ASSESSMENT REPORT
FOR

Copalia, Dafiro, Exforge, Imprida

International Non-proprietary Name: amlodipine/valsartan

Procedure No. EMEA/H/C/xxxx/WS/100/G

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Scope of the variation(s) and changes to the dossier

Medicinal product:	International non-proprietary name:
Dafiro, EMEA/H/C/000776/WS/0100/G	amlodipine / valsartan
Copalia, EMEA/H/C/000774/WS/0100/G	amlodipine / valsartan
Exforge, EMEA/H/C/000716/WS/0100/G	amlodipine / valsartan
Imprida, EMEA/H/C/000775/WS/0100/G	amlodipine / valsartan
MAH:	Novartis Europharm Ltd.

Scope of the variation(s):	Update of Summary of Product Characteristics and Package Leaflet WS-0100-G was submitted for a group of variations consisting of three Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The following variation was not considered acceptable by the CHMP: - Variation 1 (scope as applied for by the MAH): Update of section 5.1 of the SmPC with information on efficacy in patients with stage 2 hypertension and black patients based on studies VAA 2402 and VAA 2403. The following variations were considered acceptable by the CHMP: - Variation 2: Update of the current paragraph in section 5.1 of the SmPC that provides information on the relative efficacy of valsartan/amlodipine 80/5 mg compared to amlodipine 10 mg in relation to the incidence of oedema. In addition, the MAH took the opportunity to update the SmPC in line with the latest QRD template and to update the contact details of the local representatives in the Package Leaflet. - Variation 3: Update of section 5.1 of the SmPC with information on efficacy in obese patients based on studies VAA 2401, VAA 2402, VAA 2403, VAA 2404 and VAA US02 (as well as original dossier studies VAA 2201, VAA 2305, VAA 2306, VAA 2307 and VAA 2308).
Rapporteur:	Jens Heisterberg

2. Scientific discussion

2.1. Introduction

Exforge/Dafiro/Copalia/Imprida is an oral antihypertensive product consisting of a fixed dose combination a combination of valsartan, an angiotensin II receptor antagonist, and amlodipine, a calcium channel blocker.

The approved indications are:

> *"Treatment of essential hypertension.*
>
> *[Exforge/Dafiro/Copalia/Imprida] is indicated in patients whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy."*

The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

The amlodipine component inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure.

Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT_1, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked receptor subtype AT_2, which appears to counterbalance the effect of the AT_1 receptor.

The Marketing Authorisation for Exforge in the EU was granted on 17 January 2007, for Dafiro on 18 January 2007, for Copalia on 17 January 2007 and for Imprida on 17 January 2007.

Exforge, Copalia, Dafiro and Imprida have been marketed globally in over 110 countries since 2007. The currently approved doses of the fixed dose combination of valsartan/amlodipine in the EU are 80/5 mg, 160/5 mg, and 160/10 mg.

The purpose of this worksharing application is to update section 5.1 of the SmPC with additional clinical efficacy data, collected from five completed phase 3b/4 studies, in patients likely to require dual therapy including patients with stage 2 hypertension, patients not adequately responding to commonly prescribed monotherapies, and specific subgroups including black patients, diabetics and obese patients. In support of the proposed wording on consistent efficacy of the valsartan/amlodipine fixed combination in obese and diabetic patients, reference is made not only to the 5 clinical study reports completed since marketing approval, but also to 5 clinical study reports already presented in the original marketing authorisation application.

This application concerns the following medicinal products:

Medicinal product:	**International non-proprietary name:**
Dafiro	amlodipine / valsartan
Copalia	amlodipine / valsartan
Exforge	amlodipine / valsartan
Imprida	amlodipine / valsartan

The variations submitted in the group are the following:

Variation(s) requested		Type
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II
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WS-0100-G was submitted for a group of variations consisting of three Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The scopes applied for by the MAH were as follows:

- Variation 1: Update of section 5.1 of the SPC with information on efficacy in patients with stage 2 hypertension and black patients based on studies VAA 2402 and VAA 2403;

- Variation 2: Update of section 5.1 of the SPC with information on efficacy and safety of valsartan/amlodipine 160/5 mg compared to amlodipine 10 mg based on study VAA 2404. In addition the MAH took the opportunity to update the SPC in line with the latest QRD template and to update the contact details of the local representatives in the Package Leaflet;

- Variation 3: Update of section 5.1 of the SPC with information on efficacy in patients not adequately responding to any monotherapy and in obese and diabetic patients based on studies VAA 2401, VAA 2402, VAA 2403, VAA 2404 and VAA US02 (as well as original dossier studies VAA 2201, VAA 2305, VAA 2306, VAA 2307 and VAA 2308).

2.2. Clinical aspects

2.2.1. Clinical efficacy

Variation 1

The MAH proposed the following statement in section 5.1 of the SmPC as part of variation 1:

"In two additional active-controlled studies of 1,612 patients, additional blood pressure lowering effects for Exforge were observed compared to baseline in patients not adequately responding to monotherapy including ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers and diuretics.

Active controlled trials in stage 2 hypertensive patients

Two active-controlled studies of 1,195 patients with mean sitting systolic blood pressure ≥160 mmHg and <200 mmHg were conducted. In the first study in 639 patients (baseline blood pressure 171/95 mmHg), an Exforge regimen of 5 mg/160 mg force-titrated to 10 mg/160 mg significantly reduced sitting blood pressure after 4 weeks by 30/13 mmHg compared to 24/9 mmHg with a regimen of amlodipine 5 mg force-titrated to 10 mg. The second active-controlled study, specifically designed to evaluate the efficacy of Exforge in 556 black patients, compared an Exforge regimen of 5 mg/160 mg force-titrated to 10 mg/160 mg with an amlodipine regimen of 5 mg force-titrated to 10 mg. In this

study (baseline blood pressure 171/98 mmHg), Exforge significantly reduced sitting blood pressure after 4 weeks by 31/13 mmHg compared to 27/11 mmHg with amlodipine."

In support of the proposed wording, the MAH submitted studies VAA 2402 and VAA2403 which are summarized below:

Study VAA 2402

A 12-week double-blind, randomized, multicenter, parallel group study to evaluate the efficacy and safety of orally administered valsartan / amlodipine combination based therapy versus amlodipine monotherapy in Black patients with stage II hypertension.

The study was conducted in 74 centres in Colombia, Ecuador, South Africa and the USA from June 2006 to April 2007.

The primary objective was to demonstrate the superior efficacy of the combination of valsartan/amlodipine 160/10 mg and 320/10 mg treatment regimen in Black patients with stage II hypertension, by testing the hypothesis that the valsartan/amlodipine combination treatment regimen produces a superior reduction in mean seated systolic blood pressure (MSSBP) from baseline compared to amlodipine monotherapy at Week 8.

Inclusion criteria:

- Black male or female outpatients ≥ 18 years of age.

- Stage II hypertension, defined as MSSBP ≥ 160 mmHg and MSSBP < 200 mmHg, measured using a validated automated oscillometric device at Visit 2 at the study site.

- Treatment naïve patients had a MSSBP ≥ 160 mmHg and < 200 mmHg at Visit 2.

Study design, Study A2402

<table>
<tr><td>Screening/Washout</td><td colspan="5">Double-blind treatment</td></tr>
<tr><td>(1 week)</td><td colspan="5">(12 weeks)</td></tr>
<tr><td>Visit 1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td></tr>
<tr><td>Days -7 to -3</td><td>Day 1</td><td>Week 2</td><td>Week 4</td><td>Week 8</td><td>Week 12</td></tr>
<tr><td></td><td colspan="5">↓ Randomization</td></tr>
<tr><td rowspan="2"></td><td colspan="3" rowspan="2"></td><td colspan="2">+HCTZ 12.5 mg**</td></tr>
<tr><td colspan="2">+valsartan/amlodipine 320/10 mg**</td></tr>
<tr><td></td><td></td><td colspan="4">valsartan/amlodipine 160/10 mg*</td></tr>
<tr><td rowspan="2"></td><td colspan="5">valsartan/amlodipine 160/5 mg</td></tr>
<tr><td colspan="5">amlodipine 5 mg</td></tr>
<tr><td></td><td></td><td colspan="4">amlodipine 10 mg*</td></tr>
<tr><td rowspan="2"></td><td colspan="2" rowspan="2"></td><td colspan="3">+placebo**</td></tr>
<tr><td colspan="2">+HCTZ 12.5 mg**</td></tr>
</table>

*forced titration
**optional titration (MSSBP ≥130mmHg)

The *primary efficacy variable* was change from baseline in MSSBP (mmHg) at Week 8 LOCF and was analyzed using analysis of covariance (ANCOVA).

Secondary efficacy variables were change from baseline MSDBP at Week 8 (last observation carried forward; LOCF); change from baseline MSSBP and MSDBP at Weeks 2, 4 and 8 and 12; overall BP control rate after 12 weeks of treatment (MSSBP <140 mmHg and MSDBP <90 mmHg).

Treatment, country, length of washout received were fitted as factors in the model and baseline MSSBP as a covariate. The change from baseline LSM, the difference between LS means, (valsartan/amlodipine vs. amlodipine) and two-sided 95% confidence interval were presented.

The ITT population was used for analysis.

Patient disposition by treatment strategy (Randomized population)

Disposition Reason	Val/Aml N=286 n (%)	Amlodipine N=286 n (%)	Total N=572 n (%)
Screened			1042
Completed	247 (86.4)	250 (87.4)	497 (86.9)
Discontinued	39 (13.6)	36 (12.6)	75 (13.1)
Lost to follow-up	13 (4.5)	5 (1.7)	18 (3.1)
Subject withdrew consent	9 (3.1)	8 (2.8)	17 (3.0)
Adverse event(s)	7 (2.4)	9 (3.1)	16 (2.8)
Protocol deviation	8 (2.8)	7 (2.4)	15 (2.6)
Administrative problems	2 (0.7)	2 (0.7)	4 (0.7)
Abnormal test procedure result(s)	0 (0.0)	2 (0.7)	2 (0.3)
Unsatisfactory therapeutic effect	0 (0.0)	2 (0.7)	2 (0.3)
Abnormal laboratory value(s)	0 (0.0)	1 (0.3)	1 (0.2)

The ITT population was defined as the randomised patients with at least 1 post baseline measurement and consisted of 278 (97.2% of randomised) in the valsartan/amlodipine arm and 278 patients (97.2% of randomised) in the amlodipine arm.

Protocol deviations: higher in the amlodipine treatment strategy (38.1%) compared to the valsartan/amlodipine treatment strategy (32.5%). Most of these were major protocol deviations (24.1% for valsartan/amlodipine, and 26.2% for amlodipine). The most frequently reported major deviations were time of BP measurement < 20 or > 30 hours after the last dose of study medication (12.2% for valsartan/amlodipine; 14.7% for amlodipine), study drug interruption > 3 consecutive days prior to Visit 6 (4.2% for valsartan/amlodipine; 5.2% for amlodipine), and MSSBP < 160mmHg or ≥ 200 at Visit 2 (4.2% for valsartan/amlodipine; 3.5% for amlodipine).

Baseline characteristics: The mean age was 53.2 years (SD 11.01), 96% of patients were <75 years. 60.1% were females. The mean (SD) MSSBP was 170.5 (9.27) mmHg, the mean (SD) MSDBP was 98.3 (9.27) mmHg.

Results:

Adjusted least square mean changes from baseline in MSSBP and MSDBP (mmHg) at Week 8 (LOCF) by treatment strategy (Intent-to-treat population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
MSSBP (primary efficacy)						
Val/Aml (N=278)	277	170.5	-33.3 (1.20)	-6.6	(-9.12, -4.11)	<.0001*
Amlodipine (N=278)	278	170.6	-26.6 (1.18)			
MSDBP (secondary efficacy)						
Val/Aml (N=278)	277	98.4	-13.6 (0.70)	-2.76	(-4.22, -1.30)	0.0002*
Amlodipine (N=278)	278	98.1	-10.8 (0.69)			

N is the number of patients in the ITT population; n is the number of ITT patients with both baseline and endpoint non-missing values.

LS mean change from baseline in MSSBP and MSDBP (mmHg) at Week 4 (LOCF) by treatment regimen (Study A2402, ITT population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
MSSBP						
Val/Aml (N=278)	277	170.5	-30.9 (1.17)	-4.36	(-6.80, -1.92)	0.0005*
Amlodipine (N=278)	278	170.6	-26.5 (1.15)			
MSDBP						
Val/Aml (N=278)	277	98.4	-13.1 (0.68)	-2.49	(-3.91, -1.08)	0.0006*
Amlodipine (N=278)	278	98.1	-10.6 (0.67)			

N is the number of patients in the ITT population; n is the number of ITT patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 4 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is val/aml minus amlodipine.
ANCOVA model with treatment, country and length of washout as factors and baseline MSDBP as covariate.
* p-value <0.05

Blood pressure control parameters at Week 4 by treatment regimen (Study A2402 ITT, population)

Parameter	Treatment	N	No. (%) controlled	Estimated odds ratio	p-value 95% CI for odds ratio[4]
Overall BP control [1]					
	Val/Aml (N=278)	267	115 (43.1)	1.75	0.0028*
	Amlodipine (N=278)	269	82 (30.5)		(1.21, 2.52)
Diastolic BP control [3]					
	Val/Aml (N=278)	267	179 (67.0)	1.8	0.0036*
	Amlodipine (N=278)	269	152 (56.5)		(1.2, 2.7)
Systolic BP control [2]					
	Val/Aml (N=278)	267	133 (49.8)	1.7	0.0020*
	Amlodipine (N=278)	269	98 (36.4)		(1.2, 2.5)

N is the number of patients in ITT population; n is the number of ITT patients with a non-missing measurement at that timepoint.
[1] Overall BP control was defined as MSSBP <140 mmHg and MSDBP <90 mmHg.
[2] Systolic BP control was defined as MSSBP <140 mmHg.
[3] Diastolic BP control was defined as MSDBP <90 mmHg.
[4] Logistic regression model with treatment and length of washout as factors and baseline MSSBP and MSDBP as covariates
* Represents p-value less than 0.05
† Only analyzed by asymptotic method, for which p-values are not calculated

Study VAA2403

An 8-week double-blind, randomized, multicenter, parallel group study to evaluate the efficacy and safety of orally administered valsartan/amlodipine combination based therapy versus amlodipine monotherapy in patients with stage II hypertension.

The study was conducted in 75 centres in the USA and Italy from June 2006 to April 2007.

The primary objective was to demonstrate the superior efficacy of the combination of valsartan/amlodipine 160/10 mg in patients with stage II hypertension, by testing the hypothesis that the valsartan/amlodipine 160/10 mg combination regimen produces a superior reduction in MSSBP from baseline compared to amlodipine 10 mg monotherapy at week 4.

Inclusion criteria:

- Male or female outpatients ≥ 18 years of age.

- Stage II hypertension, defined as MSSBP ≥ 160 mmHg and MSSBP < 200 mmHg, measured using a validated automated oscillometric device at Visit 2 at the study site.

- Treatment naïve patients had a MSSBP ≥ 160 mmHg and < 200 mmHg at Visit 2.

Study design, 2403:

Screening/Washout	Double Blind Treatment			
1- week	8-weeks			
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Day -7 to Day -3	Day 1	Week 2	Week 4	Week 8
	↓ Randomization			
			**+ HCTZ 12.5 mg	
		*valsartan 160 mg / amlodipine 10 mg		
	valsartan 160 mg / amlodipine 5 mg			
	amlodipine 5 mg			
		*amlodipine 10 mg		
			**+ HCTZ 12.5 mg	

* Forced titration
** Optional titration (MSSBP ≥ 130 mmHg

The *primary efficacy variable* was change from baseline in MSSBP (mmHg) at Week 4 and was analyzed using analysis of covariance (ANCOVA).

Secondary efficacy variables were change from baseline MSDBP at Week 4 (LOCF); change from baseline MSSBP and MSDBP at Weeks 2, 4 and 8; Overall BP control rate after 8 weeks of treatment (MSSBP <140 mmHg and MSDBP <90 mmHg).

Treatment, country, length of washout received were fitted as factors in the model and baseline MSSBP as a covariate. The ITT population was used for analysis.

Patient disposition by treatment strategy (Randomized population):

Disposition Reason	Val/Aml N=322 n (%)	Amlodipine N=324 n (%)	Total N=646 n (%)
Completed	289 (89.8)	288 (88.9)	577 (89.3)
Discontinuations	33 (10.2)	36 (11.1)	69 (10.7)
Adverse event(s)	19 (5.9)	19 (5.9)	38 (5.9)
Subject withdrew consent	7 (2.2)	15 (4.6)	22 (3.4)
Lost to follow-up	3 (0.9)	1 (0.3)	4 (0.6)
Administrative problems	1 (0.3)	1 (0.3)	2 (0.3)
Abnormal test procedure result(s)	2 (0.6)	0 (0.0)	2 (0.3)
Protocol deviation(s)	1 (0.3)	0 (0.0)	1 (0.2)

The ITT population was defined as the randomised patients with at least 1 post baseline measurement and consisted of 318 (98.8 % of randomised) in the valsartan/amlodipine arm and 321 patients (99.1% of randomised) in the amlodipine arm.

Protocol deviations occurred in 92 patients (28.6%) in the valsartan/amlodipine treatment strategy, and in 87 patients (26.9%) in the amlodipine treatment strategy. Approximately half were major deviations (46 patients, 14.3 % for valsartan/amlodipine; 47 patients, 14.5% for amlodipine).

Baseline characteristics: The mean age was 58.1 years (SD 10.33), 94% of patients were <75 years. 50.2 % were males. The mean (SD) MSSBP was 170.5 (8.72) mmHg, the mean (SD) MSDBP was 95.2 (10.18) mmHg.

Results:

Primary efficacy analysis: Change from baseline in MSSBP (mmHg) (primary endpoint) and MSDBP (mmHg) (secondary endpoint) at Week 4 (LOCF) by treatment strategy (ITT population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
MSSBP						
Val/Aml 160/10 mg (N=318)	318	170.2	-30.1 (0.79)	-6.6	(-8.59, -4.56)	<0.0001*
Amlodipine 10 mg (N=321)	321	170.8	-23.5 (0.81)			
MSDBP						
Val/Aml 160/10 mg (N=318)	318	95.7	-12.5 (0.44)	-3.9	(-5.05, -2.78)	<0.0001*
Amlodipine 10 mg (N=321)	321	94.7	-8.6 (0.45)			

N is the number of patients in the ITT population; n is the number of ITT patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 4 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is val/aml minus amlodipine
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP or MSDBP as covariate.
* p-value < 0.05

Blood pressure control parameters at Week 4 (LOCF) by treatment regimen (Study A2403, ITT population)

Parameter	Treatment	n	No. (%) controlled	Estimated odds ratio	p-value [4] 95% CI for odds ratio
Overall BP control [1]					
	Val/Aml 160/10 mg (N=318)	307	139 (45.3)	2.7	<0.0001*
	Amlodipine 10 mg (N=321)	307	73 (23.8)		(1.9, 3.9)
Systolic BP control [2]					
	Val/Aml 160/10 mg (N=318)	307	159 (51.8)	2.9	<0.0001*
	Amlodipine 10 mg (N=321)	307	85 (27.7)		(2.0, 4.1)
Diastolic BP control [3]					
	Val/Aml 160/10 mg (N=318)	307	236 (76.9)	2.8	<0.0001*
	Amlodipine 10 mg (N=321)	307	190 (61.9)		(1.8, 4.2)

N is the number of patients in ITT population; n is the number of ITT patients with a non-missing measurement at that timepoint.
[1] Overall BP control defined as MSSBP < 140 mmHg and MSDBP < 90 mmHg.
[2] Systolic BP control defined as MSSBP < 140 mmHg.
[3] Diastolic BP control defined as MSDBP < 90 mmHg.
[4] Logistic regression model with treatment and length of washout as factors and baseline MSSBP and MSDBP as covariates
* Represents p-value less than 0.05

Discussion on Clinical Efficacy - Variation 1

Study 2402:

Patients were included in this study if they had systolic hypertension >160 mmHg and <200mmHg corresponding to grade 2/3. There were no requirements regarding the type(s) of previous

antihypertensive therapy and their dosages, and also treatment naïve patients could be included. Patients received either amlodipine 5mg (uptitrated to 10mg at week 2) or valsartan/amlodipine 160/5 mg (with uptitration to valsartan/amlodipine 160/10 at week 2). This is not in accordance with the authorised indication.

The discontinuation rate was rather high for a hypertension trial, 13.6% and 12.6%, in the valsartan/amlodipine and amlodipine arms, respectively, and approximately 25% of patients having major protocol deviations.

Patients were sufficiently balanced at baseline; a preponderance of females included is noted.

The study is only partially relevant for the European Union setting as patients in the valsartan/amlodipine arm were optionally uptitrated at week 4 to 320/10 mg, a strength which is not authorised in the EU. The applicant has therefore focused the data review largely on week 4 since this was the last visit that valsartan/amlodipine 160/10 mg could be compared to amlodipine 10 mg monotherapy. However, at that point in time those patients had not received the antihypertensive treatment with valsartan/amlodipie 160/10 mg and amlodipine 10 mg for more than 2 weeks, which is not regarded as sufficient to judge its efficacy.

In summary, it is acknowledged that valsartan/amlodipine 160/10 mg seems more effective than amlodipine 10 mg in the treatment of systolic hypertension >160mmHg and <200mmHg in a population of Black patients that was either treatment naïve or was treated with non-specified antihypertensives (i.e. not according to the authorised indication). However, a final judgement on this cannot be made as these analyses were made after 2 weeks of treatment which is considered too short. Furthermore, the conduct of the study was not adequate as indicated by the high number of discontinuations and protocol violations. This study is therefore not considered supportive of the proposed statement regarding Black patients with grade 2 hypertension.

Study 2403:

Patients were included if they had systolic hypertension >160 mmHg and <200mmHg corresponding to grade 2/3. There were no requirements regarding the type(s) of previous antihypertensive therapy; also treatment naïve patients could be included.

The primary endpoint was evaluated at week 4, i.e. 2 weeks after forced uptitration of the drugs in both treatment arms. This period is considered too short to evaluate the antihypertensive effect. Also according to the guideline on clinical investigation of medicinal products in the treatment of hypertension (CHMP/EWP/238/95 Rev.2 and EMA//238/1995/rev.3) a tested dose should remain stable for at least 4 weeks.

The discontinuation rates were comparable in both treatment arms; approximately 10% and major protocol deviations occurred in around 14% of patients in either treatment arm. LOCF seemed not to be specified to be applied for the primary analysis.

In summary, in spite of the fact that valsartan/amlodipine 160/10 mg seems more effective than amlodipine 10 mg in the treatment of systolic hypertension >160mmHg and <200mmHg in a population that was either treatment naïve or was treated with non-specified antihypertensives (i.e. not according to the authorised indication), a final judgement on this approach cannot be made as these analyses were made after 2 weeks of treatment which is considered too short. This study is therefore not considered supportive of the proposed statement regarding patients with grade 2 hypertension.

Thus, the provided studies are not considered sufficiently robust and are not in line with the authorised indication. As a consequence, the wording that was proposed by the MAH:

"In two additional active-controlled studies of 1,612 patients, additional blood pressure lowering effects for Exforge were observed compared to baseline in patients not adequately responding to monotherapy including ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers and diuretics.

Active controlled trials in stage 2 hypertensive patients

Two active-controlled studies of 1,195 patients with mean sitting systolic blood pressure ≥160 mmHg and <200 mmHg were conducted. In the first study in 639 patients (baseline blood pressure 171/95 mmHg), an Exforge regimen of 5 mg/160 mg for 2 weeks force-titrated to 10 mg/160 mg significantly reduced sitting blood pressure after 4 weeks by 30/13 mmHg compared to 24/9 mmHg with a similar regimen of amlodipine 5 mg force-titrated to 10 mg. The second active-controlled study, specifically designed to evaluate the efficacy of Exforge in 556 black patients, compared an Exforge regimen of 5 mg/160 mg force-titrated to 10 mg/160 mg for 2 weeks with a similar regimen of amlodipine 5 mg force-titrated to 10 mg. In this study (baseline blood pressure 171/98 mmHg), Exforge significantly reduced sitting blood pressure after 4 weeks by 31/13 mmHg compared to 27/11 mmHg with amlodipine."

can therefore not be accepted.

Variation 2

The MAH proposed the following wording (underlined) in section 5.1 of the SmPC as part of variation 2:

"In patients not adequately controlled on amlodipine 5 mg, amlodipine/valsartan 5 mg/80 mg may achieve blood pressure control similar to amlodipine 10 mg with less oedema and amlodipine/valsartan 5 mg/160 mg produced numerically greater reductions in blood pressure compared to amlodipine 10 mg with a 4-fold lower incidence of peripheral oedema. In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, amlodipine/valsartan 5 mg/80 mg may achieve similar blood pressure control with less oedema."

In support of the proposed wording, the MAH submitted study VAA2404, which is summarized below:

Study VAA 2404

A 12-week randomized, double-blind, multicenter, parallel group study to evaluate the efficacy, tolerability, and safety of treatment with the combination of valsartan/amlodipine 160/5 mg compared to amlodipine 10 mg in patients with essential hypertension not adequately controlled with amlodipine 5 mg alone.

The study was conducted from January to November 2007 in 148 centres in Germany, Spain, France, Italy, Switzerland, Turkey, Argentina, Sweden, Norway, Ecuador, Finland, and Chile.

The *co-primary objectives* of this study were:

- To confirm that the combination of valsartan/amlodipine 160/5mg is non-inferior to amlodipine 10mg alone when comparing the reduction of MSSBP from baseline to week 8 (LOCF) (Visit 4) between the two treatment groups (primary efficacy objective).

- To confirm that the combination of valsartan/amlodipine 160/5mg induces less peripheral edema compared to amlodipine 10mg alone up to Visit 4 (week 8) quantified as adverse event (AE) reported peripheral edema (primary safety objective).

Inclusion criteria:

- Male or female outpatients ≥ 55 years of age.

- Patients with essential hypertension measured using a validated automated oscillometric device at Visit 1 (Non-treated patients had to have a MSSBP ≥ 140 mmHg and ≤ 160 mmHg and patients pre-treated on monotherapy prior to Visit 1 had to have MSSBP ≤ 160 mmHg).

- To be eligible for randomization at Visit 2 (Day 1) all patients had to have a MSSBP ≥ 130 mmHg and ≤ 160 mmHg.

- No peripheral edema at Visit 2 (randomization)

Study design, Study 2404

<table>
<tr><td>Phase</td><td>Single-blind amlodipine run-in/ wash-out*
(4 weeks)</td><td colspan="4">Double-blind treatment</td></tr>
<tr><td>Visit</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td>Day</td><td>-28</td><td>1</td><td>28</td><td>56</td><td>84</td></tr>
<tr><td>Week</td><td>-4</td><td>Day 1</td><td>4</td><td>8</td><td>12</td></tr>
<tr><td rowspan="3"></td><td rowspan="3"></td><td colspan="4">↓ Randomization
valsartan/amlodipine 160/5 mg</td></tr>
<tr><td rowspan="2">amlodipine 5mg</td><td colspan="2" rowspan="2">amlodipine 10mg</td><td colspan="2" rowspan="2">val/amlo 160/5 mg</td></tr>
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* For patients pretreated with antihypertensive medication prior to study start, the single-blind run-in phase was also considered a wash-out period from previous medication. For patients with previous antihypertensive medication that required a gradual downward titration, the tapering down was done according to manufacturer's instructions and the last dose was taken by week -2 prior to randomization.

Primary efficacy variable: Change from baseline in MSSBP (mmHg) at week 8 LOCF.

Secondary efficacy variables were the change from baseline MSDBP at week 8 (LOCF), the change from baseline in MSSBP and MSDBP at weeks 4, 8 and 12, systolic control rate (MSSBP <130 mmHg) at weeks 4, 8 and 12, systolic response rate (MSSBP <130 mmHg or ≥ 20 mmHg reduction from baseline in MSSBP) at weeks 4, 8 and 12 and overall BP control rate (MSSBP/MSDBP <140/90 mmHg for non-diabetics and <130/80 mmHg for diabetics) at weeks 4, 8 and 12.

For the primary safety objective, investigators also evaluated patients for the presence of edema at every visit.

Statistical methods

The first primary hypothesis for non-inferiority in MSSBP reduction from baseline to Week 8 LOCF between valsartan/amlodipine 160/5 mg and amlodipine 10 mg was analyzed using analysis of covariance with treatment, region and diabetic status as fixed factors and baseline MSSBP as a covariate for the ITT population. The non-inferiority margin was 3 mmHg.

The second primary hypothesis for a difference between valsartan/amlodipine and amlodipine with regards to the proportion of patients who developed peripheral edema up to and including Week 8 was analyzed using logistic regression with treatment, region, and diabetic status as fixed factors in the model for the Safety population.

Patient disposition by treatment (Randomized population)

Total number of patients	Val/Aml 160/5mg	Aml 10mg	Total
Screened*			1644
Enrolled**			1521
Randomized***	592 (100.0)	591 (100.0)	1183 (100.0)
Completed	557 (94.1)	476 (80.5)	1033 (87.3)
Total discontinued	35 (5.9)	115 (19.5)	150 (12.7)
Primary reason for discontinuation			
Adverse event(s)	15 (2.5)	84 (14.2)	99 (8.4)
Subject withdrew consent	10 (1.7)	22 (3.7)	32 (2.7)
Protocol deviation	3 (0.5)	3 (0.5)	6 (0.5)
Lost to follow-up	2 (0.3)	3 (0.5)	5 (0.4)
Administrative problems	2 (0.3)	1 (0.2)	3 (0.3)
Unsatisfactory therapeutic effect	2 (0.3)	1 (0.2)	3 (0.3)
Subject's condition no longer requires study drug	1 (0.2)	1 (0.2)	2 (0.2)

The total number of patients in the randomized population is used as the denominator for calculating the percentages.
*Visit 1
**Visit 1; patients enrolled at Visit 1 to single-blind amlodipine 5mg run-in
***Visit 2

Protocol deviations occurred in 40.7% of the patients in the valsartan/amlodipine group, and in 47.7 % of the patients in the amlodipine group. Most of these were minor deviations (35.3 % for valsartan/amlodipine; 37.2 % for amlodipine). The most frequently reported major deviations (i.e. those that led to exclusion from the Per Protocol population) were no study medication taken for the last 3 days prior to Visit 5 (2.5 % for valsartan/amlodipine; 7.4 % for amlodipine), chronic use of NSAIDs (3.5 % for valsartan/amlodipine; 4.9 % for amlodipine) and poor compliance (≤ 80%) with study medication (1.7 % for valsartan/amlodipine; 6.6 % for amlodipine).

Baseline characteristics: The mean age was 65.5 years (SD 10.33), 86.7 % of patients were <75 years. 51.9 % were males. The mean (SD) MSSBP was 143.9 (8.09) mmHg, the mean (SD) MSDBP was 83.8 (8.60) mmHg. 77.5 % had prior antihypertensive medication.

Results:

Change in MSSBP (primary endpoint) and MSDBP (secondary endpoint) at Week 8 (LOCF) (Study A2404, ITT population)

Treatment (mg)	n	LS Mean change from baseline	Between-treatment difference (SE)*	95% CI	p-value**
MSSBP					
Val/Aml 160/5	570	-8.01	-1.72 (0.65)	(-3.00, -0.44)	<0.001
Aml 10	521	-6.30			
MSDBP					
Val/Aml 160/5	570	-4.65	-0.52 (0.39)	(-1.29, 0.26)	<0.001
Aml 10	521	-4.13			

Results were from an ANCOVA model with treatment, region and diabetic status as factors and baseline MSSBP or MSDBP as a covariate.
* Negative difference favors Val/Aml 160/5 mg
** p value <0.025 indicates statistical significance of the test for non-inferiority at a margin of 3 mmHg for MSSBP; or a margin of 2 mmHg for MSDBP

Change in MSSBP at week 8 (LOCF) (Per-protocol population)

Treatment (mg)	n	LS Mean change from baseline	Between-treatment difference (SE)*	95% CI	p-value**
Val/Aml 160/5	519	-8.32	-2.23 (0.69)	(-3.58, -0.88)	<0.001
Aml 10	434	-6.09			

Results were from an ANCOVA model with treatment, region and diabetic status as factors and baseline MSDBP as a covariate.
* Negative difference favors Val/Aml 160/5 mg
** p-value < 0.025 indicates statistical significance of the test for non-inferiority at a margin of 3 mmHg

Control and response rates by treatment group at week 8 (Study A2404 ITT population)

Parameter	Treatment (mg)	n	n (%) with control or response	Estimated Odds Ratio (SE)	95% CI	p-value
Overall BP control [1]	Val/Aml 160/5	567	324 (57.14)	1.33 (0.19)	(1.00, 1.76)	0.050
	Aml 10	510	251 (49.22)			
Systolic control [2]	Val/Aml 160/5	567	194 (34.22)	1.46 (0.22)	(1.09, 1.95)	0.011
	Aml 10	510	130 (25.49)			
Systolic response [3]	Val/Aml 160/5	567	207 (36.51)	1.47 (0.21)	(1.12, 1.93)	0.006
	Aml 10	510	139 (27.25)			

[1] Overall BP control rate defined as BP < 140/90 mmHg for non-diabetic patients and <130/80 mmHg for diabetic patients
[2] Systolic BP control rate defined as MSSBP < 130 mmHg
[3] Systolic BP responder rate defined as MSSBP < 130 mmHg or at least 20 mmHg reduction from baseline in MSSBP
Results were from a logistic regression with treatment, region and diabetic status as factors and baseline MSSBP and baseline MSDBP as covariates
Odds ratio >1 favors Val/Aml 160/5 mg

Proportion of patients with peripheral edema up to and including week 8 (Study A2404, Safety population

Treatment (mg)	n	Incidence rate n (%)	Estimated Odds Ratio (SE)	95% CI	p-value*
Val/Aml 160/5 (N=592)	592	39 (6.6)	0.15 (0.03)	(0.11, 0.22)	<0.001
Aml 10 (N=591)	591	184 (31.1)			

N is the number of patients in the Safety population; n is the number of Safety patients with a non-missing measurement at endpoint
Incidence rate: No. (%) of patients with peripheral edema
Results were from a logistic regression with treatment, region and diabetic status as factors
* p value <5% indicates statistical significance
Odds ratio <1 favors Val/Aml 160/5 mg
A patient with multiple occurrences of peripheral edema is counted only once for that treatment group

Peripheral oedema resolved in more than half of patients who switched from amlodipine to valsartan/amlodipine after week 8.

Furthermore, during the procedure in response to a CHMP request for an alternative analysis to the pre-defined last observation carried forward (LOCF) analysis performed in Study A2404, the MAH performed a mixed-effect model for repeated measures analysis which addressed the imbalance in study discontinuations between the two treatment groups.

During the preparation for the mixed-effect model analyses, inconsistencies in the original programming for deriving LOCF values in the ITT analysis (but not the Per Protocol analysis) were discovered. As a result, all of the original efficacy analyses related to blood pressure (i.e., change from baseline in msSBP and msDBP, overall BP control rate, systolic BP control rate, and systolic BP

responder rate) were repeated using corrected efficacy datasets. The results of these revised analyses are consistent with those presented in the original CSR and type II variation application, and are presented below.

In addition, the per-protocol analysis results are in line with the original conclusions, indicating that the disproportionate discontinuation rate in the amlodipine group has not impacted the treatment effect.

Study A2404 – Revised efficacy analyses

At week 8 (LOCF), the primary analysis time point, a statistically non-inferior least square (LS) mean reduction from baseline in msSBP, the primary efficacy variable, and msDBP was observed with valsartan/amlodipine 160/5 mg compared to amlodipine 5 mg.

These results are consistent with the LOCF analysis presented in the original CSR and type II variation application.

Change in msSBP and msDBP at Week 8 (LOCF) (ITT population, Study A2404)

Treatment (mg)	**n**	**LS Mean change from baseline**	**Between-treatment difference (SE)***	**95% CI**	**p-Value****
msSBP					
Val/Aml 160/5	586	-8.01	-2.06 (0.65)	(-3.34, -0.79)	<0.001
Aml 10	580	-5.95			
msDBP					
Val/Aml 160/5	586	-4.57	-0.57 (0.38)	(-1.32, 0.18)	<0.001
Aml 10	580	-3.99			

Results were from an ANCOVA model with treatment, region and diabetic status as factors and baseline msSBP as a covariate.
* Negative difference favors Val/Aml 160/5mg
** p value < 0.025 indicates statistical significance of the test for non-inferiority at a margin of 3 mmHg for msSBP; 2 mmHg for msDBP

Statistically non-inferior LS mean reductions from baseline in both msSBP and msDBP were also achieved with valsartan/amlodipine 160/5 mg compared to amlodipine 10 mg at weeks 4, 8 and 12. These results are also consistent with the analysis presented in the original CSR and type II variation application.

Change in msSBP at weeks 4, 8 and 12 (ITT population, Study A2404)

Week	Treatment (mg)	n	LS Mean change from baseline	Between-treatment difference (SE)**	95% CI	p-value**
4	Val/Aml 160/5 Aml 10	586 580	-8.29 -6.29	-2.00 (0.61)	(-3.19, -0.81)	<0.001
8	Val/Aml 160/5 Aml 10	566 515	-8.23 -6.13	-2.11 (0.66)	(-3.41, - 0.81)	<0.001
12	Val/Aml 160/5 Aml 10*	560 481	-9.13 -8.16	-0.96 (0.77)	(-2.48, 0.55)	<0.001

* Patients receiving Aml 10 mg switched to Val/Aml 160/5 mg after week 8
Results were from an ANCOVA model with treatment, region and diabetic status as factors and baseline msSBP as a covariate.
** Negative difference favors Val/Aml 160/5 mg
*** p-value < 0.025 indicates statistical significance of the test for non-inferiority at a margin of 3 mmHg

Change in msDBP at weeks 4, 8 and 12 (ITT population, Study A2404)

Week	Treatment (mg)	n	LS Mean change from baseline	Between-treatment difference (SE)**	95% CI	p-value**
4	Val/Aml 160/5 Aml 10	586 580	-5.02 -4.23	-0.79 (0.38)	(-1.53, -0.05)	<0.001
8	Val/Aml 160/5 Aml 10	566 515	-4.70 –4.06	-0.65 (0.40)	(-1.42, 0.13)	<0.001
12	Val/Aml 160/5 Aml 10*	560 481	-5.52 -4.90	-0.62 (0.42)	(-1.44, 0.20)	<0.001

In Study A2404, overall BP control was defined as BP <140/90 mmHg for non-diabetic patients and <130/80 mmHg for diabetic patients. Systolic BP control was defined as msSBP <130 mmHg. Systolic BP response was defined as msSBP <130 mmHg or at least 20 mmHg reduction from baseline in msSBP.

At weeks 4 and 8, statistically significant greater overall BP control rates, systolic BP control rates and systolic BP response rates were achieved with valsartan/amlodipine 160/5 mg compared to amlodipine 10 mg. At week 12, rates were numerically superior for valsartan/amlodipine compared to amlodipine, but no longer statistically significant as would be expected since patients in both treatment strategies had been receiving valsartan/amlodipine 160/5 mg from week 8 onwards. These results are consistent with the analysis presented in the original CSR and type II variation application.

Overall BP control rate by treatment group at weeks 4, 8 and 12 (ITT population, Study A2404)

			n (%)	Estimated		
Week (mg)	**Treatment**	**n**		**Odds Ratio**	**95% CI**	**p-value**
				(SE)		
4	Val/Aml 160/5	586	339 (57.85)	1.46 (0.20)	(1.12, 1.90)	0.005
	Aml 10	580	283 (48.79)			
8	Val/Aml 160/5	566	324 (57.24)	1.33 (0.19)	(1.00, 1.77)	0.048
	Aml 10	515	256 (49.71)			
12	Val/Aml 160/5	560	343(61.25)	1.20 (0.17)	(0.91, 1.59)	0.203
	Aml 10*	481	266 (55.30)			

* Patients receiving Aml 10 mg switched to Val/Aml 160/5 mg after week 8
Overall BP control rate defined as BP < 140/90 mmHg for non-diabetic patients and <130/80 mmHg for diabetic patients
Results were from a logistic regression with treatment, region and diabetic status as factors and baseline msSBP and baseline msDBP as covariates
Odds ratio >1 favors Val/Aml 160/5 mg

Study 2404 – A mixed-effect model for repeated measures analyses

Upon request from CHMP during the procedure, alternative analyses were conducted by the MAH using a mixed effect model for repeated measures. These analyses confirmed that the original conclusions are upheld, indicating that the disproportionate discontinuation rate in the amlodipine group has not impacted the treatment effect.

The new analyses use a likelihood-based estimation method to utilize all available data, including subjects with missing value. It accounts for the repeated measures structure in the data by adding the "visit" and "visit by treatment" interaction on top of the original model (i.e., treatment, region, and diabetes status as factors and baseline msSBP as covariate). An unstructured covariance matrix assumption was used. The patient's week 4 and week 8 blood pressure reductions were included as repeated measurements. Repeated measures analyses were performed for the change from baseline in msSBP, the primary efficacy variable, and msDBP, and are presented below.

At weeks 4 and 8, a statistically non-inferior least square (LS) mean reduction from baseline in msSBP was observed with valsartan/amlodipine 160/5 mg compared to amlodipine 10 mg (primary efficacy variable). The changes from baseline at weeks 4 and 8 were similar for both the valsartan/amlodipine and the amlodipine treatment groups confirming that the disproportionate discontinuation rate in the amlodipine group did not have an impact on the between treatment effects at week 8.

Change in msSBP at weeks 4 and 8 using mixed-effect model for repeated measures analysis (ITT population, Study A2404)

Week	Treatment (mg)	n	LS Mean change from baseline	Between-treatment difference (SE)**	95% CI	p-value**
4	Val/Aml 160/5 Aml 10	586 580	-8.13 -6.14	-1.99 (0.61)	(-3.18, -0.80)	<0.001
8	Val/Aml 160/5 Aml 10	566 515	-8.34 -6.23	-2.10 (0.66)	(-3.40, -0.81)	<0.001

Results were from a mixed-effect model for repeated measures with treatment, region, diabetic status, visit, and visit by treatment interaction as factors and baseline msSBP as a covariate.
** Negative difference favors Val/Aml 160/5 mg
*** p value < 0.025 indicates statistical significance of the test for non-inferiority at a margin of 3 mmHg

The mixed-effect model for repeated measures analysis for change from baseline in msDBP is shown in the table below.

At weeks 4 and 8, a statistically non-inferior least square (LS) mean reduction from baseline in msDBP was observed with valsartan/amlodipine 160/5 mg compared to amlodipine 10 mg. The changes from baseline at weeks 4 and 8 were similar for both the valsartan/amlodipine and the amlodipine treatment groups confirming that the disproportionate discontinuation rate in the amlodipine group did not have an impact on the between treatment effects at week 8.

Change in msDBP at weeks 4 and 8 using mixed-effect model for repeated measures analysis (ITT population, Study A2404)

Week	Treatment (mg)	n	LS Mean change from baseline	Between-treatment difference (SE)**	95% CI	p-value**
4	Val/Aml 160/5 Aml 10	586 580	-4.93 -4.14	-0.79 (0.38)	(-1.53, -0.05)	<0.001
8	Val/Aml 160/5 Aml 10	566 515	-4.73 -4.12	-0.61 (0.39)	(-1.38, 0.16)	<0.001

A summary of the blood pressure results at week 8 in Study A2404 for msSBP, the primary efficacy variable, and msDBP, which were generated in the aforementioned analyses is presented below.

Comparisons of changes in msSBP and msDBP at week 8 using different analyses (Study A2404)

Analysis	**LSM change from baseline**					
	msSBP		**p-value**	**msDBP**		**p-value**
	Val/Aml	Aml		Val/Aml	Aml	
	160/5mg	10mg		160/5mg	10mg	
Week 8 LOCF (ITT) (revised analysis)	-8.01	-5.95	P<0.001	-4.57	-3.99	P<0.001
Week 8 (ITT) (revised analysis)	-8.23	-6.13	P<0.001	-4.70	-4.06	P<0.001
Week 8 mixed-effect						
model for repeated						
measures (ITT)	-8.34	-6.23	P<0.001	-4.73	-4.12	P<0.001
(EMA requested						
analysis)						
Week 8 (PP) (original analysis)	-8.32	-6.09	P<0.001	NA	NA	NA

In addition, upon request by the CHMP during the procedure, the MAH clarified the fact that the already existing SmPC wording in section 5.1:

"In patients not adequately controlled on amlodipine 5 mg, amlodipine/valsartan 5 mg/80 mg may achieve blood pressure control similar to amlodipine 10 mg with less oedema. In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, amlodipine/valsartan 5 mg/80 mg may achieve similar blood pressure control with less oedema."

is based on data collected from the two multi-factorial studies [Study A2201] and [Study A2307] submitted as part of the original MAA for the fixed dose combination valsartan/amlodipine.

Study A2201 and Study A2307 were both multicenter, double-blind, randomized, multifactorial, placebo-controlled, parallel group trials. After a 2 week washout period, patients entered a 2-4 week single-blind placebo run-in period, followed by randomization to an 8 week double-blind treatment period with: placebo, valsartan monotherapy doses, amlodipine monotherapy doses, and the respective combinations of valsartan/amlodipine doses. Study A2201 and Study A2307 evaluated the lower and higher ends of the dose response curves, respectively. Patients were randomized with mild to moderate essential diastolic hypertension (grades 1 or 2 WHO classification msDBP ≥ 95 mmHg and < 110 mmHg). The primary objective was to assess the blood pressure lowering effects of a once daily regimen of the various combinations of valsartan and amlodipine, compared to their monotherapy components and placebo. The primary efficacy variable was mean sitting diastolic blood pressure (msDBP). Both trials enrolled male and female outpatients at least 18 years of age. Exclusion criteria were very similar for both trials.

Study design (Study A2307)

Washout	Single-blind run-in	Double-blind treatment					
(2 weeks)	(2-4 weeks)	(8 weeks)					
Visit 0	1	2	3	4	5	6	7*
Week -6 to -4	-4 to -2	0	1	2	4	6	8
		↓ Randomization					
		Placebo					
		Valsartan 160 mg OD					
		Valsartan 320 mg OD					
	Placebo	Amlodipine 10 mg OD					
		Valsartan/Amlodipine 160/10 mg OD					
		Valsartan/Amlodipine 160/5 mg OD	Valsartan/Amlodipine 320/10 mg OD				
*At the end of the 8 week double-blind treatment phase, the first 400 patients to complete all double-blind visits, with no drug related serious adverse experiences during the trial, were eligible to enroll in a one-year open-label extension.							

Baseline demographics and characteristics as presented in the table below were generally comparable between the two studies with the one exception of more Black patients enrolled in Study A2201 and more Oriental patients in Study A2307.

Based on the similarity of designs and study populations, qualitative treatment comparisons can be made across the two studies after correcting for differences in placebo response. Baseline msSBP/msDBP was 153/99 mmHg in Study A2201 and 157/99 mmHg in Study A2307.

Baseline demographics and patient characteristics (Randomized population, Study A2201 and Study A2307)

	Study A2201	Study A2307
Age (years), mean	54.4	56.9
Age category, %		
<65 years	81.8	71.4
≥ 65 years	18.2	28.6
Sex, n (%)		
Male	1022 (53.5)	629 (50.3)
Female	889 (46.5)	621 (49.7)
Race, n (%)		
Caucasian	1519 (79.5)	992 (79.4)
Black	199 (10.4)	5 (0.4)
Oriental	30 (1.6)	171 (13.7)
Other	163 (8.5)	82 (6.6)

Placebo-subtracted reductions in msDBP, the primary efficacy variable, for Study A2201 and Study A2307 are shown below. A numerically greater reduction in msDBP was observed with the combination of valsartan/amlodipine 80/5 mg (-7.8 mmHg) in Study A2201 compared to amlodipine 10 mg (-6.9 mmHg) in Study 2307.

Placebo-subtracted LS Mean Reduction in msDBP (mmHg) at Endpoint (ITT population, Study A2201)

		Valsartan				
		Placebo	40	80	160	320
	Placebo		-3.4p	-3.0p	-4.3p	-6.7p
Amlodipine	2.5	-2.6p	-4.1p	-6.6pva	-6.5pva	-7.4pa
	5	-4.7p	-7.9pva	-7.8pva	-7.5pva	-9.2pva

Placebo response: -6.8 mmHg
p = statistically significant vs. placebo (p < 0.05)
v = statistically significant vs. valsartan (p < 0.05)
a = statistically significant vs. amlodipine (p < 0.05)

Placebo-subtracted LS Mean Reduction in msDBP (mmHg) at Endpoint (ITT population, Study A2307)

			Valsartan	
		Placebo	160	320
	Placebo		-4.6p	-4.5p
Amlodipine	10	-6.9p	-8.9pva	-9.9pva

Placebo response: -8.8 mmHg
p = statistically significant vs. placebo (p < 0.05)
v = statistically significant vs. valsartan (p < 0.05)
a = statistically significant vs. amlodipine (p < 0.05)

Placebo-subtracted reductions in msSBP for Study A2201 and StudyA2307 are shown below. Consistent with the results for diastolic blood pressure, a numerically greater reduction in msSBP was observed with the combination of valsartan/amlodipine 80/5 mg (-14.0 mmHg) in Study 2201 compared to amlodipine 10 mg (-11.2 mmHg) in Study 2307.

Placebo-subtracted LS Mean Reduction in msSBP (mmHg) at Endpoint (ITT population, Study A2201)

		Valsartan				
		Placebo	40	80	160	320
	Placebo		-5.0p	-6.2p	-8.3p	-8.9p
Amlodipine	2.5	-5.7p	-8.8 pva	-10.3 pva	-10.0 pa	-11.6 pa
	5	-8.3p	-12.9 pva	-14.0 pva	-12.8 pva	-16.0 pva

Placebo-subtracted LS Mean Reductions in msSBP (mmHg) at Endpoint (ITT population, Study A2307)

			Valsartan	
		Placebo	160	320
	Placebo		-7.3p	-7.0p
Amlodipine	10	-11.2p	-14.9pva	-15.5pva

Placebo response: -12.9 mmHg

p = statistically significant vs. placebo (p < 0.05)

v = statistically significant vs. valsartan (p < 0.05)

a = statistically significant vs. amlodipine (p < 0.05)

The percentage of patients in active treatment groups achieving BP control (msDBP <90 mmHg) (minus the percent of placebo patients achieving BP control) are displayed below. Control rates with valsartan/amlodipine 80/5 mg (39.1%) in Study 2201 were similar to amlodipine 10 mg (37.5 %) in Study 2307 after adjusting for placebo control rates.

Percent of patients in active treatment groups achieving blood pressure control (minus percent of placebo patients achieving BP control) at endpoint (ITT population, Study A2201 and Study 2307)

	Control rates (%)	
Treatment (mg)	**Study A2201**	**Study A2307**
Val/Aml 320/10	---	41.5[pv]
Val/Aml 320/5	48.6[pva]	---
Val/Aml 320/2.5	34.1[pa]	---
Val/Aml 160/10	---	39.2[pv]
Val/Aml 160/5	36.2[pv]	---
Val/Aml 160/2.5	38.9[pva]	---
Val/Aml 80/5	39.1[pv]	---
Val/Aml 80/2.5	33.5[pva]	---
Val/Aml 40/5	36.8[pv]	---
Val/Aml 40/2.5	13.0[p]	---
Val 320	33.3[p]	21.2[p]
Val 160	24.4[p]	27.9[p]
Val 80	14.9[p]	---
Val 40	18.1[p]	---
Aml 10	---	37.5[p]
Aml 5	30.9[p]	---
Aml 2.5	16.1[p]	---
Placebo	33.9	42.6

p=statistically significant vs. placebo (p <0.05)

v=statistically significant vs. valsartan (p <0.05)

a=statistically significant vs. amlodipine (p <0.05)

Blood pressure control was defined as msDBP < 90 mmHg

Placebo control rate in Study A2201 was 33.9% and in Study A2307, 42.6%

In addition, pooled safety data from these 2 double-blind placebo-controlled trials Study A2201 and Study A2307, previously submitted in the original MAA, demonstrate a lower incidence of peripheral oedema with the combination of valsartan/amlodipine 80/5 mg (3/128, 2.3%) compared to amlodipine 10 mg (26/207, 12.6%).

Discussion on Clinical Efficacy - Variation 2

Study 2404

This study had a classical non responder design. Patients included were >55 years, and had mild systolic hypertension (grade 1).

The study was characterised by disproportionate discontinuations and protocol violations. Discontinuations and major protocol violations were considerably higher in the amlodipine group; almost 20% of patients discontinued treatment in the amlodipine group and 2.5% of patients discontinued treatment in the valsartan/amlodipine group. The majority of patients in the amlodipine group discontinued treatment due to adverse events.

Major protocol violations occurred in 72 out of 592 randomised patients (12%) in the valsartan/amlodipine group and in 155 out of 591 randomised patients (26%) in the amlodipine group.

The non-inferiority margin chosen was 3 mmHg for MSSBP. As this is a non-inferiority study also the PP population is relevant for the analysis. This has been provided in the study report for the primary endpoint (see above) and complements the ITT analysis.

The primary analysis used LOCF in order to account for missing data. However, due to the large difference in the rate of discontinuations between the 2 treatment arms (almost 20% in the amlodipine arm vs. 2.5% in the valsartan/amlodipine arm), this analysis may have favoured the valsartan/amlodipine arm.

Upon request by the CHMP during the procedure, the MAH provided revised primary LOCF (ITT) analyses for Study A2404 using corrected efficacy datasets as it was discovered that there were inconsistencies in the original programming for deriving LOCF values in the ITT analysis (but not the Per Protocol analysis). All of the original efficacy analyses related to blood pressure (i.e., change from baseline in msSBP and msDBP, overall BP control rate, systolic BP control rate, and systolic BP responder rate) were repeated using corrected efficacy datasets.

Furthermore, a revised analysis for change in BP at week 8 (ITT, without LOCF) was performed in Study 2404.

An additional mixed-effect model for repeated measures analysis was performed for Study 2404.

The proposed wording in section 5.1 focuses on the efficacy of valsartan/amlodipine compared to amlodipine alone in the context of oedema incidence rather than on the oedema incidence itself as described in section 4.8 of the SmPC. According to the MAH, this information provided in section 5.1 is relevant for the prescriber as it presents efficacy of valsartan/amlodipine in the approved doses of 5 mg/80 mg and 5 mg/160 mg as a benefit in relation to oedema incidence versus amlodipine in monotherapy. Thus, the proposed SmPC wording provides additional reassurance to the prescriber on efficacy of valsartan/amlodipine fixed combination in relation to oedema reduction.

Oedema was significantly more frequent in the amlodipine monotherapy group. In this respect, it should also be kept in mind that only patients 55 years or older were included in the study. Oedema is dose-dependent with amlodipine therapy and the clearance of amlodipine is reduced in the elderly, resulting in a higher exposure. It is therefore likely that the incidence of amlodipine in this study may be exaggerated due to the chosen study population.

The MAH acknowledged that patients aged 55 years and over were selected in Study A2404 to demonstrate the effect of valsartan/amlodipine compared to amlodipine monotherapy on the reduction of oedema incidence. According to the MAH, as recognised by guidelines for the management of arterial hypertension, the patient population selected in Study A2404 (≥ 55 years old) is representative of the hypertensive population at risk. Age (men >55 years; women >65 years) is considered a factor influencing prognosis of cardiovascular risk and should be used to stratify the risk of cardiovascular disease. Older patients may be more prone to develop peripheral oedema on non-dihydropyridine calcium channel blockers due to the effects of aging on the peripheral vasculature. Therefore, according to the MAH, this is the population that may have the greatest benefit with respect to attenuation in the development of oedema but does not preclude a benefit in younger patients.

It is reassuring that all the presented analyses are consistent and yield similar results. However, it should be kept in mind that, albeit statistically significant, the differences in BP reductions between valsartan/amlodipine 160/5 mg and amlodipine 10 mg are not exceptionally different and there is no obvious reason to insert a statement on *"numerically greater reductions in blood pressure compared to amlodipine 10 mg"*, derived from a not completely recognized subgroup of patients with hypertension (those ≥55 years), into section 5.1 of the SmPC. In spite of the fact that the age of ≥55 years is an agreed risk factor for males for CV disease (65 years for females), it is not recognized as a subgroup for hypertension trials.

The SmPC guideline states on section 5.1:

"…It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials, and giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced, and should summarise evidence from relevant studies supporting the indication. The magnitude of effects should be described using absolute figures. (Relative risks or odd ratio should not be presented without absolute figures)…."

Consequently, as mentioned above with reference to the SmPC guideline, the efficacy part of the proposed wording is not considered appropriate. Therefore, the proposed wording (highlighted):

"In patients not adequately controlled on amlodipine 5 mg, amlodipine/valsartan 5 mg/80 mg may achieve blood pressure control similar to amlodipine 10 mg with less oedema and amlodipine/valsartan 5 mg/160 mg produced numerically greater reductions in blood pressure compared to amlodipine 10 mg with a 4-fold lower incidence of peripheral oedema. In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, amlodipine/valsartan 5 mg/80 mg may achieve similar blood pressure control with less oedema."

is not acceptable to the CHMP and thus the context of the proposed safety information on oedema is not relevant. The existing information on oedema in section 4.8 of the SmPC is regarded sufficient for prescribers.

Furthermore, during the procedure the CHMP questioned the validity of the already existing SmPC wording in section 5.1:

"In patients not adequately controlled on amlodipine 5 mg, amlodipine/valsartan 5 mg/80 mg may achieve blood pressure control similar to amlodipine 10 mg with less oedema. In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, amlodipine/valsartan 5 mg/80 mg may achieve similar blood pressure control with less oedema."

Upon request by the CHMP, the MAH clarified that this wording was based on data collected from the two multi-factorial studies [Study A2201] and [Study A2307] submitted as part of the original MAA for the fixed dose combination valsartan/amlodipine.

Following the assessment of all data provided, the CHMP did not consider it appropriate to compare two different studies in order to obtain a statement on BP results in section 5.1 of the SmPC. The studies are not considered completely comparable with respect to the included patient population which is demonstrated by the differences in age categories (28.6% patients >65 years in study A2307 compared to 18.2% in study A2201) and ethnic origin (10.4% of Black patients in study A2201 as compared to 0.4% in study A2307. Study A2307 had in contrast a higher percentage of oriental patients, 13.7%, as compared to study A2201 (1.6%)).

Following the CHMP assessment of these data, the MAH acknowledged the CHMP comments and revised the current wording in the product information to more accurately reflect the data generated in the multi-factorial Study A2201 and Study A2307. However, according to the MAH, the percentage of patients in active treatment groups achieving BP control (msDBP <90 mmHg) could be considered similar for valsartan/amlodipine 80/5 mg (39.1%) [Study 2201] and amlodipine 10 mg (37.5 %) [Study 2307] after adjusting for placebo control rates. The CHMP, however, considered the placebo control rates very different: 33.9% (studyA2201) and 42.6% (study 2307) and furthermore, the

MSDPB and msSPB reductions for amlodipine 10 mg do not seem comparable to valsartan/amlodipine 80/5 mg but seem to lie in between the results for amlodipine 5 mg and valsartan/amlodipine 80/5 mg. These facts indicate that it is not appropriate to compare the two studies with regard to BP results.

Consequently, the suggested amendment to the existing wording as proposed by the MAH in response to the CHMP Request for supplementary information, to more accurately reflect the data generated in the multi-factorial Study A2201 and Study A2307, and the mentioning of the age range to avoid ambiguity regarding the population studied in Study A2404 was rejected by the Committee:

"*5.1 Pharmacodynamic properties*

(...)

Amlodipine/Valsartan

(...)

~~*In patients not adequately controlled on amlodipine 5mg*~~ *Patients receiving amlodipine/valsartan 5 mg/80 mg may achieve blood pressure control similar to amlodipine 10 mg with less oedema. In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, amlodipine/valsartan 5 mg/80 mg may achieve similar blood pressure control with less oedema.*

In an additional active-controlled study of 1183 patients aged 55 years or older not adequately controlled on amlodipine 5mg, amlodipine/valsartan 5 mg/160 mg produced numerically greater reductions in blood pressure compared to amlodipine 10 mg with a 4-fold lower incidence of peripheral oedema."

Moreover, the CHMP was of the view that the existing paragraph, although previously accepted by the Committee by mistake, should be removed from the SmPC since it was considered that the text might be misleading for prescribers.

In conclusion, the wording suggested by the MAH as part of variation 2 is not acceptable to the CHMP. In addition, the already approved paragraph should for the reasons outlined above be deleted from the SmPC. As part of variation 2, the MAH took the opportunity to update the SmPC in line with the latest QRD template and to update the contact details of the local representatives in the Package Leaflet, which is acceptable.

Variation 3

The MAH proposed the following wording in section 5.1 of the SmPC as part of variation 3:

a) "*In two additional active-controlled trials of 1612 patients, additional blood pressure lowering effects for Exforge were observed compared to baseline in patients not adequately responding to monotherapy including ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers and diuretics."*

and

b) "*Age, gender, race, body mass index or diabetes status did not influence the response to Exforge*."

The first part of the variation:

a) With reference to efficacy in patients not adequately responding to any monotherapy, the MAH has submitted studies VAA 2401 and VAA US02 in support of this statement and these studies are summarised below:

Study VAA2401

A double-blind, randomized, multicenter study to evaluate the effectiveness of the combination of valsartan and amlodipine in hypertensive patients not controlled on monotherapy.

The study was conducted in 118 centres in the USA, France, Spain, Canada, Norway, Belgium, Slovakia and Switzerland from February 2006 to January 2007.

The primary objective was to estimate the proportion of patients reaching blood pressure (BP) control, i.e. MSSBP <140 mmHg and MSDBP <90 mmHg for non-diabetics, or MSSBP <130 and MSDBP <80 for diabetic patients, after 16 weeks of treatment with a valsartan/amlodipine 160/10mg treatment strategy or a valsartan/amlodipine 160/5mg treatment strategy in hypertensive patients not controlled with monotherapy.

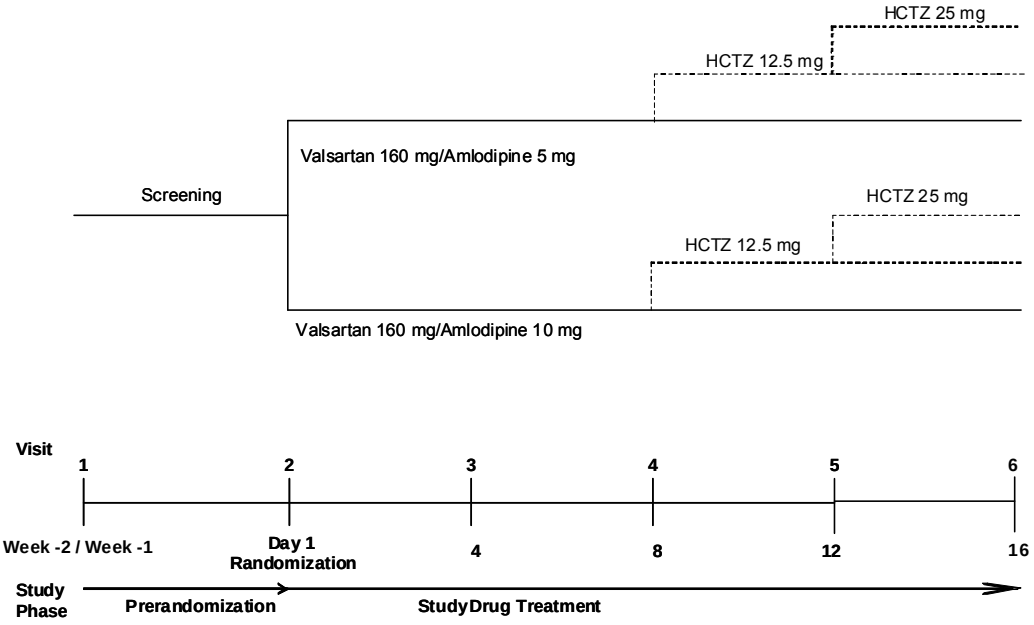
Inclusion criteria:

- Male or female patients ≥ 18 years of age;

- MSSBP of ≥ 140 mmHg and/or MSDBP ≥ 90 mmHg (Non-diabetic patients) / MSSBP ≥ 130 mmHg and/or MSDBP ≥ 80 (Diabetic patients) at Visits 1 and 2;

- Patients treated with monotherapy at a dose considered as adequate by the investigator for a minimum of two months prior to Visit 1.

Study design, 2401



The primary efficacy variable was the proportion of patients who achieved blood pressure control at endpoint (Week 16), defined as MSSBP/MSDBP <140/90 mmHg for non-diabetic patients or <130/80 mmHg for diabetic patients.

Secondary efficacy variables were the proportion of patients who reached blood pressure control at Pre-HCTZ Endpoint (Week 8), the number of BP controlled patients by study week; change from baseline in MSDBP and MSSBP, and diastolic BP control rate.

Statistical methods:

All efficacy analyses were performed using the ITT population. The unadjusted control rates (expressed as a percentage) for valsartan/amlodipine 160/5mg and valsartan/amlodipine 160/10mg at Endpoint (Week 16, LOCF) were presented with the corresponding asymptotic two-sided 95% confidence intervals. The proportion of controlled patients in each treatment group at endpoint was analyzed using a logistic regression model. Terms for treatment and diabetic status were included in the model (supplementary analysis). The point estimate for the odds ratio (valsartan/amlodipine 160/10mg vs. valsartan/amlodipine 160/5mg) and two-sided 95% confidence interval were presented.

The null hypothesis was rejected and superiority was established if the p-value <0.05.

Patient disposition by treatment strategy (Randomized population)

Disposition Reason	**Val/Aml 160/5 mg N=443 n (%)**	**Val/Aml 160/10 mg N=451 n (%)**
Completed	407 (91.9)	374 (82.9)
Discontinued	36 (8.1)	77 (17.1)
Adverse event(s)	25 (5.6)	62 (13.7)
Subject withdrew consent	7 (1.6)	9 (2.0)
Protocol violation	2 (0.5)	4 (0.9)
Administrative problems	1 (0.2)	1 (0.2)
Lost to follow-up	0 (0.0)	1 (0.2)
Unsatisfactory therapeutic effect	1 (0.2)	0 (0.0)

The ITT population was defined as the randomised patients with at least 1 post baseline measurement and consisted of 440 (99.3% of randomised) in the valsartan/amlodipine 160/5mg arm and 449 patients (99.6% of randomised) in the valsartan/amlodipine 160/10mg arm.

Protocol violations occurred in 24.8% of the patients in the valsartan/amlodipine 160/5 mg treatment strategy, and 29.3% in the valsartan/amlodipine 160/10 mg treatment strategy; however, few patients had major protocol violations, and they occurred at similar frequencies in both treatment strategies.

Baseline characteristics: Baseline characteristics were comparable between treatment arms. The mean age was 58.5 years (SD 12.17), 89.6 % of patients were <75 years. 49.6 % were males. The mean (SD) MSSBP was 150.1 (10.11) mmHg, the mean (SD) MSDBP was 90.7 (7.65) mmHg.

Prior medication: ARBs 39.4%, ACE-inhibitors 22.1%, beta blockers 14.8%, calcium channel blockers 13.9%, diuretics 8.9%, other 0.9%.

Results:

Primary endpoint

The proportion of patients reaching BP control after 16 weeks of treatment was slightly higher for valsartan/amlodipine 160/10mg (74.8%, 95%CI 70.82, 78.85) than for valsartan/amlodipine 160/5mg (72.7%, 95%CI 68.57, 76.89).

Supplementary analysis: The estimated odds of being controlled at Endpoint Week 16 were 1.35 and 1.64 for the valsartan/amlodipine 160/5 mg and 160/10 mg treatment strategies, respectively. The estimated odds ratio for valsartan/amlodipine 160/5 mg versus 160/10 mg was 0.82, favouring valsartan/amlodipine 160/10 mg over valsartan/amlodipine 160/5 mg.

Secondary endpoints

LS mean change from baseline in MSSBP and MSDBP at week 8 (LOCF) and week 16 (LOCF) by treatment regimen (Study A2401, ITT population)

BP parameter Timepoint	Treatment strategy (mg)	N	LSM change (SEM)	Difference [2]	95% CI	p-value
MSSBP	Val/Aml 160/5	440	-16.5 (0.71)	2.72	(1.33, 4.12)	0.0001 *
Endpoint week 8^	Val/Aml 160/10	449	-19.2 (0.70)			
MSSBP	Val/Aml 160/5	440	-17.5 (0.67)	2.46	(1.13, 3.80)	0.0003 *
Endpoint week 16^^	Val/Aml 160/10	449	-20.0 (0.67)			
MSDBP	Val/Aml 160/5	440	-9.3 (0.45)	2.06	(1.16, 2.96)	<.0001 *
Endpoint week 8^	Val/Aml 160/10	449	-11.3 (0.45)			
MSDBP	Val/Aml 160/5	440	-10.4 (0.42)	1.22	(0.38, 2.06)	0.0046 *
Endpoint week 16^^	Val/Aml 160/10	449	-11.6 (0.42)			

Mean baseline MSSBP was 149.8 mmHg for valsartan/amlodipine 160/5 mg and 150.4 mmHg for valsartan/amlodipine 160/10 mg.
Mean baseline MSDBP was 90.8 mmHg for valsartan/amlodipine 160/5 mg and 90.6 mmHg for valsartan/amlodipine 160/10 mg.
^ Pre-HCTZ endpoint i.e. week 8 or LOCF value
^^ Endpoint is the value at Week 16 or LOCF value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[2] Difference is Val/Aml 160/5 mg minus Val/Aml 160/10 mg ANCOVA model with treatment regimen, country and diabetic status as factors and baseline MSSBP/MSDBP as covariate.
* p-value <0.05

Study US02

A multicenter, randomized, double-blind, parallel design trial to evaluate the blood pressure lowering efficacy comparing moderate versus aggressive treatment regimen of Exforge in patients uncontrolled on angiotensin receptor blocker (ARB) monotherapy.

The study was conducted in 140 centres in the USA from March 2008 to January 2009.

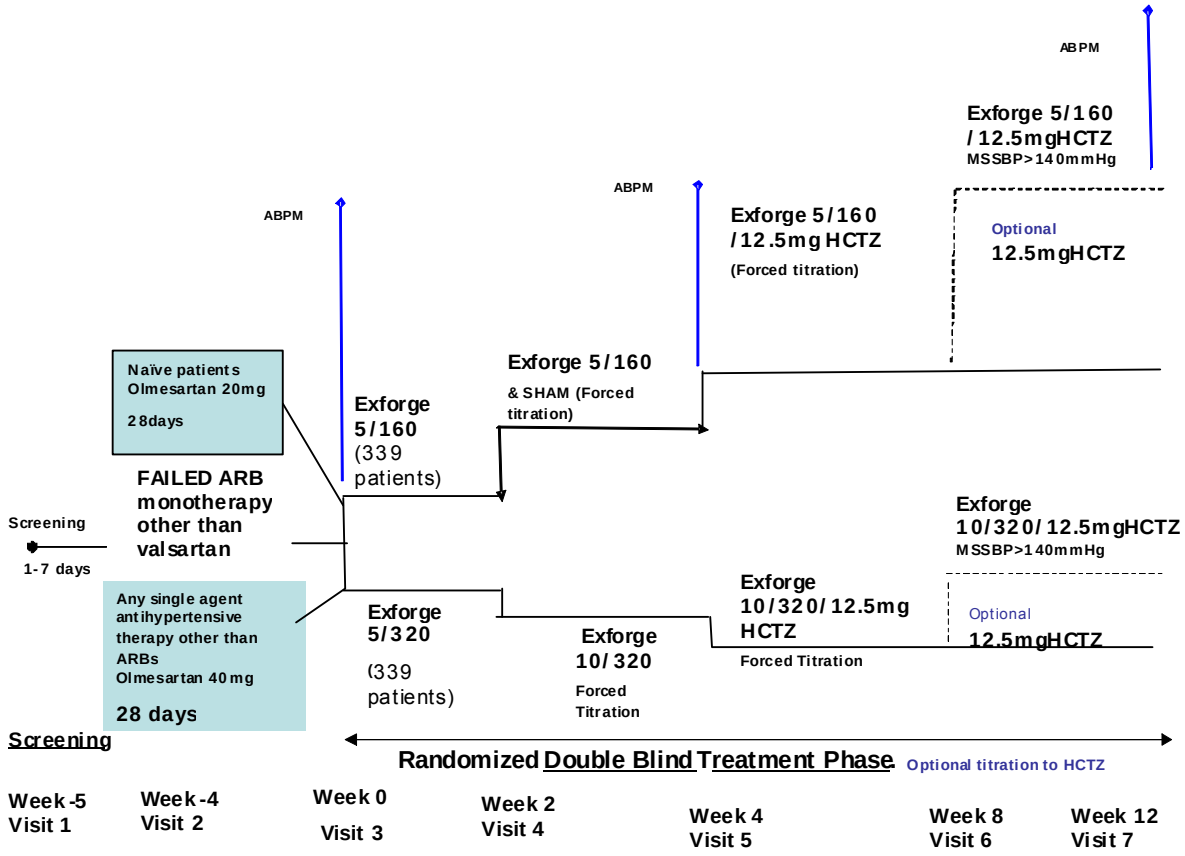
The primary objective of the study was to show that the aggressive Exforge treatment regimen was superior to the moderate Exforge treatment regimen with respect to change from baseline in mean sitting systolic blood pressure (MSSBP) at Week 4.

Inclusion criteria:

- Male or female patients ≥ 18 years of age;

- Diagnosis of uncontrolled systolic hypertension prior to study randomization on ARB monotherapy. Patients must have had a MSSBP ≥ 150 mm Hg and < 200 mm Hg ARB at Visits 1, 2, and 3 while either naïve to antihypertensive treatment or on any single agent antihypertensive therapy or on monotherapy for a minimum period of 28 days prior to randomization.

Study design, US02



The *primary efficacy variable* was the change from baseline in mean MSSBP. The main analysis time point was Week 4; other analysis time points were Weeks 2, 8, and 12.

The *key secondary efficacy variable* was change from baseline in MSDBP.

Statistical methods:

To compare the mean change from baseline to Week 4 in MSSBP between the two treatment regimens, an analysis of covariance (ANCOVA) model was utilized with baseline MSSBP, treatment, olmesartan dosage in runin phase, and sub-study based stratum (Patients were classified into 3 strata based on which type of center they belonged to. The centers that made up the 3 strata for the primary analysis

were ABPM sub-study centers, AI sub-study centers, and centers that were neither ABPM (ambulatory BP monitoring) nor AI (augmentation index) sub-study centers) as explanatory variables and with the change from baseline to Week 4 in MSSBP as the response variable. Based on this fitted model a two-sided 95% CI for the mean treatment difference between the two treatment regimens and the associated p-value was obtained. The least-squared means of each treatment arm were also computed.

Patient disposition – n (%) of patients entering Double-blind phase

	Exforge® Aggressive [a]	Exforge® Moderate [a]	Overall
Screened – n			1589
Screen failures – n			660
Olmesartan Run-in phase failure – n			201
Randomized patients – n (%)	369	359	728
Naïve, received olmesartan 20 mg	146 (39.6)	134 (37.3)	280 (38.5)
Non-naïve, received olmesartan 40 mg	103 (27.9)	104 29.0)	207 (28.4)
Non-naïve, randomized directly	120 (32.5)	121 (33.7)	241 (33.1)
Safety population – n (%) [b]	369 (100)	359 (100)	728 (100)
Intent-to-treat (ITT) population – n (%) [c]	366 (99.2)	357 (99.4)	723 (99.3)
ABPM-ITT population – n (%) [d]	44 (11.9)	36 (10.0)	80 (11.0)
AI-ITT population – n (%) [e]	38 (10.3)	35 (9.7)	73 (10.0)
Discontinued from study	33 (8.9)	37 (10.3)	70 (9.6)
Main cause of discontinuation – n (%)			
Adverse event(s)	9 (2.4)	19 (5.3)	28 (3.8)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	2 (0.5)	0 (0.0)	2 (0.3)
Patient's condition no longer required study drug	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation(s)	8 (2.2)	6 (1.7)	14 (1.9)
Patient withdrew consent	10 (2.7)	9 (2.5)	19 (2.6)
Lost to follow-up	4 (1.1)	3 (0.8)	7 (1.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)

ABPM = ambulatory blood pressure monitoring; AI = augmentation index; ITT = intent-to-treat; MSSBP = mean sitting systolic
blood pressure
a Aggressive treatment regimen with 5/320 mg initial dose. Moderate treatment regimen with 5/160 mg initial dose.
b The safety population includes all randomized patients who received at least one dose of study drug.
c The ITT population includes all randomized patients who received at least one dose of study drug and had at least one postbaseline assessment of the primary efficacy variable of MSSBP.
d The ABPM-ITT population includes all ITT patients who had both a baseline and post-baseline ABPM evaluation.
e The AI-ITT population includes all ITT patients who had both a baseline and post-baseline vascular stiffness related
assessments.
Note: The denominator for the percentages is the number of patients randomized

The ITT population was defined as the randomised patients with at least 1 post baseline measurement and consisted of 366 patients (99.2% of randomised) in the high dose arm and 357 patients (99.4% of randomised) in the moderate dose arm.

Protocol violations occurred in 24.8% of the patients in the valsartan/amlodipine 160/5 mg treatment strategy, and 29.3% in the valsartan/amlodipine 160/10 mg treatment strategy; however, few patients had major protocol violations, and they occurred at similar frequencies in both treatment strategies.

Baseline characteristics:

- The mean age was 54.7 years (SD 10.98), 82.2% of patients were <65 years. 56.6 % were females.

- The mean (SD) MSSBP was 163.6 (11.62) mmHg, the mean (SD) MSDBP was 95.3 (10.77) mmHg.

Results:

Change from baseline in MSSBP at Week 4 (LOCF) – primary efficacy variable, primary analysis time point (Study US02 ITT population)

	Valsartan/amlodipine 320/5 to 320/10 mg N = 366	**Valsartan/amlodipine 160/5 mg N = 357**	**Valsartan/amlodipine 320/5 to 320/10 vs. 160/5 mg**
Baseline			
N	366	357	
Mean ± SD (mm Hg)	163.9 ± 11.85	163.3 ± 11.40	
Week 4			
N	366	357	
Mean ± SD (mm Hg)	140.9 ± 14.61	144.4 ± 14.21	
Change from baseline			
N	366	357	
Mean ± SD (mm Hg)	-23.0 ± 14.60	-18.9 ± 13.92	
p-value [1]	< 0.0001	< 0.0001	
95% CI [2]	(-24.52, -21.52)	(-20.39, -17.50)	
Between treatment comparison			
Mean difference (95% CI)			-4.07 (-6.16, -1.99)
LS mean difference (95% CI) [3]			-3.81 (-5.73, -1.89)
p-value [3]			0.0001

[1] From a paired t-test to test if the mean change from baseline differed from zero within each treatment regimen.
[2] 95% CI for the mean change from baseline within each regimen.
[3] From an ANCOVA with baseline MSSBP, treatment, and olmesartan dosage in the Run-in phase and sub-study based stratum as explanatory variables.
Note: LOCF was used. Baseline was not carried forward.

Change from baseline in MSDBP (LOCF) at Week 4 (Study US02 ITT population)

	Valsartan/amlodipine 320/5 to 320/10 mg N = 366	**Valsartan/amlodipine 160/5 mg N = 357**	**Valsartan/amlodipine 320/5 to 320/10 vs. 160/5 mg**
Baseline			
N	366	357	
Mean ± SD (mm Hg)	95.5±11.19	95.0±10.33	
Week 4			
N	366	357	
Mean ± SD (mm Hg)	84.8 (11.47)	86.2 (9.60)	
Change from baseline (mm Hg)			
N	366	357	
Mean ± SD (mm Hg)	-10.7 ± 9.39	-8.8 ± 9.08	
p-value [1]	< 0.0001	< 0.0001	
(95% CI) [2]	(-11.64, -9.70)	(-9.73, -7.84)	
Between treatment comparison			
Mean difference (95% CI)			-1.89 (-3.24, -0.54)
LS mean difference (95% CI) [3]			-1.74 (-2.95, -0.54)
p-value [3]			0.0047

[1] From a paired t-test to test if the mean change from baseline differed from zero within each treatment regimen.
[2] 95% CI for the mean change from baseline within each regimen.
[3] From an ANCOVA with baseline MSDBP, treatment, and olmesartan dosage in the Run-in phase and sub-study based stratum as explanatory variables.
Note: LOCF was used. Baseline was not carried forward.

Second part of the variation:

b) With reference to efficacy not influenced by body mass index or diabetes status:

This proposal is based on subgroup analyses from the 9 studies that support the efficacy of valsartan/amlodipine in hypertensive patients regardless of BMI or diabetes status.

This includes post-hoc analyses of 4 studies in the original submission [Study A2201], [Study A2305], [Study A2306] and [Study A2307], and the 5 studies completed since the marketing approval [Study A2401], [Study A2402], [Study A2403], [Study A2404] and [Study US02]. The continuous variables of change from baseline in MSSBP and MSDBP are displayed.

Efficacy results by diabetic status:

The definition of diabetes varied across studies. In [Study A2401], [Study A2402], [Study A2403] and [Study A2404], diabetes status came from a specific question on the Medical History case report form. In [Study A2201], [Study A2307], [Study A2305], and [Study A2306] diabetes status was determined according to concomitant medication use at baseline and medical history, using WHODRL and MedDRA terms in place at the time of the original Exforge submission. In [Study US02], subgroup analyses based on diabetes status at baseline defined as fasting plasma glucose (FPG) > 126 mg/dL vs. FPG ≤ 126 mg/dL were performed for the primary and secondary variables. Patient diabetic status was determined post-hoc according to concomitant medication use at baseline and medical history, using WHODRL and MedDRA terms at the time of CSR completion.

Efficacy data were only analyzed within each study. No pooling for efficacy analysis was performed because of the differences in study designs, patient populations, and/or doses or dosing regimens across the trials.

The table below presents the raw mean changes from baseline at the primary endpoint (Week 8) in MSSBP and MSDBP by treatment and diabetic status in the previously submitted placebo-controlled trials [Study A2201] and [Study A2307]. The total ITT population of [Study A2201] included 198 (10.4%) diabetics. The total ITT population of [Study A2307] included 119 (9.6%) diabetics. The combinations of valsartan/amlodipine studied were effective in reducing MSDBP and MSSBP in comparison with placebo regardless of diabetic status.

Change from baseline in MSSBP and MSDBP (mmHg) at primary endpoint* by treatment regimen and diabetic status (Study A2201 and Study A2307, ITT population)

	Mean Reduction in MSSBP (mmHg)				Mean reduction in MSDBP (mmHg)			
	Study A2201		Study A2307		Study A2201		Study A2307	
Treatment (mg)	**Yes n=8-18**	**No n=106-119**	**Yes n=16-25**	**No n=182-193**	**Yes n=8-18**	**No n=106-119**	**Yes n=16-25**	**No n=182-193**
Val/Aml 320/10	--	--	-31.5	-26.4	--	--	-18.9	-18.1
Val/Aml 320/5	-19.2	-22.7	--	--	-15.3	-15.8	--	--
Val/Aml 320/2.5	-16.5	-18.2	--	--	-12.6	-14.1	--	--
Val/Aml 160/10	--	--	-25.1	-26.7	--	--	-15.0	-17.5
Val/Aml 160/5	-18.5	-19.4	--	--	-14.8	-13.9	--	--
Val/Aml 160/2.5	-17.3	-16.0	--	--	-13.1	-13.0	--	--
Val/Aml 80/5	-22.8	-20.4	--	--	-17.4	-13.9	--	--
Val/Aml 80/2.5	-17.9	-16.2	--	--	-15.5	-12.9	--	--
Val/Aml 40/5	-21.6	-19.2	--	--	-16.8	-14.1	--	--
Val/Aml 40/2.5	-13.8	-15.5	--	--	-11.9	-10.4	--	--
Val 320	-12.2	-16.8	-22.0	-18.3	-14.7	-13.0	-15.2	-12.6
Val 160	-16.6	-14.0	-17.2	-18.2	-11.3	-10.8	-12.6	-12.8
Val 80	-20.7	-11.8	--	--	-10.7	-9.3	--	--
Val 40	-10.8	-12.0	--	--	-9.0	-10.0	--	--
Aml 10	--	--	-21.3	-22.3	--	--	-14.1	-15.1
Aml 5	-12.5	-15.0	--	--	-12.8	-10.9	--	--
Aml 2.5	-20.4	-12.4	--	--	-9.4	-9.1	--	--
Placebo	-13.4	-5.6	-5.8	-11.5	-10.4	-6.1	-4.0	-8.6

Baseline MSSBP values ranged from 149.7 to 164.3 mmHg in Study A2201 and from 155.5 to 165.0 mmHg in Study A2307
Baseline MSDBP values ranged from 96.9 to 100.7 mmHg in Study A2201 and from 98.1 to 100.1 mmHg in Study A2307
*Endpoint is the value at Week 8 or the last observation carried forward in both studies.
n represents the range of patients across all treatment groups.
Authorised in EU

The table below presents the raw mean changes from baseline at the primary endpoint (Week 4 for [Study US02]; Week 8 for [Study A2401]) in MSSBP and MSDBP by treatment and diabetic status in the two reference therapy-controlled, non-responder trials completed since the marketing approval. The total ITT population of [Study A2401] included 145 (16.3%) diabetics. The total ITT population of [Study US02] included 124 (17.2%) diabetics. Clinically relevant reductions in MSDBP and MSSBP from baseline were observed with each of the dose combinations of valsartan/amlodipine regardless of diabetic status.

Change from baseline in MSSBP and MSDBP(mmHg) at primary endpoint* by treatment regimen and diabetic status (Study A2401 and Study US02, ITT population)

	Mean Reduction in MSSBP (mmHg)				Mean Reduction in MSDBP (mmHg)			
	Study A2401 *Week 8 LOCF		Study US02 *Week 4 LOCF		Study A2401 *Week 8 LOCF		Study US02 *Week 4 LOCF	
Treatment (mg)	Yes n=71-74	No n=369-375	Yes n=56-68	No n=289-310	Yes n=71-74	No n=369-375	Yes n=56-68	No n=289-310
Val/Aml 160/5	-12.5	-17.9	-17.3	-19.3	-8.1	-10.0	-8.2	-8.9
Val/Aml 160/10	-14.8	-21.1	--	--	-9.6	-12.0	--	--
Val/Aml 320/5	--	--	-25.0	-22.7	--	--	-10.7	-10.7

Baseline MSSBP values ranged from 146.3 to 151.1 mmHg in Study A2401 and from 162.8 to 165.7 mmHg in Study US02

Baseline MSDBP values ranged from 86.6 to 91.6 mmHg in Study A2401 and from 91.0 to 96.3 mmHg in Study US02

*Endpoint is the value at Week 4 for [Study US02] and Week 8 for [Study A2401]) or the last observation carried forward in both studies.

n represents the range of patients across all treatment groups

The table below presents the raw mean changes from baseline at the primary endpoint in MSSBP and MSDBP by treatment and diabetic status in the two trials completed since the marketing approval in patients with stage 2 hypertension. The time points of interest are considered to be Weeks 4 and 8 in [Study A2402] (conducted in Black patients) and Week 4 in [Study A2403]. In study A2402, Week 4 was important because it was the last visit that valsartan/amlodipine 160/10 mg was administered and Week 8 was important because it was the last visit before HCTZ could be added. In Study A2403, Week 8 was important because it was the last visit before HCTZ could be added. The total ITT population of [Study A2402] included 85 (15.3%) diabetics. The total ITT population of [Study A2403] included 70 (11.0%) diabetics. Greater reductions in both MSSBP and MSDBP were observed with the combinations of valsartan/amlodipine studied compared to amlodipine monotherapy regardless of diabetic status.

Change from baseline in MSSBP (mmHg) by treatment regimen and diabetic status (Study 2402 and Study A2403, ITT population)

	Mean Reduction in MSSBP (mmHg)				Mean Reduction in MSDBP (mmHg)			
	Study A2402		Study A2403		Study A2402		Study A2403	
Treatment (mg)	Yes n=41-44	No n=233-237	Yes n=34-36	No n=284-285	Yes n=41-44	No n=233-237	Yes n=34-36	No n=284-285
Week 4 LOCF†								
Val/Aml	-27.8	-29.1	-27.1	-30.1	-11.8	-12.5	-12.9	-12.4
Amlodipine	-21.5	-24.9	-24.0	-23.2	-8.0	-9.9	-7.2	-8.1
Week 8 LOCF†								
Val/Aml	-29.7	-31.6	--	--	-12.4	-13.1	--	--
Amlodipine	-22.3	-24.8	--	--	-8.9	-10.2	--	--

Baseline MSSBP values ranged from 170.4 to 171.8 mmHg in Study A2402 and from 170.0 to 172.9 mmHg in Study A2403
Baseline MSDBP values ranged from 94.7 to 98.9 mmHg in Study A2402 and from 88.3 to 96.7 mmHg in Study A2403
LOCF is the value at the respective week or the last observation value carried forward to the week.
n represents the range of patients across all treatment groups.

The table below shows the change from baseline in MSSBP and MSDBP at primary endpoint (Week 8) by treatment regimen and diabetic status in [Study A2404]. Diabetics (n=201) comprised 17.2% of the ITT population of this study. To be eligible for randomization in this study, patients had to have an inadequate response to amlodipine 5 mg with an MSSBP ≥ 130 mmHg and ≤ 160 mmHg, which is lower than all other studies. The reductions in MSSBP and MSDBP were numerically greater with valsartan/amlodipine 160/5 mg than with amlodipine 10 mg regardless of diabetes status

Change from baseline in MSSBP and MSDBP (mmHg) at primary endpoint* by treatment regimen and diabetic status (Study A2404, ITT population)

	Mean Reduction in MSSBP (mmHg)		Mean Reduction in MSDBP (mmHg)	
Treatment (mg)	Yes n=97-104	No n=482-483	Yes n=97-104	No n=482-483
Val/Aml 160/5	-6.1	-8.7	-3.7	-4.3
Amlodipine 10	-4.3	-6.9	-3.0	-4.1

Baseline MSSBP values ranged from 143.3 to 146.0 mmHg. Baseline MSDBP values ranged from 81.7 to 84.7 mmHg
* Endpoint is the value at Week 8 or the last observation carried forward value.
n represents the range of patients across all treatment groups.

The table below presents the raw mean changes from baseline at the primary endpoint (Week 9, after 8 weeks of treatment) in MSSBP and MSDBP by treatment and diabetic status in the two previously submitted reference therapy-controlled, non-responder trials, [Study A2305] and [Study A2306]. The total ITT population of [Study A2305] included 51 (5.4%) diabetics. The total ITT population of [Study A2306] included 34 (3.6%) diabetics. In [Study A2305], greater reductions in blood pressure were observed with the combinations of valsartan/amlodipine compared to monotherapy regardless of diabetic status. The contrary was observed in [Study A2306] which may have been due to the small numbers of diabetic patients.

Change from baseline in MSSBP and MSDBP (mmHg) at primary endpoint* by treatment regimen and diabetic status (Study A2305 and Study A2306, ITT population)

	Mean Reduction in MSSBP (mmHg)				Mean Reduction in MSDBP (mmHg)			
	Study A2305		Study A2306		Study A2305		Study A2306	
Treatment (mg)	Yes n=15-18	No n=290-304	Yes n=17	No n=451-455	Yes n=15-18	No n=290-304	Yes n=17	No n=451-455
Val/Aml 160/10	-18.7	-13.6	-7.5	-12.9	-12.5	-11.3	-10.4	-11.8
Val/Aml 160/5	-12.6	-12.0	--	--	-10.5	-9.6	--	--
Val 160	-5.3	-8.3	--	--	-7.6	-6.5	--	--
Aml 10	--	--	-12.4	-10.7	--	--	-12.2	-9.9

Baseline MSSBP values ranged from 148.5 to 161.0 mmHg in Study A2305 and from 143.8 to 148.1 mmHg in Study A2306
Baseline MSDBP values ranged from 95.7 to 97.3 mmHg in Study A2305 and from 94.1 to 95.4 mmHg in Study A2306
* Endpoints is the value at Week 9 or the last observation carried forward value. Week 9 is the patient visit after 8 weeks of treatment.
n represents the range of patients across all treatment groups

Efficacy results by BMI

The table below presents the raw mean changes from baseline at the primary endpoint (Week 8) in MSSBP and MSDBP by treatment and BMI category (obese = BMI $\geq$ 30 kg/m^2) in the previously submitted placebo-controlled trials. The total ITT population of [Study A2201] included 946 (49.8%) obese patients. The total ITT population of [Study A2307] included 384 (30.8%) obese patients. The combinations of valsartan/amlodipine studied were effective in reducing MSDBP and MSSBP in comparison with placebo regardless of BMI category. Further, for the vast majority of combination dose groups, each component of the combination therapies appeared to contribute to the total antihypertensive effect of the combination regardless of BMI category.

Change from baseline in MSSBP and MSDBP (mmHg) at primary endpoint* by treatment regimen BMI category (Study A2201 and Study A2307, ITT population)

	Mean Reduction in MSSBP (mmHg)				Mean reduction in MSDBP (mmHg)			
	Study A2201		Study A2307		Study A2201		Study A2307	
Treatment (mg)	≥ 30 kg/m² n=56-70	<30 kg/m² n=57-71	≥ 30 kg/m² n=56-78	<30 kg/m² n=129-150	≥ 30 kg/m² n=56-70	<30 kg/m² n=57-71	≥ 30 kg/m² n=56-78	<30 kg/m² n=129-150
Val/Aml 320/10	--	--	-24.9	-27.6	--	--	-16.5	-18.8
Val/Aml 320/5	-22.8	-22.0	--	--	-15.5	-15.9	--	--
Val/Aml 320/2.5	-17.2	-18.7	--	--	-13.2	-14.6	--	--
Val/Aml 160/10	--	--	-25.7	-27.0	--	--	-17.4	-17.3
Val/Aml 160/5	-19.0	-19.9	--	--	-12.7	-15.6	--	--
Val/Aml 160/2.5	-13.5	-18.6	--	--	-12.3	-13.6	--	--
Val/Aml 80/5	-20.7	-20.6	--	--	-14.0	-14.5	--	--
Val/Aml 80/2.5	-14.2	-18.6	--	--	-13.0	-13.5	--	--
Val/Aml 40/5	-21.6	-17.4	--	--	-14.4	-14.5	--	--
Val/Aml 40/2.5	-15.1	-15.6	--	--	-10.0	-11.2	--	--
Val 320	-13.1	-18.9	-15.9	-20.3	-12.2	-13.9	-11.8	-13.2
Val 160	-13.1	-15.8	-15.1	-19.4	-10.3	-11.3	-10.2	-13.7
Val 80	-10.5	-15.5	--	--	-8.1	-10.9	--	--
Val 40	-10.6	-13.1	--	--	-9.2	-10.5	--	--
Aml 10	--	--	-20.7	-22.8	--	--	-14.3	-15.3
Aml 5	-15.5	-13.9	--	--	-11.5	-10.6	--	--
Aml 2.5	-10.4	-15.9	--	--	-8.6	-9.8	--	--
Placebo	-8.4	-3.8	-8.8	-11.8	-7.5	-5.3	-6.7	-8.7

Baseline MSSBP values ranged from 148.7 to 155.8 mmHg in Study A2201 and from 155.6 to159.6 mmHg in Study A2307
Baseline MSDBP values ranged from 98.0 to 100.1 mmHg in Study A2201 and from 98.7 to 100.5 mmHg in Study A2307
*Endpoint is the value at Week 8 or the last observation carried forward in both studies.
n represents the range of patients across all treatment groups
Authorized in EU

The table below presents the raw mean changes from baseline at the primary endpoint (Week 4 for [Study US02]; Week 8 for [Study A2401]) in MSSBP and MSDBP by treatment and BMI category in the two trials completed since the marketing approval. The total ITT population of [Study A2401] included 350 (39.6%) obese patients. The total ITT population of [Study US02] included 401 (55.5%) obese patients. Clinically relevant reductions in MSDBP and MSSBP from baseline were observed with each of the dose combinations of valsartan/amlodipine, regardless of BMI category. The reductions were similar in both studies regardless of BMI category.

Change from baseline in MSSBP and MSDBP(mmHg) at primary endpoint* by treatment regimen and BMI category (Study A2401 and Study US02, ITT population)

	Mean Reduction in MSSBP (mmHg)				Mean Reduction in MSDBP (mmHg)			
	Study A2401 *Week 8 LOCF		Study US02 *Week 4 LOCF		Study A2401 *Week 8 LOCF		Study US02 *Week 4 LOCF	
Treatment (mg)	≥ 30 kg/m² n=170-180	< 30 kg/m² n=258-275	≥ 30 kg/m² n=199-202	< 30 kg/m² n=154-167	≥ 30 kg/m² n=170-180	< 30 kg/m² n=258-275	≥ 30 kg/m² n=199-202	< 30 kg/m² n=154-167
Val/Aml 160/5	-16.6	-17.3	-17.6	-20.7	-9.2	-9.9	-8.0	-9.8
Val/Aml 160/10	-17.8	-21.4	--	--	-10.2	-12.5	--	--
Val/Aml 320/5	--	--	-21.5	-24.8	--	--	-10.6	-10.8

Baseline MSSBP values ranged from 149.1 to 151.2 mmHg in Study A2401 and from 162.7 to 164.0 mmHg in Study US02
Baseline MSDBP values ranged from 86.6 to 91.6 mmHg in Study A2401 and from 93.7 to 96.8 mmHg in Study US02
n represents the range of patients across all treatment groups

The table below presents the raw mean changes from baseline at the primary endpoint in MSSBP and MSDBP in the two trials completed since the marketing approval in patients with stage 2 hypertension. For this CO Addendum, the timepoints of interest were considered to be Weeks 4 and 8 in [Study A2402] (conducted in Black patients) and Week 4 in [Study A2403]. In Study A2402, Week 4 was important because it was the last visit that valsartan/amlodipine 160/10 mg was administered and Week 8 was important because it was the last visit before HCTZ could be added. In Study A2403, Week 8 was important because it was the last visit before HCTZ could be added. The total ITT population of [Study A2402] included 321 (58.2%) obese patients. The total ITT population of [Study A2403] included 279 (43.7%) obese patients. The combination of valsartan/amlodipine studied was effective in reducing MSDBP and MSSBP in comparison with the active amlodipine control regardless of BMI category. The mean reductions at Week 4, which was common to both studies, were similar regardless of BMI category.

Change from baseline in MSSBP (mmHg) by treatment regimen and BMI category (Study A2402 and Study A2403, ITT population)

	Mean Reduction in MSSBP (mmHg)				Mean Reduction in MSDBP (mmHg)			
	Study A2402		Study A2403		Study A2402		Study A2403	
Treatment (mg)	≥ 30 kg/m² n=160-161	< 30 kg/m² n=115-116	≥ 30 kg/m² n=134-145	< 30 kg/m² n=175-184	≥ 30 kg/m² n=160-161	< 30 kg/m² n=115-116	≥ 30 kg/m² n=134-145	< 30 kg/m² n=175-184
Week 4 LOCF†								
Val/Aml	-28.8	-28.8	-28.6	-30.6	-12.6	-11.9	-12.1	-12.7
Amlodipine	-23.6	-25.5	-21.3	-25.0	-9.5	-9.9	-7.1	-8.7
Week 8 LOCF†								
Val/Aml	-31.6	-30.7	--	--	-13.5	-12.4	--	--
Amlodipine	-23.6	-25.9	--	--	-9.7	-10.5	--	--

Baseline MSSBP values ranged from 170.1 to 171.1 mmHg in Study A2402 and from 170.1 to 170.9 mmHg in Study A2403
Baseline MSDBP values ranged from 96.1 to 99.9 mmHg in Study A2402 and from 94.1 to 97.4 mmHg in Study A2403
†LOCF is the value at the respective week or the last observation value carried forward to the week.
n represents the range of patients across all treatment groups

The table below shows the change from baseline in MSSBP and MSDBP at the primary endpoint (Week 8) by treatment regimen and BMI category in [Study A2404]. The total ITT population included 417 (36.1%) obese patients. To be eligible for randomization in this study, patients had to have an inadequate response to amlodipine 5 mg with a MSSBP ≥ 130 mmHg and ≤ 160 mmHg, which is lower than all other studies. The reductions in MSSBP were numerically greater with valsartan/amlodipine 160/5 mg than with amlodipine 10 mg in both obese and non-obese patients. Clinically relevant reductions in MSDBP were observed in both treatment groups in both obese and non-obese patients. The reductions in MSDBP were numerically greater with valsartan/amlodipine 160/5 mg than with amlodipine 10 mg in the non-obese but not the obese subgroup.

Change from baseline in MSSBP and MSDBP (mmHg) at primary endpoint* by treatment regimen and BMI category (Study A2404, ITT population)

	Mean Reduction in MSSBP (mmHg)		Mean Reduction in MSDBP (mmHg)	
Treatment (mg)	≥ 30 kg/m² n=189-228	<30 kg/m² n=352-385	≥ 30 kg/m² n=189-228	<30 kg/m² n=352-385
Val/Aml 160/5	-7.7	-8.7	-3.7	-4.5
Amlodipine 10	-5.6	-6.9	-4.1	-3.8

Baseline MSSBP values ranged from 143.5 to 144.7 mmHg. Baseline MSDBP values ranged from 82.5 to 86.0 mmHg
* Endpoint is the value at Week 8 or the last observation carried forward value.

The table below presents the raw mean changes from baseline at the primary endpoint (Week 9, after 8 weeks of treatment) in MSSBP and MSDBP by treatment and BMI category in the two previously submitted reference therapy-controlled, non-responder trials. The total ITT population of [Study A2305] included 416 (44.1%) obese patients. The total ITT population of [Study A2306] included 360 (38.4%) obese patients. Reductions in both MSSBP and MSDBP were numerically greater with the combinations of valsartan/amlodipine studied compared to valsartan and amlodipine monotherapy regardless of BMI category. The reductions were similar in both studies regardless of BMI category.

Change from baseline in MSSBP and MSDBP (mmHg) at primary endpoint* by treatment regimen and BMI category (Study A2305 and Study A2306, ITT population

	Mean Reduction in MSSBP (mmHg)				Mean Reduction in MSDBP (mmHg)			
	Study A2305		Study A2306		Study A2305		Study A2306	
Treatment (mg)	≥ 30 kg/m² n=135-144	< 30 kg/m² n=170-181	≥ 30 kg/m2 n=173-187	< 30 kg/m² n=283-295	≥ 30 kg/m² n=135-144	< 30 kg/m² n=170-181	≥ 30 kg/m2 n=173-187	< 30 kg/m² n=283-295
Val/Aml 160/10	-13.3	-14.3	-11.2	-13.7	-11.0	-11.7	-10.9	-12.3
Val/Aml 160/5	-10.7	-13.0	--	--	-9.0	-10.1	--	--
Val 160	-7.7	-8.7	--	--	-6.2	-6.9	--	--
Aml 10	--	--	-10.1	-11.2	--	--	-9.2	-10.5

Baseline MSSBP values ranged from 148.6 to 150.0 mmHg in Study A2305 and from 146.0 to 148.4 mmHg in Study A2306
Baseline MSDBP values ranged from 95.7 to 97.5 mmHg in Study A2305 and from 94.6 to 95.7 mmHg in Study A2306
* Endpoint is the value at Week 9 or the last observation carried forward value. Week 9 is the patient visit after 8 weeks of treatment.
n represents the range of patients across all treatment groups

Discussion on Clinical Efficacy - Variation 3

Study 2401:

The study was not conducted in line with the authorised indication as patients with any previous hypertensive monotherapy medication could be included. Patients treated with monotherapy "at a dose considered as adequate by the investigator" for a minimum of two months could be included. This inclusion criterion is not meaningful; it is too large and unspecific in order to allow for any conclusions to be drawn on the target population.

At visit 2 (randomization) patients discontinued their previous medication and were randomized to the study medication; either val/aml 160/10 mg or val/aml 160/5 mg. Both treatment arms had the option to add HCTZ stepwise after 8 weeks if BP was uncontrolled.

The difference in discontinuations is striking in both arms, being 17% in the 160/10 mg arm and 8% in the 160/5 mg arm. The main reasons for discontinuations were adverse events.

The primary endpoint is not relevant for this variation as it is influenced by the addition of HCTZ. The applicant has also presented changes in MSSBP and MSDBP from baseline at different time points in order to be consistent in the analyses for this variation application (this was a secondary endpoint). However, this information is hardly relevant as there was no wash-out phase (before initiation of study treatment) and the baseline is an expression of previous varying monotherapy and dosages, i.e. not in accordance with the authorised indication. Furthermore due to the large differences in discontinuations between the treatment groups, LOCF may not be the appropriate way to address missing data.

Study US02:

Naïve patients and patients who remained uncontrolled with regard to systolic hypertension on any single antihypertensive medication other than ARBs were eligible for the run-in phase (treatment with olmesartan 20mg and 40mg, respectively, for 28 days). Patients treated with ARB monotherapy (other than valsartan [Diovan]) for 28 days who remained uncontrolled were eligible for the double-blind phase. This means that the conditions prior to randomisation were different, either there was a run-in therapy with 2 different doses of olmesartan or patients could directly enter the double-blind phase if being treated with another ARB than valsartan for 28 days. This is not in line with the authorised indication. Apart from this deviation, only one of the treatment arms in the double-blind phase is considered relevant from an EU perspective. The "moderate" dose of 160/5 mg is authorised, whereas

the comparator arm with the "aggressive" dose of 320/5 mg (with forced titration to 320/10 mg after 2 weeks) is not. With reference to the 160/5 mg dose, only the first 4 weeks of the double-blind period are relevant due to the forced titration thereafter with HCTZ.

Discontinuations were almost comparable between treatment groups, but discontinuations due to AEs were doubled in the 160/5 mg group as compared to the 320/5 mg group, which appears rather bizarre.

Both studies (2401 and US02) that were submitted in support of the proposed change in 5.1 concerning the efficacy in patients not adequately responding to any monotherapy including ACE inhibitors, ARBs, calcium channel blockers, beta-blockers and diuretics were not conducted in accordance with the authorised indication, i.e. in patients not adequately controlled on amlodipine or valsartan monotherapy. This is not in accordance with the SmPC guideline which states the following: *"…Such information on clinical trials should be concise, clear, relevant and balanced, and should summarise evidence from relevant studies supporting the indication."* Furthermore, the proposed statement may encourage prescribers to off-label prescriptions of Exforge.

Further, the submitted studies were not conducted in an appropriate way to support the proposed statement. Deficiencies relate to inclusion criteria, conduct of the study and handling of data.

The proposed statement:

"In two additional active-controlled trials of 1612 patients, additional blood pressure lowering effects for Exforge were observed compared to baseline in patients not adequately responding to monotherapy including ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers and diuretics"

is therefore not acceptable.

Diabetic patients:

The Applicant has presented subgroup analyses from the 9 studies submitted to support the efficacy of valsartan/amlodipine in hypertensive patients regardless of diabetes status.

Patients with type 1 diabetes as well as patients with type 2 diabetes and poor glucose control were excluded from these studies.

As mentioned by the applicant the definition of diabetes was not universal across the studies:

"The definition of diabetes varied across studies. In [Study A2401], [Study A2402], [Study A2403] and [Study A2404], diabetes status came from a specific question on the Medical History case report form. In [Study A2201], [Study A2307], [Study A2305], and [Study A2306] diabetes status was determined according to concomitant medication use at baseline and medical history, using WHODRL and MedDRA terms in place at the time of the original Exforge submission. In [Study US02], subgroup analyses based on diabetes status at baseline defined as fasting plasma glucose (FPG) > 126 mg/dL vs FPG ≤ 126 mg/dL were performed for the primary and secondary variables. For the purpose of the diabetes analyses performed for this Clinical Overview Addendum, patient diabetic status was determined post-hoc according to concomitant medication use at baseline and medical history, using WHODRL and MedDRA terms at the time of CSR completion."

Diagnosis of type 2 diabetes is usually made by WHO/ADA diagnostic criteria for fasting glucose levels (plasma glucose ≥7.0 mmol/L (126mg/dL) or plasma glucose levels 2-hours after 75 mg oral glucose load of ≥11.1 mmol/L (200mg/dL), or newly diagnosed with mixed meal tolerance test or oral glucose tolerance screening or casual glucose ≥11.1 mmol/L (200mg/dL) with symptoms.

As a consequence, diabetic status in the studies referred to is therefore not necessarily confirmed.

As mentioned previously, studies 2401, US02, 2402 and 2403 were not conducted in accordance with the authorised indication. It is therefore not considered justified to claim any inclusions in the SmPC based on post hoc subgroup analyses concerning diabetic status based on the results from these studies. Notwithstanding this fact, the reductions in MSSBP and MSDBP in studies 2401 and US02 seemed numerically lower in diabetic patients compared to non-diabetic patients.

In study 2402 the week 8 analyses for the val/aml combination is of limited value, as patients could be uptitrated from 160/10 mg to 320/10 mg at week 4.

Also in study 2404 the presented analyses were not pre-specified. Also in this study the reduction in MSSBP and MSDBP seemed numerically lower in diabetic patients compared to non-diabetic patients.

In the previously submitted studies 2201, 2307, 2305 and 2306 the subgroup analyses by diabetic status are based on very small numbers of patients by treatment group (n=8-18) which do not allow for strong conclusions.

In summary, the presented post-hoc analyses do not justify the inclusion of a statement regarding the efficacy of Exforge by diabetic status for the following reasons: 1) Different definitions were used to determine diabetic status; 2) The post-hoc analyses were either based on very small patient numbers (studies 2201, 2307, 2305, 2306), or were based on studies not conducted in accordance with the authorised indication; 3) The efficacy of Exforge does not seem as good in diabetic patients as in non-diabetic subjects.

These analyses do therefore not justify the inclusion of the proposed statement in section 5.1 regarding the efficacy of Exforge by diabetic status.

BMI:

The MAH has presented subgroup analyses for obese patients with BMI ≥30 and patients with BMI < 30. Focussing on the studies that were conducted in accordance with the authorised indication the proportion of obese patients with BMI ≥ 30 was in the range of 30 -50%. Although no statistical analyses were presented, the anti-hypertensive effect of Exforge seemed similar in obese- and non-obese subjects. The presented information on reduction in MSSBP and MSDBP are considered sufficient to allow a statement on response to Exforge by BMI to be included in section 5.1 of the SmPC with the following modification:

"Age, gender, race, *or* body mass index *(≥30kg/m^2, <30kg/m^2)* ~~or diabetes status~~ did not influence the response to Exforge.

2.2.2. Clinical safety

The safety of valsartan/amlodipine was thoroughly evaluated during the assessment of the initial marketing authorisation application and re-assessed in each of the PSURs submitted since approval of val/aml fixed dose combination in the EU. The double-blind, active- or placebo-controlled safety population in the original submission [Study A2201], [Study A2307], [Study A2305], [Study A2306], and [Study A2308] included 5175 patients, 2613 of whom received valsartan/amlodipine treatment. The studies completed since the granting of the marketing authorisation included 4014 patients, 2815 of whom received valsartan/amlodipine treatment. These studies had a double-blind treatment duration ranging from 8-16 weeks.

The focus of the safety data presented in the current dossier is the additional safety information provided for the use of valsartan/amlodipine in diabetics and obese patients (BMI ≥ 30 kg/m2); this includes safety data from 10 studies (2 placebo-controlled and 3 reference therapy-controlled studies

from the original MAA, and the 5 reference therapy-controlled studies completed since the approval of the MAA). The data presented below represent the safety population.

Subgroup assessment of AEs according to diabetic status (yes/no)

The definition of diabetes varied across studies (please refer to the efficacy section above for variation 3). The proportion of patients with diabetes in the 5 studies completed since the approval of the MAA and the controlled trials dataset from the original dossier ranged from 7.9-17.2%.

AEs by diabetic status in patients with stage 2 hypertension and in Black patients

Study A2402, Black patients:

This study included 88 diabetics (15.4%). The overall incidence of AEs in patients receiving val/aml was similar in diabetic (44.7%) and non-diabetic (44.4%) patients. The most common AEs in the valsartan/amlodipine diabetic group were bronchitis, fatigue and headache, each reported for 2 patients (4.3%). The only AE reported more frequently in diabetic patients in both the valsartan/amlodipine and amlodipine group was muscle spasms (2.1% and 4.9%, respectively).

Study A2403, stage II hypertension:

This study included 71 diabetics (11.0%). The overall incidence of AEs in patients receiving valsartan/amlodipine was similar in diabetic (34.3%) and non-diabetic (35.3%) patients with the most common AEs in the valsartan/amlodipine diabetic group being peripheral oedema (n=5 (14.3%)) and pain in extremity (n=2 (5.7%)).

Study A2404, Patients inadequately controlled on Amlodipine 5 mg alone:

This study included 204 diabetics (17.2%). The overall incidence of AEs in patients receiving valsartan/amlodipine was similar in diabetic (41.5%) and non-diabetic (44.4%) patients with the most common AEs in the valsartan/amlodipine diabetic group being peripheral oedema (n=5 (4.7%)) and rhinitis (n= 4 (3.8%)).

AEs by diabetic status in non-responder trials

Study A2401, Patients inadequately controlled on monotherapy:

This study included 146 diabetics (16.3%). The overall incidence of AEs in the total population of patients receiving valsartan/amlodipine was slightly higher in diabetics (53.4%) vs. non-diabetics (48.5%). The most frequently reported AEs in the overall valsartan/amlodipine diabetic subgroup were peripheral oedema (n=24 (16.4%)), back pain (n=6 (4.1%), hypotension (n=4 (2.7%)), and muscle spasms (n= 4 (2.7%).

Study US02, Patients inadequeately controlled on ARB monotherapy:

This study included 125 diabetics (17.2%). The overall incidence of AEs in patients receiving valsartan/amlodipine was similar in diabetic (38.4%) and non-diabetic (36.7%) patients. The most frequently reported AEs in the overall valsartan/amlodipine diabetic subgroup were peripheral oedema (n=8 (6.4%)) and dizziness (n=4 (3.2%))

AEs by diabetic status in reference- and placebo-controlled trials in the original submission

In the original submission diabetic status was available for 5175 patients in the total safety population of the pooled studies ([Study A2201], [Study A2307], [Study A2305], [Study A2306], and [Study A2308]). The overall incidence of AEs in patients receiving valsartan/amlodipine was slightly higher in diabetic (47.1%) vs. non-diabetic (41.7%) patients. Peripheral oedema (5.3%) and headache (5.3%) were the most common AEs in the valsartan/amlodipine diabetic subgroup, both frequencies being lower than in the valsartan/amlodipine non-diabetic subgroup.

Subgroup assessment of adverse events according to BMI (≥ 30 and < 30 kg/m2)

AEs by BMI category in patients with stage 2 hypertension and in Black patients

Study A2402, Black patients:

This study included 333 obese patients (58.6%). The overall incidence of AEs in patients receiving both valsartan/amlodipine and amlodipine was slightly greater in obese compared to non-obese patients (47.6% vs. 40.2% and 46.1% vs. 44.9%, respectively). The most common AE in obese and non-obese patients was peripheral oedema (14.9% vs. 9.4% (valsartan/amlodipine) and 10.9% vs. 7.6% (amlodipine).

Study A2403, stage II hypertension:

This study included 280 obese patients (43.5%). The overall incidence of AEs in patients receiving both valsartan/amlodipine and amlodipine was slightly greater in obese patients compared to non-obese patients (41.0% vs. 31.0% and 39.0% vs. 35.0%, respectively). The most common AE in obese and non-obese patients was peripheral oedema (14.9% vs. 11.2% (valsartan/amlodipine) and 16.4% vs.18.2% (amlodipine).

Study A2404, Patients inadequately controlled on Amlodipine 5 mg alone:

This study included 425 obese patients (36.3%). The overall incidence of AEs in patients receiving both valsartan/amlodipine and amlodipine was 49.3% vs. 40.9% and 65.3% vs. 50.6% in obese vs. non-obese, respectively. The most common AE in obese and non-obese patients was peripheral oedema (7.9% vs. 7.0% (valsartan/amlodipine) and 38.8% vs. 27.5% (amlodipine).

AEs by BMI in non-responder trials

Study A2401, Patients inadequately controlled on monotherapy:

This study included 352 (39.7%) obese patients. The overall incidence of AEs in the total population of patients receiving valsartan/amlodipine was 53.7% vs. 46.4% in obese vs. non-obese patients. In obese and non-obese patients, the most common AE in the overall valsartan/amlodipine group was peripheral oedema (18.5% vs. 15.5%).

Study US02, Patients inadequately controlled on ARB monotherapy:

This study included 404 obese patients (55.6%) included 404 obese patients (55.6%). The overall incidence of AEs in the total valsartan/amlodipine population was slightly higher in obese (39.1%) vs. non-obese (34.1%) patients. In obese and non-obese patients, the most common AE was peripheral oedema 7.2% vs. 5.9%).

AEs by BMI category in reference-therapy and placebo-controlled studies in the original submission

In the total safety population of the pooled studies in the original submission ([Study A2201], [Study A2307], [Study A2305], [Study A2306], and [Study A2308]) 2187 patients (42.5%) were obese (BMI data was available for 5149 patients). 42.8% were obese among patients treated with valsartan/amlodipine and amlodipine. The overall incidence of AEs was slightly greater in obese compared to non-obese patients in all treatment groups, including placebo. In both obese and non-obese patients, peripheral oedema and headache were the most common AEs overall. The incidence of peripheral oedema was less in both obese and non-obese patients receiving valsartan/amlodipine regimens compared to amlodipine.

Deaths and other serious or clinically significant adverse events

No deaths occurred in any of the studies completed since the original submission.

Discussion on Clinical Safety

The safety data presented in the submitted dossier provides supportive safety data from five new valsartan/amlodipine randomized, controlled studies. No new or altered safety signals have emerged from the new trials. Safety data have also been provided for sub-groups with and with-out diabetes as well as obese and non-obese patients (≥ 30 and < 30 kg/m2). Though obese patients had higher frequencies of overall AEs than non-obese no clinically relevant differences were observed in the safety profile of valsartan/amlodipine in diabetics and obese patients when compared to the patient populations with-out these clinical entities.

2.2.3. Conclusion

Variation 1:

The scope of this variation was the update of section 5.1 of the SmPC with information on efficacy in patients with stage 2 hypertension and in black patients based on studies VAA 2402 and VAA 2403.

Studies 2402 and 2403 were submitted to support efficacy in patients with grade 2 systolic hypertension and study 2402 was conducted in Black patients. Several deficiencies relating to the study designs for both studies have been identified. In both studies valsartan/amlodipine 160/10 mg seems more effective than amlodipine 10 mg in the treatment of systolic hypertension >160mmHg and <200mmHg in a population that was either treatment naïve or was treated with non-specified antihypertensives. This means that in neither study 2402 nor in study 2403 patients were treated in accordance with the authorised indication, as Exforge is indicated in patients whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy. The SmPC is a document that provides information on a particular medicinal product and is not issued as a general treatment recommendation. The SmPC guideline states in section 5.1 clinical efficacy and safety: *"It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials…… supporting the indication."*

Furthermore, final judgement on efficacy cannot be made as the relevant analyses were made after 2 weeks of treatment which is considered too short. According to the guideline on the clinical investigation of medicinal products in the treatment of hypertension (CHMP/EWP/238/95 Rev.2 and EMA//238/1995/rev.3) a tested dose should remain stable for at least 4 weeks.

In summary, the provided studies are not considered sufficiently robust and are not in line with the authorised indication. As a consequence, the wording that was proposed by the MAH:

"In two additional active-controlled studies of 1,612 patients, additional blood pressure lowering effects for Exforge were observed compared to baseline in patients not adequately responding to monotherapy including ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers and diuretics.

Active controlled trials in stage 2 hypertensive patients

Two active-controlled studies of 1,195 patients with mean sitting systolic blood pressure ≥160 mmHg and <200 mmHg were conducted. In the first study in 639 patients (baseline blood pressure 171/95 mmHg), an Exforge regimen of 5 mg/160 mg for 2 weeks force-titrated to 10 mg/160 mg significantly reduced sitting blood pressure after 4 weeks by 30/13 mmHg compared to 24/9 mmHg with a similar regimen of amlodipine 5 mg force-titrated to 10 mg. The second active-controlled study,

specifically designed to evaluate the efficacy of Exforge in 556 black patients, compared an Exforge regimen of 5 mg/160 mg force-titrated to 10 mg/160 mg for 2 weeks with a similar regimen of amlodipine 5 mg force-titrated to 10 mg. In this study (baseline blood pressure 171/98 mmHg), Exforge significantly reduced sitting blood pressure after 4 weeks by 31/13 mmHg compared to 27/11 mmHg with amlodipine."

can therefore not be accepted.

In view of the outcome of the CHMP assessment, the MAH agreed not to pursue the proposed wording.

Variation 2

The scope of this variation was the update of section 5.1 of the SmPC with information on the efficacy and safety of valsartan/amlodipine 160/5 mg compared to amlodipine 10 mg based on study VAA 2404.

The proposed wording in section 5.1 focuses on the efficacy of valsartan/amlodipine compared to amlodipine alone in the context of oedema incidence rather than on the oedema incidence itself as described in section 4.8 of the SmPC. According to the MAH, this information provided in section 5.1 is relevant for prescribers as it presents efficacy of valsartan/amlodipine in the approved doses of 5 mg/80 mg and 5 mg/160 mg as a benefit in relation to oedema incidence versus amlodipine in monotherapy. Thus, the proposed SmPC wording provides additional reassurance to the prescriber on efficacy of valsartan/amlodipine fixed combination in relation to oedema reduction.

Oedema was significantly more frequent in the amlodipine monotherapy group. In this respect, it should also be kept in mind that only patients 55 years or older were included in the study. Oedema is dose-dependent with amlodipine therapy and the clearance of amlodipine is reduced in the elderly, resulting in a higher exposure. It is therefore likely that the incidence of amlodipine in this study may be exaggerated due to the chosen study population.

The MAH acknowledged that patients aged 55 years and over were selected in Study A2404 to demonstrate the effect of valsartan/amlodipine compared to amlodipine monotherapy on the reduction of oedema incidence. According to the MAH, as recognised by guidelines for the management of arterial hypertension, the patient population selected in Study A2404 (≥ 55 years old) is representative of the hypertensive population at risk. Age (men >55 years; women >65 years) is considered a factor influencing prognosis of cardiovascular risk and should be used to stratify the risk of cardiovascular disease. Older patients may be more prone to develop peripheral oedema on non-dihydropyridine calcium channel blockers due to the effects of aging on the peripheral vasculature. Therefore, according to the MAH, this is the population that may have the greatest benefit with respect to attenuation in the development of oedema but does not preclude a benefit in younger patients.

Albeit statistically significant, the differences in BP reductions between valsartan/amlodipine 160/5 mg and amlodipine 10 mg are not exceptionally different and there is no obvious reason to insert a statement on *"numerically greater reductions in blood pressure compared to amlodipine 10 mg"*, derived from a not completely recognized subgroup of patients with hypertension (those ≥55 years), into section 5.1 of the SmPC. In spite of the fact that the age of ≥55 years is an agreed risk factor for males for CV disease (65 years for females), it is not recognized as a subgroup for hypertension trials.

The SmPC guideline states on section 5.1:

"…It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials, and giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced, and should summarise evidence from relevant studies supporting the indication. The magnitude of effects should be described

using absolute figures. (Relative risks or odd ratio should not be presented without absolute figures)…."

Consequently, as mentioned above with reference to the SmPC guideline, the efficacy part of the proposed wording is not considered appropriate. Therefore, the proposed wording (highlighted):

"In patients not adequately controlled on amlodipine 5 mg, amlodipine/valsartan 5 mg/80 mg may achieve blood pressure control similar to amlodipine 10 mg with less oedema and amlodipine/valsartan 5 mg/160 mg produced numerically greater reductions in blood pressure compared to amlodipine 10 mg with a 4-fold lower incidence of peripheral oedema. In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, amlodipine/valsartan 5 mg/80 mg may achieve similar blood pressure control with less oedema."

is not acceptable to the CHMP and thus the context of the proposed safety information on oedema is not relevant. The existing information on oedema in section 4.8 of the SmPC is regarded sufficient for prescribers.

Furthermore, during the procedure the CHMP questioned the validity of the already existing SmPC wording in section 5.1:

"In patients not adequately controlled on amlodipine 5 mg, amlodipine/valsartan 5 mg/80 mg may achieve blood pressure control similar to amlodipine 10 mg with less oedema. In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, amlodipine/valsartan 5 mg/80 mg may achieve similar blood pressure control with less oedema."

Upon request by the CHMP, the MAH clarified that this wording was based on data collected from the two multi-factorial studies [Study A2201] and [Study A2307] submitted as part of the original MAA for the fixed dose combination valsartan/amlodipine.

Following the assessment of all data provided, the CHMP did not consider it appropriate to compare two different studies in order to obtain a statement on BP results in section 5.1 of the SmPC. The studies are not considered completely comparable with respect to the included patient population which is demonstrated by the differences in age categories (28.6% patients >65 years in study A2307 compared to 18.2% in study A2201) and ethnic origin (10.4% of Black patients in study A2201 as compared to 0.4% in study A2307. Study A2307 had in contrast a higher percentage of oriental patients, 13.7%, as compared to study A2201 (1.6%)).

Following the CHMP assessment of these data, the MAH acknowledged the CHMP comments and revised the current product information wording to more accurately reflect the data generated in the multi-factorial Study A2201 and Study A2307. However, according to the MAH, the percentage of patients in active treatment groups achieving BP control (msDBP <90 mmHg) could be considered similar for valsartan/amlodipine 80/5 mg (39.1%) [Study 2201] and amlodipine 10 mg (37.5 %) [Study 2307] after adjusting for placebo control rates. The CHMP, however, considered the placebo control rates very different: 33.9% (studyA2201) and 42.6% (study 2307) and furthermore, the MSDPB and msSPB reductions for amlodipine 10 mg do not seem comparable to valsartan/amlodipine 80/5 mg but seem to lie in between the results for amlodipine 5 mg and valsartan/amlodipine 80/5 mg. These facts indicate that it is not appropriate to compare the two studies with regard to BP results.

Consequently, the amendment to the existing wording as proposed by the MAH in response to the CHMP Request for supplementary information, to more accurately reflect the data generated in the multi-factorial Study A2201 and Study A2307, and the mentioning of the age range to avoid ambiguity regarding the population studied in Study A2404 was rejected by the Committee:

"5.1 Pharmacodynamic properties

(...)

Amlodipine/Valsartan

(...)

~~In patients not adequately controlled on amlodipine 5mg~~ Patients receiving amlodipine/valsartan 5 mg/80 mg may achieve blood pressure control similar to amlodipine 10 mg with less oedema. In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, amlodipine/valsartan 5 mg/80 mg may achieve similar blood pressure control with less oedema.

In an additional active-controlled study of 1183 patients aged 55 years or older not adequately controlled on amlodipine 5mg, amlodipine/valsartan 5 mg/160 mg produced numerically greater reductions in blood pressure compared to amlodipine 10 mg with a 4-fold lower incidence of peripheral oedema."

Moreover, the CHMP was of the view that the existing paragraph, although previously accepted by the Committee by mistake, should be removed from the SmPC since it was considered that the text might be misleading for prescribers:

~~"In patients not adequately controlled on amlodipine 5 mg, amlodipine/valsartan 5 mg/80 mg may achieve blood pressure control similar to amlodipine 10 mg with less oedema. In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, amlodipine/valsartan 5 mg/80 mg may achieve similar blood pressure control with less oedema."~~

In conclusion, the wording suggested by the MAH as part of variation 2 is not acceptable to the CHMP. In addition, the already approved paragraph should for the reasons outlined above be deleted from the SmPC. As part of variation 2, the MAH also took the opportunity to update the SmPC in line with the latest QRD template, including a revision of the presentation of the ADRs in section 4.8, and to update the contact details of the local representatives in the Package Leaflet, which is acceptable.

In view of the outcome of the CHMP assessment, the MAH agreed not to pursue the proposed wording.

Variation 3

This variation had several scopes:

The update of section 5.1 of the SmPC with information on efficacy in patients

- not adequately responding to any monotherapy and in
- obese and diabetic patients

based on studies VAA 2401, VAA 2402,VAA 2403, VAA 2404 and VAA US02 (as well as original dossier studies VAA 2201, VAA 2305, VAA 2306, VAA 2307 and VAA 2308).

Regarding the first part of the variation:

Both studies (2401 and US02) that were submitted in support of the proposed change in 5.1 concerning the efficacy in patients not adequately responding to any monotherapy including ACE inhibitors, ARBs, calcium channel blockers, beta-blockers and diuretics were not conducted in accordance with the authorised indication, i.e. in patients not adequately controlled on amlodipine or valsartan monotherapy. This is not in accordance with the SPC guideline which states the following "…Such information on clinical trials should be concise, clear, relevant and balanced, and should summarise evidence from relevant studies supporting the indication." Furthermore, the proposed statement may encourage prescribers to off-label prescriptions of Exforge.

Further, the submitted studies were not conducted in an appropriate way to support the proposed statement. Deficiencies relate to inclusion criteria, conduct of the study and handling of data.

The proposed statement:

"In two additional active-controlled trials of 1612 patients, additional blood pressure lowering effects for Exforge were observed compared to baseline in patients not adequately responding to monotherapy including ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers and diuretics"

is therefore not acceptable.

In view of the outcome of the CHMP assessment, the MAH decided to accept the comments regarding "efficacy in patients not adequately responding to any monotherapy" and agreed not to pursue the proposed wording as part of variation 3.

Regarding the second part of the variation:

Diabetic patients:

The Applicant has presented subgroup analyses from the 9 studies submitted to support the efficacy of valsartan/amlodipine in hypertensive patients regardless of diabetes status.

Patients with type 1 diabetes as well as patients with type 2 diabetes and poor glucose control were excluded from these studies.

As mentioned by the applicant the definition of diabetes was not universal across the studies:

"The definition of diabetes varied across studies. In [Study A2401], [Study A2402], [Study A2403] and [Study A2404], diabetes status came from a specific question on the Medical History case report form. In [Study A2201], [Study A2307], [Study A2305], and [Study A2306] diabetes status was determined according to concomitant medication use at baseline and medical history, using WHODRL and MedDRA terms in place at the time of the original Exforge submission. In [Study US02], subgroup analyses based on diabetes status at baseline defined as fasting plasma glucose (FPG) > 126 mg/dL vs FPG ≤ 126 mg/dL were performed for the primary and secondary variables. For the purpose of the diabetes analyses performed for this Clinical Overview Addendum, patient diabetic status was determined post-hoc according to concomitant medication use at baseline and medical history, using WHODRL and MedDRA terms at the time of CSR completion."

Diagnosis of type 2 diabetes is usually made by WHO/ADA diagnostic criteria for fasting glucose levels (plasma glucose ≥7.0 mmol/L (126mg/dL) or plasma glucose levels 2-hours after 75 mg oral glucose load of ≥11.1 mmol/L (200mg/dL), or newly diagnosed with mixed meal tolerance test or oral glucose tolerance screening or casual glucose ≥11.1 mmol/L (200mg/dL) with symptoms.

As a consequence, diabetic status in the studies referred to is therefore not necessarily confirmed.

As mentioned previously, studies 2401, US02, 2402 and 2403 were not conducted in accordance with the authorised indication. It is therefore not considered justified to claim any inclusions in the SmPC based on post hoc subgroup analyses concerning diabetic status based on the results from these studies. Notwithstanding this fact, the reductions in MSSBP and MSDBP in studies 2401 and US02 seemed numerically lower in diabetic patients compared to non-diabetic patients.

In study 2402 the week 8 analyses for the val/aml combination is of limited value, as patients could be uptitrated from 160/10 mg to 320/10 mg at week 4.

Also in study 2404 the presented analyses were not pre-specified. Also in this study the reduction in MSSBP and MSDBP seemed numerically lower in diabetic patients compared to non-diabetic patients.

In the previously submitted studies 2201, 2307, 2305 and 2306 the subgroup analyses by diabetic status are based on very small numbers of patients by treatment group (n=8-18) which do not allow for strong conclusions.

In summary, the presented post-hoc analyses do not justify the inclusion of a statement regarding the efficacy of Exforge by diabetic status for the following reasons: 1) Different definitions were used to determine diabetic status; 2) The post-hoc analyses were either based on very small patient numbers (studies 2201, 2307, 2305, 2306), or were based on studies not conducted in accordance with the authorised indication; 3) The efficacy of Exforge does not seem as good in diabetic patients as in non-diabetic subjects.

These analyses do therefore not justify the inclusion of the proposed statement in section 5.1 regarding the efficacy of Exforge by diabetic status.

In view of the outcome of the CHMP assessment, the MAH agreed not to pursue the proposed wording in diabetic patients.

BMI:

The MAH has presented subgroup analyses for obese patients with BMI ≥30 and patients with BMI < 30. Focussing on the studies that were conducted in accordance with the authorised indication the proportion of obese patients with BMI ≥ 30 was in the range of 30 -50%. Although no statistical analyses were presented, the anti-hypertensive effect of Exforge seemed similar in obese- and non-obese subjects. The presented information on reduction in MSSBP and MSDBP are considered sufficient to allow a statement on response to Exforge by BMI to be included in section 5.1 of the SmPC with the following modification:

"Age, gender, race, *or* body mass index *(≥30kg/m^2, <30kg/m^2)* ~~or diabetes status~~ did not influence the response to Exforge.

Following the CHMP assessment, the MAH agreed to revise the proposed wording as requested by the CHMP.

3. Conclusion

WS-0100-G was submitted for a group of variations consisting of three Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

On 23 June 2011 the CHMP considered the following variations for the following medicinal products to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

This application concerns the following medicinal products:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Dafiro	amlodipine / valsartan	See Annex A
Copalia	amlodipine / valsartan	See Annex A
Exforge	amlodipine / valsartan	See Annex A
Imprida	amlodipine / valsartan	See Annex A

Variation(s) requested		Type
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

- Update of the current paragraph in section 5.1 of the SmPC that provides information on the relative efficacy of valsartan/amlodipine 80/5 mg compared to amlodipine 10 mg in relation to the incidence of oedema. In addition, the MAH took the opportunity to update the SmPC in line with the latest QRD template and to update the contact details of the local representatives in the Package Leaflet.

- Update of section 5.1 of the SmPC with information on efficacy in obese patients based on studies VAA 2401, VAA 2402, VAA 2403, VAA 2404 and VAA US02 (as well as original dossier studies VAA 2201, VAA 2305, VAA 2306, VAA 2307 and VAA 2308).

And the following variation for the following medicinal products was considered not to be acceptable by the CHMP on the following grounds:

This application concerns the following medicinal products:

Medicinal product:	International non-proprietary name:	Presentations:
Dafiro	amlodipine / valsartan	See Annex A
Copalia	amlodipine / valsartan	See Annex A
Exforge	amlodipine / valsartan	See Annex A
Imprida	amlodipine / valsartan	See Annex A

Variation(s) requested		Type
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

- (*Scope as applied for by the MAH*): Update of section 5.1 of the SmPC with information on efficacy in patients with stage 2 hypertension and black patients based on studies VAA 2402 and VAA 2403.

Grounds for refusal:

Whereas

- The studies submitted by the MAH in support of the variation are not sufficiently robust;
- The studies submitted by the MAH in support of the variation are not in line with the authorised indication;

the CHMP has recommended the refusal of the variation to the terms of the Marketing Authorisation