European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

Rasilez HCT

International Nonproprietary Name: aliskiren hemifumarate / hydrochlorothiazide

Procedure No. EMEA/H/C/000964

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Novartis Europharm Ltd. submitted on 6 December 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Rasilez HCT, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the CHMP on 21 June 2007.

The legal basis for this application refers to:
Article 10(b) of Directive 2001/83/EC, as amended – relating to applications new fixed combination products.

The application submitted is a complete dossier: a new fixed combination medicinal product.

Scientific Advice
The applicant did not seek scientific advice at the CHMP.

Licensing status:
A new application was filed in the following countries: USA, Brazil.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Giuseppe Nisticó** Co-Rapporteur: **János Borvendég**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 6 December 2007.
- The procedure started on 26 December 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 20 March 2008. . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2008.
- During the meeting on 21-24 April 2008 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 April 2008.
- A clarification meeting with the Rapporteurs on the CHMP List of Questions was held on 29 April 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 August 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 October and an updated overview on 9 October 2008.
- During the CHMP meeting on 20-23 October 2008 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- A clarification meeting with the Rapporteurs on the CHMP list of outstanding issues was held on 21 October 2008.
- The applicant submitted the responses to the CHMP consolidated list of outstanding issues 29 October 2008.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 7 November 2008.

- The applicant submitted further responses to the outstanding issues on 11 and 12 November 2008.
- The Rapporteurs circulated a further update to the Joint Assessment Report on the applicant's responses to all CHMP members on 14 November 2008.
- During the meeting on 17-20 November 2008 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Rasilez HCT on 20 November 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 November 2008 .

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Hypertension has been identified as a major risk factor for cardiovascular diseases such as stroke, myocardial infarction, and heart failure. It is widely recognised that an adequate control of hypertension is important to significantly decrease cardiovascular mortality and morbidity. For most hypertensive patients, the management of hypertension with a general target blood pressure (BP) of < 140/90 mm Hg is recommended. A lower BP target (<130/80 mm Hg) is recommended in high-risk patient populations, such as those with target organ damage, diabetes, or renal disease.

Several therapeutic choices are currently available to lower blood pressure, including diuretics, β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB) and calcium channel antagonists.

Furthermore, the inhibition of renin-angiotensin system (RAS) is an effective way to intervene in the pathogenesis of cardiovascular and renal disorders. Renin is the enzyme responsible for the conversion of angiotensinogen to angiotensin I. Then the angiotensin converting enzyme (ACE) transforms angiotensin I into the active octapeptide angiotensin II, which acts via type-1 angiotensin II receptors (AT1) to increase arterial tone, adrenal aldosterone secretion, renal sodium reabsorption, sympathetic neurotransmission, and cellular growth. Some of currently used antihypertensive drugs intervene at different points of renin-angiotensin system, e.g. β-blockers, ACE -inhibitors, angiotensin-receptor antagonists or renin-inhibitors. Despite the availability of several therapeutic choices, not all hypertensive patients achieve adequate control of blood pressure with a single antihypertensive drug. For the majority of patients a combination of two or more antihypertensive medications will be required to reach adequate blood pressure control. Thus, the development of fixed-dose combinations of different antihypertensive drugs helps to improve patient compliance over the free combination of the single monotherapies and might contribute to the improvement of their safety profile.

Aliskiren/hydrochlorothiazide fixed combination was developed to achieve target blood pressure in hypertensive patients not adequately treated with either aliskiren or hydrochlorothiazide monotherapy. Aliskiren (ALI) is the first renin-inhibitor authorized in EU via the centralized procedure in August 2007. Aliskiren inhibits renin, the enzyme responsible for the production of angiotensin I. Renin inhibitors like aliskiren do not block renin-like enzymes, such as cathepsin D or tonins, which are present in the vascular wall and which release angiotensin I from angiotensinogen. Renin has a unique specificity for its only known physiological substrate, angiotensinogen. This specific inhibition of the renin system by diminishing renin activity has the advantage to not interfere with other metabolic pathways.

Hydrochlorothiazide (HCTZ) is a well-known thiazide diuretic commonly used for the treatment of hypertension, thanks to its effect on volume/sodium depletion. Hydrochlorothiazide is used as monotherapy and in combination with other antihypertensive medicinal products such as angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers and β-blockers.

The development programme is based on non-clinical studies and clinical trials demonstrating the claimed therapeutic benefits of the proposed combination. Bridging studies were conducted in order to demonstrate bioequivalence between the free combination used in definitive clinical efficacy and safety studies to the new fixed combination film-coated tablet product. Studies included the relevant population and were conducted in accordance with the GCP requirements.

2.2 Quality aspects

Introduction

This application relates to fixed combinations of the renin inhibitor aliskiren (SPP100) and the thiazide diuretic hydrochlorothiazide in four strengths: 150 mg/12.5 mg, 150 mg/50 mg, 300 mg/12.5 mg and 300 mg/50 mg film-coated tablets.

The Rasilez-HCT film-coated tablets are formulated as immediate release solid dosage form for oral use. The product will be marketed in PA/AL/PVC or PCTFE/PVC blisters in packs containing 7, 14, 28, 30, 50, 56, 90, 98 and 280 tablets.

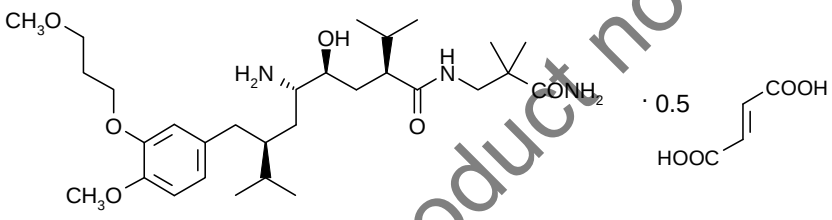
Active Substance Aliskiren hemifumarate

Aliskiren hemifumarate of Novartis has already been authorized via the centralised procedure. Information submitted in the original and supplementary documentations were evaluated and accepted by the CHMP

Aliskiren hemifumarate has four chiral centres, but is obtained as a single diastereoisomer, all S-configured.

Sufficient scientific information has been presented on physicochemical properties such as appearance, solubility in standard aqueous buffers and non-aqueous solvents, pKa, specific rotation, log P, melting point and thermal behaviour.

This molecule shows polymorphs. Satisfactory identification was performed by X-ray powder spectra, Differential Scanning Calorimetry (DSC) and ThermoGravimetric Analysis (TGA).



- Manufacture

The synthesis of the active substance can be summarized in 10 main steps.

The process predominantly involves the construction of an appropriately substituted octanamide backbone with controlling the stereochemistry.

The manufacturing process has been fully detailed, including operating conditions, quantities of solvents, reagents, catalysts.

Adequate in-process controls have been applied as well as controls of the reagents, solvents, catalysts, starting materials, and intermediates used in the manufacture of aliskiren hemifumarate. Materials used in the manufacture of aliskiren hemifumarate active substance are all of synthetic origin; therefore do not pose a risk of TSE/BSE contamination.

Critical steps include the step where the four chiral centres are stereochemically formed and the crystallisation of aliskiren hemifumarate, and relevant intermediates have been controlled accordingly.

Adequate specifications have been included for the starting materials, solvents, and intermediates.

Validation data are available and the robustness of the process has been demonstrated.

The structure of aliskiren hemifumarate has been fully elucidated with usual techniques such as elementary analysis, Infra-Red (IR) spectroscopy, Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR) spectroscopy, mass spectroscopy and X-ray powder diffractometry (XRPD), optical rotation (single diasteroisomer), particle size analysis.

- Specification

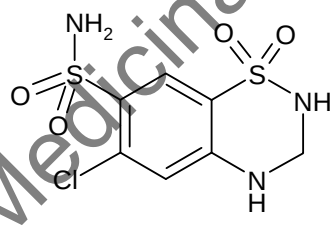
Appropriate specification has been set up and includes appearance, particle size, appearance of the solution, identification (IR, XR and optical rotation), residual solvents (GC), water content, sulfated ash, heavy metals, related substances, assay (titration and HPLC), assay of the salt (fumaric acid), microbiological quality. The skip-testing approach for the microbiological quality is considered acceptable.
Specification of the active substance including residual solvents (in line with ICH requirements) and impurities (justified by toxicological data) are appropriately justified.
Analytical methods have been adequately detailed and non-compendial methods validated in accordance with ICH guidelines.
The bulk of the active substance is packed in sealed triple bags (polyethylene PE/aluminium/ polyethylene terephthalate PET) or quadruple bags (PE /PET/aluminium/PET). The bags are stored in drums with a tamper resistant seal.
Analysis of 36 batches has demonstrated the uniformity and the consistency of the synthesis.

- Stability

Stability data on three pilot batches have been carried out under ICH long term (24 months, 25°C/60%RH) and accelerated conditions (6 months, 40°C/75%RH) as well as photostability and stress testing under different conditions.
All parameters were found in accordance with the specification and no major degradation could be observed.
Based on the discussion above it can be concluded that the active substance is stable under long-term and accelerated storage conditions. The proposed retest period is supported by the results of the stability studies.

Active Substance Hydrochlorothiazide or HCTZ

Hydrochlorothiazide or HCTZ (INN) is a white to almost white powder and fulfils the requirements of the current PhEur monograph. Its chemical structure is represented as follow:



General properties such as solubility in various aqueous and non-aqueous solvents, dissociation constants, distribution coefficients, optical rotation (inactive since does not possess an asymmetric center), water sorption properties (non-hygroscopic) and polymorphism.

- Manufacture

Commercially available hydrochlorothiazide from two suppliers, one with a CEP and one with an ASMF is further processed by the applicant. The final HCTZ is tested against the applicant's testing monograph.

Satisfactory control of reagents and solvents has been presented. No critical process steps have been identified and no intermediate product is formed during manufacture of hydrochlorothiazide. No process validation was deemed necessary.

The structure of hydrochlorothiazide is supported by the synthetic route and has been elucidated by elemental analysis, ultraviolet (UV) and infrared (IR) spectroscopy, proton (^{1}H-NMR) and carbon (^{13}C-NMR) nuclear magnetic resonance. A comprehensive analysis of polymorphism was carried out using X-ray powder diffraction spectra, Raman spectra, DSC curves and thermogravimetry.

- Specification

Appropriate specifications have been set and include appearance, physico-chemical properties, identification (IR and UV), assay (HPLC and titration), related substances, loss on drying, sulfated ash, heavy metals, microbial contamination, fulfilling the requirements of the current Ph. Eur. Analytical methods have been satisfactorily described and in-house methods have been validated in accordance with ICH requirements.

Analytical results of six batches of hydrochlorothiazide obtained from the different suppliers were presented and in line with the retained specification. Results confirm batch to batch consistency and uniformity of the quality of the substance and indicate that the process is under control.

Bulk hydrochlorothiazide is stored in metallic drums lined with two polyethylene bags which are sealed with a plastic closure. For stability hydrochlorothiazide is packed in polyethylene bags sealed with a cable binder in mini metal drums.
Appropriate specification for primary packaging material including identification test by IR, appearance, size and microbiological tests was provided along with certificate of analysis.

- Stability

Stability studies have been carried out on eight production batches of micronized hydrochlorothiazide under long term storage conditions (up to 5 years, 25°C / 60% RH), accelerated conditions (6 months data, 40°C / 75% RH) and photostability testing. The long term testing (real time testing) and accelerated testing conditions are set according to ICH and cover temperate and subtropical climates, as well as hot and tropical climates. The quality characteristics (e.g. physical characteristics like clarity and absorbance of the solution in dimethyl sulfoxide, impurity profile and assay) of the active substance are unchanged as demonstrated by comparative analytical data.

The proposed re-test period is supported by the results of the stability studies.

Medicinal Product

Rasilez HCT film-coated tablets are immediate release solid dosage forms for oral administration containing fixed combinations of the drug substances aliskiren hemifumarate (SPP100) and hydrochlorothiazide (HCTZ).
The film-coated tablets have the same shape (biconvex ovaloid tablet) but different colours and sizes.
- 150/12.5 mg: white
-300/25 mg: pale yellow
- 150/25 mg: violet white
- 300/12.5 mg: light yellow

The different strengths have the same qualitative composition with regard to the active substance and the excipients in the cores whereas the coatings are slightly different.

- Pharmaceutical Development

The main objectives for technical development of these film-coated tablets were:
• to develop an immediate release film-coated tablet
• to utilize a suitable manufacturing process to achieve a high drug load whilst keeping an acceptable tablet size.
• to achieve product bioequivalent to the selected mono-component products.

The key physico-chemical characteristics have been adequately described for the active substances aliskiren hemifumarate (SPP100) and hydrochlorothiazide (HCTZ). Compatibility between the active substances has been studied as well as compatibility with common pharmaceutical excipients during the development of SPP100 (Rasilez) film-coated tablets. Studies demonstrated compatibility with all excipients tested.

The choice of excipients is based upon their suitability for use in the manufacturing process, on compatibility results and on pharmaceutical technological experience gained from development of the existing SPP100 and HCTZ 'mono-' tablet formulations. The excipients are common excipients used for oral dosage formschosen for the ALI/HCTZ tablet formulation are all components of granulates or final blends of either the existing SPP100 or HCTZ 'mono-' tablet formulations.

Formulation development has been appropriately described including the homogeneity of this high-content drug formulation. The film-coated tablet was chosen as the most convenient and suitable dosage. A film-coating was needed to mask the bitter taste of the aliskiren hemifumarate, and to achieve dose differentiation of the strengths by different colors.

Biowaiver request

The biowaiver request for the 150/12.5 mg aliskiren/ hydrochlorothiazide fixed combination tablet is based on the rationale of the CHMP's 'Note for guidance on the investigation of Bioavailability and Bioequivalence'. Comparative dissolution data for different media are presented. Dissolution profiles proved similar by the calculated f2 factors. The composition proportionality of the 150/12.5 mg and 300/25 mg aliskiren/HCT fixed combination tablets, the similar manufacturing process for these tablets, and the acceptable *in vitro* dissolution results do fulfil the requirements for waiver of a bioequivalence study at 150/12.5 mg strength.

Manufacturing Process Development

The manufacturing process development of the drug product has been appropriately described.

- Adventitious Agents

None of the materials used for the synthesis presented TSE risk. Magnesium stearate is declared to be of vegetable origin. Lactose monohydrate is of animal origin, but is of pharmaceutical grade derived from milk sourced from healthy animals and under the same conditions as milk fit for human consumption, therefore the risk is negligible in accordance with TSE Note for Guidance (EMEA/410/01Rev.2).

- Manufacture of the Product

The manufacturing process of the finished product is considered a standard manufacturing process involving standard technology such as mixing, granulation tabletting and film-coating.

Adequate in-process controls for the manufacture of the drug product have been provided.

The manufacturing process is considered as standard. None of the process steps are considered as critical.

The excipients selected are commonly used for oral pharmaceutical dosage forms and include for the tablet core: microcrystalline cellulose, crospovidone, lactose monohydrate, wheat starch, povidone, magnesium stearate, colloidal silicon dioxide, talc, and for the coating: iron oxide, ferric oxide, macrogol and talc. All excipients are described in PhEur., except basic coating premixes that are commercially available mixtures of standard components (in line with food directive EC 95/45).
The film-coats are described as non-functional with respect to the product dissolution and stability and are needed to mask the bitter taste of the aliskiren and to differentiate the several strengths. Each excipient possesses a certificate of analysis in compliance with the proposed specification.

Rasilez HCT film-coated tablets are produced according to standard manufacturing processes: mixing, granulation, screening, drying, blending, tabletting and film-coating.

- Product Specification

Appropriate release and shelf-life specifications for the finished product have been set, and parameters tested include appearance, identification (TLC, UV and HPLC), identification of colorants, mean mass, dissolution (HPLC), loss on drying, residual solvents, related substances, microbial contamination, assay (HPLC), uniformity of dosage units (PhEur. mass uniformity and content uniformity).

All the analytical procedures are Ph Eur. methods except for assay of isopropanol in ethanol with 5% isopropyl alcohol for which an in house monograph is presented. All the non-compendial methods have been fully validated in accordance with ICH guidelines.

Five representative batches (production and pilot-scale) for each dosage strength have been tested. All batches complied with the proposed specification.

The primary packaging consists of PA/AL/PVC blister packs and PCTFE/PVC blister packs with a heat sealable lacquered aluminum foil. PA/AL/PVC blisters (Alu blisters) are double-sided aluminium blisters consisting of an aluminium forming foil (PA/AL/PVC foil) and an aluminium lidding foil.
The components of the blisters are tested for cleanliness, total thickness and identity (IR).
In addition certificates of analysis for packaging components comply with PhEur. requirements (where applicable, e.g. PVC, PA) and foodstuff legislation.

- Stability of the Product

Primary stability testing was performed on nine pilot scale batches of film-coated tablets (3 batches of each dosage strengths) kept in the commercial packaging (PCTFE/PVC and Alu blister packs) under ICH conditions. The stability program included long term (up to 18 months, 25°C/60 % RH and 30°C/75 % RH), accelerated testing (6 months, 40°C/75 % RH), other temperatures (e.g. 5°C, 50°C and –20°C) and ICH photostability testing. A bracketing approach has been applied, meaning testing only the three dosage strengths 75/12.5 mg, 300/12.5 mg and 300/25 mg to cover the extremes.

Parameters tested included: appearance, dissolution, water content, assay and degradation products. The tests cover features susceptible to change during storage and likely to influence quality and/or efficacy of the product.

No significant change in the physical properties could be observed under long-term conditions, with the exception of the water content increase with the PCTFE/PVC blister pack. Degradation products increased when tested under accelerated conditions. The film-coated tablets are not sensitive to light. The investigations show that the higher the water content of the tablets the more chemical degradation is formed.

Based on the stability data, the proposed shelf-life can be granted when the product is kept in the commercial packaging (PCTFE/PVC and Alu blister packs) with the following precautions "Do not store above 30°C. Store in the original package in order to protect from moisture" as described in product information

Discussion on chemical, pharmaceutical and biological aspects

The active substance aliskiren hemifumarate is optically active with four chiral carbons but exists as a single diastereoisomer. It is manufactured via a 10 steps stereochemically controlled synthesis. Control of stereochemistry, polymorphism and impurities have been fully discussed. Appropriate specification has been presented. Stability studies conducted according to the ICH guidelines showed that aliskiren hemifumarate is stable and support the re-test period, in very tight packaging (due to the hygroscopic nature of the substance), protected from light, at temperature not above 25°C can be granted.

The active substance HCTZ has been adequately described and characterised. Commercially available hydrochlorothiazide from 2 suppliers, one with a CEP and one with an ASMF, is further processed by the applicant. Appropriate specification has been presented. Stability studies conducted according to the ICH guidelines showed that HCTZ is stable and support the re-test period of 4 years re-test period when protected from light.

ALI/HCTZ film-coated tablets are formulated as an immediate release formulation with well-known excipients. The film-coated tablets have the same shape (biconvex ovaloid tablet) but different colours and sizes: 150/12.5 mg: white, 300/25 mg: pale yellow, 150/25 mg: violet white, 300/12.5 mg: light yellow. The four strengths have the same qualitative composition with regard to the active substance and the excipients in the cores; the coatings are slightly different

Compatibility with regard to excipients is justified by stability results. The pharmaceutical development is comprehensive and adequate. Manufacturing method has been described and allows the production of a consistent and homogeneous product. The tablets are kept in blister packs. The description and choice of the container is acceptable based on stability data. Drug product specification are satisfactory and in line with ICH guidelines. Stability data support the proposed shelf life under the precautions of storage described in the Product Information.

2.3 Non-clinical aspects

Introduction

Rasilez HCT is a fixed-dose combination of two antihypertensive drugs; aliskiren (ALI) which is an oral, potent and selective inhibitor of renin and hydrochlorothiazide (HCTZ) a well-known thiazide diuretic. Preclinical development program is aimed to support the use of ALI/HCTZ at doses of 150 mg/12.5mg, 150 mg/25 mg, 300 mg/12.5 mg and 300 mg/25 mg for the treatment of hypertensive patients not adequately treated with either aliskiren or hydrochlorothiazide monotherapy.

Aliskiren 150 mg and 300 mg received marketing authorisation in the EU in August 2007. Hydrochlorothiazide is already used as monotherapy and in combination with other antihypertensive medicinal products such as angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers and beta-blockers. The preclinical pharmacodynamic and pharmacokinetic properties from aliskiren and hydrochlorothiazide are known. Information is also available in the scientific literature as well as from the use of these medicinal products as monotherapy. No specific preclinical pharmacodynamic or pharmacokinetic studies were performed with ALI/HCTZ fixed-dose combination. Toxicity studies were conducted with aliskiren and hydrochlorothiazide as free

combinations in the rat and included a 2 week oral dose range finding study and a 13 week study toxicity study. The structure of the programme was detailed and sufficiently justified and thus, is considered appropriate for the characterisation of the preclinical safety profile of the fixed dose combination. The strategy of the non clinical development of ALI/HCTZ was in line with the available CHMP guidelines on fixed dose combinations CPMP/EWP/240/95 Rev.1: "Guideline on fixed combination medicinal products", CPMP/SWP/258498/2005: "Guideline on the non clinical development of fixed combinations of medicinal products".

The 2 week oral (gavage) dose range finding toxicity study in rats is a "GLP like" study: study, not fully comply with GLP but performed at the highest standards of scientific quality. The 13 week oral gavage toxicity study in the rat followed by a 4 week recovery and is full compliant with the GLP requirements.

Pharmacology

Preclinical studies to determine the primary pharmacodynamics of ALI/HCTZ combination were not performed. The investigations on the mechanism of action of aliskiren were conducted during the non clinical development of aliskiren. The non clinical data for hydrochlorothiazide are based on the available review of literature data.

- Primary pharmacodynamics

Aliskiren is a human renin inhibitor and has been investigated in relevant species expressing human renin gene. The studies employed double transgenic rats (dTGR) that express human genes for renin and angiotensinogen, rats that express mouse renin, and mice. These studies aimed to provide an understanding of the basic pharmacodynamic effects of aliskiren.

The rennin inhibitory potency of aliskiren was tested *in vitro*. It was demonstrated that there is a species dependent inhibition of human recombinant renin (IC_{50} = 0.6 nmol/L) and marmoset renin (IC_{50} = 2 nmol/L) with specificity and selectivity to renin *vs* other proteases. Aliskiren was inactive against the other human proteinases and HIV-1 proteinase tested (IC_{50} >5000 nM).

Aliskiren, as a human renin inhibitor has a comparatively lower potency against rat renin in comparison with humans, although the compound is effective in mice. As a result of this species specificity, the *in vivo* non clinical studies employed double transgenic rats (dTGR) that express human genes for renin and angiotensinogen, rats that express mouse renin, and mice. These studies aimed to provide an understanding of the basic pharmacodynamic effects of aliskiren with respect to its ability to inhibit the rennin-angiotensin-aldosterone system (RAAS), to reduce blood pressure, and to ameliorate organ damage in settings of hypertension with or without diabetes.

Inhibition of the RAAS *in vivo* in renovascular hypertensive hypercholesterolemic mice at a dose of 50 mg/kg was demonstrated by lowering PRA by 94% ($p<0.05$) compared with vehicle-treated hypertensive controls. In dTGR, aliskiren inhibited plasma Ang I forming capacity and lowered renal Ang I and II content. Moreover, aliskiren 0.3 mg/kg completely inhibits plasma renin activity in normotensive sodium depleted marmosets. Plasma renin activity was inhibited by 87% at 6 hours after dosing. Higher doses resulted in prolonged responses. Aliskiren is capable of lowering mean arterial blood pressure (MAP) in spontaneously hypertensive rats (SHR) when given as monotherapy. When ALI was combined with benazepril or valsartan, a synergistic blood pressure lowering effect was seen in SHR. In dTGR, aliskiren lowered MAP in a dose- and time-dependent manner. Aliskiren exhibited a rapid onset of action (< 15 min), and a prolonged duration of effect. The recovery of MAP to baseline required at the highest orally administered doses up to 48 hours. The concurrent administration of valsartan and enalaprilat with aliskiren dose-dependently lowered arterial pressure of dTGR. ALI administered intravenously was

approximately equipotent with intravenously administered valsartan and enalaprilat, but was less potent when all three agents were given by oral administration, due to its lower oral bioavailability. In addition, aliskiren showed antihypertensive effects in dTGR and in diabetic hypertensive TG(mRen-2)27 rats. Single or repeated oral and intravenous doses of ALI dose dependently lowered blood pressure in normotensive sodium depleted marmosets.

Aliskiren protected against cardio-renal damage in dTGR, preventing albuminuria in diabetic hypertensive TG(mRen-2)27 rats, normalizing serum creatinine, and inhibiting left ventricular hypertrophy and dysfunction. It displayed anti-fibrotic effects, reducing renal collagen IV immunostaining in dTGR and decreasing collagen histochemical (trichrome) staining in diabetic TG (mRen-2)27 rats. In dTGR and hypertensive-diabetic TG(mRen-2)27 rats, aliskiren inhibited the renal gene expression of the profibrogenic growth factor TGF-β. The renin inhibition resulted in anti-inflammatory effects in dTGR, reducing renal inflammatory cell infiltrates and inhibiting complement activation in the renal vasculature.

Literature data for hydrochlorothiazide are provided to summarise its antihypertensive effects in the pre-clinical models as monotherapy or in combination with RAAS blocking agents. When administered as monotherapy, hydrochlorothiazide normalized arterial pressure in the rat model of renovascular hypertension, and was cardioprotective in stroke-prone SHR, attenuating cardiac hypertrophy, myocyte hypertophy, as well as interstitial and periarterial fibrosis. In conventional SHR, hydrochlorothiazide repressed aortic hypertrophy and glomerulosclerosis. While the combination of aliskiren with hydrochlorothiazide has not been studied in the preclinical models, experiments, in which hydrochlorothiazide was combined with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers provide a rationale for expecting similar benefits from ALI/HCTZ in the treatment of hypertension. The combination of hydrochlorothiazide with either of these products lowered the MAP of the SHR, and depending on the doses, these decreases were synergistic. In SHR treated with L-NAME to induce renal injury, modest improvements were seen in renal hemodynamics, renal function, and morphological indices of glomerular and arteriolar injury with hydrochlorothiazide *vs* vehicle controls. In contrast, combination of the diuretic with either enalapril or losartan markedly improved these parameters when compared with the vehicle controls.

Aliskiren, the first in class renin inhibitor, has been studied in clinical trials as a monotherapy or in combination with hydrochlorothiazide for the treatment of hypertension, thus the pharmacodynamic interaction rationale is already clinically documented and non clinical pharmacodynamic bridging study is not needed. The number of studies performed with monotherapy as well as the submitted scientific literature is considered sufficient. The information on effects of fixed combination is already known in humans and therefore, no further animal studies are required. In summary, the data demonstrate the benefit of combining hydrochlorothiazide with angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and by supposition, with a renin inhibitor, for effective lowering of blood pressure and protection against organ damage.

- Secondary pharmacodynamics

Studies on secondary pharmacodynamics were not conducted largely due to the lack of appropriate models. Aliskiren is a human renin inhibitor, and as such it has only limited efficacy in standard rat models of hypertension. While transgenic models are accepted as being suitable for establishing renin inhibitors as antihypertensive and organ protective agents, they are artificial systems: the interactions of renin-angiontensin system components, and their activation and regulation are likely to differ from those in humans. Thus, more relevant conclusions regarding secondary pharmacodynamics could be drawn from studies conducted in humans.

- Safety pharmacology programme

The safety of hydrochlorothiazide on the nervous, cardiovascular, respiratory or renal systems has been demonstrated in extensive clinical trials and post-marketing programs. Aliskiren does not interact with a variety of other targets involved in the regulation of blood pressure and it had no significant effects in a standard battery of non clinical safety pharmacology studies that included *in vivo* assessments of central nervous system, respiratory and renal function and *in vitro* and *in vivo* cardiovascular investigations. The cardiovascular safety of aliskiren has also been confirmed in many clinical trials including a specific assessment of cardiac conduction and re-polarization. As the combination of aliskiren and hydrochlorothiazide was not expected to display concerns in safety pharmacology assays, further investigations were not conducted for aliskiren/hydrochlorothiazide fixed combination.

- Pharmacodynamic drug interactions

The drug-drug interaction potential of aliskiren and hydrochlorothiazide when given as monotherapy has been assessed and characterised during their development. The interaction potential of aliskiren and hydrochlorothiazide, as discussed in the current literature, shows that there is no overlapping substrate as well as inhibition profile on the identified active enzyme and transporter-related processes between the two compounds. This was seen in a series of in vitro and in vivo studies. The combined data on aliskiren and hydrochlorothiazide monotherapies indicate a low potential for interactions. Furthermore, the potential for drug-drug interaction between aliskiren and hydrochlorothiazide was studied clinically and the study results indicate that there were no significant pharmacokinetic interactions between the two drugs after multiple doses.

Pharmacokinetics

The non clinical and clinical pharmacokinetic and metabolism profile of aliskiren was thoroughly evaluated during its development as monotherapy. Hydrochlorothiazide is a marketed product and its pharmacokinetics and metabolism were extensively studied in non clinical and clinical studies. Therefore, overviews on pharmacokinetic of hydrochlorothiazide available form the published literature were provided. This was considered appropriate.

Absorption
The rate of absorption of aliskiren in mice, rats, and moderate in dogs, marmosets and human was rapid. The oral bioavailability was in the low percentage range. Systemic exposure was close to being dose proportional, with no gender differences observed in the tested species. The concentrations of aliskiren in plasma declined slowly, the elimination half-life being 23.1 and 36 hours in rats and marmosets, respectively. Plasma concentrations in rats and marmosets accumulated about 2-fold after multiple dosing. The pharmacokinetics of aliskiren is nonlinear. The binding to plasma proteins was moderate with free fractions (fu) between 29% in mouse and distinctly higher in marmosets (fu = 8%). The distribution between blood cells and plasma was concentration independent for rat, rabbit and human. Bioavaliability of aliskiren si low in all studied species (1-3%).

Hydrochlorothiazide is well absorbed in animal species and humans. Systemic exposure in humans increases proportionately with the dose. Bioavailability is 65% to 75% of the administered dose. Food reduces the bioavailability by approximately 10% and the C_{max} by 20% and increases the t_{max} from 1.6 to 2.9 hours.

Distribution
The volume of distribution of aliskiren at steady-state was high in the rat, moderate in human and mice, and low in the marmoset. The binding of aliskiren to plasma proteins was moderate with free fractions

between 29% in mouse and 50% in humans. Bio-distribution study after single and repeated (10 days) oral dose of 100 mg/kg to rats showed a low radioactivity tissue levels, which is expected considering the poor and moderate absorption rate. Radioactivity was eliminated within 24 hours from most organs and tissues. Aliskiren and/or its metabolites were not taken up into the brain. Accumulation of radioactivity in organs and tissues after multiple dosing was moderate and about 4-fold compared to single dose. Highest concentrations of aliskiren were observed in the liver and kidney. Considering that the kidney is a target organ of both compounds, the CHMP expressed a concern regarding the potential effect of hydrochlorothiazide on aliskiren exposure in this organ. In response, the low likelihood of accumulation of aliskiren and its metabolites in kidney tissues after multiple oral administration of aliskiren was demonstrated in a single and multiple dose administration studies to rats. For the parent compound in plasma, the accumulation factor was between 0.6 and 1.3 indicating that repeated administration of aliskiren led to no apparent increase of its exposure when compared to a single oral administration. Since aliskiren is predominantly eliminated unchanged *via* the biliary route and hydrochlorothiazide is predominantly eliminated unchanged *via* the renal route, the different clearance mechanisms as well as routes of elimination, and the lack of relevant interaction among the individual components of this combination, the overall drug-drug interaction potential within this combination is not foreseen to be clinically significant. An interaction between aliskiren and hydrochlorothiazide in the kidney appears to be very unlikely.

Exposure of the foetuses to drug-related compounds could be demonstrated after single oral doses of radiolabelled aliskiren at gestation Day 7 to rats and Day 17 to rabbits. Foetuses were exposed to aliskiren and/or its metabolites. The mean total radioactivity concentrations at 24 hours post-dose were similar to those in maternal blood. Comparable total radioactivity concentrations were found in the placentas and the amniotic fluid. Aliskiren and/or its metabolites were excreted in the milk of lactating rats (100 mg/kg, p.o.) to a very low extent (0.08% of dose in 6 days). Concentrations of the product in milk were similar to or higher than those in plasma of the mother, indicating that suckling pups are exposed to aliskiren and/or its metabolites.

Hydrochlorothiazide is moderately distributed in body tissues and its volume of distribution following oral administration corresponds to 0.83 l/kg. Hydrochlorothiazide binds to plasma proteins only to a low extent (40%-60%) and hence, its potential to interact with co-administered medications *via* protein binding is negligible. Hydrochlorothiazide crosses the placental barrier. Concentrations of the parent compound in maternal plasma and umbilical core plasma were similar. The drug was excreted into the breast milk of nursing mothers, but no measurable concentrations were found in nursing infants.

Metabolism
Aliskren was metabolised to a low to moderate extent in rats, mice, pregnant rabbits and marmosets, (about 15% to 25% of dose). The most abundant component in plasma and excreta was unchanged aliskiren. Primary metabolic pathways involved oxidations on the phenol moiety of aliskiren, like O-dealkylation and further oxidation to the carboxylic acids. These oxidation processes were found to be catalysed mainly by cytochrome P450 3A4/5 isoenzymes. Minor metabolic pathways were the formation of glucuronide metabolites and hydrolytic cleavage of aliskiren amide bond. All metabolites observed in plasma were also found in the excreta either in free or conjugated form.

Based on the data available from the literature, hydrochlorothiazide is not significantly metabolised and the majority of the dose (approximately 95%) is excreted unchanged in urine.

Excretion
In mice, rats and marmoset, aliskiren and its metabolites were predominantly eliminated into faeces (generally ≥ 88% after oral dose) indicating a high biliary excretion of the absorbed fraction of the dose.

Renal excretion was generally low in all investigated species (≤ 4.5%, p.o. and ≤ 15%, i.v.). Elimination was complete within 7 days, with the main part of a radioactive dose excreted within 24-48 hours.

Orally administered hydrochlorothiazide is excreted largely unchanged with urine. In humans, >95% of the absorbed HCTZ was excreted in urine. The elimination of the product from plasma is bi-phasic with elimination half-lives of 1-4 hours, and 5-15 hours.

Pharmacokinetic drug interactions
Aliskiren has not shown relevant interactions with cytochrome P450 isoenzymes, substrates and/or inhibitors of uptake transporters or with co-administered medication during clinical use. Virtually no pharmacokinetic interactions with other drugs *via* CYP450 enzymes have been reported in the literature for hydrochlorothiazide. Since hydrochlorothiazide is excreted largely unchanged into urine, no significant effect on hydrochlorothiazide pharmacokinetics is expected by inhibitors of metabolism or biliary excretion. Both compounds have moderate plasma protein binding and no significant interaction is expected due to competition for plasma protein binding sites. In rat and human hepatocytes, apart from the passive diffusion, a substantial part of hepatic uptake was shown to be achieved *via* the active transport. Thus, if aliskiren is a substrate of number drug-transporters, compounds with a strong inhibitory potential on these transporters may increase aliskiren concentrations.

Overall, the pharmacokinetic CYP-dependent drug interaction potential between aliskiren and hydrochlorothiazide, and other drugs is considered to be relatively low. Clinically significant interactions due to common enzymes in the metabolic pathway or due to competition to plasma protein binding sites are therefore unlikely.

Toxicology

Preclinical safety characteristics of aliskiren were established during its development as monotherapy. General toxicity in rats and marmosets as well as genotoxicity, carcinogenicity and reproductive effects were evaluated. Safety pharmacology assessments of aliskiren did not reveal significant effects on the central nervous, respiratory, cardiovascular or renal system. Premature deaths were encountered at doses ≥ 200 mg/kg/day in repeat-dose rat oral gavage studies. As aliskiren is a local irritant and can cause necrosis of the respiratory epithelium, the deaths were attributed to aspiration of the dosing solution into the respiratory tract rather than systemic toxic effects. In marmosets, two incidences of urinary stasis in decedent animals were attributed to hypotension and poor renal perfusion. Other changes in marmosets included reductions in erythropoietic parameters probably due to the effect of the renin-angiotensin system on the production of erythropoietin in the kidney. Similar findings have been previously observed with a variety of inhibitors of the renin-angiotensin system. Aliskiren had no significant effects on reproductive or immune function. Extensive genotoxicity assays showed no evidence of a genotoxic potential. Carcinogenic potential was assessed in rats and transgenic mice. Inflammatory and proliferative changes were observed in the lower gastrointestinal tract at doses of 750 or 1500 mg/kg/day in both species. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1500 mg/kg/day were not statistically significant. These findings were attributed to the known irritation potential of aliskiren. Appropriate exposure margins between rat and human faecal and mucosal gastrointestinal concentrations were demonstrated. However, in the rat carcinogenic study, no NOAEL was identified. The evaluation of the results of the cellular markers of proliferation and apoptosis following administration of aliskiren to healthy volunteers showed that aliskiren had no significant effect on epithelial cell proliferation as measured by MIB-1 immunostaining following daily oral administration of 300 mg for 8 weeks in healthy subjects. In addition, lack of effect of aliskiren on hyperplasia and mitotic activity was observed. Daily oral administration of ALI 300 mg for 8 weeks in healthy subjects did not alter apoptotic index from baseline to post-treatment. The extent of apoptosis was very small in

both placebo and aliskiren treated groups. The data presented are considered reassuring in relation to a possible risk posed by aliskiren on cell proliferation of mucosal epithelia.

Hydrochlorothiazide literature provides data on evaluation of general toxicity, carcinogenicity, genotoxicity and reproductive toxicity. Toxicity and carcinogenicity studies were conducted in mice and rats by dietary administration for 15 days, 13 weeks and 2 years. No rats died during the 15-day or 13-week studies at dietary concentrations of up to 50,000 ppm. Increased nephrosis and mineralisation at the renal corticomedullary junction were the primary toxic effects in rats. Deaths of male mice in the high dose group in the 13 week study were likely to be related to compound administration and resulted from nephrosis, calculi, inflammation and epithelial hyperplasia in the urinary bladder. Administration of hydrochlorothiazide to pregnant mice and rats did not result in any evidence of embryo or foetal toxicity. Based on all the available literature, the in vivo genotoxic potential of hydrochlorothiazide is low. There was no treatment-related effect on the survival of rats and mice or on the body weights of mice in the carcinogenicity studies. Treated rats were uniformly lighter than controls throughout the studies. In rats, severe chronic renal disease with secondary parathyroid hyperplasia and fibrous osteodystrophy of bone were found to be related to the compound. No neoplasms in rats or female mice or non-neoplastic lesions in mice were treatment-related. In high-dose male mice, the incidence of liver tumours was higher than that of concurrent controls. This was not considered to be treatment-related because of an unusually low incidence in the control group relative to historical controls. The SPC for hydrochlorothiazide monotherapy reflects the finding on non clinical studies.

Preclinical safety studies conducted with aliskiren/hydrochlorothiazide combination include a 2 week dose range-finding study and a 13 week study in rats. Based on the proposed therapeutic dose strengths of 150/12.5, 150/25, 300/12.5, 300/25 mg (ALI/HCTZ), a ratio of approximately 12:1 (aliskiren:hydrochlorothiazide) was used in the non clinical safety studies. This was believed to be adequate. The principal 13 week study was conducted in accordance with Good Laboratory Practice and currently accepted guidelines with respect to animal numbers and dose levels used. The 2 week study was considered well designed although did not full comply with GLP.

- Single dose toxicity

No single dose toxicity studies were conducted with the combination aliskiren and hydrochlorothiazide. Nevertheless, studies investigating the toxicity of aliskiren administered to rat as a single dose did not provide any information regarding the signs of an acute intoxication in humans.

- Repeat dose toxicity (with toxicokinetics)

2 week toxicity study in rat

The study was designed to establish the toxicological effects of the combination of ALI/HCTZ when administered to rats for 2 weeks, the no observable adverse effect level (NOAEL) and to estimate the toxicokinetic profile of the combination. The results of this study were used for dose selection in a subsequent 13 week toxicity study in this species. The MTD of ALI/HCTZ was 300/25 mg/kg and all animals were sacrificed on day 8 of treatment following a marked deterioration in condition which included abdominal distention, decreased locomotor activity, piloerection, rales and decreased body weight. The severity of pathological changes in multiple tissues of these animals, notably kidneys, gastrointestinal tract, bone marrow and lymphoid organs indicate that a dose of 300/25 mg/kg would not be tolerated in a longer term study. Minimal tubular basophilia present in the kidneys of some animals treated with 100/8 mg/kg/day may reflect reduced renal perfusion. The toxicological significance of the minimal lymphocytic infiltration in the medulla of the thymus in two males is unclear. Based upon minimal microscopic pathology findings in the absence of overt toxicity, the NOAEL is considered to be 100/8 mg/kg/day.

13 week toxicity study in rat
ALI/HCTZ administered at doses of 50/4, 100/8 or 150/12 mg/kg/day induced slight reversible decreases in body weight gains and food consumption in males given ≥ 100/8 mg/kg/day. Reversible decrease in potassium was seen in animals given the combination and hydrochlorothiazide alone. Reversible decrease in serum chloride levels, which was considered to reflect hydrochlorothiazide treatment related effect, was noted in all animals treated with the combination and with hydrochlorothiazide. There were minimal to mild increases in mean AST (38% compared to control group) and ALT (31% compared to control group) in two females given ALI/HCTZ at dosage 150/12 mg/kg/day. These changes were not observed with concurrent hepatic histopathologic lesions. After four weeks of recovery period, ALT and AST increases (40%) were still observed in one female given 150/12 mg/kg/day compared to the control group. Treatment-related microscopic changes recorded as minimal increased cellular vacuolisation in the zona glomerulosa was seen in all animals treated with hydrochlorothiazide alone (12 mg/kg/day) or in combination with aliskiren at a doses ≥ 50/4 mg/kg/day. In addition, the toxicological significance of the observed minimal lymphatic infiltration in the thymus medulla of two males is not clear. Further uncertainty derived from the absence of studies longer than 13 weeks is the fact, that it cannot be excluded that these effects would became more severe after chronic treatment. Thus, the CHMP requested the toxicity information observed in the rat studies to be included in the SPC. The relevant SPC section appropriately states that the findings observed in the 2 week and 13 week toxicity studies were consistent with those observed previously with aliskiren or hydrochlorothiazide monotherapies and that the increased cellular vacuolation of the adrenal gland zona glomerulosa was observed during the 13-week toxicity study in rats in animals treated with hydrochlorothiazide but not with aliskiren alone.

Toxicokinetics
Exposures to aliskiren on day 1 and in week 13 were higher in aliskiren group than in ALI/HCTZ 150/12 mg/kg/day. Higher aliskiren concentrations in females than in males were observed in animals dosed at 100/8 mg/kg/day both on day 1 and in week 13. Concentrations in females were also higher than in males dosed with aliskiren alone at 150 mg/kg/day on day 1. Based on $AUC_{(0\text{-}24h)}$, a trend to higher exposure to aliskiren in week 13 than on day 1 was observed in males. No trend to accumulation was observed in females with the exception of 150/12 mg/kg group where exposure in week 13 was higher than on day 1. Exposure to hydrochlorothiazide was similar in the hydrochlorothiazide treated group and ALI/HCTZ 150/12 mg/kg/day on day 1, whereas it was slightly lower in the hydrochlorothiazide alone group than in the combination group in week 13. Dose proportionality of exposure of each single compound could not be assessed in this study. Based on $AUC_{(0\text{-}24h)}$, no significant difference in exposure to hydrochlorothiazide was observed for animals given hydrochlorothiazide in combination with aliskiren between on day 1 and in week 13 in males. However, in females, a slightly higher exposure was seen in week 13 than on day 1. In the group given hydrochlorothiazide alone, exposure in week 13 was lower than exposure on day 1.

At the very beginning and end of the 13 week study the exposure figures for aliskiren and hydrochlorothiazide in the 100/8 mg/kg (ALI/HCTZ) group (the only common dose group for both toxicity studies) were generally well below those found on day 15 of the 2 week study. Exceptions were the day 1 and day 15 hydrochlorothiazide exposures in the females. These differences were attributed to the general animal husbandry and blood sampling condition, which can amplify the variability of toxicokinetic data especially in a short term study.

- Genotoxicity

Aliskiren alone gave negative results in a battery of *in vitro* and *in vivo* tests. Based on literature references, hydrochlorothiazide gave ambiguous evidence of *in vitro* genotoxicity: positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse

Lymphoma Cell (mutagenicity) assays, using concentrations ranging from 43 to 1300 mcg/ml, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration. No genotoxicity studies with the combination product were conducted.

- Carcinogenicity

No carcinogenic effects were reported in mice and rats receiving aliskiren. No equivocal evidence of hepatocarcinogenicity was found in male mice at high doses of hydrochlorothiazide administered for 2 years, or of an increase in tumours in female mice or rats of either sex given hydrochlorothiazide for 2 years. Hydrochlorothiazide has been used extensively as a diuretic and antihypertensive agent since 1957 and despite the equivocal non clinical genotoxicity and carcinogenicity findings, no evidence of carcinogenicity in humans have been reported. No specific carcinogenicity study has been carried out with the ALI/HCTZ. It is, however, likely that this study would have provided no significant contribution to the safety evaluation of the combination. Nevertheless, in the 13 wk repeated toxicity study a 40% increased ALT and AST, without histopathology alteration was observed at the end of the recovery period, for which an ALI/HCTZ treatment-related effect cannot be ruled out. Vacuolisation of adrenals was observed as an effect apparently not seen ever with either aliskiren or hydrochlorothiazide alone. No chronic toxicity study in rats with ALI/HCTZ has been performed and taking into consideration the uncertainty about the eventual progression of the liver and adrenal damage, explanation of the lack of the chronic study was requested by the CHMP. In response, it was proposed that the histopathology findings during the 2 or 13 week toxicity studies were attributable to expected pharmacological effects or were incidental in origin. However, there are no definitive data, which would exclude the presence of increased kidney damage due to the fixed combination and, indeed, confirm the reversibility of renal changes after repeated treatment, and therefore, the CHMP recommended to include an appropriate statement in the SPC.

- Reproduction Toxicity

Aliskiren and hydrochlorothiazide monotherapies are not recommended for use during pregnancy or for nursing mothers. There are no adequate data on the use of aliskiren during pregnancy but based on the available literature, the administration of drugs affecting the renin-angiotensin system during the second or third trimester has been associated with foetal malformations and neonatal deaths in humans. Intra-uterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with foetal or neonatal thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults. Available non-clinical or clinical data indicate that aliskiren and hydrochlorothiazide will be excreted into breast milk. A thorough evaluation of reproductive organs in male and female animals during 2 week and 13 week toxicity studies for ALI/HCTZ revealed no significant effects.

Medicinal products affecting the RAAS are contraindicated in the EU during second and third trimesters of pregnancy and additional reproductive toxicity studies to assess the effects of ALI/HCTZ on female fertility are therefore considered not to be justified and would be of limited value as the results would not alter the risk benefit analyses for the proposed patient population.

- Local tolerance

There were no additional studies on local tolerance conducted with the ALI/HCTZ combination.

- Other toxicity studies

Based on the available preclinical and clinical data for aliskiren, hydrochlorothiazide and ALI/HCTZ combination, there were no findings that would require special studies to investigate antigenicity, immunotoxicity or dependency. All metabolites and drug substance impurities for ALI/HCTZ were assessed during the individual preclinical investigations of the monotherapy components. The evaluated impurities were within specified limits in the ALI/HCTZ drug substances and the drug product. Further toxicological evaluations of metabolites or drug substance impurities were therefore not considered necessary. No additional toxicities were identified for the combination product that required further investigation in a mechanistic toxicology program.

Ecotoxicity/environmental risk assessment

According to Directive 2001/83/EC (as amended) and EMEA guideline (EMEA/CHMP/SWP/447/00) the environmental risk assessment is required for all new marketing authorisation applications for a medicinal product. The placement of aliskiren and hydrochlorothiazide on the EU market in form of the fixed combination might not constitute any significant risk to the environment. However, the CHMP does not agree that no further environmental risk assessment is required for hydrochlorothiazide because of the low contribution of ALI/HCTZ on total hydrochlorothiazide use in the EU. The absence of further studies on hydrochlorothiazide could not be justified. Therefore, in order to provide information on the additional environmental exposure and size of the population that will contribute to the increased environmental exposure of the combination product possibly due to use of the product in patients inadequately controlled by aliskiren, the following studies for hydrochlorothiazide will be performed as follow up measures:

- Transformation in aquatic sediment systems (OECD 308)
- Adsorption/Desorption (OECD 106)
- Algae Growth Inhibition Test (OECD 201)

As with all non-readily biodegradable human medicines, patients should are advised not to dispose of unused aliskiren *via* the domestic sewage.

2.4 Clinical aspects

Introduction

The clinical development program supporting the registration of the fixed combination of aliskiren/hydrochlorothiazide consisted of a multifactorial design study with adequate doses of each monotherapy components and the combination of the components, studies of the combination therapy in patients who do not adequately respond to aliskiren or hydrochlorothiazide monotherapy, and a long-term safety and efficacy study. Overall, the clinical program included a total of 8 472 patients. Since some of the studies were conducted with the free combination of aliskiren and hydrochlorothiazide, a bioequivalence development program was included to bridge the clinical efficacy and safety data obtained with free combination drugs with those obtained with the final fixed dose combination product. The summary of clinical studies are in the table below.

Topic	Source of data
Dose selection studies	None
Short-term (8 weeks) placebo-controlled efficacy study	• **Study CSPP100A2204:** double-blind, placebo-controlled 4 X 4 multifactorial study with aliskiren monotherapy, HCTZ monotherapy and aliskiren in combination with HCTZ
Short-term (8-12 weeks) active-controlled efficacy studies	**Study in patients not adequately responding to aliskiren monotherapy:** • **Study CSPP100A2332:** double-blind, active-controlled study evaluating the combination of aliskiren/HCTZ (300/12.5 mg) and aliskiren/HCTZ (300/25 mg) in non-responders to aliskiren 300 mg **Studies in patients not adequately responding to HCTZ monotherapy:** • **Study CSPP100A2333:** double-blind, active-controlled study evaluating the combination of aliskiren/HCTZ (150/25 mg) and aliskiren/HCTZ (300/25) in non-responders to HCTZ 25 mg • **Study CSPP100A2331:** double-blind, active-controlled study evaluating the combination of aliskiren/valsartan/HCTZ (300/320/25 mg), aliskiren/HCTZ (300/25 mg), and valsartan/HCTZ (320/25 mg) in non-responders to HCTZ 25 mg • **Study CSPP100A2309:** double-blind, active-controlled study evaluating the combination of aliskiren/HCTZ in comparison to HCTZ monotherapy and combination therapies of irbesartan/HCTZ and amlodipine/HCTZ in obese patients non-responders to HCTZ 25 mg **Supportive study:** • **Study CSPP100A2303*:** double-blind, active-controlled study evaluating aliskiren and lisinopril with optional addition of HCTZ in severe hypertension.
Long-term (6 to 12 months) studies	• **Study CSPP100A2302* / 2302E1:** open-label, 12-month study, evaluating aliskiren monotherapy and aliskiren in combination with HCTZ and a 4-month extension to this study • **Study CSPP100A2306*:** double-blind, active-controlled 6-month study comparing aliskiren and ramipril with optional addition of HCTZ
Other clinical studies	• **Study CSPP100A1202*:** open-label, 12-month study evaluating aliskiren monotherapy with optional addition of diuretic or calcium channel blocker in Japanese patients • **Study CRD07/CSPP100A0014*:** open-label, phase II trial of aliskiren monotherapy and aliskiren in combination with HCTZ

*In these studies, open-label addition of HCTZ was permitted or required in patients whose BP was not adequately controlled by other treatment, including aliskiren.

The claimed indication is:

Treatment of essential hypertension.
Rasilez HCT is indicated for the initial treatment of hypertensive patients unlikely to achieve target blood pressure with a single agent, such as patients with:
- markedly elevated blood pressure (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg)
- additional cardiovascular risk such as diabetes, renal impairment or known cardiovascular disease

Rasilez HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide monotherapy.
Rasilez HCT is indicated as replacement therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination.

The approved indication is:
Treatment of essential hypertension in adults.
Rasilez HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone. Rasilez HCT is indicated as substitution therapy in patients adequately

controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination.

The regulatory requirements relevant for fixed dose antihypertensive drug combinations are described in the following regulatory guidance documents:

1. Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, CPMP/EWP/238/95 Rev. 2.
2. Note for Guidance on fixed combination medicinal products, NfG/CPMP/EWP/240/95 Rev.1
3. Questions and Answers Document on the Clinical Development of Fixed Combinations of Drugs Belonging to Different Therapeutic Classes in the Field of Cardiovascular Treatment and Prevention, CHMP/EWP/191583/2005.
4. Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98).

The design and conduct of the clinical studies followed the relevant regulatory authority guidelines in effect at the time of study initiation. The clinical development program for aliskiren/hydrochlorothiazide and study designs were discussed with the National Health Authorities of France, Denmark, Sweden, and the United Kingdom, 2005.

There is no paediatric development programme. According to the European legislation valid at the time of submission, there was no need to submit a paediatric investigation plan before July 2008.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. The assessment of the clinical data did not raise concerns about their compliance with GCP. No inspection was requested.

Pharmacokinetics

This application is based on clinical trials demonstrating the claimed therapeutic advantages of the proposed aliskiren/hydrochlorothiazide combination. However, in the clinical trials the two components were administered separately and it was necessary to prove that the new fixed dose combination product is the same in terms of rate and extent of absorption of each therapeutic moiety administered concurrently as the separate monotherapy products. In order to bridge the information obtained with the free combination used in definitive clinical efficacy and safety studies to the new fixed combination film-coated tablet product, a bioequivalence development program was designed as part of the registration application. Three definitive bioequivalence studies were conducted with the dose strengths, 150/25 mg, 300/12.5 mg, and 300/25 mg of aliskiren/hydrochlorothiazide. Based on the compositional proportionality and similarity in *in vitro* dissolution properties, a bio-waiver was requested for the fourth dose strength, 150/12.5 mg of aliskiren/hydrochlorothiazide. All bioequivalence studies were carried out in fasting state. However, it is known that aliskiren has pronounced food effect. Thus, investigations whether the fixed combination product has the same property were conducted, and aliskiren and hydrochlorothiazide plasma concentrations in fasting and fed states were compared in a fourth study. Details of these new four pharmacokinetics studies are summarized below:

Study No	Study design and purpose	Patients completed treatment
CSPH100A2101	An open-label, randomized, single-dose, crossover study to determine the bioequivalence of a fixed combination of aliskiren/HCTZ 150/25 mg tablet and the free combination of aliskiren 150 mg over encapsulated tablet and HCTZ 25 mg hard gelatin capsule	68
CSPH100A2102	An open-label, randomized, single-dose, crossover study to determine the bioequivalence of a fixed combination of aliskiren/HCTZ 300/12.5 mg tablet and the free combination of aliskiren 300 mg tablet and HCTZ 12.5 mg hard gelatine capsule	64
CSPH100A2103	An open-label, randomized, single-dose, crossover study to determine the bioequivalence of a fixed combination of aliskiren/HCTZ 300/25 mg tablet and the free combination of aliskiren 300 mg tablet and HCTZ 25 mg hard gelatine capsule	66
CSPH100A2104	A randomized, open-label, single-dose, two-period, crossover study in healthy subjects to evaluate the effect of food on the bioavailability of aliskiren/HCTZ (300/25 mg) fixed combination final market image tablet	27

- Absorption

No new pharmacokinetic studies were performed with aliskiren/hydrochlorothiazide fixed combination. Based on studies previously conducted with the mono component, the oral bioavailability of aliskiren was greater following administration of capsules (2.6 ± 0.8%) than oral solution (1.9 ± 0.7%). It is unusual that oral biovailabilty of solution is less than that of the capsule (or tablet). The low bioavailability of aliskiren can be explained by the fact that aliskiren has a low intrinsic permeability and that it is effectively pumped out by multi drug resistance 1 (MDR1) transport proteins present in the gut epithelial cells. It is supposed that aliskiren undergoes an active efflux in the gut and an effective first pass excretion into bile. The observed double peaked plasma aliskiren profiles remain unexplained, but they suggest an involvement of active transporters in the liver. Absorption of hydrochlorothiazide following the oral administration is rapid with t_{max} about 2 hours, with similar absorption profiles for both suspension and tablet formulations. Absolute bioavailability of the compound is 60-80%.

Effect of food

During the development of aliskiren as a monotherapy it became apparent that meals with high fat content reduce the C_{max} by more than 85%, the AUC by approximately 70% and the bioavailability by more than 60%. Therefore, study ALI/HCTZA 2104 aimed to evaluate the effect of a high fat meal on aliskiren and hydrochlorothiazide pharmacokinetics after administration of 300/25 mg aliskiren/hydrochlorothiazide tablet under both fasting and fed conditions to 30 volunteers. The meal of a high fat breakfast (2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz (100 g) of hash brown potatoes, 8 fl oz (200 ml) of whole milk) was recommended by the FDA. For administration under fed conditions, the tablet was administered 5 min after completion of the meal. This study employed a classical single dose, two-period, two-treatment, crossover design. A fixed inter-dose interval of 16 days was observed by all subjects.

Bioavailability results for aliskiren and HCTZ pharmacokinetic parameters following single oral doses of SPH100 (aliskiren 300 mg/HCTZ 25 mg) in fixed combination tablet (Test – fed; Reference - fasted) (N=30) are presented below:

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test [a]	Reference [a]	Estimate	90% Confidence Interval
Aliskiren				
Cmax (ng/mL)	39.16	213.81	0.18	0.14 – 0.24
AUC0-tlast (h•ng/mL)	457.52	1204.74	0.38	0.33 – 0.44
AUC0-inf (h•ng/mL)	522.25	1312.96	0.40	0.34 – 0.46
HCTZ				
Cmax (ng/mL)	153.98	136.59	1.13	1.06 – 1.20
AUC0-tlast (h•ng/mL)	1103.80	978.07	1.13	1.06 – 1.20
AUC0-inf (h•ng/mL)	1143.27	1011.82	1.13	1.07 – 1.20
a: Test: Fed (Treatment 1); Reference: Fasted (Treatment 2)				

The study confirmed that a high fat meal markedly reduces aliskiren rate and extent of absorption. Bioavailability was reduced by 60-70%. Based on the geometric mean ratios, C_{max} and AUC under fed conditions were reduced by 82% and 60%, respectively, as compared with under fasted conditions. The effect of food on hydrochlorothiazide bioavailability was not statistically significant. Intra-subject coefficients of variation of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ for aliskiren were 61.67%, 34.16% and 34.47% respectively. Therefore, the CHMP was concerned about the proposed recommendation for administration of the product with a light meal. No supportive scientific data exists at present and the effect of meals with different composition to that of high fat breakfast remains unclear. The data analyses provided during the procedure reasonably demonstrate that the food effect is most probably independent of formulation and the results of the bioequivalence study under fasting conditions could be extrapolated to fed conditions. In addition, there are follow up measures to conduct a post approval studies to further assess food effect of a light meal on aliskiren.

Bioequivalence

In order to bridge the clinical efficacy and safety data obtained with free combination drugs to the fixed combinations, a bioequivalence development programme consisting of three definitive bioequivalence studies with the dose strengths 150/25 mg (study CALI/HCTZA2101), 300/12.5 mg (study CALI/HCTZA2102), and 300/25 mg (study CALI/HCTZA2103) of ALI/HCTZ. As mentioned above, a bio-waiver was requested for dose strength 150/12.5 mg of ALI/HCTZ.

Bioequivalence studies are summarised in the following table

Study No.	Objective	Population		Dosage form	Dose	N
CSPH100A2101	Definitive Bioequivalence	HS	M/F	Aliskiren (CSF)	150 mg SD	70
				HCTZ (CSF)	25 mg SD	
				Aliskiren/HCTZ tablet (FMI)	150/25 mg SD	
CSPH100A2102	Definitive Bioequivalence	HS	M/F	Aliskiren (FMI)	300 mg SD	70
				HCTZ (CSF)	12.5 mg SD	
				Aliskiren/HCTZ tablet (FMI)	300/12.5 mg SD	
CSPH100A2103	Definitive Bioequivalence	HS	M/F	Aliskiren (FMI)	300 mg SD	70
				HCTZ (CSF)	25 mg SD	
				Aliskiren/HCTZ tablet (FMI)	300/25 mg SD	

HS-healthy subjects, M-male, F-female

The design and conduct were the same in all three bioequivalence studies. The studies were correctly designed and sample sizes were adequate. Bioequivalence was evaluated after single dose, under fasting conditions. Washout periods between treatments allowed complete elimination of drugs before the next treatment period. Because food markedly reduces the bioavailability of aliskiren, and bioequivalence may depend on fed/fasting status, the studies do not allow concluding on bioequivalence under fed conditions. In addition, the recommendations of the *Note for Guidance on the investigation of bioavailability and bioequivalence* (CPMP/EWP/QWP/1401/98) were not fully followed, since the document indicates that if the SPC contains specific recommendations in relation with food intake, the study should be designed accordingly (see section *Effect of food*). Nevertheless, the results of the studies show that under fasting conditions, the fixed combination tablets are bioequivalent to the free combinations (aliskiren tablets + hydrochlorothiazide capsules) used in the clinical studies. An additional issue was the source of hydrochlorothiazide in the clinical trials conducted. In the pivotal clinical studies, so called clinical service form (CSF) hydrochlorothiazide capsules were used to prove the additional benefits of ALI/HCTZ compared to aliskiren. The CSF hydrochlorothiazide capsules were used to keep patients blinded to the treatment and this is an acceptable justification. Therapeutic equivalence between the clinical development formulation and the final market formulation was proved via bioequivalence studies. The HCTZ CSF used in ALI/HCTZ clinical trials were proven to be bioequivalent to a medicinal product approved in the EU (Co-Diovan®).

A bio-waiver was requested for the 150/12.5 mg ALI/HCTZ dose. This recommendation was based on the following justifications:

- The composition of the 150/12.5 mg ALI/HCTZ fixed combination tablet is proportional in its active and inactive ingredients to the 300/25 mg ALI/HCTZ fixed combination tablet, for which the bioequivalence was established,
- Aliskiren and hydrochlorothiazide exhibit linear and/or dose proportional pharmacokinetics
- *In vitro* dissolution of aliskiren and hydrochlorothiazide is similar in three pH media between the 300/25 mg and 150/12.5 mg fixed combination products.

The argument of linear and/or dose proportional pharmacokinetics of aliskiren and hydrochlorothiazide was questioned, since already the kinetics of aliskiren itself is slightly nonlinear. In addition, there is a nonlinear component due to the interaction between aliskiren and hydrochlorothiazide and the C_{max} of aliskiren increases even when only the hydrochlorothiazide dose increases. Still, the interaction effect is comparatively small to other drug interactions (e.g. cyclosporine).

- Distribution

Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Selective tissue accumulation also might be a reason of the observed large volume of distribution. In animal studies aliskiren concentrations were substantially higher in the kidney and in the liver than in the plasma. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.
The distribution and elimination kinetics of hydrochlorothiazide is described by a bi-exponential decay function. Hydrochlorothiazide accumulates in erythrocytes, reaching equilibrium at about 4 hours after a single dose. At 10 hours post-dosing, the concentration in erythrocytes is about 3-fold higher than in plasma. Based on literature data, hydrochlorothiazide is essentially limited in its distribution in the body to extracellular fluid space and the kidneys and the volume of distribution is approximately 3-4 litres/kg.

- Metabolism and elimination

The mean half-life of aliskiren is about 40 hours (range 34-41 hours). The drug is eliminated mainly through the hepatobiliary route mainly as unchanged drug. Following intravenous administration, the mean plasma clearance is approximately 9 l/h. Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Unchanged aliskiren was found in the faeces (78%). Approximately 0.6% of the dose is recovered in urine following oral administration. The apparent half-life of hydrochlorothiazide is 6-15 hours. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal (about 20% increase in C_{max}, day 1 *vs* 8), when administered once-daily to healthy subjects.

- Dose proportionality and time dependencies

No analysis of the results from the bioequivalence studies with the combination of aliskiren and hydrochlorothiazide were conducted. The issue of dose response was evaluated in the section on Bioequivalence. Steady-state concentration data are not available with this new fixed combination.

- Special populations

Impaired renal function: The objective of study SPP100A2209 was to compare the pharmacokinetics of aliskiren alone or in combination with irbesartan in subjects with renal impairments and healthy controls. Total exposure was significantly higher in patients with damaged kidney function. Thus, the same systemic exposure of hydrochlorothiazide may therefore be achieved with lower doses of in patients with impaired renal function compared to those with normal renal function. The SPC states that the fixed combination product should not be used in patients with severe renal impairment.

Impaired hepatic function: Hepatic impairment has no significant effect on the pharmacokinetics of aliskiren following single dose administration as shown in study SPP100A 2210. In cases of mild to moderate impaired hepatic function or progressive liver disease, the SPC advices to use of the ALI/HCTZ combination with caution. Due to the hydrochlorothiazide component, the fixed combination product should not be used in patients with severe renal impairment.

Gender: Aliskiren exposure in males compared to females was slightly lower (AUC by 24%, and C_{max} by 30%) however, this difference is not probably related to differences in body weights.

Race: In study SPP100A 2202, there was a slight difference between Caucasian and Asians regarding the kinetics of aliskiren but the observed difference was not clinically relevant.

Weight: Overweight volunteers (more than +20% from the ideal body weight) were excluded from all pharmacokinetic studies.

Elderly: The effect of age on the pharmacokinetics of aliskiren was assessed in study SPP100A2217. The detailed statistical analysis revealed that there has been 50 % increase in the total exposure (AUC) and the C_{max} has been increased by 30 %. Changes in pharmacokinetics in the elderly usually occur due to age-related physiologic perturbations and some of these may explain the increase in drug exposure. The effect of aging on small-bowel transporter systems is not yet fully established but could contribute to the observed increase. Aging is associated with a reduction in hepatic blood flow and kidney clearance which could explain this increase in exposure. Regardless of the reason for the increased exposure, the CHMP was concerned that no dose adjustment was recommended for the elderly, especially since elderly people may be more sensitive to aliskiren in combination with hydrochlorothiazide at the start of the treatment. During the procedure, additional data from a clinical study examining the efficacy and safety of aliskiren based regimens in patients with age ≥ 65 years and systolic essential hypertension were submitted. The results show an acceptable risk/benefit ratio supporting the use of ALI/HCTZ combination in these

patients. In addition, data from the ongoing studies investigating safety and efficacy of ALI in the elderly will be presented to the CHMP.

Children: Aliskiren and hydrochlorothiazide combination is not recommended for use in children.

- Pharmacokinetic interaction studies

The *in vitro* studies, described in the non clinical section of the report, showed that aliskiren does not inhibit any of the CYP450 enzymes at therapeutic concentrations (IC_{50} > 200 μM).

Sixteen *in-vivo* interaction studies were carried out with aliskiren and clinically important interactions were found:

- Co-administration of aliskiren and furosemide does not alter the pharmacokinetics of aliskiren but decreases the AUC and C_{max} of furosemide (28% and 49% respectively). Therefore, it is recommended that the effects of furosemide should be monitored and the dose adjusted, if necessary, when initiating treatment with aliskiren.
- Co-administration of aliskiren and atorvastatin does not alter the steady-state pharmacokinetics of atorvastatin or its metabolites, but increases the steady-state AUC and C_{max} of aliskiren by approximately 50%.
- Ketoconazole is a potent P-glycoprotein and CYP3 A4 inhibitor and increases aliskiren exposure by 1.8 folds. It is likely that this effect is due to the inhibition of P-glycoprotein by ketoconazole, since aliskiren is a substrate for P-glycoprotein.
- An interaction study conducted with aliskiren and cyclosporin shows that cyclosporin increased aliskiren AUC by 4.5 - 5.5 fold, and C_{max} by 2.5 fold, independently of cyclosporin dose. Cyclosporin markedly increased aliskiren $t_{1/2}$. This result confirms that P-glycoprotein is a major determinant of aliskiren clearance. Thus, a contraindication was required by the CHMP for the concomitant use of aliskiren with cyclosporin and other potent P-gp inhibitors, e.g. quinidine, verapamil, and is presented in the SPC.
- The interaction study of aliskiren with hydrochlorothiazide revealed that aliskiren decreases both, the rate and extent of absorption of hydrochlorothiazide. This effect is statistically significant and its mechanism is not understood. Increasing hydrochlorothiazide concentrations increase the C_{max} of aliskiren. But at steady-state the effect of hydrochlorothiazide is just the opposite, it decreases the C_{max} aliskiren by about 20 %. The significance of this observation is most probably of no clinical relevance, but it is important to note that steady-state data were not predictable from the single-dose data.

- Pharmacokinetics using human biomaterials

There were no pharmacokinetic studies conducted with human biomaterials.

Pharmacodynamics

- Mechanism of action

Aliskiren blocks the renin angiotensin system (RAS) by binding to renin and inhibiting the cleavage of angiotensinogen to angiotensin I (Ang I). This action results in a reduction of plasma renin activity (PRA), angiotensin I (Ang I) and angiotensin II (Ang II). Aliskiren inhibits the RAS in a dose dependent manner following single dose administration and at steady state. The evidence for RAS blockade is based on the effects of aliskiren on plasma rennin activity (PRA), Ang I and Ang II levels, urinary and plasma aldosterone levels and plasma renin concentration. Plasma renin activity is a direct measure of the

formation of Ang I in the plasma. Plasma renin concentration (PRC, active renin) measures the concentration of immunoactive renin in the plasma.

Hydrochlorothiazide is an orally active thiazide diuretic that has been proven to be effective for the treatment of hypertension. Although the mechanism is not fully understood, the antihypertensive effect of hydrochlorothiazide is believed to be related to its volume/sodium depletion. Since RAS blockade and volume depletion have been demonstrated to be among the most effective treatments of hypertension, the combination of aliskiren and hydrochlorothiazide is expected to provide more optimal blood pressure control than the monotherapies.

- Primary and Secondary pharmacology

Biomarker data (PRA and PRC) were collected as pharmacodynamic measures in two clinical studies. In study CSPP100A 2204, the treatment with all three aliskiren monotherapy doses was associated with reductions in PRA. Despite the expected increases in PRA found with hydrochlorothiazide monotherapy (range from 4% to 72%), all of the combination dose groups had PRA reductions, ranging from 46% in the ALI/HCTZ 150/25 group to 63% in the ALI/HCTZ 150/6.25 group. Greater increases in rennin concentration with increasing doses were found for the aliskiren and hydrochlorothiazide monotherapy treatment groups, with the increases somewhat greater with aliskiren than hydrochlorothiazide. Overall, these results are consistent with the known pharmacology of many antihypertensives, which leads to a compensatory rise in renin release from the juxtaglomerular cells of the kidney. They also confirm the putative mechanism of action of aliskiren, which reduces PRA through its inhibition of the active enzyme. These studies clearly affirmed the putative effects of aliskiren/hydrochlorothiazide combination, i.e. aliskiren blocks the reactive rise in PRA induced by hydrochlorothiazide.

Clinical efficacy

- Dose response study

The selection of aliskiren doses included in the efficacy studies was based on aliskiren monotherapy clinical trial data and the selected hydrochlorothiazide doses included the available marketed strengths that are commonly used for the treatment of hypertension. The final selection of the market strengths for the ALI/HCTZ combination was based on the results of the clinical study CSPP100A2204, which provides data on dose-finding as well as efficacy. It was an 8 week, double-blind, multicenter, randomised, multifactorial, placebo-controlled, parallel-group study on efficacy and safety of aliskiren alone and in combination with hydrochlorothiazide in hypertension patients.

Aliskiren and hydrochlorothiazide were studied alone and in combination. Aliskiren doses were 75, 150, and 300 mg; hydrochlorothiazide doses were 6.25, 12.5, and 25 mg; and all combinations, with the exception of 300/6.25 mg, were studied. A review of the reductions in diastolic blood pressure (DBP) and systolic blood pressure (SBP) provided by the combinations of each of the three aliskiren doses with either 12.5 or 25 mg of hydrochlorothiazide, subtracted from placebo or from the respective individual hydrochlorothiazide component dose, reveals dose-related effects.

Aliskiren combinations with HCTZ 12.5 mg – placebo-subtracted and HCTZ-subtracted effects on DBP and SBP (primary ITT population – Study CSPP100A2204)

Aliskiren/HCTZ dose (mg)	DBP – PBO-subtracted	SBP – PBO-subtracted	DBP – HCTZ-subtracted	SBP – HCTZ-subtracted
75/12.5	-4.21	-8.16	-1.03	-1.71
150/12.5	-4.97	-10.13	-1.79	-3.69
300/12.5	-6.93	-12.33	-3.76	-5.89

Aliskiren combinations with HCTZ 25 mg – placebo-subtracted and HCTZ-subtracted effects on DBP and SBP (primary ITT population – Study CSPP100A2204)

Aliskiren/HCTZ dose (mg)	DBP – PBO-subtracted	SBP – PBO-subtracted	DBP – HCTZ-subtracted	SBP – HCTZ-subtracted
75/25	-4.52	-9.84	-2.09	-3.02
150/25	-5.71	-11.99	-3.28	-5.17
300/25	-7.33	-13.74	-4.90	-6.92

The combination of aliskiren with hydrochlorothiazide was well-tolerated. The selected doses appear to be appropriate for patients with mild to moderate essential hypertension. The choice of combinations of four strengths: 150 or 300 mg aliskiren with either 12.5 mg or 25 mg hydrochlorothiazide seem appropriate, in particular for patients not adequately responding to aliskiren monotherapy. The clinical efficacy of aliskiren given alone increases in a dose-dependent manner (150 and 300mg), whereas no constant and significant blood pressure (BP) lowering effects occur when increasing hydrochlorothiazide dose from 12.5 mg to 25 mg. Based on this clinical data, the use of aliskiren combined with hydrochlorothiazide 25 mg might be questionable. However, considering the indication of ALI/HCTZ as add-on therapy or replacement therapy, the efficacy data have to be analyzed with focus on non-responder studies. All data from these studies (CSPP100A2332 and 2333) indicate that in combination with aliskiren 300 or 150 mg, hydrochlorothiazide 25 mg lowered blood pressure more than hydrochlorothiazide 12.5 mg without a substantial change in the safety profile. The difference in blood pressure reduction between the two hydrochlorothiazide doses was not statistically significant in all analyses but overall the data support a positive benefit/risk assessment for the four doses of ALI/HCTZ in the general hypertension population with inclusion of elderly patients.

- Main studies

Clinical efficacy was observed in placebo-controlled and active-controlled studies, as follows:

- *Dose-selection study:*
  1 placebo-controlled study (SPP100A2204)
- *Confirmatory efficacy studies:*
  5 active-controlled studies:
  - 4 studies in mild to moderate hypertension – not adequately responding to aliskiren or hydrochlorothiazide monotherapy (SPP100A2331, 2332, 2333, 2309)
  - 1 study in uncomplicated severe hypertension (SPP100A2303)
- *Long-term efficacy studies:*
  3 studies in total:
  - 1 double-blind, active controlled 6-month studies (SPP100A2306)

- 1 open label 12-month study, including a one-month, randomised, double-blind withdrawal period to confirm long-term efficacy (SPP100A2302) and a 4-month extension to this study (SPP100A2302E1)

Most of these short-term and long-term efficacy studies may be regarded as pivotal as they provide the principal evidence of the efficacy of aliskiren in hypertension. Each study contributes to the proof of efficacy on different level, and thus, will be accordingly described under the relevant efficacy and safety endpoint. Moreover, in some studies, comparison was made to other antihypertensive drugs, including ACE inhibitor, angiotensin receptor blocker, calcium channel blocker. Combinations of these drugs were also analysed. The following table provides a brief overview of the pivotal studies.

Overview of main studies								
Title/ Study Number	**Design**	**Study Posology**	**Study Objective**	**Subjects randomised**	**Duration**	**Gender M/F; age**	**Dg/ Incl. criteria**	**Primary Endpoint**
An 8 Week Double-Blind, Multicenter, Randomized, Multifactorial, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aliskiren Administered Alone and in Combination With Hydrochlorothiazide in Patients With Essential Hypertension								
CSPP100 A 2204	Randomised, double-blind, placebo-controlled, parallel group	75, 150, 300 aliskiren mg/day; HCTZ 6.25, 12.5, 25 mg; aliskiren/ HCTZ 150/6.25, 150/12.5, 150/25 mg; aliskiren/ HCTZ 300/12.5, 300/25 mg; placebo	Efficacy and safety of aliskiren (compared with combination with HCTZ)	2776	8 weeks	Males: 54.8%; mean age: 55 ys	Essential hypertension (mild to moderate)	Change in msDBP
An Eight-Week Multicenter Study to Evaluate the Efficacy and Safety of the Combination of Aliskiren / HCTZ (300/12.5 mg and 300/25 mg) in Comparison With Aliskiren 300 mg in Patients With Essential Hypertension Not Adequately Responsive to Aliskiren 300 mg Monotherapy								
CSPP100A 2332	Randomised, double-blind, parallel group	- Aliskiren 300 mg + 12.5 mg or 25 mg HCTZ - Aliskiren 300 mg	Efficacy and safety of aliskiren (compared with combination with HCTZ)	880	8 weeks	Males: 60.7% mean age: 55 ys	Patients not adequately responding to 300 mg aliskiren mono-therapy	Change in msDBP
An Eight-Week Multicenter Study to Evaluate the Efficacy and Safety of the Combination of Aliskiren / HCTZ (150/25 mg and 300/25 mg) in Comparison With HCTZ 25 mg in Patients With Essential Hypertension Not Adequately Responsive to HCTZ 25 mg Monotherapy								
CSPP100A 2333	Randomised, double-blind, parallel group	- Aliskiren 150 mg or 300 mg with HCTZ 25 mg - HCTZ 25 mg	Efficacy and safety of aliskiren + HCTZ (compared with HCTZ	722	8 weeks	Males: 59.1%; mean age: 54.6 ys	Patients not adequately responding to HCTZ 25 mg mono-therapy	Change in msDBP
An Eight Week, Multicenter Study to Evaluate Efficacy and Safety of the Triple Combo of Aliskiren /Valsartan/HCTZ (300/320/25 mg), Compared to the Double Combos of Aliskiren/HCTZ (300/25 mg) or Valsartan/HCTZ (320/25 mg) in Patients With Essential Hypertension Not Adequately Responsive to HCTZ 25 mg								
CSPP100A 2331	Randomised, double-blind, parallel group	- Aliskiren 300 mg with valsartan 320 mg and HCTZ 25 mg; - Aliskiren 300 mg with HCTZ 25 mg; - Valsartan 320 mg with HCTZ 25 mg: - HCTZ 25 mg	Efficacy/ safety of combined therapy (compared within arms)	641	8 weeks	Males: 56.9%; mean age: 53.2 ys	Patients not adequately responding to HCTZ 25 mg mono-therapy	Change in msDBP
A 12-Week Randomized Double-Blind Parallel Group Study to Evaluate the Efficacy and Safety of the Combination Aliskiren With HCTZ Compared to Irbesartan or								

Amlodipine With HCTZ or HCTZ Alone in Hypertensive Patients With BMI ≥ 30 kg/m2 Not Adequately Responsive to HCTZ 25 mg								
CSPP100A 2309	Randomised, double-blind, parallel group	300 mg aliskiren + 25 mg HCTZ; irbesartan/HCTZ, amlodipine/HCTZ; HCTZ	Efficacy/ safety of combined therapy	493	12 weeks	Males: 43.6%, mean age: 54.1 ys	Essential hypertension in obese patients, not adequately responsive to HCTZ	Change in msDBP
An Eight-Week, Randomized, Double-Blind, Multi-Center, Active-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of an Aliskiren-Based Regimen Compared to a Lisinopril-Based Regimen in Patients With Uncomplicated Severe Hypertension								
CSPP100A 2303	Randomised, double-blind, active controlled, parallel group	150-300 mg aliskiren ± HCTZ vs 20-40 mg lisinopril ± HCTZ	Efficacy/ safety of combined therapy	183	8 weeks	Males: 56.8%, mean age: 55 ys	Uncomplicated severe hypertension	Change in msDBP (vs baseline compared within arms)
A 12 Month, Randomized, Open-Label, Multicenter, Study to Assess the Long-term Safety of Aliskiren 150 mg Alone and 300 mg Alone or With the Optional Addition of Hydrochlorothiazide (12.5 mg or 25 mg) in Patients With Essential Hypertension.								
CSPP100A 2302	Randomised, open-label, parallel group	150 and 300 mg aliskiren (mono), 300 mg aliskiren + 12.5 or 25 mg HCTZ (combo)	Long-term safety/ efficacy of mono and combined therapy	1955	12 months	Males: 50.3-55.3%, mean age: 54.8-57 ys	Essential hypertension (mild to moderate)	Change in msDBP Long-term efficacy/safety
A 4 Month Extension to a 12 Month, Randomized, Open-Label, Multicenter, Study to Assess the Long-Term Safety of Aliskiren 150 mg Alone and 300 mg Alone or With the Optional Addition of Hydrochlorothiazide (12.5 mg or 25 mg) in Patients With Essential Hypertension								
CSPP100A2302 E1	Extension of #2302 (Randomised open-label)	150 or 300 mg aliskiren ± 12.5 or 25 mg HCTZ	Long-term safety	198	16 weeks	Males: 49.5%, mean age: 57.2 ys	Essential hypertension (mild to moderate)	Change in msDBP Long-term efficacy/safety
A 26 Week, Double-Blind, Randomized, Multicenter, Parallel Group, Active-Controlled Study Comparing Aliskiren to Ramipril With Optional Addition of Hydrochlorothiazide, Followed by a 4 Week Double-Blind, Randomized, Placebo-Controlled Withdrawal in Patients With Essential Hypertension								
CSPP100A2306	Randomised, double-blind, parallel group	150 mg, 300 mg aliskiren ± HCTZ vs. 5,10 mg ramipril ± HCTZ	Long-term efficacy/safety compared to ramipril ±HCTZ	842	26 weeks +4 weeks withdrawal	Males: 57%, mean age: 53.3 ys	Essential hypertension (mild to moderate)	Change in msDBP Long-term safety/efficacy, withdrawal effects

METHODS

Clinical studies were randomised, controlled multicenter type. There was one placebo controlled study, CSPP100A2204; all the others were active controlled, with the following reference agents: aliskiren, hydrochlorothiazide, valsartan or irbesartan, lisinopril, amlodipine and their combinations. All studies were double-blind, the only open study was CSPP100A2302, and its extension CSPP100A2302E1. Some large-scale studies were performed in well over 100 centres.

Study Participants
Efficacy was tested in patients over the age of 18 with mild to moderate hypertension (DBP from 95 and 110 mm Hg). Patients with severe or secondary hypertension were excluded in all studies except for study CSPP100A2303, in which the patient population had severe hypertension. Patients were also excluded if they had recent or ongoing cardiovascular or cerebrovascular disorders that would preclude even brief periods off antihypertensive treatment used for either BP control or protection against morbidity and mortality. The clinical studies also excluded most patients with severe renal or hepatic impairment or poorly controlled diabetes. Children and women who were pregnant or nursing were not studied. Study populations were representative of adult patients requiring treatment for hypertension and the characteristics of patients were balanced among treatment groups with some exceptions, e.g. 78,9% of patients were younger than 65 years and only 3,6 % were 75 years or older. With the exception of study CSPP100A2303 (severe hypertension group), the patients suffered from mild-to-moderate essential hypertension. Complicated cases were excluded, with the exception of co-morbidity problems with body weight and metabolism, such as obesity (higher BMI), metabolic syndrome and (controlled) diabetes mellitus, and in some cases, mild cardiovascular diseases.

Treatments
According to the results of pharmacokinetic studies, aliskiren was administered once in the morning (at 8:00 h) (OD) at a dose of 75, 150, 300 mg (in the majority of studies 150 or 300 mg) in combination with hydrochlorothiazide 6.25, 12.5 or 25 mg (in the majority of studies 12.5 or 25 mg).
The doses of comparators in the active-controlled studies:

amlodipine	5 and 10 mg
lisinopril	20 and 40 mg
valsartan	320 mg

The majority of studies were short-term (8-12 weeks: study CSPP100 1201, 2308, 2203, 2204, 2305, 2307, 2309, 2303, 2324), one study (2306) lasted for 26 weeks and 1 study (2302) lasted for 52 weeks with an additional 4-month extension (2302E1) in a subset of patients.

Objectives
With the exception of study CSPP100A2303 (see below), studies were performed in mild-to-moderate essential hypertension. The efficacy was assessed:
- in ALI/HCTZ combination therapy, compared with placebo,
- in ALI/HCTZ combination therapy compared with the drugs alone (monotherapy), i.e. to test the superiority of combined therapy to monotherapy.

In study CSPP100A2303, the efficacy of aliskiren was assessed in uncomplicated severe hypertension. In this study the efficacy of aliskiren with or without hydrochlorothiazide was compared with ramipril with or without hydrochlorothiazide. In the majority of studies patients with obesity, and metabolic syndrome and/or treated diabetes mellitus were not excluded.

The primary objective of study CSPP100A2204 was to test the superiority of aliskiren plus hydrochlorothiazide combination to monotherapy. A dose-response relationship was calculated. In the other short-term studies, the efficacy and safety of ALI/HCTZ was studied in patients who were not adequately responding to aliskiren 300 mg or hydrochlorothiazide 25 mg monotherapy. In the long-term studies, the long-term efficacy and safety of ALI/HCTZ combination was studied. The persistence of effect and possible withdrawal/rebound phenomena were also addressed.

The primary aim was to prove the concept that ALI/HCTZ combination therapy is more effective than monotherapy with either component. The posology of this combination is based on this concept.

Outcomes/endpoints
The primary and key secondary efficacy variables were changes in msDBP and msSBP. Blood pressure was measured according to *CHMP Note for Guidance on Clinical Investigation of Medicinal Products in the treatment of hypertension* (CPMP/EWP/238/95/Rev2). Other major secondary variables included the proportion of patients who were responders (DBP <90 mm Hg and/or ≥10 mm Hg less than at baseline), the proportion of patients whose BP was controlled (BP < 140/90). In some studies, dose-response surface analysis and biomarkers PRA and RC were also determined. The endpoints were considered appropriate.

Sample size
Sample sizes, assuming a dropout rate of 10% and equal randomization ratio, were calculated based on the primary variable, change from baseline in msDBP and a standard deviation of 8 mmHg. The sample size was calculated to ensure 90% power to detect statistical significance for both pair-wise comparisons under the alternative hypothesis that the treatment difference is 2.5 mmHg at a two-sided significance level of 0.05. It was needed to show that the combination is statistically superior to both monotherapy treatments. Therefore no statistical adjustment for two pair-wise comparisons was needed. If non-inferiority was statistically detected, a superiority test was performed. This sample size would have more than 90% power in the test that aliskiren is superior to ramipril under the alternative hypothesis that the treatment difference is greater than 2.5 mmHg at a two-sided significance level of 0.05. The approach for sample size calculation was considered appropriate.

Randomisation
In the appropriate studies, randomisation was performed using a randomisation list with a validated system that automates the random assignment of treatment groups to randomisation numbers in the specified ratio. The randomisation scheme was reviewed by a statistical and quality assurance expert, and locked.

Blinding (masking)
Based on the inclusion and exclusion criteria, patients eligible to enter the double-blind treatment period of the appropriate study, investigator staff, persons performing the assessments, and data analysts were blinded to the identity of the treatment from the time of randomisation until database lock, using the following methods: randomisation data were kept strictly confidential until the time of unblinding; the identity of the treatments were concealed by the use of study drugs that are all identical in packaging, labelling, schedule of administration, appearance, and odour. In studies where a comparator drug was also used, a double-dummy design was applied because the identity of the study drugs could not be disguised due to their different forms. Unblinding only occurred in case of patient emergencies and at the conclusion of the study. The investigator had the option to break the study blind in cases of emergency. Stratification, if appropriate, was performed only at data analysis. The blinding methodology was deemed acceptable.

Statistical methods
Statistical methods were appropriate for analysing blood pressure changes. The primary efficacy variable (mean change from baseline to endpoint in msDBP at trough in the ITT population) was analysed by a pre-specified two-way analysis of covariance (ANCOVA) with treatment and region as factors, and baseline as a covariate. A statistical adjustment for multiple comparisons using Dunnett's procedure was used for studies including multiple aliskiren doses. The key secondary efficacy endpoint, the msSBP, was analyzed similarly. The proportion of responders and the control rate were analysed by means of a logistic regression model with treatment and region as factors, and baseline msDBP as a covariate.

The primary pairwise comparisons performed were ALI/HCTZ combination doses against their aliskiren and HCTZ monotherapy doses. In addition, pairwise comparisons between an active treatment and placebo were also performed as supportive evaluations. The statistical test for each of the above pairwise comparisons was made at a two-sided significance level of 0.05. Ninety-five

percent confidence intervals of pairwise treatment differences were provided. The BP control rates (msSBP/msDBP < 140/90 mmHg), were analyzed for the Intent-to-treat population and each pairwise treatment comparison was made at a two-sided significance level of 0.05. Separate individual evaluations of systolic and diastolic blood were performed in a similar manner. Between-treatment comparisons of change from baseline in msSBP and msDBP were also performed.

RESULTS

Participant flow
The number of patients randomised, completed, distribution of patients per arms, and discontinued patients in the main clinical trials are shown below:

Study	Nr of patients randomised	Nr of pts completed (%)	Nr. of arms (completed pts/arms)	Nr. of pts discontinued (%)
2204	2776	2558 (92.1%)	16 (159-179 pts/arm)	204 (7.3%)
2332*	880	821 (93.3%)	3 (266-277 pts/arm)	58 (6.6%)
2333*	722	691 (95.7%)	3 (225-235 pts/arm)	29 (4%)
2331*	641	583 (91.0%)	4 (133 – 161 pts/arm)	58 (9%)
2309*	493	448 (91.6%)	4 (109-115 pts/arm)	41 (8.4%)
2303	183	165 (90.2%)	2 (54-111 pts/arm)	18 (9.8%)
2302	1955**	1625 (83.1)	2 (659-966 pts/arm)	330 (16.9%)
2302 E1	198	189 (95.5%)	1	9 (4.5%)

*double-blind period
**open label period, safety population

There were no large imbalances in the numbers of patients discontinuing for various reasons, other than a tendency for more patients to discontinue for lack of efficacy in placebo group. Addition of hydrochlorothiazide to aliskiren did not result in increased patient withdrawals. The number of patients who discontinued due to adverse events ranged between 1 and 5.2% and there was a higher discontinuation rate (16.9%) in study 2302, which had longer treatment duration (1 year) than other studies.

Recruitment
The main efficacy and safety confirming studies were conducted in Europe, Asia, North, South and Latin America. Studies were initiated and completed between 2004 and 2007. Inclusion/exclusion criteria of the relevant study were considered when recruiting patients.

Conduct of the study
If applicable, patients were randomised and entered the study with control and/or with concomitant therapies. At set time points, monitoring visits were conducted by responsible study monitors in accordance with the study protocol. Patient visits were conducted as planned in the protocol and appropriate examinations, laboratory tests and procedures were performed. Results of medical tests, adverse events and pregnancies were monitored throughout the duration of the studies and in the follow up period. Some minor procedural amendments were made to some studies aiming at uniformity of the studies. These did not affect the outcomes or statistical analyses.

Baseline data
Clinical trials included patients with mild to moderate essential hypertension, (msDBP ≥90 or 95 mmHg and <110 mmHg), except for study CSPP100A2303, which recruited patients with severe

hypertension, with msDBP ≥105 and <120 mmHg. In addition, study CSPP100A2309 enrolled exclusively patients who were obese (BMI ≥ 30 kg/m^2). Other than these differences, placebo- and active-controlled studies had comparable inclusion/exclusion criteria. The baseline demographic characteristics of the treatment groups were comparable within each study, and were generally comparable across the different studies except for differences specified in the protocols: baseline BP was higher in study CSPP100A2303 as it enrolled severe hypertensive patients and baseline body weight and BMI are greater in study CSPP100A2309 as it enrolled obese patients. Patient disposition was similar across treatment groups in all trials. There was a tendency for more patients to discontinue for lack of efficacy in placebo group and low dose monotherapy (aliskiren 75 mg and hydrochlorothiazide 6.25 mg) groups.

In general, study population was well balanced regarding the age and gender with a relative preponderance of Caucasian race.

Numbers analysed

The numbers of patients per study and per arms completed were sufficient for statistical analysis. The analysis population for efficacy is the Intent-to-Treat (ITT) population, which was defined as all randomized patients who had baseline and at least one post-baseline efficacy measurement. When ITT and per-protocol (PP) analysis were compared, no statistically significant differences were observed.

Change from baseline in msSBP and msDBP were reviewed by treatment group for the ITT population as well as age, gender, race, ethnicity, and obesity subgroups. Overall BP control rate (msSBP/msDBP < 140/90 mmHg), systolic BP control rate (msSBP < 140 mmHg), and diastolic BP control rate (msDBP < 90 mmHg) were analysed by visit and treatment group for the ITT population and for the following subgroups: age, gender, race, diabetes status, renal impairment and hypertension stage. Furthermore, for the overall population and baseline subgroup of patients with additional cardiovascular risk, the following variables were analysed by visit and treatment group: more aggressive overall BP control rate at 130/80, systolic BP control rate at 130, and diastolic BP control rate at 80. The analysis populations in each of the efficacy studies discussed are presented below:

Populations evaluated in efficacy studies (randomized populations)

Study	Population				
	Randomized	Efficacy ITT		Safety	
	N	n (%)		n (%)	
2204	2776	2752	(99.1)	2762	(99.5)
2309	489	487	(99.6)	489	(100.0)
2331	641	637	(99.4)	639	(99.7)
2332	880	872	(99.1)	879	(99.9)
2333	722	718	(99.4)	720	(99.7)
2303	183	182	(99.5)	183	(100.0)
2302	1955 [1]	1928	(98.6)	1955	(100.0)
2302E1 [2]	198	198	(100.0)	198	(100.0)
2306	842	832	(98.8)	841	(99.9)
Total	**8488**	**8408**	**(99.1)**	**8468**	**(99.8)**

Denominator = randomized patients

[1] Population referred to as "Safety population" in this open label study

[2] The 198 patients in the 2302E1 extension are counted under Study 2302, and are not counted separately toward the "Total" row.

Outcomes and estimation

Study SPP100A2204 is relevant for the combination therapy of aliskiren and hydrochlorothiazide as it reports useful data on dose-finding and potentially useful efficacy data. This placebo-controlled multifactorial study confirmed that doses of aliskiren 75, 150, and 300 mg and their combinations with hydrochlorothiazide 6.25, 12.5, or 25 mg lowered msDBP in mild to moderately hypertensive patients more effectively than placebo. Overall, both components significantly contributed to the effects of

combination therapy. The greatest least square (LS) mean reduction of msDBP was seen with ALI/HCTZ 300/25 mg.

Placebo-subtracted LS Mean Reduction in msDBP (mmHg) at Endpoint (primary ITT population – Study CSPP100A2204)

		Aliskiren		
	Placebo	75 mg	150 mg	300 mg
Placebo	---	-1.75[a]	-2.01[a]	-3.33[a]
HCTZ 6.25 mg	-2.14[a]	-3.83[a, b, c]	-3.42[a]	---
HCTZ 12.5 mg	-3.18[a]	-4.21[a, b]	-4.97[a, b, c]	-6.93[a, b, c]
HCTZ 25 mg	-2.43[a]	-4.52[a, b, c]	-5.71[a, b, c]	-7.33[a, b, c]

Placebo response: -6.93 mmHg
[a] Statistically significant difference vs. placebo ($p < 0.05$)
[b] Statistically significant difference vs. aliskiren component ($p < 0.05$)
[c] Statistically significant difference vs. HCTZ component ($p < 0.05$)

In addition, the between-treatment analysis showed that all combinations that contained aliskiren doses of 150 or 300 mg and hydrochlorothiazide 12.5 or 25 mg demonstrated statistically greater msSBP reduction than their component monotherapies with the greatest reduction seen with ALI/HCTZ 300/25 mg.

Study SPP100A2303 is important for the efficacy proof of aliskiren monotherapy, but is not of interest for the combination ALI/HCTZ. Data were analysed and are available, but do not provide adequate information on the comparison of ALI+HCTZ with aliskiren alone. This is due to the fact that hydrochlorothiazide treatment was introduced as an additional therapy at different time points in the study and there are not data on hydrochlorothiazide use alone. The main aim of this study was the assessment of the aliskiren efficacy in comparison with that of lisinopril.

Study SPP100A2306 reports information is of limited interest for the combination ALI/HCTZ. The comparison of the add-on ALI+HCTZ therapy *vs* aliskiren alone has two major limitations: 1. only a small number of patients in this study required the addition of hydrochlorothiazide; 2. the addition of hydrochlorothiazide occurred at various time points and at variable doses. There are not data about the comparison of ALI+HCTZ *vs* hydrochlorothiazide alone. The main aim of this study was the assessment of the aliskiren efficacy in comparison with that of ramipril.

Study SPP100A2309 is relevant for the combination ALI/HCTZ. In this study with obese hypertensive patients not adequately responsive to HCTZ monotherapy, ALI/HCTZ 300/25 mg produced a statistically significant superior reduction in msDBP compared to HCTZ 25 mg alone at Week 8 endpoint ($p<0.0001$). The ALI/HCTZ regimen had safety and tolerability similar to treatment with hydrochlorothiazide alone. Data support the use of the combination of aliskiren with hydrochlorothiazide as a second line indication, limitedly to obese patients pre-treated with hydrochlorothiazide. Comparisons of the efficacy of ALI/HCTZ with irbesartan/HCTZ and amlodipine/HCTZ combinations, although numerically greater, were not statistically significant.

Between-treatment analysis for change from baseline in msDBP at Week 8 endpoint in Study CSPP100A2309 (ITT population)

Treatment group	N	LSM change from baseline (SE)	
Aliskiren 300 mg / HCTZ 25 mg	113	-11.91 (0.74)	
Irbesartan 300 mg / HCTZ 25 mg	117	-11.33 (0.72)	
Amlodipine 10 mg / HCTZ 25 mg	122	-10.30 (0.71)	
HCTZ 25 mg	117	-7.89 (0.73)	
Pairwise comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
Aliskiren 300 mg / HCTZ 25 mg vs. HCTZ 25 mg	-4.02 (1.02)	(-6.02, -2.01)	<.0001*
Aliskiren 300 mg / HCTZ 25 mg vs. Irbesartan 300 mg / HCTZ 25 mg	-0.57 (1.02)	(-2.58, 1.43)	0.5757
Aliskiren 300 mg / HCTZ 25 mg vs. Amlodipine 10 mg / HCTZ 25 mg	-1.60 (1.01)	(-3.59, 0.38)	0.1135

SE=Standard Error; LSM=Least Square Mean; CI=Confidence Interval.
[1]P-values and treatment comparisons were evaluated using an ANCOVA model containing treatment, region and centered baseline.
* Indicates statistical significance at 0.05 level.

In addition, ALI/HCTZ 300/25 mg produced a statistically significant superior reduction in msSBP compared to hydrochlorothiazide 25 mg alone at week 8 endpoint ($p < 0.0001$). Comparisons with irbesartan/HCTZ and amlodipine/HCTZ combinations although numerically greater, were not statistically significant.

Study SPP100A2302 and its extension SPP100A2302E1 are relevant for the combination ALI/HCTZ and report safety data as requested for by applicable guideline for long-term use of the therapy in the treatment of hypertension.

During the open-label period, clinically meaningful reductions from baseline in sitting blood pressures were achieved with both doses of aliskiren as monotherapy and also combination therapy. The reductions were similar in both aliskiren randomization groups. The combination of ALI/HCTZ was well tolerated in patients treated for at least 180 days with the dose of 300mg/12.5mg (n=344) and or the higher dose of 300mg/25mg (N=357).

During the extension period, clinically meaningful BP reduction from baseline was maintained throughout the duration of the entire study. Greater than 17 mmHg in mean SBP and 10 mmHg in mean DBP were observed at each visit after month 4 when all the patients received the combination treatment of aliskiren 300 mg and hydrochlorothiazide 25 mg, indicating the long-term efficacy of this combination.

Mean change from baseline in msDBP and msSBP at open-label visit by treatment received in long-term Study CSPP100A2302 (open-label ITT population)

Open-label Visit	Month	Monotherapy*** N = 1060			Combo*** N = 868		
			Change (SD)			Change (SD)	
		N*	msDBP	msSBP	N*	msDBP	msSBP
4	1	1059	-10.5 (7.8)	-13.6 (12.4)	868	-6.5 (7.1)	-8.9 (12.6)
5	2	990	-12.3 (7.3)	-16.9 (12.2)	866	-6.0 (7.5)	-9.0 (12.4)
6	3	946	-13.9 (7.1)	-19.5 (12.1)	860	-8.6 (7.7)	-12.8 (14.1)
7	4	912	-14.5 (6.6)	-20.1 (11.7)	849	-10.4 (7.8)	-16.4 (14.3)
8	6	901	-14.3 (6.6)	-19.8 (12.1)	832	-11.4 (7.7)	-18.1 (14.7)
9	9	890	-14.7 (6.9)	-19.9 (12.3)	800	-12.6 (7.7)	-20.3 (14.2)
10	11/12	875	-14.7 (7.2)	-19.5 (12.6)	764	-12.8 (7.8)	-19.8 (13.8)
Endpoint**		1060	-13.3 (8.5)	-17.4 (14.5)	868	-12.1 (8.4)	-18.7 (14.6)

Note: A decrease in the mean change indicates improvement.
*N is the number of patients with values obtained at both baseline and post-baseline visit.
**Endpoint is Month 11/12, or last visit carried forward.
***Monotherapy patients are those who never took HCTZ. Combo = combination therapy (patients who took HCTZ at least once).

Study SPP100A 2331 examined the differences in the efficacy of hydrochlorothiazide, ALI/HCTZ, valsartan/HCTZ and aliskiren/valsartan/HCTZ. Thus, two out of the four arms of this study are relevant to the present application for the combination ALI/HCTZ. In this study with patients not adequately responsive to 25 mg HCTZ monotherapy, ALI/HCTZ 300/25 mg produced a statistically significant superior reduction in msDBP compared to hydrochlorothiazide 25 mg alone at week 8 ($p<0.0001$). The combination of ALI/HCTZ was well tolerated and the safety profile is similar to that of hydrochlorothiazide alone. Data support the use of ALI/HCTZ as a second line indication, limitedly to patients pre-treated with hydrochlorothiazide.

Change from baseline in msDBP at endpoint (ITT population, Study CSPP100A2331)

Treatment group		N	LSM change from baseline (SE)	
HCTZ		151	-6.4 (0.70)	
Aliskiren/HCTZ		164	-10.5 (0.67)	
Valsartan/HCTZ		154	-13.5 (0.70)	
Aliskiren/valsartan/HCTZ		168	-15.9 (0.67)	
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value[1]**
Aliskiren/valsartan/HCTZ	vs. Aliskiren/HCTZ	-5.4 (0.95)	(-7.27, -3.56)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. Valsartan/HCTZ	-2.4 (0.96)	(-4.31, -0.52)	0.0124*
Aliskiren/HCTZ	vs. HCTZ	-4.1 (0.97)	(-6.05, -2.23)	<0.0001*
Valsartan/HCTZ	vs. HCTZ	-7.1 (0.99)	(-9.08, -5.20)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. HCTZ	-9.6 (0.97)	(-11.46, -7.65)	<0.0001*

SE = Standard Error; LSM = Least Square Mean; CI = Confidence Interval
Least square mean, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
1. p-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).

In this study with patients not adequately responsive to hydrochlorothiazide monotherapy,, ALI/HCTZ 300/25 mg produced a statistically significant superior reduction in msSBP compared to hydrochlorothiazide 25 mg alone.

Study SPP100A2332 was conducted with patients not adequately responsive to aliskiren monotherapy. Both ALI/HCTZ 300/25 mg and ALI/HCTZ 300/12.5 mg groups showed a statistically significant greater msDBP reduction than the aliskiren 300 mg group for the ITT population ($p<0.001$), with further reductions of 3.58 mmHg and 3.12 mmHg (LS means), respectively, over the

aliskiren 300 mg group. The combination ALI/HCTZ was well tolerated and the safety profile is similar to that one of aliskiren alone. Data support the use of ALI/HCTZ as a second line indication, limitedly to patients pre-treated with aliskiren.

Statistical analysis of change from baseline in msDBP at endpoint, Study SPP100A2332 (ITT population)

Treatment group	N	LSM change from baseline (SE)	
Aliskiren 300 mg/HCTZ 25 mg	284	- 11.00 (0.551)	
Aliskiren 300 mg/HCTZ 12.5 mg	292	- 10.54 (0.539)	
Aliskiren 300 mg	296	- 7.42 (0.539)	
Pairwise comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-value**
Ali 300 mg/HCTZ 25mg vs. Ali 300 mg	- 3.58 (0.730)	(- 5.01, - 2.15)	< 0.001*
Ali 300 mg/HCTZ 12.5 mg vs. Ali 300 mg	- 3.12 (0.724)	(- 4.54, - 1.70)	< 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.

Both ALI/HCTZ 300/25 mg and ALI/HCTZ 300/12.5 mg groups showed a statistically significant greater msSBP reduction than the aliskiren 300 mg group for the ITT population ($p < 0.001$), with further reductions (in LS means) of 7.90 mmHg and 5.53 mmHg, respectively, over the aliskiren 300 mg group.

Study SPP100A2333 was conducted with patients not adequately responsive to hydrochlorothiazide monotherapy. Both ALI/HCTZ 300/25 mg and ALI/HCTZ 150/25 mg combination groups showed a statistically significant greater msDBP reduction than the hydrochlorothiazide 25 mg treatment group for the ITT population ($p < 0.001$), with further reductions in least squares means of 5.94 mmHg and 3.73 mmHg, respectively, over the hydrochlorothiazide 25 mg group. The combination ALI/HCTZ was well tolerated, and the safety profile is similar to that one hydrochlorothiazide alone. Data support the use of ALI/HCTZ as a second line indication, limitedly to patients pre-treated with HCTZ.

Change from baseline in msDBP at endpoint (ITT population, Study CSPP100A2333)

Treatment group	N	LSM change from baseline (SE)	
Aliskiren 300 mg/HCTZ 25 mg	232	- 10.73 (0.481)	
Aliskiren 150 mg/HCTZ 25 mg	242	- 8.52 (0.471)	
HCTZ 25 mg	244	- 4.80 (0.469)	
Pairwise comparison	**LSM difference in change from baseline**	**95% CI for LSM difference**	**P-value**
Ali 300 mg/HCTZ 25mg vs. HCTZ 25 mg	- 5.94	(- 7.24, - 4.63)	< 0.001*
Ali 150 mg/HCTZ 25 mg vs. HCTZ 25 mg	- 3.73	(- 5.02, - 2.43)	< 0.001*

SE = standard error, LSM = least squares mean, CI = confidence interval
Ali = aliskiren; HCTZ = hydrochlorothiazide
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.

Both ALI/HCTZ 300/25 mg and ALI/HCTZ 150/25 mg combination groups showed a statistically significant greater msSBP reduction than the hydrochlorothiazide 25 mg treatment group for the ITT population ($p < 0.001$), with further reductions in LSMs of 9.63 mmHg and 5.87 mmHg, respectively, over the hydrochlorothiazide 25 mg group.

Ancillary analyses
Dose-response surface analysis: For the primary efficacy variable (change from the baseline in msDBP) in study CSPP100A2204, the dose response surface was fitted in the second order. The first

order lack-of-fit test was statistically significant (p=0.0107) and the second order lack-of-fit test was not statistically significant (p=0.8717). In this fitted second order form, both the squared term of the aliskiren dose and the cross product term of the aliskiren and hydrochlorothiazide doses were not statistically significant. The negative coefficients for the first order terms indicated that the reduction in msDBP had a positive relationship to the dose of both aliskiren and hydrochlorothiazide. The positive coefficient for the second order squared term of the hydrochlorothiazide dose indicated that the magnitude of the relationship of msDBP reduction to hydrochlorothiazide dose decreased as the dose level increased. This was consistent with the primary efficacy analysis result, in which hydrochlorothiazide 12.5 mg and 25 mg had similar reductions in msDBP. This analysis was repeated for msSBP with consistent results.

- Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analyses of the clinical efficacy data from studies were conducted. This was due to the significant variability in study design, duration of treatment and patient recruitment. Studies were evaluated individually to assess the efficacy of the combination of aliskiren with hydrochlorothiazide. Pooled data were used for safety analysis only.

- Clinical studies in special populations

No children were included in clinical studies with ALI/HCTZ. The SPC advises that the combination product is not recommended for use in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

The combination therapy of ALI/HCTZ had clinically relevant additive effects overall, with individual dose combinations demonstrating numerically greater reductions in msDBP and msSBP for both genders than their component monotherapies. However, the originally claimed indication for initial treatment of hypertensive patients unlikely to achieve target blood pressure with a single agent, such as patients with markedly elevated blood pressure (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg) or patients with additional cardiovascular risk such as diabetes, renal impairment or known cardiovascular disease was not supported by solid clinical data. Therefore, the use of ALI/HCTZ combination was considered approvable only for the second-line indications, i.e. in patients whose BP is not controlled with aliskiren or hydrochlorothiazide monotherapy and for replacement therapy in patients adequately controlled with aliskiren and hydrochlorothiazide. The indication was amended appropriately.

The study population was divided into the following racial subgroups: Caucasian, Black, Asian, Native American, Pacific Islander, and other. Although the majority of the study population was Caucasian and the number of patients in other racial subpopulation treatment group is small, the results consistently support the conclusion in the overall population. Combination groups produced greater reductions than in each respective monotherapy.

In some clinical trials, patients with impaired renal function and diabetes were included. In general, the trend of greater msDBP and msSBP reduction and blood pressure control were observed with the ALI/HCTZ combination compared to the respective monotherapies. It is, however, important to note that the number of patients with diabetes or moderate renal impairment was small and thus, the data from these patients should be interpreted with caution. The ALI/HCTZ combination is contraindicated in patients with severe renal impairment.

Approach of caution should be taken when considering the use of the product in elderly population. According to pharmacokinetic data, the drug exposure increases with age; elevated plasma levels occur (exposure in subjects >65years is increased by about 50%, with respect to subjects aged 18-45 years). The dose-response relationship in the elderly population is not entirely clear. Although subgroup analyses of elderly patients do not reveal a higher incidence of adverse events in this special population, the number of elderly patients above 75 years in each treatment group is small, and therefore data in these subgroups must be interpreted with caution.

Clinical safety

Since aliskiren is approved at doses of 150 mg and 300 mg for the treatment of hypertension either as monotherapy or in combination with other antihypertensive agents and hydrochlorothiazide has been widely used for the treatment of hypertension, with 12.5 mg and 25 mg as the commonly prescribed doses, there is information available on the safety of these components in the treatment of hypertension.

Safety analyses and data for the use of ALI/HCTZ combination were derived from the overall clinical development program, including the short-term and long-term trials.

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs) including the investigator's assessment of their severity, relationship to study drug, and actions taken; the regular monitoring of haematology and blood chemistry (performed at a central laboratory); regular measurements of vital signs; and performance of physical examinations.

- Patient exposure

Overall, 8472 patients were included in the ALI/HCTZ clinical development program, with 3939 patients being exposed to aliskiren in combination with hydrochlorothiazide. Duration of exposure was presented based on the actual dose received. An adverse event started on a dose was counted towards that dose, and results were tabulated by dose. In study CSPP100A2204, two treatment groups (ALI/HCTZ 150/25 mg and ALI/HCTZ 300/25 mg) started with low dose treatment (ALI/HCTZ 150/12.5 mg) for one week followed by 7 weeks of high dose (ALI/HCTZ 150/25 mg and 300/25 mg). The high dose treatment was used as the treatment group for the entire double-blind period. All safety data were reported based on the actual treatment.

Data were pooled into 4 groups, as shown below:

Description of population	Studies supplying patients
Placebo-controlled study (Group A)	1 placebo-controlled study: CSPP100A2204
Short-term controlled studies (Group B)	Study above (CSPP100A2204), plus: 5 active-controlled studies CSPP100A2332, CSPP100A2333, CSPP100A2309, CSPP100A2331, CSPP100A2303
Long-term open-label studies (Group C)	1 open-label study and its extension: CSPP100A2302, CSPP100A2302E1
Long-term double-blind active-controlled study (Group D)	1 double-blind, active-controlled study: CSPP100A2306

The demographics, baseline BPs, co-morbid medical conditions, and use of concomitant medications of the patients in the safety database were generally representative of the target population of patients with essential hypertension.

In the placebo-controlled studies, the demographic variables were generally similar across treatment groups. The mean age of patients ranged from 54-56 years. Patients meeting criteria for obesity comprised approximately one-third to one-half of the patients in each of the treatment groups. Of those patients in whom the data were collected, approximately 8% who received ALI/HCTZ in the placebo-controlled studies had a diagnosis of diabetes. Patients with glomerular filtration rate (GFR) <60 ml/min/1.73 m² comprised 3.8% of the placebo-controlled studies population.

The demographic variables in *short-term* controlled were generally similar across treatment groups and similar to those in the placebo-controlled studies; the deviations in characteristics that did exist were those that would be expected based on the entry criteria (e.g., the inclusion of only obese patients in study CSPP100A2309, and only patients with severe hypertension in study CSPP100A2303). Approximately 9% of patients who received ALI/HCTZ in the short-term controlled studies were

known to have a diagnosis of diabetes. Patients with GFR < 60 ml/min/1.73 m² comprised 4.2% of patients who received ALI/HCTZ in the short-term controlled studies population.

The demographics and background characteristics in the *long-term* open-label and long-term double-blind studies were generally similar to those in the short-term controlled studies. The duration of exposure in the various treatment arms is summarised below:

Summary statistics for duration of exposure to study drug after randomization - all studies*

Treatment Group	Number of Patients	Duration of exposure (days)		
		Mean (SD)	Median	Range
Placebo	193	52.5 (13.2)	56	2 - 83
Mono Ali	3349	153.6 (130.2)	85	1 - 426
Mono HCTZ	1083	56.7 (14.0)	56	1 - 93
Ali/HCTZ 75/6.25 mg	188	54.7 (10.3)	56	1 - 94
Ali/HCTZ 75/12.5 mg	190	53.5 (11.5)	56	4 - 70
Ali/HCTZ 75/25 mg	186	53.9 (10.3)	56	2 - 70
Ali/HCTZ 150/6.25 mg	174	53.7 (12.5)	56	2 - 105
Ali/HCTZ 150/12.5 mg	206	66.2 (50.8)	56	7 - 335
Ali/HCTZ 150/25 mg	722	43.9 (18.5)	54	1 - 302
Ali/HCTZ 300/12.5 mg	1510	101.7 (94.4)	56	1 - 343
Ali/HCTZ 300/25 mg	1576	111.6 (116.8)	56	1 - 448
Ali/HCTZ	3939	105.3 (103.9)	56	1 - 471
Amlodipine/HCTZ	127	80.3 (14.8)	84	3 - 92
ACEI	480	117.2 (61.8)	87	3 - 229
ACEI/HCTZ	236	86.1 (35.7)	91	7 - 144
ARB/HCTZ	274	66.0 (17.5)	57	7 – 90
Ali/Val/HCTZ	168	54.5 (7.2)	56	1 - 64

- * Duration of exposure to study drug was analyzed cumulatively for patients in both Study CSPP100A 2302 and Study CSPP100A 2302E1.
- ACEI: all lisinopril or ramipril mono treatment groups
- ACEI/HCTZ: all lisinopril/HCTZ or ramipril/HCTZ combination treatment groups.
- ARB/HCTZ: all valsartan/HCTZ or Irbsartan/HCTZ combination treatment groups.
- Patients titrating to several doses within a treatment regimen were counted separately in each (dose) group.

Overall, this represents a large safety database, which is considered sufficient to meet the regulatory requirements and to demonstrate safety of aliskiren in combination with hydrochlorothiazide for the treatment of patients with hypertension. The representation of special patient population (e.g. the elderly) in the overall patients recruited is discussed below.

- Adverse events

The most frequently observed AEs in the *short-term* controlled studies are presented by treatment group in the table below:

Preferred term	Placebo N=193 n (%)	Mono Ali N=973 n (%)	Mono HCTZ N=1075 n (%)	Ali/HCTZ N=2875 n (%)
Any adverse experience	85(44.0)	312(32.1)	420(39.1)	998(34.7)
Headache	26(13.5)	56(5.8)	61(5.7)	129(4.5)
Nasopharyngitis	10(5.2)	25(2.6)	42(3.9)	92(3.2)
Dizziness	2(1.0)	6(0.6)	21(2.0)	58(2.0)
Influenza	3(1.6)	12(1.2)	9(0.8)	44(1.5)
Diarrhea	1(0.5)	14(1.4)	20(1.9)	37(1.3)
Back pain	5(2.6)	10(1.0)	14(1.3)	34(1.2)
Arthralgia	1(0.5)	7(0.7)	11(1.0)	28(1.0)
Bronchitis	3(1.6)	11(1.1)	10(0.9)	28(1.0)

Results were consistent with those in the placebo-controlled studies. The AEs experienced by ≥1% of patients taking ALI/HCTZ and that were more frequent than in patients taking placebo were dizziness, diarrhoea, and arthralgia. The only AE that was experienced by ≥2% of patients taking ALI/HCTZ and was more frequent than in patients taking placebo was dizziness, however, the difference was not statistically significant. The incidence of dizziness in ALI/HCTZ treated patients was not higher than in hydrochlorothiazide treated patients (2.0% for both groups). There was a marked increase of peripheral oedema in amlodipine/HCTZ group (11%) compared to other groups (<2%).

The most frequently reported AEs in the *long-term open-label* studies are summarized in the table below:

Preferred term	Mono Ali N=1955 n (%)	Ali/HCTZ 300/12.5 mg N=843 n (%)	Ali/HCTZ 300/25 mg N=454 n (%)	Ali/HCTZ N=871 n (%)
Any Adverse Experience	1050 (53.7)	314 (37.2)	197 (43.4)	464 (53.3)
Nasopharyngitis	135 (6.9)	38 (4.5)	15 (3.3)	53 (6.1)
Bronchitis	72(3.7)	19(2.3)	18(4.0)	36(4.1)
Dizziness	75 (3.8)	21 (2.5)	11 (2.4)	31 (3.6)
Back pain	68 (3.5)	22 (2.6)	5 (1.1)	28 (3.2)
Influenza	50 (2.6)	16 (1.9)	10 (2.2)	26 (3.0)
Headache	153 (7.8)	12 (1.4)	10 (2.2)	22 (2.5)
Arthralgia	36 (1.8)	8 (0.9)	11 (2.4)	19 (2.2)
Cough	30 (1.5)	15 (1.8)	4 (0.9)	19 (2.2)
Diarrhoea	69 (3.5)	12 (1.4)	6 (1.3)	18 (2.1)
Upper respiratory tract infection	42 (2.1)	12 (1.4)	4 (0.9)	16 (1.8)
Fatigue	41 (2.1)	10 (1.2)	2 (0.4)	12 (1.4)
Nausea	42 (2.1)	0 (0.0)	5 (1.1)	5 (0.6)

Twenty-eight patients received aliskiren/HCTZ combination treatment other than aliskiren/HCTZ 300/12.5 mg (first titrated combination dose).

The most frequently reported AE with ALI/HCTZ and aliskiren monotherapy was nasopharyngitis (6.1% and 6.9%, respectively). The incidence of headache was 2.5% in the ALI/HCTZ group and 7.8% in the aliskiren monotherapy group. There was no evidence of increase in AE rates with the addition of hydrochlorothiazide to aliskiren treatment. All the frequent AEs (≥2%) reported in the long-term open label studies were also reported in the short-term controlled trials. Addition of hydrochlorothiazide to aliskiren did not increase the incidence of diarrhoea or dizziness.

The most frequently reported AEs during the *long-term double-blind* studies are shown in the table below:

Preferred term	Mono Ali N=421 n (%)	Ali/HCTZ 300/12.5 mg N=193 n (%)	Ali/HCTZ 300/25 mg N=92 n (%)	Ali/HCTZ N=193 n (%)	Ramipril N=422 n (%)	Ramipril/ HCTZ/ N=210 n (%)
Any adverse experience	237 (56.3)	64 (33.2)	35 (38.0)	85 (44.0)	234 (55.5)	98 (46.7)
Dizziness	16 (3.8)	7 (3.6)	1 (1.1)	8 (4.1)	16 (3.8)	5 (2.4)
Nasopharyngitis	19 (4.5)	5 (2.6)	3 (3.3)	8 (4.1)	24 (5.7)	9 (4.3)
Fatigue	13 (3.1)	3 (1.6)	3 (3.3)	6 (3.1)	16 (3.8)	1 (0.5)
Headache	45 (10.7)	6 (3.1)	1 (1.1)	6 (3.1)	33 (7.8)	8 (3.8)
Bronchitis	10 (2.4)	5 (2.6)	0 (0.0)	5 (2.6)	5 (1.2)	2 (1.0)
Diarrhoea	13 (3.1)	2 (1.0)	3 (3.3)	5 (2.6)	8 (1.9)	1 (0.5)
Sinusitis	4 (1.0)	4 (2.1)	2 (2.2)	5 (2.6)	8 (1.9)	4 (1.9)
Upper respiratory tract infection	11 (2.6)	3 (1.6)	2 (2.2)	5 (2.6)	11 (2.6)	13 (6.2)
Cough	14 (3.3)	3 (1.6)	0 (0.0)	3 (1.6)	34 (8.1)	9 (4.3)
Pain in extremity	13 (3.1)	2 (1.0)	1 (1.1)	3 (1.6)	5 (1.2)	3 (1.4)
Back pain	13 (3.1)	1 (0.5)	1 (1.1)	2 (1.0)	7 (1.7)	8 (3.8)
Blood glucose increased	0 (0.0)	0 (0.0)	2 (2.2)	2 (1.0)	1 (0.2)	1 (0.5)
Nausea	10 (2.4)	1 (0.5)	1 (1.1)	2 (1.0)	5 (1.2)	3 (1.4)
Oedema peripheral	14 (3.3)	1 (0.5)	1 (1.1)	2 (1.0)	13 (3.1)	2 (1.0)
Dyspepsia	11 (2.6)	0 (0.0)	1 (1.1)	1 (0.5)	4 (0.9)	0 (0.0)

The most frequently reported AEs during long-term double-blind treatment with ALI/HCTZ were dizziness, nasopharyngitis, fatigue, and headache. Diarrhoea was reported in more patients treated with aliskiren monotherapy and the combination of ALI/HCTZ compared to patients treated with ramipril monotherapy and the combination of ramipril/HCTZ. There was no evidence of increase in the rate of overall gastrointestinal events and the rate of diarrhoea with addition of hydrochlorothiazide to aliskiren treatment. The incidence of headache was 3.1% in the ALI/HCTZ group and 10.7% in the aliskiren monotherapy group.

Adverse events suspected by the investigator to be drug-related belong mostly to with the nervous system disorders, gastrointestinal disorders, and general disorders and administration site conditions, but the rates of suspected events were low.

- Serious adverse event/deaths/other significant events

Serious adverse events: The proportion of patients with any serious adverse event (SAE) was low and generally similar across all treatment groups. In the combined group of all patients who took ALI/HCTZ, the rate was 1.3% in the placebo-controlled studies and 1.0% in the short-term controlled studies. The proportion of patients experiencing SAEs with aliskiren monotherapy was 0.5% in the placebo-controlled studies and 0.7% in the short-term controlled studies. The proportion of patients experiencing SAEs with hydrochlorothiazide monotherapy was 1.1% in the placebo-controlled studies and 1.0% in the short-term controlled studies. No placebo-treated patients experienced SAEs. In both Group A and Group B (see section *Patient exposure*) populations, for ALI/HCTZ, the system organ class with the most SAEs was nervous system disorders (< 0.3%). Results in the long-term studies were consistent with the data from the short-term studies given the relative lengths of treatment exposure in the one-year and 6-month trials and the 8-week and 12-week trials, respectively. SAEs occurred in four patients (one on aliskiren monotherapy, 3 on placebo who withdrew from aliskiren monotherapy) during the randomized withdrawal period of study CSPP100A2306.

In the bioequivalence study CALI/HCTZA2103, one subject who received one dose of ALI/HCTZ 300/25 mg, had an episode of acute cholecystitis which required hospitalisation. This was reported as an SAE not related to study medication. There were no other SAEs in the completed bioequivalence studies relevant for this combination product.

For the ALI/HCTZ group, in the placebo-controlled studies, the system organ class with the most SAEs leading to study discontinuation was cardiac disorders (0.1%), while in the short-term controlled studies, the system organ classes with the most SAEs leading to study discontinuation were cardiac disorders and nervous system disorders (0.1%). The proportion of patients with any SAE leading to

study discontinuation was low and generally similar across all treatment groups. For the ALI/HCTZ group, in both, the long-term open label and long-term double-blind studies, the system organ class with the most SAEs leading to study discontinuation was cardiac disorders (0.5% in both).

Deaths: Overall, 12 deaths occurred during or after completion of the studies which contained the treatment of aliskiren in combination with hydrochlorothiazide. Two patients are known to have taken ALI/HCTZ at any time, five patients were treated with aliskiren monotherapy, one patient was treated with hydrochlorothiazide monotherapy, and one patient was each treated with either valsartan/HCTZ, ramipril/HCTZ, placebo, or receiving no treatment. Deaths were related to cardiovascular or cerebrovascular events, as would be expected in an older hypertensive population. The causes of death were similar in all groups, and the rate was no higher in patients treated with ALI/HCTZ compared with component monotherapies, active comparators, or placebo.

In addition to the routine assessment of clinical safety during treatment and withdrawal and the evaluation of potential drug interactions with agents commonly used in the hypertensive population, the focus of the safety evaluation was also directed to potential safety concerns because aliskiren's mode of action involves blockade of the RAS:

- renal dysfunction as seen with angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs);
- angioedema as seen with ACEIs;
- cough as seen with ACEIs;
- minimal decreases in hemoglobin and hematocrit seen with ACEIs and ARBs;
- potential gastrointestinal (GI) issues based on findings during the clinical development of aliskiren (preclinical findings in the GI tract; diarrhea noted at highest aliskiren doses in clinical trials).

The most important events are described below:

Renal function: Hypokalaemia with K+<3.5 mmol/L was more common in the hydrochlorothiazide monotherapy and hydrochlorothiazide-containing combination groups than in placebo and aliskiren monotherapy groups. Hyperkalaemia with K+>5.5 mmol/L were infrequent (0 to 1.4%) in patients treated with various doses of ALI/HCTZ in the placebo-controlled trials. Only one patient treated with ALI/HCTZ had hyperkalaemia with K+≥6.0 mmol/L. No cases of elevated blood urea nitrogen (BUN) and creatinine meeting clinically significant criteria were observed in patients treated with ALI/HCTZ. In the short-term controlled studies, the incidence of hyperkalaemia with K+>5.5 mmol/L in patients treated with ALI/HCTZ (0.6%) was lower than patients treated with aliskiren monotherapy (1.6%). Only 1 case (< 0.1%) of elevated BUN, and no cases of elevated creatinine meeting clinically significant criteria were observed in patients treated with ALI/HCTZ.

It is of interest that the opposite effects of aliskiren and hydrochlorothiazide result in unaltered potassium balance, at least in the majority of patients taking ALI/HCTZ combination. There are no or insufficient data on special patient populations, i.e. patients with a preponderance to develop hyperkalaemia, e.g. diabetics and/or patients with moderate renal failure. However, in the SPC appropriate warning is placed, since 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 ALI/HCTZ.

Angioedema: Angioedema is a known serious side effect of ACEIs. It has also been reported in patients who were treated with ARBs. There was one case of angioedema reported in patients who received the combination of ALI/HCTZ in CSPP100A2302 study and the study drug was not interrupted. Following study completion, the event was completely resolved. Based on the low incidence seen in the presented clinical trials, angioedema would not be considered a safety risk for aliskiren and its combination with HCTZ. However, cases of angioedema with relevant occurrence were reported in the postmarketing use of aliskiren and the CHMP favoured the contraindication for patients with a history of angioedema to aliskiren. In addition a warning was added in the appropriate section of the SPC directing that ALI/HCTZ should be discontinued when patients with or without a

previous history who suffer angioedema with aliskiren monotherapy are warned to discontinue treatment and contact their physician. Furthermore, the risk management plan (RMP) includes directions for postmarketing use to monitor through targeted follow up clinically significant angioedema spontaneous reports irrespective of seriousness and causality. Similarly, in clinical trials clinically significant angioedema cases reported as serious adverse event reports are to be thoroughly monitored and followed up.

Cough: Cough occurred in ≤2.1% of patients in any treatment group in the placebo-controlled studies. Only two patients (0.1%) in the ALI/HCTZ combination treatment in the short-term placebo-controlled studies discontinued due to cough. Similarly, in the short-term controlled studies cough was reported in 0.5% of patients receiving placebo, 0.5% of patients receiving aliskiren monotherapy, 0.9% of patients receiving hydrochlorothiazide monotherapy, and 0.9% of patients receiving ALI/HCTZ. In the long-term open-label studies, the incidence of cough was 1.5% for aliskiren monotherapy and 2.2% for ALI/HCTZ combination therapy. In the long-term double-blind studies, the incidence of cough was 3.3% for aliskiren monotherapy and 1.6% for aliskiren in combination with HCTZ compared to 8.1% in ramipril monotherapy and 4.3 % in ramipril/HCTZ. Nevertheless, as a class effect, cough is stated in the RMP as the ongoing safety concerns for aliskiren.

Haematology: A slight decrease in mean haemoglobin from baseline was observed in the aliskiren monotherapy and ALI/HCTZ combination treatment groups. However, the percentage of patients with >20% decrease in haemoglobin was low (0% for aliskiren monotherapy and <0.1% for ALI/HCTZ combination in short-term controlled trials). There was essentially no change in haematocrit from baseline in ALI/HCTZ-treated patients. Recent studies have demonstrated that erythropoietin levels are increased by angiotensin II and that this effect is mediated by the AT1 receptor. Thus drugs blocking the RAS at sufficient doses will be expected to have minor effects on red cell production. Only one patient in the short-term controlled studies discontinued therapy due to anaemia; this patient was in the ALI/HCTZ 300/25 mg group. In the long-term open-label studies, haematology changes at endpoint were similar for monotherapy and combination therapy. At endpoint, platelet count increased slightly in both treatment groups. Other haematological variables changed little from baseline. Results in the long-term double-blind studies were generally similar.

Gastrointestinal events: Diarrhoea was observed at a higher rate in ALI/HCTZ (1.3%) as compared to placebo (0.5%) in all short-term controlled trials. Even though the difference did not reach statistical significance between ALI/HCTZ and placebo, diarrhoea is considered as an adverse reaction for the combination mainly because it is a dose related adverse reaction for aliskiren. The incidence of diarrhoea was not higher in ALI/HCTZ combination compared to aliskiren or hydrochlorothiazide alone. This event was limited in duration and most often reported as mild to moderate in severity. Diarrhoea did not lead to early withdrawal from the study in most cases, did not increase in frequency with longer duration of treatment, and was not associated with other AEs. As concerns the potential role of aliskiren in colorectal events observed in non clinical setting, the results of the planned long-term safety studies will be presented to the CHMP to give additional evaluation of the risk. Monitoring of such events and assuring safety of patients taking ALI/HCTZ was included in follow up measures.

- Laboratory findings

The effects of aliskiren and hydrochlorothiazide on potassium levels were discussed in the *Serious adverse event/deaths/other significant events* section. In summary, opposite effects of aliskiren and hydrochlorothiazide on potassium values were observed in most patients, which in majority of the cases resulted in an unchanged balance. Nevertheless, the SPC includes an appropriate warning related to electrolyte imbalance and its symptoms.

- Safety in special populations

*Elderly***:** Analysis of adverse events by age in all studies indicated no excess of dizziness, vertigo, or diarrhea in older patients (≥65 years of age). Laboratory values of haematology and clinical chemistry, vital signs, and orthostatic blood pressure changes were also evaluated according to age subgroups (<65 years, ≥65 years, ≥75 years). Results within the age subgroups were consistent with the overall

results. The overall incidence of AEs for patients ≥65 years and ≥75 years was lower in the combination therapy treatment group than in the monotherapy or placebo groups. However, the CHMP was concerned about the size of the elderly population in the clinical trials. It is important to note that the hypotensive effect of the combination ALI/HCTZ is of concern in the elderly, which can be more sensitive to the hypotensive effects than other subgroups. The exposure of the elderly to the product and the data originally presented were considered limited. Therefore, the results of a 36 week study (CSPP100A2344) were submitted during the evaluation phase. This trial was conducted to examine the efficacy and safety of aliskiren based regimens in combination with other antihypertensives in patients with age ≥65 years and systolic essential hypertension. None of the observed severe AEs in patients treated with ALI/HCTZ were hypotension or low blood pressure related events. The number of patients discontinuing the treatment due to AEs was higher in the ramipril/HCTZ group than in the ALI/HCTZ group. The conclusions about the safety profile were similar when analyses were limited to patients with age >75 years. This study provided additional information on elderly hypertensive populations and showed an acceptable risk/benefit ratio. Moreover, a commitment was included in the follow up measures to provide the CHMP with the efficacy and safety information from the currently ongoing clinical trials in elderly patients.

Patients with diabetes: Since hydrochlorothiazide is known to have been perceived to raise safety concerns in diabetic patients, the safety in diabetic patients was closely evaluated. In the placebo-controlled studies, a total of 112 patients in the ALI/HCTZ combination group had diabetes. The overall AE incidence rates were generally similar across treatment groups regardless of baseline diabetes status and diabetes did not appear to dramatically increase the total incidence of AEs within each treatment group. However, given the small number of patients evaluated, there is a need to better define the safety and risks of the product in the population and the SPC includes a statement that to date, no data are available from clinical studies that were specifically designed to evaluate the safety of the combination product in diabetic patients.

Renal impairment: In general, patients with significant renal impairment (creatinine >1.7 mg/dl for women and 2.0 mg/dl for men and/or estimated GFR <30 ml/min) were excluded from the studies conducted with aliskiren and hydrochlorothiazide. Furthermore, due to the hydrochlorothiazide component, the ALI/HCTZ combination is contraindicated for use in patients with severe renal impairment (glomerular filtration rate, GFR, < 30 ml/min). Taking into account that both of the components of the combination may accumulate in the kidney, the possible consequences of a long-lasting treatment especially in patients with already impaired renal function might be considered. Aliskiren is believed to bind to renin immediately upon its secretion. In contrast, thiazides and related diuretics accumulate in the distal tubule where they affect the renal tubular mechanisms of electrolyte re-absorption. Accordingly, no pharmacokinetic interactions are expected in the kidney.

There are no available data on the use of ALI/HCTZ in children.

- Safety related to drug-drug interactions and other interactions

No clinically significant drug-drug interactions have been observed between aliskiren and several commonly prescribed antihypertensive medications, including hydrochlorothiazide. The results of the drug-drug interaction study conducted to examine the potential for interactions between aliskiren and hydrochlorothiazide showed that there are no significant pharmacokinetic interactions. High fat meal adversely affects aliskiren and hydrochlorothiazide disposition (please see section *Pharmacokinetics*).

- Discontinuation due to adverse events

Patient disposition was similar across treatment groups in all trials, with no large imbalances in the numbers of patients discontinuing for various reasons, other than a tendency for more patients to discontinue for lack of efficacy in placebo group. The addition of hydrochlorothiazide to aliskiren did not result in increased patient withdrawals. The discontinuations due to safety reasons, e.g. AEs and laboratory abnormalities, were similar in the ALI/HCTZ treated patients when compared to aliskiren or hydrochlorothiazide treated patients, and lower when compared to placebo treated patients.

- Post marketing experience

There are no post marketing data available for the ALI/HCTZ combination. Nevertheless, the approval procedure for aliskiren was successfully completed in August 2007 and since then, clinical experience with the use of this product in the post marketing setting and/or in the clinical trials conducted post approval revealed several important safety issues, which are also applicable to the combination product:

- The results of the cyclosporine interaction study in 14 subjects showed that concomitant cyclosporine administration increased AUC 4.5 to 5.5 fold with a lower dose of aliskiren (75 mg) than the authorised strengths (150 and 300mg). Cyclosporine markedly increased aliskiren half life. Hence, there is concern that the increase in AUC would be substantially higher with the approved aliskiren dosage, even exceeding the highest dose tested in humans. An additional concern is that aliskiren might distribute to tissues from which the medicinal product is normally absent in presence of a P-gp inhibitor, or preset at low levels because of the activity of P-gp. Non clinical and clinical data converge to show that P-gp is a major determinant of aliskiren bioavailability. In addition, literature data show that P-gp mediates tissue uptake of a variety of P-gp substrates and that P-gp inhibitors can markedly increase the tissue-to-plasma concentration ratios. Given the very limited safety data at increased exposure, and the risk for very large increase in tissue exposure, the CHMP concluded that the co-administration of cyclosporine and aliskiren poses serious safety concerns. Therefore, the concomitant administration with cyclosporine, a highly potent P-gp inhibitor, as well as with other potent P-gp inhibitors (verapamil, quinidine) is contraindicated. Moreover, due to the risk for higher increase in tissue exposure than in plasma, caution should be advised during co administration with moderate P-gp inhibitors (ketoconazol, itraconazol, clarithromycin, telithromycin, erythromycin, amiodarone).
- The overall safety and tolerability of aliskiren 150 mg when given in addition to standard therapy in hypertensive patients with stable heart failure was evaluated in a clinical trial with 302 patients with mild to moderate heart failure. Addition of 150 mg aliskiren showed a reduction of BNP levels by 25 %, although the clinical significance of this reduction is unknown. The SPC contains a warning about the need for caution when the product is used in patients with heart failure.
- The effects of aliskiren (150mg/300mg) on proteinuria in 599 patients with hypertension, type II 2 diabetes mellitus and nephropathy, in whom blood pressure had been previously controlled by means of an angiotensin receptor blocker (losartan) in combination with the optional use of other antihypertensive drugs (hydrochlorothiazide and/or amlodipine) were investigated in a specific clinical trial. The addition of 300 mg aliskiren achieved an average reduction in the urinary albumin to creatinine (UACR) ratio of 12 mg/mmol (from 58 to 46 mg/mmol) compared to placebo and clinical relevance of a reduction in UACR is not established in the absence of an effect on blood pressure. Furthermore, aliskiren was associated with an increased frequency (4.2% vs. 1.9% for placebo) in serum potassium concentration (≥ 6 mmol/l). The SPC for the combination product was adequately updated.

During the post marketing use of aliskiren, a number of cases of renal failure or acute renal failure were reported. In the light of this new safety signal on renal failure from the post marketing phase, a special warning was introduced in the SPC regarding a prompt discontinuation of the treatment, should signs of renal failure occur. The Risk Management Plan has been updated accordingly. The Risk Management Plan will be reviewed on an on-going basis and updated as appropriate in the light of emerging safety data including renal dysfunction. In addition, there is a commitment to update the SPC for the aliskiren monotherapy.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional) and Summary of Product Characteristics statements**
Important identified risks		
Diarrhea	Routine PV, aggregate analyses in PSUR. Monitor through targeted follow up follow up using a questionnaire from post-marketing use and in clinical trials.	The risk is adequately reflected in SPC sections 4.4 and 4.8.
Rash	Routine PV, aggregate analyses in PSUR.	The risk is adequately reflected in SPC section 4.8. (see table 3-1)
Angioedema	Routine PV, aggregate analyses in PSUR. Monitor through targeted follow up follow up using a questionnaire from post-marketing use and in clinical trials.	The risk is adequately reflected in SPC sections 4.3; 4.4 and 4.8.
Hyperkalemia	Routine PV, aggregate analyses in PSUR. Monitor through targeted follow up using a questionnaire, of hyperkalemia in two randomized, double-blind, placebo- or active-controlled trials (SPP100E2337 and SPP100A2316).plus monitoring of laboratory and adverse event data in other clinical trials, irrespective of seriousness and causality.	The risk is adequately reflected in SPC sections 4.4; 4.5 and 4.8
Hemoglobin and hematocrit decrease	Routine PV, aggregate analyses in PSUR.	The risk is adequately reflected in SPC sections 4.8.
Renal dysfunction	Routine pharmacovigilance. Aggregate analysis in PSUR. Novartis will provide aggregate analysis , i.e cumulative review of the cases in question (all severity stages) since marketing; a listing of all cases divided by PSUR including Line Listing with complete information in CIOMS format, the review of the case narratives with focus on greater severity/specificity including causality assessment and possible mechanism of action; comparison with data deriving from clinical studies as well as from literature. Monitor renal dysfunction including the incidence of oligo_anuria and laboratory data related to renal failure events in controlled clinical trials with attention to the populations at risk (e.g., hypovolemia, blood losses, diarrhea, vomit, diabetes, use of NSAIDs, heart disease, liver disease, kidney disease, renal artery stenosis) on monotherapy and in combination with ARB/ACEI according to standard Novartis procedures.	The risk is adequately reflected in SPC sections 4.2; 4.3; 4.4; 4.8; 5.2.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional) and Summary of Product Characteristics statements
Important potential risks		
Colorectal hyperplasia	Aggregate analyses in PSUR. Monitor through targeted follow up follow up using a questionnaire from post-marketing cases, clinical trials, and post-marketing studies. Mechanistic program in place (study in marmosets). In addition to the final study reports for SPP100E2337 and SPP100A2404 an annual ad interim analysis will be submitted to EMEA.	The risk is adequately reflected in SPC sections 5.3.
Peripheral edema	In addition to routine pharmacovigilance, Novartis will provide aggregate analysis , i.e cumulative review of the cases in question (all severity stages) since marketing; a tabular listing of all cases divided by PSUR; narratives of the cases with peripheral edema; assessment of the narratives including causality assessment and possible mechanis of action; comparison with data deriving from clinical szduies as well as from literature.	No SPC statement
Hypotension	Routine PV. Monitor blood pressure in clinical trials.	The risk is adequately reflected in SPC sections 4.4; 4.8; 5.1
Identified drug interactions		
Furosemide	Routine PV, aggregate analyses in PSUR.	The risk is adequately reflected in SPC sections 4.5
Pgp inhibitors	Routine PV, aggregate analyses in PSUR.	The risk is adequately reflected in SPC sections 4.3; 4.4; 4.5
Pharmacological class effects		
Cough	Routine PV, aggregate analyses in PSUR.	The risk is adequately reflected in SPC sections 4.8
Drug-drug interaction with NSAIDs	Routine PV, aggregate analyses in PSUR.	The risk is adequately reflected in SPC sections 4.5
Important missing information		
Pregnancy	Routine PV, targeted follow up using a questionnaire, aggregate analyses in PSUR.	The risk is adequately reflected in SPC sections 4.3; 4.6
Pediatric population	Routine PV, aggregate analyses in PSUR. Monitor adverse event data in paediatric programme planned for aliskiren monotherapy	The risk is adequately reflected in SPC sections 4.2; 5.2
Severe and moderate renal impairment	Routine PV. No studies planned.	The risk is adequately reflected in SPC sections 4.2; 4.3; 4.4; 4.8; 5.2
Reno-vascular hypertension	Routine PV. No studies planned.	The risk is adequately reflected in SPC sections 4.4

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional) and Summary of Product Characteristics statements
Reduction of cardiovascular risk	Clinical CV morbidity and mortality program.	The risk is adequately reflected in SPC sections 4.4 and 5.1
Drug-drug interaction with grapefruit juice	Routine PV, aggregate analyses in PSUR.	The risk is adequately reflected in SPC sections 4.2; 4.5

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this medicinal product is considered satisfactory when used with the conditions defined in the SPC. The documentation provided for both active substances ALI and HCTZ is comprehensive and adequately detailed. The pharmaceutical development is adequate and took into consideration the properties and the stability of the active substances. The excipients used are common excipients for immediate release dosage forms. Similarly, the packaging material is well documented and no incompatibility has been noticed. The validation of the manufacturing process ensures consistency and reproducibility of the finished product. The finished product has been satisfactorily controlled and stability studies conducted under ICH conditions showed that the product is stable throughout the proposed shelf-life.

At the time of the CHMP opinion, there were some minor unresolved quality issues with no impact on the benefit/risk. The applicant undertook to provide the necessary information as follow-up measures within an agreed timeframe and to submit variations if required following the evaluation of this additional information.

Non-clinical pharmacology and toxicology

The toxicology program of ALI/HCTZ consisted of a principal, GLP compliant 13 week study in rats, with doses selected in a 2 week dose range finding non LP study. No other non clinical studies, such as pharmacology, genotoxicity, carcinogenicity, reproduction toxicology were considered necessary for the combination product as these could be derived from the previous studies with aliskiren and from the literature and bibliographic references for hydrochlorothiazide.

In the 2 week dose range finding study the severity of pathological changes in multiple tissues of rats, notably kidney, gastrointestinal tract, bone marrow and lymphoid organs indicate that a dose of 300/25 mg/kg/day would not be tolerated in a longer term study. Minimal tubular basophilia present in the kidneys of some animals treated at 100/8 mg/kg/day may reflect reduced renal perfusion. The toxicological significance of the minimal lymphocytic infiltration in the medulla of the thymus in two males is unclear but it was not present in the longer studies. The NOAEL is considered to be 100/8 mg/kg/day. In the 13 wk repeated dose toxicity ALI/HCTZ induced slight reversible decreases in body weight gains and food consumption in males given ≥ 100/8 mg/kg/day. Reversible decreases in potassium and serum chloride levels were seen in rats given the combination at all doses, as well as hydrochlorothiazide alone. There were minimal to mild increases in mean group AST and ALT in two females given ALI/HCTZ 150/12 mg/kg/day. Concurrent hepatic histopathologic lesions were not observed, but increase of liver enzyme levels was present after four weeks of recovery period in one high dose female. Treatment-related microscopic changes recorded as minimal increased cellular vacuolation in the zona glomerulosa were seen in all animals treated with hydrochlorothiazide alone (12 mg/kg/day) or in combination with aliskiren (≥ 50/4 mg/kg/day). Due to the lack of further studies longer that 13 weeks it cannot be concluded whether this effect would not became more severe after

chronic treatment and appropriate information on these finding is included in the SPC. As drugs affecting the RAAS are contraindicated in Europe during second and third trimesters of pregnancy, no specific fertility studies were carried out with the ALI/HCTZ combination. No specific carcinogenicity study was conducted with the ALI/HCTZ combination and this approach is considered appropriate based on the available data for the two single components.

Further environmental risk assessment need to be conducted for hydrochlorothiazide because of the unknown contribution of ALI/HCTZ on total hydrochlorothiazide use in the EU. In order to obtain information on the additional environmental exposure and size of the population contributing to the increased environmental exposure of the combination product possibly due to use of the product in patients inadequately controlled by aliskiren, several studies for hydrochlorothiazide will be performed as a follow up measure.

Efficacy

The fixed combination of aliskiren and hydrochlorothiazide is considered to achieve a greater antihypertensive effect than the single monotherapies. The efficacy data were derived from short- and long-term clinical studies conducted in accordance with the current regulatory guidelines using a parallel-group and an add-on design. The dose-finding was based on parallel-group data. Efficacy was tested in mild to moderate hypertension (90 or 95 to <110 mmHg DBP). The primary and secondary efficacy variables were changes in msDBP and msSBP, response rate and control rate. In addition, certain biomarkers have been evaluated (PRA and PRC).

The data, however, were insufficient for recognising a positive risk benefit balance for the originally proposed first line indication of the combination medicinal product, i.e. for the treatment of hypertensive patients with either additional cardiovascular risk or with markedly elevated blood pressure (stage 2 hypertension). Indeed, no data had been provided that demonstrated clinical efficacy and safety of the product given as a first line treatment in comparison to an add-on indication. Furthermore, in the clinical program the target population of the proposed first line indication studies was not sufficiently represented, since clinical studies excluded patients with poorly controlled diabetes, or significant cardiovascular disease, or cerebrovascular diseases, or renal impairment. In fact, the results in the small subgroup of hypertensive patients with additional cardiovascular risk indicate that the percentage of patients controlled by the combination ALI/HCTZ was not significantly higher than that obtained monotherapy treatments. Similarly, only limited data were submitted for the first line indication of ALI/HCTZ in patients with uncomplicated severe hypertension (stage 2 hypertension) to compare clinical efficacy and safety of ALI/HCTZ *vs* an add-on treatment of the single monocomponents. Therefore, the use of ALI/HCTZ combination was considered approvable only for the second-line indications, i.e. in patients whose blood pressure is not controlled with aliskiren or hydrochlorothiazide monotherapy and for replacement therapy in patients adequately controlled with aliskiren and hydrochlorothiazide.

The proposed recommendation for administration of the product with a light meal will be supported by further scientific data derived from the planned studies investigating the effect of a light meal on ALI/HCTZ bioavailability. It was observed that food markedly reduces the bioavailability of aliskiren and at present, the bioavailability of aliskiren with light meal is not fully established.

Safety

Safety of ALI/HCTZ combination was assessed in several short- and long-term clinical trials. In addition, data from the post marketing use of aliskiren monotherapy contribute to the establishment of the safety profile of this combination product. The evaluation of adverse events observed showed that diarrhoea, dizziness, headache and nasopharyngitis are the most frequently experienced adverse events. Several adverse events constitute the events of special interest, including angioedema, hyperkalaemia, diarrhoea, decreases in haemoglobin and haematocrit.

ALI/HCTZ is contraindicated in patients with severe renal impairment and further data have been submitted in order to demonstrate that the use of ALI/HCTZ is safe in hypertensive patients with mild to moderate renal impairment; this is considered acceptable. The use of the combination product is also contraindicated in patients with the history of angioedema, since several cases of this event have

been identified during the use of aliskiren. In the event of any signs suggesting an allergic reaction, patients should discontinue the treatment.

As concerns the potential safety concerns for aliskiren in elderly patients when given concomitantly with hydrochlorothiazide due to the occurrence of elevated plasma levels after aliskiren monotherapy treatment, a 36 week study (CSPP100A2344) analysing efficacy and safety of aliskiren based regimens in patients with age ≥ 65 years and systolic essential hypertension was conducted. The results indicated acceptable risk/benefit ratio supporting the use of ALI/HCTZ combination. In addition, efficacy and safety information from ongoing clinical trials in elderly patients will be closely examined to ensure the continuous monitoring and evaluation of the risk/benefit profile.

The risk of renal dysfunction as adverse event associated with aliskiren will be further assessed, as well as the clarification on risk of renal impairment from results of the ongoing clinical trials. This is mainly due to the recent reports of acute renal failure in patients with co-morbidities using aliskiren. In the meantime renal dysfunction should be considered an identified risk.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics. Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The Patient Information Leaflet (PIL) for Rasilez HCT has been tested in English in accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC. The Patient Information Leaflet for Rasilez HCT was found to contain all the necessary information in a way that is accessible and understandable to those who participated in this test.

It is considered that the tested PIL meets the requirements set for User Testing.

Risk-benefit assessment

The results of the clinical programme for ALI/HCTZ combination in the treatment of essential hypertension represent convincing evidence that, in comparison to each drug as monotherapy, the combination produces a greater antihypertensive effect. The compliance of patients with the fixed dose combination product is expected to improve. The second line indication, i.e. in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone; as replacement therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination, is considered acceptable. Clinical data are sufficient to prove the benefit of this product in these hypertensive patients.

The incidence of adverse events was similar when the combination of aliskiren and hydrochlorothiazide was compared to aliskiren monotherapy and hydrochlorothiazide monotherapy. It is to be noted that the combination ALI/HCTZ may affect potassium and/or overall electrolyte homeostasis, even though the effect of aliskiren (induction of hyperkalaemia) is opposite to that of hydrochlorothiazide (induction of hypokalaemia). Important safety concern was related to effects already observed with aliskiren monotherapy and linked to the occurrence of angioedema serious reactions or angioedema type reactions in patients with a history of angioedema associated to RAS blockers or in co-medication with RAS blockers. Aliskiren and hydrochlorothiazide combination is contraindicated in patients with the history of angioedema related to aliskiren administration. It is noteworthy that acute renal failure was reported in patients with co-morbidities during post marketing treatment with aliskiren and thus, caution should be exercised when administering the medicinal product to patients with conditions related to kidney dysfunction.

Currently, no dose adjustment is recommended in the elderly population (>65years), but further studies to better define the safety profile in elderly and in diabetic patients, as well as to better ascertain long-term safety are ongoing or in planning. The overall benefit/risk balance for

aliskiren/hydrochlorothiazide in treatment of essential hypertension is considered positive for the treatment of hypertension in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone, and as replacement therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

routine pharmacovigilance was adequate to monitor the safety of the product

AND

no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Rasilez HCT in the treatment of essential hypertension in adults, when Rasilez HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone or when indicated as a substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination, was favourable and therefore recommended the granting of the marketing authorisation.