



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Aliskiren, Amlodipine and Hydrochlorothiazide

Proprietary Product Name: Rasilamlo HCT

Sponsor: Novartis Pharmaceuticals Australia Pty
Ltd

June 2012

TGA Health Safety
Regulation

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission:</i>	New Combination (of previously approved active ingredients)
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	16 March 2012
<i>Active ingredient(s):</i>	Aliskiren Amlodipine Hydrochlorothiazide
<i>Product Name(s):</i>	Rasilamlo HCT
<i>Sponsor's Name and Address:</i>	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
<i>Dose form(s):</i>	Film coated tablet
<i>Strength(s):</i>	Aliskiren 150 mg, amlodipine 5 mg, hydrochlorothiazide 12.5 mg Aliskiren 300 mg, amlodipine 5 mg, hydrochlorothiazide 12.5 mg Aliskiren 300 mg, amlodipine 5 mg, hydrochlorothiazide 25 mg Aliskiren 300 mg, amlodipine 10 mg, hydrochlorothiazide 12.5 mg Aliskiren 300 mg, amlodipine 10 mg, hydrochlorothiazide 25 mg
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	Packs of 7 and 28.
<i>Approved Therapeutic use:</i>	Rasilamlo HCT is only indicated as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of aliskiren, amlodipine and hydrochlorothiazide taken either as three single component formulations or as dual-component formulation with single-component formulation, all components at the same dose level. Treatment should not be initiated with these fixed-dose combinations (see "Dosage and Administration").
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	One tablet daily
<i>ARTG Number (s)</i>	176176, 176182, 176185, 176187 and 176189

Product Background

Cardiovascular disease is a significant contributor to the total disease burden in Australia, accounting for nearly 18%.¹ Hypertension is the most frequently managed problem in general practice in Australia, accounting for approximately 8% of encounters and

¹ Mathers CD, Vos ET, Stevenson CE, Begg SJ. The Australian Burden of Disease Study: measuring the loss of health from diseases, injuries and risk factors. *Med J Aust* 2000; 172: 592-596.

prescriptions in general practice.² There is good evidence that blood pressure reduction decreases the risk of cardiovascular disease.³

Aliskiren belongs to a class of antihypertensives called direct renin inhibitors (DRI) that inhibit the renin angiotensin system (RAS) at the initial rate limiting step, the conversion of angiotensinogen to angiotensin I (Ang I), which is a precursor to angiotensin II, the potent vasoconstrictor in the renin angiotensin system of the kidney. Aliskiren is a Novartis drug currently registered since 2008 under the name *Rasilez* for the treatment of hypertension up to 300 mg and also registered in combination with hydrochlorothiazide (HCT) as *Rasilez HCT* for the second line treatment of hypertension in April 2010. Its product information (PI) allows for combination use with other antihypertensives.

Amlodipine is a long acting, dihydropyridine calcium channel blocker (CCB) and the most commonly prescribed drug in this class. Amlodipine was first registered in 1992 and approved for the treatment of hypertension and angina up to 10 mg, however amlodipine is not registered as a monotherapy from Novartis, but is sponsored by Pfizer as the innovator along with a number of generic sponsors. Its PI also allows for combination use with other antihypertensives.

Hydrochlorothiazide (HCT) is the most commonly prescribed thiazide type diuretic. HCT acts in the distal convoluted tubule of the kidney, affecting renal tubular mechanisms of electrolyte reabsorption and directly increasing excretion of sodium and chloride in approximately equivalent amounts.

It is registered for the treatment of hypertension up to 100 mg and use is allowed with other antihypertensives.

This AusPAR describes the evaluation of an application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register a new fixed dose combination of aliskiren, amlodipine and HCT (Rasilamlo HCT) for the treatment of hypertension as substitution therapy. Five combinations of these drugs are being proposed by the sponsor and treatment should not be initiated with these combinations. The triple combination product is proposed to improve patient compliance and achieve target blood pressure by reducing the number of tablets needed by a patient. The proposed indication for Rasilamlo HCT is:

as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of aliskiren, amlodipine and hydrochlorothiazide taken either as three single component formulations or as dual-component formulation with a single-component formulation, all components at the same dose level. Treatment should not be initiated with these fixed dose combinations (see Dosage and Administration).

The proposed dose is one tablet daily as substitution therapy.

TGA has previously evaluated and registered a triple combination called *Exforge HCT* by Novartis containing amlodipine, valsartan and hydrochlorothiazide for a substitution indication in hypertension.⁴ Aliskiren is available as monotherapy 150 mg and 300 mg tablets under the name *Rasilez*. It is also available in dual combinations as *Rasilamlo*

² Britt H, Miller GC, Knox S, et al. General practice activity in Australia 2000-01. Canberra: Australian Institute of Health and Welfare, 2001.

³ National Heart Foundation. 1999 Guide to management of hypertension for doctors. Canberra: National Heart Foundation, 1999.

⁴ AusPAR for Amlodipine and Valsartan and Hydrochlorothiazide, August 2010. Available at: <http://www.tga.gov.au/pdf/auspar/auspar-exforge.pdf>.

(aliskiren/amlodipine) 150/5, 150/10, 300/5 and 300/10 mg and *Rasilez HCT* (aliskiren/hydrochlorothiazide) 150/12.5, 150/25, 300/12.5 and 300/25 mg.^{5,6}

Regulatory Status

A similar application was approved in the US on 21 December 2010. The approved indication in the US is:

Amturnide is indicated for the treatment of hypertension. This fixed combination drug is not indicated for initial therapy of hypertension.

An application was submitted to the European Union (EU) on 6 May 2010 and approved on 22 September 2011.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Introduction

Rasilez tablets containing 150 and 300 mg of aliskiren (as hemifumarate) were approved for registration by Novartis Pharmaceuticals Australia Pty Ltd (Novartis) in June 2008 with the indication, '*Treatment of hypertension*'. There are no generics.

Rasilez HCT '150/12.5', '150/25', '300/12.5' and '300/25' fixed dose combination tablets of aliskiren (as hemifumarate) with hydrochlorothiazide (HCT) were registered by Novartis in February 2010 with the indication, '*Treatment of hypertension. Treatment should not to be initiated with this fixed dose combination*'. There are no generics.

Rasilamlo '150/5', '150/10', '300/5' and '300/10' fixed dose combination tablets of aliskiren (as hemifumarate) with amlodipine (as besylate) were registered by Novartis in August 2011 with the indication, '*Treatment of hypertension. Treatment should not to be initiated with this fixed dose combination*'. There are no generics.

Tablets containing 2.5, 5 and 10 mg of amlodipine (as the besylate) have been registered for many years (1993) for the use in the treatment of hypertension. Pfizer (Norvasc) was the innovator but there are many generics. Fixed dose combination tablets with valsartan (*Exforge*, Novartis), olmesartan medoxomil (*Sevikar*, Schering Plough), atorvastatin (as calcium; *Caduet*, Pfizer), perindopril (*Coveram*, Servier) and telmisartan (*Twynsta*, Boehringer Ingelheim) have been registered.

Monotherapy tablets containing the diuretic HCT have been registered for many years for the use in the treatment of hypertension and there are a number fixed dose combination tablets using this drug substance.

Drug Substances (active ingredients)

There are European Pharmacopoeia (EP)/British Pharmacopoeia (BP)2011 and United States Pharmacopoeia (USP) 34 monographs for HCT and BP2011 and USP34 monographs for HCT tablets.⁷

⁵ AusPAR for Aliskiren/Amlodipine, August 2011. Available at:
<http://www.tga.gov.au/pdf/auspar/auspar-rasilamlo.pdf>.

⁶ AusPAR for Aliskiren/Hydrochlorothiazide, March 2010. Available at:
<http://www.tga.gov.au/pdf/auspar/auspar-rasilez.pdf>.

⁷ EP: European Pharmacopoeia, BP: British Pharmacopoeia, USP: United States Pharmacopoeia

There is an EP/BP2011 monograph for amlodipine besilate⁸ and a USP34 monograph for amlodipine besylate. There is also an USP34 monograph for amlodipine besylate tablets, but no BP monograph.

There are no compendial monographs for aliskiren hemifumarate or aliskiren products.

The details relating to aliskiren (as hemifumarate) drug substance are the same as for the registered products.

The amlodipine besylate used in the products is covered by European Directorate of Quality Medicines (EDQM) Certificates of Suitability certifying that the material meets the EP monograph for Amlodipine Besilate. In addition, the finished product manufacturer has adopted additional tests and limits for particle size distribution and residual solvents. There is also a test and limit for alkyl besylates (which are genotoxic and can be formed from besylate ions and methanol, ethanol or iso-propanol used in the manufacture of amlodipine besylate).

The hydrochlorothiazide used in the products is covered by EDQM Certificates of Suitability certifying that the material meets the EP monograph for HCT. In addition, the finished product manufacturer has adopted additional tests and limits for particle size distribution and residual solvents.

Drug Product

The tablets are to be manufactured by Novartis Pharma Stein AG in Switzerland. Separate aliskiren and amlodipine/HCT granulations are prepared. These are then mixed, compressed, film coated and packed. The tablets contain no unusual excipients and the quality of the excipients is adequately controlled. No material of animal origin is used.

The cores of the "150/5/12.5" and "300/10/25" tablets are direct scales. The cores of the "300/5/12.5", "300/5/15", "300/10/12.5" and "300/10/25" are identical masses with the amount of microcrystalline cellulose adjusted to compensate for the different masses of amlodipine besylate and HCT present.

The tablets are well controlled with satisfactory expiry limits and release limits that allow for the changes observed on storage. The expiry limits for the aliskiren, amlodipine and HCT assays comply with the requirements of Therapeutic Goods Order (TGO) 78. The limits for the four specified degradants of aliskiren are higher than accepted for the monotherapy tablets and also above the International Council on Harmonisation (ICH) qualification threshold of 0.2%. However data was included in the nonclinical submission to support the proposed limits. Given that ethanol and isopropanol are used in the aliskiren granulate, these solvents are appropriately controlled. Further the formation of ethyl and isopropyl benzene sulfonates is theoretically possible and the sponsor has included limits for each of these.

Stability data was provided to support the proposed shelf lives of 18 months when stored below 30°C in opaque PA/Al/PVC // Al blister packs. The storage condition 'protect from moisture' is also used for all strengths and 'protect from light' for the "150/5/12.5" strength. Data was also provided to support that the tablets may be stored in bulk before packaging in the proposed blister packs.

⁸ Note the Australian Approved Name (AAN) at the time of writing was amlodipine besylate and not amlodipine besilate.

Biopharmaceutics

Clinical Background

The Phase III clinical efficacy studies were performed using the concomitant administration of 150 mg and 300 mg monotherapy aliskiren tablets (as registered in Australia), encapsulated 5 mg and 10 mg monotherapy amlodipine tablets (German *Norvasc* tablets) and 12.5 mg and 25 mg monotherapy HCT capsules manufactured specially for the studies by Novartis.

Studies submitted

The company submitted two relevant bioavailability studies, one food effect study, a justification for not generating bioavailability data using three of the tablet strengths (“150/5/12.5”, “300/5/12.5 and “150/10/12.5”), a justification for using the German *Norvasc* comparator, a justification for using the Novartis HCT comparator and the omission of a pharmacokinetic interaction study.

The test methods used in the studies to determine levels of aliskiren, amlodipine and hydrochlorothiazide in subjects’ plasma samples were evaluated and found to give accurate and precise results. The subject samples were collected at appropriate times to allow good estimation of the pharmacokinetic parameters including the maximum plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC).

Study CSAH100A2104 (Bioequivalence)

This was a single dose, five way crossover study in 80 healthy subjects (63 completed) to compare the proposed “300/10/25” fixed dose combination (FDC) tablet (and three other FDC tablets) to the concomitant administration of the monotherapies as used in the clinical efficacy studies. The results showed bioequivalence for aliskiren, amlodipine and HCT responses (Table 1).

Table 1: Comparison of pharmacokinetic data for the 300/10/25 fixed dose combination (FDC) versus the individual monotherapies

Parameter	Geometric Mean Ratio (FDC/Separate) and [90% Confidence Intervals]		
	Aliskiren	Amlodipine	Hydrochlorothiazide
AUC _{0-t}	0.98 [0.89-1.08]	0.99 [0.96-1.02]	0.91 [0.88-0.95]
C _{max}	1.02 [0.89-1.18]	0.99 [0.96-1.02]	0.90 [0.86-0.94]

Study CSAH100A2102 (Bioequivalence)

This was a single dose, two way crossover study in 109 healthy subjects (96 completed) to compare the proposed “300/5/25” FDC tablet to the concomitant administration of the monotherapies as used in the clinical efficacy studies. The results showed bioequivalence for aliskiren, amlodipine and HCT responses except that the confidence interval for the C_{max} of aliskiren was lower than 0.80-1.25 (Table 2). It was also noted that the aliskiren AUC results were statistically less than 1 (0.85). These results were referred to the Delegate to decide if they were clinically relevant.

Table 2: Comparison of pharmacokinetic data for the 300/5/25 FDC versus the individual monotherapies

Parameter	Geometric Mean Ratio (FDC/Separate) and [90% Confidence Intervals]		
	Aliskiren	Amlodipine	Hydrochlorothiazide
AUC _{0-t}	0.85 [0.80-0.90]	1.00 [0.98-1.02]	0.96 [0.93-0.98]
C _{max}	0.84 [0.76-0.93]	1.02 [0.99-1.04]	0.95 [0.91-0.98]

Study CSAH100A2101 (Food Effect)

This was a single dose, two way crossover study in 36 healthy subjects to determine the affect of food on the bioavailability of aliskiren and amlodipine from the proposed tablets (the “300/10/25” tablet was used). The results (Table 3) indicate:

- An 80% decrease in aliskiren levels with food. The time to maximum plasma concentration (T_{max}) was also reduced from 3 to 1.5 hours (h).
- No change in amlodipine levels (or T_{max}) with food
- No change in HCT levels (or T_{max}) with food.

Table 3: Comparison of pharmacokinetic data for the individual drugs for fed versus fasted

Parameter	Geometric Mean Ratio (Fed/Fasted) and [90% Confidence Intervals]		
	Aliskiren	Amlodipine	Hydrochlorothiazide
AUC _{0-t}	0.21 [0.18-0.24]	1.08 [1.04-1.12]	0.94 [0.90-0.99]
C _{max}	0.11 [0.10-0.14]	1.06 [1.01-1.10]	0.86 [0.81-0.91]

Justifications for Not Performing Bioavailability Studies**Other Strengths**

A justification was provided to justify not providing bioavailability data comparing the “150/5/12.5”, “300/5/12.5” and “300/10/12.5” strength FDC tablets to the monotherapies used in the Phase III clinical efficacy studies. The chemistry aspects of this justification were accepted. The dissolution profile results of all five strengths at pH 1, 4.5 and 6.8 were similar in relation to each analyte. Aliskiren is BCS Class 3.⁹

In relation to the clinical aspects of this justification, the pharmacokinetics of amlodipine and hydrochlorothiazide are linear over the dose range but the pharmacokinetics of aliskiren show slightly greater than linear increases with dose (that is, the best dose to examine bioequivalence is the highest dose as used). Further there were small interactions between the drug substances (*see below*). These facts were referred to the Delegate and the advisory committee (*see below*) for consideration.

⁹ The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Overseas Reference Products

No data were included comparing an Australian registered amlodipine tablet to the German *Norvasc* amlodipine tablets used in the Phase III clinical efficacy studies and bioequivalence studies. The chemistry aspects of this justification of this were acceptable. It was also noted that at the proposed maximum daily dose (10 mg), amlodipine (as besylate) can be considered BCS Class 1 and that this justification has been accepted previously in relation to other FDC tablets of Novartis containing amlodipine.⁹ Note that data has previously been provided demonstrating that encapsulation of the German *Norvasc* tablets does not change the bioavailability.

The sponsor also provided a justification for using the overseas HCT capsules used in these studies rather than HCT tablets or capsules available in Australia. In part this referred to a previous submission. That justification was relevant to this submission and acceptable. Note that hydrochlorothiazide is BCS Class 3.⁹

Omission of a Pharmacokinetic Interaction Study

Instead of a pharmacokinetic interaction study the sponsor performed a population pharmacokinetics analysis on data generated as part of the Phase III efficacy study (CSAH100A2302). The results indicate that each drug substance lowers slightly (6-22%) the bioavailability of the other drug substances (Table 4).

Table 4: Summaries of the statistical analyses of the effect of one drug on the pharmacokinetics of the other two drugs

Summary of statistical analysis of HCTZ effect on aliskiren and amlodipine pharmacokinetics

		Population predicted geometric mean ratio ¹	90% CI for ratio ¹
Aliskiren	AUC0-24 (ng.h/mL)	0.87	(0.53, 1.43)
	Cmax (ng/mL)	0.80	(0.50, 1.30)
Amlodipine	AUC0-24 (ng.h/mL)	0.94	(0.67, 1.31)
	Cmax (ng/mL)	0.94	(0.70, 1.29)

¹ 100 mg / amlodipine 10 mg / HCTZ 25 mg vs aliskiren 300 mg / amlodipine 10 mg

Table 2-3 Summary of statistical analysis of aliskiren effect on amlodipine and HCTZ pharmacokinetics

		Population predicted geometric mean ratio ¹	90% CI for ratio ¹
HCTZ	AUC0-24 (ng.h/mL)	0.89	(0.70, 1.09)
	Cmax (ng/mL)	0.86	(0.74, 1.02)
Amlodipine	AUC0-24 (ng.h/mL)	0.78	(0.56, 1.06)
	Cmax (ng/mL)	0.79	(0.59, 1.05)

¹ 300 mg / amlodipine 10 mg / HCTZ 25 mg vs amlodipine 10 mg/HCTZ 25 mg

Table 2-4 Summary of statistical analysis of amlodipine effect on aliskiren and HCTZ pharmacokinetics

		Population predicted geometric mean ratio ¹	90% CI for ratio ¹
Aliskiren	AUC0-24 (ng.h/mL)	0.95	(0.66, 1.36)
	Cmax (ng/mL)	0.78	(0.54, 1.17)
HCTZ	AUC0-24 (ng.h/mL)	0.89	(0.71, 1.13)
	Cmax (ng/mL)	0.84	(0.70, 1.04)

¹ aliskiren 300 mg / amlodipine 10 mg / HCTZ 25 mg vs aliskiren 300 mg /HCTZ 25 mg

These results are similar to previous data generated in appropriate pharmacokinetic studies using aliskiren and amlodipine only and using aliskiren and hydrochlorothiazide only, showing:

- A 29% increase in aliskiren levels in the presence of amlodipine (90% confidence intervals (CIs) for C_{max} = 0.83-1.69 and AUC = 1.07-1.55).
- No difference the amlodipine levels indicating no interaction with aliskiren (90% CIs for C_{max} = 0.93-1.05 and AUC = 0.92-1.05).
- For aliskiren and HCT, there was no change to the AUCs, but the C_{max} results are lowered to 78% for aliskiren and 74% for HCT.

These results were brought to the attention of the Delegate and the advisory committee for consideration.

Advisory Committee Considerations

Details of this submission were presented at the 140th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) in September 2011. The PSC was asked to specifically consider the validity of the population pharmacokinetic results and (subsequently) the acceptability of the justification for not performing bioequivalence studies on the "150/5/12.5", "300/5/12.5" and "300/10/12.5" strength FDC tablets.

The Committee considered that all outstanding issues should be addressed to the satisfaction of the TGA.

The PSC accepted the Sponsor's justification for:

- Using overseas sourced amlodipine (as besylate) monotherapy tablet and encapsulated tablet formulations and, hydrochlorothiazide monotherapy capsule formulation as the comparator in the bioequivalence and the clinical trial studies provided in support of this submission.
- Not providing a bioequivalence data on all strengths of the combination tablet formulation proposed for registration to the coadministration of corresponding doses of the monotherapy formulations.

The PSC was not concerned about the slight reduction in the bioavailability of each drug substance in the presence of the other drug substances in view of the fact that the observed interaction between the three drug substances was not statistically significant.

Quality Summary and Conclusions

Approval of the application was recommended with respect to chemistry and quality control.

In relation to bioavailability:

- The clinical efficacy studies used monotherapy products combined for treatment.
- For the "300/10/25" strength tablet, data was provided to demonstrate bioequivalence of this proposed fixed dose combination tablet to the monotherapy treatments used in the clinical efficacy studies.
- For the "300/5/25" strength tablet, data was provided to demonstrate bioequivalence of this proposed fixed dose combination tablet to the monotherapy treatments used in the clinical efficacy studies, except that the confidence interval for the C_{max} of aliskiren was 0.76-0.93. This was referred to the Delegate.
- The justifications for not providing bioavailability data on the "150/5/12.5", "300/5/12.5" and "300/10/12.5" strength tablets were acceptable with respect to

chemistry aspects. The clinical aspects were referred to the Delegate and the PSC was asked to consider this issue (see above).

- The justifications for the use of overseas amlodipine and hydrochlorothiazide products in the clinical efficacy and bioavailability studies have been evaluated previously and were acceptable.
- There are slight pharmacokinetic interactions between the drug substances. The clinical aspects were referred to the Delegate and the PSC was asked to consider this issue (see above).
- Food (high fat meal) reduces the bioavailability of aliskiren (but not amlodipine or hydrochlorothiazide). However the PI states patients may take the tablets with or without food, but that this should be consistent. The clinical aspects were referred to the Delegate

III. Nonclinical Findings

Introduction

The proposed fixed combination contains approved compounds indicated for long term use and the pharmacotoxicological profiles of the individual components have been previously well characterised. Despite clinical experience with concomitant use of the three drugs, nonclinical bridging studies are nevertheless considered valuable, particularly given that both aliskiren and amlodipine exert their actions on the cardiovascular system and that renal (aliskiren, amlodipine and HCT) and cardiac toxicities (amlodipine) have been identified for the individual medicines in nonclinical studies previously evaluated by the TGA.

No nonclinical studies with the triple combination were submitted. The sponsor referred to 2 week and 13 week oral (PO) repeat dose toxicity studies in rats (including toxicokinetics) conducted with the aliskiren/amlodipine and aliskiren/HCT combinations as supportive safety data. The potential of the combination to cause pharmacodynamic or specific pharmacokinetic interactions was not tested. Appropriate justifications were provided for the absence of such studies (see separate sections below). TGA adopted EU guidelines on the nonclinical development of fixed combinations of medicinal products indicate that nonclinical safety studies with the triple combination may have been considered.¹⁰ However, the availability of nonclinical data for other relevant combinations, together with the available clinical data, may mitigate any concerns, as discussed in subsequent sections.

No studies of carcinogenicity or reproductive toxicity were performed with the combination as these areas have been thoroughly evaluated for aliskiren, amlodipine and HCT and currently available clinical data do not raise any specific safety concerns in these areas.

Pharmacology

Efficacy and pharmacodynamic interactions

Nonclinical pharmacodynamic studies with the triple combination were not conducted. As justification, the sponsor argued that a large amount of experimental and clinical data are available showing greater blood pressure reductions (than monotherapy) of combinations

¹⁰ EMEA, Committee for Medicinal products for Human Use (CHMP), 24 January 2008. Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products, CHMP/SWP/258498/2005.

of calcium channel blockers (CCB; for example, amlodipine) and blockers of the renin-angiotensin aldosterone system (RAAS; for example, aliskiren) such as angiotensin-converting-enzyme inhibitor (ACE) inhibitors or angiotensin receptor blockers (ARBs). Additionally, simultaneous administration of a RAAS blocker may neutralise the diuretic induced increase in plasma renin activity associated with HCT activity.

Existing animal models for investigating the pharmacodynamics of the combination would be expected to be dominated by either (i) the aliskiren component (for example in double transgenic mice that overexpress human genes for renin and angiotensinogen) or (ii) the amlodipine/HCT component (for example in normal rats where aliskiren has weak potency of aliskiren against rat renin).

On balance, the absence of nonclinical efficacy data is reasonable given the existing clinical data for the efficacy of CCB/RAAS blockers and thiazide diuretics. Moreover, the potential for unexpected pharmacodynamic (PD) interactions is unlikely given the separate and distinct mechanism of action of each component.

Pharmacokinetics

Pharmacokinetic interactions

The pharmacokinetics of aliskiren, amlodipine and HCT have been individually characterised both nonclinically and clinically. Potential interactions at the oxidative metabolism or transporter level are considered unlikely as aliskiren is primarily eliminated by biliary efflux via MDR1, whereas amlodipine undergoes extensive metabolism, mostly mediated by cytochrome P450 (CYP) 3A4 and HCT is largely excreted unchanged in urine.

Toxicokinetic data obtained in previously evaluated 13 week toxicity studies in rats with the combinations of aliskiren/amlodipine and amlodipine/valsartan/HCT failed to reveal any significant differences between the pharmacokinetics of the relevant individual drugs in combination versus the individual drugs alone. However, combination treatment of aliskiren and HCT in a 13 week toxicity study in rats resulted in reduced exposure (AUC- and C_{max} -based) to aliskiren in the presence of HCT compared with aliskiren alone but generally increased exposure to HCT in the presence of aliskiren. According to the previous nonclinical evaluation report, reduced exposure to aliskiren in the presence of HCT was also seen clinically. The mechanism for this apparent pharmacokinetic interaction has not been discussed. However, the toxicity data obtained in the study did not indicate an accompanying toxicological interaction. Thus, the finding is unlikely to represent a cause for clinical concern.

The available data indicate that the pharmacokinetics of aliskiren, amlodipine and HCT are not likely to differ in the triple combination compared with other registered combinations, and the lack of nonclinical pharmacokinetics studies was considered acceptable.

Relative exposure

Relative exposure to aliskiren, amlodipine and HCT in toxicokinetic studies in rats with other registered combinations was calculated in previous nonclinical evaluation reports. The proposed maximum clinical daily dose of the triple combination is 300/10/25 mg aliskiren, amlodipine and HCT, which represent the same maximum doses of individual components as registered in other combinations. To assist with the assessment of the nonclinical safety of the proposed triple combination, the relevant relative exposure calculations, obtained from the key 13 week toxicity studies in previous submissions are reproduced in Table 5. No Observable Adverse Effect Levels (NOAELs) are highlighted in brackets.

Plasma protein binding of aliskiren differs between humans (50%) and rats (38%). Thus, exposure margins were adjusted to account for these differences. In contrast, plasma protein binding of amlodipine was similar in rats and humans (3% and 2%, respectively), and adjustment was not considered necessary. No data are available regarding HCT plasma protein binding, and exposure margins for this drug were calculated assuming negligible differences between rats and humans.

Exposure ratios (AUC) for aliskiren and amlodipine at NOAEL doses in all relevant studies in 13 week rat combination toxicity studies were similar to, or less than, the exposure anticipated clinically at the Maximum Recommended Human Dose (MRHD) of 300/10 mg aliskiren/amlodipine. AUC based exposure to HCT at the NOAEL in 13 week combination toxicity studies ranged from 0.5 to fourfold the anticipated clinical exposure at the MRHD of 25 mg.

Table 5: Relative exposure to aliskiren, amlodipine and HCT in previous combination toxicity studies

Study	Dose (mg/kg/day)	Drug	Sex	AUC _{0-24 h} (ng.h/mL) ^a	C _{max} (ng/mL) ^a	Exposure multiple ^a	
						AUC	C _{max}
<i>Aliskiren/amlodipine combination</i>							
Rat Day 75	30/1	Aliskiren	M	18	1.7	0.01	0.1
			F	26	7.9	0.02	0.5
		Amlod.	M	154	12.3	0.3	0.8
			F	167	15.6	0.4	1.0
	[90/3]	Aliskiren	M	126	14.9	[0.1]	[0.9]
			F	174	114	[0.1]	[7]
		Amlod.	M	594	61	[1.3]	[4]
			F	850	81.2	[1.8]	[5]
	300/10	Aliskiren	M	395	43.3	0.3	3
			F	536	81.3	0.4	5
		Amlod.	M	3990	287	9	19
			F	3710	256	8	17
	300	Aliskiren	M	366	71.1	0.3	4
			F	673	86.3	0.5	5
	10	Amlod.	M	3650	264	8	18
			F	4610	358	10	24
Human ^b	300/10 mg	Aliskiren	M/F	1235	16.8	NA	NA
		Amlod.	M/F	466	14.9	NA	NA
<i>Amlodipine/valsartan/HCT combination^c</i>							
Rat Wk 11	[0.5/1.25]	Amlod.	M	40.9	4.75	[0.08]	[0.2]
			F	65.6	6.82	[0.1]	[0.3]
		HCT	M	888	200	[0.5]	[0.9]
			F	939	221	[0.5]	[1.0]
	2/5	Amlod.	M	368	35.2	0.7	1.4
			F	460	48.7	0.9	1.9
		HCT	M	3090	672	1.6	3
			F	3590	893	1.8	4
	4/10	Amlod.	M	802	68.1	1.6	3
			F	817	98.2	1.6	4
		HCT	M	10300	1800	5	8
			F	6870	1130	3	5
	4	Amlod.	M	931	114	1.8	4
			F	1100	104	2	4
	10	HCT	M	6100	1220	3	5
			F	5640	1220	3	5
Human ^d	10/25 mg	Amlod.	M/F	504.7	25.7	NA	NA
		HCT	M/F	1969	226	NA	NA

^a Based on respective unbound fractions of 0.38 (rat) and 0.5 (human) for aliskiren and assuming similar protein binding for amlodipine and HCT; ^b Measured on Day 49; ^c Only data for amlodipine and HCT are reproduced in this table; ^d Time point not specified in previous report
Amlod. = amlodipine; NA = not applicable; NOAELs are highlighted in [brackets].

Table 5 continued

Study	Dose (mg/kg/day)	Drug	Sex	AUC _{0-24 h} (ng.h/mL) ^a	C _{max} (ng/mL) ^a	Exposure multiple ^a	
<i>Aliskiren/HCT combination</i>							
Rat Wk 13	50/4	Aliskiren	M	22	3.1	0.02	0.02
			F	17	2.9	0.02	0.02
		HCT	M	2040	352	1.6	1.9
			F	2160	570	1.7	3
	[100/8]	Aliskiren	M	70	9.1	[0.06]	[0.06]
			F	154	53.2	[0.1]	[0.3]
		HCT	M	5500	854	[4]	[5]
			F	4110	863	[3]	[5]
	150/12	Aliskiren	M	133	41.0	0.1	0.3
			F	182	52.4	0.2	0.3
		HCT	M	6100	1070	5	6
			F	7250	1320	6	7
	150	Aliskiren	M	289	70.7	0.3	0.5
			F	331	73.0	0.3	0.5
	12	HCT	M	3990	854	3	5
			F	4580	875	4	5
Human ^e	300/25 mg	Aliskiren	M/F	1105	154.5	NA	NA
		HCT	M/F	1273	187	NA	NA

^a Based on respective unbound fractions of 0.38 (rat) and 0.5 (human) for aliskiren, and assuming similar protein binding for amlodipine and HCT; ^e Measured on Day 19
NA = not applicable; NOAELs are highlighted in [brackets].

Toxicology

Toxicological interactions

The absence of nonclinical toxicity studies with the triple combination was justified on the basis that the safety profile of aliskiren/amlodipine/HCT has been adequately characterised in previous toxicity studies for each component and in different combinations. Thus, the assessment of the safety of the triple combination was primarily based on 13 week repeat dose studies conducted with the following combinations: aliskiren/amlodipine; amlodipine/valsartan/HCT; and aliskiren/HCT.

No novel, treatment related toxicities or potentiation of known toxicities were identified with any of the three previously evaluated combination products in animal studies. The observed toxicities were consistent with those seen in studies with the individual products alone and were discussed at length in those relevant evaluation reports. Most findings were related to exaggerated pharmacological effects. Briefly, hypertrophy and/or vacuolation of the zona glomerulosa of the adrenal glands was attributed to amlodipine or HCT treatment in different combinations. Aliskiren related toxicities in rats included a low incidence of haemorrhage of the stomach.

Thus, the available nonclinical data, combined with the availability of postmarket data for all three components of the combination used either individually or in various combinations, indicate that there are unlikely to be novel safety issues of clinical concern for the aliskiren/amlodipine/HCT combination.

Impurities

Aliskiren related impurities

According to the relevant TGA adopted EU guideline, the qualification threshold for aliskiren related degradation products (maximum daily dose of aliskiren is 300 mg) is NMT 0.2%.¹¹ The proposed limits for aliskiren related impurities are identical to those proposed for another new combination product containing aliskiren and amlodipine. In the nonclinical evaluation of the dual combination product, the sponsor was asked to justify the specifications for the aliskiren related impurities. The proposed specification limits for the four impurities were considered qualified by the submitted response for the dual combination and are also applicable for the proposed triple combination in this submission.

Amlodipine related impurities

According to the relevant TGA adopted EU guideline, the qualification threshold for amlodipine related degradation products (maximum daily dose of amlodipine is 10 mg) is NMT 0.5%. One amlodipine related impurity exceeds this threshold. The proposed limits for amlodipine related impurities are identical to those proposed for another new combination product containing aliskiren and amlodipine. The available nonclinical safety data was sufficient to qualify the shelf life specification limit of this amlodipine related impurity for the dual combination. This was also applicable for the current triple combination product.

HCT related impurities

There are no HCT related impurities with specification limits greater than those recommended in the relevant TGA-adopted EU guideline.

Pregnancy classification

The sponsor proposed Pregnancy Category D, which is dictated by the ability of aliskiren to block the RAAS. Previous clinical experience has shown that drugs with this activity can cause fetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters.

Nonclinical Summary and Conclusions

No nonclinical studies with the triple combination were submitted. The nonclinical safety of the triple combination was therefore assessed using previously evaluated repeat dose toxicity studies in rats of up to 13 weeks duration with different combinations of the three products (aliskiren/amlodipine, aliskiren/HCT and amlodipine/valsartan/HCT). The sponsor also submitted an analytical method for the simultaneous quantification of aliskiren and HCT in rat plasma.

The absence of nonclinical pharmacodynamics studies with the combination was justified by the sponsor on the basis of a lack of appropriate animal models as well as consideration of the large amount of experimental and clinical data showing greater blood pressure reductions (than monotherapy) of combinations of calcium channel blockers (CCB) and RAAS blockers such as ACE inhibitors or ARBs. Additionally, simultaneous administration of a RAAS blocker may neutralise the diuretic induced increase in plasma renin activity associated with HCT activity.

While increased exposure (AUC and C_{max} -based) to HCT and reduced exposure to aliskiren was observed following concurrent administration to rats in a previous 13 week study

¹¹ EMEA, ICH Topic Q 3 B (R2), June 2006. Note for Guidance on Impurities in New Drug Products, CPMP/ICH/2738/99.

there were no resulting toxicological interactions of concern. There was no evidence from previous nonclinical studies for pharmacokinetic interactions between aliskiren and amlodipine or amlodipine and HCT.

The absence of nonclinical toxicity studies with the triple combination was justified on the basis that the safety profile of aliskiren/amlodipine/HCT has been adequately characterised in previous toxicity studies for each component and in different combinations. No novel, treatment related toxicities or potentiation of known toxicities were identified in animal studies with any of the three previously evaluated combination products.

The available nonclinical data, combined with the availability of postmarket data for all three components of the combination used either individually or in various combinations, indicate that there are unlikely to be novel safety issues of clinical concern for the aliskiren/amlodipine/HCT combination. Thus, there were no nonclinical objections to the registration of Rasilamlo HCT/Riprazemlo HCT for the treatment of hypertension.

IV. Clinical Findings

Introduction

The clinical program included 3910 hypertensive patients and 1155 of whom received at least one dose of aliskiren/amlodipine/HCT combination and 568 received the combination for at least 6 months. There were 6 clinical studies in the submission: one pivotal short term active controlled; one key long term uncontrolled; and 4 supportive studies. The two main studies assessed the triple combination directly (uptitrating to the maximal dose of 300/10/25 mg) while the other 4 studies had subgroups on triple therapy who had been inadequately controlled on dual therapy. There are 3 ongoing studies for which no preliminary data were available.

As the clinical development program was conducted with the monotherapy products in free combination, a bioequivalence program with the fixed combination tablets and the 3 individual monotherapy products in free combination was conducted to allow bridging of this efficacy and safety data to support the replacement therapy indication. A definitive bioequivalence study (SAH2102) was generated for the 300/5/25 mg strength. There were two relative bioavailability studies (SAH2104 and SAH2105) performed for the 300/10/25 mg strength. Only Study SAH2104 included the variant proposed for registration in Australia (variant 002). Biowaivers were requested for the 150/5/12.5, 300/5/12.5 and 300/10/12.5 strengths. There was also a food effect study (SAH2101).

The controlled efficacy studies in the submission have been designed in accordance with the relevant guidelines on development of antihypertensives and fixed combination products (ICH E12 2000, CHMP 2004, CHMP 2009).^{12,13,14}

Pharmacokinetics

Introduction

The pharmacokinetics (PK) section of this evaluation comprises two relative bioavailability studies ([Study SAH2104] and [Study SAH2105]), one bioequivalence study [Study SAH2102], a food effect study [Study SAH2101] and a drug-drug interaction (DDI)

¹² ICH Topic E12 (2000). Principles for clinical evaluation of new antihypertensives. CPMP/ICH/54/00.

¹³ CHMP (2004). Note for guidance on clinical investigation of medicinal products in the treatment of hypertension. CPMP/EWP/238/95 Rev 2.

¹⁴ CHMP Guideline (2009) Clinical Development of Fixed Combination Medicinal Products, CHMP/EWP/240/95 Rev 1

study, which examined the interaction between aliskiren, amlodipine and HCT in a subpopulation of patients from the pivotal efficacy and safety trial [Study SAH2302] using a population PK approach.

Methods

Pharmacokinetic data analysis

The following PK parameters were determined using noncompartmental methods in WinNonlin Pro (Version 5.2): the area under the plasma concentration time curve from time zero to the last measurable time point (AUC_{last}), the area under the plasma concentration time curve from time zero to infinity (AUC_{∞}), C_{max} , T_{max} and the half-life ($t_{1/2}$).

Statistical analysis

Descriptive statistics of the PK parameters include: mean, standard deviation (SD), coefficient of variation (CV), minimum and maximum. When a geometric mean was presented it was stated as such. As T_{max} is generally evaluated by nonparametric methods, median values and ranges were given for this parameter. Log transformed AUC and C_{max} of aliskiren, amlodipine and HCT were analysed separately using a linear mixed effect model, with fixed effects from sequence, treatment, and period and random effects from subject nested in sequence.

Absorption

Bioavailability

An open label, randomised, five treatment, single dose, five period, crossover study (CSAH100A2104) examined the relative bioavailability of four fixed dose combination 300+10+25 mg aliskiren/amlodipine/HCT tablet variants relative to the free combination of the market formulations of the 300 mg aliskiren tablet, 10 mg amlodipine capsule and 25 mg HCT capsule in 80 subjects (17 female) aged 19 to 54 years; 63 completed all treatment periods. Subjects were randomised to one of five treatment sequences and were exposed to four variant formulations of the fixed dose combination tablets (variants 001- 004) and to the reference free combination, at identical dose strengths. There was a two week washout period between each dosing. Blood samples were taken prior to dosing and up to 168 hours after dosing on treatment days.

T_{max} of aliskiren occurred within 1.5-2.5 hours (h) post-dose, following administration of the four tablet variants and the free combination of aliskiren /amlodipine/HCT (300/10/25 mg) and the mean terminal half-life ($t_{1/2}$) ranged from 59 to 63 h. Similarly, T_{max} of HCT occurred within 2.0-3.0 h post-dose, whereas the $t_{1/2}$ of this drug was much shorter and ranged from 10.7 to 10.9 h for all five variants. By contrast, plasma concentrations of amlodipine rose relatively slowly, with T_{max} occurring 8 h post dose. The mean C_{max} and AUC values for all four FDC tablet formulation variants were similar to those of the free combination formulation of aliskiren/amlodipine/HCT.

Except for the C_{max} of aliskiren for the T4 formulation (90%CI: 0.95 - 1.26), the 90% confidence intervals of the estimated ratio of geometric means for all four fixed dose formulations versus the reference treatment (R) for C_{max} and AUC were contained within 0.80 to 1.25 limits and therefore, the T1, T2 and T3 fixed combinations were bioequivalent with R. This study was also discussed in *Section II* where a comparison of the FDC versus individual combinations is shown at Table 1.

Formulation T2 was chosen as the prototype formulation on the basis of the results of the relative bioavailability study and comparative *in vitro* dissolution test results.

An open label, randomised, four treatment, single dose, four period, crossover study (CSAH100A2105) examined the relative bioavailability of three fixed combinations of 300+10+25 mg aliskiren/amlodipine/HCT tablet variants relative to the free combination of the market formulations of the 300 mg aliskiren tablet, 10 mg amlodipine capsule and 25 mg HCT capsule in 72 subjects (17 female), 63 completed all treatment periods, aged 18 to 54 years. Subjects were randomised to one of four treatment sequences and were exposed to three variant formulations of the fixed combination tablets (variants 005- 007) and to the reference free combination, at identical dose strengths. There was a two week washout period between each dosing. Blood samples were taken pre dose and up to 168 hours post dose on treatment days.

The peak plasma concentrations of aliskiren and HCT were reached within 1.5-3 h post dose for all three fixed combination tablet variants and the free combination of aliskiren/amlodipine/HCT (300/10/25 mg), whereas the peak plasma concentrations of amlodipine were attained 8 h post dose. The $t_{1/2}$ for aliskiren, HCT and amlodipine ranged from 55.5 – 58.0 h, 10.5 – 11 h and 50.5 – 52.5 h, respectively. The mean AUC values for all three fixed combination tablet formulation variants were similar to those of the free combination; although the mean C_{max} values of amlodipine and HCT for all three fixed combination tablet formulation variants were similar to those of the free combination formulation, the mean C_{max} values of aliskiren for fixed combination tablet formulations were lower than those of the free combination.

The C_{max} and AUC of amlodipine and HCT for all three fixed combinations were within the 90% confidence interval of the estimated ratio of geometric means when compared to the reference treatment (R) (Table 7). However, for aliskiren, although the 90% CI for AUC_{∞} and AUC_{last} were contained within the limits for all three variants, the lower bounds of the 90% CI for C_{max} were below 0.80 for all three variants.

Table 6: Statistical analyses results of PK parameters for aliskiren, amlodipine and HCT following single dose administration of FDC tablet variants and the free combination

Analyte	Parameter	T1 vs. R	T2 vs. R	T3 vs. R
Aliskiren	AUC(0-inf) [hr*ng/mL]	0.91 (0.83,1.01)	0.91 (0.83,1.00)	0.90 (0.82,0.99)
	AUC(0-last) [hr*ng/mL]	0.91 (0.83,1.01)	0.91 (0.82,1.00)	0.90 (0.81,0.99)
	C_{max} [ng/mL]	0.81 (0.70,0.93)	0.79 (0.68,0.91)	0.81 (0.70,0.93)
Amlodipine	AUC(0-inf) [hr*ng/mL]	0.99 (0.96,1.03)	0.98 (0.95,1.01)	1.00 (0.97,1.03)
	AUC(0-last) [hr*ng/mL]	0.98 (0.94,1.03)	0.97 (0.93,1.02)	0.97 (0.92,1.01)
	C_{max} [ng/mL]	0.99 (0.96,1.03)	1.00 (0.97,1.04)	1.02 (0.98,1.05)
HCTZ	AUC(0-inf) [hr*ng/mL]	0.97 (0.93,1.02)	0.95 (0.90,0.99)	0.95 (0.91,1.00)
	AUC(0-last) [hr*ng/mL]	0.95 (0.91,0.99)	0.94 (0.91,0.98)	0.95 (0.91,0.99)
	C_{max} [ng/mL]	0.90 (0.85,0.95)	0.94 (0.89,0.99)	0.93 (0.89,0.98)

T1 - (Variant 005: Fast SPP-release monolayer tablet) SAH100 300+10+25 mg

(aliskiren/amlodipine/HCTZ), N = 63

T2 - (Variant 006: Target SPP-release monolayer tablet) SAH100 300+10+25 mg

(aliskiren/amlodipine/HCTZ), N = 64

T3 - (Variant 007: bilayer tablet) SAH100 300+10+25 mg (aliskiren/amlodipine/HCTZ), N = 65

R - One 300 mg SPP100 (aliskiren) tablet, one 10 mg amlodipine capsule and one 25 mg HCTZ

capsule, N = 66

Note: Subjects who complete at least two periods (one reference treatment, and one test treatment) with valuable/complete PK data were included in the PK data analysis

Bioequivalence

An open label, randomised, two treatment, crossover, single dose study (CSAH100A2102) evaluated the bioequivalence between a fixed dose combination of 300/5/25 mg aliskiren/amlodipine/HCT tablet and a free combination of market formulation of the 300 mg aliskiren tablet and clinical service formulations of 5 mg amlodipine and 25 mg HCT capsule in 109 healthy Asian males, aged 18 to 41 years. Ninety six subjects completed the trial; they were administered a single oral dose of either fixed combination (aliskiren 300mg + amlodipine 5 mg + HCT 25 mg) or free combination administered as one 300 mg aliskiren tablet, one 5 mg amlodipine capsule and one 25 mg HCT capsule, under fasted conditions.

As in previous studies, aliskiren was absorbed rapidly reaching peak concentrations within 2.0 h for the free combination and 1 h and for the fixed combination and the $t_{1/2}$ for the two formulations were 63.9 h and 66.0 h, respectively. Although the mean aliskiren AUC_{last} and AUC_{∞} were similar, the C_{max} was 16% lower for the fixed combination compared to the free combination. Amlodipine attained peak concentrations within 8.0 h for both the free and fixed combinations and the mean $t_{1/2}$ was 4.6 h and 53.6 h, respectively. The other PK parameters for amlodipine were also similar between the fixed and free combination. Peak concentrations of HCT were attained within 2.0 h and 3.0 h for the free and fixed combinations and both the free and fixed combinations had a mean $t_{1/2}$ of 9.6 h. The mean HCT C_{max} , AUC_{last} , and AUC_{∞} were similar for both combinations. Statistical analysis of the PK results indicated that the fixed and free combinations are bioequivalent for both amlodipine and HCT. By contrast, for aliskiren the two formulations were not strictly bioequivalent as the geometric mean ratio for C_{max} was 0.84 and the 90% CIs ranged from 0.76 – 0.93. This study was also discussed in above where a comparison of the FDC versus individual combinations is shown at Table 2.

The evaluator noted that it was not clear whether the fixed combination batch used in this study is of the same formulation as Variant 002, which is described as the prototype formulation in Study CSAH100A2104.

An open label, single dose, three period, crossover study (SPH100A2105) assessed the bioequivalence of a 25 mg dose of HCT following administration of the Clinical Service Form (CSF) capsule and European (EU) marketed tablet or Canadian (CA) marketed tablet formulations in 36 healthy subjects (6 female), aged 21 to 54 years. Subjects were randomised to receive a single oral dose of 25 mg HCT from each of the following sources: Treatment 1, CSF capsule formulation (Test); Treatment 2, EU marketed tablet formulation (Reference); and Treatment 3, CA marketed tablet formulation (Reference) and there was at least a 5 day washout period between dosing.

Following a single oral dose of 25 mg CSF capsule, EU marketed tablet and CA marketed tablet, the T_{max} of HCT occurred within 2-3 h. The C_{max} and AUC values of HCT following a single oral administration of 25 mg CSF capsule were similar to those of the 25 mg EU marketed and 25 mg CA marketed tablets. The $t_{1/2}$ (10.1 – 10.3 h) and CL/F (20.0 – 21.7 L/hr) values were consistent with earlier reported PK results for HCT.

The HCT AUCs for all 3 tablets were bioequivalent; although the C_{max} of the CSF and EU marketed forms were bioequivalent, the C_{max} of the CSF and Canadian tablets were not (Table 8).

Table 7: Geometric means and ratios of geometric means for PK parameters of HCT

Parameter (Unit)	Treatment	Geometric Mean *	Ratio of test to each reference *	90% CI of the ratio*
AUC _{0-∞} (hr*ng/mL)	CSF capsule(T)	1208.07		
	EU-marketed tablet(R)	1153.41	1.05	[1.00,1.09]
	CA-marketed tablet(R)	1112.84	1.07	[1.03,1.12]
AUC _{0-t} (hr*ng/mL)	CSF capsule(T)	1252.58		
	EU-marketed tablet(R)	1193.77	1.05	[1.01,1.09]
	CA-marketed tablet(R)	1156.73	1.07	[1.03,1.12]
C _{max} (ng/mL)	CSF capsule(T)	173.24		
	EU-marketed tablet(R)	156.02	1.11	[1.05,1.17]
	CA-marketed tablet(R)	142.27	1.20	[1.14,1.27]

*back-transformed from log scale.

HCTZ 25mg CSF capsule formulation (Test), N = 34

HCTZ 25mg EU-marketed tablet formulation (Reference), N = 34

HCTZ 25mg CA-marketed tablet formulation (Reference), N = 33

T = Test formulation, R = Reference formulation

Influence of food

The effect of food on the PKs of a fixed dose combination of aliskiren /amlodipine/ HCT 300/10/25 mg tablet under fasted¹⁵ and fed¹⁶ conditions was examined in an open label, randomised, two treatment, single dose, crossover study (CSAH100A2101) in 36 healthy males, aged 19 to 45 years. There was a wash out period of at least 14 days between doses and blood samples for the determination of the PK parameters were taken pre dose and up to 168 hours post dosing.

The AUC, C_{max}, T_{max} and t_{1/2} for amlodipine and HCT were similar under fed and fasted conditions. By contrast, a high fat meal reduced aliskiren exposure by 78% and C_{max} by 89% compared to fasted conditions. The T_{max} and t_{1/2} of aliskiren were also affected by food with the T_{max} 1.5 h under fasted conditions increasing to 3 h under fed conditions whereas, the t_{1/2} decreased from 65 h to 54 h under fasted and fed conditions respectively.

Unlike aliskiren, examination of the geometric mean ratios for amlodipine and HCT revealed no significant food effects. This study was also discussed in *Section II* where a comparison of the fed versus fasted ratios is shown at Table 3.

Intra- and inter-individual variability

Three PK studies (CSAH100A2104, CSAH100A2105 and CSAH100A2101) examined the intra subject coefficients of variation (CV) for the calculated PK parameters. No treatment related sequence effect (p > 0.1) was identified for any of the PK parameters studied in the

¹⁵ Following an overnight fast of at least 10 hours, subjects were administered the study drug with 240 mL of water. On dosing days, no breakfast was provided, nor was food allowed for at least 4 hours post-dose.

¹⁶ Following an overnight fast of at least 10 hours, subjects were administered the study drug 30 minutes after consuming a FDA-standard, high-fat, breakfast meal. A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal was recommended as a test meal according to FDA guidelines.

first 2 studies. Overall, the CVs for the intra subject PK parameters for the three drugs were similar across all 3 studies; the intra-subject %CV for AUC_{∞} ranged from 33.4-34.9%, 9.9-10.1% and 10.9-15.7% for aliskiren, amlodipine and HCT respectively. The intra-subject %CV for C_{max} ranged from 44.7-52.2%, 10.2-11.5% and 14.9-18.2% for aliskiren, amlodipine and HCT respectively. The intra-subject results for a fourth study (CSAH100A2102) were also included and it indicated slightly lower %CVs for all three drugs. The inter subject %CVs for AUC_{∞} ranged from 26.8-53.8, 22.5-37.1 and 16-26.5 for aliskiren, amlodipine and HCT, respectively; the inter-subject %CVs for C_{max} ranged from 26.7-55.0, 14.6-50.6 and 13.4-24.6 for aliskiren, amlodipine and HCT, respectively, across all four studies.

Pharmacokinetics in target population

A randomised, single-blind, parallel group, multiple oral dose study (CSAH100A2302) evaluated the effect of a light meal on the pharmacokinetics of aliskiren using the market 300 mg tablet formulation in 122 subjects (50 female), aged 23 to 64 years, with mild to moderate essential hypertension. Mild to moderate hypertension was defined as patients with newly diagnosed hypertension or subjects who had not received antihypertensive medication for at least 2 weeks prior to screening who had a mean sitting diastolic blood pressure (msDBP) ≥ 95 and < 110 mm Hg and mean sitting systolic blood pressure (msSBP) < 180 mmHg at Visit 1/Visit 3 and at Visit 6. In addition, it included patients with history of hypertension and on current antihypertensive medication at Visit 1 who had a msDBP < 110 mmHg at Visit 1 and a msDBP ≥ 95 and < 110 mmHg and a msSBP < 180 mm Hg at Visit 3 and at Visit 6. Patients were randomised to either the fed or fasted group. Patients in the fed group were instructed to take their medication after a light breakfast¹⁷ whilst those in the fasted group were instructed to take their medication after an overnight fast and to continue fasting for at least 1 h post dose. Patients took medication daily for 4 weeks (28 days) and blood samples were taken for the determination of the PKs on Days 1 and 28 pre-dose and up to 24 h following dosing.

Compared to the PK parameters for patients taking aliskiren in the fasted state, there was a significant reduction in aliskiren exposure (AUC and C_{max}) following dosing in the fed state. In addition, the T_{max} was attained within 4 h in the fed state compared to 2 h in the fasted state.

The estimates for the geometric mean fed versus fasted ratios were low (≤ 0.33) as were the upper 90% CIs for AUC and C_{max} (≤ 0.41) and all comparisons were highly significant ($p < 0.001$) indicating that the bioavailability of aliskiren is significantly affected when taken with a light meal and is lower than when patients were fasted (Table 9). There was a 67% reduction in aliskiren AUC_{0-t} and a 76% reduction in aliskiren C_{max} at steady state when aliskiren was taken with a light meal.

Table 8: Geometric mean ratio (fed/fasted) and 90% CIs for aliskiren PK parameters on Day 28

PK parameter	Adjusted geometric mean		Ratio of geometric means	
	Fed	Fasted	Estimate	90% CI
N	40	41		
AUC_{0-t} (hr.ng/mL)	862	2594	0.33	0.27, 0.41
C_{max} (ng/mL)	97.1	410	0.24	0.17, 0.32

¹⁷ A light breakfast contained 200 mL of semi-skimmed milk, 10 g sugar and 2 pre-packed snacks with a total intake of 410 calories (45% carbohydrate, 13% fat, 42% lipids).

Evaluator's overall conclusions on pharmacokinetics

Following treatment with a fixed combination tablet containing aliskiren /amlodipine/HCT (300/10/25 mg) (Variant 002) in the fasted state the C_{max} , AUC_{∞} , T_{max} and $t_{1/2}$ were 180 ng/mL, 1324 ng.hr/mL, 1.25 h and 60.15 h, respectively for aliskiren, 128.4 ng/mL, 1095 ng.hr/mL, 3 h and 10.78 h, respectively for HCT and 4.5 ng/mL, 280 ng.hr/mL, 8 h and 48.4 h, respectively for amlodipine. The PK parameters for the three drugs in the fixed combination were bioequivalent with a free combination dose of aliskiren /amlodipine/HCT (300/10/25 mg).

Although the fixed dose combination of 300/5/25 mg aliskiren/amlodipine/HCT tablet was bioequivalent to a free combination of market formulation of 300/5/25 mg aliskiren/amlodipine/HCT in regards to amlodipine and HCT, for aliskiren the two formulations were not strictly bioequivalent as the geometric mean ratio for C_{max} was 0.84 and the 90% CI ranged from 0.76 – 0.93. However, the bioequivalence criteria were met for AUC (0.85, 90% CI: 0.80, 0.90).

No PK studies examined the bioequivalence of fixed combination doses containing 12.5 mg HCT.

Following treatment with a fixed combination tablet containing aliskiren /amlodipine/HCT (300/10/25 mg) a high fat meal reduced aliskiren exposure by 78% and C_{max} by 89% compared to fasted conditions, whereas, the T_{max} and $t_{1/2}$ of aliskiren increased by 1.5 h and 11 h under fed compared to fasted conditions. By contrast, the PKs of amlodipine and HCT were not affected by food.

The pharmacokinetic peak and total exposure of aliskiren at steady state was reduced by more than 65% when it was taken with light meal compared to the fasted state.

No studies examined drug interactions between the individual components of the fixed combination.

Although strict PK bioequivalence does not exist between the fixed 300/5/25 mg aliskiren/amlodipine/HCT tablet and the comparable free combination, dissolution studies comparing the 300/5/25 mg and the 300/10/25 mg formulations used in the bioequivalence studies, CSAH100A2104 and CSAH100A2102, indicates that the two formulations are similar. In addition, in their request for a biowaiver in the quality section (see *Section II*), the sponsor addressed all of the clinical issues required.

In regards to the sponsor statement:

“Norvasc (amlodipine) tablets were sourced from Europe. Novartis Australia has not been able to confirm whether these tablets are identical to the ones supplied in Australia by Pfizer, however Novartis understands that a study comparing the bioequivalence of amlodipine (Rasilamlo HCT/Riprazemlo HCT) and the Australian Norvasc is not required since amlodipine is a Biopharmaceuticals Classification Scheme Class I drug (high solubility and high permeability) and as such is unlikely to be significantly affected by finished product formulations differences”

Have dissolution studies been conducted comparing the Novartis and Pfizer forms of amlodipine?

Pharmacodynamics

Introduction

A single study examined the effects of a light meal on the pharmacodynamic (PD) effects of aliskiren in 122 subjects (50 females) with mild to moderate hypertension.

Mechanism of action

Mechanism of action of the individual components of the combination is well established and no new data was provided in this submission.

Primary pharmacology

A randomised, single blind, parallel group, multiple oral dose study (CSAH100A2302) evaluated the effect of a light meal on the pharmacodynamics of aliskiren using the market 300 mg tablet formulation in 122 subjects (50 female) aged 23 to 64 years, with mild to moderate hypertension. A detailed outline of the study methods and the pharmacokinetic results relating to this study can be found under *Efficacy* below. The primary PD objective of the study was to evaluate the effect of light meals on the plasma renin activity (PRA). The secondary PD objectives included an evaluation of the effect of light meals on plasma renin and angiotensin II (Ang II) concentration. PRA, plasma renin concentration (PRC) and Ang II levels were determined by radioimmunoassay.

On Day 28, the baseline adjusted geometric mean PRA area under the effect-time curve (AUE_{24h}) was reduced by 62% and 65% compared to baseline for the fed and fasted treatment groups, respectively. The geometric mean ratio of fed versus fasted on Day 28 versus baseline was 1.07 and the 90% confidence intervals ranged from 0.95 – 1.21 indicating that there was no difference in the AUE_{24h} between the fed and the fasted treatment groups.

The trough PRA levels from baseline to Day 28 decreased by 62% and 64 % in the fed and fasted groups, respectively. The estimate of fed to fasted ratio for this change was 1.04 and the 90% CI included one (0.88 - 1.23), indicating that there was no difference between the fed and the fasted treatment groups (one sided $p=0.70$). By contrast, the estimate of fed to fasted ratio for the change in trough PRC from baseline to Day 28 was 0.62 and the 90% confidence limit ranged from 0.42 to 0.91 indicating that food significantly increased trough PRC (one sided $p=0.040$). The estimate of fed to fasted ratio for the change in trough Ang II levels from baseline to Day 28 was 1.06 and the 90% CI ranged from 0.91 to 1.25 indicating that there was no difference between the fed and the fasted treatment groups for trough Ang II (one sided $p=0.51$).

Between baseline and Day 28 the trough mean sitting systolic and diastolic BP were reduced by 10-12 mmHg with the differences between the treatment groups being less than 1 mmHg for both measures. The 90% confidence interval for msSBP and msDBP were -3.45 to 4.13 and -1.89 to 3.15, respectively, indicating that there were no differences in trough msSBP and msDBP changes from baseline to Day 28 when aliskiren was taken with a light meal when compared with fasted conditions.

Evaluator's overall conclusions on pharmacodynamics

Mechanism of action of the individual components of the combination is well established and no new data was provided in this submission.

A light meal had no effect on the change in PRA AUE_{24hrs} from baseline to Day 28 induced by aliskiren. There was no significant food effect upon the aliskiren induced change in: trough PRA; trough Ang II, trough msSBP or trough msDBP from baseline to Day 28. A light meal significantly increased trough PRC levels on Day 28 (1.6 fold) compared to fasted conditions following administration of aliskiren.

No studies have examined the PD interaction between the components of the fixed combination.

Efficacy

Introduction

The clinical section of the submission contained 6 clinical studies (Table 10). There were 2 studies with the aliskiren/amlodipine/HCT combination, one short term active controlled study (SAH2302) and one long term, open label, uncontrolled study (SAH2301), which provide the main efficacy data. There were 3 studies of aliskiren with add on amlodipine and HCT: one short term active controlled study (SPP2441); one long term active controlled study (SPP2411); and one long term open label study (SPP2360). The submission also included a long term, open label, study of aliskiren/amlodipine with optional add-on HCT (SPA2301). This study was also submitted for evaluation in the aliskiren/amlodipine combination application.⁵

Table 9: Overview of efficacy studies

Topic Purpose	Details
Pivotal study	
Pivotal short-term, active-controlled study	Study SAH2302: double-blind, 8-week, active-controlled, 4-group, parallel study evaluating the triple combination of aliskiren/amlodipine/HCTZ in comparison to dual combinations of aliskiren/amlodipine, aliskiren/HCTZ, or amlodipine/HCTZ
Key long-term efficacy and safety study	
Long-term efficacy and safety study of the (aliskiren/amlodipine/HCTZ) triple combination	Study SAH2301: open-label, 28 to 54-weeks study evaluating the long-term safety and efficacy of the aliskiren/amlodipine/HCTZ triple combination
Other supportive Studies¹	
Long-term active-controlled study in elderly patients	Study SPP2344: double-blind, 36-week, active-controlled study evaluating aliskiren-based regimen (with optional add-on of HCTZ and amlodipine) in comparison to ramipril-based regimen (with optional add-on of HCTZ and amlodipine) in elderly hypertensive patients
Short-term active-controlled study	Study SPP2411: double-blind, 8-week, parallel-group, active-controlled dose-escalation study evaluating the combination of aliskiren/HCTZ in comparison to HCTZ (with optional addition of amlodipine) in older patients (≥ 55 years)
Long-term open-label studies	Study SPA2301: open-label 54-week study evaluating the long-term safety and efficacy of aliskiren/amlodipine with optional addition of HCTZ Study SPP2360: open-label, 24-week, non-comparative study in which patients were treated with an aliskiren-based regimen that included an optional add-on of HCTZ and amlodipine to control BP

¹ By study design, patients in these studies whose BP was not controlled by aliskiren/HCTZ or aliskiren/amlodipine received the add-on of amlodipine or HCTZ. Therefore, a proportion of patients in these studies were treated with the combination of aliskiren/amlodipine/HCTZ.
BP=blood pressure and HCTZ=hydrochlorothiazide

The primary efficacy measure was change from baseline in the mean sitting systolic blood pressure (msSBP), with mean sitting diastolic BP (msDBP) and BP response rates as secondary endpoints. There were no pooled efficacy data due to the different study designs and treatments.

All study medication was in free combinations with none of the clinical efficacy and safety trials using the fixed triple combination tablet proposed for marketing.

Dose response studies

There were no dose response studies included in the submission. The proposed dosage in the combination tablets is the same as the doses used in the respective monotherapies for hypertension treatment, that is, 150 mg and 300 mg for aliskiren, 5 mg and 10 mg for amlodipine, and 12.5 and 25 mg for HCT.

Main (pivotal) Studies

SAH2302 (short term active controlled – aliskiren/amlodipine/HCT)

Design

Study CSAH100A2302 (SAH2302) was an 8 week double blind, multicentre, randomised, active controlled, parallel group study to evaluate the efficacy and safety of the combination aliskiren/amlodipine/HCT in 1189 patients with moderate to severe hypertension.

There were 3 study periods: Period 1 was a washout of up to 4 weeks; Period 2 was a single blind placebo run in period of 1 to 4 weeks duration to establish baseline BP and eligibility; and Period 3 was an 8 week randomised, double blind treatment period. Subjects were randomised to one of 4 treatment groups: (1) aliskiren 150 mg/amlodipine 5 mg; (2) aliskiren 150 mg/HCT 12.5 mg; (3) amlodipine 5 mg/HCT 12.5 mg; and (4) aliskiren 150 mg/HCT 12.5 mg for 3 days followed by aliskiren 150 mg/amlodipine 5 mg/HCT 12.5 mg. After 4 weeks doses were force titrated up for the remaining 4 weeks to: (1) aliskiren 300 mg/amlodipine 10 mg; (2) aliskiren 300 mg/HCT 25 mg; (3) amlodipine 10 mg/ HCT 25 mg; and (4) aliskiren 300 mg/amlodipine 10 mg/HCT 25 mg. Subgroups of patients had PK samples at Week 6 and ambulatory BP monitoring (ABPM) at baseline and Week 12.

Ambulatory BP monitoring (ABPM) was performed in a subset of patients over two 24 hour periods at the start and end of double blind treatment. Electronic case report forms (eCRF) were used and there was a central laboratory for blood analysis and biomarker measurement.

Treatment

Aliskiren 150 mg and 300 mg were tablets, amlodipine 5 mg, amlodipine 10 mg, HCT 12.5 mg and HCT 25 mg were capsules. There were identical matching placebo capsules and tablets. Subjects took 2 capsules and 2 tablets once a day in the morning (8 am), except on study visit days when it was taken after the study procedures.

Prohibited concomitant medications included: any antihypertensives (beta blocker ophthalmic preparations were allowed); potassium supplements; Monoamine Oxidase (MAO) inhibitor antidepressants; systemic corticosteroids; thyroid medications or hormone replacement therapy unless stable dose for 3 months prior to the study; phosphodiesterase type 5 inhibitors within 48 hours of a study visit; antiarrhythmics except digoxin; cholestyramine or colestipol resins; and cyclosporin or P-glycoprotein inhibitors.

Objectives

The primary objective was to demonstrate that the fixed dose triple combination of aliskiren/amlodipine/HCT was superior to the double combinations of aliskiren/amlodipine, aliskiren/HCT and amlodipine/HCT in lowering mean sitting systolic blood pressure (msSBP) in patients with moderate to severe hypertension. Secondary objectives included the comparison of the triple combination to the double combinations on: superiority in lowering mean sitting diastolic BP (msDBP); BP control rates (msSBP/msDBP <140/90 mmHg); DBP responder rates (msDBP <90 mmHg or a reduction \geq 10 mmHg from baseline); SBP responder rates (msSBP <140 mmHg or a reduction \geq 20 mmHg from baseline); 24 hour mean ambulatory DBP (MADBP) and SBP (MASBP); drug-drug interaction potential; and safety and tolerability.

Study participants

Inclusion criteria were: ≥ 18 years of age; male or female; met BP criteria and discontinued all antihypertensive medication prior to placebo period; and have moderate to severe hypertension. This was defined as either (1) msSBP ≥ 160 mmHg and < 200 mmHg at the qualifying BP visit and msSBP ≥ 145 mmHg and < 200 mmHg and msDBP ≥ 95 mmHg and < 120 mmHg at the visit prior to qualifying visit or (2) msSBP ≥ 180 mmHg and < 200 mmHg with msDBP ≥ 95 mmHg and < 120 mmHg, or msDBP ≥ 110 mmHg and < 120 mmHg with msSBP ≥ 150 mmHg and < 200 mmHg after at least one week of treatment with placebo.

Exclusion criteria were: inability to discontinue antihypertensive medication; on 4 or more antihypertensives at Visit 1; hypertension with msSBP ≥ 200 mmHg or msDBP ≥ 120 mmHg during placebo run in; pregnancy or lactation; women of child bearing potential unless using approved birth control; secondary hypertension; history of hypertensive encephalopathy, cerebrovascular accident, transient ischaemic attack (TIA), myocardial infarction (MI), coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI); heart failure (New York Heart Association [NYHA] Class II-IV¹⁸); serum potassium ≥ 5.5 mEq/L (mmol/L); Type I or II diabetes mellitus which was not well controlled; angina pectoris requiring medication (except nitrates); second or third degree heart block with or without a pacemaker or life threatening arrhythmia in last 12 months; major gastrointestinal surgery with bowel resection; active inflammatory bowel disease within 12 months; active gastritis, ulcers or bleeding within 3 months; hepatic disease including alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $> 3x$ the upper limit of normal (ULN), history of hepatic encephalopathy, oesophageal varices or portocaval shunt; renal impairment with serum creatinine $> 1.5x$ ULN, dialysis or history of nephrotic syndrome; known or suspected contraindications to CCB, thiazide diuretics, sulphonamides or renin inhibitors; malignancy within the past 5 years; gouty arthritis; drug and alcohol abuse within 12 months; likely to need a forbidden medication; and for the ABPM substudy an upper arm circumference > 42 cm and shift workers.

Patients were withdrawn if: msDBP ≥ 120 mmHg or msSBP ≥ 200 mmHg during the placebo or low treatment dose period; if msDBP ≥ 110 mmHg or msSBP ≥ 180 mmHg during the higher dose treatment period; if clinically significant hypotension and/or msDBP < 60 mmHg and msSBP < 100 mmHg at any time during the study; or if pregnant.

Outcomes/endpoints

The primary efficacy variable was the change from baseline to the end of the study (Week 8) in msSBP. The BP was defined as the average of the available readings of sitting SBP from one visit. Secondary variables included the change from baseline in msDBP, percent of patients achieving BP control, SBP response, DBP response and changes from baseline

¹⁸ NYHA Class

Symptoms

I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest . Mostly bedbound patients.

in ABPM. The hourly mean ambulatory DBP (MADBP) and SBP (MASBP) was the average of readings taken in the corresponding hour.

Statistical considerations

A sample size of 246 completed patients per group had a 90% power to detect a 5 mmHg difference in msSBP between the triple combination and double combination treatments at a two sided significance level of 0.05, assuming a standard deviation (SD) of 15 mmHg. Allowing for a dropout rate of 15%, 290 patients per arm and 1160 in total were required. For the ABPM substudy, 592 patients were required (700 to allow for dropout), or 148 completed per group, to give the study an 80% power to detect a difference of 5 mmHg between the triple combination and double combination treatment in change from baseline in MASBP assuming a standard deviation of 13 mmHg.

Patients were randomised in a 1:1:1:1 ratio to one of the 4 treatment arms by an interactive voice response system (IVRS).

Amlodipine and HCT were capsules and aliskiren a tablet, so to maintain the study blind a double dummy design was used with patients taking 2 capsules and 2 tablets of study medication throughout the study. All tablets and capsules were placebo in the single blind run in period.

To assess the superiority of the triple combination compared to the 3 double combinations on lowering msSBP an analysis of co variance (ANCOVA) model was used with treatment and region as factors and the baseline as a covariate. The overall null hypothesis was rejected with all three individual null hypotheses were rejected, that is, a greater reduction in msSBP than all 3 double combinations. Additional analyses assessed treatment by region and by baseline interactions. The primary analysis was msSBP change at Week 8. Analysis was also conducted at Week 4 after the low dose period and for msDBP at Week 4 and 8.

The proportion of patients responding to each treatment at Week 4 and 8, as well as BP control rates, were analysed using logistic regression models with treatment and region as factors and baseline BP as a covariate. The hourly change from baseline in MADBP or MASBP was analysed by repeated measures ANCOVA.

The primary analysis population was the “full analysis set” (FAS) which was all randomised patients excluding those misrandomised (that is, did not qualify but were inadvertently randomised). Supportive analysis was conducted on the “per protocol” set (PPS) which was all FAS patients who completed the study without any major protocol deviation. The last post baseline BP measurement during double blind treatment was carried forward to analysis (LOCF).

The study was conducted in 2008-2009 in 181 centres in Europe, Israel, North America and Australia.

Participant flow

There were 1909 patients enrolled and 1189 who completed the single blind placebo run in period. Of the 720 who discontinued the single blind period, the most common reason was abnormal test procedure (25.4%) which included the BP criteria. There were 1191 patients randomised, 2 misrandomised who did not receive double blind treatment and 1106 (92.9%) who completed the study. Premature discontinuation rates (7.0% overall) were similar between the 3 groups, aliskiren/amlodipine/HCT (7.7%), aliskiren/amlodipine (7.3%) and aliskiren/HCT (7.0%), and lower for amlodipine/HCT (5.7%). Discontinuation due to AEs was greatest in the aliskiren/amlodipine/HCT group (3.5%) compared to 0.7% to 2.7% in the other groups. Protocol deviations that led to

exclusion from the PPS occurred in 15.7% of patients, were balanced across treatment groups and most (13.5%) related to msSBP and msDBP not meeting study requirements. The FAS included 1189 (99.8%) subjects and the PPS included 939 (78.8%) subjects.

Baseline data

Groups were comparable with respect to baseline demography and characteristics. Most subjects were Caucasian (84.1%) or Black (10.0%), the mean age was 55.1 years with 19.1% aged ≥ 65 years and 60.5% were male. Forty nine percent of subjects were obese (body mass index [BMI] ≥ 30 kg/m²), 51.7.0% had the metabolic syndrome¹⁹ and 14.4% diabetes. The mean duration of hypertension was 9.4 years (excluding the 3.4% of patients who were treatment naïve). Baseline BP measurements were also comparable across treatment groups with a msDBP of 103.3 to 104.9 and msSBP of 171.5 to 173.2 mmHg. The most frequently reported medical conditions were hyperlipidaemia (10.7%) obesity (9.5%) hypercholesterolaemia (8.6%), dyslipidaemia (9.1%), diabetes (13.8%), osteoarthritis (10.4%), back pain (6.4%), depression (5.7%) and asthma (4.0%).

Outcomes and estimation

Primary outcome

At the Week 8 endpoint, the change from baseline in msSBP with the aliskiren/amlodipine/HCT was -37.92 mmHg. There was a statistically significant ($p < 0.001$) greater reduction in the msSBP with the triple combination compared to the respective double combinations. The least squares mean (LSM) difference in change from baseline in msSBP for aliskiren/amlodipine/HCT compared to the double combinations ranged from -6.55 to -9.93 mmHg (Table 11). Results from the PPS analysis supported those found with the FAS.

Table 10: Statistical analysis of change from baseline in msSBP at Week 8 endpoint (FAS)

Treatment group	N	LSM change from baseline (SE)	
Alii/Aml 300/10 mg	282	-31.37 (0.90)	
Alii/HCTZ 300/25 mg	296	-27.99 (0.88)	
Aml/HCTZ 10/25 mg	295	-30.77 (0.88)	
Alii/Aml/HCTZ 300/10/25 mg	308	-37.92 (0.86)	
Pairwise comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
Alii/Aml/HCTZ vs Alii/Aml	-6.55 (1.22)	(-8.96, -4.15)	< 0.001*
Alii/Aml/HCTZ vs Alii/HCTZ	-9.93 (1.21)	(-12.31, -7.56)	< 0.001*
Alii/Aml/HCTZ vs Aml/HCTZ	-7.15 (1.21)	(-9.53, -4.78)	< 0.001*

SE = standard error, LSM = least squares mean, CI = confidence interval.

Least squares means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region and baseline.

P-Values and treatment comparisons were evaluated at the average baseline level.

* indicates statistical significance at 0.05 level.

Secondary Outcomes

For msDBP at Week 8 the change from baseline with the triple combination was -20.63 mmHg. Again there was a statistically significant greater reduction with the triple

¹⁹ Metabolic Syndrome if any 3 of the following 5 are true: 1. Waist circumference > 102 cm (40 in) for men, or > 88 cm (35 in) for women; 2. Triglycerides ≥ 150 mg/dL (1.69 mmol/L); 3. HDL cholesterol < 40 mg/dL (1.04 mmol/L) for men, or < 50 mg/dL (1.29 mmol/L) for women; 4. SBP ≥ 130 or DBP ≥ 85 mmHg; 5. Fasting glucose ≥ 110 mg/dL (6.1 mmol/L).

combination compared to all 3 double combinations ($p < 0.001$). The LSM difference in change from baseline in msDBP ranged from -2.60 to -6.30 mmHg (Table 12).

Table 11: Statistical analysis of change from baseline in msDBP at Week 8 endpoint (FAS)

Treatment group	N	LSM change from baseline (SE)
Ali/Aml 300/10 mg	282	-18.03 (0.57)
Ali/HCTZ 300/25 mg	296	-14.32 (0.55)
Aml/HCTZ 10/25 mg	295	-17.03 (0.55)
Ali/Aml/HCTZ 300/10/25 mg	308	-20.63 (0.54)

Pairwise comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
Ali/Aml/HCTZ vs Ali/Aml	-2.60 (0.77)	(-4.11, -1.08)	< 0.001*
Ali/Aml/HCTZ vs Ali/HCTZ	-6.30 (0.76)	(-7.80, -4.81)	< 0.001*
Ali/Aml/HCTZ vs Aml/HCTZ	-3.59 (0.76)	(-5.09, -2.10)	< 0.001*

SE = standard error; LSM = least squares mean, CI = confidence interval.

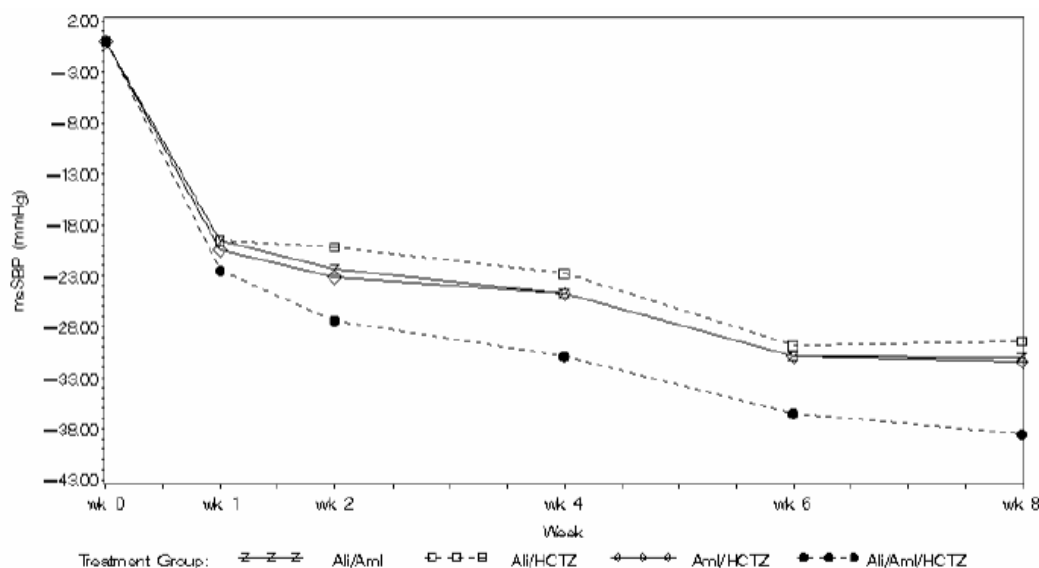
Least squares means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region and baseline.

P-Values and treatment comparisons were evaluated at the average baseline level.

* indicates statistical significance at 0.05 level.

At Week 4, the triple combination of aliskiren/amlodipine/HCT 150/5/12.5 mg showed a statistically significant greater reduction in msSBP and msDBP compared to the respective double combinations ($p < 0.003$). The additional reduction in SBP ranged from 5.55 to 8.70 mmHg and for DBP ranged from 2.17 to 5.13 mmHg. BP reduction was seen from Week 1 and maintained over the study duration (Figure 1).

Figure 1: Average change from baseline in msSBP by treatment group and week (FAS)



At Week 8, the mean change from baseline in standing BP was -35.3/-17.8 mmHg with the triple combination which was greater than the double combinations (range: -25.0 to -28.8/-11.6 to -15.8 mmHg).

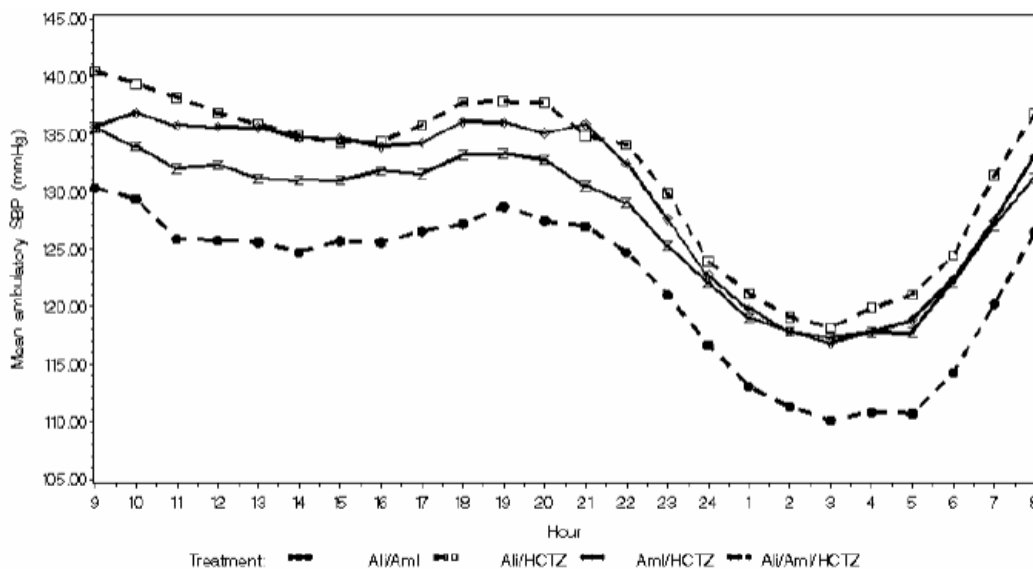
BP control was defined as msDBP < 90 mmHg and msSBP < 140 mmHg. At Week 8, the BP control rate was significantly greater with the triple combination (62.3%) compared to 33.1% for aliskiren/HCT, 39.0% for amlodipine/HCT and 41.3% for aliskiren/amlodipine ($p < 0.001$ for all comparisons).

Systolic BP response (msSBP < 140 mmHg or at least 20 mmHg reduction from baseline) was greater with the triple combination (89.0% at Week 8) compared to each double combinations (aliskiren/HCT 72.3% p<0.001, amlodipine/HCT 81.7% p=0.011, and aliskiren/amlodipine 82.3% p=0.026). SBP response was also significantly greater at Week 4.

Diastolic BP response (msDBP < 90 mmHg or a \geq 10 mmHg reduction from baseline) was 89.6% for triple combination at Week 8. This was significantly greater than 69.3% for aliskiren/HCT (p<0.001) and 82.0% for amlodipine/HCT (p=0.009), however DBP response was not improved on aliskiren/amlodipine (86.5%, p=0.223). There were similar findings at Week 4.

For a subset of 576 patients (147 treated with aliskiren/amlodipine/HCT), the mean 24 hour ambulatory DBP and SBP was significantly reduced with the triple combination compared to the respective double combinations with differences of 4.99 to 9.02 mmHg for SBP and 2.61 to 6.33 mmHg for DBP (p<0.001 for all comparisons). Treatment effect was maintained over 24 hours with the once daily dose (Figure 2). As 35 patients had over 5 hours of missing ABPM readings, a *post hoc* sensitivity analysis was conducted. Results of this were consistent with the main analysis.

Figure 2: Average of hourly mean ASBP at Week 8 endpoint by hour and treatment



The hour displayed stands for chronological clock hours.

Subgroup analysis

Severe hypertension was defined as msSBP \geq 180 mmHg at baseline. In this subgroup, the reduction from baseline in msSBP was 49.53 mmHg with a significant improvement over the double combinations of -9.58 to -11.42 mmHg (p<0.001 for the 3 pairwise comparisons). The reduction in msDBP was 22.53 mmHg and this was also significantly greater in the 3 comparisons (p<0.001). For patients with severe hypertension, the BP control rate at Week 8 was 57.5% for the triple combination compared to 16.2%, 19.3% and 25.0% for the aliskiren/HCT, aliskiren/amlodipine and amlodipine/HCT double combinations, respectively. *Post hoc* analysis in the sponsor's *Summary of Clinical Efficacy* found that in patients with baseline msSBP \geq 190 mmHg, the triple combination 300/10/25 mg resulted in a BP control rate of 50.0% compared to 11.4% to 21.2% with dual combinations.

For Caucasians and Blacks, the triple combination therapies resulted in a greater reduction in DBP and SBP than the double therapy, while numbers in other racial groups were too small to draw meaningful conclusions. For males and females, and those aged <65 years, ≥ 65 years and ≥ 75 years, the triple combination resulted in a greater reduction in msDBP and msSBP than the double combination. The response to triple therapy was greater in females than males with a BP reduction at Week 8 of 43.5/21.6 mmHg compared to 33.3/19.4 mmHg. For those aged ≥ 75 years the reduction in BP at Week 8 was 50.9/29.2 mmHg compared to 36.4/20.1 mmHg in those aged less than 65 years. Triple therapy also had a greater BP reduction than dual therapy across the BMI groups.

Biomarkers

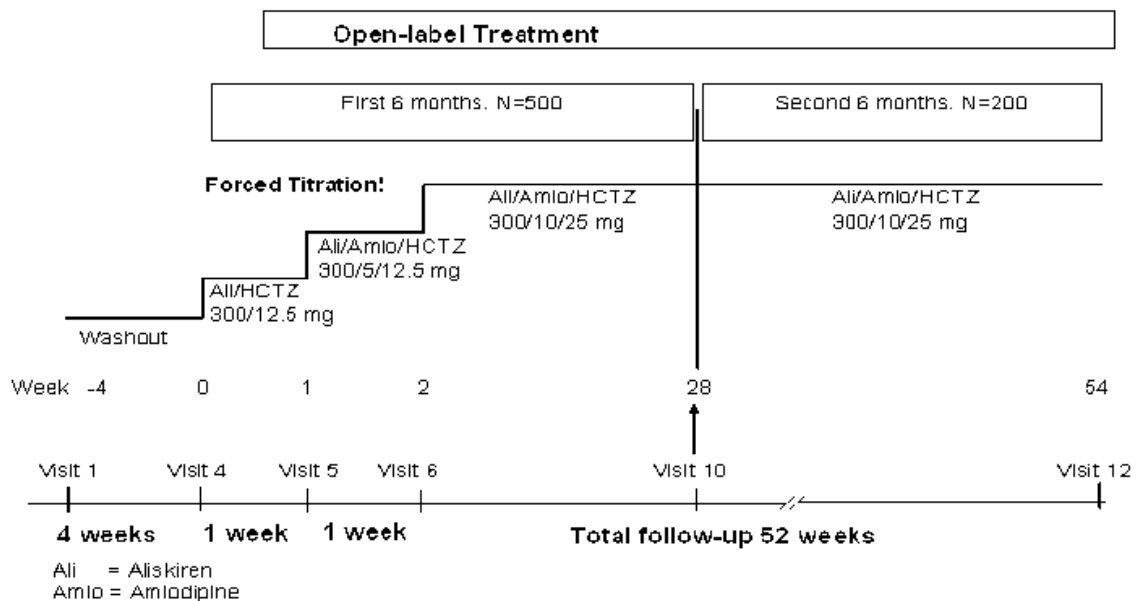
About half the subjects had plasma renin concentration (PRC) and plasma renin activity (PRA) measured. At the study end, there was a reduction in the geometric mean PRA of 34%, 63% and 64% in the aliskiren/amlodipine/HCT, aliskiren/amlodipine and aliskiren/HCT groups respectively, while PRA increased by 170% in the amlodipine/HCT group. An increase in PRC was seen in all groups and was greatest with the triple combination (1419%) compared to 716%, 721% and 158% in the aliskiren/amlodipine and aliskiren/HCT groups and amlodipine/HCT groups, respectively.

SAH2301 (long term uncontrolled – aliskiren/amlodipine/HCT)

Design

Study CSAH100A2301 (SAH2301) was a 28 to 54 week, open label, multicentre study assessing the long term safety of the combination aliskiren/amlodipine/HCT in patients with moderate to severe essential hypertension. After 1 to 4 weeks of washout there was a 54 week open label treatment period. Treatment commenced with aliskiren/HCT 300/12.5 mg, after 1 week this was force titrated to aliskiren/amlodipine/HCT 300/5/12.5 mg and then after another week to aliskiren/ amlodipine/HCT 300/10/25 mg which continued to study end (Figure 3).

Figure 3: Study SAH2301 design



Treatment

Study medication was the individual tablets of aliskiren 300 mg and of amlodipine 5mg (2 tablets being given for the 10 mg dose) and capsules of HCT (12.5 mg and 25 mg strengths).

Down titration or removal of any study medication was not allowed. Temporary discontinuation for no more than 14 days was allowed for adverse events. The study drug was discontinued if: msSBP \geq 180 mmHg and/or msDBP \geq 110 mmHg at any time after 4 weeks of high dose triple therapy; or if there was symptomatic hypotension and/or msDBP $<$ 60 mmHg or msSBP $<$ 100 mmHg.

Prohibited medications included: other antihypertensives (except ophthalmic preparations); potassium supplements; MAO inhibitors; systemic corticosteroids; thyroid medication and hormone replacement therapy (unless stable dose for 3 months); phosphodiesterase type 5 inhibitors (within 48 hours of a study visit); antiarrhythmics (except digoxin); cholestyramine and colestipol resins; and cyclosporin.

Objectives

The primary objective of the study was long term safety, secondary objectives included evaluation of long term BP lowering efficacy, BP control rates and BP response rates.

Study participants

Inclusion criteria were: males and females \geq 18 years; and essential hypertension with msDBP \geq 100 mmHg and $<$ 120 mmHg and/or msSBP \geq 160 mmHg and $<$ 200 mmHg (at Visit 1 and 2 for newly diagnosed, or after washout for previously treated patients). Exclusion criteria were essentially the same as study SAH2302 with the addition of: on 3 or more antihypertensives with msDBP \geq 110 mmHg and/or msSBP \geq 180 mmHg, or on 4 or more antihypertensives; atrial flutter or fibrillation during screening; serum potassium $<$ 3.5 mEq/L (mmol/L) or \geq 5.5 mEq/L at Visit 1; and history of angioedema to ACE inhibitors (ACEI) or angiotensin receptor blockers (ARB).

Outcomes/endpoints

As this was primarily a safety study, efficacy endpoints were secondary and included the change from baseline in msDBP and msSBP, blood pressure control, msDBP response and msSBP response. Efficacy was assessed on the treated population of all patients who took at least one dose of study medication ("treated population") with last observation carried forward (LOCF).

Statistical considerations

The sponsor stated the sample size of 500 patients was selected to meet the ICH guideline requirements of more than 300 for 6 months and more than 100 for 12 months at high dose. Only the first 206 patients completing the first 6 month period of the study were continued into the second 6 month period.

The study was open label and not randomised. As this was a single group study, only summary statistics were provided.

The study was conducted between 2008 and 2009 at 82 centres in Belgium, Egypt, Germany, Poland, Slovakia, Spain, Turkey and the USA.

Participant flow

There were 635 patients who entered the washout and 564 (87.4%) continued onto study treatment. Discontinuations during washout (11.2%) were mainly for abnormal test procedures (not meeting BP criteria). There were 206 patients who completed 6 months

of treatment and continued onto the second 6 month period. There were 71 (12.6%) patients who discontinued prematurely, 60 in the first and 11 in the second 6 month period. The main reason was adverse events (6.9%) with peripheral oedema being the most frequent adverse event (AE) leading to discontinuation (2.3%). Protocol deviations occurred in 11.7% of patients, with 5.7% being major deviations, the most frequent of which was use of prohibited concomitant medications (2% medications for hypertension).

Baseline data

The mean age was 55.9 years (range: 20 to 81 years), 23.9% were ≥ 65 years, 4.8% were ≥ 75 years, 57.8% were male, 89.9% were Caucasian and 7.4% were Black. Over half (51.8%) were obese with a BMI ≥ 30 kg/m², 52.1% had metabolic syndrome and the mean duration of hypertension was 8.9 years. The msDBP and msSBP were 101.8 and 166.1 mmHg, respectively. The most frequent medical conditions at baseline (by primary System Organ Class [SOC]) were *Metabolism and Nutrition Disorders* (63.1%), *Musculoskeletal and Connective Tissue Disorders* (34.9%), *Surgical and Medical Procedures* (31.7%) and *Gastrointestinal Disorders* (22.3). The most frequent diagnoses were hypercholesterolaemia (18.1%), hyperlipidaemia (16.3%), diabetes mellitus (12.9%) and osteoarthritis (12.9%).

The most frequently reported medication classes were dihydropyridine CCBs (27.3%), ACE inhibitors (24.8%), hydroxymethyl glutamyl coenzyme A (HMG COA) reductase inhibitors (23.6%), beta blocking agents (22.7%) and ARBs (20.9%). The most commonly used prior medications were HCT (15.6%) and acetylsalicylic acid (14.7%).

Outcomes and estimation

Secondary outcomes

The triple combination aliskiren/amlodipine/HCT 300/10/25 mg started to reduce BP after 2 weeks of treatment at the high dose (study treatment Week 4). The reduction in msSBP/msDBP was 34.2/20.3 mmHg at Week 28 and 37.3/21.8 mmHg at Week 54 (Table 13).

Table 12: Summary statistics for the change from baseline in msDBP and msSBP by visit

Week (Visit)	Total N =564	
	n*	Mean (SD)
Week 1 (Visit 5)	564	-9.6 (8.11)
Week 2 (Visit 6)	559	-14.4 (8.02)
Week 4 (Visit 7)	552	-18.9 (8.31)
Week 6 (Visit 8)	544	-20.1 (8.39)
Week 16 (Visit 9)	531	-20.8 (8.61)
Week 28 (Visit 10)	508	-20.6 (8.61)
Week 28 Endpoint**	564	-20.3 (8.92)
Week 41 (Visit 11)	205***	-21.7 (8.30)
Week 54 (Visit 12)	199	-21.8 (8.60)
Week 54 Endpoint**	205	-21.8 (8.66)

SD = standard deviation.

* n is the number of patients with msDBP measurements at both baseline and post-baseline visits.

** Week 28 Endpoint is the last non-missing post-baseline measurement value on or before Week 28, and Week 54 Endpoint is the last non-missing measurement value after Week 28.

*** Of the 564 treated patients, only the first 206 patients who completed the first 6-month period entered the second 6-month period. The number of patients who had any post-baseline measurements during the second six month treatment was 205, instead of 206. This was because patient SAH100A2301-0515-00006 had Visit 10 and entered the second six month period but withdrew consent before Visit 11 without completing final visit procedures (PT-Listing 16.2.1-1.2 and PT- Listing 16.2.9-

Week (Visit)	Total N =564	
	n*	Mean (SD)
Week 1 (Visit 5)	564	-17.5 (12.87)
Week 2 (Visit 6)	559	-25.4 (13.41)
Week 4 (Visit 7)	552	-32.2 (13.52)
Week 6 (Visit 8)	544	-33.8 (13.61)
Week 16 (Visit 9)	531	-35.0 (13.73)
Week 28 (Visit 10)	508	-34.9 (13.61)
Week 28 Endpoint**	564	-34.2 (14.16)
Week 41 (Visit 11)	205***	-37.8 (13.34)
Week 54 (Visit 12)	199	-37.4 (14.67)
Week 54 Endpoint**	205	-37.3 (14.63)

SD = standard deviation.

* n is the number of patients with msSBP measurements at both baseline and post-baseline visits.

** Week 28 Endpoint is the last non-missing post-baseline measurement value on or before Week 28, and Week 54 Endpoint is the last non-missing measurement value after Week 28.

*** Of the 564 treated patients, only the first 206 patients who completed the first 6-month period entered the second 6-month period. The number of patients who had any post-baseline measurements during the second six month treatment was 205, instead of 206. This was because patient SAH100A2301-0515-00006 had Visit 10 and entered the second six month period but withdrew consent before Visit 11 without completing final visit procedures (PT-Listing 16.2.1-1.2 and PT- Listing 16.2.9-

The proportion of patients with BP control (msSBP/msDBP < 140/90 mmHg) was 69.1% at Week 28 and 77.1% at Week 54. A response on msDBP (< 90 mmHg or \geq 10 mmHg decrease from baseline) was achieved in 91.8% of patients at Week 28 and 96.6% of patients at Week 54. Systolic BP response (msSBP < 140 mmHg or a \geq 20 mmHg reduction from baseline) was 90.2% at Week 28 and 93.7% at Week 54. Efficacy was seen across the subgroups of gender, age (\pm 65 years) and race (Caucasian, Black).

Biomarkers

A subset of patients (n=129) had PRA, PRC and plasma aldosterone measured at baseline and at Week 28. There was an increase of 1545.8% in the geometric mean PRC and decrease of 41.8% in PRA. There was also an increase in aldosterone levels of 44.5% from baseline.

Supportive studies

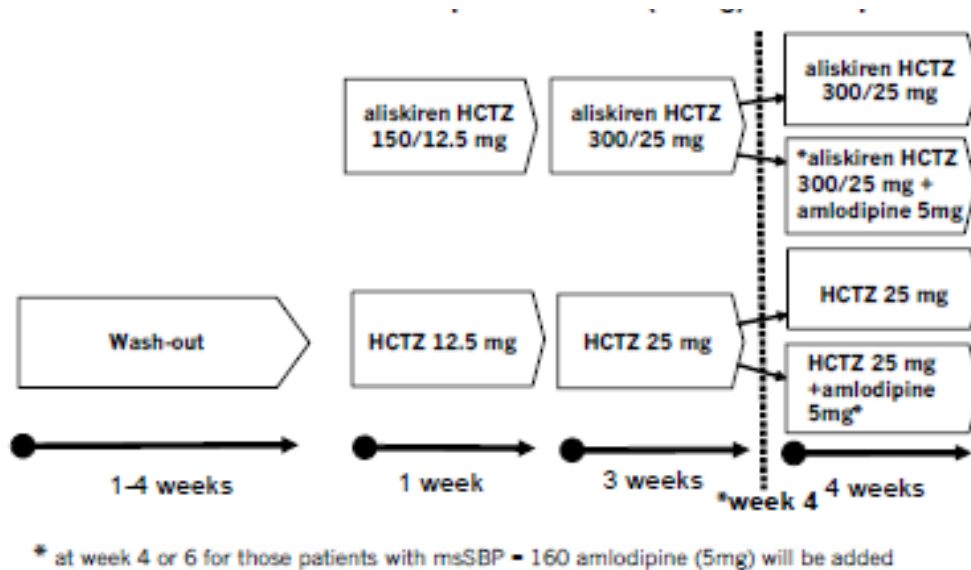
SPP2411 (short term active controlled - aliskiren/HCT based regimen)

Design

Study CSPP100A2411 (SPP2411) was a Phase IV, 8 week randomised, double blind, parallel group study to evaluate the efficacy and safety of the combination of aliskiren/HCT (300/25 mg) in comparison with HCT 25 mg in older patients (≥ 55 years) with Stage 2 systolic hypertension (msSBP ≥ 160 mmHg and < 200 mmHg).

After a 1 to 4 week washout period, subjects entered an 8 week double blind treatment period. During the first 4 weeks doses were escalated from aliskiren/HCT 150/12.5 mg or HCT 12.5 mg to aliskiren/HCT 300/25 mg or HCT 25 mg (Figure 4). Open label amlodipine 5 mg could be added after 4 weeks if msSBP was ≥ 160 mmHg.

Figure 4: Study SPP2411 design



Treatment

Aliskiren/HCT 150/12.5 mg and 300/25 mg were tablets and HCT 12.5 mg and 25 mg and amlodipine 5mg were capsules. Medication was taken once a day in the morning. Patients were discontinued if msDBP ≥ 110 mmHg or msSBP ≥ 200 mmHg at any time, or if there was clinically significant hypotension and/or msSBP < 100 mmHg or msDBP < 60 mmHg.

Prohibited concomitant medications from the start of the washout until the end of the study were the same as in Study SAH2301 with the addition of any other diuretics, alpha adrenergic blockers, drugs which may have adverse interactions with HCT, oral or topical nitrates, antipsychotics, serotonin receptor antagonists, any potentially nephrotoxic or hepatotoxic agent within 6 months, and chronic administration of sympathomimetics (for example, in nasal decongestants and bronchodilators).

Objectives

The primary objective was to demonstrate a greater reduction in msSBP with aliskiren/HCT than with HCT at Week 4. Secondary objectives included reduction in msDBP, comparison of aliskiren/HCT \pm amlodipine compared to HCT \pm amlodipine, SBP and DBP response rates, BP control rates, safety and biomarker evaluation.

Study participants

The study included males and females ≥ 55 years with essential hypertension with msSBP ≥ 160 mmHg and < 200 mmHg. Exclusion criteria were msSBP ≥ 200 mmHg and/or msDBP ≥ 100 mmHg, with the rest being essentially the same as previously described trials (SAH2303 and SAH2301). Grade III and IV hypertensive retinopathy, long QT syndrome²⁰ or QT > 450 milliseconds (ms) in males and > 470 ms in females and significant valvular heart disease were also exclusion criteria.

Outcomes/endpoints

The primary efficacy variable was the change from baseline to Week 4 in msSBP. Change from baseline to Week 8 in msSBP as well as msDBP at Week 4 and 8 for the total population and subgroups were secondary variables.

Statistical considerations

A sample size of 388 completed patients, 194 per group, gave the study 80% power to detect a 4 mmHg difference in msSBP assuming a SD of 14 mmHg ($\alpha=0.05$). Allowing a drop out of 10%, 432 subjects were to be enrolled.

Patients were randomised in a 1:1 ratio using an IVRS.

Placebo capsules of HCT 12.5 and 25 mg and placebo tablets of aliskiren/HCT 150/12.5 mg and 300/25 mg were used in a double dummy design to blind the study, with 2 tablets and 1 capsule of study medication taken per day (in the morning) during the 8 week blinded period.

A difference in msSBP of 4 mmHg was chosen for superiority. The change from baseline in msSBP and msDBP was analysed by ANCOVA model. Proportion of responders and BP control rates used a logistic regression model. The analysis population was the FAS with LOCF. Misrandomised subjects were excluded from the FAS. The PPS provided supportive data.

The study was conducted in 2008-2009 at 80 centres in the USA.

Participant flow

There were 451 subjects randomised, 228 to the aliskiren/HCT and 223 to the HCT groups with 409 (90.7%) completing the study. Of the 42 patients (9.3%) who prematurely discontinued, more were in the aliskiren/HCT (24, 10.5%) than the HCT group (18, 8.1%) with a higher rate due to AEs in the aliskiren/HCT group (5.7% versus 3.1%). Major protocol deviations occurred in 45/451 (10.0%) patients with a higher rate in the aliskiren/HCT than HCT group (12.3% versus 7.6%) with the major reason being use of a drug to treat hypertension (7.0% versus 1.3%). Of the 451 patients randomised one was in error, so there were 450 (99.8%) in the FAS. The PPS included 379 (84.0%) patients with a lower proportion in the aliskiren/HCT group (184, 80.7% versus 195, 87.4%).

Baseline data

The groups were similar in age (mean 64.8 years) and duration of hypertension (mean 10.9 years) but in the aliskiren/HCT group there were fewer males (44.3% versus 55.2%), Caucasians (76.3% versus 80.3%), Hispanic/Latino (10.1% versus 14.3%), diabetics (17.5% versus 22.0%), patients with metabolic syndrome (25.9% versus 28.7%) and the estimated glomerular filtration rate (eGFR) was lower (mean 75.9 versus 79.9

²⁰ Long QT syndrome (LQTS) is a congenital disorder characterized by a prolongation of the QT interval on ECG and a propensity to ventricular tachyarrhythmias, which may lead to syncope, cardiac arrest, or sudden death.

mL/min/1.73m²). Significant differences were found for gender (p=0.021), height (p=0.019) and eGFR (p=0.019). Baseline BP was comparable between groups with msSBP of 168.8 mmHg and msDBP 91.4 mmHg. The most frequent baseline medical conditions were hyperlipidaemia (29.8% aliskiren/HCT, 31.8% HCT), osteoarthritis (25.4%, 29.1%), gastroesophageal reflux disease (17.5%, 17.9%) and hypercholesterolaemia (17.1%, 14.3%).

Outcomes and estimation

Primary outcome

The changes from baseline to Week 4 in the least square mean (LSM) msSBP was -29.3 mmHg for aliskiren/HCT and -22.3 mmHg for the HCT group. The difference of -7.0 mmHg (95% CI: -9.7, -4.4) was significant (p<0.0001) (Table 14). Analysis of the PPS found a similar significant difference of -6.9 mmHg in favour of aliskiren/HCT (p<0.0001).

Table 13: Between treatment analysis of the change from baseline in msSBP at Week 4 endpoint (FAS)

Treatment group	N	LSM change from baseline (SE)	
Aliskiren/HCTZ	225	-29.3 (1.0)	
HCTZ	222	-22.3 (1.0)	
Pairwise comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
Aliskiren/HCTZ vs. HCTZ	-7.0 (1.4)	(-9.7, -4.4)	< 0.0001*

Abbreviations: CI = confidence interval, SE = standard error, LSM = least squares mean.

*Indicates statistical significance at the 0.05 level.

N = the number of patients with values at both Baseline and this endpoint.

Baseline was Day 1. Week 4 endpoint was the value at Visit 7 (Week 4) or LOCF of post-baseline prior to Visit 7 (Week 4).

Least squares mean, confidence interval, and p-value were from an ANCOVA containing treatment, region, and baseline mean sitting systolic blood pressure as covariate. The difference in LSM was for aliskiren/HCTZ – HCTZ.

Secondary Outcomes

The msSBP reduction in both groups was maintained to 8 weeks (aliskiren/HCT -33.2 mmHg, -25.7 mmHg HCT) with a similar significant difference at this time point (-7.5 mmHg, p<0.0001). For patients with a baseline msDBP ≥ 90 mmHg, there was no significant difference in the change from baseline to Week 4 in msDBP (-1.5 mmHg, p=0.168) though the difference was significant at Week 8 (-3.2 mmHg, p=0.005). For all patients, irrespective of baseline msDBP, the difference at Week 8 in msDBP was -3.6 mmHg (p <0.0001).

There was a statistically significantly higher percentage of responders (msSBP < 140 mmHg or ≥ 20 mmHg difference from baseline) in the aliskiren/HCT group versus the HCT alone group at Week 4 (73.3% versus 55.9%, p=0.0001) and at Week 8 (83.1% versus 67.6%, p=0.0002). The percentage of patients achieving blood pressure control (defined as msSBP < 140 mmHg and msDBP < 90 mmHg) was higher in the aliskiren/HCT group versus the HCT alone group at Week 4 (49.8% versus 33.3%, p=0.0001) and at Week 8 (62.2% versus 39.2%, p < 0.0001).

In this study there were relatively few patients requiring add-on amlodipine; 29 in the aliskiren/HCT group and 49 in the HCT group. This proportion was significantly lower in the aliskiren/HCT group (12.8% versus 22.0%, p=0.0051). *Post hoc* analyses in the sponsor's *Summary of Clinical Efficacy* of the 29 patients treated with aliskiren/amlodipine/HCT found the mean change from baseline in msSBP/msDBP was -23.3/-6.1 mmHg with a BP control rate of 24.1%.

SPP2344 (long term controlled - aliskiren based regimen)*Design*

Study CSPP100A2344SPP2344 (CSPP100A2344) was a 36 week, randomised, double blind, parallel group, active controlled study to evaluate the efficacy and safety of aliskiren based regimen to a ramipril based regimen in 901 patients ≥ 65 years with systolic essential hypertension. The study was conducted in 2006-2008 at 100 centres in the USA.

There was an initial eligibility/washout period of up to 4 weeks (up to 2 weeks for patients on previous antihypertensive medication and up to 4 weeks if not previously treated). Patients were then randomised in a 1:1 ratio to receive aliskiren 150 mg or ramipril 5 mg. Patients with inadequate BP control (msSBP ≥ 140 mmHg) were uptitrated to aliskiren 300 mg (two 150 mg tablets) or ramipril 10 mg and then had add-on open label HCT (12.5 mg then 25 mg) and then amlodipine (5 mg then 10 mg). Quality of life (QoL) was assessed using the Psychological General Well-Being Index (PGWBI) and the Medical Outcomes Study (MOS) Sleep Scale (short form).

Treatment

Aliskiren 150 mg or matching placebo were tablets, ramipril 5 mg or 10 mg and matching placebo were capsules. Patients took 2 tablets and one capsule each day in a double dummy design. The open label treatments were amlodipine 5 mg and 10 mg tablets and HCT 12.5 mg capsules and 25 mg tablets. All medication was taken in the morning. Prohibited medications were similar to the previous study, SPP2411.

Objectives

The primary objective was to evaluate the msSBP lowering effect of aliskiren at 12 weeks by testing non inferiority to ramipril. Superiority was tested if non inferiority was achieved. Secondary objectives included msSBP and msDBP at Week 36, response rates and BP control rates at Week 12 and 36, quality of life (QoL) and safety. Exploratory objectives in subsets of patients included biomarkers, effect on arterial compliance, GFR, proteinuria, and B-type natriuretic peptide (BNP).

Study participants

For inclusion, patients ≥ 65 years with essential hypertension needed msSBP ≥ 140 mmHg and < 180 mmHg and msDBP ≤ 110 mmHg after washout (Visit 2) and at randomisation with ≤ 20 mmHg difference in msSBP. Exclusion criteria were: renal artery stenosis; Grade III or IV hypertensive retinopathy; history of hypertensive encephalopathy; ejection fraction $< 40\%$; class III or IV heart failure; history of TIA, stroke, MI, CABG, PCI within 6 months; unstable angina pectoris; life threatening or symptomatic arrhythmia; valvular heart disease; and the need for any antihypertensive medications (except beta blockers for angina or alpha blockers for benign prostatic hypertrophy).

Subjects were withdrawn if msDBP ≥ 110 mmHg or msSBP ≥ 180 mmHg or if significant hypotension or msDBP < 60 mmHg or msSBP < 100 mmHg.

Outcomes/endpoints

The primary efficacy variable was the change from baseline to Week 12 in msSBP.

Statistical considerations

A sample of 774 completed patients (387 per group) were needed for the study to have a 90% power for the non inferiority test at a one sided significance level of 0.025 assuming a non-inferiority margin for msSBP of 3.5 mmHg with a standard deviation of 15 mmHg. Assuming a 15% drop out rate by Week 12, 912 patients (456 per group) were required to be randomised.

Patients were randomised using an IVRS in a 1:1 ratio to the aliskiren and ramipril based treatments stratified by two age groups (≥ 65 and < 75 years and ≥ 75 years). Placebo tablets of aliskiren 150 mg and placebo capsules of ramipril 5 mg/10 mg were used in a double dummy design with 2 tablets and 1 capsule taken daily throughout the study.

For assessment of non inferiority of the aliskiren based regimen to ramipril based regimen, the non inferiority margin was a 3.5 mmHg reduction in msSBP with a one sided significance level of 0.025. If the non inferiority test was significant then superiority was tested at a two sided significance level of 0.05. Tests used an ANCOVA model with regimen, age strata and region as factors and baseline msSBP as a covariate. The ITT population with LOCF was used for the primary analysis. For assessment of msDBP, a non inferiority margin of 2 mmHg was used. Analysis was repeated on the PP population (completed Week 12 without any major protocol deviations) and completer population (ITT population who completed 36 weeks of treatment without any major protocol deviations). Logistic regression was used for responder and BP control analysis.

Participant flow

There were 1325 patients enrolled and 901 randomised with 221 (24.5%) discontinuing prematurely. While the overall discontinuation rate was similar between groups, the rate due to AEs was lower in the aliskiren than the ramipril group (7.7% versus 11.3%) and due to lack of efficacy was higher in the aliskiren group (6.8% versus 5.4%). The rate of major protocol deviations leading to exclusion from the PPS was high in both groups (30.2% and 30.6% in the aliskiren and ramipril groups, respectively) and was predominantly entry BP related (msSBP < 140 mmHg or > 180 mmHg). The ITT population included 891 (98.9%), the PP population 493 (54.7%) and the Completer population 432 (47.9%).

Baseline data

Groups were comparable and the mean age was 72.1 years, 85.1% were Caucasian, 8.0% Black, 47.6% male, 40.2% obese, 20.6% diabetic, 17.4% had an eGFR < 60 mL/min/1.73m² and the mean duration of hypertension was 11.7 years. Baseline BP was comparable with a msSBP of 156.6 mmHg in both groups and a msDBP of 85.5 mmHg and 86.0 mmHg in the aliskiren and ramipril groups, respectively.

Outcomes and estimation

The study found a reduction in msSBP with aliskiren based regimen that was non inferior (3.5 mmHg non inferiority margin) to the ramipril based regimen at 12 and 36 weeks (Table 15). These results were confirmed in the PP population at Week 12 and the completer population at Week 36. The result was also statistically superior at Week 12 though not at Week 36. The LSM change from baseline in msSBP at Week 36 was -19.9 mmHg and -18.0 mmHg in the aliskiren and ramipril groups, respectively. There was also a non inferior and significantly superior reduction in msDBP at Week 12 and 36 with reduction of -8.24 mmHg and -7.02 mmHg, respectively at Week 36. This was also confirmed on the PP and completer populations at Week 12 and 36, respectively. BP control rates (msBP $< 140/90$ mmHg) were significantly higher with aliskiren (46.3% versus 39.3% at Week 12 and 65.6% versus 57.5% at Week 36 in the aliskiren and ramipril groups, respectively). At Week 36, there were 46.3% and 55.5% of patients in the aliskiren and ramipril groups respectively taking add-on HCT, while 11.5% (n=52) and 15.7% (n=66), respectively, were requiring additional add-on amlodipine.

Table 14: Between treatment analysis for the change from baseline in msSBP (ITT population)

Endpoint	Treatment regimen	N	LSM change from baseline (SE)
Week 12 endpoint	Aliskiren	451	-13.96 (0.754)
	Ramipril	439	-11.64 (0.759)
Week 12	Aliskiren	382	-15.54 (0.737)
	Ramipril	390	-12.01 (0.724)
Week 36 endpoint	Aliskiren	451	-19.97 (0.788)
	Ramipril	439	-18.05 (0.794)
Week 36	Aliskiren	348	-23.25 (0.643)
	Ramipril	338	-21.69 (0.643)

Endpoint	Pairwise comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value non-inferiority test	P-value superiority test
Week 12 endpoint	Aliskiren vs. Ramipril	-2.32 (1.028)	(-4.34, -0.30)	<0.0001*	0.0241*
	Aliskiren vs. Ramipril	-3.52 (0.988)	(-5.46, -1.58)	<0.0001*	0.0004*
Week 36 endpoint	Aliskiren vs. Ramipril	-1.92 (1.074)	(-4.03, 0.19)	<0.0001*	0.0747
	Aliskiren vs. Ramipril	-1.56 (0.866)	(-3.26, 0.14)	<0.0001*	0.0716

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval

LSM, SE, p-value and 95% CI are obtained from analysis of covariance model with terms for treatment regimen, age strata and region, and baseline msSBP as a covariate.

Non-inferiority margin used in the non-inferiority test was 3.5 mmHg. One-sided significance level of 0.025 was used for the non-inferiority test.

* Indicates statistical significance.

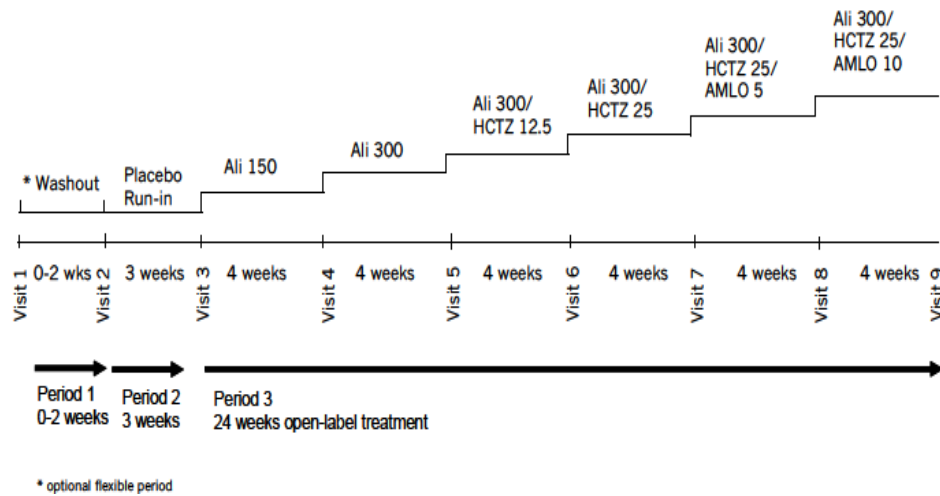
Posthoc analyses in the SCE found that at the Week 36 endpoint, the triple combination aliskiren/amlodipine/HCT showed a reduction in msSBP/msDBP of 30.8/14.1 mmHg compared to 25.7/9.0 mmHg in the ramipril/amlodipine/HCT group. The BP control rate was higher with the aliskiren triple compared to the ramipril triple combination (61.5% versus 54.4%) at Week 36.

SPP2360 (long term uncontrolled – aliskiren based regimen)

Design

Study CSPP100A2360 (SPP2360) was a Phase IV, 24 week, open label, multicentre study assessing the efficacy and tolerability of an aliskiren based regimen in 256 patients with uncomplicated mild to moderate hypertension.

After a 0 to 2 week washout, there was a 3 week placebo run-in to establish BP eligibility and then a 24 week open label treatment period. Treatment commenced with aliskiren 150 mg and at a 4 week intervals was modified (up-titrated or additional therapy to a maximum of aliskiren 300 mg, HCT 25 mg and amlodipine 10 mg) until target BP was reached (Figure 5). Participants were withdrawn if msSBP \geq 180 mmHg and/or msDBP \geq 110 mmHg at any time or if clinically significant hypotension developed. Down titration of medication was not allowed.

Figure 5: Study SPP2360 design

Treatment

Study treatment was with aliskiren 150 mg and 300 mg tablets, HCT 12.5 mg and 25 mg capsules and amlodipine 5 mg and 10 mg tablets. Placebo aliskiren 150 mg tablets were used in the run-in period. All medication was taken once a day in the morning.

Prohibited medications were similar to other studies and included: other antihypertensives, diuretics, potassium supplements, MAO inhibitors, systemic corticosteroids, thyroid medication and hormone replacement therapy (unless stable dose for 3 months), phosphodiesterase 5 (PDE5) inhibitors and serotonin receptor agonists (within 48 hours of a study visit), sympathomimetics, antiarrhythmics, cyclosporine, cholestyramine and colestipol resins.

Objectives

The primary objective of the study was to assess the percentage of patients reaching target BP with an aliskiren based, stepwise treatment regimen. Target BP was defined as msBP <140/90 mmHg for non-diabetics and msBP < 130/80 mmHg for diabetics. Secondary objectives included: BP control rates in subgroups of mild/moderate hypertension, diabetics/ non-diabetics, and treatment (monotherapy, double and triple combination therapy); change from baseline in msSBP and msDBP; BP response rates and safety.

Study participants

Inclusion criteria were: ≥ 18 years; mild to moderate hypertension with an msSBP ≤ 140 mmHg and < 180 mmHg and/or msDBP ≥ 90 mmHg and < 110 mmHg (at Visit 1 and 3). Exclusion criteria were: severe hypertension (msSBP ≥ 180 mmHg and/or msDBP ≥ 110 mmHg); secondary hypertension; significant cardiac disease (valvular disease, Class II to IV heart failure, arrhythmias); hypertensive retinopathy (Grade III or IV); malignancy; hepatic or renal impairment (ALT or AST $> 3 \times$ ULN, oesophageal varices, hepatic encephalopathy, creatinine $> 1.5 \times$ ULN, nephritic syndrome or dialysis); type I or uncontrolled type 2 diabetes (4 weeks of stable medication required for type 2); upper arm circumference > 42 cm; pregnancy or lactation; more than 1 class of antihypertensive medication for patients with mild and more than 2 classes for moderate hypertension at Visit 1; potassium < 3.5 or ≥ 5.2 mEq/L or dehydration at Visit 1; and aliskiren within 3 months.

Outcomes/endpoints

The primary efficacy variable was the proportion of patients who reached the target BP (defined above). Efficacy was assessed on the FAS of all patients who took at least one dose of active study medication. Patients were designated as completing if the target BP was met or all study visits were completed without reaching target BP.

Statistical considerations

With a sample of 230 patients receiving study medication, assuming 10% of patients' data were censored (207 reaching Week 24) and a probability of reaching target BP of 50% (with SD of 0.035) and the 95% CI would have range of 7% from the observed BP control rate.

The study was open label and not randomised.

The target BP control rate was summarised using life table survival estimates at each visit. The 95% CI of the control rate was estimated using Greenwood's variance formula. The event was defined as the subject reaching the target BP at the visit. Treatment steps were aliskiren monotherapy (baseline to but not including Week 8), aliskiren/HCT (Week 8 to Week 16) and aliskiren/HCT/amlodipine (Week 16 to Week 24). Primary analysis was repeated on the PPS. Overall control rate and 95% CI was summarised using Kaplan-Meier survival estimates for the FAS. Cox proportional hazard model was used to assess the influence of baseline msSBP on control rate. LOCF was used for the change in BP from baseline.

The study was conducted between 2008 and 2009 at 29 centres in France, Hungary, Romania and Slovakia.

Participant flow

There were 274 patients enrolled and 256 who continued onto active study treatment. The discontinuation rate was 9.4% and was mainly due to consent withdrawal (5.9%) with a lower rate for AEs (1.6%). Any and major protocol deviations occurred in 32.4% and 13.3% of patients, respectively. Approximately 11% of the study population were misclassified as completing the study when the incorrect target BP was applied (diabetic or non diabetic). These subjects are included in the FAS but not in the PPS. The FAS included 256 patients and the PPS included 220 (85.9%).

Baseline data

The average age was 55.4 years (range: 24 to 89 years), 20.7% were ≥ 65 years, 55.9% were male, 99.2% Caucasian, 37.1% had a BMI ≥ 30 kg/m² and the mean duration of hypertension was 6.6 years with 9.0% being treatment naïve. There were 34.4% with diabetes and 7.4% had baseline eGFR < 60 mL/min/1.73m². The patients who ended up on triple therapy were older (mean 57.1 years), more likely to be obese (41.2%) and have diabetes (42.0%) and less likely to be treatment naïve (3.4%). The baseline msSBP/msDBP was 155.7/91.7 mmHg with those ending up on triple therapy having a higher mean baseline BP of 157.1/92.0 mmHg. The most frequent diagnoses at baseline were dyslipidaemia (21.9%), hypercholesterolaemia (11.7%) and obesity (11.3%).

Outcomes and estimation

Primary outcome

In the FAS, the cumulative probability of reaching BP control was 86.12% (95% CI: 81.52, 90.7%). The probability was 18.7%, 47.27% and 86.12% at the end of the aliskiren, aliskiren/HCT and aliskiren/HCT/amlodipine treatments steps, respectively (Table 17). The PPS analysis produced similar rates of 19.09%, 49.55% and 87.27% at the end of the 3

steps, respectively. For the patients who had not achieved target BP and needed triple combination, the BP control rate was 31.1% (37/119) for aliskiren/amlodipine/HCT 300/5/25 mg and 61% (47/77) for aliskiren/amlodipine/HCT 300/10/25 mg dose.

Table 15: Estimated rate of patients reaching the BP target (FAS)

Visit	Effective sample size N (%)	Target BP achieved n (%)	Cumulative number target BP achieved n (%)	Number censored n' (%)	Estimated cumulative control rate	95% CI
3 – 4	254.0 (99.2)	1 (0.4)	1 (0.4)	4 (1.6)	0.39	(-0.38, 1.16)
4 – 5	248.0 (96.9)	19 (7.4)	20 (7.8)	6 (2.3)	8.02	(4.65, 11.40)
5 – 6	224.0 (87.5)	26 (10.2)	46 (18.0)	4 (1.6)	18.70	(13.82, 23.58)
6 – 7	193.5 (75.6)	37 (14.5)	83 (32.4)	5 (2.0)	34.25	(28.26, 40.23)
7 – 8	151.5 (59.2)	30 (11.7)	113 (44.1)	5 (2.0)	47.27	(40.91, 53.63)
8 - 9	116.5 (45.5)	37 (14.5)	150 (58.6)	5 (2.0)	64.01	(57.79, 70.24)
9	76.5 (29.9)	47 (18.4)	197 (77.0)	1 (0.4)	86.12	(81.52, 90.7)

CI = Confidence interval

N - Number of patients entered in that interval accounting for censored patients during that interval.

n' - Number of patients who are censored in that interval.

Visit [x-y] : visit x to just before visit y (visit y is not included).

Estimated cumulative control rate and 95% CI are obtained using life table survival estimates.

The 95% confidence interval of control rate was calculated using Greenwood's variance formula and its limits could be less than 0 or greater than 100 when estimated control rates were close to zero or 100.

BP target: msSBP < 140 mmHg and msDBP < 90 mmHg (for non-diabetic patients)
msSBP < 130 mmHg and msDBP < 80 mmHg (for diabetic patients)

The total number of patients in the Full Analysis Set is the denominator for calculating percentages.

Treatment step 'Aliskiren', 'Aliskiren + HCTZ', and 'Aliskiren + HCTZ + Aml' can be read from visit interval '[5-6]', '[7-8]', and '[9-]', respectively.

Patients who completed Visit 9 without having achieved the target BP were considered to be censored at Visit 9+ (i.e. at a timepoint a short time later than the timepoint for reaching the target).

Secondary outcomes

The mean decrease from baseline to endpoint in msSBP/msDBP was 25.33/12.40 mmHg. A decrease in msSBP of 9.75 mmHg, 17.98 mmHg and 27.99 mmHg and for msDBP of 5.47 mmHg, 7.75 mmHg, and 13.59 mmHg was found at the end of the aliskiren, aliskiren/HCT and aliskiren/HCT/amlodipine treatments steps, respectively. The estimated cumulative probability of reaching the target DBP or SBP response²¹ at the end of the triple therapy step was 96.8% (95% CI: 94.47, 99.12) and 97.78% (95% CI: 95.86, 99.69).

The cumulative probability of BP control at the end of the aliskiren/HCT/amlodipine treatment step was 91.48% for patients with mild hypertension ($140 \leq \text{msSBP} < 160$ mmHg and/or $90 \leq \text{msDBP} < 100$ mmHg) and was 79.24% for those with moderate hypertension ($160 \leq \text{msSBP} < 180$ mmHg and/or $100 \leq \text{msDBP} < 110$ mmHg). For diabetic patients at the end of the triple therapy step, the cumulative probability of BP control was 72.58% compared to 92.74% in non-diabetics with a mean decrease in msSBP/msDBP of 29.75/11.48 mmHg compared to 22.98/15.12 mmHg in non-diabetics.

SPA2301 (long term uncontrolled – aliskiren/amlodipine based regimen)

Design

Study CSPA100A2301 (SPA2301) was a 54 week, open label, multicentre study assessing the long term safety of the combination aliskiren/amlodipine 300/10 mg in patients with essential hypertension. After a 1 to 4 week washout there was a 54 week open label treatment period. In the first 2 weeks treatment was aliskiren/amlodipine 150/5 mg which was then force titrated to aliskiren/amlodipine 300/10 mg for the next 52 weeks.

²¹ SBP response was defined as a target msSBP of < 140 mmHg (non-diabetics) or < 130 mmHg (diabetics) or a reduction of ≥ 20 mmHg from baseline. DBP response was a target msDBP of < 90 mmHg (non-diabetics) or < 80 mmHg (diabetics) or a reduction of ≥ 10 mmHg from baseline.

After 72 days of treatment, patients with a msSBP ≥ 140 mmHg and/or msDBP ≥ 90 mmHg for two consecutive visits could have optional add-on HCT 12.5 mg with an increase to 25 mg if BP remained elevated. Down titration of medications was not allowed. Study drug was discontinued if: msDBP ≥ 110 mmHg or msSBP ≥ 180 mmHg; if there was symptomatic hypotension or msDBP < 60 mmHg or msSBP < 100 mmHg; or if serum potassium was > 5.5 Eq/L on a repeated sample.

Treatment

Open label aliskiren tablets (150 mg and 300 mg), amlodipine tablets (5 mg) and HCT capsules (12.5 mg and 25 mg) were used. Prohibited medications were similar to SPP2360.

Objectives

The primary objective of the study was long term safety, secondary objectives included evaluation of long term BP lowering efficacy, BP control rates and msDBP response rates.

Study participants

Inclusion criteria were: ≥ 18 years; essential hypertension with msDBP ≥ 90 mmHg and < 110 mmHg (at Visit 1 and 2 for newly diagnosed, or after 2 to 4 weeks washout for previously treated patients). Patients with severe hypertension were excluded (msDBP ≥ 110 mmHg and/or msSBP ≥ 180 mmHg) and other exclusion criteria were essentially the same as SAH2302.

Outcomes/endpoints

Efficacy endpoints were secondary and included the change from baseline in msDBP, msSBP, blood pressure control (msSBP/msDBP $< 140/90$ mmHg) and msDBP response (msDBP < 90 mmHg or a ≥ 10 mmHg decrease from baseline). Efficacy was assessed on the treated population of all patients who took at least one dose of study medication with LOCF.

Statistical considerations

The sponsor stated the sample size of 500 patients was selected to meet ICH guideline requirements of more than 300 for 6 months and more than 100 for 12 months at high dose, assuming a discontinuation rate of 20% in the first 6 months and 30% in the second 6 months. The study was open label and not randomised. As this was a single group study, only summary statistics were provided.

The study was conducted between 2006-2008 at 89 centres in Belgium, Switzerland, Germany, Denmark, Finland, Iceland, India and the USA.

Participant flow

There were 652 patients who entered the washout and 556 (85.3%) continued onto study treatment. Discontinuations during washout (14.7%) were mainly for abnormal test procedures (9.4%) and consent withdrawal (2.3%). There were 452/556 (81.3%) patients who completed 12 months of treatment and 104/556 (18.7%) who prematurely discontinued, 12.1% were for AEs and 2.3% withdrew consent. Peripheral oedema was the most frequent AE leading to discontinuation (6.5%). Protocol deviations occurred in 26.1% of patients with most relating to use of prohibited concomitant medications (7.9% systemic corticosteroids, 6.7% medications for hypertension) and 2.0% not meeting inclusion/exclusion criteria.

Baseline data

Of the 556 treated patients, 470 (84.5%) received aliskiren/amlodipine and 86 (15.5%) received aliskiren/amlodipine plus add-on HCT at some time during the study. The average age was 54.4 years (range: 21 to 88 years), 18.2% were ≥ 65 years, 59.4% were male, 48.7% had a BMI ≥ 30 kg/m², 42.6% had metabolic syndrome and the mean duration of hypertension was 8.1 years. The patients who received add-on HCT were more likely to have metabolic syndrome (60.5% versus 39.4%), be obese (64% versus 46%) and have longer duration of hypertension (10.2 years versus 7.7 years). The baseline msDBP and msSBP were 97.6 and 153.5 mmHg, respectively. Baseline BP in those who received add-on HCT was slightly higher than in the aliskiren/amlodipine alone group (159.1/99.4 mmHg versus 152.5/96.3 mmHg). The most frequent medical conditions at baseline (by primary SOC) were *Metabolism and Nutrition Disorders* (49.6%), *Musculoskeletal and Connective Tissue Disorders* (42.8%), *Surgical and Medical Procedures* (30.6%), *Gastrointestinal Disorders* (28.1%), *Psychiatric Disorders* (22.1%) and *Nervous System Disorders* (20.3%). The most frequent diagnoses were hypercholesterolaemia (18.2%) and hyperlipidaemia (16.2%).

Outcomes and estimation

Secondary outcomes

The msDBP started to reduce at Week 2 with the aliskiren/amlodipine 150/5 mg dose (mean reduction -8.3 mmHg) and a maximal reduction (-15.1 mmHg) was seen by Week 10 after 8 weeks of the forced titration to aliskiren/amlodipine 300/10 mg. This reduction was maintained to the study end at Week 54 (mean reduction -15.5 mmHg) (Table 17, Figure 6). The reduction in msSBP commenced within 2 weeks of treatment, and was maximal at Week 28 (mean reduction -25.9 mmHg) and was also maintained to study end (-24.2 mmHg) (Figure 7). For the group of subjects who ended up on triple therapy, the change from baseline in msSBP/msDBP was -16.0/-9.3 mmHg at Week 10 when HCT was added and -23.7/-14.2 mmHg at Week 54.

Table 16: Summary statistics for the change from baseline (Visit 4) in msDBP by visit

Week (Visit)	Aliskiren/Amlodipine* N = 470		Aliskiren/Amlodipine /HCTZ** N = 86		Total N = 556	
	N***	Mean (SD)	N***	Mean (SD)	N***	Mean (SD)
Week 2 (Visit 5)	467	-8.7 (6.94)	86	-5.9 (6.05) ^a	553	-8.3 (6.89)
Week 4 (Visit 6)	459	-14.0 (6.88)	85	-11.9 (5.58) ^a	544	-13.7 (6.73)
Week 6 (Visit 7)	453	-15.7 (6.96)	86	-11.5 (7.36) ^a	539	-15.1 (7.19)
Week 10 (Visit 8)	440	-16.3 (6.69)	86	-9.3 (7.22) ^a	526	-15.1 (7.24)
Week 14 (Visit 9)	429	-17.1 (6.84)	85	-13.1 (7.64)	514	-16.4 (7.12)
Week 28 (Visit 10)	416	-16.7 (7.15)	81	-14.7 (8.22)	497	-16.4 (7.36)
Week 41 (Visit 11)	396	-17.0 (7.26)	75	-15.4 (6.86)	471	-16.8 (7.21)
Week 54 (Visit 12)	383	-16.3 (7.13)	74	-15.3 (6.55)	457	-16.1 (7.04)
Endpoint****	467	-15.7 (7.61)	86	-14.2 (7.90)	553	-15.5 (7.67)

*'Aliskiren /Amlodipine' is the group of patients who took only Aliskiren/Amlodipine (without HCTZ) throughout the study.

**'Aliskiren /Amlodipine/HCTZ' is the group of patients who took HCTZ at some time during the study (HCTZ was only added to eligible patients after visit 8).

*** N*** is the total number of patients with msDBP observations at both baseline and post-baseline visits.

a: Use of HCTZ was not permitted until after week 10 (visit 8).

**** Endpoint is the value at Week 54 (visit 12) or last observation carried forward (LOCF) based on the availability of measurements.

Figure 6: Study SPA2301 - average of msDBP by week (treated population)

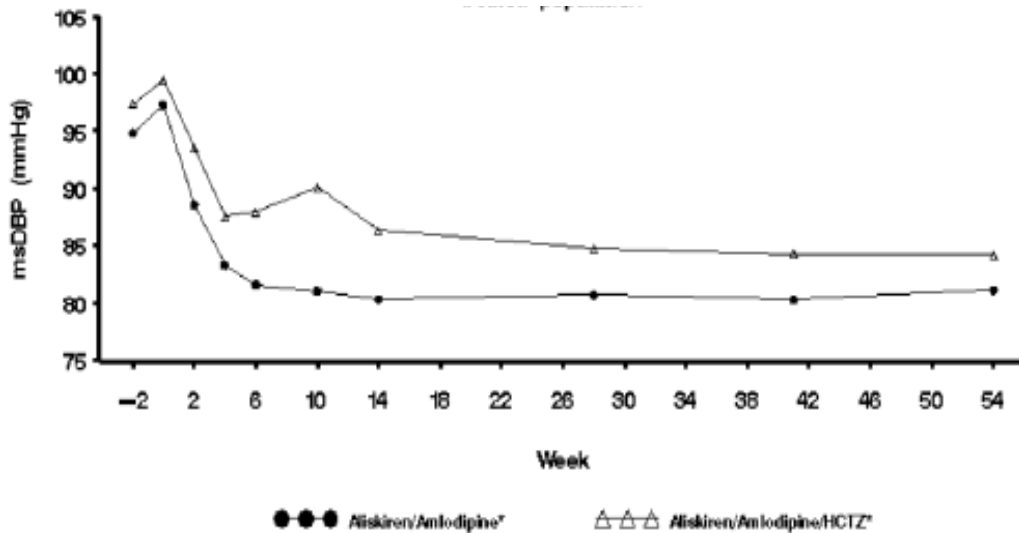
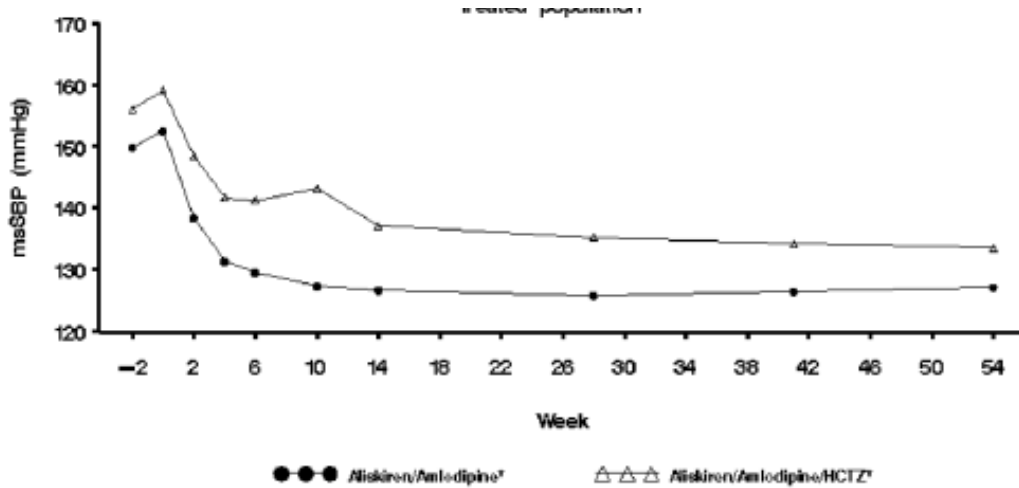


Figure 7: Study SPA2301 - average of msSBP by week (treated population)



* 'Aliskiren/Amlodipine' is the group of patients who took only Aliskiren/Amlodipine (without HCTZ) throughout the study.
 * 'Aliskiren/Amlodipine/HCTZ' is the group of patients who took HCTZ at some time during the study.
 - Week 0 (day 1) = Visit 4.

Note: Addition of HCTZ was permitted for qualifying patients after Week 10.

At the study endpoint (54 weeks with LOCF), the proportion of patients with BP control (msSBP/msDBP < 140/90 mmHg) was 74.3% overall (77.3% for those on aliskiren/amlodipine, and 58.1% for those on aliskiren/amlodipine plus HCT). A response on msDBP (< 90 mmHg or ≥ 10 mmHg reduction from baseline) was achieved in 89.7%, 90.6% and 84.9% in the overall population, the aliskiren/amlodipine and the aliskiren/amlodipine/HCT groups, respectively. Efficacy was seen across all subgroups of gender, age (±65 years) and race (Caucasian, Black, and Asian).

Biomarkers

A subset of patients (aliskiren/amlodipine n=274; aliskiren/amlodipine/HCT n=55) had high sensitivity C-reactive protein (hsCRP), plasma rennin activity (PRA), and plasma aldosterone measured at baseline and at study end. PRA decreased by 70% and 50% in the

aliskiren/amlodipine and aliskiren/amlodipine/HCT groups, respectively. There was little effect in either group on plasma aldosterone or hsCRP.

Ongoing studies

There are 3 ongoing studies where patients have received aliskiren/amlodipine/HCT: SPA2307, SPAUS02 and SPHDE01. No preliminary results were available.

Study CSPA100A2307 (SPA2307) is a randomised, 32 week, double blind, parallel group, multicentre study comparing the efficacy and safety of initiating treatment with combination (aliskiren/amlodipine) therapy in comparison with the sequential add-on treatment strategies in patients with essential hypertension.

Study CSPA100AUS02 (SPAUS02) is a short term (8 week), multicentre, randomised, double blind, active controlled, parallel group, forced titration study to evaluate the efficacy and safety of aliskiren/amlodipine/HCT compared to aliskiren/amlodipine in US minority patients with Stage 2 hypertension.

Study CSPH100ADE01 (SPHDE01) is an open label, single arm, multicentre study to evaluate the efficacy and safety of aliskiren in combination with HCT in hypertensive patients not responding to candesartan plus HCT. Patients still not responding (msDBP > 90 mmHg and/or msSBP >140 mmHg) after being treated with aliskiren/HCT are offered participation in an open label 4 week extension with amlodipine 5 mg in addition to the aliskiren 300 mg/HCT 25 mg.

Evaluators overall conclusions on clinical efficacy

The clinical program included 3910 hypertensive patients, 1155 of whom received at least 1 dose of the aliskiren/amlodipine/HCT combination with 568 who received the combination for at least 6 months and 182 for at least 12 months. There were 6 main clinical studies with two that assessed the triple combination directly, one short term controlled (SAH2302) and one long term uncontrolled (SAH2301). There were 3 studies with data on the triple combination in patients not controlled on aliskiren/HCT; one short term controlled (SPP2411), one long term controlled (SPP2344) and one long term uncontrolled (SPP2360). The last study had data on patients not controlled by aliskiren/amlodipine (SPA2301) and this study had also been evaluated in the submission for the aliskiren/amlodipine fixed combination.

None of these clinical trials used the fixed combination proposed for marketing; aliskiren/amlodipine/HCT treatment was in free combinations of tablets and capsules. There were no dose selection studies as doses in the triple combination are the same as the registered monotherapies. There were no pooled efficacy data due to study design and population differences.

The two trials of the triple combination, as well as SPP2411 in older patients, included patients with moderate to severe hypertension (msSBP \geq 160 mmHg and < 200 mmHg and/or msDBP \geq 100 mmHg and 120 mmHg). The other 3 trials, which allowed dose escalation to triple therapy, included patients with mild to moderate hypertension (msSBP \geq 140 mmHg and < 180 mmHg and msDBP \leq 110 mmHg). The main exclusion criteria, which were similar across trials, were secondary hypertension, evidence of significant hepatic or renal impairment, heart failure, diabetes with poor glucose control, a history of myocardial infarction, cerebrovascular accident or hypertensive encephalopathy.

The primary efficacy variable was the change from baseline in msSBP in SAH2302, SPP2344 and SPP2411, while in SPP2360 it was target BP control rate. Studies SAH2301 and SPA2301 were safety studies with msSBP and msDBP as secondary variables. The short term controlled studies used the FAS which excluded misrandomised patients.

The controlled studies in the submission have been designed in accordance with the relevant guidelines on development of antihypertensives and fixed combination products (ICH E12 2000, CHMP 2004, CHMP 2009).^{22,23,24} This included appropriate BP measurements, an adequate run in period of 2 to 4 weeks, treatment duration of 8 weeks, parallel design, randomisation and blinding.

SAH2302 was the pivotal efficacy study which randomised 1191 patients with moderate to severe hypertension (msSBP \geq 160 mmHg and $<$ 200 mmHg and/or msDBP \geq 100 mmHg and $<$ 120 mmHg). In this parallel group study there was a high rate of obesity (49%) and metabolic syndrome (52%) and 14% had diabetes. After 8 weeks of treatment, the combination of aliskiren/amlodipine/HCT 300/10/25 mg resulted in statistically significant and clinically meaningful reductions in msSBP and msDBP compared to the three respective double combinations (differences -6.55 to -9.93 mmHg for msSBP and -2.60 to -6.30 mmHg for msDBP). Efficacy was also seen at Week 4 with the lower dose (150/5/12.5 mg) combination. BP control ($<$ 140/90 mmHg) at Week 8 was significantly greater with the triple combination (62.3%) compared to the double combinations (33.1% to 41.3%). There was also a significant reduction in mean 24 hour ambulatory DBP and SBP and this effect was maintained over the 24 hour period with once daily dosing. Efficacy of the triple combination was seen in patients with severe hypertension (SBP \geq 180 mmHg) (reduction of 49.53/22.53 mmHg) with a BP control rate of 57.5% compared to 16.2 to 25.0% with the double combinations. The triple combination was effective across subgroups of gender, age, Caucasians and Blacks though there were too few subjects in other racial groups to draw conclusions.

SAH2301 was an open label long term study of the triple combination in 564 patients with moderate to severe essential hypertension. After 6 months of treatment the combination aliskiren/amlodipine/HCT 300/10/25 mg resulted in a BP control rate of 69% and a long term msSBP/msDBP reduction of 34.2/20.3 mmHg. A DBP response was noted in 91.8% and SBP response in 90.2% of patients at Week 28. In the smaller group of subjects (n=206) who continued into the second 6 months of treatment, the effect was maintained to Week 54. Efficacy was seen across subgroups of age and gender.

The other 4 studies in the submission had optional add-on treatment in patients not adequately controlled with dual therapy and so are considered to provide supportive data only (Table 18).

²² ICH Topic E12 (2000). Principles for clinical evaluation of new antihypertensives. CPMP/ICH/54/00.

²³ CHMP (2004). Note for guidance on clinical investigation of medicinal products in the treatment of hypertension. CPMP/EWP/238/95 Rev 2.

²⁴ CHMP Guideline (2009) Clinical Development of Fixed Combination Medicinal Products, CHMP/EWP/240/95 Rev 1

Table 17: Summary of study treatment and doses in Studies SPP2344, SP2411, SPP2360 and SPA2301

Study SPP2344*	Day 1	Optional from Week 4	Optional from Week 12	Optional from Week 16	Optional from Week 22 to 28
	Ali 150 mg	Ali 300 mg	Ali/HCTZ 300/12.5 mg	Ali/HCTZ 300/25 mg	Ali/Aml/HCTZ 300/5/25 to 300/10/25 mg
	Ram 5 mg	Ram 10 mg	Ram/HCTZ 10/12.5 mg	Ram/HCTZ 10/25 mg	Ram/Aml/HCTZ 10/5/25 to 10/10/25 mg
Study SPP2411*	Day 1	Week 1		Optional from Week 4 to 6	
	Ali/HCTZ 150/12.5 mg	Ali/HCTZ 300/25 mg		Ali/Aml/HCTZ 300/5/25 mg	
	HCTZ 12.5 mg	HCTZ 25 mg		Ali/HCTZ 5/25 mg	
Study SPP2360*	Day 1	Week 4	Week 8	Week 12	Week 16 to 20
	Ali 150 mg	Ali 300 mg	Ali/HCTZ 300/12.5 mg	Ali/HCTZ 300/25 mg	Ali/Aml/HCTZ 300/5/25 to 300/10/25 mg
Study SPA2301*	Day 1	Week 2		Optional from Week 10	
	Ali/Aml 150/5 mg	Ali/Aml 300/10 mg		Ali/Aml/HCTZ 300/10/12.5 to 300/10/25 mg	
	Single- or double-component dose-escalation				Dose-escalation to triple combination therapy

* Dose increase or add-on only occurred in patients whose BP was not controlled.

SPP2411, an 8 week controlled study, assessed the efficacy of the combination of aliskiren/HCT (300/25mg) in comparison with HCT 25 mg in 451 older patients (≥ 55 years) with Stage 2 systolic hypertension (msSBP ≥ 160 mmHg and < 200 mmHg). Open label amlodipine 5 mg could be added after 4 weeks if msSBP was ≥ 160 mmHg and this was required in 12.8% and 22.0% of the aliskiren/HCT and HCT groups, respectively. *Post hoc* analyses in the group on triple therapy found a reduction in BP of 23.3/6.1 mmHg at Week 8.

The number of patients in this study on triple therapy was small (n=29), the treatment duration was only 2 to 4 weeks, and analyses were *post hoc*. There were also imbalances in baseline characteristics in this study (statistically significant for gender, height and eGFR) as well as a higher rate of major protocol deviations in the aliskiren/HCT group (in particular those relating to use of a drug to treatment hypertension 7.0% versus 1.3%). For these reasons the efficacy data from this study are of limited value for this evaluation.

Study SPP2344 was a 36 week randomised, controlled study comparing an aliskiren based regimen with a ramipril based regimen in 901 elderly patients (≥ 65 years) with systolic essential hypertension. There were 52 patients (11.5%) who ended up on the triple combination of aliskiren 300 mg, HCT 25 mg and amlodipine (either 5 mg or 10 mg). *Post hoc* analyses found a higher BP control rate with the aliskiren based triple combination at Week 36 (61.5% versus 54.4%) with a msSBP/msDBP reduction of 30.8/14.1 mmHg. The high rate of major protocol deviations (30%), the small numbers on triple therapy and the *post hoc* nature of analyses led the evaluator to conclude that the efficacy data from this study were of limited utility.

SPP2360 was an open label study of a stepped aliskiren based treatment in 256 patients with mild to moderate essential hypertension. There were 119 who did not achieve target BP on mono or dual therapy and so received aliskiren/amlodipine/HCT triple combination (5 or 10 mg amlodipine). The stepped treatment algorithm was effective with an incremental improvement in BP control rates and responder rates with each treatment

step as well as incremental reductions in msSBP and msDBP. The estimated cumulative BP control rate was 18.7%, 47.27% and 86.12% at the end of the aliskiren, aliskiren/HCT and aliskiren/HCT/amlodipine treatments steps, respectively. For subjects requiring triple therapy, the BP control rate was 31.1% for aliskiren/amlodipine/HCT 300/5/25 mg and 61% for aliskiren/amlodipine/HCT 300/10/25 mg dose. Target BP control rates were chosen as the primary efficacy measure rather than reduction in BP as the sponsor felt this was more clinically relevant. Given the efficacy was demonstrated in SAH2302, the evaluator agrees that this was reasonable. Supportive results were found on analysis of the PPS which was important as there was misclassification of target BP in 11% of subjects.

Study SPA2301 was an open label study of aliskiren/amlodipine in 556 patients with essential hypertension. There were 86 (15.5%) who also received add-on HCT (12.5 or 25 mg). In this group on triple therapy, the BP control rate was 58.1%, the msDBP response rate was 84.9% and the msSBP/msDBP reduction was 23.7/14.2 mmHg. A DBP response (<90 mmHg or ≥ 10 mmHg reduction from baseline) was noted in 84.9% of patients. The addition of HCT resulted in further BP reduction in those inadequately controlled with aliskiren/amlodipine alone. This study was evaluated in with the aliskiren/amlodipine combination therapy.⁵

The long term Study SAH2301 demonstrated sustained reduction in BP over a treatment period of up to 54 weeks with no evidence of tolerance resulting in loss of efficacy. Effects on treatment cessation were not assessed in the development program of the combination therapy and, as the product information for the three therapies do not mention withdrawal effects or rebound hypertension, the evaluator agreed with the sponsor that such assessment is not be necessary.

Subgroup analyses found the triple therapy was more effective than dual therapy in lowering BP across subgroups of age, gender, BMI and race. Females and elderly (≥ 75 years) were noted to have a greater BP reduction. After 8 weeks of treatment, msSBP/msDBP reduction in patients ≥ 75 years was 50.9/29.2 mmHg. There were no notable findings in the different racial groups but the numbers of non-Caucasians were low.

The clinical program excluded patients with secondary hypertension or with high cardiovascular risk such as post MI or heart failure requiring treatment and therefore no efficacy conclusion could be drawn in these populations.

Once daily dosing was supported by data from ABPM conducted in Study SAH2302 which showed sustained BP lowering over the 24 hour monitoring period.

Safety

Introduction

Safety assessments included monitoring of adverse events (AEs) and serious adverse events (SAEs), vital signs, physical examination, haematology and biochemistry assessments. The study population was males and females 18 years of age or more with mild to severe hypertension who received at least one dose of study medication. Patients with unstable diabetes, hepatic or renal impairment, significant cardiac disease including myocardial infarction and heart failure requiring treatment, and cerebrovascular disease were excluded. Pregnant and lactating women and premenopausal women not using contraception were also excluded. Where doses were titrated, safety data was presented by the final titrated dose received. Data were pooled into three groups (Table 19).

Table 18: Population groupings for safety assessment

Database	Studies	Total number of patients treated (safety population)/ No. of patients treated with aliskiren/amlodipine/HCTZ
Safety Dataset Group B (short-term, double-blind, all controlled)	SAH2302	1188/ 309
Safety Dataset Group C (all long-term, open-label studies)	SAH2301, SPA2301	1120/ 647
Safety Dataset Group D (long-term, double-blind study)	SPP2344	896/ 51

Two studies were not included with pooled data due to design issues which allowed termination of patients with BP control prior to triple therapy (SPP2360) and the short treatment duration of 2 to 4 weeks with triple therapy (SPP2411). There were 3 ongoing studies (SPA2307, SPAUS02 and SPHDE01) for which deaths and serious adverse events (SAEs) up to the cut off date of 26 November 2009 were included in the safety analysis. The adverse event data from the six clinical pharmacology and biopharmaceutic studies (753 subjects) were not pooled in the overall safety analysis.

Patient exposure

Safety data was collected from 3910 patients; 1155 patients received at least one dose of aliskiren/amlodipine/HCT combination and 568 patients who were exposed for 6 months and 182 patients for 12 months. The mean duration of exposure in the 6 clinical trials was 159.3 days (Table 20). In Group B (the short term controlled study), mean exposure for the 309 patients treated with triple therapy was 55.4 days. In Group C (long term open label studies), 647 patients were treated with aliskiren/amlodipine/HCT, with 568 for at least 6 months (180 days or more) and 182 for at least 12 months (360 days or more). In Group D, there were 51 patients who received triple therapy starting from Week 22 with a mean exposure of 84.0 days. In the two additional studies, the mean exposure to aliskiren/amlodipine/HCT was 47.0 days for the 119 patients in SPP2360 and 24.3 days for the 29 patients in SPP2411.

Table 19: Duration of exposure to study drug (Safety Set) all studies

Duration of Exposure (days)	Ali/Aml/ HCTZ N=1155	Ali/Aml N=843	Ali/HCTZ N=1490	Mono Ali N=708	Ramipril/Aml/ HCTZ N=68
≥ 1	1155 (100.0)	843 (100.0)	1490 (100.0)	708 (100.0)	68 (100.0)
≥ 14	1133 (98.1)	827 (98.1)	902 (60.5)	676 (95.5)	68 (100.0)
≥ 28	1101 (95.3)	818 (97.0)	877 (58.9)	651 (91.9)	65 (95.6)
≥ 42	1037 (89.8)	800 (94.9)	814 (54.6)	622 (87.9)	65 (95.6)
≥ 56	938 (81.2)	736 (87.3)	686 (46.0)	576 (81.4)	58 (85.3)
≥180	568 (49.2)	412 (48.9)	4 (0.3)	172 (24.3)	0 (0.0)
≥270	257 (22.3)	394 (46.7)	0 (0.0)	3 (0.4)	0 (0.0)
≥360	182 (15.8)	372 (44.1)	0 (0.0)	0 (0.0)	0 (0.0)
Statistics					
n	1155	843	1490	708	68
Mean	159.3	211.1	45.3	108.9	82.5
SD	120.99	155.54	43.22	82.99	24.21
Median	126.0	138.0	55.0	83.0	97.0
Minimum	2	1	1	1	16
Maximum	392	407	195	284	125

Duration of Exposure (days)	Ramipril/ HCTZ N=244	Aml/HCTZ N=345	Mono Ramipril N=443	HCTZ N=223	Total N=3910
≥ 1	244 (100.0)	345 (100.0)	443 (100.0)	223 (100.0)	3910 (100.0)
≥ 14	237 (97.1)	342 (99.1)	424 (95.7)	216 (96.9)	3799 (97.2)
≥ 28	235 (96.3)	321 (93.0)	410 (92.6)	207 (92.8)	3720 (95.1)
≥ 42	231 (94.7)	285 (82.6)	399 (90.1)	162 (72.6)	3633 (92.9)
≥ 56	225 (92.2)	219 (63.5)	390 (88.0)	134 (60.1)	3286 (84.0)
≥180	4 (1.6)	0 (0.0)	135 (30.5)	0 (0.0)	1693 (43.3)
≥270	0 (0.0)	0 (0.0)	4 (0.9)	0 (0.0)	678 (17.3)
≥360	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	637 (16.3)
Statistics					
n	244	345	443	223	3910
Mean	119.9	51.8	132.0	48.3	160.8
SD	49.47	13.26	81.74	14.16	124.72
Median	139.5	56.0	88.0	56.0	88.0
Minimum	1	3	1	7	1
Maximum	244	84	288	69	407

Patient characteristics:

In Group B overall, the mean age was 55.1 years with 19.1% ≥ 65 years, 60.5% male, 49% obese, 14% had diabetes and the baseline msSBP/msDBP was 172.4/103.8 mmHg. In Group C patients treated with triple therapy, the mean age was 55.9 years with 23.5% ≥ 65 years, 59% male, 53% obese, 21% had diabetes and the baseline msSBP/msDBP was 165.2/101.5 mmHg. In Group D patients treated with triple therapy, the mean age was 71 years with 29% ≥ 75 years, 49% male, 44% obese, 27% had diabetes and the baseline msSBP/msDBP was 165.7/92.1 mmHg. The predominant medical conditions were hyperlipidaemia, hypercholesterolaemia and osteoarthritis.

Adverse events

In Group B, the overall AE incidence with aliskiren/amlodipine/HCT was slightly greater than the component dual therapy groups (36.2% versus 32.3-33.6%). Peripheral oedema

was the most frequent AE occurring in 7.1% and 8.0% of the aliskiren/amlodipine/HCT and aliskiren/amlodipine groups, respectively, compared to 2.0% and 4.0% of the aliskiren/HCT and amlodipine/HCT groups, respectively (Table 21). Peripheral oedema was also found to be more frequent in women than men (12.2% versus 3.8%) treated with aliskiren/amlodipine/HCT. The other frequent AEs, dizziness (3.6%), headache (3.6%), nasopharyngitis (2.6%), fatigue (1.9%) and cough (0.3%) did not occur more frequently than in the dual therapy groups. A statistical evaluation of AEs occurring at a rate of $\geq 1\%$ in the aliskiren/amlodipine/HCT group found that peripheral oedema occurred more frequently in the triple therapy group compared to the aliskiren/HCT group ($p=0.0032$) but not more frequently than in aliskiren/amlodipine group ($p=0.757$).

Table 20: Number (%) of patients with most frequent AEs (at least 2% for any group) Group B

Preferred term	All Ali/Aml N=287 n (%)	All Ali/HCTZ N=297 n (%)	All Aml/HCTZ N=295 n (%)	All Ali/Aml/HCTZ N=309 n (%)
Any adverse experience	96 (33.4)	96 (32.3)	99 (33.6)	112 (36.2)
Oedema peripheral	23 (8.0)	6 (2.0)	12 (4.1)	22 (7.1)
Dizziness	7 (2.4)	10 (3.4)	5 (1.7)	11 (3.6)
Headache	9 (3.1)	12 (4.0)	15 (5.1)	11 (3.6)
Nasopharyngitis	2 (0.7)	6 (2.0)	10 (3.4)	8 (2.6)
Fatigue	1 (0.3)	6 (2.0)	4 (1.4)	6 (1.9)
Cough	4 (1.4)	0	6 (2.0)	1 (0.3)

In Group C, the overall AE rate was 50.1% and 74.3% of the aliskiren/amlodipine/HCT and aliskiren/amlodipine patients, respectively. The most frequent AEs were peripheral oedema (9.9%), headache (3.9%), bronchitis (3.7%), nasopharyngitis (3.4%), influenza (2.6%), diarrhoea (2.3%) and dizziness (1.9%). None of these AEs occurred more frequently with triple therapy compared to aliskiren/amlodipine (Table 22).

In the small group D (51 subjects), the AE incidence was similar to ramipril/amlodipine/HCT (27.5% versus 30.9%). In these elderly subjects (≥ 65 years), the most frequent AEs were cough (3.9%), dizziness (3.9%) and peripheral oedema (3.9%) (Table 23).

In healthy volunteers in the pharmacology and biopharmaceutic studies aliskiren/amlodipine /HCT was well tolerated.

Adverse events that were most likely to be assessed as drug related by the investigator included peripheral oedema, headache and dizziness. AE intensity was generally mild or moderate. In Group B, 6 patients (1.9%) treated with aliskiren/amlodipine/HCT had a severe AE (acute coronary syndrome, supraventricular arrhythmia, gastroenteritis, eczema, hypertension and muscle spasms). In Group C, severe AEs were reported in 6.0% of patients overall and 3.9% of patients on aliskiren/amlodipine/HCT. Severe peripheral oedema occurred in 0.8% and 1.3% of the aliskiren/amlodipine/HCT and aliskiren/amlodipine groups, respectively.

Table 21: Number (%) of patients with most frequent AEs (at least 2% for any group) Group C

Preferred term	Alii/Aml N=556 n (%)	Alii/Aml/HCTZ* N=647 n (%)
Any adverse experience	413 (74.3)	324 (50.1)
Oedema peripheral	114 (20.5)	64 (9.9)
Headache	37 (6.7)	25 (3.9)
Bronchitis	30 (5.4)	24 (3.7)
Nasopharyngitis	26 (4.7)	22 (3.4)
Influenza	29 (5.2)	17 (2.6)
Back pain	25 (4.5)	16 (2.5)
Diarrhoea	15 (2.7)	15 (2.3)
Upper respiratory tract infection	37 (6.7)	15 (2.3)
Dizziness	28 (5.0)	12 (1.9)
Arthralgia	24 (4.3)	11 (1.7)
Cough	13 (2.3)	11 (1.7)
Pain in extremity	12 (2.2)	10 (1.5)
Fatigue	15 (2.7)	9 (1.4)
Nausea	13 (2.3)	9 (1.4)
Urinary tract infection	12 (2.2)	8 (1.2)
Sinusitis	21 (3.8)	7 (1.1)
Palpitations	12 (2.2)	6 (0.9)
Vertigo	13 (2.3)	6 (0.9)
Musculoskeletal pain	12 (2.2)	2 (0.3)
Joint swelling	17 (3.1)	1 (0.2)

* In Study SAH2301 patients also received one week of treatment with aliskiren/HCTZ, prior to being force titrated to aliskiren/amlodipine/HCTZ; the AEs reported during this treatment are given in [SCS PT-Table 4.1-7]

Table 22: Number (%) of patients with most frequent AEs (at least 2% for any group) Group D

Preferred term	Alii/Aml/HCTZ (N=51) n (%)	Ramipril/Aml /HCTZ (N=68) n (%)	Total Ali (N=452) n (%)	Total Ramipril (N=444) n (%)
Any adverse experience	14 (27.5)	21 (30.9)	328 (72.6)	336 (75.7)
Cough	2 (3.9)	1 (1.5)	19 (4.2)	59 (13.3)
Dizziness	2 (3.9)	3 (4.4)	34 (7.5)	37 (8.3)
Oedema peripheral	2 (3.9)	1 (1.5)	22 (4.9)	18 (4.1)
Arthralgia	1 (2.0)	0	17 (3.8)	8 (1.8)
Back pain	1 (2.0)	0	21 (4.6)	15 (3.4)
Diarrhoea	1 (2.0)	0	30 (6.6)	22 (5.0)
Fatigue	1 (2.0)	1 (1.5)	28 (6.2)	20 (4.5)
Insomnia	1 (2.0)	3 (4.4)	16 (3.5)	15 (3.4)
Nasopharyngitis	1 (2.0)	0	23 (5.1)	20 (4.5)
Nausea	1 (2.0)	0	19 (4.2)	16 (3.6)
Sinusitis	1 (2.0)	0	15 (3.3)	12 (2.7)
Upper respiratory tract infection	1 (2.0)	1 (1.5)	35 (7.7)	28 (6.3)
Urinary tract infection	1 (2.0)	2 (2.9)	17 (3.8)	25 (5.6)
Bronchitis	0	0	7 (1.5)	16 (3.6)
Constipation	0	0	11 (2.4)	13 (2.9)
Headache	0	1 (1.5)	42 (9.3)	40 (9.0)
Rash	0	0	14 (3.1)	4 (0.9)

AEs of other treatment groups can be found in [SCS-PT-Table 4.1-11]

Preferred terms are sorted in descending frequency, as reported in the Alii/Aml/HCTZ column

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE preferred term for that treatment.

A patient with multiple adverse events within a primary system organ class is counted only once in the total row

AEs relating to low blood pressure

In Group B, the dizziness rate was 3.6% in the triple therapy group compared to 3.4% in aliskiren/HCT, 2.4% in aliskiren/amlodipine and 1.7% in amlodipine/HCT groups. There were also two cases of postural dizziness, one case of presyncope and one case of hypotension in the 150/5/12.5 mg group and one syncope case in the 300/10/25 mg group compared to one case of presyncope in the other treatment groups combined. In Group C, dizziness was less frequent in the aliskiren/amlodipine/HCT group than the aliskiren/amlodipine group (1.9% versus 5.0%) though there were more AEs of hypotension (1.1% versus 0%) and similar rates of syncope (0.6% versus 0.5%) and orthostatic hypotension (0.5% in both groups). There was one case of orthostatic intolerance with presyncope and circulatory collapse in the aliskiren/amlodipine/HCT group. In Group D, the dizziness rate was 3.9% in the aliskiren/amlodipine/HCT group compared to 4.4% in the ramipril/amlodipine/HCT group.

Serious adverse events and deaths

Deaths

There were no deaths in the clinical program in patients treated with aliskiren/amlodipine/HCT. In Group B, there were two deaths during the single blind placebo period and none during double blind treatment. In Group C there were no deaths. There were three deaths in Group D (cerebrovascular accident, pancreatic carcinoma and coronary artery disease) with none in the aliskiren/amlodipine/HCT group. In Study SPP2360, there were two deaths during the single blind placebo period.

SAEs

In Group B, SAEs occurred in 1.9% (6/309) of aliskiren/amlodipine/HCT treated patients compared to 0.7% to 1.0% in the dual therapy groups. Of the 6 events, 4 were in the 150/5/12.5 mg dose and 2 in the 300/10/25 mg dose group. The events were: acute coronary syndrome, supraventricular arrhythmia, goitre, hypertension, psychosomatic disease and syncope. Four of these events (1.3%) led to treatment discontinuation, which was higher than other groups (0% to 0.3%).

In Group C, the SAE rate was 2.6% with 7 SAEs (1.1%) leading to discontinuation (atrial fibrillation, palpitations, osteoarthritis, cerebrovascular accident, drug dependence, interstitial lung disease and hypotension). In Group D, there was one (2.0%) SAE (bladder cancer) in the aliskiren/amlodipine/HCT group. There were no SAEs in patients treated with aliskiren/amlodipine/HCT in Studies SPP2360 and SPP2411 and none in the biopharmaceutical studies.

Laboratory findings and vital signs

Haematology

In Group B, the mean change from baseline in haemoglobin for the aliskiren/amlodipine/HCT treated patients was -1.9 g/L compared to -2.8 g/L in the aliskiren/amlodipine group. There was one patient (0.3%) with a > 20% reduction from baseline in haematocrit and 1.3% of patients shifted from normal to low haemoglobin in the aliskiren/amlodipine/HCT group. There was little change in mean haemoglobin in Group C (0.2 g/L) and Group D (-0.7 g/L).

Clinical chemistry

In Group B, there were small decreases in potassium in groups receiving HCT (-0.217 mmol/L and -0.369 mmol/L in the aliskiren/amlodipine/HCT and amlodipine/HCT groups, respectively) with 11.0% and 19.0% having a potassium < 3.5 mmol/L at any post baseline visit. There were also 3.0% of subjects with hyperkalaemia (potassium > 5.5

mmol/L) at any visit. No patients met criteria for increase in blood urea nitrogen (BUN) or creatinine in the aliskiren/amlodipine/HCT group. There were also small increases in uric acid in the HCT groups (40.8 $\mu\text{mol/L}$ and 56.9 $\mu\text{mol/L}$ in the aliskiren/amlodipine/HCT and amlodipine/HCT groups, respectively) with a shift from normal to a high value in 7.0% and 6.5% of these groups, respectively.

In Group C, there was a mean decrease of -0.136 mmol/L in potassium and increase of 30.9 $\mu\text{mol/L}$ in uric acid in the aliskiren/amlodipine/HCT group which was not evident in the aliskiren/amlodipine treated subjects (-0.031 mmol/L and -4.7 $\mu\text{mol/L}$, respectively). The incidence of hypokalaemia with the triple therapy was 11.7% compared to 1.9% with aliskiren/amlodipine. In Group D, hypokalaemia was similar in the aliskiren based triple therapy to the ramipril based triple therapy (3.9% versus 4.4%).

Vital signs

There were no relevant changes in body weight or pulse rate in the safety groups. Orthostatic hypotension was defined as a decrease in SBP of at least 20 mmHg or DBP of at least 10 mmHg on moving from sitting to standing. In Group B, the orthostatic hypotension rate at any post baseline visit was 15.3% in patients treated with aliskiren/amlodipine/HCT compared to 11.8% to 15.5% in the dual therapy groups. In the long term open label studies (Group C), the overall incidence of orthostatic hypotension at any visit was higher in aliskiren/amlodipine/HCT than aliskiren/amlodipine treated patients (16.6% versus 8.6%). In Group D, the incidence at any visit was higher with aliskiren based triple therapy than ramipril based triple therapy (25.5% versus 20.6%).

Safety in special populations

Age

Safety data was assessed by age groups of ± 65 years and ± 75 years. In Group B in subjects treated with aliskiren/amlodipine/HCT, the AE incidence in those aged ≥ 65 years was higher than those aged < 65 years (44.1% versus 34.4%), though discontinuation rates due to AEs were similar (3.6% versus 3.4%). When AEs possibly related to hypotension were examined in the elderly (≥ 65 years) there was an increase in dizziness (6.8% versus 2.8% in those < 65 years). In Group C, there was an increase in dizziness, syncope, hypotension and orthostatic hypotension with increasing age. In Group D aliskiren/amlodipine/HCT treated patients, AEs incidence was 30.6% and 20.0% in those < 75 years ($n=36$) and ≥ 75 years ($n=15$), respectively, but the numbers were small.

Gender

The rate of peripheral oedema was higher in women than men treated with aliskiren/amlodipine/HCT (12.2% versus 3.8% in Group B and 16.1% versus 5.5% in Group C). There were no other notable differences in safety findings by gender.

Renal function

AEs and laboratory values were examined for patients with moderate renal impairment (eGFR 30-60 mL/min/1.73m²) and compared to those with mild (eGFR 60-90 mL/min/1.73m²) and normal renal function (eGFR ≥ 90 mL/min/1.73m²). In Group B, 4.2% (50/1188) of the population had moderate renal impairment and there were no evident differences in AE frequency or nature. In patients with reduced renal function at baseline, there was one AE of renal impairment reported in the aliskiren/amlodipine/HCT group (150/5/12.5 mg dose). In those with moderate renal impairment at baseline, there was a higher incidence of potassium < 3.5 mmol/L in those treated with HCT (22.2%, 18.2% and 9.1% in the aliskiren/amlodipine/HCT, amlodipine/HCT, and aliskiren/HCT groups, respectively).

In Group C, 5.9% had moderate renal failure at baseline and the frequency of AEs was similar between those with renal impairment and normal renal function. There were two cases of renal failure in patients with mild renal impairment at baseline. In patients with moderate renal impairment treated with aliskiren/amlodipine/HCT, the incidence of hypokalaemia was 12.0%. In Group D, 17.4% of these elderly patients had moderate renal impairment. For patients treated with aliskiren/amlodipine/HCT, the AE incidence was higher in those with moderate compared to mild renal impairment or normal function (42.9% versus 25.8% and 23.1%) though the numbers were small.

Diabetes

For diabetics and non diabetics treated with aliskiren/amlodipine/HCT, the AE incidence was 24.2% versus 24.6% in Group B, 44.5% versus 51.6% in Group C and 42.9% versus 21.6% in Group D. There were no notable differences in the nature of AEs in diabetics. For patients without diabetes at baseline treated with aliskiren/amlodipine/HCT, there were two AEs of diabetes in Group B and one in Group C.

Obesity

Nearly half the population studied were obese (BMI ≥ 30 kg/m²) and AE frequency in Group B was 34.9% and in Group C was 51.2% which was similar to the overall population.

Discontinuation due to adverse events

In Group B (short term study), discontinuation due to safety reasons²⁵ occurred in 4.2% of the aliskiren/amlodipine/HCT group which was higher than the other dual therapy groups (1.7-3.4%). The rate of discontinuation due to AEs did not increase with the higher dose (2.3% in the 150/5/12.5 mg group compared to 1.4% in the 300/10/25 group). In Group C (long term, open label studies) there was no increase in safety related discontinuation with triple therapy (12.8% versus 7.2% for aliskiren/amlodipine and aliskiren/amlodipine/HCT groups, respectively). The most frequent AE leading to discontinuation was peripheral oedema which occurred in 2.5% of triple therapy subjects. In Group D (long term, controlled study), safety related discontinuation was similar between the aliskiren and ramipril groups (24.7% versus 24.3%) with only one (1.9%) subject in the triple therapy group discontinuing for safety reasons.

Postmarketing experience

The submission stated that the combination product has not yet been marketed in any country up to its compilation date of November 2009. The sponsor estimated, from first marketing to 31 October 2009, the exposure to aliskiren is approximately 626,000 patient treatment years (PTY), for amlodipine (monotherapy and combination therapies) the exposure is approximately 335 million PTY and for HCT the exposure is approximately 506 million PTY. There were 119 cases (427 events) on the sponsor's database of reported events with concurrent use of aliskiren, amlodipine and HCT, with the most common serious cases being dyspnoea, hypotension, dizziness, and palpitations.

Evaluator's overall conclusions on clinical safety

Safety data were collected from 3910 patients; 1155 patients received at least one dose of aliskiren/amlodipine/HCT combination, 568 patients were exposed for 6 months and 182 patients were exposed for 12 months. The mean duration of exposure was 159 days in the 6 trials. Exposure data was not provided by dose but due to the design of Studies SAH2302 and SAH2301 most exposure would be to the highest dose of 300/10/25 mg. Safety data

²⁵ "Safety reasons" included AEs, death, abnormal laboratory value or abnormal test procedure result.

were collected from populations predominantly exposed to the highest dose. In Group B, patients received 3 days of aliskiren/HCT 150/12.5 mg then 4 weeks of 150/5/12.5 mg and 4 weeks of 300/10/25 mg. In Group C, patients were uptitrated to 300/10/25 mg. Patients had mild to severe hypertension, with a mean age of 55 years in the short term study and 56 years in the long term open label studies. Around half the patients were obese and diabetes prevalence ranged from 14% to 27% in the safety groups.

The overall AE incidence was slightly higher with the triple therapy than the dual therapies (36.2% versus 32.3-33.6%) in the short term studies. Peripheral oedema was the most frequent AE (7.1% short term, 9.9% long term studies) though this was not greater than with aliskiren/amlodipine (8.0% in short term studies, $p=0.757$). Peripheral oedema was found to be more frequent in women compared to men (12.2% versus 3.8% in Group B) and was the AE most frequently leading to discontinuation of aliskiren/amlodipine/HCT treatment (2.5% in long term open label studies).

The other frequent AEs of dizziness (3.6%), headache (3.6%), nasopharyngitis (2.6%), fatigue (1.9%) and cough (0.3%) did not occur more frequently than in the dual therapy groups in the short term controlled study (Group B).

In general, AEs in patients treated with aliskiren/amlodipine/HCT were mild to moderate in severity with only 1.9% of AEs in the short term studies and 3.9% of AEs in the long term open label studies being assessed as severe.

Low blood pressure related AEs were examined and the rate of dizziness was similar to aliskiren/HCT (3.6% versus 3.4%) but greater than the other two dual combinations (1.7% and 2.4%). In the long term open label studies, there were low rates of dizziness (1.9%), hypotension (1.1%) and syncope (0.6%) in the aliskiren/amlodipine/HCT treated patients although there was one report of orthostatic intolerance and circulatory collapse. In the elderly subjects in Group D, the dizziness rate was comparable to the ramipril based triple therapy (3.9% versus 4.4%). Orthostatic hypertension at any visit was similar with the triple therapy than dual therapies in the short term study (15.3% versus 11.8-15.5%), however in the long term open label studies it was more frequent than with aliskiren/amlodipine (16.6% versus 8.6%).

There were no deaths in patients treated with aliskiren/amlodipine/HCT but there were two each in the single blind periods of Studies SAH2302 and SPP2360 and three in Study SPP2344 in other treatment groups. The SAE rate was generally low though slightly higher than dual therapy in Group B (1.9% versus 0.7% to 1.0%). In Group C and D, the SAE rate was 2.6% and 2.0%, respectively. Treatment discontinuation rates due to SAEs were 1.3% and 1.1% in Group B and C, respectively.

Laboratory assessment did not reveal any unexpected findings. There was a small mean decrease in haemoglobin (-1.9 g/L in short term studies) which was less than in the aliskiren/amlodipine group (-2.8 g/L) and little change with the long term treatment (0.2 g/L in Group C). As expected with HCT treatment, there was some decrease in potassium (-0.217 mmol/L in Group B) with 11% of patients having a potassium < 3.5 mmol/L at any post baseline visit, though this was less than seen with amlodipine/HCT (19%). There were also small increases in serum uric acid (40.8 μ mol/L) and 7% of patients shifting from normal to high value. Similar results were seen in the long term studies. There were no notable findings on BUN and creatinine. The current Australian submission was noted to have no discussion on the findings of other biochemistry assessments (lipids, glucose and LFTs).

The AE incidence was higher in the elderly ≥ 65 years (44.1% versus 34.4%) with a higher rate of dizziness (6.8% versus 2.8%). Other AEs relating to low blood pressure also increased with increasing age.

In the small numbers with moderate renal impairment (4.2% in Group B and 5.9 % in Group C), there was a higher incidence of hypokalaemia (22.2% and 12.0% in Group B and C, respectively).

There were no notable safety findings by gender, in the obese or in diabetics. There were too few non Caucasians to draw meaningful conclusions of safety in other racial groups.

Post marketing data is limited; the most frequent severe cases reported with concurrent use of aliskiren, amlodipine and HCT were dyspnoea, hypotension, dizziness, and palpitations.

The effect of treatment withdrawal (such as rebound hypertension) was not assessed in the clinical program, though no effects are noted on the product information for the monotherapies.

Safety of aliskiren/amlodipine/HCT has not been assessed in pregnancy. There were two pregnancies in the clinical program (Study SAH2302) which were terminated and neither was in the triple therapy group. As drugs acting on the renal angiotensin system and thiazide diuretics have known fetal and neonatal risks, aliskiren/amlodipine/HCT should not be used in pregnancy, in women planning to become pregnant, or during lactation.

Overall, the aliskiren/amlodipine/HCT combination appeared well tolerated with a safety profile consistent with that reported for the component monotherapies. There were no new safety signals evident from the data submitted. There was, however, a general trend for slightly higher AE rate (36.2% versus 32.3 to 33.6%) and an increase in safety related treatment discontinuation with the addition of the third treatment component compared to dual therapy (4.2% versus 1.7 to 3.4%).

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Pharmacokinetics

- Can the sponsor verify that Variant 4 (Study SPA100A22101) was the formulation used in Studies SPA100A22102 to SPA100A22104.
- Is there any data, which specifically examines the PK interaction between the components of the fixed combination or with other drugs with which it is likely to be co administered?
- Can dissolution data be provided regarding the Novartis and Pfizer forms of amlodipine?

Efficacy

In Study SAH2302, amlodipine 5 mg and 10 mg capsules were used in the free combination. In Study SAH2301 amlodipine 5 mg (x2) was used in the free combination triple therapy. From the clinical study report of SAH2301 it is not clear which formulation was used as both tablets and capsules were mentioned. Please provide information on the formulations used in these two main clinical trials and comment on this in relation to biopharmaceutic studies that are to bridge to the proposed fixed combination for marketing.

In the short term clinical trial SAH2302, the treatment compliance was not reported, although it was stated the monitors checked compliance at monitoring visits. Please provide the details and commentary on treatment compliance from this study.

Safety

Longer term gastrointestinal toxicity studies were to be submitted in relation to aliskiren. Please comment on these data, if available, and if any relevant details need inclusion in the aliskiren/amlodipine/ HCT product information.

It appears from reading the statistical tables that there were no notable changes in LFTs, glucose, calcium or lipids in the safety datasets, however the results of these assessments in the 3 pooled safety datasets were not discussed in the submission. A summary, including any results meeting the pre specified criteria for significance, and commentary should be provided on these laboratory assessments. Are there any data from this which would warrant inclusion on the product information?

Clinical Summary and Conclusions

Clinical Aspects

Pharmacokinetics

Following treatment with a fixed combination tablet containing aliskiren/amlodipine/HCT (300/10/25 mg) (Variant 002) in the fasted state the PK parameters for the three drugs in the fixed combination were bioequivalent with a free combination dose of aliskiren/amlodipine/HCT (300/10/25 mg). By contrast, a study examining the bioequivalence between a fixed combination of aliskiren /amlodipine/HCT (300/5/25 mg) and free combination of the drugs showed that the two dosage forms were bioequivalent for amlodipine and HCT although the two formulations did not strictly meet the criteria for bioequivalence for aliskiren C_{max} ; the geometric mean ratios for C_{max} and AUC were 0.84 (90% CI 0.76, 0.93) and 0.85 (90% CI: 0.80, 0.90), respectively.

However, *in vitro* dissolution data were provided for the batches, dosage strengths 300/10/25 mg and 300/5/25 mg aliskiren/amlodipine/HCT, used in the two bioequivalence studies CSAH100A2104 and CSAH100A2102. In addition, data were provided for the dosage strengths 150/5/12.5 mg, 300/10/12.5 mg, and 300/5/12.5 mg aliskiren/amlodipine/HCT for which a biowaiver was requested. These studies have been conducted according to the FDA Guidance.

Following treatment with a fixed combination tablet containing aliskiren/amlodipine/HCT (300/10/25 mg) a high fat meal reduced aliskiren exposure by 78% and C_{max} by 89% compared to fasted conditions, whereas, the T_{max} and $t_{1/2}$ of aliskiren increased by 1.5 h and 11 h under fed compared to fasted conditions, respectively. By contrast, the PKs of amlodipine and HCT were not affected by food. In addition, the pharmacokinetic peak and total exposure of aliskiren at steady state was also reduced by more than 65% when it was taken with light meal compared to the fasted state. A light meal also resulted in a significant increase (1.6 fold) in trough PRC though there was no change in trough PRA or trough msSBP or msDBP. No studies examined drug interactions between the components of the fixed combination.

Clinical Efficacy

The clinical development program for the aliskiren/amlodipine/HCT combination therapy was thorough and the study design and methodology was in line with the relevant guidelines for the investigation of products for the treatment of hypertension. There were six clinical trials in the current submission: one pivotal short term (SAH2302) and one key open label long term (SAH2301), together with one supportive short term trial (SPP2411) and three supportive long term trials (SPP2344, SPP2360 and SPA2301). These included 3910 patients with mild to severe hypertension, 1155 of whom were exposed to aliskiren/amlodipine/HCT.

The two trials of the triple combination, as well as SPP2411 in older patients, included patients with moderate to severe hypertension (msSBP \geq 160 mmHg and $<$ 200 mmHg and/or msDBP \geq 100 mmHg and 120 mmHg). The other three trials, which allowed dose escalation to triple therapy, included patients with mild to moderate hypertension (msSBP \geq 140 mmHg and $<$ 180 mmHg and msDBP \leq 110 mmHg). Patients with secondary hypertension and high cardiovascular risk groups (significant hepatic or renal impairment, heart failure, poorly controlled diabetes, a history of myocardial infarction or cerebrovascular disease) were excluded from the development program.

None of these clinical trials used the fixed combination proposed for marketing, aliskiren/amlodipine/HCT treatment was in free combinations of tablets and capsules. There were no dose selection studies as doses in the triple combination are the same as the registered monotherapies. There were no pooled efficacy data due to study design and population differences.

The primary efficacy variable was change from baseline in msSBP in Studies SAH2302, SPP2344 and SPP2411, while in Study SPP2360 it was target BP control rate. Studies SAH2301 and SPA2301 were safety studies with msSBP and msDBP as secondary variables.

SAH2302 was the pivotal efficacy study which randomised 1191 patients with moderate to severe hypertension. After 8 weeks of treatment, the combination of aliskiren/amlodipine/HCT 300/10/25 mg resulted in statistically significant and clinically meaningful reduction in msSBP and msDBP compared to the respective double combinations (differences -6.55 to -9.93 mmHg for msSBP and 2.60 to -6.30 mmHg for msDBP). Efficacy was also seen at Week 4 with the lower dose (150/5/12.5 mg) combination. BP control ($<$ 140/90 mmHg) was significantly greater with the triple combination (62.3%) compared to the double combinations (33.1% to 41.3%). There was also a significant reduction in mean 24 hour ambulatory DBP and SBP and this effect was maintained over the 24 hour period with once daily dosing.

SAH2301 was an open label long term study of the triple combination in 564 patients with moderate to severe essential hypertension. After 6 months of treatment, the combination aliskiren/ amlodipine/HCT 300/10/25 mg resulted in a BP control rate of 69% and a long term msSBP/msDBP reduction of 34.2/20.3 mmHg. A DBP response was noted in 91.8% and SBP response in 90.2% of patients at Week 28. In the smaller group of subjects (n=206) who continued into the second 6 months of treatment, the effect was maintained to Week 54.

Subgroup analyses found the triple therapy was more effective than dual therapy in lowering BP across subgroups of age, gender, BMI and race. Females and elderly (\geq 75 years) were noted to have a greater BP reduction. There were no notable findings in the different racial groups but the numbers of non-Caucasians were low. Efficacy, that was superior to dual therapy, was also noted in patients with severe hypertension (SBP \geq 180 mmHg) with a reduction of msSBP/msDBP of 49.53/22.53 mmHg and a BP control rate of 57.5% after 8 weeks of treatment.

The other four studies in the current submission had optional add-on treatment in patients not adequately controlled with dual therapy. Data from these studies provided supportive evidence of additional BP reduction with the addition of the third agent.

Once daily dosing was supported by data from ABPM conducted in SAH2302 which showed sustained BP lowering over the 24 hour monitoring period. Aliskiren/amlodipine/HCT resulted in BP reduction over one year of treatment with no evidence of tolerance resulting in loss of efficacy.

Clinical Safety

Safety data were collected from 3910 patients (1155 patients received at least one dose of aliskiren/amlodipine/HCT combination, 568 patients were exposed for 6 months and 182 patients were exposed for 12 months. The mean duration of exposure was 159 days. Patients had mild to severe hypertension, with a mean age of 55 years in the short term study and 56 years in the long term open label studies. Around half the patients were obese and diabetes prevalence ranged from 14% to 27% in the safety groups. Overall, there were 301 patients aged ≥ 65 years with 124.5 person years exposure and 67 patients aged ≥ 75 years with 26.8 person years exposure. Exposure by dose was not provided, though in Group B and C safety sets it was predominantly to the highest dose (300/10/25 mg). While the safety database size was within guideline requirements, the number of patients over 75 years was limited.

The overall AE incidence was slightly higher with the triple therapy than the dual therapies (36.2% versus 32.3-33.6%) in Group B (short term controlled study). The nature of AEs was in line with known effects of the monotherapies and there were no new safety signals. Peripheral oedema was the most frequent AE (7.1% Group B, 9.9% Group C long term open label studies) although this incidence was not greater than with aliskiren/amlodipine. Peripheral oedema was the AE most frequently leading to discontinuation of aliskiren/amlodipine/HCT treatment (2.5% in Group C). The other frequent AEs of dizziness (3.6%), headache (3.6%), nasopharyngitis (2.6%), fatigue (1.9%) and cough (0.3%) did not occur more frequently than in the dual therapy groups in the short term controlled study (Group B).

Low blood pressure related AEs such as dizziness, hypotension and syncope and occurred at low rates in the Group C (1.9%, 1.1% and 0.6%, respectively). Rates were similar to aliskiren/HCT (3.6% versus 3.4% Group B) though greater than the other two dual combinations (1.7% and 2.4%) in Group B. In the elderly subjects in Group D, the dizziness rate was comparable to the ramipril based triple therapy (3.9% versus 4.4%). Orthostatic hypertension at any visit was similar with the triple therapy and dual therapies in Group B but more frequent than with aliskiren/amlodipine with longer term treatment (16.6% versus 8.6%).

In general, AEs in patients treated with aliskiren/amlodipine/HCT were mild to moderate in severity with only 1.9% of AEs in Group B and 3.9% of AEs in Group C being assessed as severe. There were no deaths in patients treated with aliskiren/amlodipine/HCT. The SAE rate was low (2.6% in long term study) however in Group B it was higher than in the dual therapy groups (1.9% versus 0.7% to 1.0%). Treatment discontinuation rates due to SAEs were 1.3% and 1.1% in Group B and C, respectively.

Laboratory assessment did not reveal any unexpected findings. There was a small mean decrease in haemoglobin in the short term and little change with the long term treatment (0.2 g/L). As expected with HCT treatment, there was some decrease in potassium (-0.217 mmol/L in Group B) with 11% of patients having a potassium < 3.5 mmol/L at any post baseline visit, though this was less than seen with amlodipine/HCT (19%). A small proportion of subjects (3%) were found to have hyperkalaemia at a post baseline visit. There were also small increases in serum uric acid (40.8 $\mu\text{mol/L}$) and 7% of patients shifting from normal to high value. Similar results were seen in the long term studies. There were no notable findings with respect to BUN and creatinine.

There were no notable safety findings by gender, in the obese or in diabetics. There were too few non Caucasians to draw meaningful conclusions of safety in other racial groups. The AE incidence was higher in the elderly ≥ 65 years (44.1% versus 34.4%) with a higher rate of dizziness (6.8% versus 2.8%, Group B). Other AEs relating to low blood pressure

also increased with increasing age. In the small numbers with moderate renal impairment there was a higher incidence of hypokalaemia (22.2% and 12.0% in Group B and C, respectively).

Post marketing data is limited; the most frequent severe cases reported with concurrent use of aliskiren, amlodipine and HCT were dyspnoea, hypotension, dizziness, and palpitations.

Overall, the aliskiren/amlodipine/HCT combination appeared well tolerated with a safety profile consistent with that reported for the component monotherapies. There were no new safety signals evident from the data submitted. There was, however, a general trend for higher AE rate (36.2% versus 32.3 to 33.6%) and an increase in safety related treatment discontinuation with the addition of the third treatment component compared to dual therapy (4.2% versus 1.7 to 3.4%).

Benefit risk assessment

Benefits

The aliskiren/amlodipine/HCT combination tablet includes one drug, aliskiren, which is the first in its class with two others that are well known and widely used. The modes of action of the three treatments are complementary.

The clinical efficacy and safety program was comprehensive and designed in accordance with relevant guidelines.

The aliskiren/amlodipine/HCT combination of 300/10/25 mg was bioequivalent with the free combination.

The aliskiren/amlodipine/HCT combination, at doses of 300/10/25 mg and 150/5/12.5 mg, resulted in clinically meaningful and statistically significant antihypertensive effect together with greater BP control rates than the respective dual therapies.

The antihypertensive effect was maintained over 24 hours on ABPM, and was sustained over 1 year of treatment with no evidence of tolerance. Efficacy was seen in patients with mild to severe hypertension and was also seen across subgroups of age, gender, race, BMI and diabetes.

Aliskiren/amlodipine/HCT had an acceptable safety profile similar to the component monotherapies and there were no new safety signals with the combination therapy.

The treatment is a once a day dosing of a single tablet which may assist in patient compliance and improved treatment acceptance.

Risks

The pharmacokinetic peak and total exposure of aliskiren at steady state was reduced by more than 65% when it was taken with light meal compared to the fasted state.

With the addition of a third component to the antihypertensive treatment regimen there was a small, but noticeable, increase in adverse events including adverse events leading to treatment discontinuation. The main risk with aliskiren/amlodipine/HCT was peripheral oedema which is a recognised effect of amlodipine.

Adverse events related to low blood pressure (such as dizziness and syncope) did occur (3.6% of patient short term) but the rate was similar to that of aliskiren/HCT (3.4%). The risk of low BP related events increased with increasing age. The triple therapy resulted in a number of patients with hypokalaemia (11%) and increased uric acid (7%) but these numbers were not greater than those with amlodipine/HCT dual therapy. The risk of hypokalaemia was greater in patients with renal impairment. There were also a small

proportion of patients with hyperkalaemia. There was a small decrease in haemoglobin in the short term which was not found with longer term treatment.

As reported in postmarketing data for aliskiren monotherapy, there could potentially be risks of angioedema, rash and renal dysfunction with the combination therapy.

While SPP2344 was a 36 week study in patients ≥ 65 years, there very few were on triple therapy in this study and overall the long term exposure in patients ≥ 75 years was low. The data on racial groups other than Caucasians were limited and there were no data on pregnancy.

One of the main areas for lack of efficacy and safety data is in patients with high cardiovascular risk as those with severe hepatic and renal impairment, heart failure, history of myocardial infarction or cerebrovascular disorders were excluded from the clinical program.

There are currently no morbidity or mortality outcome data available for aliskiren but it was noted that a clinical trial assessing this is in progress.

Rebound hypertension was not assessed but it is not anticipated to be an issue as withdrawal effects are not mentioned in the respective monotherapy production information.

Information on the monotherapies notes numerous drug interactions and these will obviously continue to add to the risk profile of the combination treatment.

Balance

It is reported that between 50 to 75% of patients with hypertension will not achieve their target BP with monotherapy (Hansson 1998) and in this group combination antihypertensive therapy has a clinical place.²⁶ As this combination may need to include three therapies there is an evident clinical place for a combination tablet to increase patient acceptance and compliance. Amlodipine and hydrochlorothiazide are well known products with established safety profiles and have complementary actions with aliskiren.

The sponsor has proposed to market the following strengths: 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg, 300/10/25 mg. This covers a wide number of strength combinations but does not cover all eight possibilities. The doses not included are those with a 150 mg aliskiren base. The evaluator believes this would not affect clinical practice as it would be expected that patients requiring three antihypertensive medications would be on the higher aliskiren dose. Given the known risk of peripheral oedema with the 10 mg dose of amlodipine, it is important that the combinations with the 5 mg dose have been included.

As there are 5 proposed strengths of the combination, the trade names should include the strengths of each component in order to avoid possible confusion between the doses,.

Bioequivalence between the fixed and free combination has been demonstrated for the 300/10/25 mg dose while the 300/5/25 mg dose resulted in a 15% decrease in exposure to aliskiren. However, only the C_{max} fell outside the guideline defined 90% confidence of 0.80-1.25 and the more clinically important measure of AUC just met the criteria. The guidelines state that "in certain cases a wider interval may be acceptable. The interval must be prospectively defined for example, 0.75-1.33, and justified addressing in

²⁶Hanssen L, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351:1755-62.

particular any safety or efficacy concerns for patients switched between formulations”²⁷. The evaluator believed that this marginal finding on the aliskiren C_{max} ratio should not pose a problem with clinical efficacy particularly given the results on AUC, the positive data on the other components and the supportive dissolution data. For the 150/5/12.5 mg, the 300/10/12.5 mg and 300/5/12.5 mg doses the manufacturing process is identical, the composition proportional or similar, the pharmacokinetics linear and dose proportional and the *in vitro* dissolution profiles comparable. This supports the sponsor’s request for biowavers for these doses.

As this program was conducted with the free combination, the establishment of bioequivalence is critical. The clinical development program found positive clinical efficacy and acceptable safety data together with bioequivalence for the highest dose of 300/10/25 mg dose and acceptable bioequivalence data for the other 4 doses and therefore the evaluator concluded that the aliskiren/amlodipine/HCT combination tablet is an appropriate replacement therapy for the concurrent use of separate tablets at the same dose.

The trials did not include a number of patients groups (secondary hypertension, severe hepatic or renal impairment, cardiovascular or cerebrovascular disorders and pregnancy) and this should be adequately addressed in the PI. The risks of low blood pressure related events, electrolyte disturbance and drug interactions also need to be thoroughly covered in the product and consumer medicine information. Data coming from the clinical outcome study with aliskiren will be important to ensure there is no change to the risk benefit balance of this aliskiren based product.

As drugs acting on the renal angiotensin system and thiazide diuretics have known fetal and neonatal risks, aliskiren/amlodipine/HCT should not be used in pregnancy, in women planning to become pregnant or during lactation.

In summary, the evaluator finds the risk benefit balance in favour of a replacement indication in the treatment of primary hypertension, that is, in patients who are already being treated with aliskiren, amlodipine and HCT concurrently at the same dose level as the combination.

Conclusions

It was concluded that the overall benefit risk balance of aliskiren/amlodipine/HCT combination tablet is positive for the indication of:

Rasilamlo HCT/Riprazemlo HCT is indicated as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on triple combination of aliskiren, amlodipine and hydrochlorothiazide taken either as three single component formulation or as dual-component formulation with a single component formulation, all components at the same dose level. Treatment should not be initiated with these fixed dose combinations.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP which was reviewed by the TGA’s Office of Product Review (OPR). The summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 24.

²⁷ CPMP (2001) Note for guidance on the investigation of bioavailability and bioequivalence. CPMP/EWP/QWP/1401/98. London.

Table 23: Ongoing safety concerns for the individual components in Rasilamlo HCT.
Table continued across two pages.

Important identified risks	Diarrhea Rash Angioedema Hyperkalemia Renal dysfunction Peripheral edema
Important potential risks	Colorectal hyperplasia Hypotension Ischemic colitis
Important identified interactions	Decrease in furosemide systemic levels Increased aliskiren systemic levels with the potent Pgp inhibitor, ciclosporin A Increased aliskiren systemic levels with moderate Pgp inhibitors ketoconazole and verapamil.
Important potential interactions	Increased aliskiren systemic levels with other moderate (itraconazole, clarithromycin, telithromycin, erythromycin, amiodarone) and potent Pgp inhibitors (quinidine)
Pharmacological class effects	Cough
Pharmacological class interactions	NSAIDs: increase in BP and renal function deterioration.
Important missing information	Pregnancy Pediatric patients Patients with severe and moderate renal dysfunction Patients with reno-vascular hypertension Patients with cardiovascular morbidity and mortality reduction

Ongoing Safety Concerns for Amlodipine

System organ class	Reported ADRs
Blood and Lymphatic System Disorders	Leukopenia and thrombocytopenia
Cardiac Disorders and Vascular Disorders	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), vasculitis, and hypotension.
Central and Peripheral Nervous System	Neuropathy peripheral, tremor, dizziness, dysgeusia, headache, paraesthesia, and somnolence.
Gastrointestinal & Hepatobiliary	Gastritis, gingival hyperplasia, pancreatitis, altered bowel habit, hepatic enzyme elevation, hepatitis, dyspepsia, nausea/vomiting, abdominal pain upper, diarrhea, and dry mouth.
General	Malaise, weight increased, weight decreased, asthenia, and non-cardiac chest pain.
Immune System Disorders	Hypersensitivity
Infections and Infestations	Rhinitis
Musculoskeletal System	Arthralgia, myalgia, and muscle spasm.
Nervous System Disorder	Syncope
Psychiatric	Mood changes and insomnia.
Respiratory System	Dyspnea and cough.
Skin and Appendages	Alopecia, angioedema, rash, erythema multiforme, purpura, skin discoloration, urticaria, hyperhidrosis, and pruritus.
Special Senses	Tinnitus and visual disturbance.
Urinary System	Increased urinary frequency, nocturia, micturition disorder, and pollakiuria.
Metabolic and Nutritional	Hyperglycemia
Reproductive System	Impotence and gynecomastia.

Ongoing Safety Concerns for HCTZ

System organ class	Reported ADRs
Electrolytes and Metabolic Disorders	Hyponatraemia and hypochloroemic alkalosis, hypomagnesaemia, rise in serum levels of cholesterol, triglycerides, and uric acid.
Cardiac Disorders and Vascular Disorders	Orthostatic hypotension (common) which may be aggravated by alcohol, anaesthetics or sedatives; arrhythmia (rare), and vasculitis necrotizing (very rare).
Central and Peripheral Nervous System	Headache, dizziness, and paresthesia (rare).
Gastrointestinal & Hepatobiliary	Mild nausea and vomiting (common); abdominal discomfort, constipation, diarrhea, cholestasis or jaundice (rare); and pancreatitis (very rare).
Blood and Lymphatic System Disorders	Thrombocytopenia, sometimes with purpura (rare); leukopenia, agranulocytosis, bone marrow depression, hemolytic anaemia (very rare)

The sponsor states in the RMP that “no new safety observations following administration of aliskiren, amlodipine and HCT as a free combination have emerged from the clinical trial program in hypertension which would constitute a new risk or provide evidence of increased severity, specificity and frequency of known or potential risks already described for aliskiren.”

The OPR reviewer noted that the summary of the ongoing safety concerns was considered acceptable and was supported by the nonclinical and clinical evaluators. The nonclinical evaluator noted that all potential clinically relevant toxicological findings had been

adequately identified and described in the Safety Specification in the RMP. The clinical evaluator noted that the sponsor indicated that ischaemic colitis was included as new potential risk due to isolated reports with aliskiren. There were no new safety signals identified in this evaluation, however there was low long term exposure to the triple combination in the very elderly (≥ 75 years) and therefore monitoring of this group was recommended. Risks for the aliskiren/amlodipine/HCT combination need to be considered the same as for the three component monotherapies.

The OPR reviewer noted this recommendation of the clinical evaluator and recommended the sponsor include a subgroup analysis in the Periodic Safety Update Report (PSUR) for this group.

Pharmacovigilance plan

Routine pharmacovigilance was proposed by the sponsor to monitor ongoing safety concerns associated with aliskiren, amlodipine and HCT.²⁸ This routine pharmacovigilance includes ongoing and proposed clinical trials and also questionnaires/checklists for follow up of significant adverse event cases in these trials and also spontaneous adverse event reports.

As a consequence of the sponsor's statement reproduced above, it intends to apply the same pharmacovigilance (PV) activities for the fixed combination as those planned for aliskiren monotherapy.

In the aliskiren/HCT combination (Rasilez HCT) RMP, only routine pharmacovigilance (including clinical trials) and routine risk minimisation activities were proposed. This RMP or previous versions of this RMP were not evaluated by the TGA because the submission was prior to the RMP requirement.

In the aliskiren/amlodipine combination (Rasilamlo) RMP, routine pharmacovigilance (including clinical trials) and routine risk minimisation activities were proposed and considered sufficient by the TGA RMP evaluator.

Diarrhoea, angioedema, hyperkalaemia (Identified risks), colorectal hyperplasia (Potential risk) and patients with cardiovascular morbidity and mortality (Important missing information) were proposed to be monitored by the ongoing trials:

- Study SPP100E2337: A long term, placebo controlled, double blind, randomised cardiovascular morbidity and mortality study with safety
- Study SPP100A2340E1: A randomised, placebo controlled, double blind, parallel group study to evaluate the efficacy and safety of aliskiren on the prevention of left ventricular remodelling in high risk post acute myocardial infarction patients when added to optimised standard therapy (cardiovascular morbidity and mortality only).

Proposed studies include:

- A database cohort study to assess the incidence of ischaemic colitis in adult treated hypertensive patients (ischaemic colitis [potential risk])

²⁸ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- Study SPP100A2255: Single blind multiple dose placebo controlled, double dummy study to investigate the pharmacodynamic and pharmacokinetic interaction between aliskiren and furosemide in patients with heart failure (decrease in frusemide systemic levels [potential risk])

It was considered that routine pharmacovigilance was satisfactory to monitor the ongoing safety concerns associated with aliskiren. The OPR reviewer was satisfied with the ongoing studies but found it difficult to assess the details of the proposed studies as the protocols were not provided. It was recommended that the sponsor provide these protocols and a justification explaining how each study is appropriately designed to provide a greater understanding of its assigned safety concern(s).

Risk minimisation activities

The sponsor indicated that the objective of the Risk Minimization Plan is to minimise or prevent the risks discussed in the RMP. This RMP is based on the latest version of the approved aliskiren monotherapy RMP, updated with new clinical trial data and targeted follow up of certain already identified and potential risks to support the fixed combination for the treatment of hypertension (no new risks identified for the fixed combination). Risk minimisation activities for the fixed combination will follow the approved plan for aliskiren monotherapy. In a summary of “Planned actions” the sponsor stated that routine risk minimisation activities were sufficient for all ongoing safety concerns identified with aliskiren.²⁹

The OPR reviewer agreed that routine risk minimisation activities were considered appropriate to mitigate the risks associated with aliskiren, amlodipine and HCT.

Summary of recommendations

It was recommended to the Delegate that the sponsor:

- Confirm if the risk minimisation activities associated with the core data sheet are equivalent to the Australian product information or identify where differences exist. These equivalences or differences may be identified in an Australian specific annex.
- Provide protocols for the two proposed studies and a justification explaining how each study is appropriately designed to provide a greater understanding of its assigned safety concern(s).
- Include a sub group analysis in the PSUR for the very elderly (≥ 75 years). The clinical evaluator suggested monitoring of this group is needed due to the low long term exposure.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate’s overview and recommendations:

Quality

The quality evaluator recommended approval with respect to chemistry and quality control and noted there was adequate differentiation amongst the different strength tablets. In relation to bioavailability the sponsor submitted two studies, a food effect study, a justification for not submitting bioavailability data for three of the proposed

²⁹ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

combinations, a justification for using the German *Norvasc* product, a justification for using a Novartis HCT product and a population pharmacokinetic analysis in lieu of a pharmacokinetic interaction study. The advice of PSC was that all outstanding issues should be addressed to the satisfaction of the TGA. The PSC accepted the sponsor's justification for:

- Using overseas sourced amlodipine (as besylate) monotherapy tablet and encapsulated tablet formulations and, hydrochlorothiazide monotherapy capsule formulation as the comparator in the bioequivalence and the clinical trial studies provided in support of this submission.
- Not providing a bioequivalence data on all strengths of the combination tablet formulation proposed for registration to the coadministration of corresponding doses of the monotherapy formulations.

The PSC was not concerned about the slight reduction in the bioavailability of each drug substance in the presence of the other drug substances in view of the fact that the observed interaction between the three drug substances was not statistically significant.

The following findings were noted:

- The fixed dose tablet of 300/10/25 mg was found to be bioequivalent with the monotherapies used in the clinical studies.
- The fixed dose tablet of 300/5/25 mg was found to be bioequivalent with the monotherapies used in the clinical studies except the confidence interval for the C_{max} of aliskiren was slightly beyond the normal limits (0.76-0.93).
- The justification for not providing bioavailability data on 150/5/12.5, 300/5/12.5 and 300/10/12.5 was acceptable.
- The justification for the use of overseas amlodipine and HCT was acceptable.
- A population pharmacokinetic interaction study indicated that each drug lowers the bioavailability of the other components by 5-22%. The evaluator noted that these results are similar to previous pharmacokinetic studies using aliskiren and amlodipine alone and aliskiren and HCT alone.
- Food (high fat breakfast) delayed the absorption of aliskiren from 1.5 to 3 hours for T_{max} , reduced C_{max} by 90% and AUC by 80% compared to fasted conditions. Amlodipine and HCT were unaffected compared to the fasted state.

Nonclinical

The nonclinical evaluator had no objections to the registration of Rasilamlo HCT for the proposed indication. No nonclinical studies were submitted for the triple combination and data relied on previously evaluated toxicity studies using different combinations (aliskiren with amlodipine, aliskiren with HCT and amlodipine with valsartan and HCT). The evaluator indicated it was unlikely there would be any novel safety concerns with this combination given the previous nonclinical data and the availability of postmarket data with each drug as either monotherapy or combination.

Clinical

Clinical evaluation

The clinical evaluator recommended approval. The concerns noted by the evaluator in this submission included:

- Small increase in adverse events when a third drug is added to the combination
- Some electrolyte changes
- Long term exposure on the triple combination in the elderly is low
- Lack of data in severe hepatic or renal impairment, cardiovascular or cerebrovascular disorders, pregnancy, secondary hypertension and clinical outcomes for cardiovascular morbidity or mortality

Pharmacology

The bioequivalence studies have been summarised above under *Quality* above. Clinical aspects of the justification for not submitting bioequivalence studies using the lower strength combinations were acceptable. No new pharmacodynamic data were submitted. The food study showed no significant effects of food on the aliskiren induced change in trough plasma renin activity, trough systolic BP or trough diastolic BP.

Efficacy

SAH2302

This was an 8 week, randomised, double blind, double dummy, multicentre, active controlled parallel group study of aliskiren/amlodipine/HCT in 1189 patients (mean 55 years, 19% >65 years) with moderate to severe hypertension (mean 9 years) comparing four treatment groups: 150/5, 150/12.5, 5/12.5 and 150/12.5 mg for 3 days followed by 150/5/12.5. After 4 weeks, patients were force titrated to 300/10, 300/25, 10/25 and 300/10/25 mg. Groups were comparable with respect to baseline demographics and characteristics (49% obese, 52% metabolic syndrome, 14% diabetes). Baseline BP was about 172/104 mmHg. The results showed:

- The primary efficacy endpoint of change in mean sitting systolic BP (msSBP) at Week 8 showed the triple combination of 300/10/25 mg achieved a change of -38 mmHg which was statistically significantly superior to all three dual combinations of between 6.55-9.93 mmHg (see below).
- The change in mean sitting diastolic BP (msDBP) at Week 8 showed the triple combination of 300/10/25 mg achieved a change of -21 mmHg which was statistically significantly superior to all three dual combinations of between 2.6-6.3 mmHg.
- At Week 4, the triple combination of 150/5/12.5 mg showed a significant result for reduction in msSBP and msDBP compared to the dual combinations.
- Blood pressure control (<140/90 mmHg) was statistically significantly greater on the triple combination (62%) compared to all three dual combinations (33-41%).
- Systolic response rate (msSBP<140 mmHg or ≥20 mmHg reduction) was statistically significantly greater on the triple combination (89%) compared to all three dual combinations (72-82%). Diastolic response rate (msDBP<90 mmHg or ≥10 mmHg reduction) was statistically significantly greater on the triple combination (90%) compared to the two dual combinations (69-82%) but not compared to aliskiren/amlodipine (87%).
- Ambulatory BP monitoring showed the effect was over 24 hours and significantly greater on the triple combination.
- A subgroup analysis showed the benefit was seen in severe hypertension, males and females and those < 65 years, ≥ 65 years and ≥75 years. The BP reduction in females

was greater than males and the effect in those ≥ 75 years (51/29 mmHg) was greater than those < 65 years (36/20 mmHg).

Table 25: Study SAH2302 Primary efficacy results.

Treatment group	N	LSM change from baseline (SE)	
Aii/Aml 300/10 mg	282	-31.37 (0.90)	
Aii/HCTZ 300/25 mg	296	-27.99 (0.88)	
Aml/HCTZ 10/25 mg	295	-30.77 (0.88)	
Aii/Aml/HCTZ 300/10/25 mg	308	-37.92 (0.86)	
Pairwise comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
Aii/Aml/HCTZ vs Aii/Aml	-6.55 (1.22)	(-8.96, -4.15)	< 0.001*
Aii/Aml/HCTZ vs Aii/HCTZ	-9.93 (1.21)	(-12.31, -7.56)	< 0.001*
Aii/Aml/HCTZ vs Aml/HCTZ	-7.15 (1.21)	(-9.53, -4.78)	< 0.001*

SE = standard error, LSM = least squares mean, CI = confidence interval.

Least squares means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region and baseline.

P-Values and treatment comparisons were evaluated at the average baseline level.

* indicates statistical significance at 0.05 level.

SAH2301

This was a 54 week, multicentre, uncontrolled, open label, long term safety study with secondary efficacy measurements of the 300/10/25 mg triple combination in 564 patients (mean 56 years, 24% > 65 years) with moderate to severe hypertension (mean 9 years). Baseline demographics and characteristics were 52% were obese, 52% had metabolic syndrome and 13% had diabetes. Baseline BP was about 166/102 mmHg. The results showed:

- The reduction in msSBP/msDBP at Week 28 was 34/20 mmHg and at Week 54 was 37/22 mmHg.
- BP control was 69% at Week 28 and 77% at Week 54.
- Systolic response rate was 90% at Week 28 and 94% at Week 54.
- Diastolic response rate was 92% at Week 28 and 97% at Week 54.
- Efficacy was seen across the subgroups of gender and age.

SPP2411

This was a Phase IV, 8 week, randomised, double blind, parallel study of 300/25 mg versus 25 mg in 451 patients > 55 years (mean 65 years) with Stage 2 systolic hypertension (160- < 200 mmHg msSBP for a mean 11 years). Open label amlodipine was allowed from Week 4 if msSBP ≥ 160 mmHg. Baseline BP was 169/91 mmHg. The primary efficacy endpoint of change in msSBP was statistically significant at Week 4 of -29 versus -22 mmHg, $p < 0.0001$, which was maintained to Week 8. Systolic response and BP control were also greater on 300/25 versus 25 mg. Only 29 patients were on the triple combination and there were significant baseline differences in age, gender and eGFR status, therefore this study contributed little information.

SPP2344

This was a 36 week, randomised, double blind, parallel design active controlled non inferiority study of aliskiren 150 mg titrated to 300 mg versus ramipril 5 mg titrated to 10 mg in 901 patients ≥ 65 years (mean 72 years) with systolic hypertension (140- < 180 mmHg msSBP for a mean 12 years). Both groups could also add HCT 12.5 mg to 25 mg and then amlodipine 5 mg to 10 mg if required. The non inferiority margin was set at 3.5

mmHg for msSBP. Baseline BP was 157/86 mmHg. The primary efficacy endpoint of change in msSBP at Week 12 showed the aliskiren regimen was non inferior to the ramipril regimen. By Week 36, the change in msSBP was -19.9 mmHg in the aliskiren arm versus -18 mmHg in the ramipril arm. At Week 36, the triple combination (aliskiren/amlodipine/HCT) had a reduction in BP of 90.8/14.1 mmHg versus the ramipril triple combination of 25.7/9 mmHg. However, only 11.5% of patients ended the study on the 300/amlodipine/25 combination and being a subgroup analysis with significant protocol deviations, then this study is of limited value.

SPP2360

This was a Phase IV, 24 week, open label uncontrolled study of aliskiren 150 mg uptitrated at 4 weekly intervals to a maximum of 300/10/25 mg in 256 patients with mild to moderate hypertension (mean 6.6 years). The primary efficacy endpoint of the cumulative proportion of patients reaching target BP (<140/90 mmHg for non-diabetics and <130/80 mmHg for diabetics) was 86% by the time they reached the triple combination. For those 119 patients who did not reach target BP and needed the triple combination, the BP control rate was 31% for 300/5/25 mg and 61% for 300/10/25 mg.

SPA2301

This was a 54 week open label, uncontrolled safety study of 300/10 mg in 556 patients with essential hypertension. After 72 days, HCT at 12.5 to 25 mg could be added. A total of 452 patients (81%) completed 12 months of treatment, however only 86 patients received the triple combination. Efficacy, a secondary endpoint, for the triple combination showed -24/-14 mmHg at Week 54. BP control for this group was 58% at Week 54 and the diastolic response was 85%.

Safety

Exposure data for the triple combination was from 1155 patients with 568 patients exposed for 6 months and 182 patients exposed for 12 months. Patients were grouped according to study type (B for short term studies, C for all long term studies and D for long term double blind studies). Where doses were titrated, data were presented for the final titrated dose. Adverse event incidence in Group B was 36% on the triple combination versus 32-34% on the dual combinations. Peripheral oedema was the most frequent adverse event at 7.1% on the triple combination, 8% on the aliskiren/amlodipine combination, 4.1% on the amlodipine/HCT combination and 2% on the aliskiren/HCT combination. It was greater in women than men on the triple combination (12.2 versus 3.8%). Dizziness occurred at a similar rate to aliskiren/HCT but greater than other dual combinations. Other adverse events occurred at a similar rate to the dual combinations. In Group C patients, the adverse event rate was 50.1% on the triple combination versus 74.3% on the aliskiren/amlodipine combination, with peripheral oedema being the most common AE but occurring less on the triple combination than the dual combination (9.9 versus 20.5%). Other events occurred at a similar rate to aliskiren/amlodipine. There were no deaths on the triple combination. Serious adverse events in Group B occurred at 1.9% (n=6) versus 0.7-1% of the dual combinations. Of the 6 events, 4 were on the lowest dose triple combination. In Group C, 7 patients (2.6%) had a serious adverse event. Discontinuations due to adverse events were slightly higher on the triple combination (4.2 versus 1.7-3.4%) compared to the dual combinations.

Laboratory assessment showed a small mean decrease in haemoglobin (-1.9 g/L in short term studies) which was less than in the aliskiren/amlodipine group (-2.8 g/L) with little change with long term treatment (0.2 g/L in Group C). There was a small decrease in potassium (-0.217 mmol/L in Group B) with 11% of patients having a potassium < 3.5 mmol/L at any post baseline visit. However, this was less than seen with amlodipine/HCT

(19%). There were small increases in serum uric acid (40.8 µmol/L) and 7% of patients shifted from normal to high values. Similar results were seen in the long term studies. There were no notable findings with respect to BUN and creatinine. Orthostatic hypotension in Group B occurred in 15.3% on the triple combination and 11.8-15.5% on the dual combinations. However in the long term studies it was higher at 16.6% on the triple combination and 8.6% on the dual combination.

Adverse events were higher in the elderly (44.1 versus 34.4%) with higher rates of dizziness (6.8 versus 2.8%). Events related to low blood pressure increased with increasing age. In the small numbers with moderate renal impairment (4.2% in Group B and 5.9% in Group C), there was a higher incidence of hypokalaemia (22.2% and 12.0% in Group B and C, respectively). There have been no postmarketing data with this product but the free combination has revealed the most common adverse events were dyspnoea, dizziness, hypotension and palpitations.

Risk Management Plan

The Office of Product Review accepted the RMP, Version 2.0 for Rasilamlo HCT including the sponsor's response to the evaluation report which was considered acceptable. There were no outstanding matters.

Risk-Benefit Analysis

Delegate Considerations

Efficacy

The clinical dataset included 6 studies of which two directly assessed a triple combination and four studies which assessed a triple combination as a subgroup. Although all these studies used the triple combination as free combinations of tablets/capsules, bioequivalence data has been provided to show they are equivalent to a fixed dose tablet. The studies included patients with mild-severe hypertension and the elderly with systolic hypertension, however excluded patients with secondary hypertension, significant hepatic or renal disease, heart failure, history of myocardial infarction and stroke. Efficacy has been demonstrated for the triple combinations of 300/10/25 mg and 150/5/12.5 mg and there was some data to support the 300/5/25 mg combination however the evidence to support the other combinations is less clear. Given these are intermediate doses and the proposed indication is for substitution only in patients already controlled on these combinations then this is probably acceptable. There are also three other possible combinations using an aliskiren 150 mg base that were not chosen by the sponsor, however the clinical evaluator thought this was acceptable since the higher dose combinations would most likely be required. There were no adequately designed multifactorial studies or add-on therapy studies as would be expected for a second line indication in hypertension treatment, however the sponsor was only applying for a substitution indication.

Safety and RMP

The exposure for the triple combination was acceptable and the product appeared to have a safety profile that was consistent with the respective monotherapies and mostly at rates similar to the dual component formulations. There was a trend to higher adverse event rates and discontinuations due to adverse events with the triple combination and peripheral oedema was the most common although not higher than the aliskiren/amlodipine combination which is currently registered (Rasilamlo). Adverse events related to lowered blood pressure were noted. There were no deaths and serious adverse events were slightly higher on the triple combination. Changes in laboratory values were mostly minor although hypokalaemia was greater in patients with moderate

renal impairment. There were increased rates of adverse events in the elderly. The RMP was found to be acceptable.

Bioavailability and food effect

Bioequivalence was demonstrated for the combinations of 300/10/25 mg and 300/5/25 mg with their components and an acceptable justification was provided for the three other strengths of 150/5/12.5, 300/5/12.5 and 300/10/12.5 mg. An acceptable justification was also provided for using overseas sourced amlodipine and HCT which was previously accepted in other submissions. Food had a significant effect in lowering the exposure to aliskiren and the sponsor proposed to address this with a dosing recommendation that the product be taken without regard to food but that patients should establish a routine pattern for taking the tablets with regard to meals and that high fat meals reduce the absorption of aliskiren substantially. This type of statement has been previously accepted for Rasilez HCT and Rasilamlo. An interaction was seen between the three components which lowered the exposure of the other components however this was similar to previous studies using aliskiren and amlodipine alone and aliskiren and HCT alone and the clinical data provides reassurance in this regard as to the efficacy and safety effects.

List of Questions

The clinical evaluator had a list of questions for the sponsor that have been mostly addressed in the sponsor's response. A population pharmacokinetic analysis was undertaken for drug interactions amongst the component drugs rather than a prospective pharmacokinetic drug-drug interaction study, which showed reductions in exposure for each component drug. Despite these reductions, clinical data were available to provide efficacy and safety effects. Another issue concerned gastrointestinal (GI) toxicity with aliskiren for which a 54 week GI toxicity study using colonoscopy is under evaluation by TGA. The submission lacked discussion on changes in lipids, glucose and LFTs with the triple combination however the sponsor presented information in their response to the clinical evaluation report which showed some increases in glucose on the triple combination. The proposed PI includes a statement in relation to thiazides and glucose tolerance.

Data deficiencies

There were no studies in severe hypertension or isolated systolic hypertension. There were no studies on withdrawal effects or in patients with high cardiovascular risk factors. There are limited data in those over 75 years of age and no data in those with severe renal or hepatic impairment and no clinical outcome studies on cardiovascular morbidity and mortality.

Summary

Overall the submission appears approvable with Rasilamlo HCT having been investigated in a number of studies by the sponsor and an acceptable efficacy profile has been demonstrated for two of the proposed doses. There is a lack of data at the intermediate doses but the sponsor is applying for a substitution indication for patients already on these doses. An acceptable safety profile was also seen that was similar to the monotherapies with no new safety signals although some rates of adverse events were increased. There still remains no cardiovascular morbidity and mortality outcome data with aliskiren but there is a trial underway from the sponsor. Although the submitted data would not be sufficient for a second line hypertension indication, given this is a substitution indication and patients will already be on all three component drugs before being prescribed Rasilamlo HCT, the data appears sufficient.

The Delegate proposed to approve the submission to register Rasilamlo HCT for the indication:

Rasilamlo HCT is only indicated as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of aliskiren, amlodipine and hydrochlorothiazide taken either as three single component formulations or as dual-component formulation with a single-component formulation, all components at the same dose level. Treatment should not be initiated with these fixed dose combinations.

The sponsor should address the following issues in the Pre Advisory Committee on Prescription Medicines (ACPM) response:

1. Please provide a summary of the efficacy data that specifically supports the three intermediate doses of 300/5/12.5, 300/5/25, 300/10/12.5 mg from the submitted data.
2. Clarify exactly why compliance was not recorded for Study SAH2302.

Response from Sponsor

The sponsor accepted the Delegate's recommendation and addressed the issues raised in the Delegate's overview.

Efficacy and safety data for the three intermediate doses

The proposed range of Rasilamlo HCT doses covers 5 out of the 8 possible dose combinations based on approved doses of the monotherapies.

Based on the known dose dependent adverse reaction profile of amlodipine in the dose range 5-10 mg (for example, oedema) and hydrochlorothiazide in the dose range 12.5-25 mg (for example, hypokalaemia) and the relative absence of dose dependent adverse reactions with aliskiren in the range 150-300 mg, it is believed that physicians would first increase aliskiren to a maximal dose before uptitrating the other agents to reach BP control. Accordingly, the doses proposed for registration include the initial dose of 150/5/12.5 mg and then the different combinations of doses based on aliskiren 300 mg.

The Rasilamlo HCT clinical development program evaluated the benefit/risk of the triple combination. Given the high number of doses possible with the triple combination, it was not possible to design a multifactorial study comparing the triple to each respective double combinations at all dose levels. Accordingly, Novartis decided to use a parallel design for the pivotal efficacy and safety trial, Study SAH2302, using the highest dose. Given the high number of doses possible with the triple combination, it was not possible to design a multifactorial study comparing the triple to each respective double combinations at all dose levels. Accordingly, the sponsor decided to use a parallel design for the pivotal efficacy and safety trial, Study SAH2302, using the highest dose.

The rationale for the design of the pivotal Study SAH2302 was based on the fact that if contribution to the efficacy of the triple combination could be robustly demonstrated for each dual therapy at the highest doses, one could assume contribution at the lower doses and that any potential safety issues with the lower doses of the triple combination could be identified from the use of the highest dose. Study SAH2302 provided efficacy data demonstrating the superiority of the maximal dose of the triple combination of aliskiren/amlodipine/HCT 300/10/25 mg over each dual combination in terms of msSBP, msDBP, ABPM and blood pressure control rate. The maximal triple combination dose in Study SAH2302 was well tolerated with a safety profile similar to the respective dual combinations. Adverse events potentially related to low blood pressure occurred at a low incidence and rarely led to discontinuation in patients treated with the triple combination.

Four additional studies in the original Rasilamlo HCT submission provided positive supportive data for the efficacy and safety of the triple combination at intermediate doses of 300/5/25 mg and 300/10/12.5 mg. These studies included patients whose blood pressure was not controlled by aliskiren/HCT double combination (Studies SPP2344, SPP2411 and SPP2360) and patients whose blood pressure was not controlled by aliskiren/amlodipine double combination (Study SPA2301). Additionally, there was one study where a dose of 300/5/12.5 mg was administered to 561 patients for one week before forced titration to a higher dose (Study SAH2301). Since the submission of the submission, 4 additional clinical trials (Studies SPA2307, SPAUS02, SPADE01 and SPHDE01) have been completed that also support the clinical efficacy and safety of the triple combination at the aforementioned intermediate doses. The sponsor provided a summary of these studies.

The sponsor also summarised the additional blood pressure reductions achieved with intermediate triple therapy doses in patients not controlled with dual therapy in the four clinical trials (Studies SPP2344, SPP2411, SPP2360 and SPA2301) included in the original submission. These trials used an optional titration approach driven by the patients' blood pressure target, mimicking real life practice, and consistently demonstrated the benefit in terms of additional blood pressure control of the triple combination in patients not adequately treated with double combination.

Consistent incremental BP reductions were also observed in the 4 trials completed after the original submission (Studies SPAUS02, SPA2307, SPHDE01 and SPADE01). In summary, the contribution of each dual therapy component to the efficacy of the triple combination of aliskiren/amlodipine/HCT was demonstrated using maximal doses in Study SAH2302. The maximal triple therapy dose of 300/10/25 mg was well tolerated in this study. Four clinical studies included in the current submission provide supportive efficacy data for the intermediate doses of 300/5/25 mg and 300/10/12.5 mg. Consistent results have been observed in four additional studies completed subsequent to the submission.

Compliance in Study SAH2302

As noted in the sponsor's response to the clinical evaluation report, investigators and/or study personnel routinely monitored patient compliance with study drug administration at each visit using pill counts and information provided by the patient. This information was recorded in source documentation at each visit but, as per Novartis data collection standards, it was not recorded in the case report forms, nor analysed at the end of the study.

Study SAH2302 was conducted to demonstrate the superior antihypertensive efficacy of the triple combination of aliskiren/amlodipine/HCT compared to the dual combinations of aliskiren/amlodipine, aliskiren/HCT and amlodipine/HCT. In order to reduce investigator and patient bias, a double blind, double dummy study design was required. As a result, the measurement of compliance with respect to the use of the free combination of three medicinal product units versus the fixed combination of one medicinal product unit could not be performed in a controlled fashion in Study SAH2302. To maintain the study blind in Study SAH2302, all patients received the same number of units of study medication daily. All study medication was administered in free combination form, rather than in fixed dose combination form.

Fixed combinations are recognised to provide greater convenience by reducing the number of dosage forms and simplifying treatment and have been demonstrated to significantly improve medication compliance in hypertensive populations versus free

combination.³⁰ This benefit is expected with all fixed dose combinations as reflected in the TGA adopted EU guidance on fixed dose combinations.²⁴ This benefit can therefore also be expected from Rasilamlo HCT even if not investigated specifically in the clinical trials.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy

It was noted the rationale for the triple combination product proposed improvement in patient compliance and achievement of target blood pressure by reducing the number of tablets needed by a patient. Further, all three active ingredients have been evaluated separately and in various combinations, and have previously been approved by the TGA.

The clinical dataset included six studies of which two directly assessed a triple combination. Efficacy was demonstrated for the triple combinations of 300/10/25 mg and 150/5/12.5 mg and there was some data to support the 300/5/25 mg combination; however, the evidence to support the other intermediate dose combinations was less clear. Although not ideal, given the proposed indication is for substitution only in patients already controlled on these combinations it was considered acceptable.

Safety

There were no particular safety signals of concern noted. The product appeared to have a safety profile that was consistent with the respective monotherapies and mostly at rates similar to the dual component formulations. There was a trend to higher adverse event rates and discontinuations due to adverse events with the triple combination and peripheral oedema was the most common. Adverse events related to a lowered blood pressure were noted. Serious adverse events were slightly higher on the triple combination. Hypokalaemia was increased in patients with moderate renal impairment. There were increased rates of adverse events in the elderly.

Food had a significant effect in lowering the exposure to aliskiren compared to the other actives in the combination. The sponsor has proposed to address this with an explanatory statement in the Product Information (PI) which was considered appropriate.

It was noted that there were no studies in severe hypertension, on withdrawal effects or in patients with high cardiovascular risk factors. There are limited data in those over 75 years of age and no data in those with severe renal or hepatic impairment. While surrogate endpoints are acceptable within the EU guidelines adopted by the TGA, the lack of clinical outcome studies on cardiovascular morbidity and mortality was disappointing.

The ACPM also recommended amendments to the Product Information (PI) and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

The ACPM advised that the implementation by the sponsor of the recommendations to the satisfaction of the TGA, in addition to the evidence provided for the aliskiren, amlodipine and hydrochlorothiazide combination would support the safe and effective use of this product.

³⁰ Bangalore S, Kamalakkanna G, Parkar S, et al. Fixed dose combinations improve medication compliance: A Meta-Analysis. *Am Journal Medicine* 2007; 120: 713-19.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Rasilamlo HCT 150/5/12.5, Rasilamlo HCT300/5/12.5, Rasilamlo HCT300/5/25, Rasilamlo HCT 300/10/12.5 and Rrasilamlo HCT300/10/25 tablets containing aliskiren (as hemifumarate)/amlodipine (as besylate)/hydrochlorothiazide 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg and 300/10/25 mg, for the following indication:

Rasilamlo HCT is only indicated as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of aliskiren, amlodipine and hydrochlorothiazide taken either as three single component formulations or as dual-component formulation with single-component formulation, all components at the same dose level. Treatment should not be initiated with these fixed-dose combinations (see "Dosage and Administration").

The following Specific Conditions apply to these therapeutic goods:

1. The full implementation of the Risk Management Plan version 2.0 (dated 5 April 2010) for Rasilamlo HCT including any commitments or amendments pursuant to the response by the sponsor, Novartis Pharmaceuticals Australia Pty Ltd, to the RMP evaluation report of 21 June 2011 and of any future versions of the Risk Management Plan as may be agreed between the sponsor and the Office of Product Review of the TGA.
2. There is presently underway an evaluation of the results of the ALTITUDE study by the Office of Product Review of the TGA. Amendments to the Product Information documents arising from this evaluation must be implemented in the Product Information documents of all aliskiren containing products as will be agreed between the sponsor, Novartis Pharmaceuticals Australia Pty Ltd and the Office of Product Review. Furthermore, all such amendments must be implemented in a harmonized fashion across the full range of aliskiren containing products.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

www.tga.gov.au

Reference/Publication #

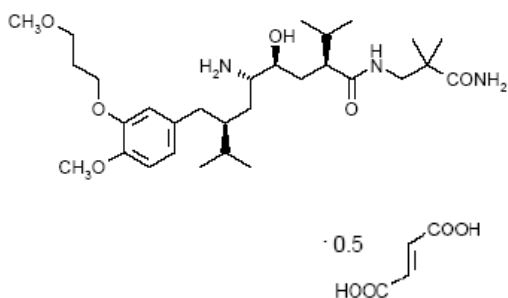
RASILAMLO HCT[®] 150/5/12.5
RASILAMLO HCT[®] 300/5/12.5
RASILAMLO HCT[®] 300/5/25
RASILAMLO HCT[®] 300/10/12.5
RASILAMLO HCT[®] 300/10/25

(aliskiren hemifumarate/amlodipine besylate/hydrochlorothiazide)

NAME OF THE MEDICINE

Active ingredients (INN): aliskiren hemifumarate, amlodipine besylate and hydrochlorothiazide

Structural formula:



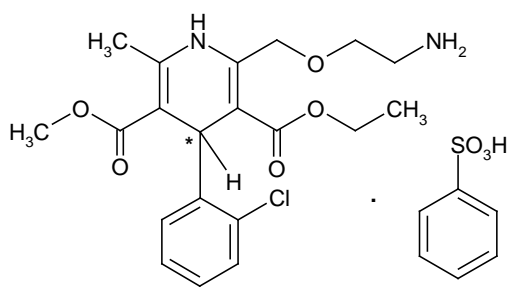
Aliskiren (as hemifumarate)

(2S,4S,5S,7S-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-(4-methoxy-3-(3-methoxypropoxy)phenyl)-octanamide)

CAS: 173334-58-2

Molecular formula: C₃₀H₅₃N₃O₆ · 0.5 C₄H₄O

Molecular weight: 609.8 (551.8 as free base)



and enantiomer

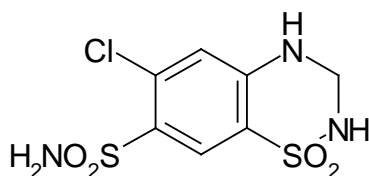
Amlodipine (as the besylate salt)

(3-ethyl 5-methyl (4R)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate)

CAS: 111470-99-6

Molecular formula: C₂₀H₂₅ClN₂O₅ · C₆H₆O₃S

Molecular weight: 567.06 (408.9 as free base)



Hydrochlorothiazide

(6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide)

CAS : 58-93-5

Molecular formula: C₇H₈ClN₃O₄S₂

Molecular weight: 297.72

DESCRIPTION

Aliskiren hemifumarate is a white to slightly yellowish powder. It is freely soluble in water, over a wide range of pH.

Amlodipine besylate is a white or almost white powder that is slightly soluble in water and sparingly soluble in ethanol.

Hydrochlorothiazide is a white or almost white powder, very slightly soluble in water and freely soluble in dimethylsulfoxide.

RASILAMLO HCT 150/5/12.5, RASILAMLO HCT 300/5/12.5, RASILAMLO HCT 300/5/25, RASILAMLO HCT 300/10/12.5 and RASILAMLO HCT 300/10/25 are available as film-coated tablets in five strengths containing aliskiren (150 or 300 mg), amlodipine besylate (5 or 10 mg) and hydrochlorothiazide (12.5 or 25 mg) as: 150/5/12.5 mg, 300/5/12.5 mg, 300/10/12.5 mg, 300/10/12.5 mg and 300/10/25 mg.

Excipients: Cellulose microcrystalline, crospovidone, silica - colloidal anhydrous, magnesium stearate, hypromellose, titanium dioxide, macrogol 4000, purified talc, black and red iron oxide. RASILAMLO HCT 300/5/25 and RASILAMLO HCT 300/10/25 also contain yellow iron oxide.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Renin inhibitor (ATC code C09XA54) combinations with dihydropyridine derivatives (amlodipine) and thiazide diuretics (hydrochlorothiazide).

Aliskiren, amlodipine and hydrochlorothiazide

RASILAMLO HCT combines three antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: aliskiren belongs to the direct renin inhibitor class, amlodipine belongs to the calcium antagonist class, and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. When combined, the consolidated effects of inhibition of the Renin-Angiotensin System (RAS), calcium channel-mediated vasodilatation and sodium chloride excretion result in a reduction of blood pressure to a greater degree than the corresponding dual combination.

A population pharmacokinetic analysis in patients with hypertension did not indicate any clinically relevant changes in the steady-state exposure (AUC) or C_{max} of aliskiren, amlodipine and hydrochlorothiazide compared to the corresponding dual therapies.

Aliskiren

Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the Renin-Angiotensin System at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other agents that inhibit the RAS (Angiotensin Converting Enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases plasma

renin activities (PRA) in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents. Elevated PRA has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients. The clinical implications of the differences in effect on PRA are not known at the present time.

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment (12 months), and was independent of age, gender, body mass index and ethnicity.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the ACEI ramipril, the calcium channel blocker amlodipine, the angiotensin receptor antagonist valsartan, and the beta blocker atenolol. These combinations were efficacious and well tolerated.

In diabetic hypertensive patients, aliskiren as monotherapy was safe and effective. In combination with ramipril, aliskiren provided additive blood pressure reductions compared to the component monotherapies. The antihypertensive effects of aliskiren were independent of age, gender, body mass index and ethnicity.

Beneficial effects of aliskiren on mortality and cardiovascular morbidity and target organ damage are currently unknown.

In a 3-month pilot safety study of 302 patients with a current diagnosis or history of hypertension and mild stable heart failure (ALOFT), all of whom were receiving standard therapy for stable heart failure (ACE inhibitor or ARB, a beta blocker and for a third of patients an aldosterone antagonist), addition of aliskiren 150 mg was well tolerated. B-type natriuretic peptide (BNP) levels were reduced by 25% in the aliskiren arm (n=137) compared to placebo (n=127). The clinical significance of the reduction in BNP levels is however unknown. Over the 3 months period, no statistically significant changes in echocardiographic measures of left atrial or left ventricular size or function nor signs and symptoms of heart failure were detected and the overall grading of patients according to NYHA classification remained unchanged.

Amlodipine

The amlodipine component of RASILAMLO HCT 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. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Amlodipine has demonstrated beneficial clinical effects in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Hydrochlorothiazide

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high affinity receptor in the renal cortex with the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na⁺Cl⁻ symporter which affects mechanisms of electrolyte reabsorption. Inhibition of the Na⁺Cl⁻ symporter directly increases excretion of sodium and chloride in approximately equivalent amounts. It also indirectly reduces plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and decreases in serum potassium.

Pharmacokinetics

Aliskiren

Following oral absorption, peak plasma concentrations of aliskiren are reached after 1 to 3 hours. The absolute bioavailability of aliskiren based on a pharmacokinetic study with capsule formulation is approximately 2.6%, however, this is indicative only as this figure refers to capsule/solution formulations and the precise value for the film coated tablets is unknown. Food reduces the C_{max} and exposure (AUC) but has minimal impact on pharmacodynamics thus can be taken without respect to food. High-fat meal significantly reduced the peak concentration (C_{max}) and total exposure (AUC) of aliskiren by 85% and 71% respectively, and the time to reach C_{max} was delayed by about 1 hour. Steady-state-plasma concentrations are reached within 5 to 7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Aliskiren is evenly distributed systemically after oral administration. Following intravenous administration, mean volume of distribution at steady state is approximately 135 L indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47 to 51%) and independent of the concentration.

The mean elimination half-life is about 40 hours (range 34 to 41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (91%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, the mean plasma clearance is approximately 9 L/h.

Exposure to aliskiren increased more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and C_{max} , respectively. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Amlodipine

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins in hypertensive patients. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.

Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Hydrochlorothiazide

The absorption of hydrochlorothiazide after an oral dose is rapid (T_{max} about 2 hours), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60-80% after oral administration.

The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated administration, and accumulation is minimal when administered once daily.

The distribution and elimination kinetics have generally been described by a bi-exponential decay function, with a terminal half-life of 6-15 hours. Greater than 95% of the absorbed dose is excreted as unchanged compound in the urine.

Aliskiren/amlodipine/hydrochlorothiazide

Following oral administration of a fixed combination tablet of aliskiren, amlodipine and hydrochlorothiazide, peak concentrations were achieved for aliskiren within 1-2 hours, for amlodipine within 8 hours and for hydrochlorothiazide within 2-3 hours. The rate and extent of absorption of aliskiren, amlodipine and hydrochlorothiazide following administration of a fixed combination tablet are similar to when administered as individual dosage forms.

The results from a food effect study using a standard high-fat meal with the 300/10/25 mg fixed combination tablet showed that food reduced the rate and extent of absorption of aliskiren in the fixed combination tablet with a similar magnitude of effect as for aliskiren monotherapy. Food had no effect on the pharmacokinetics of amlodipine or hydrochlorothiazide in the fixed combination tablet.

Pharmacokinetics in children: No pharmacokinetic data are available in the paediatric population.

Pharmacokinetics in the elderly: No adjustment of the initial dose of RASILAMLO HCT is required for elderly patients (see 'DOSAGE AND ADMINISTRATION').

Pharmacokinetics in patients with impaired renal function: No dose adjustment is required for patients with mild to moderate renal impairment. No data are available for RASILAMLO HCT in patients with severe renal impairment (creatinine clearance < 30 mL/min). However, as expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide. Therefore, RASILAMLO HCT is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see 'CONTRAINDICATIONS').

Pharmacokinetics in patients with impaired hepatic function: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60% in AUC. Therefore caution should be exercised when administering RASILAMLO HCT to patients with mild to moderate hepatic impairment.

No data are available on patients with severe hepatic impairment when treated by RASILAMLO HCT. However, because of hydrochlorothiazide, RASILAMLO HCT is contraindicated in patients with severe hepatic impairment (see 'CONTRAINDICATIONS').

CLINICAL TRIALS

RASILAMLO HCT

In hypertensive patients, once-daily administration of RASILAMLO HCT provided clinically meaningful reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The greater blood pressure reduction for RASILAMLO HCT over each dual combination was seen at every hour including the early morning hours with the 24-hour ambulatory blood pressure monitoring.

RASILAMLO HCT was studied in a double-blind, randomized, active-controlled study in 1181 patients of which 773 were classified as moderately hypertensive (msSBP 160-180 mmHg) and 408 as severely hypertensive (msSBP > 180 mmHg) at baseline. A large number of patients were obese (49%) and over 14% of the total population had diabetes.

In this study, RASILAMLO HCT at a dose of 300/10/25 mg produced statistically significant mean blood pressure reductions (systolic/diastolic) from baseline of 37.9/20.6 mmHg compared

to 31.4/18.0 mmHg with aliskiren/amlodipine combination (300/10 mg), 28.0/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 30.8/17.0 mmHg with amlodipine/hydrochlorothiazide (10/25 mg) in patients with moderate to severe hypertension. In patients with severe hypertension (SBP \geq 180 mmHg), the reduction in blood pressure from baseline for RASILAMLO HCT and the dual combinations respectively was 49.5/22.5 mmHg compared to 38.1/17.6 mmHg with aliskiren/amlodipine combination (300/10 mg), 33.2/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 39.9/17.8 mmHg with amlodipine/hydrochlorothiazide (10/25 mg). The effect of RASILAMLO HCT was evident as early as one week after initiation of therapy, with the majority of the antihypertensive effect achieved within two weeks of titration to maximal dose. The blood-pressure-lowering effect in patients with moderate to severe hypertension, was independent of age, gender, race, ethnicity and body mass index.

RASILAMLO HCT was associated with a significant reduction in plasma renin activity (PRA) (34%) from baseline while the dual combination of amlodipine with hydrochlorothiazide increased PRA by 170 %.

In a 28 to 54 week open label safety study in 564 patients with moderate to severe hypertension, RASILAMLO HCT at a dose of 300 /10/25 mg produced mean blood pressure reductions (systolic/diastolic) of 37.3/21.8 mmHg over 28 to 54 weeks of treatment. Efficacy of RASILAMLO HCT was maintained over one year of treatment, with no evidence of loss of effect.

In a randomized, double blind, active controlled, 36-week study in elderly (\geq 65 years of age) hypertensive patients, RASILAMLO HCT at a dose of 300/10/25 mg produced clinically meaningful SBP/DBP reductions of 31.9/14.7 mmHg from baseline in patients whose blood pressure was not controlled (SBP \geq 140 mmHg) with aliskiren/HCTZ dual combination treatment.

Age, gender, and race did not significantly influence the response to RASILAMLO HCT.

No Studies were conducted in severe hypertension or in patients with high cardiovascular risk factors. Withdrawal and rebound effects on efficacy have not been studied.

Patients with severe hepatic and renal impairment, cardiovascular or cerebrovascular disorders, pregnancy or secondary hypertension were excluded from the clinical trials.

There have not been sufficient studies carried out to support the use of this product in the context of add-on or step-up dose titration from the dual combinations (see "DOSAGE AND ADMINISTRATION").

No clinical outcome studies have been conducted on cardiovascular morbidity and mortality with RASILAMLO HCT.

INDICATIONS

RASILAMLO HCT is only indicated as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of aliskiren, amlodipine and hydrochlorothiazide taken either as three single component formulations or as dual-component formulation with a single-component formulation, all

components at the same dose level. Treatment should not be initiated with these fixed-dose combinations (see “DOSAGE AND ADMINISTRATION”).

CONTRAINDICATIONS

- Hypersensitivity to the active substances, dihydropyridine derivatives, other sulfonamide-derived drugs, or to any of the excipients;
- Pregnancy (see ‘Use in Pregnancy’);
- Severe hepatic impairment;
- Severe renal impairment (creatinine clearance <30 mL/min);
- Anuria;
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia;
- History of angioedema with aliskiren;
- Hereditary or idiopathic angioedema;
- Severe hypotension;
- Shock (including cardiogenic shock);
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis);
- Haemodynamically unstable heart failure after acute myocardial infarction;
- Concomitant use of RASILAMLO HCT and Angiotensin Converting Enzyme inhibitors (ACEi) or Angiotensin II Receptor Blockers (ARB) in patients with type 2 diabetes mellitus;
- Concomitant administration with cyclosporine, a highly potent P-gp inhibitor, and other potent P-gp inhibitors such as itraconazole, verapamil and quinidine (see ‘INTERACTIONS WITH OTHER DRUGS’).

PRECAUTIONS

Risk for Renal dysfunction/Serum electrolyte changes: Based on experience with the use of other substances that affect the renin-angiotensin system (RAS), aliskiren may increase potassium, serum creatinine and blood urea nitrogen. Increases in serum potassium may be exacerbated by the concomitant use of other agents acting on the RAAS or use of NSAIDs.

Patients with diabetes mellitus are at an increased risk of hyperkalemia during aliskiren therapy.

Worsening of renal function may occur in patients receiving aliskiren and other RAAS agents or NSAIDs concomitantly, or in those with pre-existing renal disease, diabetes mellitus or with other conditions pre-disposing to renal dysfunction such as hypovolaemia, heart failure or liver disease.

Consistent with standard medical practice, close monitoring of serum electrolytes to detect possible electrolyte (potassium) imbalances is advised at initiation of therapy with RASILMLO HCT and periodic monitoring thereafter.

Thiazide diuretics can precipitate new onset hypokalemia or exacerbate pre-existing hypokalemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis, or ECG alterations), RASILAMLO HCT should be discontinued. Correction of hypokalemia and any coexisting hypomagnesaemia is recommended prior to the initiation of thiazides. Potassium and magnesium serum concentrations should be

checked periodically. All patients receiving thiazide diuretics should be monitored frequently for imbalances in electrolyte particularly potassium.

The renin-aldosterone link is mediated by angiotensin II, so with coadministration of aliskiren the reduction in serum potassium is less pronounced than observed under monotherapy with hydrochlorothiazide (see 'INTERACTIONS WITH OTHER DRUGS, and 'ADVERSE REACTIONS').

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals. Diuretics, including hydrochlorothiazide, can precipitate new onset hyponatraemia and hypochloaemic alkalosis or exacerbate pre-existing hyponatraemia. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been reported in isolated cases. Regular monitoring of serum sodium concentrations is recommended.

Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Warning signs of fluid or electrolyte imbalance are dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with aliskiren may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotrophic hormone (ACTH).

Conversely, due to the aliskiren component of RASILAMLO HCT, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with RASILAMLO HCT, risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Caution is required when co-administering potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes with RASILAMLO HCT.

There is no evidence that RASILAMLO HCT would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Sodium and/or volume depleted patients: In patients with marked volume- and/or salt-depletion (e.g. those receiving high doses of diuretics) symptomatic hypotension could occur after initiation of treatment with RASILAMLO Tradename HCT. This condition should be corrected prior to administration of RASILAMLO HCT, or the treatment should start under close medical supervision.

In patients with uncomplicated hypertension treated with RASILAMLO HCT in short-term controlled trials, the incidence of hypotension was low (0.3%).

Hypotension: As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke. If an excessive fall in blood pressure occurs with RASILAMLO HCT, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once pressure has stabilised.

Angioedema: As with other agents acting on the renin-angiotensin system, angioedema has been reported rarely in patients treated with aliskiren. If angioedema occurs, RASILAMLO HCT should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to ensure a patent airway should be provided.

Acute Angle-Closure Glaucoma: Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to week of a drug initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulfonamide or penicillin allergy.

Non-steroidal anti-inflammatory drugs (NSAIDs including Cox-2 selective inhibitors): As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren with an NSAID requires caution, especially in elderly patients (see 'INTERACTIONS WITH OTHER DRUGS').

Patients with pre-existing renal impairment: When RASILAMLO HCT is used in patients with impaired renal function, periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. There is no experience regarding the administration of RASILAMLO HCT in patients who have recently undergone kidney transplantation. No dosage adjustment is necessary in patients with renal impairment whose GFR is ≥ 30 ml/min/1.73 m². However, in patients with mild to moderate renal impairment (≥ 30 ml/min/1.73 m² but < 60 ml/min/1.73 m²), RASILAMLO HCT should be administered with caution.

As for other agents acting on the renin-angiotensin system, caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (eg. Due to blood loss, severe prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease or kidney disease. Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

A *post-hoc* analysis of clinical trial data has shown that the incidence of an increased blood creatinine to above a pre-defined threshold of 176.8 μ mol/L was higher in patients taking aliskiren with pre-existing reduced eGFR (eGFR < 60 mL/min/1.732) compared to patients taking

aliskiren with normal eGFR and also in patients taking aliskiren with a history of renal disease compared to patients taking aliskiren without a history of renal disease.

Hyperkalaemia: Patients receiving other medicinal products that inhibit the rennin angiotensin-system (RAS), and/or those with reduced kidney function and/or diabetes mellitus are at an increased risk of hyperkalaemia during aliskiren therapy.

Increases in serum potassium >5.5 meq/L were infrequent with Rasilez alone (0.9% compared to 0.6% with placebo). However, when used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). Routine monitoring of electrolytes and renal function is indicated in this population. Concomitant use of Rasilez with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium. If concomitant use is considered necessary, caution should be exercised.

Patients with renal artery stenosis: No data are available on the use of RASILAMLO Tradename HCT in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. However, as with other agents acting on the renin-angiotensin system, there is an increased risk of renal insufficiency, including renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Patients with hepatic impairment: Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Amlodipine is extensively metabolised by the liver and the plasma elimination half life is 56 hours in patient with impaired hepatic function. Worsening of the liver function test may occur. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%. Therefore caution should be exercised when administering RASILAMLO HCT to patients with hepatic impairment and careful monitoring should be performed.

No adjustment of the initial dose is required for patient with mild to moderate hepatic impairment. RASILAMLO HCT is contraindicated in patients with severe hepatic impairment (see 'CONTRAINDICATIONS')

Systemic lupus erythematosus: Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances: Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may occur during thiazide therapy. To date, no data are available from clinical studies that were specifically-designed to evaluate the safety of RASILAMLO HCT in diabetic patients.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Like other diuretics, hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Thiazides decrease urinary calcium excretion and may cause mild elevation of serum calcium in the absence of known disorders of calcium metabolism. Since hydrochlorothiazide can increase serum calcium concentrations, it should be used with caution in patients with hypercalcemia. Marked hypercalcemia unresponsive to thiazide withdrawal or ≥ 12 mg/dL may be evidence of an underlying thiazide independent hypercalcemic process.

Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic clarification is necessary.

Use in patients with heart failure/Post-myocardial infarction: RASILAMLO HCT should be used with caution in patients with heart failure due to limited clinical efficacy and safety data. Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV). In general, calcium channel blockers should be used with caution in patients with heart failure. As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death.

Care should be taken to differentiate peripheral oedema from the effects of increasing left ventricular dysfunction.

Patients with acute myocardial infarction: Worsening of angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

Children and adolescents: The safety and efficacy of RASILAMLO HCT in children and adolescents (below the age of 18 years) have not been established.

General: In the event of severe and persistent diarrhoea, RASILAMLO HCT therapy should be stopped.

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur, but are more likely in patients with a prior history allergy or bronchial asthma such a history.

Food intake: Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially.

Effects on ability to drive and use machines: As with other antihypertensive agents, it is advisable to exercise caution when driving or operating machinery.

Carcinogenicity

No carcinogenicity studies have been conducted with the aliskiren, amlodipine, hydrochlorothiazide combination. However, aliskiren, amlodipine and hydrochlorothiazide have been tested individually for carcinogenicity with generally negative results.

Aliskiren: The carcinogenic potential of aliskiren was assessed in a 2-year rat study and a 6-month transgenic mouse study. There was no significant increase in the incidence of neoplastic lesions in mice given up to 1500 mg/kg/day PO (ER <1 based on AUC). Inflammatory and proliferative changes were observed in the lower gastro-intestinal tract at dietary doses of 750 or 1500 mg/kg/day in both mice and rats (ER <1 and 3 based on AUC, respectively). One colonic adenoma and one caecal adenocarcinoma were found in two separate rats at the dietary dose of 1500 mg/kg/day (ER 3 based on AUC). These tumour incidences were not statistically significant versus untreated controls. The results from a subsequent 104-week oral toxicity study in marmoset monkeys showed the absence of any treatment-related histopathological changes in the gastro-intestinal tract at oral doses of 10 and 20 mg/kg/day (up to 5 times greater than clinical exposure to unbound aliskiren at the maximum recommended daily dose, based on AUC). Overall, the data suggests that these tumour incidences may not be clinically relevant.

Amlodipine: The carcinogenic potential of amlodipine has not been fully elucidated. Amlodipine did not induce any tumours when tested in rats at oral doses up to 2.5 mg/kg. This dose gave rise to plasma levels that are similar to those achieved clinically.

Hydrochlorothiazide: Two-year feeding studies in mice and rats showed no evidence of carcinogenic potential in female mice at doses up to approximately 600 mg/kg/day, or in male and female rats at doses up to approximately 100 mg/kg/day. However, there was equivocal evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide alone at approximately 600 mg/kg/day.

Genotoxicity

No genotoxicity studies have been conducted with the aliskiren, amlodipine and hydrochlorothiazide combination. The combination of aliskiren and amlodipine was negative in *in vivo* assays of bacterial reverse mutation and chromosomal damage. Aliskiren, amlodipine and hydrochlorothiazide have been tested individually for genotoxicity with generally negative results.

Aliskiren: Aliskiren was negative in a series of assays for gene mutation, chromosomal damage and DNA damage.

Amlodipine: Amlodipine did not induce gene mutation in bacteria or mouse lymphoma cells, and was not clastogenic in human lymphocytes, Chinese hamster V79 fibroblast cells (*in vitro*), or mouse bone marrow cells (*in vivo*).

Hydrochlorothiazide: Hydrochlorothiazide did not induce gene mutation in bacteria or chromosome damage in mammalian cells in several *in vitro* and *in vivo* assays. However, positive results were obtained in a mammalian cell assay for gene mutation (mouse lymphoma cell assay) and in two other tests (sister chromatid exchange assay in Chinese hamster ovary cells and nondisjunction assay in *Aspergillus nidulans*).

Effects on fertility

No specific fertility studies were conducted with the aliskiren/amlodipine/hydrochlorothiazide combination;

Aliskiren: Aliskiren did not affect fertility or general reproductive performance when given to rats at oral doses up to 226 mg/kg/day (ER 1 based on AUC).

Amlodipine: There was no effect on fertility of rats treated with amlodipine at oral doses up to 18 mg/kg/day.

Hydrochlorothiazide: The effects of hydrochlorothiazide on fertility have not been investigated.

Use in Pregnancy (Category D)

There is no clinical experience with the use of RASILAMLO HCT in pregnant women Use in pregnancy is contraindicated.

Aliskiren: Aliskiren should not be used during pregnancy or in women planning to become pregnant. Physicians prescribing any agents acting on the RAAS (renin-angiotensin-aldosterone system) should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, RASILAMLO HCT should be discontinued as soon as possible.

Drugs that act on the RAAS can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors (a specific class of drugs acting on the RAAS). The use of drugs that act directly on the RAAS during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydraminos has been reported, presumably resulting from decreased fetal renal function. Oligohydraminos in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug, In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects.

Infants with histories of in utero exposure to renin inhibitor should be closely observed for hypotension, oliguria and hyperkalemia.

Aliskiren was not teratogenic when administered at maternotoxic oral doses of 543 mg/kg/day to rats or 90 mg/kg/day to rabbits. An embryofetal NOAEL was established in rats with an oral dose of 270 mg/kg/day and in rabbits with 90 mg/kg/day, equivalent to <1. and 4- fold the MRHD based on AUC, respectively. Post-natal development in rats was unaffected by oral doses up to 181 mg/kg/day (ER <1. based on AUC).

Amlodipine: The safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine had no teratogenic effects in rats (18 mg/kg) or rabbits (10 mg/kg). Amlodipine (7 mg/kg) administered orally to rats at or near parturition induced a prolongation of gestation time, increase in the number of stillbirths and a decreased postnatal survival. Calcium channel blockers carry the potential to produce foetal hypoxia associated with maternal hypotension. Accordingly they should not be used in pregnant women unless the potential benefit outweighs the risk to the foetus.

Hydrochlorothiazide: Intrauterine exposure to thiazide diuretics is associated with fetal or neonatal thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.

Use in Lactation

It is not known whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats. The safety of amlodipine in human lactation has not been established. Hydrochlorothiazide crosses the placenta and is excreted in human milk. It is therefore not advisable for women who are breast-feeding to use RASILAMLO HCT.

INTERACTIONS WITH OTHER DRUGS

It is important to take into account that RASILAMLO HCT may increase the antihypertensive effect of other antihypertensive agents (e.g. alpha blockers, other diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia).

Concomitant use not recommended

RASILAMLO HCT individual component	Known interactions with the following agents	Effect of the interaction with other medicinal products
Aliskiren	<i>Potent Pgp inhibitors (cyclosporine and itraconazole)</i>	A single dose drug interaction study in healthy subjects has shown that cyclosporine (200 mg and 600 mg) increases C_{max} of aliskiren 75 mg by approximately 2.5 fold and the AUC by approximately 5 fold. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5 fold and 5.8 fold, respectively. Therefore, the concomitant use of these drugs is not recommended (see 'CONTRAINDICATIONS').
Aliskiren and HCT	<i>Lithium</i> <i>Non-steroidal anti-inflammatory drugs and Cox-2 selective inhibitors</i>	Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazides. Despite the lack of experience with concomitant use of aliskiren and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs with agents acting on the renin-angiotensin system may result in deterioration of renal function, including possible acute renal failure, which is usually reversible. The antihypertensive effect of agents acting on the renin-angiotensin system, including aliskiren, may be attenuated by NSAIDs. Concomitant administration of NSAIDs (e.g. salicylic acid derivatives, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of RASILAMLO HCT. Concurrent

hypovolemia may induce acute renal failure. (see “PRECAUTIONS”)

Caution required with concomitant use

RASILAMLO HCT individual component	Known interactions with the following agents	Effect of the interaction with other medicinal products
Aliskiren	<p><i>Moderate Pgp inhibitors (ketoconazole, verapamil)</i></p> <p><i>Frusemide</i></p>	<p>Co-administration of ketoconazole (200 mg) with aliskiren (300 mg) resulted in a 80% increase in plasma levels of aliskiren (AUC and C_{max}). Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Co-administration of a single oral dose of 300 mg aliskiren with 240 mg verapamil increased AUC and C_{max} of aliskiren by ~2-fold. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. As a result no dose adjustment for aliskiren is necessary. Yet P-gp inhibitors are expected to increase tissue concentrations more than plasma concentrations. Therefore caution should be exercised when aliskiren is administered with ketoconazole or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone)</p> <hr/> <p>When aliskiren was co-administered with frusemide, the AUC and C_{max} of frusemide were reduced by 28% and 49% respectively. It is therefore recommended that the effects be monitored when initiating and adjusting frusemide therapy to avoid possible under-dosing.</p>

	<i>Potassium and potassium sparing diuretics</i>	Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of aliskiren with the following medicines may lead to increases in serum potassium: Potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium. If co-medication is considered necessary, caution is advisable (see 'PRECAUTIONS')
Amlodipine	<i>CYP3A4 inhibitors (diltiazem, ketoconazole, itraconazole, ritonavir)</i>	A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50% and the effect of amlodipine is increased). The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded. Caution should therefore be exercised when co-administering amlodipine with CYP3A4 inhibitors.
	<i>CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum).</i>	Co-administration may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal. In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin (glyceryl trinitrate), digoxin, warfarin, atorvastatin, aluminium/magnesium antacid, cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, ethanol and oral hypoglycaemic drugs.
	<i>Simvastatin</i>	Co-administration of multiple doses of 10 mg of amlodipine with 80mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.
HCT	<i>Alcohol, anesthetics and sedatives</i>	Concomitant administration with alcohol, barbiturates or narcotics may potentiate orthostatic hypotension.
	<i>Amantadine</i>	Thiazides, including hydrochlorothiazide may increase the risk of adverse reactions caused by Amantadine.

<i>Anticholinergic agents (e.g. atropine, biperiden)</i>	The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, prokinetic drug such as cisapride may decrease the bioavailability of thiazide diuretics.
<i>Antidiabetic agents (e.g. insulin and oral antidiabetic agents) - Metformin</i>	Thiazide diuretics, including hydrochlorothiazide, may increase blood glucose. It may be necessary to readjust the dosage of insulin and of oral antidiabetic agents (see “PRECAUTIONS”) Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.
<i>Beta blockers and diazoxide</i>	Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide may enhance the hyperglycaemic effect of diazoxide.
<i>Carbamazepine</i>	Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatremia. Such patients should therefore be advised about the possibility of hyponatremic reactions, and should be monitored accordingly.
<i>Cholestyramine and colestipol resins (ion exchange resins)</i>	Single doses of cholestyramine or colestipol resins reduced the absorption of hydrochlorothiazide by up to 85 and 43 percent respectively. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimize the interaction.
<i>Corticosteroids, ACTH</i>	Electrolyte depletion, particularly hypokalaemia, may be increased.
<i>Cyclosporin</i>	Concomitant treatment with cyclosporin may increase the risk of hyperuricemia and gout-type complications.
<i>Cytotoxic agents (e.g. cyclophosphamide, methotrexate)</i>	Co-administration of thiazide diuretics, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

<i>Digitalis glycosides</i>	Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects, favouring the onset of digitalis-induced cardiac arrhythmias (see “PRECAUTIONS”).
<i>Iodine contrasting agents</i>	In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be re-hydrated before the administration.
<i>Medicinal product affecting serum potassium level (kaliuretic diuretics, amphotericin, carbenoxolone, penicillin G, salicylic acid derivative)</i>	The hypokalemic effect of diuretics may be increased by concomitant administration of kaliuretic diuretics, amphotericin, carbenoxolone, penicillin G, and salicylic acid derivatives or antiarrhythmics. If these medicinal products are to be prescribed with hydrochlorothiazide, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see “PRECAUTIONS, Serum electrolyte changes”).
<i>Medicinal product affecting serum sodium level</i>	The hyponatraemic effect of diuretics may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc. Caution is advised in long-term administration of these drugs (see “PRECAUTIONS”).
<i>Medicinal products used in the treatments for gout (probenecid, sulfipyrazone and allopurinol)</i>	Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol. Thiazides may also increase serum uric acid levels, and the dose of uricosuric agents such as probenecid or sulfipyrazone may need to be increased.
<i>Methyldopa</i>	There have been reports in the literature of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.
<i>Non-depolarising skeletal muscle relaxants (e.g. tubocurarine)</i>	Thiazides, including hydrochlorothiazide, potentiate the action of non-depolarising muscle relaxants (e.g. curare derivatives).
<i>Other diuretics and antihypertensive agents</i>	The antihypertensive effect may be increased with concomitant use of other antihypertensive drugs. Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g.

guanethidine, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, Angiotensin Receptor Blockers (ARBs) and Direct Renin Inhibitors (DRIs).

The thiazide component of RASILAMLO HCT may enhance the hyperglycaemic effect of beta-blockers and diazoxide.

<i>Pressor amines(e.g. noradrenalin, adrenaline)</i>	The effect of pressor amines may be decreased but the clinical significance of this effect is not sufficient to preclude their use.
<i>Tetracyclines</i>	Concomitant administration of tetracyclines and thiazide diuretics increases the risk for tetracycline induced increase in urea. This interaction is probably not applicable to doxycycline.
<i>Vitamin D and Calcium salts</i>	Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics may lead to hypercalcaemia by increasing tubular calcium reabsorption.

No interactions

RASILAMLO HCT individual component	Known interactions with the following agents	Effect of the interaction with other medicinal products
Aliskiren	<i>acenocoumarol, atenolol, celecoxib, fenofibrate, pioglitazone, allopurinol, isosorbide-5-mononitrate, irbesartan, digoxin, ramipril, valsartan, metformin, amlodipine, atorvastatin, cimetidine and hydrochlorothiazide</i>	Aliskiren has a low potential for interactions with other medicinal products. Compounds that have been investigated in aliskiren clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, fenofibrate, pioglitazone, allopurinol, isosorbide-5-mononitrate, irbesartan, digoxin, ramipril, valsartan, metformin, amlodipine, atorvastatin, cimetidine and hydrochlorothiazide and no clinically relevant interactions have been identified. As a result no dose adjustment for aliskiren or these co-administered medications is necessary

	<i>CYP 450 interactions (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and CYP3A)</i>	Aliskiren does not inhibit the CYP450 isoenzymes. Aliskiren does not induce CYP3A4. Aliskiren is metabolised minimally by the cytochrome P450 enzymes. Therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce, or are metabolised by these enzymes.
	<i>Pgp substrates or weak Pgp inhibitors (atenolol, digoxin, amlodipine, and cimetidine)</i>	No relevant interactions with atenolol, digoxin, amlodipine, and cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C _{max} increased by 50%.
Amlodipine	<i>Grapefruit juice</i>	Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers. In a study in 20 healthy volunteers, co administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg had no significant effect on the pharmacokinetics of amlodipine.
	<i>Sildenafil</i>	A single 100 mg dose of sildenafil in 16 patients with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.
	<i>Other drugs</i>	In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, Maalox [®] (Aluminium hydroxide gel, Magnesium hydroxide and Simeticone), cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

ADVERSE EFFECTS

RASILAMLO HCT

RASILAMLO HCT has been administered to more than 1155 patients in completed clinical trials including 182 patients for one year or more. Treatment with RASILAMLO HCT was well tolerated at doses up to 300 mg/10 mg/25 mg with an overall incidence of adverse events similar

to the corresponding dual combinations. The incidence of adverse events did not show any association with gender, age, body mass index, race or ethnicity. Adverse events have generally been mild and transient in nature. Discontinuation of therapy due to a clinical adverse event occurred in 3.6 % of patients treated with RASILAMLO HCT versus 2.4% in aliskiren/amlodipine, 0.7% in aliskiren/hydrochlorothiazide and 2.7% in amlodipine/hydrochlorothiazide.

Table 1 Number (%) of patients with most frequent AEs (at least 2% for any group) by preferred term (safety set)

Preferred term	All Ali/Aml N=287 n (%)	All Ali/HCTZ N=297 n (%)	All Aml/HCTZ N=295 n (%)	All Ali/Aml/HCTZ N=309 n (%)
General disorders and administration site conditions				
Oedema peripheral	23 (8.0)	6 (2.0)	12 (4.1)	22 (7.1)
Fatigue	1 (0.3)	6 (2.0)	4 (1.4)	6 (1.9)
Nervous system disorders				
Dizziness	7 (2.4)	10 (3.4)	5 (1.7)	11 (3.6)
Headache	9 (3.1)	12 (4.0)	15 (5.1)	11 (3.6)
Infections and infestations				
Nasopharyngitis	2 (0.7)	6 (2.0)	10 (3.4)	8 (2.6)
Respiratory, thoracic and mediastinal disorders				
Cough	4 (1.4)	0	6 (2.0)	1 (0.3)

There were no new adverse reactions which occurred specifically with RASILAMLO HCT in addition to those known to be associated with the individual monotherapies.

Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine. The incidence of edema for RASILAMLO HCT in a short-term double active-controlled study was 7.1% compared to 8.0% for aliskiren/amlodipine, 4.1% for amlodipine/hydrochlorothiazide and 2.0% for aliskiren/hydrochlorothiazide dual combinations.

Adverse reactions previously reported with one of the individual components may occur with RASILAMLO HCT even if not observed in clinical trials.

In long term treatment, increased rates of adverse events (e.g. dizziness and hypotension) were observed in the elderly compared to younger patients.

In a short term trial, the percentages of patients who had a >50% increase in glucose were as follows: RASILAMLO HCT (5.0%), amlodipine/HCTZ (4.8%), aliskiren/HCTZ (1.4%), and aliskiren/amlodipine (1.8%). In long-term trials, the incidence was 3.1% with RASILAMLO HCT and no patients with aliskiren/amlodipine.

Aliskiren

The following table of adverse events is based on five placebo-controlled studies involving a total of 5664 patients (Study Protocols 1201, 2201, 2203, 2204 and 2308). Of the 2316 patients receiving aliskiren monotherapy, 1542 received one of the marketed doses. All adverse events showing an incidence of 1% or more in the aliskiren group are included in the following table, irrespective of their causal association with the study drug.

	Placebo N=781 n(%)	Aliskiren 150 mg N=774 n(%)	Aliskiren 300 mg N=768 n(%)
Headache	68 (8.7)	42 (5.4)	44 (5.7)
Nasopharyngitis	45 (5.8)	33 (4.3)	29 (3.8)
Diarrhoea	9 (1.2)	9 (1.2)	18 (2.3)
Dizziness	17 (2.2)	9 (1.2)	19 (2.5)
Fatigue	12 (1.5)	5 (0.6)	13 (1.7)
Upper respiratory tract infection	12 (1.5)	7 (0.9)	13 (1.7)
Back pain	11 (1.4)	12 (1.6)	7 (0.9)
Cough	5 (0.6)	11 (1.4)	7 (0.9)
Bronchitis	3 (0.4)	6 (0.8)	9 (1.2)
Nausea	11 (1.4)	3 (0.4)	12 (1.6)
Influenza	5 (0.6)	9 (1.2)	5 (0.7)

The adverse drug reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10000$, $< 1/1000$); very rare ($< 1/10000$), including isolated report. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Gastrointestinal disorders

Common: Diarrhoea

Skin and subcutaneous tissue disorders

Uncommon: Rash

Rare: Angioedema

Immune system disorders

Rare: Hypersensitivity

Cardiovascular:

Uncommon: Peripheral oedema,

Treatment with aliskiren was well tolerated with an overall incidence of adverse experiences similar to placebo up to 300 mg. Adverse events have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction is diarrhoea. Other adverse drug reactions that occurred during treatment with aliskiren include rash and angioedema. In controlled clinical trials, angioedema occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or hydrochlorothiazide. In the event of any signs suggesting an allergic reaction (in particular difficulties in breathing, or swallowing, or swelling of the face, extremities, eyes, lips and/or tongue) patients should discontinue treatment and contact the physician. The incidence of cough was similar in placebo (0.6%) and aliskiren treated (0.9%) patients.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/L and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other agents

acting on the renin-angiotensin system, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers. These decreases led to slight increases in rates of anaemia with aliskiren compared to placebo (0.1% for any aliskiren use vs 0% for placebo).

Serum potassium: Increases in serum potassium were minor and infrequent in patients with essential hypertension treated with aliskiren alone (0.9% compared to 0.6% with placebo). However, in one study where aliskiren was used in combination with an angiotensin converting enzyme inhibitor (ACEI) in a diabetic population increases in serum potassium were more frequent (5.5%) (See 'CONTRAINDICATIONS'). Close monitoring of electrolytes and renal function is indicated when using aliskiren.

Other Laboratory findings: In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of Rasilez. In clinical studies in hypertensive patients, Rasilez had no clinically important effects on total cholesterol, fasting glucose or uric acid, however, minor (<1%) decreases in HDL and increases in triglycerides that were not dose related were noted.

Blood Urea Nitrogen, Creatinine: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 7% of patients with essential hypertension treated with Rasilez alone vs. 6% on placebo.

Serum Uric Acid: Aliskiren monotherapy produced small median increases in serum uric acid levels (about 6 µmol/L) while HCTZ produced larger increases (about 30 µmol/L). The combination of aliskiren with HCTZ appears to be additive (about a 40 µmol/L increase). The increases in uric acid appear to lead to slight increases in uric acid-related AEs: elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Creatine Kinase: Increases in creatine kinase of >300% were recorded in about 1% of aliskiren monotherapy patients vs. 0.5% of placebo patients. Five cases of creatine kinase rises, three leading to discontinuation and one diagnosed as subclinical rhabdomyolysis and another as myositis, were reported as adverse events with aliskiren use in the clinical trials. No cases were associated with renal dysfunction.

No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with aliskiren.

Post-Marketing Experience

Metabolic and Nutritional

Unknown frequency: Blood creatinine increased

Immune system

Unknown frequency: Hypersensitivity
Angiodema requiring airway management and
Hospitalisation

Skin and subcutaneous tissue disorders

Very Rare: Rash, severe cutaneous adverse reactions including Stevens-Johnson syndrome* and toxic epidermal necrolysis

Investigations

Common: Hyperkalaemia

Renal and urinary disorders

Uncommon: Renal impairment

Rare: Renal failure

Nervous system disorder

Common: Dizziness

Vascular disorders

Uncommon: Hypotension

Very rare: Necrotising vasculitis*

Cardiovascular:

Unknown frequency Peripheral oedema

Other:

Unknown frequency Blood creatinine increased

*Causality was unclear in these adverse events which occurred very rarely, were poorly documented or were confounded.

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk.

Amlodipine

Other additional adverse events reported with amlodipine monotherapy, irrespective of their causal association with the study drug, were as follows:

Blood and Lymphatic System Disorders: leukopenia, thrombocytopenia

Cardiac Disorders and Vascular Disorders: arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), vasculitis, hypotension, palpitations, myocardial infarction, flushing

Central and Peripheral Nervous System: neuropathy peripheral, tremor, dizziness, dysgeusia, headache, paraesthesia, somnolence, syncope, hypoesthesia, paresthesia, hypertonia

Gastrointestinal & Hepatobiliary: gastritis, gingival hyperplasia, pancreatitis, altered bowel habit, hepatic enzyme elevation, hepatitis, jaundice, dyspepsia, nausea/vomiting, abdominal pain upper, diarrhea, dry mouth

General: malaise, weight increased, weight decreased, asthenia, pain, non-cardiac chest pain, fatigue, oedema

Immune System Disorders: hypersensitivity

Infections and Infestations: rhinitis

Musculoskeletal System: arthralgia, myalgia, muscle spasm, back pain

Psychiatric: mood changes, insomnia

Respiratory System: dyspnea, cough

Skin and Appendages: alopecia, angioedema, rash, erythema multiforme, purpura, skin discoloration, urticaria, hyperhidrosis, pruritus, photosensitivity, Stevens-Johnson syndrome

Special Senses: tinnitus, visual disturbance, diplopia

Urinary System: increased urinary frequency, nocturia, micturition disorder, pollakiuria

Metabolic and Nutritional: hyperglycemia

Reproductive System: impotence, gynecomastia

Hydrochlorothiazide

Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in RASILAMLO HCT. The following additional adverse experiences have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Metabolism and Nutrition Disorders: Mainly at higher doses, hypokalemia, blood lipids increased hyponatraemia, hypomagnesaemia, hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state, hypochloremic alkalosis.

Cardiac Disorders and Vascular Disorders: orthostatic hypotension (common) which may be aggravated by alcohol, anaesthetics or sedatives; arrhythmia (rare); vasculitis necrotizing (very rare)

Central and Peripheral Nervous System: headache, dizziness, paresthesia (rare)

Gastrointestinal & Hepatobiliary: mild nausea and vomiting (common); abdominal discomfort, constipation, diarrhea, cholestasis or jaundice (rare); pancreatitis (very rare)

Blood and Lymphatic System Disorders: thrombocytopenia, sometimes with purpura (rare); leukopenia, agranulocytosis, bone marrow failure, hemolytic anaemia (very rare)

Immune System Disorders: hypersensitivity reactions (very rare)

Psychiatric: depression, sleep disorders (rare)

Respiratory System: respiratory distress including pneumonitis and pulmonary edema (very rare)

Skin and Subcutaneous Disorders: Urticaria and other forms of rash (common); photosensitivity reaction (rare); toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus (very rare)

Special Senses: visual impairment (rare)

Metabolic and Nutritional: decreased appetite (common)

Reproductive System: impotence (common)

Adverse drug reactions from post marketing experiences:

The following adverse drug reactions have been identified based on the post-marketing experiences. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequencies. Therefore the frequency assigned is "not known".

Frequency "not known": Acute renal failure, renal disorder, aplastic anemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma.

DOSAGE AND ADMINISTRATION

RASILAMLO HCT is only indicated as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of aliskiren, amlodipine and hydrochlorothiazide taken either as three single component formulations or as dual-component formulation with a single-component formulation, all components at the same dose level.

Therefore, if blood pressure is not controlled on one of the three possible dual combination therapies, then any third monotherapy must be first added as an individual therapy until dose titration is complete and BP control established before the triple fixed-dose combination may be introduced.

Similarly, there can be no direct dose-titration within the RASILAMLO HCT product range. If a patient's blood pressure is uncontrolled at one of the lower dosage of the combination, dose titration must be carried out with the separately administered components.

Renal impairment: No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see 'PRECAUTIONS - Impaired renal function' and 'PHARMACOLOGY – Pharmacokinetics'). Due to the hydrochlorothiazide component, RASILAMLO HCT is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see 'CONTRAINDICATIONS').

Hepatic impairment: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%. Due to the amlodipine component, caution should be exercised when administering RASILAMLO HCT to patients with mild to moderate hepatic impairment. A lower dose of amlodipine may be required. Due to the hydrochlorothiazide component, RASILAMLO HCT is contraindicated in patients with severe hepatic impairment (see 'CONTRAINDICATIONS').

Use in elderly patients (over 65 years): No initial dosage adjustment is required for elderly patients. A lower dose of amlodipine may be recommended in small, frail and elderly patients.

Use in children and adolescents: The safety and efficacy of RASILAMLO HCT has not been established in children and adolescents (below 18 years of age) and therefore RASILAMLO HCT is not recommended in this population.

Administration: The recommended dose is one tablet per day. RASILAMLO HCT can be taken with or without food. Patients should establish a routine pattern for taking RASILAMLO HCT with regard to meals. Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially. It is recommended to take RASILAMLO HCT with some water.

OVERDOSAGE

Symptoms: There is no experience of overdose with RASILAMLO HCT. The most likely manifestation of overdose would be hypotension related to the antihypertensive effect of the combination of aliskiren, amlodipine and hydrochlorothiazide.

Overdosage with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

Treatment: If symptomatic hypotension should occur, supportive treatment should be initiated. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Amlodipine and aliskiren are unlikely to be removed by haemodialysis whereas clearance of hydrochlorothiazide will be achieved by dialysis.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Presentations:

RASILAMLO HCT 150/5/12.5 (150mg aliskiren, 5mg amlodipine and 12.5mg hydrochlorothiazide): violet white, ovaloid convex shaped, film-coated tablets with a bevelled edge with debossing “YIY” on one side and “NVR” on the reverse side of the tablet. Blister packs of 7 and 28.

RASILAMLO HCT 300/5/12.5 (150mg aliskiren, 5mg amlodipine and 12.5mg hydrochlorothiazide): light pink, ovaloid convex shaped, film-coated tablets with a bevelled edge with debossing “LIL” on one side and “NVR” on the reverse side of the tablet. Blister packs of 7 and 28.

RASILAMLO HCT 300/5/25 (300mg aliskiren, 5mg amlodipine and 25mg hydrochlorothiazide): pale orange brown, ovaloid convex shaped, film-coated tablets with a bevelled edge with debossing “OIO” on one side and “NVR” on the reverse side of the tablet. Blister packs of 7 and 28.

RASILAMLO HCT 300/10/12.5 (300mg aliskiren, 10mg amlodipine and 12.5mg hydrochlorothiazide): light red, ovaloid convex shaped, film-coated tablets with a bevelled edge with debossing “UIU” on one side and “NVR” on the reverse side of the tablet. Blister packs of 7 and 28.

RASILAMLO HCT 300/10/25 (300mg aliskiren, 10mg amlodipine and 25mg hydrochlorothiazide): brown, ovaloid convex shaped, film-coated tablets with a bevelled edge with debossing “VIV” on one side and “NVR” on the reverse side of the tablet. Blister packs of 7 and 28.

Not all pack sizes may be marketed.

Storage conditions:

Store below 30 degrees Celsius. Protect from moisture. Additional storage condition for RASILAMLO HCT 150/5/12.5: Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

North Ryde NSW 2113

® = Registered Trademark

POISON SCHEDULE OF THE MEDICINE

RASILAMLO HCT is a Schedule 4 medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

Approved by the Therapeutic Goods Administration: 16 March 2012

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