Subject 0104-0019 (atrial fibrillation), Subject 0126-0017 (hypertensive crisis, ruptured cerebral aneurysm, and subarachnoid hemorrhage), Subject 0223-0017 (diabetes mellitus), Subject 0225-0005 (acute myocardial infarction), and Subject 0260-0028 (pancreatitis).

There were 5 serious adverse events of note:

- Subject 0352-0002 had acute prerenal failure on OM 40 mg + AML 5 mg + HCTZ 12.5 mg. The subject was discontinued from the study;
- Subject 0356-0001 had presyncope on OM 40 mg + AML 5 mg + HCTZ 12.5 mg. The subject was not discontinued from the study;
- Subject 0136-0012 had hypotension on OM 40 mg + AML 5 mg + HCTZ 12.5 mg. The subject was not discontinued from the study;
- Subject 0025-0013 had acute renal failure and hyperkalemia on OM 40 mg + AML 5 mg + HCTZ 25 mg. The subject was not discontinued from the study;
- Subject 0316-0056 had syncope on OM 40 mg + AML 5 mg + HCTZ 25 mg. The subject was discontinued from the study.

OTHER STUDIES AND INFORMATION

The sponsor conducted a search of electronic medical literature databases to confirm that all preclinical and clinical experience with CS-8635 has been reported in this submission. According to the sponsor

search terms included OM in combination with hypertension, cardiovascular risk reduction, stroke, and myocardial infarction; AML in combination with hypertension, cardiovascular risk reduction, stroke, and myocardial infarction; HCTZ in combination with hypertension, cardiovascular risk reduction, stroke, and myocardial infarction; OM and AML in combination with hypertension, cardiovascular risk reduction, stroke, and myocardial infarction; OM and HCTZ in combination with hypertension, cardiovascular risk reduction, stroke, and myocardial infarction; AML and HCTZ in combination with hypertension, cardiovascular risk reduction, stroke, and myocardial infarction; and OM, AML, and HCTZ in combination with hypertension,

cardiovascular risk reduction, stroke, and myocardial infarction.

The search period extended from 17 April 2009 (the date of database lock for the first 12 weeks of double-blind treatment in Study CS8635-A-U301) through the final safety update cutoff date of 06 November 2009. Based on the search terms, 86 publications were found that contained preclinical or clinical data. Seventy-three of these 86 publications contained preclinical or clinical data on the component monotherapies.

A list of these 73 publications was provided in the Safety Update.

Appendices

Figure 3.1: Overview of Study

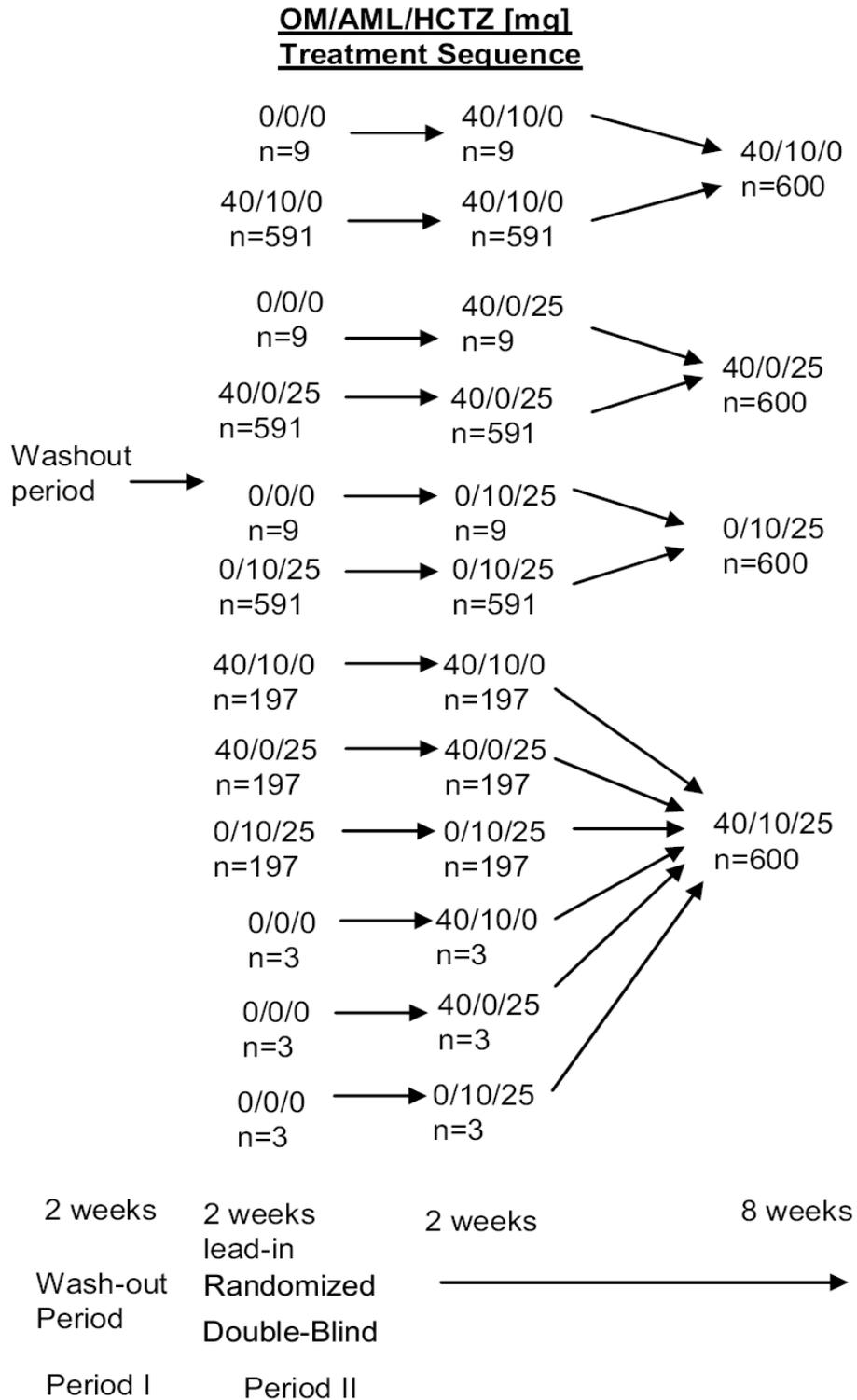


Table 10.14: Listing of Subjects with Serious Adverse Events – Safety Set

Randomized Tmt Group Subject Number	Adverse Event Preferred Term	Relationship to Study Medication	Resulted in Discontinuation
OM40/AML10			
0091-0004	appendicitis appendicitis perforated	not related not related	no no
0112-0044	pneumonia	unlikely	yes
0121-0068	hypersensitivity osteoarthritis	not related not related	no no
0125-0020	gastrointestinal hemorrhage	not related	no
0200-0013	angina pectoris	possible	yes
0313-0009	acute myocardial infarction coronary artery disease	not related not related	no no
0325-0003 [a]	colon cancer	not related	no
0329-0006	arthritis bacterial	not related	no
0334-0010	right ventricular failure sleep apnea syndrome	not related not related	yes yes
0340-0002	osteoarthritis	not related	no
OM40/HCTZ25			
0015-0021	arteriospasm coronary	unlikely	yes
0035-0018	cerebellar infarction	not related	yes
0065-0012	non-cardiac chest pain	not related	yes
0076-0005	cerebrovascular accident	not related	no
0091-0001	ovarian cyst	not related	no
0147-0036	musculoskeletal chest pain	not related	no
0156-0025	chest pain	unlikely	yes
0184-0001	chest pain hypertension	unlikely unlikely	yes yes
0233-0002	bladder cancer	not related	no
0248-0037	adrenal adenoma hyperkalemia renal failure acute	not related not related not related	yes no no
0257-0007	cerebrovascular accident	unlikely	yes
0350-0004	acute myocardial infarction	unlikely	yes
0356-0001	diabetes mellitus	not related	no
AML10/HCTZ25			
0052-0015	hiatus hernia	not related	no
0065-0005	fall hip fracture	not related not related	yes yes
0085-0010	non-cardiac chest pain	unlikely	no
0093-0021	cellulitis	not related	no
0111-0066	renal cell carcinoma	not related	no
0128-0023	ataxia hemiparesis	not related not related	no no
0173-0011	fall lumbar vertebral fracture	not related not related	no yes
0196-0017	renal failure acute syncope	possible probable	yes yes
0208-0016	lobar pneumonia	unlikely	no
0295-0003	hypertensive crisis	not related	yes
0297-0001	prostate cancer	not related	no
0316-0027	hydronephrosis hypokalemia hyponatremia pyelonephritis sepsis	not related not related not related not related not related	no no no no no

Table 10.14: Listing of Subjects with Serious Adverse Events – Safety Set (Continued)

Randomized Tmt Group Subject Number	Adverse Event Preferred Term	Relationship to Study Medication	Resulted in Discontinuation
OM40/AML10/HCTZ25			
0070-0190 [b]	uterine leiomyoma	not related	yes
0071-0017	prostate cancer	not related	no
0102-0020	coronary artery disease	not related	yes
0111-0041	osteomyelitis	not related	no
	peroneal nerve palsy	not related	no
0111-0071 [b]	diabetes mellitus	not related	yes
0121-0010 [c]	alcohol poisoning	not related	yes
0125-0024 [d]	bipolar disorder	not related	yes
	drug dependence	not related	yes
0150-0009	dyspnea	not related	no
	pulmonary artery atresia	not related	no
0152-0032	obstructive airways disorder	not related	no
	syncope	not related	no
0204-0015	acute pre-renal failure	unlikely	no
0224-0013 [d]	prostate cancer	not related	no
0336-0024	intervertebral disc degeneration	not related	no
	vertebral injury	not related	no
0343-0023	duodenitis	not related	no
	gastritis	not related	no
	rectal hemorrhage	not related	no
0354-0013	coronary artery disease	not related	no
	non-cardiac chest pain	not related	no

The Safety Set included subjects who received at least 1 dose of study medication and had at least 1 post-dose safety assessment.

Treatment-emergent adverse events were adverse events that emerged during treatment having been absent pre-treatment, or worsened relative to the pre-treatment state.

Drug-related was defined as definitely, probably, or possibly related to randomized study medication.

- a. The serious adverse event occurred while the subject was receiving placebo.
- b. The serious adverse event occurred while the subject was receiving OM40/HCTZ25.
- c. The serious adverse event occurred while the subject was receiving AML10/HCTZ25.
- d. The serious adverse event occurred while the subject was receiving OM40/AML10.

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; Tmt = treatment.

Source: Post-text Table 15.3.2.1

Discontinuations for adverse events

OM40/AML10/HCTZ25	
0015-0009 [a]	edema peripheral
0015-0024 [b]	dizziness palpitations pollakiuria
0016-0004 [a]	cough dizziness nausea
0018-0019	anxiety blood creatinine phosphokinase increased blood potassium decreased burning sensation dizziness dry mouth flushing loss of consciousness
0039-0006	dizziness headache
0052-0013	edema peripheral [c] petechia
0070-0190 [b]	anemia uterine leiomyoma vaginal hemorrhage

Randomized Tmt Group Subject Number	Adverse Event Preferred Term
OM40/AML10/HCTZ25 (continued)	
0073-0012	hypotension
0088-0002	hypotension
0095-0001 [c]	fatigue irritability myalgia
0102-0020	coronary artery disease
0110-0018 [b]	cough
0111-0071 [b]	diabetes mellitus
0112-0019 [c]	diarrhea dizziness headache
0112-0022 [b]	hypotension
0121-0010 [a]	alcohol poisoning [f]
0125-0024 [c]	bipolar disorder drug dependence
0126-0007	dizziness
0145-0006 [c]	dyspnea face edema edema peripheral
0155-0016	edema peripheral
0156-0008 [a]	dizziness headache
0159-0015 [c]	hypertension hypoxia systemic lupus erythematosus
0164-0013	edema peripheral weight increased
0164-0024	palpitations
0166-0026	blood pressure decreased
0176-0010 [a]	abdominal pain asthenia decreased appetite disorientation dizziness headache
0183-0021	blood creatinine increased blood urea increased
0183-0023	hypotension
0183-0031	extrasystoles
0192-0020 [c]	dizziness fatigue edema peripheral
0202-0001	blood creatinine increased blood urea increased
0214-0008	constipation edema peripheral
0216-0017 [b]	dizziness dizziness dyspnea heart rate increased night sweats

Randomized Tmt Group Subject Number	Adverse Event Preferred Term	Relationship to Study Medication	Serious
OM40/AML10/HCTZ25 (continued)			
0220-0002 [d]	edema peripheral	not related	no
0228-0010	hyperkalemia	probable	no
0237-0007	dizziness headache	probable possible	no no
0251-0010 [b]	vertigo	unlikely	no
0257-0020	blood creatinine increased blood urea increased	possible possible	no no
0259-0006 [c]	edema peripheral	not related	no
0260-0015 [c]	musculoskeletal pain neck pain	not related not related	no no
0275-0019 [c]	convulsion loss of consciousness	unlikely unlikely	no no
0312-0008 [c]	headache	possible	no
0316-0123 [b]	dyspnea	unlikely	no
0318-0046	dizziness fatigue hypotension	definite definite definite	no no no
0322-0004 [a]	mood swings	not related	no
0322-0012 [b]	fatigue heart rate increased	probable probable	no no
0331-0032	edema peripheral rash	probable probable	no no
0340-0013 [b]	fibromyalgia	unlikely	no

The Safety Set included subjects who received at least 1 dose of study medication and had at least 1 post-dose safety assessment.

Discontinuation from the study is based on “action taken” on adverse event case report form.

Drug-related was defined as definitely, probably, or possibly related to randomized study medication.

- a. The adverse event leading to discontinuation first occurred while the subject was receiving AML10/HCTZ25.
- b. The adverse event leading to discontinuation first occurred while the subject was receiving OM40/HCTZ25.
- c. The adverse event leading to discontinuation first occurred while the subject was receiving OM40/AML10.
- d. The adverse event leading to discontinuation first occurred before Subject 0220-0002 received study medication. After the adverse event began, the subject received OM40/AML10 prior to discontinuing from the study.
- e. The adverse event leading to discontinuation first occurred during the screening period.
- f. This event resulted in the death of the subject.

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; Tmt = treatment.

Source: Post-text Table 15.3.2.2

Shift table for creatinine

Table 15.3.4.10
Shift Table for Creatinine (mg/dL)
Safety Set

Final Randomized Treatment	Baseline	Week 12/Early Termination					Total
		Low n (%)	Normal n (%)	High n (%)	Missing n (%)		
OM40/AML10 (N= 628)	Low	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)	
	Normal	2 (0.3)	575 (91.6)	5 (0.8)	21 (3.3)	603 (96.0)	
	High	0 (0.0)	9 (1.4)	14 (2.2)	0 (0.0)	23 (3.7)	
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Total	3 (0.5)	585 (93.2)	19 (3.0)	21 (3.3)	628 (100.0)	
OM40/HCTZ25 (N= 637)	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Normal	0 (0.0)	568 (89.2)	30 (4.7)	22 (3.5)	620 (97.3)	
	High	0 (0.0)	2 (0.3)	15 (2.4)	0 (0.0)	17 (2.7)	
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Total	0 (0.0)	570 (89.5)	45 (7.1)	22 (3.5)	637 (100.0)	
AML10/HCTZ25 (N= 600)	Low	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	
	Normal	2 (0.3)	556 (92.7)	8 (1.3)	24 (4.0)	590 (98.3)	
	High	0 (0.0)	3 (0.5)	6 (1.0)	0 (0.0)	9 (1.5)	
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Total	3 (0.5)	559 (93.2)	14 (2.3)	24 (4.0)	600 (100.0)	
OM40/AML10/HCTZ25 (N= 626)	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Normal	0 (0.0)	550 (87.9)	26 (4.2)	33 (5.3)	609 (97.3)	
	High	0 (0.0)	3 (0.5)	14 (2.2)	0 (0.0)	17 (2.7)	
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Total	0 (0.0)	553 (88.3)	40 (6.4)	33 (5.3)	626 (100.0)	

Baseline is defined as the last available measurement on or before the first dose date of double-blind study medication
Week 12/Early Termination is defined as the last available planned measurement in the double-blind period.

Change in selected chemistry parameters

Table 15.3.4.1
Change in Chemistry Parameters From Baseline to Week 12/Early Termination (ET)
Safety Set

Parameter (unit)/ Final Randomized Treatment	n [1]	--- Baseline [2] ---			-- Week 12/ET [3] --			Change			p-value [4]
		Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	
BUN (mg/dL)											
OM40/AML10	607	14.0	13.0	4.23	14.8	14.0	4.81	0.8	1.0	3.93	<.0001
OM40/HCTZ25	615	14.0	14.0	4.23	17.5	17.0	5.97	3.5	3.0	5.00	<.0001
AML10/HCTZ25	576	13.8	13.0	3.96	15.0	14.5	5.00	1.2	1.0	4.44	<.0001
OM40/AML10/HCTZ25	593	14.1	14.0	4.37	17.4	16.0	6.19	3.4	3.0	5.22	<.0001
Creatinine (mg/dL)											
OM40/AML10	607	0.947	0.910	0.2756	0.922	0.900	0.2317	-0.025	-0.020	0.1876	0.0010
OM40/HCTZ25	615	0.940	0.910	0.2121	1.007	0.970	0.2623	0.067	0.040	0.1659	<.0001
AML10/HCTZ25	576	0.931	0.920	0.2067	0.939	0.920	0.2569	0.007	0.000	0.1505	0.2333
OM40/AML10/HCTZ25	593	0.920	0.890	0.2181	0.983	0.930	0.2694	0.063	0.040	0.1546	<.0001
Creatinine Clearance (mL/min) [5]											
OM40/AML10	578	121.8	110.5	52.84	121.8	113.7	48.97	-0.0	2.9	26.88	0.9828
OM40/HCTZ25	587	117.7	110.0	44.65	109.5	103.6	40.95	-8.2	-5.6	24.50	<.0001
AML10/HCTZ25	555	120.5	113.0	45.36	118.6	113.2	42.78	-2.0	0.7	23.16	0.0476
OM40/AML10/HCTZ25	560	119.5	114.0	42.07	112.5	106.9	42.57	-7.0	-5.6	19.54	<.0001
Glucose (mg/dL)											
OM40/AML10	579	110.2	101.0	33.55	114.1	101.0	44.77	4.0	1.0	34.63	0.0060
OM40/HCTZ25	596	109.9	100.0	34.51	113.3	102.5	44.54	3.4	2.0	39.58	0.0374
AML10/HCTZ25	556	107.7	100.0	32.71	117.0	104.0	46.66	9.3	4.0	40.52	<.0001
OM40/AML10/HCTZ25	563	108.5	99.0	32.47	113.6	101.0	41.34	5.1	3.0	34.04	0.0005
Uric Acid (mg/dL)											
OM40/AML10	583	6.17	6.00	1.504	6.00	5.90	1.518	-0.18	-0.20	0.900	<.0001
OM40/HCTZ25	599	6.17	6.00	1.512	7.25	7.20	1.733	1.09	1.10	1.144	<.0001
AML10/HCTZ25	560	6.15	6.10	1.584	6.61	6.40	1.796	0.46	0.50	1.152	<.0001
OM40/AML10/HCTZ25	566	6.07	6.00	1.464	7.03	6.90	1.816	0.96	1.00	1.165	<.0001

- [1] n is the number of subjects with both baseline and endpoint measurements.
- [2] Baseline is defined as the last available measurement on or before the first dose date of double-blind study medication
- [3] Week 12/ET is defined as the last available planned measurement in the double-blind period.
- [4] Two-sided p-value is obtained from t-test testing whether mean change is equal to 0 within the treatment group.
- [5] Creatinine Clearance is calculated using the Cockcroft-Gault formula.

Table 2.11: Listing of Subjects with Serious Adverse Events During the Open-Label Period – Period III Safety Set – Study CS8635-A-U301

Onset Regimen Subject No.	Adverse Event Preferred Term	Severity	Relationship to Study Medication	Outcome	Resulted in Discontinuation
OM40/AML5/HCTZ12.5					
0035-0013	Osteoarthritis	Severe	Not related	Recovered/resolved	No
0047-0009	Dehydration	Severe	Not related	Recovered/resolved	Yes
	Pneumonia	Severe	Not related	Recovered/resolved	Yes
0059-0022	Inguinal hernia	Moderate	Not related	Recovered/resolved	No
0066-0036	Abdominal wall abscess	Mild	Not related	Recovered/resolved	No
0069-0002	Conjunctival melanoma	Moderate	Not related	Recovered/resolved with sequelae	No
0070-0139	Asthenia	Moderate	Not related	Recovered/resolved	No
	Chest pain	Moderate	Not related	Recovered/resolved	No
	Coronary artery disease	Moderate	Not related	Recovered/resolved	No
0073-0005	Metrorrhagia	Severe	Not related	Recovered/resolved	No
	Supraventricular tachycardia	Moderate	Not related	Recovered/resolved	No
	Uterine leiomyoma	Severe	Not related	Recovered/resolved	No
0074-0005	Ischemic cerebral infarction	Severe	Not related	Recovered/resolved with sequelae	No
0080-0010	Cholelithiasis	Moderate	Not related	Recovered/resolved	Yes
	Gallbladder cancer	Severe	Not related	Recovered/resolved with sequelae	Yes
0090-0014	Contusion	Moderate	Not related	Recovered/resolved with sequelae	No
	Rib fracture	Moderate	Not related	Recovered/resolved with sequelae	No
	Road traffic accident	Moderate	Not related	Recovered/resolved	No
	Sternal fracture	Moderate	Not related	Recovered/resolved with sequelae	No
0091-0004	Affect liability	Moderate	Not related	Recovered/resolved	Yes
	Suicidal ideation	Moderate	Not related	Recovered/resolved	Yes
0091-0008	Transient ischemic attack	Mild	Not related	Recovered/resolved	No
	Venous thrombosis limb	Severe	Not related	Recovered/resolved with sequelae	No
0104-0012	Acute coronary syndrome	Moderate	Not related	Recovered/resolved with sequelae	Yes
	Angina unstable	Moderate	Not related	Recovered/resolved	No
0112-0012	Fall	Severe	Unlikely	Recovered/resolved with sequelae	Yes
	Traumatic brain injury	Severe	Unlikely	Recovered/resolved with sequelae	Yes
0114-0004	Angina pectoris	Moderate	Not related	Recovered/resolved	No
	Renal failure acute	Moderate	Not related	Recovered/resolved	No
0122-0009	Multiple myeloma	Severe	Not related	Not recovered/not resolved	Yes
0128-0039	Osteoarthritis	Severe	Not related	Recovered/resolved	No
0136-0012	Accidental overdose	Severe	Not related	Recovered/resolved	Yes
	Hypotension	Severe	Definite	Recovered/resolved	No
0166-0017	Acute myocardial infarction	Severe	Not related	Recovered/resolved	Yes
	Atrial fibrillation	Severe	Not related	Recovered/resolved	Yes
	Atrioventricular block	Severe	Not related	Recovered/resolved	Yes
	Coronary artery disease	Severe	Not related	Recovered/resolved	Yes
	Pneumonia aspiration	Severe	Not related	Recovered/resolved	Yes
	Respiratory failure	Severe	Not related	Recovered/resolved	Yes
0168-0009	Abscess limb	Moderate	Not related	Recovered/resolved with sequelae	No
	Hyperglycemia	Severe	Not related	Recovered/resolved	No
	Staphylococcal skin infection	Moderate	Not related	Recovered/resolved	No
0171-0034	Pharyngeal abscess	Severe	Not related	Fatal	Yes
0194-0007	Parathyroid tumor benign	Moderate	Not related	Recovered/resolved with sequelae	No
0208-0004	Atrial fibrillation	Moderate	Not related	Recovered/resolved	Yes
	Atrial flutter	Moderate	Not related	Recovered/resolved	Yes
	Clavicle fracture	Moderate	Not related	Recovered/resolved	Yes
	Rib fracture	Moderate	Not related	Recovered/resolved	Yes
	Road traffic accident	Moderate	Not related	Recovered/resolved	Yes
	Sternal fracture	Moderate	Not related	Recovered/resolved	Yes
	Tibia fracture	Moderate	Not related	Recovered/resolved	Yes
0208-0027	Abdominal abscess	Moderate	Not related	Recovered/resolved with sequelae	No
	Abdominal abscess	Moderate	Not related	Recovered/resolved	No
	Diverticulitis	Severe	Not related	Recovered/resolved	No
	Diverticulitis	Severe	Not related	Recovered/resolved	No
0251-0006	Acute myocardial infarction	Severe	Not related	Recovered/resolved	Yes
0260-0012	Dehydration	Severe	Not related	Recovered/resolved	No
	Dyspnea	Severe	Not related	Recovered/resolved	No
0263-0003	Diverticulitis	Severe	Not related	Recovered/resolved	No

Table 2.11: Listing of Subjects with Serious Adverse Events During the Open-Label Period – Period III Safety Set – Study CS8635-A-U301 (Continued)

Onset Regimen Subject No.	Adverse Event Preferred Term	Severity	Relationship to Study Medication	Outcome	Resulted in Discontinuation
OMI40/AML5/HCTZ12.5 (continued)					
0265-0005	Breast cancer	Moderate	Not related	Not recovered/not resolved	No
	Breast cancer	Severe	Not related	Not recovered/not resolved	No
0272-0014	Dehydration	Moderate	Not related	Recovered/resolved	No
	Gastroenteritis	Severe	Not related	Recovered/resolved	No
	Renal failure acute	Mild	Not related	Recovered/resolved	No
0287-0010	Coronary artery disease	Severe	Not related	Recovered/resolved	No
	Coronary artery disease	Severe	Unlikely	Recovered/resolved	No
0293-0001	Ankle fracture	Moderate	Not related	Recovered/resolved with sequelae	No
	Joint dislocation	Moderate	Not related	Recovered/resolved with sequelae	No
0320-0011	Intervertebral disc degeneration	Severe	Not related	Recovered/resolved	No
	Spinal column stenosis	Severe	Not related	Recovered/resolved	No
0340-0002	Osteoarthritis	Severe	Not related	Recovered/resolved	No
0340-0004	Breast cancer stage I	Severe	Not related	Not recovered/not resolved	No
0343-0008	Concussion	Severe	Not related	Recovered/resolved	No
	Joint dislocation	Severe	Not related	Recovered/resolved	No
	Road traffic accident	Severe	Not related	Recovered/resolved	No
0343-0040	Arrhythmia	Moderate	Not related	Recovered/resolved	No
0352-0002	Acute prerenal failure	Moderate	Possible	Recovered/resolved	No
	Gastroenteritis	Moderate	Unlikely	Recovered/resolved	No
0354-0010	Bronchitis	Severe	Not related	Recovered/resolved	No
	Hematuria	Severe	Not related	Recovered/resolved	No
0356-0001	Presyncope	Moderate	Probable	Recovered/resolved	No
OMI40/AML5/HCTZ25					
0020-0001	Hypertension	Mild	Unlikely	Recovered/resolved	No
	Non-cardiac chest pain	Moderate	Unlikely	Recovered/resolved	No
0021-0010	Uterine leiomyoma	Severe	Not related	Recovered/resolved	No
0025-0013	Hyperkalemia	Severe	Possible	Recovered/resolved	No
	Hypoxia	Moderate	Not related	Recovered/resolved	No
	Mental status changes	Moderate	Not related	Recovered/resolved	No
	Pneumonia	Moderate	Not related	Recovered/resolved	No
	Pulmonary embolism	Moderate	Not related	Recovered/resolved	No
	Renal failure acute	Severe	Possible	Recovered/resolved	No
0050-0020	Angina pectoris	Mild	Not related	Recovered/resolved	No
0059-0018	Pneumonia	Moderate	Not related	Recovered/resolved	No
0183-0007	Prostate cancer stage II	Severe	Not related	Recovered/resolved	No
0187-0008	Pulmonary embolism	Moderate	Not related	Recovered/resolved with sequelae	No
0211-0005	Pneumonia bacterial	Severe	Not related	Recovered/resolved	No
0316-0056	Hypokalemia	Moderate	Unlikely	Recovered/resolved	Yes
	Syncope	Moderate	Possible	Recovered/resolved	Yes
0337-0004	Obesity	Mild	Not related	Recovered/resolved with sequelae	No
0354-0011	Pain in extremity	Moderate	Not related	Recovered/resolved	No
OMI40/AML10/HCTZ12.5					
0012-0007	Abortion spontaneous	Severe	Not related	Recovered/resolved	No
0031-0019	Dehydration	Severe	Unlikely	Recovered/resolved	No
0044-0011	Angina unstable	Severe	Unlikely	Recovered/resolved	No
0070-0065	Vertigo positional	Moderate	Unlikely	Recovered/resolved	No
0104-0031	Rectal hemorrhage	Severe	Not related	Recovered/resolved	No
0136-0004	Lung adenocarcinoma	Moderate	Not related	Not recovered/not resolved	No
0138-0015	Dizziness	Mild	Unlikely	Recovered/resolved	No
	Tinnitus	Mild	Unlikely	Recovered/resolved	No
0163-0014	Deep vein thrombosis	Severe	Not related	Recovered/resolved	No
	Forearm fracture	Moderate	Not related	Recovered/resolved with sequelae	No
	Osteoarthritis	Severe	Not related	Recovered/resolved with sequelae	No
	Road traffic accident	Moderate	Not related	Recovered/resolved with sequelae	No
0197-0006	Musculoskeletal chest pain	Severe	Unlikely	Recovered/resolved	No
0224-0017	Abscess intestinal	Severe	Not related	Recovered/resolved	No

Table 2.11: Listing of Subjects with Serious Adverse Events During the Open-Label Period – Period III Safety Set – Study CS8635-A-U301 (Continued)

Onset Regimen Subject No.	Adverse Event Preferred Term	Severity	Relationship to Study Medication	Outcome	Resulted in Discontinuation
OMI40/AML10/HCTZ12.5 (continued)					
0251-0001	Death	Severe	Not related	Fatal	Yes
0253-0009	Chronic obstructive pulmonary disease	Moderate	Unlikely	Recovered/resolved	No
	Lobar pneumonia	Moderate	Unlikely	Recovered/resolved	No
	Sepsis	Moderate	Unlikely	Recovered/resolved	No
0279-0020	Renal cancer	Severe	Not related	Recovered/resolved	No
0316-0027	Fall	Moderate	Unlikely	Recovered/resolved	No
0330-0010	Atrial fibrillation	Severe	Not related	Recovered/resolved with sequelae	Yes
	Myocardial ischemia	Severe	Not related	Recovered/resolved with sequelae	Yes
0331-0022	Pleuritic pain	Moderate	Not related	Recovered/resolved	No
0334-0013	Coronary artery disease	Severe	Not related	Recovered/resolved with sequelae	No
OMI40/AML10/HCTZ25					
0007-0050	Bile duct stone	Severe	Not related	Recovered/resolved	No
	Cholelithiasis	Severe	Not related	Recovered/resolved	No
0021-0005	Non-cardiac chest pain	Severe	Not related	Recovered/resolved	No
	Pneumonia	Severe	Not related	Recovered/resolved	No
	Rib fracture	Severe	Not related	Recovered/resolved	No
0030-0002	Atrial fibrillation	Mild	Unlikely	Recovered/resolved with sequelae	No
	Transient ischemic attack	Severe	Unlikely	Recovered/resolved	Yes
0031-0015	Ovarian cyst	Moderate	Not related	Recovered/resolved	No
	Uterine leiomyoma	Moderate	Not related	Recovered/resolved	No
0031-0021	Cervical myelopathy	Moderate	Not related	Recovered/resolved	No
	Cervical spinal stenosis	Moderate	Not related	Recovered/resolved	No
	Myelomalacia	Moderate	Not related	Recovered/resolved	No
0042-0011	Cardiac arrest	Severe	Not related	Fatal	Yes
0052-0001	Atrial fibrillation	Moderate	Not related	Recovered/resolved with sequelae	No
0102-0010	Hypertension	Moderate	Not related	Recovered/resolved	No
0102-0048	Cholecystitis acute	Severe	Not related	Not recovered/not resolved	Yes
0104-0019	Atrial fibrillation	Moderate	Not related	Recovered/resolved with sequelae	Yes
0107-0011	Cervical spinal stenosis	Severe	Not related	Recovered/resolved	No
0111-0005	Cerebrovascular accident	Moderate	Not related	Recovered/resolved with sequelae	No
0111-0008	Uterine leiomyoma	Mild	Not related	Recovered/resolved	No
0111-0041	Osteomyelitis	Moderate	Not related	Recovered/resolved with sequelae	No
0111-0067	Uterine leiomyoma	Moderate	Not related	Recovered/resolved	No
0121-0045	Osteoarthritis	Severe	Not related	Recovered/resolved	No
0126-0017	Hypertensive crisis	Severe	Not related	Recovered/resolved	Yes
	Ruptured cerebral aneurism	Moderate	Not related	Recovered/resolved	Yes
	Subarachnoid hemorrhage	Moderate	Not related	Recovered/resolved	Yes
0147-0014	Prostate cancer	Moderate	Not related	Recovered/resolved	No
0147-0051	Colitis	Severe	Not related	Recovered/resolved	No
0164-0006	Prostate cancer	Moderate	Not related	Not recovered/not resolved	No
0166-0008	Suicidal ideation	Severe	Not related	Recovered/resolved	No
0174-0001	Tendon rupture	Severe	Not related	Recovered/resolved	No
0178-0002	Anastomotic ulcer	Moderate	Not related	Recovered/resolved	No
	Syncope	Moderate	Not related	Recovered/resolved	No
0186-0008	Prostate cancer	Severe	Not related	Recovered/resolved	No
0187-0015	Diabetic ketoacidosis	Severe	Not related	Recovered/resolved	No
0198-0007	Pyelonephritis	Moderate	Unlikely	Recovered/resolved	No
0223-0017	Diabetes mellitus	Severe	Not related	Recovered/resolved with sequelae	Yes
0225-0005	Myocardial infarction	Severe	Unlikely	Recovered/resolved	Yes
0260-0028	Pancreatitis	Severe	Not related	Recovered/resolved	Yes
0264-0003	Intravascular papillary endothelial hyperplasia	Severe	Not related	Recovered/resolved with sequelae	No
0264-0007	Deep vein thrombosis	Moderate	Not related	Recovered/resolved with sequelae	No
	Joint dislocation	Moderate	Not related	Recovered/resolved with sequelae	No
	Road traffic accident	Moderate	Not related	Recovered/resolved with sequelae	No
	Tibia fracture	Moderate	Not related	Recovered/resolved with sequelae	No

Table 2.11: Listing of Subjects with Serious Adverse Events During the Open-Label Period – Period III Safety Set – Study CS8635-A-U301 (Continued)

Onset Regimen Subject No.	Adverse Event Preferred Term	Severity	Relationship to Study Medication	Outcome	Resulted in Discontinuation
OM40/AML10/HCTZ25 (continued)					
0279-0001	Diabetes mellitus	Severe	Not related	Recovered/resolved with sequelae	No
	Hyperglycemia	Severe	Not related	Recovered/resolved with sequelae	No
0287-0011	Gastroenteritis	Severe	Unlikely	Recovered/resolved	No
	Renal failure acute	Severe	Unlikely	Recovered/resolved	No
	Syncope	Severe	Unlikely	Recovered/resolved with sequelae	No
0303-0016	Nephrolithiasis	Moderate	Not related	Recovered/resolved	No
0336-0014	Cellulitis	Moderate	Not related	Recovered/resolved with sequelae	No
0342-0004	Femoral artery occlusion	Severe	Not related	Recovered/resolved	No

Drug-related was defined as definitely, probably, or possibly related to randomized study medication.

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

Source: Study CS8635-A-U301 Post-text Table 8

Table 2.12: Listing of Subjects who Discontinued due to Adverse Events During the Open-Label Period – Period III Safety Set – Study CS8635-A-U301

Onset Regimen Subject No.	Adverse Event Preferred Term	Severity	Relationship to Study Medication	Serious
OM40/AML5/HCTZ12.5				
0014-0009	Blood chloride decreased	Severe	Possible	No
	Blood sodium decreased	Moderate	Possible	No
0020-0004	Blood urea increased	Moderate	Possible	No
0022-0008	Headache	Severe	Probable	No
	Photosensitivity reaction	Moderate	Probable	No
0022-0018	Pitting edema	Severe	Not related	No
0025-0002	Angina pectoris	Moderate	Unlikely	No
0045-0014	Creatinine renal clearance decreased	Mild	Definite	No
0047-0009	Dehydration	Severe	Not related	Yes
	Pneumonia	Severe	Not related	Yes
0069-0001	Erectile dysfunction	Moderate	Probable	No
0070-0088	Dry mouth	Mild	Probable	No
	Angioedema	Mild	Probable	No
0070-0123	Hypercalcemia	Mild	Not related	No
0070-0127	Rash generalized	Mild	Possible	No
0080-0010	Gallbladder cancer	Severe	Not related	Yes
	Cholelithiasis	Moderate	Not related	Yes
0083-0027	Vertigo	Moderate	Possible	No
	Lethargy	Mild	Possible	No
0091-0004	Affect lability	Moderate	Not related	Yes
	Suicidal ideation	Moderate	Not related	Yes
0097-0019	Alanine aminotransferase increased	Moderate	Possible	No
	Aspartate aminotransferase increased	Moderate	Possible	No
0104-0012	Acute coronary syndrome	Moderate	Not related	Yes
0110-0007	Muscle spasms	Severe	Possible	No
0110-0012	Dizziness	Moderate	Possible	No
0112-0012	Traumatic brain injury	Severe	Unlikely	Yes
	Fall	Severe	Unlikely	Yes
	Post concussion syndrome	Severe	Possible	No
	Pneumonia aspiration	Severe	Not related	No
	Pneumonia staphylococcal	Severe	Not related	No
0112-0018	Hypotension	Moderate	Definite	No
0114-0002	Blood creatinine increased	Moderate	Probable	No
	Blood uric acid increased	Moderate	Probable	No
	Blood urea increased	Moderate	Probable	No
	Blood phosphorous increased	Moderate	Probable	No
	Blood calcium decreased	Moderate	Probable	No
0120-0001	Bundle branch block right	Mild	Unlikely	No
0122-0007	Dizziness	Severe	Definite	No
0122-0009	Multiple myeloma	Severe	Not related	Yes
0122-0017	Pruritus	Mild	Definite	No
	Lip swelling	Moderate	Definite	No
0125-0005	Gamma-glutamyltransferase increased	Moderate	Probable	No
0132-0014	Hypotension	Mild	Probable	No
0136-0012	Accidental overdose	Severe	Not related	Yes
0152-0038	Weight increased	Mild	Not related	No
0154-0012	Dizziness	Mild	Possible	No
0163-0018	Hypotension	Moderate	Possible	No
0163-0035	Hypotension	Moderate	Possible	No

Table 2.18: Listing of Subjects Who Discontinued from the Study due to Adverse Events – Treated Subjects – Study CS-8663-404

Onset Regimen Subject No.	Adverse Event Preferred Term	Severity	Relationship to Study Medication	Serious
Azor10/40 + HCTZ12.5				
1010-0013	Syncope	Moderate	Probable	No
1018-0003	Syncope	Mild	Probable	No
1020-0002	Non-small cell lung cancer stage IIIB	Severe	Not related	Yes
1020-0010	Dizziness	Moderate	Probable	No
1027-0012	Dizziness	Mild	Possible	No
1027-0015	Dizziness	Mild	Possible	No
1035-0006	Renal pain	Mild	Probable	No
1037-0004	Dizziness	Severe	Possible	No
1039-0015	Dizziness Syncope Nausea	Mild Mild Moderate	Possible Possible Possible	No No No
1048-0003	Hypotension	Mild	Not related	No
1053-0005	Dizziness Vision blurred Chest pain Dyspnea	Moderate Moderate Moderate Moderate	Possible Possible Possible Possible	No No No No
1054-0011	Dizziness	Moderate	Probable	No
1057-0004	Dizziness	Moderate	Probable	No
1064-0006	Hypotension	Moderate	Definite	No
1075-0008	Malaise Nausea	Moderate Moderate	Probable Probable	No No
1081-0002	Fatigue Muscular weakness	Moderate Moderate	Unlikely Unlikely	No No
1083-0006	Presyncope	Mild	Unlikely	Yes
1085-0005	Dizziness	Mild	Possible	No
1087-0010	Painful defecation	Severe	Definite	No
1097-0008	Dizziness Nausea	Moderate Moderate	Definite Definite	No No
1104-0005	Hypotension	Mild	Probable	No
1106-0001	Arthralgia	Mild	Unlikely	No
1168-0003	Dizziness	Moderate	Possible	No
1184-0004	Hypotension	Moderate	Definite	No
Azor10/40 + HCTZ25				
1025-0009	Hypotension	Moderate	Definite	No
1048-0004	Hypotension	Mild	Not related	No
1054-0009	Dizziness	Moderate	Probable	No
1071-0001	Dizziness Asthenia Hypotension	Moderate Moderate Mild	Definite Definite Definite	No No No
1104-0001	Asthenia Headache	Moderate Moderate	Possible Possible	No No

Table 2.18: Listing of Subjects Who Discontinued from the Study due to Adverse Events – Treated Subjects – Study CS-8663-404 (Continued)

Onset Regimen Subject No.	Adverse Event Preferred Term	Severity	Relationship to Study Medication	Serious
Azor10/40 + HCTZ25 (continued)				
1104-0003	Angioedema	Mild	Probable	No
1109-0001	Hypotension	Moderate	Definite	No
1109-0005	Hypotension	Moderate	Definite	No
1109-0007	Hypotension	Moderate	Definite	No
1168-0015	Dizziness	Severe	Possible	No

Note: Three subjects (Subject 1034-0012 and Subject 1187-0012 on Azor10/40 + HCTZ12.5 and Subject 1187-0009 on Azor10/40 + HCTZ25) listed in Post-text Table 9.12 were misclassified as having been discontinued from the study when they only discontinued treatment with HCTZ. Therefore, these 3 subjects are not included in this table or in the count of subjects who discontinued from Study CS-8663-404.

Drug-related was defined as definitely, probably, or possibly related to randomized study medication.

Azor10/40 = combination of amlodipine 10 mg and olmesartan medoxomil 40 mg; HCTZ = hydrochlorothiazide.

Source: Study CS-8663-404 Post-text Table 9.12

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARYANN GORDON
04/22/2010

FANHUI KONG
04/22/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 NA Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?				WAIVE
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				SEE STATISTICS
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
34.	Are all datasets to support the critical safety analyses available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

MARYANN GORDON, MD	11-16-09
Reviewing Medical Officer	Date

_____	_____
Clinical Team Leader	Date

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

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/s/

MARYANN GORDON
11/16/2009