Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Olmesartan medoxomil, Amlodipine (as besilate) and Hydrochlorothiazide

Proprietary Product Name: Sevikar HCT

Sponsor: Merck Sharp & Dohme Australia Pty Ltd

Date of first round CER: 14 November 2012
Date of second round CER: 21 February 2013
Date of supplementary CER: 23 August 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
ALT	Alanine transaminase
AML	Amlodipine
ANCOVA	Analysis of Covariance
ARB	Angiotensin receptor blocker
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
AV	Atrioventricular
BE	bioequivalence
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CCB	Calcium channel blocker
CHD	Coronary Heart disease
CHF	Congestive heart failure
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products
CS-8635	SEVIKAR-HCT
CS-8663	40 mg olmesartan medoxomil + 10 mg amlodipine besylate - SEVIKAR
CSR	Clinical study report
DBP	Diastolic blood pressure
DSPD	Daiichi Sankyo Pharma Development

Abbreviation	Meaning
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EuroQoL	European Quality of Life
FDA	Food and Drug Administration
FDC	Fixed dose combination
GCP	Good Clinical Practices
GGT	Gamma-glutamyltransferase
HbA1c	Glycosylated hemoglobin
HCT	Hydrochlorothiazide
HCTZ	Hydrochlorothiazide
HD	high dose
HIV	Human immunodeficiency virus
HRQoL	Health Related Quality of Life
IRB	Institutional Review Board
IVRS	Interactive voice response system
JNC7	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LD	Low dose
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MIF	Market Image Formulation
MINICHAL	Short form of the Spanish Hypertension Quality of Life Questionnaire
msDBP	Mean seated diastolic blood pressure

Abbreviation	Meaning
msSBP	Mean seated systolic blood pressure
NMSC	Non-melanoma skin cancer
NYHA	New York Heart Association
OL	Open label
OM	Olmesartan
OM	Olmesartan medoxomil
PD	pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
popPK	Population PK
PRO	Patient reported outcomes
PT	Preferred term
RFI	Reference Clinical Formulation I
RFII	Reference Clinical Formulation II
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SeDBP / sDBP	Seated diastolic blood pressure
SeSBP / sSBP	Seated systolic blood pressure
SOC	System organ class
STTT	Subject treated to target
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal

1. Introduction

This submission is to register a new fixed dose combination tablet containing olmesartan medoxomil, amlodipine besylate and hydrochlorothiazide.

There are three components of this fixed dose combination (FDC): olmesartan medoxomil (Olmetec) the prodrug of the active olmesartan which is an angiotensin II antagonist; amlodipine besylate a calcium channel blocker; and hydrochlorothiazide a thiazide diuretic. Each of these agents is currently registered for the treatment of hypertension. In addition, the dual combinations of olmesartan/hydrochlorothiazide (Olmetec Plus) and olmesartan/ amlodipine (Sevikar) are also registered for the treatment of hypertension.

2. Clinical rationale

The current approved product information for Sevikar (olmesartan and amlodipine) includes a statement that if blood pressure lowering is insufficient then hydrochlorothiazide addition is recommended. The triple combination has been developed to offer treatment in a single tablet where a patient requires all three agents to adequately reduce blood pressure. The Sponsor's justification for the product is that *"A fixed-dose triple combination treatment of OM + AML + HCTZ will not only help more subjects achieve blood pressure goals, but will provide a more convenient way of administering an antihypertensive regimen".* The sponsor also states that *"fixed-dose combinations, particularly for subjects with more severe hypertension, may improve the control of hypertension by enhancing compliance, by achieving blood pressure goals rapidly, and by reducing physician inertia in prescribing adequate antihypertensive therapy."*

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Module 5
  - Six clinical pharmacology studies including: four bioavailability studies (CS8635-A-U101, CS8635-A-U102, CS8635-A-U103, CS8635-A-U104); one bioequivalence study (CS8635-A-E105) and one food effect study (CS8635-A-U106). All these studies provided pharmacokinetic data and none provided pharmacodynamic data.
  - One population pharmacokinetic analysis.
  - One pivotal phase III efficacy/safety study (CS8635-A-U301).
  - One phase IV open label study (SP-OLM-03-05).
  - Two open label extension studies which had been previously evaluated (CS8663-A-U301 and CS8663-A-E303).
  - An Integrated Summary of Safety, literature references and study data listings.
- Module 1
  - Application letter, application form, draft Australian PI and CMI, FDA-approved product label and the proposed European Summary of Product Characteristics.
- Module 2

– Clinical Overview, Summary of Biopharmaceutics and associated analytical methods, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety, literature references and synopses of individual studies.

3.2. Guidance

There was no formal presubmission meeting in relation to this dossier. The Sponsor stated in the Clinical Overview that a meeting was held with the US FDA and it was agreed that a single pivotal phase III trial demonstrating superiority in blood pressure (BP) lowering of the triple combination over the highest dosage dual combination (each of the three dual combinations) was sufficient, pending review, to support registration. There was no statement from the Sponsor in the dossier regarding adherence to relevant clinical development guidelines.

3.3. Paediatric data

The submission did not include paediatric data.

3.4. Good clinical practice

In each clinical study report, the sponsor declared that studies were conducted according to Good Clinical Practice guidelines.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 (below) shows the studies relating to each pharmacokinetic topic.

Table 1 Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Primary aim of the study
PK in healthy adults	*General PK*		
	Single dose	N/A	
	Multi-dose	N/A	
	Bioequivalence†		
	Single dose	CS8635-A-E105	Compare the PK of MIF versus the two reference clinical formulations at 2 dose strengths.
		CS8635-A-U101	BA of Benicar HCT and Norvasc when given together and when administered alone.
		CS8635-A-U102	BA of CS-8663 and HCT when given together and when administered alone.
		CS8635-A-U103	BA of CS-8635 (Pilot Formulation A) and of a two-

PK topic	Subtopic	Study ID	Primary aim of the study
			tablet regimen (Benicar HCT plus Antacal)
		CS8635-A-U104	BA of CS-8635 (Pilot Formulation B) and of a two-tablet regimen (Benicar HCT plus Antacal)
	Multi-dose	N/A	
	Food effect	CS8635-A-U106	PK CS-8635 MIF [0/10/25 mg under fed and fasting conditions
PK in Target population	Single dose	N/A	
	Multi-dose	N/A	
PK in special populations	Hepatic impairment	N/A	
	Renal impairment	N/A	
	Neonates/ infants/children /adolescents	N/A	
	Elderly	N/A	
	Other special populations	N/A	
Genetic/gender-related PK	Males vs. females	N/A	
	other genetic variable	N/A	
PK interactions	Olmesartan/ amlodipine/HCT	CS8635-A-U101 CS8635-A-U102	PK interaction between 3 active components
Population PK analyses	Target population	CS8635-A-U301	

* Indicates the primary aim of the study.

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Relevance of test products to the Australian market

· **Benicar**

Although the studies detailed in the evaluation did not use Australian sourced formulations, it must be noted that Benicar is marketed in Australia as Olmetec using the same formulation.Benicar and Olmetec are bioequivalent.Therefore, all pharmacokinetic results from the clinical pharmacology program pertaining to Benicar are considered applicable to Olmetec, and vice versa.

· **Benicar HCT and Azor**

In addition, Benicar HCT and Azor are the US trade names for Olmetec Plus and Sevikar, respectively, which are registered in Australia.

· **Amlodipine**

In the submitted studies (Studies U101, U103/U104 and E105) three different formulations of amlodipine besylate are used, these are Norvasc (manufactured by Pfizer), Antacal (Merck) and Antacal (Errekappa Euroterapici), respectively; however in Australia, although the PBS lists amlodipine besylate under a variety of trades including Norvasc (Pfizer) and amlodipine (Sandoz), the tradename Antacal does not appear in this list, nor do Merck and Errekappa Euroterapici appear as producers of amlodipine besylate in Australia.

· **Hydrochlorothiazide**

In Australia, the PBS lists only one tradename for HCT that being Dithiazide, which is manufactured by Phebra Pty Ltd as a 25 mg tablet.Study U102 gives the manufacturer of the HCT used as IVAX Pharmaceuticals and in study E105 the HCT used is manufactured by Salutas Pharma GmBH.In addition, the Summary of Biopharmaceutic Studies describes IVAX sourced and 1APharma sourced HCT as having similar dissolution profiles.

> **Comment:** However, it is not known whether the amlodipine besylate and HCT forms described above are bioequivalent, comprised of similar constituents and have similar dissolution profiles to the corresponding drugs marketed in Australia; therefore, it could be argued that the BE/BA testing program described in the evaluation materials may have little relevance for the Australian Market.

4.2.2. Pharmacokinetics in healthy subjects

Following administration of a single dose of the Market Image Formulation (MIF) of SEVIKAR-HCT (40mg olmesartan medoxomil/10 mg amlodipine/25 mg HCT) to healthy subjects the C_{max} and AUC_{inf} of the olmesartan component was 908 ng/mL and 6277 ng.h/mL, respectively, and the T_{max} and $t_{½}$ were 1.5 and 17.4 hours respectively.For the amlodipine component, the corresponding PK parameters were 7.5 ng/mL, 372 ng.h/mL, 7 hours and 41.5 hours, respectively, and for HCT component the values were 193 ng/mL, 1223 ng.h/mL, 1.5 hours and 10.2 hours, respectively.

4.2.2.1. Absorption

4.2.2.1.1. Sites and mechanisms of absorption

The population PK study (Study CS8635-A-U301) indicated that the PK of olmesartan was adequately characterised by a two-compartmental model with first-order absorption and time lag; creatinine clearance was a significant predictor of the apparent oral clearance.The PK of amlodipine was adequately characterised by two-compartmental model with first-order absorption and a time lag; age was a significant predictor of the apparent oral clearance, and the

PK of HCT was adequately characterised by two-compartmental model with first-order absorption and a time lag; sex, age and creatinine clearance were significant predictors of the apparent oral clearance.

4.2.2.2. Bioavailability

4.2.2.2.1. Absolute bioavailability

No new information is provided.

4.2.2.2.2. Bioavailability relative to an oral solution or micronised suspension

Not applicable.

4.2.2.2.3. Bioequivalence of clinical trial and market formulations

No studies examined the bioequivalence of the Market Image Formulation (MIF) of SEVIKAR-HCT and individual doses of the three active components.In addition, no studies in the evaluation materials examined the bioequivalence between the FDC combinations containing two active ingredients and the corresponding components when given as a free combination.

When given as a triple combination in the pivotal efficacy study CS8635-A-U301, the triple formulations investigated comprised a FDC combination of olmesartan/HCT 40/25 mg (Benicar HCT) + amlodipine 10 mg (Antacal).

Study CS8635-A-E105 examined the PK of olmesartan, amlodipine and HCT in healthy subjects when administered as the MIF versus the two reference clinical formulations, i.e. Benicar HCT + Antacal and Azor + HCT at dose strengths of 40/10/25 (olmesartan medoxomil/AML/HCT) and 20/5/12.5 mg.Bioeqivalence was established in terms of exposure (AUC_{last}, $AUC_{0\text{-}inf}$ and C_{max}) to olmesartan, amlodipine and HCT.

> **Comments**: It must be noted that the bioequivalence for the three intermediate doses of the MIF, i.e. 40/5/12.5 mg OM/AML/HCT, 40/5/25 mg OM/AML/HCT and 40/10/12.5 mg OM/AML/HCT have not been examined.To this end, the sponsor states:"Based on similar tablet composition, equivalent dissolution profiles, lack of drug-drug interaction of CS-8635 components, bioequivalence of the lowest and highest market image formulations and the dose proportional composition of the 5 market image formulations, all of the market formulations were considered to be bioequivalent to the their corresponding clinical formulations."
>
> However, the guideline on "Clinical on Clinical Development of Fixed Combination Medical Products" (CHMP/EWP/240/95 Rev. 1) states that if: "The combination contains known active substances and it is a substitution indication (i.e. use in patients adequately controlled with the individual products given concurrently, at the same dose level as in the combination, but as separate tablets) or the new fixed combination contains known active ingredients that have not been used in combination before. In these cases bioequivalence should be demonstrated between the free combination of the recognised reference formulations of the individual mono-components and the marketing formulation (fixed combination)."Clearly this guideline has not been adhered to by the sponsor as the bioequivalence between SEVIKAR-HCT MIF and the mono-components has not been established, nor has a formal Request or Justification for a Biowaiver been provided by the sponsor in the evaluation materials.

4.2.2.2.4. Bioequivalence of different dosage forms and strengths

Study CS8635-A-E105 indicated that the PKs of the three active components of the low dose MIF (20/5/12.5 mg OM/AML/HCT) and the high dose MIF (40/10/25 mg OM/AML/HCT) were bioequivalent when dose normalised indicating dose proportional PKs for the two MIF dose strengths.

It must be noted that the dose proportionality for the three intermediate doses of the MIF, i.e. 40/5/12.5 mg OM/AML/HCT, 40/5/25 mg OM/AML/HCT and 40/10/12.5 mg OM/AML/HCT have not been examined, please see the previous discussion in Section 4.2.2.2.3 of this report.

Two further studies examined the bioequivalence and bioavailability of the various combinations of FDC containing two active components + the third active component compared with when these components were administered alone.

The first of these, Study CS8635-A-U101, examined the bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered together as Benicar HCT (40 mg Olmesartan medoxomil plus 25 mg hydrochlorothiazide) and Norvasc (10 mg amlodipine besylate) and when administered alone in healthy subjects.This study indicated that Benicar HCT + Norvasc was bioequivalent with Benicar HCT in regards to olmesartan and HCT AUC and C_{max}.In addition, Benicar HCT + Norvasc was bioequivalent with Norvasc in terms of amlodipine AUC and C_{max}.

Study CS8635-A-U102 examined the bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered together as CS-8663 (40 mg olmesartan medoxomil + 10 mg amlodipine besylate) and 25 mg hydrochlorothiazide, and when administered alone in healthy subjects.This study indicated that CS-8663 + HCT was bioequivalent with CS-8663 in regards to olmesartan and amlodipine AUC and C_{max}, and that CS-8663 + HCT was bioequivalent with HCT in terms of HCT AUC and C_{max}.

The following two studies examined the relative bioavailability of pilot formulations of the triple FDC and Benicar HCT + Antacal.

Study CS8635-A-U103 examined the relative bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered as a fixed dose triple component formulation (CS-8635 Pilot Formulation A) and as a two-tablet regimen (Benicar HCT plus Antacal) in healthy subjects.This study indicated that the two treatments were bioequivalent in regards to the AUC and C_{max} of the three active components.

Study CS8635-A-U104 determined the relative bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered as a fixed dose triple component formulation (CS-8635 Pilot Formulation B) and as a two-tablet regimen (Benicar HCT plus Antacal) in healthy subjects.This study indicated that the two treatments were also bioequivalent in regards to the AUC and C_{max} of the three active components.

4.2.2.2.5. Bioequivalence to relevant registered products

No fixed dose combinations containing the 3 active components are currently registered.

4.2.2.2.6. Influence of food

Study CS8635-A-U106 examined the PKs of the highest strength FDC of the SEVIKAR-HCT MIF (40/10/25 mg) under fasting and fed conditions in 33 healthy subjects.This study indicated that the PK of the active components olmesartan and amlodipine were bioequivalent in regards AUC and C_{max} in the presence or absence of food.By contrast, although the AUC of HCT was bioequivalent between fasted and fed subjects, for the C_{max} of HCT the bioequivalence criteria were not met in fasted and fed subjects and under fed conditions HCT C_{max} was approximately 23% lower when compared to the parameters calculated after single dose administration under fasting conditions.

4.2.2.2.7. Dose proportionality

See Section 4.2.2.2.4 of this report.

4.2.2.2.8. Bioavailability during multiple-dosing

No new information is provided.

4.2.2.2.9. Effect of administration timing

No new information is provided.

4.2.2.3. Distribution

No new information is provided.

4.2.2.4. Metabolism

No new information is provided.

4.2.2.5. Excretion

No new information is provided.

4.2.2.6. Intra- and inter-individual variability of pharmacokinetics

Two studies (CS8635-A-U101 and CS8635-A-U102) examined the intra-subject variability in AUC and C_{max} for the three active components.For olmesartan AUC_{inf} and C_{max} intra-subject CV ranged from 14.3% to 20.2% and 17.1% to 21.1%, respectively).For amlodipine AUC_{inf} and C_{max}, intra-subject CV ranged from 8.3% to 11.9% and 9.3% to 10.6%, respectively, and for HCT AUC_{inf} and C_{max}, intra-subject CV ranged from 7.1 to 12.5% and 18.5% to 20.0%, respectively.

4.2.3. Pharmacokinetics in the target population

No information is provided.

4.2.4. Pharmacokinetics in other special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

No new information is provided.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

No new information is provided.

4.2.4.3. Pharmacokinetics according to age

No new information is provided.

4.2.4.4. Pharmacokinetics related to genetic factors

No new information is provided.

Pharmacokinetics {in other special population / according to other population characteristic}

4.2.4.4.1. Race

The results of the exposure-response model in the population PK study (Study CS8635-A-U301) indicated that black race was a clinically significant covariate, decreasing the maximal possible effect on blood pressure of olmesartan without influencing PK parameters.

4.2.5. Pharmacokinetic interactions

4.2.5.1. Pharmacokinetic interactions demonstrated in human studies

Two studies examined the drug-drug interaction between the three active components.

Study CS8635-A-U101, which examined the PK of the active components following administration of Benicar HCT (OM/HCT) and Norvasc (AML), demonstrated that the PK parameters were similar when the drugs were administered concomitantly compared to when the drugs are administered alone; indicating that there was no drug-drug interaction between OM 40 mg, AML 10 mg, and HCT 25 mg administered as Benicar HCT (OM/HCT) and Norvasc (AML).

Study CS8635-A-U102, which examined the PK profiles of OM 40mg and AML 10 mg administered as CS-8663 (OM/AML) and HCT 25 mg, and when each drug was administered alone, demonstrated that PK parameters were similar when the drugs were administered concomitantly compared to when the drugs are administered aloneTherefore indicating that it is unlikely that a drug-drug interaction exists between OM 40 mg, AML 10 mg, and HCT 25 mg when administered as CS-8663 (OM/AML) and HCT.

4.2.5.2. Clinical implications of in vitro findings

No new data was provided.

4.2.6. Population PK modelling

The population PK study (Study CS8635-A-U301) used data from three clinical development programs: CS866 (OM+HCT), CS-8663 (OM+AML), and CS-8635 (OM+AML+HCT) and the dataset contained a total of thirteen Phase 1 Clinical Pharmacology studies and two Phase 3 studies (CS8663-A-U301 and CS8635-A-U301).Modelling of the data indicated that all three compounds were best described by a two-compartment mammillary PK model, which consisted of a central and one peripheral compartment, and the covariates identified as important modifiers of the PKs of the drugs are summarised in Section 4.2.2.1.1, entitled *"Sites and mechanisms of absorption"*, of this report.

4.3. Evaluator's overall conclusions on pharmacokinetics

- Other than BE/BA and food studies the Applicant provides no new information on the PK of SEVIKAR-HCT or its individual active components.
- Following administration of a single dose of the MIF of SEVIKAR-HCT (40mg olmesartan medoxomil/10 mg amlodipine/25 mg HCT) to healthy subjects the C_{max} and AUC_{inf} of the olmesartan component was 908 ng/mL and 6277 ng.h/mL, respectively, and the T_{max} and $t_{½}$ were 1.5 and 17.4 hours respectively.For the amlodipine component, the corresponding PK parameters were 7.5 ng/mL, 372 ng.h/mL, 7 hours and 41.5 hours, respectively, and for HCT component the values were 193 ng/mL, 1223 ng.h/mL, 1.5 hours and 10.2 hours, respectively.
- Population PK modelling indicated that: the PK of olmesartan was adequately characterised by a two-compartmental model with first-order absorption and time lag; creatinine clearance was a significant predictor of the apparent oral clearance; the PK of amlodipine was adequately characterised by two-compartmental model with first-order absorption and a time lag; age was a significant predictor of the apparent oral clearance; and the PK of HCT was adequately characterised by two-compartmental model with first-order absorption and a time lag; sex, age and creatinine clearance were significant predictors of the apparent oral clearance.
- No studies examined the bioequivalence of the MIF of SEVIKAR-HCT and individual doses of the three active components. No formal Justification for a Biowaiver has been provided by the sponsor.
- The MIF and two reference clinical formulations (Benicar HCT + Antacal and Azor + HCT) were bioequivalent at 2 dose strengths (40/10/25 mg OM/AML/HCT and 20/5/12.5 mg).
- The three active components of the low dose MIF (20/5/12.5 mg OM/AML/HCT) and the high dose MIF (40/10/25 mg OM/AML/HCT) were bioequivalent when dose normalised indicating dose proportional PKs for the two MIF dosage strengths.
- Benicar HCT + Norvasc was bioequivalent with Benicar HCT in regard to olmesartan and HCT AUC and C_{max}, and Benicar HCT + Norvasc was bioequivalent with Norvasc in terms of amlodipine AUC and C_{max}.

- CS-8663 (OM/AML) + HCT was bioequivalent with CS-8663 in regards to olmesartan and amlodipine AUC and C_{max}, and that CS-8663 + HCT was bioequivalent with HCT in terms of HCT AUC and C_{max}.
- Two pilot formulations (Formulation A and B) of the fixed dose triple combination were bioequivalent with a two-tablet regimen (Benicar HCT plus Antacal) in regard to the AUC and C_{max} of the three active components.
- The PKs of the 3 active components of SEVIKAR-HCT following a single dose were bioequivalent in regards to olmesartan and amlodipine AUC and C_{max} in fasted and fed subjects. By contrast, although the AUC of HCT was bioequivalent between the two groups, the C_{max} of HCT was not bioequivalent and was approximately 23% lower in fed subjects. Given the bioequivalence result on AUC, this food effect on C_{max} is not felt to be so clinically relevant.
- PPK modelling indicated that being of Black race was a clinically significant covariate, which decreased the maximal possible effect on blood pressure of olmesartan without influencing PK parameters
- There was no drug-drug interaction between the active components of the triple combination therapy.
- It is not known whether the amlodipine besylate and HCT forms used in the BE/BA studies are comprised of similar constituents and have similar dissolution profiles to the forms of the drugs marketed in Australia; therefore, it could be argued that the BE/BA testing program described in the evaluation materials may have little relevance for the Australian Market.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Other than population PK study described in the Section 4.2.6, no new studies were provided in the evaluation materials that specifically examined PD activity of the triple formulation.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

5.2.1.1. Olmesartan Medoxomil

Olmesartan medoxomil (the prodrug form of active olmesartan) is an orally active angiotensin II antagonist intended for use in treating hypertension.Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract.Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle.Its action is independent of the pathways for angiotensin II synthesis. With chronic daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours.

5.2.1.2. Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mode of action of AML differs from, and is complementary to, that of olmesartan.Amlodipine is a

peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.As a result, following administration of therapeutic doses to patients with hypertension, AML produces vasodilation resulting in a reduction of supine and standing blood pressures.With chronic daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours.

5.2.1.3. Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic.Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts.Indirectly, the diuretic action of HCTZ reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium.The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with this diuretic.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

No new data has been provided in the evaluation materials.

5.2.2.2. Secondary pharmacodynamic effects

No new data has been provided in the evaluation materials.

5.2.3. Time course of pharmacodynamic effects

No new data has been provided in the evaluation materials.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

No studies directly examined the relationship between drug concentration and PD effect; however, the population PK study (Study CS8635-A-U301), described in detail in the PK section of this report, indicated that the drug effects of olmesartan and amlodipine exposure on seated trough DBP and SBP could be described by an E_{max} model, whereas the drug effect of HCT exposure was described by a linear model. In addition, the blood pressure lowering effects of olmesartan, amlodipine, and HCT in monotherapy, dual combination therapy, and triple combination therapy were well characterised by a model composed of the sum of the individual effects and interaction among the components.

The exposure-response model generated indicated that the baseline seated trough DBP and SBP were significant covariates, with more blood pressure lowering effect associated with higher baseline blood pressure. Unsurprisingly, the simulation results also indicated that blood pressure lowering effects of CS-8635 triple combination therapies were superior to their respective mono and dual treatment of the olmesartan, amlodipine and HCT, and the predicted systolic and diastolic blood pressure lowering effects were in order of 20/5/12.5 mg < 40/5/12.5 mg < 40/10/12.5 mg ≈ 40/5/25 mg < 40/10/25 mg for OM/AML/HCT, respectively.

5.2.5. Genetic, gender- and age-related differences in pharmacodynamic response

No new data has been provided in the evaluation materials.

5.2.6. Pharmacodynamic interactions

No new data has been provided in the evaluation materials.

5.3. Evaluator's overall conclusions on pharmacodynamics

PPK modelling indicated:

1. the effects of olmesartan and amlodipine on seated trough DBP and SBP were described by an E_{max} model, whereas the drug effect of HCT exposure was described by a linear model;
2. the blood pressure lowering effects of olmesartan, amlodipine, and HCT in monotherapy, dual combination therapy, and triple combination therapy were well characterised by a model composed of the sum of the individual effects and interaction among the components;
3. the baseline seated trough DBP and SBP were significant covariates, with more blood pressure lowering effect associated with higher baseline blood pressure; and
4. the simulation results also indicated that blood pressure lowering effects of CS-8635 triple combination therapies were superior to their respective mono and dual treatment of the olmesartan, amlodipine and HCT.

6. Dosage selection for the pivotal studies

The doses proposed in the FDC are the same as those currently available in the respective monotherapies and dual therapies, i.e. 20 mg and 40 mg for olmesartan (OM), 5 mg and 10 mg for amlodipine (AML), and 12.5 mg and 25 mg for hydrochlorothiazide (HCTZ).

7. Clinical efficacy

7.1. Treatment of hypertension

7.1.1. Pivotal efficacy study

7.1.1.1. Study CS8635-A-U301

7.1.1.1.1. Study design, objectives, locations and dates

Study CS8635-A-U301 was a phase III, multicentre, randomised, parallel group study. There were three periods: Period 1 was a washout (3 weeks maximum duration) to determine eligibility; Period 2 was a 12 week double-blind treatment period; and Period 3 was a 40 week open label treatment period and a 2 week follow up. The study was conducted between May 2008 and February 2009 at 317 centres in the US.

The primary objective was to determine if the triple combination of OM 40 mg + AML 10 mg + HCTZ 25 mg had a clinically significant benefit versus the respective dual therapy components in controlling blood pressure after 12 weeks of treatment.

After washing out antihypertensive medications, subjects with confirmed eligible BP were randomised to one of 4 treatment groups OM 40 mg + AML 10 mg, OM 40 mg + HCTZ 25 mg, AML 10 mg + HCTZ 25 mg, or OM 40 mg + AML 10 mg + HCTZ 25 mg. This randomisation included a treatment sequence to arrive at the final dose. The sequence included either a dual combination or placebo for the first 2 weeks. After 2 weeks the placebo subjects then received dual therapy for 2 weeks. This resulted in all subjects receiving dual therapy between weeks 2 and 4. From week 4 to 12 treatment reflected the four randomised groups (Table 2).

Table 2. Study CS8635-A-U301. Period II treatment assignment

		n	Day 1 to Week 2	Week 2 to Week 4	Week 4 to Week 12
800 subjects		591	OM/AML/HCTZ 40/10/0 mg		OM/AML/HCTZ 40/10/0 mg (600 subjects)
	naïve	9	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/10/0 mg	
		3	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/10/0 mg	OM/AML/HCTZ 40/10/25 mg (200 subjects)*
		197	OM/AML/HCTZ 40/10/0 mg		
800 subjects		591	OM/AML/HCTZ 40/0/25 mg		OM/AML/HCTZ 40/0/25 mg (600 subjects)
	naïve	9	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/0/25 mg	
		3	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/0/25 mg	OM/AML/HCTZ 40/10/25 mg (200 subjects)*
		197	OM/AML/HCTZ 40/0/25 mg		
800 subjects		591	OM/AML/HCTZ 0/10/25 mg		OM/AML/HCTZ 0/10/25 mg (600 subjects)
	naïve	9	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 0/10/25 mg	
		3	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 0/10/25 mg	OM/AML/HCTZ 40/10/25 mg (200 subjects)*
		197	OM/AML/HCTZ 0/10/25 mg		

*In total, the OM 40 mg + AML 10 mg + HCTZ 25 mg treatment group was comprised of approximately 600 subjects, consisting of 200 subjects from each of the three dual combination assignments at Week 4.
AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

In the 40 week Period III, all subjects were switched to open label OM 40 mg + AML 5 mg + HCTZ 12.5 mg. Those not achieving target BP (<140/90 mmHg or <130/80 mmHg for those with diabetes, chronic renal disease or chronic cardiovascular disease) after 2 weeks were randomly titrated (using an IVRS) to OM 40 mg + AML 10 mg + HCTZ 12.5 mg or OM 40 mg + AML 5 mg + HCTZ 25 mg. A further titration to OM 40 mg + AML 10 mg + HCTZ 25 mg was allowed at investigator discretion. Once target BP was reached, subjects remained on this dose. Down titration of triple therapy was allowed for hypotension or intolerance, however dual therapy was not allowed.

There were two sub-studies, one with ambulatory BP monitoring (ABPM) and one with pharmacokinetic assessments. A placebo control group was included in the study during the first 2 weeks of Period II. The subjects entering this group were treatment naïve or newly diagnosed. The CRF was electronic and central laboratories were used for blood samples, ECG and ABPM reading. The patient reported outcome (PRO) questionnaires were paper-based. There was one protocol amendment consisting of minor revisions.

7.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria were adults ≥18 years with hypertension (after medication washout) defined as a mean sitting BP (msBP) ≥140/100 mmHg or a msBP ≥160/90 mmHg with a difference in mean sitting systolic BP (msSBP) and mean sitting diastolic BP (msDBP) between 2 consecutive visits before randomisation of ≤20/10 mmHg. Women needed a negative pregnancy test and had to be postmenopausal or using appropriate contraception.

Exclusion criteria were: msDBP <90 mmHg or msSBP <140 mmHg off medication; uncontrolled hypertension; at risk of hypotension such as volume depletion; history of hypertensive encephalopathy; history of myocardial infarction, PTCA, CABG or unstable angina within 6 months; NYHA Class III or IV congestive cardiac failure; secondary hypertension; renal artery stenosis, uncorrected coarctation of the aorta; symptomatic bradycardia; haemodynamically significant cardiac valvular disease; heart block more than first degree AV block, atrial fibrillation or flutter; uncontrolled diabetes (HBA1c >9.0%); liver disease with ALT/AST or total bilirubin >3x ULN; renal insufficiency with creatinine clearance <30 mL/min; hepatitis B or C or HIV positive; malignancy within 2 years except for NMSC; current drug or alcohol abuse; and lactating females.

7.1.1.1.3. Study treatments

Subjects took 5 tablets at the same time each day during Period II as shown in Table 3.The medications used in the study were OM/HCTZ 40/25 mg (Benicar HCT), OM/AML 40/10 mg (Azor), AML 10 mg (Antacal) and HCTZ 12.5 mg. The triple combination was achieved by taking OM/HCTZ 40/25 mg with AML 10 mg (Benicar HCT + Antacal). On the days of study visits, subjects took their morning dose after the visit completion to ensure blood pressure measurements at trough drug levels. Subjects were not to smoke for at least 2 hours prior to the clinic visit. Compliance was measured on returned tablet count.

Table 3. Study CS8635-A-U301. Study Treatments in Period II

Study Treatment	Tablets per Day
OM/AML/HCTZ 0/0/0 mg	OM/AML 0/0 + AML 0 + 2 × HCTZ 0 + OM/HCTZ 0/0
OM/AML/HCTZ 0/10/25 mg	OM/AML 0/0 + AML 10 + 2 × HCTZ 12.5 + OM/HCTZ 0/0
OM/AML/HCTZ 40/10/0 mg	OM/AML 40/10 + AML 0 + 2 × HCTZ 0 + OM/HCTZ 0/0
OM/AML/HCTZ 40/0/25 mg	OM/AML 0/0 + AML 0 + 2 × HCTZ 0 + OM/HCTZ 40/25
OM/AML/HCTZ 40/10/25 mg	OM/AML 0/0 + AML 10 + 2 × HCTZ 0 + OM/HCTZ 40/25

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.
Source: Study protocol (Appendix 16.1.1)

Prohibited medications included other antihypertensives (stable doses of nitrates were permitted); phosphodiesterase inhibitors within 2 days of study visit; vasoactive agents; antithyroid agents (unless >3 months of stable use); amphetamines and weight loss medications; oral corticosteroids within 24 hours of study visit and inhaled or topical corticosteroids within 12 hours of visits.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome was the change from baseline in msDBP at week 12 with last observation carried forward (LOCF). Blood pressure was measured using a validated cuff (Omron Model HEM 705CP). Three measurements were made at each visit with the subject seated (at least 5 minutes) and the mean value used. The baseline msDBP and msSBP was the mean of the randomisation visit and the visit prior. The 24 hour ABPM was assessed at baseline prior to randomisation and at week 12.

The secondary efficacy outcomes were:

- Change from baseline in msSBP at Week 12 with LOCF;
- Change from baseline in msDBP and msSBP at Weeks 6, 8, 10, and 12;
- Change in msDBP and msSBP from baseline at Week 2 (to compare the placebo and each dual combination treatment);
- Proportion of subjects who reached blood pressure goal (<140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease);
- Proportion of subjects who reached blood pressure targets at Weeks 6, 8, 10, 12, and Week 12 with LOCF (i.e. <140/90 mmHg, <130/85 mmHg, <130/80 mmHg, <120/80 mmHg, msDBP <90 mmHg, and msSBP <140 mmHg); and
- Change from baseline in 24-hour ABPM at 12 weeks. This included the change from baseline in mean daytime (8 am to 4 pm), mean night time (10 pm to 6 am) and mean 24-hour ABPM; change from baseline in mean ABPM during the last 2, 4, and 6 hours of the dosing interval; and the percentage of subjects achieving mean 24-hour, daytime, nighttime, and last 2, 4 and 6 hour ABPM blood pressure targets.

Other efficacy outcomes included:

- Changes in msDBP and msSBP from week 4 to 12 for responders and non-responders at week 4.
- Proportion of subjects reaching blood pressure goal at Week 12 for both responders and non-responders at Week 4;
- Patient reported outcomes as recorded on 2 instruments: European Quality of Life (EuroQoL) and short form of the Spanish Hypertension Quality of Life Questionnaire (MINICHAL); and
- Change in microalbuminuria from Day 1 to Week 12 (or Early Termination).

Blood samples for PK assessments were collected predose and at 0.5 to 2 hour and 5 to 10 hours post dose in the PK substudy.

7.1.1.1.5. Randomisation and blinding methods

Subjects were randomised via an IVRS which also managed the treatment sequencing. Randomisation was stratified by age (<65/≥65 years), diabetic status (yes/no) and race (Black/ non-Black). All five active medication tablets had a corresponding matching placebo to maintain the study blind in Period II. Period III was open label.

7.1.1.1.6. Analysis populations

The primary analysis was on the full analysis set (FAS) with LOCF. The FAS included all randomised subjects who received at least one dose of study medication and had a baseline and at least one post baseline msDBP assessment. The per protocol (PP) set included all subjects in the FAS who completed Period II or withdrew before completing Period II due to insufficient treatment effect, and had no major protocol violations.

7.1.1.1.7. Sample size

The standard deviation (SD) for the primary efficacy variable (msDBP) was assumed to be 8.5 mmHg and the minimum treatment effect difference between the triple and dual combinations after 12 weeks of treatment was 2.0 mmHg. With these assumptions, the study required a sample of 534 subjects per arm in order to have a 97% power for each pairwise comparison, and a 90% overall power, at a 0.05 significance level. Allowing for dropouts (11%), 600 subjects per group and 2400 in total were required.

[Information redacted by the TGA Delegate]

For the comparison of placebo to dual therapy after 2 weeks of treatment in the subset of newly diagnosed/treatment naïve subjects, a sample of 22 placebo-treated subjects would have a 90% power to detect a 6.0 mmHg difference in msDBP, assuming a SD of 8.5 mmHg and α=0.05. Allowing for dropouts and randomisation requirements, a sample of 36 subjects was chosen.

7.1.1.1.8. Statistical methods

Treatment comparisons were analysed using an ANCOVA model with baseline msDBP as a covariate and fixed effects of randomised treatment, age group, race group and diabetic status. The least squares (LS) mean change in msDBP or msSBP with its 95% CI and two sided p value, testing a within treatment group change from baseline, were presented. The triple combination OM 40 mg + AML 10 mg + HCTZ 25 mg was compared to the three dual combinations, OM 40 mg + AML 10 mg, OM 40mg + HCTZ 25 mg and AML 10 mg + HCTZ 25. The proportion of subjects reaching target BP was analysed using a Chi-square test and pairwise comparisons performed using Cochran Mantel Haenzel test adjusting for stratification factors.

7.1.1.1.9. Participant flow

There were 6724 subjects enrolled and 2492 randomised to double-blind treatment. There were 2491 in the safety set and 2302 who received at least one dose of medication at week 4 or later which was the final randomised dose. The FAS included 2458 (98.6%) subjects and the PP

population 2025 (81.3%). There were 440 subjects (17.7%) in the ABPM substudy. Table 4 shows the number of subjects randomised to each group and treatment sequence. There were 628 in the OM 40/AML 10 mg, 637 in the OM 40/HCTZ 25 mg, 600 in the AML 10/HCTZ 25 mg and 627 subjects in the OM 40/AML 10/HCTZ 25 mg group.

Table 4. Study CS8635-A-U301. Subject disposition by randomised Treatment Group – Day 1 to Week 12 – Randomised 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 overall discontinuation rate was 15.1% with the highest rate in the triple combination group (17.7%) and a range of 11.3% to 16.6% in the dual combination groups. Adverse events were the most frequent reason for discontinuation (6.2%) with similar rates in the OM 40/AML 10/HCTZ 25 (7.7%), OM 40/HCTZ 25 (7.2%) and AML 10/HCTZ 25 groups (6.3%) and slightly lower in the OM 40/AML 10 group (3.5%). Other reasons for discontinuation were consent withdrawal (3.3%) and loss to follow up (3.2%). Excluding the first four weeks of the study, the discontinuation rate was higher with triple than dual triple combination (10.3% vs 6.4-8.6%) and the main reason was an adverse event (4.0% vs 1.2-2.2%).

7.1.1.1.10. Major protocol violations/deviations

The types of major protocol deviations were not discussed in the clinical study report and only provided as listings. The PP population included 81.3% of subjects which indicates the major deviation rate was around 18.7%. The proportion of subjects in the PP population was slightly lower in the triple therapy group compared to the dual therapy groups (78.1% vs 80.5-84.1%). The compliance rate was high and ranged from 98.0% to 98.5% across the 4 groups.

7.1.1.1.11. Baseline data

Demographic and baseline characteristics were on the whole balanced between groups and no significant differences were found. There were slightly more males (52.9%), two thirds of subjects were Caucasian (66.8%) and approximately 30% Black. The mean age was 55.1 years and the mean BMI 33.1 kg/m^2. The mean duration of hypertension was 9.9 years and 33.5% were treatment naïve. There were slightly fewer elderly subjects (≥65 years) in the AML 10/HCTZ 25 mg group compared to the other groups (16.0% vs 19.1%-20.7%). About 40% of

subjects were current or ex-smokers, about 9% had a history of cardiovascular disease and 15-16% were diabetic.

At baseline, the msDBP was 100.9 mmHg and the msSBP was 168.5 mmHg. While subjects were meant to have Stage 2 hypertension, 11.2% had Stage 1 (SBP 140-<160 mmHg and DBP 90-<100 mmHg) due to changes in BP between determining eligibility and baseline measurements and also protocol violations.

During randomised treatment the most commonly used concomitant medications were HMG CoA reductase inhibitors (19.4%), platelet inhibitors (19.3%) and propionic acid derivatives (18.6%).

7.1.1.1.12. Results for the primary efficacy outcome

The mean change from baseline to week 12 (with LOCF) in the msDBP was -21.5 mmHg for the triple combination and -17.8 mmHg, -16.5 mmHg and -14.8 mmHg for the OM40/AML 10, OM40/HCTZ 25 and AML 10/HCTZ 25 mg groups, respectively. The reduction in msDBP was statistically significant in all groups (p<0.0001) (Table 5). The reduction in msDBP was greater with OM 40/AML 10/HCTZ 25 mg and the LS mean difference between the triple therapy and the three dual therapy groups ranged from -3.8 to -6.7 mmHg (p<0.0001).

Table 5. Study CS8635-A-U301. 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

	Between treatment comparisons [5]	
Comparisons	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

7.1.1.1.13. Results for other efficacy outcomes

At week 12 with LOCF, the LS mean reduction in msSBP was 37.1 mmHg for the triple therapy and 27.5 to 30.0 mmHg for the dual therapy groups with all reductions being statistically significant (p<0.0001). The LS mean difference between triple and dual therapy in msSBP was also significant (p<0.0001) and ranged from -7.1 to -9.6 mmHg.

As per study design, triple therapy commenced at week 4. By week 6, 90-95% of the maximum msDBP reduction was achieved with a small additional reduction between weeks 6 and 12. The reduction in msDBP was significantly greater with the triple therapy at weeks 6, 8, 10 and 12. The greater reduction with triple therapy over weeks 6 to 12 was also evident on msSBP.

The proportion of subjects reaching their BP target[1] at week 12 (LOCF) was 64.3% with triple therapy compared to 34.9% to 46.6% in the dual therapy groups. This improved rate with triple therapy was statistically significant (p<0.0001). Target attainment was significant greater with the triple therapy at weeks 6, 8, 10 and 12 and also was greater when different blood pressure targets were analysed.

Analysis of data at week 2 found that all dual therapy groups had a significantly greater reduction in msDBP than placebo (LS mean difference of -11.9, -10.8 and -8.8 mmHg for OM 40/AML 10 mg, OM 40 /HCTZ 25 mg and AML 10/HTCZ 25 mg, respectively, p<0.0001). Similarly, there was a greater reduction in msSBP at week 2 (LS mean difference -22.9, -22.6 and -19.6 mmHg for the three respective groups, p<0.0001).

ABPM: In the ABPM substudy, there was a statistically significant greater mean reduction in 24 hour DBP and SBP from baseline to week 12 with the triple therapy compared to each dual therapy. The greater reduction in DBP and SBP was seen across the 24 hour period. These greater mean reductions in DBP and SBP were consistent across assessment of daytime, nighttime and last 2, 4 and 6 hours. Target attainment on ambulatory BP was also significantly greater for the triple therapy compared to the dual combinations.

Exploratory endpoints: An assessment was undertaken of BP reduction in subjects who were responders and non-responders at week 4 on dual therapy. For non-responders, switching to triple therapy from week 4 to 12 resulted in a reduction of msDBP of 7.5 to 8.3 mmHg compared to 2.5 to 3.4 mmHg for those staying on dual therapy and a reduction in msSBP of 11.9 to 16.7 mmHg compared to 3.9 to 5.7 mmHg for those remaining on dual therapy. Target attainment at week 12 was also greater for non-responders (at week 4) who switched to triple therapy (50.8% to 57.3% vs 19.7% to 26.0% for dual therapy).

Quality of life: There were no statistically significant changes from baseline to week 12 in the mean score on the EuroQoL in any of the treatment groups. There were also no significant differences between results in the triple compared to dual therapy groups.

Subgroups: A significantly greater effect on msDBP and msSBP reduction with triple compared to dual therapy was seen in those aged <65 and ≥65 years. There were limited number of subjects over 75 years and results were not statistically significant. Target attainment was also greater with triple therapy in those aged <65 and ≥65 years, and while numerically greater in the ≥75 year age group, did not reach statistically significance.

The effect of triple therapy (reduction in msDBP, msSPB and target attainment) was consistent across males and females, those with stage 1 or stage 2 hypertension[2], those with severe or

[1] 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.
[2] 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.

mild/moderate hypertension[3], Blacks, non-Blacks, Hispanics/Latinos, diabetics, BMI <30 or ≥30 kg/m^2.

In subjects with renal impairment (creatinine clearance ≥30 and ≤60 mL/min), the triple therapy resulted in a numerically greater reduction in msSBP and msDBP, however the difference was only statistically significant compared to OM 40/HCTZ 25 on both measurements. Target attainment rates were not significantly different to any of the three dual therapies. However, interpretation was limited by the small number of subjects in this subgroup.

7.1.1.1.14. Summary

Study CS8635-A-U301 was a phase III, multicentre, randomised, parallel group study in 2492 adult subjects with hypertension. After a run-in of at least 2 weeks on high dose dual therapy, subjects remained on dual therapy or were titrated to the maximal dose triple therapy. This triple combination dose of OM 40/AML 10/HCTZ 25 (taken as Benicar HCT + Antacal) was found to significantly reduce msDBP and msSBP to a greater level than any of the three dual therapy combinations. The addition of the HCTZ 25 mg component to the dual therapy contributed a BP reduction of 7.1/3.8 mmHg, amlodipine 10 mg contributed 7.4/4.9 mmHg and olmesartan 40 mg contributed 9.6/6.7 mmHg. Target BP goal attainment rates were significantly greater with triple therapy. The 24 hour ambulatory BP monitoring substudy in 440 subjects confirmed the difference between triple and dual therapy over the 24 hour dosing interval. Results were consistent across subgroups of age, gender, race and hypertension severity. There were too few subjects over 75 years or with renal impairment to allowing meaningful comparisons.

> **Comment:** Data from the 40 week open label Period III (weeks 12 to 52) were not provided. Given the first part of the study was completed in 2009 these should be available and are necessary to provide data on the persistence of efficacy and tolerance as well as important long term safety data.

7.1.2. Other efficacy studies

The dossier included two clinical study reports (CS8663-A-U301 and CS8663-A-E303) which had previously been evaluated as part of the submission for Sevikar (olmesartan/amlodipine). These studies were sponsored by Daiichi Sankyo. It was noted that the Clinical Evaluation Report for Sevikar (dated 21 August 2009) only provided data to week 10 (rather than the full 28 weeks) of Period IV of study CS8663-A-E303 for that evaluation.

7.1.2.1. Study CS8663-A-U301

Study CS8663-A-U301 was a randomised, factorial, 8 week study evaluating the efficacy and safety of coadministered olmesartan and amlodipine compared to monotherapy in 1400 adults with mild to severe hypertension (mean baseline BP of 163.6/101.5 mmHg). The dossier included the clinical study report for Period III of the trial which was an open label, 44 week (week 8 to 52) extension study. There were 1684 subjects who entered the extension and were treated with olmesartan 40 mg + amlodipine 5 mg. This was uptitrated to amlodipine 10 mg if their BP was not adequately controlled. The addition of HCTZ 12.5 mg and then 25 mg was then offered for further BP control. There were 1400 (83%) subjects who completed the extension study. The blood pressure goal was <140/90 mmHg or <130/80 mmHg for diabetic patients.

At week 52, there were 287 patients on OM 40 mg + AML 10 mg + HCTZ 12.5 mg with a msDBP of 81.0 mmHg and a msSBP of 130.7 mmHg. Two thirds (67%) of these subjects had reached

[3] The mild or moderate hypertension class includes 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 ≥180 or diastolic blood pressure ≥110 mmHg.

their BP goal. There were 419 subjects on OM 40 mg + AML 10 mg + HCTZ 25 mg with a msDBP of 83.4 mmHg and a msSBP of 136.8 mmHg with 46.3% reaching BP target.

> **Comment:** The Clinical Evaluation Report for Sevikar stated that the long term data showed an initial decrease in BP during the first few weeks of treatment with any dose regimen. Thereafter, BP tended to stabilise. This pattern would be expected since patients not achieving target BP were up-titrated to a higher dose; however, the data do demonstrate that the efficacy of each dose regimen was maintained over the long term in patients remaining on that dose.

7.1.2.2. Study CS8663-A-E303

Study CS8663-A-E303 was a phase III randomised, 52 week study of add-on olmesartan in 755 adult subjects with moderate to severe hypertension inadequately controlled on amlodipine 5 mg. The first three periods of the study were 8 weeks each and were: open label amlodipine; double blind fixed dose; and double blind with dose titration. The dossier included the CSR for Period IV of this study which covered a 28 week open label extension (weeks 24 to 52) in 692 subjects. In this period, subjects received olmesartan 40 mg and amlodipine 5 mg which could be uptitrated to amlodipine 10 mg. After this HCTZ 12.5 mg and then 25 mg could be added if required. Uptitration was required for msSBP/DBP ≥140/90 mmHg.

For the 692 subjects in Period IV, the baseline mean sitting BP (start of randomised treatment at week 8) was 154.5/97.0 mmHg. The completion rate of Period IV was high (97%). At week 52 after three possible titration steps, 67% of subjects had reached the BP target. At this time, 68 subjects were on OM 40 mg + AML 10 mg + HCTZ 12.5 mg with a msSBP/msDBP of 138.3/87.3 mmHg and 47.1% had reached the BP goal. There were a further 27 subjects on OM 40 mg + AML 10 mg + HCTZ 25 mg with a msSBP/msDBP of 145.6/89.7 mmHg and 9 (33.3%) reached the BP goal.

7.1.3. Study SP-OLM-03-05

Design and Methods: This was a 22 week, phase IV, open label, non-comparative, multicentre study of olmesartan and sequential add-on treatment of HCTZ and amlodipine in 694 subjects with mild to moderate hypertension. It was sponsored by Daiichi Sankyo and conducted between April 2006 and April 2008 at 58 centres in 9 European countries.

The primary objective was to evaluate the rate of subjects treated to target (STTT) overall and at each combination treatment step. The target BP (at trough) was msSBP ≤130 mmHg and msDBP ≤85 mmHg for non-diabetics and msSBP <130 mmHg and msDBP <80 mmHg in diabetics. BP was measured with mercury sphygmomanometers after 10 minutes rest in the sitting position. There were three sitting and one standing BP measurements.

Subjects were adults with mild to moderate essential hypertension with msSBP≥140 and <180 mmHg and/or msDBP ≥90 and <110 mmHg. Exclusion criteria were: severe hypertension; pregnancy or not using acceptable contraceptives; secondary hypertension; hypotension (BP >105/60 mmHg); differences in SBP of >20 mmHg or DBP of >10 mmHg at 3 consecutive readings; clinical significant laboratory abnormalities; 2nd or 3rd degree AV block, atrial fibrillation, bradycardia (<50 bpm) or cardiac arrhythmia requiring treatment; severe heart failure (NYHA stage III or IV); valvular heart disease; myocardial infarction, unstable angina, PTCA, stroke or TIA in the past 6 months; conditions (such as ischaemic heart disease and cerebrovascular disease) with a risk of stroke or MI from excessive BP reduction; hepatic impairment, cholestasis or biliary obstruciotn; malabsorption; galactose intolerance; autoimmune disease; poorly controlled diabetes; gout; HIV infection or other uncontrolled infection; malignancy with 5 years or requiring treatment; and other antihypertensive medications.

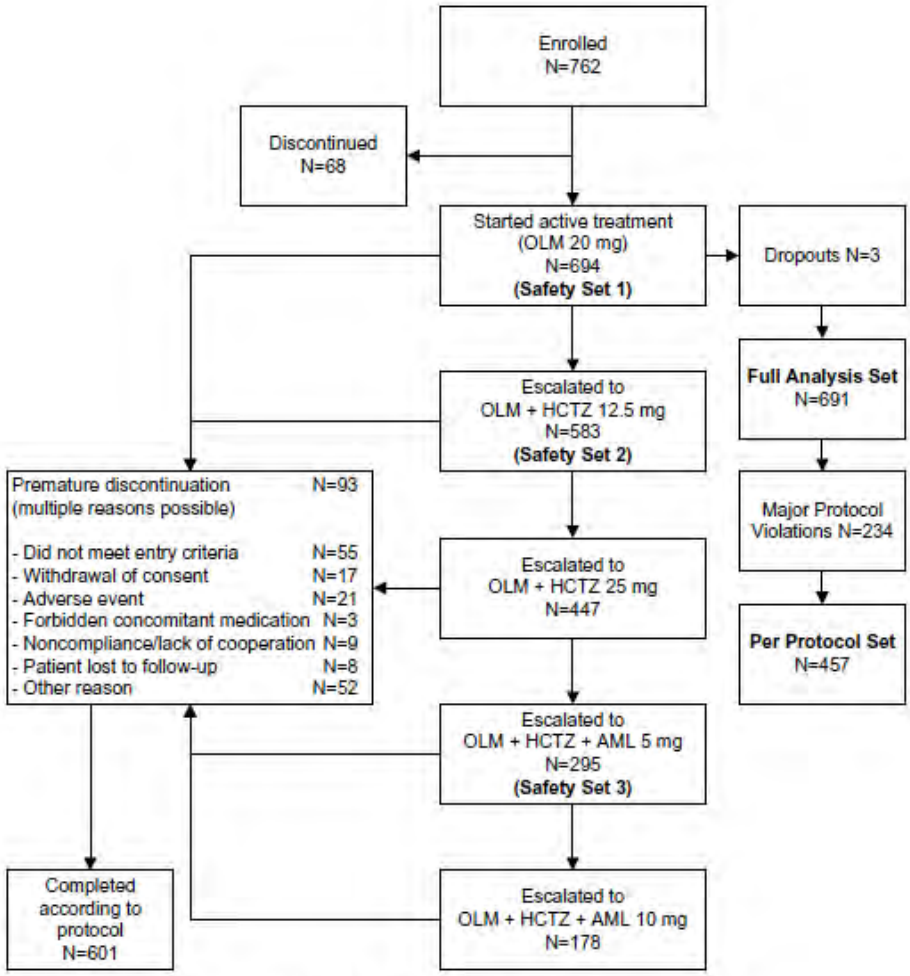
After a 2 week placebo run-in period, there were 5 active treatment periods of 4 weeks duration each. If the entry criteria were met, subjects were treated with the following sequential steps:

- 20 mg OLM od;
- 20 mg OLM plus 12.5 mg HCTZ (fixed combination) od;
- 20 mg OLM plus 25 mg HCTZ (fixed combination) od;
- 20 mg OLM plus 25 mg HCTZ (fixed combination) plus 5 mg AML od;
- 20 mg OLM plus 25 mg HCTZ (fixed combination) plus 10 mg AML od.

Subjects reaching BP target on active treatment were discontinued from the study. All study medication was taken once daily in the morning (except on clinic visit days when it was taken after the BP measurement). Treatment was open label and non-randomised. The primary analysis was conducted on the FAS with LOCF. Analysis was descriptive and prognostic factors were assessed using logistic regression.

Results: There were 762 subjects enrolled and 694 who commenced study treatment with 86.6% completing the study according to the protocol. Premature discontinuation rate was 13.4% with the main reasons being not meeting eligibility criteria (7.2%), adverse events (2.8%) and consent withdrawal (2.2%). Participant flow is shown in Figure 1. The major protocol violation rate was high at 34% and included inappropriate visit schedules (14%), premature discontinuation which was not for achieving target BP (12%), treatment non-compliance (10%) and inclusion/exclusion criteria violations (7%). There were 691 subjects (90.7%) in the FAS and 457 (60.0%) in the PP set. There were 103 subjects who received the triple combination of OM/HCTZ/AML 20/25/5 mg and 59 who received OM/HCTZ/AML 20/25/10 mg.

Figure 1. Study SP-OLM-03-05. Disposition of patients



(based on information in Tables 1.1, 2.4, 5.2, 5.24 and 5.25 in Section 14)

Study subjects had a mean age of 58.2 years, mean BMI of 28.9 kg/m^2, 81% were classed as overweight or obese, 97.7% were Caucasian and 51% male. Cardiac risk factors included diabetes (13.1%), dyslipidaemia (39.5%), family history (17.0%) and atherosclerosis (5.8%).

In the FAS the rate of subjects treated to target was 71.8% (95% CI: 68.4, 75.1%) and in the PP set the rate was 84.5% (95% CI: 81.1, 87.8%). The proportion of subjects attaining target BP was 12.3% with olmesartan 20 mg, 16.4% with OM/HTCZ 20/12.5 mg, 19.2% with OM/HTCZ 20/25 mg, 14.9% with OM/HTCZ/AML 20/25/5 mg and 8.5% with OM/HTCZ/AML 20/25/10 mg. From a baseline msSBP/msDBP of 158.1/94.7 mmHg, there was a mean change to the last available assessment of –29.6/-15.7 mmHg. Results were comparable in the PP population. The statistically significant prognostic factors for requiring dual therapy were moderate or severe hypertension, diabetes or abnormal BMI, while for triple therapy were moderate or severe hypertension, age >65 years and diabetes. There was some difference in prognostic factors in the PP population with moderate and severe hypertension and diabetes being the main factors associated with the need for triple therapy.

Summary: This open label, non-comparative phase IV study in 694 adults with mild to moderate hypertension found that a BP target of ≤130/85 mmHg (or <130/80 mmHg in diabetics) could be achieved in 72% with a stepped treatment algorithm of olmesartan 20 mg, hydrochlorothiazide and amlodipine. The mean overall BP reduction was 30/16 mmHg.

7.1.4. Analyses performed across trials (pooled analyses and meta-analyses)

None provided.

7.2. Evaluator's conclusions on clinical efficacy for hypertension

The efficacy of the triple combination was based on one large pivotal study CS8635-A-U301. This was a phase III, multicentre, randomised, parallel group study in 2492 adult subjects with hypertension, 627 of whom received the triple combination. After a run-in of at least 2 weeks on high dose dual therapy, subjects remained on dual therapy or were titrated to the maximal dose triple therapy. The triple combination dose of OM 40/HCTZ 25 + AML 10 was found to significantly reduce msDBP and msSBP to a greater level than any of the three dual therapy combinations. The addition of the HCTZ 25 mg component to the dual therapy contributed a BP reduction of 7.1/3.8 mmHg, amlodipine 10 mg contributed 7.4/4.9 mmHg and olmesartan 40 mg contributed 9.6/6.7 mmHg. Target BP attainment rates at week 12 were significantly greater with triple therapy than dual therapy (64.3% vs 34.9% to 46.6%). The 24 hour ambulatory BP monitoring substudy in 440 subjects confirmed the difference between triple and dual therapy over the 24 hour dosing interval. Results were consistent across subgroups of age, gender, race and hypertension severity.

In this study there were too few subjects over 75 years or with renal impairment to allow meaningful comparisons. There were also very few Asian subjects. Triple therapy treatment in the study was achieved by using a combination of BENICAR HCT (OM/HTCZ 40/25) with ANTACAL 10 mg (amlodipine) so it was important to see that bioequivalence of these products to the proposed FDC was demonstrated.

The study was reported to have a 40 week open label Period III (weeks 12 to 52), however the data were not provided in the dossier. Given the first part of the study was completed in 2009, these should be available and are necessary to provide data on the persistence of efficacy and tolerance.

The pivotal study was a head to head comparison of triple versus dual therapy in subjects with moderate hypertension. It did not directly assess the efficacy of triple therapy in subjects who had not adequately responded to dual therapy, although this was done on an exploratory basis and was suggestive of a positive response.

Some supportive efficacy data was provided in study SP-OLM-03-05. This was an open label, non-comparative phase IV study in 694 adults with mild to moderate hypertension. Subjects received a stepped treatment algorithm of olmesartan 20 mg, hydrochlorothiazide (12.5 and 25 mg) and amlodipine (5 and 10 mg). Using this treatment sequence a BP target of ≤130/85 mmHg (or <130/80 mmHg in diabetics) could be achieved in 72% of subjects with a mean overall BP reduction of 30/16 mmHg.

The dossier also included clinical study reports of the extension arms of studies CS8663-A-U301 and CS8663-A-E303. These studies had previously been evaluated (2009) for the Sevikar (Olmesartan/Amlodipine) submission. The data showed that efficacy of dose regimens was maintained over the long term (to 52 weeks).

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

In the pivotal efficacy study (CS8635-A-U301) the following safety data were collected:

- General adverse events (AEs) were assessed at each visit.
- Adverse events of interest included oedema, headache, hypotension, dizziness and vertigo,syncope, renal impairment, hepatic related events, hyper- and hypokalaemia, glycaemic control related events, falls, gout and hyperuricaemia.
- Laboratory tests, including chemistry, haematology and urinalysis, were performed at screening, day one and then week 12, 20 and 52.
- Vital signs, ECGs, and physical examination.
- The non-pivotal efficacy studies provided safety data, as follows:
- Study CS8663-A-U301, CS8663-A-E303 provided data on adverse events, specific AEs and clinical laboratory assessments. Subjects entering the open label periods of these studies were included in the integrated analysis of safety of the Phase 3 open label cohort.
- Study SP-OLM-03-05 provided data on adverse events and clinical laboratory assessments. Data were divided into three safety sets: safety set 1 was subjects who received olmesartan; safety set 2 was those who received HTCZ; and safety set 3 was those who received amlodipine at least once, i.e. triple therapy.

The clinical pharmacology studies CS8635-A-U101, -U102, -U103, -U104, -E105 and -U106 provided data on adverse events. Data were included in an integrated analysis of safety for the phase I cohort.

The Safety set was defined as all randomised subjects who received at least one dose of study medication and had at least one post dose safety assessment. In the pivotal study, the primary assessment of adverse events was on the Safety Set 2 from day 1 to week 12. The Safety Set 2 was defined as the subjects who took at least one dose of study medication at or beyond the week 4 visit when treatment with triple therapy commenced.

Data from the 40 week open label extension of the pivotal study was not included in the dossier.

8.2. Pivotal studies that assessed safety as a primary outcome

None.

8.3. Patient exposure

In the pivotal study Safety Set 2, there were 574 subjects exposed to triple therapy for a mean duration of 53.6 days. Due to study design, the mean duration of exposure to dual therapy was longer (82.7 to 83.0 days).

In the phase 3 open label cohort (uncontrolled extensions of studies CS6883-A-U301 and -E303), there were 829 subjects who received OM 40/AML 10/HTCZ 12.5 for a mean duration of 111.6 days and 468 who received OM 40/AML 10/HTCZ 25 for mean duration of 175.0 days. The mean exposure to dual therapy AML 10/HCTZ 25 was 79.5-100.9 days. Due to the difference in duration of exposure, comparisons between triple and dual therapy group rates are not directly possible.

In the phase IV study, 294 subjects received triple combination (OM 20/AML 10/HTCZ 12.5 or OM 20/AML 10/HTCZ 25 for a mean duration of 45.6 days.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal study

Over the 12 weeks of the pivotal study, the rate of treatment emergent AEs (TEAEs) was 58.4% in the triple combination group compared to 51.7% to 58.9% in the dual combination groups. In the triple combination group, the severity of TEAEs was generally mild (31.9%) or moderate (22.3%) with severe TEAEs being less frequent (4.2%). Similar proportions were seen across the dual therapy groups (Table 6).

Table 6. Overview of Adverse Events by Final Randomised Treatment – Number (%) of subjects – Day 1 to Week 12 – Safety Set 2

Category	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					
Any TEAE	308 (51.7)	319 (55.0)	325 (58.9)	335 (58.4)	1287 (55.9)
Any drug-related [1] TEAE	138 (23.2)	121 (20.9)	164 (29.7)	162 (28.2)	585 (25.4)
Maximum severity of TEAEs					
Any TEAE					
Mild	160 (26.8)	177 (30.5)	160 (29.0)	183 (31.9)	680 (29.5)
Moderate	124 (20.8)	125 (21.6)	147 (26.6)	128 (22.3)	524 (22.8)
Severe	24 (4.0)	17 (2.9)	18 (3.3)	24 (4.2)	83 (3.6)
Drug-related [1] TEAEs					
Mild	84 (14.1)	78 (13.4)	104 (18.8)	103 (17.9)	369 (16.0)
Moderate	45 (7.6)	39 (6.7)	58 (10.5)	52 (9.1)	194 (8.4)
Severe	9 (1.5)	4 (0.7)	2 (0.4)	7 (1.2)	22 (1.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with SAEs					
Any SAE	9 (1.5)	7 (1.2)	9 (1.6)	10 (1.7)	35 (1.5)
Any drug-related [1] SAE	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Subjects with AE leading to study discontinuation [2]					
Any AE	7 (1.2)	12 (2.1)	11 (2.0)	23 (4.0)	53 (2.3)
Any TEAE	6 (1.0)	12 (2.1)	11 (2.0)	23 (4.0)	52 (2.3)
Any drug-related [1] TEAE	4 (0.7)	5 (0.9)	5 (0.9)	18 (3.1)	32 (1.4)
SAE	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)	6 (0.3)

Safety Set 2 included subjects who received at least 1 dose of double-blind study medication at or beyond Week 4. Treatment-emergent adverse events were AEs 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.

1. Drug-related was defined as definitely, probably, or possibly related to randomized study medication.
2. Based on "action taken" on Adverse Event electronic case report form.

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

Source: CS8635-A-U301 CSR Post-text Table 15.3.1.1

In the triple therapy group, the most frequent SOCs involved were nervous system disorders (19.3%), infections and infestations (14.8%) and general disorders and administration site conditions (15.9%). These rates were no greater than in the dual therapy groups. The most common TEAEs in the triple compared to dual therapy groups were dizziness (11.3% vs 3.4-10.7%), oedema (7.7% vs 1.6-9.8%), headache (6.4% vs 6.0-7.0%) and fatigue (4.2% vs 5.3-6.5%).

TEAEs of special interest are summarised in Table 7. Oedema was associated with amlodipine and was not higher with the triple combination than with AML 10/HCTZ 25 (7.7% vs 9.8%). Treatment with the triple compared to dual therapy resulted in a higher rate of hypotension (2.1% vs 0-0.7%) and syncope (1.0% vs 0-0.5%). Dizziness/vertigo was similar to OM 40/HCTZ 25 (11.3% vs 10.7%) and the rate of falls/injuries/fractures was similar (1.2% vs 1.0-1.8%). The rate of renal impairment AEs was higher (2.1% vs 0.2-1.3%) as was hyperkalaemia (0.9% vs 0.3-0.5%). Hepatic-related events and gout/hyperuricaemia/increased uric acid adverse events were no greater with the triple therapy.

Table 7. Number (%) of subjects with Treatment-Emergent Adverse Events in Adverse Events Categories of Special Interest– – Day 1 to Week 12 – Safety Set 2

Adverse Event Category [1]	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 (%)
Edema	46 (7.7)	9 (1.6)	54 (9.8)	44 (7.7)	153 (6.6)
Hypotension	0 (0.0)	4 (0.7)	1 (0.2)	12 (2.1)	17 (0.7)
Headache	42 (7.0)	38 (6.6)	33 (6.0)	37 (6.4)	150 (6.5)
Dizziness and vertigo	33 (5.5)	62 (10.7)	19 (3.4)	65 (11.3)	179 (7.8)
Syncope	0 (0.0)	0 (0.0)	3 (0.5)	6 (1.0)	9 (0.4)
Renal impairment AEs	1 (0.2)	5 (0.9)	7 (1.3)	12 (2.1)	25 (1.1)
Hepatic-related AEs	1 (0.2)	2 (0.3)	6 (1.1)	2 (0.3)	11 (0.5)
Hyperkalemia	2 (0.3)	3 (0.5)	3 (0.5)	5 (0.9)	13 (0.6)
Hypokalemia	3 (0.5)	6 (1.0)	39 (7.1)	9 (1.6)	57 (2.5)
Glycemic control	10 (1.7)	8 (1.4)	16 (2.9)	3 (0.5)	37 (1.6)
Injury, falls, and fractures	6 (1.0)	9 (1.6)	10 (1.8)	7 (1.2)	32 (1.4)
Gout, hyperuricemia, and increased uric acid	3 (0.5)	3 (0.5)	7 (1.3)	2 (0.3)	15 (0.7)

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 AEs 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.
1. See Section 1.1.2.1.5 for the Medical Dictionary for Regulatory Activities terms included in the various adverse event categories of interest.
AE = adverse event; AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.
Source: CS8635-A-U301 CSR Post-text Table 15.3.1.15

8.4.1.2. Other studies

In the phase 3 open label cohort, the rate of TEAEs in those who received triple therapy was 54.5% and 39.7% in those who received OM40/AML 10/HCTZ 25 and OM 40/AML 10/HCTZ 12.5, respectively. TEAEs were mild or moderate with triple therapy and severe TEAEs were less frequent (27.9%, 25.3%, 4.3%, respectively). The most frequent TEAEs included peripheral oedema (14.1%), oedema (3.8%), dizziness (5.2%), headache (3.7%), cough (3.0%), URTI (3.6%) and headache (3.7%). The rates for these events were higher with the maximal dose triple therapy 40/10/25 mg than with the triple therapy with the lower HCTZ component of 12.5 mg. TEAEs of special interest showed a similar pattern to the short term study. Renal-related AEs were reported in 1.6% and glycaemic control AEs in 4.2% of triple therapy subjects.

In the phase I cohort, the AE rate with the varying doses of triple therapy ranged from 35.9% to 50.0%. Most AEs were mild (28.7-41.7%) or moderate (5.6-13.9%) in severity. There was only one severe AE which occurred in a subject treated with OM 20/AML 5/HTCZ 12.5 and was not classed as treatment-related. The most frequent AEs were headache and dizziness.

In the phase IV study (SP-OLM-03-05), the AE rate was similar in the three safety sets (33.2% to 39.0%). The most frequent AEs were dizziness (5.0%), bronchitis (3.2%) and back pain (2.2%) in safety set 1, dizziness (5.1%), bronchitis (2.9%), and peripheral oedema (1.9%) in safety set 2, and dizziness (4.1%), peripheral oedema (3.4%) and bronchitis (2.4%) in safety set 3.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal study

Treatment-related TEAEs were reported in 28.2% of the triple therapy compared to 20.9% - 29.7% of the dual therapy groups. The most frequent treatment-related TEAEs were dizziness (6.4%), peripheral oedema (6.1%) and headache (3.0%). These rates were no higher than a dual combination group. The rate of hypotension was greater with the triple than dual therapies (1.2% vs 0-0.3%), as was increased creatinine (1.2% vs 0-0.5%). The rate of treatment-related hypokalaemia was 0.5% vs 0.2-3.4% in the triple and dual therapy groups, respectively (Table 8). Most treatment-related events were mild or moderate. Severe treatment-related TEAEs occurred in 1.2% of subjects in the triple therapy compared to 0.4-1.5% in the dual therapy groups.

Table 8. Summary of subjects with Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (≥% 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 drug-related TEAEs	138 (23.2)	121 (20.9)	164 (29.7)	162 (28.2)	585 (25.4)
Nervous system disorders	45 (7.6)	66 (11.4)	38 (6.9)	61 (10.6)	210 (9.1)
Dizziness	17 (2.9)	37 (6.4)	13 (2.4)	37 (6.4)	104 (4.5)
Headache	19 (3.2)	15 (2.6)	10 (1.8)	17 (3.0)	61 (2.6)
Lethargy	6 (1.0)	4 (0.7)	3 (0.5)	1 (0.2)	14 (0.6)
General disorders and administration site conditions	57 (9.6)	27 (4.7)	64 (11.6)	56 (9.8)	204 (8.9)
Edema peripheral	30 (5.0)	3 (0.5)	33 (6.0)	35 (6.1)	101 (4.4)
Fatigue	20 (3.4)	20 (3.4)	25 (4.5)	15 (2.6)	80 (3.5)
Gastrointestinal disorders	17 (2.9)	24 (4.1)	24 (4.3)	21 (3.7)	86 (3.7)
Nausea	4 (0.7)	8 (1.4)	5 (0.9)	6 (1.0)	23 (1.0)
Dry mouth	3 (0.5)	6 (1.0)	8 (1.4)	1 (0.2)	18 (0.8)
Musculoskeletal and connective tissue disorders	20 (3.4)	10 (1.7)	20 (3.6)	20 (3.5)	70 (3.0)
Joint swelling	13 (2.2)	0 (0.0)	11 (2.0)	7 (1.2)	31 (1.3)
Muscle spasms	5 (0.8)	6 (1.0)	6 (1.1)	9 (1.6)	26 (1.1)
Investigations	4 (0.7)	9 (1.6)	24 (4.3)	21 (3.7)	58 (2.5)
Blood potassium decreased	1 (0.2)	2 (0.3)	13 (2.4)	3 (0.5)	19 (0.8)
Blood creatinine increased	0 (0.0)	3 (0.5)	2 (0.4)	7 (1.2)	12 (0.5)
Metabolism and nutrition disorders	6 (1.0)	7 (1.2)	23 (4.2)	10 (1.7)	46 (2.0)
Hypokalemia	1 (0.2)	2 (0.3)	19 (3.4)	3 (0.5)	25 (1.1)
Renal and urinary disorders	14 (2.3)	10 (1.7)	9 (1.6)	9 (1.6)	42 (1.8)
Pollakiuria	8 (1.3)	7 (1.2)	5 (0.9)	8 (1.4)	28 (1.2)
Vascular disorders	2 (0.3)	5 (0.9)	4 (0.7)	12 (2.1)	23 (1.0)
Hypotension	0 (0.0)	2 (0.3)	0 (0.0)	7 (1.2)	9 (0.4)

Safety Set 2 included subjects who received at least 1 dose of double-blind study medication at or beyond Week 4.
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.
Drug-related was defined as definitely, probably, or possibly related to randomized study medication.
AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil;
TEAE = treatment-emergent adverse event.
Source: CS8635-A-U301 CSR Post-text Table 15.3.1.11

8.4.2.2. Other studies

In the phase 3 open label cohort, the rate of treatment-related TEAEs with triple therapy was 24.3% which was higher than dual therapy olmesartan/amlodipine (11.1%-15.1%). Most were mild (16.6%) or moderate (7.4%) with only 2 (0.2%) severe treatment-related TEAEs both of which were in subjects who received OM 40/AML10/HCTZ 12.5 mg. The most frequent events were peripheral oedema (10.5%), oedema (2.5%), dizziness (2.8%), hypotension (1.7%), increased blood creatinine (1.0%) and pollakiuria (1.2%).

Treatment-related AEs in the phase I cohort were reported in 11.1 to 20.8% of subjects treated with triple therapy (varying doses). In the phase IV study the rate of treatment-related TEAEs was 19.7%, 19.9% and 21.7% in safety sets 1, 2 and 3, respectively. The most frequent treatment related events in safety set 3 were peripheral oedema (3.4%) and dizziness (3.1%).

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal study

There was one death in CS8635-A-U301. This subject was on AML10 mg / HCTZ 25 mg and died prior to week 4 from 'alcohol poisoning' and was not included in safety set 2.

The rate of SAEs while taking triple therapy was 1.6% (n=9) compared to 1.3% to 1.8% while taking a dual therapy and 2.8% while on placebo. There was one subject in the triple therapy group who discontinued the study due to an SAE (coronary artery disease). There were three treatment-related SAEs in two subjects (angina pectoris in a subject on OM 40/AML 10 and acute renal failure and syncope in s a subject on AML10/HCTZ 25) neither of whom were on triple therapy. A listing of SAEs was provided.

8.4.3.2. Other studies

There was one death in the phase 3 open label cohort. This subject on OM40 mg + AML10 mg died from a gunshot wound.

The rate of SAEs in the phase 3 open label cohort was 1.8% and 3.8% for subjects while taking OM40/AML 10/HCTZ 12.5 mg and OM 40/AML 10/HCTZ 25 mg, respectively. The SAE rate while on OM 40/AML 5 and OM 40/AML 10 was 1.8% for each. The SAEs which resulted in discontinuation in subjects treated with triple therapy included: hepatic malignant neoplasm, psychotic disorder, chest pain, dizziness and small intestine obstruction.

There were no deaths and seven (1.0%) SAEs in the phase IV study (cellulitis, rectal cancer, acute myocardial infarction, myocardial infarction, lung disorder, inguinal hernia, and spinal osteoarthritis). None of the SAEs were considered treatment-related.

There were no deaths or other SAEs in the phase I cohort.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal study

The discontinuation rate from double-blind treatment due to adverse events was 7.7% with triple therapy compared with 3.5%, 7.2% and 6.3% for the dual combinations of OM 40/AML 10, OM 40/HCTZ 25 and AML 10/HTCZ 25, respectively. There were 4 discontinuations due to severe treatment-related TEAEs: one dizziness in the OM 40/ALM 10 group; one nausea in the AML 10/HCTZ 25 group; and one hyperkalaemia and one headache in the triple combination group.

The most frequent TEAEs leading to discontinuation were dizziness (1.0% vs 0.2-0.3%), peripheral oedema (0.9% vs 0.2% both) and hypotension (0.7% vs 0-0.3%) in the triple vs dual therapy groups.

8.4.4.2. Other studies

The overall discontinuation rate due to AEs in the phase 3 open label cohort was 3.6%. The AE discontinuation rate while taking dual therapy was 1.4-1.5% and while taking OM 40/AML 10/HCTZ 12.5 was 1.3% and for OM 40/AML 10/HCTZ 25 increased to 2.5%. Events leading to discontinuation occurring in more than one subject on triple therapy included oedema and increased blood creatinine.

In the phase IV study, 2.7 % of subjects discontinued due to a TEAE, the most common of which was dizziness.

In the phase I cohort, 3.2% of subjects (n=8) discontinued the study due to an AE: 1.7% of the OM 40/AML 10/HCTZ 25 mg group, 0.7% of the OM 40/HCTZ 25 mg + AML 10 mg group, 4.2% of the OM 40/AML 10 mg + HCTZ 25 mg group, and 2.9% of the HCTZ 25 mg group. There was one papular rash in a subject on OM 40/HCTZ 25 + AML 10 which was felt to be definitely treatment related.

8.5. Laboratory tests

The sponsor defined "markedly abnormal" laboratory parameters as follows: 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, haemoglobin <9 g/dL for males and <8 g/mL for females, hematocrit <30%, red blood cells <3 $\times 10^6$/µL, white blood cells >20 $\times 10^3$/µL and platelet count <100 $\times 10^3$/µL.

8.5.1. Liver function

8.5.1.1. Pivotal study

There were small statistically significant increases from baseline to week 12 in the mean levels of ALT and AST across the treatment groups. In the OM40/AML 10/HCTZ 25 group, the mean change in ALT and AST was 1.2 and 0.4 U/L, respectively and marked elevation of ALT, AST and total bilirubin occurred in 1.3%, 2.7% and 0.2%, respectively. These proportions were similar to that seen in the dual therapy groups.

8.5.1.2. Other studies

In the phase 3 open label cohort, there were no clinically notable mean changes from baseline to week 12 in liver function. Marked elevations of AST, ALT and GGT (0.9%, 1.5% and 5.8%) were slightly more frequent with OM40/AML 10/HCTZ 25 than with OM40/AML 10/HCTZ 12.5 or the dual combinations of OM40/AML 5 or 10.

In the phase IV study there were small changes between baseline and final visit in laboratory parameters but there were no new safety signals related to these assessments.

8.5.2. Kidney function

8.5.2.1. Pivotal study

In the triple therapy group, the rate of increased creatinine >1.4 mg/dL and creatinine clearance ≤60 mL/min was 6.4% and 5.4%, respectively, which was no higher than the OM40/ HCTZ 25 mg group (7.1% and 6.6%, respectively).

The incidence of renal impairment AEs was greater with triple than dual therapy (2.1% vs 0.2-1.3%). Overall there were 27 subjects with renal impairment AEs (increased creatinine, increased blood urea, renal impairment, acute or chronic renal failure, renal failure, azotemia or renal pain) in the pivotal study with 12 of these in the triple therapy group. Of the 14 laboratory-related AEs leading to discontinuation, 5 were in the triple therapy group and 3 of these were due to increased creatinine and increased urea.

8.5.2.2. Other studies

In the phase 3 open label cohort, there were no clinically notable mean changes from baseline to week 12 in creatinine or blood urea. There were, however, 11.3% of subjects on OM 40/AML 10/HCTZ 25 with creatinine >1.4 mg/dL compared to 1.3% to 4.0% in the other groups. The rate of renal AEs was higher with triple therapy compared to the other groups (1.7% vs 0.1-0.7%).

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal study

The mean change from baseline to week 12 for sodium and potassium was shown. There were no clinically relevant differences between the treatment groups. The rate of increased potassium (>5.0 mmol/L) was no higher with triple therapy than with OM 40/AML 10 (5.9% vs 7.6%) and the rate of low potassium (<3.5 mmol/L) was similar to OM 40/HCTZ 25(2.2% vs 2.4) and less than with AML 10/HCTZ 25 (9.8%).

There were 2 subjects with laboratory related SAEs: one hyperkalaemia in a subject on OM40 /HCTZ 25 and one hypokalaemia and hyponatraemia in a subject on AML 10/HCTZ 25. The rate of TEAEs of hyperkalaemia was slightly higher with triple therapy (0.9% vs 0.3-0.5%). The rate of hypokalaemia TEAEs (1.6%) was slightly higher than OM 40/AML 10 and OM 40/HCTZ 25 (0.5% and 1.0%, respectively), with the highest rate seen in the AML 10/HCTZ 25 group (7.1%).

8.5.3.2. Other studies

In the phase 3 open label cohort the mean change from baseline in sodium and potassium was not remarkable. Increased potassium rates were lower with triple than dual olmesartan/amlodipine therapy (2.4-2.8% vs 4.5-5.3%) while low potassium was higher (4.0-11.3% vs 1.3-2.1%).

8.5.4. Haematology

8.5.4.1. Pivotal study

There were small changes in haematology parameters between baseline and week 12 that were not clinically significant. There were few markedly abnormal haematology results and no evident differences between groups.

8.5.4.2. Other studies

In the phase 3 open label cohort the mean change from haematology parameters was not remarkable and marked abnormalities were infrequent.

8.5.5. Electrocardiograph

8.5.5.1. Pivotal study

There were no clinically relevant changes in ECGs in the pivotal study.

8.5.5.2. Other studies

There were no notable changes from baseline in ECG findings in the two phase 3 open label extension studies.

8.5.6. Vital signs

There were no clinically relevant changes in heart rate, body weight, or physical examination in the pivotal study or the two phase 3 open label extension studies

8.6. Post-marketing experience

Data from the phase IV study has been included in Sections 8.4 and 8.5 above. No other post-marketing data was submitted in the study.

8.7. Safety issues with the potential for major regulatory impact

The safety issues with the triple therapy are the same as those already labelled for the individual components, in particular the risk in pregnancy and renal impairment.

8.8. Other safety issues

8.8.1. Safety in special populations

Age: Exposure to triple therapy was similar across the age groups in the pivotal study (53.8 days in subjects <65 years of age, 54.1 days in subjects ≥65 years of age, and 55.8 days in subjects ≥75 years of age). The rate of TEAEs was similar between these age groups treated with triple therapy (57.7%, 61.0% and 56.3%) although the number in the ≥75 years group was small (n=16).

The rate of SAEs was higher in the ≥65 years than in the <65 years group (5.1% vs 0.9%) treated with triple therapy and higher in the ≥65 years treated with triple compared to dual therapy (5.1% vs 1.6-3.4%). The rate of study discontinuation due to AEs in the triple therapy group was similar between those ≥65 years and <65 years (4.2% vs 3.9%) and in the elderly group was similar to AML 10/ HCTZ25 (4.5%).

Compared to those aged <65 years, the elderly on triple therapy had a higher rate of oedema (12.7% vs 6.4%), dizziness (11.8% vs 9.3%), renal impairment AEs (3.4% vs 1.8%) and hypotension (2.5% vs 2.0%). When the elderly were treated with triple therapy compared to dual therapy they had higher rates of oedema, hypotension and syncope. The addition of olmesartan reduced the risk of hypokalaemia (0.8% vs 6.7% with AML 10/HCTZ 25).

> **Comment:** The numbers in the ≥75 years age group were too small in the pivotal study to allow meaningful conclusions to be drawn on the relative safety in this age group.

In the phase 3 open label cohort, subjects aged ≥65 years treated with triple therapy had an TEAE rate of 64.5%, 27.9% had a treatment-related TEAE, 4.4% had a severe TEAE, 8.2% had an SAE and 3.8% discontinued due to an AE. As with the pivotal study the risk of adverse events was greater in the elderly than in those aged <65 years. The most frequent TEAEs were oedema (16.5% with OM 40 /AML 10/HCTZ 25 and 16.8% with OM 40/AML 10/HCTZ 12.5) followed by dizziness (6.2% and 5.8%, respectively).

Gender: The rate of TEAEs was higher in females than males treated with triple therapy in the pivotal study (61.9% vs 51.3%) as was the rate of treatment-related TEAEs (33.6% vs 23.3%), while SAEs were less frequent (0.7% vs 2.7%) and discontinuation due to any TEAE was similar (4.4% vs 3.7%). When treated with triple therapy, females compared to males had higher rate of oedema (11.3% vs 4.3%), headache (8.4% vs 4.7%), hypotension (2.6% vs 1.7%), hypokalaemia (2.2% vs 1.0%) and falls/injuries/factures (1.8% vs 0.7%) and a lower rate of renal impairment AEs (0.7% vs 3.3%).

In the phase 3 open label cohort, when treated with maximal dose triple therapy, females had a higher rate of oedema (16.6% vs 12.0%) and dizziness (7.1% vs 4.0%) than males.

Race: The rate of TEAEs was higher in non-Black than Black subjects when treated with triple therapy (61.3% vs 51.2%) and black subjects had lower rates of oedema (3.0% vs 9.6%), dizziness and vertigo (7.2% vs 13.0%) and hypotension (1.2% vs 2.5%) and a higher rate of hypokalemia (2.4% vs 1.2%)

Ethnicity: Compared to the rest of the study population, Hispanics/Latinos had a slightly lower TEAE rate when treated with triple therapy group (50.0% vs 60.0%). Triple therapy resulted in a higher rate of hypokalaemia in this subgroup compared to the rest of the study population (3.3% vs 1.2%) and headache (12.0% vs 5.4%) and a lower rate of dizziness (5.9% vs 12.2%).

Hypertension stage[4]: There were 253 subjects with stage 1 hypertension and 1996 with stage 2 with similar exposure (53.7 vs 54.9 days). In those treated with triple therapy, the TEAE rate was similar between stage 1 and 2 (61.3% vs 57.4%) as was the SAE rate (1.6% vs 1.8%).

[4] Stage 1 hypertension = subjects with SBP from 140 mmHg to <160 mmHg and DBP from 90 mmHg to <100 mmHg. Stage 2 hypertension = subjects with SBP ≥160 mmHg or DBP ≥100 mmHg.

Subjects with stage 2 hypertension treated with triple therapy had a higher rate of oedema (8.4% vs 1.6%) but a lower rate of hypotension (1.8% vs 4.8%) and renal impairment AEs (1.8% vs 3.2%). Compared to dual therapy, triple therapy resulted in higher rates of hypotension and syncope in both the stage 1 and stage 2 hypertension subgroups.

Hypertension severity: In those treated with triple therapy, the TEAE rate was higher in those with severe hypertension compared to those with mild/moderate severity (63.6% vs 56.1%). In the triple therapy group, the rate of renal impairment AEs was higher in those with severe hypertension compared to mild/moderate hypertension (3.9% vs 1.4%). In subjects with severe hypertension the rates of AEs of interest were no higher with triple compared to one of the dual therapy combinations.

Body Mass Index: Assessment of those with BMI <30 kg/m^2 and ≥30 kg/m^2 found in those treated with triple therapy, there were higher rates of oedema in the obese subjects (9.7% vs 4.2%) and lower rates of hypotension (1.4% vs 3.3%) and renal impairment AEs (1.7% vs2.8%).

Renal impairment: When treated with triple therapy, subjects with renal impairment had a higher rate of renal impairment AEs compared to those without renal impairment (11.1% vs 1.8%). Other events were not notable.

Diabetes: In the triple therapy group, the rate of TEAEs in diabetics was slightly higher than non-diabetics (63.0% vs 57.5%), as was the rate of severe TEAEs (6.5% vs 3.7%), while SAEs were similar (2.2% vs 1.7%). The AE profile, for those on triple therapy, between diabetics and non-diabetics was similar apart from a higher rate of renal impairment AEs (3.3% vs 1.9%), hyperkalaemia (2.2% vs 0.6%) and glycaemic control (2.2% vs 0.2%). Diabetics on triple therapy, compared to dual therapy, had increased rates of hypotension, dizziness, syncope and hyperkalaemia.

8.8.2. Safety related to drug-drug interactions and other interactions

In study CS 8635-A-U301 the most commonly used concomitant medications during the double-blind treatment were HMG CoA reductase inhibitors (statins), propionic acid derivatives, platelet aggregation inhibitors (excluding heparin), anilides and plain multivitamins. Use of these medications with triple therapy did not appear to result in an increase in TEAE rates.

8.9. Evaluator's overall conclusions on clinical safety

The pivotal study CS8635-A-U301 provided the primary safety data in which there were 574 subjects exposed to triple therapy for a mean duration of 53.6 days. This mean exposure to triple combination included a titration period which was slightly shorter than the dual therapy periods of around 83 days. Exposure was at the highest dose of the triple therapy (40/10/25 mg). The placebo group in the pivotal study was too small (n=36) to provide data for safety comparisons. The open label cohort provided long term data in which there were 829 subjects who received OM 40/ALM 10/HTCZ 12.5 for a mean duration of 111.6 days and 468 who received OM 40/ALM 10/HTCZ 25 for mean duration of 175.0 days.

Overall, the safety risks seen were in line with what is known for the individual components and there were no new safety signals with co-administration of the three components.

The rate of TEAEs was similar between triple and dual therapy groups (58.4% vs 51.7-58.9%) and events were generally mild (31.9% vs 26.8-30.5%) or moderate (22.3% vs 20.8-26.6%) in severity. Severe TEAEs were less frequent and rates were in line with dual therapy (4.2% vs 2.9-4.0%).

There were two deaths in the safety dataset; one from "alcohol poisoning" and the other from a gunshot wound. Both subjects were on dual therapy. SAE rates were similar to dual therapy in the short term (1.6% vs 1.3-1.8%) and rates remained low in the longer term population (1.8% and 3.8% for OM 40/AML 10/HCTZ 12.5 mg and OM 40/AML 10/HCTZ 25 mg, respectively).

The SAEs which resulted in discontinuation is subjects treated with triple therapy included: hepatic malignant neoplasm, psychotic disorder, chest pain, dizziness, small intestine obstruction and coronary artery disease.

Discontinuation of treatment due to adverse events occurred in 7.7% of subjects in the pivotal study which was marginally higher than dual therapy (3.5% to 7.2%). The most frequent TEAEs leading to discontinuation were dizziness (1.0% vs 0.2-0.3%), peripheral oedema (0.9% vs 0.2% both) and hypotension (0.7% vs 0-0.3%). In the longer term, the discontinuation rate due to AEs was slighter higher with the maximal dose compared to OM 40/AML 10/HCTZ 12.5 (2.5% vs 1.3%). The rate of treatment-related TEAEs was again no greater than dual therapy (28.2% vs 20.9% - 29.7%).

The most common TEAEs in the triple compared to dual therapy groups were dizziness/vertigo (11.3% vs 3.4-10.7%), oedema (7.7% vs 1.6-9.8%), headache (6.4% vs 6.0-7.0%) and fatigue (4.2% vs 5.3-6.5%). Oedema is known to occur with amlodipine and was also notable in subjects with this as one of the therapy components. While the rate of dizziness/vertigo was similar to OM40/HCTZ 25 (11.3% vs 10.7%) it was more frequent than the other dual therapies (3.4-5.5%). The rates of hypotension (2.1% vs 0-0.7%) and syncope (1.0% vs 0-0.5%) were higher with triple than dual therapy.

There was a risk of high potassium with triple therapy, which was not higher than OM40/HCTZ (5.9% vs 7.6%), although the risk of TEAEs of hyperkalaemia was greater than with dual therapy (0.9% vs 0.3-0.5%). The rate of low potassium was similar to OM40/HCTZ (2.2% vs 2.4) and less than with AML 10/HCTZ 25 (9.8%)

The rates of increased creatinine (6.4%) and creatinine clearance ≤60 mL/min (5.4%) were not higher with triple therapy than with OM40/ HCTZ 25 mg (7.1% and 6.6%, respectively). There was however an increased risk of renal impairment TEAEs with triple therapy (2.1% vs 0.2-1.3%). The rates of glycaemic control events and gout, hyperuricaemia and increased uric acid events were no greater with the triple therapy than other groups.

ECG findings were unremarkable. There were small increases in liver function with marked elevation of ALT, AST and total bilirubin occurring in 1.3%, 2.7% and 0.2% of subjects respectively, though this was no greater than with dual therapy.

There were no new safety signals across subgroups of gender, race (Blacks), ethnicity (Hispanics), diabetes, hypertension stage and severity, BMI. In subjects aged ≥65 years the rate of SAEs was higher in those treated with triple therapy (5.1% vs 1.6-3.4%) although discontinuation rate due to TEAEs was not (4.2% vs 0.9-4.5%). The number of subjects aged ≥75 years was too small to draw conclusions in this age group. Compared to those aged <65 years, the elderly had higher risks of oedema, dizziness, renal impairment AEs and hypotension when treated with triple therapy.

Treatment withdrawal effects were not studied with the triple combination. As such effects are not associated with the component products this would not be an expected issue with the triple therapy.

Safety data from the 40 week extension of the pivotal study were not included in the dossier and need to be submitted.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of olmesartan/amlodipine/hydrochlorothiazide in the proposed usage are:

- A clinically meaningful and statistically significant antihypertensive effect together with greater BP control rates than the respective dual therapies.
- The addition of the HCTZ 25 mg component to the dual therapy contributed a BP reduction of 7.1/3.8 mmHg, amlodipine 10 mg contributed 7.4/4.9 mmHg and olmesartan 40 mg contributed 9.6/6.7 mmHg.
- The antihypertensive effect was maintained over 24 hours on ABPM, and appears to be sustained over 6 months of treatment with no evidence of tolerance, although the long term data from study CS8635-A-U301 need to be submitted to confirm this.
- Efficacy was seen in patients with mild to severe hypertension and was also seen across subgroups of age, gender, race, BMI, and diabetes.
- The treatment is a once a day dosing of a single tablet which may assist in patient compliance and improved treatment acceptance. The modes of action of the three treatments are complementary.
- An acceptable safety profile similar to the component monotherapies with no new safety signals identified.
- The MIF was bioequivalent with the combination of Benicar HCT (olmesartan/ hydrochlorothiazide) and Antacal (amlodipine) and the combination of Azor (olmesartan/ amlodipine) and hydrochlorothiazide for both the highest 40/10/25 mg and lowest 20/5/12.5 mg doses. Benicar HCT and Azor have the same formulations as the Australian products Olmetec Plus and Sevikar, respectively
- There were no drug interactions between the active components of the triple combination.

9.2. First round assessment of risks

The risks of olmesartan/amlodipine/hydrochlorothiazide in the proposed usage are:

- The BP lowering effects of the triple combination have only been studied with the maximum dose and not the 4 lower proposed doses.
- Greater risks of hypotension, dizziness/vertigo, and syncope than with dual therapy and a resultant slightly higher rate of discontinuation due to adverse events.
- Renal impairment adverse events which occurred at a higher rate than with dual therapy. The therapy should be used with caution in patients with renal impairment and is contraindicated in severe renal impairment.
- Other frequent events were oedema, headache, nausea, fatigue, hyperkalaemia and hypokaleamia. Oedema is associated with amlodipine 10 mg and was not greater than with AML 10/HCTZ 25.
- The known risks to the foetus of agents acting on the renin-angiotensin system and thiazides are known to be excreted in breast milk.
- There are currently no morbidity or mortality outcome data available for olmesartan.
- There were limited data on subjects aged 75 years and over.
- There is a lack of efficacy and safety data in patients with high cardiovascular risk as those with severe hepatic and renal impairment, heart failure, a recent history of myocardial infarction or cerebrovascular disorders were excluded from the clinical program.
- Numerous possible drug interactions.

- There are no data addressing the comparability of the monotherapies of amlodipine and hydrochlorothiazide used in the BE/BA program with those available on the Australian market.
- There are no bioequivalence data between the three single components and the MIF triple combination.
- The bioequivalence of the middle three doses (40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg) of the triple combination has not been evaluated.

9.3. First round assessment of benefit-risk balance

It has been reported that many patients with hypertension will not achieve their target BP with monotherapy and may require a combination of two or more agents. Given patients in this group may require three therapies, there is an evident clinical place for a combination tablet to increase patient acceptance and compliance. Amlodipine and hydrochlorothiazide are well known products with established safety profiles and have complementary actions with olmesartan medoxomil so the combination is a rational choice for three agents which are currently registered in Australia.

The clinical development program was conducted in line with recommendations for fixed dose combinations (CHMP 2009). The pivotal study's design and BP assessment methods (at trough and with standardised methods and conditions) were also in line with guidelines (EMA 2010). The study used diastolic BP as the primary endpoint and so it was important to see a statistically significant and clinically beneficial effect on systolic BP as the latter is the preferred primary variable (EMA 2010).

As is frequently the case with this type of clinical trial, patients with more severe co-morbidities were excluded (e.g. recent myocardial infarction, NYHA class ≥III cardiac failure, creatinine clearance <30 mL/min). In addition, there were few subjects 75 years or older. These issues need to be adequately covered in the PI. Rebound hypertension was not assessed, although it is not anticipated to be an issue as withdrawal effects are not mentioned in the respective monotherapy production information documents.

The maximal dose triple combination (OM 40/HCTZ 25 + AML 10) was found to significantly reduce msDBP and msSBP to a greater level than any of the three dual therapy combinations without compromising safety. The safety profile from the pivotal trial and the long term safety cohort was as would be expected from the monotherapies and no new safety signals were identified. The triple therapy did result in an increased risk of renal impairment AEs as well as of dizziness, hypotension and syncope. These risks have been adequately covered in the PI and CMI. Other risks such as the known foetal and neonatal risks are also clearly specified and the product is contraindicated in pregnancy and during lactation.

The pivotal study CS8635-A-U301was reported to have a 40 week open label Period III (weeks 12 to 52), however the data were not provided in the dossier. Given the first part of the study was completed in 2009, these should be available and are necessary to provide data on the persistence of efficacy and tolerance as well as very relevant long term safety data.

The current indication (*SEVIKAR HCT is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy*) is too broad and implies that the triple therapy could be used as a second line treatment for hypertension. It is acknowledged that patients with severe hypertension may require triple therapy to reach their BP goals. Nevertheless, in line with hypertension treatment guidelines (NHF 2010, NICE 2011), the evaluator recommends that therapy should be via a stepwise addition of agents and treatment with two agents used prior to the addition of a third. Therefore, triple therapy should be reserved for third line treatment. Consequently, there are two appropriate situations where a triple therapy could be used - substitution and add-on therapy. Substitution should be dose for

dose in those adequately controlled on the three individual therapies. Add-on therapy should be when an additional therapy is being considered in those whose BP is not adequately controlled on dual therapy.

The clinical development program was based on one pivotal study. This study demonstrated superiority in BP reduction of the triple therapy compared to the three possible dual therapies in patients with moderate to severe hypertension. While this study provided some evidence of efficacy as add-on therapy in patients not adequately controlled on dual therapy, this was in an exploratory subgroup analysis. Guidance documents for products in the treatment of hypertension (EMA 2010) clearly state that for development of second or third line therapy *"it is mandatory that at least one or two pivotal clinical study/-ies is/are performed in a population of patients whose blood pressure cannot be normalised with one or all of the mono-components"*. That is, in order to support an indication of add-on therapy, studies are required *"to demonstrate a statistically significant and clinically relevant additional blood pressure reduction of the combination in patients who did not respond adequately to standard therapeutic doses of one or more of the mono-components"* together with safety concerns that *"do not outweigh the additional benefit of the combination".* The pivotal study did not have this design and the dossier did not include any specific add-on therapy studies. Consequently, the evaluator cannot support an indication for add-on therapy and only recommends use for therapy substitution.

In the pivotal trial, the triple combination was achieved using Benicar HCT (olmesartan/ hydrochlorothiazide) and Antacal (amlodipine), therefore the establishment of bioequivalence to the MIF is critical. This was demonstrated for the highest (40/10/25 mg) and lowest (20/5/12.5 mg) doses. Bioequivalence was also demonstrated with another dual therapy Azor (olmesartan/ amlodipine) combined with hydrochlorothiazide for the lowest and highest dose. The products Benicar HCT and Azor are the same formulations as the products, Olmetec Plus and Sevikar, which are available in Australia. It is unknown, however, whether the amlodipine besylate and hydrochlorothiazide forms used in the bioequivalence studies are comprised of similar constituents and whether they have similar dissolution profiles as those available on the Australian market. As such, prior to any approval this issue would need to be satisfactorily addressed. Assuming this is achieved, then the bioequivalence data would allow substitution of the dual plus single component therapy at the lowest and highest dose of the triple combination. By contrast, there were no data provided, or biowavers requested, for bioequivalence of the middle three proposed strengths (40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg). As a result, the evaluator cannot support the registration of these three middle doses. Likewise, without data that demonstrate bioequivalence between the three mono-components and the MIF triple combination, the evaluator does not support direct substitution between single components and the triple combination.

Given these facts, the evaluator proposes the following indication: [**Information redacted by the TGA delegate]**

> *SEVIKAR HCT is only indicated as substitution therapy for the treatment of hypertension in adult patients whose blood pressure is already adequately controlled on the triple combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component formulation (olmesartan medoxomil/amlodipine or olmesartan medoxomil/hydrochlorothiazide) and a single component formulation (hydrochlorothiazide or amlodipine), all components at the same dose level. This fixed dose combination is not indicated for initial therapy.*

There are five strengths proposed: 20/5/12.5, 40/5/12.5, 40/5/25, 40/10/12.5 and 40/10/25. The missing combinations are the olmesartan 20 with amlodipine and hydrochlorothiazide doses of 5/25, 10/12/5, 10/25. This covers five of the possible eight strength combinations and doses not included are those with a olmesartan 20 mg base.Should further positive bioequivalence data be made available, the evaluator believes having five of the possible eight dose combinations would not affect clinical practice as it would be expected those requiring

three antihypertensive medications would be on the higher olmesartan dose. Given the known risk of peripheral oedema with the 10 mg dose of amlodipine, it is important that the combinations with the 5 mg dose have been included.

As there are five proposed strengths of the combination, in order to avoid possible confusion between the doses, the tradename should include the strengths of each component.

The triple combination does not include the 2.5 mg amlodipine dose. This dose is used in the small, frail and elderly patients, as well as those with hepatic insufficiency. The lack of this amlodipine dose has not been described in the draft PI and needs to be included.

The dosage instructions in the draft PI do not adequately explain how to move patients from dual to triple combination. In addition, the titration explanation for the triple therapy combination doses has missed titrating through two of the middle doses. This would need to be altered if an add-on indication was granted. However, as the evaluator is only recommending an indication based on replacement therapy, such changes are not necessary and dosage would need to be amended to include only information relevant to dose for dose substitution.

The draft product information has combined data from the PIs of the three component therapies and the dual combination therapies with little overall attention to the flow of the document or inclusion of repetitive information. This has a resulted in a PI which needs substantial modifications to make it relevant to the triple therapy. The suggested alterations are listed[5].

In summary, the evaluator finds there are positive clinical efficacy data together with safety risks in line with dual therapy which result in a benefit-risk balance in favour of a replacement or substitution indication in the treatment of primary hypertension. However, the bioequivalence and bioavailability testing program described in the dossier is not directly targeted to the Australian market. In particular, comparability of the monotherapy components of amlodipine and hydrochlorothiazide used in the BE/BA studies to those available in Australia has not been addressed. If this was satisfactorily addressed then the replacement indication could cover patients who are already adequately controlled on triple therapy (olmesartan, amlodipine and hydrochlorothiazide) taken as a dual component plus single component formulation at the same dose level. The lack of bioequivalence with three mono-components means this substitution cannot be covered in the replacement indication. In addition, due to the lack of bioequivalence data or request for biowaivers for the middle three proposed doses, this replacement indication should only cover the two doses of 20/5/12.5 mg and 40/10/25 mg.

In line with treatment guidelines and rational, sensible use of therapeutic products, the evaluator does not support the use of a triple therapy for second line use. In addition, due to the lack of clinical studies, the indication for add-on therapy where the patient is inadequately controlled on dual therapy is also not supported. This is in line with recent guidelines from the EMA on the clinical investigations required to support an add-on therapy indication for hypertension treatments.

Finally, the product information needs substantial changes and long term efficacy and safety data needs to be confirmed by the evaluation of the 40 week extension study of the pivotal efficacy trial (CS8635-A-U301).

10. First round recommendation regarding authorisation

The evaluator does not recommended authorisation of Sevikar HCT in the proposed indication of:

[5] The section on evaluation of product literature is not included in this extract from the Clinical Evaluation Reports.

SEVIKAR HCT is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy.

However, following satisfactory responses to the questions raised in Section 11 and compliance with requested changes to the PI/CMI[6], then substitution therapy could be recommended. The evaluator also recommends inclusion of the dosage strengths in the product name.

The recommended indication is:

SEVIKAR HCT is indicated as substitution therapy for the treatment of hypertension in adult patients whose blood pressure is already adequately controlled on the triple combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component formulation (olmesartan medoxomil/amlodipine or olmesartan medoxomil/hydrochlorothiazide) with a single component formulation (hydrochlorothiazide or amlodipine), all components at the same dose level. This fixed dose combination is not indicated for initial therapy.

11. Clinical questions

11.1. Pharmacokinetics

The sponsor is requested to provide any information regarding the similarities between the forms of amlodipine besylate and hydrochlorothiazide used in the bioequivalence/ bioavailability development program and those available on the Australian market, for example BE studies or dissolution profiles etc.

The sponsor is requested to provide a formal Justification for a Biowaiver in regards to the bioequivalence and dose proportionality of the three intermediate doses of the SEVIKAR-HCT MIF i.e. 40/5/12.5 mg OM/AML/HCT, 40/5/25 mg OM/AML/HCT and 40/10/12.5 mg OM/AML/HCT.

The sponsor is requested to please justify why studies examining the bioequivalence between the recognised reference formulations of the individual mono-components and the FDC SEVIKAR-HCT MIF have not been undertaken in accordance with EU guidelines CHMP/EWP/240/95 Rev. 1.

11.2. Pharmacodynamics

None.

11.3. Efficacy

For study CS8635-A-U301, data from the 40 week open label Period III (weeks 12 to 52) were not provided in the dossier. The first part of the study was completed in 2009 so the data should be available. As this extension study may provide relevant information on the persistence of efficacy and tolerance, the sponsor is requested to submit the full clinical study report for evaluation as part of this submission. Relevant changes to the draft PI may also need to be proposed in relation to these efficacy data. The sponsor needs to be aware of the fact that submission of this extra data may require re-negotiation of the dates of the remaining milestones under the Streamlined Submission Process, possibly via the mechanism of a mutual stop the clock.

[6] Details of these are not included in this extract from the Clinical Evaluation Reports

11.4. Safety

As stated above, the 40 week open label Period III of study CS8635-A-U301 should also provide relevant long term safety and tolerability data on the triple combination. The sponsor is requested to provide these data, unedited and unredacted and containing all relevant line listings of adverse events, for evaluation as part of this submission. Relevant changes to the draft PI may also need to be proposed in relation to these safety data. The sponsor needs to be aware of the fact that submission of this extra data may require re-negotiation of the dates of the remaining milestones under the Streamlined Submission Process, possibly via the mechanism of a mutual stop the clock.

Are there any post-marketing data with the triple combination following marketing in the US and elsewhere? If so, this safety information needs to be provided and included in a designated section in the Australian PI. In addition, are there any relevant safety data from the fixed dose combinations of olmesartan/amlodipine or olmesartan/hydrochlorothiazide which need to be included? If so, the sponsor is requested to provide these data, unedited, unredacted and containing all relevant line listings of adverse events, for evaluation as part of this submission. The sponsor needs to be aware of the fact that submission of this extra data may require re-negotiation of the dates of the remaining milestones under the Streamlined Submission Process, possibly via the mechanism of a mutual stop the clock.

11.5. PI and CMI

There are extensive comments regarding the draft PI and CMI.

[These are not included in this Extract from the Clinical Evaluation Reports].

12. Second round evaluation of clinical data submitted in response to questions

The following section provides an evaluation of responses to clinical questions raised under section 11 as well as to questions regarding the biopharmaceutical aspects of the submission, which were also evaluated in a separate TGA report.

12.1. Biopharmaceutic aspects

TGA clinical question 1:

Please justify the absence of bioavailability data for the proposed Sevikar HCT 40/5/12.5, 40/10/12.5 and 40/5/25 tablet presentations [addressing the chemistry and clinical requirements set out in section 4 of Appendix 154 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM)].

Company response:

Sevikar HCT contains 3 active ingredients (olmesartan, amlodipine and hydrochlorothiazide). These active ingredients are also contained, as individual or in combination, in Olmetec (olmesartan - AUST R 102134, 102138, 102139), Olmetec Plus (olmesartan/hydrochlorothiazide - AUST R 115732, 115737, 115738, 115661) and Sevikar (olmesartan/amlodipine - AUST R 157565, 157564, 157563, 157562). The proposed dosing recommendations for Sevikar HCT are consistent with those approved for Olmetec, Olmetec Plus and Sevikar.

Study E105 demonstrated that the high dose strength (40/10/25) and the low dose strength (20/5/12.5) of Sevikar HCT were bioequivalent to their respective reference formulations (TGA Biopharmaceutics evaluation report). In addition, this study also showed no pharmacokinetic

interaction between the active ingredients and dose proportional pharmacokinetics for olmesartan, amlodipine and hydrochlorothiazide between the low dose strength (20/5/12.5) and high dose strength Sevikar HCT (40/10/25) tablets.

From a clinical perspective, dose proportional reductions in blood pressure (BP) for olmesartan, amlodipine and hydrochlorothiazide between the low dose and the high dose strength of Sevikar HCT were also observed; i.e. the largest reduction in BP and the lowest reduction in BP were attained with the highest and lowest dose strength of Sevikar HCT, respectively. The intermediate dose combinations producing BP lowering effects was within this range.

Dissolution profiles for Sevikar HCT tablets (n=12) used in this bioequivalent study were assessed and compared to the intermediate dose combinations of Sevikar HCT tablets. According to the F2 similarity testing, all dissolution profiles at pH 1.2, pH 4.5 and pH 6.8 for the intermediate dose combinations (40/5/12.5; 40/10/12.5 and 40/5/12.5) were assessed as similar to the reference profiles of the lowest dose strength (20/5/12.5) and the high dose strength (40/10/25) of Sevikar HCT tablets utilized in the pivotal BE study (Study E105).

Therefore, the results from the bioequivalence study with the highest and lowest dose Sevikar HCT can be extrapolated to the intermediate dose combinations.

Please refer to the response to TGA clinical question 5 [below] where a Biowaiver has been presented.

Evaluator's comments:

The bioequivalence study with the highest and lowest dose Sevikar HCT can be extrapolated to the intermediate dose combinations on the proviso that the sponsor provides validation of the experimental methods for the FDC dissolution studies conducted in pH 1.2 phosphate buffer and pH 4.5 phosphate buffer (see question 5 below).

TGA clinical question 2:

Please confirm that the formulations for the Benicar HCT tablets used in the provided biopharmaceutic studies are quantitatively identical to Olmetec Plus formulations registered in Australia. If this is not the case, please provide a justification as to why data establishing bioequivalence between the Benicar HCT tablets used in the provided biostudies and Olmetec Plus or other comparable Australian supplied fixed dose combinations are not required (addressing the chemistry and clinical requirements set out in section 4 of Appendix 15 of the ARGPM).

Company response:

We can confirm that the formulation for Benicar HCT and Olmetec Plus, registered in Australia, are identical.

Evaluator's comments:

The evaluator is satisfied that the two formulations are identical and no further response is required from the sponsor.

TGA clinical question 3:

With regard to the Antacal, Azor and Hydrochlorothiazide tablets used in the provided biopharmaceutic studies, please confirm that these reference products are quantitatively identical in formulation to products registered for supply in Australia, or, if this is not the case, please provide a justification as to why data establishing bioequivalence between the reference products used in the provided biostudies and comparable Australian supplied monotherapies/fixed dose combinations are not required (addressing the chemistry and clinical requirements set out in section 4 of Appendix 15 of the ARGPM).

Company response:

- Azor

We can confirm that the formulation for Azor and Sevikar, registered in Australia, are identical.

· Antacal

Antacal (amlodipine) is a product of Heinrich Mack Nachf GmbH & Co, Germany, a subsidiary of Pfizer. The excipients contained in Antacal (Europe) and Norvasc (Australia) are identical and are presented below

[Table redacted].

Furthermore, results from Study E105 confirm that Antacal is bioequivalent to amlodipine component of Azor (which is Sevikar in Australia)

· Hydrochlorothiazide

Two hydrochlorothiazide tablets were used in the biopharmaceutical studies:

- Hydrochlorothiazide tablet of Ivax Pharmaceuticals (USA) – Study 102
- Hydrochlorothiazide tablet of 1A Pharma GmbH, Germany. The product is manufactured by Salutas Pharma GmbH, a part of Sandoz/Norvatis – Study E105

As outlined in Module 2.7.1, section 3.1.2.5 (page 38), the bioequivalence of HCTZ Clinical Formulations to HCTZ component of Benicar HCT (Olmetec Plus in Australia) was demonstrated.

In Study E105, HCTZ administered alone (1A Pharma product) and HCTZ administered as Benicar HCT (same as Olmetec Plus in Australia) were shown to be bioequivalent. This is consistent with the results from the in-vitro dissolution comparisons between Benicar HCT (Olmetec Plus in Australia) and the 1A Pharma HCTZ tablets which demonstrated superimposable dissolution curves.

In addition, *in vitro* dissolution testing of the 1APharmac HCTZ and IVAX HCTZ compared to Benicar HCT (Olmetec Plus) demonstrated that the 1A Pharma HCTZ and IVAX HCTZ tablets were equivalent to the HCTZ component of Benicar HCT (Olmetec Plus in Australia) as shown by the f2 values in the table below.

[Table redacted].

Evaluator's comments:

In regards to the Sevikar/Azor component, since the formulations are identical no further response is required from the sponsors.

In regards to the Antacal component, as the excipients of NORVASC and ANTACAL are identical, they are both products of the same parent company Pfizer and as Antacal is bioequivalent to amlodipine component of Azor no further response is required by the sponsor.

In regards to the HCTZ component, the evaluator accepts that at the highest and lowest dose the HCTZ administered alone (1A Pharma product) and HCTZ administered as Benicar HCT (same as Olmetec Plus in Australia) were bioequivalentas described in Study E105.

However, the "Guideline on the investigation of bioequivalence" (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) states that:

"Comparative *in vitro* dissolution experiments should follow current compendial standards. Hence, thorough description of experimental settings and analytical methods including validation data should be provided. It is recommended to use 12 units of the product for each experiment to enable statistical evaluation.

Complete documentation of *in vitro* dissolution experiments is required including a study protocol, batch information on test and reference batches, detailed experimental conditions,

validation of experimental methods, individual and mean results and respective summary statistics."

To this end the sponsor has provided the following information regarding the dissolution studies summarised in the preceding table:

- batch number of test and reference batches;
- stated that the method used for dissolution testing was taken from USP;
- respective summary statistics; and
- individual and mean results for 12 replicate experiments.

Whereas, the sponsor has not provided the following information:

- detailed experimental conditions; and
- validation of experimental methods.

In cases where a USP method has been followed then full validation of the methodology is not required; however, the sponsor must at least demonstrate that in their hands the method is performing as expected i.e. according to USP acceptance criteria. The sponsor has not provided this information in either PPD Project Number 7005-001 or the Summary of Biopharmaceutical studies.

Evaluator's conclusion

Prior to registration of SEVIKAR-HCT for substitution therapy the sponsor should provide information regarding the exact experimental conditions used in the HCTZ dissolution studies as well as evidence that in the sponsor's hands the method used complies with USP acceptance criteria.

12.2. Pharmacokinetics

TGA clinical question 4:

The sponsor is requested to provide any information regarding the similarities between the forms of amlodipine besylate and hydrochlorothiazide used in the bioequivalence/ bioavailability development program and those available on the Australian market, for example BE studies or dissolution profiles etc.

Company response:

Please refer to the company response to the TGA clinical question 3 above.

Evaluator's comments:

The evaluator is satisfied that the two formulations are identical and no further response is required from the sponsor.

TGA clinical question 5:

The sponsor is requested to provide a formal Justification for a Biowaiver in regards to the bioequivalence and dose proportionality of the three intermediate doses of the SEVIKAR-HCT MIF i.e. 40/5/12.5mg OM/AML/HCT, 40/5/25 mg OM/AML/HCT and 40/10/12.5 mg OM/AML/HCT.

Company response:

Merck Sharp & Dohme (Australia) Pty Limited ("MSD") proposes that the data submitted with the Category 1 application for the new fixed combination product (SEVIKAR HCT) for hypertension consisting of:

- Olmesartan medoxomil, an angiotensin II receptor antagonist

- Amlodipine besilate (a calcium channel blocker)
- Hydrochlorothiazide (a diuretic)

are sufficient to show the bioequivalence and dose proportionality over the range of strengths for Sevikar HCT.

The Guideline for Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev. 1, adopted by TGA effective 28 May 2010) states*: 6.2.2 Pharmacokinetic studies …If the application covers several strengths, then demonstration of bioequivalence study with only one strength may be acceptable. Biowaiver for an additional strength may be applicable when the conditions for this as detailed in the guideline on bioequivalence are fulfilled for all individual active substances.*

In accordance with this guidance, MSD provides the following Justification for a Biowaiver in regard to the bioequivalence and dose proportionality of the three intermediate dose strengths proposed in this application. The principles outlined in this request for a Biowaiver have also been presented to, and accepted by, the FDA in relation to the MAA that was evaluated in the USA.

Based on similar, dose proportional composition, equivalent dissolution profiles, lack of component drug-drug interaction, bioequivalence between the highest dose strengths and lowest dose strengths, taking Sevikar HCT as a fixed dose combination of OM/AML/HCTZ is bioequivalent to taking these same compounds concomitantly as separate tablets. Each of these elements is discussed in more detail below.

Dose proportional composition and dissolution profiles

All of the five dose combinations for Sevikar HCT proposed in this application contain pregelatinised starch, silicified microcrystalline cellulose, croscarmellose sodium and magnesium stearate with Opadry II as a film coating agent.

The formulations for the 40/25/10 mg strength and the 20/12.5/5 mg strength are direct scales of each other for all components except the colouring agent in the coating. For the intermediate strengths (40/5/12.5, 10/5/25, 40/10/12.5) the formulation is similar to that for the 40/10/25 strength with some minor variations in excipient quantities to accommodate for the different quantities of active ingredients. The composition for each dose combination is shown in a Table (below).

[Table redacted].

Dissolution profiles at pH 6.8, 4.5 and 1.2 were determined for the FDC market image formulation of OLM, AML and HCTZ. All five dose combinations proposed for marketing in this application were evaluated. The dissolution profiles of the five strengths were similar, and equivalency was demonstrated across all three pH's for OLM, AML and HCTZ between the five strengths. For olmesartan, dissolution was approximately 90% at pH 6.8 and pH 1.2 but was only approximately 12 to 22 % at pH 4.5.

Overall the five tablet strengths of the proposed marketing formulations were compositionally similar and exhibited equivalent dissolution profiles across all pH conditions used.

Component drug-drug interactions

Potential drug interaction between olmesartan 40 mg, amlodipine 10 mg and hydrochlorothiazide 25 mg were evaluated in two randomized, open-label, single dose, 3-way crossover studies (CS8635-A-U101 and CS8635-A-U102).

The following PK parameters were calculated: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $t_{½}$ and CL/F. Pharmacokinetic parameters were similar between the treatment arms (OLM/HCTZ with or without AML; OLM/AML with or without HCTZ) for all active ingredients. The ratio of geometric LSM and 90% corresponding CI were within 80-125% for all PK parameters in all cases. Thus

administering two or more of OM, AML and HCTZ ingredients together did not affect the PK behaviour of any of the individual active ingredients.

The results of these studies indicate that there is no drug-drug interaction between the three active ingredients based on the PK parameters evaluated.

Bioequivalence between the highest dose strength and the lowest dose strength

Bioequivalence was investigated between the highest dose strength (OM40/AML10/HCTZ25) and the lowest dose strength (OM20/AML5/HCTZ12.5) fixed combination tablet (market formulation) as compared to two reference formulations used in the clinical efficacy program (CS8635-A-E105).

Bioequivalence was demonstrated between the high dose reference formulation and the high dose market formulation and between the low dose reference formulation and the low dose market formulation. Statistical comparisons of PK parameters showed the ratios of LSM and 90% CI to be within 80-125% for all parameters when comparing both high dose formulations and both low dose formulations.

Dose proportionality was evaluated in the same study. This study evaluated the dose proportionality of Sevikar HCT in dose strength ranges of 20-40 mg OM, 5-10 mg AML and 12.5 to-25 mg HCTZ using an ANOVA model for the low (20/5/12.5 mg) and high (40/10/25 mg) dose formulations. The ratio and 90% CIs for the dose normalized PK parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max} were within 80-125% for all three active ingredients. Based on these results, the dose proportional pharmacokinetics has been demonstrated for olmesartan, amlodipine and hydrochlorothiazide between the low and high dose formulations.

By demonstrating that the proposed marketing formulations are bioequivalent for the lowest and highest dose strength combinations, and that PK parameters show dose proportionality across the entire range of proposed marketing strengths for all active ingredients, the bioequivalence of all proposed marketing formulations to the corresponding clinical formulation can be extrapolated.

Conclusion

Based on similar tablet composition, equivalent dissolution profiles, lack of drug-drug interaction of Sevikar HCT components, bioequivalence of the lowest and highest market image formulations and the dose proportional composition of the 5 market image formulations, all of the market formulations were considered to be bioequivalent to the their corresponding clinical formulations.

Evaluator's comments:

A Biowaiver is appropriate for the intermediate-dose strengths of the FDC tablets on the proviso that the Sponsor provides validation of the experimental methods used in the dissolution studies conducted on the FDC tablets in pH 1.2 phosphate buffer and pH 4.5 phosphate buffer. Note: validation has only been provided for dissolution in the pH 6.8 buffer (Module 3.2.P.5.3 Validation of analytical procedures).

TGA clinical question 6:

The sponsor is requested to please justify why studies examining the bioequivalence between the recognised reference formulations of the individual mono-components and the FDC SEVIKAR-HCT MIF have not been undertaken in accordance with EU guidelines CHMP/EWP/240/95 Rev. 1.

Company response:

The EU Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev. 1, adopted by TGA effective 28 May 2010) states:

> *6.2 Pharmacodynamic and Pharmacokinetic studies*

The possibility of interactions between the substances should always be considered. Appropriate data should be submitted either to establish that such interactions do not occur or that they are clearly recognized and defined.

6.2.2 Pharmacokinetic studies

…The need for pharmacokinetic documentation depends on the type of fixed combination, as follows…

ii) The combination contains known active substances and it is a substitution indication (i.e. use in patients adequately controlled with the individual products given concurrently, at the same dose level as in the combination, but as separate tablets) or the new fixed combination contains known active ingredients that have not been used in combination before. In these cases bioequivalence should be demonstrated between the free combination of the recognised reference formulations of the individual monocomponents and the marketing formulation (fixed combination).

…For the latter two cases (ii and iii), the applicant should in general evaluate to what extent the various substances affect each others' respective pharmacokinetic patterns (interaction) based either on previous knowledge or on experimental evidence. In some cases, a pharmacokinetic interaction (i.e. combination with a metabolism inhibitor) constitutes the rationale of the fixed combination. These interactions should normally be studied in healthy volunteers.

One of the key objectives of the Clinical Pharmacology program for the fixed dose combination of olmesartan (OM), amlodipine (AML), and hydrochlorothiazide (HCTZ) was to evaluate drug-drug interactions among the constituents of the fixed-dose combination.

There were 2 drug-drug interaction studies (CS8635-A-U101 and CS8635-A-U102).

In Study CS8635-A-U101, pharmacokinetic profiles were generated for olmesartan 40 mg, amlodipine 10 mg, and hydrochlorothiazide 25 mg when administered as Benicar HCT (OM/HCTZ) and Norvasc (AML) and when each drug was administered alone. The results indicate that PK parameters are similar when the drugs are administered concomitantly compared to when the drugs are administered alone. There is no drug-drug interaction between OM 40 mg, AML 10 mg, and HCTZ 25 mg administered as Benicar HCT (OM/HCTZ) and Norvasc (AML).

In Study CS8635-A-U102, PK profiles were generated for AML 10 mg and HCTZ 25 mg administered as SEVIKAR (OM/AML) and HCTZ 25 mg, and when each drug was administered alone. The results indicate that PK parameters are similar when the drugs are administered concomitantly compared to when the drugs are administered alone. There is no drug-drug interaction between OM 40 mg, AML 10 mg, and HCTZ 25 mg administered as SEVIKAR (OM/AML) and HCTZ.

These 2 studies confirmed that no pharmacokinetic drug-drug interactions occurred when the individual components of the FDC SEVIKAR-HCT (OM40/AML10/HCTZ25 mg) are administered concomitantly. These results were also supported by the bioequivalence of area under the curve (AUC) and maximum observed plasma drug concentration (C_{max}) established between the administration of SEVIKAR-HCT as Benicar HCT + AML or as SEVIKAR + HCTZ, compared to the administration of each of these presentations individually (Benicar HCT, AML, SEVIKAR, or HCTZ). The rate and extent of bioavailability of OM/AML/HCTZ in the fixed-dose formulations tested were also found to be bioequivalent to those in a separate tablet with 3 components (OM/AML/HCTZ) or 2 components (SEVIKAR + HCTZ or Benicar HCT + AML) under fasting conditions.

Overall, these clinical pharmacology studies address the requirements established under EU guidance CPMP/EWP/240/95. The studies indicate that taking olmesartan + amlodipine + hydrochlorothiazide as a fixed-dose combination is bioequivalent to taking these same

compounds concomitantly as separate tablets. Further, the study data demonstrates that there were no drug-drug interactions between OM, AML, and HCTZ when administered as individual tablets (OM, AML, and HCTZ), combination tablets (Benicar HCT +AML and Azor + HCTZ) or administered as the FDC SEVIKAR-HCT.

Evaluator's comments:

As the sponsor describes the EU Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev. 1) states that in cases where the FDC contains known active substances and it is a substitution indication: "bioequivalence should be demonstrated between the free combination of the recognised reference formulations of the **individual monocomponents** and the marketing formulation (fixed combination)."

In the present application the individual mono-components **have not** been studied in accordance with the guidelines. Therefore, it is recommended that SEVIKAR-HCT should only be registered as a substitution therapy in patients whose blood pressure is already adequately controlled on the triple combination of olmesartan, amlodipine and hydrochlorothiazide taken as a dual–component formulation with a single-component formulation, all components at the same dose level on the proviso that the Sponsor provides the relevant information regarding the dissolution studies described in the evaluator's responses to question 3 and question 5 above.

TGA clinical question 7:

For study CS8635-A-U301, data from the 40 week open label Period III (weeks 12 to 52) were not provided in the dossier. The first part of the study was completed in 2009 so the data should be available. As this extension study may provide relevant information on the persistence of efficacy and tolerance, the sponsor is requested to submit the full clinical study report for evaluation as part of this submission. Relevant changes to the draft PI may also need to be proposed in relation to these efficacy data. The sponsor needs to be aware of the fact that submission of this extra data may require re-negotiation of the dates of the remaining milestones under the Streamlined Submission Process, possibly via the mechanism of a mutual stop the clock.

The Sponsor included a copy of the CSR for study CS8635-A-U301. The Sponsor contended that long term efficacy and safety of the three products used in combination had previously been submitted to the TGA in relation to the Sevikar dossier and in the form of the PSURs for Olmetec. It was noted that the triple combination was introduced into the PSURs from 25 April 2010 (PSUR #17).

Study CS8635-A-U301 included Period III which was a 40 week open label treatment period (weeks 12 to 52) during which all subjects switched to OM 40 + AML 5 + HCTZ 12.5. After 2 weeks subjects not their achieving BP goal were randomly titrated to OM 40 + AML 10 + HCTZ 12.5 or OM 40 + AML 5 + HCTZ 25 and then if necessary to OM 40 + AML 10 + HCTZ 25. There were 2112 subjects who entered period III with 15% discontinuing, 6% due to an AE. The Period completion rate was 85%. There were 2098 (99.3%) in the efficacy dataset.

At week 12 the msDBP and msSBP was 82.3 mmHg and 134.8 mmHg, respectively. At the week 52 endpoint, the msDBP ranged from 77.8 to 82.5 mmHg and msSBP ranged from 125.0 to 136.8 mmHg. There was no statistically significant difference in mean change from week 14 to 16 in msDBP or msSBP between the two initial titration regimens. There were 51.3% of subjects at BP goal at week 12 and by week 52 the proportion of subjects who had reached their BP goal ranged from 44.5% to 79.8%. At week 52, the mean reduction in msDBP was -19.4 to -22.1 mmHg and msSBP was -37.2 to -39.1 mmHg.

Efficacy was maintained in subgroups of age, gender, race, ethnicity, diabetes and renal impairment. Subjects with severe or stage 2 hypertension, or BMI ≥30 kg/m^2, at baseline had higher BP at week 52 than those with less severe hypertension or BMI <30 kg/m^2.

Evaluator's comments:

This open label period of the study CS8635-A-U301 demonstrated maintenance of efficacy over 12 months when treatment was titrated to the maximal triple therapy dose. Efficacy was consistent across the subgroups.

TGA clinical question 8:

As stated above, the 40 week open label Period III of study CS8635-A-U301 should also provide relevant long term safety and tolerability data on the triple combination. The sponsor is requested to provide these data, unedited and unredacted and containing all relevant line listings of adverse events, for evaluation as part of this submission. Relevant changes to the draft PI may also need to be proposed in relation to these safety data. The sponsor needs to be aware of the fact that submission of this extra data may require re-negotiation of the dates of the remaining milestones under the Streamlined Submission Process, possibly via the mechanism of a mutual stop the clock.

The Sponsor included the CSR for Period III of CS8635-A-U301, although again stated that the Sevikar dossier submitted in 2008 included long term data on the triple combination and further data were provided in the PSURs. The Sponsor also stated that any additional safety data from study U301 would have already been included in the Sevikar PI.

The safety population for the open label Period III of CS8635-A-U301 included 2112 subjects of whom 869 subjects received OM 40 + AML 5 + HCTZ 12.5 mg, 246 received OM 40 + AML 5 + HCTZ 25 mg, 239 received OM 40 + AML 10 + HCTZ 12.5 mg and 758 subjects received OM 40 + AML 10 + HCTZ 25 mg as their final dosing regimen. During the 40 week open label period, the mean exposure to the highest dose (40/10/25) was twice that of the lower dose combinations (200.8 days vs 104-117.3 days).

During this period the AE rates was 71.7%, with the highest rate in the highest dose group (59.1%) compared to the other doses (36.4% to 46.8%). The rate of treatment-related AEs was 25.4%. The rate of mild, moderate and severe AEs was 33.9%, 30.4% and 7.4%, respectively. The rate of SAEs was 5.0% with 6 events (in 5 subjects) deemed treatment-related (2 acute renal failure, and 1 each of hyperkalaemia, presyncope, syncope and hypotension). There were 3 deaths which were not considered treatment related (pharyngeal abscess, unknown cause, artery obstruction syndrome). Discontinuations due to AEs occurred in 6.0% of subjects and 3.4% had a treatment-related AE leading to discontinuation.

The most frequent AEs were URTI (28.7%), dizziness (7.8%), nasopharyngitis (6.1%), peripheral oedema (5.7%) urinary tract infection (4.6%) and headache (4.7%). AEs of special interest are summarised in Table 9. The most frequent was dizziness and vertigo (9.2%) followed by oedema (6.3%0,glycaemic control (5.2%), headache (4.8%), hepatic related AEs (4.0%), gout, hyperuricaemia and increased uric acid (4.0%) and renal impairment AEs (3.0%).

Table 9. Number (%) of subjects with Adverse Events in Adverse Events Categories of Special Interest– Period III Safety Set

Adverse Event Category [1]	OM40/ AML5/ HCTZ12.5 (N = 2112) n (%)	OM40/ AML5/ HCTZ25 (N = 627) n (%)	OM40/ AML10/ HCTZ12.5 (N = 652) n (%)	OM40/ AML10/ HCTZ25 (N = 790) n (%)	Total (N = 2112) n (%)
Edema	45 (2.1)	12 (1.9)	27 (4.1)	55 (7.0)	133 (6.3)
Hypotension	25 (1.2)	3 (0.5)	8 (1.2)	8 (1.0)	44 (2.1)
Headache	48 (2.3)	16 (2.6)	17 (2.6)	26 (3.3)	101 (4.8)
Dizziness and vertigo	108 (5.1)	24 (3.8)	25 (3.8)	47 (5.9)	194 (9.2)
Syncope	5 (0.2)	1 (0.2)	3 (0.5)	7 (0.9)	16 (0.8)
Renal impairment AEs	30 (1.4)	12 (1.9)	8 (1.2)	14 (1.8)	63 (3.0)
Hepatic-related AEs	51 (2.4)	10 (1.6)	7 (1.1)	18 (2.3)	85 (4.0)
Hyperkalemia	17 (0.8)	4 (0.6)	2 (0.3)	3 (0.4)	26 (1.2)
Hypokalemia	26 (1.2)	3 (0.5)	1 (0.2)	19 (2.4)	48 (2.3)
Glycemic control	67 (3.2)	5 (0.8)	12 (1.8)	31 (3.9)	112 (5.3)
Injury, falls, and fractures	29 (1.4)	3 (0.5)	10 (1.5)	23 (2.9)	64 (3.0)
Gout, hyperuricemia, and increased uric acid	49 (2.3)	9 (1.4)	6 (0.9)	22 (2.8)	84 (4.0)

1. See Section 6.7.1.7.1 for the Medical Dictionary for Regulatory Activities terms included in the various adverse event categories of interest.

AE = adverse event; AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

Source: Post-text Table 15.3.1.6

The rate of marked chemistry abnormalities was generally greater with OM 40/AML10/HCTZ 25 although exposure duration may have contributed to this.

Evaluator's comments:

The rates of AEs were highest with the highest dose of triple therapy, although the exposure duration to this dose was also greater. Adverse event-related discontinuations over the 40 week period remained relatively low indicating treatment tolerance. Treatment-related SAEs were infrequent (0.2%).The AE profile was consistent with earlier data evaluated and no particular safety signals were evident.

TGA clinical question 9:

Are there any post-marketing data with the triple combination following marketing in the US and elsewhere? If so, this safety information needs to be provided and included in a designated section in the Australian PI. In addition, are there any relevant safety data from the fixed dose combinations of olmesartan/amlodipine or olmesartan/hydrochlorothiazide which need to be included? If so, the sponsor is requested to provide these data, unedited, unredacted and containing all relevant line listings of adverse events, for evaluation as part of this submission.

The Sponsor stated that the triple combination has been included in the Olmetec PSURs since the 17th report. The most recent PSUR (#21), which was submitted to the TGA in December 2012, was included in the response. The Sponsor maintained that all safety information arising from post-marketing data obtained with the triple combination olmesartan medoxomil with hydrochlorothiazide and amlodipine has already been included in the ADVERSE EVENTS section of the PI under subheadings for the individual components.

The Olmesartan medoxomil PSUR number 866-021 dated 10 December 2012 reported an estimated patient exposure to olmesartan with amlodipine and hydrochlorothiazide during this period 401,850. There were 173 medically confirmed reports with the triple therapy with an ADR report rate per 10,000 patients of 4.3. With the triple therapy there were 20 serious cases and one death reported of lactic acidosis and acute renal failure. The most frequent events were oedema peripheral, nausea, dizziness, drug ineffective, oedema and pain in extremity.

The company core datasheets for OM+AML and OM+AML+HCTZ were updated to include the interaction between amlodipine and simvastatin as follows: 'Co-administration of multiple

doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin to 20 mg daily in patients on amlodipine.'

Following findings of increased cardiovascular deaths in two studies of olmesartan in diabetic patients (ROADMAP and ORIENT), additional analyses regarding cardiovascular risks were performed. This meta-analysis and an epidemiological study were completed and the Sponsor reported that they did not show an increased cardiovascular risk with olmesartan compared to the control group nor raise any concerns regarding the safety of olmesartan compared to other ARBs or ACE inhibitors. The results were submitted to the Pharmacovigilance Risk Assessment Committee in the EU. This committee requested that the main findings from these studies [ROADMAP and ORIENT] be included in the PI of all olmesartan-containing products. In addition, the risk management plan for the triple combination was updated to include cardiovascular risk [in diabetic patients].

Evaluator's comments:

The information relating to the interaction between amlodipine and simvastatin is not currently in the draft Sevikar HCT PI and should be included. The information relating to cardiovascular risk should be considered for inclusion in the PI and RMP[7].

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of olmesartan/amlodipine/hydrochlorothiazide in the proposed usage are largely unchanged from those identified in Section 9.1 apart from the following two points:

- A maintenance of efficacy over 12 months of treatment with no additional safety signals.
- The MIF was bioequivalent with the combination of Benicar HCT (olmesartan/ hydrochlorothiazide) and Antacal (amlodipine) and the combination of Azor (olmesartan/ amlodipine) and hydrochlorothiazide for both the highest 40/10/25 mg and lowest 20/5/12.5 mg doses. In addition, based on data provided in the biowaiver, the middle three dose strengths (40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg) are also considered equivalent to the clinical formulations.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of olmesartan/amlodipine/ hydrochlorothiazide in the proposed usage are unchanged from those identified in Section 9.2 with the exception of the following points.

- As it has been confirmed that the amlodipine used in the BE/BA program is equivalent to that available on the Australian market, this risk is no longer applicable. In relation to equivalence of hydrochlorothiazide available in Australia, further information is required on the dissolution testing.[8]
- The risk regarding lack of bioequivalence of the three intermediate dose strengths is no longer valid as the data presented in the biowaiver was acceptable (subject to data on dissolution study methodology).

[7] The TGA Office of Product Review had granted a waiver from the need to submit an RMP for this application.
[8] Satisfactory data were subsequently provided to TGA.

13.3. Second round assessment of benefit-risk balance

After evaluation of the Sponsor's responses to questions, the evaluators make the following points.

The pivotal study CS8635-A-U301 had a 40 week open label Period III (weeks 12 to 52) and the data from this indicated that efficacy is maintained and no additional safety signals were evident over this period.

The Sponsor provided data which established the equivalence for amlodipine used in the clinical program with those on the Australian market. By contrast, the Sponsor has failed to provide the necessary dissolution data (experimental conditions and validation of methods) that would allow the evaluator to assume the formulations of HCTZ used in the clinical trials are equivalent to that available in Australia. Prior to registration, the Sponsor should provide information regarding the exact experimental conditions used in the HCTZ dissolution studies as well as evidence that in the Sponsor's hands the method used complies with USP acceptance criteria.[9]

As noted in the first round evaluation, bioequivalence was found for the highest and lowest dose strength but no biowaiver was requested for the three other dose strengths (40/5/12.5 mg, 40/5/25 mg and 40/10/12.5 mg). This has now been provided and included data showing similar and dose proportional tablet composition, comparable dissolution profiles, a lack of drug-drug interaction between the components of the triple therapy and dose proportional pharmacokinetics. The experimental methods used in the dissolution studies conducted on the FDC tablets were not provided. Assuming this is provided and is satisfactory, then, given the findings listed above, the evaluator believes a biowaiver is appropriate.

On the assumption that the two issues above relating to dissolution testing have been addressed, then the bioequivalence data allow substitution of the dual plus single component therapy (olmesartan/amlodipine plus HCTZ or olmesartan/HCTZ plus amlodipine) with the triple combination.

It still remains that bioequivalence between the MIF triple combination and the three mono-components has not been established and so an indication which supports direct substitution between single components and the triple combination is not supported.

The evaluator's recommendation regarding the indication remains as outlined after the first round evaluation. That is, the triple combination should only be used as third line therapy as direct substitution for patients already controlled on a dual component and single component formulation. There are insufficient clinical data to support an add-on therapy indication.

It is still recommended that as there are five proposed dose strengths of the combination, in order to avoid possible confusion between the doses, the tradename should include the strengths of each component.

The draft product information needs substantial modification[10]. The Sponsor needs to ensure that the PI only includes information that is relevant to direct dose for dose substitution from dual plus single therapy to triple therapy.

It is also recommended that the Sponsor provide information to the TGA relating to recent discussions with the European Agency on cardiovascular risk which resulted in recommendations to include further data in the product information of olmesartan-containing medicines. This should include a discussion on whether additional data should also be required in the relevant Australian product information documents.

[9] Satisfactory data were subsequently provided to the TGA.
[10] Details of comments on product literature not included in this extract from the Clinical Evaluation Report

In summary, the evaluator finds there are positive clinical efficacy data together with safety risks in line with dual therapy which result in a benefit-risk balance in favour of a replacement or substitution indication in the treatment of primary hypertension. This replacement indication must only cover patients who are already adequately controlled on triple therapy (olmesartan, amlodipine and hydrochlorothiazide) taken as a dual component plus single component formulation at the same dose level.

14. Second round recommendation regarding authorisation

The evaluator does not recommended authorisation of Sevikar HCT in the proposed indication of:

> *SEVIKAR HCT is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy.*

If the Sponsor satisfactorily addresses the questions relating to the dissolution testing for hydrochlorothiazide and the fixed dose combination, and complies with the requested changes to the PI/CMI, then an indication covering substitution therapy is recommended.

The recommended indication is:

> *SEVIKAR HCT is only indicated as substitution therapy for the treatment of hypertension in adult patients whose blood pressure is already adequately controlled on the triple combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component formulation (olmesartan medoxomil/amlodipine or olmesartan medoxomil/hydrochlorothiazide) with a single component formulation (hydrochlorothiazide or amlodipine), all components at the same dose level. This fixed dose combination is not indicated for initial therapy.*

The evaluator recommends inclusion of the dosage strengths in the product name. In addition, details of data relating to cardiovascular risks with the olmesartan-containing products that were submitted to the European Agency, and the resultant recommended changes to the product information, need to be provided for evaluation.[11]

15. Comments on clinical aspects of the RMP

The Sponsor provided new clinical information after the first round evaluation. There was no proposed change to the RMP for olmesartan. The evaluator has noted that the PSUR submitted for the second round of evaluation stated that the Risk Management Plan was updated to include cardiovascular risk. This inclusion should be verified and considered for the local RMP[12].

16. References

CHMP (2009) Guideline on clinical development of fixed combination medicinal products. CHMP/EWP/240/95 Rev 1. London.

CPMP (2001) Note for guidance on the investigation of bioavailability and bioequivalence. CPMP/EWP/QWP/1401/98. London.

EMA (2010). Guideline on clinical investigation of medicinal products in the treatment of hypertension. EMA/238/1995/Rev.3. London.

[11] Relevant information was provided to the TGA and taken into account by the Delegate.

[12] The TGA Office of Product Review had granted a waiver from the need to submit an RMP for this application.

NHF (2010). National Heart Foundation of Australia (National Blood Pressure and Vascular Disease Advisory Committee). Guide to management of hypertension 2008. Updated December 2010.

NICE (2011). Hypertension: Clinical management of primary hypertension in adults. Clinical Guideline CG127. August 2011.

17. Supplementary clinical evaluation report

Note: This supplementary clinical evaluation report was prepared after this application was considered at the June 2013 Advisory Committee on Prescription Medicines.

17.1. Background

Supplementary data to the original submission has been provided by the sponsor in response to the Delegate's proposed action to reject the submission to register the triple fixed-dose combination tablet Sevikar HCT containing olmesartan medoxomil (OM), amlodipine (AML) & hydrochlorothiazide (HCTZ) in various dosage strength combinations, for the indication *"Sevikar HCT is indicated for the treatment of hypertension.The fixed dose combination is not indicated for initial therapy".*The Delegate instead proposed to approve it for a substitution or replacement indication only.This recommendation was based on an assessment that the efficacy of the product had not been satisfactorily established for an indication which included add-on therapy.

The sponsor has submitted two pivotal randomised, double-blind Phase 3 studies evaluating the safety and efficacy of adding HCTZ to OM/AML combinations in subjects not adequately controlled on the dual-combination (CS8635-A-E303), and the additional effect of the OM/AML/HCTZ triple-combinations compared to the corresponding OM/AML dual-combination in subjects with hypertension (CS8635-A-E302).These data meet the requirements for evaluation of fixed-dose combinations as add-on antihypertensive therapy specified in the Committee for Proprietary Medicinal Products guideline CPMP/EWP/238/95 Rev 2.

17.2. Scope of the supplementary clinical dossier

The supplementary data consisted of:

- Module 5
  - Two pivotal randomised double-blind phase III efficacy/safety studies (CS-8635-A-E302 and CS-8635-A-E303).
- Module 1
  - Type II variation Final Variation Assessment Report [European Agency report]
- Module 2
  - Clinical Overview for add-on therapy indication

17.3. Good clinical practice

The sponsor has stated that the submitted studies were conducted according to Good Clinical Practice guidelines and applicable regulatory requirements.

17.4. Pharmacokinetics

Not applicable - previously evaluated in first and second round CER.

17.5. Pharmacodynamics

Not applicable - previously evaluated in first and second round CER.

17.6. Dosage selection for the pivotal studies

The doses proposed for the triple combination therapies are consistent with the respective currently available mono- and dual therapies – OM: 20 mg and 40 mg; AML: 5 mg and 10 mg, and HCTZ: 12.5 mg and 25 mg.

17.7. Clinical efficacy

17.7.1. Pivotal efficacy studies

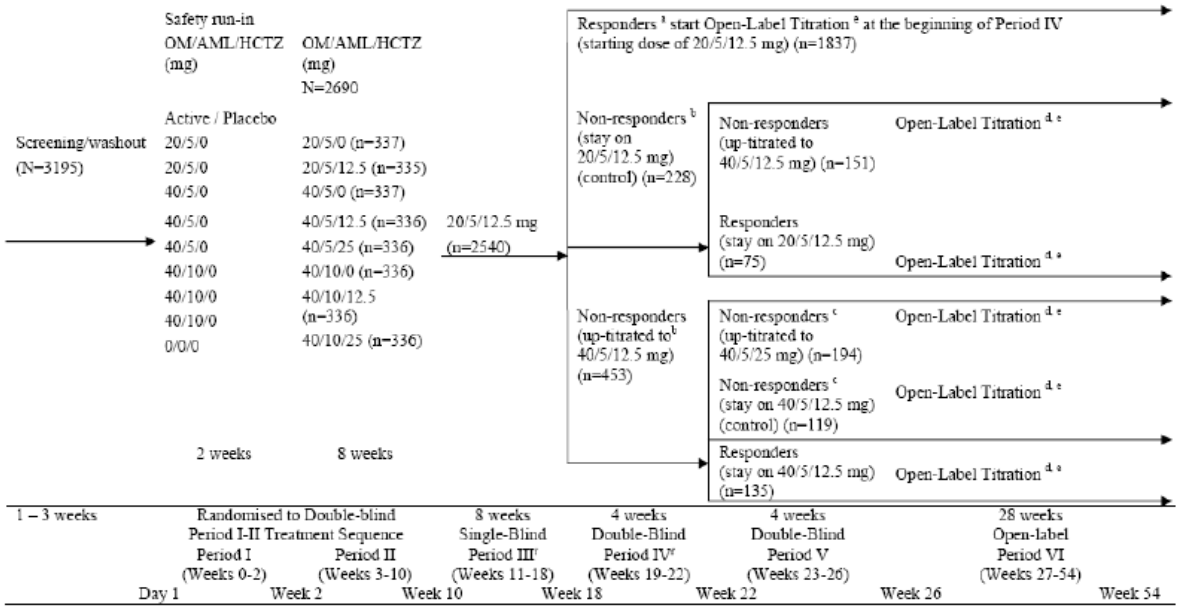
17.7.1.1. Study CS8635-A-E302

17.7.1.1.1. Study design, objectives, locations and dates

Study CS8635-A-E302 was a randomised, double-blind (DB), parallel group study evaluating the efficacy and safety of the triple-combinations of 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) compared with the corresponding OM/AML dual-combinations (20/5 mg, 40/5 mg, or 40/10 mg) in subjects with moderate to severe hypertension after 10 weeks of treatment.

The study was conducted in 161 centres in Europe, between May 2009 and July 2010, and had a duration of up to 59 weeks.This included a 3-week screening and taper-off period, a 10-week parallel-group period (comprised of a 2-week DB safety run-in [Period I], and an 8-week DB treatment period [Period 2]), an 8-week single-blind period [Period III], two 4-week DB, randomised, controlled, titration periods [Periods IV & V], a 28-week open-label treatment period [Period VI], and a 2-week safety follow-up period (Figure 2, below).The results from the open-label treatment period were included as a separate clinical study report.

Figure 2: Overall Study Design and Disposition of Study Subjects



a: Responders (subjects reaching BP goal) to Period III medication were on open-label medication (20/5/12.5 mg for the first 4 weeks with subsequent up- or down-titrations allowed). If necessitated by medical reasons, subjects could be titrated during the first 4 weeks as well.**b**: Only non-responders (subjects not reaching BP goal) to Period III medication were re-randomised in Period IV.**c**: At the end of Period IV, subjects not at their BP goal on 40/5/12.5 mg were re-randomised in Period V to either 40/5/12.5 mg (control group) or 40/5/25 mg for an additional 4 weeks.**d**: All Period III non-responders, who were still in the study at the end of Period V, started open-label medication in Period VI at a dose of 40/5/25 mg for the first 4 weeks with subsequent titrations allowed following 4 weeks of treatment in Period VI (2 weeks for subjects who could not tolerate 4 weeks of treatment in Period VI).**e**: Allowed doses during the open-label period of the study were

OM/AML/HCTZ 20/5/12.5, 40/5/12.5, 40/5/25, 40/10/12.5, and 40/10/25 mg.**f**: Subjects with uncontrolled BP (SBP ≥160 mmHg or DBP≥100 mmHg) in Periods III or IV were able to visit/call the investigator after 2 weeks of treatment during that particular period. If the investigator assessed that the subject required up-titration of his/her medication, the investigator called the Interactive Voice Response System to receive instructions as to which dose the subject should receive in the next period. The subject was then able to move directly into the next period earlier than scheduled, without completing the period they were in.AML = amlodipine; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; SBP = systolic blood pressure.

> **Evaluator's comment:** It should be noted that this study design compares the effect of dual versus triple therapy in hypertensive subjects, but does not reflect the clinical situation in which only non-responders to dual therapy would be considered for triple therapy.This study is therefore considered as supportive relative to Study CS8635-A-E303.

The primary objective of this study (Day 1 to Week 10) was to determine if the OM/AML/HCTZ triple-combination therapies are more efficacious than the corresponding OM/AML dual-combination therapies in lowering seated diastolic blood pressure (SeDBP) in subjects with hypertension.

Secondary objectives included:

- Day 1 to Week 10
  - To evaluate the antihypertensive efficacy for SeDBP and seated systolic blood pressure (SeSBP) lowering with co-administration of various doses of OM/AML/HCTZ compared to the corresponding dual-combinations of OM/AML.
  - To evaluate the number (%) of subjects reaching BP goal (defined as BP <140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease [defined as creatinine clearance ≥30 mL/min and ≤60 mL/min], or chronic cardiovascular disease).
  - To evaluate the number (%) of subjects reaching BP thresholds of <140/90 mmHg, <130/85 mmHg, <130/80 mmHg, <120/80 mmHg, SeDBP <90 mmHg, and SeSBP <140 mmHg.
  - To perform exploratory evaluations of the results of the Patient Reported Outcomes (PRO) questionnaires at baseline and Week 10.
- Week 10 to Week 54
  - To gain long-term efficacy and safety experience with administration of a sequential algorithm of triple-combination treatments of OM/AML/HCTZ while treating subjects to BP goal (<140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease).
  - To evaluate the number (%) of subjects reaching BP goal / thresholds for the triple-combination therapies.
  - To evaluate the benefit of triple-combination therapy up-titration from OM/AML/HCTZ 20/5/12.5 mg to OM/AML/HCTZ 40/5/12.5 mg (Period IV) and from OM/AML/HCTZ 40/5/12.5 mg to OM/AML/HCTZ 40/5/25 mg (Period V) under randomised, DB, controlled conditions.
  - To evaluate the benefit of triple-combination therapy up-titration from OM/AML/HCTZ 40/5/25 mg to OM/AML/HCTZ 40/10/25 mg (Period VI) under open-label conditions.
  - To perform exploratory evaluations of the results of the PRO questionnaire results at Week 26 and Week 54.

17.7.1.1.2. Inclusion and exclusion criteria

Subjects had to satisfy all of the following criteria to be included in the study:

- Male or female subjects 18 years of age or older;
- Had mean trough seated BP ≥160/100 mmHg (SeSBP ≥160 mmHg and SeDBP ≥100 mmHg) at screening for subjects not on antihypertensive medication (newly diagnosed subjects or subjects who had not taken any antihypertensive medication for at least 3 weeks) or after washout of prior antihypertensive medication for subjects who discontinued their antihypertensive medication;
- The difference in mean SeSBP/SeDBP between the visit prior to randomisation and the randomisation visit must have been ≤20/10 mmHg.Subjects who were not on antihypertensive medication must have met this requirement at the screening visit (Visit 1) and the randomisation visit (Visit 3). Subjects washing out of antihypertensive medication must have met this requirement at least by Visit 2 (or Visit 2.1, if needed) and Visit 3. All subjects undergoing washout of their prior antihypertensive medication had the opportunity to revisit the study site for additional visits during washout (Visits 2 and 2.1) to assess eligibility for randomisation;
- Signed the informed consent form after the nature of the study and the disclosure of his/her data had been explained; and
- Female subjects of childbearing potential were using adequate contraception.If a female became pregnant during the study, she had to be withdrawn from the study immediately.

The full list of exclusion criteria are presented in the dossier, with the main exclusion criteria listed below:

- Had serious disorders which may have limited the ability to evaluate the efficacy or safety of the study medications;
- History of CV event within the past 6 months;
- Clinically significant abnormal laboratory values at screening;
- Secondary hypertension of any aetiology such as renal disease, phaeochromocytoma, or Cushing's syndrome;
- Severe heart failure, vascular stenosis;
- Clinically relevant hepatic impairment, renal disease;
- Newly diagnosed subjects with a mean trough SeSBP >200 mmHg or mean trough SeDBP >115 mmHg or any subject with bradycardia (heart rate <50 bpm at rest);
- Mean trough SeSBP >145 / 160 / 180 mmHg or mean trough SeDBP >95 /100 / 110 mmHg while taking 3 / 2/ 1 antihypertensive medication(s), respectively.

17.7.1.1.3. Study treatments

To maintain the blind during Periods I to V, each subject received 3 tablets of study medication per day.The tablet type distribution for the treatment groups in each of the blinded periods is displayed in Table 10, below (also see Figure 2 above).

Table 10: Study treatments. Study CS8635-A-E302

Study Treatment	Tablets per Day
Period I	
OM/AML 20/5 mg	OM/AML 20/5 + 2 × HCTZ 0
OM/AML 40/5 mg	OM/AML 40/5 + 2 × HCTZ 0
OM/AML 40/10 mg	OM/AML 40/10 + 2 × HCTZ 0
OM/AML 0/0 mg	OM/AML 0/0 + 2 × HCTZ 0
Period II	
OM/AML 20/5 mg	OM/AML 20/5 + 2 × HCTZ 0
OM/AML/HCTZ 20/5/12.5 mg	OM/AML 20/5 + HCTZ 12.5 + HCTZ 0
OM/AML 40/5 mg	OM/AML 40/5 + 2 × HCTZ 0
OM/AML/HCTZ 40/5/12.5 mg	OM/AML 40/5 + HCTZ 12.5 + HCTZ 0
OM/AML/HCTZ 40/5/25 mg	OM/AML 40/5 + 2 × HCTZ 12.5
OM/AML 40/10 mg	OM/AML 40/10 + 2 × HCTZ 0
OM/AML/HCTZ 40/10/12.5 mg	OM/AML 40/10 + HCTZ 12.5 + HCTZ 0
OM/AML/HCTZ 40/10/25 mg	OM/AML 40/10 + 2 × HCTZ 12.5
Period III	
OM/AML/HCTZ 20/5/12.5 mg	OM/AML 20/5 + HCTZ 12.5 + HCTZ 0
Period IV	
OM/AML/HCTZ 20/5/12.5 mg	OM/AML 20/5 + HCTZ 12.5 + HCTZ 0
OM/AML/HCTZ 40/5/12.5 mg	OM/AML 40/5 + HCTZ 12.5 + HCTZ 0
Period V	
OM/AML/HCTZ 20/5/12.5 mg	OM/AML 20/5 + HCTZ 12.5 + HCTZ 0
OM/AML/HCTZ 40/5/12.5 mg	OM/AML 40/5 + HCTZ 12.5 + HCTZ 0
OM/AML/HCTZ 40/5/25 mg	OM/AML 40/5 + 2 × HCTZ 12.5

All subjects received OM/AML/HCTZ 20/5/12.5 mg in Period III.Subjects not achieving BP goal at the end of Period III or who were considered by the investigator to have uncontrolled BP (SBP ≥160 mmHg or DBP ≥100 mmHg) after 2 weeks of treatment and were moved into the next period earlier than scheduled, were randomly assigned to continue on their triple-combination treatment or to have their dose up-titrated in Period IV.Subjects who had reached BP goal at the end of Period III directly entered open-label (OL) titration (Period VI).

Subjects not achieving BP goal at the end of Period IV or who were considered by the investigator to have uncontrolled BP (SBP ≥160 mmHg or DBP ≥100 mmHg) after 2 weeks of treatment and were moved into the next period earlier than scheduled, were randomly assigned to continue on their triple-combination treatment or to have their dose up-titrated in Period V. Subjects who had reached BP goal at the end of Period IV continued on their triple-combination treatment in Period V.

Period VI was an open-label titration period.Subjects who completed Periods IV and V received OM/AML/HCTZ 40/5/25 mg for the first 4 weeks of Period VI to maintain the blind of previous periods.Subjects who entered directly from Period III received OM/AML/HCTZ 20/5/12.5 mg for the first 4 weeks of Period VI.During Period VI, doses could be up- or down-titrated at the discretion of the investigator to the following triple combinations at any time in order to achieve blood pressure goal, avoid hypotension, and maintain tolerability:

- OM/AML/HCTZ 20/5/12.5 mg,
- OM/AML/HCTZ 40/5/12.5 mg,
- OM/AML/HCTZ 40/5/25 mg,
- OM/AML/HCTZ 40/10/12.5 mg, or
- OM/AML/HCTZ 40/10/25 mg.

17.7.1.1.4. Efficacy variables and outcomes

The primary efficacy variable was the change in mean trough SeDBP from baseline to Week 10 with last observation carried forward (LOCF).

The main secondary efficacy variables relevant to the add-on indication included the following:

- Changes in mean trough SeDBP and SeSBP from baseline to Weeks 4, 6, 8, and 10;
- Number (%) of subjects achieving trough seated BP goal (<140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease [creatinine clearance ≥30 mL/min and ≤60 mL/min], or chronic cardiovascular disease) during Period II; and
- Number (%) of subjects achieving trough seated BP thresholds (ie, <140/90 mmHg, <130/85 mmHg, <130/80 mmHg and <120/80 mmHg, SeDBP <90 mmHg, and SeSBP <140 mmHg) during Period II.

Other secondary efficacy variables included the following:

- Changes in mean trough SeDBP and SeSBP from Week 10 to Weeks 14 and 18;
- Changes in mean trough SeDBP and SeSBP from immediately before the first dose to last dose of each triple-combination titration step in Periods III–V, especially for the purposes of comparing the following titration steps:
  - OM/AML/HCTZ 20/5/12.5 mg vs. OM/AML/HCTZ 40/5/12.5 mg in Period IV, and
  - OM/AML/HCTZ 40/5/12.5 mg vs. OM/AML/HCTZ 40/5/25 mg in Period V;
- Number (%) of subjects achieving trough seated BP goal during Period III, Period IV, and Period V;
- Number (%) of subjects achieving trough seated BP thresholdsduring Period III, Period IV, and Period V; and
- Changes in PRO questionnaire results from baseline to Weeks 10 and 26.

Seated BP was assessed by a Sponsor-provided model of a calibrated, validated sphygmomanometer (Greenlight 300 Sphygmomanometer, Accoson, Harlow, Essex, United Kingdom).Three assessments of SeDBP were made at each visit; the mean of these 3 evaluations was used as the SeDBP for that visit. Baseline cuff SeDBP was the mean of the randomization visit and the visit prior to randomization.

> **Evaluator's comment:** The efficacy assessments are widely used and generally recognised as reliable and valid. The method used for measuring BP appears appropriate and is in accordance with the relevant European Guideline adopted in Australia (Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension CPMP/EWP/238/95 Rev. 2).The efficacy endpoints (SeDBP, SeSBP, and proportion achieving trough seated BP goal) are also consistent with this Guideline.The main focus of this evaluation will be the efficacy results relevant to the add-on indication (Period I-II).

17.7.1.1.5. Randomisation and blinding methods

Eligible subjects were randomly assigned to a treatment sequence in Periods I–II.The distribution of subjects to treatment sequences for Periods I–II and to treatment groups in Period IV and Period V was managed by an Interactive Voice Response System (IVRS).

A total of 2,690 subjects were randomised in a 1:1:1:1:1:1:1:1 ratio to the 8 treatment groups in Period II (approximately 336 subjects per treatment arm), stratified by age group (<65 years, ≥65 years), diabetic status (yes, no), and study site.If the treatment in Period II was a triple-combination, the treatment in Period I was determined (ie, dual-combination treatment).If the assigned Period II treatment was a dual-combination, there was a second randomisation step (27:2 ratio to dual-combination or placebo) performed at the same time to determine the treatment in Period I.

Randomisation was not required in Period III as it was a single-blind period in which all subjects received the same regimen (OM/AML/HCTZ 20/5/12.5 mg).

At the start of Periods IV and V, only subjects not achieving BP goal on the regimen in the previous treatment period were re-randomised in a 2:1 ratio to the high or low dose groups, stratified by age group, diabetic status, and study site.

No person involved in conducting the study or the statistical analysis had access to the randomisation code before the blind was officially broken.

17.7.1.1.6. Analysis populations

Analysis sets for periods I–II

The Randomised Set included all subjects who were randomised to Periods I–II and had a randomisation date.

Safety Set 1 included all subjects who received at least 1 dose of DB study medication in Periods I–II.

The Primary Safety Set included all subjects who received at least 1 dose of DB study medication in Period II. The primary analysis of adverse event (AE) safety data was performed on Primary Safety Set.

The primary analysis of efficacy data was on the Full Analysis Set 1 (FAS1). The FAS1 included all randomised subjects who received at least 1 dose of DB study medication in Periods I–II and who provided at least 1 SeDBP measurement after randomisation in Periods I–II.

The Per-Protocol Analysis Set 1 (PPS1) included all subjects in the FAS1, excluding the following:

- Subjects who violated major inclusion/exclusion criteria;
- Subjects who deviated from the protocol guidelines during the study prior to the end of Period II (eg, poor compliance, prohibited medications) in a sufficiently serious manner to warrant data (but not subject) exclusion; or
- Subjects who withdrew from the study for any reason prior to the end of Period II, with the exception of withdrawal due to insufficient BP control.

Similar efficacy and safety data sets were defined for each of the other study Periods.

17.7.1.1.7. Sample size

The sample size calculation was based on the primary efficacy variable (i.e., change in mean trough SeDBP from baseline to Week 10 with LOCF).From previous studies, the standard deviation (SD) for the primary efficacy variable was assumed to be 8.5 mmHg, and the expected minimum treatment effect difference between the triple and dual-combinations after 10 weeks of treatment was ≥2.5 mmHg.By setting the 2-sided significance level at 0.05 and further assuming the resulting p-values would be compared to 0.0167 (=0.05/3) to judge for statistical significance when using Hommel's procedure, it was estimated that 2,320 randomised subjects (290 per dual or triple-combination in Period II) would be required to detect a difference of 2.5 mmHg between triple and corresponding component dual-combination with 80% power. This sample size took into account a possible 15% drop out rate during Periods I–II.

To assess the magnitude of the placebo effect and to ascertain that the reduction in BP in treatment groups was not a regression to the mean, at least 60 subjects were to be assigned randomly to placebo treatment in Period I.Sixty subjects were required to complete 2 weeks of placebo treatment in order to have 95% power to detect a placebo-subtracted active treatment effect of 4 mmHg for dual-combinations.

17.7.1.1.8. Statistical methods

Treatment comparisons for change from baseline in SeDBP were performed between triple-combination treatments and their corresponding dual-combination treatments using an Analysis of Covariance (ANCOVA) model. Baseline BP was included as a covariate and treatment, age group (≥65 years, <65 years), and diabetic status (yes, no) as fixed effects.Least-squares (LS) treatment means / differences, standard errors (SE), corresponding 95% confidence interval (CI), and p-values are presented for change from baseline and between treatment comparisons.Hommel's procedure was applied to control the Type I error rate of the treatment comparisons (Periods I-II only).The secondary efficacy analyses involving the change in BP from baseline were performed in a similar manner.

The proportion of subjects who achieved BP goal and BP thresholds were summarised for each treatment group.Treatment comparisons were performed using the Cochran-Mantel-Haenszel test stratified by age group and diabetic status at a 0.05 significance level.

The titration effects in Period IV and Period V were analysed by ANCOVA models with seated BP at the end of the previous period as a covariate and treatment, age group, and diabetic status as fixed effects.

Subgroup analyses for the change from baseline in seated BP and the proportion of subjects who achieved BP goal at Week 10 with LOCF was performed for age group, gender, hypertension severity, diabetic status, and body mass index (BMI) category. For each of these subgroup variables, two-sided p-values for testing the significance of triple-combination treatment against each dual-combination treatment were derived from an ANCOVA model that included baseline BP as a covariate and treatment as a fixed effect. The difference in LS means between triple and component dual-combinations treatments are also presented. For the proportion of subjects achieving BP goal, comparisons between triple and dual-combinations were performed using individual Fisher's Exact tests at a 0.05 significance level.

17.7.1.1.9. Participant flow

The disposition of subjects from Day 1 through Week 26 of the study is summarised in Figure 2 above and in Table 11 below.Disposition by treatment group was also shown in the dossier.Of the 3,195 subjects enrolled in the study, 2,690 (84.2%) continued into Period I / II (335-337 subjects per treatment group), and 2,540 (79.5%) entered Period III.At the end of Period III, 1,837 subjects were responders and therefore entered directly into the open-label Period VI, while the remaining 681 non-responders entered Period IV either randomised to the same dose (n=228) or to a higher dose (n=453).

Table 11: Disposition of Subjects (CS8635-A-E302)

	Screening/ Washout N (%)	Period I / II N (%)	Period III N (%)	Period IV N (%)	Period V N (%)
Entered	3195	2690	2540	681	676
Completed	2690 (84.2)	2543 (94.5)	2520 (99.2)	677 (99.4)	672 (99.4)
Discontinued	503 (15.7)	146 (5.4)	20 (0.8)	4 (0.6)	4 (0.6)
Adverse event	6 (0.2)	75 (2.8)	5 (0.2)	2 (0.3)	0 (0.0)
Withdrawal by subject	68 (2.1)	46 (1.7)	10 (0.4)	1 (0.1)	2 (0.3)
Did not satisfy all incl/excl criteria	402 (12.6)	-	-	-	-

	Screening/ Washout N (%)	Period I / II N (%)	Period III N (%)	Period IV N (%)	Period V N (%)
Protocol violation	7 (0.2)	21 (0.8)	3 (0.1)	1 (0.1)	1 (0.1)
Lost to follow-up	5 (0.2)	1 (0.0)	2 (0.1)	0 (0.0)	1 (0.1)
Other	15 (0.5)	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Did not continue to next period	0 (0.0)	3 (0.1)	2 (0.1)	1 (0.1)	0 (0.0)
Other	2[a]	1[b]	1837[c] (72.3)	-	2[d]

a Discontinuation information prior to randomisation for subjects (**[Information redacted]**)and (**[Information redacted]**)was not recorded on the CRF. The source documentation was then lost for the three subjects hence the CRF data was left as is and the site was subsequently closed due to quality issues. **b** 1 subject had a randomisation date recorded on the eCRF, but was not formally randomised via the IVRS system. Therefore, the subject is represented in the randomised category but is not represented in either of the completed or discontinued categories. **c** 1837 subjects were responders and therefore entered into open-label Period VI. **d** Includes 2 subjects who received OM40/AML5/HCTZ12.5 in Period IV, were BP goal responders, but were incorrectly given OM20/AML5/HCTZ12.5 and OM40/AML5/HCTZ25, respectively

During the screening / washout period, 503 (15.7%) subjects discontinued prior to randomisation, primarily because of failure to satisfy all inclusion/exclusion criteria (402 [12.6 %] subjects).The next highest percentage of discontinuations occurred during Period I / II, when 146 (5.4%) subjects discontinued, primarily because of an AE (75 [2.8%] subjects).Discontinuations were <1% in Periods III to V.

With the exception of discontinuations due to AEs (which were higher in the treatment groups receiving AML 10 mg [particularly OM/AML 40/10 mg]), discontinuations were generally evenly distributed among the Period II treatment groups.

17.7.1.1.10. Major protocol violations/deviations

Subjects (**[Information redacted]**) (not formally randomised), (**[Information redacted]**), and (**[Information redacted]**) (discontinuation information not recorded on the eCRF) were recruited at a site that was "subsequently closed due to quality issues".In addition, serious GCP violations were observed during monitoring activities and confirmed via an audit for site 2109, resulting in two subjects ((**[Information redacted]**) and (**[Information redacted]**)) being excluded from the PPS1 analysis set.

> **Evaluator's comment:** It is not clear whether other subjects were recruited from these sites, and if so, how these subjects were handled during the analyses.The sponsor will be asked to clarify this.

17.7.1.1.11. Baseline data

Baseline demographic and other baseline characteristics for the Randomised Set by Period II randomised treatment are summarised.Of the 2,690 subjects in the Randomised Set, 1,247 (46.4%) were male, the majority (99.9%) were Caucasian, the mean age was 56.5 years, and 3.7% were aged ≥ 75 years.This was comparable across all the treatment groups.The mean duration of hypertension (8.4 years), proportion of subjects with diabetes (14.6%), chronic renal disease (2.0%), or chronic cardiovascular disease (28.5%) were also generally similar across the treatment groups.Baseline mean SeDBP and SeSBP ranged from 103.5 to 104.0 mmHg and 167.7 to 168.7 mmHg, respectively.

Evaluator's comment: The baseline characteristics of the study subjects represent a relatively young population compared with what might be expected in clinical practice given that the prevalence of hypertension is known to increase with age[13].In addition, patients with diabetes and chronic renal disease were relatively under-represented.

17.7.1.1.12. Results for the primary efficacy outcome

There was a statistically significant mean reduction in SeDBP from baseline to Week 10 for each treatment group (p<0.0001 for all treatment groups) (Table 12, below).The LS mean reduction in SeDBP ranged from -20.5 mmHg to -22.1 mmHg among the component dual-combination therapy groups and from -22.5 mmHg to -23.9 mmHg among the triple-combination therapy groups.

The mean reduction in SeDBP was greater with each triple-combination therapy compared to the corresponding dual component OM/AML therapy.While the LS mean treatment difference was relatively small (range: -1.3 mmHg to -1.9 mmHg), the difference was statistically significant for all comparisons:

- OM/AML/HCTZ 20/5/12.5 mg vs. OM/AML 20/5 mg (LS mean treatment difference of -1.9 mmHg; p=0.0071);
- OM/AML/HCTZ 40/5/12.5 mg vs. OM/AML 40/5 mg (LS mean treatment difference of -1.3 mmHg; p=0.0323);
- OM/AML/HCTZ 40/5/25 mg vs. OM/AML 40/5 mg (LS mean treatment difference of -1.8 mmHg; p=0.0080);
- OM/AML/HCTZ 40/10/12.5 mg vs. OM/AML 40/10 mg (LS mean treatment difference of -1.9 mmHg; p=0.0071); and
- OM/AML/HCTZ 40/10/25 mg vs. OM/AML 40/10 mg (LS mean treatment difference of -1.7 mmHg; p=0.0107).

Table 12: Change in SeDBP (mmHg) From Baseline to Week 10 with LOCF – Periods I–II –Full Analysis Set 1 (CS8635-A-E302)

	OM20/ AML5 (N = 337)	OM20/ AML5/ HCTZ12.5 (N = 334)	OM40/ AML5 (N = 334)	OM40/ AML5/ HCTZ12.5 (N = 336)	OM40/ AML5/ HCTZ25 (N = 335)	OM40/ AML10 (N = 335)	OM40/ AML10/ HCTZ12.5 (N = 336)	OM40/ AML10/ HCTZ25 (N = 332)
n [1]	337	334	334	336	335	335	336	332
Baseline mean (SD) [2]	104.0 (2.77)	103.5 (2.76)	103.8 (2.93)	103.9 (2.77)	103.7 (2.90)	103.6 (2.96)	103.9 (3.15)	103.8 (3.23)
Week 10 LOCF mean (SD) [3]	84.1 (8.06)	81.9 (8.04)	83.4 (8.38)	82.1 (7.88)	81.5 (8.30)	82.4 (8.19)	80.7 (8.78)	80.8 (8.68)
Mean change (SD)	-19.9 (8.01)	-21.6 (7.88)	-20.5 (7.94)	-21.8 (7.99)	-22.2 (8.14)	-21.2 (8.14)	-23.3 (8.72)	-23.0 (8.57)
LS mean change (SE)	-20.5 (0.47)	-22.5 (0.48)	-21.2 (0.48)	-22.5 (0.48)	-23.0 (0.48)	-22.1 (0.48)	-23.9 (0.47)	-23.8 (0.48)
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Between treatment comparisons								
LS mean (SE)		-1.9 (0.62)		-1.3 (0.62)	-1.8 (0.62)		-1.9 (0.62)	-1.7 (0.62)
95% CI		(-3.2, -0.7)		(-2.5, -0.1)	(-3.0, -0.6)		(-3.1, -0.7)	(-3.0, -0.5)
p-value		0.0019		0.0323	0.0039		0.0024	0.0053
Adjusted p-value [4]		0.0071		0.0323	0.0080		0.0071	0.0107

LS mean, SE, 95% CI, and 2-sided p-values were obtained from an ANCOVA model with baseline BP as a covariate and treatment, age group, and diabetic status as fixed effects.**1**. n is the number of subjects with values at both time points.**2**. Baseline for BP was defined as the average of the visit values from the randomisation visit and the visit prior to the randomisation visit.**3**. Week 10 with LOCF was defined as the last available measurement during Periods I–II.**4.** Adjusted p-values were obtained from Hommel's procedure to control the overall Type 1 error at 0.05 level.

Evaluator's comment:While statistically significant reductions in the mean trough SeDBP were reported, the clinical significance could be considered marginal.In determining the sample size, the sponsor designated an expected minimum treatment

[13] Barr ELM *et al*. The Australian Diabetes, Obesity & Lifestyle Study. AusDiab Report 2005

effect difference between the triple and dual-combinations after 10 weeks of treatment of ≥2.5 mmHg.This difference was not reached for any of the treatment comparisons.However, data from overviews of observational studies and randomized trials suggest that a 2 mmHg reduction in DBP would result in a 6% reduction in the risk of CHD and a 15% reduction in risk of stroke and TIAs[14], which is clinically relevant.

17.7.1.1.13. Results for other efficacy outcomes

· Change in SeDBP and SeSBP from Baseline to Week 2 with LOCF – FAS1

To confirm the antihypertensive efficacy of the dual-combination therapies, a placebo control group was included from baseline to Week 2.Each treatment group had a statistically significant mean reduction in SeDBP and SeSBP (p<0.0001 for all treatment groups).

The LS mean reduction in SeDBP was -10.2 mmHg for the placebo group and ranged from -15.2 mmHg to -16.8 mmHg among the dual-combination treatment groups.The reduction in SeDBP was significantly greater with each dual-combination therapy (-5.0 mmHg, -5.0 mmHg, and -6.6 mmHg for OM/AML 20/5 mg, OM/AML 40/5 mg, and OM/AML 40/10 mg, respectively) compared to treatment with placebo (p<0.0001 for each treatment comparison).

For SeSBP, the LS mean reduction in was -15.8 mmHg for the placebo group and ranged from -24.7 mmHg to -27.5 mmHg in the dual-combination treatment groups.The reduction in SeSBP was significantly greater with each dual-combination therapy (-8.9 mmHg, -9.3 mmHg, and -11.7mmHg for OM/AML 20/5 mg, OM/AML 40/5 mg, and OM/AML 40/10 mg, respectively) compared to treatment with placebo (p<0.0001 for each treatment comparison).

· Change in SeSBP During Periods I–II

The mean change in SeSBP from baseline to Week 10 with LOCF for the FAS1 is shown in Table 13, below.Each treatment group had a statistically significant mean reduction in SeSBP from baseline to Week 10 (p<0.0001 for all treatment groups). The LS mean reduction in SeSBP ranged from -33.2 mmHg to -36.2 mmHg among the triple-combination therapy groups and from -29.9 mmHg to -32.8 mmHg among the component dual-combination therapy groups.

Triple-combination OM/AML/HCTZ therapies resulted in significantly greater mean reductions in SeSBP compared to the component OM/AML therapies:

– OM/AML/HCTZ 20/5/12.5 mg vs. OM/AML 20/5 mg (LS mean treatment difference of -3.4 mmHg; p=0.0006);

– OM/AML/HCTZ 40/5/12.5 mg vs. OM/AML 40/5 mg (LS mean treatment difference of -3.3 mmHg; p=0.0008);

– OM/AML/HCTZ 40/5/25 mg vs. OM/AML 40/5 mg (LS mean treatment difference of -4.9 mmHg; p<0.0001);

– OM/AML/HCTZ 40/10/12.5 mg vs. OM/AML 40/10 mg (LS mean treatment difference of -2.7 mmHg; p=0.0034); and

– OM/AML/HCTZ 40/10/25 mg vs. OM/AML 40/10 mg (LS mean treatment difference of -3.4 mmHg; p=0.0006).

[14] Cook N, Cohen J, Herbert P, *et al* (1995). Implications of Small Reductions in Diastolic Blood Pressure for Primary Prevention. Archives of Internal Medicine; 155: 701-709.

Table 13: LS Mean Differences in Change in SeBP (mmHg) and % of Subjects Reaching BP Goal Between Each Triple and Corresponding Dual Combination From Baseline to Week 10 With LOCF – Periods I-II – FAS 1 (CS8635-A-E302)

		OM20/ AML5/ HCTZ12.5 (N = 334)	OM40/ AML5/ HCTZ12.5 (N = 336)	OM40/ AML5/ HCTZ25 (N = 335)	OM40/ AML10/ HCTZ12.5 (N = 336)	OM40/ AML10/ HCTZ25 (N = 332)
SeDBP (primary endpoint)						
vs. OM20/AML5 (N = 337)	LS mean (SE)	-1.9 (0.62)				
	Adjusted p-value [1]	0.0071				
vs. OM40/AML5 (N = 334)	LS mean (SE)		-1.3 (0.62)	-1.8 (0.62)		
	Adjusted p-value [1]		0.0323	0.0080		
vs. OM40/AML10 (N = 335)	LS mean (SE)				-1.9 (0.62)	-1.7 (0.62)
	Adjusted p-value [1]				0.0071	0.0107
SeSBP (secondary endpoint)						
vs. OM20/AML5 (N = 337)	LS mean (SE)	-3.4 (0.93)				
	Adjusted p-value [1]	0.0006				
vs. OM40/AML5 (N = 334)	LS mean (SE)		-3.3 (0.93)	-4.9 (0.93)		
	Adjusted p-value [1]		0.0008	<0.0001		
vs. OM40/AML10 (N = 335)	LS mean (SE)				-2.7 (0.93)	-3.4 (0.93)
	Adjusted p-value [1]				0.0034	0.0006
Subjects Reaching Blood Pressure Goal						
vs. OM20/AML5 (N = 337)	n (%)	177 (53.0%) vs. 144 (42.7%)				
	Adjusted p-value [1]	0.0295				
vs. OM40/AML5 (N = 334)	n (%)		176 (52.4%) vs. 155 (46.4%)	197 (58.8%) vs. 155 (46.4%)		
	Adjusted p-value [1]		0.2529	0.0037		
vs. OM40/AML10 (N = 335)	n (%)				190 (56.5%) vs. 166 (49.6%)	179 (53.9%) vs. 166 (49.6%)
	Adjusted p-value [1]				0.2033	0.2529

- Proportion of Subjects Reaching BP Goal During Periods I–II

  The percentage of subjects achieving BP treatment goal at Week 10 for the FAS1 ranged from 52.4% to 58.8% for the triple-combination treatment groups compared to 42.7% to 49.6% for the component dual-combination treatment groups (Table 13, above).

  While treatment with all OM/AML/HCTZ triple-combination therapies resulted in numerically greater percentages of subjects reaching their treatment goal compared to the corresponding component dual-combination therapies, the overall results were only statistically significant for OM/AML/HCTZ 20/5/12.5 mg and OM/AML/HCTZ 40/5/25 mg:

  – OM/AML/HCTZ 20/5/12.5 mg vs. OM/AML 20/5 mg (53.0% vs. 42.7%; p=0.0295);
  – OM/AML/HCTZ 40/5/25 mg vs. OM/AML 40/5 mg (58.8% vs. 46.4%; p=0.0037);
  – OM/AML/HCTZ 40/5/12.5 mg vs. OM/AML 40/5 mg (52.4% vs. 46.4%; p=0.2529);
  – OM/AML/HCTZ 40/10/12.5 mg vs. OM/AML 40/10 mg (56.5% vs. 49.6%; p=0.2033); and
  – OM/AML/HCTZ 40/10/25 mg vs. OM/AML 40/10 mg (53.9% vs. 49.6%; p=0.2529).

- Proportion of Subjects Reaching BP Thresholds During Periods I–II

  Treatment with the triple-combination therapies resulted in higher percentages of subjects reaching all diastolic and systolic BP thresholds at Week 10 compared to the component dual-combination therapies.

The efficacy results for Periods III to VI relate to up-titration of OM (Period IV) or HCTZ (Period V) in subjects already receiving triple combination therapy and are therefore not directly relevant to the add-on indication.These results overall demonstrated that increasing either the OM dose (from 20 to 40 mg) or HCTZ dose (from 12.5 to 25 mg) in non-responders to the lower dose resulted in a numerically greater mean reduction in SeDBP and SeSBP compared with the lower dose regimen.

17.7.1.1.14. Subgroup analyses

Subgroup analyses are presented for age group, gender, hypertension severity, diabetic status, and BMI category for data from Periods I–II only.

> **Evaluator's comment**:While the sponsor reported the statistical significance of the comparison of triple-therapy vs. dual therapy in the subgroup analyses, the evaluator has not reported this as it does not appear that Hommel's (or any other) procedure was applied to control the Type I error rate of treatment comparisons in the subgroup analyses.

Age: mean reductions in SeDBP were numerically higher and SeSBP numerically lower (but similar) in the group of subjects ≥65 years of age compared with subjects <65 years of age irrespective of treatment group (Table 14, below).The pattern was less clear for subjects aged ≥75 years, but the small numbers (n ≤ 18 for each treatment group) limited meaningful interpretation of this group.The numerical benefits of triple therapy over dual therapy for both SeDBP to and SeSBP were comparable to that seen in the overall population (bearing in mind the small number of subjects in some age and treatment groups).The percentage of subjects reaching BP goal was generally lower in those aged ≥65 years than in those aged <65 years, but the numerical benefit of triple- over dual-therapy remained.

Table 14: Mean Changes in SeDBP and SeSBP (mmHg) From Baseline to Week 10 With LOCF – Age Subgroups (CS8635-A-E302)

	SeDBP				SeSBP			
	<65 Years		≥65 Years		<65 Years		≥65 Years	
Treatment	N[1]	Change Mean (SD)	N[1]	Change Mean (SD)	N[1]	Change Mean (SD)	N[1]	Change Mean (SD)
OM20/AML5	263	-19.5 (7.88)	74	-21.1 (8.37)	263	-32.3 (12.61)	74	-27.6 (12.15)
OM20/AML5/HCTZ12.5	262	-21.0 (7.56)	72	-23.5 (8.74)	262	-34.6 (11.42)	72	-33.5 (13.89)
OM40/AML5	261	-20.2 (7.80)	73	-21.3 (8.45)	261	-32.8 (11.23)	73	-28.3 (12.21)
OM40/AML5/HCTZ12.5	262	-21.3 (7.99)	74	-23.7 (7.77)	262	-35.5 (11.78)	74	-34.3 (12.89)
OM40/AML5/HCTZ25	262	-21.6 (7.88)	73	-24.3 (8.75)	262	-37.1 (12.60)	73	-34.6 (13.43)
OM40/AML10	261	-20.5 (7.89)	74	-23.6 (8.61)	261	-34.6 (12.52)	74	-33.0 (12.04)
OM40/AML10/HCTZ12.5	261	-22.9 (8.49)	75	-24.5 (9.45)	261	-37.7 (11.97)	75	-34.4 (17.61)
OM40/AML10/HCTZ25	261	-22.5 (8.45)	71	-25.1 (8.73)	261	-37.1 (12.50)	71	-39.1 (13.10)

Gender: female subjects appeared to have numerically higher (but similar) LS mean reductions in SeDBP and SeSBP compared to male subjects (SeDBP range -20.6 to -23.8 vs. -18.8 to -22.7 mmHg; SeSBP range -32.3 to -37.9 vs. -29.6 to -37.0 mmHg) across all treatment groups.Triple combination therapy resulted in greater reductions in SeDBP and SeSBP than the corresponding dual combination therapy.The percentage of subjects reaching BP goal and the numerical benefit of triple over dual therapy was comparable in males and females, and similar to the overall results.

Hypertension severity (mild or moderate - SeSBP from 140 mmHg to <180 mmHg and SeDBP from 90 mmHg to <110 mmHg at baseline; severe - SeSBP ≥180 mmHg or SeDBP ≥110 mmHg at baseline): LS mean reductions in SeDBP were similar in subjects with mild or moderate (SeDBP range -19.5 to -23.1 mmHg) and severe hypertension (SeDBP range -19.0 to -24.3 mmHg) across all treatment groups.LS mean reductions in SeSBP were lower in subjects with mild or moderate hypertension (SeSBP range -30.4 to -36.5 mmHg) compared with subjects with severe hypertension (SeSBP range -35.5 to -46.2 mmHg) across all treatment groups.Triple

combination therapy generally resulted in greater reductions in SeDBP and SeSBP than the corresponding dual combination therapy.The small number of subjects with severe hypertension (n ≤ 40 for each treatment group), make the results difficult to interpret in this subgroup.The percentage of subjects reaching BP goal was lower in those subjects with severe hypertension compared with those with mild or moderate hypertension, but a numerical benefit of triple over dual therapy remained irrespective of hypertension severity.

Diabetic status: LS mean reductions in SeDBP and SeSBP were similar in subjects with (SeDBP range -19.8 to -24.7 mmHg; SeSBP range -29.6 to -36.5 mmHg) and without diabetes (SeDBP range -19.5 to -23.0 mmHg; SeSBP range -31.2 to -37.7 mmHg) across all treatment groups.Triple combination therapy generally resulted in greater reductions in SeDBP and SeSBP than the corresponding dual combination therapy.The small number of subjects with diabetes (n ≤ 51 for each treatment group), limit meaningful interpretation in this subgroup.Bearing in mind that the BP goal was more stringent in subjects with diabetes (<130/80 vs. <140/90 mmHg), the percentage of subjects reaching BP goal was lower in those subjects with diabetes compared with those without diabetes.There was a numerical benefit of triple over dual therapy for all treatment comparisons in subjects without diabetes, but in subjects with diabetes a benefit was seen only for OM/AML/HCTZ 20/5/12.5 mg, OM/AML/HCTZ 40/10/12.5 mg, and OM/AML/HCTZ 40/10/25 mg.

BMI: subjects with BMI <30 kg/m^2 appeared to have numerically higher (but similar) LS mean reductions in SeDBP and SeSBP compared to subjects with BMI ≥30 kg/m2 (-20.3 to -24.5 vs. -19.3 to -21.9 mmHg SeDBP; -31.4 to -40.6 vs. -30.4 to -35.3 mmHg SeSBP) across all treatment groups.Triple combination therapy resulted in greater reductions in SeDBP and SeSBP than the corresponding dual combination therapy in both BMI categories.The percentage of subjects reaching BP goal was lower in those subjects with BMI ≥30 kg/m^2 compared with those with BMI <30 kg/m^2, but a numerical benefit of triple over dual therapy remained irrespective of BMI category.

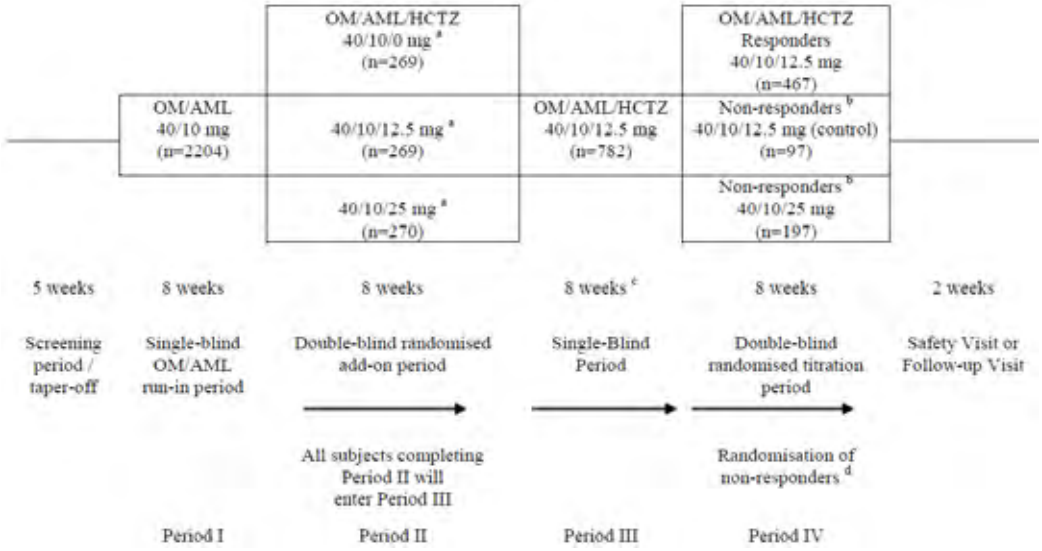
17.7.1.2. Study CS8635-A-E303

17.7.1.2.1. Study design, objectives, locations and dates

Study CS8635-A-E303 was a Phase III, randomised, DB, parallel-group study evaluating the efficacy and safety of add-on HCTZ (12.5 mg or 25 mg) in subjects with moderate to severe hypertension not achieving target BP on fixed dose combination OM/AML 40/10 mg alone.It was conducted in 187 centres in Europe, between April 2009 and September 2010.

The study had a duration of up to 39 weeks, and included a 5-week screening and taper-off period, an 8-week, single-blind, run-in period (Period I), an 8-week, randomised, DB, add-on period (Period II), an 8-week, single-blind period (Period III), and an 8-week, DB, randomised titration period (Period IV) (Figure 3, below).

Figure 3: Overall Study Design and Disposition of Study Subjects (CS8635-A-E303)



a: Responders were defined as subjects achieving seated blood pressure goal (defined as seated blood pressure <140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease [defined as creatinine clearance ≥30 mL/min and ≤60 mL/min], or chronic cardiovascular disease). Only subjects who met the requirements for SeSBP and SeDBP were randomised in Period II. **b**: Subjects not achieving seated blood pressure goal (non-responders) were randomised in Period IV. **c**: Subjects with mean trough SeSBP ≥160 mmHg or mean trough SeDBP ≥100 mmHg could have been randomised to Period IV after at least 2 weeks of Period III by proceeding directly to Visit 8; subjects with SeSBP ≥200 mmHg, SeDBP ≥115 mmHg, 24-hour DBP >104 mmHg (assessed by 24-hour ABPM) or bradycardia (heart rate <50 bpm) at any time during the study were immediately withdrawn from the study. **d**: Subjects not achieving seated blood pressure goal (non-responders) at the end of Period III were randomised in a 1:2 ratio to receive OM/AML/HCTZ 40/10/12.5 mg or OM/AML/HCTZ 40/10/25 mg in Period IV.

The primary objective of this study (Period II) was to determine whether the addition of HCTZ 12.5 mg or HCTZ 25 mg to OM/AML 40/10 mg provides additional antihypertensive efficacy (SeDBP) in subjects with moderate to severe hypertension not adequately controlled on OM/AML alone.

Secondary objectives included:

- Week 8 to Week 16 (Period II)
  - To evaluate the antihypertensive efficacy for SeDBP and SeSBP of the triple-combinations of OM/AML/HCTZ 40/10/12.5 mg and OM/AML/HCTZ 40/10/25 mg compared to OM/AML 40/10 mg using conventional BP measurement.
  - To evaluate the antihypertensive efficacy from baseline (Week 8) to Week 16 in daytime, night-time, and 24-hour DBP and SBP assessed by 24-hour ambulatory blood pressure monitoring (ABPM).
  - To evaluate the number (%) of subjects achieving BP goal (defined as seated blood pressure <140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease [defined as creatinine clearance ≥30 mL/min and ≤60 mL/min], or chronic cardiovascular disease), and BP thresholds of <140/90 mmHg, <130/85 mmHg, <130/80 mmHg, and <120/80 mmHg, SeDBP <90 mmHg, and SeSBP <140 mmHg at Weeks 12 and 16.
  - To evaluate the safety and tolerability of OM/AML/HCTZ triple-combination therapy during Weeks 8 to 16.
- Week 16 to Week 32 (Period III / IV)

- To evaluate the antihypertensive efficacy of up-titration to OM/AML/HCTZ 40/10/25 mg in subjects not achieving BP goal on OM/AML/HCTZ 40/10/12.5 mg based on changes from Week 24 to Week 32 in conventional BP measurement and in daytime, night-time, and 24-hour DBP and SBP assessed by 24-hour ABPM.
- To evaluate the number (%) of subjects achieving BP goal and BP thresholds at Week 32.
- To evaluate the safety and tolerability of triple-combination OM/AML/HCTZ therapy during Weeks 16 to 32.

17.7.1.2.2. Inclusion and exclusion criteria

Subjects had to satisfy all of the following criteria to be included in the study:

- Male or female subjects 18 years of age or older;
- Mean trough seated BP ≥160/100 mmHg (SeSBP ≥160 mmHg and SeDBP ≥100 mmHg) at screening for subjects not on antihypertensive medication (newly diagnosed subjects) *and a mean 24-hour DBP of at least 85 mmHg with at least 30% of daytime DBP readings over 90 mmHg*;

  OR

- Mean trough seated BP of ≥150/95 mmHg (SeSBP of ≥150 mmHg and SeDBP of ≥95 mmHg) at screening *and a mean 24-hour DBP of at least 80 mmHg and with at least 30% of daytime DBP readings over 85 mmHg* for subjects on monotherapy;

  OR

- Mean trough seated BP of ≥140/90 mmHg (SeSBP of ≥140 mmHg and SeDBP ≥90 mmHg) at screening *and a mean 24-hour DBP of at least 80 mmHg with at least 30% of daytime DBP readings over 85 mmHg* for subjects on any combination of antihypertensive medications that included either HCTZ, OM, or AML for a duration of at least 4 weeks;

  OR

- Mean trough SeSBP ≥160 mmHg and mean trough SeDBP ≥100 mmHg, at the end of the taper-off period *and a mean 24-hour DBP of at least 85 mmHg with at least 30% of daytime DBP readings over 90 mmHg* for subjects on any other combination of antihypertensive medications that included neither HCTZ, OM, nor AML;
- Freely signed the informed consent form after the nature of the study and the disclosure of his/her data had been explained; and
- Female subjects of childbearing potential were using adequate contraception.If a female became pregnant during the study, she had to be withdrawn from the study immediately.

  Evaluator's comment:The ABPM inclusion criteria (italicised text above) were removed in Protocol Amendment 02 (issued 9 October 2009) to allow the enrolment of subjects who met all other inclusion/exclusion criteria.This was to facilitate subjects entering Period II after it was found that 1,039 subjects enrolled in Period I failed these criteria (see Section on participant flow).The European Agency assessor was concerned that this may have increased the recruitment of subjects with 'white coat' hypertension and the sponsor was asked to address whether subjects still met the inclusion criteria with respect to conventional SeDBP and SeSBP (Module 1 European Agency report).The Sponsor's response indicated that all but one subject at screening had a BP ≥140/90 mmHg, with the majority having a BP ≥160/100 mmHg.This resolved the issue to the European Agency assessor's satisfaction (Module 1 European Agency report).This explanation is acceptable.

The full list of exclusion criteria are presented, with the main exclusion criteria listed below:

- Serious disorders which may have limited the ability to evaluate the efficacy or safety of the study medications;
- History of CV event within the past 6 months;
- Clinically significant abnormal laboratory values at screening;
- Secondary hypertension of any aetiology such as renal disease, phaeochromocytoma, or Cushing's syndrome;
- Severe heart failure, vascular stenosis;
- Clinically relevant hepatic impairment, renal disease;
- Mean SeSBP >200 mmHg or mean SeDBP >115 mmHg or bradycardia (heart rate <50 bpm at rest);

17.7.1.2.3. Study treatments

During Period I, each eligible subject received 1 tablet of study medication (OM/AML 40/10 mg) per day.To maintain the blind during Periods II to IV, each subject received 3 tablets of study medication per day (1 x OM/AML 40/10 mg, and 2 x HCTZ [12.5 mg or matching placebo). The tablet type distribution for the treatment groups in each of the blinded periods is displayed in Table 15, below (also see Figure 3, and section on randomisation and blinding methods).

Table 15: Study treatments (CS8635-A-E303)

Study Treatment	Tablets per Day
Period I	
OM/AML 40/10 mg	OM/AML 40/10
Period II	
OM/AML 40/10 mg	OM/AML 40/10 + 2 × HCTZ 0
OM/AML/HCTZ 40/10/12.5 mg	OM/AML 40/10 + HCTZ 12.5 + HCTZ 0
OM/AML/HCTZ 40/10/25 mg	OM/AML 40/10 + 2 × HCTZ 12.5
Period III	
OM/AML/HCTZ 40/10/12.5 mg	OM/AML 40/10 + HCTZ 12.5 + HCTZ 0
Period IV	
OM/AML/HCTZ 40/10/12.5 mg	OM/AML 40/10 + HCTZ 12.5 + HCTZ 0
OM/AML/HCTZ 40/10/25 mg	OM/AML 40/10 + 2 × HCTZ 12.5

17.7.1.2.4. Efficacy variables and outcomes

The primary efficacy variable was the change in mean trough SeDBP from baseline (end of OM/AML run-in period [Week 8]) to the end of the DB Period II (Week 16) with LOCF.

The secondary efficacy variables included the following:

- Changes in mean trough SeDBP and SeSBP from baseline to Weeks 12, 16, 24, and 32;
- Changes in daytime, night-time, and 24-hour DBP and SBP, assessed by 24-hour ABPM from baseline to Weeks 16, 24, and 32;
- Number (%) of subjects achieving trough seated BP goal (<140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease) during Period II, Period III, and Period IV;
- Number (%) of subjects achieving trough seated BP thresholds (ie, <140/90 mmHg, <130/85 mmHg, <130/80 mmHg, <120/80 mmHg, SeDBP <90 mmHg, and SeSBP <140 mmHg) during Period II, Period III, and Period IV; and
- Clinical benefit of up-titration from OM/AML/HCTZ 40/10/12.5 mg to 40/10/25 mg during Period IV in terms of conventional BP and ABPM parameters.

Seated BP was assessed by a Sponsor-provided model of a calibrated, validated sphygmomanometer (Greenlight 300 Sphygmomanometer, Accoson, Harlow, Essex, United Kingdom).Three assessments of SeDBP were made at each visit; the mean of these 3 evaluations was used as the SeDBP for that visit.Baseline cuff SeDBP was the mean of the randomization visit and the visit prior to randomization.

17.7.1.2.5. Randomisation and blinding methods

Periods I and III were single-blind with all eligible subjects receiving OM/AML 40/10 mg (Period I) and OM/AML/HCTZ 40/10/12.5 mg (Period III).The distribution of subjects to treatment groups in Period II and Period IV was managed by an IVRS.Randomisation was stratified by age group (<65 years, ≥65 years), diabetic status (yes, no), and study site.

Subjects were randomly assigned to a treatment sequence in Period II if they satisfied the BP criteria (mean trough SeSBP ≥140 mmHg, and mean trough SeDBP ≥90 mmHg) at the end of Period I (1:1:1 ratio to continue on OM/AML 40/10 mg, or to receive either OM/AML/HCTZ 40/10/12.5 mg, or OM/AML/HCTZ 40/10/25 mg treatment).Subjects who achieved the BP goal at the end of Period III directly continued on their triple-combination treatment in Period IV.Subjects not achieving BP goal at the end of Period III were randomly assigned in a 1:2 ratio to continue to receive OM/AML/HCTZ 40/10/12.5 mg or to have their dose up-titrated to OM/AML/HCTZ 40/10/25 mg in Period IV.Subjects with a mean trough SeSBP ≥160 mmHg or a mean trough SeDBP ≥100 mmHg after at least 2 weeks of treatment in Period III were randomised directly into Period IV.

No person involved in conducting the study or the statistical analysis had access to the randomisation code before the blind was officially broken.

17.7.1.2.6. Analysis populations

Randomised Set 1 included all subjects who were randomised to Period II and had a randomisation date.Randomised Set 2 included all subjects who were randomised to Period IV and had a randomisation date.

- Analysis Set for Period I

  Safety Set 1 included all subjects who received at least 1 dose of single-blind study medication in Period I.

- Analysis Sets for Period II

  Safety Set 2 included all randomised subjects who received at least 1 dose of DB study medication in Period II.

  The Full Analysis Set 1 (FAS1) included all Randomised Set 1 subjects who received at least 1 dose of DB study medication in Period II and who provided at least 1 SeDBP measurement after randomisation in Period II.

  The Per-Protocol Analysis Set 1 (PPS1) included all subjects in the FAS1, excluding the following:

  – Subjects who violated major inclusion/exclusion criteria;
  – Subjects who deviated from the protocol guidelines during the study prior to the end of Period II (eg, poor compliance, prohibited medications) in a sufficiently serious manner to warrant data (but not subject) exclusion; or
  – Subjects who withdrew from the study for any reason prior to the end of Period II, with the exception of withdrawal due to insufficient blood pressure control.

- Analysis Set for Period III

The Period III Analysis Set included all subjects who received at least 1 dose of single-blind study medication in Period III.

- Analysis Sets for Period IV

  Safety Set 3 included all subjects who entered Period IV and received at least 1 dose of DB study medication in Period IV. For safety presentations in Period IV, responder and non-responder subjects who received OM/AML/HCTZ 40/10/12.5 mg were grouped together.

  The Full Analysis Set 2 (FAS2) included all Randomised Set 2 subjects who received at least 1 dose of DB study medication in Period IV and who provided at least 1 SeDBP measurement after randomisation in Period IV.

  The Per-Protocol Analysis Set 2 (PPS2) included all subjects in the FAS2, with the same exclusions as per PPS1 but with respect to Period IV.

17.7.1.2.7. Sample size

The sample size calculation was based on the primary efficacy variable (i.e. change in mean trough SeDBP from baseline to Week 16 with LOCF).From previous studies, the SD of the primary efficacy variable was assumed to be 8.5 mmHg in the sample size calculation. By setting the 2-sided significance level at 0.05, it was estimated that 666 randomised subjects (222 per arm) would be required to complete Period II to detect a difference of 2.5 mmHg between add-on HCTZ 12.5 mg or 25 mg and add-on placebo with 80% power. Assuming a possible dropout rate of 15%, it was calculated that 262 subjects per arm were needed for a total of 786 subjects. It was estimated that 60% of the subjects would reach goal at the end of Period I, therefore 1,965 subjects were planned to be enrolled.

17.7.1.2.8. Statistical methods

The same statistical methods were used in Study CS8635-A-E303 as were used in CS8635-A-E302, with the exception that Dunnett's test was used to adjust the p-values in order to control the overall 2-sided type-I error at a 0.05 level of significance (Period II only).

17.7.1.2.9. Participant flow

The disposition of subjects from Period I through Period IV of the study is summarised in Figure 3 and for Period II in Table 16.

Table 16: Subject Disposition (Period II) – Randomised Set 1 (CS8635-A-E303)

Category	OM40/ AML10 (N = 269) n (%)	OM40/ AML10/ HCTZ12.5 (N = 269) n (%)	OM40/ AML10/ HCTZ25 (N = 270) n (%)	Total (N = 808) n (%)
Randomised	269	269	270	808
Completed Period II	260 (96.7)	263 (97.8)	262 (97.0)	785 (97.2)
Discontinued in Period II	9 (3.3)	6 (2.2)	8 (3.0)	23 (2.8)
Adverse event	4 (1.5)	2 (0.7)	3 (1.1)	9 (1.1)
Withdrawal by subject	1 (0.4)	2 (0.7)	1 (0.4)	4 (0.5)
Protocol violation	1 (0.4)	1 (0.4)	2 (0.7)	4 (0.5)
Randomisation in error	0 (0.0)	1 (0.4)	2 (0.7)	3 (0.4)
Failure to comply with protocol requirements	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.2)
Did not continue to Period III	2 (0.7)	1 (0.4)	0 (0.0)	3 (0.4)
Safety Set 2	269 (100.0)	268 (99.6)	269 (99.6)	806 (99.8)
Full Analysis Set 1	269 (100.0)	268 (99.6)	269 (99.6)	806 (99.8)
Per-Protocol Analysis Set 1	254 (94.4)	257 (95.5)	259 (95.9)	770 (95.3)

Although 3,420 subjects were enrolled in the study, only 2,204 (64.4%) subjects entered Period I.Of the 1,216 (35.6%) subjects who discontinued prior to Period I, the primary reason for

discontinuation was failure to satisfy all inclusion/exclusion criteria (1,039 [30.4%] subjects), in particular, failure to meet the ABPM criteria.The ABPM criteria were subsequently removed to allow the enrolment of subjects who met all other inclusion/exclusion criteria.

Of the 2,204 subjects who entered Period I, 2,086 (94.7%) subjects completed the period, with the primary reasons for discontinuation being AEs (49 [2.2%] subjects), subject withdrawal from the study (30 [1.4%] subjects), protocol violation (22 [1.0%] subjects), and other reasons (13 [0.6%] subjects). In total, 1,235 (56.0%) of these subjects met BP criteria for randomisation into Period II, and 808 subjects were actually randomised.The reasons the other 427 subjects did not continue to Period II were: the close of randomisation (418 subjects), subject withdrawal (3 subjects), withdrawal from the study by mistake (1 subject), ABPM technical reasons (2 subjects), failure to comply with protocol requirements (1 subject), AE (1 subject), and 24-hour ABPM exceeded 104 mmHg (1 subject).Few subjects withdrew from Period II (2.8%), III (1.9%), or IV (1.6%).

17.7.1.2.10. Major protocol violations/deviations

There were no major protocol violations / deviations, although a number of protocol amendments were made.Substantial Protocol Amendment 02 removed the ABPM inclusion criterion at screening and end of Period I.Potential bias resulting from this amendment was investigated by conducting sensitivity analyses of the primary and secondary endpoints in the context of an ANCOVA model.Results for the endpoints were found to be similar in the subjects randomised before (n=372) or after the amendment (n=436), with no evidence of bias.

17.7.1.2.11. Baseline data

Baseline demographic and other baseline characteristics for the Randomised Set by Period II randomised treatment are summarised.Of the 808 subjects in the Randomised Set, 469 (58.0%) were male, the majority (99.9%) were Caucasian, the mean age was 55.8 years, and 3.7% were aged ≥ 75 years.This was comparable across all the treatment groups.The mean duration of hypertension (9.9 years), proportion of subjects with diabetes (12.9%), chronic renal disease (2.5%), or chronic cardiovascular disease (36.0%) were also generally similar across the treatment groups.At screening, 280 (34.7%) subjects had mild hypertension (baseline SBP <160 mmHg and DBP <100 mmHg and SBP ≥140 mmHg or DBP ≥90 mmHg), 466 (57.8%) had moderate hypertension, and 60 (7.4%) had severe hypertension.Baseline mean SeDBP and SeSBP ranged from 93.6 to 93.7 mmHg and 147.9 to 148.8 mmHg, respectively.

17.7.1.2.12. Results for the primary efficacy outcome

There was a statistically significant mean reduction in SeDBP from baseline to Week 16 for each treatment group (p<0.0001 for all treatment groups) (Table 17, below).The LS mean reductions in SeDBP were -7.1 mmHg and -8.9 mmHg for the OM/AML/HCTZ 40/10/12.5 mg and OM/AML/HCTZ 40/10/25 mg group, respectively compared to -6.1 mmHg for the OM/AML 40/10 mg group.Both triple combination therapies resulted in a greater mean reduction in SeDBP compared to OM/AML 40/10 mg dual combination therapy, but this was only statistically significant for OM/AML/HCTZ 40/10/25 mg (LS mean treatment difference of -2.8 mmHg; p<0.0001).

Table 17: Change in SeDBP (mmHg) From Baseline to Week 16 With LOCF – Period II – FAS1 (CS8635-A-E303)

	OM40/ AML10 (N = 269)	OM40/ AML10/ HCTZ12.5 (N = 268)	OM40/ AML10/ HCTZ25 (N = 269)
n [1]	269	268	269
Baseline mean (SD) [2]	93.6 (3.39)	93.7 (3.67)	93.7 (3.34)
Week 16 with LOCF mean (SD) [3]	87.3 (7.29)	86.4 (7.20)	84.6 (8.04)
Mean change (SD)	-6.2 (7.23)	-7.3 (6.87)	-9.1 (7.70)
LS mean change (SE)	-6.1 (0.55)	-7.1 (0.55)	-8.9 (0.55)
p-value	<0.0001	<0.0001	<0.0001
Between treatment comparisons [4]			
LS mean (SE)		-1.0 (0.62)	-2.8 (0.62)
95% CI		(-2.2, 0.2)	(-4.0, -1.6)
p-value		0.1187	<0.0001
Adjusted p-value [5]		0.2062	<0.0001

Least-squares mean, standard error, 95% CI, and 2-sided p-values were obtained from an ANCOVA model with baseline blood pressure as a covariate and treatment, age group, and diabetic status as fixed effects.**1**. n is the number of subjects with values at both time points.**2**. Baseline was defined as the last measurement prior to the first dose of randomised study medication in Period II.**3**. Week 16 with LOCF was defined as the last available measurement during Period II.**4**. Between treatment comparisons include comparisons of triple combinations vs. OM/AML 40/10 mg.**5**. Adjusted p-values were obtained from Dunnett's test to control the overall Type 1 error at 0.05 level.

17.7.1.2.13. Results for other efficacy outcomes

· Change in SeSBP During Period II

Each treatment group had a statistically significant reduction in mean SeSBP at Week 16 with LOCF (p<0.0001 for all treatment groups), with greater reductions with both triple combination therapies (range -8.6 to -10.5 mmHg) compared with OM/AML 40/10 mg dual combination therapy (-6.9 mmHg).The between treatment difference was only statistically significant for OM/AML/HCTZ 40/10/25 mg.

· Proportion of Subjects Reaching BP Goal / Thresholds During Period II

The percentage of subjects achieving BP treatment goal at Week 16 with LOCF for the FAS1 was 24.2% for the OM/AML 40/10 mg group, 29.5% for the OM/AML/HCTZ 40/10/12.5 mg group, and 41.3% for the OM/AML/HCTZ 40/10/25 mg group.Treatment with the triple-combination therapies also resulted in higher percentages of subjects reaching all BP thresholds at Weeks 12, 16 and 16 with LOCF compared to the dual-combination therapy.The difference was more likely to be statistically significant with OM/AML/HCTZ 40/10/25 mg.

· Change in Ambulatory BP During Period II

Each treatment group had a statistically significant mean reduction in mean 24-hour, daytime, and night-time ambulatory DBP from baseline to Week 16 with LOCF for the FAS1 (p<0.0001; p≤0.0003; p≤0.0001; respectively, for all treatment groups).Similarly, there were statistically significant mean reductions in ambulatory SBP over the same time period (24-hour p≤0.0104; daytime p≤0.0149; and night-time p≤0.0497 for all treatment groups).BP differences were significantly greater for both triple combination therapies compared to OM/AML 40/10mg dual combination therapy:

24-hour ambulatory DBP and SBP

– OM/AML/HCTZ 40/10/12.5 mg vs. OM/AML 40/10 mg (LS mean difference of -1.9 mmHg [p=0.0018] and -3.2 mmHg [p=0.0002])

- OM/AML/HCTZ 40/10/25 mg vs. OM/AML 40/10 mg (LS mean difference of -3.2 mmHg [p<0.0001] and -4.6 mmHg [p<0.0001])

Daytime ambulatory DBP and SBP

- OM/AML/HCTZ 40/10/12.5 mg vs. OM/AML 40/10 mg (LS mean difference of -2.0 mmHg [p=0.0024] and -3.4 mmHg [p=0.0002])
- OM/AML/HCTZ 40/10/25 mg vs. OM/AML 40/10 mg (LS mean difference of -3.6 mmHg [p<0.0001] and -5.1 mmHg [p<0.0001])

Night-time ambulatory DBP and SBP

- OM/AML/HCTZ 40/10/12.5 mg vs. OM/AML 40/10 mg (LS mean difference of -1.6 mmHg [p=0.0300] and -2.7 mmHg [p=0.0095])
- OM/AML/HCTZ 40/10/25 mg vs. OM/AML 40/10 mg (LS mean difference of -2.3 mmHg [p=0.0012] and -3.6 mmHg [p=0.0004])

· Proportion of Subjects Reaching BP Goal / Threshold Based on ABPM (24-Hour, Daytime, Night-time) During Period II

For all ABPM outcomes, a higher proportion of subjects receiving treatment with either triple combination therapy reached the BP treatment goal compared with subjects receiving dual combination therapy.These results were not always statistically significant.Similarly, treatment with triple combination therapy generally resulted in a higher proportion of subjects reaching each ABPM BP threshold at Week 16 with LOCF compared to OM/AML 40/10 mg dual combination therapy.

The efficacy results for Periods III and IV relate to a single-blind period on OM/AML/HCTZ 40/10/12.5 mg (Period III) or up-titration to OM/AML/HCTZ 40/10/25 mg in non-responders (Period IV) in subjects already receiving triple combination therapy and are therefore not directly relevant to the add-on indication.These results overall demonstrated that further reductions in SeDBP and SeSBP were observed in Period III, with greater mean reductions in SeDBP and SeSBP in those Period III non-responders up-titrated to OM/AML/HCTZ 40/10/25 mg compared with those remaining on OM/AML/HCTZ 40/10/12.5 mg.

17.7.1.2.14. Subgroup analyses

Subgroup analyses are presented for age group, gender, hypertension severity, diabetic status, and BMI category for mean SeDBP, SeSBP and proportion of subjects reaching BP Goal for Period II only.

> **Evaluator's comment**:While the sponsor reported the statistical significance of the comparison of triple-therapy vs. dual therapy in the subgroup analyses, the evaluator has not reported this as it does not appear that Dunnett's (or any other) test was applied to control the Type I error rate of treatment comparisons in the subgroup analyses.

Age: mean reductions in SeDBP and SeSBP were similar in the group of subjects ≥65 years of age compared with subjects <65 years of age (Table 18, below).There were few subjects aged ≥75 years (n<13 for each treatment group limits ability to interpret results), but reductions in SeDBP (-7.2 to -13.0 mmHg) and SeSBP (-7.6 to -14.0 mmHg) tended to be greater than in the younger age groups.The benefits of triple therapy over dual therapy for both SeDBP and SeSBP were comparable to that seen in the overall population (bearing in mind the small number of subjects aged ≥75 years).The percentage of subjects reaching BP goal was lower in those aged ≥65 years and ≥75 years than in those aged <65 years, but the numerical benefit of triple- over dual-therapy remained.

Table 18: Mean Changes in SeDBP and SeSBP (mmHg) From Baseline to Week 16 With LOCF – Age Subgroups (CS8635-A-E303)

	SeDBP				SeSBP			
	<65 Years		≥65 Years		<65 Years		≥65 Years	
Treatment	N[1]	Change Mean (SD)	N[1]	Change Mean (SD)	N[1]	Change Mean (SD)	N[1]	Change Mean (SD)
OM40/AML10	213	-6.1 (7.14)	56	-6.8 (7.62)	213	-8.1 (9.36)	56	-8.6 (10.05)
OM40/AML10/HCTZ12.5	213	-7.4 (6.71)	55	-6.8 (7.50)	213	-10.3 (10.33)	55	-10.3 (9.29)
OM40/AML10/HCTZ25	215	-9.0 (7.44)	54	-9.4 (8.72)	215	-12.6 (10.93)	54	-9.5 (12.10)

Gender: female subjects appeared to have numerically higher (but similar) mean reductions in SeDBP and SeSBP compared to male subjects (-6.9 to -10.4 vs. -5.7 to -8.0 mmHg SeDBP; -9.3 to -12.8 vs. -7.3 to -11.3 mmHg SeSBP) across the treatment groups.Both triple combination therapies resulted in greater reductions in SeDBP and SeSBP than the dual combination therapy.The percentage of subjects reaching BP goal and the numerical benefit of triple over dual therapy was comparable in males and females, and similar to the overall results.

Hypertension severity: mean reductions in SeDBP and SeSBP were higher in subjects with mild or moderate (SeSBP <180 mmHg and SeDBP <110 mmHg at screening) compared with severe (SeSBP ≥180 mmHg or SeDBP ≥110 mmHg at screening) hypertension in the OM/AML 40/10 mg and OM/AML/HCTZ 40/10/12.5 mg treatment groups, but lower in the subjects receiving OM/AML/HCTZ 40/10/25 mg.Triple combination therapy generally resulted in greater reductions in SeDBP and SeSBP than the dual combination therapy.The small number of subjects with severe hypertension (n ≤ 26 for each treatment group), make the results difficult to interpret in this subgroup.The percentage of subjects reaching BP goal was generally lower in those subjects with severe hypertension compared with those with mild or moderate hypertension, and a numerical benefit of triple over dual therapy generally remained irrespective of hypertension severity.

Diabetic status: mean reductions in SeDBP and SeSBP were similar in subjects with and without diabetes across all treatment groups (SeDBP range -4.8 to -9.2 mmHg; SeSBP range -4.0 to -12.4 mmHg).Triple combination therapy resulted in greater reductions in SeDBP and SeSBP than the corresponding dual combination therapy.The small number of subjects with diabetes (n ≤ 37 for each treatment group), make the results difficult to interpret in this subgroup.Bearing in mind that the BP goal was more stringent in subjects with diabetes (<130/80 vs. <140/90 mmHg), the percentage of subjects reaching BP goal was lower in those subjects with diabetes compared with those without diabetes.There was a numerical benefit of triple over dual therapy for all treatment comparisons.

BMI: subjects with BMI <30 kg/m^2 appeared to have numerically higher (but similar) mean reductions in SeDBP and SeSBP compared to subjects with BMI ≥30 kg/m^2 (-6.5 to -9.7 vs. -5.9 to -8.5 mmHg SeDBP; -8.7 to -11.9 vs. -7.7 to -12.0 mmHg SeSBP) across the treatment groups.Both triple combination therapies resulted in greater reductions in SeDBP and SeSBP than the dual combination therapy.The percentage of subjects reaching BP goal was similar in subjects with BMI ≥30 kg/m^2 and in those with BMI <30 kg/m^2, and a numerical benefit of triple over dual therapy remained irrespective of BMI category.

17.7.2. Other efficacy studies

Not applicable.

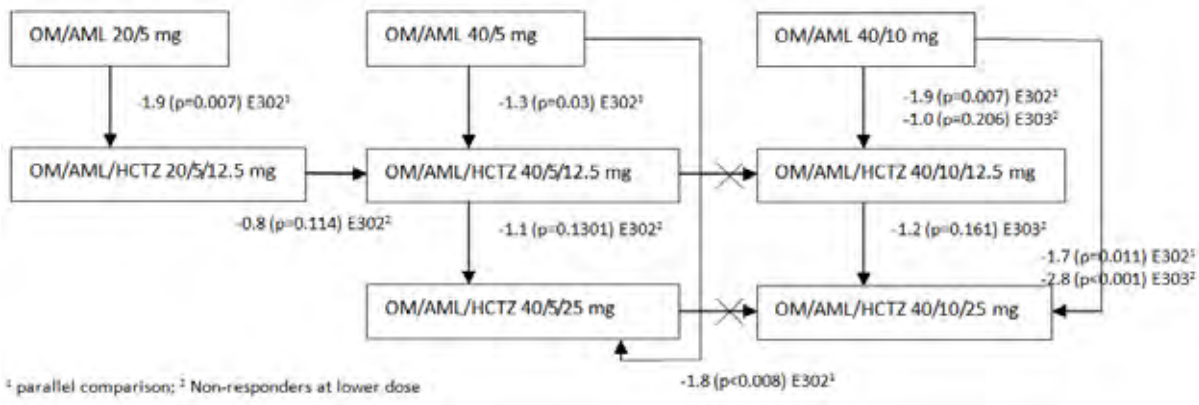
17.7.3. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

17.7.4. Evaluator's conclusions on clinical efficacy for hypertension

The supplementary studies CS8635-A-E302 and CS8635-A-E303 were submitted primarily to establish the efficacy of the triple combination product as add-on-therapy in subjects with moderate to severe hypertension.Study CS8635-A-E303 is considered to more closely resemble the clinical situation because it compared the effects of adding HCTZ to OM/AML therapy in subjects who had not adequately responded to OM/AML therapy alone, whereas in study CS8635-A-E302 subjects were randomised to dual or triple therapy irrespective of their response to dual therapy.In both studies the primary efficacy endpoint was change in mean trough SeDBP with last observation carried forward, with change in mean trough SeSBP, and percentage achieving BP treatment goal being the most important secondary endpoints. Figure 4 (below) summarises the change in SeDBP from both studies.

Figure 4: Summary of change in SeDBP at tested dose addition / titrations (adapted from a Figure in the European Agency report) (CS8635-A-302 & CS8635-A-303).



The results from Study CS8635-A-E303 demonstrated clinically meaningful differences in SeDBP and SeSBP reductions when subjects who were non-responders to OM/AML 40/10 mg had HCTZ 12.5mg or 25 mg added to their dual combination therapy from Week 8 to Week 16 (Period II).The reduction in SeSBP/SeDBP in subjects who continued OM/AML 40/10 mg treatment during Period II was -6.9/-6.1 mmHg, compared with a reduction of -8.6/-7.1 mmHg in subjects who were randomized to OM/AML/HCTZ 40/10/12.5 mg, and a reduction of -10.5/-8.9 mmHg in subjects who were randomized to OM/AML/HCTZ 40/10/25mg.The SeSBP/SeDBP least-squares (LS) mean treatment difference was statistically significant between subjects who remained on OM/AML 40/10 mg and those who had their dose up-titrated to OM/AML/HCTZ 40/10/25 mg (-3.6/-2.8 mmHg, p<0.0001), but not in those who had their dose up-titrated to OM/AML/HCTZ 40/10/12.5 mg (-1.8/-1.0, p=0.0777/p=0.2062).These results are supported by the 24 hour ABPM results, which demonstrated that subjects on either triple combination therapy had statistically and clinically meaningful differences in SeSBP/SeDBP compared with subjects who continued OM/AML 40/10 mg (-3.2/-1.9 [p=0.002/p=0.0018] and -4.6/-3.2 mmHg [p<0.0001] in subjects on OM/AML/HCTZ 40/10/12.5 mg and OM/AML/HCTZ 40/10/25 mg, respectively).Similar results were also obtained for daytime and night-time ABPM.Further support is provided by the percentage of subjects who reached their BP treatment goal, which was higher in subjects receiving OM/AML/HCTZ 40/10/12.5 mg (29.5%) and OM/AML/HCTZ 40/10/25 mg (41.3%) than in those remaining on OM/AML 40/10 mg (24.2%).Results were consistent across subgroups of age, gender, BMI, diabetic status, and hypertension severity.Although the study did not investigate the benefits of adding HCTZ to OM/AML 20/5 mg or OM/AML 40/5 mg, this was previously discussed with the European Agency who stated: "If the benefit of add-on therapy is demonstrated using the highest doses of the baseline 2-drug therapy, then it can be assumed that benefit would also result from addition of the third component to lower doses of the 2-drug combinations.".

Study CS8635-A-E302 provided supportive evidence from a parallel group comparison, with the triple therapy combinations of 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 resulting in statistically significant greater LS mean reductions in SeDBP/SeSBP (of ~2 / ~ 3 mmHg, respectively) and a higher proportion of subjects reaching their BP treatment goal (52–59%) compared to the respective dual component therapies (43–50%) (Table 13, above).

The case for the addition of OM to AML/HCTZ or AML to OM/HCTZ was addressed in the parallel group Study CS8635-A-U301 (evaluated in the original submission), that explored the following dual vs. triple therapy comparisons in hypertensive subjects who were randomised to dual or triple therapy irrespective of their response to dual therapy:

- OM/AML 40/10 mg vs OM/AML/HCTZ 40/10/25 mg
- OM/HCTZ 40/25 mg vs OM/AML/HCTZ 40/10/25 mg
- AML/HCTZ 10/25 mg vs OM/AML/HCTZ 40/10/25 mg

It demonstrated a statistically significant mean difference between each triple therapy and the dual therapy groups for SeDBP (-3.8 to -6.7 mmHg, p<0.001), SeSBP (-7.1 to -9.6 mmHg, p<0.001), and proportion of subjects reaching their BP treatment goal (64.3% vs. 34.9 to 46.6%, p<0.0001).This study also conducted an exploratory analysis of the BP outcomes in subjects who were non-responders at Week 4 on dual therapy.Non-responders switched to triple therapy had greater reductions in SeDBP / SeSBP (-7.5 to -8.3 mmHg / -11.9 to -16.7 mmHg) compared with those remaining on dual therapy (-2.5 to -3.4 mmHg / -3.9 to -5.7 mmHg), and a higher proportion of subjects who reached BP goal (50.8 to 57.3% vs 19.7 to 26.0%).While this was only an exploratory endpoint, the results for the OM/AML vs OM/AML/HCTZ comparison are consistent with those from Study CS8635-A-E303.It therefore seems not unreasonable to assume that the results for the other dual vs triple component comparisons reflect what would have been observed in an add-on trial.

In summary, while there is only one formal add-on comparison and one exploratory analysis of add-on therapy in non-responders to dual combination therapy, the totality of data consistently demonstrates that subjects receiving the triple combination of various doses of OM/AML/HCTZ have clinically relevant, better antihypertensive outcomes than subjects on the respective dual combination therapies (Table 19).

Table 19: Summary of Major Endpoints for each Dual vs. Triple Therapy Comparison

Study Number	Dual Therapy	Triple Therapy	SeDBP	SeSBP	BP Goal
CS8635-A-E302 (parallel group)	OM/AML 20/5 mg	OM/AML/HCTZ 20/5/12.5 mg	ü ü	ü ü	ü ü
	OM/AML 40/5 mg	OM/AML 40/5/12.5 mg	ü ü	ü ü	ü
		OM/AML 40/5/25 mg	ü ü	ü ü	ü ü
	OM/AML 40/10 mg	OM/AML/HCTZ 40/10/12.5 mg	ü ü	ü ü	ü
		OM/AML/HCTZ 40/10/25 mg	ü ü	ü ü	ü
CS8635-A-E303 (in non-responders)	OM/AML 40/10 mg	OM/AML/HCTZ 40/10/12.5 mg	ü	ü	ü
		OM/AML/HCTZ 40/10/25 mg	ü ü	ü ü	ü ü
CS8635-A-U301	OM/AML 40/10 mg	OM/AML/HCTZ 40/10/25 mg	ü ü	ü ü	ü ü

Study Number	Dual Therapy	Triple Therapy	SeDBP	SeSBP	BP Goal
	OM/HCTZ 40/25 mg		ü ü	ü ü	ü ü
	AML/HCTZ 10/25 mg		ü ü	ü ü	ü ü
CS8635-A-U301 (exploratory analysis in non-responders)	OM/AML 40/10 mg	OM/AML/HCTZ 40/10/25 mg	ü	ü	ü
	OM/HCTZ 40/25 mg		ü	ü	ü
	AML/HCTZ 10/25 mg		ü	ü	ü

ü ü = statistically significant benefit of triple vs. dual therapy; ü = numerical benefit of triple vs. dual therapy.

17.8. Clinical safety

17.8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy studies (CS8635-A-E302 and CS8635-A-E303) the following safety data were collected:

- Adverse events (whether observed by the investigator or reported by the subject) were collected from screening until 14 days after the last dose of study medication was taken,
- Clinical laboratory evaluations (chemistry, haematology, and urinalysis) were measured at screening, Week 0, and periodically thereafter until final visit/ET. Laboratory safety variables were also measured at the follow-up visit if considered necessary by the investigator. If clinically significant laboratory abnormalities were noted at final visit/ET, additional laboratory samples were obtained and the abnormality was followed to resolution,
- Vital signs (seated BP, weight and heart rate) were measured prior to having blood drawn for laboratory evaluations and after the subject had been sitting for at least 5 minutes, and were obtained at all scheduled visits.The BP was computed as an average of 3 measurements,
- ECGs (12-lead) were performed at screening, and periodically thereafter, including at the follow-up visit if considered necessary by the investigator,
- Physical examinations were performed at screening (baseline), and periodically thereafter, including at any time at the discretion of the investigator.

Based on the investigator's discretion, subjects who experienced a clinically significant increase or decrease in BP after baseline measurement were classified as experiencing an adverse event and coded as "blood pressure increase" or "blood pressure decrease", respectively.

17.8.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

17.8.3. Patient exposure

Study CS8635-A-E302

Mean exposure to each dosing regimen for the Safety Sets were as follows (Table 20, below):

- Period I (Safety Set 1) - 14.1 to 14.2 days (and placebo 14.5 days)
- Period II (Primary Safety Set) - 54.1 to 55.6 days

- Period III (Analysis Set) – 55.3 days
- Period IV (Safety Set 2) – 27.6 to 27.9 days
- Period V(Safety Set 3) – 28.3 to 28.6 days (titration period for responders / non-responders)
- Period VI (OL Analysis Set) - 108.4 days to 205.6 days.

Table 20: Extent of mean exposure to medications (Study CS8635-A-E302)

Extent of Exposure (Days)	OM20/ AML5	OM20/ AML5/ HCTZ 12.5	OM40/ AML5	OM40/ AML5/ HCTZ 12.5	OM40/ AML5/ HCTZ 25	OM40/ AML10	OM40/ AML10/ HCTZ 12.5	OM40/ AML10/ HCTZ 25
Period I (n)	650	NA	983	NA	NA	985	NA	NA
Mean	14.1		14.2			14.1		
Period II (n)	333	330	332	334	332	325	329	332
Mean	55.6	55.2	55.2	55.4	55.3	55.2	54.1	54.6
Period III (n)	NA	2540	NA	NA	NA	NA	NA	NA
Mean		55.3						
Period IV (n)	NA	228	NA	453	NA	NA	NA	NA
Mean		27.6		27.9				
Period VI (n)	NA	1846	NA	439	807	NA	236	172
Mean		205.6		127.4	128.3		108.4	120.0

Study CS8635-A-E303

Mean exposure to each dosing regimen for the Safety Sets were as follows (Table 21, below):

- Period I (Safety Set 1) – 56.6 days
- Period II (Safety Set 2) – 55.8 to 56.0 days
- Period III (Period III Analysis Set) – 55.9 days
- Period IV (Safety Set 3) – 56.5 to 56.8 days

Table 21: Extent of mean exposure to medications (Study CS8635-A-E303)

Extent of Exposure (Days)	OM40/AML10	OM40/AML10/ HCTZ12.5	OM40/AML10/ HCTZ25
Period I (n)	2203	NA	NA

Extent of Exposure (Days)	OM40/AML10	OM40/AML10/ HCTZ12.5	OM40/AML10/ HCTZ25
Mean	56.6	-	-
Period II (n)	269	268	270
Mean	55.9	56.0	55.8
Period III (n)	NA	782	NA
Mean	-	55.9	-
Period IV (n)	NA	564	197
Mean	-	56.8	56.5

17.8.4. Adverse events

· **Study CS8635-A-E302**

The primary analyses of adverse event safety data was performed on the Primary Safety Set. The counting of AEs under treatment groups for the Primary Safety Set was based on Period II randomised treatment groups. Treatment-emergent adverse events (TEAEs) were assigned to the treatment that a subject received from Week 2 to Week 10. For the primary analysis of AE data, TEAEs that started and/or resolved while the subject was taking their Period I dual combination treatment were still assigned to the Period II randomised treatment. This analysis was set up to reflect the manner in which triple combination therapy is anticipated to be used clinically (ie, subjects will likely first titrate through dual combination therapy before receiving triple combination therapy).

17.8.4.1. All adverse events (irrespective of relationship to study treatment)

· **Study CS8635-A-E302**

During the 10 weeks of Periods I-II, 763 (28.8%) of the 2,645 subjects who received at least 1 dose of DB study medication in Period II had a TEAE.Across the treatment groups, the overall percentage of subjects with a TEAE ranged from 24.9% to 32.2%, and most were considered mild or moderate in severity.The most common TEAEs were in the system organ classes (SOCs) general disorders and administration site conditions (7.1%), nervous system disorders (6.7%), and infections and infestations (6.5%) (Table 22, below).The TEAEs reported most frequently overall included: peripheral oedema (4.8%), headache (3.9%), nasopharyngitis (2.5%), dizziness (2.1%), dyslipidaemia (1.6%), and asthenia (1.6%).There was a higher incidence of peripheral oedema and asthenia in the treatment groups receiving AML 10 mg as one of the components of the combination therapy (6.3% to 9.2% and 2.4% to 2.7%, respectively) compared to the treatment groups receiving AML 5 mg (2.1% to 4.8% and 0.3% to 1.8%, respectively).Hypotension and palpitations were observed in a higher percentage of subjects on OM/AML/HCTZ 40/10/12.5 mg (2.4% and 2.7%, respectively), with palpitations also higher in the group receiving OM/AML/HCTZ 40/10/25 mg (1.8%) compared to the other treatment groups (0.0% to 1.2%).

Table 22: TEAEs by SOC and Preferred Term (PT, ≥3% in Any Treatment Group) – Periods I–II – Primary Safety Set (CS8635-A-E302)

System Organ Class Preferred Term	OM20/ AML5 (N = 333) n (%)	OM20/ AML5/ HCTZ12.5 (N = 329) n (%)	OM40/ AML5 (N = 332) n (%)	OM40/ AML5/ HCTZ12.5 (N = 334) n (%)	OM40/ AML5/ HCTZ25 (N = 331) n (%)	OM40/ AML10 (N = 325) n (%)	OM40/ AML10/ HCTZ12.5 (N = 329) n (%)	OM40/ AML10/ HCTZ25 (N = 332) n (%)	Total (N = 2645) n (%)
Subjects with TEAEs	83 (24.9)	89 (27.1)	101 (30.4)	105 (31.4)	93 (28.1)	94 (28.9)	106 (32.2)	92 (27.7)	763 (28.8)
General Disorders and Administration Site Conditions	16 (4.8)	15 (4.6)	19 (5.7)	17 (5.1)	14 (4.2)	39 (12.0)	34 (10.3)	33 (9.9)	187 (7.1)
Oedema Peripheral	11 (3.3)	9 (2.7)	16 (4.8)	7 (2.1)	7 (2.1)	30 (9.2)	26 (7.9)	21 (6.3)	127 (4.8)
Asthenia	1 (0.3)	2 (0.6)	3 (0.9)	6 (1.8)	5 (1.5)	8 (2.5)	8 (2.4)	9 (2.7)	42 (1.6)
Nervous System Disorders	22 (6.6)	22 (6.7)	20 (6.0)	27 (8.1)	23 (6.9)	14 (4.3)	22 (6.7)	28 (8.4)	178 (6.7)
Headache	15 (4.5)	12 (3.6)	8 (2.4)	16 (4.8)	13 (3.9)	7 (2.2)	13 (4.0)	18 (5.4)	102 (3.9)
Dizziness	5 (1.5)	8 (2.4)	5 (1.5)	8 (2.4)	8 (2.4)	4 (1.2)	7 (2.1)	10 (3.0)	55 (2.1)
Infections and Infestations	14 (4.2)	17 (5.2)	25 (7.5)	36 (10.8)	24 (7.3)	14 (4.3)	21 (6.4)	21 (6.3)	172 (6.5)
Nasopharyngitis	7 (2.1)	7 (2.1)	11 (3.3)	13 (3.9)	8 (2.4)	4 (1.2)	9 (2.7)	7 (2.1)	66 (2.5)
Influenza	0 (0.0)	1 (0.3)	1 (0.3)	4 (1.2)	2 (0.6)	2 (0.6)	2 (0.6)	3 (0.9)	15 (0.6)
Respiratory Tract Infection Viral	1 (0.3)	3 (0.9)	0 (0.0)	2 (0.6)	3 (0.9)	0 (0.0)	4 (1.2)	1 (0.3)	14 (0.5)
Respiratory Tract Infection	0 (0.0)	0 (0.0)	2 (0.6)	5 (1.5)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	11 (0.4)
Metabolism and Nutrition Disorders	8 (2.4)	14 (4.3)	14 (4.2)	16 (4.8)	10 (3.0)	5 (1.5)	11 (3.3)	9 (2.7)	87 (3.3)
Dyslipidaemia	1 (0.3)	8 (2.4)	11 (3.3)	9 (2.7)	5 (1.5)	4 (1.2)	3 (0.9)	2 (0.6)	43 (1.6)
Musculoskeletal and Connective Tissue Disorders	10 (3.0)	10 (3.0)	7 (2.1)	11 (3.3)	9 (2.7)	7 (2.2)	13 (4.0)	13 (3.9)	80 (3.0)
Back Pain	3 (0.9)	4 (1.2)	2 (0.6)	1 (0.3)	2 (0.6)	2 (0.6)	5 (1.5)	5 (1.5)	24 (0.9)
Arthralgia	2 (0.6)	1 (0.3)	1 (0.3)	5 (1.5)	2 (0.6)	3 (0.9)	1 (0.3)	2 (0.6)	17 (0.6)
Muscle Spasms	0 (0.0)	1 (0.3)	1 (0.3)	4 (1.2)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	8 (0.3)
Cardiac Disorders	6 (1.8)	7 (2.1)	6 (1.8)	4 (1.2)	8 (2.4)	4 (1.2)	14 (4.3)	10 (3.0)	59 (2.2)
Tachycardia	4 (1.2)	3 (0.9)	3 (0.9)	2 (0.6)	4 (1.2)	3 (0.9)	4 (1.2)	3 (0.9)	26 (1.0)
Palpitations	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	3 (0.9)	0 (0.0)	9 (2.7)	6 (1.8)	24 (0.9)
Respiratory, Thoracic and Mediastinal Disorders	12 (3.6)	8 (2.4)	7 (2.1)	6 (1.8)	5 (1.5)	7 (2.2)	7 (2.1)	5 (1.5)	57 (2.2)
Cough	4 (1.2)	3 (0.9)	4 (1.2)	5 (1.5)	0 (0.0)	2 (0.6)	5 (1.5)	2 (0.6)	25 (0.9)
Vascular Disorders	0 (0.0)	3 (0.9)	4 (1.2)	7 (2.1)	6 (1.8)	6 (1.8)	15 (4.6)	6 (1.8)	47 (1.8)
Hypotension	0 (0.0)	2 (0.6)	2 (0.6)	2 (0.6)	4 (1.2)	1 (0.3)	8 (2.4)	4 (1.2)	23 (0.9)

Primary Safety Set included subjects who received at least 1 dose of double-blind study medication in Period II.TEAEs were AEs that emerged during treatment having been absent pre-treatment, or worsened relative to the pre-treatment state. TEAEs were defined as having a start date on or after the first dose of Period I study medication and up to the first dose of Period III study medication for subjects continuing into Period III, or up to and including 14 days after the last dose date of study medication in Periods I–II for early terminated subjects. 1. Drug-related was defined as definitely, probably, or possibly related to randomised study medication.

A further 410 of 2,540 (16.1%) subjects had TEAEs in Period III (8-weeks duration), 60 of 681 (8.8%) in Period IV (4-weeks duration), 61 of 676 (9.0%) in Period V (4-weeks duration), and 893 of 2509 (35.6%) in Period VI (≥ 28-weeks duration).The majority of TEAEs were mild or moderate in severity in all Periods.The AEs reported were generally consistent with those reported in Periods I-II.

- **Study CS8635-A-E303**

In Period I (all subjects on OM/AML 40/10 mg), 432 (19.6%) subjects had a TEAE.In Period II, 115 (14.3%) subjects had a TEAE. The percentage of subjects with a TEAE was similar across the treatment groups, ranging from 13.4% to 15.0% (Table 23, below).The most common TEAEs experienced occurred in the SOCs infections and infestations (4.0%), general disorders and administration site conditions (2.2%), and metabolism and nutrition disorders (2.1%).The TEAEs reported most frequently overall included: peripheral oedema (2.1%), upper respiratory tract infection (1.5%), and bronchitis (0.9%).There was a slightly higher incidence of peripheral oedema in the OM/AML 40/10 mg group (3.0%) compared to the OM/AML/HCTZ 40/10/12.5 mg (1.5%) and OM/AML/HCTZ 40/10/25 mg (1.9%) groups.

Table 23: TEAEs by SOC and Preferred Term (PT, ≥3% in Any Treatment Group) – Period–II –Safety Set 2 (CS8635-A-E303)

System Organ Class Preferred Term	OM40/ AML10 (N = 269) n (%)	OM40/ AML10/ HCTZ12.5 (N = 267) n (%)	OM40/ AML10/ HCTZ25 (N = 270) n (%)	Total (N = 806) n (%)
Subjects with TEAEs	36 (13.4)	40 (15.0)	39 (14.4)	115 (14.3)
Infections and Infestations	11 (4.1)	9 (3.4)	12 (4.4)	32 (4.0)
Upper Respiratory Tract Infection	6 (2.2)	4 (1.5)	2 (0.7)	12 (1.5)
Bronchitis	3 (1.1)	3 (1.1)	1 (0.4)	7 (0.9)
General Disorders and Administration Site Conditions	8 (3.0)	4 (1.5)	6 (2.2)	18 (2.2)
Oedema Peripheral	8 (3.0)	4 (1.5)	5 (1.9)	17 (2.1)
Nervous System Disorders	1 (0.4)	4 (1.5)	4 (1.5)	9 (1.1)
Headache	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.4)
Injury, Poisoning and Procedural Complications	0 (0.0)	3 (1.1)	2 (0.7)	5 (0.6)
Fall	0 (0.0)	3 (1.1)	1 (0.4)	4 (0.5)
Vascular Disorders	2 (0.7)	0 (0.0)	3 (1.1)	5 (0.6)
Hypotension	1 (0.4)	0 (0.0)	3 (1.1)	4 (0.5)

In Period III (all subjects on OM/AML/HCTZ 40/10/12.5 mg), 99 (12.7%) subjects had a TEAE.The most common TEAEs occurred in the system organ classes infections and infestations (2.7%), investigations (1.9%), musculoskeletal and connective tissue disorders (1.8%), metabolism and nutrition disorders (1.7%), general disorders and administration site conditions (1.4%), and nervous system disorders (1.3%). The only specific TEAE that occurred in ≥1% of subjects during Period III was peripheral oedema (1.2%).

In Period IV, 129 (17.0%) subjects had a TEAE.The most common TEAEs occurred in the SOCs general disorders and administration site conditions (3.4%), investigations (3.2%), infections and infestations (2.9%), and metabolism and nutrition disorders (2.8%).The TEAEs reported in ≥1% of subjects during Period IV were peripheral oedema (1.8%), and asthenia (1.4%).The incidence of peripheral oedema was higher (3.6%) and asthenia lower (0.0%) in the OM/AML/HCTZ 40/10/25 mg treatment group compared with the OM/AML/HCTZ 40/10/12.5 mg treatment group (1.2% and 2.0%, respectively).

Most TEAEs across all treatment groups in all Periods were considered mild or moderate in severity.

17.8.4.2. Treatment-related adverse events (adverse drug reactions)

- **Study CS8635-A-E302**

In total, 310 (11.7%) subjects had a drug-related AE, with the percentage ranging from 8.5% (OM/AML/HCTZ 20/5/12.5 mg group) to 17.3% (OM/AML/HCTZ 40/10/12.5 mg group).There was a slightly higher incidence of drug-related AEs in the groups receiving AML 10 mg (13.6% to 17.3%) as one of the components of combination therapy compared to the groups receiving AML 5 mg (8.5% to 10.5%).Most drug-related AEs were considered mild or moderate in severity.While the percentages were slightly lower, the pattern of drug-related AEs by SOC and PT was similar to that seen with overall TEAEs.

Table 24: Drug-related AEs by SOC and PT (≥1% in Any Treatment Group) – Periods I–II – Primary Safety Set (CS8635-A-E302)

System Organ Class Preferred Term	OM20/ AML5 (N = 333) n (%)	OM20/ AML5/ HCTZ12.5 (N = 329) n (%)	OM40/ AML5 (N = 332) n (%)	OM40/ AML5/ HCTZ12.5 (N = 334) n (%)	OM40/ AML5/ HCTZ25 (N = 331) n (%)	OM40/ AML10 (N = 325) n (%)	OM40/ AML10/ HCTZ12.5 (N = 329) n (%)	OM40/ AML10/ HCTZ25 (N = 332) n (%)	Total (N = 2645) n (%)
Subjects with drug-related TEAEs	32 (9.6)	28 (8.5)	35 (10.5)	29 (8.7)	33 (10.0)	51 (15.7)	57 (17.3)	45 (13.6)	310 (11.7)
General Disorders and Administration Site Conditions	13 (3.9)	13 (4.0)	16 (4.8)	9 (2.7)	11 (3.3)	35 (10.8)	31 (9.4)	28 (8.4)	156 (5.9)
Oedema Peripheral	10 (3.0)	9 (2.7)	15 (4.5)	6 (1.8)	7 (2.1)	29 (8.9)	25 (7.6)	20 (6.0)	121 (4.6)
Asthenia	0 (0.0)	2 (0.6)	1 (0.3)	2 (0.6)	2 (0.6)	5 (1.5)	6 (1.8)	7 (2.1)	25 (0.9)
Nervous System Disorders	10 (3.0)	10 (3.0)	10 (3.0)	13 (3.9)	9 (2.7)	6 (1.8)	11 (3.3)	14 (4.2)	83 (3.1)
Dizziness	4 (1.2)	5 (1.5)	4 (1.2)	6 (1.8)	6 (1.8)	2 (0.6)	6 (1.8)	10 (3.0)	43 (1.6)
Headache	6 (1.8)	5 (1.5)	3 (0.9)	5 (1.5)	1 (0.3)	2 (0.6)	4 (1.2)	6 (1.8)	32 (1.2)
Vascular Disorders	0 (0.0)	3 (0.9)	3 (0.9)	4 (1.2)	6 (1.8)	4 (1.2)	11 (3.3)	5 (1.5)	36 (1.4)
Hypotension	0 (0.0)	2 (0.6)	2 (0.6)	2 (0.6)	4 (1.2)	1 (0.3)	8 (2.4)	4 (1.2)	23 (0.9)
Cardiac Disorders	4 (1.2)	3 (0.9)	2 (0.6)	4 (1.2)	5 (1.5)	1 (0.3)	6 (1.8)	6 (1.8)	31 (1.2)
Tachycardia	4 (1.2)	2 (0.6)	2 (0.6)	2 (0.6)	3 (0.9)	1 (0.3)	2 (0.6)	2 (0.6)	18 (0.7)
Palpitations	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.6)	2 (0.6)	0 (0.0)	4 (1.2)	4 (1.2)	13 (0.5)
Skin and Subcutaneous Tissue Disorders	5 (1.5)	3 (0.9)	2 (0.6)	1 (0.3)	0 (0.0)	2 (0.6)	2 (0.6)	2 (0.6)	17 (0.6)
Erythema	4 (1.2)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	8 (0.3)

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

A further 92 of 2,540 (3.6%) subjects had drug-related AEs in Period III, 13 of 681 (1.9%) in Period IV, 16 of 676 (2.4%) in Period V, and 273 of 2509 (10.9%) in Period VI.The majority of drug-related TEAEs were mild or moderate in severity in all Periods.There were no specific drug-related TEAEs (PT) that occurred at an incidence ≥1% for any treatment group in Periods III or IV.In Period V, the most common drug-related TEAEs (PT) were oedema peripheral (n=6, 0.9%) and dry mouth (n=2, 0.3%).

- **Study CS8635-A-E303**

In Period I, 171 (7.8%) subjects had a drug-related TEAE.The only drug-related TEAE (preferred term) that occurred at an incidence ≥1% was peripheral oedema (5.0%).

In Period II, 43 (5.3%) subjects had a drug-related TEAE. The percentage of subjects with a drug-related TEAE was similar across the treatment groups, ranging from 5.2% to 5.6%.The most common drug-related TEAEs experienced by subjects during Period II occurred in the system organ class general disorders and administration site conditions (2.2%). The most common drug-related TEAEs (preferred term) were peripheral oedema (2.1%) and hypotension (0.5%).

Table 25: Drug-related AEs by SOC and PT (≥1% in Any Treatment Group) – Period II –Safety Set 2 (CS8635-A-E303)

System Organ Class Preferred Term	OM40/ AML10 (N = 269) n (%)	OM40/ AML10/ HCTZ12.5 (N = 267) n (%)	OM40/ AML10/ HCTZ25 (N = 270) n (%)	Total (N = 806) n (%)
Subjects with drug-related TEAEs	14 (5.2)	14 (5.2)	15 (5.6)	43 (5.3)
General Disorders and Administration Site Conditions	8 (3.0)	4 (1.5)	6 (2.2)	18 (2.2)
Oedema Peripheral	8 (3.0)	4 (1.5)	5 (1.9)	17 (2.1)
Vascular Disorders	1 (0.4)	0 (0.0)	3 (1.1)	4 (0.5)
Hypotension	1 (0.4)	0 (0.0)	3 (1.1)	4 (0.5)

Safety Set 2 included all subjects who received at least 1 dose of double-blind study medication in Period II.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 Period II study medication and up to the first dose of

Period III study medication for subjects continuing into Period III, or up to and including 14 days after the last dose date of study medication in Period II for early terminated subjects.

In Period III 16 (2.0%) subjects had a drug-related TEAE.During Period III, no specific drug-related TEAEs (preferred term) occurred at an incidence ≥1%. The most common drug-related TEAEs (preferred term) were peripheral oedema (0.9%) and blood uric acid increased (0.4%).

In Period IV, 27 (3.5%) subjects had a drug-related TEAE: 16 (2.8%) subjects in the OM/AML/HCTZ 40/10/12.5 mg group and 11 (5.6%) subjects in the OM/AML/HCTZ 40/10/25 mg group.The most common drug-related TEAEs experienced by subjects during Period IV occurred in the system organ classes general disorders and administration site conditions (1.7%) and investigations (0.9%). The most common drug-related TEAE (preferred term) was peripheral oedema (1.7%).

In all Periods across all treatment groups, most drug-related TEAEs were considered mild or moderate in severity.

17.8.4.3. Deaths and other serious adverse events

- **Study CS8635-A-E302**

Two deaths were reported in Periods I-II: 1 x pulmonary embolism (**[Information redacted]**) in the OM/AML/HCTZ 40/5/25 mg group, and 1 x bronchopneumonia (**[Information redacted]**) in the OM/AML/HCTZ 40/10/25 mg group.A further 3 deaths occurred during the open-label period of the study while on OM/AML/HCTZ 20/5/12.5 mg: pulmonary embolism (**[Information redacted]**), suicide (**[Information redacted]**), and cardiogenic shock (**[Information redacted]**).None of the deaths were considered to be related to study medication by the investigator.

In Periods I-II, SAEs were reported in 14 (0.5%) subjects.All of the SAEs occurred in the treatment arms containing OM 40 mg, but none were considered to be related to study medication (Table 26, below).The only SAE that occurred more than once was osteoarthritis (2 events); SAEs that led to discontinuation included: acute myocardial infarction, pulmonary embolism, and bronchopneumonia.

Table 26: Deaths and SAEs by Period II Randomised Treatment Group – Number (%) of Subjects – Periods I–II – Primary Safety Set (CS8635-A-E302)

Category	OM20/ AML5 (N = 353) n (%)	OM20/ AML5/ HCTZ12.5 (N = 329) n (%)	OM40/ AML5 (N = 332) n (%)	OM40/ AML5/ HCTZ12.5 (N = 334) n (%)	OM40/ AML5/ HCTZ25 (N = 331) n (%)	OM40/ AML10 (N = 325) n (%)	OM40/ AML10/ HCTZ12.5 (N = 329) n (%)	OM40/ AML10/ HCTZ25 (N = 332) n (%)	Total (N = 2645) n (%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.1)
Subjects with SAEs during randomised treatment period									
Any SAE	0 (0.0)	0 (0.0)	3 (0.9)	1 (0.3)	3 (0.9)	2 (0.6)	2 (0.6)	3 (0.9)	14 (0.5)
Any drug-related [1] SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with AE leading to discontinuation of study medication during Period II [2]									
Any AE	3 (0.9)	6 (1.8)	8 (2.4)	2 (0.6)	5 (1.5)	8 (2.5)	11 (3.3)	9 (2.7)	52 (2.0)
Any TEAE	3 (0.9)	6 (1.8)	8 (2.4)	2 (0.6)	5 (1.5)	8 (2.5)	11 (3.3)	9 (2.7)	52 (2.0)
Any drug-related [1] TEAE	3 (0.9)	5 (1.5)	6 (1.8)	2 (0.6)	3 (0.9)	8 (2.5)	11 (3.3)	8 (2.4)	46 (1.7)
SAE	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)	4 (0.2)

1. Drug-related was defined as definitely, probably, or possibly related to randomised study medication.**2**. Based on "action taken" on AE Electronic Case Report Form.

A further 11 (0.4%) subjects had an SAE in Period III, 1 (0.2%) in Period IV, and 2 (0.3%) in Period V.During Periods III to V, only 1 SAE (hypokalaemia) was considered related (definitely) to study medication.In the OL phase, 53 (2.1%) subjects had an SAE: 32 (1.7%) subjects on OM/AML/HCTZ 20/5/12.5 mg, 5 (1.1%) subjects on OM/AML/HCTZ 40/5/12.5 mg, 10 (1.2%) subjects on OM/AML/HCTZ 40/5/25 mg, 3 (1.3%) subjects on OM/AML/HCTZ 40/10/12.5 mg, and 3 (1.7%) subjects on OM/AML/HCTZ 40/10/25 mg.Two SAEs in one patient were considered definitely related to study medication (BP decreased and dizziness), and 3 SAEs in

another patient were considered probably related (eye haemorrhage and retinal detachment), or possibly related (gastritis).Both patients were receiving OM/AML/HCTZ 20/5/12.5 mg.

- **Study CS8635-A-E303**

Two deaths were reported during the study.During Period I, Subject 4208-0008 died from a pulmonary embolism whilst on OM/AML 40/10 mg, and during Period IV, Subject 4009-0036 died from cardio-respiratory arrest whilst on OM/AML/HCTZ 40/10/25 mg.Neither death was considered to be related to study medication by the investigator.

SAEs were reported in 15 (0.7%), 5 (0.6%), 9 (1.2%), and 3 (0.4%) subjects in Periods I, II, III, and IV, respectively.None of the reported SAEs were considered to be related to study medication.SAEs that led to discontinuation included: hyperuricaemia, pulmonary embolism, cerebral infarction, cardiac failure and intracardiac thrombus, hypertensive crisis, and myocardial infarction.

17.8.4.4. Discontinuation due to adverse events

- **Study CS8635-A-E302**

In total, 52 (2.0%) subjects discontinued study medication during Periods I-II due to an AE, with 46 (1.7%) subjects considered to have discontinued due to a drug-related AE.Discontinuations due to drug-related AEs were higher in the treatment groups receiving AML 10 mg as one of the components of the combination therapy (2.4% to 3.3%) compared to the treatment groups receiving AML 5 mg (0.6% to 1.8%) (Table 26, above).The most common AEs leading to discontinuation were in the SOCs general disorders and administration site conditions (0.9%), vascular disorders (0.6%), nervous system disorders (0.3%), cardiac disorders (0.2%), and skin and subcutaneous tissue disorders (0.2%).The AEs reported most frequently overall included: peripheral oedema (0.8%), asthenia (0.5%), and hypotension (0.5%).

A further 5 (0.2%) subjects had AEs that led to discontinuation in Period III, 2 (0.3%) in Period IV, and none in Period V.

In Period VI, 23 (0.9%) subjects discontinued study medication due to an AE, with 12 (0.5%) considered due to a drug-related AE.Eleven (0.6%) subjects were on OM/AML/HCTZ 20/5/12.5 mg and 1 (0.1%) subject on OM/AML/HCTZ 40/5/25 mg at the onset of the AE.

- **Study CS8635-A-E303**

During Period I, 49 (2.2%) subjects discontinued due to a TEAE and 38 (1.7%) subjects discontinued due to a drug-related TEAE.Peripheral oedema (n=26) was the most frequently reported TEAE leading to discontinuation.

In total, 9 (1.1%) subjects discontinued from the study due to an AE during Period II: 4 (1.5%) subjects on OM/AML 40/10 mg, 2 (0.7%) subjects on OM/AML/HCTZ 40/10/12.5 mg, and 3 (1.1%) subjects on OM/AML/HCTZ 40/10/25 mg. Seven (0.9%) subjects discontinued from the study due to a drug-related TEAE during Period II.Peripheral oedema (n=2) and hypotension (n=3) were the most frequently reported TEAEs leading to discontinuation.

In total, 5 (0.6%) subjects discontinued due to an AE during Period III while receiving OM/AML/HCTZ 40/10/12.5 mg. Four (0.5%) subjects discontinued due to a TEAE and 1 (0.1%) subject discontinued due to a drug-related TEAE.Peripheral oedema was the most frequently reported TEAE leading to discontinuation (n=2).

In total, 5 (0.7%) subjects discontinued due to an AE (4 considered treatment emergent) during Period IV: 4 (0.7%) subjects on OM/AML/HCTZ 40/10/12.5 mg and 1 (0.5%) subject on OM/AML/HCTZ 40/10/25 mg. Three of the TEAEs (all in subjects on OM/AML/HCTZ 40/10/12.5 mg) were considered drug-related (peripheral oedema [n=2], and atrial fibrillation [n=1]).

17.8.5. Laboratory tests

17.8.5.1. Chemistry Parameters

· **Study CS8635-A-E302**

Results were presented for selected chemistry parameters, including ALT, AST, BUN, creatinine, sodium, potassium, and glucose (both fasting and non-fasting).There were small mean changes in all these parameters across the treatment groups with some of these changes reaching within-group statistical significance. However, the changes were not clinically meaningful within treatment groups or between the triple and dual-component treatment groups for any Period of the study.

· **Study CS8635-A-E303**

From baseline to Week 8/ET for Safety Set 1 and to Week 16/ET for Safety Set 2, there were small mean changes in the selected chemistry parameters of ALT, AST, BUN, creatinine, sodium, potassium, and glucose across the treatment groups with some of these changes reaching within-group statistical significance. However, there were no clinically meaningful changes in any of these parameters among the treatment groups.

17.8.5.2. Electrocardiograph

· **Study CS8635-A-E302 / CS8635-A-E303**

There were no clinically meaningful changes in 12-lead ECG parameters for any subject across any Period of either study.

17.8.5.3. Vital signs

· **Study CS8635-A-E302 / CS8635-A-E303**

There were no clinically meaningful changes in heart rate in any of the treatment groups across any Period of either study.

17.8.6. Post-marketing experience

Not reported for the supplementary data.

17.8.7. Safety issues with the potential for major regulatory impact

Not applicable for the supplementary data.

17.8.8. Other safety issues

17.8.8.1. Safety in special populations

· **Study CS8635-A-E302**

Age: Adverse events were compared in subjects <65 years of age, ≥65 years of age, and ≥75 years of age for the Primary Safety Set (Table 27).While there was an increase in overall AEs with age, the type and pattern of AEs by treatment group was generally similar irrespective of age group, and reflected what was observed in the overall population.The small number of subjects aged ≥75 years limits interpretation of data in this subgroup.

Table 27: Overview of Adverse Events – Number (%) of Subjects by Period II Treatment Group – Age Subgroup – Primary Safety Set (CS8635-A-E302)

	<65 Years of Age N = 2068	≥65 Years of Age N = 577	≥75 Years of Age N = 97
TEAE n (%):	584 (28.2)	179 (31.0)	37 (38.1)
Peripheral oedema	98 (4.7)	29 (5.0)	8 (8.2)

	<65 Years of Age N = 2068	≥65 Years of Age N = 577	≥75 Years of Age N = 97
Headache	83 (4.0)	19 (3.3)	3 (3.1)
Nasopharnyngitis	49 (2.4)	17 (2.9)	3 (3.1)
Asthenia	32 (1.5)	10 (1.7)	3 (3.1)
Drug-related TEAE n (%)	239 (11.6)	71 (12.3)	14 (14.4)
Deaths n (%)	2 (0.1)	0 (0.0)	0 (0.0)
SAE n (%)	12 (0.6)	2 (0.3)	0 (0.0)
Discontinued due to AE n (%)	34 (1.6%)	18 (3.1%)	6 (6.2%)

Gender: Across all treatment groups AEs were observed in a higher proportion of females compared to males, but the type and pattern of AEs observed was generally similar, and reflected what was observed in the overall population (Table 28, below).

Table 28: Overview of Adverse Events – Number (%) of Subjects by Period II Treatment Group – Gender Subgroup – Primary Safety Set (CS8635-A-E302)

	Females N = 1417	Males N = 1228
TEAE n (%)	462 (32.6)	301 (24.5)
Peripheral oedema	104 (7.3)	23 (1.9)
Headache	69 (4.9)	33 (2.7)
Nasopharnyngitis	38 (2.7)	28 (2.3)
Asthenia	28 (2.0)	14 (1.1)
Dizziness	37 (2.6)	18 (1.5)
Drug-related TEAE n (%)	210 (14.8)	100 (8.1)
Deaths n (%)	0 (0.0)	2 (0.2)
SAE n (%)	4 (0.3)	10 (0.8)
Discontinued due to AE n (%)	33 (2.3%)	19 (1.5%)

Hypertension severity / Diabetic Status: AEs were observed at similar rates in subjects with mild to moderate and severe hypertension and in subjects with and without diabetes (Table 29, below).

Table 29: Overview of Adverse Events – Number (%) of Subjects by Period II Treatment Group – Hypertension Severity / Diabetic Status Subgroup – Primary Safety Set (CS8635-A-E302)

	Mild or Moderate Hypertension N = 2370	Severe Hypertension N = 275	With Diabetes N = 387	Without Diabetes N = 2258
TEAE n (%)	700 (29.5)	63 (22.9)	115 (29.7)	648 (28.7)
Peripheral oedema	115 (4.9)	12 (4.4)	23 (5.9)	104 (4.6)
Headache	92 (3.9)	10 (3.6)	14 (3.6)	88 (3.9)
Nasopharnyngitis	58 (2.4)	8 (2.9)	8 (2.1)	58 (2.6)
Asthenia	38 (1.6)	4 (1.5)	7 (1.8)	35 (1.6)
Dizziness	49 (2.1)	6 (2.2)	9 (2.3)	46 (2.0)
Drug-related TEAE n (%)	281 (11.9)	29 (10.5)	43 (11.1)	267 (11.8)
Deaths n (%)	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
SAE n (%)	14 (0.6)	0 (0.0)	2 (0.5)	12 (0.5)
Discontinued due to AE n (%)	49 (2.1%)	3 (1.1%)	8 (2.1%)	44 (1.9%)

- **Study CS8635-A-E303**

Age: Adverse events were compared in subjects <65 years of age, ≥65 years of age, and ≥75 years of age during Period II (Safety Set 2) (Table 30 below).There was no consistent pattern in overall AEs or drug-related AEs with age or treatment group.The small number of subjects aged ≥75 years limits interpretation of data in this subgroup.

Table 30: Overview of Adverse Events (≥1% Overall*) – Number (%) of Subjects by Period II Treatment Group – Age Subgroup –Safety Set 2 (CS8635-A-E303)

	<65 Years of Age N = 641	≥65 Years of Age N = 165	≥75 Years of Age N = 30
TEAE n (%)	95 (14.8)	20 (12.1)	5 (16.7)
Peripheral oedema	10 (1.6)	7 (4.2)	1 (3.3)
URTI	9 (1.4)	3 (1.8)	0 (0.0)
Bronchitis	5 (0.8)	2 (1.2)	0 (0.0)
Drug-related TEAE n (%)	35 (5.5)	8 (4.8)	1 (3.3)
Deaths n (%)	0 (0.0)	0 (0.0)	0 (0.0)
SAE n (%)	4 (0.6)	1 (0.6)	0 (0.0)
Discontinued due to AE n (%)	8 (1.2)	2 (1.2)	0 (0.0)

*In age subgroups <65 or ≥65 Years of Age only, as an n=1 in those ≥75 Years of Age is the equivalent of 3.3% (no AE was reported more than once in this age group overall).

Gender: AEs were observed in a higher proportion of females compared to males, but the type and pattern of AEs observed was generally similar, and reflected what was observed in the overall population (Table 31 below).

Table 31: Overview of Adverse Events (≥1% Overall*) – Number (%) of Subjects by Period II Treatment Group – Gender Subgroup –Safety Set 2 (CS8635-A-E303)

	Females N = 337	Males N = 469
TEAE n (%) Peripheral oedema URTI Bronchitis	50 (14.8%) 6 (1.8) 5 (1.5) 4 (1.2)	65 (13.9%) 11 (2.3) 7 (1.5) 3 (0.6)
Drug-related TEAE n (%)	23 (6.8%)	20 (4.3%)
Deaths n (%)	0 (0.0)	0 (0.0)
SAE n (%)	2 (0.6%)	3 (0.6%)
Discontinued due to AE n (%)	7 (2.1%)	3 (0.6%)

Hypertension severity: AEs were observed at similar rates in subjects with mild to moderate and severe hypertension.The small number of subjects with severe hypertension limits interpretation of data in this subgroup (Table 32, below).

Table 32: Overview of Adverse Events – Number (%) of Subjects by Period II Treatment Group – Hypertension Severity Subgroup –Safety Set 2 (CS8635-A-E303)

	Mild or Moderate Hypertension N = 746	Severe Hypertension N = 60
TEAE n (%) Peripheral oedema URTI	107 (14.3%) 15 (2.0) 11 (1.5)	8 (13.3%) 2 (3.3) 1 (1.7)
Drug-related TEAE n (%)	40 (5.4%)	3 (5.0%)
Deaths n (%)	0 (0.0)	0 (0.0)
SAE n (%)	4 (0.5%)	1 (1.7%)
Discontinued due to AE n (%)	10 (1.3%)	0 (0.0)

Diabetic Status: AEs were observed at similar rates in subjects with and without diabetes.The small number of subjects with diabetes limits interpretation of data in this subgroup (Table 33).

Table 33: Overview of Adverse Events – Number (%) of Subjects by Period II Treatment Group – Diabetic Status Subgroup –Safety Set 2 (CS8635-A-E303)

	With Diabetes N = 104	Without Diabetes N = 702
TEAE n (%)	13 (12.5%)	102 (14.5%)
Peripheral oedema	1 (1.0)	16 (2.3)
URTI	0 (0.0)	12 (1.7)
Bronchitis	2 (1.9)	5 (0.7)
Hyperglycaemia	4 (3.8)	1 (0.1)
Drug-related TEAE n (%)	3 (2.9%)	40 (5.7%)
Deaths n (%)	0 (0.0)	0 (0.0)
SAE n (%)	2 (1.9%)	3 (0.4%)
Discontinued due to AE n (%)	1 (1.0%)	9 (1.3%)

17.8.8.2. Safety related to drug-drug interactions and other interactions

None reported in the submitted data.

17.8.9. Evaluator's overall conclusions on clinical safety

In both studies, the triple combination therapies were well tolerated and the incidence of adverse events was low in all treatment groups. No new safety concerns were identified for the triple combination OM/AML/HCTZ therapies or the component dual combination OM/AML therapies.The types of TEAEs observed with the triple combination therapies were similar to those seen with the component dual combination therapies, with no clinically meaningful differences in any of the safety parameters between the triple and dual combination therapies.In Study CS8635-A-E302, a higher incidence of drug-related peripheral oedema was observed in the triple combination and component dual combination treatment groups which included AML 10 mg as a component compared with the groups with the AML 5 mg dose.Among the subgroups evaluated (age, gender, hypertension severity, and diabetic status), there were slight differences in safety observed between some of the subgroups, however these did not appear to be clinically important.Overall, the safety profiles of the triple combination therapies in both studies were consistent with the safety profiles for the component therapies.

17.9. Supplementary round benefit-risk assessment

17.9.1. Supplementary round assessment of benefits

Study CS-8635-A-303 demonstrated that in non-responders to dual therapy OM/AML 40/10 mg, the addition of HCTZ 12.5 or 25 mg provides an additional clinically relevant diastolic and systolic BP lowering effect whether measured by conventional or 24-hour ambulatory BP monitoring.These data were supported by the demonstration of greater reductions in diastolic and systolic BP in subjects receiving triple-combination therapy compared to the corresponding dual-combinations in the parallel group Study CS-8635-A-302.

Study CS8635-A-U301 (evaluated in the original submission) also demonstrated greater reductions in diastolic and systolic BP in subjects receiving triple-combination therapy (OM/AML/HCTZ 40/10/25 mg) compared to the dual-combinations of OM/AML 40/10 mg,

OM/HCTZ 40/25 mg, or AML/HCTZ 10/25 mg.This result was also seen in an exploratory analysis of those subjects who were non-responders to the dual therapies at Week 4, with results for the OM/AML vs OM/AML/HCTZ comparison being consistent with those from Study CS8635-A-E303.It therefore seems not unreasonable to assume that the results for the other comparisons reflect what would have been observed in an add-on trial.

While the studies did not explore add-on therapy for every dose combination for the dual combination therapies, the EMA has previously stated that "If the benefit of add-on therapy is demonstrated using the highest doses of the baseline 2-drug therapy, then it can be assumed that benefit would also result from addition of the third component to lower doses of the 2-drug combinations."

17.9.2. Supplementary round assessment of risks

The safety profiles of the triple-combination and dual-combination therapies in both studies provided as supplementary data were consistent with the safety profiles for the component therapies, and with those evaluated for the same dose combinations in the original submission.

17.9.3. Supplementary round assessment of benefit-risk balance

On the basis of positive clinical efficacy data and a similar safety profile to the combined individual component therapies, the benefit-risk balance of the triple combination of OM/AML/HCTZ is favourable for add-on therapy in the treatment of hypertension.

17.10. Supplementary round recommendation regarding authorisation

The evaluator recommends approval of the submission for SEVIKAR HCT, subject to modification of the PI[15].

17.11. Supplementary clinical question

17.11.1. Efficacy

Subjects (**[Information redacted]**) (not formally randomised), (**[Information redacted]**), and (**[Information redacted]**) (discontinuation information not recorded on the eCRF) were recruited at a site that was "subsequently closed due to quality issues".In addition, serious GCP violations were observed during monitoring activities and confirmed via an audit for site 2109, resulting in two subjects (**[Information redacted]**) being excluded from the PPS1 analysis set.

Please confirm whether other subjects were recruited from these sites, how these subjects were handled during the analyses, and what impact this had on the results.

[Note: The sponsor subsequently provided an adequate response to the above question.]

[15] Details of recommended revisions to the PI are not included in this Extract from the clinical evaluation reports.

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