SCIENTIFIC DISCUSSION

1. Introduction

Essential hypertension (EHTN) affects approximately 1 billion individuals worldwide. It has been identified as a major risk factor for cardiovascular diseases such as stroke, myocardial infarction (MI), and congestive heart failure (CHF): it's widely recognised that an adequate control of EHTN is important to significantly decrease cardiovascular mortality and morbidity. All international guidelines for the management of EHTN 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 target organ damage, diabetes mellitus or renal disease. Several therapeutic choices are currently available to lower BP, including diuretics, β-blockers (BB), angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB) and calcium channel blockers (CCB). 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 (AGT) to angiotensin I (Ang I). Then the ACE transforms Ang I into the active octapeptide angiotensin II (Ang II), which acts via type-1 angiotensin II receptors 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 RAS. BB reduce the release of renin from the juxtaglomerular apparatus and lower BP. ACE inhibitors reduce the conversion of Ang I to Ang II. They also inhibit the inactivation of bradykinin and substance P, causing some typical side effects of ACE inhibitors, such as cough and angioedema. ARBs block the interaction of Ang II with the AT1 receptor.

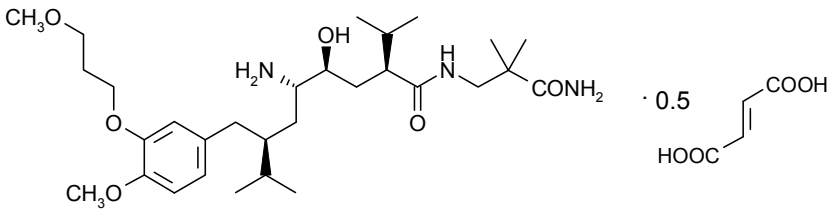
Aliskiren (ALI) contains a new chemical entity, aliskiren, which belongs to the pharmacotherapeutic group of Renin inhibitor (RI), ATC code: C09XA02. It is proposed as film-coated tablets in strengths of 150 and 300 mg for treatment of EHTN. The recommended dose is 150 mg once daily. In patients whose BP is not adequately controlled, the dose may be increased to 300 mg once daily. ALI is proposed to be used alone or in combination with other antihypertensive agents. ALI exhibits a new mode of action compared with other drugs acting on the RAS. It selectively inhibits human renin, the enzyme responsible for the conversion of AGT to Ang I; therefore the final production of the potent vasoconstrictor Ang II (increase arterial tone, adrenal aldosterone secretion, renal sodium reabsorption, sympathetic neurotransmission and cellular growth) is inhibited by blocking the renin system at its very origin. Ang II also inhibits renin release, thus providing a negative feedback to the system. Elevated PRA has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients. All agents that inhibit this system, including RIs, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACE inhibitors and ARB, it is accompanied by increased levels of PRA. During treatment with ALI, however, the feedback loop effects are neutralised. As a result, PRA, Ang I, and Ang II are all reduced. RIs like ALI do not block the degradation of bradykinin, so they might have a lower hypotensive effect compared with ACE inhibitors, although they show fewer side effects. In addition RIs do not block renin-like enzymes, such as cathepsin D or tonins, which are present in the vascular wall and which release Ang I from AGT. Renin has a unique specificity for its only known physiological substrate, AGT. This specific inhibition of the renin system by diminishing renin activity has the advantage to not interfere with other metabolic pathways.

The development program consisted of efficacy and safety studies of ALI as monotherapy or in combination with other classes of anti-hypertensive drugs, including a diuretic (HCTZ), an ARB (valsartan [VAL]), an ACEI (ramipril [RAM]), CCB (amlodipine, [AML]), and BB (atenolol [ATE]).. All completed studies were conducted in patients with essential HTN. Specific studies were conducted in hypertensive patients with diabetes, obesity, systolic HTN (in patients over 65 years of age), and severe HTN. Studies are being conducted in populations with diabetic nephropathy, congestive heart failure, and left ventricular hypertrophy, as well as in hypertensive patients unresponsive to other agents. The Scientific Advice was given by the CHMP (EMEA/H/SA/466/1/2004/III) and followed during the development process. No clinical development in pediatric population was submitted with this application.

2. Quality aspects

Introduction
The applicant has applied to obtain a marketing authorisation for Rasilez, immediate release film-coated tablets as 150 mg and 300 mg dosage strengths. It contains aliskiren, an orally potent and selective inhibitor of human renin.

Active Substance
Aliskiren hemifumarate has 4 chiral centres, but is obtained as a single diastereoisomer, all S-configured. Sufficient scientific information has been presented on physicochemical properties such as appearance, solubility in standard aqueous buffers and in non-aqueous solvents, pKa, specific rotation, log P, melting point and thermal behaviour. This molecule shows polymorphs. Satisfactory identification was performed by X-ray powder spectra, DSC and TGA analysis.



- Manufacture

The synthesis of the active substance can be summarized in 10 main steps. The process predominantly involves the construction of an appropriately substituted octanamide backbone with controlling the stereochemistry. The manufacturing process has been fully detailed, including operating conditions, quantities of solvents, reagents, catalysts. Adequate in-process controls have been applied as well as controls of the reagents, solvents, catalysts, starting materials, and intermediates used in the manufacture of aliskiren hemifumarate. Critical steps include the step where the 4 chiral centres are stereochemically formed and the crystallisation of aliskiren hemifumarate, and relevant intermediates have been controlled accordingly. Adequate specifications have been included for the starting materials, solvents, and intermediates. Validation data are available and the robustness of the process has been demonstrated. The structure of aliskiren hemifumarate has been fully elucidated with usual techniques such as elementary analysis, IR spectroscopy, ^{1}H-NMR and ^{13}C-NMR spectroscopy, mass spectroscopy and X-ray powder diffractometry (XRDP), optical rotation (single diasteroisomer), particle size analysis.

- Specification

Appropriate specification has been set up and includes appearance, particle size, appearance of the solution, identification (by IR, by XR and optical rotation), residual solvents, water content, sulfated ash, heavy metals, related substances, assay (by titration and HPLC), assay of the salt (fumaric acid), microbiological quality. The skip-testing approach for the microbiological quality is considered acceptable. Specification of the active substance including residual solvents (in line with ICH requirements) and impurities (justified by toxicological data) are appropriately justified. Analytical methods have been adequately detailed and non-compendial methods validated in accordance with ICH guidelines. The bulk of the active substance is packed in sealed triple bags (polyethylene PE/aluminium/ polyethylene terephthalate PET) or quadruple bags (PE /PET/aluminium /PET). The bags are stored in drums with a tamper resistant seal. Results based on the analysis of 31 batches have demonstrated the uniformity and the consistency of the synthesis.

- Stability

Stability data on 3 pilot batches have been carried out under ICH long term (24 months, 25°C/60%RH) and accelerated conditions (6 months, 40°C/75%RH) as well as photostability and stress testing under different conditions. All parameters were found in accordance with the specification and no major degradation could be observed. Post-approval, the applicant will perform stability studies on

3 production batches according to the registered protocol. The proposed re-test period is supported by the results of the stability study.

Medicinal Product
The formulation is an immediate release oral formulation available in two strengths 150 mg and 300 mg. Film-coated tablets were chosen as it is the most convenient and suitable dosage form. The 2 strengths have different shapes and colors. They have the same qualitative composition with regard to the active substance and the excipients in the cores whereas the coatings are slightly different.

- Pharmaceutical Development

The choice of the active substance has been adequately described. In particular the choice of the hemifumarate salt is justified. The choice of excipients is based upon their suitability with the manufacturing process, on compatibility and on pharmaceutical technological experience gained from development of similar immediate release oral solid dosage forms. Excipients used are microcrystalline cellulose, crospovidone, povidone, magnesium stearate and silica, colloidal anhydrous, and premix coating mixtures. All excipients comply with PhEur or USP specifications, except the basic coating premixes that are commercially available mixtures of standard components used for film-coat. The excipients are common excipients used for oral dosage forms. The colorants titanium dioxide and iron oxide comply with Directive 95/45/EEC. Film-coating is only used to mask the bitter taste of the active substance and has no impact on the dissolution properties. Satisfactory specification as well as certificates of analysis are presented for each excipient and analytical methods have been described and validated when non-compendial. The manufacturing development of the drug product has been described in detail, Differences between clinical formulation and the formulation to be marketed were discussed and the biopharmaceutical equivalence demonstrated. The manufacturing process development of the drug product has been appropriately described and validated. The description of the manufacturing process changes showed that the manufacturing process is robust and consistently yields a drug product which meets the proposed requirements. Adequate in-process controls have been selected to monitor the manufacturing process. For primary stability studies drug product were packaged in different standard packaging types commonly used for solid oral dosage forms. Rasilez will be marketed in PA/AL/PVC blister packs (Alu-Alu blisters).

- Adventitious Agents

All excipients are of vegetable or mineral origin therefore no TSE risk assessment is needed.

- Manufacture of the Product

The manufacturing process is considered a standard manufacturing process involving standard technology such as mixing, granulation, compressing and film-coating unit operations and is appropriately controlled by in-process controls. No process steps were considered as critical.

- Product Specification

Specification for the film-coated tablets at release and at the end of shelf-life include parameters such as dimensions, appearance, identification (UV and HPLC), identification of the colorants (colour reaction), mean mass, dissolution test (UV, PhEur, USP), water content (Karl-Fischer), residual solvents (GC), related substances (HPLC), microbial quality (PhEur, USP), uniformity of dosage (mass variation and content uniformity, PhEur), assay (HPLC). Specification has been justified.. Furthermore, the applicant has discussed and analysed the possible formation of chiral impurities in the drug product during shelf life. Impurity limits are in line with ICH/Q6A and justified by toxicological studies and batch data. Residual solvents are in line with ICH guidelines. Analytical methods have satisfactorily described and validated in accordance with ICH guidelines. Batch analysis of 4 batches of each strength have been presented. The results comply with the specification and confirm the consistency of the product.

The primary packaging for the film-coated tablets consists of PA/Al/PVC blister packs (Alu-Alu blisters). The components of the PA/Al/PVC blisters are tested for cleanliness, total thickness and identity (IR). In addition the Applicant states that the packaging components comply with PhEur requirements and/or EU foodstuff legislation.

- Stability of the Product

Stability studies have been conducted in 3 types of blisters including the commercial packaging. Stability program under ICH conditions consisted of long term testing at 25°C/60% RH and 30°C/70% RH (changed to 30°C/75 % RH as of 1st October 2005), accelerated testing at 40°C/75% RH, as well as testing under other conditions (-20°C/ambient RH, 5°C/ambient RH, 50°C/ambient RH) and special tests (photostability, microbial limit test, freeze/thaw cycle). Parameters such as appearance, dissolution, water content, degradation products and assay have been tested. Only the commercial packaging (PA/Al/PVC blister) was retained. Based on stability data, the proposed shelf life can be accepted under the precautions of storage described in the Product Information.

Discussion on chemical, pharmaceutical and biological aspects

The active substance aliskiren hemifumarate is optically active with four chiral carbons but exists as a single diastereoisomer. It is manufactured via a 10 steps stereochemically controlled synthesis. Control of stereochemistry, polymorphism and impurities have been fully discussed. Appropriate specification has been presented. Stability studies conducted according to the ICH guidelines showed that aliskiren hemifumarate is stable and the re-test period of 2 years, in very tight packaging (due to the hygroscopic nature of the substance), protected from light, at temperature not above 25°C can be granted. Rasilez film-coated tablets 150 mg and 300 mg are formulated as an immediate release formulation with well-known excipients.The two strengths have the same qualitative composition with regard to the active substance and the excipients in the cores; the coatings are slightly different. Compatibility with regard to excipients is justified by stability results. The pharmaceutical development is comprehensive and adequate. Manufacturing method has been described and allows the production of a consistent and homogeneous product.The tablets are kept in PA/AL/PVC blister packs (Alu-Alu blisters). The description and choice of the container is acceptable based on stability data. Drug product specification are satisfactory and in line with ICH guidelines. Stability data support the proposed shelf life under the precautions of storage described in the Product Information.

3. Non-clinical aspects

Introduction

The non-clinical development program sufficiently follows the worldwide regulatory guidance and it was considered complete by the CHMP (SA procedure EMEA/H/SA/466/I/2004/III). A sufficient number of *in vitro* tests showed the selectivity of ALI to renin. Since renin displays strong species-dependent substrate specificity, the main *in vivo* experimental models used BP response to a human renin. They provided insight into the PD properties demonstrating antihypertensive effects of ALI, with range of effective doses between 0.3 mg/kg to 50 mg/kg, depending on the models and on the administration route. The toxicity studies employed rats and marmosets, species used as pharmacological models, which displayed metabolic profiles similar to humans. Safety margin calculations have been performed considering the human exposure after the highest expected clinical dose of 300 mg. All non-clinical studies in the toxicology program were performed with oral route, except one study in rats when ALI was administered intravenously and local tolerance studies. In the PD program, oral, iintravenous and osmotic minipump administration have been used. ALI showed generally a non-linear pharmacokinetics (PK) with low bioavailability and overproportional exposure after oral dosing in all species. Many of the administration/distribution/metabolism/elimination (ADME) studies were conducted using a ^{3}H and ^{14}C labelled drug substances.

Pharmacology

- Primary pharmacodynamics

In vitro studies with ALI showed its potency in inhibition of human recombinant renin and marmoset renin. ALI is less potent in various non-primate species. Moreover, ALI was inactive or only weakly active against human aspartic proteinases and HIV-1 proteinase. *In vivo* ALI was tested in marmosets, mice, and two stains of transgenic rats: (1) double transgenic rats (dTGR) expressing the human genes for renin, and (2) transgenic rats (TGR), that express mouse renin. Spontaneously hypertensive rats (SHR), in which ALI monotherapy evokes a weak antihypertensive response, were used to test the antihypertensive effect of combining this RI with other inhibitors of the RAS. The *in vivo* models for

testing antihypertensive properties of human rennin inhibitors are limited and not fully representative of the human disease. In particular the elevated species-specificity of renin rendered useless the classic preclinical models of EHTN like SHR rats. This problem has been partially solved by using transgenic models that are considered representative of the "state of the art" for RIs and suitable to demonstrate ALI primary PD effects, as well as the choice of comparators and statistical analysis. In particular in the TGR rat the acute BP lowering effect of ALI given in a single oral dose was rapid and seems to be dose-depedent between 3 and 100 mgEq/kg. The highest dose resulted in prolonged effect persisting for greater than 24 hours after dosing. The acute antihypertensive effect of ALI was 10-fold less strong, than that of enalapril. After repeated dose for 10 days (1, 3 or 10 mgEq/kg/day orally once daily) no loss or gain in effect over the 10 days study was demonstrated. A small but significant increase in HR occurred following daily dosing with ALI at 10 mgEq/kg. Enalapril (ENA) at a dose of 1 1 mgEq/kg/day induced a significant tachycardia. The *in vivo* potency of ALI given orally was an order of magnitude less potent than that of VAL and ENA. Given i.v. these three agents exhibited comparable dose response profiles. The ALI PK/PD relationship is relatively log-linear over a 10-fold range of doses and over the entire duration of action from peak to recovery. In marmosets single ALI dose between 0.3 and 1 mg/kg lowered mean arterial blood pressure (MAP) to a significantly greater extent compared with either benazepril or VAL. In these animals ALI plasma levels increased dose dependently. PRA was completely inhibited 1.5 and 3 hrs after the lowest p.o. dose of 0.3 mg/kg. PRA was still inhibited by 87% after 6 hrs and had returned to above baseline levels after 24 h. After the higher p.o. doses, the complete inhibition of PRA persisted even longer; PRA was completely inhibited (100%) for at least 24 h after administration of the 3 and 10 mg/kg doses. Lower doses of ALI were required for inhibition of PRA than to lower MAP. In renin-dependent mice ALI given at 50 mg/kg/day s.c. for four weeks prevented the development of the renovascular HTN and significantly inhibited the rise of BP in renin-independent mice. ALI inhibited PRA in renin-dependent mice by 58% relative to vehicle-treated animals. The studies performed in dTGR to investigate organ protective effect of ALI are not considered really suitable for evaluation due to high variability. In diabetic-hypertensive TGR rats ALI given s.c. for 10 weeks significantly lowered the BP. In summary the studies performed *in vitro* and *in vivo* proved the significant and selective inhibitory effect against human renin, and antihypertensive effect of ALI in different animal models. According to the pharmacological studies ALI, as a RI, provide the pharmacologic rationale for the use in the treatment of EHTN.

- Secondary pharmacodynamics

Secondary pharmacodynamic studies were not conducted, but there are no concerns derived from the lack of these data.

- Safety pharmacology programme

CNS, cardiovascular, respiratory and renal safety pharmacology investigations performed did not indicate undue risk for patients with regard to CNS adverse effects and QT prolongation-related even considering the available clinical data including a specific assessment of cardiac conduction. No effects on the rate and force of contraction of isolated guinea pig atria were observed. ALI affinity for main body receptors was analysed in *in vitro* and *in vivo* data and it is considered unlikely that the compound will interact with the tested receptors at therapeutic doses *in vivo*. In summary, no significant effects from safety pharmacology studies were observed at employed doses, which could preclude the use of ALI in man.

- Pharmacodynamic drug interactions

The effect on BP and HR of combining ALI with other RAS-blocking agents was studied in telemetered SHR. When ALI and VAL were administered simultaneously at submaximal doses (30 mg/kg/day and 1 mg/kg/day s.c., respectively) an apparent synergistic BP lowering effect occurred. The decrease in BP was particularly pronounced with the combination during the second week of administration, at a time when the antihypertensive effects in the monotherapy groups had dissipated. A similar synergy was observed with the combination of ALI (30 mg/kg/day) and a higher dose of VAL (3 mg/kg/day). Combinations of ALI and VAL or ALI and benazepril caused significant ($p<0.05$) increases in the HR compared with vehicle controls and with the respective monotherapies. The elevation in HR diminished somewhat after the first week, consistent with baroreceptor resetting over time. However, a minimal, but sustained tachycardia was observed during the second week of

drug administration. While chronic RAS inhibition is generally not associated with significant elevations of HR, the extent and speed of the BP fall when ALI was combined with either VAL or benazepril led to tachycardia in SHR.

Pharmacokinetics (and toxicokinetics)

Conventional ADME studies were conducted extensively using single oral dose, to determine the PK behaviour, the type of decay plasma concentration time curves and the linearity of kinetics. Moreover supporting information on repeated administration was derived from numerous toxicokinetic data available. The conventional ADME studies have been performed in rats and marmosets after single and repeated oral doses mainly measuring the parent compound which represents the predominant systemically available component in the plasma. ALI shows a low bioavailability after oral administration (absolute oral bioavailability in rats, marmosets and humans is 3.4, 16 and about 2%, respectively). The exact mechanism of the low bioavailability has not been elucidated. Doses administered in the TK studies were suitable to cover the range of doses as those studied in patients only in term of mg/kg. Plasma exposure however, based on dose normalized Cmax and AUC values, in relevant animals species was in many cases lower than in humans. However, it was demonstrated that safety ratios calculated on plasma ALI levels were less informative that safety margins based on faecal and mucosal concentrations. The plasma profile of rats and marmosets and humans shows a slowly terminal elimination half life at 23, 26 and 24 hours respectively with contribution of an entero-hepatic recirculation. There is no trend of Cl decrease with repeated doses. ALI is highly bound (approximately 92%) to plasma proteins in marmoset as determined from *in vitro* studies, and moderately bound (about 50%) in rats and humans. Most of the ALI seems mainly confined to the blood circulation. ALI is slightly metabolized in humans and marmosets (20%) and moderately in rodents (50%). The pattern of metabolites of ALI observed in liver microsomes of human, rat, and marmoset were qualitatively comparable. Primary metabolic pathways were oxidation. These oxidation processes had been found to be catalysed largely by CYP3A4/5 enzymes. The elimination of ALI from the body occurred almost exclusively via the faeces, whereas less than 12% of the administered dose was excreted with the urine, mainly as unchanged compound. Cyclosporin or ritonavir are advised to probe interactions involving MDR1, because these drugs block several metabolic and transport pathways. The applicant provided a commitment to submit results of the ALI-cyclosporin interaction trial. The terminal elimination half-lives (t½) for ALI was 23.1 hours in rats and 36 hours in marmosets. Independently of the route of administration, in all investigated species, excretion of radioactivity after p.o. dosing occurred mainly via bile/faeces and was virtually complete within 7 days. Available data of ALI kinetics after single and repeated administration in rats, monkeys and humans shows that **t**he plasma concentration-time profiles and the derived PK parameters showed substantial variability. However, when all studies were considered together, it is possible to conclude that generally the exposure increased in an approximately dose-proportional manner. Dose dependent or dose-linear exposure was more obvious in gavage studies than in dietary dose studies. No accumulation beyond steady state levels was found. The observed steady state kinetics indicates that no autoinduction of clearance processes occurred during the treatment. In three rat studies, and possibly in the mouse carcinogenicity study, some trend to higher exposure of females was seen. In the marmoset study, exposure of males may have been higher than that of females. Considering all data and the variability of the individual data, it was concluded that there was no general gender difference in exposure, in none of the investigated animal species. In mechanistic toxicology studies investigating the gastrointestinal irritation potential of ALI in rats and marmosets concentrations of ALI were measured in feces. The fecal concentrations of ALI increased roughly with dose. ALI was also measured in the lumen and mucosa of various intestinal segments in rats. The concentrations did not show significant differences between the intestinal segments. In summary, the usually safety margin calculation, comparing human and animals Cmax and AUC, is complicated by the high variability and low bioavailability, showing a plasma picture that could be probably different in patients, however more suitable safety margins are based on faecal and mucosal concentrations comparison between animals and humans.

Toxicology

- Single dose toxicity

These studies, as conducted with ALI, do not provide information regarding the signs and symptoms

of an acute intoxication in humans. A single species, the rat was used, treatment was carried out in a few animals by gavage at 1000 then at a 2000 mg/kg limit dose. As no alterations were found it was concluded that the acute oral toxicity (LD50) of ALI in rats is higher than 2000 mg/kg.

- Repeat dose toxicity

The daily administration of ALI to rats for 13-weeks was associated with premature deaths of a total of 17 animals treated at 200 or 600 mg/kg/day. Findings in these animals comprised respiratory disturbances and histopathological alterations in the respiratory tract. Decreased red blood cell parameters at the dose 600 mg/kg/day were attributable to the pharmacological action of the test item. Other histopathological changes in animals found dead or killed before schedule and in surviving animals comprised minimal to slight, dose-related hypertrophy/hyperplasia of the cecal mucosa at 200 and 600 mg/kg, which may showed a tendency towards reversibility after the 4-week recovery period. The dose of 60 mg/kg/day was identified as the no-observed-effect-level (NOEL) under the conditions of this study. The daily administration of ALI to rats for 26 weeks at doses up to 250 mg/kg/day resulted in dose dependent plasma toxicokinetics, mild clinical signs and slight reductions in body weight gain. The only histopathological change of note at 250 mg/kg/day was minor inflammatory and degenerative changes of the respiratory epithelium at the tracheal bifurcation and the lungs, which were associated with the noisy breathing noted clinically. On the basis of the above results, a NOAEL was defined as 50 mg/kg/day for rats treated with daily oral doses of ALI for 26 weeks. This study was extensively discussed during the evaluation process. Finally, it was considered by the CHMP to be suitable following the applicant explanations regarding the contamination of control and GLP compliance status of necroscopy and histopathology examinations.The daily administration of ALI for 13 weeks in marmosets up to 50 mg/kg/day, resulted in dose dependent plasma toxicokinetics, increased incidence of vomiting and post-dose salivation and frequent incidences of diarrhea were noted at the high dose. Blood alterations consisted of moderate reductions in RBCs, with minimal increases in reticulocyte counts. Mild to moderate increase in urea and/or creatinine concentration were occasionally found. There were no treatment-related changes during the electrocardiography and BP measurements. NOEL was not established for female animals in this study; the NOEL for male animals was 5 mg/kg/day. The daily administration of ALI for 39 weeks in marmosets up to 20 mg/kg/day resulted in no clinical signs observed throughout the experimental period that could be ascribed to treatment with ALI. Principal drug-related findings following oral administration of ALI included minimal to moderate microscopic renal lesions in animals of either sex at the high dose level of 20 mg/kg/day. These drug-related changes partly correlated with increased creatinine and blood urea values seen on occasions in animals receiving the test material at 5 and 20 mg/kg/day. Furthermore, the renal microscopic findings were associated with elevated kidney weights in high dose males at the terminal sacrifice. Changes proved to be fully reversible at the end of the recovery period. Based on these findings, the NOEL for this study was the low dose of 2 mg/kg/day. The toxicity profile in mice and rats was consisted of inflammatory and degenerative changes of the respiratory epithelium and hypertrophy/hyperplasia of the cecal mucosa. Diarrhea was the primary gastrointestinal effect of ALI in marmosets but there were no associated treatment-related histopathological findings.

- Genotoxicity

Most studies conducted to evaluate the genotoxic potential of ALI were compliant with current ICH Guidance, however, a non-GLP study was also performed early in the development program as a screen to assist in internal decision making. Studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with and without metabolic activation did not reveal any evidence for a genotoxic potential of ALI including studies in target organs identified in the rat carcinogenicity study. In a rat comet assay by the oral route at high doses (1000 mg/kg and 2000 mg/kg) ALI did not induce DNA migration in liver cells, colon cells and cecum mucosa cells of Crl:WI (Han) rats.

- Carcinogenicity

The carcinogenic potential of ALI was assessed following dietary administration to transgenic mice for 26 weeks or Wistar rats for 104 weeks. In the 104-week dietary carcinogenicity study in rats ALI in feed admixtures was not carcinogenic at doses up to 1500 mg/kg/day in females, and at doses up to 750 mg/kg/day in males. One colonic adenoma and one cecal adenocarcinoma were observed in males at 1500 mg/kg/day which were not statistically significant but were of uncertain relationship to ALI

treatment given the low incidence of these neoplasms in historical controls. No treatment-related tumors were observed. Diffuse hyperplasia in the small intestine and cecum as well as the focal atypical mucosal hyperplasia were noted in the colon at 1500 mg/kg/day. The main target organs for non-neoplastic lesions were small and large intestine, mesenteric lymphonode and gall bladder in both sexes, and reproductive organs and bone marrow in females. A dose of 250 mg/kg/day cannot be considered the NOEL under the conditions of the present study, because at the low dose used i.e. 250 mg/kg/day, the number of cecum mucosal hyperplasia increased of two fold and this was considered a certain adverse effect. The 5.3 section of the SmPC has been updated to reflect this aspect. In the 26-week dietary study in transgenic mice ALI did not induced treatment-related tumors. Diffuse hyperplasia in the small intestine and cecum as well as the focal atypical mucosal hyperplasia was noted in the colon at 1500 mg/kg/day. Hence the compound was not considered to show any carcinogenic potential in this study. The main target organs for non-neoplastic lesions were small and large intestine, mesenteric lymph node and gall bladder in both sexes, and reproductive organs and bone marrow in females. Based on AUC(0-24h) values, a trend to over-exposure of animals with increasing dose was seen in both males and females. M. A dose of 250 mg/kg/day can be considered as the NOEL under the conditions of the present study

- Reproduction Toxicity

Studies on fertility and early embryonic development, embryo-fetal and prenatal-postnatal development studies were performed in rats and rabbits by oral route.

Fertility and early embryonic development study in rats
The administration of ALI at doses of 50, 150 and 250 mg/kg/day elicited no parental toxicity and no AEs on fertility or early embryonic development in rats following oral gavage administration

Embryo-fetal development study in rats
The purpose of the study was to investigate any adverse effects of ALI on the pregnant rat and the development of the embryo and fetus consequent to exposure of the pregnant female from implantation to closure of the hard palate following administration by daily oral gavage dose levels of 0, 60, 300 or 600 mg/kg/day of ALI on gestation days 6 through to 17. There were no treatment-related maternal mortalities or effects on necropsy observations, and no effects of treatment on reproductive parameters, fetal body weights, sex ratios or fetal gross, visceral or skeletal examinations.

Embryo-fetal development range-finding study in rabbits
The purpose of this study was to provide information on dose selection for a subsequent embryo-fetal development study of ALI in rabbits. No treatment-related effects were noted in clinical or necropsy observations, food consumption, body weight parameters or evaluated reproductive parameters. Oral administration of ALI to pregnant rabbits on gestation days 7 through 20 produced no adverse effects at doses as high as 100 mg/kg/day.

Embryo-fetal development range-finding study in rabbits
The purpose of this follow-up study was to provide additional information on dose selection for a subsequent embryo-fetal development study of ALI (at dose levels of 200, 400, 600 or 1000 mg/kg/day) in rabbits. Treatment-related mortalities and sacrifices occurred at doses ≥400 mg/kg/day and no animals survived to terminal sacrifice in these groups. There were no effects on reproductive parameters or fetal gross examinations at 200 mg/kg/day, which was the only dose group to survive to terminal C-section.

Embryo-fetal development study in rabbits
The purpose of this study was to investigate any adverse effects of ALI (at doses of 0, 50, 100 or 200 mg/kg/day) on the embryonic and fetal development of the rabbit when administered orally, by gavage. The doses of 50 or 100 mg/kg/day elicited mild maternal toxicity in terms of slight reductions in body weight gain, food and water intake but without adverse effects on the embryo or fetus.

Pre- and postnatal development study in rats
The purpose of the study was to assess the effects of ALI (at doses of 50, 150 or 250 mg/kg/day) on

the pre- and postnatal development, including maternal function, of the rats receiving ALI orally, by gavage, from day 6 of gestation to day 21 post-partum, inclusive. The ALI administration to female rats during gestation and lactation elicited no maternal toxicity and no adverse effects on the development or reproductive performance.

In summary, effects on the fetal or pre/postnatal development are observed in animal studies with drugs affecting the RAS. Reproductive toxicity studies did not show such effects for ALI. Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofoetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats or 100 mg/kg/day in rabbits. Fertility, pre-natal development and post-natal development were unaffected in rats at doses up to 250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1 to 4 and 5 times higher, respectively, than the maximum recommended human dose (300 mg).

- Local tolerance

A series of studies has been performed in order to characterised to irritation potential of ALI. ALI did not increase the haemolytic potential at any concentration tested. It induced severe acute inflammation with ulceration in the trachea, larynx and bronchi, and bronchopneumonia in rats receiving intra-tracheal administration of a single 0.05 mL dose of the product at a concentration of 20 mg/mL. ALI administered by subcutaneous injection to rats at doses of 10, 30 or 100 mg/kg/day for 2 wk, induced sore formation, brown or black discoloration, swelling and erythema. The incidence and severity of these changes was broadly dose-related ranging from minimal at 10 mg/kg/day to moderate/severe at 100 mg/kg/day. Haematoma formation and necrosis were also recorded at the injection sites of animals treated at 30 or 100 mg/kg/day. ALI applied topically with occlusive bandage to non-abraded New Zealand white rabbit skin did not induce reactions. ALI was administered to three New Zealand white rabbits as single intravenous (i.v.), perivenous (p.v.) or intra-arterial (i.a.) injections (0.3 mL) as a 1 mg/mL solution and the animals has been observed for 7 days. After i.v. and p.v. administration a slight erythema was observed for up to 4 -5 days. Intra-arterial application resulted not only in slight erythema but also slight oedema for up to 4 days after treatment. In addition, slight to moderate haematomas developed at all injection sites after application and remained visible for between 4 and 7 days. These findings were present also with the vehicle and were common in the rabbit following i.v., p.v.or i.a. injection due to the low vascular stability of this animal. Macroscopic or microscopic evaluation of the sites of injection showed that there were no apparent differences between the local reactions at injection sites treated with ALI or vehicle. The administration of ALI at a concentration of 20 mg/ml into the trachea of anaesthetized rats resulted in rapid necrosis of the epithelium and after s.c. route in view of the severity of the observed findings, the animals were killed with the minimum of delay and the changes in the skin were confirmed at necropsy. It was concluded that the s.c. administration of it to rats at doses of 10, 30 or 100 mg/kg/day caused signs of minimal to marked local irritation at the injection sites, while the product appeared equally tolerated in the rabbit by the i.v., p.v. and i.a. routes of administration in comparison to control group.

Ecotoxicity/environmental risk assessment

The maximum anticipated daily dose of ALI is 300 mg. After oral intake, ALI is absorbed to 1.5 - 3%. The absorbed fraction is excreted largely unmetabolised, with an overall metabolism rate of less than 1% of dose. In total, > 99% of dose is being excreted as unchanged ALI into the environment. The available evidence suggests ALI to have a very low chronic toxicity towards aquatic organisms. The data further shows that soil and sediment can be regarded of low concern regarding the environmental exposure of ALI. The assessment therefore focused on the aquatic environment, i.e. sewage treatment plants, surface water and ground water. As demonstrated by the respective studies, ALI is not removed from the water phase by either hydrolysis or photolysis to a significant extent. The highest respective risk ratio is 0.00028, which is far below unity, and is the accepted risk ratio. The present assessment suggests that, based on the scientific information available, the placement of the foreseen amounts of ALI on the EU market does not constitute any significant risk to the environment. No specific labeling or risk mitigation measures are deemed necessary. As with all non-readily biodegradable human medicines, patients should be advised not to dispose of unused ALI via domestic sewage.

Discussion on the non-clinical aspects

The transgenic rats and marmoset models and methodology used are considered representative of the "state of the art" for RIs. The *in vivo* models for testing antihypertensive properties of human RIs are limited and not fully representative of the human disease. In particular the elevated species-specificity of renin rendered useless the classic preclinical models of HTN like SHR rats. This problem has been partially solved by using models in which RAS was activated either in the absence or in the presence of hypertensive state. Another source of difficulties in RIs preclinical studies is due to their low biovailability by oral route, which imposed subcutaneous continuous administration in sub-chronic studies. Administered through a subcutaneous route ALI caused marked cutaneous irritative damage so that some studies were stopped before the end of the treatment. From the studies submitted it is possible to conclude that ALI is a potent specific RI both *in vitro* and *in vivo*. After oral administration ALI exerts a strong and long-lasting BP lowering effect without any effect on HR. Safety pharmacology studies did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings during repeat-dose toxicity studies in animals were consistent with the known local irritation potential or the expected pharmacological effects of aliskiren. In spite of a single *in vitro* reassuring data showing a less sensitivity to ALI effects for human colon in comparison to rat colon, the overall *in vivo* data do not permit to completely rule out a risk of intestinal hyperplasia for humans after long-term administration. Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic mouse study. No carcinogenic potential was detected. One colonic adenoma and one cecal adenocarcinoma recorded in rats at the dose of 1500 mg/kg/day were not statistically significant. Although ALI has known irritation potential, safety margins obtained in humans at the dose of 300 mg during a study on healthy volunteers were considered to be appropriate at 9-11-fold based fecal concentrations or 6-fold based on mucosa concentrations in comparison with 250 mg/kg/day in the rat carcinogenicity study. Aliskiren was devoid of any mutagenic potential in the *in vitro* and *in vivo* mutagenicity studies. The assays included *in vitro* assays in bacterial and mammalian cells and *in vivo* assessments in rats. Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofoetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats or 100 mg/kg/day in rabbits. Fertility, pre-natal development and post-natal development were unaffected in rats at doses up to 250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1 to 4 and 5 times higher, respectively, than the maximum recommended human dose (300 mg). There are no data on the use of ALI in pregnant women. Aliskiren was not teratogenic in rats or rabbits. ALI was secreted in the milk of lactating rats.

4. Clinical aspects

Introduction

The development program consisted of efficacy and safety studies of ALI as monotherapy or in combination with other classes of anti-hypertensive drugs, including a diuretic (hydrochlorothiazide [HCTZ]), an ARB (VAL), an ACEI (RAM), CCB (AML) and BB (ATE). All completed studies were conducted in patients with essential HTN. Specific studies were conducted in hypertensive patients with diabetes, obesity, systolic HTN (in patients over 65 years of age), and severe HTN. Ongoing studies are being conducted in populations with diabetic nephropathy, CHF, and left ventricular hypertrophy, as well as in hypertensive patients unresponsive to other agents.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. The assessment of the clinical documentations did not raise concerns about compliance with GCP.

Pharmacokinetics

- Absorption

Following oral absorption, peak plasma concentrations of ALI are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Steady-state-plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose. Meals with a high fat content reduce C_{max} by 85% and AUC

by 70%. Administration following a high fat meal reduces the drug bioavailability by 60-70%. This means that assumption of drug under fasting condition increases the drug bioavailability approximately 3-fold, with respect to assumption with food. The effect of different meal contents, and in particular of a lighter breakfast, has not been investigated. Nor has been investigated whether the food effect is influenced by the drug product formulation.

- Distribution

Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. ALI plasma protein binding is moderate (47-51%) and independent of the concentration.

- Metabolism

The mean half-life is about 40 hours (range 34-41 hours). ALI is mainly eliminated as unchanged compound in the faeces (78%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration.

- Elimination

In all species, ALI is mainly eliminated as unchanged drug by biliary excretion into the faeces. Unchanged drug accounted for 77.5% of the faecal radioactivity but most of the unchanged drug eliminated with faeces was unabsorbed drug. The drug is eliminated mainly through the hepatobiliary route mainly as unchanged drug. Following intravenous administration, the mean plasma clearance is approximately 9 l/h. Terminal half-life was found to be 23.7 ± 7.6 hours after i.v. administration; similar values were found after oral administration. In subsequent studies, substantially higher mean values were found, ranging from 30 to 60 hours. Exposure to aliskiren increased more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6 fold increase in AUC and C_{max}, respectively. At steady state the nonlinearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Consequences of possible genetic polymorphism

Given the complex PK involving different transport systems there may be a genetic background for variability of PK and outliers. Yet, at present there is limited information on genetic polymorphism of transporters and the clinical relevance of transporter genetic variations is not well established. Therefore, and taking into account the data on efficacy and safety, investigation of the consequences of possible genetic polymorphism of transport systems were not considered necessary.

- Dose proportionality and time dependencies

The PKs is slightly nonlinear in the whole range of investigated doses probably due to the saturation of a pre-systemic elimination process. Systemic exposure after multiple dose administration of the 300 mg dose has been evaluated in several studies in healthy subjects. Time needed to reach steady-state could not be determined accurately; it was comprised between 7 and 12 days. Comparison between AUC following a single dose and AUC at steady-state indicate a 1.5 to 2-fold accumulation of ALI. Apparent clearance did not change with repeated administration.

- Special populations

Renal impairment

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Relative AUC and C_{max} of aliskiren in subjects with renal impairment ranged between 0.8 to 2 times the levels in healthy subjects following single dose administration and at steady state. These observed changes, however, did not correlate with the severity of renal impairment. No adjustment of the initial dosage of Rasilez is required in patients with mild to severe renal impairment, however caution should be exercised in patients with severe renal impairment.

Hepatic impairment

The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe liver disease. Consequently, no adjustment of the initial dose of Rasilez is required in patients with mild to severe hepatic impairment

Gender
The influence of gender on PKs was evaluated using data from 7 selected studies in healthy subjects. Data show that the mean AUC value in females was 31% higher than in males, the mean Cmax value 45% higher than in males. Pooled data analysis indicated that gender difference was caused by weight.

Race
One study compared PK and PD between Caucasians and Japanese following a single dose and at steady-state. There was an about 20% increase in the total exposure of ALI in the Japanese group compared to the Caucasians, which probably has no clinical consequence. This difference might be due to Cyp 3A4 or MDR1 polymorphism. Pooled data from 7 steady-state studies in healthy volunteers were used to investigate the effect of ethnic origin on PK. There were no apparent differences in PK parameters among ethnicities

Weight
Pooled data from 17 multiple dose studies were examined for the influence of weight on PK. The correlation analysis indicated a significant negative correlation between PK and weight. The correlations were not statistically significant when PK values were adjusted by weight. The actual impact of weight on PK was examined through regression analysis of PK on weight based on log-transformed data. It can be noted that with a 20%, 40% or 60% increment in weight, the predicted drop should be around 14%, 24% or 31%, respectively, in AUC and 18%, 30% or 40% in Cmax. These changes in PK are considered not clinically significant.

Elderly
The influence of age on ALI PK was investigated in a single-dose (300 mg) study in healthy subjects. Elderly subjects (16 subjects 65-75 and 13 subjects >75 years) were matched to young subjects (18 to ≤45 years) by gender, weight, and race. PK analysis showed a 50% increase in the total exposure and a 30% increase in Cmax, with no difference between subjects aged 65-74 and those aged ≥75 years. There was a trend toward an increase of half-life in the elderly group, with concomitant decrease of apparent clearance and apparent volume of distribution. The increase in drug exposure may be explained by several changes in pharmacokinetics usually occurring in the elderly due to age-related physiologic perturbations.

Type II diabetic patients
One study evaluated ALI PK (and PD) following a single 300 mg dose in 30 type II diabetic patients *vs.* 30 healthy volunteers, selected to match type 2 diabetes with regard to age, weight and race. The diabetic group was not homogenous with regard to sex and race. In addition, sex rates in the two groups slightly differed (male/female: 16/14 in diabetic patients, 13/17 in healthy volunteers). Diabetic patients were not homogenous with regard to the drug assumed for treating diabetes (metformin, glipizide, glybenclamide). At least one of these drugs, metformin, has been shown to influence ALI PK, decreasing Cmax and AUC. Because of the small sample size, this lack of homogeneity added further sources of variability, thus hampering the detection of differences due to the diabetic state. Healthy subjects had a 14% higher clearance than type 2 diabetic patients. The increase in CL/F led to slight increases in Cmax (13%), AUC0-t (13%) and t1/2 (10%) in type2 diabetic patients relative to healthy subjects. PD effect appeared to be lower in diabetic patients. In particular, Ang II levels were higher in diabetics 24 hours post-dose, but it is not known whether this difference was statistically significant.

- Pharmacokinetic interaction studies

As it is described in the SPC ALI has no known clinically relevant interactions with medicinal products commonly used to treat HTN or diabetes. Compounds that have been investigated in clinical PK studies include acenocoumarol, atenolol, celecoxib, pioglitazone, allopurinol, isosorbide-5-mononitrate, ramipril and hydrochlorothiazide. No interactions have been identified. Co-

administration of ALI with either valsartan (↓28%), metformin (↓28%), amlodipine (↑29%) or cimetidine (↑19%) resulted in between 20% and 30% change in C_{max} or AUC of aliskiren. When administered with atorvastatin, steady-state ALI AUC and C_{max} increased by 50%. Co-administration of ALI had no significant impact on atorvastatin, VAL, metformin or AML PK. As a result no dose adjustment for ALI or these co-administered medicinal products is necessary. Digoxin bioavailability may be slightly decreased by ALI. Preliminary data suggest that IRB may decrease ALI AUC and C_{max}. In experimental animals, it has been shown that P-gp is a major determinant of aliskiren bioavailability. Inducers of P-gp (St. John's wort, rifampin) might therefore decrease the bioavailability of aliskiren. The Applicant has planned an interaction study with cyclosporine, a P-gp inhibitor as a part of the follow-up measures. ALI does not inhibit the CYP450 isoenzymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A). ALI does not induce CYP3A4. ALI is metabolised minimally by the cytochrome P450 enzymes, therefore interactions with agents that inhibit, induce or are metabolised by these enzymes are not expected. As a result no dose adjustment for ALI is necessary. Based on experience with the use of other substances that affect the RAS, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other substances that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium. If co-medication is considered necessary, caution is advisable. When ALI was co-administered with furosemide, the AUC and C_{max} 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 underutilisation in clinical situations of volume overload. Co-administration of ketoconazole 200 mg twice daily with ALI resulted in a 1.8-fold increase in plasma levels of ALI (AUC and C_{max}). The change in plasma levels in the presence of ketoconazole is expected to be within the range that would be achieved if the dose were doubled; ALI doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be safe in well-controlled clinical trials. Preclinical studies indicate that ALI and ketoconazole co-administration enhances ALI gastrointestinal absorption and decreases biliary excretion. The effects of ALI on warfarin pharmacokinetics have not been evaluated. Meals with a high fat content have been shown to reduce the absorption of ALI substantially. Interaction with isosorbide-5-mononitrate: the study showed a trend towards reduction of isosorbide-5-mononitrate AUC.

Pharmacodynamics

- Mechanism of action

All agents that block the RAS, including RIs, inhibit the negative feedback loop, leading to a compensatory rise in RC. When this rise occurs during treatment with ACEIs and ARBs, it is accompanied by increased levels of PRA. The decreasing effect of ALI on PRA is maintained despite the compensatory increase in RC.

- Primary and Secondary pharmacology

PD has been poorly investigated. The relevant information comes from a single dose-finding study. ALI at doses of 40-640 mg dose-dependently inhibited PRA following single dose administration and at steady state. A concomitant increase of RC was observed with doses ≥ 80 mg. Maximal inhibition of PRA was reached within one hour of administration. PRA was inhibited for up to 24 hours at doses of 80 mg and higher. ALI dose-dependently reduced plasma Ang I and Ang II levels following single dose administration and at steady state. ALI at the 160 mg dose suppressed Ang II levels to a similar extent as enalapril 20 mg with somewhat greater suppression at the 640 mg dose. The observed changes in PRA, Ang I and Ang II provided direct evidence for RAS blockade. Urinary aldosterone excretion over 24 hours was reduced by ALI at doses of 80-640 mg following single dose administration (up to 56%) and at steady state (up to 31%). Treatment with ALI reduced plasma aldosterone concentrations following single dose administration at 3 hours post-dose. This effect persisted for up to 24 hours at the highest dose (640 mg). The suppression of aldosterone with ALI is attributable to a decrease in Ang II-mediated activation of the AT1 receptor, which triggers secretion of aldosterone, providing additional evidence for RAS blockade. PRA and RC were also collected in 2 of the PLA-controlled studies, and in 2 of the long-term studies (Study 2306 and Study 2302) as PD measures. Data indicate that during treatment with ALI, the increase in RC does not overcome the drug's effect in decreasing PRA or BP whether ALI is used as monotherapy or in combination with other antihypertensive agents. PD was also studied in Type II diabetic subjects, in comparison with

healthy subjects after single dose (300 mg)**.** PRA was significantly inhibited in both healthy subjects (60 %) and in patients with type 2 diabetes (72%). Baseline PRA was higher in patients with diabetes (1.8 ± 3.2 ng/mL/h) compared to the healthy subjects (1.2 ± 0.9 ng/mL/h). RC increased by 8.6 and 9.5-fold in diabetics and healthy subjects, respectively. Baseline RC was also higher in diabetic patients. One study compared PRA inhibition under fasted and fed status after a single dose (150 mg), formulated as two different film-coated tablets. ALI given as the film coated tablet after food resulted in a less pronounced decrease in PRA compared to the fasted state, with 50% of subjects showing detectable levels of PRA at all time-points following dosing, but no statistical analysis was performed. No bibliographic reference was found showing that food has an acute effect on PRA. Also, the relationship between PRA levels and the antihypertensive effect has not been established.

Relationship between plasma concentration and effect
The PK/PD relationship has been very poorly investigated. The PRA-ALI concentration plots show a flat anticlockwise hysteresis loop for PRA at steady state, suggesting that activity increases when the drug is distributed to the kidney. The Ang II-ALI concentration profile is similar to the PRA-ALI profile, but there is no flattening following multiple dose administration.

Clinical efficacy

- Introduction

All efficacy studies but one (1201) were done in 3 or more countries and included various ethnic groups. Study 1201 was limited to Japanese individuals. All studies had a randomised, double-blind, parallel-group design and included washout (WO) and/or RI periods. Inclusion criterium was a diagnosis of mild-to-moderate EHTN for all of the studies but one (2303). Study 2303 was specifically designed on severe EHTN.

Data for comparison of aliskiren as a single drug vs PLA were collected in five studies (2201, 2203, 2204, 2308, and 1201). These studies were done with use of different ALI doses for analyses on dose-response relationship. Data for analyses on the ALI effects in combination with other registered antihypertensive drugs (comparison of ALI+other drug vs other drug alone) were collected in six studies (2203, 2204, 2305, 2307, 2309, and 2304). Data for comparison of ALI vs other registered antihypertensive drugs (ALI vs another drug) were collected in nine studies (2201, 2203, 2303, 2307, 2309, 2324, 2323, 2306, and 2304). The comparison was between regimens based on the administration of one drug in five studies (2201, 2307, 2323, 2324, and 2304), between regimens based on the administration of more drugs in the remaining studies (2203, 2303, 2309, 2323, and 2306). Other registered antihypertensive drugs included in the studies were two different ARB (IRB and VAL), two different ACEi (LIS and RAM), one CCB (AML), one diuretic (HTC), and one BB (ATE).

Active treatment with ALI lasted 8 wk for eight studies that included all the five studies vs PLA. In the other four studies, active treatment lasted between 6 and 26 wk. Analyses of duration of withdrawal (DW) effects were included in four studies (2201, 2308, 1201, and 2306). DW lasted between 4 d and 4 wk. All studies included male and female patients. Age distribution was relatively similar across all studies (median or mean age of about 55 y, age range including young and older ages) with exception of study 2324 that was specifically designed for analyses on individuals with ages ≥65y. The primary end-point was the change induced by active treatment in msDBP in ten of the twelve studies. Two studies focused on msSBP: the 2303 study in severe EHTN and the 2324 study in individuals with age ≥ 65y.

Results of studies on efficacy will be described focusing on three points: dose-response relation and effects of ALI as a single antihypertensive drug (comparison vs PLA of ALI at different doses); effects of ALI in combination with other antihypertensive drugs (comparison of ALI + other drug vs other drug alone); comparison of ALI to other drugs (comparison of ALI vs other drug between regimens based on the use of one or more drugs).

Brief overview of the clinical studies is presented in table 1 below:

Study Nr.	Nr. of centers	Design	Study Posology	Study Objective	Subjects by arm/ entered/ completed	Duration	Gender M/F; age	Dg/ Incl. criteria	Primary Endpoint
1201 5.3.5.1 Part 5	29	Randomized, placebo-controlled, 4 arm dose-finding	75 mg, 150 mg, 300 mg ALI/day; placebo	Efficacy/ safety/ dose finding	455 entered; 434 (104-111/arm) completed:	8 weeks	males (70-80%), mean age: 53.5 ys	EHTN (m-t-m)	Change in msDBP
2308 5.3.5.1. Part 4	68	Randomized, double-blind, placebo-controlled, parallel group	150 mg, 300 mg, 600 mg ALI/day - placebo	Efficacy/ safety/ dose finding	672 entered; 608 (163-167/arm completed	8 weeks	Males (58-63%), mean age: 52-54 ys (10-16% over 65 ys)	EHTN (m-t-m)	Change in msDBP
2203 5.3.5.1 Part 2	94	Randomized, double-blind, placebo-controlled	75, 150, 300 mg ALI/day; valsartan 80, 160, 320 mg; ALI/valsartan 75/80, 150/160, 300/320 mg, valsartan/HCTZ 160/12.5 mg; placebo	Efficacy/ safety of ALI (compared with valsartan combinations)	1123 entered; 1034 (58-177/arm) completed	8 weeks	Males 55.9%, median age: 57 (range: 19-88 ys)	EHTN (m-t-m)	Change in msDBP
2327 5.3.5.1 Part 2	312	Randomized, double-blind, placebo-controlled, parallel group	150, 300 mg ALI/day; valsartan 160, 320 mg; ALI/valsartan 150/160, 300/320 mg; placebo	Efficacy/ safety of ALI (compared with valsartan combinations)	1797 entered; 1601 (384-412/arm) completed	8 weeks	Males 60.89%, median age: 52 (range: 24-84 ys)	EHTN (m-t-m)	Change in msDBP
2204 5.3.5.1 Part 3	207	Randomized, double-blind, placebo-controlled, parallel group	75, 150, 300 ALI mg/day; HCTZ 6.25, 12.5, 25 mg; ALI/ HCTZ 150/6.25, 150/12.5, 150/25 mg; ALI/ HCTZ 300/12.5, 300/25 mg; PLA	Efficacy and safety of ALI (compared with combinations with HCTZ)	2776 entered; 2558 (159-179 per arm) completed	8 weeks	Males: 54.8%; mean age: 55 ys (range: 19-87 ys)	EHTN (m-t-m)	Change in msDBP
2305 5.3.5.1 Part 7	81	Randomized, double-blind, parallel group	ALI/amlodipine 150/5 mg; amlodipine 5, 10 mg	Efficacy of combination therapy	545 entered; 523 (170-182/arm)	4 weeks amlodipine +6	Males: 53.6%, mean age	EHTN (m-t-m; not fully response to	Change in msDBP

					completed	weeks combined	53 ys	amlodipine)	
2307 5.3.5.1 Part 8	125	Randomized, double-blind, parallel group	150 mg ALI (with dose escalation to 300 mg); RAM 5 or10 mg; ALI/RAM 300/10 mg	Efficacy of combination therapy	837 entered; 742 (246-249/arm) completed	8 weeks	Male: 58.7%, mean age: 59.8 ys (range: 26-85)	EHTN (m-t-m) with diabetes mellitus	Change in msDBP
2309 5.3.5.1 Part 9	69	Randomized, double-blind, parallel group	300 mg ALI + 25 mg HCTZ; irbesartan/HCTZ, amlodipine/HCTZ; HCTZ	Efficacy/safety of combined therapy	489 entered; 448 (109-115/arm) completed	12 weeks	Males: 43.6%), mean age: 54.1 ys	EHTN (m-t-m) with obesity, not adequately responsive to HCTZ)	Change in msDBP
2303 5.3.5.1 Part 6	26	Randomized, double-blind, parallel group	150-300 mg ALI ± HCTZ vs 20-40 mg lisinopril ± HCTZ	Efficacy of combined therapy	183 entered; 165 (54-111/arm) completed	8 weeks	Male: 56.8%, mean age: 55 ys)	Uncomplicated severe EHTN	msDPB (vs baseline compared within arms)
2324 5.5.5.1 Part 10	58	Randomized, double-blind, parallel group	75, 150, 300 mg ALI / 10 mg lisinopril	Efficacy/ safety	355 entered; 330 (79-88/arm) completed	8 weeks	Male: 40.3%, mean age: 73.5 ys (range: 65-90 ys)	EHTN (m-t-m in aged (≥65 ys) persons	Change in mean 24-h SBP (ABPM)
2306 5.3.5.1 Part 12	93	Randomized, double-blind, parallel group	150 mg, 300 mg ± HCTZ vs. 5,10 mg RAM ± HCTZ	Long-term efficacy/ safety compared to RAM (±HCTZ)	842 entered; 687 (338-349/arm) completed	26 weeks + 4 weeks withdrawal	Male: 57%, mean age: 53.3 ys)	EHTN (m-t-m)	Change in msDBP
2323 5.3.5.1 Part 11	173	Randomized, double-blind, parallel group	150 mg, 300 mg ALI ± 5/10 mg amlodipine vs 12.5/25 mg HCTZ ± 5/10 mg amlodipine	Long term efficacy/ safety, compared to HCTZ	1124 entered; 978 (469-509/arm) completed	26 weeks + 26 weeks extension	Male: 54.1-56%, median age: 56-57 ys	EHTN (m-t-m)	Change in msDBP
2302 5.3.5.2	185	Randomized, open-label	150 and 300 mg ALI (mono), 300 mg ALI + 12.5/25 mg HCTZ (combo)	Long-term safety/efficacy of mono and combo therapy	1951 entered (open label); 1625 (659-966/arm) completed	52 weeks	Male: 50.3-55.3%, mean age: 54.8-57 ys	EHTN (m-t-m)	Safety/ change in msDBP
2302E	78	Extension of	300 mg ALI + 25 mg	Long-term	198 entered;	16 weeks	Male:	EHTN (m-t-	Long-term

1		#2302 (Randomized open-label)	HCTZ	safety	189 completed		49.5%, mean age: 57.2 ys	m)	safety/ change in msDBP
2201 5.3.5.1 Part 1	56	Randomized, double-blind, PLA-controlled, parallel group	150, 300, 600 mg ALI (and 150 mg irbesartan)	Efficacy, also compared with irbesartan	ITT: 649, PP: 559	8 weeks	Male: 50.2%, median age: 56	EHTN (m-t-m)	msDBP (vs baseline compared with arms)
2304		Randomised, double blind	300 mg ALI vs ATE 100mg/ALI300 mgvs ATE 100m	Efficacy of combined therapy	23/arm	6 weeks + 6 weeks		EHTN (m-t-m)	Change in nsDBP

METHODS

Study Participants

All studies include participants with a large range of age and of both sexes. Data are more numerous for men than women in all studies. Age distribution was relatively similar across all studies (median or mean age of about 55 y, age range including young and older ages) with exception of study 2324 that was specifically designed for analyses on individuals with age ≥65y. Studies in special populations were done for diabetes mellitus (Study 2307), obesity (Study 2309), and older ages (Study 2324). The studies included pre- and post- menopausal women, and patients with BMI<20 kg/m^2. In all studies, the presence of a renal disorder was an exclusion criteria (as a secondary form of HTN and/or a condition altering the kinetics of any medicinal product). Prevalence of overweight/obesity likely differed among participants in pivotal studies as suggested by the difference in the median BMI. This difference was a major confounder in the analysis of results since life-style are important for BP regulation and blood response to antihypertensive treatment.

Treatments

All study medication (investigational and reference material) was provided by the Applicant as capsules packaged in bottles labelled with batch and formulation numbers. Each dose was taken with water at approximately 8:00 a.m., except on the morning of the office/clinic visit. No instruction was given for fasting/fed conditions.

Objectives

With the exception of Study 2303, studies were performed in mild-to-moderate EHTN. The efficacy was assessed: (I) in monotherapy, compared with PLA, (II) in combined therapy compared with PLA, (III) in combined therapy compared with a reference drug, (IV) in combined therapy compared with a reference drug in combination. In one study (2303), the efficacy of ALI was assessed in uncomplicated severe HTN. In this study the efficacy of ALI with or without HCTZ was compared with RAM with or without HCTZ. In this study, however, the number of patients treated with ALI was relatively small. One study (2324) analysed the efficacy of ALI in elderly (age over 65 years) patients with mild-to-moderate EHTN. The efficacy of ALI in patients with diabetes mellitus was measured in Study 2307. In the majority of studies patients with obesity, and metabolic syndrome and/or diabetes were included.

Outcomes/endpoints

The primary end-point was the change induced by active treatment in msDBP in ten of the twelve studies. Two studies focused on msSBP: the 2303 study in severe EH and the 2324 study in individuals with age ≥ 65y. Five studies investigated the effects of ALI withdrawal using ALI as a single drug (2201, 2308, 1201, and 2306). Primary endpoint was in almost all studies the change in msDBP as a 'surrogate endpoint'. BP was measured according to *CHMP Note for Guidance on Clinical Investigation of Medicinal Products in the treatment of hypertension* (CPMP/EWP/238/95/Rev2). In none of the studies there were mortality, morbidity data analyzed or target organ damage assessed. In the 'diabetes' study (2307), the microalbuminuria was measured, but the study was too short to obtain significant changes. Key secondary endpoints were changes in systolic BP, proportion of patients with successful response (diastolic BP <90 mmHg or ≥10 mmHg reduction from baseline), proportion of patients with BP control (<140/90), effects on plasma renin concentration and activity.

Sample size

Overall, the studies completed the protocol in 9476 individuals out of the 10,743 randomised individuals. Among individuals with completed protocols, 3,507 were treated with aliskiren as a single antihypertensive drug, 2,684 were treated with aliskiren in combination with other antihypertensive drugs, 2,851 were treated with other registered antihypertensive drugs, and 664 were treated with PLA. Percent of completed patients was higher in studies lasting 6-8 wk than in studies lasting 12-26 wk.

Randomisation
Was performed using a randomization list produced by the Applicant using a validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio. The randomization scheme was reviewed by a Biostatistics Quality Assurance Group and locked by them after approval.

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 were blinded to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) randomization data were kept strictly confidential until the time of unblinding and were not accessible by anyone else directly involved in the study except for those individuals as defined in (2) the identity of the treatments were concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor. If a comparator drug was alos used, a double-dummy design was used because the identity of the study drugs could not be disguised due to their different forms. Unblinding only occurred in the case of patient emergencies and at the conclusion of the study.

Statistical methods
The primary efficacy variable (mean change from baseline to endpoint in msDBP at trough in the ITT population) was analyzed by a pre-specified two-way analysis of covariance (ANCOVA) with treatment and region as factors, and baseline as a covariate. A statistical adjustment for multiple comparisons using Dunnett's procedure was used for studies including multiple ALI doses. The key secondary efficacy endpoint, msSBP, was analyzed similarly. The proportion of responders and the control rate were analyzed by means of a logistic regression model with treatment and region as factors, and baseline msDBP as a covariate. In many cases pairwise comparisons between parameters of each ALI dose and PLA were also done. When comparing ALI to other antihypertensive drugs the statistical hypothesis was non-inferiority, if non-inferiority was statistically detected, a superiority test was performed. This is acceptable; however, in the majority of the active-controlled studies, treatment was too short (8 weeks) to compare antihypertensive effects. Moreover, due to the (m-to-m EHTN) population, there was a significant PLA effect. Therefore, in all active-controlled studies, at least in all short-term studies, PLA control should have been included.

RESULTS

Recruitment
Patients with m-to-m EHTN were recruited in American, European, and Asian countries. Patients who were on antihypertensive drug treatment entered a single-blind, PLA, run-in period after wash-out from previous treatment. Patients who were not on any antihypertensive drug treatment entered directly into the run-in period. After the run-in period, patients who met the inclusion/exclusion criteria were randomised to investigational or reference treatment.

Conduct of the study
After randomization, patients entered a double-blind study with control of concomitant therapies, measurement of treatment compliance; standardized morning visits at given time-points. The visits included medical examinations and lab tests in agreement with GCP. Results of medical examinations (physical conditions, ECGs, anthropometrical data, etc.), adverse events, pregnancies, and lab tests were monitored during the studies.

Baseline data
Baseline characteristics were similar for the different groups of the study. Median BMI was substantially lower in one study (1201) than in the remaining studies suggesting a lower prevalence of overweight/obesity. Prevalence of overweight (BMI 25-25.99 kg/m^2) was not reported in any study.

Prevalence of menopausal status was not reported in any study. Prevalence of treatment with estrogens was reported. This information is relevant since estrogens affect the RAS.

Numbers analysed
Number of patients/arm is adequately reported for each study with detailed information on patients not completing the study protocol.

- **Dose response studies and BP effects of ALI as a single drug**

Table 2 summarizes the results of 8-wk studies on clinical efficacy investigating the dose-response relationship and the effects of ALI as a single drug in comparison to PLA. Thus, data are shown as mean difference vs PLA in the BP change induced by ALI from baseline to endpoint (intent-to-treat population). The mean difference is negative (with minus sign) when the BP reduction induced by ALI was greater than the BP reduction induced by PLA. The mean difference is positive in the opposite case.

Table 2 – BP effects of ALI as a single drug in m-to-m EHTN: mean BP change from baseline to endpoint corrected for effects of PLA				
Study 2201				
	ALI dose			
	75 mg	150 mg	300 mg	600 mg
Difference vs PLA in msDBP change, mm Hg	---	-2.6*	-5.6***	-5.0***
Difference vs PLA in msSBP change, mm Hg	---	-6.1***	-10.5***	-10.4***
*P vs PLA: *<0.05, **<0.01, ***<0.001*				
Study 2203				
	ALI dose			
	75 mg	150 mg	300 mg	600 mg
Difference vs PLA in msDBP change, mm Hg	-1.7^{ns}	-1.7^{ns}	-3.7***	----
Difference vs PLA in msSBP change, mm Hg	-2.2^{ns}	-2.1^{ns}	-5.0***	----
*P vs PLA: ^{ns}not significant, *<0.05, **<0.01, ***<0.001*				
Study 2204				
	ALI dose			
	75 mg	150 mg	300 mg	600 mg
Difference vs PLA in msDBP change, mm Hg	-1.8*	-2.0*	-3.3***	---
Difference vs PLA in msSBP change, mm Hg	-1.9^{ns}	-4.8***	-8.3***	---
*P vs PLA: ^{ns}not significant, *<0.05, **<0.01, ***<0.001*				
Study 2308				
	ALI dose			
	75 mg	150 mg	300 mg	600 mg
Difference vs PLA in msDBP change, mm Hg	----	-5.4***	-6.2***	-7.6***
Difference vs PLA in msSBP change, mm Hg	----	-9.3***	-10.9***	-12.1***
*P vs PLA: *<0.05, **<0.01, ***<0.001*				
Study 1201				
	ALI dose			
	75 mg	150 mg	300 mg	600 mg
Difference vs PLA in msDBP change, mm Hg	-4.0***	-4.5***	-7.5***	----
Difference vs PLA in msSBP change, mm Hg	-5.7***	-5.9***	-11.2***	----
*P vs PLA: *<0.05, **<0.01, ***<0.001*				
Study 2327				
	ALI dose			
	75 mg	150 mg	300 mg	600 mg
Difference vs PLA in msDBP change, mm Hg	----	----	-4.95***	----
Difference vs PLA in msSBP change, mm Hg	----	----	-8.40***	----
*P vs PLA: *<0.05, **<0.01, ***<0.001*				

All the studies were done in mild-to-moderate (m-to-m) EHTN patients. The 75 mg dose was investigated in three studies and induced a consistent BP reduction (significant for msSBP and msDBP) only in study 1201, not in studies 2203 and 2204. Study 1201 was with low power and low representativity because it was with the lowest number of patients and was limited to individuals from Japan. As compared to patients of other studies, patients of study 1201 differed substantially also for their anthropometrical characteristics (median BMI 25.1 kg/m^2 vs median BMI >28 kg/m^2 for patients of other studies). Thus, a BP reduction for the 75 mg dose cannot be considered as proved. The 600 mg dose induced a BP reduction smaller than the 300 mg dose in one of the two studies with complete data (2201). Thus, the evidence is not reached that an increase in the dose from 300 to 600 mg induces an increase in the BP reduction. The trend between ALI dose and BP reduction was not linear in study 2201 (range of dose 150-600 mg) and in study 2203 (range of dose 75-300 mg). Altogether, the results support the existence of a dose-response relationship only for doses in the range 150-300 mg because, after correction for PLA effects, the BP reduction was greater for dose 300 mg than for dose 150 mg in all the five studies. In all studies, the BP reduction induced by both doses was stable after 4-wk treatment and slowly disappeared after DW. The 150 mg dose did not induce a significant BP reduction in study 2203. This negative result cannot be explained by a limited power of the study as per the pre-study calculations and the finding of a significant BP reduction in similar studies with lower power (2201 and 1201). Data indicate a large inter-study variability in the BP reduction not only for the 150 mg dose but also for 300 mg dose. This variability deserves further data analysis. It could reflect variability among different study groups in the patients' characteristics or in the ALI bioavailability (food effect on ALI absorption: no breakfast vs light breakfast vs full breakfast). For the DW period, study results show that msDBP and msSBP slowly increased over the value found at the end of active treatment. The BP increase was detectable already 4 d after DW (study 2201) and stayed constant up to 4 wk (study 2306).
Study 2308 differed from the above discussed studies with regards to the definition of the EHTN, which was defined as a msDBP ≥ 95 mm Hg and < 110 mm Hg. This is not a general definition of EHTN. That is why despite the majority of patients had systolic and diastolic HTN the results of the study cannot be extrapolated to patients with isolated systolic HTN, since in this study, as in the majority of the presented clinical studies, the inclusion criteria were limited to patients with diastolic arterial HTN. The primary hypothesis of the study was that ALI was superior to PLA in reducing msDBP. All ALI treatment groups significantly reduced ambulatory BP better than PLA during both day- and nighttime as measured in ambulatory blood pressure monitoring (ABPM). The responder rates (when "responder" was defined as a patient with a msDBP < 90 mm Hg and/or a ≥ 10 mm Hg reduction from Baseline) for the ALI groups were significantly superior to PLA. Given the inclusions criteria in this study according to the CHMP the responder rate should include only patients in whom DBP achieved values lower than 90 mm Hg.

In summary, clinical studies represent convincing evidence that ALI, used as monotherapy is an effective antihypertensive medicinal product for the short term period and for longer periods (6 months to 1 year). There was a variability in the BP effects among different studies. The variability in the BP effects might reflect a variable bioavailability of the medicinal product as it was administered without respect to fast/fed conditions. The long-term efficacy of aliskiren as a single antihypertensive drug was investigated as per relevant guideline.

- **Effects of ALI in combination with other drugs**

Table 3 summarizes the results of studies on clinical efficacy investigating the use of ALI in combination with other antihypertensive drugs. In these studies, the clinical efficacy is evaluated comparing the effects of the combination ALI+other drug to the effects of the other drug alone used as reference. Data are shown as mean difference vs other drug in the BP change induced by the combination ALI+other drug from baseline to endpoint. The mean difference is negative (with minus sign) when the BP reduction induced by the combination ALI+other drug was greater than the BP reduction induced by the reference drug, positive (with plus sign) in the opposite case.

Table 3 – BP effects of ALI in combination with other drugs: mean BP change induced by ALI from baseline to endpoint compared to effects of other drug alone			
	ALI dose		
	75 mg	150 mg	300 mg
Study 2203 – comparison ALI+VAL vs VAL alone **8 wk, m-to-m EHTN**			
VAL 80 mg			
Difference vs other drug alone in msDBP change, mmHg	-1.3^{ns}	----	----
Difference vs other drug alone in msSBP change, mmHg	-3.2^{ns}	----	----
VAL 160 mg			
Difference vs other drug alone in msDBP change, mmHg	----	-1.1^{ns}	----
Difference vs other drug alone in msSBP change, mmHg	----	-1.1^{ns}	----
VAL 320 mg			
Difference vs other drug alone in msDBP change, mmHg	----	----	-1.7^{ns}
Difference vs other drug alone in msSBP change, mmHg	----	----	-1.5^{ns}
P vs other drug alone: ^{ns}not significant			
Study 2204 – comparison ALI+HCT vs HCT alone **8 wk, m-to-m EHTN**			
HCT 6.25 mg			
Difference vs other drug alone in msDBP change, mmHg	-1.7*	-1.3^{ns}	----
Difference vs other drug alone in msSBP change, mmHg	-3.3*	-4.4**	----
HCT 12.5 mg			
Difference vs other drug alone in msDBP change, mmHg	-1.0^{ns}	-1.8*	-3.8***
Difference vs other drug alone in msSBP change, mmHg	-1.7^{ns}	-3.7**	-5.9***
HCT 25 mg			
Difference vs other drug alone in msDBP change, mmHg	-2.1*	-3.3***	-4.9***
Difference vs other drug alone in msSBP change, mmHg	-3.0*	-5.2***	-6.9***
*P vs other drug alone: ^{ns}not significant, *<0.05, **<0.01, ***<0.001*			
Study 2305 – comparison ALI+AML vs AML alone **6 wk, m-to-m EHTN**			
AML 5 mg			
Difference vs other drug alone in msDBP change, mmHg	----	-3.6***	----
Difference vs other drug alone in msSBP change, mmHg	----	-6.0***	----
*P vs other drug alone: ***<0.001*			
Study 2307 – comparison ALI+RAM vs RAM alone **8 wk, diabetics T1/T2 m-to-m EHTN**			
RAM 10 mg			
Difference vs other drug alone in msDBP change, mmHg	----	----	-2.1**
Difference vs other drug alone in msSBP change, mmHg	----	----	-4.6***
*P vs other drug alone: **<0.01, ***<0.001*			
Study 2309 – comparison ALI+HCT vs HCT alone **8-wk time point (12-wk study), obese m-to-m EHTN**			
HCT 25 mg			
Difference vs other drug alone in msDBP change, mmHg	----	----	-4.0***
Difference vs other drug alone in msSBP change, mmHg	----	----	-7.2***
*P vs other drug alone: *<0.05, **<0.01, ***<0.001*			
Study 2304 – comparison ALI alone vs ALI+ATE vs ATE alone			
Difference vs other drug alone in msDBP change, mmHg	----	----	-0.49^{ns}
Difference vs other drug alone in msSBP change, mmHg	----	----	-3.02*
Study 2327 - Comparison ALI alone vs ALI+VAL			

VAL 320 mg			
Difference vs other drug alone in msDBP change, mmHg	----	----	-2.47***
Difference vs other drug alone in msSBP change, mmHg	----	----	-4.44***
*P vs other drug alone: *<0.05, **<0.01, ***<0.001*			

These studies investigated doses of ALI ranging between 75 and 300 mg, not 600 mg.

Results of study 2203 show that, after 8-wk of treatment in m-to-m EHTN, the BP reduction induced by the combination ALI+VAL is not greater than the BP reduction induced by VAL alone. This negative finding is consistent at various doses of both drugs. The study cannot give information on ALI doses 150-300 mg in combination with low dose VAL (80 mg). Thus, ALI did not induce significant BP effects when used in combination with VAL in m-to-m EHTN in this preliminary study.

Results of a second study 2327 with a robust design to assess the ALI/VAL combination, where ALI was studied alone and in combination with VAL indicate that the combination of ALI and VAL reduced ms DBP and ms SBP more than either ALI or VAL monotherapy.

Results of study 2204 show that, after 8-wk treatment in m-to-m EHTN, the BP reduction induced by the combination ALI+HCT is greater than the BP reduction induced by HCT alone. This trend is detectable in all arms of the study but becomes consistently significant (for DBP and SBP) with use of regimens combining ALI doses of 150-300 mg with HCT doses of 12.5-25 mg. The difference in the BP reduction between ALI+HCT and HCT alone tends to be greater with increasing the ALI dose for any given HCT dose as well as with increasing the HCT dose for any given ALI dose. The findings appear independent of PLA effects because HCT alone (12.5-25 mg) reduced BP more than PLA. Thus, when used in combination with HCT, ALI induces a further and significant BP reduction over the HCT effects.

Results of study 2305 show that, after 6-wk treatment, the BP reduction induced by the combination ALI+AML is greater than the BP reduction induced by AML alone. The lack of a PLA group impeached to differentiate the effects of 5 mg AML from a PLA. In fact, the results could reflect a BP reduction induced by ALI over the BP reduction induced either by AML or by a PLA. A role for a PLA effect is likely for two reasons. First, the BP reduction induced by 5 mg AML alone was modest and similar to BP reduction induced by PLA in other studies. Second, the 6-wk duration of active treatment was not long enough to hypothesize an attenuation of a PLA effect. In patients who did not adequately respond to 5 mg of the calcium channel blocker AML, the addition of ALI 150 mg had a blood-pressure-lowering effect similar to that obtained by increasing AML dose to 10 mg, but had a lower incidence of oedema (ALI 150 mg/AML 5 mg 2.1% vs. AML 10 mg 11.2%). Thus, the study does not prove that, when used in combination with AML, ALI induces BP reduction only in patients non-responding to AML.

Results of study 2307 in diabetic hypertensives show that, after 8-wk treatment, the BP reduction induced by the combination ALI+RAM is greater than the BP reduction induced by RAM alone. The study does not include a PLA group. A role for a PLA effect does not seem likely because the BP reduction induced by RAM alone was greater to the BP reduction induced by PLA in other studies enclosed in this submission. Thus, the study suggests but does not prove that, when used in combination with RAM, ALI induces in diabetic hypertensives a further BP reduction over the RAM effects. Furthermore the Study 2307 combines diabetic patients with type 1 and 2 pooled, a subset analysis of type 1 and type 2 should be performed

Results of study 2309 in obese hypertensives show that, after 8-wk treatment, the BP reduction induced by the combination ALI+HCT is greater than the BP reduction induced by HCT alone. These results confirm the evidence in favour of the combination ALI+HCT investigated also by study 2204. The lack of a PLA group does not appear important because study 2204 shows that the synergistic effect of the combination ALI+HCT was independent of PLA effects. Thus the study confirms that, when used in combination with HCT, ALI induces a further and significant BP reduction over the HCT effects.

Results of study 2304 where ALI was studied alone and in combination with ATE indicate that the combination of ALI and ATE reduced msDBP more that ALI alone but not more than ATE alone. However, the combination reduced systolic BP more than either ALI or ATE monotherapy.

Altogether, the results support the view that other antihypertensive agents affect the efficacy of ALI. However, none of these studies was done with use of a crossover design. Thus, the possibility cannot be excluded that inter-group differences in the individual factors responsible for high BP level (volume expansion, high adrenergic tone, renin- angiotensin system activatio, etc.) biased the BP response to treatment in the various arms of the studies. The efficacy of ALI as antihypertensive drug is maintained in the presence of treatment with a diuretic (HTC, studies 2204 and 2309) and BB (ATE). ALI in combination with an angiotensin receptor antagonist (VAL) showed an additive antihypertensive effect in the study specifically designed to investigate the effect of the combination therapy (study 2327). Results are inconclusive for the possible effects of ACE-i (study 2307, in diabetics only, without control for PLA) and of CCB (study 2305, BP reduction by ALI proved only in patients non-responding to AML). There are no data available for non-dihydropiridinic CCB.

- **Effects of ALI in comparison to other antihypertensive medicinal products**

Tables 4 and5 summarizes the results of studies on clinical efficacy investigating the use of ALI in comparison to other antihypertensive medicinal products. Clinical efficacy is evaluated comparing the ALI effects to the effects of the other drug used as reference. Data are shown as mean difference vs other drug in the BP change induced from baseline to endpoint. The mean difference is negative (with minus sign) if the BP reduction induced by ALI was greater than the BP reduction induced by the reference drug, positive (with plus sign) in the opposite case.

Table 4 – BP effects of ALI vs other drug in mono-therapy regimens:
Difference between ALI and other drug in mean BP change from baseline to endpoint

	ALI dose			
	75 mg	150 mg	300 mg	600 mg
Study 2201 – comparison ALI to 150 mg IRB m-to-m EHTN, 8 wk				
Difference ALI vs IRB in msDBP change, mm Hg	----	-0.4^{ns}	-2.9**	-2.6*
Difference ALI vs IRB in msSBP change, mm Hg	----	+1.1^{ns}	-3.3^{ns}	-3.2^{ns}
*P vs IRB: ^{ns}not significant, *<0.05, **<0.01*				
Study 2307 – comparison ALI to 10 mg RAM, diabetics T1/T2, m-to-m EHTN, 8 wk				
Difference ALI vs RAM in msDBP change, mm Hg	----	----	-0.6^{ns}	----
Difference ALI vs RAM in msSBP change, mm Hg	----	----	-2.7*	----
*P vs RAM: ^{ns}not significant, *<0.05*				
Study 2324 – comparison ALI to 10 mg LIS Ages ≥65, m-to-m EHTN, 8 wk				
Difference ALI vs LIS in msDBP change, mm Hg	-0.2^{ns}	-0.8^{ns}	-1.0^{ns}	----
Difference ALI vs LIS in msSBP change, mm Hg	+1.9^{ns}	+1.5^{ns}	+0.4^{ns}	----
P vs LIS: ^{ns}not significant				
Study 2323 – Comparison ALI vs 25 mg HCT m-to-m EHTN, 12 wk (26-wk study, 8-wk time point not given)				
Difference ALI vs HCT in msDBP change, mm Hg	----	----	-2.0***	----
Difference ALI vs HCT in msSBP change, mm Hg	----	----	-2.8***	----
*P vs HCT:***<0.001*				
Study 2304 – Comparison ALI vs ATE 100 mg m-to-m EHTN, (6 weeks + 6 weeks)				
Difference ALI vs ATE in msDBP change, mm Hg	----	----	+2.39**	----
Difference ALI vs ATE in msSBP change, mm Hg	----	----	-0,08^{ns}	----
*P vs HCT:***<0.001*				

Results of the study 2201 show that, after 8-wk treatment in m-to-m EHTN, the BP reduction induced by ALI is not consistently different compared to the BP reduction induced by IRB at various doses of ALI. Thus, ALI has BP effects not different from those ones of IRB in m-to-m EHTN.

Results of the study 2307 show that, after 8-wk treatment in diabetics with m-to-m EHTN, the BP reduction induced by 300 mg ALI is not consistently different compared to the BP reduction induced by 10 mg RAM. Thus, ALI has BP effects not different from those ones of RAM in diabetics with m-to-m EHTN.

Results of the study 2324 show that, after 8-wk treatment in individuals with age ≥ 65 y and m-to-m EHTN, the BP reduction induced by various doses of ALI is not different compared to the BP reduction induced by 10 mg LIS. Thus, ALI has BP effects not different from those ones of LIS in older hypertensives.

Results of the study 2323 show that, after 12-wk treatment in m-to-m EHTN (26-wk study, data not given for 8-wk time-point), the BP reduction induced by 300 mg ALI is slightly higher than the BP reduction induced by 25 mg HCT. Thus, ALI has BP effects not different from those ones of HCT in m-to-m EHTN.

Table 5 – BP effects of ALI vs other drug in multi-therapy regimens : difference between ALI and other drug in mean BP change from baseline to endpoint	
Study 2203 – Comparison ALI+VAL vs HCT+VAL m-to-m EHTN, 8-wk Doses: ALI = 150 mg, VAL = 160 mg, HCT = 12.5 mg	
Difference ALI vs HCT in msDBP change, mm Hg	+1.4[ns]
Difference ALI vs HCT in msSBP change, mm Hg	+2.2[ns]
P vs HCT: [ns]not significant	
Study 2303 – Comparison ALI+HCT vs LIS+HCT severe EHTN, 8-wk Doses: ALI = 150/300 mg, LIS = 20-40 mg, HCT = 25 mg	
Difference ALI vs LIS in msDBP change, mm Hg	+1.6[ns]
Difference ALI vs LIS in msSBP change, mm Hg	+2.3[ns]
P vs LIS: [ns]not significant	
Study 2309 – Comparison ALI+HCT vs IRB+HCT vs AML+HCT obese m-to-m EHTN, 8-wk end-point (12-wk study) Doses: ALI = 300 mg, IRB = 300 mg, HCT = 25 mg, AML 10 mg	
Difference ALI vs IRB in msDBP change, mm Hg	-0.6[ns]
Difference ALI vs IRB in msSBP change, mm Hg	-0.4[ns]
Difference ALI vs AML in msDBP change, mm Hg	-1.6[ns]
Difference ALI vs AML in msSBP change, mm Hg	-2.2[ns]
P vs IRB or AML: [ns]not significant	
Study 2323 – Comparison ALI+AML vs HCT+AML m-to-m EHTN, 26 wk Doses: ALI = 300 mg, HCT = 25 mg, AML 5/10 mg	
Difference ALI vs HCT in msDBP change, mm Hg	-1.2**
Difference ALI vs HCT in msSBP change, mm Hg	-1.7*
*P vs HCT: *<0.05, **<0.01*	
Study 2306 – Comparison ALI+HCT vs RAM+HCT m-to-m EHTN, 26 wk Doses: ALI = 150/300 mg, RAM = 5/10 mg, HCT = 12.5/25 mg	
Difference ALI vs RAM in msDBP change, mm Hg	-1.2*
Difference ALI vs RAM in msSBP change, mm Hg	-2.6**
*P vs RAM: *<0.05, **<0.01*	

Results of study 2203 show that, after 8-wk treatment in m-to-m EHTN, the BP reduction induced by ALI+VAL is not different compared to the BP reduction induced by HCT+VAL. Thus, in combination with VAL, ALI has BP effects not different from those ones of HCT in m-to-m EHTN.

Results of study 2303 show that, after 8-wk treatment in severe EHTN, the BP reduction induced by ALI+HCT is not different compared to the BP reduction induced by LIS+HCT. Thus, in combination with HCT, ALI has BP effects not different from those ones of LIS in severe EHTN.

Results of study 2309 show that, after 8-wk treatment in obese individuals with m-to-m EHTN, the BP reduction induced by ALI+HCT is not different compared to the BP reduction induced by IRB+HCT and AML+HCT. This is a 12-wk-study. However, data are shown for the 8-wk time-point for comparability with other studies. Thus, in combination with HCT, ALI has BP effects not different from those ones of IRB and AML in obese individuals with m-to-m EHTN.

Results of study 2323 show that, after 26-wk treatment in m-to-m EHTN, the BP reduction induced by ALI+AML is slightly higher than the BP reduction induced by HCT+AML. Thus, in combination with AML, ALI has BP effects not lower than those ones of HCT in m-to-m EHTN.

Results of study 2306 show that, after 26-wk treatment in m-to-m EHTN, the BP reduction induced by ALI+HCT is slightly higher than the BP reduction induced by RAM+HCT. Thus, in combination with HCT, ALI has BP effects not lower than those ones of HCT in m-to-m EHTN.

Altogether, the results provide the evidence that the efficacy of ALI is not inferior in comparison to diuretics, ARB, ACEi, CCB and BB. Data are missing for other antihypertensive drugs (non-dihydropiridinic CCB, non-thiazide diuretics, etc.).

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

Demographic subgroups of age, sex, race, ethnicity, obesity and renal function for their efficacy response and dosing needs. Summary statistics of the change from baseline to endpoint for msDBP, msSBP, responder rate, and control rate were produced by treatment group for each of the demographic subgroups. Number of hypothesis tests were performed for the subgroup analyses. The results were generally consistent and indicated that ALI was more effective than PLA regardless of age, sex, race, ethnicity, obesity or renal function. The population was pooled according to the following 3 age groups: <65 years, ≥65 years, and ≥75 years. The mean baseline SBP was higher in the older age group, while DBP was slightly lower, consistent with the known prevalence of systolic HTN and increased pulse pressure in the elderly. Responder rates and control rates, which are based on both SBP and DBP, were lower for PLA in the older patients, while the PLA-subtracted rates were comparable for all treatments.

Change from baseline to endpoint in msDBP and msSBP by age group, ITT population (pooled PLA-controlled studies: 2201, 2203, 2204, 2308, 1201):

Treatment	N		Baseline Mean		Endpoint Mean		Change from Baseline			
							Mean		Placebo-subtracted	
Age group	<65	>=65	<65	>=65	<65	>=65	<65	>=65	<65	>=65
msDBP										
Placebo	637	139	99.3	98.4	93.5	90.2	-5.8	-8.2		
Ali 75 mg	359	116	99.6	98.5	91.2	88.1	-8.4	-10.4	-2.6	-2.2
Ali 150 mg	623	143	99.4	98.3	90.4	86.9	-9.0	-11.4	-3.2	-3.2
Ali 300 mg	621	143	99.5	98.4	88.2	87.3	-11.3	-11.2	-5.5	-3.0
Ali 600 mg	243	52	99.5	98.2	87.4	86.2	-12.1	-12.0	-6.3	-3.8
msSBP										
Placebo	637	139	151.4	158.5	145.3	154.2	-6.0	-4.3		
Ali 75 mg	359	116	151.4	157.9	142.0	147.0	-9.4	-10.9	-3.4	-6.6
Ali 150 mg	623	143	151.9	159.5	140.8	146.4	-11.1	-13.1	-5.1	-8.8
Ali 300 mg	621	143	152.5	157.8	137.2	144.2	-15.2	-13.5	-9.2	-9.2
Ali 600 mg	243	52	150.6	159.6	135.2	144.1	-15.4	-15.6	-9.4	-11.3

Females had a slightly greater PLA response than males for reductions in SBP and DBP and for both responder rate and control rate. When the PLA subtracted responses were compared, they were similar for both genders. There is no evidence of a gender difference in response to ALI. Overall, the PLA-subtracted treatment effects for ALI as measured by changes in SBP, DBP, responder rate, and control rate were smaller for blacks than for Caucasians, and greater for Asians than for Caucasians at the two higher doses of ALI. These differences may simply be a chance effect due to relatively small numbers of black patients in the ALI treatment groups. The differences may also have been driven, in part, by the lower PLA responses for all variables in both blacks and Asians than in Caucasians. No meta-analysis was performed.

- **Clinical studies in special populations**

Studies in special populations were done for diabetes mellitus, obesity, and older ages. No separate analysis was performed for patients with type 1 and type 2 diabetes (study 2307). Obesity was highly prevalent in most of studies but one (1201). No study was done in non-overweight individuals.

- **Discussion on clinical efficacy**

In hypertensive patients, once-daily administration of ALI at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic BP that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal BP-lowering effect was observed after 2 weeks. The BP-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. ALI has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older. ALI monotherapy studies have shown BP lowering effects comparable to other classes of antihypertensive agents including ACEI and ARB. Compared to a diuretic (HCTZ), ALI 300 mg lowered systolic/diastolic BP by 17.0/12.3 mmHg, compared to 14.4/10.5 mmHg for HCTZ 25 mg after 12 weeks of treatment. In diabetic hypertensive patients, ALI monotherapy was safe and effective. Aliskiren was studied in combination with HCTZ, ARB, ACE, CCB and BB. These combinations were well tolerated. Combination therapy studies have shown clear additive BP-lowering-effects of ALI when added to HCTZ. In patients who did not adequately respond to 5 mg of the CCB (AML), the addition of ALI 150 mg had a BP-lowering effect similar to that obtained by increasing AML dose to 10 mg, but had a lower incidence of oedema (ALI 150 mg/AML 5 mg 2.1% vs. AML 10 mg 11.2%). In diabetic hypertensive patients, ALI provided additive BP reductions when added to RAM, while the combination of ALI and RAM had a lower incidence of cough (1.8%) than ramipril (4.7%). ALI in combination with VAL showed an additive antihypertensive effect in the study specifically designed to investigate the effect of the combination therapy. Beneficial effects of aliskiren on mortality and cardiovascular morbidity and target organ damage are currently unknown.

Clinical safety

- **Introduction**

ALI is a new chemical entity and a member of a new class of drugs, RIs, that to date does not include any agents in clinical use. Therefore, little data exist outside the ALI clinical program regarding the potential safety risks of drugs in this pharmacologic class. Preclinical safety pharmacology studies with ALI revealed no significant effects on the CNS, cardiovascular, respiratory, or renal systems. Local irritation at the site of administration was a key feature of the toxicity studies and is hypothesized to be related to the increased incidence of inflammatory and proliferative changes in the gastrointestinal tract during the carcinogenicity studies at doses well in excess of the maximum tolerated. The key studies supporting the safety claim include all larger studies examining relevant doses and duration of therapy in the claimed indication. These consist of 2 dose selection studies, 9 adequate and well-controlled confirmatory efficacy and safety studies (4 PLA-controlled and 5 active-controlled) and 4 long-term studies, including an open-label 12-month study with a PLA-controlled withdrawal period and a 4-month extension and 2 double-blind, active controlled 6-month studies. Additional safety data were obtained from pilot efficacy studies,

clinical pharmacology and biopharmaceutical studies, and ongoing studies from 13 clinical trials and 6 clinical pharmacology studies.

- **Patient exposure**

Safety data were obtained in a total of 11,566 treated patients. Of these patients, 9611 received treatment only in controlled studies, 1525 received treatment only in the long-term open-label study, and 430 received treatment in the PLA-controlled (Study 2203) and subsequently received treatment in the long-term (Study 2302). There were 7896 patients who received at least one dose of ALI of whom 2,367 were exposed to ALI for 6 months and 1,270 for 12 months. Of these, 5734 were exposed to ALI monotherapy (of whom 1,398 for up to 1 year) and at least 3100 received ALI in combination with other antihypertensives. There were 5664 patients who received treatment in the PLA-controlled studies and 2412 who received treatment in the short-term active-controlled studies. Of the patients in the five 8-week, phase II-III, PLA-controlled studies using ALI doses of 75 to 600 mg, 2316 received ALI monotherapy, 1642 ALI in combination with other antihypertensives, 925 other antihypertensives and 781 PLA. Of the patients in the short-term active-controlled studies, 676 received ALI monotherapy, 654 received ALI in combination with other antihypertensives, and 1149 received the active control.

- **Adverse events**

Overall number of AEs was lower in patients treated with ALI than in patients treated with PLA (37.7% vs 40.2%). Among the common AEs, diarrhoea, cough, peripheral oedema, fatigue, rash, and influenza were more incident in patients treated with ALI than in patients treated with PLA. Among these AEs: (I) diarrhoea was the most common AE and was 2-time more frequent in patients treated with ALI than patients treated with PLA (2.4% vs 1.2%), (II) cough was the second most common AE but was substantially less frequent in patients treated with ALI than in patients treated with ACE-inhibitors (1.0% vs 3.8%), (III) peripheral oedema was substantially less frequent in patients treated with ALI than in patients treated with AML (0.9% vs 7.3%).

- **Serious adverse event/deaths/other significant events**

The proportion of patients with any SAE was similar across all treatment groups in both populations; in the combined group of all patients who took ALI, the rate was 0.8% in the PLA-controlled studies and 0.9% in the short-term controlled studies, compared to 0.6 % for the PLA-treated patients. In both populations, the system organ class with the most SAEs was cardiac disorders. Results were consistent with the data from the short-term studies given the relative lengths of treatment exposure in the one-year and 6-month trials and the 8-week trials, respectively. Three SAEs occurred during the randomized withdrawal period in Study 2306 and none occurred during the withdrawal period in Study 2302. There were no drug-related SAEs in the healthy volunteers or patients included in the completed and ongoing clinical pharmacology studies Two patients in the early dose-ranging study (Study 04HTNDR) had SAEs. There were no SAEs during active treatment in any of the other trials. Summaries of the SAEs leading to study discontinuation in the PLA-controlled studies, the short-term controlled studies, the long-term double-blind studies, and the long-term open-label studies are presented by system organ class and preferred term in. In all populations, the system organ class with the most SAEs leading to study discontinuation was cardiac disorders and the proportion of patients with any SAE leading to study discontinuation was similar across all treatment groups. Two patients in the early dose-ranging study discontinued due to SAEs (Study 04HTNDR). There were no SAEs leading to study discontinuation in the clinical pharmacology studies, except for one patient discontinued due to pregnancy. Overall, 32 deaths occurred during completed or ongoing studies with ALI through 01-June 2006: 11 patients known to have taken ALI at any time, 8 patients randomized to active treatment in ongoing studies whose treatment codes have not been unblinded, 4 patients on PLA, 4 during initial washout, and 5 on active comparators. Most deaths were related to cardiovascular or cerebrovascular events, as would be expected in an older hypertensive population. The causes of death were similar in all groups, and the rate was no higher in patients-treated with ALI compared with active comparators or PLA. The overall frequency of SAEs was not significantly higher for the ALI groups compared with the PLA groups. The proportion of patients with any SAE leading to study discontinuation was similar across all treatment groups.

- **Laboratory findings**

Drugs that inhibit the RAS system may be associated with changes in renal function in susceptible individuals. These changes may manifest as increases in potassium, urea nitrogen (BUN) and serum creatinine, especially in patients with pre-existing renal disease or diabetes. In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of ALI. In clinical studies in hypertensive patients, ALI had no clinically important effects on total cholesterol, high density lipoprotein cholesterol (HDL-C), fasting triglycerides, fasting glucose or uric acid. Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other agents acting on the RAS, such as ACEi and ARB. Increases in serum potassium were minor and infrequent in patients with EHTN treated with ALI alone (0.9% compared to 0.6% with placebo). However, in one study where ALI was used in combination with an ACEI in a diabetic population, increases in serum potassium were more frequent (5.5%). Therefore as with any agent acting on the RAS system, routine monitoring of electrolytes and renal function is indicated in patients with diabetes mellitus, kidney disease, or heart failure.

- Safety in special populations

Elderly: overall, subgroup analysis results were consistent with main safety analysis results. The frequency of SAEs was not higher for ALI than for PLA in subjects ≥ 65 years of age. Patients with diabetes mellitus: ALI alone and in combination with RAM was assessed in type II diabetic patients with m-t-m EHTN (Study 2307). ALI was well tolerated in this study with overall AE rates for ALI, RAM, and the combination that did not exceed those in the pooled data base. Diabetic patients were more likely to develop laboratory abnormalities including elevations of BUN>14.28 mmol/L, creatinine >176.8 μmol/L, and hyperkalaemia, but these were not different in the different treatment groups in Study 2307 except for the greater rate of hyperkalaemia with ALI/RAM combination treatment.

Renal dysfunction: Although renal excretion is not a significant pathway for ALI elimination (<1%), clinical pharmacology (Study 2209) revealed increased exposure both after single doses and at steady state in renally impaired subjects compared to normal controls. This increase in exposure did not correlate with the severity of renal impairment and was maximal in the moderately impaired group. Although this finding may have been due to chance, adverse events and laboratory abnormalities were examined in an exploratory analysis of patients with at least moderate renal dysfunction (estimated GFR < 60 ml/min/1.73m²) compared to those with normal or only mildly decreased renal function. Patients with at least moderate renal dysfunction were infrequent but comprised 4.2% of the population in the all-controlled studies. Overall AEs were similar in patients with at least moderate renal dysfunction and without renal dysfunction among those treated with ALI alone (40.0% vs. 37.6%) and those treated with ALI alone or in combination with other agents (38.7% vs. 37.8%). There was no excess of gastrointestinal adverse events (the only class of adverse events associated with ALI therapy) in the patients with lower GFR, and during treatment with ALI these patients were not more likely to experience adverse events related to the renal and urinary disorders system organ class than those with normal GFR (1.2 % vs 1.3%). Among patients treated with ALI monotherapy, specified percent change in BUN occurred in 8.6% of patients with estimated GFR < 60 compared to 7.0% of patients with GFR ≥ 60. There were no patients with low GFR with the specified percent change in creatinine. Although the number of patients with impaired renal function receiving 600 mg of ALI was small (n=12), none had meaningful changes in BUN or creatinine.

Children: No clinical trials were performed in children.

Pregnancy and lactation: Other substances that act directly on the RAS have been associated with serious foetal malformations and neonatal death. As for any medicine that acts directly on the RAS, ALI will be contraindicated during pregnancy (2nd and 3rd trimester) and should not be used in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is

detected during therapy, ALI should be discontinued as soon as possible. It is not known whether ALI is excreted in human milk. Its use is therefore not recommended in women who are breast-feeding.

- **Safety related to drug-drug interactions and other interactions**

In vitro studies showed that ALI does not inhibit any of the CYP450 enzymes at therapeutic concentrations. Although specific studies were not performed to assess metabolic induction, it was not seen in animal or human studies. The interaction potential of ALI with other co-medications frequently used in the hypertensive and diabetic population was determined in several drug interaction studies. In addition, the effect of maximum inhibition of P-glycoprotein was also investigated using a probe inhibitor ketoconazole. ALI showed a low potential for interaction with many concomitant medications. Co-administration of irbesartan, furosemide, digoxin, RAMl, HCTZ, ATE, celecoxib, fenofibrate, pioglitazone, allopurinol, and isosorbide-5-mononitrate with ALI had no effect on ALI steady-state pharmacokinetics. Co-administration of VAL and metformin resulted in a 25-30% reduction in ALI steady-state AUC and C_{max}. Co-administration of AML resulted in a 29% increase in ALI steady-state AUC. Coadministration of cimetidine resulted in 20% and 25% increases in ALI steady-state AUC and C_{max} respectively. Co-administration of ALI did not affect the steady-state pharmacokinetics of digoxin, VAL, AML, metformin, RAM, HCT, pioglitazone, ATE, celecoxib, isosorbide-5- mononitrate, fenofibrate, and allopurinol. Coadministration of ALI did not have an effect on acenocoumarol exposure or PD effect as assessed by PT and INR. Coadministration of ALI and furosemide does not alter the PK of ALI but decreases the AUC and C_{max} of furosemide (28% and 49% respectively). It is, therefore, recommended that the effects of furosemide be monitored and the dose adjusted, if necessary, when initiating treatment with ALI. Co-administration of ALI and atorvastatin does not alter the steady-state PK of atorvastatin or its metabolites, but increases the steady-state AUC and C_{max} of ALI by approximately 50%. Ketoconazole, a potent P-glycoprotein and CYP3 A4 inhibitor, increases exposure to ALI 300 mg by 1.8 fold [Study 2334]. It is likely that this is due to the inhibition of P-glycoprotein and CYP3A4 by ketoconazole since ALI is a substrate for P-glycoprotein and is metabolized by CYP3A4, although less than 1.4% of an oral dose is recovered as excreted metabolites. It is not anticipated that dose adjustment will be required when inhibitors of P-glycoprotein and ALI are used concomitantly at recommended doses as these exposures would be within the range studied in the clinical trials. The fact that some drugs, potentially co-administered with ALI, can significantly affect the disposition (AUC and Cmax) of ALI requires further studies.

- **Discontinuation due to adverse events**

Few patients overall discontinued prematurely in PLA-controlled studies (2.3%) or in the short-term controlled studies (2.4%). In the PLA-controlled studies, the PLA group had the largest proportion of patients with AEs leading to study discontinuation (3.5%). The rate of discontinuation was 1.7% in the all-ALI group and 1.9% in the ALI monotherapy group. The only notable difference among individual AEs was for headache, which led to discontinuation in 1.0% of the PLA-treated patients and 0.3% of all-ALI-treated patients and therefore accounted for about half of the excess rate for all AEs in the PLA group compared with the ALI groups. There was no evidence for a dose-response relationship for any events leading to discontinuation in the ALI treatment groups. In the short-term controlled studies, the ACE inhibitor group had the largest proportion of patients with AEs leading to study discontinuation (4.0%). The rate of discontinuation was 2.2% in the ALI group and 2.0% in the ALI monotherapy group and the pattern of events was similar to that seen in the PLA-controlled studies. Overall, the most frequently reported AEs leading to discontinuation in the long-term double-blind studies were headache (13 patients, 0.7%) and dizziness (8 patients, 0.7%). Similarly, the most frequently reported AEs leading to discontinuation in the long-term open-label studies were headache (15 patients, 0.8%) and dizziness (13 patients, 0.7%). There were no discontinuations due to AEs during the randomized withdrawal period of Study 2302. Discontinuations during the randomized withdrawal period of Study 2306 were predominantly in those randomized to PLA (3 of 3 for ALI regimen and 3 of 4 for RAM regimen).

- **Discussion on clinical safety**

Studies were pooled for analyses on the overall safety profile. The safety population consisted of adults

with m-to-m EHTN with exception of patients of study 2303 (with severe EHTN) and study 2307 (with m-to-m EHTN and type 1 or type 2 diabetes mellitus). Studies lasting more than 8 weeks in general had the optional addition of other antihypertensive agents in patients whose BP was uncontrolled. However, a significant number of patients were exposed to Aliskiren as monotherapy for 6 months and 1 year. List of investigated AEs was complete. Overall number of AEs was lower in patients treated with ALI than in patients treated with PLA (37.7% vs 40.2%). Among the common AEs, diarrhoea, cough, peripheral oedema, fatigue, rash, and influenza were more incident in patients treated with ALI than in patients treated with PLA. As far as data of laboratory tests are concerned, effects of 8-wk treatment with ALI were of minor statistical or medical significance

5. 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, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activates (routine and additional)**
Important identified risks		
Diarrhoea	Routine PV, aggregate analyses in PSUR, Monitor through targeted follow up from post-marketing use and in clinical trials.	Routine
Rash	Routine PV, aggregate analyses in PSUR.	Routine
Hyperkalemia	Routine PV, review of clinical trials, aggregate analyses in PSUR.	Routine
Haemoglobin and haematocrit decrease	Routine PV, aggregate analyses in PSUR.	Routine
Important potential risks		
Colorectal hyperplasia	Routine PV, aggregate analyses in PSUR, Monitor through targeted follow up from post-marketing use and in clinical trials.	Routine
Peripheral oedema	Routine PV, aggregate analyses in PSUR.	Routine
Hypotension	Routine PV, aggregate analyses in PSUR.	Routine
Identified drug interactions		

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activates (routine and additional)
Furosemide	Routine PV, aggregate analyses in PSUR.	Routine
Potential drug interactions		
P-glycoprotein inhibitors	PK interaction study with cyclosporine A, routine PV, aggregate analyses in PSUR.	Routine
Pharmacological class effects		
Cough	Routine PV, aggregate analyses in PSUR.	Routine
Angioedema	Routine PV, aggregate analyses in PSUR, Monitor through targeted follow up from post-marketing use and in clinical trials.	Routine
Renal dysfunction	Routine PV, aggregate analyses in PSUR Monitor in clinical trials of population at risk.	Routine
Important missing information		
Pregnancy	Routine PV, aggregate analyses in PSUR.	Routine
Pediatric population	Routine PV, aggregate analyses in PSUR.	Routine
Severe renal impairment	No studies planned.	Routine
Reno-vascular hypertension	No studies planned.	Routine
Reduction of cardiovascular risk	Routine PV, aggregate analyses in PSUR. Clinical CV morbidity and mortality program.	Routine

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

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

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

At the time of the CHMP opinion, there were some outstanding quality issues with no impact on the benefit/risk. The applicant undertook to provide the necessary information as follow-up measures within

an agreed timeframe and to submit variations if required following the evaluation of this additional information.

Non-clinical pharmacology and toxicology

The studies performed *in vitro* and *in vivo* proved the significant and selective inhibitory effect against human renin, and antihypertensive effect of ALI in different animal models. According to the pharmacological studies ALI, as a RI, provide the pharmacologic rationale for the use in the treatment of the HTN. ALI was evaluated for its possible effects on CNS, cardiovascular, respiratory and renal systems as well as for its interaction with a series of CNS receptors. Only minor effects were observed and these do not produce serious side effects. The primary PD program and safety pharmacology studies provided sufficient information regarding the affinity, the selectivity and the non-clinical PD efficacy of ALI. The overall actual data are considered reassuring for short and long term ALI administration to humans, but are less definitive for chronic administration. A complete toxicology safety evaluation program was conducted to support the chronic administration of ALI to adult patients. The toxicology program was consistent with the *ICH M3 Guideline on Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* as well as all other relevant guidelines. The rat and marmoset were selected as the rodent and non-rodent species for toxicity testing as both species are used routinely as animal models in toxicity evaluations. Furthermore, both the rat and the marmoset were used as pharmacological models for the evaluation of ALI PD, and both species displayed metabolic profiles similar to humans. The toxicity profile in mice and rats was consisted of inflammatory and degenerative changes of the respiratory epithelium and hypertrophy/hyperplasia of the cecal mucosa. Diarrhea was the primary gastrointestinal effect of ALI in marmosets but there were no associated treatment-related histopathological findings. Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofoetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats or 100 mg/kg/day in rabbits. Fertility, pre-natal development and post-natal development were unaffected in rats at doses up to 250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1 to 4 and 5 times higher, respectively, than the maximum recommended human dose (300 mg).

Efficacy

The claimed indication for RAS is treatment of EHTN, alone or in combination with other antihypertensive agents. Inclusion criterium was a diagnosis of m-t-m EHTN for all of the studies but one that was specifically designed for severe HTN. Overall, the studies completed the protocol in 9,476 individuals out of the 10,743 randomised individuals. Among individuals with completed protocols, 3,507 were treated with ALI as a single antihypertensive drug, 2,684 were treated with ALI in combination with other antihypertensive drugs, 2,851 were treated with other registered antihypertensive drugs, and 664 were treated with PLA. The primary end-point was the change induced by active treatment in msDBP in ten of the twelve studies. Two studies focused on msSBP. Clinical studies represent the evidence that ALI, used as mono-therapy, is an effective antihypertensive medicinal product. In clinical trials the change in msDBP varied from -1.7 to -7.6 mmHg for the effects of ALI as a single drug in m-to-m EHTN. There is some variability in the BP effects among different studies. The variability in the BP effects might reflect a variable bioavailability of the drug. In fact, drug administration was not standardized with regard to fed/fasting conditions although other studies show that ALI absorption is substantially affected by food ingestion. The long-term efficacy of ALI as a single antihypertensive drug was investigated as per suggested guidelines. Clinical studies address also the BP effects of ALI used as in combination with other antihypertensive drugs. These studies represent convincing evidence that ALI is an effective antihypertensive drug when used in combination with thiazide diuretics and with BB (ATE). ALI when used in combination with ARB (VAL) was effective in the study specifically designed to investigate the effect of the combination therapy. As far as the combination with other drugs, study results are partially conclusive for combination with CCB, or limited to a specific subgroup of patients (combination with RAM). The change in msDBP induced by combination with ALI varied from -1.0 to -4.9 mmHg compared to effects of other drug alone. Subgroup analyses were adequately performed for patients without overweight, and pre/post menopausal women, but not for type 1 and type 2 diabetes mellitus

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

Safety
Studies were pooled for analyses of an overall safety profile. The safety population consisted of adults with m-t-m EHTN with exception of one study (with severe EHTN). Studies lasting more than 8 weeks in general had the optional addition of other antihypertensive agents in patients whose BP was uncontrolled. However, a significant number of patients were exposed to Aliskiren as monotherapy for 6 months and 1 year. Overall number of AEs was lower in patients treated with ALI than in patients treated with PLA. Among the common AEs, diarrhoea, cough, peripheral oedema, fatigue, rash, and influenza were more incident in patients treated with ALI than in patients treated with PLA. Among these AEs: diarrhoea was the most common AE and was 2-time more frequent in patients treated with ALI than patients treated with PLA (2.4% vs 1.2%). Cough was the second most common AE but was substantially less frequent in patients treated with ALI than in patients treated with ACEi (1.0% vs 3.8%). Peripheral oedema was substantially less frequent in patients treated with ALI than in patients treated with AML (0.9% vs 7.3%). As far as data of laboratory tests are concerned, effects of treatment with ALI were of minor statistical or medical significance. From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Having considered the safety concerns in the RMP, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these concerns.

- **User consultation**

The user testing provided was adherent to the EC Guideline. The results reported met the readability success criteria.

Risk-benefit assessment
The benefits of the new RI ALI, in lowering BP in a large cohort of patients with m-t-m EHTN and in a group of patients with severe HTN are well documented. There is some variability in the BP effects among different studies very likely due to a variable bioavailability of the drug and no standardisation of administration with regard to fed/fasting conditions. No specific clinical trials were carried out to show ALI beneficial effect in hypertensive patients with concomitant morbidities. Ali was well tolerated when given alone and in combination with other antihypertensive drugs and particularly effective in combination with diuretics (HCTZ). A structured review and evaluation of the entire ALI safety database has led to the identification of adverse drug reactions related to administration of ALI: diarrhoea and rash. Data on ALI safety are not available in children, pregnant or nursing females, patients with severe renal or hepatic impairment, recent or ongoing major cardiovascular disorders or cerebrovascular disorders, or secondary HTN. Long-term studies in general had the optional addition of other antihypertensive agents in patients whose BP was uncontrolled. However, a significant number of patients were exposed to Aliskiren as monotherapy for up to 1 year. A rapid and reversible local toxicity of ALI in the lower intestinal mucosa is a species-specific finding in rodents and did not occur in humans, as shown by colonoscopy, after 8 wk treatment with ALI. In addition, ALI did not behave as a classical tumour promoter agent. A specific RMP ensure the monitoring, during long-term treatment with ALI, GI adverse reactions and potential carcinogenetic lesions. In conclusion, the therapeutic antihypertensive effects of ALI given alone or in combination with other antihypertensive agents outweigh the negative effects.
A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

routine pharmacovigilance was adequate to monitor the safety of the product

AND

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

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Rasilez in the treatment of essential hypertension was favourable and therefore recommended the granting of the marketing authorisation.

LIST OF ABBREVIATIONS

ACE(i)	Angiotensin converting enzyme (inhibitor)
ADME	Absorption, Distribution, Metabolism and Excretion
AE	adverse event
ALI	Aliskiren
ALT	alanine aminotransferase/glutamic pyruvic transaminase/SGPT
Ang I/II	angiotensin I/II
AMLO	amlodipine
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMS	accelerator mass spectrometry
Ang I, II	Angiotensin I, II
AOGEN	Angiotensinogen
ANP	Atrial natriuretic peptide
$ApoE^{-/-}$	Apolipoprotein E knock out
ARB	Angiotensin receptor blocker
AST	aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
AT-III	Anti-thrombin-III
ATE	Atenolol
AUC	Area under the curve
AUC(0-t)	Area under the plasma/blood concentration-time curve from time zero to time t, using the log-linear trapezoidal rule.
AUC(0-∞)	Area under the plasma/blood concentration-time curve from time zero to infinity.
BrdU	Bromodeoxyuridine
AUC AUC	area under the curve of the time vs. ALI concentration profile
βMHC	Beta myosin heavy chain
BAV	bioavailability
BB	betablockers
BMI	body mass index
BUN	blood urea nitrogen
BP	Blood pressure
^{14}C	carbon-14 radioisotope
CAR	carcinogenicity study
CCB	calcium channel blockers
CHO	Chinese hamster ovary
CK	creatine kinase
CL	Clearance
Cmax	Maximum plasma/blood concentration after a single dose
CNS	Central nervous system
CRP	C-reactive protein
CSF	Colony stimulating factor (or cerebrospinal fluid)
Css	steady-state concentration
rhCYP	recombinant human cytochrome P450
d	day
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DRF	dose range finding study
dTGR	Double transgenic rat
EH	hepatic extraction ratio
EHTN	essential hypertension
EFD	embryo-fetal development study
EFT	embryo-fetal transfer distribution study
EHR	enterohepatic recirculation
ELISA	Enzyme-linked immunosorbent assay
F%	absolute oral bioavailability
FACS	Fluorescein activated cell scanning
FDA	Food and Drug Administration
fu	fraction unbound (in plasma)

GLP	Good Laboratory Practice
h	hour
^{3}H	tritium radioisotope
HbA1c	glycosylated hemoglobin
hERG	Human ether-a-go-go-related gene
Hg	Mercury
HIV	Human immunodeficiency virus
^{1}H-NMR	proton nuclear magnetic resonance spectroscopy
HPLC	High performance liquid chromatography
HPLC-MS-MS	HPLC coupled to tandem mass spectrometry (MS2)
HPLC-UV	high performance liquid chromatography coupled to ultraviolet detection
HR	Heart rate
HTN	Hypertension
5HT	5-hydroxytryptamine
HV	healthy volunteer
i.a.	intraarterial
ICH	International Conference on Harmonisation
IC_{25}	Concentration required to inhibit by 25%
IC_{50}	Concentration required to inhibit by 50%
i.d.	intraduodenal
INN	international non-proprietary name, generic drug name
i.p.	intraperitoneal dosing
IRMA	Immunoradiometric assay
i.t.	intra-tracheal dosing
i.v.	intravenous dosing
1K1C	1 kidney 1 clip model of hypertension
2K1C	2 kidney 1 clip model of hypertension
kg	kilogram
LC-MS	Liquid chromatography coupled to mass spectrometry
LC-MS-MS	Liquid chromatography coupled to tandem mass spectrometry
LDH	lactic acid dehydrogenase
LLNA	Local lymph node assay
LOD	Limit of detection
LOQ	Limit of quantification
LLOQ	Lower limit of quantification
LLNA	Local lymph node assay
LSC	Liquid scintillation counting
M	Male
MADBP	mean ambulatory diastolic blood pressure
MAP	Mean arterial blood pressure
MDR1	Multidrug resistance protein (P-glycoprotein (P-gp); *ABCB1*)
MF	market formulation
mg	milligram
mgEq	milligram equivalent
mm	millimeter
mM	millimolar
µM	micromolar
mRen-2 rat	Transgenic rats expressing mouse ren-2 gene
MRP2	Multidrug resistance-associated protein 2 (*ABCC2*)
msDBP/SBP	mean sitting diastolic BP/systolic BP
MTD	Maximum tolerated dose
N	Experimental number
n.d.	not determined
NK cells	Natural killer cells
nM	nanomolar
NMDA	N-methyl-D-aspartate
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NSAID	nonsteroidal anti-inflammatory drug

hOATP	human Organic anion transporting polypeptide
rOatp	h: human, r: rat
hOCT	human Organic cation transporter
o.d.	*omnia die*/once a day
PK/PD	Pharmacokinetic/pharmacodynamic
p.o.	Per oral dosing
PKWS	Pharmacokinetics written summary
PRA	Plasma renin activity
PRC	Plasma renin concentration
QWBA	Quantitative whole body autoradiography
QWBAL	Quantitative whole body autoradioluminography
RAM	ramipril
RAS	Renin angiotensin system
SAE	Serious Adverse Event
SBS	Summary of biopharmaceutic studies and associated analytical methods
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	standard deviation
SE	standard error
s.c.	subcutaneous
SEM	Standard error of the mean
SHR	Spontaneously hypertensive rats
SOP	Standard Operating Procedure
SPP 100 ALI	
SSRI	selective serotonin reuptake inhibitor
STZ	Streptozotocin
t½	terminal half-life
t½λz	terminal elimination half-life (unit: h)
t_{max}	time to the maximum observed plasma/blood concentration
TGF-β	Transforming growth factor-beta
TGR(mRen-2)27	Transgenic rats expressing mouse ren-2 gene
TK	Toxicokinetic
TKWS	Toxicokinetic written summary
TNF-α	Tumor necrosis factor-alpha
TWA	Time-weighted average
ULN	upper limit of normal
UAE	Urinary albumin excretion
VAL	valsartan
Vdβ	distribution volume at terminal elimination phase (unit: L or L/kg)
Vss	Steady-state volume of distribution
v/v	volume per volume
WBC	white blood cell
WHO	World Health Organization
wk	week
w/v	weight per volume
w/w	weight per weight