EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

for

Rasilamlo

International Nonproprietary Name: aliskiren / amlodipine

Procedure No. EMEA/H/C/002073

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 3 December 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Rasilamlo, 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 EMA/CHMP on 23 July 2009.

The applicant applied for the following indication treatment of hypertension.

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for new fixed combination products.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/118/2009 on the granting of a product-specific waiver for the following condition:

Essential Hypertension

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Daniela Melchiorri** Co-Rapporteur: **János Borvendég**

- The application was received by the EMA on 3 December 2009.
- The procedure started on 23 December 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 March 2010 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 March 2010 (Annex 2).
- During the meeting on 19-22 April 2010, 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 22 April 2010 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 August 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 October 2010 (Annex 4).
- During the CHMP meeting on 18-21 October 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 November 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 November 2010, which was adopted during the CHMP meeting on 13-16 December 2010. The CHMP agreed on the Second List of Outstanding Issues to be addressed in writing by the applicant (Annex 6).
- The applicant submitted the responses to the Second List of Outstanding Issues on 14 January 2011 and oral explanation was held during the CHMP meeting on 17-20 January 2011. The Third List of Outstanding Issues was adopted in January 2011 (Annex 7).
- The applicant submitted the responses to the Third List of Outstanding Issues on 31 January 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the Third List of Outstanding Issues to all CHMP members on 7 and 11 February 2011. (Annex 8).
- During the meeting on 14-17 February 2011, 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 Rasilamlo on 17 February 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 February 2011 (Annex 9).

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's widely recognised that an adequate control of hypertension is important to significantly decrease cardiovascular mortality and morbidity. All international guidelines for the management of hypertension recommend a general target blood pressure (BP) < 140/90 mm Hg for most hypertensive patients. A lower BP target (<130/80 mm Hg) is recommended in high-risk patient populations such as those with 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. Inhibition of the 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:

- β-blockers reduce the release of renin from the juxtaglomerular apparatus and lower blood pressure.
- ACE-inhibitors reduce the conversion of angiotensin I to angiotensin II. They also inhibit the inactivation of bradykinin and substance P, causing some typical side-effects of ACE inhibitors, such as cough and angioedema.
- Angiotensin-receptor antagonists (ARB) block the interaction of angiotensin II with the AT1 receptor.
- Renin-inhibitors directly inhibit renin, blocking the RAS at its very origin.

Despite the availability of several therapeutic choices, in the majority of hypertensive patients blood pressure cannot be adequately controlled by one antihypertensive drug alone. In most patients, a combination of two or more antihypertensive medications will be required to reach adequate blood pressure control. In this scenario, development of new fixed-dose combinations of different antihypertensive drugs helps to improve patient compliance over the free combination of single monotherapies as well as the safety profile related to the current available treatments. Therefore, aliskiren, a DRI (direct renin inhibitor), and amlodipine, a long-acting dihydropyridine calcium channel blocker (CCB), were selected as the active substances to be combined in a fixed combination product for the treatment of hypertension based on their complementary mechanisms of action, pharmacological and pharmacokinetic characteristics, and their clinical profiles.

Aliskiren acts by inhibiting the RAS at the initial rate limiting step, the conversion of angiotensinogen to angiotensin I. Treatments which block the RAS are widely favoured methods of treating hypertension. Aliskiren was authorised in EU via the centralized procedure in August 2007. Amlodipine inhibits the calcium-dependent contraction of vascular smooth muscle cells and, through this effect, lowers total peripheral resistances to blood flow and blood pressure. Previous studies show additive antihypertensive effects of CCB with drugs which block the RAS. Amlodipine was approved for the treatment of hypertension, angina, and in some countries for angiographically documented coronary artery disease several years ago.

The main objective of the clinical programme provided in this Marketing Authorisation Application was to demonstrate the efficacy and safety of the fixed combination of aliskiren with amlodipine in the treatment of hypertension. Combination of aliskiren/amlodipine at doses of 150mg/5mg, 150mg/10mg, 300mg/5mg and 300mg/10mg was selected.

2.2. Quality aspects

2.2.1. Introduction

Rasilamlo film-coated tablets are a fixed combination product consisting of two active substances: Aliskiren hemifumarate and Amlodipine besylate.

Aliskiren hemifumarate (SPP100) is an anti-hypertensive agent that inhibits the renin-angiotensin system and Amlodipine besylate is a dihydropyridine calcium channel blocker. Both Aliskiren hemifumarate and amlodipine besylate are already present in mono and combination products already approved.

To cover the therapeutic needs, the tablets are formulated in four strengths 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg with a combination of Aliskiren hemifumarate equivalent to 150 mg or 300 mg of Aliskiren free base and with Amlodipine besylate equivalent to 5 mg or 10 mg of Amlodipine free base.

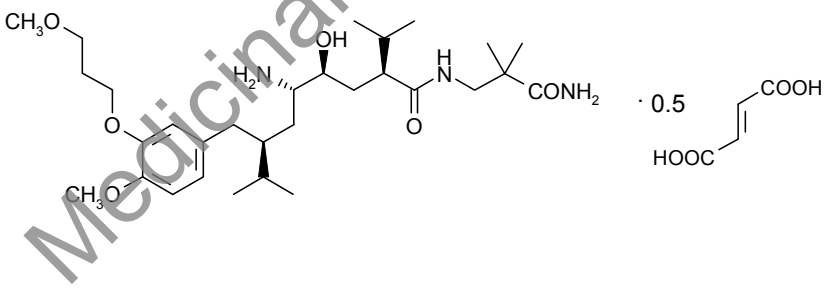
The primary packaging of tablets consists of Polyamide/Aluminium/Polyvinylchloride (PA/Alu/PVC) blister packs (Alu blisters) and Polytetrafluoroethylene PCTFE/PVC blister packs backed with a heat sealable lacquered aluminium foil

2.2.2. Active Substance

Active Substance Aliskiren hemifumarate

Aliskiren hemifumarate of Novartis has already been authorized via the centralised procedure both in monotherapy and in a combination product, with hydrochlorothiazide, owned by the Applicant.

Aliskiren hemifumarate exists as a white to slightly yellowish powder. It has four chiral centres, but is obtained as a single diastereoisomer, all S-configured.
Sufficient scientific information has been presented for the 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.



Manufacture

Aliskiren hemifumarate (SPP100) drug substance is manufactured according to two synthetic pathways: B and C.

The drug substance is manufactured with total synthesis including ten and six main stages using routes [synB] and [synC], respectively. Addition of synthesis C in alternative to synthesis B has been the object of a type II variation. The alternate synthesis C has been developed to reduce the complexity of the process, while improving the overall quality and safety.

Adequate in-process controls including the control of the stereochemistry and control of the critical steps 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.
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 drug substance (SPP100) is supported by the synthetic routes.
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 (by ESI, Electron Spray Ionisation) and X-ray powder diffractometry (XRPD), optical rotation (single diasteroisomer), particle size analysis.

Specification
The drug substance specifications using the different syntheses differ only in the requirements for residual solvents and impurities
Appropriate specification has been set up for the active substance obtained by route B and route C and includes appearance, particle size, appearance of the solution, identification (IR, XR and optical rotation), residual solvents (Gas Chromatography 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. An overview on the related substances of aliskiren hemifumarate has been presented covering potential process impurities and degradation products (from synthesis B and C). Levels observed and the origin of related substances has been extensively discussed and found satisfactory. The limits are in line with ICH Q3A.

Analytical methods have been adequately detailed and non-compendial methods validated in accordance with ICH guidelines.
The bulk of the active substance is packed and stored in very tight packaging. The bags are stored in drums with a tamper resistant seal.

Batch analysis from batches obtained by the route B (12 batches) and the route C (6 batches) has demonstrated the uniformity and the consistency of the syntheses.
Data presented show the release testing of batches manufactured by syntheses B and A which were used in clinical trials, toxicological studies and / or primary stability studies. Comparative analytical data of three more recent batches of aliskiren hemifumarate manufactured by the synthetic route B and three batches of drug substance manufactured by the synthetic route C. All the results were found compliant with the specifications.

Stability

Stability summary and conclusions for synthesis B

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. Very tight packaging has to be used.
In addition six production batches have been placed under stability. The stability reports submitted contain data covering 36 months of long term and 6 months of accelerated stability studies.

The parameters tested were including: appearance, identity (IR, X-ray diffraction, optical rotation), impurities (HPLC), water content (Karl-Fischer), clarity and colour of the solution and assay (HPLC). All parameters were found in accordance with the specification and no major degradation could be observed under long-term and accelerated conditions.

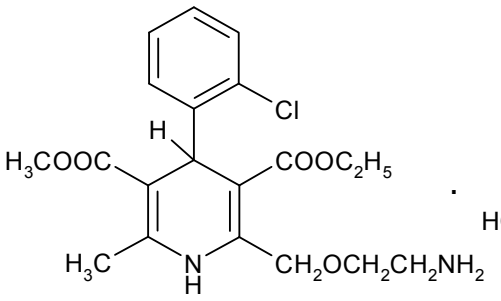
Stability summary and conclusions for synthesis C

Stability data on four development batches and three production-scale batches have been carried out under ICH long term and accelerated conditions (24 months, 25°C/60%RH, 30°C/ 65% RH and 40°C/ 75% RH and 18 months respectively). The results obtained show that they are similar to the data obtained for aliskiren hemifumarate manufactured by synthesis B and confirm the storage precautions (store below 25°C, protect from light in very tight packaging).

Based on the discussion above, the data for synthesis B support a retest period of 30 months stored not above 25°C in a very tight packaging. Stability data on pilot and commercial batches from synthesis C are available for up to 24 and 18 months, respectively, and a re-a test period of 24 months stored not above 25°C in a very tight packaging can be granted.

Active Substance Amlodipine Besilate

Amlodipine besilate (INN) is an active substance described in the Ph.Eur and is manufactured by two active substance manufacturers. Both manufacturers have presented Certificates of Suitability (CEP). The three CEPs, current version, are provided in the regional section of the dossier



Amlodipine is a White or almost white powder. Physico-chemical properties such as solubility in various solvents, melting point, polymorphism and chirality have been described. The substance is used as a racemic mixture (R and S isomers). There is no polymorphism of Amlodipine besylate described in the literature.

All the information relating to the manufacturing process, control of materials, critical steps and intermediates, manufacturing development, elucidation of the structure and impurities is covered by the CEP therefore no information was included in the dossier.

Specification

Adequate specification from the active substance suppliers include the following tests: description, particle size (laser diffraction), appearance of solution, identity (IR, XR, HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (Karl-Fisher), sulfated ash (Ph.Eur.), optical rotation (Ph.Eur.), heavy metals (ICP-OES), microbial contamination.
Upon receipt from the commercial manufacturers, the active substance is tested in accordance with internal Novartis testing monographs specific for each supplier.
The monographs are based on the requirements for amlodipine besilate as found in the Ph. Eur. monograph, and include additional tests needed to conform to Novartis internal standards.
The applicant has put in place additional tests needed by comparison to the Ph.Eur. monograph to ensure the consistency of quality for the active substance between and within each supplier The specification has been adequately justified and especially limits for impurities, heavy metals, residual solvents have been toxicologically justified.

In addition, amlodipine besilate is controlled for the content in besylate esters that are known to be genotoxic. Moreover, according to the Q&A document on the CHMP Guideline on the Limits of Genotoxic Impurities (EMA/CHMP/SWP/431994/2007) the tolerated amounts of besylate esters should not be cumulated since the benzenesulfonate impurities are structurally related. The limits for besylate esters in amlodipine besylate have been restricted to NMT 75 ppm each and NMT 150 ppm for the sum. This was found acceptable.
In summary, the active substance is controlled according to the requirements of the Ph. Eur. monograph with the addition of the following tests, which are not source specific: identification by XRPD and HPLC, Heavy metals, clarity of solution, colour of solution and microbial limits. Requirements for additional impurities and residual solvents are included in the specifications and are active substance source specific.

All analytical procedures used for testing the active substance have been properly described. Compendial methods are used for clarity and colour of the solution, identification by IR, water content by Karl Fischer, sulphated ash, optical rotation, related substances by HPLC and assay by HPLC.
In-house analytical methods are used for particle size determination (laser light diffraction), identification by X-ray diffraction, Identification by HPLC, impurities by HPLC, residual solvents by GC, heavy metals by ICP/OES and microbial enumeration test. Non-compendial methods have been validated in line with ICH guidelines.

Nine batches from both active substance manufacturers were tested for compliance with the specifications of the test monographs. Certificates of analysis showed that all the batches meet the Ph.Eur. test requirements and all additional testing requirements from the applicant. Results of analysis demonstrate that the quality of the active pharmaceutical ingredient batches of both suppliers is comparable.

For one manufacturer, the drug substance is filled in clear polyethylene bag, tied in a black polyethylene bag, tied and in HDPE container. For the other manufacturer, it consists of a polyethylene inner bag in a black polyethylene outer bag in or without (Process II) a cardboard box or polypropylene pail with lid.
The certificates of compliance with the Ph.Eur. and the foodstuff legislation for the packaging materials have been provided

Stability
For one manufacturer, a retest period of 5 years and 1 year (depending on the synthetic route) have been granted on the CEPs. For the other manufacturer, since the CEP provides no re-test period, long-term and accelerated stability data are provided but the Applicant commits to test each batch of amlodipine besilate before producing the drug product.

In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Finished Medicinal Product

The Rasilamlo film-coated tablets are immediate release solid dosage forms for oral administration containing fixed combinations of the active substances aliskiren hemifumarate and amlodipine besilate. The four different tablet strengths have the same shape (ovaloid convex shaped) but different colour and sizes:

150 mg aliskiren/5 mg amlodipine film-coated tablets are light yellow, ovaloid convex shaped, bevelled edged film-coated tablet with debossing "T2" on one side and "NVR" on the reverse side of the tablet.

150 mg aliskiren/10 mg amlodipine film-coated tablets are yellow, ovaloid convex shaped, bevelled edged film-coated tablet with debossing "T7" on one side and "NVR" on the reverse side of the tablet.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

300 mg aliskiren/5 mg amlodipine film-coated tablets are dark yellow, ovaloid convex shaped, bevelled-edged film-coated tablet with debossing "T11" on one side and "NVR" on the reverse side of the tablet.

300 mg aliskiren/10 mg amlodipine film-coated tablets are brown yellow, ovaloid convex shaped, bevelled-edged film-coated tablet with debossing "T12" on one side and "NVR" on the reverse side of the tablet.

The excipients used for the core tablets are common standard Pharmaceutical excipients: microcrystalline cellulose, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, ethanol with 5% isopropanol.
The Coating premixes (white, yellow and red) are commercially available materials containing iron oxides and/or titanium oxides, macrogol, talc and hypromellose.
There are differences in the ratios of the film-coating pre-mixes that make the various strengths distinguishable.
The components of the premixes are given and comply with the standard of the Ph.Eur. or with the Directive 2008/128/EC. The difference in the premixes is the colourant (iron oxide and titanium dioxide.

The primary packaging consists of tablets are PA/Alu/PVC blister packs (Alu blisters) and PCTFE/PVC blister packs backed with a heat sealable lacquered aluminium foil

Pharmaceutical development

Aliskiren is a single diastereoisomer with 4 S-configured chiral centers. Its hemifumarate salt was selected for the drug product, because it was the only one which showed crystallinity. Aliskiren hemifumarate is a white to slightly yellowish hygroscopic crystalline powder with high solubility and low permeability according to the BCS (class 3). Aliskiren does not possess adequate compactability properties therefore needs granulation. Aliskiren has shown very good chemical compatibility with all the excipients used in the formulation, proved by previously approved formulations. Given the high solubility, particle size is not a concern however the particle size is checked to be under 1000 µm (90%). The crystalline form is checked in the specifications.

Amlodipine besylate is described in the US Pharmacopoeia and Ph.Eur. From the literature it is known to be well absorbed (90% in humans) and with a good solubility. No classification according BCS is given, however given the low dose it may be considered as a high solubility drug. Particle size may be an issue and therefore is controlled by laser diffraction. Amlodipine besylate is sourced from two drug substance suppliers with CEPs.

Compatibility studies with mixtures of the actives with a variety of excipients were carried out and analyzed using the validated chromatography currently utilized in the Aliskiren / Hydrochlorothiazide project. The major identified impurity in samples showing significant degradation was formed by the reaction of the major components. No other major impurities were observed and therefore, the tested excipients were deemed to be compatible.

The excipients selected are standard ingredients in tablet formulations, and are in compliance with internationally accepted pharmacopoeial standards. The concentrations of each excipient are within the usual range of application.

The tablet cores are coated with a non-functional coating to provide a distinctive tablet colour to identify the different dosage strengths. The basic coating premixes are a combination of ingredients established for use in medicinal products. The premixes themselves do not appear in any pharmacopoeia; but the ingredients meet compendial requirements and/or international standards.

The formulation development focused on obtaining a tablet formulation using the existing commercial granulates of Aliskiren hemifumarate and Amlodipine besylate. Aliskiren hemifumarate granules (without extra-granular material or lubricant) are manufactured using the validated process developed for the approved Rasilez product. Amlodipine granules were manufactured using the commercial validated process for the amlodipine granulation portion. Four strengths of the fixed combination were

developed. A suitable extragranular phase was found and compression conditions were chosen then scaled up to industrial scale.

The 150/10 mg and 300/10 mg film-coated tablet formulation were tested in bioequivalence studies. Both formulations successfully demonstrated bioequivalence to the free forms of aliskiren and amlodipine. As a result of the positive bioavailability and bioequivalence studies, this disintegrant level was maintained for all strengths.

The composition of drug substance and excipients in the 150/5 mg tablet is weight and dose proportional to the 300/10 mg tablet which proved bioequivalent to the free combination. The qualitative composition of the 150/5 and 150/10 mg formulations as well as of the 300/5 and 300/10 mg formulations are qualitatively identical and quantitatively similar (the amount of drug is compensated by a corresponding amount of the excipient cellulose microcrystalline and the total percentage difference in excipient concentration is 0.7 %). Therefore the formulations can be considered as dose proportional all together and a biowaiver for the two formulations that have not been subjected to bioequivalence studies can be considered.

The biowaiver request for the 150/5 mg and 300/5 mg film-coated tablets based on compositional proportionality (300/10mg – 150/5 mg), compositional similarity (300/10 mg – 300/5 mg), identical manufacturing process and similar dissolution profiles of the waived strengths to the profile of 300/10 mg BE batch in four dissolution media is acceptable.

A 20 % overage is included in the film coating suspension to compensate for any losses that may occur during the film-coating process

Based on the available stability data, the following packaging materials are claimed to be sufficiently protective and compatible with the film-coated tablets: PA/Alu/PVC blister packs (Alu blisters) and PCTFE/PVC blister packs.

Adventitious agents

There are no excipients of human or animal origin used in the manufacture of the finished product .A declaration that the magnesium stearate used is of vegetable origin is provided.

Manufacture of the product

Details of the manufacturing process and appropriate in-process controls including parameters such as mean mass, individual mass, thickness, hardness, friability, disintegration time have been provided.

The manufacture of the tablets can be summarized in three main steps: granulation, Final compression and film coating. In summary, the manufacturing process uses standard processes, granulation, blending, compression and coating. The tablet cores are coated and packaged. All strengths are manufactured with the same process.

The manufacturing process development was briefly addressed. The manufacture of the tablets can be summarized in three main steps: granulation, Final compression and film coating

All strengths are manufactured by combining and blending the granulates of the active substance with extragranular components and compression of the tables. The manufacturing process presents critical points, concerning the homogeneity of granulates blends and the content uniformity of tablet cores. These have been addressed in the process validation. Even though the homogenous distribution of active ingredients in the final powder mixture is supported by the homogeneity results presented in the validation report and is ensured by the preset mixing parameters, the applicant, upon request, has specified in section 3.2P.3.3. the exact value of the mixing parameters (time and speed).
Information on the measures taken to avoid moisture, period and conditions of the manufacturing process, and holding time and storage conditions for the cores and film-coated tablets have also been provided. The ICP proposed are accepted.
Complete validation data on three batches per each strengths have been provided according to an acceptable scheme and show that the manufacturing process is reliable and reproducible.

Control of Excipients

All the excipients used in the core formulation comply with the quality requirements of the applicable compendial monograph.
Monographs for the premixes themselves do not appear in any pharmacopoeia, however, their respective ingredients meet compendial requirements and international standards. These include, Macrogol/PEG 4000 (Ph. Eur.), Talc (Ph. Eur.), Hypromellose (Ph. Eur.), Titanium dioxide (Ph. Eur.) and iron oxides (red, yellowcontrolled according to commission directive 2008/128/EC and/or the NF.

Certificates of analysis for all pharmacopoeia excipients have been provided. Satisfactory in-house specifications and certificates of analysis are provided for the coating. Satisfactory method validation data has also been provided where applicable.
In addition, where relevant, additional testing has been carried out (functionality test and residual solvents in line with ICH requirements)

Specifications

Adequate specifications at release and at the end of shelf-life for all strengths (150/5 mg, 150/10 mg, 300/5 mg, 300/10 mg) of the finished product include: appearance (visual test), identification of aliskiren and amlodipine (TLC and HPLC), identification of colorants titanium and iron (colour reaction), dissolution test (HPLC), residual solvents (GC), water content (Karl-Fisher), related substances (HPLC), microbial contamination (microbial enumeration test), uniformity of dosage units (content uniformity HPLC), assay for aliskiren and amlodipine (HPLC).

Analytical methods have been adequately described and validated in accordance with the ICH guidelines Q2R1.

Batch analytical data
Batch results have been provided for at least 3 pilot batches per strength, the results were found in compliance with the specification.

Container closure system

The primary packaging for SPA100 150/5 mg, 150/10 mg, 300/5 mg and 300/100 mg film-coated tablets are PA/Alu/PVC blister packs (Alu blisters) and PCTFE/PVC blister packs backed with a heat sealable lacquered aluminum foil.

The components of the blisters are tested for cleanliness, total thickness and identity (IR). In addition the packaging components comply with Ph. Eur. requirements (where applicable) and/or foodstuff legislation.

Stability of the product

Stability results have been presented on 3 pilot batches for each strength 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg film-coated tablets in two different packaging configurations (PA/Alu/PVC (Alu) blister packs and in PCTFE/PVC blisters).

The batches have been stored under ICH long term testing at 25°C/60%RH and 30°C/65%RH (12 months), accelerated testing at 40°C/75%RH (6 months), as well as other temperatures (e.g. -20°C, 5°C and 50°C). Special tests (e.g. photostability and microbial enumeration) have also been performed.

The characteristics tested during the stability study were appearance, water content, accompanying substances, dissolution, assay and degradation products as well as microbiology. The tests covered parameters susceptible to change during storage and likely to influence quality and/or efficacy of the product.

Parameters remained within the specification when the product was kept at 25C and no significant change could be observed, slight increase was observed under intermediate conditions but out of specification results were found under accelerated conditions. Photostability data showed that the product is stable in the proposed packages.

Stability data support the proposed shelf life under the precautions of storage described in the Product Information.

2.2.4. 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 2 stereochemically controlled syntheses (route B and route C). Controls 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. Based on the discussion above, the data support synthesis B support a retest period of 30 months stored not above 25°C in a very tight packaging. Stability data on pilot and commercial batches from synthesis C are available for up to 24 and 18 months, respectively, and a re-a test period of 24 months stored not above 25°C in a very tight packaging can be granted.

The active substance amlodipine besilate is covered by Certificates of Suitability CEP from 2 suppliers. Adequate specification has been presented. For one manufacturer, a retest period of 5 years and 1 year (depending on the synthetic route) have been granted on the CEPs. For the other manufacturer, since the CEP provides no re-test period. Long-term and accelerated stability data are provided but the Applicant commits to test each batch of amlodipine besilate before to produce the drug product.

Rasilamlo film-coated tablets 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg are formulated as an immediate release formulation with well-known excipients. 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 description and choice of the container is acceptable based on stability data. Drug product specification is satisfactory and in line with ICH guidelines. Stability results have been presented on 3 pilot batches for each strength in two different packaging configurations (PA/Alu/PVC (Alu) blister packs and in PCTFE/PVC blisters).
Stability data support the proposed shelf life under the precautions of storage described in the Product Information.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this medicinal product is considered satisfactory when used with the conditions defined in the SPC. The documentation provided for the active substance aliskiren hemifumarate and amlodipine besilate is comprehensive and adequately detailed. The pharmaceutical development is adequate and took into consideration the properties and the stability of the 2 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.

2.3. Non-clinical aspects

2.3.1. Introduction

No preclinical pharmacodynamic or special pharmacokinetic studies were performed with Rasilamlo. Rationale for not performing these studies is discussed in detail in each section. The 2-week and 13-week toxicity studies conducted in rats evaluated the nonclinical safety profile of aliskiren and amlodipine when used in combinations. Toxicokinetic analyses of the two components, aliskiren and amlodipine, were included in the toxicity studies. The preclinical safety programme is consistent with the CHMP guidance (EMEA/CHMP/SWP/258498/2005) on the non-clinical safety evaluation of fixed combinations. Based on the proposed highest therapeutic dose strength of 300/10 mg (aliskiren/amlodipine), a ratio of approximately 30:1 was used in the toxicity studies. The principal 13-week study was conducted in accordance with GLP. In addition, two genotoxicity assays including Ames and the chromosome aberration assays were performed on Rasilamlo. No further studies were performed for genotoxicity, carcinogenicity and reproductive toxicity since the assessment of potential in these areas was adequately performed with aliskiren or amlodipine and there were no safety concerns from the assessment. The nonclinical programme took into consideration the approved SmPC for aliskiren and amlodipine and allowed for the characterisation of the nonclinical safety profile of the combination while avoiding unnecessary repetition of animal studies. In support of the programme, literature data were also provided.

2.3.2. Pharmacology

2.3.2.1. ***Primary pharmacodynamic studies***

Studies on pharmacodynamics for the fixed combination of aliskiren and amlodipine (SPA100) were not conducted primarily due to the lack of appropriate animal models. Aliskiren is highly specific for human renin and has limited activity in standard rat models of hypertension. The highly artificial human renin transgenic models used to demonstrate the efficacy of aliskiren cannot be used to model the activity of the combination drug in man. The individual efficacy of aliskiren and amlodipine has been demonstrated extensively and there are no expectations of a lowered effectiveness when combined. This approach is considered acceptable.

2.3.2.2. ***Secondary pharmacodynamic studies***

No special studies were conducted with aliskiren/amlodipine, due to the lack of appropriate animal models as described in the above sections.

2.3.2.3. ***Safety pharmacology programme***

No special studies were conducted with aliskiren/amlodipine, due to the fact that the safety of aliskiren and amlodipine on the central nervous, cardiovascular and respiratory systems has been demonstrated in previous studies with the individuals components and the combination was tested in repeated dose toxicity studies.

2.3.2.4. ***Pharmacodynamic drug interactions***

Due to the distinct mechanisms of amlodipine and aliskiren, specific pharmacodynamic drug interaction investigations were not conducted for the aliskiren/amlodipine fixed combination.

2.3.3. Pharmacokinetics

The pharmacokinetics and metabolism of the aliskiren and amlodipine are well characterised and have been extensively studied preclinically as well as clinically. Based on the Guideline on the Non-clinical Development of Fixed Combinations of Medicinal Products (CHMP/EMEA/CHMP/SWP/258498/2005), if the pharmacokinetic profiles of the single components are adequately characterised in animals, additional non-clinical documentation on pharmacokinetic interactions is generally not needed. Accordingly, no new pharmacokinetic study with the aliskiren/amlodipine combination has been submitted and the preclinical pharmacokinetic documentation is a compilation of results from previous studies and literature data.

Absorption and bioavailability

The rate of absorption of aliskiren was rapid in mice, rats, and moderate in dogs, marmosets and humans. The oral bioavailability in mouse, rat, marmoset and human was low and ranged between 1.5% and 3%. Systemic exposure was roughly dose proportional with no gender differences observed in the toxicology species. There was no accumulation in blood or plasma of the rat after daily oral administration of the drug for 10 days. After oral dosing, the concentration-time profiles of aliskiren and aliskiren-related components in plasma were highly variable and peaked between 0.25 and 3 hours in all species investigated, including humans. The plasma clearance (CL) was low in marmosets (0.036 L/h/kg) and humans (0.13 L/h/kg), and moderate to high in rats (1.2 L/h/kg) and mice (2.01 L/h/kg). Oral doses of amlodipine were well absorbed in mice, rats and dogs, and nearly completely absorbed in humans. Unlike other calcium antagonists, amlodipine did not undergo relevant pre-systemic metabolism. Absolute oral bioavailability is 67-90% in humans, and 88-100% in dogs, mice and rats. There is no food-effect in humans. Rats showed higher plasma clearance and shorter half-life than human, dog and mouse and a plasma clearance which exceeds liver blood flow 2.2 fold. This may indicate dose-dependent kinetics in the rat with first-pass metabolism. The pharmacokinetics of R-(+)- and S-(-)-amlodipine after single enantiomer administration were comparable to that of each enantiomer after administration of the racemate. No racemization occurred in vivo in human plasma.

The absorption and bioavailability of aliskiren/amlodipine combination is not expected to act differently from the individual components aliskiren and amlodipine. There was no significant effect on the exposure of either drug components after single and multiple dosing of the combination. The pharmacokinetics of individual components aliskiren and amlodipine and its combination in a 2- and 13-week oral (gavage) toxicity study in male and female rats indicate no potential clinically significant interactions (see section Toxicology).

Distribution and protein binding

The volume of distribution of aliskiren at steady-state was high in the rat, moderate in humans and mice, and low in the marmoset. After single intravenous dosing of 10 mg/kg radio-labelled aliskiren to pigmented rats, radioactivity was extensively distributed throughout the body, with the highest levels at 5min post-dose in the liver and kidney. However, after oral dosing, there was no evidence of drug-related material being bound. Aliskiren-related radioactivity was eliminated within 24 hours from most organs and tissues. Aliskiren and/or its metabolites were not taken up into the central nervous system. The binding of aliskiren to plasma proteins was moderate with free fractions (fu) of 29% (mouse), 38% (rat) and 50% (human). In marmosets, a distinctly higher plasma protein binding was observed (fu = 8%). The distribution between blood cells and plasma was independent of the concentration for rat, and human. Amlodipine was highly distributed into tissues with a large volume of distribution around 21-32 L/kg across species. The myocardial concentration increased after a bolus injection and reached

a maximum in 2min and then remained on a plateau. Myocardial uptake was threefold higher than lung uptake. Both enantiomers of amlodipine displayed similar myocardial kinetics. Amlodipine was highly bound to human plasma proteins (98% at a drug concentration of 50ng/mL). Protein binding was similar in dogs and rats.

The blood distribution and plasma protein binding of aliskiren and amlodipine have been investigated as described above and it is not expected to act differently when administered in combination. Therefore, additional blood distribution and plasma protein binding studies with the combination were not conducted.

Metabolism

Examination of ^{14}C-labeled aliskiren metabolism in mice, rats, marmosets, humans and pregnant rabbits showed that the drug was metabolised to a low to moderate extent in humans, marmosets, rats and mice. The primary metabolic pathways involved oxidative reactions on the phenol moiety of aliskiren, like O-dealkylation and further oxidation to the carboxylic acid metabolites. These oxidation processes had been found to be catalysed largely by cytochrome P450 3A4/5 enzymes. Minor metabolic pathways were the formation of glucuronide metabolites and hydrolytic cleavage of aliskiren at the amide bond level. All metabolites observed in plasma were also found in the excreta either in free or conjugated form. In animals and humans, amlodipine was eliminated mainly through extensive, though slow metabolism, with a low first pass extraction in mouse, dog and humans. In rats, a substantial first-pass extraction is indicated. Metabolism was catalysed mainly by hepatic CYP3A4 and was similar in rats, dogs, mice and humans. Only a small fraction of the dose (up to 5%) was recovered in urine as unchanged drug. In human, rat and dog, the first step of metabolism was oxidation of the dihydropyridine ring of the racemic compound to the pyridine analogue. Further metabolism involved oxidation/hydrolysis of the side-chain ester(s) and oxidation/degradation of the aminoethoxymethyl side chain.

The metabolism of the individual components, aliskiren and amlodipine, was extensively studied as described above. Additional metabolism studies with the combination aliskiren/amlodipine were therefore not necessary.

Excretion

In mice, rats, marmosets and humans, aliskiren and its metabolites were predominantly eliminated with faeces (≥88% of the absorbed oral dose) indicating high biliary excretion of the absorbed fraction of the administered dose. In bile duct-cannulated rats, about 13% and 70% of orally and intravenously administered radio-labelled aliskiren were excreted in bile, respectively. Renal excretion was generally low in all investigated species, including humans. Excretion was complete within 7 days, with the main fraction of a radioactive dose excreted within 24-48 hours. About 50% of amlodipine oral dose was recovered in urine and faeces of rats and dogs. Following the administration of single 5mg intravenous and 15mg oral doses of ^{14}C-radiolabeled amlodipine to healthy volunteers, 59% (p.o.) and 62% (i.v.) of the dose were recovered in faeces, and 23% (i.v., p.o.) in urine. Excretion after 12 days accounted for 84% of the administered dose.

The elimination and excretion of the individual components, aliskiren and amlodipine, was extensively studied as described in the above sections. Elimination and excretion of the individual components is not expected to act differently when administered in combination. Therefore, additional studies investigating the elimination and excretion of the fixed dose combination were not necessary.

Pharmacokinetic drug interactions

Aliskiren is not expected to inhibit CYP450-catalysed metabolism of co-administered drugs. The clinical relevance of drug transporter interactions between aliskiren and various co-medications was assessed in numerous clinical studies. The AUC of the MDR1 (P-gp) substrate digoxin was only weakly affected by aliskiren co-administration. Similarly, aliskiren did not alter pharmacokinetics of the MDR1 and CYP3A4 substrate cyclosporine A. *In vitro* studies showed that aliskiren had a minimal effect on the MRP2 efflux pump as demonstrated with the MRP2 substrate valsartan. Interactions of aliskiren with substrates of several uptake transporters were only weak or not present in clinical drug-drug interaction studies with digoxin, metformin, atenolol or cimetidine. Further, multiple once oral daily dosing of aliskiren (300 mg) showed no clinically relevant pharmacokinetic interactions when administered in combination with valsartan (320 mg), amlodipine (10 mg), hydrochlorothiazide (25 mg) or ramipril (10 mg). Ketoconazole, a very potent inhibitor of CYP3A4 and also moderate MDR1 inhibitor, showed a moderate (1.8 fold) increase in aliskiren exposure. A single oral dose of Cyclosporine A (200 or 600 mg), a potent MDR1 and weak CYP3A4 inhibitor, co-administered with a single oral dose of

aliskiren (75 mg) resulted in a 4- to 5-fold and 2.5 fold increase in aliskiren AUC and C_{max}, respectively. Accordingly, aliskiren should not be used in combination with potent MDR1 (P-gp) inhibitors.

In studies *in vitro*, amlodipine showed a strong competitive inhibition of CYP1A1, and a moderate inhibition of CYP2B6. The observations suggest a moderate to low potential of amlodipine to inhibit CYP1A1- and/or CYP2B6-mediated metabolic clearance. In studies *in vitro*, amlodipine was found to be an inhibitor of MDR1. Amlodipine moderately inhibited the transport of daunorubicin, however, *in vitro* amlodipine did not inhibit the MDR1-mediated transport of digoxin. Therapeutic amlodipine steady-state concentrations are comparatively low; therefore the systemic *in vivo* interaction potential with MDR1 appears to be very low. Amlodipine did not affect the pharmacokinetics of the cardiovascular drugs digoxin, telmisartan, or benazepril. Amlodipine increased AUC and C_{max} of simvastatin by 28% and 43%, respectively, though without an effect on cholesterol. It caused a minor increase of cyclosporine A plasma levels. Grapefruit juice, which inhibits CYP3A4 and MDR1, or sildenafil, a CYP3A substrate in the gut did not change the pharmacokinetics of amlodipine. Cimetidine, telmisartan and benazepril did not significantly alter the pharmacokinetics of amlodipine. The potent CYP3A inhibitor diltiazem caused an increase in plasma C_{max} and AUC of amlodipine by up to 57%.

Aliskiren-amlodipine: The absorbed part of aliskiren is metabolised by CYP3A4 to a very limited extent (~ 1% of the dose) in humans. Animal data indicated that absorbed aliskiren is eliminated via hepatobiliary route and mainly as unchanged drug. In humans, amlodipine was eliminated mainly through extensive metabolism. Direct biliary excretion of unchanged amlodipine is much less significant. Thus, the clearance mechanisms of aliskiren and amlodipine are not anticipated to interfere with each other. The effect of co-administration of aliskiren (300 mg) and amlodipine (10 mg) on the steady-state pharmacokinetics of each drug was determined in an open-label study conducted in healthy volunteers. Amlodipine steady-state pharmacokinetics is comparable when given alone or in combination with aliskiren. Co-administration of amlodipine with aliskiren resulted in an 18% and a 29% increase in aliskiren steady-state C_{max} and AUC, respectively. These changes were not considered clinically significant. Administration of aliskiren with amlodipine to healthy volunteers was safe and well tolerated.

In summary, due to the double action of amlodipine, it might be expected that there are some changes in aliskiren exposure but a strong effect is not expected since none of these effects are strong and they are in fact counteracting. As it was stated, there is some increase in the exposure of aliskiren (18% and a 29% increase in aliskiren steady-state C_{max} and AUC,) which is in line with the reasoning presented above. The pharmacokinetic interactions were sufficiently described for the individual compounds. The significant interactions identified in preclinical and clinical studies are adequately described in the SmPC of Rasilamlo.

2.3.4. Toxicology

2.3.4.1. ***Single dose toxicity***

No nonclinical studies investigating single dose toxicity were conducted with the fixed dose combination of aliskiren/amlodipine. Previous studies conducted with the single components aliskiren and amlodipine did not suggest that the individual components of the fixed association would behave differently when given in combination.

2.3.4.2. ***Repeat dose toxicity (with toxicokinetics)***

Two repeated dose toxicity studies in rats were conducted with aliskiren/amlodipine. All animals were dosed orally by gavage. The high doses (300/10 mg/kg/day) selected for both 2-week and 13-week toxicity studies were based on the results of the previous toxicity data with aliskiren and amlodipine and considered to be at, or above, the maximum tolerated dose for repeated administration in rat. Oral administration of aliskiren/amlodipine to rats for 2- or 13-weeks resulted in changes in clinical observations, clinical pathology parameters and histopathological changes in large intestine and adrenals. All the changes noted in the studies were attributed to either aliskiren or amlodipine, respectively, based on previous findings with each component. In the 2-week rat study, the main adverse effects of aliskiren/amlodipine were noted in the large intestine at doses of 100/3 and 300/10 mg/kg/day, including inflammation and hypertrophy/hyperplasia. These changes are consistent with those previously observed for aliskiren in repeated-dose toxicity study in rats. In the 13-week rat study, the adverse effects were mainly noted in the high dose groups. The findings included premature

deaths and clinical signs of shallow/deep/laboured breathing. The findings were consistent with those observed in the previously conducted 13-week rat study with aliskiren and associated with local irritation of aliskiren as a result of aspiration of the dosing solution into the respiratory tract rather than systemic toxic effects. The findings in the adrenals were clearly related to the amlodipine treatment since there were no similar findings noted in aliskiren alone group. Also the number of animals with the findings in the adrenals was higher in the amlodipine treated group than in the combination groups. Most of the findings were reversible following the 4-week recovery period. In summary, there was no new toxicity or increased severity of the known toxicity associated with each component noted in the 13-week oral toxicity study in rats with aliskiren/amlodipine. The NOAEL was considered to be 90/3 mg/kg/day for aliskiren/amlodipine in this study. In summary, there were no toxicities identified in the 2-week and 13-week oral toxicity study in rats that would be prohibitive for use of the FDC in humans.
The overview of the studies and the findings identified is presented in the table below.

Repeated dose toxicity studies with aliskiren/amlodipine

Species (strain) Study no. Batch no. GLP status	Duration (weeks)	Route of administration, Vehicle /formulation	Dose (mg/kg/day)	No of animals per group	Major findings
Rat (Wistar) Study no. 0670746 Batch nos. 0724052 for SPP100, 000883505H for amlodipine Non-GLP	2 weeks	Oral (gavage) 0.5% Klucel-HF solution in 0.5% klucel	30/1, 100/3 and 300/10 (aliskiren /amlodipine)	5M and 5F	<u>30/1 mg/kg/day</u> No significant findings. <u>100/3 mg/kg/day</u> inflammatory cell infiltration and mucosal basophilia in the cecum (1f) <u>300/10 mg/kg/day</u> slight ↓ body weight gain and food consumption. Minimal to slight ↑ neutrophiles, slight ↑ platelet count. Enlarged mesenteric lymphnodes. Minimal inflammatory cell infiltration, mucosal basophilia and hypertrophy and hyperplasia in cecum and colon. Lymphoid hyperplasia.
Rat (Wistar) Study no. 0670747 Batch nos. 08/1 for SPA100, C0168 for SPP100, ACAA0464 for amlodipine GLP	13-week and 4-week recovery	Oral (gavage) 0.5% Klucel-HF suspension in 0.5% klucel	Aliskiren /amlodipine: 30/1, 90/3, 300/10 Aliskiren alone: 300 mg/kg/day Amlodipine alone: 10 mg/kg	10 M and 10 F in main groups 5 M and 5 F in recover groups	<u>30/1 mg/kg/day</u> No significant findings <u>90/3 mg/kg/day</u> No significant findings <u>300/10 mg/kg/day</u> Mortality. Clinical signs of shallow, deep and labored breathing, abnormal breathing sound and salivation. ↓ in lymphocyte counts, ↓ in globulin concentration. Increased heart weight. Pale discoloration or foci of the adrenals. Minimal hypertrophy and vacuolation of the zona glomerulosa <u>300 mg/kg/day</u> Mortality. Clinical signs of shallow, deep and labored breathing, abnormal breathing sound and salivation. ↓ in globulin concentration. ↓heart weigh. <u>10 mg/kg/day</u> ↓ in lymphocyte counts. Increased heart weight. Pale discoloration or foci of the adrenals. Minimal hypertrophy and vacuolation of the zona glomerulosa

NOAEL = No adverse effect level

The 2-week study is considered to be the dose finding study. There was no new toxicity or increased severity of the known toxicity associated with each component noted in the 13-week oral toxicity study in rats with aliskiren/amlodipine. The NOAEL was considered to be 90/3 mg/kg/day for the FDC. The exposure multiples at dose of NOAEL in the 13-week rat toxicity study when comparing with the exposure levels at the projected highest human dose (300/10 mg/day for aliskiren/amlodipine) are

relatively low. Overall, these studies raised no major concerns on the potential toxicity of aliskiren/amlodipine FDC.

2.3.4.3. ***Genotoxicity***

Genotoxic potential of aliskiren and amlodipine was fully evaluated as part of the monotherapy development programmes and no genotoxic potential was identified for either aliskiren or amlodipine. It is, therefore, acceptable that no specific genotoxicity tests with Rasilamlo were needed. However, two genotoxicity tests were performed to qualify the impurities detected in the drug substance of Rasilamlo, including the mutagenicity test using Salmonella typhimurium and the chromosome aberration test with cultured human peripheral blood lymphocytes. The results from these assays were negative on genotoxicity potential of impurities of Rasilamlo.

2.3.4.4. ***Carcinogenicity***

No carcinogenicity studies were conducted with Rasilamlo since this area has been adequately investigated for the monocomponents. The safety profile of Rasilamlo is expected to be same as those for the two components.

2.3.4.5. ***Reproduction Toxicity***

No reproductive and developmental toxicity studies were conducted with Rasilamlo, since these have been conducted with the monotherapies. This approach is acceptable.

2.3.4.6. ***Toxicokinetic data***

Toxicokinetic analyses of the two components, aliskiren and amlodipine, were included in the toxicity studies and no new safety signals have been identified.

2.3.4.7. ***Local Tolerance***

No specific local tolerance studies were conducted with Rasilamlo and this is considered acceptable.

2.3.4.8. ***Other toxicity studies***

No specific studies have been conducted with Rasilamlo.

2.3.5. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) for aliskiren/amlodipine fixed dose combination tablets (150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg) was provided in accordance with the CHMP guideline EMEA/CHMP/SWP/4447/00. The active molecules were assessed separately. Predicted environmental concentrations for aliskiren and amlodipine exceed the threshold value of 0.01 µL and trigger a Phase II – Tier A for both substances. Aliskiren shows low acute and chronic toxicity towards aquatic organisms. Based on the low adsorption coefficient determined for sludge, partitioning to soil is not expected for aliskiren. Bioaccumulation is not expected. The value of log Koc < 4 in the adsorption/desorption study suggests a low to moderate sorption to soil and sludge and aliskiren has no significant potential to inhibit the microbial activity of activated sludge, and is not readily biodegradable. Photodegradation is expected to be minimal. Although a highly conservative approach in predicted environmental concentrations (PEC) calculation has been adopted, the determined PEC values are well below the recommended threshold values indicated in the CHMP guidelines. Results of Tier B risk assessment on sediment dwelling organisms, in particular on the midge larvae *Chironomus riparius*, suggests that no risk for the sediment compartment due to exposure to aliskiren is expected.

However, amlodipine shows significant chronic toxicity to aquatic species with the green algae species *Pseudokirchneriella subcapitata* being the most sensitive species tested. Moreover, amlodipine has the potential to inhibit the microbial activity of activated sludge at concentrations higher than 10 mg/L and toxicity to fish early-life stage seems to appear at concentration of 1mg/L. Nevertheless, amlodipine is neither considered to be stable in the surface water, based on its photolability, nor is it persistent in

sediment compartments. The PEC values are below the recommended threshold values indicated in the CHMP guidelines. Amlodipine is not expected to bioaccumulate.

According to the results of the test entitled "Transformation in Aquatic Sediment Systems test" conducted with amlodipine, DT_{90} sediment equals 35–53 days. It means that more than 10% of the test substance is present in the sediment after 14 days thus, triggering a Tier B risk assessment on sediment dwelling organisms. Moreover, Metabolite Met5 is present in the sediment up to 99 days accounting for 37.1% of the applied test substance radioactivity. As regards Met5, a Tier B risk assessment on toxicity to sediment dwelling organisms should be provided as this was agreed as part of the post-authorisation follow-up measure. According to the OECD 308, metabolites with concentration >10% in total system water/sediment should be identified, as it's the case for Met1, Met2, Met6, Met8, and Met10. Thus, the CHMP has requested the relevant documentation as follow-up measure. The results from these additional studies were not considered required by the Committee before the adoption of the positive CHMP opinion and it is confirmed that these applications comply with Article 6 of Regulation 726/2004 having regard to the requirements of Article 8(3) (ca) of Directive 2001/83.

2.3.6. Discussion on non-clinical aspects

No specific studies with the aliskiren/amlodipine fixed combination have been conducted concerning primary and secondary pharmacodynamics, safety pharmacology, animal pharmacokinetics, single-dose toxicity, genotoxic potential, carcinogenic potential, reproductive and developmental toxicity and special toxicity studies. For all of the above aspects, reference is made to previous studies conducted with the single components aliskiren and amlodipine, conducted either in animals or in humans, and assuming that the individual components of the fixed association were not expected to behave differently when given in combination. As far as pharmacodynamics was concerned, the lack of special studies was also justified by the unavailability of appropriate animal models. Animal toxicokinetic –but not pharmacokinetic- data have been obtained from sub-groups of animals within the pivotal 2-week and 13-week repeated dose toxicity studies. Further support for limiting the number of specific studies in the pre-clinical development plan derived from the indications of the EMEA/CHMP/SWP/258498/2005 guideline in order to reduce the use of experimental animals. Overall, the pre-clinical developmental plan was limited to a minimum essential number of studies. The CHMP considered this approach acceptable.

Two non-clinical toxicity studies were performed using free or fixed combination of aliskiren and amlodipine to support the present application. The 2-week aliskiren oral dose range finding study in rats in combination with amlodipine was conducted in-house according to GLP-like standards. The 13-week GLP study was a 13-week oral gavage toxicity study in the rat followed by a 4-week recovery, conducted and reported in compliance with the current requirements of the GLP regulations. Overall, these studies raised no major concerns on the potential toxicity of Rasilamlo FDC. While the assessment of environmental risk for aliskiren was considered acceptable, there is a post-authorisation follow-up measure to be conducted in order to better clarify the environmental toxicity of amlodipine.

2.3.7. Conclusion on the non-clinical aspects

Overall, the pre-clinical developmental plan was limited to a minimum essential number of studies. This is acceptable. The available nonclinical safety data including the results obtained from the 2-week and 13-week oral toxicity studies in rats, genotoxicity studies with Rasilamlo impurities and the environmental risk assessment did not identify any new safety issues. The nonclinical safety profile of aliskiren/amlodipine appears to be consistent with those established for aliskiren and amlodipine when used as monotherapy. Based on the available clinical safety data with the two monotherapy, aliskiren and amlodipine, it is concluded that the FDC should be well tolerated when used in human at the proposed dosage. The environmental toxicity profile of amlodipine will be better characterised in frame of an agreed follow-up measure.

2.4. Clinical aspects

2.4.1. Introduction

This is an application in frame of the centralised procedure submitted in accordance with Article 3(2)(a) of Regulation (EC) No 726/2004 and with Article 10b of Directive 2001/83/EC, as amended (fixed combination application). A full dossier has been submitted, including a Risk Management Plan and an Environmental Risk Assessment.

The marketing authorisation application is made for the fixed combination of aliskiren/amlodipine (Rasilamlo) in doses of 150/5 mg, 150/10mg, 300/5mg and 300/10 mg for the treatment of hypertension. The original application claims a first-line therapy indication in a defined population of patients unlikely to achieve blood pressure control with a single agent, an add-on indication and a substitution indication. Relevant clinical studies (please see below) have been submitted in support of this claim, however, following the CHMP evaluation of the clinical results provided at the start or during the procedure, the therapeutic indication for Rasilamo was amended.

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
2. Guideline on clinical development of fixed combination medicinal products, CPMP/EWP/240/95
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/191583/05.
4. Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).
5. Questions & Answers on the Bioavailability and Bioequivalence Guideline (CHMP/EWP/40326/06).

Guidance on the clinical development programme from the EU health authorities has not been sought given the similarities with the aliskiren/hydrochlorothiazide FDC development programme (Rasilez HCT, aliskiren/hydrochlorothiazide, was approved in 2008).

2.4.2. 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 following clinical data have been submitted in support of the evaluation of Rasilamlo dossier.

Tabular overview of clinical studies

OVERVIEW OF CLINICAL STUDIES FOR RASILAMLO
Short-term parallel study SPA2305
Main Study SPA2305: 8 week, double-blind, placebo-controlled 3 x 3 multifactorial study with aliskiren monotherapy, amlodipine monotherapy, and aliskiren/amlodipine combination, with a 24-hour ABPM substudy. Placebo-controlled study about first-line use of aliskiren/amlodipine combination.
Short-term, active-controlled, add-on studies
Main Study SPA2303: 8 week, double-blind, active-controlled study evaluating the combination of aliskiren/amlodipine (300/5 mg) and aliskiren/amlodipine (300/10 mg) compared to aliskiren 300 mg in non-responders to aliskiren 300 mg. Focus on aliskiren/amlodipine combination in patients not controlled by aliskiren monotherapy. **Main Study SPA2304:** 8 week, double-blind, active-controlled study evaluating the combination of aliskiren/ amlodipine (150/10 mg) and aliskiren/amlodipine (300/10 mg) compared to amlodipine 10 mg in non-responders to amlodipine 10 mg. Focus on aliskiren/amlodipine combination in patients not controlled by amlodipine monotherapy.
Supportive Study SPP2305: double-blind, active-controlled study evaluating the combination of aliskiren/amlodipine (150/5 mg) compared to amlodipine 5 mg and amlodipine 10 mg in non-responders to amlodipine 5 mg. Focus on aliskiren/amlodipine combination in patients not controlled by amlodipine monotherapy.
Long-term studies
Main Study SPA2301: open-label 54-week study evaluating the long-term safety and efficacy of aliskiren/amlodipine 300/10 mg with optional addition of HCTZ. Uncontrolled study on the long-term use of the aliskiren/amlodipine combination.
Supportive Study SPP2323*: double-blind 26-week study, evaluating aliskiren monotherapy (300 mg) vs. HCTZ (25 mg) with optional addition of amlodipine. **Supportive Study SPP2323E1*:** a 26-week extension to Study SPP2323. Patients continued on same treatment from double-blind study. Focus on long-term use of the aliskiren/amlodipine combination
Additional data submitted during the procedure
Supportive study SPA2306: 8-week, double-blind, randomized, parallel group, multi-center study comparing the efficacy and safety of the combination of aliskiren/amlodipine 300/10 mg to amlodipine 10 mg monotherapy in patients with moderate to severe hypertension.
Main study SPA2307: 32 week, double-blind, parallel group, multicenter study to compare the efficacy and safety of initiating treatment with combination (aliskiren/amlodipine) therapy in comparison with the sequential add-on treatment strategies in patients with essential hypertension.
Supportive SPAUS01: 8 week, multicenter, randomized, double-blind, active control, parallel group study to evaluate the efficacy and safety of aliskiren administered in combination with amlodipine (150/5 mg, 300/10 mg) versus amlodipine alone (5 mg, 10 mg) in African American patients with Stage 2 hypertension.
Supportive study SAH2302: 8 week, double-blind, randomized, parallel group, active-controlled study to evaluate the efficacy and safety of the combination of aliskiren/amlodipine/HCTZ in patients with moderate to severe hypertension (pivotal study in Rasilamlo HCT dossier [aliskiren/amlodipine/HCTZ]).
Supportive study SPP100ADE03: a multi-center, open-label, prospective, observational (non-interventional) study to investigate the BP-lowering effect, patient quality of life, safety and tolerability over a period of 9-12 months of treatment with aliskiren as antihypertensive monotherapy or as add-on treatment to any other antihypertensive medication in patients with hypertension.
Supportive study SPP100A2238: An open label pilot study to determine interstitial and tissue concentrations of aliskiren and effects on the Renin-Angiotensin System (RAS) in fat and skeletal muscle of hypertensive patients with abdominal obesity.

2.4.3. Pharmacokinetics

Rasilamlo is a fixed combination of two drug substances already approved in EU, aliskiren and amlodipine. In support of the submission, the new fixed dose combination was compared with the free combination in two pivotal bioequivalence studies. Biowaivers were requested for the remaining strengths. The main goals of these studies were to justify the substitution (third-line) indication and to allow bridging to existing efficacy and safety data generated for the first and second line indications. Overall, four pharmacokinetic studies were submitted as listed in the table below.

Summary of biopharmaceutic studies

Study No.	Objective	Population	Dosage form	Dose	N
CSPA100A2101	Relative Bioavailability	HSM/F	Aliskiren (RT)	300 mg SD	60
			Amlodipine (RT)	10 mg SD	
			Aliskiren/amlodipine tablet variants	300/10 mg SD	
CSPA100A2102	Definitive Bioequivalence	HS M	Aliskiren (RT)	300 mg SD	120
			Amlodipine (RT)	10 mg SD	
			Aliskiren/amlodipine tablet (FMI)	300/10 mg SD	
CSPA100A2103	Definitive Bioequivalence	HS M	Aliskiren (RT)	150 mg SD	120
			Amlodipine (RT)	10 mg SD	
			Aliskiren/amlodipine tablet (FMI)	150/10 mg SD	
CSPA100A2104	Food-Effect	HS M	Aliskiren/amlodipine tablet (FMI)	300/10 mg SD	36

HS = Healthy subjects; M = Male; F= Female; RT = Registered tablet; FMI = Final market image product; SD = Single dose

In the pivotal efficacy phase III trials, the Final Market Image (FMI) aliskiren/amlodipine fixed combination tablets were used, while the free combination was used in the long term safety trial. Therefore, bioequivalence (BE) had to be demonstrated between the FMI formulation and the free combination formulations. In addition, demonstration of BE between FMI combination tablets and the free combination formulations also fulfils the requirement of the Guideline on clinical development of fixed combination medicinal products, requiring a BE study to be performed between the free combination of the recognised reference formulations of the individual monocomponents and the final marketed formulation. Two definitive BE studies were conducted with the dose strengths of 150/10 mg and 300/10 mg of aliskiren/amlodipine. The studies employed an open-label, randomised, single dose, two period, two sequence, crossover design. Washout between treatments was 14 days. The subjects enrolled were male healthy subjects. The studies were correctly designed and carried out. The results of the studies show that under fasting conditions, the fixed combination FMI tablets are bioequivalent to the free combination forms. Bioequivalence was evaluated under fasting conditions, while the SmPC recommends taking Rasilamlo after light meal. But based on recommendations in the CHMP Guidance, EMEA/CHMP/EWP/40326/2006, the study results are acceptable because the SmPC recommends to take Rasilamlo with food to avoid large concentration fluctuations and consequently to improve its tolerability. The results of these two pivotal bioequivalence studies are acceptable.

Biowaivers are considered appropriate for the 150/5 mg and 300/5 mg dose strengths based on the compositional proportionality/similarity, linear pharmacokinetics within the registered dose range, and similarity *in vitro* dissolution properties.

The influence of a high-fat meal on the bioavailability of the 300/10 mg fixed combination FMI tablet was investigated in an open-label, randomised, single dose, two period, two sequence, crossover study CSPA100A2104. Based on the geometric mean ratios, aliskiren AUC and C_{max} under fed conditions were reduced by 80% and 90%, respectively, when compared to fasted conditions. Bioavailability of amlodipine was not significantly affected by food. The study confirms a marked decrease in aliskiren bioavailability was elicited by food. The decrease found in the present study was higher than that found in previous studies with aliskiren alone or aliskiren/HCTZ (AUC reduction 60 to 70%) and similar to

that found with aliskiren/valsartan (AUC: -76%; C_{max}: -88%). Overall, these data suggest that the effect of food may also be dependent on formulation.

2.4.3.1. ***Absorption, distribution and elimination***

Pharmacokinetics of aliskiren and amlodipine have been reviewed and assessed in previous studies and below is a summary of their profiles based on data available from these investigations.
Aliskiren shows a very low bioavailability (2.6%). Absorption is probably also mediated by unidentified active transporters. Food markedly decreased aliskiren bioavailability by about 70%. Aliskiren is only moderately bound to plasma protein (47-51%), is poorly metabolised and is excreted mainly as unchanged drug into the bile, its urinary excretion being minimal. Hepatic uptake and biliary excretion are predominantly mediated by transporters. Plasma clearance was found to be 0.13 L/h/kg. Terminal half-life is about 40 h (ranging from 30 to 60 hours) and was found to be slightly longer in the elderly (>65 years). In the elderly (>65 years), exposure is increased by about 50%, with respect to subjects aged 18-45 years. In subjects with renal impairment, C_{max} and C_{min} are both about 2-fold higher than in subjects with normal renal function. The increase appears to be not related to the decrease of renal function. In subjects with hepatic impairment, exposure is not increased. Time needed to reach steady-state is 7-12 days. The accumulation factor is 1.5-2. Apparent clearance did not change with repeated administration. Pharmacokinetics slightly deviated from linearity in the whole range of investigated doses. Pharmacokinetics of aliskiren was found to be highly variable. The inter-subject variability for C_{max} and AUC was 40-70% and 30-50%, respectively. The intra-subject variability for aliskiren C_{max} and AUC was 40% and 20%, respectively. Aliskiren does not inhibit any of the CYP450 enzymes at therapeutic concentrations. *In vivo* data suggest that aliskiren is not an enzyme inducer. When administered with atorvastatin, steady-state aliskiren AUC and C_{max} increased by 50%. An interaction study with ciclosporin has shown that ciclosporin increased aliskiren AUC by 4.5 to 5.5-fold, and C_{max} by 2.5-fold, independently of ciclosporin dose. Ciclosporin markedly increased aliskiren $t_{1/2}$. This result confirms that P-gp is a major determinant of aliskiren clearance.

Amlodipine is almost completely absorbed from the gastrointestinal tract, absolute bioavailability being between 52% and 88%. Absorption is not influenced by food. Amlodipine has a high volume of distribution (Vd) of 21 L/Kg, which could be due to high membrane affinity of the drug. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients. Amlodipine is extensively (about 90%) converted to inactive metabolites *via* hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. The elimination half-life of amlodipine is approximately 40 hrs. Amlodipine exhibits linear pharmacokinetics between 5 mg and 10 mg. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%. The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with hepatic insufficiency have a decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%; therefore, a lower initial dose of amlodipine may be required.

2.4.3.2. ***Dose proportionality and time dependencies***

No specific pharmacokinetic studies were conducted.

2.4.3.3. ***Special populations***

No specific pharmacokinetic studies were conducted.

2.4.3.4. ***Pharmacokinetic interaction studies***

Interaction between aliskiren (300 mg/day) and amlodipine (10 mg/day) was investigated at a steady-state in young healthy subjects. In the SPP100A2218 study, drug products were administered under fasting conditions. Amlodipine co-administration significantly increased aliskiren AUC_{ss}, C_{max} and C_{min}. Inspection of aliskiren time-courses indicated that amlodipine co-administration likely altered the absorption features of aliskiren. The mechanism of the effect of amlodipine is unknown but may be related to inhibition or modulation of P-glycoprotein activity by amlodipine, aliskiren PK being very sensitive to P-glycoprotein inhibitors. Hence, the effect of amlodipine might depend on the dose ratio of the two drugs and thus, might be greater with the 150/10 mg combination, which was not investigated. In addition, food decreases aliskiren absorption, but the overall effect of amlodipine

and food is unknown even though the proposed SmPC recommends that the drug product should be taken with food. Finally, interaction data in the elderly are missing. The CHMP considered that these data may be important because of the likely differences in the absorption of aliskiren in different age groups. The published pharmacodynamic studies indicate that an interaction at the absorption site between amlodipine and aliskiren is theoretically possible and that the extent of their interaction depends on the dose (plasma concentration) ratio. However, the data from the pivotal clinical trial provide sufficient evidence that an eventual interaction has no clinically significant effects.

2.4.3.5. ***Pharmacokinetics using human biomaterials***

No specific studies were conducted.

2.4.4. Pharmacodynamics

No specific pharmacodynamic interaction studies with the aliskiren/amlodipine combination have been performed. The pharmacodynamic properties of aliskiren and amlodipine are well characterised and relevant information is reflected in their SmPCs.

2.4.5. Discussion on clinical pharmacology

The main issue under discussion in the initial phase of the evaluation was that the bioequivalence studies were performed under fasting conditions, whereas the proposed SmPC recommends administration of the medicinal product with a light meal. Since available data show that food has a marked effect on aliskiren bioavailability and that the effect of food may also be dependent on formulation, it was considered that a BE study under fed conditions was therefore needed to support the substitution indication. Nevertheless, the indication substitution therapy has finally been withdrawn during the procedure.

Interaction between aliskiren (300 mg/day) and amlodipine (10 mg/day) was investigated at steady-state in healthy subjects and products were administered under fasting conditions. Amlodipine co-administration increased aliskiren AUC_{ss}, C_{max} and C_{min} and appears to alter the absorption features of aliskiren. The mechanism of this effect may be related to inhibition or modulation of P-glycoprotein activity by amlodipine. The effect of amlodipine was considered to be dependant on the dose ratio of the two drugs and food. However, clinical data from clinical trial CSPA100A2305 were presented and showed that the association of aliskiren 150 mg and amlodipine 10 mg does not lead to unpredictable clinical effects. Patients on the FDC 150/10 mg dose showed good efficacy and safety when the drug was administered without regards to food intake. The standard error for the DBP reduction observed with 150/10 mg was the same as for other doses, indicating that there was no greater variability with this dose. Moreover, no new safety issues were identified with any of the aliskiren/amlodipine combination doses studied, including 150/10 mg. Therefore, the data from clinical trials provide sufficient evidence that an eventual interaction has no clinically significant effects. The recently published data on rifampicin decreasing the bioavailability of aliskiren by about 50% have been included in the SmPC of Rasilamlo, as required by the CHMP.

2.4.6. Conclusions on clinical pharmacology

Rasilamlo is a fixed combination of two drug substances already approved in EU, aliskiren and amlodipine. Their pharmacokinetic and pharmacodynamic profiles have been adequately characterised during the drug development of each substance. The core clinical pharmacology studies were the bioequivalence studies performed to bridge the data between the Final Market Image aliskiren/amlodipine fixed combination tablets used in the pivotal efficacy phase III trials and the free combination used in the long term safety trial. Two definitive BE studies were conducted with the dose strengths of 150/10 mg and 300/10 mg of aliskiren/amlodipine. The studies were correctly designed and carried out. The results of the studies show that under fasting conditions, the fixed combination FMI tablets are bioequivalent to the free combination forms. Demonstration of BE under fed conditions is not deemed necessary as the substitution and first line therapy indications have been withdrawn. The biowaiver request for the 150/5 mg and 300/5 mg strengths is acceptable, being supported by all the data and information required by the valid CHMP guidelines on bioequivalence. Interaction between aliskiren (300 mg/day) and amlodipine (10 mg/day) was investigated at steady-state in healthy subjects under fasting conditions. In the study, drug products were administered under fasting

conditions. Amlodipine co-administration increased aliskiren disposition. Although theoretically the extent of interaction may depend on the dose ratio, and also be different under fed conditions, data from clinical trials show that the clinical consequence of this presumed interaction is not significant.

2.4.7. Clinical efficacy

2.4.7.1. ***Dose response study(ies)***

The clinical program does not include true dose-response studies but the proposal of four different dosages of the FDC is acceptable because they include all the dosages available in the market for the two monocomponents, aliskiren and amlodipine.

2.4.8. Main study(ies)

As summarised below, the clinical programme includes 4 main studies for analyses on efficacy and/or safety

Short-term parallel study

Study SPA2305: *double-blind, placebo-controlled 3 x 3 multifactorial study with aliskiren monotherapy, amlodipine monotherapy, and aliskiren/amlodipine combination, with a 24-hour ABPM substudy.*

Placebo-controlled study about first-line use of aliskiren/amlodipine combination

Short-term, active-controlled, add-on studies

Study SPA2303: *double-blind, active-controlled study evaluating the combination of aliskiren/amlodipine (300/5 mg) and aliskiren/amlodipine (300/10 mg) compared to aliskiren 300 mg in non-responders to aliskiren 300 mg.*

Focus on aliskiren/amlodipine combination in patients not controlled by aliskiren monotherapy

Study SPA2304: *double-blind, active-controlled study evaluating the combination of aliskiren/ amlodipine (150/10 mg) and aliskiren/amlodipine (300/10 mg) compared to amlodipine 10 mg in non-responders to amlodipine 10 mg.*

Focus on aliskiren/amlodipine combination in patients not controlled by amlodipine monotherapy

Study SPP2305: *double-blind, active-controlled study evaluating the combination of aliskiren/amlodipine (150/5 mg) compared to amlodipine 5 mg and amlodipine 10 mg in non-responders to amlodipine 5 mg.*

Focus on aliskiren/amlodipine combination in patients not controlled by amlodipine monotherapy

Long-term studies

Study SPA2301: *open-label 54-week study evaluating the long-term safety and efficacy of aliskiren/amlodipine 300/10 mg with optional addition of HCTZ.*

Uncontrolled study on the long-term use of the aliskiren/amlodipine combination

Study SPP2323: *double-blind 26-week study, evaluating aliskiren monotherapy (300 mg) vs. HCTZ (25 mg) with optional addition of amlodipine.*

Study SPP2323E1: *a 26-week extension to Study SPP2323. Patients continued on same treatment from double-blind study.*

Focus on long-term use of the aliskiren/amlodipine combination

Study SPA2305 was a multifactorial comparison of 4 doses of aliskiren/amlodipine to each of the monotherapy components. It served to support the use of the combination as first-line therapy, since patients whose BP was unlikely to be controlled by a single agent, such as those with stage 2 hypertension and co-morbidities (diabetes and renal impairment) were included, and since all randomised patients received aliskiren/amlodipine fixed combination treatment without titration from

monotherapy. Mean 24-hour ABPM was evaluated in a subset of the study patient population in support of the once-daily dosing. However, this study failed to provide convincing evidence in support of the first line indication of Rasilamlo. In light of the above and considering that the first line indication was not approvable, the results of this study will not be the main focus of the report, and will be mentioned as supportive data in the appropriate sections.

Studies SPA2303, SPA2304 and SPP2305 were double-blind, randomised, active-controlled and performed in patients not adequately controlled by one or the other monotherapy. These studies provide the data to support the use of the combination as add-on therapy in accordance with the CHMP Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2004. Study SPA2303 was conducted in patients who were inadequately controlled by aliskiren 300 mg, study SPA2304 and study SPP2305 in patients inadequately controlled by amlodipine (10 mg and 5 mg, respectively). These studies are considered the be the main clinical trials in support of the add-on indication for Rasilamlo.

Supportive study SPA2301 was an uncontrolled, open-label study to investigate on long-term use of the maximum dose of aliskiren/amlodipine (1 year). This study is in line with the requirements of the ICH Guideline on Extent of Population Exposure to Assess Clinical Safety E1, 1995, which addresses the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life threatening disease. Study SPP2323 and its extension Study SPP2323E1 evaluated long-term (52 weeks) use of aliskiren based regimen *vs* HCT-based regimen. Since these studies allowed the optional addition of amlodipine they provide additional data about the long-term use of aliskiren/amlodipine combination.

Methods

Study Participants

Studies SPA2303, SPA2304, SPP2305: The populations evaluated in the short-term, active controlled, non-responder studies were those who required combination therapy due to inadequate BP control with monotherapy. Study SPA2303 in patients not adequately controlled with aliskiren 300 mg monotherapy, study SPA2304 and study SPP2305 in patients not adequately controlled with amlodipine (10 mg and 5 mg, respectively) monotherapy. Patients enrolled in the active-controlled non-responder studies were required to have an msDBP of ≥90 mmHg and <110 mmHg after the 4-week run-in with aliskiren or amlodipine. Differences between short-term, active-controlled, non-responder studies included a larger percentage of Black patients in study SPP2305 (≥ 16.3% within each treatment group) compared with study SPA2303 (0% to 0.4% within each treatment group) and none in study SPA2304. There was a larger percentage of Asian patients in study SPA2303 (>26.5% within each treatment group) *vs* study SPP2305 (10.0% to 12.4%) and study SPA2304 (0% to 0.4%).
Exclusion criteria were generally similar across all trials. Patients with severe hypertension, secondary hypertension, evidence of significant hepatic or renal impairment, unstable diabetes, significant cardiac disease, and history of hypertensive encephalopathy or cerebrovascular accident were not included in most trials. Concomitant medications that could significantly affect BP or were known to interact with the study drug were also excluded. However, the CHMP noted that drug taking was not standardised in terms of food intake.

Treatments

Studies SPA2303, SPA2304, SPP2305: All trials had 3 phases and began with a 1- to 4-week washout phase to allow patients to taper off previous antihypertensive treatments, followed by a 4-week single-blind active run-in period. Non-responding patients were then randomised to 8 weeks of double-blind treatment in Study SPA2303 and Study SPA2304, and 6 weeks of double-blind treatment in Study SPP2305. Summary of treatments is provided in the table below.

Summary of short-term, active-controlled non-responder trials

Study No.	Study objective, population	Patients random. / treated	Treatment duration	Dosage	Primary efficacy endpoint
Patients not adequately responding to aliskiren 300 mg monotherapy					
SPA2303	Efficacy/safety in patients with hypertension not responding to aliskiren 300 mg	820 / 818	8 weeks	3 treatment groups: ali/aml 300/5 mg ali/aml 300/10 mg aliskiren 300 mg	Change in msDBP
Patients not adequately responding to amlodipine monotherapy					
SPA2304	Efficacy/safety in patients with hypertension not responding to amlodipine 10 mg	847 / 843	8 weeks	3 treatment groups: ali/aml 150/10 mg ali/aml 300/10 mg amlodipine 10 mg	Change in msDBP
SPP2305	Efficacy/safety in patients with hypertension not responding to amlodipine 5 mg	545 / 544	6 weeks	3 treatment groups: ali/aml 150/5 mg; amlodipine 10 mg; amlodipine 5 mg	Change in msDBP

Objectives

The primary objective was change from baseline in msDBP for all short-term and long-term controlled studies, which is consistent with ICH Guideline on Clinical Evaluation of New Hypertensive Drugs E12, 2000. Secondary efficacy variables in all studies included change from baseline to Endpoint in msSBP, BP control rates (msSBP <140 mmHg and msDBP <90 mmHg), as well as aggressive BP control rates for msSBP <130 mmHg and msDBP <80 mmHg), DBP response defined as an msDBP <90 mmHg or a ≥10 mmHg decrease compared to baseline, SBP response defined as msSBP <140 mmHg or a ≥20 mmHg decrease compared to baseline, mean ABPM (in Study SPA2305), and the biomarkers (PRA and/or PRC) as exploratory objective. The CHMP considered the objectives of the studies as adequately defined.

Outcomes/endpoints

Study SPA2303: Efficacy variables included changes from baseline (Visit 4) to Endpoint in msDBP and msSBP, the proportions of patients achieving a BP control target of <140/90 mmHg, and the proportions of patients achieving a response (msDBP: <90 mmHg or a ≥10 mmHg reduction from baseline and msSBP: <140mmHg or ≥20 mmHg reduction from baseline).

Study SPA2304: Efficacy variables included changes from baseline (Visit 5) to endpoint in mean sitting diastolic blood pressure (msDBP) and mean sitting systolic blood pressure (msSBP), the proportions of patients achieving a blood pressure control target of msSBP/msDBP< 140 / 90 mmHg, and the proportions of patients achieving a diastolic blood pressure response (msDBP < 90 mmHg or a ≥10 mmHg reduction from baseline).

Study SPP2305: The primary efficacy variable was the change from baseline (Visit 4, Day 1) to endpoint (Visit 7, Day 42) in msDBP at trough, as measured by the Omron HEM-705CP automatic blood pressure monitor and appropriate size cuff. The secondary efficacy variables included the change from baseline (Visit 4, Day 1) to endpoint (Visit 7, Day 42) in msSBP at trough, the proportion of responders (msDBP <90 mm Hg or a reduction or ≥10 mm Hg from baseline, and the proportion of patients achieving blood pressure control (msSBP< 140 mm Hg and msDBP < 90 mm Hg) in each treatment group.

Sample size

A total of 5570 patients were treated in studies: SPA2305, SPA2303, SPA2304, SPP2305, SPA2301, SPP2323 and SPP2323E1, including 2835 patients who received at least 1 dose of any aliskiren/amlodipine combination, and 86 patients who received hydrochlorothiazide add-on to aliskiren/amlodipine combination. Among these 5570 treated patients, 21 patients in Study SPP2323 were excluded from the safety analyses because they were only treated with placebo for a short period of time and never re-randomized to receive aliskiren or hydrochlorothiazide treatment in this long-term study. Sample size of the studies matches the zero hypotheses.

Randomisation

All eligible patients were randomised to one of the treatment arms using the IVRS system if appropriate, which assigned a randomization number to the patient following the confirmation of inclusion/exclusion criteria. The randomisation number was not communicated to the investigator. Randomisation was stratified by centre. The randomisation scheme for patients was reviewed and approved by a member of the Biostatistics Quality Assurance Group.

Blinding (masking)

Once patients fulfilled the entry criteria to enter the double-blind treatment period, patients, investigator staff, persons performing the assessments, and data analysts remained blind to the identity of the treatment from the time of randomization until database lock, using the following methods: a/ randomization data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study; b/ the identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, schedule of administration, appearance and odour. A double-dummy design was used because the identity of the medications could not be disguised due to their different forms. Unblinding only occurred in the case of patient emergencies (see below) and at the conclusion of the study. Emergency unblinding was only undertaken when it was essential for effective treatment of the patient.

Statistical methods

For studies SPA2305, SPA2303, SPA2304, SPP2305, SPP2323 and SPP2323E1, the primary efficacy variable (change from baseline in msDBP) was analysed by a pre-specified, 2-way analysis of covariance (ANCOVA) with treatment and region as factors, and baseline as a covariate. The region was pre-specified prior to unblinding treatment codes for analyses. The same model was used to analyze the change from baseline in msSBP. The response rates and the overall BP control rate were analysed by means of a logistic regression model with treatment and region as factors, and baseline BP measurement as a covariate. The statistical methods, as proposed, were considered acceptable.

Results

Participant flow

Study SPA2303

Patient disposition for each treatment group during the double-blind period (Entered Single-Blind Set)

Disposition	Aliskiren/ amlodipine 300/10 mg n (%)	Aliskiren/ amlodipine 300/5 mg n (%)	Aliskiren 300 mg n (%)	Total n (%)
Single-blind analysis set				1086
Completed single-blind				818
Discontinued single-blind				268
Randomized analysis set	**283[1]**	**277[1]**	**260**	**820[1]**
Completed	262 (92.6)	271 (97.8)	244 (93.8)	777 (94.8)
Discontinued	20 (7.1)	5 (1.8)	16 (6.2)	41 (5.0)
Reason for discontinuation (double-blind)				
Adverse Event(s)	11 (3.9)	1 (0.4)	3 (1.2)	15 (1.8)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	9 (3.5)	9 (1.1)
Patient's condition no longer required study drug	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Patient withdrew consent	3 (1.1)	2 (0.7)	3 (1.2)	8 (1.0)
Lost to follow-up	3 (1.1)	1 (0.4)	0 (0.0)	4 (0.5)
Protocol deviation	2 (0.7)	1 (0.4)	1 (0.4)	4 (0.5)

Percentage (%) was calculated using the Randomized Analysis Set as the denominator.
[1] Two patients (SPA100A2303-0457-00006 and SPA100A2303-0601-00030) were randomized in error and were assigned a randomization number (1 patient in each of the aliskiren/amlodipine 300/10 mg and aliskiren/amlodipine 300/5 mg groups). Both of these patients were discontinued from the single-blind run-in treatment period without taking any double-blind study medication. Therefore, these 2 patients were not counted as discontinued from the double-blind treatment period.

Study SPA2304

Patient disposition by treatment group (Randomized Set)

Disposition	Ali/Aml 300/10 mg n (%)	Ali/Aml 150/10 mg n (%)	Aml 10 mg n (%)	Total n(%)
Single-blind set				1358
Completed				843
Discontinued				515
Randomized set	279	285[1]	283[1]	847[1]
Completed	261 (93.6)	266 (93.3)	255 (90.1)	782 (92.3)
Discontinued	18 (6.5)	17 (6.0)	26 (9.2)	61 (7.2)
Reason for discontinuation				
Adverse Event(s)	9 (3.2)	10 (3.5)	14 (5.0)	33 (3.9)
Abnormal laboratory value(s)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.2)
Unsatisfactory therapeutic effect	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)
Patient's condition no longer requires study drug	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Patient withdrew consent	3 (1.1)	1 (0.4)	6 (2.1)	10 (1.2)
Lost to follow-up	0 (0.0)	2 (0.7)	1 (0.4)	3 (0.4)
Administrative problems	1 (0.4)	2 (0.7)	0 (0.0)	3 (0.4)
Protocol deviation	3 (1.1)	0 (0.0)	2 (0.7)	5 (0.6)

Percentage (%) was calculated using the randomized set as the denominator.

[1] Four patients were randomized in error and were assigned a randomization number (2 in aliskiren/amlodipine 150/10 mg group and 2 in amlodipine 10 mg group). All these patients were discontinued from the single-blind period without taking any double-blind study medication. Therefore, these patients were not counted as discontinued from the double-blind period.

Study SPP2305

Patient disposition for each treatment group during the double-blind period (All enrolled patients)

	Aliskiren 150 mg + Amlodipine 5 mg	Amlodipine 5 mg	Amlodipine 10 mg	Total
Number (%) of patients				
Enrolled				762
Randomized	187	180	178	545
Completed	182 (97.3)	171 (95.0)	170 (95.5)	523 (96.0)
Discontinued	5 (2.7)	9 (5.0)	8 (4.5)	22 (4.0)
Main reason for discontinuation				
Death	0	0	0	0
Adverse event(s)	5 (2.7)	4 (2.2)	5 (2.8)	14 (2.6)
Abnormal test procedure result	0	1 (0.6)	0	1 (0.2)
Patient withdrew consent	0	3 (1.7)	1 (0.6)	4 (0.7)
Lost to follow-up	0	1 (0.6)	2 (1.1)	3 (0.6)

Recruitment

For studies SPA2305, SPA2303 and SPA2304 the study period was between September 2008 and June 2009. Study SPP2305 was conducted between February and October 2005.

Conduct of the study

Studies SPA2303 and SPA2304
The protocols of studies SPA2303 and SPA2304 were not amended. All analyses were carried out as specified in the protocol. No changes in the studies' conduct occurred.

Study SPP2305
The protocol of the study SPP2305 was amended twice. Amendment 1, issued before any patients were enrolled in the study concerned the collection of blood samples for the analysis of PRA in a subset of patients at Visit 4 and Visit 7. Furthermore, the use of an automatic blood pressure monitor rather than a standard mercury sphygmomanometer for the assessment of blood pressure at each visit in the study was required. Amendment 2, issued after the inclusion of 27.6% of patients, allowed an optional two week extension of the washout period prior to the start of single-blind amlodipine in this study. This option was needed as the initial two week washout did not allow sufficient time for blood pressure to rise above normal ranges for a large number of the subjects initially screened. This amendment did not have impact on patient safety as patients with msDBP ≥ 110 mmHg or msSBP ≥ 180 mmHg at any time during the study were to be discontinued from the trial.

Baseline data

Studies SPA2303, SPA2304 and SPP2305
The baseline data are summarised in the table below.

Demographics and baseline characteristics in active-controlled non-responder studies (Randomized patients)

	Study SPA2303 Non-responders to aliskiren 300 mg			Study SPA2304 Non-responders to amlodipine 10 mg			Study SPP2305 Non-responders to amlodipine 5 mg		
Demographic Characteristic Category/statistic	**Ali / aml 300/10mg**	**Ali / aml 300/5mg**	**Ali 300 mg**	**Ali / aml 300/10mg**	**Ali / aml 150/10mg**	**Amlodipine 10mg**	**Ali / aml 150/5mg**	**Amlodipine 5 mg**	**Amlodipine 10 mg**
Age (yrs)									
N	283	277	260	279	285	283	187	180	178
mean (SD)	54.6 (10.67)	54.4 (10.69)	54.7 (10.99)	55.2 (10.19)	54.4 (10.70)	54.3 (10.92)	53 (11.9)	54 (10.9)	54 (10.6)
Age Group n (%)									
<65 yrs	233 (82.3)	222 (80.1)	208 (80.0)	232 (83.2)	231 (81.1)	231 (81.6)	156 (83.4)	144 (80.0)	148 (83.1)
≥65 yrs	50 (17.7)	55 (19.9)	52 (20.0)	47 (16.8)	54 (18.9)	52 (18.4)	31 (16.6)	36 (20.0)	30 (16.9)
>75 yrs	12 (4.2)	8 (2.9)	12 (4.6)	6 (2.2)	3 (1.1)	8 (2.8)	8 (4.3)	4 (2.2)	3 (1.7)
Sex n (%)									
Female	120 (42.4)	101 (36.5)	103 (39.6)	116 (41.6)	113 (39.6)	99 (35.0)	82 (43.9)	85 (47.2)	86 (48.3)
Male	163 (57.6)	176 (63.5)	157 (60.4)	163 (58.4)	172 (60.4)	184 (65.0)	105 (56.1)	95 (52.8)	92 (51.7)
Race n (%)									
Caucasian	191 (67.5)	180 (65.0)	173 (66.5)	277 (99.3)	283 (99.3)	282 (99.6)	128 (68.4)	128 (71.1)	122 (68.5)
Black	0 (0.0)	1 (0.4)	0 (0.0)	--	-	--	34 (18.2)	33 (18.3)	29 (16.3)
Asian	75 (26.5)	76 (27.4)	70(26.9)	1 (0.4)	0 (0.0)	1 (0.4)	21 (11.2)	18 (10.0)	22 (12.4)
Native American	1 (0.4)	0 (0.0)	1 (0.4)	--	-	--	NA	NA	NA
Other	16 (5.7)	20 (7.2)	16 (6.2)	1 (0.4)	2 (0.7)	0 (0.0)	4 (2.1)	[illegible]	5 (2.8)
Ethnicity n (%)									
Hispanic or Latino	24 (8.5)	22 (7.9)	19 (7.3)	8 (2.9)	9 (3.2)	8 (2.8)	NA	NA	NA
Chinese	--	--	--	1 (0.4)	0 (0.0)	0 (0.0)	NA	NA	NA
Indian (Indian Subcontinent)	47 (16.6)	50 (18.1)	45 (17.3)	--	-	--	NA	NA	NA
Mixed ethnicity	2 (0.7)	0 (0.0)	0 (0.0)	--	-	--	NA	NA	NA
Other	210 (74.2)	205 (74.0)	196 (75.4)	270 (96.8)	276 (96.8)	275 (97.2)	NA	NA	NA
Duration of Hypertension (yrs)									
N	279	271	257	275	278	279	179	176	171
mean (SD)	7.9 (6.51)	7.9 (6.69)	7.6 (6.53)	8.3 (7.66)	8.2 (7.35)	7.8 (7.51)	8 (7.6)	8 (6.8)	8 (7.5)
naïve patients, n (%)	4 (1.4)	6 (2.2)	3 (1.2)	4 (1.4)	7 (2.5)	5 (1.8)	NA	NA	NA
Body Mass Index (kg/m^2)									
N	283	277	258	276	284	281	187	179	177
mean (SD)	29.2 (5.14)	29.1 (5.07)	29.1 (5.26)	30.3 (5.13)	30.0 (4.87)	29.6 (4.87)	30 (5.5)	30 (5.7)	30 (5.7)
BMI status n (%)									
BMI <20 kg/m^2	8 (2.8)	3 (1.1)	3 (1.2)	1 (0.4)	3 (1.1)	3 (1.1)	NA	NA	NA
20 <= BMI <25 kg/m^2	39 (13.8)	54 (19.5)	55 (21.2)	33 (11.8)	35 (12.3)	38 (13.4)	NA	NA	NA
25 <= BMI <30 kg/m^2	126 (44.5)	118 (42.6)	102 (39.2)	111 (39.8)	114 (40.0)	114 (40.3)	NA	NA	NA
BMI >= 30 kg/m^2	110 (38.9)	102 (36.8)	98 (37.7)	131 (47.0)	132 (46.3)	126 (44.5)	82 (43.9)	80 (44.4)	81 (45.5)
Baseline msDBP and msSBP (mmHg)									
n	283	277	260	279	285	283	187	180	178
msDBP Mean (SD)	96.2 (5.12)	96.5 (5.13)	96.3 (4.62)	94.4 (3.97)	94.8 (3.92)	94.6 (4.07)	95.7 (4.4)	96.2 (4.8)	96.5 (4.5)
msSBP Mean (SD)	151.7(12.51)	150.8(12.82)	151.9(12.90)	149.7(11.98)	151.7(11.62)	149.4(11.71)	150.5 (11.1)	150.5 (13.2)	150.8 (12.0)
Metabolic Syndrome n (%)#									
Yes	127(44.9)	120(43.5)	126(48.5)	151 (54.1)	135 (47.4)	119 (42.0)	80 (42.8)	71 (39.4)	74 (41.6)
No	156(55.1)	156(54.2)	134(51.5)	126 (45.2)	149 (52.3)	163 (57.6)	103 (55.1)	108 (60.0)	102 (57.3)
Diabetes- yes– n (%)	28(9.9)	28(10.1)	36(13.8)	50 (17.9)	38 (13.3)	37 (13.1)	26 (13.9)	26 (14.4)	27 (15.2)

SD = standard deviation; NA = not available

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

The CHMP noted that in studies SPA2303, SPA2304 and SPP2305 the number of patients between 65-75 years of age was relatively small (16.9%) and patients >75 years of age only 1.7%. No data on patients with renal impairment or CV risks have been provided. The number of patients with diabetes was only 15.2%.

Numbers analysed

Populations evaluated in all active- and placebo-controlled trials

		Population			
		Randomized	Completed	Efficacy* (FAS)	Safety
Design	Study No.	N	n (%)	n (%)	n (%)
Placebo-controlled	SPA2305	1688	1539 (91.2)	1685 (99.8)	1685 (99.8)
Active-controlled	SPA2303	820	777 (94.8)	818 (99.8)	818 (99.8)
	SPA2304	847	782 (92.3)	843 (99.5)	843 (99.5)
	SPP2305	545	523 (96.0)	541* (99.3)	544 (99.8)
	Total	3900	3621	3887	3890

*The ITT population was used in Study SPP2305 (not the FAS); definition of ITT: "all randomized patients who received at least 1 dose of double-blind study drug and who had a baseline and at least 1 post-baseline primary efficacy measurement" and definition of FAS: "All randomized patients. This was the primary efficacy set for all studies except SPP2305. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization. Misrandomized patients were excluded from the FAS. Misrandomized patients were those who discontinued the study permanently prior to the randomization visit, but were allocated a randomization number by error and did not take any double-blind study medication."

Outcomes and estimation

Studies SPA2303, SPA2304 and SPP2305

Changes from baseline in msDBP and msSBP: The below tables present the statistical analyses of changes from baseline in msDBP and msSBP at Endpoint in the active-controlled non-responder trials. For all 3 active-controlled non-responder trials, the aliskiren/amlodipine combination treatment was clinically and statistically superior to the respective monotherapies in reduction of msDBP and msSBP. In study SPA2304, when aliskiren was added to amlodipine 10 mg, aliskiren/amlodipine 300/10 mg and aliskiren/amlodipine 150/10 mg were both clinically and statistically superior to amlodipine 10 mg at Endpoint in reduction of msDBP (-3.76 and -1.72 mmHg over amlodipine 10 mg, respectively) and msSBP (-6.22 and -2.81 mmHg over amlodipine 10 mg, respectively). Similarly, in study SPA2303, when amlodipine was added to aliskiren 300 mg, aliskiren/amlodipine 300/10 mg and aliskiren/amlodipine 300/5 mg were both clinically and statistically superior to aliskiren 300 mg at Endpoint in reduction of msDBP (-7.23 and -4.71 mmHg over aliskiren 300 mg, respectively) and msSBP (-11.62 and - 8.01 mmHg over aliskiren 300 mg, respectively). In Study SPP2305, the combined aliskiren/amlodipine 150/5 mg treatment group showed a significantly greater reduction ($p < 0.0001$) in msDBP compared to the amlodipine 5 mg treatment group at Endpoint, with an additional mean reduction in msDBP of 3.62 mmHg and in msSBP of 6.02 mmHg. Aliskiren/amlodipine 150/5 mg had a numerically greater (but not statistically significant) SBP/DBP reduction than amlodipine 10 mg, with an incremental change of 1.35/0.42 mmHg.

Study SPA2303

Statistical analysis of LS mean reduction of msDBP and msSBP (mmHg) from baseline to Endpoint in Study SPA2303 (FAS)

msDBP (primary efficacy variable)			
Treatment Group	**N**	**LSM change from baseline (SE)**	
Aliskiren/amlodipine 300/10 mg	281	-13.07 (0.463)	
Aliskiren/amlodipine 300/5 mg	274	-10.54 (0.467)	
Aliskiren 300 mg	260	-5.84 (0.480)	
Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Aliskiren/amlodipine 300/10 mg vs aliskiren 300 mg	-7.23 (0.638)	(-8.49, -5.98)	<0.0001*
Aliskiren/amlodipine 300/5mg vs aliskiren 300 mg	-4.71 (0.642)	(-5.97, -3.45)	<0.0001*
msSBP (key secondary efficacy variable)			
Treatment Group	**N**	**LSM change from baseline (SE)**	
Aliskiren/amlodipine 300/10 mg	281	-18.04 (0.780)	
Aliskiren/amlodipine 300/5 mg	274	-14.43 (0.786)	
Aliskiren 300 mg	260	-6.42 (0.809)	
Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Aliskiren/amlodipine 300/10 mg vs aliskiren 300 mg	-11.62 (1.074)	(-13.73, -9.51)	<0.0001*
Aliskiren/amlodipine 300/5 mg vs aliskiren 300 mg	-8.01 (1.082)	(-10.13, -5.88)	<0.0001*

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

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

* Indicates statistical significance at 0.05 level

N includes patients who had baseline and post-baseline measurements. Three patients (1 in aliskiren/amlodipine 300/10 mg and 2 in aliskiren/amlodipine 300/5 mg) were excluded from the analysis due to lack of post-baseline assessment.

Study SPA2304

Statistical analysis of LS mean reduction of msDBP and msSBP (mmHg) from baseline to Endpoint in Study SPA2304 (FAS)

msDBP (primary efficacy variable)			
Treatment group	**N**	**LSM change from baseline (SE)**	
Aliskiren/amlodipine 300/10 mg	277	-10.99 (0.462)	
Aliskiren/amlodipine 150/10 mg	281	-8.95 (0.460)	
Amlodipine 10 mg	279	-7.23 (0.459)	
Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Aliskiren 300mg/ amlodipine 10mg vs amlodipine 10mg	-3.76 (0.644)	(-5.03, -2.50)	<0.0001*
Aliskiren 150mg/ amlodipine 10mg vs amlodipine 10mg	-1.72 (0.642)	(-2.98, -0.46)	0.0077*
msSBP (key secondary efficacy variable)			
Treatment group	**N**	**LSM change from baseline (SE)**	
Aliskiren/amlodipine 300/10 mg	277	-14.42 (0.684)	
Aliskiren/amlodipine 150/10 mg	281	-11.01 (0.681)	
Amlodipine 10 mg	279	-8.20 (0.680)	
Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Aliskiren 300mg/ amlodipine 10mg vs amlodipine 10mg	-6.22 (0.953)	(-8.09, -4.35)	<0.0001*
Aliskiren 150mg/ amlodipine 10mg vs amlodipine 10mg	-2.81 (0.953)	(-4.69, -0.94)	0.0033*

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

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

* Indicates statistical significance at 0.05 level

Study SPP2305

Statistical analysis of LS mean reduction of msDBP and msSBP (mmHg) from baseline to Endpoint in Study SPP2305 (ITT)

msDBP (primary efficacy variable)		
Treatment Group	**N**	**LSM change from baseline (SE)**
Aliskiren/amlodipine 150/5 mg	187	-8.46 (0.60)
Amlodipine 10 mg	177	-8.04 (0.62)
Amlodipine 5 mg	177	-4.84 (0.62)

Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Aliskiren/amlodipine 150/5 mg vs amlodipine 5 mg	-3.62 (0.83)	(-5.25, -1.99)	<0.0001*
Aliskiren/amlodipine 150/5 mg vs amlodipine 10 mg	-0.42 (0.83)	(-2.05, 1.21)	0.6167

msSBP (key secondary efficacy variable)		
Treatment Group	**N**	**LSM change from baseline (SE)**
Aliskiren/amlodipine 150/5 mg	187	-10.98 (0.88)
Amlodipine 10 mg	177	-9.63 (0.90)
Amlodipine 5 mg	177	-4.96 (0.90)

Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Aliskiren/amlodipine 150/5 mg vs amlodipine 5 mg	-6.02 (1.21)	(-8.40, -3.64)	<0.0001*
Aliskiren/amlodipine 150/5 mg vs amlodipine 10 mg	-1.35 (1.21)	(-3.73, 1.03)	0.2666

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

* Indicates statistical significance at 0.05 level

BP control rate: BP control rates (percentages of patients with BP control, defined as having msSBP <140 mmHg and msDBP <90 mmHg) are summarized below. For the percentage of patients achieving BP control, statistical superiority to component monotherapies was observed in all studied doses of aliskiren/amlodipine combinations, with the exception of aliskiren/amlodipine 150/10 mg vs. amlodipine 10 mg in Study SPA2304, in which aliskiren/amlodipine 150/10 mg showed a numerically greater BP control rate in comparison to amlodipine 10 mg that did not reach statistical significance.

Study SPA2303

Between-treatment comparison for BP control rates at Endpoint in Study SPA2303 (FAS)

Pairwise Comparison			Treatment A	Treatment B	
A	vs.	B	n/N (%)	n/N (%)	p-value
Ali/aml 300/10mg	vs	ali 300 mg	184/281 (65.5)	82/260 (31.5)	<0.0001*
Ali/aml300/ 5mg	vs	ali 300mg	155/274 (56.6)	82/260 (31.5)	<0.0001*

* Indicates statistical significance at 0.05 level.

The percentage of patients with BP control was analyzed using a logistic-regression model with treatment and region as factors and baseline msDBP as a covariate. Baseline was the Day 1 value.

N includes patients who had both baseline and post-baseline measurements. Three patients (1 in aliskiren/amlodipine 300/10 mg group and 2 in aliskiren/amlodipine 300/5 mg group) were excluded from the analysis due to lack of post-baseline assessment.

Study SPA2304

Between-treatment comparison for BP control rates at Endpoint in Study SPA2304 (FAS)

Pairwise Comparison			Treatment A	Treatment B	
A	vs.	B	n/N (%)	n/N (%)	p-value
Ali/aml 300/10 mg	vs.	aml 10 mg	163/277 (58.8)	107/279 (38.4)	<0.0001*
Ali/aml 150/10 mg	vs.	aml 10 mg	117/281 (41.6)	107/279 (38.4)	0.3248

* Indicates statistical significance at 0.05 level

The percentage of patients with BP control was analyzed using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate. Baseline is the Day 1 value.

Study SPP2305

Between-treatment comparison for BP control rates at Endpoint in Study SPP2305 (ITT)

Pairwise Comparison			Treatment A	Treatment B	
A	vs.	B	n/N (%)	n/N (%)	p-value
Ali/aml 150/5 mg	vs.	aml 5 mg	80/187 (42.78)	40/177 (22.60)	<0.0001*
Ali/aml 150/5 mg	vs.	aml 10 mg	80/187 (42.78)	67/177 (37.85)	0.5229

* Indicates statistical significance at 0.05 level

BP response rate: DBP response rates (percentages of patients with msDBP <90 mmHg and/or a ≥10 mmHg reduction from baseline in msDBP) were summarised in the active controlled trials. With the exception of one comparison, statistical superiority in the DBP response rate was observed in all studied doses of aliskiren/amlodipine combinations compared to component monotherapies. The exception was the aliskiren/amlodipine 150/10 mg vs. amlodipine 10 mg comparison in study SPA2304, where the aliskiren/amlodipine 150/10 mg combination showed a numerically greater DBP response rate in comparison to amlodipine 10 mg that did not reach statistical significance. Results for SBP response rates (percentages of patients with msSBP <140 mmHg or a reduction from baseline ≥20 mmHg) showed statistical superiority to component monotherapies in all studied doses of aliskiren/amlodipine combinations in study SPA2303 and study SPA2304. SBP response rate was not performed for study SPP2305.

Ancillary analyses

Overall BP control rate, DBP control rate and SBP control rate: For patients whose BP was uncontrolled (>140/90 mmHg) at baseline, each of the aliskiren/amlodipine combination dose groups had a statistically or at least numerically greater proportion of patients with overall BP control (msSBP/msDBP < 140/90 mmHg) than component monotherapy or placebo groups at Endpoint. The greatest BP control rate was seen with the aliskiren/amlodipine 300/10 mg group (68.1%) and with 10mg amlodipine group it was 50.3%. The DBP control rate (msDBP < 90 mmHg) and SBP control rate (msSBP < 140 mmHg) were similar to the overall BP control rates.

Blood pressure control rate in patients uncontrolled at baseline by renal function and diabetic status: In general, the aliskiren/amlodipine combination therapies resulted in a higher percentage of controlled patients (msSBP/msDBP < 140/90 mmHg) at Endpoint than component monotherapies or placebo regardless of renal impairment or diabetic status, as stated by the applicant. However, patients with 30≤eGFR were excluded from all of the studies and the proportion of patients with moderate renal failure and of patients with diabetes were small and limit the interpretation data.

Time to BP control in patients uncontrolled at baseline: The greater BP control rate and aggressive BP control rates with aliskiren/amlodipine 300/10 mg combination over monotherapies and placebo were seen as early as week 1 and maintained throughout the study, with a similar trend observed for other doses. These results indicate that a greater proportion of patients treated with aliskiren/amlodipine combination will achieve BP control earlier than with either component monotherapy. The detailed statistical analysis broken down to weeks after starting the treatment is not presented.

Stage 2 hypertension: Study SPA2305 included 1074 stage 2 hypertension patients, of which 463 received combination therapy. Patients with stage 2 hypertension treated with aliskiren/amlodipine combination demonstrated clinically meaningful and numerically greater reductions in msDBP and msSBP compared with placebo and the component monotherapies. Although the sample size for the subgroup of stage 2 patients may not have sufficient power to detect treatment differences, the greater reductions in msDBP and msSBP with aliskiren/amlodipine combinations showed statistical superiority in most comparisons, with the exception of comparisons to amlodipine 10 mg for aliskiren/amlodipine 150/10 mg (msDBP and msSBP) and aliskiren/amlodipine 300/10 mg (msSBP). Even in this hypertensive population, over 60% of patients achieved BP control with the high-dose combination (aliskiren/amlodipine 300/10 mg). Stage 2 patients receiving the fixed combination therapies had statistically greater BP control rates than placebo or component monotherapies at Endpoint, with the exception of aliskiren/amlodipine 150/10 mg vs. amlodipine 10 mg which showed a clinical meaningful incremental BP control rate of 13.4%, though the difference did not reach statistical significance. In conclusion, the results of the ancillary analyses gave support for the enhanced antihypertensive effect of the combination of aliskiren/amlodipine over placebo and in the majority of the cases also over the monotherapies.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1.1 Summary of Efficacy for trial SPA100A2303

Title: A randomized, eight-week double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren / amlodipine (300/5 mg and 300/10 mg) in comparison with aliskiren 300 mg in patients with essential hypertension not adequately responsive to aliskiren 300 mg monotherapy.			
Study identifier	SPA2303		
Design	SPA2303 study design consisted of a 7-day washout period, a 4 week single blind run-in treatment period in which patients received aliskiren 300 mg, and an 8 week double-blind study drug treatment period (3 periods). At Visit 4 (Day 1), patients not adequately responsive to aliskiren 300 mg (msDBP ≥90 mmHg and <110 mmHg) were equally randomized to receive 1 of 3 treatments: aliskiren/amlodipine (300/5 mg), aliskiren/amlodipine (300/10 mg), or aliskiren 300 mg for 8 weeks. All patients were asked to return to the study clinic every 2 weeks during single-blind run-in and double-blind period. The study duration for each patient, inclusive of all phases, was approximately 13 weeks.		
	Duration of main phase:		8-weeks
	Duration of Run-in phase:		4-weeks
	Duration of Extension phase:		Not applicable
Hypothesis	Superiority		
Treatments groups	Aliskiren/amlodipine 300/10 mg		aliskiren/amlodipine 300/10 mg, 8 weeks, 283 randomized
	Aliskiren/amlodipine 300/5 mg		aliskiren/amlodipine 300/5 mg, 8 weeks, 277 randomized
	Aliskiren 300 mg		aliskiren 300 mg, 8 weeks, 260 randomized
Endpoints and definitions	Primary endpoint	Change from baseline in msDBP	Demonstrate the efficacy of the combination therapies of aliskiren/amlodipine (300/10 mg and 300/5 mg) in hypertensive patients who did not show sufficient BP response to a 4-week treatment of aliskiren 300 mg by testing the hypothesis of superior reduction in msDBP from baseline to end of study when compared to aliskiren 300 mg.

	Secondary endpoint	Change from baseline in msSBP	Evaluate the efficacy of the combination therapies of aliskiren/amlodipine (300/5 mg and 300/10 mg) in hypertensive patients who did not adequately respond to a 4-week treatment of aliskiren 300 mg by testing the hypothesis of superior reduction in msSBP from baseline to end of study when compared to aliskiren 300 mg
Database lock	19June2009		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat 8-weeks			
Descriptive statistics and estimate variability	Treatment group	Aliskiren/ amlodipine 300/10 mg	Aliskiren / amlodipine 300/5 mg	Aliskiren 300 mg
	Number of subject	281	274	260
	Change in msDBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-13.5	-11.0	-6.3
	Standard Deviation	7.37	7.48	8.53
	Change in msSBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-18.5	-14.3	-6.9
	Standard Deviation	14.01	13.46	14.17

Effect estimate per comparison	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/amlodipine 300/10 mg vs. aliskiren 300 mg
		Least Square Mean Difference	-7.23
		Standard Error	0.638
		P-value	<0.0001
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/ amlodipine 300/5 mg vs. aliskiren 300 mg
		Least Square Mean Difference	-4.71
		Standard Error	0.642
		P-value	<0.0001
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren/ amlodipine 300/10 mg vs. aliskiren 300 mg
		Least Square Mean Difference	-11.62
		Standard Error	1.074
		P-value	<0.0001

	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren/ amlodipine 300/5 mg vs. aliskiren 300 mg
		Least Square Mean Difference	-8.01
		Standard Error	1.082
		P-value	<0.0001
Notes	Not applicable		
Analysis description	**Primary Analysis** The primary endpoint was analyzed using a two-way analysis of covariance model with treatment and region as two factors, and the baseline as a covariate. A hierarchical multiple testing strategy was used for the analyses of primary endpoint, change from baseline in msDBP. First, aliskiren/amlodipine (300/10 mg) was compared to aliskiren 300 mg. If aliskiren/amlodipine (300/10 mg) was statistically superior to aliskiren 300 mg, then further assessment for efficacy of aliskiren/amlodipine (300/5 mg) compared to aliskiren 300 mg was made. No multiple comparison adjustment needed to be made.		

Table 1.2 Summary of Efficacy for trial SPA100A2304

Title: A randomized, eight week double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren / amlodipine (150/10 mg and 300/10 mg) in comparison with amlodipine 10 mg in patients with essential hypertension not adequately responsive to amlodipine 10 mg monotherapy.				
Study identifier	SPA2304			
Design	SPA2304 study design consisted of a 7-day washout period, a 4 week single blind run-in treatment period in which patients received amlodipine 10 mg, and an 8 week double-blind study drug treatment period (3 periods). At Visit 4 (Day 1), patients not adequately responsive to amlodipine 10 mg (msDBP ≥90 mmHg and <110 mmHg) were equally randomized to receive 1 of 3 treatments: aliskiren/amlodipine (300/10 mg), aliskiren/amlodipine (150/10 mg), or amlodipine 10 mg for 8 weeks. All patients were asked to return to the study clinic every 2 weeks during single-blind run-in and double-blind period. The study duration for each patient, inclusive of all phases, was approximately 13 weeks.			
	Duration of main phase:		8-weeks	
	Duration of Run-in phase:		4-weeks	
	Duration of Extension phase:		Not applicable	
Hypothesis	Superiority			
Treatments groups	Aliskiren/amlodipine 300/10 mg		Aliskiren/amlodipine 300/10 mg, 8 weeks, 279 randomized	
	Aliskiren/amlodipine 150/10 mg		Aliskiren/amlodipine 150/10 mg, 8 weeks, 285 randomized	
	Amlodipine 10 mg		Amlodipine 10 mg, 8 weeks, 283 randomized	
Endpoints and definitions	Primary endpoint	Change from baseline in msDBP	Demonstrate the efficacy of the combination therapies of aliskiren/amlodipine (150/10 mg and 300/10 mg), in hypertensive patients who did not adequately respond to a 4-week treatment of amlodipine 10 mg by testing the hypothesis of superior reduction in msDBP from baseline to end of study when compared to amlodipine 10 mg monotherapy.	
	Secondary endpoint	Change from baseline in msSBP	Evaluate the efficacy of the combination therapies of aliskiren/amlodipine (150/10 mg and 300/10 mg) in hypertensive patients who did not adequately respond to a 4-week treatment of amlodipine 10 mg by testing the hypothesis of superior reduction in msSBP from baseline to end of study when compared to amlodipine 10 mg	
Database lock	26June2009			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat 8-weeks			
Descriptive statistics and estimate variability	Treatment group	Aliskiren/ amlodipine 300/10 mg	Aliskiren / amlodipine 150/10 mg	Amlodipine 10 mg
	Number of subject	277	281	279

	Change in msDBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-10.8	-8.9	-7.1
	Standard Deviation	7.73	7.70	8.05
	Change in msSBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-14.1	-11.5	-7.7
	Standard Deviation	12.37	12.46	11.52

Effect estimate per comparison	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/amlodipine 300/10 mg vs. amlodipine 10 mg
		Least Square Mean Difference	-3.76
		Standard Error	0.644
		P-value	<0.0001
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/amlodipine 150/10 mg vs. amlodipine 10 mg
		Least Square Mean Difference	-1.72
		Standard Error	0.642
		P-value	0.0077
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren/amlodipine 300/10 mg vs. amlodipine 10 mg
		Least Square Mean Difference	-6.22
		Standard Error	0.953
		P-value	<0.0001
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren/amlodipine 150/10 mg vs. amlodipine 10 mg
		Least Square Mean Difference	-2.81
		Standard Error	0.953
		P-value	0.0033
Notes	Not applicable		
Analysis description	**Primary Analysis** The primary endpoint was analyzed using a two-way analysis of covariance model with treatment and region as two factors, and the baseline as a covariate. A hierarchical multiple testing strategy was used for the analyses of primary endpoint, change from baseline in msDBP. First, aliskiren/amlodipine (300/10 mg) was compared to amlodipine 10 mg. If aliskiren/amlodipine (300/10 mg) was statistically superior to amlodipine 10 mg, then further assessment for efficacy of aliskiren/amlodipine (150/10 mg) compared to amlodipine 10 mg was made. No multiple comparison adjustment needed to be made.		

Table 1.3 Summary of Efficacy for trial SPA100A2305

Title: 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 amlodipine in patients with essential hypertension.			
Study identifier	SPA2305		
Design	SPA2305 study design consisted of a washout period, a 2 to 4 week single blind placebo run-in period, and an 8 week double-blind study drug treatment period (3 periods). All patients were to have a msDBP of ≥ 90 mmHg and < 110 mmHg at the visit prior to randomization, and a msDBP ≥ 95 mmHg at the randomization visit, in order to enter period 3 of the study. At Visit 3 (Day 1), patients who fulfilled the inclusion/exclusion criteria were randomized in a double-blind fashion to one of the nine treatment groups: aliskiren 150 mg, aliskiren 300 mg, amlodipine 5 mg, amlodipine 10 mg, the combination of aliskiren/amlodipine 150/5 mg, 150/10 mg, 300/5 mg, 300/10 mg or placebo. Patients who were randomized to amlodipine 10 mg and aliskiren/amlodipine 150/10 mg or 300/10 mg started their initial treatment with amlodipine 5 mg, aliskiren/amlodipine 150/5 mg, 300/5 mg respectively, and were force titrated to their randomization dose after one week. The study duration for each patient, inclusive of all phases, was approximately 13 weeks.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8-weeks 4-weeks Not applicable
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo, 8 weeks, 198 randomized
	Aliskiren 150 mg		Aliskiren 150 mg, 8 weeks, 195 randomized
	Aliskiren 300 mg		Aliskiren 300 mg, 8 weeks, 203 randomized
	Amlodipine 5 mg		Amlodipine 5 mg, 8 weeks, 185 randomized
	Amlodipine 10 mg**		Amlodipine 10 mg, 8 weeks, 181 randomized
	Aliskiren/amlodipine 150/5 mg		Aliskiren/amlodipine 150/5 mg, 8 weeks, 181 randomized
	Aliskiren/amlodipine 150/10 mg**		Aliskiren/amlodipine 150/10 mg, 8 weeks, 183 randomized
	Aliskiren/amlodipine 300/5 mg		Aliskiren/amlodipine 300/5 mg, 8 weeks, 178 randomized
	Aliskiren/amlodipine 300/10 mg**		Aliskiren/amlodipine 300/10 mg, 8 weeks, 184 randomized
	**		Patients who were randomized to amlodipine 10 mg, aliskiren/amlodipine 150/10 mg or 300/10 mg started their initial treatment with amlodipine 5 mg, aliskiren/amlodipine 150/5 mg, 300/5 mg respectively, and were force titrated to their randomization dose after one week.
Endpoints and definitions	Primary endpoint	Change from baseline in msDBP	Demonstrate the efficacy of the combination of aliskiren/amlodipine is superior to both monotherapies in patients with essential hypertension by testing the hypothesis of superior reduction in msDBP from baseline to end of study when compared with monotherapy across the doses in the study.

	Secondary endpoint	Change from baseline in msSBP	Demonstrate that the efficacy of the combination of aliskiren/amlodipine is superior to both monotherapies in patients with essential hypertension by testing the hypothesis of superior reduction in msSBP from baseline to end of study when compared with monotherapies across the doses in the study.
Database lock	26June2009		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat 8-weeks			
Descriptive statistics and estimate variability	*Treatment group*	*Placebo*	*Aliskiren 150 mg*	*Aliskiren 300 mg*
	Number of subject	198	193	201
	Change in msDBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-5.1	-7.8	-10.1
	Standard Deviation	9.25	8.99	9.70
	Treatment group	*Amlodipine 5 mg*	*Amlodipine 10 mg*	*Aliskiren / amlodipine 150/5 mg*
	Number of subject	184	179	179
	Change in msDBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-10.8	-13.8	-13.8.
	Standard Deviation	8.77	8.32	9.11
	Treatment group	*Aliskiren / amlodipine 150/10 mg*	*Aliskiren / amlodipine 300/5 mg*	*Aliskiren/ amlodipine 300/10 mg*
	Number of subject	179	175	183
	Change in msDBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-16.0	-14.7	-16.1
	Standard Deviation	7.58	9.89	8.20
	Treatment group	*Placebo*	*Aliskiren 150 mg*	*Aliskiren 300 mg*

	Number of subject	198	193	201
	Change in msSBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-6.3	-10.0	-15.8
	Standard Deviation	15.45	15.33	15.64
	Treatment group	*Amlodipine* *5 mg*	*Amlodipine* *10 mg*	*Aliskiren / amlodipine 150/5 mg*
	Number of subject	184	179	179
	Change in msSBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-15.4	-20.9	-20.6.
	Standard Deviation	14.46	13.70	16.22
	Treatment group	*Aliskiren / amlodipine 150/10 mg*	*Aliskiren / amlodipine 300/5 mg*	*Aliskiren/ amlodipine 300/10 mg*
	Number of subject	179	175	183
	Change in msSBP (mmHg) from baseline at Wk 8 (LOCF) Mean	-23.1	-21.1	-22.5
	Standard Deviation	14.72	15.73	16.41

Effect estimate per comparison	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren 150 mg vs. Placebo
		Least Square Mean Difference	-2.64
		Standard Error	0.88
		P-value	0.003
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren 300 mg vs. Placebo
		Least Square Mean Difference	-4.85
		Standard Error	0.87
		P-value	<0.001
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Amlodipine 5 mg vs. Placebo
		Least Square Mean Difference	-5.66
		Standard Error	0.89
		P-value	<0.001
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Amlodipine 10 mg vs. Placebo
		Least Square Mean Difference	-8.47

		Standard Error	0.90
		P-value	<0.001
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/amlodipine 150/5 mg vs. aliskiren 150 mg
		Least Square Mean Difference	-6.00
		Standard Error	0.90
		P-value	<0.001
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/amlodipine 150/5 mg vs. amlodipine 5 mg
		Least Square Mean Difference	-2.98
		Standard Error	0.91
		P-value	0.001
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/amlodipine 150/10 mg vs. aliskiren 150 mg
		Least Square Mean Difference	-8.17
		Standard Error	0.90
		P-value	<0.001
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/amlodipine 150/10 mg vs. amlodipine 10 mg
		Least Square Mean Difference	-2.33
		Standard Error	0.92
		P-value	<0.011
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/amlodipine 300/5 mg vs. aliskiren 300 mg
		Least Square Mean Difference	-4.79
		Standard Error	0.90
		P-value	<0.001
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/amlodipine 300/5 mg vs. amlodipine 5 mg
		Least Square Mean Difference	-3.98
		Standard Error	0.92
		P-value	<0.001
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/amlodipine 300/10 mg vs. aliskiren 300 mg
		Least Square Mean Difference	-6.26
		Standard Error	0.89
		P-value	<0.001
	Primary endpoint (Change from baseline in msDBP)	Comparison groups	Aliskiren/amlodipine 300/10 mg vs. amlodipine 10 mg
		Least Square Mean Difference	-2.63
		Standard Error	0.92
		P-value	0.004

	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren 150 mg vs. Placebo
		Least Square Mean Difference	-3.88
		Standard Error	1.41
		P-value	0.006
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren 300 mg vs. Placebo
		Least Square Mean Difference	-8.58
		Standard Error	1.40
		P-value	<0.001
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Amlodipine 5 mg vs. Placebo
		Least Square Mean Difference	-9.03
		Standard Error	1.43
		P-value	<0.001
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Amlodipine 10 mg vs. Placebo
		Least Square Mean Difference	-14.25
		Standard Error	1.44
		P-value	<0.001
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren/amlodipine 150/5 mg vs. aliskiren 150 mg
		Least Square Mean Difference	-9.97
		Standard Error	1.45
		P-value	<0.001
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren/amlodipine 150/5 mg vs. amlodipine 5 mg
		Least Square Mean Difference	-4.82
		Standard Error	1.47
		P-value	0.001
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren/amlodipine 150/10 mg vs. aliskiren 150 mg
		Least Square Mean Difference	-13.20
		Standard Error	1.45
		P-value	<0.001
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren/amlodipine 150/10 mg vs. amlodipine 10 mg
		Least Square Mean Difference	-2.83
		Standard Error	1.48
		P-value	0.056
	Secondary endpoint	Comparison groups	Aliskiren/amlodipine 300/5 mg vs. aliskiren 300 mg

	(Change from baseline in msSBP)	Least Square Mean Difference	-6.45
		Standard Error	1.45
		P-value	<0.001
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren/amlodipine 300/5 mg vs. amlodipine 5 mg
		Least Square Mean Difference	-6.00
		Standard Error	1.48
		P-value	<0.001
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren/amlodipine 300/10 mg vs. aliskiren 300 mg
		Least Square Mean Difference	-7.82
		Standard Error	1.43
		P-value	<0.001
	Secondary endpoint (Change from baseline in msSBP)	Comparison groups	Aliskiren/amlodipine 300/10 mg vs. amlodipine 10 mg
		Least Square Mean Difference	-2.16
		Standard Error	1.47
		P-value	0.143
Notes	Not applicable		
Analysis description	**Primary Analysis** To assess whether both monotherapy treatments (aliskiren and amlodipine) contribute to the overall effect in blood pressure reduction of the combination treatment, the primary endpoint was analyzed by Hung's AVE test (Hung 2000). If the AVE test was statistically significant (in favor of the combination treatment), it would be concluded that the aliskiren/amlodipine combination treatment is superior in reducing the msDBP from baseline to the end of study compared to aliskiren and amlodipine monotherapies. Furthermore, if the AVE test is positive, the following additional analysis will be further performed to quantify the add-on effects for a given aliskiren/amlodipine combination dose due to the respective monotherapy doses by performing a two-way analysis of covariance model with treatment and region as two factors, and the baseline as a covariate.		

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

Additional analysis of the efficacy of the fixed dose combination were performed in patients with stage 2 hypertension combining data from different studies (SPA2305, SPA2306, SPAUS01 and SPA2307) Specifically, the BP lowering effect of the high dose combination *versus* monotherapy was investigated. The analysis across the above mentioned studies confirmed the efficacy of the high dose combination in patients with stage 2 hypertension.

2.4.8.2. ***Clinical studies in special populations***

Very limited efficacy data for the fixed dose combination in patients with stage I hypertension with additional cardiovascular risk have been submitted. At present, a sound conclusion on the efficacy of

the FDC in patients with stage I hypertension with additional cardiovascular risk is therefore not possible.

2.4.8.3. ***Supportive study(ies)***

Short-term studies

Supportive study SPP2305

This is a 6-week double-blind multicenter, randomised parallel-group study for comparison of FDC (aliskire/amlodipine (Ali/Aml) 150/5 mg) to amlodipine alone (5 and 10 mg) in patients with untreated essential hypertension stage 1-2 (msDBP ≥95 mm Hg and <110 mm Hg) not controlled by 5 mg Aml alone. The effects of the combination aliskiren 150 + amlodipine 5 mg were compared to data of Placebo + Aml 5 mg in patients with hypertension stage 1-2 not controlled after 4-week treatment with Aml alone 5 mg. Thus, this study integrates the main information of the preceding study (main study SPA2304) which investigated only the comparison between aliskiren/amlodipine 150 mg/10 mg and Aml 10 mg alone. The design of the study included a 2-4 weeks washout period, a 4-week single-blind run in period in which patients received Aml 5 mg monotherapy, and a 6-week double-blind treatment period (3 periods and 7 visits). The study, inclusive of all phases lasted 12-14 wk/patient.

Effects on blood pressure: Treatment with the combination at the Ali/Aml 150/5 mg dosage induced a blood pressure reduction greater than Aml 5 mg alone. In the comparison of Ali150/Aml5 mg *vs* Aml 5 mg, the LSM difference in change from baseline to study end was -5.9 mm Hg for average msSBP, and – 3.5 mm Hg for average msDBP. These differences were statistically significant (P<0.001). The percentage of patients with controlled hypertension at the end of the study was approximately 1.9-time higher using the combination, than Aml alone (43% vs 23%, P<0.001)). Findings tend to be consistent in subgroup analyses but there were a low number of patients in some subgroups. The treatment with 5 mg Aml alone was associated with higher incidence of drug-related AEs than Ali150 mg + Aml5 mg but the incidence of serious AEs was higher during the treatment with combination. It is impossible to assess the confounding on these data due to the fact that aliskiren administration was not standardized with a light meal as per CHMP recommendations.

Long-term studies

Summary of trials providing long-term data

Study No.	Study objective, population	Patients random. / treated	Treatment duration	Dosage	Key efficacy endpoints
Uncontrolled, long-term trial					
SPA2301	Long-term open-label safety/efficacy in target population	556*	54 weeks	aliskiren/amlodipine 150/5 mg for 2 weeks, then aliskiren/amlodipine 300/10 mg for 52 weeks (optional add-on of HCTZ 12.5 mg/25 mg)	Change in msDBP, msSBP
Active-controlled long-term trials					
SPP2323	Long-term double-blind efficacy/safety in target population	1124 / 1124**	26 weeks	First 6 weeks: aliskiren 150 mg, HCTZ 12.5 mg, or placebo; Last 20 weeks: aliskiren 300 mg, or HCTZ 25 mg, (optional add-on of amlodipine 5 mg/10 mg at pre-specified visits)	Change in msDBP, msSBP
SPP2323E1	Long-term double-blind efficacy/safety in target population	965*	26 weeks	aliskiren 300 mg, or HCTZ 25 mg, (optional add-on of amlodipine 5 mg/10 mg at pre-specified visits)	Change in msDBP, msSBP

*Treated patients only.

**Among 1124 patients, 21 were treated only with placebo and did not receive aliskiren or HCTZ treatment and were not included in the SCS analysis.

Study **SPA2301** and Study **SPP2323** with its extension **Study SPP2323E1** provide supportive evidence of efficacy.

Study SPA2301

Study SPA2301 was performed to assess long-term (1 year) safety (primary endpoint) and efficacy (secondary endpoint) of the maximum dose of Ali/Aml (300/10 mg) combination. This study included 556 patients, of which 470 were treated with Ali/Aml without requiring the addition of hydrochlorothiazide (HCT). Patients who received the optional HCTZ add-on treatment were considered more resistant to therapy and more difficult to treat. The mean duration of treatment with Ali/Aml 300/10 mg (without HCT) for the 546 pooled patients who continued into the 52-week high-dose treatment period was 282.5 days, indicating an adequate exposure to study medication. In the group of patients treated with the FDC alone, number of patients was 101 for age group ≥65 years and 24 for age group ≥75 years.

Effects on blood pressure: Clinically meaningful mean reductions from baseline in msDBP and msSBP were seen as early as Week 2, and this effect was maintained over the entire 54 weeks of the study. Approximately 16% of the study population required the addition of HCT to the Ali/Aml regimen.

Change from baseline in msDBP and msSBP (mmHg) by time on treatment in Study SPA2301 (Treated population)

	Ali/aml [a]			Ali/aml/HCTZ [b]			Total		
	mean change			mean change			mean change		
Week	n [c]	msDBP	msSBP	n [c]	msDBP	msSBP	n [c]	msDBP	msSBP
Week 2	467	-8.7	-14.1	86	-5.9[d]	-10.6[d]	553	-8.3	-13.5
Week 4	459	-14.0	-21.2	85	-11.9[d]	-17.4[d]	544	-13.7	-20.6
Week 6	453	-15.7	-22.9	86	-11.5[d]	-17.9[d]	539	-15.1	-22.1
Week 10	440	-16.3	-25.0	86	-9.3[d]	-16.0[d]	526	-15.1	-23.5
Week 14	429	-17.1	-25.6	85	-13.1	-21.8	514	-16.4	-25.0
Week 28	416	-16.7	-26.4	81	-14.7	-23.8	497	-16.4	-25.9
Week 41	396	-17.0	-25.7	75	-15.4	-24.8	471	-16.8	-25.6
Week 54	383	-16.3	-25.0	74	-15.3	-25.4	457	-16.1	-25.0
Endpoint [e]	467	-15.7	-24.2	86	-14.2	-23.7	553	-15.5	-24.2

[a] 'Aliskiren /amlodipine' is the group of patients who took only aliskiren/amlodipine (without HCTZ) throughout the study.
[b] 'Aliskiren/amlodipine/HCTZ' is the group of patients who took HCTZ at some time during the study (HCTZ was only added to eligible patients after Week 10).
[c] N is the total number of patients with msDBP and msSBP observations at both baseline and post-baseline visits.
[d] Use of HCTZ was not permitted until after Week 10.
[e] Endpoint is the value at Week 54 or last observation carried forward (LOCF) based on the availability of measurements.

Blood pressure control rate and BP response rate: The BP control rate (msSBP <140 mmHg and msDBP <90 mmHg) was 31.1% after 2 weeks and increased to 74.3% at the endpoint. A large majority of patients (89.7%) achieved a DBP response (percentages of patients with msDBP <90 mmHg and/or a ≥ 10 mmHg reduction from baseline in msDBP) at Endpoint. Consistent with the results observed for BP reductions, a higher percentage of patients treated with Ali/Aml/HCT achieved BP control and DBP response after Week 10 following the addition of HCT. Data on efficacy are of limited relevance because this is an open-label uncontrolled study. These uncontrolled long-term data on efficacy substantially confirm the observations of 8-week, double-blind, controlled studies.

Studies SPP2323 + SPP2323E1

Study SPP2323 and its extension SPP2323E1 provide supportive data for long-term efficacy of the Ali/Aml combination. Although primarily designed to evaluate Ali and HCT, the optional addition of Aml provides some relevant long-term experience with the combination of Ali and Aml when used with another antihypertensive agent. Based on the design of this study, a patient whose BP was not controlled with aliskiren 300 mg or HCTZ 25 mg had optional add-on of amlodipine. The first timepoint with optional amlodipine 5 mg add-on was Week 12 and the first time point with optional Aml 10 mg add-on was Week 18. The demographic distribution of patients was similar to that seen in the short-term, controlled studies. The study was adequately carried out and completed by 978 (87%) of the 1124 randomised patients. Overall, the number of patients with age ≥65 years was 256 (≤129 per arm). Overall number of patients with age ≥75 years was 38 (19 per arm). Prevalence of diabetes was around 11% in both arms. The mean duration of exposure to double-blind study medication (329.8 days for aliskiren and 311.9 days for HCT) was similar for the 2 regimens. A slightly greater proportion of patients in the HCT-based regimen received Aml when compared to the Ali-based regimen.

Blood pressure reduction: The Ali-based regimen was statistically superior to the HCT-based regimen in reduction of msDBP and msSBP at the Week 26 endpoint and for msDBP at the Week 52 endpoint. For msSBP at Week 52, the Ali-based regimen was non-inferior to the HCT regimen and was numerically, but not statistically superior to the HCT-based regimen. A further reduction in msDBP and msSBP, and an increased percentage of patients achieving BP control, was observed after Week 12 following the addition of Aml to the Ali-based or the HCT-based treatment group. A specific analysis carried out in patients treated with the combination Ali/Aml, showed a clinically meaningful reduction from baseline in both msSBP and msDBP, indicating that in patients whose BP was not controlled with Ali monotherapy, adding Aml provides additional BP lowering effect.

During the procedure, additional data were submitted from supportive studies SPA2306, SPAUS01 and SAH2302 conducted specifically in patients with stage 2 hypertension and examining the BP lowering

effect of the high dose combination versus monotherapy. Overall, data from these studies confirmed the efficacy of the high dose combination in patients with stage 2 hypertension. Limited efficacy data for the FDC in patients with stage 1 hypertension with additional cardiovascular (CV) risk have also been submitted. A sound conclusion on the efficacy of the FDC in patients with Stage 1 hypertension with additional cardiovascular (CV) risk is thus impossible at present.

2.4.9. Discussion on clinical efficacy

The CHMP considered that the clinical data submitted in support of the first line indication are not sufficient. In fact, several issues prevent granting of the first line indication:
i) Currently, the clinical experience with aliskiren is considered limited. In the absence of data supporting the existence of a wide therapeutic experience, the benefit-risk of the combination in the first-line indication needs to be explored further with special attention paid to the doses, as used in the fixed combination tablet. An in depth evaluation of the benefit of the FDC in the indication first line therapy has not been performed at present. In addition, the long term safety profile (> 1 year) of aliskiren has not been adequately characterized.

ii) In the clinical study SPA2307, approximately 1/3 of patients with stage 2 hypertension were adequately controlled after 16-week treatment with a mono-regimen (27.3% with aliskiren and 33.8% with amlodipine, respectively). A sizeable percentage of patients would therefore be unnecessarily exposed to two pharmacological agents and to an increased risk of adverse events. Approximately 58% of patients were controlled with the combination therapy at the Week 16 time point, i.e, 30% more patients with the combination than with the respective monotherapies. Data about benefits of early blood pressure control in patients with uncomplicated hypertension were not provided, not quoted nor reported by the clinical development program. In addition, some data show that incidence of AEs was higher while on treatment with the FDC (Study SPA2303). Although results from Study SPA 2307 do not seem to suggest the possibility of an increased risk of adverse effect with the combination therapy compared to monotherapy, Study SPA2307 was designed to show efficacy as primary objective, therefore no conclusive evaluation of the risk profile for the combination versus the individual monotherapy regimes is possible.

iii) Study SPA2305, the pivotal study submitted in support the first-line indication, failed to show superiority in BP control of the intermediate dose combination Ali/Aml 150/10 mg compared to 10 mg amlodipine monotherapy; in addition, no difference in BP lowering effect was observed between Ali/Aml 150/10 mg and 300/10 mg FDCs.

Following the CHMP's recommendation for not granting the authorisation for the use of Rasilamlo in the first line indication, the claim for this indication was withdrawn by the applicant.

Overall, data support the use of the FDC as a second line treatment, although the additional benefit of the FDC with 150 mg aliskiren versus monotherapy with 10 mg amlodipine seems to be limited. The efficacy of 150 mg aliskiren in the presence of food has been demonstrated in the elderly population (Study SPP2405). A significant BP lowering effect is achieved with the 75 mg dose, and a plateau in the BP lowering effect of aliskiren is apparent at 150 mg dose, with no difference between 150 mg and 300 mg. This does not occur in the adult population where a dose-effect curve is evident in the dose range 75-300 mg, and the 75 mg dose is largely ineffective. Food intake in the adult population may thus decrease the absorption of 150 mg aliskiren and potentially reduce the BP lowering effect of aliskiren.

In addition, study SPP100A2110 supports the relevance of meal-induced reduction in plasma AUC of aliskiren at steady state. For example, this study shows that aliskiren-induced increase in plasma renin concentration was approximately 2-fold higher when the drug was given in fasting state compared to the fed state.

Geometric mean ratio (Fed/Fasted) and 90% confidence intervals for the change from baseline in trough PRA, PRC and Ang II on Day 28 (Primary PD analysis data set)

	Treatment	N	Geometric mean		Baseline-adjusted* geometric mean of Day 28 to baseline ratio	Geometric mean ratio of Fed/Fasted	
			Baseline	Day 28		Estimate	90% CI
Trough PRA (ng/mL/h)	Fed	39	0.30	0.12	0.38	1.04	0.88, 1.23
	Fasted	38	0.35	0.12	0.36		
Trough PRC (ng/L)	Fed	38	2.99	20.19	6.38	0.62	0.42, 0.91
	Fasted	38	3.67	41.62	11.16		
Trough Ang II (pmol/L)	Fed	40	4.82	4.36	0.90	1.06	0.91, 1.25
	Fasted	41	4.91	4.16	0.85		

N values vary due to missing values.

*Analysis was of change from baseline with baseline as covariate

Study SPP100ADE03 was submitted during the evaluation of the application. It does not directly solve the specific issue of the superiority of the FDC (in particular the combination with 150 mg aliskiren) versus the respective monotherapies because it does not contain a direct comparison of the combination versus the monotherapies. On the other hand, results of this study are reassuring about the extent of BP lowering effect of 150 mg aliskiren when taken after a light meal.

It is to be noted that the originally requested third line (substitution) indication was not approvable and was withdrawn during the procedure. The CHMP identified two main issues preventing the approval of the substitution therapy for Rasilamo: a/ the demonstration of a wide therapeutic experience and b/ the demonstration of the bioequivalence between the monocomponents of the FDC and the FDC under fed conditions (light meal). A wide therapeutic experience for aliskiren/amlodipine combination is at present not available. In addition, overall pharmacokinetic data show not only that food induces a large decrease in aliskiren absorption, but also that the effect of food may be dependent on formulation. In the absence of both, the proof of a wide therapeutic experience and results from a bioequivalence study under fed conditions, the indication substitution therapy cannot be granted at present.

GCP inspection-related issues

In the context of the assessment of a related application for the triple fixed dose combination Rasilamlo HCT, the CHMP requested a GCP inspection of the clinical study SAH100A2302 (pivotal efficacy study submitted within the application for the triple combination Rasilamlo HCT). As this study is also part of the application for Rasilamlo double combination, the outcome of this inspection and the responses to its findings were required to be submitted as part of the responses to the outstanding issues identified by the CHMP for the Rasilamlo application. The conclusion of the GCP Inspectors was that the data from study SAH100A2302 raised questions regarding GCP compliance at a global level and similar non-compliance issues could be found at other study sites. A major objection concerning the potential impact of the inspections findings on the Rasilamlo dossier was raised by the CHMP, and this issue was requested to be addressed in an oral explanation. The oral explanation focused on two points:

i. The protocols and conduct of the studies supporting the Rasilamlo application, in relation to the critical issues raised for study SAH2302 with an adequate description of the procedures put in place for the control of the quality and validity of Rasilamlo efficacy data, and providing evidence supporting the adequacy of the Sponsor's Monitoring Plan

ii. Impact of the exclusion of the minority of cases with aberrant BP readings on the overall results of the SPA programme.

In response, the following was claimed:

i. It was stated that the prevalence of aberrant BP readings in studies of the SPA programme, pivotal for the Rasilamlo application,was substantially lower than in studies of the SAH programme.

ii. It was stated that overall results from the studies of the SPA programme did not change after the exclusion of the minority of patients with aberrant BP readings.

Following the oral explanation, the CHMP concluded that the presentation did not lift the doubts on the quality of efficacy data control and successful training of the investigators in the clinical studies of the SPA programme. This could represent a concern in view of the observation that the analysis of the pivotal add-on trials of the SPA program, studies 2303 and 2304, after removal of aberrant readings, showed a minimal, although significant blood pressure lowering effect of Rasilamlo in patients not responding to amlodipine 5 and 10 mg. As stated in the CHMP guidelines for the assessment of clinical trials, it is important to critically assess, apart from statistical significance, the clinical relevance of the observed changes. Given the limited additional efficacy of Rasilamlo in patients not responding to amlodipine and the significant number of aberrant readings admitted by the applicant, it was the CHMP's opinion that the impact of variability in BP pressure readings on the clinical significance of the efficacy data should have been further investigated. The CHMP considered that a new GCP inspection was not needed, but nevertheless, the lack of: i. information on baseline characteristics (pre-treatment) of patients without aberrant BP measurements, and ii. detailed statistics and efficacy and safety data for patients without aberrant readings precluded an adequate evaluation of the efficacy data.. Therefore, a new set of additional information was requested. The CHMP requested to submit, for the three Rasilamlo pivotal studies SPA2302, SPA2304, and SPA2305 data on:

a) Prevalence of aberrant readings (BP measurements differing by 10 or more mm Hg) at visit 2 (initiation of 4-week run-in period and treatment with monocomponent), at visit 4 (end of monotherapy) and at study end.

b) Detailed descriptive statistics and efficacy and safety data (the latter limited to hypotension-related adverse events) for patients without aberrant readings.

The additional set of results provided in response showed that, across each one of the three studies, the baseline characteristics of the different arms did not substantially differ and, therefore, were unlikely to have biased the main results. The aliskiren/amlodipine combination was superior to the respective monotherapies in reducing BP in patients without aberrant readings, and the statistical significance was preserved for both add-on studies. However, the continuous increase in the percentage of patients with aberrant BP readings in the course of the assessment is considered a matter of concern. Not a single case of aberrant BP was disclosed at the time of the original application although this data were readily available in the final data file used for analysis, as confirmed during the oral explanation. After the inspection on studies of the SAH program, the presence of cases with aberrant BP readings was estimated to be 30% and this was also reported in the Oral Explanation. This percentage rose up to above 40% in the very last analysis submitted in response to the CHMP list of outstanding issues. In response to the issue raised by the CHMP concerning the overall reliability of BP data on the basis of the evidence that the percentage of patients with aberrant BP readings seems to increase constantly through the whole assessment procedure, the following clarification was provided:

i. In the assessment report, the derived value for the total percentage of patients in the per protocol set of less than 60% is based on exclusion of all patients with aberrant BP readings at visit 2 (pre-randomisation), baseline or endpoint. If the aberrant data from the pre-randomisation visit are excluded, the total percentage of patients with aberrant readings is 28.6% for study SPA2303 and 34.9% for study SPA2304.

ii. Occurrence of an aberrant BP reading per se was not a protocol deviation according to the study protocols. Aberrant BP measurements could have qualified as protocol deviations only when a second set of BP measurements was not performed. This occurred in 11.6% of patients (at baseline or endpoint) in study SPA2303 and 16.3% of patients in study SPA2304. When considering the other protocol deviations leading to exclusion from the PPS, which were unrelated to aberrant BP, a total of 4.5% of major protocol deviations (PDs) were reported for study SPA2303 and 7.7% for study SPA2304 (as presented in the study reports and in the response to the list of outstanding issues). Therefore, even when applying the most conservative calculation by adding the aberrant BP PDs to major PDs and not adjusting for double-counting, the maximum total of protocol deviations that could have occurred is 16.1% for study SPA2303 and 24.0% for study SPA2304. Therefore, based upon this definition, the PPS constitutes at worst >80% for study SPA2303 and > 76% for study SPA2304.

Summary of aberrant BP data in studies SPA2303, SPA2304 and SPA2305

	SPA2303	SPA2304	SPA2305
Total number of patients in Full Analysis Set (FAS) †	**818**	**843**	**1685**
No. (%) of patients without aberrant BP ≥ 10 mm Hg (as defined in study protocols)			
At visit 2 (pre-randomisation), baseline or endpoint*	479 (58.6%)	454 (53.9%)	N/A
At baseline or endpoint**	584 (71.4%)	549 (65.1%)	1069 (63.4%)
No. (%) of patients in analysis set excluding patients with aberrant BP ≥ 10 mmHg which were not repeated (i.e. protocol deviations)			
At baseline or endpoint**	723 (88.4%)	706 (83.7%)	1384 (82.1%)
No. (%) of patients without aberrant BP ≥ 20 mmHg (per CHMP guideline)			
At baseline or endpoint**	778 (95.1%)	798 (94.7%)	1555 (92.3%)

* Included in response to 3rd LOI (seq. 0005)
** Included in response to the 2nd List of outstanding issues (dated 10th January 2011; seq. 0004)

† FAS includes all randomized patients excluding mis-randomized patients. Mis-randomized patients are patients who discontinued the study permanently prior to the randomization visit, but were allocated a randomization number by error. There are total of 2, 4 and 3 randomized patients respectively in study SPA2303, SPA2304 and SPA2305 that were randomized in error and excluded from FAS and did not receive double-blind study medication

The CHMP came to the conclusion that overall data, after the exclusion of patients with aberrant BP readings, consistently show an additional benefit of the FDC over monotherapy with the components of the FDC. This is considered sufficiently reassuring on the reliability of the results.

The additional analyses performed by the Applicant have confirmed that limited information is available in patients with age ≥65 years, in particular limited efficacy data for the add-on indication and no information in patients aged 75 years and older. The limited efficacy data in patients aged 65 years and older is reflected in the Rasilamlo SmPC.

2.4.10. Conclusions on the clinical efficacy

It is concluded that overall data do not support the use of Rasilamlo as first line therapy because the clinical experience is considered limited and a non-negligible percent of patients do not need the FDC to achieve blood pressure control, even in the presence of stage 2 hypertension. The Applicant has withdrawn the first-line indication.
With regard to the second-line indication, overall add-on studies show a greater BP reduction effect of the FDC in comparison with therapy in patients not controlled with monotherapy, all studies were conducted regardless of food intake. Data from the newly submitted observational Study SPP100ADE03 indirectly reassure on the efficacy in the adult population of both 150 mg and 300 mg aliskiren when taken after a light meal. Overall the issues raised by the GCP inspections are considered sufficiently addressed and clarified in the oral explanation and in written response to the list of outstanding issues.
The lack of the demonstration of bioequivalence between the FDC and the free combination after a light meal prevents the approval of the substitution indication. The Applicant has withdrawn the substitution indication.

The indication applied for:

> *Treatment of essential hypertension in adults.*
>
> *Rasilamlo is indicated for the initial treatment of stage 2 hypertensive patients (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) who are likely to need multiple medicinal products to achieve blood pressure control.*
>
> *Rasilamlo is indicated in patients whose blood pressure is not adequately controlled with aliskiren or amlodipine (or another dihydropyridine calcium channel blocker) used alone.*
>
> *Rasilamlo is indicated as substitution therapy in patients adequately controlled with aliskiren and amlodipine, given concurrently, at the same dose level as in the combination.*

Indication granted by the CHMP:

> *Rasilamlo is indicated for the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled with aliskiren or amlodipine used alone.*

2.5. Clinical safety

Patient exposure

Overall, 5549 patients were included in the safety analysis of aliskiren/amlodipine clinical development programme as submitted for initial evaluation. This included studies SPA2305, SPA2303, SPA2304, SPP2305, SPA2301, SPP2323, and SPP2323E1. In total, 2835 patients were exposed to aliskiren/amlodipine combination. The total number of patients exposed to aliskiren/amlodipine in long-term 6-month and 1-year studies was 612 and 372, respectively. During the evaluation, additional safety data from new studies SPA2307, SPA2306, SPAUS01, and SAH2302 were submitted.

Pooled analysis from Studies SPA2306, SPAUS01 and SAH2302 included 2115 patients with stage 2 hypertension, with 750 exposed to aliskiren/amlodipine combination. Data is provided for the monotherapy amlodipine and combination of aliskiren/amlodipine. The overall extent of drug exposure is shown in the below table.

Duration of exposure to study drug after randomization (safety set, pooled data from Studies SPA2306, SPAUS01 and SAH2302)

Duration of Exposure (days)	Mono Aml N=464 n (%)	Ali/Aml N=750 n (%)	Total* N=2115 n (%)
≥ 1	464 (100.0)	750 (100.0)	2115 (100.0)
≥ 14	450 (97.0)	729 (97.2)	2062 (97.5)
≥ 28	435 (93.8)	720 (96.0)	2020 (95.5)
≥ 42	422 (90.9)	705 (94.0)	1983 (93.8)
≥ 56	335 (72.2)	567 (75.6)	1569 (74.2)
Statistics			
n	464	750	2115
Mean (SD)	53.6 (11.81)	54.9 (10.51)	54.9 (10.59)
Median	56.0	56.0	56.0
Range	1 - 73	1 – 83	1 - 84

* including other treatment groups not presented in the table

Adverse events

In short-term and long-term studies, the two main non-serious adverse events observed with the use of the fixed dose combination of Ali/Aml were: peripheral oedema and diarrhoea. The table below summarises data about completion, discontinuation of treatment, serious AEs, and deaths during the

short-term studies (8-week treatment, study SPA2305, study SPA2304, and study SPA2303). There was no death. Incidence of serious AEs was 0.4% lower during active treatment in comparison with placebo. Discontinuation of treatment due to side effects was 0.7% more frequent during active treatment in comparison with placebo.

Summary of safety data of aliskiren/amlodipine for the 8-week treatment in clinical studies SPA2305, SPA2304, and SPA2303

	Active treatment (Ali and/or Aml)	Placebo
N patients randomized	3157	198
% completed	92.8%	84.8%
% discontinued	7.1%	15.2%
% discontinued because of AEs	2.2%	1.5%
% discontinued because of lab disorders	0.1%	0.0%
% with serious AEs	0.6%	1.0%
Deaths	0	0

The incidence of most common AEs in the same clinical studies (study SPA2305, study SPA2304, and study SPA2303) is given below. Peripheral oedema was the most common AE. It was a frequent cause of treatment discontinuation and was much more common during treatment with amlodipine than during the treatment with aliskiren. The possible protective effect of aliskiren against this side effect was one of the secondary objectives of the clinical programme. However, on the basis of safety data accumulated for all aliskiren-containing products, including those that were authorised earlier, peripheral oedema was identified as one of the AEs related to aliskiren treatment and thus, adequate information has been reflected in the SmPC.

Summary of Adverse Events observed with aliskiren/amlodipine for the 8-week treatment in clinical studies SPA2305, SPA2304, and SPA2303

Common AEs	% incidence during active treatment (Ali and/or Aml)	
Peripheral oedema	~7%	most common cause of discontinuation incidence up to 25% using10 mg Aml incidence <1% using aliskiren alone
Dizziness	~2%	never severe, never cause of discontinuation, incidence <1% using monocomponents
Diarrhea	~2%	never severe, never cause of discontinuation incidence <1% using amlodipine alone
Lab disorders	~4%	mild increase in serum K, creatinine or glucose

Effective antihypertensive treatment is essential in the control of proteinuria and microalbuminuria. Aliskiren appears to play a specific role in this regard, as was observed in several previous studies. Vice versa, the effect of dihydropyridines (and amlodipine) on proteinuria and microalbuminuria is controversial. The clinical programme included information about standard urinalysis by dipstick but no reliable assessment of proteinuria or microalbuminuria was reported. Dipstick is a low-sensitivity method. Thus, it was considered impossible to assess whether the antiproteinuric effect of aliskiren is present when given in association with amlodipine. Additional data on this issue were presented in an observational study SPPDE03 conducted in Germany. Aliskiren and amlodipine were administered as a dual combination or as part of a multidrug combination. These data show that amlodipine did not prevent the expected reduction in albuminuria from aliskiren. It is also noted that there are other planned trials in which patients with CV diseases or risk including renal impairment (eGFR <60) will be enrolled and the urine albumin/creatinine ratio will be measured.

In study SPA2307, the total overall adverse events were similar in all treatment groups. The most frequent AE in all treatment groups was peripheral oedema. The incidence of peripheral oedema was highest in amlodipine based add-on regimen (24.1%) followed by aliskiren/amlodipine initial treatment

regimen (21.4%). It was lowest in aliskiren based add-on regimen (16.8%). Other AEs and laboratory findings were largely unremarkable. No events of hypotension were reported in the study.

Number (percent) of patients with adverse events (at least 2 percent for any treatment regimen) starting in the double-blind period by treatment regimen and preferred term (Safety set, Study SPA2307)

Preferred term	Ali/Aml regimen N=617 n (%)	Ali regimen N=315 n (%)	Aml regimen N=315 n (%)
Any Adverse events	410 (66.5)	215 (68.3)	207 (65.7)
Oedema peripheral	132 (21.4)	53 (16.8)	76 (24.1)
Joint swelling	47 (7.6)	20 (6.3)	21 (6.7)
Headache	31 (5.0)	20 (6.3)	16 (5.1)
Dizziness	30 (4.9)	11 (3.5)	12 (3.8)
Back pain	27 (4.4)	11 (3.5)	7 (2.2)
Diarrhoea	18 (2.9)	11 (3.5)	7 (2.2)
Muscle spasms	18 (2.9)	3 (1.0)	1 (0.3)
Arthralgia	17 (2.8)	9 (2.9)	9 (2.9)
Nasopharyngitis	17 (2.8)	9 (2.9)	8 (2.5)
Pain in extremity	16 (2.6)	7 (2.2)	8 (2.5)
Urinary tract infection	14 (2.3)	3 (1.0)	4 (1.3)
Constipation	13 (2.1)	5 (1.6)	6 (1.9)
Cough	13 (2.1)	11 (3.5)	3 (1.0)
Influenza	13 (2.1)	10 (3.2)	2 (0.6)
Upper respiratory tract infection	13 (2.1)	7 (2.2)	10 (3.2)
Fatigue	12 (1.9)	7 (2.2)	4 (1.3)
Oropharyngeal pain	4 (0.6)	7 (2.2)	1 (0.3)

Pooled analysis from Studies SPA2306, SPAUS01 and SAH2302
Oedema, Headache, Dizziness were the most frequent AEs (≥ 2% for either treatment group). The incidence of total AEs, and of peripheral edema and headache were higher in the amlodipine monotherapy group than in the aliskiren/amlodipine combination group. The incidence of dizziness was similar between the two groups.

The availability of long-term safety data only for the high dose combination gives information about safety under the worst possible conditions, i.e. with the use of the highest dose. Thus, the long-term safety profile appears acceptable and it is likely to be better with the low dose FDC. The below summary table provides data about long-term incidence of common AEs in study 2301 which lasted 52-weeks.

Number (%) of patients with common adverse events (>=2.0%)
(Treated population)

Preferred term	Aliskiren 150 mg/Amlodipine 5mg alone N=556 n (%)	Aliskiren 300 mg/Amlodipine 10mg alone N=546 n (%)	Aliskiren /Amlodipine alone N=556 n (%)	Aliskiren 300 mg/Amlodipine 10mg/HCTZ N=86 n (%)	Total N=556 n (%)
Any Adverse Events	131(23.6)	389(71.2)	413(74.3)	49(57.0)	424(76.3)
Oedema peripheral	8(1.4)	108(19.8)	114(20.5)	12(14.0)	126(22.7)
Upper respiratory tract Infection	5(0.9)	32(5.9)	37(6.7)	5(5.8)	40(7.2)
Bronchitis	3(0.5)	27(4.9)	30(5.4)	4(4.7)	34(6.1)
Dizziness	5(0.9)	24(4.4)	28(5.0)	2(2.3)	30(5.4)
Influenza	5(0.9)	24(4.4)	29(5.2)	2(2.3)	31(5.6)
Arthralgia	2(0.4)	22(4.0)	24(4.3)	1(1.2)	25(4.5)
Back pain	3(0.5)	22(4.0)	25(4.5)	3(3.5)	28(5.0)
Nasopharyngitis	6(1.1)	22(4.0)	26(4.7)	1(1.2)	27(4.9)
Headache	19(3.4)	19(3.5)	37(6.7)	3(3.5)	38(6.8)
Sinusitis	4(0.7)	17(3.1)	21(3.8)	1(1.2)	22(4.0)
Joint swelling	1(0.2)	16(2.9)	17(3.1)	0(0.0)	17(3.1)
Diarrhoea	3(0.5)	13(2.4)	15(2.7)	3(3.5)	18(3.2)
Musculoskeletal pain	0(0.0)	12(2.2)	12(2.2)	0(0.0)	12(2.2)
Cough	3(0.5)	11(2.0)	13(2.3)	1(1.2)	14(2.5)
Gastroenteritis	0(0.0)	11(2.0)	11(2.0)	1(1.2)	12(2.2)
Pain in extremity	1(0.2)	11(2.0)	12(2.2)	2(2.3)	13(2.3)
Urinary tract infection	2(0.4)	10(1.8)	12(2.2)	1(1.2)	13(2.3)
Nausea	4(0.7)	9(1.6)	13(2.3)	2(2.3)	15(2.7)
Palpitations	3(0.5)	9(1.6)	12(2.2)	0(0.0)	12(2.2)
Vertigo	4(0.7)	9(1.6)	13(2.3)	0(0.0)	13(2.3)
Viral infection	0(0.0)	9(1.6)	9(1.6)	2(2.3)	10(1.8)
Abdominal pain upper	0(0.0)	8(1.5)	8(1.4)	2(2.3)	10(1.8)
Dyspepsia	3(0.5)	6(1.1)	8(1.4)	3(3.5)	10(1.8)
Fatigue	9(1.6)	6(1.1)	15(2.7)	0(0.0)	15(2.7)
Muscle spasms	1(0.2)	5(0.9)	6(1.1)	5(5.8)	11(2.0)
Joint sprain	0(0.0)	3(0.5)	3(0.5)	3(3.5)	6(1.1)
Tachycardia	2(0.4)	3(0.5)	4(0.7)	2(2.3)	6(1.1)
Bursitis	0(0.0)	1(0.2)	1(0.2)	2(2.3)	3(0.5)
Fungal infection	0(0.0)	1(0.2)	1(0.2)	2(2.3)	3(0.5)

Number (%) of patients with common adverse events (>=2.0%)
(Treated population, 52-week long-term Study SPA2301)

Preferred term	Aliskiren 150 mg/Amlodipine 5mg alone N=556 n (%)	Aliskiren 300 mg/Amlodipine 10mg alone N=546 n (%)	Aliskiren /Amlodipine alone N=556 n (%)	Aliskiren 300 mg/Amlodipine 10mg/HCTZ N=86 n (%)	Total N=556 n (%)
Any Adverse Events	131(23.6)	389(71.2)	413(74.3)	49(57.0)	424(76.3)
Oedema peripheral	8(1.4)	108(19.8)	114(20.5)	12(14.0)	126(22.7)
Upper respiratory tract infection	5(0.9)	32(5.9)	37(6.7)	5(5.8)	40(7.2)
Bronchitis	3(0.5)	27(4.9)	30(5.4)	4(4.7)	34(6.1)
Dizziness	5(0.9)	24(4.4)	28(5.0)	2(2.3)	30(5.4)
Influenza	5(0.9)	24(4.4)	29(5.2)	2(2.3)	31(5.6)
Arthralgia	2(0.4)	22(4.0)	24(4.3)	1(1.2)	25(4.5)
Back pain	3(0.5)	22(4.0)	25(4.5)	3(3.5)	28(5.0)
Nasopharyngitis	6(1.1)	22(4.0)	26(4.7)	1(1.2)	27(4.9)
Headache	19(3.4)	19(3.5)	37(6.7)	3(3.5)	38(6.8)
Sinusitis	4(0.7)	17(3.1)	21(3.8)	1(1.2)	22(4.0)
Joint swelling	1(0.2)	16(2.9)	17(3.1)	0(0.0)	17(3.1)
Diarrhoea	3(0.5)	13(2.4)	15(2.7)	3(3.5)	18(3.2)
Musculoskeletal pain	0(0.0)	12(2.2)	12(2.2)	0(0.0)	12(2.2)
Cough	3(0.5)	11(2.0)	13(2.3)	1(1.2)	14(2.5)
Gastroenteritis	0(0.0)	11(2.0)	11(2.0)	1(1.2)	12(2.2)
Pain in extremity	1(0.2)	11(2.0)	12(2.2)	2(2.3)	13(2.3)
Urinary tract infection	2(0.4)	10(1.8)	12(2.2)	1(1.2)	13(2.3)
Nausea	4(0.7)	9(1.6)	13(2.3)	2(2.3)	15(2.7)
Palpitations	3(0.5)	9(1.6)	12(2.2)	0(0.0)	12(2.2)
Vertigo	4(0.7)	9(1.6)	13(2.3)	0(0.0)	13(2.3)
Viral infection	0(0.0)	9(1.6)	9(1.6)	2(2.3)	10(1.8)
Abdominal pain upper	0(0.0)	8(1.5)	8(1.4)	2(2.3)	10(1.8)
Dyspepsia	3(0.5)	6(1.1)	8(1.4)	3(3.5)	10(1.8)
Fatigue	9(1.6)	6(1.1)	15(2.7)	0(0.0)	15(2.7)
Muscle spasms	1(0.2)	5(0.9)	6(1.1)	5(5.8)	11(2.0)
Joint sprain	0(0.0)	3(0.5)	3(0.5)	3(3.5)	6(1.1)
Tachycardia	2(0.4)	3(0.5)	4(0.7)	2(2.3)	6(1.1)
Bursitis	0(0.0)	1(0.2)	1(0.2)	2(2.3)	3(0.5)
Fungal infection	0(0.0)	1(0.2)	1(0.2)	2(2.3)	3(0.5)

All patients took aliskiren 150 mg/amlodipine 5 mg for 2 weeks and then the dose was titrated to 300/10 mg for additional 52 weeks.

Serious adverse event/deaths/other significant events

Overall, most AEs were rated by the investigator as mild or moderate in intensity and were most often reported in only one to two patients. No pattern was observed. Severe peripheral oedema was most often observed when the higher dose of amlodipine (10 mg) was given alone or in combination with aliskiren; however, in the short-term, placebo-controlled and all controlled studies, the incidence of severe peripheral oedema was lower in the aliskiren/amlodipine combination treated patients than in the amlodipine treated patients. In the long-term, open-label study, severe peripheral oedema was reported in 7 patients (1.3%) treated with aliskiren/amlodipine 300/10 mg. In long-term, double-blind study, severe peripheral oedema was reported for 0.4% of all patients treated with aliskiren/amlodipine and 1.5% of all patients treated with HCT/Aml. Severe diarrhoea was reported in 2 patients (aliskiren/amlodipine 300/10 mg) in the long-term, open-label study, and was not observed in the other analysis groups. There were no deaths reported in any of the pivotal clinical studies.

Number (%) of patients with deaths, serious adverse events, and adverse events and abnormal laboratory values leading to permanent discontinuation of study drugs (Treated population)

	Aliskiren 150 mg / Amlodipine 5 mg alone N=556 n(%)	Aliskiren 300 mg / Amlodipine 10 mg alone N=546 n(%)	Aliskiren/ Amlodipine alone N=556 n(%)	Aliskiren 300 mg / Amlodipine 10 mg/ HCTZ N=86 n(%)	Total N=556 n(%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	13 (2.4)	13 (2.3)	2 (2.3)	15 (2.7)
AE discontinuations*	8 (1.4)	52 (9.5)	60 (10.8)	6 (7.0)	66 (11.9)
Drug-related AE discontinuations	5 (0.9)	44 (8.1)	49 (8.8)	3 (3.5)	52 (9.4)
SAE discontinuations	0 (0.0)	3 (0.5)	3 (0.5)	1 (1.2)	4 (0.7)
Discontinuation for abnormal lab values	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

One patient (0003_00007) whose AE started during washout period discontinued due to this AE during the active treatment period. This patient is not reflected in the count of AE discontinuations

In study SPA2307, the severity of AEs during double-blind treatment was mainly mild (30.2% of patients) to moderate (30.5% of patients), and to a much lesser extent severe (6.1% of patients). For the most frequently reported AE of peripheral oedema, the majority of cases were mild (11.7% of patients in the aliskiren/amlodipine initial treatment regimen, 6.0% in the aliskiren based add-on regimen and 10.8% in the amlodipine based add-on regimen) or moderate (7.8% of patients in the aliskiren/amlodipine initial treatment regimen, 7.9% in the aliskiren based add-on regimen and 11.1% in the amlodipine based add-on regimen). The percentage of severe cases was low (< 3%) and similar across treatment groups. No patient died during this study.

Number (percent) of patients with deaths, serious adverse events and discontinuation due to adverse events and abnormal laboratory values during the double-blind period (Safety set, Study SPA2307)

	Ali/Aml regimen N=617 n (%)	Ali regimen N=315 n (%)	Aml regimen N=315 n (%)	Total N=1247 n (%)
Deaths	0	0	0	0
SAEs	14 (2.3)	9 (2.9)	9 (2.9)	32 (2.6)
AE discontinuations	85 (13.8)	45 (14.3)	58 (18.4)	188 (15.1)
Drug-related AE discontinuations	77 (12.5)	40 (12.7)	52 (16.5)	169 (13.6)
SAE discontinuations	8 (1.3)	4 (1.3)	2 (0.6)	14 (1.1)
Discontinuations for abnormal lab values	0	0	0	0

Pooled analysis from Studies SPA2306, SPAUS01 and SAH2302
The incidence of SAE was low for both groups (4 patients, 0.9%, in amlodipine group and 4 patients, 0.5%, in aliskiren/amlodipine group). Angioedema was not reported in any patient in the 3 studies that formed the pooling database. Two deaths were reported in Study SAH2302. Both were reported in patients who had not been exposed to active study medication, and therefore were not suspected to be related to study medication.

Laboratory findings

Decreases in haemoglobin and hematocrit have been reported with agents acting on the RAS, including aliskiren. In the short-term studies, aliskiren/amlodipine treated patients had slight mean decreases from baseline in haemoglobin (-1.8 g/L and -2.0 g/L for placebo controlled and all controlled studies); however, the changes were small and not clinically meaningful. In the long-term studies, the slight decreases in haemoglobin for the aliskiren/amlodipine treated patients was consistent with the results of the short-term studies (-1.9 g/L and -0.1 g/L, for open-label and double-blind studies). In the short-term and long-term studies, analyses by age, gender, race, and ethnicity, baseline renal function and BMI status showed a pattern of laboratory values not different from those in the overall population.

Changes from baseline in most biochemistry parameters were generally small and not clinically meaningful when compared across treatment groups within the 4 analysis sets. There were no clinically meaningful changes in potassium, calcium, creatinine, BUN, lipids or glucose with the treatment of aliskiren/amlodipine (short-term, placebo-controlled; short-term, all controlled; long-term, open-label study and long-term, double-blind).

The effect of aliskiren on ECG parameters was thoroughly investigated during its development, and aliskiren did not prolong the QT-interval as assessed by the QTcF or the QTcI compared to placebo. No correlation between QT interval and C_{max} or AUC was observed.

Orthostatic BP change was defined as a decrease of ≥20 mmHg in SBP or a decrease of ≥10 mmHg in DBP when moving from a sitting position to a standing position. The incidence of orthostatic BP changes with aliskiren/amlodipine was infrequent, and was often higher at baseline than at any individual post-baseline visit for all treatment groups. When orthostatic BP changes at any visit post-baseline were considered, the incidence with aliskiren/amlodipine (8.1%) treatment was lower than placebo (10.1%) in the short-term, placebo-controlled study. In the short-term, all controlled studies, the incidence with aliskiren/amlodipine (7.6%) treatment was similar to amlodipine monotherapy (6.9%), and aliskiren monotherapy (6.6%). In the long-term studies, orthostatic BP change was infrequent at each individual post-baseline visit.

In study SPA2307, the laboratory results did not reveal any particular safety concerns for the combination. The number of patients meeting pre-specified high potassium level of >5.5 mmol/L was similar in aliskiren/amlodipine initial treatment regimen and amlodipine based add-on regimen, while it was slightly higher in the aliskiren based add-on regimen (2.0%).
Pooled analysis from studies SPA2306, SPAUS01 and SAH2302 showed that the proportion of patients meeting the criterion of serum potassium >5.5 mmol/L was small in both aliskiren/amlodipine group (0.6%) and amlodipine group (0.2%). More patients in the amlodipine monotherapy group (4.7%) met the criterion of serum potassium <3.5 mmol/L than in aliskiren/amlodipine group (2.6%). The number of patients meeting the criterion of serum BUN >14.28 mmol/L or creatinine >176.8 ìmol/L at any post-baseline visit was small in both groups (1 to 2 patients).

Safety in special populations

The initially submitted studies encompassed a total of 640 elderly (≥65 yr old) and 109 (≥75 yr old) very elderly patients treated with Rasilamlo in studies of duration up to one year. These safety data in elderly populations (≥65yr and especially ≥75yr) obtained from the clinical trials were considered too limited. Additional data became available from the newly submitted studies for the evaluation of aliskiren/amlodipine combination in elderly patients (overall n=434 for age ≥65 and n=90 for age ≥ 75). The number of elderly and very elderly patients is summarized in the below table.

Number of elderly patients treated with aliskiren/amlodipine or amlodipine (Studies SPA2306, SPAUS01 and SAH2302)

	≥65 yr old		≥75 yr old	
	Aliskiren/amlodipine	**amlodipine**	**Aliskiren/amlodipine**	**amlodipine**
SPA2306 (Randomized Set)	76	74	17	16
SPAUS01 (Safety or full Analysis Set)	22	24	6	5
SAH2302 (Randomized Set)	50	No amlo mono group	10	No amlo mono group
Total	148	193	33	37

The paucity of data in patients >75 years old, and in patients with co-morbidity does not allow a sound evaluation of efficacy and safety of the FDC in these patient populations. This information is adequately reflected in the SmPC of Rasilamlo.

The already known data on aliskiren as well as the new data derived from the clinical study CSPP100A2405 (efficacy of aliskiren 75 mg, 150 mg and 300 mg compared to placebo in elderly patients with essential hypertension after a light meal) indicate that there is no significant increase in the efficacy with increasing aliskiren dosage >75 mg/day in the elderly population. Indeed, not only was there no significant difference in SBP and DBP between the doses of 150 and 300 mg aliskiren, but the absolute BP reduction was numerically greater with 150mg. It is considered necessary to include information on the limited information from elderly in the SmPC along with an advice to exercise caution when these patients are being treated with Rasilamlo.

Safety related to drug-drug interactions and other interactions

Study SPP2218 was an open-label, multiple dose study specifically designed to evaluate the pharmacokinetic drug-drug interaction between amlodipine and aliskiren when given alone or in combination to healthy subjects. Twenty-five healthy subjects were enrolled and 18 completed the study. Conclusions from this study, together with safety data from other clinical trials, show that co-administration of aliskiren and amlodipine during steady-state conditions had no significant effect on the pharmacokinetics of either drug.

Aliskiren: Previous studies have shown that aliskiren has no known clinically relevant interactions with medicinal products commonly used to treat hypertension or diabetes. A drug drug interaction with furosemide (decreased furosemide exposure and peak concentration) has been conducted and is described in the aliskiren prescribing information. Aliskiren is a substrate for P-glycoprotein and increased aliskiren exposure and peak concentration have been identified with concomitant use of P-gp Inhibitors. This effect is substantial with cyclosporin A and itraconazole. Contraindication for concomitant use of aliskiren with cyclosporine and itraconazole is present in the SmPC of Rasilamlo.
Due to the lack of data a potential interaction between grapefruit juice and aliskiren cannot be excluded. Grapefruit juice should not be taken together with Rasilamlo as stated in the SmPC.

Amlodipine: Several studies have shown that, in monotherapy, amlodipine has been safely administered with other hypertensive drugs. A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4, since the plasma concentration increases by approximately 50% and the effect of amlodipine is increased. The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded. Co-administration with CYP3A4 inducers may lead to reduced plasma concentrations of amlodipine. The information on potential interactions between amlodipine and other drugs has been adequately reflected in the SmPC of Rasilamlo.

Discontinuation due to adverse events

Discontinuation of treatment due to side effects was 0.7% more frequent during active treatment in comparison with placebo. Peripheral oedema was a frequent cause of treatment discontinuation. The incidence was lower in aliskiren/amlodipine treated patients than in amlodipine treated patients (short-term, placebo controlled and short-term, all controlled trials). In the long-term studies, the incidence of discontinuation due to adverse events in aliskiren/amlodipine patients was lower when compared to the total population (long-term, open-label) and when compared to all hydrochlorothiazide/amlodipine patients (long-term, double-blind). No other particular pattern or clustering of events according to preferred term was observed.

In study SPA2307, more patients discontinued due to AE in the amlodipine (18.4%) regimen compared to aliskiren/amlodipine (13.8%) or aliskiren (14.3%) regimen. Most of the AE discontinuations were suspected to be drug-related with the incidence higher in the amlodipine (16.5%) regimen than in the aliskiren/amlodipine (12.5%) and aliskiren regimen (12.7%). SAEs-related discontinuations were low (<1.5% in all treatment groups). No patients discontinued study due to abnormal laboratory findings. Presented safety data indicated that the combination regimen of aliskiren/amlodipine was well tolerated.

Pooled analysis from Studies SPA2306, SPAUS01 and SAH2302 showed that more patients in amlodipine monotherapy group discontinued from the studies due to any reason or due to AEs compared to the aliskiren/amlodipine group.

Post marketing experience

The fixed combination of aliskiren/amlodipine was not marketed in any country at the time of the first MAA submission for Rasilamlo and until 26 August 2010, when the first marketing authorisation was granted in US. According to the Applicant's update, the number of total Standard Units (tablets) sold was 780 with a cut-off date of 09-Oct-2010.
Based on sales data, patient exposure to aliskiren was estimated to be approximately over 460,000 patient-treatment-years (PTY); while for amlodipine it was approximately 325 million PTY. Applicant's search conducted for all cases with concurrent use of aliskiren and amlodipine (as single active ingredients or in combination products) produced 320 cases reporting 1268 events. The review of these cases did not result in any new safety findings, as the events were either known to be associated with the use of amlodipine and/or aliskiren or related to the underlying disease. Based on the submitted data, approximately 779.000 patients have used aliskiren as monotherapy or in combination with another anti-hypertensive drug since its first introduction on the market until January 2010. Roughly 19% of the patients are taking aliskiren in combination with amlodipine, with an estimated total number of aliskiren-amlodipine treated patients of 149,643. On this regard a 30% discontinuation rate (best case scenario for patients treated with anti-hypertensive drugs at 6 months) should be applied to these figures. This reduces the number of long-term exposed patients to nearly 105,000.

2.5.1. Discussion on clinical safety

Based on the analysis of overall short-term safety data in the general hypertensive population there is no evidence that Rasilamlo may induce, in the short term, changes in the nature, incidence, and seriousness of AEs or laboratory abnormalities, that could raise serious concerns in comparison with the monocomponents. To date, data in patients with severe hypertension and patients with co-morbidities are limited or lacking. Very limited safety data are available in patients with hypertension stage 1 with additional cardiovascular risks. The paucity of data in patients $\geq$75 years old, and in patients with co-morbidity does not allow a sound evaluation of Rasilamlo safety in these patient populations.

Safety in stage 2 hypertensive patients: In study SPA2305, no increase in the incidence of AEs was observed in stage 2 hypertensive patients in comparison with the general population. Peripheral oedema was, as expected, the most common. The nature and frequency of AEs reported was similar to that of the overall population. No additional safety concerns in stage 2 hypertension patients were observed. Similar results were obtained from the pooled analysis from studies SPA2306, SPAUS01 and SAH2302, analysing data from 750 patients, 567 of which were exposed for > 8 weeks to the combination of aliskiren/amlodipine.

The most frequently reported AEs were: peripheral oedema and headache, the incidence of which was higher in the amlodipine than in the aliskiren/amlodipine group. The incidence of diarrhoea was 1.5 % for aliskiren/amlodipine combination and 1.3 % for amlodipine. One patient had hypotension in aliskiren/amlodipine group. Angioedema was not reported in any of the studies. The proportion of patients who had serum potassium >5.5 mmol/L was 0.6 % in aliskiren/amlodipine group and 0.2 % in almodipine group. The number of patients who had BUN >14.8 mmol/L or creatinine >176.8 μmol/L was small in both groups

Long-term (1 year) safety data do not seem to indicate additional safety concerns elicited by Rasilamlo in comparison with those already known for the monocomponents. Post-marketing data show the use of the free combination of aliskiren and amlodipine in nearly 105,000 patients. This number is somewhat reassuring. However, these data should be supported by information on the long-term safety profile of the combination therapy in the clinical practice. This information is lacking. The long-term safety profile (> 1 year) of the aliskiren/amlodipine combination is at present not fully established.

From the safety database all the adverse reactions reported in clinical trials and the post-marketing use of aliskren and/or amlodipine have been included in the Summary of Product Characteristics.

2.5.2. Conclusions on the clinical safety

Based on the short- and long-term (1 year) observations, there is no evidence that in stage 2 hypertensive patients or in the general hypertensive population - with the exclusion of severe

hypertensive patients and patients with co-morbidities, for whom data are lacking - Rasilamlo could induce such incidence and seriousness of AEs or laboratory abnormalities, which may raise serious concerns in comparison with the safety profile of the monocomponents. However, long term safety data (> 1 year) for the FDC are still limited.

2.6. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

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)
Important identified risks		
Diarrhoea	Routine pharmacovigilance activities.	SmPC Special warnings and precautions for use (Section 4.4): In the event of severe and persistent diarrhoea, aliskiren/amlodipine therapy should be stopped. Listed in section 4. 8 Undesirable Effects
Rash	Routine pharmacovigilance activities.	SmPC Listed in section 4.8 Undesirable Effects
Angioedema	Routine pharmacovigilance activities.	SmPC Contraindication in patients with history of angioedema with aliskiren and in patients with hereditary or idiopathic angioedema (Section 4.3). Special warnings and precautions for use (Section 4.4): Information is given about the risk of angioedema, and the symptoms suggestive of angioedema. Patients with history of angioedema may be at increased risk of experiencing angioedema and advice is given to monitor patients during treatment, especially at the beginning of the treatment. If angioedema occurs, Rasilamlo should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		provided. Listed in section 4.8 Undesirable Effects
Hyperkalaemia	Routine pharmacovigilance activities.	SmPC Special warnings and precautions for use (Section 4.4) and Interaction with other medicinal products and other forms of interaction (Section 4.5): Patients receiving other medicinal products that inhibit the renin-angiotensin-aldosterone system (RAAS), and/or those with reduced kidney function and/or diabetes mellitus are at an increased risk of hyperkalaemia during aliskiren therapy. Caution is advised when co-administered with agents which increase potassium levels. Listed in 4.8 Undesirable effects As with any medicinal product acting on the RAAS, routine monitoring of electrolytes and renal function is indicated in patients with diabetes mellitus, kidney disease, or heart failure.
Renal dysfunction including blood creatinine increased	Routine pharmacovigilance activities.	SmPC Posology (Section 4.2) and Special warnings and precautions for use (Section 4.4): Caution should be exercised in hypertensive patients with severe renal impairment due to the absence of safety information for aliskiren in this patient population. Special warnings and precautions for use (Section 4.4): - Renal impairment As for other medicinal products acting on the renin-angiotensin-aldosterone system, caution should be exercised when Rasilamlo is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe or prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease or kidney disease. Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued. - Renal artery stenosis No controlled clinical data are available on the use of Rasilamlo in patients with unilateral or bilateral renal artery stenosis,

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		or stenosis to a solitary kidney. However, as with other medicinal products acting on the renin-angiotensin-aldosterone system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore, caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued. Listed in section 4.8 Undesirable effects
Peripheral edema	Routine pharmacovigilance activities.	SmPC Listed in section 4.8 Undesirable effects
Hypotension	Routine pharmacovigilance activities.	SmPC Contraindicated in patients with severe hypotension (Section 4.3): Special warnings and precautions for use (Section 4.4): In patients with marked volume- and/or salt-depletion (e.g. those receiving high doses of diuretics or as a result of dietary salt restriction, diarrhoea or vomiting) symptomatic hypotension could occur after initiation of treatment with Rasilamlo. This condition should be corrected prior to administration of Rasilamlo, or the treatment should start under close medical supervision. In patients with uncomplicated hypertension treated with Rasilamlo in short-term controlled trials, the incidence of hypotension was low (0.2%). Listed in section 4.8 Undesirable effects
Decrease in furosemide systemic levels	Routine pharmacovigilance activities.	SmPC Interaction with other medicinal products and other forms of interaction (Section 4.5): When aliskiren was co-administered with furosemide, the AUC and Cmax of furosemide were reduced by 28% and 49% respectively. It is therefore recommended to monitor the effects when initiating and adjusting furosemide therapy to avoid possible under-utilisation in clinical situations of volume overload.
Increased aliskiren systemic levels with the potent Pgp inhibitors: Ciclosporin A and Itraconazole.	Routine pharmacovigilance activities.	SmPC Contraindication (Section 4.3) and interaction (Section 4.5) The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent Pgp inhibitors, and other potent P-gp inhibitors is contraindicated.
Increased aliskiren	Routine pharmacovigilance activities.	SmPC

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
systemic levels with moderate Pgp inhibitors, ketoconazole and verapamil		Special warnings and precautions for use and interactions with medicinal products (Section 4.4 and 4.5): Moderate Pgp inhibitors: Caution should be exercised when aliskiren is administered with moderate P-gp inhibitors such as ketoconazole and verapamil (see section 4.5). .
Interaction with grapefruit juice	Routine pharmacovigilance activities.	SmPC Posology and method of administration (Section 4.2): Grapefruit juice should not be taken together with Rasilamlo.
Food interaction	Routine pharmacovigilance activities.	SmPC Posology and method of administration (Section 4.2): Rasilamlo should be taken with a light meal. Interaction with other medicinal products and other forms of interaction (section 4.5) Food interactions Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially.
Cough	Routine pharmacovigilance activities.	SmPC Listed in section 4.8 Undesirable effects
Interaction with NSAIDs	Routine pharmacovigilance activities.	SmPC: Interaction with other medicinal products and other forms of interaction (Section 4.5): As with other medicinal products acting on the renin-angiotensin-aldosterone system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren with an NSAID requires caution, especially in elderly patients.
Important potential risks		
Colorectal hyperplasia	Routine pharmacovigilance activities.	SmPC Listed in section 5.3 preclinical safety data.
Ischemic colitis	Routine pharmacovigilance activities.	SmPC No risk minimization activity is currently required.
Increased aliskiren systemic levels	Routine pharmacovigilance activities.	SmPC Interaction with other medicinal products and other forms of interaction (Section

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
with other moderate (Clarithromycin, telithromycin, erythromycin, amiodarone) or potent Pgp inhibitors (quinidine)		4.5): Caution should be exercised when aliskiren is administered with other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone). Contraindication (Section 4.3): The concomitant use of quinidine is contraindicated.
Important missing information		
Pregnancy and lactation	Routine pharmacovigilance activities.	SmPC Contraindication (Section 4.3): Second and third trimesters of pregnancy. Fertility, pregnancy and lactation (Section 4.6): - Women of child-bearing potential/contraception in males and females: Healthcare professionals prescribing Rasilamlo should counsel women of childbearing potential about the potential risk during pregnancy. A switch to a suitable alternative antihypertensive treatment should be carried out in advance of a planned pregnancy since Rasilamlo should not be used in women planning to become pregnant. - Pregnancy: Rasilamlo should not be used during the first trimester of pregnancy. Rasilamlo is contraindicated during the second and third trimesters. If pregnancy is detected during therapy, Rasilamlo should be discontinued accordingly as soon as possible. - Breast-feeding: It is unknown whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Since there is insufficient/limited information on the excretion of aliskiren and amlodipine in human or animal breast milk, a risk to the newborns/infants cannot be excluded. It is therefore not advisable for women who are breast-feeding to use Rasilamlo. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Rasilamlo therapy taking into account the benefit of breast-feeding for the child and the benefit of

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		therapy for the woman.
Paediatric patients	Routine pharmacovigilance activities.	SmPC. Posology (Section 4.2): Paediatric population: The safety and efficacy of Rasilamlo in children and adolescents below age 18 have not been established. No data are available.
Severe renal dysfunction	Routine pharmacovigilance activities.	SmPC Posology (Section 4.2) and Special warnings and precautions for use (Section 4.4): Renal impairment Caution should be exercised in hypertensive patients with severe renal impairment due to the absence of safety information for Rasilamlo in this patient population.
Reno-vascular hypertension	Routine pharmacovigilance activities.	SmPC Special warnings and precautions for use (Section 4.4): Caution should be exercised in hypertensive patients with severe renal impairment due to the absence of safety information for aliskiren in this patient population
Cardiovascular morbidity and mortality reduction	Routine pharmacovigilance activities.	SmPC Listed in section 5.1 Pharmacodynamic properties.
Hepatic impairment	Routine pharmacovigilance activities.	SmPC Posology and method of administration (Section 4.2) and Special warnings and precautions for use (Section 4.4) Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%. Therefore caution should be exercised when administering Rasilamlo to patients with hepatic impairment.
Interaction with clopidogrel	N/A	SmPC No risk minimization activity is currently required.

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.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.7. Benefit-Risk Balance

Benefits

The current indication concerns the use of the FDC 150mg/5mg, 150mg/10mg, 300mg/5mg, 300mg/10mg film-coated tablets in patients whose blood pressure is not adequately controlled with aliskiren or amlodipine used alone (second line). First-line and substitution indications have been withdrawn.

- Beneficial effects

The majority of hypertensive patients need two or more medications for adequate blood pressure control. New fixed-dose combinations of antihypertensive drugs could improve the patients' compliance over the free combination of the single monotherapies.

The parallel group study SPA2305 and the add-on studies indicate that Rasilamlo induces a higher dose-dependent antihypertensive effect and a higher rate of controlled hypertension in comparison to mono-regimens.

- Uncertainty in the knowledge about the beneficial effects.

The population of hypertensive patients that would benefit from initial therapy with the FDC has not been clearly identified. In addition, no demonstration of the clinical relevance of early BP control with the use of the FDC in first-line therapy in non-high risk patients with stage 2 hypertension has been provided. Consequently, the first-line indication was not granted, and was withdrawn.

There is limited information available in patients with age ≥65 years, in particular limited efficacy data for the add-on indication and no information in patients aged 75 years and older. This is correctly reflected in the SmPC.

However, the information on elderly will be further updated based on the assessment of results from study 2405 in elderly patients. Therefore, the Applicant is committed to submit the relevant type II variation for all aliskiren containing products according to the CHMP requests.

Limited information on BE of the FDC when administered under fed conditions. The lack of bioequivalence data in the fed state is correctly reflected in the SmPC

Risks

A significant percentage (about 30%) of patients initially treated with the FDC combination could have their BP potentially controlled by the monotherapy, and thus, be unnecessarily exposed to two drugs and to the risk of higher number of adverse events. Consequently, the first-line indication was not granted.

Food decreases aliskiren absorption. Available data suggest that the effect of food may also be dependent on formulation. No bioequivalence study of the FDC in the fed state has been performed. This has led to the withdrawal of the indication in substitution therapy.

Theoretically, the use of the FDC could imply the sum or the potentiating of the AEs of the two monocomponents, the incidence of new AEs secondary to an unknown interaction between the two monocomponents, and AEs secondary to too rapid and/or excessive blood pressure reduction.

- Unfavourable effects

In short-term studies, incidence of AEs was slightly higher during treatment with the FDC in comparison to monotherapies. Discontinuation of treatment due to AEs was slightly more frequent during treatment with the FDC in comparison to monotherapies. Long-term safety data are limited and are available only for the high-dose combination, hence under the worst possible conditions because the long-term safety profile is expected to be better with the use of the low-dose FDC.

In short-term and long-term studies, the FDC was characterised by two non-serious AEs: peripheral oedema and diarrhoea and both have been included in the SmPC. Peripheral oedema was the most common AE and a frequent cause of treatment discontinuation. It was more common during the treatment with amlodipine than during treatment with aliskiren. Diarrhea occurred approximately in 3% of patients and was more common during treatment with aliskiren than during treatment with amlodipine. Diarrhea was severe only in approximately 0.5% of patients but was not related to the treatment.

- Uncertainty in the knowledge about the unfavourable effects

Limited information is available form patients with age ≥75 years. This is reflected in the SmPC with a warning on the use of aliskiren in patients older than 75 years old.

Benefit-risk balance

- Importance of favourable and unfavourable effects

As regards the first-line indication:

i) The lack of a wide therapeutic experience for the combination therapy with aliskiren and amlodipine,
ii) The unnecessary exposure to the FDC of a significant number of patients (30%) whose BP is adequately controlled by the monotherapy,
iii) The lack of demonstration of the clinical relevance of early BP control with the use of the FDC in first-line therapy in non-high risk patients with stage 2 hypertension

are considered major issues that overweight the potential benefit represented by the faster control of BP levels obtained with the FDC as compared to the sequential add-on treatment strategy. For these reasons, the first-line indication was not granted and was withdrawn.

In reference to the second-line indication, the FDC induced a higher dose-dependent antihypertensive effect and a higher rate of controlled hypertension in comparison to mono-regimens. Although the effect of food on the additional benefit of the FDC combination *versus* amlodipine monotherapy can not be clearly estimated, the entity of the BP lowering effect of the components of the FDC when administered after a light meal is reassuring on the beneficial effects of the FDC in patients not controlled by monotherapy.

No important safety concern for the FDC has emerged from short term safety studies. However, the long-term safety profile of the FDC is not completely elucidated yet.

- Benefit-risk balance

For the second line indication, the beneficial effect of the FDC combination is considered sufficiently demonstrated, although there was a considerable fraction of aberrant BP readings. Their clinical relevance on the overall efficacy of Rasilamlo is however not considered significant.

For the first line indication, the observation that 1/3 of patients with stage 1-2 hypertension were controlled after 16 weeks of treatment with the mono-regimen, and that a higher number of AEs are associated with the FDC in comparison with the monotherapy, together with the lack of demonstration of the clinical relevance of early BP control with the use of the FDC in first-line therapy in non-high risk patients with stage 2 hypertension renders the benefit-risk balance for this indication negative. The first-line indication was withdrawn.

The benefit-risk balance for *the substitution indication* is negative because of the lack of a bioequivalence study in the fed state. This has led to its withdrawal.

2.7.1. Discussion on the benefit-risk balance

The overall benefit/risk of Rasilamlo is considered positive for the indication: *treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled with aliskiren or*

amlodipine used alone. The benefit/risk of Rasilamlo is considered negative for the first line indication and for the substitution indication.

2.7.2. Risk management plan

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.

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

2.8. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Rasilamlo in the treatment of Rasilamlo is indicated for *the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled with aliskiren or amlodipine used alone* was favourable and therefore recommended the granting of the marketing authorisation.