CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-217

MEDICAL REVIEW(S)

CLINICAL and STATISTICAL JOINT REVIEW

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Reviewer Name	Shen Xiao, M.D., Ph.D. Ququan Liu, M.D., M.S.
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Established Name	Aliskiren/Valsartan
(Proposed) Trade Name	Valturna™
Therapeutic Class	Antihypertensive (Renin inhibitor combined with angiotensin II receptor blocker)
Applicant	Novartis
Priority Designation	S
Formulation	Oral tablet
Dosing Regimen	Aliskiren/Valsartan: 150/160 mg, and 300/320 mg
Indication	Treatment of hypertension
Intended Population	Adult patients with hypertension

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Abbreviations

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ABPM	ambulatory blood pressure monitoring
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferases (SGOT)
AUC	area under the curve
BID	twice a day
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CAT	coaxial tomography
CK	creatine kinase
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DSI	Division of Scientific Investigation (FDA)
ECG	electrocardiogram
EEG	electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	Good Laboratory Practices
HbA1c	hemoglobin A1c
HGB	hemoglobin
HCTZ	hydrochlorothiazide
HF	heart failure
ICH	International Conference on Harmonization
IRB	institutional review board
ISE	Integrated Summary (Review) of Efficacy
ISS	Integrated Summary (Review) of Safety
ITT	intention-to-treat
LOCF	last observation carried forward
LSM	least squares mean
LVH	left ventricular hypertrophy
MI	myocardial infarction

MRI	magnetic resonance imaging
MSDBP	mean seated diastolic blood pressure
MSSBP	mean seated systolic blood pressure
NDA	New Drug Application
NOS	not otherwise specified
NS	not significant
OD	once a day
PD	pharmacodynamics
PEY	person-exposure-year
PK	pharmacokinetic
PRA	plasma renin activity
PRC	plasma renin concentration
PTCA	percutaneous coronary angioplasty
QD	once a day
QTc	QT interval corrected (for heart rate)
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cells
RMP	Risk Management Plan
SAE	serious adverse event
SAS	Statistical Analysis System
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SLE	systemic lupus erythromatosus
SPA	special protocol assessment
TIA	transient ischemic attack
ULN	upper limit of normal
US	United States

1 Executive Summary

1.1 Recommendation on Regulatory Action

From clinical and statistical perspectives we recommend that , Valturna™ , the combination of aliskiren and valsartan, be approved for the treatment of hypertension. This combination product demonstrated clinically and statistically significant reductions in both diastolic and systolic blood pressure compared to placebo and each respective monotherapy in one randomized, double-blind, placebo-controlled trial and one long-term open-label trial (one year).

The antihypertensive effect was generally attained after 2 weeks of therapy. With the estimates of the probability of reaching a BP goal (systolic BP <140 or 130 mmHg and diastolic BP <90 or 80 mmHg), a greater probability of achieving systolic or diastolic goal with the combination over monotherapies was observed. Therefore, this combination should be also approved for the first-line therapy which means that aliskiren/valsartan can be indicated for the initial treatment of hypertensive patients who are likely to need multiple drugs to achieve their blood pressure goals.

The adverse event profile of the combination is similar to each component monotherapy. Regarding the incidences of significant AEs identified during aliskiren monotherapy clinical development program, the angioedema, GI events, cough, and anemia are also similar in the aliskiren/valsartan combination therapy compared to each monotherapy. Small mean decreases from baseline were seen in red blood cell count, hemoglobin and hematocrit in both monotherapies and combination therapy. These changes were small, but were slightly more pronounced with the combination therapy than with monotherapy.

Four patients (0.7%) in the aliskiren/valsartan combination group had a clinically significant increase in creatinine (>176.8 μmol/L), compared to 2 patients in both the aliskiren monotherapy group (0.2%) and the valsartan monotherapy group (0.3%). Of the four patients in aliskiren/valsartan group, two had values that returned to within normal range without the disruption of the study drug by the end of study or study follow-up. In the one year open label study, two patients (0.3%) had a creatinine value > 176.8 umol/L. One had value that returned to within normal range without the disruption of the study drug by the end of study. Using the criteria of creatinine >132.6 μmol and >30% from baseline, there three patients (0.5%) in the aliskiren/valsartan group and none were either monotherapy groups or placebo group at the end of study. There were also three patients in the long-term open label study.

Increased serum level of potassium seems the major finding in this combination therapy compared to each of monotherapy. The incidence rate of hyperkalemia (serum potassium >5.5 mEq/L) was increased in the combination therapy compared to each monotherapy or placebo. The majority of the elevations were transient. No patient was discontinued during the study because of the hyperkalemia in the short-term studies. Two patients (0.3%) were discontinued due to the hyperkalemia in the one year long-term study. The incidence of hyperkalemia does

not appear to increase with long term treatment of aliskiren/valsartan compared to short term treatment. Overall, AE profile is considered to be acceptable for antihypertensive therapy.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

The sponsor provided a risk management plan for aliskiren/valsartan fixed combination focusing on the risks including hyperkalemia, diarrhea, rash, angioedeam, decreases in hemoglobin and hematocrit, hypotension, renal dysfunction, cough, pregnancy, pediatric, moderate and severe renal impairment, renal vascular hypertension, and cardiovascular morbidity and mortality.

The risk management activities will include the regular pharmacovigilance activities and risk minimization activities.

The risk minimization activities for fixed combination aliskiren/valsartan at the dose range (150 mg/160 mg, 300 mg/320 mg) proposed for human use for the treatment of hypertension will follow the approved plan for aliskiren monotherapy detailed in the aliskiren RMP and the existing labeling for valsartan.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Aliskiren (Tekturna) is an inhibitor of renin, the enzyme that converts angiotensinogen to angiotensin I in the first and rate-limiting step of the renin-angiotensin-aldosterone system (RAAS). Aliskiren is the first and the only approved renin inhibitor so far.

Valturna™ is a new combination product of aliskiren with valsartan for the treatment of patients with essential hypertension. It is formulated as film-coated tablets for oral administration. The recommended doses of the combination of aliskiren/valsartan included 150/160 mg and 300/320 mg.

The sponsor provided four clinical studies in this original NDA for the evaluation of efficacy and safety to support this combination product for the treatment of hypertension. These studies included one pivotal study, two short-term placebo control studies and one long-term open label study.

There were 1797 patients in the pivotal trial and a total of 3520 patients were evaluated in the safety database and extent of exposure.

1.3.2 Efficacy

The overall clinical design is to assess whether both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment. There are a total of 4 studies provided to support the efficacy claim. The Study SPP 100A 2327 is the pivotal study which provides a critical appraisal for the efficacy. Other studies provide efficacy support for both short term and long term use.

The primary endpoint was change from baseline in seated trough (i.e., prior to next treatment at the end of the 24-hour inter dosing interval) cuff diastolic blood pressure (DBP) at Week 8. Seated trough cuff systolic blood pressure (SBP), percent responders (DBP < 90 mmHg and/or ≥ 10 mmHg less than baseline), and control rate (SBP<140 and DBP <90 mmHg) were analyzed as the major secondary endpoints.

In the pivotal study, the tested drugs and doses included 1) aliskiren 150 titrated to 300 mg monotherapy; 2) valsartan 160 titrated to 320 mg; 3) aliskiren 150/160 titrated to 300/320 mg; and 4) the placebo.

The study results showed that the combinations of aliskiren/valsartan in both dosages produced clinically and statistically significant reductions in the DBP compared to placebo and each respective monotherapy.

For the secondary endpoint of SBP in this pivotal study, the pairwise comparison showed that the combination of aliskiren/valsartan produced a greater reduction of SBP at Weeks 4 (low dose) and 8 (high dose) from baseline, compared with the placebo and each monotherapy.

The dose-response relationship study showed that reduction in msDBP was positively related to the dose of both aliskiren and valsartan. For the response rate (defined as DBP < 90 mmHg or fall in DBP ≥ 10 mmHg compared to baseline) and the control rate (defined as DBP < 90 mmHg and SBP < 140 mmHg), the combinations produced greater effects than the corresponding monotherapy.

There are similar reductions of BP between ages of <65 years (no children were included) and ≥65 years, gender, renal function impairment, diabetes and baseline obesity of BMI< 30 kg/m^2 and BMI≥ 30 kg/m^2 after the combined therapy. Regarding the race difference, however, it is not clear whether the combination is more effective than monotherapy in African Americans. Only the diastolic BP value at full dose appears to show a incremental reduction.

To be considered for first-line therapy with this combination, estimates of the probability of reaching a BP goal (systolic BP <140 or 130 mmHg and diastolic BP <90 or 80 mmHg) at endpoint were determined by analyses using a logistic regression model with baseline as a covariant. The probability of achieving systolic or diastolic goal was higher with the combination than with either monotherapy.

There are two other short term active-controlled studies (Studies CSPP 100A 2203 and 2331) submitted with this NDA to support the efficacy. Study 2203 is a Phase IIB, randomized, double-blind, placebo-controlled, multifactorial, multi-center, parallel-group study of aliskiren alone compared to placebo; the combination of aliskiren and valsartan compared to their component monotherapies; and the combination of valsartan and HCTZ compared to the combination of aliskiren and valsartan in patients with uncomplicated essential hypertension (msDBP ≥ 95 mmHg and < 110 mmHg). The BP lowering effects in msDBP and msSBP of the combination of aliskiren and valsartan (75/80 mg, 150/160 mg and 300/320 mg) compared with their component monotherapies were not reach statistical significance. However, since there is a substantial placebo effect (placebo mean change from baseline: -8.6 mm Hg in msDBP and -10.0 mm Hg in msSBP) in this study, it may be difficult to make accurate interpretation of the overall study results. Please see detailed information in the appendix for this study.

Study 2331 is a multicenter, randomized, double-blind, parallel group supportive study conducted in 639 hypertensive patients who were not adequately responsive to HCTZ 25 mg monotherapy. The total duration of study participation for each patient, inclusive of all phases, was approximately 12 weeks, and consisted of a 4-week single-blind run-in period and a 8-week randomized double-blind, treatment period (4 weeks of low-dose treatment, followed by 4 weeks of high-dose treatment), with 4 treatment groups. The primary efficacy variable was the change from baseline in msDBP at the endpoint. Change from baseline in msSBP was a key secondary efficacy variable. The combination of aliskiren and valsartan with 25 mg HCTZ resulted in statistically greater mean reductions in msDBP and msSBP at the Week 4 (low dose) and Week 8 (high dose) endpoints than either respective low-dose or high-dose combination of monotherapy with HCTZ (aliskiren/HCTZ or valsartan/HCTZ). Combination of aliskiren with valsartan without HCTZ was not performed in this study. The study results support the use of aliskiren/valsartan with other antihypertensives such as HCTZ.

The assessment for long-term use of this product was conducted in a 12-month long-term open-label study: Study CSPV 100A 2301. This is a 54 week, open-label, multicenter study evaluating the long-term safety of the combination of aliskiren/valsartan 300/320 mg in patients with essential hypertension (msDBP ≥ 90 mmHg and < 110 mmHg). Long-term safety was the primary objective, and long-term efficacy was the secondary objective. This study was comprised of a 1-4 week washout phase, and a 54 week treatment phase. During the first two weeks of the treatment, aliskiren/valsartan was in 150/160 mg and then titrated to 300/320 mg for the remaining 52 weeks. Optional addition of HCTZ (12.5 mg with increase to 25 mg) was allowed for patients not adequately controlled (after 10 weeks of treatment). In the overall population, a clinically significant mean reduction from baseline in msDBP and msSBP from baseline was observed as early as Week 2 (after initial treatment with aliskiren/valsartan 150

mg/160 mg) and continued throughout the study (following treatment with aliskiren/valsartan 300 mg/320 mg).

1.3.3 Safety

Overall, the adverse events including the mortality rate, SAEs, common AEs, discontinuation rates due to AEs, etc., in the combination of aliskiren and valsartan were generally comparable with each of monotherapy.

Increased serum level of potassium seems the major finding in the combination compared to each of monotherapy. The higher incidence of hyperkalemia (serum potassium >5.5 mEq/L) was reported for aliskiren/valsartan fixed combination compared with the monotherapy aliskiren or valsartan or compared to placebo. The majority of the elevations were transient. No patient was discontinued due to this adverse event in the short-term studies. In the long-term (12 months) open label study, 6 patients (1.0%) with hyperkalemia were reported as AEs . The incidents occurred in five patients treated with aliskiren 300 mg / valsartan 320 mg and one patient while treated with aliskiren/valsartan/HCTZ. Two of the patients discontinued due to hyperkalemia: one event lasted for 38 days, and one event was continuing at discontinuation. The remaining four patients with hyperkalemia had events that did not require additional treatment or study drug interruption. Two of these patients completed the study, and two discontinued participation for reasons unrelated to hyperkalemia.

Small mean decreases from baseline were seen in red blood cell count, hemoglobin and hematocrit in both monotherapies and combination therapy. These changes were small, but were slightly more pronounced (-0.26 g/dL) than with monotherapy regimens (-0.04 g/dL in aliskiren or -0.13 g/dL in valsartan) or placebo (+0.07 g/dL).

Four patients (0.7%) in the aliskiren/valsartan combination group had a clinically significant increase in creatinine (>176.8 µmol/L), compared to 2 patients in both the aliskiren monotherapy group (0.2%) and the valsartan monotherapy group (0.3%). Of the four patients in aliskiren/valsartan group, two had values that returned to within normal range without the disruption of the study drug by the end of study or study follow-up. In the one year open label study, two patients (0.3%) had a creatinine value > 176.8 µmol/L. One had value that returned to within normal range without the disruption of the study drug by the end of study. Using the criteria of creatinine >132.6 µmol and >30% from baseline, there three patients (0.5%) in the aliskiren/valsartan group including the two patients with creatinine > 176.8µmol/L and none were either monotherapy groups or placebo group at the end of study. There were also three patients in the long-term open label study including one patient with creatinine > 176.8µmol/L.

Other important AEs which were found in aliskiren monotherapy (NDA 21-985) including diarrhea, cough, angioedema, slight increase in uric acid and anemia were similar in the combination monotherapy compared to the aliskiren monotherapy.

Based on the provided short- and long-term studies, the AE profile with this combination product is considered to be acceptable for this antihypertensive combination therapy.

1.3.4 Dosing Regimen and Administration

Valturna™, the combination of aliskiren with valsartan, should be indicated for the treatment of hypertension. This treatment should include 1) an add-on therapy: a patient whose blood pressure is not adequately controlled with aliskiren alone or valsartan (or another angiotensin receptor blocker) alone may be switched to combination therapy with aliskiren/valsartan; 2) replacement therapy: aliskiren/valsartan may be substituted for the titrated components (aliskiren and valsartan); and 3) initial therapy: aliskiren/valsartan is indicated for the initial treatment of hypertensive patients who are likely to need multiple drugs to achieve their blood pressure goals.

The sponsor proposed 2 fixed dosage strengths: 150/160 mg and 300/320 mg which have been tested in the pivotal study. Based on the pivotal study, all of these doses produced clinically and statistically significant reductions in both msDBP and msSBP compared to placebo and each respective monotherapy at the same dose levels. In the safety analysis, the adverse event profile of these combination is similar to each component monotherapy. Therefore, it is reasonable to approve these two dosages.

1.3.5 Drug-Drug Interactions

No other drug-drug interaction studies were conducted.

1.3.6 Special Populations

Aliskiren/valsartan was effective regardless of gender, age, and disease factors including obesity, stages of hypertension, renal impairment and diabetes. Regarding the race in this study, the comparison is focused on Caucasians and Blacks due to the lack of patients from other races. It seems that both the monotherapies and the combination therapy are more effective in Caucasians than in Blacks.

Children were not studied. Since the Division previously waived the pediatric requirement for other aliskiren fixed dose combination products on the basis that data in pediatric patients will not be available for each of the components at the projected time of submission. The sponsor requested a waiver of the pediatric requirement for this combination. We considered this request is reasonable.

Studies of either aliskiren monotherapy or the combination of aliskiren with valsartan were not conducted in pregnant women. The sponsor is proposing a black box warning in the label regarding use in pregnancy as is currently included in the labels for all ACEIs and ARBs. There are three pregnant cases in the studies. While there have not been definite fetal abnormalities reports following these pregnancies, the experience with human pregnancies is obviously limited.

2 Introduction and Background

2.1 Product Information

Valturna™ is a new combination product of Aliskiren (Tekturna®) with Valsartan (Diovan®). Aliskiren is a novel anti-hypertensive agent, which acts by inhibiting the enzyme renin to block the conversion of angiotensinogen to angiotensin I (Ang I), the precursor of angiotensin II (Ang II). Valsartan is an Ang II receptor blocker/antagonist (ARB) that inhibits the interaction of Ang II and its receptor, and therefore blocks the hypertensive and other effects of Ang II.

Blockade of the renin-angiotension system (RAS) by an ARB in combination with a renin inhibitor may offer a better blockade by inhibiting both at the receptor level and at the first step of the cascade. Therefore, Valturna™ is expected to provide more optimal blood pressure control than the component monotherapies through the complementary effects of the two drugs. This fixed-dose combination tablet of aliskiren/valsartan was developed for use in the targeted population of patients with essential hypertension.

Valturna™ is a film-coated tablet in a immediate release solid dosage form for oral administration containing fixed combinations of the drug substances Aliskiren hemifumarate and Valsartan. Light red, ovaloid film-coated tablet, standard convex with beveled edges, with debossing “HDU” on one side and “NVR” on the reverse side of the tablet with length of approximately 17mm and width of approximately 7mm means 150/160 mg dosage and Light brown, ovaloid film-coated tablet, shallow convex with bevelled edges, with debossing “SNB” on one side and “NVR” on the reverse side of the tablet with length of approximately 22 mm and width of approximately 12 mm means 300/320 mg dosage.

2.2 Currently Available Treatment for Indications

Many drugs are approved for the treatment of hypertension. The most relevant approved drugs are those that also work by inhibiting the renin-angiotensin-aldosterone system (RAAS). RAAS
inhibitors approved for hypertension include the renin inhibitor (Aliskiren), angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone receptor antagonists (eplerenone, spironolactone). Regarding the combination product, there are several products of fixed combination doses of ACEIs/HCTZ or ARBs/HCTZ available for the treatment of hypertension. In addition, the fixed combination doses of aliskiren/HCTZ (Tekturna HCT®) were approved in January 2008.

2.3 Availability of Proposed Active Ingredient in the United States

Aliskiren is approved for use as either monotherapy or in combination with other antihypertensive agents in once daily doses of 150 and 300 mg. A fixed dose combination of aliskiren and HCTZ (Tekturna HCT®) was approved for the treatment of hypertension in January 2008 as the second line therapy.

Valsartan is approved for use as monotherapy or in combination with other antihypertensive agents in once daily doses of 80 mg to 320 mg. It has been marketed for hypertension in combination with hydrochlorothiazide (Diovan HCT®), and in combination with amlodipine (Exforge®). Diovan HCT® and Exforge® were approved (July 2008) as initial treatment for hypertension in patients likely to need multiple drugs to achieve their BP goals.

2.4 Important Issues With Pharmacologically Related Products

RAAS inhibitors share certain adverse events (AEs). Because all affect aldosterone, all can cause increases in serum potassium. All, either through effects on aldosterone or angiotensin II or both, can cause decreases in renal function. In addition to these AEs shared by all RAAS inhibitors, ACEIs cause cough, presumably through effects of ACE on the bradykinin pathway. ACEIs, and to a lesser extent ARBs, cause angioedema. Whether the latter
is mediated through the bradykinin pathway is not clear. It is assumed that renin inhibitors should not cause these latter AEs. However, this has not been confirmed in clinical trials. Finally, ARBs have recently been implicated in rare cases of rhabdomyolysis.

As a combination of renin inhibitor and ARB, it is possible that Valturna™ may increase the incidence for some above adverse effects caused by RAAS inhibitors.

2.5 Pre-submission Regulatory Activity

At the pre-NDA meeting for Valturna™ submission on February 22, 2007, the Division agree that Study CSPP100A2327 can be used as the pivotal registration study for the fixed dose combination tablet of aliskiren/valsartan with dose strengths of 150/160 mg and 300/320 mg (given once a day as two 150/160 mg tablets). Study CSPV100A2301 has a planned duration of treatment for 54 weeks (including the initial 2-week low dose treatment) and can be used to obtain long-term safety data. At least 300 patients have been treated for 6 months in this study.

2.6 Other Relevant Background Information

N/A

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable)

CMC reviewer, Dr. Prafull Shiromani, found several deficiencies and sent a letter to Sponsor dated March 27, 2009. He also notes that the environmental assessment and biowaiver and dissolution assessments are completed. He has reported at the review meetings that he believes the sponsor can address all deficiencies. Please see his review for details on the deficiencies noted.

3.2 Animal Pharmacology/Toxicology

No preclinical pharmacodynamic or pharmacokinetic studies were performed with the new combination product. Toxicity studies were conducted with aliskiren and valsartan as free combinations in the rat and included dose range-finding and 13-week studies. The toxicity studies were accompanied by toxicokinetic monitoring of the drugs components aliskiren and valsartan. Based on the proposed therapeutic dose strengths of 150/160 and 300/320 mg (aliskiren/valsartan), a ratio of approximately 1:1 was used in these preclinical safety studies.

The animal pharmacology and toxicology reviewer, Dr. G. Jagadeesh, judges this application approvable from the pharmacology and toxicology perspective. Please see Dr. Jagadeesh's review for the pre-clinical findings.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The primary source of clinical data for this review was the initial NDA submission dated November 25, 2008. This submission included one pivotal efficacy trial (Study CSPP100A2327), two supportive efficacy studies (Studies CSPP100A2203, 2331), and a long term safety trial (Study CSPV100A2301).

4.2 Tables of Clinical Studies

The sponsor conducted four clinical studies for the evaluation of efficacy and safety to support this combination product for the treatment of the primary hypertension in the initial submission. In addition, the sponsor has conducted PK/PD, and bioavailability and bioequivalence studies in healthy volunteers with this combination product. Please see the FDA clinical pharmacologist's review for tabulations and reviews of those studies. Studies for efficacy and safety evaluation of this product included in this initial NDA are displayed in the following Table 1.

Table 1: Studies Supporting Efficacy and Safety in Hypertension

Studies	Country & Study Dates	Study Design, Purpose, Population Studied Evaluations	Total No., Race (w,b,a,o), Age Range (mean), Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status
#SPP 2327	Germany, Spain, US start: 27-Jun-05 end: 5-Sep-06	DB, randomized, multi-center, parallel group, placebo and active controlled dose escalation study with aliskiren (150 mg and 300 mg) alone and in	1797 (1343 w, 286 b, 29 a, 139 o) age: 24-84 years (52.2) groups: 4 (1092m, 705f) 437 (255 m, 182 f) 455 (281 m, 174 f) 446 (275 m, 171 f) 459 (281 m, 178 f)	1 - 2 wk washout 3 - 4 wk run-in 4 wk DB at low dose followed by forced titration to 4 wk DB at high dose Aliskiren 150 mg titrated to 300 mg Valsartan 160 mg	Completed

		combination with valsartan (160 mg and 320 mg) in hypertension.		titrated to 320 mg Aliskiren/valsartan 150/160 mg titrated to 300/320 mg	
#SPP 2203	Denmark, France, Germany, Poland, US start: 15-Mar-04 end: 12-Oct-04	DB, randomized, multicenter, factorial, placebo-controlled, parallel-group study of aliskiren and valsartan in hypertension	1123 (1034w,76b,1a, 12o) **age:** 19-88 (56) **groups:** 11 (628m, 495f) 177(97m, 80f) 179 (99m, 80f) 178 (101m, 77f) 175 (100m, 75f) 58 (38m, 20f) 59 (29m, 30f) 60 (31m, 29f) 60 (30m, 30f) 60 (35m, 25f) 58 (32m, 26f) 59 (36m, 23f)	2 wk washout, 3-4 wk placebo run-in, 8 wk DB. Placebo Aliskiren 75 mg Aliskiren 150 mg Aliskiren 300 mg Valsartan 80 mg Valsartan 160 mg Valsartan 320 mg Alisk 75 /Val 80 mg Alisk150 / Val 160 mg Alisk 300/Val 320mg Val 160/HCTZ12.5 mg	Completed
# SPP 2331	Germany, Spain and USA start: Oct 31 2005 end: Jan 11 2007	8-wk, DB, randomized, parallel group, multicenter study with aliskiren/ valsartan/HCTZ (300/320/25 mg), aliskiren/HCTZ (300/25mg) and valsartan/HCTZ (320/25 mg) in hypertension not adequately responding to HCTZ 25 mg.	641[554w, 58b, 13a, 16o] age: 23 – 84 (53.2) groups: 4 (365m, 276f) 152 (94m. 58f) 166 (92m, 74f) 155 (88m, 67f) 168 (91m, 77f)	4 wk HCTZ run-in 8 wk double blind (DB) HCTZ 12.5 mg titrated to HCTZ 25 mg ALI/HCTZ 150/25 mg titrated to ALI/HCTZ 300/25 mg VAL/HCTZ 160/25 mg titrated to VAL/HCTZ 320/25 mg ALI/VAl/HCTZ 150/160/25 mg titrated to ALI/VAL/HCTZ 300/320/25 mg	Completed
#SPV 2301	Canada, Germany, Netherlands, US **start:** 09-Oct-2006 **end:** 09-Jan-2008	54-week, Open-label, multi-center study to assess the long-term safety and tolerability of the combination of aliskiren 300 mg with valsartan 320 mg in essential hypertension.	601 (508w, 76b, 8a,9o) **age:** 23-85 (55) **groups:** aliskiren/valsartan 404 (223m, 181f) aliskiren/valsartan/HCTZ 197 (107m, 90f)	2- 4 wk washout 2 wk at aliskiren 150 mg and valsartan 160 mg , 52 wk at aliskiren 300 mg and valsartan 320 mg with option of add on HCTZ 12.5 mg after 2 months on high dose of aliskiren and valsartan and dose of HCTZ to be increased to 25 mg, if BP is not controlled.	Completed

4.3 Review Strategy

This medical officer initially reviewed all of the four trials as shown in table 1. Both the medical officer and statistician performed detailed reviews of the pivotal placebo-controlled trial (protocol CSPP100A 2327) for approval from an efficacy aspect. The efficacy section of this study has also been reviewed by Dr. Thomas Marciniak in the NDA 21-985 (Aliskiren monotherapy). Some of his review data were referred in the efficacy section of this review. For

an integrated review of safety, the medical officer relied primarily upon analyses of all of the trials from table 1.

4.4 Data Quality and Integrity

Sponsor reported that GCP non-compliance issues were identified and confirmed at one study site (Site 38; washout period N=42 patients; treatment phase N=40 patients) in the long-term study, Study CSPV 100A 2301. These patients were, therefore, excluded from the analyses presented in that study report, as data for these patients were considered unreliable. The decision to exclude the data from analysis was made prior to completion of the study.

Since this NDA is a drug combination application and all of the studies have been conducted in nearly all of the same sites as the approved NDA 21-985 (Aliskiren monotherapy) and NDA 22-107 (Fixed combination therapy of Aliskiren/HCTZ), where some of them have been audited by DSI, I do not think any additional audits are required.

From the provided dataset, we did not identify any problems or major discrepancy which might confound the efficacy and safety results of this NDA.

4.5 Compliance with Good Clinical Practices

Based on the sponsor's claims, all studies were conducted in full compliance with Good Clinical Practice other than the one site in Study CSPV 100A 2301 and in accordance with the following directives:

1. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients).

2. Directive 91/507/EEC: The Rules Governing Medicinal Products in the European Community.

3. US 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning informed patient consent and Institutional Review Board approval.

4.6 Financial Disclosures

The sponsor provided a detailed lists of all the clinical investigators participating in studies SPP100A2327, SPP100A2203, SPP100A2331, and SPV100A2301 conducted at US and non-US sites. From the list, one investigator from study (b) (6) received $25000 of speaker fees, one investigator from study (b) (6) received $25000 of speaker fees, and no clinical investigators are full or part-time employees of the sponsor. One investigator is the spouse employee of the sponsor.

Since only three investigators have the potential conflicts of interest, these should not prejudice the results greatly even if there were overt manipulation.

5 Clinical Pharmacology

In order to support the registration of two doses of aliskiren/valsartan fixed combinations for registration, 150/160 mg and 300/320 mg, a relative bioavailability study, a bioequivalence study, and, a food effect study were conducted. The data showed that the fixed combination tablet (300/320 mg, aliskiren/valsartan) is bioequivalent to the free combination of aliskiren 300 mg tablet and 2x160 mg valsartan capsule (clinical service form). Based on the dose proportionality/ linearity data of the two individual drugs, which showed that the two strengths of the fixed combination tablets are proportionally similar, and *in vitro* dissolution profiles in three different pH media, a biowaiver is accepted for 150/160 mg of aliskiren/valsartan dose strength. The food effect with 300/320 mg aliskiren/valsartan tablets is similar to 300 mg aliskiren film-coated tablets (Tekturna®) and 300/25 mg aliskiren/HCTZ film-coated tablets (Tekturna-HCT®). Since in the pivotal efficacy and safety studies with the aliskiren/valsartan combination, the treatments were administered to patients without regard to food, it is recommended that aliskiren/valsartan tablets be taken with a similar pattern as the one recommended for Tekturna® and Tekturna HCT® in order to achieve a consistent clinical effect.

The pharmacokinetics and pharmacodynamics of aliskiren and valsartan are well established and have been presented in previous submission (NDA 21-985) for aliskiren monotherapy and no new PK/PD studies were performed with this fixed combination for this indication. Data from pervious submission were very briefly summarized in the following. Please see the FDA clinical pharmacology review for detailed information.

5.1 Pharmacokinetics

Following oral administration of the fixed combination of aliskiren/valsartan 300/320 mg under fasted conditions, peak plasma concentrations of aliskiren and valsartan are reached in 1 hour and 3 hour (median values), respectively. The mean elimination half-lives of aliskiren and valsartan are about 34 hours and 12 hours, respectively. The rate and extent of absorption of both aliskiren and valsartan from the fixed combination tablets are similar to those from the free combination.

No specific drug-drug interaction studies were conducted with the combination of aliskiren/valsartan and other drugs. Coadministration of valsartan decreased AUCτ and Cmax for aliskiren by 26% and 28%, respectively. Aliskiren decreased the AUCτ and Cmax of valsartan by 14% and 12%, respectively. Based on the supporting PK/PD data and safety/efficacy profile in various clinical studies, this magnitude of change is not considered clinically relevant.

5.2 Pharmacodynamics

In the drug-drug interaction study with healthy volunteers, valsartan alone increased PRA while aliskiren alone inhibited PRA. Co-administration of aliskiren prevented the reactive rise in PRA observed with valsartan. Plasma aldosterone levels decreased following administration of either valsartan alone, aliskiren alone or the combination. Plasma aldosterone levels tended to be lower following the administration of the combination, consistent with greater RAS blockade.

In mildly sodium-depleted normotensive subjects, a single oral dose of 160 mg valsartan increased PRA, Ang I and Ang II, whereas these were reduced to placebo levels by single oral doses of 300 mg aliskiren alone or 150/80 mg aliskiren/valsartan combination. In addition, compared with placebo, 300 mg aliskiren and the 150/80 mg aliskiren/valsartan combination suppressed urine aldosterone excretion for up to 24 hour after a single oral dose, whereas the effect of 160 mg valsartan on urinary aldosterone concentration persisted for no more than 12 to 18 hour. Both 300 mg aliskiren and the 150/80 mg aliskiren/valsartan combination reduced 24-hour cumulative urine aldosterone excretion to a significantly greater extent than 160 mg valsartan.

In sodium-repleted normotensive subjects, a single oral dose of 320 mg valsartan increased PRA, Ang I and Ang II, whereas 300 mg of aliskiren decreased them for 48 hour. In combination, 150 mg of aliskiren neutralized the valsartan (160 mg)- induced increase in plasma angiotensins for 48 hour. The reduction in urinary aldosterone excretion with the 150/160 mg aliskiren/valsartan combination was similar to 300 mg of aliskiren and greater than that of 320 mg of valsartan and placebo.

5.3 Exposure-Response Relationships

Study was not conducted.

6 Integrated Review of Efficacy

6.1 Indication

The indication for the proposed aliskiren/valsartan fixed-dose combination tablets (Valturna^{MT}) is the treatment of essential hypertension including the following conditions:

- Add-on Therapy: A patient whose blood pressure is not adequately controlled with aliskiren alone or valsartan (or another angiotensin receptor blocker) alone may be switched to combination therapy with aliskiren/valsartan.
- Replacement Therapy: Aliskiren/valsartan may be substituted for the titrated components (aliskiren and valsartan).
- Initial Therapy: Aliskiren/valsartan is indicated for the initial treatment of hypertensive patients who are likely to need multiple drugs to achieve their blood pressure goals.

6.1.1 Methods

There are four studies were provided to support the efficacy claim as tabulated in Section 4.2.

Study SPP 100A 2327 is the pivotal study which provides a critical appraisal for supporting the efficacy.

Studies SPP 100A 2203 and 2331 are active-controlled supportive studies to evaluate the short-term efficacy of aliskiren/valsartan and aliskiren/valsartan/HCTZ comparing to each monotherapy.

The long-term open label Study SPV 100A 2301 provide supportive evidence of sustained long-term efficacy.

For the primary evaluation of efficacy, our review focuses on the Study SPP 100A 2327 for the initial evaluation of the antihypertensive effects. Since this study has been reviewed by Dr. Thomas Marciniak, part of his review data and comments were also referred here. We then examine results of the other studies to answer other critical questions such as the long term effect, population variation, subgroup analysis, etc.

6.1.2 General Discussion of Endpoints

The primary endpoint in the pivotal study (SPP 100A 2327) and other two, multicenter, randomized, double-blind, controlled, parallel group trials (SPP 100A 2203 and SPP 100A 2331) was change from baseline in seated trough (i.e., prior to next treatment at the end of the 24-hour inter dosing interval) cuff diastolic blood pressure (DBP). Seated trough cuff systolic blood pressure (SBP) and overall blood pressure control rate (SBP<130, and 140 mmHg and DBP <80, 90 mmHg) were analyzed as the important secondary endpoints. In addition, ambulatory blood pressure measurement (ABPM) done in Study SPP 100A 2327 was also analyzed.

6.1.3 Study Design

The overall clinical design in this program is to assess whether both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment. The clinical studies in this program included a pivotal efficacy trial (Study CSPP 100A 2327), two supportive efficacy studies (Studies CSPP 100A 2203 and 2331) and one long-term open label study (Study CSPV 100A 2301) in patients with mild to moderate hypertension (≥90 or ≥95 to < 110 mmHg diastolic BP).

The dose selection in the combination was based on aliskiren monotherapy clinical trial data and the available marketed doses of valsartan that are commonly used for the treatment of hypertension.

Study CSPP100A 2327 serves as the pivotal efficacy trial for this submission. This is a double-blind, randomized, parallel group, placebo-controlled dose escalation study in patients with

essential hypertension. It was an international, four-arm (the two monotherapies, the combination, and placebo) study with a forced doubling of initial doses at four weeks and evaluations at four and eight weeks. It enrolled the usual patients with mild-to moderate essential hypertension (office cuff DBP 95-109 mmHg with mean 8-hour ABPM DBP > 90 mmHg) as an inclusion criterion.

The study randomized 1797 patients, and 1796 were treated. The primary efficacy endpoint was to evaluate the efficacy of the combination of aliskiren 300 mg and valsartan 320 mg in patients with essential hypertension by testing the hypothesis of greater reduction in msDBP from baseline to end of study (Week 8 endpoint) when compared to both monotherapy components. Major secondary endpoints included change from baseline in msSBP, BP response and control rates, 24-hour ambulatory BP, and some biomarkers such as plasma renin activity (PRA), plasma renin concentration (PRC) and plasma aldosterone level. A study design diagram was summarized in the following table 2.

Table 2: Study design.

Period	Screening	Single-blind run-in	Double-blind treatment	
Duration	1-2 weeks	3-4 weeks	Initial dose – 4 weeks	Titrated dose – 4 weeks
			Placebo	Placebo
			Aliskiren 150 mg	Aliskiren 300 mg
	Washout	Placebo		
			Valsartan 160 mg	Valsartan 320 mg
			Aliskiren/valsartan 150/160 mg	Aliskiren/valsartan 300/320 mg

To support the use of the aliskiren/valsartan combination as initial therapy, a supplemental analysis was performed on this study. This analysis is to estimate the probability of reaching a BP goal based on baseline BP, at Week 4 and Week 8 endpoints by treatment group using a logistic regression model with baseline msSBP and msDBP, respectively, as a covariate, for the following BP goals:
• DBP control (msDBP < 90 mmHg),
• Aggressive DBP control (msDBP < 80 mmHg),
• SBP control (msSBP < 140) mmHg, and
• Aggressive SBP control (msSBP < 130 mmHg).

In addition to the pivotal study 2327, other studies also provided efficacy information in sub-groups of the study population and the long-term efficacy information. For the details of the study designs and the individual study results, please see Appendix 10.1.

6.1.4 Efficacy findings

6.1.4.1 Primary Endpoint (DBP) and Major Secondary Endpoints

The changes from baseline for seated trough cuff DBP in the pivotal study (Study CSPP 100A 2327) were summarized in the following table 3. The data showed that the combination of aliskiren/valsartan had a statistically significantly greater change from baseline in the mean sitting DBP at Week 8, compared with aliskiren and valsartan monotherapies.

Table 3:Sponsor's change from baseline in mean sitting diastolic blood pressure (mmHg) at week 8 endpoint in study 2327 (ITT population)

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-4.07 (0.41)	
Aliskiren	430	-9.02 (0.42)	
Valsartan	453	-9.69 (0.41)	
Aliskiren/Valsartan	438	-12.17 (0.41)	
Pairwise Comparison	**LS M difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value+**
Aliskiren vs. Placebo	-4.95 (0.58)	(-6.07, -3.82)	<.0001*
Valsartan vs. Placebo	-5.62 (0.57)	(-6.73, -4.51)	<.0001*
Aliskiren/Valsartan vs. Placebo	-8.09 (0.57)	(-9.22, -6.97)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-3.15 (0.58)	(-4.29, -2.01)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-2.47 (0.57)	(-3.60, -1.35)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
+ P-Values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level

For the secondary endpoint of SBP in this pivotal study, the changes from baseline was summarized in the following table 4. The data showed that the combination of aliskiren/valsartan produced a greater reduction of SBP at Week 8 from baseline, compared with the placebo and each monotherapy.

Table 4: Sponsor's change from baseline in mean sitting systolic blood pressure (mmHg) at week 8 endpoint in study 2327 (ITT population)

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-4.56 (0.65)	
Aliskiren	430	-12.96 (0.67)	
Valsartan	453	-12.75 (0.65)	
Aliskiren/Valsartan	438	-17.20 (0.67)	
Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value+**
Aliskiren vs. Placebo	-8.40 (0.93)	(-10.22, -6.58)	<.0001*
Valsartan vs. Placebo	-8.20 (0.91)	(-9.99, -6.40)	<.0001*
Aliskiren/Valsartan vs. Placebo	-12.64 (0.92)	(-14.45, -10.8)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-4.24 (0.94)	(-6.07, -2.40)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-4.44 (0.92)	(-6.26, -2.63)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
+ P-Values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Source: PT-Table 14.2-2.1b

At the lower doses, the combination of aliskiren/valsartan 150/160 mg also demonstrated statistically greater reductions in msDBP and msSBP compared with the aliskiren 150 mg and valsartan 160 mg monotherapy treatment groups at Week 4 endpoint as showed in the following tables 5 and 6.

Table 5 : Sponsor's Change from Baseline in DBP at Week 4 in Study 2327 (Aliskiren 150 mg and Valsartan 160 mg)

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-4.80 (0.36)	
Aliskiren	430	-7.46 (0.37)	
Valsartan	453	-8.68 (0.36)	
Aliskiren/Valsartan	438	-10.50 (0.37)	
Pairwise Comparison	**LS M difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value+**
Aliskiren vs. Placebo	-2.66 (0.51)	(-3.66, -1.66)	<.0001*
Valsartan vs. Placebo	-3.88 (0.50)	(-4.87, -2.89)	<.0001*
Aliskiren/Valsartan vs. Placebo	-5.70 (0.51)	(-6.69, -4.70)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-3.04 (0.51)	(-4.05, -2.03)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-1.82 (0.51)	(-2.82, -0.82)	0.0004*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
+ P-Values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level

Table 6: Sponsor's Change from Baseline in SBP at Week 4 in Study 2327 (Aliskiren 150 mg and Valsartan 160 mg)

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-5.24 (0.58)	
Aliskiren	430	-10.69 (0.60)	
Valsartan	453	-10.85 (0.58)	
Aliskiren/Valsartan	438	-15.29 (0.59)	
Pairwise Comparison	**LS M difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value+**
Aliskiren vs. Placebo	-5.44 (0.83)	(-7.07, -3.82)	<.0001*
Valsartan vs. Placebo	-5.61 (0.82)	(-7.21, -4.01)	<.0001*
Aliskiren/Valsartan vs. Placebo	-10.05 (0.82)	(-11.66, -8.43)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-4.60 (0.84)	(-6.24, -2.96)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-4.44 (0.83)	(-6.06, -2.82)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
+ P-Values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level

Regarding the blood pressure control, the proportions of patients achieving BP control targets (msDBP < 90 mm Hg and msSBP < 140 mm Hg) for the four groups at Week 8 endpoint were: 49.32% for aliskiren/valsartan, 37.44% for aliskiren, 33.77% for valsartan, and 16.48% for placebo. The pairwise comparisons between the treatments indicate that the proportion achieving the BP control target in the aliskiren/valsartan treatment was statistically significantly higher compared with both monotherapy groups. Similar results were observed at Week 4 endpoint. Data were summarized in the following tables 7 and 8. The greater BP control rates in the aliskiren/valsartan combination group vs. either respective monotherapy or placebo were seen at all time points starting as early as Week 2 as shown in the following figure 1.

Table 7: Between treatment comparison for control rate of blood pressure at Week 8 endpoint by treatment group (ITT population)

Pairwise Comparison	Treatment A		Treatment B		
	n/N	(%)	n/N	(%)	P-Value
Aliskiren vs. Placebo	161/430	(37.44)	75/455	(16.48)	<.0001*
Valsartan vs. Placebo	153/453	(33.77)	75/455	(16.48)	<.0001*
Aliskiren/Valsartan vs. Placebo	216/438	(49.32)	75/455	(16.48)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	216/438	(49.32)	161/430	(37.44)	0.0005*
Aliskiren/Valsartan vs. Valsartan	216/438	(49.32)	153/453	(33.77)	<.0001*

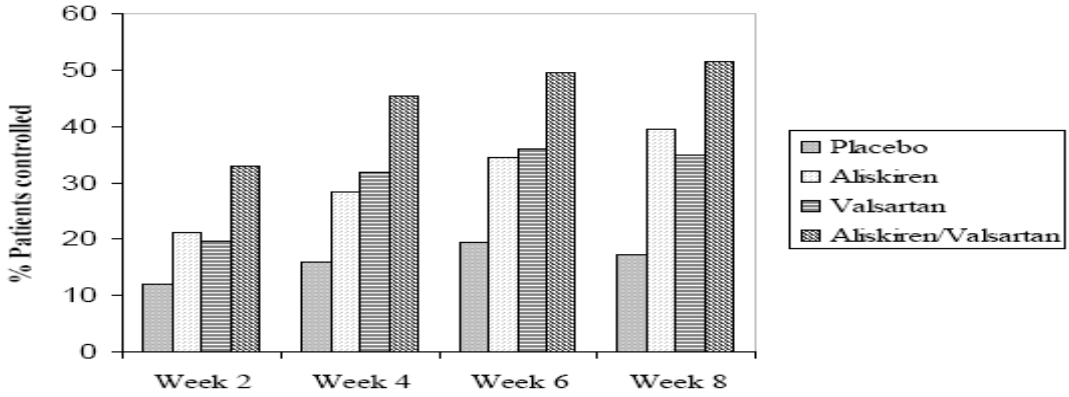
A patient with control in BP is defined as having as a mean sitting diastolic blood pressure < 90 mm Hg and a mean sitting systolic blood pressure < 140 mm Hg.
The control rate was analyzed by using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.
*indicates statistical significance at 0.05 level.

Table 8: Between treatment comparison for control rate of blood pressure at Week 4 endpoint by treatment group (ITT population)

Pairwise Comparison	Treatment A		Treatment B		
	n/N	(%)	n/N	(%)	P-Value
Aliskiren vs. Placebo	119/430	(27.67)	70/455	(15.38)	<.0001*
Valsartan vs. Placebo	143/453	(31.57)	70/455	(15.38)	<.0001*
Aliskiren/Valsartan vs. Placebo	194/438	(44.29)	70/455	(15.38)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	194/438	(44.29)	119/430	(27.67)	<.0001*
Aliskiren/Valsartan vs. Valsartan	194/438	(44.29)	143/453	(31.57)	0.0001*

A patient with control in BP is defined as having as a mean sitting diastolic blood pressure < 90 mm Hg and a mean sitting systolic blood pressure < 140 mm Hg.
The control rate was analyzed by using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.
*indicates statistical significance at 0.05 level.

Figure 1: Overall BP control rates (%) during treatment (ITT population) (Study 2327)



In the ambulatory blood pressure analyses, aliskiren/valsartan was statistically superior to both monotherapies in reducing both the ambulatory DBP and SBP from baseline at Week 8 endpoint. The pairwise comparisons between the combination treatment and each of the respective monotherapy treatment groups in mean 24-hour ambulatory DBP and SBP are presented in the following tables 9 and 10. Change from baseline in hourly mean ambulatory DBP and SBP at Week 8 endpoint is shown graphically by postdosing hour and treatment in figures 2 and 3.

Table 9: Change from baseline in Mean 24-hour ambulatory DBP at Week 8 endpoint (ITT population)

Treatment	N	LS Mean in change from baseline (SE)	
Placebo	81	-1.07 (0.49)	
Aliskiren	79	-7.08 (0.49)	
Valsartan	100	-7.12 (0.44)	
Aliskiren/Valsartan	94	-10.31 (0.45)	
Pairwise Comparison	**LS Mean Difference (SE)**	**95% CI for LSM difference**	**P – value**
Aliskiren vs. Placebo	-6.00 (0.70)	(-7.38, -4.63)	<.0001*
Valsartan vs. Placebo	-6.05 (0.65)	(-7.33, -4.76)	<.0001*
Aliskiren/Valsartan vs. Placebo	-9.24 (0.66)	(-10.55, -7.93)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-3.24 (0.67)	(-4.55, -1.93)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-3.20 (0.63)	(-4.43, -1.96)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least squares means and the associated standard errors, confidence intervals, and p-values were from a two-way repeated-measures analysis-of-covariance model with treatment, region, and post-dosing hours as factors and baseline mean 24-hour ambulatory DBP as a covariate with treatment by post-dosing-hour interaction and autoregressive order 1 covariance structure (AR1).
LS means were evaluated at the average baseline mean 24-hour ambulatory DBP.
* indicates statistical significance at 0.05 level

Table 10: Change from baseline in Mean 24-hour ambulatory SBP at Week 8 endpoint (ITT population).

Treatment	N	LS Mean in change from baseline (SE)	
Placebo	81	-1.33 (0.67)	
Aliskiren	79	-9.75 (0.67)	
Valsartan	100	-10.11 (0.60)	
Aliskiren/Valsartan	94	-14.42 (0.62)	
Pairwise Comparison	**LS Mean Difference (SE)**	**95% CI for LSM difference**	**P – value**
Aliskiren vs. Placebo	-8.42 (0.95)	(-10.29, -6.55)	<.0001*
Valsartan vs. Placebo	-8.78 (0.89)	(-10.53, -7.02)	<.0001*
Aliskiren/Valsartan vs. Placebo	-13.09 (0.91)	(-14.89, -11.3)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-4.67 (0.91)	(-6.46, -2.88)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-4.32 (0.86)	(-6.01, -2.62)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least squares means and the associated standard errors, confidence intervals, and p-values were from a two-way repeated-measures analysis-of-covariance model with treatment, region, and post-dosing hours as factors and baseline mean 24-hour ambulatory SBP as a covariate with treatment by post-dosing-hour interaction and autoregressive order 1 covariance structure (AR1).
LS means were evaluated at the average baseline mean 24-hour ambulatory SBP.
* indicates statistical significance at 0.05 level

Figure 2: Change from baseline in hourly mean ambulatory DBP at Week 8 endpoint by post-dosing hour and treatment (ITT population, Study 2327)

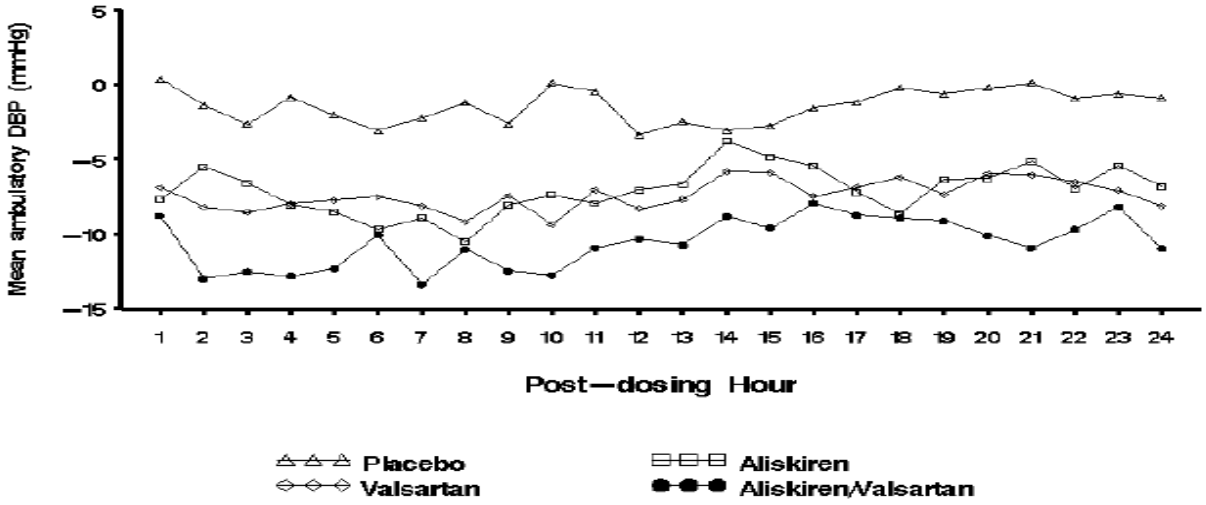
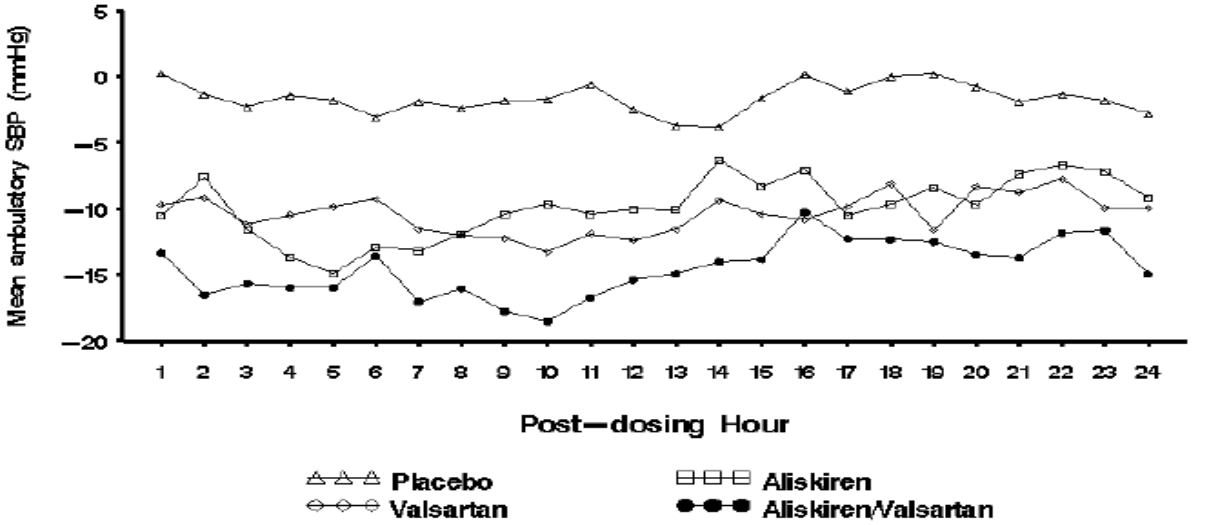


Figure 3: Change from baseline in hourly mean ambulatory SBP at Week 8 endpoint by post-dosing hour and treatment (ITT population, Study 2327)



In the biomarker evaluations by using the geometric means analysis, renin concentration increased from baseline by 19.0% in the placebo group, 468.2% in the aliskiren group, 137.8% in the valsartan group, and 911.5% in the aliskiren/valsartan group at Week 8 endpoint. The elevation of renin concentration with the combination therapy exceeded the sum of the increases seen with each monotherapy, suggesting a synergistic effect on RAS blockade. At Week 8 endpoint, aldosterone increased from baseline by 7.3% in the placebo group while it decreased from baseline in the active treatment groups; the greatest decrease was seen in the combination group (-5.9% in the aliskiren group, -25.2% in the valsartan group, and -30.5% in the aliskiren/valsartan group) based on the change in the geometric means. PRA values increased from baseline to Week 8 endpoint in both the placebo (18.2%) and valsartan (159.6%) groups, while it decreased in both the aliskiren and aliskiren/valsartan groups (-72.6% and -

43.9%, respectively) based on the change in the geometric means. The addition of aliskiren to valsartan therapy was shown to inhibit PRA despite the fact that valsartan monotherapy increases PRA and the combination produces a reactive rise in renin concentration. Data were summarized in the following table 11.

Table 11: Change from baseline of plasma biomarkers - Study 2327 (ITT population)

Treatment	PRC change from baseline		PRA change from baseline		Aldosterone change from baseline	
	GM	%*	GM	%*	GM	%*
Placebo	1.190	19.0	1.182	18.2	1.073	7.3
Aliskiren 300 mg	5.682	468.2	0.274	-72.6	0.941	-5.9
Valsartan 320 mg	2.378	137.8	2.596	159.6	0.748	-25.2
Aliskiren/valsartan 300/320 mg	10.115	911.5	0.561	-43.9	0.695	-30.5

GM = Geometric mean of change from baseline defined as Geometric mean at Week 8 endpoint/Baseline.
*%=(GM-1)x100

6.1.4.2 Long term efficacy

The long-term efficacy was evaluated in Study CSPV 100A 2301. This is a 54 week, open-label, multicenter study evaluating the long-term safety of the combination of aliskiren/valsartan 300/320 mg in patients with essential hypertension (msDBP ≥ 90 mmHg and < 110 mmHg). Long-term safety was the primary objective, and long-term efficacy was the secondary objective. This study was comprised of a 1-4 week washout phase, and a 54 week treatment phase. During the first two weeks of the treatment, aliskiren/valsartan was in 150/160 mg and then 300/320 mg for the remaining 52 weeks. Optional addition of HCTZ (12.5 mg with increase to 25 mg) was allowed for patients not adequately controlled (after 10 weeks of treatment).

In the overall population, a clinically significant mean reduction from baseline in msDBP and msSBP from baseline was observed as early as Week 2 (after initial treatment with aliskiren/valsartan 150 mg/160 mg) and continued throughout the study (following treatment with aliskiren/valsartan 300 mg/320 mg) as summarized in the following table 12.

Table 12: Change from baseline in msDBP and msSBP (mmHg) by time on treatment – Study V2301 (Treated population)

	Aliskiren/valsartan*			Aliskiren/valsartan/HCTZ*			Total		
		Mean change			Mean change			Mean change	
Week	n#	msDBP	msSBP	n#	msDBP	msSBP	n#	msDBP	msSBP
Week 2	398	-9.1	-12.5	197	-5.6	-8.1	595	-7.9	-11.0
Week 4	386	-12.2	-16.9	196	-8.1	-11.0	582	-10.8	-15.0
Week 6	370	-14.0	-20.5	197	-7.7	-12.2	567	-11.8	-17.6
Week 10	357	-15.6	-23.1	197	-6.9	-10.0	554	-12.5	-18.4
Week 14	346	-15.7	-23.0	197	-10.1	-16.7	543	-13.7	-20.7
Week 18	339	-16.4	-24.1	194	-12.7	-19.9	533	-15.0	-22.6
Week 28	335	-16.1	-24.8	189	-13.7	-23.5	524	-15.2	-24.3
Week 41	327	-15.9	-24.7	178	-13.9	-23.5	505	-15.2	-24.3
Week 54	322	-14.5	-21.8	169	-13.6	-23.1	491	-14.2	-22.3
Endpoint~	398	-13.6	-19.7	197	-13.1	-22.1	595	-13.4	-20.5

* Aliskiren/valsartan group was patients who received only aliskiren/valsartan. Aliskiren/valsartan/HCTZ group was patients who received HCTZ in addition to aliskiren/valsartan at any time in the study.
# n number of patients with observations at baseline and timepoint. Endpoint was Week 54 value or LOCF.

Overall, more than 85% of patients achieved BP response, and more than 70% achieved BP

control between Week 18 and Week 54 as shown in the following tables 13 and 14. Please be noted that this is an open-labeled without placebo controlled study and it has no randomized withdraw study. Therefore, it would be difficult to evaluate its real efficacy.

Table 13: Patients achieving blood pressure control by visit and treatment group – Study V2301 (Treated population)

	Aliskiren/valsartan* N=404		Aliskiren/valsartan/HCTZ* N=197		Total N=601	
Week (Visit)	**Total**	**n (%)**	**Total**	**n (%)**	**Total**	**n (%)**
Week 2 (Visit 5)	398	166 (41.7)	197	29 (14.7)	595	195 (32.8)
Week 4 (Visit 6)	386	226 (58.5)	196	41 (20.9)	582	267 (45.9)
Week 6 (Visit 7)	370	259 (70.0)	197	38 (19.3)	567	297 (52.4)
Week 10 (Visit 8)	357	308 (86.3)	197	29 (14.7)	554	337 (60.8)
Week 14 (Visit 9)	346	300 (86.7)	197	73 (37.1)	543	373 (68.7)
Week 18 (Visit 10)	339	302 (89.1)	194	105 (54.1)	533	407 (76.4)
Week 28 (Visit 11)	335	297 (88.7)	189	111 (58.7)	524	408 (77.9)
Week 41 (Visit 12)	327	284 (86.9)	178	111 (62.4)	505	395 (78.2)
Week 54 (Visit 13)	322	248 (77.0)	169	104 (61.5)	491	352 (71.7)
Endpoint~	398	284 (71.4)	197	114 (57.9)	595	398 (66.9)

Blood pressure control defined as msDBP < 90 mmHg and msSBP < 140 mmHg.
Total was the number of patients with observations at both baseline and timepoint.
n is the number of patients meeting the criteria for blood pressure control.
Proportions are calculated from the number of patients meeting the criteria for blood pressure control divided by the number of patients with observations at both baseline and endpoint (n/Total).
* Aliskiren/valsartan group is defined as patients who received only aliskiren/valsartan.
Aliskiren/valsartan/HCTZ group is defined as patients who received HCTZ in addition to aliskiren/valsartan at any time during the study.
~ Endpoint was the value at Week 54 or the LOCF based upon the availability of measurements

Table 14: Patients achieving a blood pressure response in msDBP by visit and treatment group – Study V2301 (Treated population)

	Aliskiren/valsartan* N=404		Aliskiren/valsartan/HCTZ* N=197		Total N=601	
Week (Visit)	**Total**	**n (%)**	**Total**	**n (%)**	**Total**	**n (%)**
Week 2 (Visit 5)	398	257 (64.6)	197	80 (40.6)	595	337 (56.6)
Week 4 (Visit 6)	386	312 (80.8)	196	106 (54.1)	582	418 (71.8)
Week 6 (Visit 7)	370	329 (88.9)	197	99 (50.3)	567	428 (75.5)
Week 10 (Visit 8)	357	343 (96.1)	197	90 (45.7)	554	433 (78.2)
Week 14 (Visit 9)	346	330 (95.4)	197	128 (65.0)	543	458 (84.3)
Week 18 (Visit 10)	339	326 (96.2)	194	146 (75.3)	533	472 (88.6)
Week 28 (Visit 11)	335	318 (94.9)	189	156 (82.5)	524	474 (90.5)
Week 41 (Visit 12)	327	311 (95.1)	178	145 (81.5)	505	456 (90.3)
Week 54 (Visit 13)	322	289 (89.8)	169	137 (81.1)	491	426 (86.8)
Endpoint~	398	336 (84.4)	197	155 (78.7)	595	491 (82.5)

Blood pressure response defined as a msDBP < 90 mmHg or a ≥ 10 mmHg reduction from baseline (Visit 4) value.
Total is the number of patients with observations at both baseline and timepoint.
n is the number of patients meeting the criteria for blood pressure control.
Proportions are calculated from the number of patients meeting the criteria for blood pressure control divided by the number of patients with observations at both baseline and timepoint.
* Aliskiren/valsartan group defined as patients who received only aliskiren/valsartan.
Aliskiren/valsartan/HCTZ group defined as patients who received HCTZ in addition to aliskiren/valsartan at any time during the study.
~ Endpoint was the value at Week 54 or the LOCF based upon the availability of measurements.

6.1.4.3 Sub-groups of the study population

The subgroups of the study population were examined to search for differences in efficacy related to the age, gender, race/ethnicity or the disease factors including obesity, diabetes, renal impairment and hypertension stage at baseline. The FDA statistician also examined and compared the efficacy across regions.

Approximately 85% of patients were aged under 65. Baseline msDBP was similar between age and treatment groups. Mean change from baseline at Week 4 endpoint and Week 8 endpoint for both age categories (less than 65, 65 or older) was greatest in the aliskiren/valsartan combination treatment group. For msSBP baseline pressures were lower in the under 65 age group by approximately 8-10 mmHg. At both Week 4 and Week 8 endpoints msSBP had decreased in all treatment groups, with the greatest mean decrease observed for the aliskiren/valsartan combination in both age groups.

Control rates for patients aged less than 65 and those aged 65 and over were greatest for the aliskiren/valsartan combination at Week 8 endpoint. At Week 4 endpoint in patients aged under 65 the control rate was greatest for the aliskiren/valsartan (150/160 mg) combination. For the patients aged 65 or over, control rates at Week 4 endpoint were similar for the aliskiren/valsartan and valsartan treatment groups. Data were summarized in the following tables 15 and 16.

Table 15: Change from baseline to Week 4 Endpoint and Week 8 Endpoint in msDBP and msSBP by age group – Study 2327 (ITT population)

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										
Week 4 Endpoint										
Placebo	391	64	100.7	99.3	95.6	94.7	-5.0	-4.7		
Ali 150 mg	380	50	100.2	100.6	92.8	91.9	-7.5	-8.7	-2.5	-4.0
Val 160 mg	397	56	100.4	100.2	91.5	90.9	-8.9	-9.2	-3.9	-4.5
Ali/Val 150/160 mg	385	53	100.1	99.6	89.3	90.2	-10.8	-9.4	-5.8	-4.7
Week 8 Endpoint										
Placebo	391	64	100.7	99.3	96.6	94.0	-4.0	-5.3		
Ali 300 mg	380	50	100.2	100.6	91.1	92.0	-9.2	-8.6	-5.2	-3.3
Val 320 mg	397	56	100.4	100.2	90.7	89.2	-9.7	-11.0	-5.7	-5.7
Ali/Val 300/320 mg	385	53	100.1	99.6	87.9	87.1	-12.2	-12.5	-8.2	-7.2
msSBP										
Week 4 Endpoint										
Placebo	391	64	153.3	160.1	147.8	154.6	-5.5	-5.5		
Ali 150 mg	380	50	152.8	163.1	142.1	151.0	-10.7	-12.2	-5.2	-6.7
Val 160 mg	397	56	153.2	161.8	142.0	150.4	-11.1	-11.4	-5.6	-5.9
Ali/Val 150/160 mg	385	53	151.7	160.4	136.7	144.8	-15.0	-15.6	-9.5	-10.1
Week 8 Endpoint										
Placebo	391	64	153.3	160.1	148.6	155.0	-4.7	-5.1		
Ali 300 mg	380	50	152.8	163.1	139.9	148.7	-12.9	-14.5	-8.2	-9.4
Val 320 mg	397	56	153.2	161.8	140.0	149.6	-13.1	-12.2	-8.4	-7.1
Ali/Val 300/320 mg	385	53	151.7	160.4	135.0	141.4	-16.7	-19.0	-12.0	-13.9

Table 16: Overall BP control rates (%) at Week 4 (low dose) and Week 8 (high dose) endpoints, by demographic subgroup – Study 2327 (ITT population)

	Low-Dose Week 4 Endpoint (LOCF)				High-Dose Week 8 Endpoint (LOCF)			
	Placebo	Aliskiren 150 mg	Valsartan 160 mg	Ali/Val 150/160	Placebo	Aliskiren 300 mg	Valsartan 320 mg	Ali/Val 300/320
Total, N	**455**	**430**	**453**	**438**	**455**	**430**	**453**	**438**
% of patients	**15.38**	**27.67**	**31.57**	**44.29**	**16.48**	**37.44**	**33.77**	**49.32**
Age group[a]								
< 65 years	391	380	397	385	391	380	397	385
n (% of patients)	63 (16.1)	109 (28.7)	127 (32.0)	179 (46.5)	65 (16.6)	147 (38.7)	139 (35.0)	193 (50.1)
≥ 65 years	64	50	56	53	64	50	56	53
n (% of patients)	7 (10.9)	10 (20.0)	16 (28.6)	15 (28.3)	10 (15.6)	14 (28.0)	14 (25.0)	23 (43.4)
Sex								
Male	278	252	279	270	278	252	279	270
n (% of patients)	40 (14.4)	65 (25.8)	79 (28.3)	117 (43.3)	43 (15.5)	95 (37.7)	89 (31.9)	133 (49.3)
Female	177	178	174	168	177	178	174	168
n (% of patients)	30 (16.9)	54 (30.3)	64 (36.8)	77 (45.8)	32 (18.1)	66 (37.1)	64 (36.8)	83 (49.4)
Race[a]								
Caucasian	346	321	327	333	346	321	327	333
n (% of patients)	46 (13.3)	90 (28.0)	102 (31.2)	155 (46.5)	57 (16.5)	128 (39.9)	109 (33.3)	180 (54.1)
Black	68	69	88	58	68	69	88	58
n (% of patients)	12 (17.6)	15 (21.7)	26 (29.5)	21 (36.2)	10 (14.7)	15 (21.7)	27 (30.7)	22 (37.9)
Ethnicity[a]								
Hispanic	73	66	74	72	73	66	74	72
n (% of patients)	13 (17.8)	15 (22.7)	26 (35.1)	26 (36.1)	14 (19.2)	25 (37.9)	21 (28.4)	32 (44.4)
Obesity, BMI (kg/m^2)[a]								
20 ≤BMI< 30	239	204	220	227	239	204	220	227
n (% of patients)	37 (15.5)	60 (29.4)	70 (31.8)	103 (45.4)	40 (16.7)	75 (36.8)	75 (34.1)	116 (51.1)
BMI ≥ 30	210	217	228	198	210	217	228	198
n (% of patients)	31 (14.8)	55 (25.3)	73 (32.0)	84 (42.4)	32 (15.2)	81 (37.3)	77 (33.8)	94 (47.5)

a: The number of patients in racial subpopulations Asian, Native American, Pacific Islander, and other; in the age subpopulation ≥ 75 years; in ethnicity subpopulations Chinese, Indian, Japanese, and mixed; and in obesity subpopulation BMI < 20 kg/m^2 were too small for meaningful comparisons.

Regarding the race in this study, only five patients were classed as a Pacific islanders, three patients were native Americans, and the Asian and Others sub-populations were also very small making interpretation of these data difficult. Therefore, the comparison is focused on Caucasians and Blacks. After the placebo subtraction, the msDBP change from baseline to Week 8 endpoint for the aliskiren/valsartan combination therapy was -8.8 mmHg, -5.1 mmHg for aliskiren and -6.0 mmHg for valsartan in Caucasians. In Black patients, the mean change from baseline to Week 8 endpoint in msDBP was -6.1 mmHg, -4.0 mmHg and -4.4 mmHg for the aliskiren/valsartan 300/320mg combination, aliskiren 300 mg, and valsartan 320 mg treatment groups, respectively. Similarly, the aliskiren/valsartan combination treatment group had the greatest mean reduction in msSBP at Week 4 and Week 8 endpoints for both Blacks and Caucasians. Data were summarized in the following table 17. It seems that both the monotherapies and the combination therapy are more effective in Caucasians than Blacks.

Table 17: Change from baseline to Week 4 Endpoint and Week 8 Endpoint in msDBP and msSBP by race – Study 2327 (ITT population, Statistician review table)

	Half Dose at 4 weeks				Full Dose at 8 weeks			
	White		Black		White		Black	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Aliskiren	-6.1	-2.9	-4.2	-1.9	-8.6	-5.0	-6.2	-4.0
Valsartan	-6.4	-4.2	-4.4	-3.0	-9.1	-6.0	-4.7	-4.5
Combo	-11.0	-6.4	-4.7	-3.3	-13.6	-8.7	-6.5	-6.1

Change from baseline in msDBP and msSBP by gender is shown in the following table 18. Approximately 60% of patients were male. Baseline msDBP and msSBP were similar between males and females. The change from baseline was greatest in the aliskiren/valsartan treatment group for both genders at Week 4 and Week 8 endpoints.

Table 18: Change from baseline to Week 4 Endpoint and Week 8 Endpoint in msDBP and msSBP by gender – Study 2327 (ITT population)

Treatment	n		Baseline Mean		Endpoint Mean		Change from baseline Mean		Placebo subtracted	
Gender	M	F	M	F	M	F	M	F	M	F
msDBP										
Week 4 Endpoint										
Placebo	278	177	100.7	100.1	95.9	94.8	-4.8	-5.3		
Ali 150 mg	252	178	100.5	99.9	93.2	91.9	-7.3	-8.0	-2.5	-2.7
Val 160 mg	279	174	100.7	99.8	91.9	90.7	-8.8	-9.2	-4.0	-3.9
Ali/Val 150/160 mg	270	168	100.4	99.6	89.7	89.0	-10.6	-10.7	-5.8	-5.4
Week 8 Endpoint										
Placebo	278	177	100.7	100.1	96.5	95.9	-4.2	-4.2		
Ali 300 mg	252	178	100.5	99.9	91.5	90.7	-9.0	-9.3	-4.8	-5.1
Val 320 mg	279	174	100.7	99.8	91.1	89.5	-9.6	-10.3	-5.4	-6.1
Ali/Val 300/320 mg	270	168	100.4	99.6	88.2	87.2	-12.2	-12.4	-8.0	-8.2
msSBP										
Week 4 Endpoint										
Placebo	278	177	153.4	155.4	148.8	148.7	-4.6	-6.8		
Ali 150 mg	252	178	153.5	154.7	143.1	143.2	-10.4	-11.5	-5.8	-4.7
Val 160 mg	279	174	153.8	155.0	142.5	144.0	-11.2	-11.0	-6.6	-4.2
Ali/Val 150/160 mg	270	168	152.1	153.6	137.4	138.1	-14.8	-15.5	-10.2	-8.7
Week 8 Endpoint										
Placebo	278	177	153.4	155.4	149.0	150.1	-4.4	-5.3		
Ali 300 mg	252	178	153.5	154.7	140.5	141.6	-13.0	-13.1	-8.6	-7.8
Val 320 mg	279	174	153.8	155.0	140.8	141.9	-13.0	-13.1	-8.6	-7.8
Ali/Val 300/320 mg	270	168	152.1	153.6	135.8	135.7	-16.4	-17.9	-12.0	-12.6

In the disease factors analysis, all body mass index (BMI) sub-populations showed the greatest mean decrease from baseline in msDBP and msSBP in the aliskiren/valsartan combination treatment group as shown in the following table 19.

Table 19: Blood pressure changes at Week 8 endpoint by body mass index -Study 2327 (ITT population).

BMI category	Placebo		Aliskiren 300 mg		Valsartan 320 mg		Aliskiren/valsartan 300/320 mg	
	Mean change from baseline msDBP (mmHg)							
	n	Mean	n	Mean	n	Mean	n	Mean
< 20 Kg/m^2	3	-3.2	5	-12.5	3	-6.3	8	-15.0
20 to < 30 Kg/m^2	239	-4.6	204	-9.2	220	-10.2	227	-12.8
≥ 30 Kg/m^2	210	-3.8	217	-8.9	228	-9.7	198	-11.7
	Mean change from baseline msSBP (mmHg)							
	n	Mean	n	Mean	N	Mean	n	Mean
< 20 Kg/m^2	3	-5.3	5	-17.5	3	-6.3	8	-31.6
20 to < 30 Kg/m^2	239	-4.2	204	-12.9	220	-14.0	227	-17.6
≥ 30 Kg/m^2	210	-5.3	217	-13.1	228	-12.3	198	-15.8

N = number of patients at baseline and Week 8 endpoint

In patients with mild to moderate renal impairment, the aliskiren/valsartan combination showed greater reductions in msDBP and msSBP, as well as greater BP control rate, than the component monotherapies as shown in the following table 20.

Table 20: Number of patients by disease characteristics at baseline (Study 2327) (ITT population)

Characteristic Category/Statistic	Placebo N=455	Aliskiren N=430	Valsartan N=453	Aliskiren/ Valsartan N=438
Hypertension stage 2, n	279	253	270	242
GFR (ml/min/1.73 m^2), n				
30 ≤ GFR < 60	13	9	10	11
60 ≤ GFR < 90	210	216	219	215
GFR ≥ 90	255	195	219	200
Diabetes (yes), n	39	59	49	44

In the subgroup analysis for patients with stage 2 hypertension, both aliskiren/valsartan combination doses proposed for registration (150/160 mg and 300/320 mg) demonstrated statistically significantly greater msDBP and msSBP reductions than the respective monotherapies. In addition, Statistically significantly greater BP control rates in both the low-dose and high-dose aliskiren/valsartan combinations versus component monotherapies were also observed in overall control rate (percentages of patients with msSBP < 140 mmHg and msDBP < 90 mmHg) in these population. Data were summarized in the following tables 21 and 22.

Table 21: Placebo-subtracted LS mean reduction in msSBP / msDBP (mmHg) at Week 4 (low dose) and Week 8 (high dose) endpoints (Stage 2 hypertension patients) (Study 2327).

	Placebo	Aliskiren 150 mg (Week 4)	Aliskiren 300 mg (Week 8)
Change in msDBP (mmHg) (primary efficacy variable)			
Placebo	----	-2.51[a]	-5.08[a]
Valsartan 160 mg (Week 4)	-3.71[a]	-6.15[a, b, c]	---
Valsartan 320 mg (Week 8)	-5.52[a]	---	-8.75 [a, b, c]
Change in msSBP (mmHg) (key secondary efficacy variable)			
Placebo	----	-5.59[a]	-8.91[a]
Valsartan 160 mg (Week 4)	-6.04[a]	--11.1 [a, b, c]	---
Valsartan 320 mg (Week 8)	-9.03[a]	---	-14.35 [a, b, c]

Endpoint is the LOCF to Week 4/8. Placebo change from baseline:
msDBP was -4.56 mmHg and -3.94 mmHg,. Week 4 and Week 8 endpoints, respectively.
msSBP was -5.85 mmHg and -4.76 mmHg, Week 4 and Week 8 endpoints respectively.
Statistically significant difference (p <0.05): **a**: vs. placebo; **b**: vs. aliskiren component; **c**: vs. valsartan component

Table 22: Overall BP control rates (%) at Week 4 (low dose) and Week 8 (high dose) endpoints (Stage 2 hypertension) (Study 2327)

	Placebo (Week 4 / Week 8)	Aliskiren 150 mg (Week 4)	Aliskiren 300 mg (Week 8)
Overall BP Control Rate (%)**—Stage 2 hypertension**			
Placebo (Week 4 / Week 8)	7.2 / 9.0	14.6[a]	24.5[a]
Valsartan 160 mg (Week 4)	18.1[a]	31.0 [a, b, c]	-----
Valsartan 320 mg (Week 8)	22.6[a]	----	38.4 [a, b, c]

Endpoint is the LOCF to Week 4/8. Blood Pressure Control = msDBP < 90 mm Hg and msSBP < 140 mm Hg
Please refer to Table 4-5 for number of patients in each treatment group with Stage 2 hypertension
Statistically significant difference (p <0.05): **a**: vs. placebo; **b**: vs. aliskiren component; **c**: vs. valsartan component

Regarding a BP control goal of 130/80 mmHg in patients with diabetes or renal disease, a greater proportion of patients with diabetes or different levels of renal impairment treated with either the low-dose or high-dose aliskiren/valsartan combination achieved greater overall BP control rates (defined as msSBP < 130 mmHg and/or msDBP < 80 mmHg) relative to component monotherapies as shown in the following table 23.

Table 23: Overall BP control rates (%) of 130/80 mmHg at Week 4 (low dose) and Week 8 (high dose) endpoints (Study 2327)

BP control (mmHg), % of patients	Low Dose Week 4 (LOCF) msSBP < 130 / msDBP < 80	High Dose Week 8 (LOCF) msSBP < 130 / msDBP < 80
Total		
Placebo (N=455)	1.8	1.5
Aliskiren (N=430)	4.4	7.9
Valsartan (N=453)	6.0	5.5
Aliskiren/Valsartan (N=438)	9.8	16.2
Diabetes (yes)		
Placebo (N=39)	2.6	2.6
Aliskiren (N=59)	6.8	13.6
Valsartan (N=49)	8.2	6.1
Aliskiren/Valsartan (N=44)	9.1	20.5
Renal function: 30 ≤ GFR < 60 (ml/min/1.73 m2)—moderate impairment		
Placebo (N=13)	0	0
Aliskiren (N=9)	0	0
Valsartan (N=10)	0	0
Aliskiren/Valsartan (N=11)	18.2	36.4
Renal function: 60 ≤ GFR < 90 (ml/min/1.73 m2)—mild impairment		
Placebo (N=210)	1.4	1.9
Aliskiren (N=216)	4.2	8.3
Valsartan (N=219)	5.5	5.9
Aliskiren/Valsartan (N=215)	7.9	11.6
Renal function: GFR ≥ 90 (ml/min/1.73 m2)—no impairment		
Placebo (N=225)	2.2	1.3
Aliskiren(N=195)	5.1	7.7
Valsartan (N=219)	6.8	5.5
Aliskiren/Valsartan (N=200)	11.0	19.5

The efficacy was examined and compared across all regions. The result was shown in Table 24. It appears that there are some variations in the efficacy of the combination of Aliskiren/Valsartan across regions, some regions show a higher efficacy (i.e. Spain) and some show a lower efficacy (i.e. Germany South). However, this inconsistent efficacy may not be a big concern, because the trend in reduction of msDBP is obviously shown across regions and the variations may be due to a lower power of a smaller sample size of region.

Table 24 Statistical analysis of change form baseline in mean sitting diastolic blood pressure at Week 8 endpoint by region (ITT, Statistician review table)

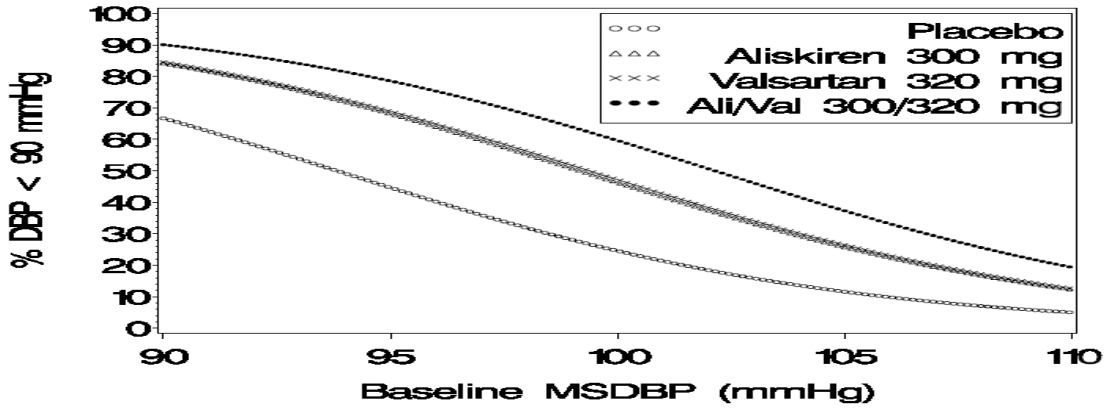
Region (N)	**Treatment Group**	**LSM change from baseline**
US West (288)	Placebo	-4.1
	Aliskiren	-11.3
	Valsartan	-9.4
	Aliskiren/Valsartan	-13.4
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-9.3 (-6.6, -12.1)
	Aliskiren/Valsartan vs. Aliskiren	-2.2 (-0.6, 5.0)
	Aliskiren/Valsartan vs. Valsartan	-4.0 (-1.2, -6.8)
	Treatment Group	**LSM change from baseline**
US West North & West	Placebo	-1.9
	Aliskiren	-9.9

South Central (313)	Valsartan	-10.5
	Aliskiren/Valsartan	-12.1
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-10.2 (-7.4, -12.9)
	Aliskiren/Valsartan vs. Aliskiren	-2.2 (-0.5, 5.0)
	Aliskiren/Valsartan vs. Valsartan	-1.6 (-1.1, 4.4)
	Treatment Group	**LSM change from baseline**
US south Atlantic, East South Central and Puerto Rico (277)	Placebo	-6.6
	Aliskiren	-7.8
	Valsartan	-11.1
	Aliskiren/Valsartan	-12.7
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-6.1 (-3.3, -9.0)
	Aliskiren/Valsartan vs. Aliskiren	-4.9 (-2.0, -7.9)
	Aliskiren/Valsartan vs. Valsartan	-1.6 (-1.2, 4.4)
	Treatment Group	**LSM change from baseline**
US Northeast & East North Central (213)	Placebo	-3.2
	Aliskiren	-8.1
	Valsartan	-8.9
	Aliskiren/Valsartan	-11.8
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-8.6 (-5.1, -12.1)
	Aliskiren/Valsartan vs. Aliskiren	-3.7 (-0.1, -7.2)
	Aliskiren/Valsartan vs. Valsartan	-2.9 (-0.6, 6.3)
	Treatment Group	**LSM change from baseline**
Germany North (288)	Placebo	-6.2
	Aliskiren	-9.9
	Valsartan	-10.8
	Aliskiren/Valsartan	-14.1
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-7.9 (-5.3, -10.6)
	Aliskiren/Valsartan vs. Aliskiren	-4.2 (-1.5, -7.0)
	Aliskiren/Valsartan vs. Valsartan	-3.3 (-0.7, -5.9)
	Treatment Group	**LSM change from baseline**
Germany South (266)	Placebo	-3.0
	Aliskiren	-7.9

	Valsartan	-8.9
	Aliskiren/Valsartan	-9.6
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-6.6 (-3.7, -9.5)
	Aliskiren/Valsartan vs. Aliskiren	-1.8 (-1.2, 4.7)
	Aliskiren/Valsartan vs. Valsartan	-0.7 (-2.3, 3.8)
	Treatment Group	**LSM change from baseline**
Spain (131)	Placebo	-3.8
	Aliskiren	-7.8
	Valsartan	-7.7
	Aliskiren/Valsartan	11.7
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-7.9 (-3.7, -12.0)
	Aliskiren/Valsartan vs. Aliskiren	-4.0 (-0.2, 8.1)
	Aliskiren/Valsartan vs. Valsartan	-4.0 (-0.1, 8.2)

To be considered for first-line therapy with this combination, estimates of the probability of reaching a BP goal (systolic BP <140 or 130 mmHg and diastolic BP <90 or 80 mmHg) at endpoint were determined by analyses using a logistic regression model with baseline as a covariant. Extensive model assessment of goodness-of-fit was required. A statistical review for this analysis and model assessments was prepared in a separate review. As shown in the following figures 4 and 5, as baseline BP increased, the probability of achieving BP control decreased in all groups. However, at all levels of baseline BP, the probability of achieving systolic or diastolic goal was higher with the combination than with either monotherapy. The greater probability of achieving systolic or diastolic goal with the combination over monotherapies was also observed for low dose aliskiren/valsartan 150/160 mg at the week 4 endpoint.

Figure 4: Probability of DBP (< 90 mmHg) control and SBP (< 140 mmHg) control at Week 8 endpoint (ITT population, Study 2327)



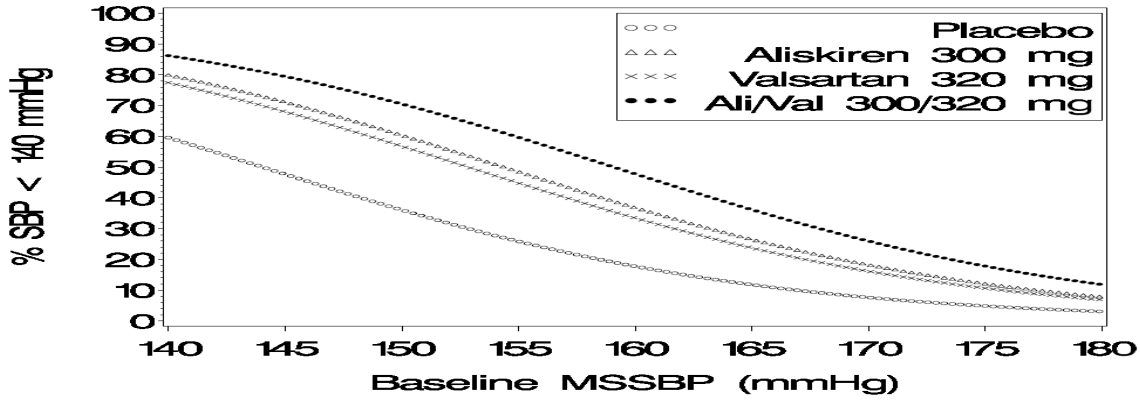
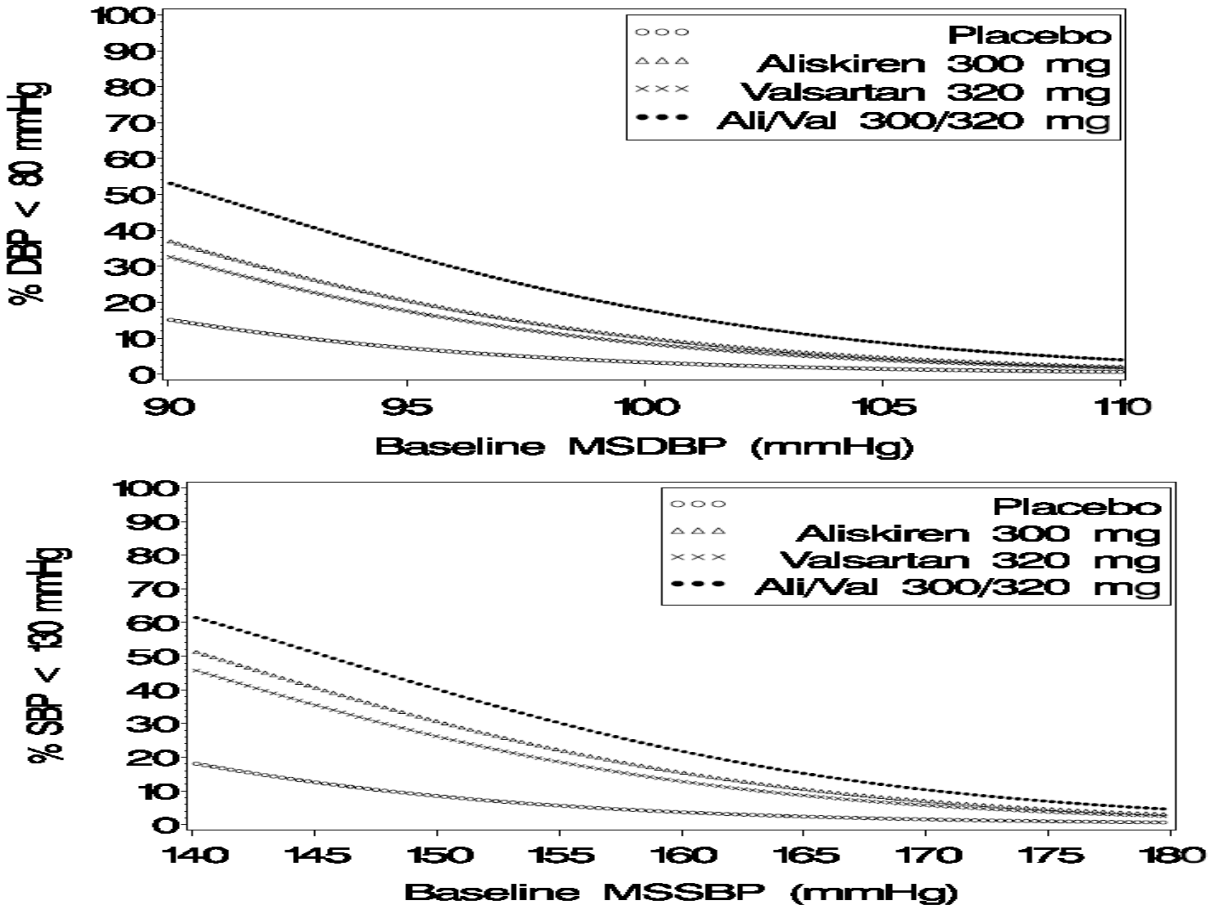


Figure 5: Probability of DBP control (< 80 mmHg) and SBP (<130 mmHg) control at Week 8 endpoint (ITT population, Study 2327)



6.1.4.4 Other supportive trials or Data

Two short term active-controlled studies (Studies CSPP 100A 2203 and 2331) were submitted for analysis of the efficacy.

Study 2203 is a Phase IIB, randomized, double-blind, placebo-controlled, multifactorial, multi-center, parallel-group study of aliskiren alone compared to placebo; the combination of aliskiren and valsartan compared to their component monotherapies; and the combination of valsartan and HCTZ compared to the combination of aliskiren and valsartan in patients with uncomplicated essential hypertension (msDBP $\geq$ 95 mmHg and < 110 mmHg). The study was designed as a pivotal trial for efficacy and safety of aliskiren monotherapy and as proof-of-concept for the combination; and therefore, the combination groups had only approximately one-third the sample size of the aliskiren monotherapy group. The study was comprised of 2 periods:a single-blind placebo run-in period (3-4 weeks), and a randomized, double-blind 8-week treatment period with 11 treatment groups (aliskiren 75 mg, 150 mg or 300 mg; valsartan 80 mg, 160 mg or 320 mg; combination of aliskiren and valsartan 75/80 mg, 150/160 mg, or 300/320 mg; valsartan and HCTZ 160/12.5 mg; and placebo). The primary objective was to confirm the BP lowering effects of aliskiren 75 mg, 150 mg and 300 mg given alone versus placebo at endpoint, and a secondary objective (proof of concept) was to assess the BP lowering effects of the combination of aliskiren and valsartan (75/80 mg, 150/160 mg and 300/320 mg) compared with their component monotherapies at endpoint.

The BP lowering effects in msDBP and msSBP of the combination of aliskiren and valsartan (75/80 mg, 150/160 mg and 300/320 mg) compared with their component monotherapies were not reaching statistical significance. Since there is a substantial placebo effect (placebo LSM change from baseline: -8.6 mm Hg in msDBP and -10.0 mm Hg in msSBP) in this study, it may be difficult to make accurate interpretation of the overall study results. Please see detailed information in the appendix for this study.

Study 2331 is a multicenter, randomized, double-blind, parallel group supportive study conducted in 639 hypertensive patients who were not adequately responsive to HCTZ 25 mg monotherapy. The total duration of study participation for each patient, inclusive of all phases, was approximately 12 weeks, and consisted of a 4-week single-blind run-in period and a 8-week randomized double-blind, treatment period (4 weeks of low-dose treatment, followed by 4 weeks of high-dose treatment), with 4 treatment groups. The primary efficacy variable was the change from baseline in msDBP at the endpoint. Change from baseline in msSBP was a key secondary efficacy variable.

The combination of aliskiren and valsartan with 25 mg HCTZ resulted in statistically greater mean reductions in msDBP and msSBP at the Week 4 (low dose) and Week 8 (high dose) endpoints than either respective low-dose or high-dose combination of monotherapy with HCTZ (aliskiren/HCTZ or valsartan/HCTZ). The study results support the use of aliskiren/valsartan with other antihypertensives such as HCTZ. Data were summarized in the following table 25.

Table 25 Statistical analysis of change from baseline in msDBP and msSBP at Week 4 (low dose) and Week 8 (high dose) Endpoints (ITT population) (Study 2331)

		msDBP		msSBP	
		Low Dose Week 4 (LOCF)	High Dose Week 8 (LOCF)	Low Dose Week 4 (LOCF)	High Dose Week 8 (LOCF)
Treatment group	**N**	**LSM change from baseline(SE)**			
HCTZ	151	-6.5 (0.71)	-6.4 (0.70)	-7.2 (1.08)	-6.3 (1.12)
Ali/HCTZ	164	-10.0 (0.68)	-10.5 (0.67)	-12.7 (1.03)	-15.0 (1.08)
Val/HCTZ	154	-12.1 (0.70)	-13.5 (0.70)	-14.6 (1.07)	-18.3 (1.12)
Ali/val/HCTZ	168	-14.6 (0.67)	-15.9 (0.67)	-18.5 (1.02)	-21.6 (1.07)
Pairwise Comparison		**LSM difference in change from baseline (p-value)**			
Ali/val/HCTZ	vs. Ali/HCTZ	-4.6 (<0.0001*)	-5.4 (<0.0001*)	-5.8 (<0.0001*)	-6.5 (<0.0001*)
Ali/val/HCTZ	vs. Val/HCTZ	-2.5 (0.0109*)	-2.4 (0.0124*)	-3.9 (0.0097*)	-3.3 (0.0350*)
Ali/HCTZ	vs. HCTZ	-3.5 (0.0005*)	-4.1 (<0.0001*)	-5.5 (0.0002*)	-8.7 (<0.0001*)
Val/HCTZ	vs. HCTZ	-5.6 (<0.0001*)	-7.1 (<0.0001*)	-7.5 (<0.0001*)	-12.0 (<0.0001*)
Ali/val/HCTZ	vs. HCTZ	-8.1 (<0.0001*)	-9.6 (<0.0001*)	-11.3 (<0.0001*)	-15.3 (<0.0001*)

Ali = Aliskiren; Val= Valsartan; HCTZ = hydrochlorothiazide. Endpoint is the LOCF to Week 4/8.

Low dose: treatment up to week 4; aliskiren 150 mg/ valsartan 160 mg/ HCTZ 25 mg
High dose: treatment from week 4 to week 8; aliskiren 300 mg/ valsartan 320 mg/ HCTZ 25 mg

SE = Standard Error; LSM = Least Square Mean
Least square mean, and p-values were from an ANCOVA model containing treatment, region, and baseline.
[1] p-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.

6.1.5 Clinical Microbiology

Clinical microbiology is not applicable for this oral formulation.

6.1.6 Efficacy Conclusions

Based on the pivotal study, the combination of aliskiren/valsartan at doses of 300/320 mg and 150/160 mg produced clinically and statistically significantly greater reductions in both diastolic and systolic blood pressure compared to each respective monotherapy. Both individual monotherapy components contributed to the antihypertensive effect of the combination in the overall population. Further BP reduction was observed when the aliskiren/valsartan 150/160 mg dose was increased to aliskiren/valsartan 300/320 mg.

A greater proportion of patients achieving a BP control target of < 140/90 mm Hg was observed in the combination therapy as compared with each respective monotherapy in the overall patient population. This greater BP control rates with aliskiren/valsartan combination over respective monotherapies were attained within 2 weeks after treatment. In the long-term open label study without placebo control, the combination of aliskiren/valsartan has shown a long-term treatment effect for patients with essential hypertension. However, randomized withdraw study was not performed.

In the subgroup analysis, the greater BP lowering effect of the combination therapy of aliskiren/valsartan over the respective monotherapies was observed consistently, regardless of gender, age and disease factors including obesity, diabetes, renal impairment, and stages (stages 1 and 2) of hypertension. Regarding the race in this program, the comparison is focused on the comparison of Caucasians and Blacks due to the small sample size of other races. It seems that both the monotherapies and the combination therapy are more effective in Caucasians than in African Americans.

Based on the probability analysis, the predicted BP control targets of both < 140/90 mmHg and 130/80 mmHg was greater with the combination of aliskiren/valsartan as compared to aliskiren or valsartan monotherapy, regardless of baseline BP.

Data from both the subgroup analysis and the probability analysis of BP control targets support the use of aliskiren/valsartan as initial therapy

7 Integrated Review of Safety

7.1 Methods and Findings

The data sources for supporting the safety claims of this combination product in the original submission were mainly from the three trials including 2 placebo-controlled short-term trials (Studies CSPP 100A 2203 and 2327) and one open-label long-term trial (Study CSPV 100A 2301). Safety data were obtained in a total of 3520 treated patients including 2919 patients from the two short-term placebo controlled studies and 601 patients from the one long-term open-label study with 1225 being exposed to the aliskiren/valsartan combination.

In addition, 639 patients received treatment in a short-term active-controlled supportive study in patients unresponsive to HCTZ 25mg in Study CSPP 100A 2331, including 168 patients who were exposed to aliskiren/valsartan/HCTZ 300/320/25 mg, which provides the safety data of aliskiren/valsartan on top of HCTZ.

Data were summarized in the following tables 26, 27, and 28.

Table 26: Placebo-controlled short-term trials

Study	Study objectives	Patients randomized	Treatment duration	Treatment/dose	Type of control/blinding
CSPP100A2327	Efficacy/safety in hypertensive patients. This was the pivotal trial for this submission.	1797	8 weeks	Placebo; aliskiren 300 mg (titrated from 4 weeks of 150 mg); valsartan 320 mg (titrated from 4 weeks of 160 mg); aliskiren/valsartan 300/320 mg (titrated from 4 weeks of 150/160 mg)	Placebo controlled double-blind
CSPP100A2203	Efficacy/safety in hypertensive patients. Study is proof of concept for the aliskiren/ valsartan combinations.	1123	8 weeks	Placebo; aliskiren 75 mg, 150 mg, 300 mg; valsartan 80 mg, 160 mg, 320 mg; aliskiren/valsartan 75/80 mg, 150/160 mg, 300/320 mg; valsartan/HCTZ 160/12.5 mg	Placebo controlled double-blind

Table 27: Open-label long-term trial

Study	Study objectives	Patients randomized	Treatment duration	Treatment/dose	Type of control/blinding
CSPV100A2301	Safety in hypertensive patients. Long-term exposure.	641*	54 weeks	Aliskiren/valsartan 300/320 mg (titrated from 2 weeks of 150/160 mg) with the option to add HCTZ (12.5 to 25 mg) after 10 weeks	Open-label

* Among 641 randomized patients all 40 randomized patients at site 38 were excluded from study analysis and also from the SCS safety population due to serious GCP noncompliance issues, see details [SPV100A2301 Report-section 9.8]

Table 28: Additional supportive short-term trial

Study / objectives	Patients randomized	Treatment duration	Treatment/dose	Type of control/blinding
CSPP100A2331 / Efficacy and safety of aliskiren/valsartan/ HCTZ in patients with hypertension not adequately controlled with HCTZ monotherapy	641*	4 weeks	Run-in period HCTZ run-in 12.5 mg 1 week, 25 mg 3 weeks	Single-blind
		8 weeks	Randomized treatment period Aliskiren/HCTZ 150/25 mg titrated to 300/25 mg after 4 weeks Valsartan/HCTZ 160/25 mg titrated to 320/25 mg after 4 weeks Aliskiren/valsartan/HCTZ 150/160/25 mg (initial one week of valsartan/HCTZ 160/25 mg) titrated to 300/320/25 mg after 4 weeks HCTZ 25 mg	Double-blind

* Patients were randomized as they entered double-blind period 2.

7.1.1 Deaths

There were 4 deaths occurred during or after completed studies in the two short-term trials. There were no deaths in patients treated with the aliskiren/valsartan combination. There were no deaths in the open-label long-term study (Study V2301). Data were summarized in the following table 29. In addition, one death was recorded in supportive safety study 2331: a 46 year old black female in the valsartan 300 mg/HCTZ 25 mg group died from 'sudden cardiac death' on Day 43 of the study.

Table 29: Death in all three completed studies

Treatment Group Patient No. Age, Gender, Race Treatment duration	Cause of death System organ class preferred term	Comments	Attributed relationship to study drug	
			Investigator	Novartis
During study treatment period				
Placebo				
[2203/0003-00018] 70 year old Caucasian male Died Day 16 of double-blind period (last dose received on Day 16 presumed)	Natural causes. General disorders and admin site conditions. - sudden death	Baseline mean sitting BP 145/97 mmHg at entry. Patient found dead, no unusual circumstances, no autopsy was performed.	Natural causes, not related.	Not noted
Aliskiren mono 300 mg				
[2327/0054-00016] 69 year old Caucasian female Died Day 41 in follow-up period (last dose received on Day 40)	Myocardial infarction Cardiac disorders - myocardial infarction	Baseline ECG normal, mean sitting BP 169/101mmHg at entry. Patient died suddenly, autopsy was performed.	Not related.	Not noted
Valsartan mono 160 mg				
[2327/0548-00026] 45 year old male, 'Other' race Died Day 13 of double-blind period (last dose received on Day 13 presumed)	Disease progression. Vascular disorders - arteriosclerosis	Medical history of left ventricular hypertrophy, diet-controlled diabetes and hyperlipoproteinemia. The patient was found dead at home.	Not related, due to progression of athero-sclerosis.	Not noted
[2203/0506-00019] 52-year-old Caucasian male Died on study day 26 after having been discontinued from the study	Automobile accident	Not noted.	Not related	Not noted

7.1.2 Serious Adverse Events

The incidence rate of other SAEs was lowest in the aliskiren/valsartan group (0.6%), and generally similar across other treatment groups (1.0% -1.3%), in the short-term placebo-controlled studies. There was no system organ class with more than one SAEs in the aliskiren/valsartan group. The system organ class with the most frequent SAEs overall was cardiac disorders, however none were reported in the aliskiren/valsartan regimen. The most frequently reported SAE overall was myocardial infarction reported in one patient in the placebo regimen and two patients in monotherapy aliskiren regimens. Four patients (0.6%) had SAEs while receiving aliskiren/valsartan (aortic aneurysm, intervertebral disc protrusion, prostate cancer, wrist fracture, and thyroidectomy). In comparison, SAEs were reported in 7 patients (1.1%) in the placebo group (atrial flutter, myocardial infarction, ventricular tachycardia, sudden death, CVA, cystitis, headache, hypertension, hypertensive crisis). Data were summarized in the following table 30. No patients reported an SAE in the aliskiren/valsartan/ HCTZ group.

Table 30: Serious AEs by primary system organ class, in the short-term placebo-controlled studies.

	Plac-ebo	Aliskiren				Valsartan				Aliskiren/Valsartan				Val/HCT Z
Primary System organ class	N=635 n (%)	75mg N=179 n (%)	150mg N=615 n (%)	300mg N=569 n (%)	Mono All N=969 n (%)	80mg N=58 n (%)	160mg N=514 n (%)	320mg N=487 n (%)	Mono All N=632 n (%)	75/ 80mg N=60 n (%)	150/ 160mg N=506 n (%)	300/ 320mg N=473 n (%)	All Ali/Val N=624 n (%)	160mg /12.5mg N=59 n (%)
Any organ class	7 (1.1)	1 (0.6)	4 (0.7)	5 (0.9)	10 (1.0)	0	6 (1.2)	2 (0.4)	8 (1.3)	0	2 (0.4)	2 (0.4)	4 (0.6)	0
Cardiac disorders	2 (0.3)	1 (0.6)	0	2 (0.4)	3 (0.3)	0	1 (0.2)	0	1 (0.2)	0	0	0	0	0
GI disorders	0	0	1 (0.2)	1 (0.2)	2 (0.2)	0	0	0	0	0	0	0	0	0
Gen disorders	1 (0.2)	0	1 (0.2)	0	1 (0.1)	0	0	0	0	0	0	0	0	0
Infections and infestations	1 (0.2)	0	0	0	0	0	1 (0.2)	0	1 (0.2)	0	0	0	0	0
Injury, poisoning and procedural comp.	0	0	0	0	0	0	1 (0.2)	0	1 (0.2)	0	1 (0.2)	0	1 (0.2)	0
Musculoskeletal and connective tissue	0	0	0	0	0	0	0	0	0	0	0	1 (0.2)	1 (0.2)	0
Neoplasms benign, malignant and unspec.	0	0	0	0	0	0	1 (0.2)	1 (0.2)	2 (0.3)	0	0	1 (0.2)	1 (0.2)	0
Nervous system	2 (0.3)	0	1 (0.2)	0	1 (0.1)	0	0	1 (0.2)	1 (0.2)	0	0	0	0	0
Pregnancy, puerp. & perinatal conditions	0	0	0	1 (0.2)	1 (0.1)	0	0	0	0	0	0	0	0	0
Renal and urinary	0	0	1 (0.2)	0	1 (0.1)	0	0	0	0	0	0	0	0	0
Resp., thoracic and mediastinal disorders	0	0	0	0	0	0	1 (0.2)	0	1 (0.2)	0	0	0	0	0
Skin & subcutaneous	0	0	0	0	0	0	1 (0.2)	0	1 (0.2)	0	0	0	0	0
Surgical and medical	0	0	0	0	0	0	0	0	0	0	1 (0.2)	0	1 (0.2)	0
Vascular disorders	2 (0.3)	0	0	1 (0.2)	1 (0.1)	0	1 (0.2)	0	1 (0.2)	0	0	1 (0.2)	1 (0.2)	0

In the open-label long-term study, SAEs were observed in 22 patients (3.7%). The most frequently affected primary system organ classes were cardiac disorders (0.8%) and vascular disorders (0.7%). Two patients had SAEs that were suspected to be related to study medication. Both these patients were receiving aliskiren 300mg/valsartan 320 mg at the time of the events. One patient (0084-00004), with a significant medical history that included syncope and hypercholesterolemia, and concomitant medications during the study of naproxen, amitryptiline, rosuvastatin calcium and diclofenac, was hospitalized with SAEs of subdural hematoma, intracerebral bleeding and syncope, which were continuing at the time when patient permanently discontinued from the study. Another patient (0503-00007) had severe hypotension and required hospitalization, resolved after 2 days and required discontinuation from study medication. Data were summarized in the following table 31.

Table 31: Serious adverse events by primary system organ class in long-term open-label study (treated population)

	Aliskiren/valsartan				
Primary System Organ Class	Alis 150mg / vals 160 mg N = 601 n (%)	Alis 300mg / vals 320 mg N = 585 n (%)	Aliskiren /valsartan all N=601 n (%)	Aliskiren/ valsartan/ HCTZ N = 197 n (%)	Total N = 601 n (%)
Any organ class	3 (0.5)	14 (2.4)	17 (2.8)	5 (2.5)	22 (3.7)
Cardiac disorders	2 (0.3)	2 (0.3)	4 (0.7)	1 (0.5)	5 (0.8)
Eye disorders	1 (0.2)	0	1 (0.2)	0	1 (0.2)
Gastrointestinal disorders	0	1 (0.2)	1 (0.2)	0	1 (0.2)
General disorders and admin. site conditions	0	1 (0.2)	1 (0.2)	0	1 (0.2)
Hepatobiliary disorders	0	1 (0.2)	1 (0.2)	0	1 (0.2)
Infections and infestations	0	1 (0.2)	1 (0.2)	1 (0.5)	2 (0.3)
Injury, poisoning and procedural complications	0	3 (0.5)	3 (0.5)	0	3 (0.5)
Metabolism and nutrition disorders	0	0	0	1 (0.5)	1 (0.2)
Musculoskeletal and conn. Tissue disorders	0	2 (0.3)	2 (0.3)	1 (0.5)	3 (0.5)
Neoplasms benign, malignant and unspecified	0	1 (0.2)	1 (0.2)	1 (0.5)	2 (0.3)
Nervous system disorders	1 (0.2)	1 (0.2)	2 (0.3)	0	2 (0.3)
Psychiatric disorders	0	1 (0.2)	1 (0.2)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	0	1 (0.2)	1 (0.2)	1 (0.5)	2 (0.3)
Vascular disorders	0	3 (0.5)	3 (0.5)	1 (0.5)	4 (0.7)

Preferred terms are sorted in descending frequency, as reported in aliskiren 300 mg / valsartan 320 mg alone.
A patient with multiple episodes of an adverse event is counted only once.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In the short-term, placebo-controlled studies, there were no meaningful differences among groups, other than a higher number of dropouts in the placebo and aliskiren 75 mg groups due to lack of efficacy, and there was no indication that use of the aliskiren/valsartan combination was associated with more withdrawals for safety reasons. Overall, >87% of patients completed the studies, with the highest rate of discontinuations seen in the placebo group, primarily due to lack of efficacy. The dropout rate due to safety (AEs, abnormal laboratory values, and abnormal test procedures) in the aliskiren/valsartan 300/320 mg combination group was similar to the placebo group and other monotherapy groups. Data were summarized in the following table 32.

Table 32: Overall profile of dropout rates in short-term, placebo-controlled studies.

				Discontinued n (%)			
Treatment Group	Randomized	Treated n (%)	Completed n (%)	Total	Safety	Lack of efficacy	Other
Placebo	636	635 (99.8)	558 (87.7)	78 (12.3)	18 (2.8)	41 (6.4)	19 (3.0)
Ali 75 mg	179	179 (100.0)	158 (88.3)	21 (11.7)	5 (2.8)	10 (5.6)	6 (3.4)
Ali 150 mg	178	178 (100.0)	165 (92.7)	13 (7.3)	3 (1.7)	4 (2.2)	6 (3.4)
Ali 300 mg	612	612 (100.0)	550 (89.9)	62 (10.1)	17 (2.8)	17 (2.8)	28 (4.6)
Mono Ali	969	969 (100.0)	873 (90.1)	96 (9.9)	25 (2.6)	31 (3.2)	40 (4.1)
Val 80 mg	58	58 (100.0)	54 (93.1)	4 (6.9)	0	2 (3.4)	2 (3.4)
Val 160 mg	59	59 (100.0)	52 (88.1)	7 (11.9)	2 (3.4)	0	5 (8.5)
Val 320 mg	515	515 (100.0)	467 (90.7)	48 (9.3)	15 (2.9)	14 (2.7)	19 (3.7)
Mono Val	632	632 (100.0)	573 (90.7)	59 (9.3)	17 (2.7)	16 (2.5)	26 (4.1)
Ali/Val 75/80 mg	60	60 (100.0)	55 (91.7)	5 (8.3)	0	2 (3.3)	3 (5.0)
Ali/Val 150/160 mg	60	60 (100.0)	56 (93.3)	4 (6.7)	1 (1.7)	0	3 (5.0)
Ali/Val 300/320 mg	504	504 (100.0)	464 (92.1)	40 (7.9)	10 (2.0)	7 (1.4)	23 (4.6)
All Ali/Val	624	624 (100.0)	575 (92.1)	49 (7.9)	11 (1.8)	9 (1.4)	29 (4.6)
Val/HCTZ	59	59 (100.0)	56 (94.9)	3 (5.1)	0	0	3 (5.1)

Safety = Adverse event(s), death, abnormal laboratory values, abnormal test procedure result(s)
Other = Administrative problems, subject's condition no longer requires study drug, lost to follow up, subject withdrawal consent, protocol violation, or other

In the long-term open-label study, overall, 80.9% of patients completed the study. The total discontinuation due to AE and laboratory abnormalities was low (7.2%) considering the length of the study. The difference in safety discontinuations between aliskiren/valsartan (9.2%) and aliskiren/valsartan/HCTZ (3.0%) as shown in the following table 33 is probably due to a combination of factors such as shorter duration of exposure to aliskiren/valsartan/HCTZ and all patients having already been exposed to the aliskiren/valsartan treatment before receiving HCTZ.

Table 33: Overall profile of dropout rates in long-term open-label study

			Discontinued n (%)			
Treatment Group	Enrolled	Completed n (%)	Total	Safety	Lack of efficacy	Other
Aliskiren/valsartan	404	320 (79.2)	84 (20.8)	37 (9.2)	15 (3.7)	32 (7.9)
Alisk/valsartan/HCTZ	197	166 (84.3)	31 (15.7)	6 (3.0)	8 (4.1)	17 (8.6)
Total	**601**	**486 (80.9)**	**115 (19.1)**	**43 (7.2)**	**23 (3.8)**	**49 (8.2)**

Safety = Adverse event(s), death, abnormal laboratory values, abnormal test procedure result(s).
Other = Administrative problems, subject's condition no longer requires study drug, lost to follow up, subject withdrawal consent, protocol violation, or other.

7.1.3.2 Adverse events associated with dropouts

In the short-term placebo-controlled studies, the incidence of AEs leading to discontinuation was 2.7% in patients treated with placebo, 2.0% in patients treated with aliskiren monotherapy, 2.7% in patients treated with valsartan monotherapy, and 1.4% of patients treated with aliskiren/ valsartan combination treatment. Headache was the most frequent AE leading to discontinuation, reported in 5 (0.8%) patients receiving placebo, 2 (0.2%) patients receiving aliskiren monotherapy, and 4 (0.6%) patients receiving valsartan monotherapy. No patient receiving aliskiren/valsartan combination treatment discontinued due to headache. Fatigue was reported for 1 patient (0.2%) with placebo, 1 (0.1%) with aliskiren monotherapy, 2 (0.3%) with valsartan monotherapy, and 3 (0.5%) patients treated with aliskiren/valsartan combination treatment, and dizziness was reported for 1 patient (0.2%) with placebo, 3 (0.5%) with valsartan monotherapy, and none in aliskiren monotherapy or aliskiren/valsartan combination treatment. All other preferred terms reported as the reason for discontinuation were experienced by only one or two patients in any treatment group.

SAEs leading to study discontinuation in short-term placebo-controlled studies are summarized by system organ class in the following table 34. The proportion of patients with any SAE leading to study discontinuation was generally similar across all treatment groups. In the aliskiren /valsartan combination group, no patients discontinued due to an SAE. In other treatment groups SAEs necessitating discontinuation were in 5 (0.8%) patients on placebo, 8 (0.8%) on aliskiren monotherapy, and 6 (0.9%) on valsartan monotherapy. The system organ class with the most SAEs leading to study discontinuation was cardiac disorders (6 patients in total); Vascular disorder recorded 3 patients who discontinued, while all other system organ classes only recorded 1 or 2 patients discontinuing due to an SAE.

Table 34: Serious adverse events leading to discontinuation, by primary system organ class and treatment groups in short term, double-blind, placebo controlled studies

	Placebo	Aliskiren				Valsartan				Aliskiren/Valsartan			
Primary System Organ Class	N=635 n (%)	75mg N=179 n (%)	150mg N=615 n (%)	300mg N=569 n (%)	Mono All N=969 n (%)	80mg N=58 n (%)	160mg N=514 n (%)	320mg N=487 n (%)	Mono All N=632 n (%)	75/ 80mg N=60 n (%)	150/ 160mg N=506 n (%)	300/ 320mg N=473 n (%)	All Ali/Val N=624 n (%)
Any organ class	5 (0.8)	1 (0.6)	4 (0.7)	3 (0.5)	8 (0.8)	0	4 (0.8)	2 (0.4)	6 (0.9)	0	0	0	0
Cardiac disorders	2 (0.3)	1 (0.6)	0	2 (0.4)	3 (0.3)	0	1 (0.2)	0	1 (0.2)	0	0	0	0
Gastrointestinal disorders	0	0	1 (0.2)	0	1 (0.1)	0	0	0	0	0	0	0	0
Gen disorders	1 (0.2)	0	1 (0.2)	0	1 (0.1)	0	0	0	0	0	0	0	0
Neoplasms benign, malignant and unspec.	0	0	0	0	0	0	1 (0.2)	1 (0.2)	2 (0.3)	0	0	0	0
Nervous system	0	0	1 (0.2)	0	1 (0.1)	0	0	1 (0.2)	1 (0.2)	0	0	0	0
Pregnancy, puerp. & perinatal conditions	0	0	0	1 (0.2)	1 (0.1)	0	0	0	0	0	0	0	0
Renal and urinary disorders	0	0	1 (0.2)	0	1 (0.1)	0	0	0	0	0	0	0	0
Skin & subcutaneous tissue disorders	0	0	0	0	0	0	1 (0.2)	0	1 (0.2)	0	0	0	0
Vascular disorders	2 (0.3)	0	0	0	0	0	1 (0.2)	0	1 (0.2)	0	0	0	0

Note: the valsartan 160 mg / HCTZ 12.5 mg treatment group is omitted from this table for space-saving presentation. No SAEs were reported in this group

In the long term, open-label study, discontinuations due to adverse events were 6.7% overall. Dizziness was the most frequently specified AE leading to discontinuation (6 patients, 1%). Headache and hypotension each led to the discontinuation of 4 (0.7%) patients. Three patients (0.5%) discontinued due to fatigue, 2 patients each (0.3%) discontinued due to diarrhea and hyperkalemia, and one patient (aliskiren/valsartan/HCTZ group) discontinued due to rash. Discontinuation due to other individual AEs occurred in less than 1% of total patients. Regarding SAEs lead discontinuation, 8/601 (1.3%) patients discontinued study treatment due to SAEs. In two of these patients the SAEs were considered related to study drug. Both patients were hospitalized, and had study drug permanently discontinued as described in the section of 7.1.2.

In the supportive study 2311, approximately 3% of patients in total discontinued from the study due to AEs, 4 (2.6%) patients on HCTZ monotherapy, 5 (3.0%) patients on aliskiren/HCTZ dual therapy, 5 (3.2%) patients on valsartan/HCTZ dual therapy, and 4 (2.4%) patients on aliskiren/valsartan/HCTZ triple therapy. Dizziness resulted in the discontinuation of three patients, hypotension in a further three, and peripheral edema in two. Other preferred terms were only reported by one patient each.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Renal function

Drugs that inhibit the renin-angiotensin-aldosterone system may be associated with changes in renal function in susceptible individuals, especially in patients with pre-existing renal disease or diabetes. In the placebo-controlled studies, increases in BUN over 14.28 mmol/L were observed in two patients (one in aliskiren monotherapy, one in valsartan monotherapy

regimens). Increases in creatinine to >176.8 μmol/L (2 mg/dl) were reported in four patients (0.7%) receiving aliskiren/ valsartan and two patients in each of the monotherapy regimens (0.2% and 0.3% in the aliskiren and valsartan groups, respectively. In addition, increases both in creatinine to > 132.6 μmol/L (1.5 mg/dl) and > 30% from baseline were observed in 9 patients receiving aliskiren/valsartan and 4 patients receiving aliskiren, 2 patients receiving valsartan and no patients in placebo. Of these 14 patients, abnormal values of serum creatinine in 3 patients (0.5%) in the aliskiren/valsartan group were not returned to normal range at the end of study or follow up.

One patient in aliskiren/valsartan group had renal failure reported as an AE. This was reported for a 58-year old woman following treatment for 15 days with aliskiren/valsartan 150/160 mg. Elevated creatinine (97.2 μmol/L) was reported at Visit 1 (Day -30); however, BUN was within normal limits (8.9 mmol/L). At Study Day 1 (baseline), creatinine (70.7 μmol/L) and BUN (7.9 mmol/L) were within normal limits, and treatment was initiated. On Day 15, the patient experienced an elevated creatinine (88.4 μmol/L) and BUN (10.7 mmol/L). The investigator suspected that the renal failure was related to study drug, but did not discontinue treatment. The duration of renal failure was 16 days. By Day 30, creatinine was back within normal limits (70.7 μmol/L); and BUN was lower but still elevated (9.3 mmol/L). The patient completed the study, at which time (Day 57) creatinine (70.7 μmol/L) and BUN (7.9 mmol/L) were within normal limits.

Similar results were observed in the long-term, open-label study, where the incidence of elevated BUN was reported in 5 patients (0.9%) > 14.28 mmol/L and elevated creatinine in two patients (0.3%) > 176.8 umol/L. There were 12 patients with elevated serum creatinine in both >30% increase from baseline and > 132.6 umol/L. Nine was returned to baseline at the end of study without the disruption of the drug study.

Please see detailed information in laboratory findings in the section of 7.1.7.

7.1.3.3.2 Hyperkalemia

Drugs that inhibit the renin system are known to lead to increases in potassium concentrations. Hyperkalemia was not reported as an AE in the placebo-controlled studies but some specified elevations in potassium were seen in laboratory measurements. In the long term open label study, hyperkalemia was reported as an AE in 6 (1.0%) of patients in the total group, with one (0.2%) further patient reporting 'blood potassium increased', two of the patients discontinued due to hyperkalemia: one event lasted for 38 days (0526-00001), and one event was ongoing at discontinuation (0503-00001).

In the short-term, placebo-controlled pivotal study, the combination of aliskiren/valsartan was associated with a higher proportion of patients with hyperkalemia (defined as K^+ >5.5 mmol/L at any post baseline visit) than in other treatment groups. Patient numbers (%) were: aliskiren/ valsartan 20/624 (3.4%), placebo 13/635 (2.1%), aliskiren 7/632 (1.2%) and valsartan 9/969 (1.0%). This incidence rate of hyperkalemia (K^+ >5.5 mmol/L) in placebo (2.1%) was higher than any other previous aliskiren studies. By checking the original data, the reviewer found that 6 patients in the placebo group have the serum level of potassium more than 7.5 mmol/L (7.5 to 9.4 mmol/L) without any further examination and AE report. There was only one patient

with such serum level of potassium (7.7mmol/L) in the aliskiren group and none in other study groups. Therefore, the reviewer believes that the incidence rates of hyperkalemia in the placebo group in this pivotal study is not correct.

In this pivotal study, 14 of the 20 aliskiren/valsartan combination patients who had potassium >5.5 mmol/L during the study had the values return to below 5.5 mmol/L at a later visit without treatment interruption. Elevated serum potassium during therapy with the combination of aliskiren/ valsartan was more frequent in males (16 patients 4.5%) than females (4 patients 1.7%). A higher proportion of patients with eGFR <60 mL/min/1.73m2 had hyperkalemia (K+ >5.5 mmol/L) (3/18 patients 17.6%) compared to patients with normal renal function (17/570 patients 3.0%). Diabetes did not appear to impact on serum potassium levels. Serum potassium measurements >5.5mmol/L were not seen in any of the 63 diabetic patients in the all aliskiren/valsartan treatment group. Again, there were some measured errors in this pivotal study since several patients had serum level of potassium more than 7 mmol/L without any re-examination and AE reports.

In the long-term Study, overall, 20/601 patients (3.3%) had at least one time potassium > 5.5 mmol/L, and this occurred more frequently in patients not receiving HCTZ add-on. Three patients (0.5%) had serum potassium ≥6.0 mmol/L. 6 patients (1.0%) with hyperkalemia were reported as AEs. The incidents occurred in five patients treated with aliskiren 300 mg / valsartan 320 mg and one patient while treated with aliskiren/valsartan/HCTZ. Two of the patients discontinued due to hyperkalemia: one event lasted for 38 days, and one event was continuing at discontinuation. The remaining four patients with hyperkalemia had events that did not require additional treatment or study drug interruption. Two of these patients completed the study, and two discontinued participation for reasons unrelated to hyperkalemia. Among the 20 patients whose potassium values exceeded 5.5 mmol/L, 16 had transient elevations that returned to below 5.5 mmol/L at subsequent or final visits. In aliskiren/valsartan patients with a low eGFR of <60 only 1/22 patients (4.8%) not receiving HCTZ and 1/13 (7.7%) receiving HCTZ had a potassium measurement of >5.5 mmol/L. Neither of these had levels of ≥ 6.0mmol/L, however the small number of patients in the low eGFR category make any conclusions difficult. Like in the short-term placebo-controlled studies, diabetic status in this study did not appear to have an impact of potassium elevation either. Potassium >5.5mmol/L were seen in 2/67 (3.0%) diabetic patients and in 18/521 (3.4%) non-diabetic patients. Detailed information was provided in the laboratory findings in the section of 7.1.7.

7.1.3.3.3 GI toxicity

Dose-related diarrhea was observed in aliskiren monotherapy (original review of NDA 21-985). In the short term controlled studies, the incidence of diarrhea was similar between the combination group and the aliskiren monotherapy group, and higher than the placebo and valsartan groups: 6 (0.9%) patients in the placebo group, 16 (1.7%) in the aliskiren group, 5 (0.8%) in the valsartan group, and 9 (1.4%) in the aliskiren/valsartan group. None of the diarrhea events were serious adverse events. There were two cases of diarrhea rated as severe in Study 2203 (one in the aliskiren/valsartan 150/160 mg group, and one in the aliskiren 300 mg group), and no cases of severe diarrhea in Study 2327. None of the AEs of diarrhea in aliskiren/valsartan group resulted in study drug discontinuation in these trials.

In the long-term open label study, diarrhea was reported in 42 (7.0%) patients during the 1-year study. None of the diarrhea AEs were serious. Only two patients (0.3%) discontinued due to diarrhea (moderate in severity, study-drug related) while receiving aliskiren 300 mg/valsartan 320 mg. Only one patient (aliskiren/valsartan 150/160mg) experienced an AE of diarrhea rated as severe. In the aliskiren/valsartan/HCTZ group of Study 2331, diarrhea was reported in 2 (1.2%) of patients and was not severe.

7.1.3.3.4 Cough

Cough was common in ACE inhibitors. It seems that the incidence rate of cough was slightly lower in aliskiren monotherapy than in the ACE inhibitors (NDA 21, 985). In this NDA, the incidence rate of cough was low and was reported only by less than 2% of any treatment group in the placebo-controlled studies and there was no evidence of a dose response relationship for cough in patients treated with aliskiren/ valsartan, where the overall rate was 0.5%, compared with 0.8% in the placebo group, 1.0% with aliskiren monotherapy, and 0.5% with valsartan monotherapy.

In the long-term study, cough was reported in 29 patients (4.8%), with similar rates whether or not optional HCTZ was added.

7.1.3.3.5 Anemia

Small decreases in hemoglobin and hematocrit are seen with other agents acting on the RAS, such as ACEIs and ARBs. A slight decrease in mean hemoglobin was also observed in the aliskiren monotherapy in the original NDA (NDA 21-985). In the short-term studies in this NDA, the incidence rate of decreased hematocrit/hemoglobin was higher in the aliskiren/valsartan group than in placebo and monotherapy groups. The mean change of hemoglobin from baseline was 0.7 g/dL in placebo; -0.4 g/L in aliskiren; -1.3 g/L in valsartan; and -2.6 g/L in the combination. The mean changes in hematocrit were ranged from +0.005 in the placebo group to –0.009 in the aliskiren/valsartan 150/160 mg group. There was only one patient (aliskiren/valsartan 300/320 mg) with >20% decrease in hemoglobin, and the hemoglobin level remained within the normal range. The anemia reported as an AE was reported in one patient each in the aliskiren and valsartan monotherapy treatment groups, and one in the aliskiren/valsartan combination group. No patients discontinued therapy due to anemia. None of the patients had hematology abnormalities considered AEs that led to study drug discontinuation. Details of hematology findings are summarized in Section 7.1.7.

In the long-term study, the mean change in hematocrit in the total group was +0.001 from baseline. Addition of HCTZ to the aliskiren/valsartan combination did not make any difference to the mean hematocrit. Eight patients (1.4%) had hemoglobin decrease more than 20% from the baseline.

7.1.3.3.6 Angioedema

Angioedema is a known serious side effect of ACEIs. It has also been reported in patients who were treated with ARBs but the causality relationship between the event and ARB treatment has not been clearly established. In short-term studies, there were no angioedema cases reported in aliskiren or aliskiren/valsartan groups. There was one event of angioedema in the

valsartan group, (valsartan 160 mg): a 57 year-old Caucasian female with a prior history of facial angioedema while receiving an ACEI, experienced angioneurotic edema on Study day 28. Study drug was stopped on day 33 and the condition resolved spontaneously without treatment three days later. The patient discontinued from the study at this time due to this event.

There were no reports of angioedema in the long-term study. There was one case of general edema and one case of eyelid edema.

7.1.4 Other Search Strategies

I reviewed the submitted data sets to determine if the adverse events were consistent with what was reported in the Clinical Study Reports.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The sponsor reported that the information about adverse events was collected in clinical trials. An adverse event (AE) was defined as any undesirable sign, symptom or medical condition occurring after starting study drug even if the event was not considered to be related to study drug. AEs could be volunteered by the subject, discovered during general questioning by the investigator or detected through physical examination, laboratory test or other means. Medical conditions/diseases present before starting study treatment were only considered AEs if they worsened after starting study treatment. AEs occurring before starting study treatment but after signing the informed consent form were recorded on the Medical History/Current Medical Conditions Case Report Form (CRF). Each AE was also described by its duration (start and end dates), the severity grade (mild, moderate, severe), its relationship to the study drug (suspected/not suspected), the actions taken, and the outcome.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The AE terms used in this application were the preferred terms included in the Medical Dictionary for Drug Regulatory Affairs (MedDRA). Because this dictionary is periodically updated, the terms may differ slightly from those used in some of the individual study reports. As a result, there may be minor differences in the counts of certain categories of events. However, these coding variations apply equally to all treatment groups and should be acceptable.

7.1.5.3 Incidence of common adverse events

For common adverse events the sponsor tabulated event rates in two pooled studies including the short-term placebo-controlled studies and the long-term open-label studies.

7.1.5.4 Common adverse event tables

The most frequently (≥ 2% in any treatment group) observed AEs in the short-term placebo controlled studies are summarized in the following table 35. No dose dependency of adverse events was observed for the aliskiren/valsartan combination or for either of its component monotherapy groups. Headache was the most common AE in all treatment groups with the highest incidence seen in placebo (8.8%). The incidence of dizziness was low in aliskiren/valsartan treated patients (0.8% and 1.6% in 300/320 mg group and the combined dose groups, respectively), which is numerically lower than that in placebo, aliskiren monotherapy and valsartan monotherapy.

Diarrhea, the identified ADR during the aliskiren monotherapy program, especially notable at doses higher than 300 mg, was uncommon with aliskiren/valsartan treatment (up to 300/320 mg) with an incidence of 1.4%, similar to that of aliskiren monotherapy (1.7%). None of the diarrhea events were serious adverse events.

Fatigue was occurring more frequently in the aliskiren/valsartan combination (2.6% in the combined dose groups) compared with the placebo group (1.4%). The incidence of fatigue in the individual dose groups of aliskiren/valsartan (ranging from 1.3% in 300/320 mg group to 2.0% in 150/160 mg group) was similar to placebo. Fatigue was 2% and 2.2% in the aliskiren and valsartan monotherapy groups respectively, similar to that in the aliskiren/valsartan group.

Nasopharyngitis was reported as an AE in 2.6% in patients treated with aliskiren/valsartan combination similar to patient treated with the placebo (2.2%), and lower than the valsartan monotherapy group (3.5%),. The incidence of nasopharyngitis in aliskiren monotherapy group was 1.9%.

Rash was uncommon. The incidence of rash (including generalized, pruritic, and butterfly rashes) was low and similar between the treatment groups (8 patients overall; 2 patients with aliskiren/valsartan, 4 with aliskiren monotherapy; 1 with valsartan monotherapy; and 1 with placebo).

Table 35: Number (%) of patients with most frequent AEs (>= 2% for any group) (safety population) by preferred term in short term, double-blind, placebo controlled studies

	Placebo	Aliskiren				Valsartan				Aliskiren/Valsartan				Val/HCTZ
Preferred term	N=635 n (%)	75mg N=179 n (%)	150mg N=615 n (%)	300mg N=569 n (%)	Mono All N=969 n (%)	80mg N=58 n (%)	160mg N=514 n (%)	320mg N=487 n (%)	Mono All N=632 n (%)	75/ 80mg N=60 n (%)	150/ 160mg N=506 n (%)	300/ 320mg N=473 n (%)	All Ali/Val N=624 n (%)	160mg /12.5mg N=59 n (%)
Any adverse experience	225 (35.4)	63 (35.2)	164 (26.7)	121 (21.3)	321 (33.1)	19 (32.8)	143 (27.8)	102 (20.9)	221 (35.0)	20 (33.3)	124 (24.5)	93 (19.7)	210 (33.7)	13 (22.0)
Headache	56 (8.8)	15 (8.4)	21 (3.4)	10 (1.8)	45 (4.6)	3 (5.2)	20 (3.9)	13 (2.7)	34 (5.4)	3 (5.0)	15 (3.0)	11 (2.3)	28 (4.5)	0
Fatigue	9 (1.4)	7 (3.9)	6 (1.0)	6 (1.1)	19 (2.0)	0	11 (2.1)	3 (0.6)	14 (2.2)	1 (1.7)	10 (2.0)	6 (1.3)	16 (2.6)	0
Naso-pharyngitis	14 (2.2)	1 (0.6)	10 (1.6)	7 (1.2)	18 (1.9)	1 (1.7)	16 (3.1)	5 (1.0)	22 (3.5)	2 (3.3)	8 (1.6)	6 (1.3)	16 (2.6)	0
Back pain	11 (1.7)	2 (1.1)	7 (1.1)	7 (1.2)	16 (1.7)	1 (1.7)	3 (0.6)	7 (1.4)	11 (1.7)	2 (3.3)	5 (1.0)	3 (0.6)	10 (1.6)	1 (1.7)
Dizziness	11 (1.7)	4 (2.2)	8 (1.3)	7 (1.2)	19 (2.0)	0	6 (1.2)	7 (1.4)	13 (2.1)	1 (1.7)	5 (1.0)	4 (0.8)	10 (1.6)	0
Nausea	12 (1.9)	4 (2.2)	4 (0.7)	4 (0.7)	12 (1.2)	0	7 (1.4)	3 (0.6)	10 (1.6)	0	8 (1.6)	2 (0.4)	9 (1.4)	0
Bronchitis	6 (0.9)	2 (1.1)	3 (0.5)	4 (0.7)	7 (0.7)	2 (3.4)	1 (0.2)	5 (1.0)	8 (1.3)	1 (1.7)	0	5 (1.1)	6 (1.0)	0
Dyspnea	2 (0.3)	0	1 (0.2)	2 (0.4)	2 (0.2)	0	1 (0.2)	1 (0.2)	2 (0.3)	2 (3.3)	0	3 (0.6)	5 (0.8)	0

Source: [SCS-PT-Table 4.1-3]

The common AEs in the long-term open-label study are summarized in table 36. Dizziness, nasopharyngitis, and headache were the most frequent AEs overall. Dizziness was reported by 50 (8.3%) of aliskiren/valsartan group patients. Only one case was reported as severe. One patient had a serious adverse event of dizziness, but the patient did not discontinue from the study. Six (1.0%) patients in the aliskiren/valsartan regimen discontinued from the study due to (nonserious) adverse events of dizziness.

Diarrhea was reported by 34 (5.7%) of aliskiren/valsartan group patients. Most episodes were mild (23, 3.8%), and only one was reported as severe. No patient had a serious adverse event of diarrhea, however, two (0.3%) patients in the aliskiren/valsartan regimen discontinued from the study due to episodes of diarrhea. The one severe diarrhea case resolved after 3 days, and was reported in a patient with an active history of gastro-esophageal reflux disease and diverticulitis. The addition of HCTZ to aliskiren/valsartan did not seem to alter markedly the AE profile of aliskiren/valsartan.

Table 36: Number (%) of patients with most frequent AEs (>= 2% for any group) by preferred term (treated population), in long term open-label study

Preferred term	Aliskiren 150 mg /valsartan 160 mg alone N = 601 n (%)	Aliskiren 300 mg / valsartan 320 mg alone N = 585 n (%)	Aliskiren/ valsartan N=601 n (%)	Aliskiren/ valsartan/ HCTZ N = 197 n (%)	Total N=601 n (%)
Any AEs	124 (20.6)	381 (65.1)	423 (70.4)	120 (60.9)	458 (76.2)
Dizziness	16 (2.7)	39 (6.7)	50 (8.3)	6 (3.0)	56 (9.3)
Nasopharyngitis	6 (1.0)	39 (6.7)	43 (7.2)	11 (5.6)	53 (8.8)
Headache	16 (2.7)	33 (5.6)	45 (7.5)	4 (2.0)	48 (8.0)
Diarrhea	8 (1.3)	27 (4.6)	34 (5.7)	10 (5.1)	42 (7.0)
Upper resp. tract infection	2 (0.3)	25 (4.3)	27 (4.5)	6 (3.0)	32 (5.3)
Bronchitis	3 (0.5)	24 (4.1)	27 (4.5)	4 (2.0)	31 (5.2)
Cough	1 (0.2)	23 (3.9)	24 (4.0)	7 (3.6)	29 (4.8)
Back pain	4 (0.7)	19 (3.2)	22 (3.7)	8 (4.1)	30 (5.0)
Arthralgia	3 (0.5)	18 (3.1)	20 (3.3)	4 (2.0)	24 (4.0)
Sinusitis	2 (0.3)	18 (3.1)	20 (3.3)	6 (3.0)	25 (4.2)
Urinary tract infection	2 (0.3)	17 (2.9)	18 (3.0)	1 (0.5)	19 (3.2)
Nausea	3 (0.5)	15 (2.6)	18 (3.0)	3 (1.5)	21 (3.5)
Fatigue	4 (0.7)	13 (2.2)	17 (2.8)	6 (3.0)	23 (3.8)
Influenza	1 (0.2)	12 (2.1)	13 (2.2)	1 (0.5)	14 (2.3)
Vomiting	1 (0.2)	12 (2.1)	13 (2.2)	2 (1.0)	15 (2.5)
Pharyngolaryngeal pain	1 (0.2)	11 (1.9)	12 (2.0)	1 (0.5)	13 (2.2)
Myalgia	3 (0.5)	10 (1.7)	13 (2.2)	1 (0.5)	14 (2.3)
Pain in extremity	3 (0.5)	10 (1.7)	13 (2.2)	4 (2.0)	17 (2.8)
Edema peripheral	1 (0.2)	9 (1.5)	10 (1.7)	2 (1.0)	12 (2.0)
Constipation	4 (0.7)	8 (1.4)	12 (2.0)	2 (1.0)	14 (2.3)
Dyspepsia	2 (0.3)	7 (1.2)	9 (1.5)	4 (2.0)	13 (2.2)
Osteoarthritis	1 (0.2)	7 (1.2)	8 (1.3)	5 (2.5)	13 (2.2)
Muscle spasms	0	6 (1.0)	6 (1.0)	5 (2.5)	11 (1.8)
Hypercholesterolemia	9 (1.5)	5 (0.9)	14 (2.3)	0 (0.0)	14 (2.3)
Rash	1 (0.2)	5 (0.9)	6 (1.0)	6 (3.0)	12 (2.0)

Preferred terms are sorted in descending frequency, based on the aliskiren 300 mg/valsartan 320 mg column.
A patient with multiple episodes of an adverse event is counted only once.
*For 13 out of the 14 cases, the AE of hypercholesterolemia was reported based on the lab results at Visit 4 (baseline) which occurred prior to the initiation of the study drug.
Source: [SCS-PT-Table 4.1-7]

In the aliskiren/valsartan add-on to HCTZ Study 2331, the common AEs (occurring in at least 2% of patients) from both the aliskiren/valsartan/HCTZ and the aliskiren/HCTZ groups were

generally similar or less than found in the other treatment groups. Back pain and vertigo were the only common AE that occurred in more patients in the aliskiren/valsartan/HCTZ group (4 patients, 2.4%) than in any of the other groups. None of the cases was severe, and no patient discontinued study medication due to these events. Data were summarized in the following table 37.

Table 37: Number (%) of patients with adverse events (>= 2% for any group) by preferred term in double-blind period in any treatment group (Study 2331 safety population)

Preferred term	HCTZ N = 152 n (%)	Aliskiren / HCTZ N = 165 n (%)	Valsartan / HCTZ N = 154 n (%)	Alis/Valsartan / HCTZ N = 168 n (%)
Any adverse event	64 (42.1)	60 (36.4)	72 (46.8)	62 (36.9)
Dizziness	3 (2.0)	3 (1.8)	13 (8.4)	10 (6.0)
Headache	8 (5.3)	4 (2.4)	9 (5.8)	5 (3.0)
Fatigue	4 (2.6)	2 (1.2)	3 (1.9)	4 (2.4)
Back pain	1 (0.7)	2 (1.2)	2 (1.3)	4 (2.4)
Vertigo	0 (0.0)	2 (1.2)	1 (0.6)	4 (2.4)
Nasopharyngitis	10 (6.6)	5 (3.0)	4 (2.6)	3 (1.8)
Cough	2 (1.3)	2 (1.2)	4 (2.6)	3 (1.8)
Hyperlipidemia	3 (2.0)	2 (1.2)	3 (1.9)	3 (1.8)
Diarrhea	4 (2.6)	2 (1.2)	3 (1.9)	2 (1.2)
Bronchitis	3 (2.0)	0 (0.0)	2 (1.3)	2 (1.2)
Upper resp. tract infection	3 (2.0)	3 (1.8)	2 (1.3)	1 (0.6)
Eczema	3 (2.0)	1 (0.6)	1 (0.6)	1 (0.6)
Edema peripheral	3 (2.0)	0 (0.0)	1 (0.6)	1 (0.6)
Pollakiuria	0 (0.0)	4 (2.4)	2 (1.3)	0 (0.0)

Preferred terms are sorted in descending frequency, as reported in the Aliskiren/Valsartan/HCTZ column.
A patient with multiple occurrences of any adverse events within a preferred term is counted only once.
Source: [Study 2331-PT-Table 14.3.1-1.1b]

7.1.5.5 Identifying common and drug-related adverse events

In the short-term, placebo-controlled studies, the most frequently reported AE suspected to be study drug related in patients receiving the combination treatment was fatigue, reported in 13 patients, (2.1%) overall, and although this was higher than in the placebo (0.9%) and monotherapy regimens (0.6% and 1.1% in the aliskiren and valsartan regimens, respectively), no dose-related increase in the rate was observed. Other AEs just like the aliskiren and valsartan monotherapy, the common drug-related adverse events in the combination study of aliskiren/valsartan included diarrhea, cough, headache and dizziness. Based on both the short term and long term study data, the incidence rates of these AEs were comparable to the individual monotherapy. These AEs were also analyzed in Sections 7.1.3.2 and 7.1.3.3.

7.1.5.6 Additional analyses and explorations

Additional analyses of AEs are presented in Sections 7.1.3.2, and 7.1.3.3.

7.1.6 Less Common Adverse Events

Analyses of less common AEs are presented in Sections 7.1.3.2, and 7.1.3.3.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The development program included typical safety lab testing (chemistry, hematology, and urinalysis) at baseline and end of study. In addition, because aliskiren affects the rennin-angiotensin system, additional testing for renal function and potassium levels was done.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Like the previous safety study reports, summary of the data of laboratory parameters was presented in short-term placebo-controlled studies and long-term open-label studies. The patients treated only in monotherapy were considered as monotherapy treatment group while the patients treated with at least one dose of combination were considered as combination treatment group.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Lab tests that showed changes in measures of central tendency were hemoglobin(decrease, with corresponding decreases in RBC and hematocrit), creatinine and blood urea nitrogen (increase), potassium (increase and decrease), and uric acid (increase). The changes from baseline in the placebo-controlled studies in hemoglobin are shown in Table 38, in creatinine in Table 39, in urea in Table 40, in potassium in Table 41, and in uric acid in Table 42. The mean and median changes for these lab values from the following tables are small and similar.

Table 38: Change from baseline in hemoglobin (in g/L) in placebo-controlled studies.

		Baseline			Post baseline Endpoint			Post baseline Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=635)	601	147.5	14.35	147.0	148.2	14.39	148.0	0.7	7.08	1.0
Ali 75 mg (N=179)	168	145.1	12.92	146.0	144.7	12.35	145.5	-0.3	6.18	0.0
Ali 150 mg (N=178)	173	145.3	12.09	146.0	145.9	11.58	146.0	0.6	6.40	1.0
Ali 300 mg (N=612)	560	146.5	14.07	147.0	145.9	13.86	147.0	-0.6	6.82	-1.0
Mono Ali (N=969)	901	146.0	13.50	147.0	145.7	13.17	146.0	-0.4	6.64	0.0
Val 80 mg (N=58)	57	145.0	11.73	143.0	144.5	10.11	143.0	-0.5	6.32	-2.0
Val 160 mg (N=59)	55	142.0	13.94	141.0	141.2	11.14	140.0	-0.9	6.74	-2.0
Val 320 mg (N=515)	481	146.7	14.51	148.0	145.2	13.85	146.0	-1.5	8.01	-2.0
Mono Val (N=632)	593	146.1	14.26	147.0	144.8	13.34	145.0	-1.3	7.75	-2.0
Ali/Val 75/80 mg (N=60)	54	143.0	10.83	145.0	142.6	12.10	144.0	-0.4	8.12	-1.0
Ali/Val 150/160 mg (N=60)	56	145.2	12.23	147.0	143.0	11.84	142.5	-2.3	6.90	-2.0
Ali/Val 300/320 mg (N=504)	476	147.5	14.78	148.0	144.6	14.05	147.0	-2.9	8.30	-3.0
All Ali/Val (N=624)	586	146.9	14.28	148.0	144.3	13.69	145.5	-2.6	8.18	-3.0
Val/HCTZ 160/12.5 mg (N=59)	57	146.8	10.80	146.0	144.4	10.54	144.0	-2.4	6.26	-3.0

Table 39: Change from baseline in creatinine (in µmol/L) in placebo-controlled studies.

		Baseline			Post baseline Endpoint			Post baseline Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=635)	622	79	15	80	81	16	80	1	9	0
Ali 75 mg (N=179)	173	79	17	80	80	19	80	1	9	0
Ali 150 mg (N=178)	176	79	16	80	81	17	80	2	9	1
Ali 300 mg (N=612)	588	79	16	80	80	16	80	1	9	0
Mono Ali (N=969)	937	79	16	80	80	17	80	1	9	0
Val 80 mg (N=58)	58	78	13	78	81	14	80	3	7	4
Val 160 mg (N=59)	57	77	16	75	77	16	76	-0	11	0
Val 320 mg (N=515)	505	79	17	80	80	17	80	1	11	0
Mono Val (N=632)	620	79	17	80	80	17	80	1	11	0
Ali/Val 75/80 mg (N=60)	57	79	16	76	77	15	73	-1	9	0
Ali/Val 150/160 mg (N=60)	58	82	17	80	83	16	80	0	10	1
Ali/Val 300/320 mg (N=504)	484	86	155	80	82	19	80	-4	156	0
All Ali/Val (N=624)	599	85	140	80	81	18	80	-4	140	0
Val/HCTZ 160/12.5 mg (N=59)	58	79	15	78	83	16	82	4	8	3

Table 40: Change from baseline in BUN (in mmol/L) in placebo-controlled studies.

		Baseline			Post baseline Endpoint			Post baseline Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=635)	622	5.20	1.437	5.00	5.32	1.364	5.30	0.12	1.169	0.00
Ali 75 mg (N=179)	173	5.53	1.581	5.30	5.57	1.529	5.40	0.03	1.192	0.00
Ali 150 mg (N=178)	176	5.76	1.545	5.70	5.78	1.579	5.50	0.02	1.200	-0.10
Ali 300 mg (N=612)	588	5.26	1.483	5.10	5.47	1.509	5.40	0.20	1.270	0.20
Mono Ali (N=969)	937	5.41	1.524	5.30	5.54	1.529	5.40	0.14	1.245	0.00
Val 80 mg (N=58)	58	5.49	1.438	5.60	5.63	1.527	5.45	0.15	1.187	0.20
Val 160 mg (N=59)	57	5.52	1.661	5.20	5.58	1.627	5.40	0.07	1.288	-0.20
Val 320 mg (N=515)	505	5.04	1.396	5.00	5.39	1.431	5.30	0.36	1.244	0.40
Mono Val (N=632)	620	5.12	1.435	5.00	5.43	1.459	5.30	0.31	1.245	0.40
Ali/Val 75/80 mg (N=60)	57	5.60	1.576	5.30	5.69	1.501	5.40	0.08	1.243	0.30
Ali/Val 150/160 mg (N=60)	58	5.94	1.288	5.80	6.06	1.781	6.00	0.13	1.604	-0.10
Ali/Val 300/320 mg (N=504)	484	5.27	1.796	5.00	5.64	1.620	5.40	0.37	1.765	0.40
All Ali/Val (N=624)	599	5.37	1.744	5.20	5.68	1.628	5.50	0.32	1.708	0.30
Val/HCTZ 160/12.5 mg (N=59)	58	5.18	1.251	5.10	6.16	1.587	6.15	0.98	1.300	1.00

Table 41: Change from baseline in BUN (in mmol/L) in placebo-controlled studies.

		Baseline			Post baseline Endpoint			Post baseline Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=635)	606	4.273	0.5002	4.200	4.243	0.3853	4.200	-0.030	0.4666	0.000
Ali 75 mg (N=179)	167	4.332	0.3985	4.300	4.334	0.3643	4.300	0.002	0.3874	0.000
Ali 150 mg (N=178)	168	4.273	0.3273	4.300	4.347	0.3683	4.300	0.074	0.3538	0.100
Ali 300 mg (N=612)	577	4.255	0.3893	4.200	4.321	0.3871	4.300	0.066	0.3636	0.100
Mono Ali (N=969)	912	4.272	0.3811	4.300	4.328	0.3793	4.300	0.056	0.3668	0.100
Val 80 mg (N=58)	56	4.366	0.3549	4.350	4.346	0.3991	4.300	-0.020	0.4949	-0.100
Val 160 mg (N=59)	52	4.294	0.3006	4.300	4.369	0.3433	4.400	0.075	0.2814	0.100
Val 320 mg (N=515)	499	4.251	0.3865	4.200	4.297	0.3969	4.300	0.046	0.4086	0.000
Mono Val (N=632)	607	4.265	0.3781	4.200	4.308	0.3930	4.300	0.042	0.4081	0.000
Ali/Val 75/80 mg (N=60)	55	4.278	0.3023	4.300	4.304	0.3410	4.300	0.025	0.4142	0.000
Ali/Val 150/160 mg (N=60)	54	4.317	0.4013	4.300	4.339	0.2904	4.300	0.022	0.3484	0.000
Ali/Val 300/320 mg (N=504)	479	4.292	0.3990	4.300	4.394	0.4525	4.300	0.102	0.4368	0.100
All Ali/Val (N=624)	588	4.293	0.3907	4.300	4.381	0.4311	4.300	0.088	0.4279	0.100
Val/HCTZ 160/12.5 mg (N=59)	54	4.219	0.3376	4.200	4.217	0.3994	4.200	-0.002	0.3317	0.000

Table 42: Change from baseline in uric acid (in mmol/L) in placebo-controlled studies.

		Baseline			Post baseline Endpoint			Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=635)	610	356.35	88.666	350.00	360.51	90.233	350.00	4.16	50.491	0.00
Ali 75 mg (N=179)	170	348.81	84.649	340.00	355.45	88.025	350.00	6.65	43.803	0.00
Ali 150 mg (N=178)	174	348.45	81.702	340.00	362.48	90.412	365.00	14.06	53.870	19.00
Ali 300 mg (N=612)	569	348.04	85.127	345.00	361.43	91.309	356.90	13.39	51.394	11.90
Mono Ali (N=969)	913	348.26	84.305	340.00	360.52	90.471	350.90	12.26	50.580	10.00
Val 80 mg (N=58)	57	348.02	90.291	340.00	363.14	91.536	360.00	15.12	46.230	20.00
Val 160 mg (N=59)	54	342.67	90.726	330.00	355.81	96.092	340.00	13.13	49.407	10.00
Val 320 mg (N=515)	494	352.57	87.204	350.00	359.00	90.856	356.90	6.43	49.244	5.90
Mono Val (N=632)	605	351.26	87.716	350.00	359.11	91.254	351.00	7.84	48.998	10.00
Ali/Val 75/80 mg (N=60)	55	333.64	81.908	310.00	345.44	77.159	340.00	11.80	51.872	6.00
Ali/Val 150/160 mg (N=60)	56	367.66	107.047	385.00	377.30	102.136	395.00	9.64	43.587	3.00
Ali/Val 300/320 mg (N=504)	476	350.20	84.311	345.00	363.39	91.062	356.90	13.19	57.133	10.00
All Ali/Val (N=624)	587	350.31	86.663	345.00	363.03	91.093	360.00	12.72	55.438	10.00
Val/HCTZ 160/12.5 mg (N=59)	57	345.60	86.763	330.00	377.30	85.244	370.00	31.70	55.163	40.00

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The criteria for notable laboratory values defined by sponsor were showed in the following table 43.

Table 43: Criteria for notable laboratory values

Laboratory Variables	Low	High
Hematology		
Hemoglobin	>20% decrease	>50% increase
Hematocrit	>20% decrease	>50% increase
RBC count	>20% decrease	>50% increase
WBC count	>50% decrease	>50% increase
Platelet count	>50% decrease	>75% increase
Biochemistry		
Sodium	>5% decrease	
Potassium	>20% decrease	>20% increase
Chloride	>10% decrease	>10% increase
Calcium	>10% decrease	>10% increase
Creatinine		>50% increase
BUN		>50% increase
Glucose	>50% decrease	>50% increase
SGOT (AST)		>150% increase
SGPT (ALT)		>150% increase
Alkaline phosphatase		>100% increase
Total bilirubin		>100% increase
Uric acid		>50% increase
CK		>300%

In addition criteria that are of clinical significance were identified for BUN, creatinine, and potassium: BUN (> 14.28 mmol/L), creatinine (> 176.82 umol/L), or potassium (< 3.5 mmol/L, > 5.5 mmol/L, or ≥ 6.0 mmol/L).

In the short-term controlled studies, a decrease from baseline in mean hemoglobin was observed in the aliskiren and valsartan monotherapy and aliskiren/valsartan combination treatment groups (mean change from baseline: placebo, 0.7 g/dL; aliskiren, -0.4 g/L; valsartan, -1.3 g/L; and aliskiren/valsartan, -2.6 g/L). There were three AEs of anemia reported (one in each of the treatment groups aliskiren, valsartan, and the aliskiren/valsartan combination). The hematological data in the long-term open label study are similar to those seen in the short-term studies. A > 20% decrease in hemoglobin was seen in 8 patients (1.4%).

In the short-term studies, the aliskiren/valsartan combination shows a slightly higher number of patients with serum potassium increases of >20%, whereas the proportion of patients in this group with >50% increase in uric acid was similar to that seen with aliskiren monotherapy, and the proportion of patients with >50% increase in BUN in the aliskiren/valsartan combination was similar to that seen with valsartan monotherapy. For creatinine, the percentage of patients with increases of >50% was slightly higher in the aliskiren/valsartan combination group. This elevation was observed in 2.0% patients compared to 0.9% and 1.1% in the aliskiren and valsartan monotherapy groups. Data were summarized in the following table 44.

Table 44: Summary of changes from baseline in potassium, uric acid, BUN, and creatinine for placebo, monotherapy, and combination therapy treatment groups: short term, placebo controlled studies

	Placebo (N=635)	Mono Ali (N=969)	Mono Val (N=632)	All Ali/Val (N=624)
Potassium (mmol/L)				
N	606	912	607	588
Baseline (SD)	4.27 (0.500)	4.27 (0.381)	4.26 (0.378)	4.29 (0.391)
Mean (SD) change	-0.030 (0.467)	0.056 (0.367)	0.042 (0.408)	0.088 (0.428)
> 20% increase n (%)	30 (5.0)	38 (4.2)	31 (5.1)	49 (8.3)
Uric Acid (µmol/L)				
N	610	913	605	587
Baseline (SD)	356.35 (88.666)	348.26 (84.305)	351.26 (87.716)	350.31 (86.663)
Mean (SD) change	4.16 (50.491)	12.26 (50.580)	7.84 (48.998)	12.72 (55.438)
> 50% increase n (%)	6 (1.0)	13 (1.4)	4 (0.7)	8 (1.4)
BUN (mmol/L)				
N	622	937	620	599
Baseline (SD)	5.20 (1.437)	5.41 (1.524)	5.12 (1.435)	5.37 (1.744)
Mean (SD) change	0.12 (1.169)	0.14 (1.245)	0.31 (1.245)	0.32 (1.708)
> 50% increase n (%)	48 (7.7)	77 (8.2)	81 (13.1)	91 (15.2)
Creatinine (µmol/L)				
N	622	937	620	599
Baseline (SD)	79 (15)	79 (16)	79 (17)	85 (140)
Mean (SD) change	1 (9)	1 (9)	1 (11)	-4 (140)*
> 50% increase n (%)	2 (0.3)	8 (0.9)	7 (1.1)	12 (2.0)

* The mean creatinine change from baseline in this group was due to an implausibly high outlying baseline value in Study 2327 (patient Study 2327 0617-00014, 3474.1 µmol/L) that returned to normal post-baseline.
Source: [SCS-PT-Table 5.2-1 and SCS-PT-Table 5.2-2]

A summary of potassium, BUN, and creatinine by specified criteria that were considered clinically significant were summarized in the following tables 45 and 46.

The incidence of hyperkalemia (potassium > 5.5 mmol/L) with aliskiren/ valsartan combination (3.4%) was slightly higher than placebo (2.1%), valsartan monotherapy (1.2%), and aliskiren monotherapy (1.0%). However, the incidence rate of hyperkalemia (K^+ >5.5

mmol/L) in placebo (2.1%) was much higher than any other previous studies. By checking the original data, 6 patients in the placebo group have the serum level of potassium more than 7.5 mmol/L (7.5 to 9.4 mmol/L) without any further examination and AE report. One patient has serum level of potassium at 7.7 mmol/L in the aliskiren group and none of patients have such high level of potassium in any other groups. Therefore, there must be some medical errors for the serum level of potassium measurement such as hemolysis, etc in this short-term pivotal study.

Among the 20 patients in the aliskiren/valsartan treatment group whose potassium values exceeded 5.5 mmol/L, most increases were transient, and 14 patients potassium values were within the normal or below 5.5 mmol/L at the end of the study without treatment interruption. None of these 20 patients had hyperkalemia reported as an AE. The incidence of hypokalemia (K+ < 3.5 mmol/L) was lower in patients treated with aliskiren/valsartan (2.2%) or aliskiren monotherapy (1.6%) than patients treated with valsartan monotherapy or placebo (both 3.5%).

In the long-term study, hyperkalemia (K+ > 5.5 mmol/L) was seen in16 patients (4.1%) treated with aliskiren/valsartan, and 4 patients (2.0%) treated with aliskiren/valsartan/ HCTZ (3.4% of patients overall). Among these 20 patients whose potassium values exceeded 5.5 mmol/L, 16 had transient elevations that returned to normal at subsequent or final visits. Three patients (0.8%) had serum potassium ≥ 6.0 mmol/L; none of whom received HCTZ add-on. While a > 20% increase in potassium was reported in 74 patients (12.6%) overall, for the majority of cases, 62 patients (10.5%), values remained within the normal range. There were total 6 patients (1.0%) with hyperkalemia reported as AEs. The incidents occurred in five patients treated with aliskiren 300 mg / valsartan 320 mg and one patient while treated with aliskiren/valsartan/HCTZ. Two of the patients discontinued due to hyperkalemia: one event lasted for 38 days, and one event was continuing at discontinuation. The remaining four patients with hyperkalemia had events that did not require additional treatment or study drug interruption. Two of these patients completed the study, and two discontinued participation for reasons unrelated to hyperkalemia.

In the short-term studies, there were only two cases of elevated BUN (BUN > 14.28 mmol/L), neither in the aliskiren/valsartan combination group. A slight mean increase in BUN in the aliskiren/valsartan combination group (0.32 mmol/L) was observed as compared to valsartan monotherapy (0.31mmol/L), aliskiren group (0.14 mmol/L) and the placebo group (0.12 mmol/L). The percentage of patients with > 50% increases in BUN in the aliskiren/valsartan combination therapy (15.2%) was comparable to the valsartan monotherapy (13.1%), and higher than either the aliskiren monotherapy (8.2%) or placebo (7.7%) groups. The majority of these increases were not outside the laboratory normal range for BUN. There is no indication of an higher incidence of elevated BUN in the elderly or in patients with mild renal impairment. In the long-term study, two patients (0.5%) treated with aliskiren/valsartan (without additional HCTZ) had elevated BUN (BUN > 14.28 mmol/L). An overall mean increase from baseline in BUN of 0.96 mmol/L overall was seen, with the greatest increase (1.42 mmol/L) in the aliskiren/valsartan/ HCTZ group. A > 50% increase in BUN was reported in 197 patients (33.5%); 131 patients (22.3%) were within the normal range.

Regarding the change of creatinine from baseline, 4 patients (0.7%) in the aliskiren/valsartan combination group had a clinically significant increase in creatinine, compared to 2 patients in both the aliskiren monotherapy group (0.2%) and the valsartan monotherapy group (0.3%), and no patients in the placebo group. Of the four patients in aliskiren/valsartan group with creatinine values > 176.8 umol/L, two had values that returned to within normal range without the disruption of the study drug by the end of study or study follow-up. The percentage of patients with > 50% increase from baseline in creatinine were greater in the aliskiren/valsartan combination group (2.0%) relative to placebo (0.3%), aliskiren (0.9%), or valsartan (1.1%). There was no apparent dose-dependence for aliskiren (aliskiren 150 mg, 1.1% and aliskiren 300 mg, 1.0% of patients with > 50% increase). In the long-term open label study overall, two patients (0.3%) had a creatinine value > 176.8 umol/L. One was returned to baseline at the end of study. There were 21 patients (3.6%) with > 50% increase from baseline in creatinine. In addition, there were 12 patients with both >30% increase from baseline and > 132.6 umol/L (1.5mg/dl which may indicate a renal insufficiency). Nine was returned to baseline at the end of study.

Regarding the change of uric acid, the percentage of patients with > 50% increase from baseline in serum uric acid were same between the aliskiren/valsartan group (1.4%) and aliskiren group (1.4%) and higher relative to valsartan (0.7%) or placebo (1.0%). A mean increase in uric acid was seen with aliskiren/valsartan (12.72 µmol/L) and aliskiren monotherapy (12.26 µmol/L) that was a little bit greater than valsartan (7.84 µmol/L) or placebo (4.16µmol/L). In the long-term study, a mean increase from baseline in uric acid of 25.9 umol/L overall was seen, with a greater increase (44.8 µmol/L) in aliskiren/ valsartan/ HCTZ treated patients. A> 50% increase in uric acid was reported in 22 patients (3.8%); 16 patients (2.8%) were within the normal range. Two cases of gout were found in the short-term studies, one in placebo and one in the combination group at the time of lower dose.

Table 45: Summary of potassium, BUN and creatinine by specified criteria in short term, double-blind, placebo controlled studies.

	Placebo	Aliskiren				Valsartan				Aliskiren/Valsartan				Val/HCTZ
Laboratory test	N=635 n (%)	75mg N=179 n (%)	150mg N=178 n (%)	300mg N=612 n (%)	Mono All N=969 n (%)	80mg N=58 n (%)	160 mg N=59 n (%)	320mg N=515 n (%)	Mono All N=632 n (%)	75/ 80mg N=60 n (%)	150/ 160 mg N=60 n (%)	300/ 320mg N=504 n (%)	All Ali/Val N=624 n (%)	160mg /12.5mg N=59 n (%)
Potassium														
Total subjects*	606 (100)	167 (100)	168 (100)	577 (100)	912 (100)	56 (100)	52 (100)	499 (100)	607 (100)	55 (100)	54 (100)	479 (100)	588 (100)	54 (100)
High (≥ 6.0 mmol/L)	6 (1.0)	0	0	4 (0.7)	4 (0.4)	0	0	5 (1.0)	5 (0.8)	0	0	2 (0.4)	2 (0.3)	0
High (> 5.5 mmol/L)	13 (2.1)	1 (0.6)	0	8 (1.4)	9 (1.0)	0	0	7 (1.4)	7 (1.2)	0	1 (1.9)	19 (4.0)	20 (3.4)	0
Low (< 3.5 mmol/L)	21 (3.5)	2 (1.2)	1 (0.6)	12 (2.1)	15 (1.6)	1(1.8)	0	20 (4.0)	21 (3.5)	0	0	13 (2.7)	13 (2.2)	0
Blood Urea Nitrogen (BUN)														
Total subjects*	622 (100)	173 (100)	176 (100)	588 (100)	937 (100)	58 (100)	57 (100)	505 (100)	620 (100)	57 (100)	58 (100)	484 (100)	599 (100)	58 (100)
High (> 14.28 mmol/L)	0	0	0	1 (0.2)	1 (0.1)	0	0	1 (0.2)	1 (0.2)	0	0	0	0	0
Creatinine														
Total subjects*	622 (100)	173 (100)	176 (100)	588 (100)	937 (100)	58 (100)	57 (100)	505 (100)	620 (100)	57 (100)	58 (100)	484 (100)	599 (100)	58 (100)
High (> 176.8 µmol/L)	0	1 (0.6)	0	1 (0.2)	2 (0.2)	0	0	2 (0.4)	2 (0.3)	0	0	4 (0.8)	4 (0.7)	0

* Number of subjects contributing data; a patient must have both baseline and post-baseline values to be included
Among 20 patients in the combination treatment group whose potassium values exceeded 5.5 mmol/L during the double-blind treatment, 14 patients had potassium values that returned to below 5.5 mmol/L at the end of the study without treatment interruption
Source: [SCS-PT-Table 5.3-1]

Table 46: Summary of potassium, BUN and creatinine by specified criteria – in long term, open-label study.

Laboratory test	Aliskiren/valsartan* N = 404 n (%)	Alis/valsartan/HCTZ * N = 197 n (%)	Total N = 601 n (%)
Potassium			
Total subjects*	391 (100)	197 (100)	588 (100)
Low < 3.5 mmol/L	6 (1.5)	17 (8.6)	23 (3.9)
High > 5.5 mmol/L	16 (4.1)	4 (2.0)	20 (3.4)
High ≥ 6.0 mmol/L	3 (0.8)	0	3 (0.5)
Blood urea nitrogen			
Total subjects*	391 (100)	197 (100)	588 (100)
High > 14.28 mmol/L	2 (0.5)	3 (1.5)	5 (0.9)
Creatinine			
Total subjects*	391 (100)	197 (100)	588 (100)
High > 176.8 µmol/L	1 (0.3)	1 (0.5)	2 (0.3)

* 'Aliskiren/valsartan/HCTZ' group are patients who received HCTZ in addition to aliskiren/valsartan at any time during the study. 'Aliskiren/valsartan' group did not receive HCTZ during the study.
Percentages based on the number of patients with laboratory results.
Source: [Study V2301-Table 12-8]

In the subgroup analysis, biochemistry laboratory results meeting specified criteria for potassium, BUN and creatinine were evaluated in demographic subgroups including gender, race, age, ethnicity and in baseline characteristics obesity, baseline renal impairment (GFR), and diabetic status. Among the 18 patients treated with aliskiren/valsartan who had GFR < 60 in the short term studies, there were no patients who met the specified criteria in BUN (>14.28 mmol/ L), one patient with creatinine >176.8 µmol/L, and 3 (17.6%) with potassium>5.5mmol/L. Although the number of patients with impaired renal function receiving aliskiren/valsartan was small (n=18), none had meaningful changes in BUN or creatinine, and just one had a potassium ≥6.0mmol/L. These subgroup analyses showed a pattern of laboratory values meeting specific criteria not different from those seen in the overall population.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no marked outliers for lab abnormalities and No patients discontinued due to abnormal values in laboratory abnormalities in the aliskiren/valsartan combination therapy.

7.1.7.4 Additional analyses and explorations

We did not perform any additional analyses or explorations other than those presented above.

7.1.7.5 Special assessments

Special assessments for renal function and potassium are also addressed in Section 7.1.7.3. I did not identify any other laboratory value concerns for which special assessment are needed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Blood pressure and pulse were routinely measured at most visits for the efficacy evaluations.

Weight was typically measured during baseline and at the end. Temperature and respirations were not routinely recorded. The main discussion is the orthostatic pressure.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Like at the beginning of the safety review, all dataset included short-term placebo controlled studies and long-term open label study.

7.1.8.3 Standard analyses and explorations of vital signs data

There were no clinically significant changes from baseline in body weight or sitting and standing pulse rate in any of the treatment groups in the pooled populations. Results were presented in the individual study reports.

Orthostatic pressure was analyzed in both the short-term controlled studies and long-term open label study. Orthostatic blood pressure changes were defined as a decrease of at least 20 mm Hg in systolic blood pressure or a decrease of at least 10 mm Hg in diastolic blood pressure when a patient moves from a sitting position to a standing position. In short-term controlled studies, the incidence of orthostatic blood pressure changes is summarized in the following table 47. Overall, orthostatic BP was seen at a broadly similar frequency at baseline and endpoint. When orthostatic BP changes at any visit post baseline were considered, the incidence with aliskiren/valsartan treatment was similar to the respective monotherapies. Orthostatic blood pressure change was reported at one or more visits in 49 (8.0%) patients in the aliskiren/valsartan regimen, 36 (5.7%) patients in the placebo regimen, 65 (6.8%) patients in aliskiren monotherapy and 40 (6.4%) patients in valsartan monotherapy. The AEs of hypotension and orthostatic hypotension were each reported in two patients receiving aliskiren/valsartan treatment and in none of the patients receiving placebo or valsartan.

Table 47: Incidence of orthostatic blood pressure change –short-term placebo-controlled studies

	Placebo	Aliskiren				Valsartan				Aliskiren/Valsartan				Val/ HCTZ 160mg /12.5mg N=59 n (%)
Timepoint	N=635 n (%)	75mg N=179 n (%)	150mg N=178 n (%)	300mg N=612 n (%)	Mono All N=969 n (%)	80mg N=58 n (%)	160mg N=59 n (%)	320mg N=515 n (%)	Mono All N=632 n (%)	75/ 80mg N=60 n (%)	150/ 160mg N=60 n (%)	300/ 320mg N=504 n (%)	All Ali/Val N=624 n (%)	
Baseline														
N*	635	179	178	612	969	58	59	515	632	60	60	504	624	59
n (%)	6 (0.9)	4 (2.2)	3 (1.7)	10 (1.6)	17 (1.8)	0	0	6 (1.2)	6 (0.9)	2 (3.3)	1 (1.7)	9 (1.8)	12 (1.9)	0
Endpoint														
N*	631	177	177	605	959	58	58	513	629	60	60	496	616	58
n (%)	7 (1.1)	0	9 (5.1)	6 (1.0)	15 (1.6)	1 (1.7)	0	7 (1.4)	8 (1.3)	2 (3.3)	3 (5.0)	15 (3.0)	20 (3.2)	2 (3.4)
Any visit														
N*	631	177	177	605	959	58	58	513	629	60	60	496	616	58
n (%)	36 (5.7)	12 (6.8)	24 (13.6)	29 (4.8)	65 (6.8)	4 (6.9)	4 (6.9)	32 (6.2)	40 (6.4)	7 (11.7)	6 (10.0)	36 (7.3)	49 (8.0)	4 (6.9)

Orthostatic blood pressure change is defined as a decrease ≥20mmHg in systolic BP or a decrease ≥10 mmHg in diastolic BP when a patient moves from a sitting position to a standing position.
* N is the number of patients with both sitting and standing BP at baseline and timepoint, respectively; the total for any visit is the number of patients with both sitting and standing BP data at that post-baseline visit.
- n is the number of patients who had orthostatic blood pressure change.
Source: [SCS-PT-Table 6.1-1]

In the long term, open-label study, the incidence of orthostatic blood pressure changes is summarized in the following table 48. Overall, orthostatic BP change was similar in frequency to baseline at endpoint. When orthostatic blood pressure changes at any visit post-baseline were counted, the incidence was 11.3%. There were four patients with mild, non-serious AEs of orthostatic hypotension. One of them discontinued from the study due to dizziness.

Table 48: Incidence of orthostatic BP change – long-term, open-label study

	Ali/Val (N=404)		Ali/Val/HCTZ (N=197)		Total (N=601)	
Visit	Total*	n (%)	Total*	n (%)	Total*	n (%)
Baseline	404	4 (1.0)	197	3 (1.5)	601	7 (1.2)
Week 28	335	1 (0.3)	188	1 (0.5)	523	2 (0.4)
Week 54	322	8 (2.5)	169	3 (1.8)	491	11 (2.2)
Endpoint	397	9 (2.3)	197	3 (1.5)	594	12 (2.0)
Any visit	397	41 (10.3)	197	26 (13.2)	594	67 (11.3)

- Orthostatic blood pressure change is defined as a decrease ≥20mmHg in systolic BP or a decrease ≥10 mmHg in diastolic BP when a patient moves from a sitting position to a standing position.
* Total is the number of patients with both sitting and standing BP at baseline and endpoint, respectively; the total for any visit is the number of patients with both sitting and standing BP data at that post-baseline visit.
- n is the number of patients who had orthostatic blood pressure change.
Source: [Study V2301-Table 12-9]

Orthostatic blood pressure changes were also examined in demographic and background subgroups (age, sex, race, ethnicity, obesity) in the short-term placebo-controlled studies and in the long-term open-label study. The incidence of orthostatic changes were slightly more frequent in female than male patients treated with aliskiren/valsartan (10.0% vs. 6.5%), in patients ≥ 65 years than in younger patients (9.1% vs. 7.7%), and in Caucasian patients compared to Black patients (8.7% vs. 6.8%).

7.1.8.4 Additional analyses and explorations
I did not perform any additional analyses of vital signs.

7.1.9 Electrocardiograms (ECGs)

No post-baseline ECGs were performed in studies included in this submission. In the previous NDA review (NDA 21, 985), aliskiren monotherapy does not appear to have an appreciable effect on QT interval. Valsartan is not known to cause adverse ECG changes.

7.1.10 Immunogenicity

Aliskiren and valsartan are both small molecules that by themselves should have little immunogenic potential. Aliskiren did not show a pattern of increase adverse events of potentially immunogenic etiology, e.g., aliskiren was not associated with increased rates of urticaria compared to placebo.

7.1.11 Human Carcinogenicity

Additional risk of the human carcinogenicity was not observed in the combination of aliskiren with valsartan as compared to the aliskiren monotherapy in the long-term open label study.

7.1.12 Special Safety Studies

Special safety studies were not performed with the combination of aliskiren and valsartan.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

In the aliskiren development program there was no suggested potential for rebound hypertension on withdrawal of aliskiren treatment, with blood pressure returning to pretreatment levels slowly. AEs were infrequent during the randomized withdrawal from treatment, similar between the treatment groups, and primarily of mild severity. Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure. Therefore, there is no reason to suspect this combination that has the potential for abuse in humans.

7.1.14 Human Reproduction and Pregnancy Data

Studies of either aliskiren monotherapy or the combination of aliskiren with valsartan were not conducted in pregnant women. There were a total of 3 pregnancies in enrolled female patients during all completed studies in the aliskiren/valsartan program. Two pregnancies were reported in the short-term placebo-controlled studies, one in Study 2327, and one in Study 2203 as summarized in the following. The other pregnant patient, treated during a placebo run-in period, subsequently had an abortion. In addition, a spousal pregnancy in Study 2327 (treatment valsartan 320 mg) was reported for the wife of a male patient, but no additional information is available.

In Study 2327, patient 0537-00002- (aliskiren/valsartan 150/160 mg) was found to be pregnant on (b) (6), and was withdrawn from the study upon learning of the pregnancy (Day 28). Her last menstrual period was (b) (6), and she had been using barrier methods of contraception. The patient subsequently had an uneventful delivery of a healthy neonate.

In Study 2203, in the aliskiren 300 mg group, patient 0513-00026 had a positive pregnancy test result 42 days after starting study drug. The patient discontinued study drug and subsequently underwent a routine delivery without complication.

In Study 2203, patient 0001-00053 presented with a positive pregnancy test during the single-blind run-in period and was discontinued from the study due to this event. A planned abortion was performed.

7.1.15 Assessment of Effect on Growth

The product has not been studied in children

7.1.16 Overdose Experience

There were no reports of overdose in the clinical trials.

7.1.17 Post-marketing Experience

Aliskiren/valsartan as a fixed-dose combination product has not yet marketed anywhere in the world.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary clinical data sources were summarized in tables 25, 26 and 27 in section 7.1.

7.2.1.1 Study type and design/patient enumeration

There are three datasets in this application for the safety analysis including 1) Two short-term placebo-controlled studies; 2) One long-term open-label studies; and 3) One supportive short-term study which is the aliskiren/valsartan add-on HCTZ study.

7.2.1.2 Demographics

The demographics of patients were summarized in the following tables 48-51. The treatment groups were well matched and reflect the aliskiren/valsartan combination target patient population. A wide age range of the adult population, including the elderly was studied (range 22-82 years, mean 53.4 years for aliskiren/valsartan combination and 19-88 years, mean 53.7 years overall). Women comprised approximately 40% of the population in both the aliskiren/valsartan combination group (40.4%) and overall (41.1%). Of the patients in the aliskiren/valsartan combination group, 80.1% were Caucasian, and 11.9% were Black, similar proportions to that in the overall population (81.4% and 12.4% respectively). In the 'ethnicity' category 10-12% of the population were considered 'Hispanic or Latino' in the aliskiren/valsartan combination group and in the overall population. The majority of the rest of the patients for whom ethnicity information was collected were categorized as 'other' (4.9% of the total patient population).

Within the short-term placebo-controlled study population, baseline disease characteristics obesity, diabetic status and kidney function (measured by glomerular filtration rate) were similar across treatment groups, and were as expected for this hypertensive population. Patients with GFR < 60 mL/min/1.73m2 comprised 2.9% of the studies population and were reasonably well distributed across the treatment groups. In the all aliskiren/valsartan combination group, approximately 10% of the population was diabetic at baseline. Across all treatment groups, approximately a third to half of all patients were obese (BMI $\geq$ 30 kg/m^2). Data were summarized in the tables 49 and 50.

Table 49: Demographic characteristics in short term, double-blind, placebo controlled studies

		Age			Gender n (%)		Race n (%)†			
Treatment group	N	mean(SD)	< 65 years	≥ 65 years	Male	Female	Caucasian	Black	Asian	Other
Placebo	636	53 (11.0)	534 (84.0)	102 (16.0%)	378 (59.4)	258 (40.6)	511 (80.3)	83 (13.1)	8 (1.3)	33 (5.2)
Ali 75 mg	179	55 (13.1)	127 (70.9%)	52 (29.1%)	99 (55.3)	80 (44.7)	169 (94.4)	10 (5.6)	0	0
Ali 150 mg	178	56 (12.4)	137 (77.0%)	41 (23.0%)	101 (56.7)	77 (43.3)	166 (93.3)	10 (5.6)	0	2 (1.1)
Ali 300 mg	612	53 (11.1)	514 (84.0%)	98 (16.0%)	355 (58.0)	257 (42.0)	490 (80.1)	80 (13.1)	7 (1.1)	31 (5.1)
Mono Ali	969	54 (11.8)	778 (80.3%)	191 (19.7%)	555 (57.3)	414 (42.7)	825 (85.1)	100 (10.3)	7 (0.7)	33 (3.4)
Val 80 mg	58	56 (13.0)	39 (67.2%)	19 (32.8%)	38 (65.5)	20 (34.5)	55 (94.8)	2 (3.4)	0	1 (1.7)
Val 160 mg	59	55 (11.8)	48 (81.4%)	11 (18.6%)	29 (49.2)	30 (50.8)	53 (89.8)	5 (8.5)	1 (1.7)	0
Val 320 mg	515	53 (10.5)	449 (87.2%)	66 (12.8%)	312 (60.6)	203 (39.4)	380 (73.8)	93 (18.1)	7 (1.4)	34 (6.6)
Mono Val	632	53 (10.9)	536 (84.8%)	96 (15.2%)	379 (60.0)	253 (40.0)	488 (77.2)	100 (15.8)	7 (1.1)	36 (5.7)
Ali/Val 75/80 mg	60	56 (12.2)	46 (76.7%)	14 (23.3%)	30 (50.0)	30 (50.0)	53 (88.3)	5 (8.3)	0	2 (3.3)
Ali/Val 150/160 mg	60	58 (11.2)	43 (71.7%)	17 (28.3%)	35 (58.3)	25 (41.7)	53 (88.3)	6 (10.0)	0	1 (1.7)
Ali/Val 300/320 mg	504	53 (10.6)	436 (86.5%)	68 (13.5%)	307 (60.9)	197 (39.1)	394 (78.2)	63 (12.5)	8 (1.6)	37 (7.3)
All Ali/Val	624	53 (10.9)	525 (84.1%)	99 (15.9%)	372 (59.6)	252 (40.4)	500 (80.1)	74 (11.9)	8 (1.3)	40 (6.4)
Val/HCTZ 160/12.5 mg	59	57 (12.2)	43 (72.9%)	16 (27.1%)	36 (61.0)	23 (39.0)	53 (89.8)	5 (8.5)	0	1 (1.7)
Total	2920	54 (11.3)	2416 (82.7%)	504 (17.3%)	1720 (58.9)	1200 (41.1)	2377 (81.4)	362 (12.4)	30 (1.0)	143 (4.9)

† On source table 3.1-1, but not included here for brevity, there were also 3 Native Americans and 5 Pacific Islanders in the Group A population.
Source: SCS-PT-Table 3.1-1

Table 50: Disease baseline characteristics in short term, double-blind, placebo controlled studies.

		Obesity*		Diabetic	GFR (mL/min/1.73m2) n (%)			
		No (BMI <30)	Yes (BMI ≥30)					
Treatment group	N	n (%)	n (%)	n (%)	GFR<30	30≤GFR<60	60≤GFR<90	GFR≥90
Placebo	636	355 (55.8)	277 (43.6)	54 (8.5)	0	19 (3.0)	324 (50.9)	286 (45.0)
Ali 75 mg	179	105 (58.7)	74 (41.3)	16 (8.9)	0	13 (7.3)	90 (50.3)	74 (41.3)
Ali 150 mg	178	118 (66.3)	60 (33.7)	15 (8.4)	0	7 (3.9)	102 (57.3)	69 (38.8)
Ali 300 mg	612	316 (51.6)	292 (47.7)	72 (11.8)	0	12 (2.0)	311 (50.8)	276 (45.1)
Mono Ali	969	539 (55.6)	426 (44.0)	103 (10.6)	0	32 (3.3)	503 (51.9)	419 (43.2)
Val 80 mg	58	37 (63.8)	21 (36.2)	3 (5.2)	0	1 (1.7)	30 (51.7)	27 (46.6)
Val 160 mg	59	33 (55.9)	25 (42.4)	2 (3.4)	0	4 (6.8)	31 (52.5)	24 (40.7)
Val 320 mg	515	264 (51.3)	249 (48.3)	57 (11.1)	0	12 (2.3)	253 (49.1)	245 (47.6)
Mono Val	632	334 (52.9)	295 (46.7)	62 (9.8)	0	17 (2.7)	314 (49.7)	296 (46.8)
Ali/Val 75/80 mg	60	29 (48.3)	30 (50.0)	4 (6.7)	0	0	37 (61.7)	23 (38.3)
Ali/Val 150/160 mg	60	33 (55.0)	27(45.0)	10 (16.7)	0	4 (6.7)	36 (60.0)	19 (31.7)
Ali/Val 300/320 mg	504	273 (54.2)	226 (44.8)	50 (9.0)	1 (0.2)	13 (2.6)	251 (49.8)	228 (45.2)
All Ali/Val	624	335 (53.7)	283 (45.4)	64 (10.3)	1 (0.2)	17 (2.7)	324 (51.9)	270 (43.3)
Val/HCTZ 160/12.5mg	59	32 (54.2)	27 (45.8)	2 (3.4)	0	0	36 (61.0)	23 (39.0)
Total	2920	1595 (54.6)	1308 (44.8)	285 (9.8)	1 (0.0)	85 (2.9)	1501 (51.4)	1294 (44.3)

* Obesity is yes if BMI ≥ 30 kg/m2. Obesity 'yes' and 'no' may sum to less than 100% due to some patients with missing information
Source: [SCS-PT-Table 3.1-1]

In the long-term open-label study, demographic and other baseline disease characteristics were generally comparable across the treatment groups. Overall, the majority of patients were Caucasian (84.5%), and greater proportion of study patients were males (54.9%). Half of the population was obese (BMI ≥ 30). The mean age was 55 years and ranged from 23 to 85 years. Most patients were younger than 65 years old (80%). The aliskiren/valsartan/HCTZ group had a greater proportion of patients who were Black (21.8% vs. 8.2% aliskiren/valsartan) and who were obese (BMI ≥ 30; 58.4% vs. 46.8% aliskiren/valsartan). Demographic and background

characteristics in the long-term open label study were generally similar to those in short term studies. Data were summarized in table 51.

Table 51: Demographics by treatment group in long term open-label study

Demographic variable		Aliskiren/ valsartan * N=404	Aliskiren/ valsartan/HCTZ * N=197	Total N=601
Age (years)	mean (SD)	55.0 (11.59)	55.1 (10.39)	55.0 (11.20)
	median	56.0	54.0	55.0
	range (min – max)	23.0 – 85.0	32.0 – 80.0	23.0 – 85.0
Age group – n (%)	< 65 years	319 (79.0)	162 (82.2)	481 (80.0)
	≥ 65 years	85 (21.0)	35 (17.8)	120 (20.0)
	< 75 years	391 (96.8)	189 (95.9)	580 (96.5)
	≥ 75 years	13 (3.2)	8 (4.1)	21 (3.5)
Gender – n (%)	Male	223 (55.2)	107 (54.3)	330 (54.9)
	Female	181 (44.8)	90 (45.7)	271 (45.1)
Race – n (%)	Caucasian	357 (88.4)	151 (76.6)	508 (84.5)
	Black	33 (8.2)	43 (21.8)	76 (12.6)
	Asian	6 (1.5)	2 (1.0)	8 (1.3)
	Native American	2 (0.5)	0 0	2 (0.3)
	Pacific Islander	2 (0.5)	0 0	2 (0.3)
	Other	4 (1.0)	1 (0.5)	5 (0.8)
Obesity – n (%)	BMI ≥ 30 kg/m^2	189 (46.8)	115 (58.4)	304 (50.6)
	BMI < 30 kg/m^2	213 (52.7)	82 (41.6)	295 (49.1)
Diabetes	Yes – n (%)	45 (11.1)	25 (12.7)	70 (11.6)
GFR (mL/min/1.7m^2) n (%)	30 ≤ GFR < 60	22 (5.4)	13 (6.6)	35 (5.8)
	60 ≤ GFR < 90	206 (51.0)	105 (53.3)	311 (51.7)
	GFR ≥ 90	176 (43.6)	79 (40.1)	255 (42.4)

* 'Aliskiren/valsartan/HCTZ' group are patients who received HCTZ in addition to aliskiren/valsartan at any time during the study. 'Aliskiren/valsartan' group did not receive HCTZ during the study.
Source: [Study V2301-Table 11-1], [SCS PT-Table 3.1-2]

There were no other defined populations for safety. Study 2331 that provides supportive safety for combination therapy has details of demographic and baseline characteristic in the following table 52.

Table 52: Demographics in Study 2331.

Demographic variable		HCTZ N = 152	Aliskiren / HCTZ N = 166	Valsartan / HCTZ N = 155	Aliskiren / Valsartan / HCTZ N = 168	Total N = 641
Sex – n (%)	Female	58 (38.2)	74 (44.6)	67 (43.2)	77 (45.8)	276 (43.1)
	Male	94 (61.8)	92 (55.4)	88 (56.8)	91 (54.2)	365 (56.9)
Race – n (%)	Caucasian	131 (86.2)	141 (84.9)	135 (87.1)	147 (87.5)	554 (86.4)
	Black	13 (8.6)	16 (9.6)	14 (9.0)	15 (8.9)	58 (9.0)
	Asian	3 (2.0)	5 (3.0)	4 (2.6)	1 (0.6)	13 (2.0)
	Native American	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
	Other	5 (3.3)	4 (2.4)	2 (1.3)	4 (2.4)	15 (2.3)
Ethnicity – n (%)	Hispanic/Latino	28 (18.4)	20 (12.0)	26 (16.8)	31 (18.5)	105 (16.4)
	Indian (Indian subcont.)	1 (0.7)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.3)
	Mixed ethnicity	0 (0.0)	4 (2.4)	0 (0.0)	1 (0.6)	5 (0.8)
	Other	123 (80.9)	142 (85.5)	128 (82.6)	136 (81.0)	529 (82.5)
Age Group – n (%)	<65	136 (89.5)	143 (86.1)	123 (79.4)	141 (83.9)	543 (84.7)
	≥ 65	16 (10.5)	23 (13.9)	32 (20.6)	27 (16.1)	98 (15.3)
	≥ 75	3 (2.0)	4 (2.4)	6 (3.9)	4 (2.4)	17 (2.7)
Age (yrs)	n	152	166	155	168	641
	Mean (SD)	52.6 (9.93)	52.3 (10.90)	55.0 (11.40)	52.9 (10.83)	53.2 (10.81)
Duration of hypertension (yrs)	n	149	161	151	162	623
	Mean (SD)	8.0 (7.42)	7.8 (7.38)	9.2 (8.96)	8.6 (8.06)	8.4 (7.98)
Body mass index (BMI) (kg/m^2)	n	152	166	154	166	638
	Mean (SD)	31.8 (6.13)	31.3 (6.28)	31.3 (5.85)	31.9 (6.21)	31.6 (6.12)
Obesity* – n (%)	Yes	80 (52.6)	84 (50.6)	78 (50.3)	96 (57.1)	338 (52.7)
	No	72 (47.4)	82 (49.4)	76 (49.0)	70 (41.7)	300 (46.8)
Metabolic syndrome# – n (%)	Yes	80 (52.6)	87 (52.4)	76 (49.0)	96 (57.1)	339 (52.9)
	No	72 (47.4)	79 (47.6)	78 (50.3)	72 (42.9)	301 (47.0)
	Not available	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Diabetes – n (%)	Yes	21 (13.8)	20 (12.0)	19 (12.3)	18 (10.7)	78 (12.2)
	No	131 (86.2)	146 (88.0)	136 (87.7)	150 (89.3)	563 (87.8)

SD = standard deviation.
* Obesity = yes if BMI ≥ 30 kg/m^2.
# Metabolic Syndrome=Yes, if any 3 of the following are true:
1. Waist circumference >102 cm (40 in) for men, or > 88 cm (35 in) for women;
2. Triglycerides ≥ 150 mg/dL (1.69 mmol/L);
3. HDL cholesterol <40 mg/dL (1.04 mmol/L) for men, or <50 mg/dL (1.29 mmol/L) for women;
4. SBP ≥ 130 / or DBP ≥ 85 mmHg;
5. Fasting glucose ≥ 110 mg/dL (6.1 mmol/L).

Source: PT-table 14.1-3.1a

7.2.1.3 Extent of exposure (dose/duration)

The overall extent of drug exposure from all studies in the clinical development program is summarized in the following table 53. This table summarizes all treatments, all doses, and all treatment durations for all subjects who received at least one dose of study drug. Study 2327 exposed patients at both low and high doses, and exposure has been collected and presented accordingly. In the exposure table, patients who stayed in the study past Visit 7 when the dose was titrated up may therefore appear in both low and high dose exposure categories. Overall, 3520 patients were included in the aliskiren/valsartan combination clinical development program, with 1225 being exposed to the aliskiren/valsartan combination alone. Other groups received either placebo, aliskiren or valsartan monotherapy, valsartan with HCTZ, or aliskiren/valsartan with HCTZ. In the aliskiren/valsartan group, 349 patients were exposed for at least 180 days, and 316 for at least 360 days. In the short-term, placebo controlled studies, there were total 2919 patients including 624 of whom received the aliskiren/valsartan combination treatment.

Table 53: Duration of exposure to study drug after randomization – Safety/treated population (all studies)

Duration of Exposure(days)	Placebo N=635	Mono Ali N=969	Mono Val N=632	Ali/Val 75/80 mg N=60	Ali/Val 150/160 mg N=1107	Ali/Val 300/320 mg* N=1058	All Ali/Val N=1225	Val/HCTZ 160/12.5 mg N=59	ALI/VAL/HCTZ N=197
>= 1	635 (100%)	969 (100%)	632 (100%)	60 (100%)	1107 (100%)	1058 (100%)	1225 (100%)	59 (100%)	197 (100%)
>= 14	616 (97.0%)	938 (96.8%)	623 (98.6%)	58 (96.7%)	983 (88.8%)	1039 (98.2%)	1196 (97.6%)	58 (98.3%)	196 (99.5%)
>= 28	584 (92.0%)	905 (93.4%)	608 (96.2%)	56 (93.3%)	312 (28.2%)	941 (88.9%)	1162 (94.9%)	57 (96.6%)	194 (98.5%)
>= 42	571 (89.9%)	888 (91.6%)	586 (92.7%)	56 (93.3%)	58 (5.2%)	604 (57.1%)	1142 (93.2%)	57 (96.6%)	189 (95.9%)
>= 180	0	0	0	0	0	345 (32.6%)	349 (28.5%)	0	164 (83.2%)
>= 270	0	0	0	0	0	332 (31.4%)	332 (27.1%)	0	130 (66.0%)
>= 360	0	0	0	0	0	270 (25.5%)	316 (25.8%)	0	0
Statistics									
n	635	969	632	60	1107	1058	1225	59	197
Mean	52.3	53.2	53.9	53.4	21.5	145.1	147.3	55.2	253.1
SD	12.23	11.44	9.49	11.16	10.86	149.40	141.98	8.69	85.04
Median	56.0	56.0	56.0	56.0	16.0	57.0	59.0	56.0	300.0
Minimum	1	1	1	8	1	1	1	2	2
Maximum	74	73	70	66	70	386	400	68	333

Note: includes exposure from Studies 2203, 2327, and V2301
- Patients titrating to several doses within a treatment group were counted separately in each Ali/Val dose group.
* Subjects were treated with aliskiren/valsartan 150/160 mg for one week followed by 7 weeks of aliskiren/valsartan 300/320 mg in study 2203. The low dose period is aggregated with the high dose.
Source: [SCS-PT-Table 2.3-1]

Long-term data was provided in 1 uncontrolled study of 1-year duration. The overall mean exposure to aliskiren/valsartan combination was 236.8 days (median, 357 days). A total of 601 patients were exposed to the aliskiren/valsartan combination, starting dose 150/160 mg, and titrated to 300/320 mg with optional HCTZ add-on for up to 1 year. Most patients (80.0%) in this population received at least 360 days of treatment. Three hundred and forty five patients were treated with aliskiren 300 mg/valsartan 320 mg for at least 6 months (180 days) and 270 patients were treated for at least 12 months (360 days) without the need for the addition of HCTZ. Of the 197 patients who received add-on HCTZ, 164 were treated with aliskiren/valsartan/HCTZ for at least 6 months. Data were summarized in tables 53 and 54.

Table 54: Long-term duration of exposure in long-term open-label study.

	Aliskiren 150 mg/ valsartan 160 mg alone N = 601	Aliskiren 300 mg/ valsartan 320 mg alone N = 585	Aliskiren/ valsartan/HCTZ N = 197	Pooled * aliskiren 300 mg/ valsartan 320 mg N = 585	Total N = 601
Mean	14.1	236.8	253.1	322.0	327.6
SD	2.15	146.52	85.04	102.58	113.89
Median	14.0	357.0	300.0	364.0	378.0
Min - max	1 – 25	1 – 386	2 – 333	1 – 390	1 – 405

SD = standard deviation min - max = minimum and maximum values for the parameter
* Includes aliskiren 300 mg / valsartan 320 mg and aliskiren / valsartan / HCTZ groups.
Source: [Study V2301-PT-Table 14.3-1.1]

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Not available

7.2.2.2 Postmarketing experience

The fixed-dose combination of aliskiren/valsartan is not marketed in any country to date. However, both aliskiren and valsartan are currently approved in many countries worldwide. The reviewer agreed with the sponsor that it is not possible to estimate the exposure to the free combination of aliskiren and valsartan. Therefore, the adequate assessment of spontaneous reports involved the concomitant (free combination) use of these drug could not be performed.

No new safety observations following the administration of aliskiren have emerged from the cumulative assessment of postmarketing reports (as of 31 Mar 08) constituting a new risk or providing evidence of increased severity, specificity, and frequency of known or potential risks already described for aliskiren monotherapy.

Because valsartan has been on market in more than 100 countries for many years with the patient exposure estimated approximately (b) (4), extensive clinical experience reported in numerous reviews and major clinical trials have supported its use as first-line therapy for the treatment of hypertension. The safety profile of valsartan has been well defined.

7.2.2.3 Literature

Using the words “combination of aliskiren and valsartan” or “Valturna”, I did not find new or additional safety issues related to this combination in the public literature search.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience appears to have been adequate to evaluate the product safety based on the two short-term studies, one long-term study and one supportive study.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

I do not consider that the pre-clinical testing is needed.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical laboratory testing was adequate. Measurements of lab parameters expected to be affected by RAAS inhibitors, e.g., renal function and serum electrolytes, were frequent enough to detect significant problems.

Thorough QT study was not performed with the product. However, full QT study with aliskiren has been conducted and no abnormal findings were observed. Valsartan was approved in 1996 and no abnormal QT interval has been reported since then. Therefore, I do not think there is a potential QT impact with the combination of aliskiren and valsartan.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The potential for a pharmacokinetic and PD drug interaction between aliskiren and valsartan was assessed in healthy subjects. At steady state, when administered together, the mean AUC_{last} and C_{max} for aliskiren decreased by about 25% and that of valsartan decreased by about 15%. The 90% confidence intervals for AUC and C_{max} ratios for both aliskiren and valsartan were not within the no effect boundaries (80 to 125%). The observed plasma renin concentrations following administration of the combination was higher than that observed with either aliskiren or valsartan alone. The observed decrease in plasma renin activity following administration of the combination was similar to that observed with aliskiren alone. Given the observed inter-subject variability in aliskiren and valsartan PK (~ 50% CV) and the observed PD effects of the combination. Dr. Menon-Andersen, the clinical pharmacology reviewer, considered that the decreased AUC and C_{max} observed in this study should not be of any clinical significance.

Based on the review of NDA 21, 985 for aliskiren monotherapy and the metabolic profile of valsartan, the metabolic, clearance, and interaction workup of this combination were considered to be adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The evaluation for potential adverse events was adequate with the following limitations:
a). Higher incidence rate was found in patients with combination group than each monotherapy and placebo control groups. However, due to the significant measurement errors (6 patients in

the placebo group have serum level of potassium in the range of 7.5 to 9.4 mmol/L without any adverse events), the exact incidence rate can not be calculated.
b). A higher proportion of patients with moderate renal impairment (GFR <60 mL/min/1.73m2) had hyperkalemia (K^+>5.5 mmol/L) compared to patients with normal renal function in short-term studies. However, the number of patients with moderate renal impairment was too small to make the conclusion.

7.2.8 Assessment of Quality and Completeness of Data

The reviewer did not identify any problems with major discrepancies among the CRFs and Medwatch forms, and study reports. DSI inspection was not conducted.

7.2.9 Additional Submissions, Including Safety Update

In the 120 day safety update, no new clinical studies were provided. Data from the sponsor's global safety database for aliskiren and valsartan as concomitant medication did not reveal any safety signals other than the ones reported in the NDA.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The types of adverse events in the combination of aliskiren and valsartan were generally comparable with each of monotherapy. Higher incidence rates of decreased hemoglobin/hematocrit, increased serum levels of BUN, creatinine, uric acid, and potassium were observed in the combination group compared to each monotherapy and placebo control groups. However, other than the hyperkalemia, changes of hemoglobin/hematocrit, BUN, creatinine and uric acid do not seem to provide additionally clinically meaningful changes compared to each monotherapy.

Increased serum level of potassium seems the major finding in the combination compared to each of monotherapy. However, due to the significantly medical measurement errors (6 patients in the placebo group have the serum levels of potassium in the range of 7.5 to 9.4 mmol/L without any adverse events), the exact incidence rate can not be calculated. The majority of the elevations of potassium were transient. In the aliskiren monotherapy study, higher incidence rate of hyperkalemia was observed in diabetic patients. In this study, however, no patients in the short-term placebo-controlled studies with diabetes and only one patient in the long-term open-label study with diabetes had abnormal elevations in serum K^+. A higher proportion of patients with moderate renal impairment (GFR <60 mL/min/1.73m2) had hyperkalemia (K^+>5.5 mmol/L) compared to patients with normal renal function in short-term studies. Since the number of patients with moderate renal impairment was small, the result is inconclusive and further studies in this population are needed. The incidence of hyperkalemia does not appear to increase with long term (12 months) treatment of aliskiren/valsartan compared to short term treatment. In the long-term (12 months) open label study, there were 6 patients (1.0%) with hyperkalemia (≥ 6.0 mmol/L) patients. The incidents occurred in five patients treated with aliskiren 300 mg / valsartan 320 mg and one patient while treated with aliskiren/valsartan/HCTZ. Two of the patients discontinued due to hyperkalemia: one event

lasted for 38 days, and one event was continuing at discontinuation. The remaining four patients with hyperkalemia had events that did not require additional treatment or study drug interruption. Two of these patients completed the study, and two discontinued participation for reasons unrelated to hyperkalemia.

Other drug-related adverse events including diarrhea, rash, cough, anemia, and angioedema are comparable between the combination of aliskiren/valsartan and each of their monotherapy. Overall, AE profile is considered to be acceptable for antihypertensive therapy.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1Pooled data vs. individual study data

Individual data were summarized in the appendices in Section 10. The pooled data were summarized in Section 7.

7.4.1.2 Combining data

The rates were calculated by pooling the counts of patients with events in the numerators and counts of patients in the denominators. The rates were compared between the combined product of aliskiren with valsartan to each monotherapy of valsartan or aliskiren.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Dose-dependency of all AEs were counted by calculating rates for each dosage

7.4.2.2 Explorations for time dependency for adverse findings

No significantly time-dependent adverse events were observed with this product either in the short-term studies or long-term study.

7.4.2.3 Explorations for drug-demographic interactions

Subgroup specific rates were analyzed when sufficient events were available in subgroups, by age, race, gender, and disease factors including obesity, impaired renal function, and diabetes.

7.4.2.4 Explorations for drug-disease interactions

In small sample analyses, adverse events in patients with obesity, diabetes or mild impaired renal function, in general, were comparable to the overall population. However, the results may not be conclusive.

7.4.2.5 Explorations for drug-drug interactions

In addition to this combined product of aliskiren with valsartan, the AE rates were also analyzed in aliskiren with valsartan and HCTZ.

7.4.3 Causality Determination

Causality determinations other than associations suggested by increased rates were not performed.

8 Additional Clinical Issues

8.1 Dosing Regimen and Administration

The combination of aliskiren/valsartan generally produced clinically and statistically significant reductions in both diastolic and systolic blood pressure compared to placebo and each respective monotherapy in the studied dose ranges of 150 mg or 300 mg of aliskiren in combination with valsartan 160 mg or 320 mg. Therefore, the sponsor proposed clinical doses of aliskiren/ valsartan including 150/160 and 300/320 are acceptable.

8.2 Drug-Drug Interactions

The sponsor did not conduct any drug-drug interactions.

8.3 Special Populations

Aliskiren/valsartan was effective regardless of gender, age, ethnicity, and disease factors of obesity, diabetes and mild impaired renal function.

8.4 Pediatrics

The sponsor did not conduct pediatric studies.

8.5 Advisory Committee Meeting

This NDA has not been and is not planned to be discussed at an advisory committee meeting.

8.6 Literature Review

In the Pubmed literature searches by using "aliskiren and valsartan" or "valturna", there were no additional findings of combined product other than in this NDA.

8.7 Postmarketing Risk Management Plan

The sponsor provided a risk management plan for aliskiren/valsartan fixed combination focusing on the risks including diarrhea, rash, hyperkalemia, angioedeam, decreases in hemoglobin and hematocrit, hypotension, renal dysfunction, cough, pregnancy, pediatric, moderate and severe renal impairment, renal vascular hypertension, and cardiovascular morbidity and mortality. The reviewer believe that the proposed postmarketing risk management plan with NDA is adequate.

The risk management activities will include the proposed pharmacovigilance activities and proposed risk minimization activities.

The pharmacovigilance activities will include the following:

(b) (4)

The risk minimization activities for fixed combination aliskiren/valsartan at the dose range (150 mg/160 mg, 300 mg/320 mg) proposed for human use for the treatment of hypertension will follow the approved plan for aliskiren monotherapy detailed in the aliskiren RMP and the existing labeling for valsartan.

The complete and ongoing studies of the risk management plan for both aliskiren monotherapy and the combination therapy were summarized in the following table 55 .

Table 55: Summary of complete and ongoing studies of RMP

Action	Timelines	Milestones
Important identified risks		
Diarrhea – Obtain further data on mechanism of diarrhea and further placebo comparative clinical trial data on clinically significant diarrhea events arising in a large scale morbidity/mortality study.	Ongoing study (CSPP100E2337) with first patient enrolled Oct-2007 (planned enrollment, N=8600). 4-year follow-up planned with two interim analyses.	Clinical trial report of **Study CSPP100E2337** (see summary of study protocol in [RMP Annex 3]) The final study report will be available by end of 2nd Q of 2012.
Angioedema – Obtain further placebo comparative clinical trial data, including targeted follow-up on angioedema events arising in a large scale morbidity/mortality study.	Ongoing study (CSPP100E2337) with first patient enrolled Oct-2007 (planned enrollment, N=8600). 4-year follow-up planned with two interim analyses.	Clinical trial report of **Study CSPP100E2337** (see summary of study protocol in [RMP Annex 3]) The final study report will be available by end of 2nd Q of 2012
Hyperkalemia – Obtain placebo comparative clinical trial data on hyperkalemia events arising in a large scale morbidity/mortality study.	Ongoing study (CSPP100E2337) with first patient enrolled Oct-2007 (planned enrollment, N=8600). 4-year follow-up planned with two interim analyses.	Clinical trial report of **Study CSPP100E2337** (see summary of study protocol in [RMP Annex 3]) The final study report will be available by end of 2nd Q of 2012
Obtain active control data on hyperkalemia events arising in a hypertension and obesity study.	Completed study (CSPP100E2316) with first patient enrolled Oct-2005 and last patient 28-Nov-2007 (actual enrollment, N=466).	Clinical trial report of **Study CSPP100A2316** finalized 13 May-2008 (see summary of study report in [RMP Annex 3]) The final study report will be available by end of 2nd Q of 2012
Important potential risks		
Colorectal hyperplasia –	A 2-year study in marmosets is running (1939-017) to investigate effects of aliskiren in the GI tract after chronic exposure in a relevant animal species. This will allow elucidation of the effects of aliskiren on GI histopathology, proliferation assays, and aliskiren concentrations in plasma, GI tissue and lumen. Final report expected end of 2009.	A draft report is planned for end Q1 2009.
Obtain placebo comparative clinical trial data on colorectal events, including targeted follow-up, arising in a large scale morbidity/mortality study.	Ongoing study (CSPP100E2337) with first patient enrolled Oct-2007 (planned enrollment, N=8600) 4-year follow-up planned with two interim analyses.	Clinical trial report of **Study CSPP100E2337** (see summary of study protocol in [RMP Annex 3]) The final study report will be available by end of 2nd Q of 2012
Obtain active control comparative clinical trial data in a colonoscopy study of aliskiren 300 mg/day for 1 year.	Study started February 2008 (Study CSPP100A2404).	Clinical trial report of **Study CSPP100A2404** (see summary of study protocol in [RMP Annex 3]) The final study report will be available in Feb 2010 (N=640 patients).
Renal dysfunction – Obtain placebo comparative clinical trial data on renal dysfunction events arising in a large scale morbidity/mortality study.	Ongoing study (CSPP100E2337) with first patient enrolled Oct-2007 (planned enrollment, N=8600). 4-year follow-up planned with two interim analyses.	Clinical trial report of **Study CSPP100E2337** (see summary of study protocol in [RMP Annex 3]) The final study report will be available by end of 2nd Q of 201
Obtain active control data on renal dysfunction events arising in a hypertension and obesity study.	Completed study (CSPP100E2337) with first patient enrolled Oct-2005 and last patient 28-Nov-2007 (actual enrollment, N=466).	Clinical trial report of **Study CSPP100A2316** finalized 13 May-2008 (see summary of study report in [RMP Annex 3])

8.8 Other Relevant Materials

All the materials are incorporated in this NDA and have been reviewed.

9 Overall Assessment

9.1 Conclusions

The combination of aliskiren/valsartan generally produced clinically and statistically significant reductions in both diastolic and systolic blood pressure compared to placebo and each respective monotherapy in the studied dose ranges of aliskiren/valsartan at doses of 150/160 mg or 300/320 mg. Both individual monotherapy components seem to contribute to the antihypertensive effect of the combination in the overall population. This anti-hypertensive effect was attained within 2 weeks after treatment. In the long-term open label study, the combination of aliskiren/valsartan is effective as a long-term treatment for patients with essential hypertension, demonstrating persistent BP reduction over a 12-month treatment period. However, randomized withdraw study was not conducted. Therefore, the long-term effect in this open-label study is inconclusive. In the subgroup analysis, the greater BP lowering effect of the combination therapy of aliskiren/valsartan over the respective monotherapies was observed consistently, regardless of gender, age and disease factors including obesity, diabetes, renal impairment, and stages of hypertension. Regarding the different effect of this product on race, it seems that either aliskiren/valsartan monotherapy or the combination has more effective in Caucasian than in African American. Other races can not be determined due to the small sample size.

Based on the probability analysis, the predicted BP control targets of both < 140/90 mmHg and 130/80 mmHg was greater with the combination of aliskiren/valsartan as compared to aliskiren or valsartan monotherapy, regardless of baseline BP. Therefore, data from both the subgroup analysis and the probability analysis of BP control rates support the use of aliskiren/valsartan as an initial therapy

In the integrated safety data analysis, the incidence of overall as well as individual AEs were similar in aliskiren/valsartan combination therapy to each component monotherapy. Regarding the incidences of significant AEs identified during aliskiren monotherapy clinical development program, the angioedema, GI events, cough, and anemia are also similar in the aliskiren/ valsartan combination therapy compared to each monotherapy. Small mean decreases from baseline were seen in red blood cell count, hemoglobin and hematocrit in both monotherapies and combination therapy. These changes were small, but were slightly more pronounced with the combination therapy than with monotherapy. Four patients (0.7%) in the aliskiren/valsartan combination group had a clinically significant increase in creatinine (>176.8 μmol/L), compared to 2 patients in both the aliskiren monotherapy group (0.2%) and the valsartan monotherapy group (0.3%). Of the four patients in aliskiren/valsartan group, two had values that returned to within normal range without the disruption of the study drug by the end of study or study follow-up. In the one year open label study, two patients (0.3%) had a creatinine

value > 176.8 umol/L. One had value that returned to within normal range without the disruption of the study drug by the end of study. Using the criteria of creatinine >132.6 µmol and >30% from baseline, there three patients (0.5%) in the aliskiren/valsartan group including the two patients with creatinine > 176.8µmol/L and none were either monotherapy groups or placebo group at the end of study. There were also three patients in the long-term open label study including one patient with creatinine > 176.8µmol/L.

Increased serum level of potassium is the major finding in the aliskiren/valsartan combination therapy compared to each of monotherapy. The incidence rate of hyperkalemia (serum potassium >5.5 mEq/L) was higher in the combination compared with the aliskiren, valsartan monotherapy or placebo. The majority of the elevations were transient. A higher proportion of patients with moderate renal impairment (GFR <60 mL/min/1.73m2) had hyperkalemia (>5.5 mmol/L) compared to patients with normal renal function in short-term studies; however, the number of patients with moderate renal impairment was small and therefore, the data are inconclusive. No patient was withdrawn due to hyperkalemia in short-term studies. The incidence of hyperkalemia does not appear to increase with long term (12 months) treatment of aliskiren/valsartan compared to short term treatment. There were total 6 patients (1.0%) with hyperkalemia reported as AEs. The incidents occurred in five patients treated with aliskiren 300 mg / valsartan 320 mg and one patient while treated with aliskiren/valsartan/HCTZ. Two of the patients discontinued due to hyperkalemia: one event lasted for 38 days, and one event was continuing at discontinuation. The remaining four patients with hyperkalemia had events that did not require additional treatment or study drug interruption. Two of these patients completed the study, and two discontinued participation for reasons unrelated to hyperkalemia.

Regarding the higher proportion of patients with moderate renal impairment (GFR <60 mL/min/1.73m^2) had hyperkalemia (>5.5 mmol/L) compared to patients with normal renal function in short-term studies, more patients with moderate and severe renal impairment should be studied with this combination. It should be noted, however, all patients with renal impairment should be carefully monitored for their plasma level of potassium when RAAS blockers are administered. Therefore, overall, AE profile is considered to be acceptable for antihypertensive therapy.

9.2 Recommendation on Regulatory Action

From clinical and statistical perspectives, the combination of aliskiren/valsartan should be approved for the treatment of hypertension. This combination generally produced clinically and statistically significant reductions in both diastolic and systolic blood pressure compared to placebo and each respective monotherapy. In addition, based on the probability analysis, the predicted BP control targets of both < 140/90 mmHg and 130/80 mmHg was greater with the combination of aliskiren/valsartan as compared to aliskiren or valsartan monotherapy, regardless of baseline BP. Therefore, data from both the subgroup analysis and the probability analysis of BP control rates support the use of aliskiren/valsartan as an initial therapy. Its adverse event profile is similar to each component therapy.

Based on the analysis of provided data sets, the recommended dosage strengths of aliskiren/valsartan should be 150/160 mg and 300/320 mg once-a-day.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity (RMP)

Since the sponsor has provided detailed RMP especially for the hyperkalemia, no additional risk management activities are needed. Please see the section of 8.7.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are required at this time.

9.3.3 Other Phase 4 Requests

No other phase 4 studies are requested.

9.4 Labeling Review

The labeling review will be discussed in the upcoming labeling meetings.

9.5 Comments to Applicant

No additional comments are provided to the sponsor.

10 Appendices

10.1 Review of Individual Study Reports

10.1.1 SPP100A 2327: An 8-week randomized, double-blind, parallel group, multicenter, placebo and active controlled dose escalation study to evaluate the efficacy and safety of aliskiren (150 mg and 300 mg) administered alone and in combination with valsartan (160 mg and 320 mg) in patients with hypertension

10.1.1.1 Sites and Investigators

Study centers: United States (202 centers), Germany (85 centers), and Spain (25 centers).
Investigator(s): (b) (4) et al

10.1.1.2. Study dates

First patient enrolled: 27-Jun-2005; Last patient completed: 05-Sep-2006

10.1.1.3. Study design

This was a double-blind, randomized, parallel group, multi-center, placebo and active control dose escalation study comparing the efficacy and safety of aliskiren administered alone and in combination with valsartan in patients with essential hypertension (office cuff msDBP ≥ 95 mm Hg and < 110 mm Hg). The study had four periods and 7 to 9 visits.

Period 1 (Screening / Washout): Patients on current antihypertensive medications were to discontinue their antihypertensive medications under the supervision of the study investigator and enter a one-week washout period before entering the single-blind period. Patients who were newly diagnosed with uncomplicated essential hypertension or patients who had not received antihypertensive medications for at least 4 weeks prior to Visit 1 must have had an office cuff msDBP ≥ 95 mm Hg and < 110 mm Hg at Visit 1. For these patients, Visit 1 and Visit 2 were combined and the patients were enrolled directly into the three to four week single-blind placebo run-in period.

Period 2 (Single-blind placebo run-in): At Visit 2 (Day -21 or Day -28), all patients entered a three to four week single-blind placebo run-in period in order to establish a baseline blood pressure and eligibility for randomization based upon the inclusion and exclusion criteria defined in the protocol. At Visit 3 (Day -7 or Day -14) the blood pressure eligibility criteria of office cuff msDBP ≥ 90 mm Hg and < 110 mm Hg was assessed and patients were discontinued if office msDBP ≥ 110 mm Hg. At Visit 4 (Day -1 or Day -7) the blood pressure eligibility criteria of office cuff msDBP ≥ 95 mm Hg and < 110 mm Hg and the difference in office msDBP ≤ 10 mm Hg during the last two consecutive visits (Visit 3 and 4) of the single-blind placebo run-in period were assessed:

• If a patient met the eligibility criteria defined above at Visit 4 then the Visit 4 was converted into Visit 5, the blood pressure measured at Visit 4 was entered on the eCRF as the Visit 5 blood pressure and the patient was evaluated using mean 8-hr daytime ABPM at Visit 5.
• If a patient had an office msDBP < 90 mm Hg at Visit 4, then that patient was to be discontinued from the study.
• If the patient had a difference in office msDBP > 10 mm Hg during the last two consecutive visits (Visit 3 and 4) or if the patient had an office msDBP < 90 mm Hg at Visit 3 and ≥ 90 mm Hg at Visit 4, or if the patient has an office cuff msDBP ≥ 90 mm Hg but < 95 mm Hg at Visit 4 then the patient was allowed one additional week of single blind placebo run-in before the occurrence of Visit 5 (in this case, the duration between Visit 4 and Visit 5 would be for one week), in order to establish blood pressure eligibility.
• If after one additional week of run-in placebo, the patient did not meet the office msDBP ≥ 90 mm Hg at Visit 4 and msDBP ≥ 95 mm Hg at Visit 5 or the difference in msDBP ≤ 10 mm Hg during the last two consecutive visits (Visit 4 and Visit 5), then the patient was to be discontinued from the study.

Period 3 (Initial four-week double-blind treatment): After verification of the above office msDBP criteria the patients had an ABPM device placed on them for evaluation of 8-hour daytime ABPM and patients continued to receive single blind placebo medication. (In those patients included in the subset having a 24-hour ABPM evaluation, the first 8 hours of this 24-

hour evaluation provided the mean 8-hour daytime ABPM data required as part of the entry criteria). On the second day of Visit 5, the evaluation of the ABPM from Day -1 must have demonstrated a mean 8-hour daytime ambulatory DBP ≥ 90 mm Hg in order for the patient to be randomized. If the quality control failed on the first attempt for 8-hour ABPM, the second attempt of 8- hour ABPM was allowed within 48 hours. The second attempt was not allowed for patients whose 8-hour daytime ABPM passed quality control but failed to meet mean 8-hour daytime DBP criteria of ≥ 90 mm Hg. Only one repeat ABPM was allowed for each patient.

All patients who fulfilled the inclusion/exclusion criteria (in addition to the above defined blood pressure criteria) were randomized in a double-blind fashion to one of the four treatment arms: aliskiren monotherapy, valsartan monotherapy, the combination of aliskiren and valsartan, or placebo. The initial therapy in the respective treatment arm was aliskiren 150 mg o.d., valsartan 160 mg o.d., the combination of aliskiren 150 mg / valsartan 160 mg o.d., or placebo o.d.

Period 4 (Final four-week double-blind treatment):
After 4 weeks of treatment on the period 3 regimen, at Visit 7 (Day 29), all patients were force-titrated to elevated doses of their respective treatment arms to: aliskiren 300 mg o.d., valsartan 320 mg o.d., the combination of aliskiren 300 mg / valsartan 320 mg o.d., or placebo o.d. for an additional four weeks of treatment. Treatment ended at Visit 9. In addition to 8-hour daytime ABPM described above, a subset of patients (approximately 500 patients) had the 24-hour ABPM evaluated at baseline (Visit 5) and at the end of study (Visit 9 or early termination) at selected centers, with the goal of completing 400 total patients. Centers were selected based on interest and expertise in ABPM procedures. The study duration for each patient, inclusive of all phases, was a minimum of approximately 11 weeks and a maximum of approximately 14 weeks.

Study population: Approximately 1784 patients (446 in each of the 4 treatment arms) with essential hypertension who met selection criteria were to be randomized in this study from approximately 194 Centers in the US and Europe. A subset of approximately 500 patients (125 per treatment arm) were to be enrolled into the 24-hour ABPM at Visit 5, with the goal of 400 patients (100 per treatment arm) completing both 24-hour ABPM evaluations (at Visits 5 and 9), at a selected number of centers. These centers were expected to enroll patients who would undergo 24-hour ABPM at Visit 5 (prior to randomization and corresponding to the last dose of placebo medication) and at Visit 9 (end of study/early discontinuation and corresponding to the last dose of double-blind medication).

The study design was summarized in the following Figure 6.

Figure 6: Study design

Phase	Pre-randomization				Double-Blind Treatment				
Period	Screening / Washout	Single-blind Placebo Run-in			Initial four-weeks of treatment		Final four-weeks of treatment		
Visit	1[1,2]	2[2]	3	4	5[3]	6	7[4]	8	9
Duration[5]	1-2 week(s)	2 weeks	1 week	1 day or 1 week	4 weeks		4 weeks		
Day[6]	-28 or -42	-21 or -28	-7 or -14	-1 or -7	1	15	29	43	56
Randomization					X				
Rx group 1		Placebo			Aliskiren 150 mg o.d.		Aliskiren 300 mg o.d.		
Rx group 2		Placebo			Valsartan 160 mg o.d.		Valsartan 320 mg o.d.		
Rx group 3		Placebo			Aliskiren 150 mg / Valsartan 160 mg o.d.		Aliskiren 300 mg / Valsartan 320 mg o.d.		
Rx group 4		Placebo			Placebo		Placebo		

[1] If the patient was required to be tapered off the current anti-hypertensive medication then the tapering was to occur at Visit 1. The patient was to be washed out of their anti-hypertensive medication for at least 1 week prior to Visit 2.

[2] For currently untreated patients Visit 1 and Visit 2 were combined into one Visit.

[3] Visit 5 consisted of 2 days. Randomization occurred on the second day of Visit 5.

[4.] Titration occurred at Day 29 (Visit 7) of double-blind treatment.

[5.] Duration refers to the time between current visit and next Visit.

[6] If the placebo run-in period was extended for 1 week to meet randomization criteria then, Visit 1 became Day -42 (if the duration between Visit 1 and Visit 2 was 2 weeks), Visit 2 became Day -28, Visit 3 became Day -14 and Visit 4 became Day -7.

10.1.1.4. Study objectives

The primary objective of this study was to evaluate the efficacy of the combination of aliskiren 300 mg and valsartan 320 mg in patients with essential hypertension by testing the hypothesis of superior reduction in msDBP from baseline to end of study when compared to both monotherapy components.

10.1.1.5. Inclusion, exclusion criteria and stop rule

Inclusion Criteria: Male or female outpatients, 18 years of age and older, with a history of essential hypertension; newly diagnosed or patients who had not been treated within 4 weeks of Visit 1 must have had an office cuff msDBP ≥ 95 mm Hg and < 110 mm Hg at Visit 1. Prior to the randomization, patients were required to have an office cuff msDBP ≥ 90 mm Hg at Visit 3 and office cuff msDBP ≥ 95 mm Hg at Visit 4 or Patients must have an office cuff msDBP ≥ 90 mm Hg at Visit 4 and office cuff msDBP ≥ 95 mm Hg at Visit 5 during single blind placebo run in period. In addition patient must have an office cuff msDBP < 110 mm Hg at visits 3, 4, and 5. Patients must have had a difference of ≤ 10 mm Hg in their msDBP during

the last two consecutive visits (at Visit 3 and Visit 4 or at Visit 4 and Visit 5) of the single blind placebo run-in period. Patients must have had a mean 8-hour daytime ABPM DBP ≥ 90 mm Hg at Visit 5.

Exclusion Criteria:
1. Previously treated in an aliskiren study and who qualified to be randomized or enrolled into the active drug treatment period.
2. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/ml).
3. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners had been sterilized by vasectomy or other means, UNLESS they met the following definition of postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/m or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy OR were using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception (implantable, patch, oral), and double-barrier methods. Reliable contraception was to be maintained throughout the study and for 7 days after study drug discontinuation.
4. Severe hypertension (an office cuff msDBP ≥ 110 mm Hg and/or msSBP ≥ 180 mm Hg).
5. History or evidence of a secondary form of hypertension.
6. Known Keith-Wagener grade III or IV hypertensive retinopathy.
7. Previous and current diagnosis of heart failure (NYHA Class II-IV).
8. History of hypertensive encephalopathy or cerebrovascular accident, transient ischemic cerebral attack (TIA), myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention (PCI).
9. Serum sodium less than lower limit of normal, serum potassium ≥ 5.3 mEq/L at Visit 1.
10. History of Type 1, or Type 2 diabetes and glycosylated hemoglobin (HbA1c) > 8 % at Visit 1.
11. Current angina pectoris requiring pharmacological therapy.
12. Second or third degree heart block without a pacemaker.
13. Atrial fibrillation or atrial flutter at Visit 1, or potentially life threatening or any symptomatic arrhythmia during the 12 months prior to Visit 1.
14. Clinically significant valvular heart disease.
15. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs including, but not limited to, any of the following:
• History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
• History of active inflammatory bowel disease during the 12 months prior to Visit 1.
• Currently active gastritis, duodenal or gastric ulcers, or gastrointestinal bleeding during the 3 months prior to Visit 1.
• Any history of pancreatic injury, pancreatitis, or evidence of impaired pancreatic function/injury as indicated by abnormal lipase or amylase during the 12 months prior to Visit 1.

• Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 3 x ULN at Visit 1, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt.
• Evidence of renal impairment as determined by any one of the following: serum creatinine > 1.5 x ULN at Visit 1, a history of dialysis, or a history of nephritic syndrome.
• Current treatment with cholestyramine or colestipol resins.
16. History of hypersensitivity to any of the study drugs or to drugs belonging to the same therapeutic class (ARBs or renin inhibitors) as the study drugs.
17. History of angioedema due to usage of an ARB or ACE.
18. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
19. History or evidence of drug or alcohol abuse within the last 12 months.
20. Any surgical or medical condition, which in the opinion of the investigator, may have placed the patient at higher risk from his/her participation in the study, or was likely to prevent the patient from complying with the requirements of the study or completing the study.
21. Arm circumference > 42 cm.
22. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half lives
of enrollment, whichever was longer.
23. History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
24. Any condition that in the opinion of the investigator or the Novartis Medical Monitor would confound the evaluation and interpretation of efficacy and/or safety data.
25. Persons directly involved in the execution of this protocol.

Stop rule: Patients with an office cuff msDBP ≥ 110 mm Hg or an office cuff msSBP ≥ 180 mm Hg at any time during the screening/washout, single-blind placebo run-in, or double-blind treatment period of the study must have been permanently discontinued from the study; Patients with signs or symptoms of clinically significant hypotension and / or an office cuff msDBP < 60 mm Hg and / or an office cuff msSBP < 100 mm Hg at any time during the study (i.e., screening/washout, single-blind placebo run-in, or double-blind treatment period) were to be thoroughly evaluated by the investigator and if clinically warranted, were to be permanently discontinued from the study; Pregnancy

Patients who discontinued during the double-blind treatment period (prior to Visit 9) were to be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit were performed. The 24-hour ABPM was only completed on those patients who successfully completed 24-hour ABPM at Visit 5. For those patients who discontinued early after completing 24-hour ABPM at Visit 5, an attempt was to be made to assess the 24-hour ABPM at Visit 9 provided an additional dose of double-blind medication had been administered on the day 24-hour ABPM was to be applied.

10.1.1.6 Efficacy and safety assessment.

Sitting and standing blood pressure were measured at trough (24 hours ± 3 hours post dose)

and recorded at all study visits.

The mean 8-hour daytime ABPM was measured for all patients at Visit 5 prior to randomization. All patients who met the office msDBP criteria had an ABPM device applied to assess mean 8-hour daytime ABPM DBP at Visit 5. The 24-hour ABPM was performed in a subset of patients at Visit 5 and Visit 9.

The ABPM was placed on the nondominant arm after sphygmomanometer readings between 7:00 am and 10:00 am. The subject was then instructed regarding ABPM procedures and was required to return to the clinic in 24 hours for removal of the device. Patients who were not participating in the 24-hour ABPM sub-study removed the ABPM device after 8 hours of recording and returned to the clinic the next day. Only those patients who completed the 24-hour ABPM at Visit 5 successfully had a Visit 9 ABPM evaluation completed. At Visit 9, the patient completed the last office blood pressure/pulse evaluation prior to application of the ABPM device. The monitor was removed the next day, and the data were transferred into a personal computer and loaded into a specialized software package.

Safety Assessments**:** Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine performed at (study center / central laboratory) and regular assessments of vital signs, physical condition and body weight.

10.1.1.7. Statistical and Analytical Plans

The primary variable at Week 8 endpoint was analyzed using a two-way analysis of covariance model with treatment and region as two factors, and baseline as a covariate. The participating countries in the study were US, Germany, and Spain; US centers were divided into 4 regions, Germany's centers were divided into 2 regions, and Spain was considered a single region. The regions were pre-specified prior to unblinding treatment codes for analyses. To assess whether both monotherapy treatments (aliskiren and valsartan) contribute to the effect in blood pressure reduction of the combination treatment, the primary variable at Week 8 endpoint was analyzed using the model. Two pair-wise treatment comparisons (combination versus aliskiren and combination versus valsartan) were made based on the model. The combination was considered more effective than both monotherapy treatments if both pair-wise comparisons were statistically significant in favor of the combination. Therefore, the statistical test for each of the pair-wise comparisons was made at the two-sided significance level of 0.05. No statistical adjustment of the type I error was needed. Ninety-five percent confidence intervals were provided to quantify add-on effects for the combination dose.

The second efficacy variable is change from baseline (Visit 5) in mean sitting systolic blood pressure (msSBP). The same analysis for msDBP (described above) was performed for msSBP.

For the low-dose combination of aliskiren and valsartan and low-dose monotherapy, for the primary variable, all the analyses described above were performed at Week 4 endpoint for the

intent-to-treat population. Week 4 endpoint measurement was calculated as the last post baseline measurement prior to or on Week 4.

For the responder analysis, the proportion of patients in each treatment achieving a response in mean sitting diastolic blood pressure during the double-blind period was compared using a logistic regression model with treatment and region as the factors and baseline msDBP value as a covariate at Week 4 and Week 8 endpoints, for the primary efficacy population. Pair-wise treatment comparisons were made at a two-sided significance level of 0.05. The response was defined as a mean sitting diastolic blood pressure < 90 mm Hg or a ≥ 10 mm Hg decrease compared to baseline (pre-dose measurement at the randomization Visit 5).

For ABPM analysis, the hourly mean ambulatory diastolic blood pressure (MADBP) post dosing was calculated for each post-dosing hour over 24 hours by taking the average of the readings taken in the corresponding post-dosing hour. The post-dosing clock time according to the dosing time at visit 9 was the benchmark to define the post-doing hours for the calculation of the hourly MADBP at Visits 5 and 9. To assess the treatment effects on change from baseline (visit 5) in hourly MADBP (hour 1, 2, 3, …, 24), the analysis of covariance (ANCOVA) for repeated measures was employed for hourly changes from baseline. The hourly change from baseline in MADBP was calculated by taking the difference between the corresponding hourly MADBP at Visit 9 and Visit 5 for a given post-dosing hour. A two-way repeated-measures analysis-of-covariance model with treatment, region, and post-dosing hours (hour 1, 2, 3, …, or 24) as factors and baseline mean 24-hour MADBP as a covariate was performed. Treatment by post-dosing-hour interaction was included in the model. Hourly changes from baseline were summarized to assess the intra-dosing effects. In addition, the 24-hour mean differences with 95% confidence interval in change from baseline of MADBP between the treatment groups were assessed as supportive efficacy results. SAS PROC MIXED procedure with autoregressive order 1 covariance structure (AR1) was used for the analysis. The same analysis as MADBP above was done for mean ambulatory systolic blood pressure (MASBP) with the exception of using the baseline MASBP value as the covariate.

Similar analysis of covariance (ANCOVA) models for repeated measures were used to assess the treatment effect on the change from baseline in daytime/nighttime MADBP and MASBP. Each patient's daytime mean was the average of the hourly means between 6 am and 10 pm (> 6 am and ≤ 10 pm) while the nighttime mean was the average of the hourly means between 10 pm and 6 am (> 10 pm and ≤ 6 am). Change from baseline in daytime/nighttime MADBP/MASBP was calculated in the same fashion as that described above. The factors in the model included: region, treatment, time (daytime, nighttime), treatment-by-time interaction, and the baseline mean 24-hour MADBP/MASBP as a covariate.

The proportion of patients in each treatment achieving a blood pressure control target (msSBP/msDBP < 140/90 mm Hg) during the double-blind period were compared using a logistic regression model with treatment and region as the factors and baseline msDBP value as a covariate at Week 4 and Week 8 endpoints for the primary efficacy. Pair-wise treatment comparisons were made at a two-sided significance level of 0.05.

Determination of Sample Size: A sample size of 1604 completed patients (401 per arm) was targeted. Assuming a dropout rate of 10%, 1784 patients (446 per arm) with an equal randomization ratio of 1:1:1:1 were to be randomized. The sample size was calculated for the primary variable, change from baseline in mean sitting diastolic blood pressure, assuming a standard deviation of 8 mm Hg (based on previous data). The objective was to show that the combination is statistically superior to both monotherapy treatments. To achieve this objective with an overall power of 90%, the sample size was calculated to simultaneously detect a treatment difference of at least 2 mm Hg for both corresponding pair wise treatment comparisons (combination versus aliskiren and combination versus valsartan), at a two-sided significance level of 0.05.

10.1.1.8. Protocol amendments and violations.

Protocol Amendment 1 (05-May-2005) was issued prior to start of the study, before any patients were enrolled. The amendment revised the original plan to include a long-term extension to CSPP100A2327. Based on Amendment 1, the long-term study was postponed until after results from the core study were available. This allowed further assessment of the efficacy and safety of the combination of aliskiren and valsartan before exposing patients to long term treatment with this combination.

Protocol Amendment 2 (05-Dec-2005) was issued after approximately 1650 patients had been enrolled, before any un-blinding took place. Changes in Amendment 2 are summarized in the following:
• The patient population in this study is those with mild to moderate hypertension, defined as sitting cuff DBP ≥ 95 mm Hg and ABPM DBP ≥ 90 mm Hg at the end of the placebo run-in phase. The original protocol also required that the patient had a sitting cuff DBP of ≥ 95 mm Hg at the visit preceding the randomization visit. This was to enhance the likelihood for the patient to be qualified at the randomization visit. However, in doing so it also excluded some patients whose sitting DBP may have taken a little longer to reach 95 mm Hg. Those patients are hypertensive and this protocol amendment allowed such patients to be included in the study.
• From the mechanism of action and clinical experience so far with aliskiren and valsartan, it does not appear that the two drugs when used alone or in combination result in an increased risk of hypokalemia. Thus, there is no need to specify the lower limit of serum potassium as an exclusion criterion at the study entry.
• Typographical errors with respect to the indication for the ratio of PRA to plasma aldosterone were corrected to reflect the ratio of plasma aldosterone to PRA.

Local Amendment 3 (06-Dec-2005), applicable in USA only, was issued prior to the completion of recruitment in the USA, after approximately 1650 patients had been enrolled and before any unblinding took place. The original protocol excluded diabetic patients with glycosylated hemoglobin (HbA1c) above 8%. However, such patients have the same or greater need for blood pressure treatment as they do for blood sugar treatment. In studies to date, including a recent trial in diabetic patients with hypertension, there were no increased safety risks associated with the use of aliskiren observed in this population. Therefore, the local protocol amendment allowed the inclusion of diabetic patients in this study regardless of baseline HbA1c status, i.e., the requirement that this value be less than 8 was eliminated.

Major protocol violations are summarized in table 56. The overall incidence of major protocol violations was higher in the placebo group (10.9%) than in the other treatment groups (5.4% in the aliskiren/valsartan group, 6.4% in the valsartan group, and 6.9% in the aliskiren group). Compared with the other treatment groups, a greater proportion of patients in the placebo group used drugs approved for treatment of hypertension, had msDBP < 95 mm Hg at Visit 5, and had a > 10 mm Hg change in msDBP between Visit 3 or 4 and Visit 5.

Table 56: Summary of major protocol violations by treatment group (randomized population)

Protocol violation	Placebo N=459 n (%)	Aliskiren N=437 n (%)	Valsartan N=455 n (%)	Aliskiren/ Valsartan N=446 n (%)	Total N=1797 n (%)
Any major protocol violation	50 (10.9)	30 (6.9)	29 (6.4)	24 (5.4)	133 (7.4)
Mean 8 hr ABPM DBP < 90 mm Hg at V5	9 (2.0)	9 (2.1)	6 (1.3)	11 (2.5)	35 (1.9)
msDBP < 95 mm Hg at V5	14 (3.1)	9 (2.1)	2 (0.4)	5 (1.1)	30 (1.7)
Drug approved for treatment of HTN V2-V9	15 (3.3)	3 (0.7)	5 (1.1)	2 (0.4)	25 (1.4)
msDBP change >10 mm Hg between V3 or V4 & V5	12 (2.6)	1 (0.2)	5 (1.1)	6 (1.3)	24 (1.3)
Med affect BP & used 48h prior key eff V	2 (0.4)	4 (0.9)	5 (1.1)	2 (0.4)	13 (0.7)
msDBP ≥ 110 mm Hg at V1, V2, V3, V4, V5	3 (0.7)	2 (0.5)	3 (0.7)	3 (0.7)	11 (0.6)
msSBP ≥ 180 mm Hg at V1, V2, V3, V4, V5	3 (0.7)	3 (0.7)	4 (0.9)	1 (0.2)	11 (0.6)
msDBP < 90 mm Hg at the visits prior to V5	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)
Blind was broken between V5-V9	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Pt randomized, no double blind med taken	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Protocol violations are sorted in descending order of frequency as presented in the "Total" column.
Source: PT-Table 14.1-1.3

10.1.1.9. Demographic and other baseline characteristics

Of the 3980 patients enrolled in the single-blind period, 1797 patients (45.2%) were randomized; 459 patients were randomized to placebo; 437 patients to the aliskiren group, 455 to the valsartan group, and 446 to the aliskiren/valsartan group. Of the randomized patients, 89.1% (1601 out of 1797) completed the double-blind treatment phase.

The treatment groups were generally comparable with respect to the demographics and baseline characteristics. The patients randomized to the study were on average 52.2 years old, ranging from 24 to 84 years of age, with 12.5% who were 65 years old or older and 1.9% who were 75 years old or older. There were 60.8% male and 39.2% female patients in the study. The majority of the patients were Caucasian (74.7%) or Black (15.9%). Approximately half of the patients (48.1%) were obese (BMI ≥ 30 kg/m2). The duration of hypertension of the non-treatment-naïve patients in the study (approximately 95% of the total) ranged from 1 year to 48 years with an overall mean of 8.2 years. The average baseline msDBP in each group ranged from 100.1 mmHg (aliskiren/valsartan) to 100.4 mm Hg (placebo) and the average baseline msSBP ranged from 152.8 mm Hg (aliskiren/valsartan) to 154.2 mm Hg (valsartan). Data were summarized in the following tables 57 and 58.

Table 57: Patient demographic and background characteristics by treatment group (randomized population).

Demographic Characteristic Category/Statistic	Placebo N= 459	Aliskiren N= 437	Valsartan N= 455	Aliskiren/ Valsartan N= 446
Sex n (%)				
Male	281 (61.2%)	255 (58.4%)	281 (61.8%)	275 (61.7%)
Female	178 (38.8%)	182 (41.6%)	174 (38.2%)	171 (38.3%)
Race n (%)				
Caucasian	349 (76.0%)	326 (74.6%)	328 (72.1%)	340 (76.2%)
Black	69 (15.0%)	70 (16.0%)	88 (19.3%)	59 (13.2%)
Asian	7 (1.5%)	7 (1.6%)	7 (1.5%)	8 (1.8%)
Native American	0 (0.0%)	2 (0.5%)	0 (0.0%)	1 (0.2%)
Pacific Islander	1 (0.2%)	2 (0.5%)	1 (0.2%)	1 (0.2%)
Other	33 (7.2%)	30 (6.9%)	31 (6.8%)	37 (8.3%)
Ethnicity n (%)				
Hispanic or Latino	73 (15.9%)	67 (15.3%)	75 (16.5%)	75 (16.8%)
Chinese	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Indian (India Subcontinent)	0 (0.0%)	1 (0.2%)	0 (0.0%)	3 (0.7%)
Japanese	2 (0.4%)	2 (0.5%)	2 (0.4%)	0 (0.0%)
Mixed ethnicity	3 (0.7%)	4 (0.9%)	2 (0.4%)	4 (0.9%)
Other	381 (83.0%)	363 (83.1%)	376 (82.6%)	362 (81.2%)
Age (yrs)				
N	459	437	455	446
Mean (SD)	52.6 (10.36)	51.9 (10.42)	52.4 (10.42)	52.1 (10.34)
Age group n (%)				
< 65	395 (86.1%)	386 (88.3%)	399 (87.7%)	393 (88.1%)
≥ 65	64 (13.9%)	51 (11.7%)	56 (12.3%)	53 (11.9%)
< 75	448 (97.6%)	431 (98.6%)	445 (97.8%)	439 (98.4%)
≥ 75	11 (2.4%)	6 (1.4%)	10 (2.2%)	7 (1.6%)
Duration of Hypertension (yrs)				
N	438	413	435	417
Mean (SD)	8.3 (7.01)	7.9 (7.04)	8.4 (7.82)	8.2 (7.88)
n (naive patients)	21 (4.6%)	24 (5.5%)	20 (4.4%)	29 (6.5%)
Body Mass Index (kg/m^2)				
N	456	433	453	441
Mean (SD)	30.4 (5.56)	30.6 (5.84)	30.7 (5.51)	30.2 (5.73)
Obesity n (%)				
BMI < 30 (kg/m^2)	244 (53.2%)	211 (48.3%)	225 (49.5%)	239 (53.6%)
BMI ≥ 30 kg/m^2)	212 (46.2%)	222 (50.8%)	228 (50.1%)	202 (45.3%)
Metabolic Syndrome# n (%)				
Yes	204 (44.4%)	208 (47.6%)	217 (47.7%)	208 (46.6%)
No	254 (55.3%)	227 (51.9%)	238 (52.3%)	236 (52.9%)

SD=standard deviation.
Note: # Metabolic Syndrome=Yes, if any 3 of the following are true: 1. Waist circumference > 102 cm (40 in) for men, or >88 cm (35 in) for women; 2. Triglycerides >= 150 mg/dL (1.69 mmol/L); 3. HDL cholesterol < 40 mg/dL (1.04 mmol/L) for men, or < 50mg/dL (1.29 mmol/L) for women; 4. SBP>=130 mm Hg and /or DBP>=85 mm Hg; 5. Fasting glucose >= 110 mg/dL (6.1 mmol/L).
Source: PT-Table 14.1-3.1a

Table 58: Summary of baseline (Visit 5) values for mean sitting diastolic and systolic blood pressure, standing diastolic and systolic blood pressure (randomized population)

Parameter Statistic	Placebo N= 459	Aliskiren N= 437	Valsartan N= 455	Aliskiren/ Valsartan N= 446
msDBP (mm Hg)				
N	459	437	455	446
Mean (SD)	100.4 (4.20)	100.2 (3.85)	100.3 (3.84)	100.1 (4.04)
Median	99.3	99.3	99.3	99.3
Min	90.3	91.3	94.7	81.3
Max	116.0	109.3	112.0	119.3
msSBP (mm Hg)				
N	459	437	455	446
Mean (SD)	154.1 (12.77)	153.9 (11.71)	154.2 (12.66)	152.8 (12.17)
Median	154.7	154.0	153.3	152.0
Min	124.0	128.7	120.0	120.0
Max	182.7	182.0	188.0	190.0
Standing diastolic BP (mm Hg)				
N	459	437	455	446
Mean (SD)	102.3 (5.58)	101.6 (5.60)	101.8 (5.49)	101.5 (5.70)
Median	102.0	100.0	101.0	101.0
Min	88.0	77.0	88.0	84.0
Max	122.0	126.0	124.0	124.0
Standing systolic BP (mm Hg)				
N	459	437	455	446
Mean (SD)	155.4 (13.79)	154.9 (13.48)	155.7 (13.56)	153.6 (13.15)
Median	156.0	156.0	155.0	154.0
Min	122.0	118.0	118.0	110.0
Max	186.0	196.0	202.0	193.0

SD=standard deviation.
Source: PT-Table 14.1-3.2a

10.1.1.10. Efficacy

The primary efficacy variable was change from baseline in msDBP at the Week 8 endpoint. Using the primary efficacy population (ITT), the aliskiren/valsartan 300/320 mg group showed a statistically significant reduction in msDBP than the aliskiren 300 mg and valsartan 320 mg treatment groups at Week 8 endpoint, with further reductions of 3.15 mm Hg and 2.47 mm Hg in least squares means compared to aliskiren and valsartan, respectively as shown in the following table 59. Similar results were obtained using the per-protocol population.

Table 59: Statistical analysis of change from baseline in mean sitting diastolic blood pressure at Week 8 endpoint (intent-to-treat population)

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-4.07 (0.41)	
Aliskiren	430	-9.02 (0.42)	
Valsartan	453	-9.69 (0.41)	
Aliskiren/Valsartan	438	-12.17 (0.41)	
Pairwise Comparison	**LS M difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value+**
Aliskiren vs. Placebo	-4.95 (0.58)	(-6.07, -3.82)	<.0001*
Valsartan vs. Placebo	-5.62 (0.57)	(-6.73, -4.51)	<.0001*
Aliskiren/Valsartan vs. Placebo	-8.09 (0.57)	(-9.22, -6.97)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-3.15 (0.58)	(-4.29, -2.01)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-2.47 (0.57)	(-3.60, -1.35)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
+ P-Values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level
Source: PT-Table 14.2-1.1b

For the major secondary endpoint, the aliskiren/valsartan 300/320 mg group also showed a statistically significant reduction in msSBP compared with the aliskiren 300 mg and valsartan 320 mg treatment groups at Week 8 endpoint (both p-values < 0.0001) as shown in the following table 60.

Table 60: Statistical analysis of change from baseline in mean sitting systolic blood pressure at Week 8 endpoint (intent-to-treat population)

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-4.56 (0.65)	
Aliskiren	430	-12.96 (0.67)	
Valsartan	453	-12.75 (0.65)	
Aliskiren/Valsartan	438	-17.20 (0.67)	
Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value+**
Aliskiren vs. Placebo	-8.40 (0.93)	(-10.22, -6.58)	<.0001*
Valsartan vs. Placebo	-8.20 (0.91)	(-9.99, -6.40)	<.0001*
Aliskiren/Valsartan vs. Placebo	-12.64 (0.92)	(-14.45, -10.8)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-4.24 (0.94)	(-6.07, -2.40)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-4.44 (0.92)	(-6.26, -2.63)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
+ P-Values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Source: PT-Table 14.2-2.1b

In the low dose group, aliskiren/valsartan 150/160 mg also demonstrated statistical reductions in msDBP and msSBP compared with the aliskiren 150 mg and valsartan 160 mg monotherapy treatment groups. The changes from baseline in least squares means for each group and the difference between the combination and the two monotherapies are shown in tables 61 (msDBP) and 62 (msSBP). msDPB and msSBP change from baseline by week is presented graphically in Figures 7 and 8.

Table 61: Statistical analysis of change from baseline in mean sitting diastolic blood pressure at Week 4 endpoint (intent-to-treat population)

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-4.80 (0.36)	
Aliskiren	430	-7.46 (0.37)	
Valsartan	453	-8.68 (0.36)	
Aliskiren/Valsartan	438	-10.50 (0.37)	
Pairwise Comparison	**LS M difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value+**
Aliskiren vs. Placebo	-2.66 (0.51)	(-3.66, -1.66)	<.0001*
Valsartan vs. Placebo	-3.88 (0.50)	(-4.87, -2.89)	<.0001*
Aliskiren/Valsartan vs. Placebo	-5.70 (0.51)	(-6.69, -4.70)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-3.04 (0.51)	(-4.05, -2.03)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-1.82 (0.51)	(-2.82, -0.82)	0.0004*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
+ P-Values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level
Source: PT-Table 14.2-1.2b

Table 62: Statistical analysis of change from baseline in mean sitting systolic blood pressure at Week 4 endpoint (intent-to-treat population)

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-5.24 (0.58)	
Aliskiren	430	-10.69 (0.60)	
Valsartan	453	-10.85 (0.58)	
Aliskiren/Valsartan	438	-15.29 (0.59)	
Pairwise Comparison	**LS M difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value+**
Aliskiren vs. Placebo	-5.44 (0.83)	(-7.07, -3.82)	<.0001*
Valsartan vs. Placebo	-5.61 (0.82)	(-7.21, -4.01)	<.0001*
Aliskiren/Valsartan vs. Placebo	-10.05 (0.82)	(-11.66, -8.43)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-4.60 (0.84)	(-6.24, -2.96)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-4.44 (0.83)	(-6.06, -2.82)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
+ P-Values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level
Source: PT-Table 14.2-2.2b

Figure 7: Change from baseline in msDBP by Week (intent-to-treat population)

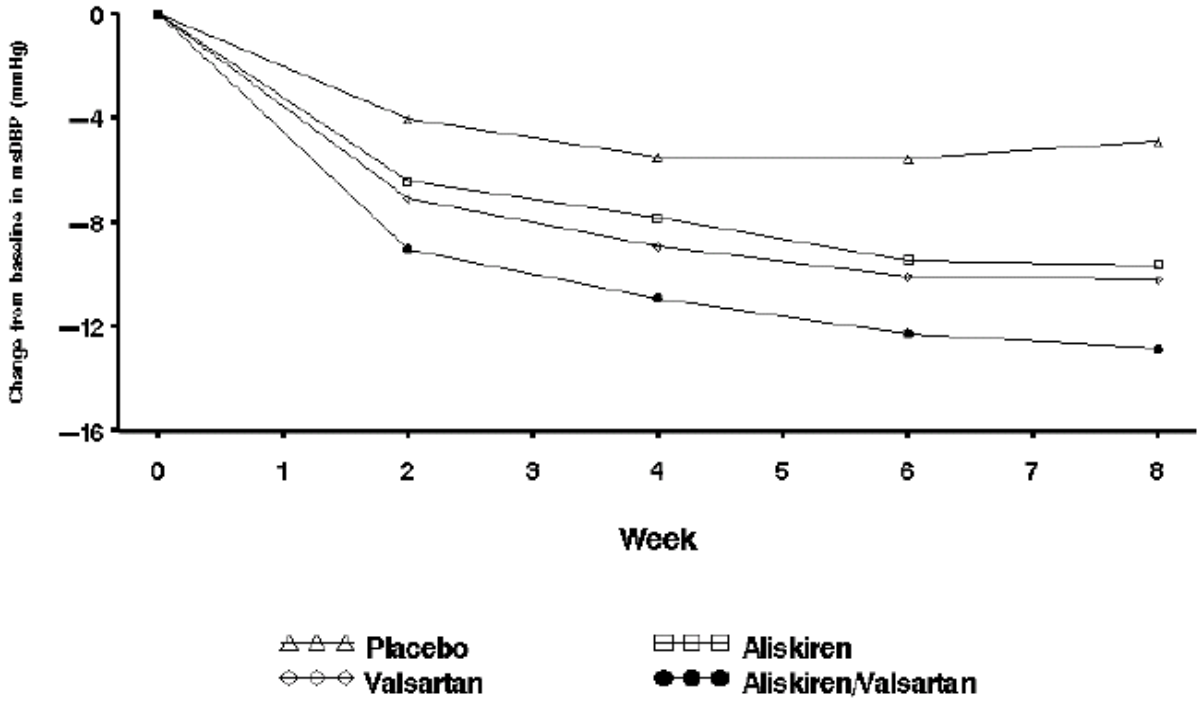
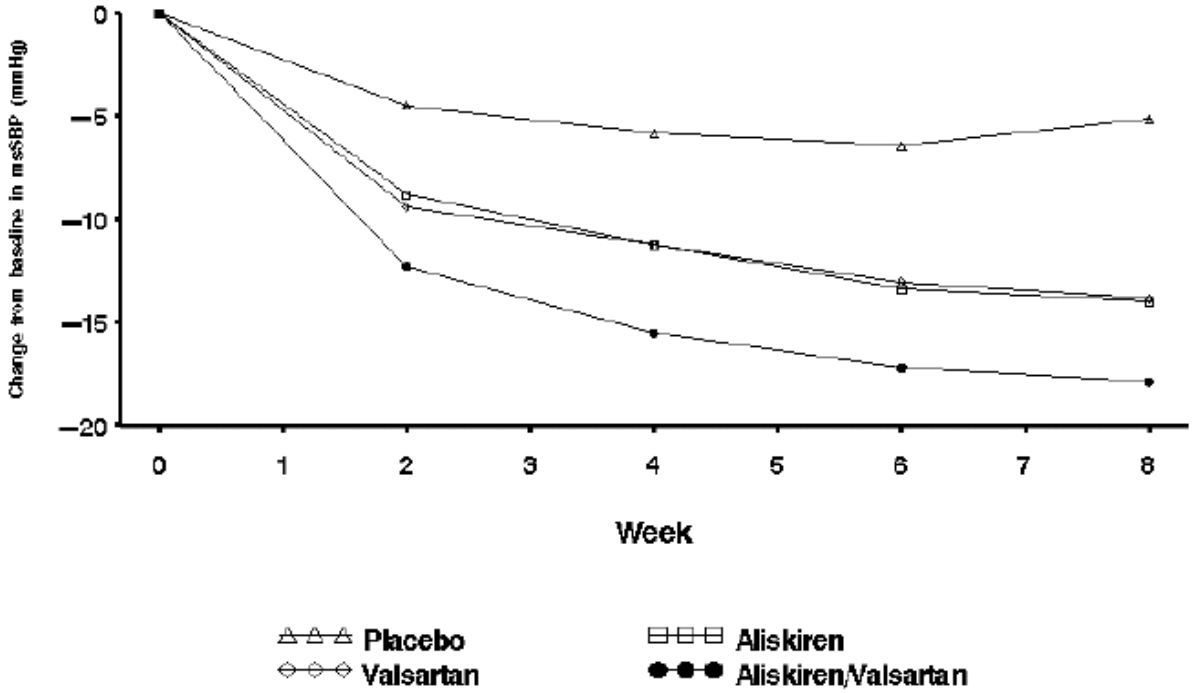


Figure 8: Change from baseline in msSBP by Week (intent-to-treat population)



Blood pressure control rates were summarized in the following tables 63 and 64. The proportions of patients achieving BP control targets (msDBP < 90 mm Hg and msSBP <140 mm Hg) for the four groups at Week 8 endpoint were: 49.32% for aliskiren/valsartan, 37.44% for aliskiren, 33.77% for valsartan, and 16.48% for placebo. The pair wise comparisons between the treatments indicate that the higher proportion achieving the BP control target with the aliskiren/valsartan treatment was statistically significant compared with both monotherapy groups.

Table 63: Between treatment comparison for control rate of blood pressure at Week 8 endpoint by treatment group (intent-to-treat population)

Pairwise Comparison	Treatment A		Treatment B		
	n/N	(%)	n/N	(%)	P-Value
Aliskiren vs. Placebo	161/430	(37.44)	75/455	(16.48)	<.0001*
Valsartan vs. Placebo	153/453	(33.77)	75/455	(16.48)	<.0001*
Aliskiren/Valsartan vs. Placebo	216/438	(49.32)	75/455	(16.48)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	216/438	(49.32)	161/430	(37.44)	0.0005*
Aliskiren/Valsartan vs. Valsartan	216/438	(49.32)	153/453	(33.77)	<.0001*

A patient with control in BP is defined as having as a mean sitting diastolic blood pressure < 90 mm Hg and a mean sitting systolic blood pressure < 140 mm Hg.
The control rate was analyzed by using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.
*indicates statistical significance at 0.05 level.
Source: PT-Table 14.2-2.9

Table 64: Between treatment comparison for control rate of blood pressure at Week 4 endpoint by treatment group (intent-to-treat population)

Pairwise Comparison	Treatment A		Treatment B		
	n/N	(%)	n/N	(%)	P-Value
Aliskiren vs. Placebo	119/430	(27.67)	70/455	(15.38)	<.0001*
Valsartan vs. Placebo	143/453	(31.57)	70/455	(15.38)	<.0001*
Aliskiren/Valsartan vs. Placebo	194/438	(44.29)	70/455	(15.38)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	194/438	(44.29)	119/430	(27.67)	<.0001*
Aliskiren/Valsartan vs. Valsartan	194/438	(44.29)	143/453	(31.57)	0.0001*

A patient with control in BP is defined as having as a mean sitting diastolic blood pressure < 90 mm Hg and a mean sitting systolic blood pressure < 140 mm Hg.
The control rate was analyzed by using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.
*indicates statistical significance at 0.05 level.
Source: PT-Table 14.2-2.10

Response rates were summarized in the following tables 65 and 66. Response was defined as a msDBP < 90 mm Hg or a ≥ 10 mm Hg decrease compared to baseline. The analyses showed that aliskiren/valsartan was statistically superior to both aliskiren and valsartan monotherapy in achieving msDBP response.

Table 65: Number (%) of responders in msDBP (mm Hg) at Week 8 endpoint by treatment group (intent-to-treat population)

Pairwise Comparison	Treatment A		Treatment B		
	n/N	(%)	n/N	(%)	P-Value
Aliskiren vs. Placebo	230/430	(53.49)	136/455	(29.89)	<.0001*
Valsartan vs. Placebo	250/453	(55.19)	136/455	(29.89)	<.0001*
Aliskiren/Valsartan vs. Placebo	288/438	(65.75)	136/455	(29.89)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	288/438	(65.75)	230/430	(53.49)	0.0003*
Aliskiren/Valsartan vs. Valsartan	288/438	(65.75)	250/453	(55.19)	0.0010*

Responder is defined as a patient with msDBP < 90 mm Hg or ≥ 10 mm Hg reduction from baseline msDBP.
P-Values were from a logistic regression model with treatment and region as factors and baseline as a covariate.
Baseline is the Visit 5 value.
+Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).
N = Number of patients with baseline and Week 8 endpoint msDBP values.
*indicates statistical significance at 0.05 level.
Source: PT-Table 14.2-2.7

Table 66: Number (%) of responders in msDBP (mm Hg) at Week 4 endpoint by treatment group (intent-to-treat population)

Pairwise Comparison	Treatment A		Treatment B		
	n/N	(%)	n/N	(%)	P-Value
Aliskiren vs. Placebo	190/430	(44.19)	153/455	(33.63)	0.0014*
Valsartan vs. Placebo	236/453	(52.10)	153/455	(33.63)	<.0001*
Aliskiren/Valsartan vs. Placebo	256/438	(58.45)	153/455	(33.63)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	256/438	(58.45)	190/430	(44.19)	<.0001*
Aliskiren/Valsartan vs. Valsartan	256/438	(58.45)	236/453	(52.10)	0.0472*

Responder is defined as a patient with msDBP < 90 mm Hg or ≥ 10 mm Hg reduction from baseline msDBP.
P-Values were from a logistic regression model with treatment and region as factors and baseline as a covariate.
Baseline is the Visit 5 value.
+Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).
N = Number of patients with baseline and Week 4 endpoint msDBP values.
*indicates statistical significance at 0.05 level.
Source: PT-Table 14.2-2.8

The pairwise comparisons between the combination treatment and each of the respective monotherapy treatment groups in mean 24-hour ambulatory DBP and SBP are summarized in the following tables 67 and 68. Change from baseline in hourly mean ambulatory DBP and SBP at Week 8 endpoint is shown graphically by post-dosing hour and treatment in figures 9 and 10. The analyses showed that aliskiren/valsartan was statistically superior to both monotherapies in reducing ambulatory DBP and SBP. In addition, the analyses showed that aliskiren/valsartan was statistically superior to both monotherapies in reducing ambulatory DBP and SBP during both the daytime and the nighttime.

Table 67: Table 65. Change from baseline in Mean 24-hour ambulatory DBP at Week 8 endpoint (intent-to-treat population)

Treatment	N	LS Mean in change from baseline (SE)	
Placebo	81	-1.07 (0.49)	
Aliskiren	79	-7.08 (0.49)	
Valsartan	100	-7.12 (0.44)	
Aliskiren/Valsartan	94	-10.31 (0.45)	
Pairwise Comparison	**LS Mean Difference (SE)**	**95% CI for LSM difference**	**P – value**
Aliskiren vs. Placebo	-6.00 (0.70)	(-7.38, -4.63)	<.0001*
Valsartan vs. Placebo	-6.05 (0.65)	(-7.33, -4.76)	<.0001*
Aliskiren/Valsartan vs. Placebo	-9.24 (0.66)	(-10.55, -7.93)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-3.24 (0.67)	(-4.55, -1.93)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-3.20 (0.63)	(-4.43, -1.96)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least squares means and the associated standard errors, confidence intervals, and p-values were from a two-way repeated-measures analysis-of-covariance model with treatment, region, and post-dosing hours as factors and baseline mean 24-hour ambulatory DBP as a covariate with treatment by post-dosing-hour interaction and autoregressive order 1 covariance structure (AR1).
LS means were evaluated at the average baseline mean 24-hour ambulatory DBP.
* indicates statistical significance at 0.05 level
Source: PT-Table 14.2-2.11

Table 68: Change from baseline in Mean 24-hour ambulatory SBP at Week 8 endpoint (intent-to-treat population)

Treatment	N	LS Mean in change from baseline (SE)	
Placebo	81	-1.33 (0.67)	
Aliskiren	79	-9.75 (0.67)	
Valsartan	100	-10.11 (0.60)	
Aliskiren/Valsartan	94	-14.42 (0.62)	
Pairwise Comparison	**LS Mean Difference (SE)**	**95% CI for LSM difference**	**P – value**
Aliskiren vs. Placebo	-8.42 (0.95)	(-10.29, -6.55)	<.0001*
Valsartan vs. Placebo	-8.78 (0.89)	(-10.53, -7.02)	<.0001*
Aliskiren/Valsartan vs. Placebo	-13.09 (0.91)	(-14.89, -11.3)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-4.67 (0.91)	(-6.46, -2.88)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-4.32 (0.86)	(-6.01, -2.62)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least squares means and the associated standard errors, confidence intervals, and p-values were from a two-way repeated-measures analysis-of-covariance model with treatment, region, and post-dosing hours as factors and baseline mean 24-hour ambulatory SBP as a covariate with treatment by post-dosing-hour interaction and autoregressive order 1 covariance structure (AR1).
LS means were evaluated at the average baseline mean 24-hour ambulatory SBP.
* indicates statistical significance at 0.05 level
Source: PT-Table 14.2-2.13

Figure 9: Change from baseline in hourly mean ambulatory DBP at Week 8 endpoint by post-dosing hour and treatment (intent-to-treat population)

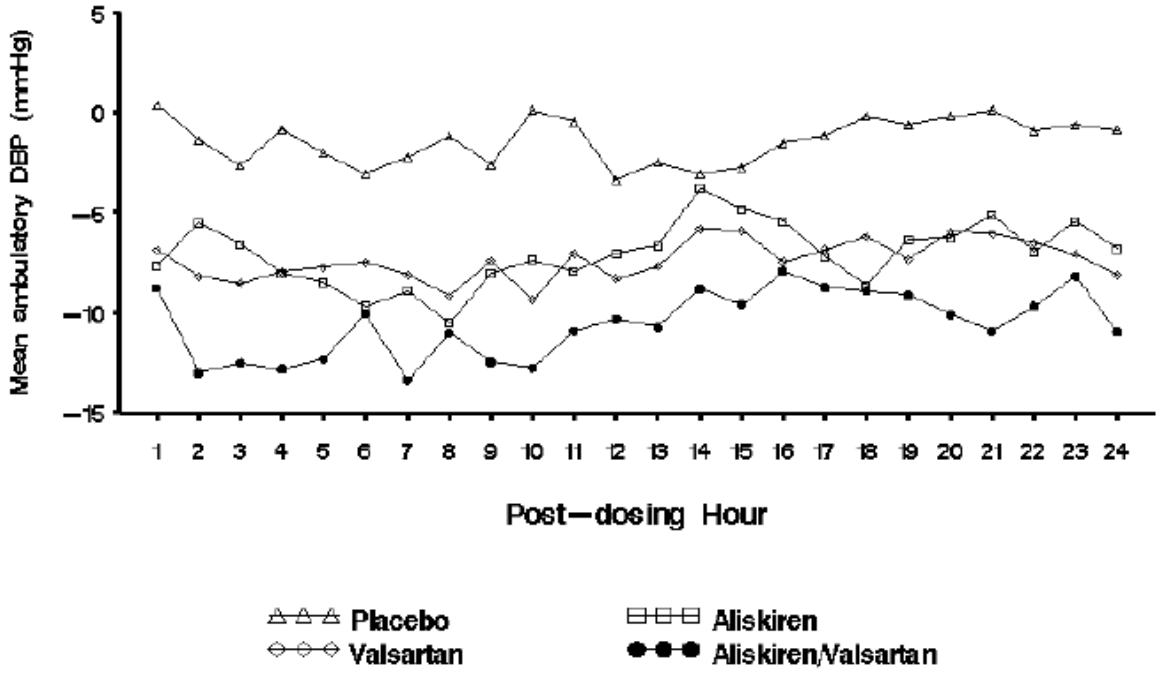
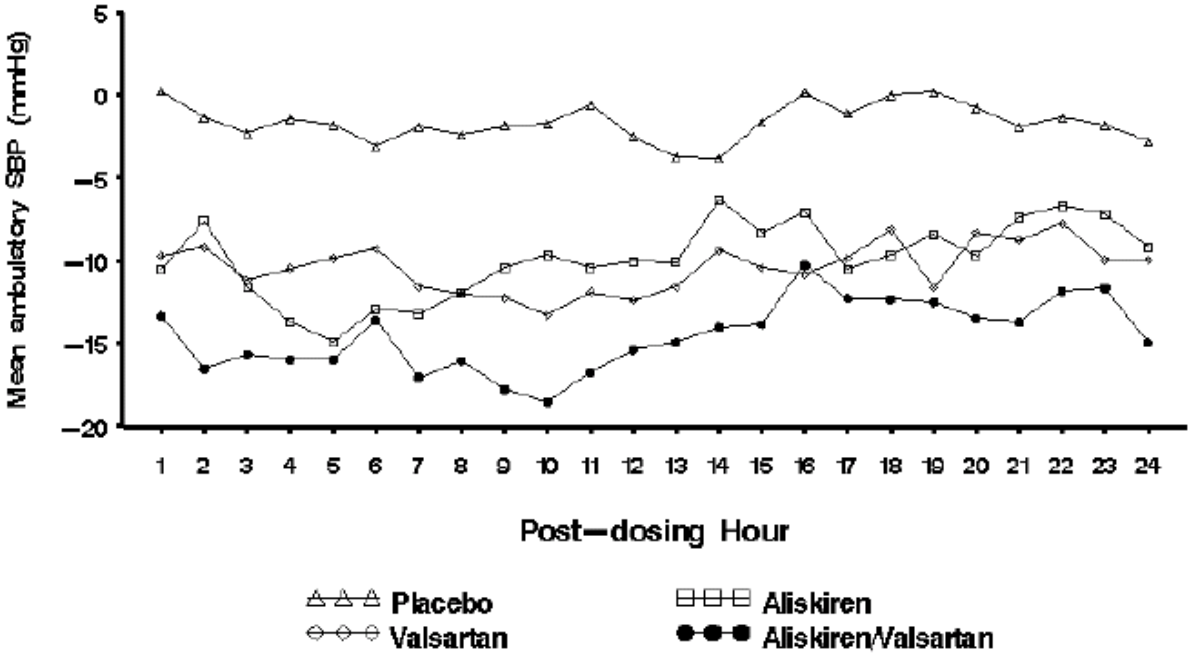


Figure 10: Change from baseline in hourly mean ambulatory SBP at Week 8 endpoint by post-dosing hour and treatment (intent-to-treat population)



The subgroup analysis results were generally similar to those seen in the overall population. Black patients in all active treatment groups had clinically meaningful reductions in msDBP and msSBP. However, the magnitude of the reduction was smaller.

The efficacy was also examined and compared across all regions. The result was shown in Table 69. It appears that there are some variations in the efficacy of the combination of Aliskiren/Valsartan across regions, some regions show a higher efficacy (i.e. Spain) and some show a lower efficacy (i.e. Germany South). However, this inconsistent efficacy may not be a big concern, because the trend in reduction of msDBP is obviously shown across regions and the variations may be due to a lower power of a smaller sample size of region.

Table 69 Statistical analysis of change form baseline in mean sitting diastolic blood pressure at Week 8 endpoint by region (ITT)

Region (N)	**Treatment Group**	**LSM change from baseline**
US West (288)	Placebo	-4.1
	Aliskiren	-11.3
	Valsartan	-9.4
	Aliskiren/Valsartan	-13.4
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-9.3 (-6.6, -12.1)
	Aliskiren/Valsartan vs. Aliskiren	-2.2 (-0.6, 5.0)
	Aliskiren/Valsartan vs. Valsartan	-4.0 (-1.2, -6.8)
	Treatment Group	**LSM change from baseline**
US West North & West South Central (313)	Placebo	-1.9
	Aliskiren	-9.9
	Valsartan	-10.5
	Aliskiren/Valsartan	-12.1
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-10.2 (-7.4, -12.9)
	Aliskiren/Valsartan vs. Aliskiren	-2.2 (-0.5, 5.0)
	Aliskiren/Valsartan vs. Valsartan	-1.6 (-1.1, 4.4)
	Treatment Group	**LSM change from baseline**
US south Atlantic, East South Central and Puerto Rico (277)	Placebo	-6.6
	Aliskiren	-7.8
	Valsartan	-11.1
	Aliskiren/Valsartan	-12.7
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-6.1 (-3.3, -9.0)

	Aliskiren/Valsartan vs. Aliskiren	-4.9 (-2.0, -7.9)
	Aliskiren/Valsartan vs. Valsartan	-1.6 (-1.2, 4.4)
	Treatment Group	**LSM change from baseline**
US Northeast & East North Central (213)	Placebo	-3.2
	Aliskiren	-8.1
	Valsartan	-8.9
	Aliskiren/Valsartan	-11.8
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-8.6 (-5.1, -12.1)
	Aliskiren/Valsartan vs. Aliskiren	-3.7 (-0.1, -7.2)
	Aliskiren/Valsartan vs. Valsartan	-2.9 (-0.6, 6.3)
	Treatment Group	**LSM change from baseline**
Germany North (288)	Placebo	-6.2
	Aliskiren	-9.9
	Valsartan	-10.8
	Aliskiren/Valsartan	-14.1
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-7.9 (-5.3, -10.6)
	Aliskiren/Valsartan vs. Aliskiren	-4.2 (-1.5, -7.0)
	Aliskiren/Valsartan vs. Valsartan	-3.3 (-0.7, -5.9)
	Treatment Group	**LSM change from baseline**
Germany South (266)	Placebo	-3.0
	Aliskiren	-7.9
	Valsartan	-8.9
	Aliskiren/Valsartan	-9.6
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-6.6 (-3.7, -9.5)
	Aliskiren/Valsartan vs. Aliskiren	-1.8 (-1.2, 4.7)
	Aliskiren/Valsartan vs. Valsartan	-0.7 (-2.3, 3.8)
	Treatment Group	**LSM change from baseline**
Spain (131)	Placebo	-3.8
	Aliskiren	-7.8
	Valsartan	-7.7
	Aliskiren/Valsartan	11.7
	Pair-wise comparison	**LSM difference (95% CI)**
	Aliskiren/Valsartan vs. placebo	-7.9 (-3.7, -12.0)

	Aliskiren/Valsartan vs. Aliskiren	-4.0 (-0.2, 8.1)
	Aliskiren/Valsartan vs. Valsartan	-4.0 (-0.1, 8.2)

Biomarkers including plasma renin concentration, plasma aldosterone, PRA, the ratio of plasma aldosterone and PRA, and the ratio of plasma aldosterone and renin concentration were measured. Using the geometric means analysis, renin concentration increased from baseline by 19.0% in the placebo group, 468.2% in the aliskiren group, 137.8% in the valsartan group, and 911.5% in the aliskiren/valsartan group at Week 8 endpoint. The elevation of renin concentration with the combination therapy exceeded the sum of the increases seen with each monotherapy, suggesting a synergistic effect on RAS blockade.

At Week 8 endpoint, aldosterone increased from baseline by 7.3% in the placebo group while it decreased from baseline in the active treatment groups; the greatest decrease was seen in the combination group (-5.9% in the aliskiren group, -25.2% in the valsartan group, and -30.5% in the aliskiren/valsartan group) based on the change in the geometric means. PRA values increased from baseline to Week 8 endpoint in both the placebo (18.2%) and valsartan (159.6%) groups, while it decreased in both the aliskiren and aliskiren/valsartan groups (-72.6% and -43.9%, respectively) based on the change in the geometric means. The addition of aliskiren to valsartan therapy was shown to inhibit PRA despite the fact that valsartan monotherapy increases PRA and the combination produces a reactive rise in renin concentration.

10.1.1.11. Safety

Exposure to study drug is summarized in following table 70; in all treatment groups, the mean and median durations of exposure reflected the planned treatment duration of 8 weeks.

Table 70: Duration of exposure (days) to double-blind study medication (safety population)

	Placebo N= 458 n (%)	Aliskiren N= 437 n (%)	Valsartan N= 455 n (%)	Aliskiren/Valsartan N= 446 n (%)
Exposure (days)				
N	458	437	455	446
Mean (SD)	51.8 (12.71)	52.3 (12.60)	53.7 (9.76)	53.3 (11.64)
Median	56.0	56.0	56.0	56.0
Min	1	1	1	1
Max	72	69	68	98*

SD = standard deviation

*In one patient in the aliskiren/valsartan group, the duration of exposure was listed as 98 days based on the date of the last study visit/dose of study drug, although the patient (0667/00002) had only been dispensed enough study drug for 8 weeks of double-blind treatment. This patient experienced several delays in study visits due to personal issues including a death in the family (Appendix Listing 16.2.9-1.2).

Source: PT-Table 14.3-1.1

The overall rates of AEs were 36.7% in placebo group, 34.1% in aliskiren group, 36.7% in valsartan group, and 35.0% in aliskiren/valsartan group. The most frequently reported AEs were headache, nasopharyngitis, dizziness, fatigue, and nausea; all other AEs occurred in < 2.0% of patients in any treatment group. The placebo group had the highest incidence of

headache among the four treatments. In addition, diarrhea was reported in 3 (0.7%) patients in the placebo group, 7 (1.6%) in the aliskiren group, 3 (0.7%) in the valsartan group, and 3 (0.7%) in the aliskiren/ valsartan group. Data were summarized in the following tables 71 and 72.

Table 71: Number (%) of patients with overall AEs in double-blind period by treatment group and body system (safety population)

Primary system organ class	Placebo N=458 n (%)	Aliskiren N=437 n (%)	Valsartan N=455 n (%)	Aliskiren/ Valsartan N=446 n (%)	Total N=1796 n (%)
Any Adverse Events	168(36.7)	149(34.1)	167(36.7)	156(35.0)	640(35.6)
Infections and infestations	39 (8.5)	36 (8.2)	61(13.4)	55(12.3)	191(10.6)
Nervous system disorders	59(12.9)	28 (6.4)	44 (9.7)	35 (7.8)	166 (9.2)
Gastrointestinal disorders	31 (6.8)	37 (8.5)	20 (4.4)	26 (5.8)	114 (6.3)
Musculoskeletal and connective tissue disorders	26 (5.7)	22 (5.0)	27 (5.9)	21 (4.7)	96 (5.3)
Respiratory, thoracic and mediastinal disorders	19 (4.1)	13 (3.0)	16 (3.5)	14 (3.1)	62 (3.5)
General disorders and administration site conditions	11 (2.4)	14 (3.2)	20 (4.4)	12 (2.7)	57 (3.2)
Cardiac disorders	9 (2.0)	2 (0.5)	10 (2.2)	7 (1.6)	28 (1.6)
Injury, poisoning and procedural complications	9 (2.0)	11 (2.5)	5 (1.1)	7 (1.6)	32 (1.8)
Metabolism and nutrition disorders	14 (3.1)	11 (2.5)	14 (3.1)	7 (1.6)	46 (2.6)
Skin and subcutaneous tissue disorders	5 (1.1)	8 (1.8)	9 (2.0)	7 (1.6)	29 (1.6)
Investigations	6 (1.3)	5 (1.1)	6 (1.3)	6 (1.3)	23 (1.3)
Vascular disorders	5 (1.1)	5 (1.1)	2 (0.4)	6 (1.3)	18 (1.0)
Ear and labyrinth disorders	4 (0.9)	3 (0.7)	3 (0.7)	5 (1.1)	15 (0.8)
Psychiatric disorders	4 (0.9)	7 (1.6)	2 (0.4)	4 (0.9)	17 (0.9)
Eye disorders	9 (2.0)	4 (0.9)	7 (1.5)	3 (0.7)	23 (1.3)
Renal and urinary disorders	1 (0.2)	6 (1.4)	5 (1.1)	3 (0.7)	15 (0.8)
Hepatobiliary disorders	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.4)	4 (0.2)
Neoplasms benign, malignant and unspecified(incl cysts and polyps)	1 (0.2)	0 (0.0)	3 (0.7)	2 (0.4)	6 (0.3)
Blood and lymphatic system disorders	1 (0.2)	2 (0.5)	1 (0.2)	1 (0.2)	5 (0.3)
Immune system disorders	1 (0.2)	2 (0.5)	4 (0.9)	1 (0.2)	8 (0.4)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Reproductive system and breast disorders	2 (0.4)	5 (1.1)	5 (1.1)	1 (0.2)	13 (0.7)
Social circumstances	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Surgical and medical procedures	1 (0.2)	3 (0.7)	0 (0.0)	1 (0.2)	5 (0.3)
Congenital, familial and genetic disorders	0 (0.0)	4 (0.9)	1 (0.2)	0 (0.0)	5 (0.3)
Endocrine disorders	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)

Organ systems are sorted in descending frequency, as reported in the aliskiren/valsartan column.
A patient with multiple adverse events within a primary system organ class is counted only once.
Source: PT-Table 14.3.1-1.1a

Table 72: Number (%) of patients with the most frequent adverse events (> = 2.0% in any treatment group) during the double-blind period by frequency (safety population)

Preferred term	Placebo N= 458 n (%)	Aliskiren N= 437 n (%)	Valsartan N= 455 n (%)	Aliskiren/ Valsartan N= 446 n (%)
Any Adverse Events	168 (36.7)	149 (34.1)	167 (36.7)	156 (35.0)
AE > 2% in any group				
Headache	41 (9.0)	14 (3.2)	25 (5.5)	19 (4.3)
Nasopharyngitis	9 (2.0)	16 (3.7)	20 (4.4)	12 (2.7)
Dizziness	9 (2.0)	8 (1.8)	11 (2.4)	8 (1.8)
Fatigue	5 (1.1)	4 (0.9)	10 (2.2)	8 (1.8)
Nausea	11 (2.4)	6 (1.4)	7 (1.5)	7 (1.6)

Source: PT-Table 14.3.1-1.1a

The number of patients who died or had other serious or significant adverse events is summarized in tables 73 and 74. Two patients died during the double-blind period, one in the aliskiren monotherapy group and one in the valsartan monotherapy group. One patient is a 69-year-old Caucasian female in the aliskiren group, died on study Day 41 (treatment: aliskiren 300 mg) due to myocardial infarction. Another patient is a 45-year-old male of "Other" race in the valsartan group, died on Day 13 (treatment: valsartan 160 mg); the principal cause of death was reported as hypertensive arteriosclerotic cardiovascular disease (preferred term arteriosclerosis), with an SAE of sudden death (preferred term arteriosclerosis) listed.

A total of 22 patients experienced SAEs (including deaths) during the double-blind period, including 3 patients (0.7%) in the combination aliskiren/valsartan group, 5 patients (1.1%) in placebo, 8 patients (1.8%) in aliskiren monotherapy, and 6 patients (1.3%) in valsartan monotherapy. The most frequently affected system organ class overall was vascular disorders (5 patients, 0.3%). Myocardial infarction was reported in two (0.5%) patients in the aliskiren monotherapy group, all other SAEs occurred in ≤ 1 patient each.

Few patients discontinued due to adverse events that began during the double-blind period. The incidence was lower in the combination group (6 patients, 1.3%) compared with placebo (11 patients, 2.4%), aliskiren monotherapy (8 patients, 1.8%), or valsartan monotherapy (12 patients, 2.6%). Data were summarized in the following table 75.

Table 73: Number (%) of patients who died or had other serious or significant adverse events during double-blind period (safety population)

	Placebo N= 458 n (%)	Aliskiren N= 437 n (%)	Valsartan N= 455 n (%)	Aliskiren/ Valsartan N= 446 n (%)	Total N=1796 n (%)
Deaths	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.1)
SAEs	5 (1.1)	8 (1.8)	6 (1.3)	3 (0.7)	22 (1.2)
AE discontinuations	11 (2.4) [a,b]	8 (1.8) [a,b]	12 (2.6) [a]	6 (1.3) [b]	37 (2.1) [a,b]
---Drug-related AE discontinuations	5 (1.1)	2 (0.5)	5 (1.1)	4 (0.9)	16 (0.9)
---SAE discontinuations	3 (0.7)	6 (1.4)	5 (1.1)	0 (0.0)	14 (0.8)
Discontinuations for abnormal lab values	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Includes two patients in the placebo group, one in the aliskiren group, and one in the valsartan group who had AEs leading to discontinuation but are not counted as discontinuing due to AEs in Table 10-1 because the primary reason for discontinuation was other than AE.
[b] Four patients in the aliskiren group, one in the placebo group, and one in the aliskiren/valsartan group were discontinued during the double-blind period due to AEs that began during the single-blind period; these patients are not included in this table but are counted as discontinuing due to AEs in Table 10-1.
Source: PT-Tables 14.1-1.2 and 14.3.1-1.5 and PT-Listings 14.3.2-1.1 to 14.3.2-1.3

Table 74: Number (%) of patients with serious adverse events during the double-blind period by preferred term (safety population)

Preferred term	Placebo N=458 n (%)	Aliskiren N=437 n (%)	Valsartan N=455 n (%)	Aliskiren/ Valsartan N=446 n (%)	Total N=1796 n (%)
-Any Preferred term					
-Total	5 (1.1)	8 (1.8)	6 (1.3)	3 (0.7)	22 (1.2)
Angina pectoris	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Aortic aneurysm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Arteriosclerosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Atrial flutter	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Breast cancer	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Bronchitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Cerebrovascular accident	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Cystitis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Facial paresis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Gastritis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Grand mal convulsion	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Headache	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypertension	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypertensive crisis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Intervertebral disc protrusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Intestinal polyp	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Myocardial infarction	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.1)
Non-cardiac chest pain	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Ovarian cancer	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Peripheral vascular disorder	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Pneumonia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Prostate cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Pulmonary oedema	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Renal failure acute	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Thyroidectomy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Ventricular tachycardia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

- Preferred terms are sorted in alphabetical order.

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

Source: PT-Table 14.3.1-1.4

Table 75: Number (%) of patients with adverse events leading to discontinuation by preferred term and treatment group (safety population)

Preferred term	Placebo N= 458 n (%)	Aliskiren N= 437 n (%)	Valsartan N= 455 n (%)	Aliskiren/ Valsartan N= 446 n (%)	Total N=1796 n (%)
Any AE Leading to Discontinuation	11 (2.4) [a,b]	8 (1.8) [a,b]	12 (2.6) [a]	6 (1.3) [b]	37 (2.1) [a,b]
Nausea	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.2)
Angina pectoris	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.1)
Disorientation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Dyspnoea	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)
Fatigue	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.1)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Arrhythmia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Arteriosclerosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Atrial flutter	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood pressure increased	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Breast cancer	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Dizziness	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)	3 (0.2)
Epistaxis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Facial paresis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Gastritis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Grand mal convulsion	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Headache	4 (0.9)	1 (0.2)	3 (0.7)	0 (0.0)	8 (0.4)
Hypertension	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypertensive crisis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Myocardial infarction	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.1)
Non-cardiac chest pain	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.1)
Oedema peripheral	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Ovarian cancer	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Renal failure acute	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Swelling face	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Ventricular tachycardia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vertigo	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

[a] Includes two patients in the placebo group (0085/00002, 0579/00031), one in the aliskiren group (0054/00016), and one in the valsartan group (0548/00026) who had AEs leading to discontinuation but are not counted as discontinuing due to AEs in Table 10-1 because the primary reason for discontinuation was other than AE.
[b] Four patients in the aliskiren group (0090/00004, 0521/00003, 0555/00007, and 0646/00004), one in the placebo group (0578/00007), and one in the aliskiren/valsartan group (0119/00032) were discontinued during the double-blind period due to AEs that began during the single-blind period with no evidence of worsening during the double-blind period; these patients are not included in this table but are counted as discontinuing due to AEs in Table 10-1.
Source: PT-Table 14.3.1-1.5, PT-Listing 14.3.2-1.2, PT-Listing 14.3.2-1.3

In the laboratory analysis, there was a larger mean decrease from baseline in hemoglobin (g/dL) values in the aliskiren/valsartan combination group (-2.9) compared with the aliskiren (-0.8) and valsartan monotherapy (-1.4) groups and the placebo group (0.3). Increases in creatinine, BUN, and potassium were reported most frequently in the aliskiren/valsartan combination group, followed by the valsartan monotherapy, aliskiren monotherapy, and placebo groups. There were slight increase of uric acid in patients in the aliskiren/valsartan combination group compared to each monotherapy and placebo.

There were more patients in the combination group met the pre-specified clinically notable values in potassium (> 5.5 mmol/L) and creatinine (> 176.8 umol/L) compared with placebo and the monotherapy groups. In the placebo group, however, 6 patients had serum level of

potassium more than 7.5 mmol/L (7.5-9.4 mmol/L without any adverse event report), one patient in the aliskiren group (7.7mmol/L) and none in other groups. Therefore, hemolysis may occur in these samples.

Among the 18 patients in the combination treatment group whose potassium values exceeded 5.5 mmol/L during the double-blind treatment, 13 had potassium values within the normal range at the end of the study without the disruption of treatment. Of the four patients in the combination group with creatinine values > 176.8 umol/L during the double-blind period, two had values that returned to within normal range by the end of study or study follow-up. None of the four patients with creatinine values >176.8 umol/L had associated clinically notable increases in BUN. Data were briefly summarized in the following table 76. Considering the increase of creatinine, there were 10 patients in the aliskiren/valsartan group compared to 3 in aliskiren monotherapy group, 1 in valsartan group and none in placebo, who had increased creatinine more 30% from baseline and more than 1.5mg/dl. There were three patients (0.3%) in aliskiren/valsartan group who still had abnormal values of creatinine at the end of study.

Table 76: Percentage of patients with specified criteria in potassium, creatinine, and BUN (safety population)

Laboratory test	Criterion	Placebo (N=458) n (%)	Aliskiren (N=437) n (%)	Valsartan (N=455) n (%)	Aliskiren/ Valsartan (N=446) n (%)
Potassium	< 3.5 mmol/L	17 (3.8)	11 (2.6)	20 (4.5)	12 (2.8)
	> 5.5 mmol/L	12 (2.7)	7 (1.7)	7 (1.6)	18 (4.2)
	≥ 6.0 mmol/L	6 (1.3)	4 (1.0)	5 (1.1)	2 (0.5)
Creatinine	> 176.8 umol/L	0	1 (0.2)	2 (0.4)	4 (0.9)
Blood Urea Nitrogen (BUN)	> 14.28 mmol/L	0	1 (0.2)	1 (0.2)	0

Source: PT-Table 14.3-2.3, PT-Listing 14.3.4-1.3

There were no significant difference of vital signs between the combination and each monotherapy. There were slightly more patients in the aliskiren/valsartan group experienced orthostatic blood pressure changes at one or more time point during the study as shown in the following table 77. However, only one patient (in the aliskiren/valsartan group) discontinued due to an AE of hypotension and three patients (2 in the valsartan group, 1 in the placebo group) discontinued due to an AE of dizziness.

Table 77: Number (%) of patients with orthostatic blood pressure change (safety population)

	Placebo		Aliskiren		Valsartan		Aliskiren/ Valsartan	
	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
Baseline	455	5 (1.1)	435	7 (1.6)	452	2 (0.4)	445	9 (2.0)
Week 2	455	9 (2.0)	430	8 (1.9)	453	10 (2.2)	437	8 (1.8)
Week 4	429	5 (1.2)	412	7 (1.7)	440	8 (1.8)	420	7 (1.7)
Week 6	411	8 (1.9)	393	4 (1.0)	427	5 (1.2)	414	7 (1.7)
Week 8	399	3 (0.8)	383	5 (1.3)	414	6 (1.4)	407	9 (2.2)
Week 4 Endpoint	455	5 (1.1)	430	7 (1.6)	453	8 (1.8)	438	9 (2.1)
Week 8 Endpoint	455	3 (0.7)	430	5 (1.2)	453	6 (1.3)	438	11 (2.5)
Any visit (post-baseline)	455	24 (5.3)	430	20 (4.7)	453	28 (6.2)	438	31 (7.1)

Orthostatic blood pressure change is defined as a decrease of at least 20 mm Hg in systolic blood pressure or a decrease of at least 10 mm Hg in diastolic blood pressure when a patient moves from a sitting position to a standing position.

Note: as described in Section 10-2, one patient in the placebo group (0563/00004) accidentally received one dose of double-blind study medication instead of single-blind medication at a visit prior to randomization. As a result, Visit 3 safety evaluations for this patient were used as baseline evaluations instead of Visit 5 values.

Source: PT-Table 14.3-3.4

10.1.1.15. Summary and conclusion

The combination of aliskiren and valsartan showed greater msDBP and msSBP reduction when compared with the respective monotherapies. There was significantly greater 24-hour ABPM DBP and SBP reduction with the combination when compared with monotherapy of aliskiren or valsartan. Further, the combination of aliskiren and valsartan produced greater proportions or patients achieving BP control (< 140/90 mm Hg) and proportion of patients achieving a response (msDBP < 90 mm Hg or a reduction of ≥ 10 mm Hg from baseline) when compared with monotherapy of aliskiren or valsartan. The combination of aliskiren and valsartan demonstrated additional efficacy in BP reduction regardless of race, sex or age group. Black patients in the aliskiren monotherapy group had smaller reductions in msDBP and msSBP compared with Caucasian patients. There seems to be some variations in efficacy across regions, however, it may be just due to a lower power of a smaller sample size of region. Biomarker results indicated that the combination of aliskiren and valsartan neutralized the reactive increase in PRA caused by valsartan. Aldosterone also showed a greater mean decrease in the combination of aliskiren and valsartan group compared to both monotherapies.

The reported SAEs, discontinuations due to AEs, and common AEs in general were comparable between the combination and each monotherapy. A slight numerical increase in patients with prespecified clinically notable high values of potassium and creatinine was observed in the combination group. Considering the increase of creatinine, there were 10 patients in the aliskiren/valsartan group compared to 3 in aliskiren monotherapy group, 1 in valsartan group and none in placebo, who had increased creatinine more 30% from baseline and more than 1.5mg/dl. There were three patients (0.3%) in aliskiren/valsartan group who still had abnormal values of creatinine at the end of study. Overall, the combination of aliskiren and valsartan demonstrated a safety profile comparable to both monotherapies and placebo.

10.1.2. SPP100A 2203: A randomized, double-blind, multicenter, multifactorial, placebo controlled, parallel-group study to confirm the efficacy and safety of aliskiren monotherapy,

and evaluate efficacy and safety of combinations of aliskiren and valsartan in hypertensive patients

10.1.2.1. Sites and Investigators

Investigators: (b) (4) et al.
Study center(s): Denmark: 5 centers, France: 11 centers, Germany: 41 centers, Poland: 8 centers and USA: 29 centers

10.1.2.2. Study Dates

First patient enrolled: 15-Mar-2004
Last patient completed: 12-Oct-2004

10.1.2.3. Study Design

This was a randomized, double-blind, placebo-controlled, multifactorial, multi-center, parallel-group study of aliskiren alone compared to placebo, the combination of aliskiren and valsartan compared to their component monotherapies, and the combination of valsartan and HCTZ compared to the combination of aliskiren and valsartan in patients with uncomplicated essential hypertension (MSDBP ≥ 95 mmHg and < 110 mmHg). Patients who required tapering of antihypertensive medications had their medications tapered and discontinued after signing an informed consent and before entering the single-blind run-in period. Qualified patients entered a 3- to 4-week single-blind placebo run-in period in order to establish a baseline blood pressure and eligibility for randomization based upon the inclusion and exclusion criteria defined in the protocol. Patients who did not meet the blood pressure eligibility criteria (MSDBP ≥ 95 mmHg and < 110 mmHg and an absolute difference in MSDBP ≤ 10mmHg from visit 2) after 3 weeks, were allowed one additional week of placebo single-blind run-in in order to establish blood pressure eligibility. At the conclusion of this single-blind placebo run-in period, approximately 1064 patients who fulfilled the inclusion and exclusion criteria were planned to be randomized in a double-blind fashion to one of eleven treatment arms: aliskiren 75 mg, 150 mg or 300 mg o.d.; valsartan 80 mg, 160 mg or 320 mg o.d.; the combination of aliskiren and valsartan 75/80 mg, 150/160 mg, or 300/320 mg o.d.; valsartan and HCTZ 160/12.5 mg o.d.; or placebo o.d. The first week post randomization was a forced titration period for patients randomized to aliskiren and valsartan 300/320 mg o.d. During this period, patients randomized to this treatment group received aliskiren and valsartan 150/160 mg o.d. for one week, while patients randomized to the remaining ten treatment groups received their respective assigned doses. The overall study design was summarized in the following figure 11.

Figure 11: Study design

Single-blind run-in			Double-blind treatment					
2 weeks	1 week	1 week, optional	8 weeks					
Visit 1	Visit 2	Optional visit[1] 201	3	4	5	6	7	8
Day -21	Day -7		1	7	14	28	42	56
			↓ Randomization					
			Aliskiren 75 mg o.d.					
			Aliskiren 150 mg o.d.					
			Aliskiren 300 mg o.d.					
			Valsartan 80 mg o.d.					
			Valsartan 160 mg o.d.					
			Valsartan 320 mg o.d.					
			Aliskiren 75 mg/valsartan 80 mg o.d.					
			Aliskiren 150 mg/valsartan 160 mg o.d.					
			Aliskiren 300 mg/valsartan 320 mg o.d. (titrated from aliskiren 150 mg/valsartan 160 mg o.d. on day 7)					
			Valsartan 160 mg/HCTZ 12.5 mg o.d.					
			Placebo o.d.					

[1] If optional visit 201 was required to meet randomization criteria, visit 1 became day -28, visit 2 became day -14 and the optional visit became day -7.
Maximum duration of individual patient participation, including single-blind run-in: 12 weeks (changed from 10 via amendment 1).
Total duration of protocol: 33 weeks (changed from 31 via amendment 1).

10.1.2.4. Objectives

The primary objective as stated in the original protocol was to assess the blood pressure lowering effects of the combination of aliskiren and valsartan (75/80 mg, 150/160 mg and 300/320 mg) compared with their component monotherapies administered for 6 weeks in patients with MSDBP ≥ 95 mmHg and < 110 mmHg. Then it has been changed to confirm the blood pressure lowering effects of aliskiren 75 mg, 150 mg and 300 mg given alone versus placebo administered for 8 weeks in patients with mean sitting diastolic blood pressure ([MSDBP] ≥ 95 mmHg and < 110 mmHg) in the amendment 1.

The secondary objectives of this study were to: assess the safety and tolerability of aliskiren 75 mg, 150 mg, and 300 mg given alone verses placebo administered for 8 weeks in this study population; assess the blood pressure lowering effects of the combination of aliskiren and valsartan (75/80 mg, 150/160 mg and 300/320 mg) compared with their component monotherapies administered for 8 weeks in patients with MSDBP ≥ 95 mmHg and < 110 mmHg (changed from the primary to a secondary objective); assess the safety and tolerability of the combination of aliskiren and valsartan (75/80 mg, 150/160 mg, and 300/320 mg) compared with their component monotherapies administered for 8 weeks in this study population; compare the blood pressure lowering effects and the safety and tolerability of the combination of valsartan 160 mg and HCTZ 12.5 mg to the combinations of aliskiren and valsartan (150/160 mg, 300/320 mg) in this study population; explore the impact of treatment on selected biomarkers including plasminogen activator inhibitor [PAI- 1], fibrinogen,

interleukin 6 [IL-6], high sensitivity C-reactive protein (hsCRP) , and procollagen Type III N terminal propeptide [P3NP]) of cardiovascular risk at selected centers.

10.1.2.5. Number of Subjects, Randomization, and Blinding

Approximately 1064 patients with uncomplicated essential hypertension (MSDBP ≥ 95 mmHg and < 110 mmHg) were planned to be randomized in this study from approximately 95 international centers. A total of 954 patients were expected to complete the study (151 patients in each of the three aliskiren monotherapy arms and the placebo arm, and 50 in the remaining seven treatment arms). Randomization was performed by region using an interactive voice response system (IVRS).

10.1.2.6. Inclusion, Exclusion Criteria and stop rules

The inclusion criteria were the following: Outpatients 18 years of age and older; Both male and female patients were eligible. Female patients must have been either post-menopausal for one year, surgically sterile, or using effective contraceptive methods such as hormonal or implant contraceptive (the dose had been stable for at least 3 months prior to visit 1), barrier method with spermicide or an intrauterine device; Patients with essential diastolic hypertension measured by calibrated standard mercury sphygmomanometer; Patients must have had a MSDBP ≥ 90 mmHg and < 110 mmHg at visit 2 (day -7), and a MSDBP ≥ 95 mmHg and < 110 mmHg at visit 3 (day 1); Patients must have had an absolute difference of ≤ 10 mmHg in their average sitting diastolic blood pressure during the last two visits (visit 2 and 3) of the single-blind run-in period of the study;

The exclusion criteria were the following:
1. Patients previously treated with aliskiren.
2. Severe hypertension (MSDBP ≥ 110 mmHg and/or MSSBP ≥ 180 mmHg).
3. Inability to discontinue all prior antihypertensive medications for a period of up to 12 weeks.
4. History or evidence of a secondary form of hypertension, such as coarctation of the aorta, hyperaldosteronism, Cushing's disease, unilateral or bilateral renal artery stenosis, pheochromocytoma, etc.
5. Known Keith-Wagener grade III or IV hypertensive retinopathy.
6. History of hypertensive encephalopathy or cerebrovascular accident at any time prior to visit 1.
7. Transient ischemic cerebral attack during the 12 months prior to visit 1.
8. History of heart failure (NYHA Class I-IV).
9. Coronary bypass surgery or any percutaneous coronary intervention during the 6 months prior to visit 1.
10. History of myocardial infarction within 12 months prior to visit 1.
11. Unstable angina pectoris.
12. Second or third degree heart block without a pacemaker.
13. Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia.
14. Clinically significant valvular heart disease.
15. Type 1 diabetes.

16. Type 2 diabetes mellitus with poor glucose control as defined by fasting HbA1c >8% at visit 1.
17. Serum sodium and/or serum potassium outside the limits of normal, or dehydration at visit 1.
18. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug; including, but not limited to, any of the following:
• History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
• Currently active or previously active inflammatory bowel disease during the 12 months prior to visit 1.
• Currently active gastritis, duodenal or gastric ulcers, or gastrointestinal/rectal bleeding during the 3 months prior to visit 1.
• Any history of pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury as indicated by abnormal lipase or amylase.
• Evidence of hepatic disease as determined by any one of the following: SGOT or SGPT values exceeding 2 x upper limit of normal (ULN) at visit 1, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt.
• Evidence of renal impairment as determined by any one of the following: serum creatinine > 1.5 x ULN at visit 1, a history of dialysis, or a history of nephritic syndrome.
• Current obstruction of the urinary tract or difficulty in voiding (due to mechanical or inflammatory conditions) that is likely to require intervention during the course of the study, or is regarded as clinically meaningful by the investigator.
19. History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the past five years.
20. History of any severe or life-threatening disease(s).
21. History of drug or alcohol abuse within the last 12 months.
22. Pregnant or nursing women.
23. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.
24. Known or suspected contraindications to the study medications, including history of allergy to angiotensin receptor blockers and/or to thiazide diuretics or other sulfonamide derived drugs.
25. History of systemic lupus erythematosus.
26. History of gouty arthritis.
27. History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
28. Any condition that in the opinion of the investigator or the Novartis medical monitor would jeopardize the evaluation of efficacy or safety.
29. Participation in any investigational drug trial within one month of visit 1.
30. Unwillingness or inability to give informed consent.
31. Persons directly involved in the execution of this protocol.

Stop rules: Patients with MSDBP ≥ 110 mmHg or MSSBP ≥ 180 mmHg at any time during the single blind or double-blind treatment phases were to be permanently discontinued from the trial. Patients with signs or symptoms of hypotension with MSDBP < 60 mmHg and/or a

MSSBP < 100 mmHg at any time during the single-blind or double-blind treatment phases were also to be permanently discontinued from the study. Study treatment could have been temporarily interrupted for documented reasons such as AEs.

10.1.2.6 Visit schedule and assessments

Patients were observed for a planned maximum period of 12 weeks. An additional visit (Pre-screen) was required for patients who needed to have antihypertensive medication(s) tapered prior to the initiation of the single-blind run-in period. Each evaluation was conducted in the morning between 7:00 and 10:00 A.M., allowing a range of +/-3 days for scheduling purposes. The schedule and assessments were summarized in the following table 77.

Table 78: Evaluation and visit schedule

Study Period	Screening Period				8 Weeks active treatment					
Visit	Pre-Screen 0	1	2	Optional Visit 201[2]	3	4	5	6	7	8[3]
Day		-21	-7	-7	1	7	14	28	42	56
Informed Consent	X*	X								
Inclusion/Exclusion Criteria	X	X	X	X	X					
Taper antihypertensive medication	X									
Medical History	X	X								
Height	X*	X								
Weight	X*	X								X
Blood Pressure and Pulse	X[4]	X	X	X	X[2]	X	X	X	X	X
Complete Physical Examination	X*	X								X
ECG	X*	X			X					X
Complete Laboratory Evaluations	X*	X			X					X
Serum/Urine Pregnancy Test[1]	X*	X			X					X
Electrolytes/BUN/Creatinine only							X			
Pharmacogenetic Sample					X					
Biomarkers					X					X
Adverse Events			X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Drug Accountability			X	X	X	X	X	X	X	X
IVRS	X	X	X	X	X	X	X	X	X	X
Randomization					X					
Screening Log	X	X								
Dispense Study Medications		X	X	X	X	X	X	X	X	
Study Medication Record			X	X	X	X	X	X	X	X
End of Study Information										X
Complete required eCRFs	X	X	X	X	X	X	X	X	X	X

[1] Women of child bearing potential only. To be performed on serum samples by central laboratory at visit 1 and 8 (changed from 6 by amendment 1). A urine pregnancy test was completed by on-site study staff at visit 3 before the first dose of study medication. The test results must have been negative in order for patients to be randomized.

[2] If the patient did not meet the blood pressure eligibility criteria (MSDBP > 95 mmHg but < 110 mmHg, or a > 10 mmHg change from visit 2), the single-blind run-in period could be extended by 1 week for a maximum of 4 weeks total, and visit 3 could be rescheduled (optional visit 201 eCRFs were completed and laboratory samples were not obtained at this point if the patient was to be rescheduled for visit 3). If optional visit 201 was required to meet randomization criteria, visit 1 became day -28, visit 2 became day -14 and the optional visit 201 became day -7.

[3] Or upon early termination.

[4] Vital signs for the Pre-screen visit (0) were only to be recorded in the source document and not entered in the eCRF.

X* Patients who required tapering of antihypertensive medications entered at the pre-screening visit, and were not required to repeat these procedures at visit 1.

10.1.2.7 Statistical Considerations

The primary efficacy variable was analyzed by a two-way analysis of covariance model with treatment and region as factors and baseline as a covariate. To assess the primary objective of aliskiren monotherapy versus placebo, the null hypothesis of no treatment difference among the three aliskiren doses (75, 150, and 300 mg) and placebo was tested versus the alternative hypothesis that at least one aliskiren dose has a treatment effect different from placebo. To

maintain an overall two-sided significance level at 5%, Dunnett's procedure was used to adjust for the multiple comparisons of the aliskiren doses versus placebo. This test was primary for the assessment of the primary objective. If the primary test was statistically significant in favor of aliskiren, aliskiren treatment was considered superior to placebo. Furthermore, the pairwise comparisons with 95% confidence intervals between each of the aliskiren doses and placebo were provided. The following analyses were performed to assess the add-on effects for a given combination dose compared to the respective monotherapy doses. For a given combination dose, the null hypotheses to be tested were that the combination dose was at most as good as one of its respective monotherapy doses versus that the combination was better than each monotherapy. The statistical test for each of the pairwise comparisons was made at a two-sided significance level of 0.05. Ninety-five percent confidence intervals were provided to quantify the add-on effects for combination doses. The combination dose was considered superior to monotherapy if the result was in favor of the combination. The pairwise comparisons between each aliskiren/ valsartan combination dose (150/160 mg, 300/320 mg) and the valsartan 160 mg/HCTZ 12.5 mg combination were also performed. Similar analyses were performed at week 4 and week 8. In addition, the percent of responders was analyzed by means of a logistic regression model with treatment and region as factors and baseline as a covariate. The proportion of patients with control of blood pressure during the double-blind treatment period in each treatment group was compared using a logistic regression model with treatment and region as the factors and baseline as a covariate at endpoint, week 4, and week 8 for the primary efficacy population. Pairwise treatment comparisons were made at a two-sided significance level of 0.05. As a response assessment, a first-order response surface analysis with the dose as predictor variable was performed for the change from baseline in MSDBP at endpoint and week 8 for the primary efficacy population and at endpoint for the per-protocol population to examine the relationship between the blood pressure lowering effect and the dose. The test for lack-of-fit was performed at a significance level of 0.1. If the lack-of-fit was statistically significant, a second-order dose-response surface was considered. Summary statistics for the primary and secondary efficacy variables and safety variables were provided.

10.1.2.8. Protocol Changes and Violations

Amendment 1, issued before the inclusion of the first patient, introduced the following changes:
1. The number of subjects randomized into the placebo and aliskiren monotherapy groups was increased to provide 90% power to detect a 3.5 mmHg difference between any aliskiren dose group and placebo.
2. Numbers of subjects in the combination groups as well as the active control group (valsartan/HCTZ) were slightly reduced to provide enough information to explore three combinations of aliskiren and valsartan.
3. The study treatment duration was extended from 6 weeks to 8 weeks, resulting in two additional visits.
4. The protocol allowed for the inclusion of type 1 and type 2 diabetic patients and patients who were taking insulin who had a baseline HbA1c $\leq$ 8%.
5. hsC-reactive protein was added to the biomarkers of cardiovascular risk measured at baseline and end of study.
6. The OMRON HEM705-CP automated blood pressure device was replaced with the standard calibrated mercury sphygmomanometer for blood pressure assessment.

Few major protocol violations resulted in exclusion from the per-protocol population as shown in the following table 77. Most involved the use of excluded medications, i.e., pre-specified non-antihypertensive agents known to affect BP (1.9% overall), BP values that were outside the protocol-specified criteria (4.7% total for all BP violations), and the chronic use of sympathomimetics (1.2% overall). The treatment groups of the aliskiren 300 mg/valsartan 320 mg (12.1%) and the aliskiren 150 mg group have the highest major violation rates (12.1% and 112.%, respectively) and others of the number of major protocol violations was generally even across treatment groups.

Prior to unblinding the study, it was found that seven patients had taken study drug with incorrect medication numbers. Of these seven patients, one took study drug with the incorrect medication number in the placebo run-in phase, and one was identified by the IVRS company as having received the same treatment to which they had been randomized. The other five patients who took study drug with the incorrect medication number did so only with up to a one-week supply of study drug, and thus received the assigned treatment for most of the double-blind period. These patients at the drug doses of aliskiren 75 mg, aliskiren 150 mg, aliskiren 300 mg, and valsartan 320 mg, were excluded from the per-protocol analysis and were included in the safety population according to their assigned treatment arms. The blind was broken prior to week 8 for one patient in the valsartan 160 mg group who experienced angioneurotic edema on day 28.

Other protocol violations that did not result in exclusion from the per-protocol population occurred in small numbers overall and at similar rates across treatment groups. These minor violations involved surgical or medical conditions that could significantly alter the absorption, distribution, metabolism, or excretion of any drug (2.4% overall); MSDBP>110 mmHg or MSSBP >180 after visit 3 (1.4% overall for each); the use of systemic corticosteroids (1.5% overall), thyroid medication (0.3% overall), and antiarrhythmic drugs including digoxin (0.3% overall); type 2 diabetes with poor glucose control (0.4% overall); and history of malignancy within the past 5 years (0.2% overall). Data were summarized in the following table 79.

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Table 79: Summary of any major protocol violations by treatment group (all randomized patients)

Major protocol violation	Placebo N=177 n (%)	ALI 75 N=179 n (%)	ALI 150 N=178 n (%)	ALI 300 N=176 n (%)	VAL 80 N=58 n (%)	VAL 160 N=59 n (%)	VAL 320 N=60 n (%)
Any major protocol violation	12 (6.8)	12 (6.7)	20 (11.2)	13 (7.4)	4 (6.9)	4 (6.8)	3 (5.0)
Drug approved for the treatment of hypertension (V1 - V8)	2 (1.1)	2 (1.1)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Chronic administration of sympathomimetic drugs (V1 - V8)	4 (2.3)	3 (1.7)	2 (1.1)	1 (0.6)	1 (1.7)	0 (0.0)	0 (0.0)
Wrong treatment allocation	0 (0.0)	2 (1.1)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	1 (1.7)
MSDBP > 110 mmHg at V1, V2, V201, V3	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MSSBP > 180 mmHg at V1, V2, V201, V3	0 (0.0)	1 (0.6)	3 (1.7)	2 (1.1)	0 (0.0)	1 (1.7)	0 (0.0)
MSDBP < 90 mmHg at V2	4 (2.3)	3 (1.7)	3 (1.7)	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
MSDBP < 95 mmHg at V3 or 201	0 (0.0)	1 (0.6)	2 (1.1)	1 (0.6)	3 (5.2)	1 (1.7)	1 (1.7)
Patient has > 10 mmHg at MSDBP between V2 or 201 and V3	3 (1.7)	1 (0.6)	2 (1.1)	3 (1.7)	1 (1.7)	0 (0.0)	0 (0.0)
Blind was broken prior to week 8 (V8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Other excluded non-antihypertensive meds that affect BP	4 (2.3)	2 (1.1)	6 (3.4)	3 (1.7)	0 (0.0)	1 (1.7)	0 (0.0)

Major protocol violation	ALI 75/VAL 80 N=60 n (%)	ALI 150/VAL 160 N=60 n (%)	ALI 300/VAL 320 N=58 n (%)	VAL 160/HCTZ 12.5 N=59 n (%)	Total N=1123 n (%)
Any major protocol violation	3 (5.0)	5 (8.3)	7 (12.1)	4 (6.8)	87 (7.7)
Drug approved for the treatment of hypertension (V1 - V8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.6)
Chronic administration of sympathomimetic drugs (V1 - V8)	1 (1.7)	0 (0.0)	1 (1.7)	0 (0.0)	13 (1.2)
Wrong treatment allocation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)
MSDBP > 110 mmHg at V1, V2, V201, V3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
MSSBP > 180 mmHg at V1, V2, V201, V3	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	9 (0.8)
MSDBP < 90 mmHg at V2	0 (0.0)	1 (1.7)	2 (3.4)	0 (0.0)	16 (1.4)
MSDBP < 95 mmHg at V3 or 201	1 (1.7)	2 (3.3)	1 (1.7)	2 (3.4)	15 (1.3)
Patient has > 10 mmHg at MSDBP between V2 or 201 and V3	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	12 (1.1)
Blind was broken prior to week 8 (V8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Other excluded non-antihypertensive meds that affect BP	1 (1.7)	1 (1.7)	3 (5.2)	0 (0.0)	21 (1.9)

Major violation: leading to exclusion from per-protocol population.
A patient can appear in more than one category.
Source: PTT 7.2-1

10.1.2.9. Subject Demographics and Baseline Characteristics

The baseline characteristics appear balanced among groups. The duration of patient exposure in the double-blind medication was similar across the active treatment groups, and consistent with the 8-week treatment duration. Data were summarized in the following tables 80 and 81.

Table 80: Demographics and baseline characteristics

Demographic Variable	Placebo N=177	ALI 75 N=179	ALI 150 N=178	ALI 300 N=175	VAL 80 N=58	VAL 160 N=59
Age (years)						
n	177	179	178	175	58	59
Mean	55.2	55.4	56.2	56.7	56.0	55.1
SD	12.24	13.09	12.39	11.86	12.98	11.81
Median	55.0	57.0	56.0	58.0	56.5	55.0
Min	24.0	19.0	21.0	21.0	26.0	19.0
Max	88.0	81.0	85.0	79.0	80.0	78.0
Age group						
<65 years	139(78.5%)	127(70.9%)	137(77.0%)	128(73.1%)	39(67.2%)	48(81.4%)
>=65 years	38(21.5%)	52(29.1%)	41(23.0%)	47(26.9%)	19(32.8%)	11(18.6%)
<75 years	165(93.2%)	173(96.6%)	168(94.4%)	166(94.9%)	55(94.8%)	56(94.9%)
>=75 years	12(6.8%)	6(3.4%)	10(5.6%)	9(5.1%)	3(5.2%)	3(5.1%)
Sex						
Male	97(54.8%)	99(55.3%)	101(56.7%)	100(57.1%)	38(65.5%)	29(49.2%)
Female	80(45.2%)	80(44.7%)	77(43.3%)	75(42.9%)	20(34.5%)	30(50.8%)
Race						
Caucasian	162(91.5%)	169(94.4%)	166(93.3%)	164(93.7%)	55(94.8%)	53(89.8%)
Black	14(7.9%)	10(5.6%)	10(5.6%)	10(5.7%)	2(3.4%)	5(8.5%)
Asian	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Other	0(0.0%)	0(0.0%)	2(1.1%)	1(0.6%)	1(1.7%)	1(1.7%)
Height (cm)						
n	177	179	178	175	58	59
Mean	170.7	169.6	169.8	170.3	170.7	169.7
SD	10.72	9.86	10.30	9.53	9.22	10.02
Median	170.0	169.0	170.0	170.0	171.0	168.0
Min	142.0	147.0	144.0	149.0	154.0	152.0
Max	198.0	196.0	197.0	197.0	196.0	192.0
Weight at visit 1 (kg)						
n	176	179	178	175	58	58
Mean	85.1	86.6	83.4	85.7	84.6	87.0
SD	17.43	17.65	16.45	16.59	14.46	18.28
Median	84.4	83.0	82.7	83.0	84.1	83.5
Min	47.5-	46.0	50.5	52.0	59.0	55.5
Max	147.7	156.0	138.0	143.4	124.4	159.0
BMI (kg/m^2)						
n	176	179	178	175	58	58
Mean	29.1	30.1	28.8	29.5	29.0	30.1
SD	5.00	5.46	4.22	5.12	4.21	5.69
Median	28.4	29.1	28.2	28.7	28.6	28.7
Min	20.1	18.7	17.9	20.3	21.0	21.4
Max	46.6	57.3	43.6	46.6	44.3	51.9

Demographic Variable	VAL 320 N=60	ALI 75/ VAL 80 N=60	ALI 150/ VAL 160 N=60	ALI 300/ VAL 320 N=58	VAL 160/ HCTZ 12.5 N=59	Total N=1123
Age (years)						
n	60	60	60	58	59	1123
Mean	56.8	55.5	57.7	57.1	56.9	56.1
SD	10.67	12.18	11.15	11.72	12.21	12.17
Median	57.0	55.5	61.0	57.5	58.0	57.0
Min	30.0	22.0	27.0	23.0	22.0	19.0
Max	80.0	82.0	74.0	82.0	79.0	88.0
Age group						
<65 years	50 (83.3%)	46 (76.7%)	43 (71.7%)	43 (74.1%)	43 (72.9%)	843 (75.1%)
>=65 years	10 (16.7%)	14 (23.3%)	17 (28.3%)	15 (25.9%)	16 (27.1%)	280 (24.9%)
<75 years	55 (91.7%)	57 (95.0%)	60 (100%)	54 (93.1%)	53 (89.8%)	1062 (94.6%)
>=75 years	5 (8.3%)	3 (5.0%)	0 (0.0%)	4 (6.9%)	6 (10.2%)	61 (5.4%)
Sex						
Male	31 (51.7%)	30 (50.0%)	35 (58.3%)	32 (55.2%)	36 (61.0%)	628 (55.9%)
Female	29 (48.3%)	30 (50.0%)	25 (41.7%)	26 (44.8%)	23 (39.0%)	495 (44.1%)
Race						
Caucasian	52 (86.7%)	53 (88.3%)	53 (88.3%)	54 (93.1%)	53 (89.8%)	1034 (92.1%)
Black	5(8.3%)	5(8.3%)	6(10.0%)	4(6.9%)	5(8.5%)	76(6.8%)
Asian	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.1%)
Other	3(5.0%)	2(3.3%)	1(1.7%)	0(0.0%)	1(1.7%)	12(1.1%)
Height (cm)						
n	60	59	60	58	59	1122
Mean	168.7	168.0	170.5	168.3	170.7	169.9
SD	10.21	9.69	9.70	9.91	10.54	10.03
Median	168.0	167.0	169.0	170.0	171.0	170.0
Min	149.0	150.0	148.0	147.0	150.0	142.0
Max	187.0	188.0	191.0	190.0	191.0	198.0
Weight at visit 1 (kg)						
n	60	59	60	58	59	1120
Mean	82.5	86.5	88.2	84.1	86.0	85.3
SD	16.57	18.97	15.53	15.32	17.81	16.93
Median	82.0	85.0	86.0	86.2	84.0	83.8
Min	54.2	53.6	50.0	56.0	49.2	46.0
Max	132.1	141.4	120.5	129.1	140.0	159.0
BMI (kg/m^2)						
n	60	59	60	58	59	1120
Mean	28.9	30.6	30.3	29.8	29.4	29.5
SD	4.59	6.07	4.50	5.49	5.01	5.03
Median	28.2	30.3	29.7	28.9	29.7	28.7
Min	21.7	21.7	19.3	16.6	19.2	16.6
Max	43.5	54.3	40.4	52.4	40.2	57.3

SD = standard deviation.
Source: PTT 7.4-1a

Table 81: Duration of exposure to double-blind study medication (all randomized patients)

Duration (days)	Placebo N=177	ALI 75 N=179	ALI 150 N=178	ALI 300 N=175	VAL 80 N=58	VAL 160 N=59
n	177	179	178	175	58	59
Mean	53.5	52.4	53.9	55.5	55.4	53.4
SD	10.83	12.83	10.05	7.16	6.11	12.12
Median	56.0	56.0	56.0	56.0	56.0	56.0
Minimum	3.0	1.0	7.0	7.0	33.0	1.0
Maximum	74.0	72.0	73.0	73.0	70.0	67.0
Duration (days)	**VAL 320 N=60**	**ALI 75/ VAL 80 N=60**	**ALI 150/ VAL 160 N=60**	**ALI 300/ VAL 320 N=58**	**VAL 160/ HCTZ 12.5 N=59**	**Total N=1123**
n	60	60	60	58	59	1123
Mean	55.1	53.4	55.5	54.6	55.2	54.1
SD	6.94	11.16	7.55	9.20	8.80	9.97
Median	56.0	56.0	56.0	56.0	56.0	56.0
Minimum	28.0	8.0	8.0	8.0	1.0	1.0
Maximum	65.0	66.0	70.0	67.0	68.0	74.0

SD = standard deviation
Note: Treatment duration for the double-blind randomization period is calculated as (last study drug date - first study drug date + 1), or (last visit date - first study drug date + 1) if the last study drug date is missing or incomplete.
Source: PTT 8.1-1

10.1.2.10. Efficacy

A statistically significant reduction of both msDBP and msSBP was observed in aliskiren treated groups compared to the placebo. However, there were no statistically significant differences between the aliskiren/valsartan combinations and each of their monotherapies. Data were summarized in the following tables 82 and 83.

Table 82: Statistical analysis of change from baseline in MSDBP (mmHg) at week 8 (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Placebo	163	-8.4 (0.62)
Aliskiren 75 mg	158	-11.2 (0.63)
Aliskiren 150 mg	165	-10.8 (0.62)
Aliskiren 300 mg	166	-12.8 (0.62)
Valsartan 80 mg	54	-11.3 (1.07)
Valsartan 160 mg	52	-11.3 (1.09)
Valsartan 320 mg	56	-11.4 (1.05)
Aliskiren 75 mg/Valsartan 80 mg	55	-12.2 (1.06)
Aliskiren 150 mg/Valsartan 160 mg	57	-12.0 (1.04)
Aliskiren 300 mg/Valsartan 320 mg	55	-13.0 (1.06)
Valsartan 160 mg/HCTZ 12.5 mg	56	-13.6 (1.05)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1]
Aliskiren 75 mg vs. Placebo	-2.83 (0.87)	(-4.55,-1.12)	0.0012+*
Aliskiren 150 mg vs. Placebo	-2.38 (0.86)	(-4.08,-0.69)	0.0059+*
Aliskiren 300 mg vs. Placebo	-4.35 (0.86)	(-6.04,-2.65)	<0.0001+*
Valsartan 80 mg vs. Placebo	-2.84 (1.23)	(-5.25,-0.44)	0.0207*
Valsartan 160 mg vs. Placebo	-2.87 (1.25)	(-5.31,-0.43)	0.0214*
Valsartan 320 mg vs. Placebo	-2.96 (1.21)	(-5.34,-0.59)	0.0145*
Aliskiren 75 mg/Valsartan 80 mg vs. Aliskiren 75 mg	-0.91 (1.22)	(-3.31, 1.49)	0.4560
Aliskiren 75 mg/Valsartan 80 mg vs. Valsartan 80 mg	-0.90 (1.50)	(-3.84, 2.04)	0.5464
Aliskiren 75 mg/Valsartan 80 mg vs. Placebo	-3.75 (1.22)	(-6.14,-1.36)	0.0022*
Aliskiren 150 mg/Valsartan 160 mg vs. Aliskiren 150 mg	-1.25 (1.20)	(-3.61, 1.11)	0.2979
Aliskiren 150 mg/Valsartan 160 mg vs. Valsartan 160 mg	-0.76 (1.50)	(-3.71, 2.18)	0.6103
Aliskiren 150 mg/Valsartan 160 mg vs. Placebo	-3.63 (1.20)	(-5.99,-1.27)	0.0026*
Aliskiren 300 mg/Valsartan 320 mg vs. Aliskiren 300 mg	-0.22 (1.22)	(-2.61, 2.17)	0.8572
Aliskiren 300 mg/Valsartan 320 mg vs. Valsartan 320 mg	-1.60 (1.48)	(-4.51, 1.31)	0.2812
Aliskiren 300 mg/Valsartan 320 mg vs. Placebo	-4.56 (1.22)	(-6.96,-2.17)	0.0002*
Valsartan 160 mg/HCTZ 12.5 mg vs. Placebo	-5.22 (1.21)	(-7.60,-2.84)	<.0001*
Aliskiren 150 mg/Valsartan 160 mg vs. Valsartan 160 mg/HCTZ 12.5 mg	1.59 (1.47)	(-1.30, 4.47)	0.2808
Aliskiren 300 mg/Valsartan 320 mg vs. Valsartan 160 mg/HCTZ 12.5 mg	0.66 (1.48)	(-2.26, 3.57)	0.6587

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval
+The overall Dunnett's procedure between aliskiren monotherapy and placebo shows statistical significance between placebo and one aliskiren treatment. The smallest Dunnett's adjusted p-value among these comparisons is <0.0001.
1 P-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.

Table 83: Statistical analysis of mean change from baseline in MSSBP at week 8 (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Placebo	163	-10.3 (0.91)
Aliskiren 75 mg	158	-13.8 (0.93)
Aliskiren 150 mg	165	-12.9 (0.91)
Aliskiren 300 mg	166	-15.8 (0.90)
Valsartan 80 mg	54	-12.5 (1.57)
Valsartan 160 mg	52	-16.1 (1.60)
Valsartan 320 mg	56	-16.7 (1.54)
Aliskiren 75 mg/Valsartan 80 mg	55	-15.3 (1.56)
Aliskiren 150 mg/Valsartan 160 mg	57	-16.3 (1.53)
Aliskiren 300 mg/Valsartan 320 mg	55	-17.9 (1.55)
Valsartan 160 mg/HCTZ 12.5 mg	56	-19.0 (1.54)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1]
Aliskiren 75 mg vs. Placebo	-3.55 (1.28)	(-6.06,-1.04)	0.0057*^
Aliskiren 150 mg vs. Placebo	-2.59 (1.27)	(-5.08,-0.10)	0.0413*^
Aliskiren 300 mg vs. Placebo	-5.54 (1.26)	(-8.02,-3.06)	<.0001*^
Valsartan 80 mg vs. Placebo	-2.17 (1.80)	(-5.71, 1.36)	0.2284
Valsartan 160 mg vs. Placebo	-5.82 (1.83)	(-9.41,-2.24)	0.0015*
Valsartan 320 mg vs. Placebo	-6.42 (1.78)	(-9.91,-2.93)	0.0003*
Aliskiren 75 mg/Valsartan 80 mg vs. Aliskiren 75 mg	-1.47 (1.80)	(-5.00, 2.05)	0.4124
Aliskiren 75 mg/Valsartan 80 mg vs. Valsartan 80 mg	-2.85 (2.20)	(-7.16, 1.46)	0.1946
Aliskiren 75 mg/Valsartan 80 mg vs. Placebo	-5.02 (1.79)	(-8.53,-1.51)	0.0051*
Aliskiren 150 mg/Valsartan 160 mg vs. Aliskiren 150 mg	-3.40 (1.76)	(-6.86, 0.06)	0.0540
Aliskiren 150 mg/Valsartan 160 mg vs. Valsartan 160 mg	-0.17 (2.20)	(-4.48, 4.15)	0.9401
Aliskiren 150 mg/Valsartan 160 mg vs. Placebo	-5.99 (1.77)	(-9.46,-2.52)	0.0007*
Aliskiren 300 mg/Valsartan 320 mg vs. Aliskiren 300 mg	-2.10 (1.78)	(-5.60, 1.40)	0.2398
Aliskiren 300 mg/Valsartan 320 mg vs. Valsartan 320 mg	-1.22 (2.18)	(-5.50, 3.05)	0.5743
Aliskiren 300 mg/Valsartan 320 mg vs. Placebo	-7.64 (1.79)	(-11.15,-4.13)	<.0001*
Valsartan 160 mg/HCTZ 12.5 mg vs. Placebo	-8.69 (1.78)	(-12.17,-5.20)	<.0001*
Aliskiren 150 mg/Valsartan 160 mg vs. Valsartan 160 mg/HCTZ 12.5 mg	2.70 (2.16)	(-1.54, 6.93)	0.2120
Aliskiren 300 mg/Valsartan 320 mg vs. Valsartan 160 mg/HCTZ 12.5 mg	1.04 (2.18)	(-3.23, 5.32)	0.6319

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval
*The overall Dunnett's procedure between aliskiren monotherapy and placebo shows statistical significance between placebo and one aliskiren treatment. The smallest Dunnett's adjusted p-value among these comparisons is <0.0001.
[1] P-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Source: PTT 9.2-3b

For the response rate(MSDBP < 90 mm Hg or a ≥ 10 mm Hg reduction from baseline), aliskiren treated groups was statistically significantly superior to placebo. However, there were no statistically significant difference between the aliskiren/valsartan combination groups and the each monotherapies except that the aliskiren 75 mg/valsartan 80 mg combination was statistically significantly superior to both monotherapies. Data were summarized in the following table 84.

Table 84: Number (%) of responders in MSDBP (mmHg) at endpoint by treatment group (ITT population).

Pairwise Comparison A vs. B	Treatment A n/N (%)	Treatment B n/N (%)	P-Value
Aliskiren 75 mg vs. Placebo	106/177 (59.9)	85/176 (48.3)	0.0183*
Aliskiren 150 mg vs. Placebo	105/177 (59.3)	85/176 (48.3)	0.0211*
Aliskiren 300 mg vs. Placebo	119/175 (68.0)	85/176 (48.3)	<.0001*
Aliskiren 75 mg/Valsartan 80 mg vs. Aliskiren 75 mg	45/ 60 (75.0)	106/177 (59.9)	0.0247*
Aliskiren 75 mg/Valsartan 80 mg vs. Valsartan 80 mg	45/ 60 (75.0)	32/ 58 (55.2)	0.0184*
Aliskiren 75 mg/Valsartan 80 mg vs. Placebo	45/ 60 (75.0)	85/176 (48.3)	0.0002*
Aliskiren 150 mg/Valsartan 160 mg vs. Aliskiren 150 mg	40/ 60 (66.7)	105/177 (59.3)	0.3658
Aliskiren 150 mg/Valsartan 160 mg vs. Valsartan 160 mg	40/ 60 (66.7)	38/ 58 (65.5)	0.9244
Aliskiren 150 mg/Valsartan 160 mg vs. Placebo	40/ 60 (66.7)	85/176 (48.3)	0.0126*
Aliskiren 300 mg/Valsartan 320 mg vs. Aliskiren 300 mg	44/ 58 (75.9)	119/175 (68.0)	0.3237
Aliskiren 300 mg/Valsartan 320 mg vs. Valsartan 320 mg	44/ 58 (75.9)	38/ 60 (63.3)	0.1554
Aliskiren 300 mg/Valsartan 320 mg vs. Placebo	44/ 58 (75.9)	85/176 (48.3)	0.0004*
Valsartan 160 mg/HCTZ 12.5 mg vs. Placebo	46/ 58 (79.3)	85/176 (48.3)	<.0001*
Aliskiren 150 mg/Valsartan 160 mg vs. Valsartan 160 mg/HCTZ 12.5 mg	40/ 60 (66.7)	46/ 58 (79.3)	0.1017
Aliskiren 300 mg/Valsartan 320 mg vs. Valsartan 160 mg/HCTZ 12.5 mg	44/ 58 (75.9)	46/ 58 (79.3)	0.5510

Responder is defined as a patient with trough MSDBP < 90 mmHg and/or at least 10 mmHg reduction from baseline.
P-Values were from a logistic regression model with treatment and region as factors and baseline as a covariate.
Baseline is the week 0 value.
N = Number of patients with both baseline and endpoint MSDBP values.
* indicates statistical significance at 0.05 level.
Source: PTT 9.2-7

In the dose-response analysis of change from baseline in MSDBP, the dose response was fitted in the first order. Statistically significant linear dose relationships were shown for both aliskiren and valsartan dose (p=0.0002 for aliskiren dose and p=0.0117 for valsartan dose). The lack-of-fit test was not statistically significant (p = 0.6549). In this fitted first-order form, the negative first-order term indicated that the reduction in MSDBP had a positive relationship to the aliskiren and valsartan dose. The predicted and raw means in MSDBP for each treatment group are presented in table 85. Similar to the results for MSDBP, for change from baseline in MSSBP at endpoint, a first order dose-response surface was fitted.

Table 85: Dose-response surface analysis for change from baseline in MSDBP (mmHg) at endpoint (intent-to-treat population)

Treatment Group	N	Predicted Mean	Raw Mean
Placebo	176	-9.2	-8.4
Aliskiren 75 mg	177	-9.9	-10.1
Aliskiren 150 mg	177	-10.5	-10.1
Aliskiren 300 mg	175	-11.8	-12.1
Valsartan 80 mg	58	-9.7	-10.3
Valsartan 160 mg	58	-10.2	-10.9
Valsartan 320 mg	60	-11.2	-11.1
Aliskiren 75 mg/Valsartan 80 mg	60	-10.4	-11.6
Aliskiren 150 mg/Valsartan 160 mg	60	-11.5	-11.9
Aliskiren 300 mg/Valsartan 320 mg	58	-13.8	-12.9

Note: The dose-response surface was fitted in first-order [change from baseline in MSDBP] = -9.207 - 0.009*(aliskiren dose) - 0.006*(valsartan dose).
Source: PTT 9.2-11

10.1.2.11. Safety

The overall AEs based on system organ class, preferred term and treatment group were summarized in the following table 86. The overall rate of AEs was 31.2%, and ranged from 22.0% in the valsartan 160 mg/HCTZ 12.5mg group to 35.2% in the aliskiren 75 mg group. The most frequently affected primary system organ classes overall were nervous system

disorders (9.5%) and infections and infestations (6.1%). Adverse events that occurred in ≥ 2% of patients in any treatment group during the double-blind treatment period are summarized in the table 87. The most frequent adverse events overall were headache (5.7%) and fatigue (2.8%). The incidence rate of headache ranged from 0% in the valsartan 160 mg/HCTZ 12.5 group to 8.5% in the placebo group. The incidence rate of fatigue ranged from 0% in the valsartan 80 mg group to 6.7% in the aliskiren 150 mg/valsartan 160 mg group.

Regarding the severity of AEs, overall, headache (4 patients, 0.4%) and fatigue (3 patients, 0.3%) were the most frequently reported AEs rated as severe. AEs classified as severe were reported in 8.3% of patients in the aliskiren 75 mg/valsartan 80 mg group, 3.4% in the aliskiren 300 mg and valsartan 160 mg groups, 3.3% in the valsartan 320 mg and aliskiren 150mg/ valsartan 160 mg groups, 2.8% in the placebo and aliskiren 75 mg groups, 1.7% in the valsartan 80 mg and aliskiren 300 mg/valsartan 320 mg groups, 1.1% in the aliskiren 150 mg group, and 0% in the valsartan 160 mg/HCTZ 12.5 mg group.

Table 86: Number (%) of patients with AEs in the double-blind randomization period, by treatment group and primary system organ class (Safety population)

Primary System Organ Class	Placebo N=177 n (%)	ALI 75 N=179 n (%)	ALI 150 N=178 n (%)	ALI 300 N=175 n (%)	VAL 80 N=58 n (%)	VAL 160 N=59 n (%)
-Any primary system organ class	57(32.2)	63(35.2)	59(33.1)	50(28.6)	19(32.8)	17(28.8)
Gastrointestinal disorders	8(4.5)	11(6.1)	5(2.8)	16(9.1)	4(6.9)	4(6.8)
Nervous system disorders	21(11.9)	23(12.8)	16(9.0)	13(7.4)	5(8.6)	5(8.5)
Infections and infestations	14(7.9)	9(5.0)	12(6.7)	10(5.7)	6(10.3)	2(3.4)
Musculoskeletal and connective tissue disorders	7(4.0)	13(7.3)	9(5.1)	9(5.1)	1(1.7)	2(3.4)
General disorders and administration site conditions	9(5.1)	14(7.8)	9(5.1)	8(4.6)	2(3.4)	3(5.1)
Injury, poisoning and procedural complications	3(1.7)	8(4.5)	6(3.4)	5(2.9)	2(3.4)	3(5.1)
Skin and subcutaneous tissue disorders	1(0.6)	3(1.7)	3(1.7)	5(2.9)	3(5.2)	1(1.7)
Ear and labyrinth disorders	1(0.6)	3(1.7)	2(1.1)	4(2.3)	0(0.0)	1(1.7)
Vascular disorders	0(0.0)	1(0.6)	2(1.1)	4(2.3)	2(3.4)	0(0.0)
Psychiatric disorders	2(1.1)	0(0.0)	2(1.1)	3(1.7)	2(3.4)	2(3.4)
Respiratory, thoracic and mediastinal disorders	5(2.8)	6(3.4)	9(5.1)	3(1.7)	0(0.0)	2(3.4)
Immune system disorders	0(0.0)	0(0.0)	0(0.0)	2(1.1)	1(1.7)	0(0.0)
Investigations	0(0.0)	0(0.0)	4(2.2)	2(1.1)	0(0.0)	0(0.0)
Metabolism and nutrition disorders	3(1.7)	0(0.0)	1(0.6)	1(0.6)	0(0.0)	0(0.0)
Pregnancy, puerperium and perinatal conditions	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
Renal and urinary disorders	1(0.6)	1(0.6)	2(1.1)	1(0.6)	1(1.7)	1(1.7)
Blood and lymphatic system disorders	0(0.0)	1(0.6)	2(1.1)	0(0.0)	0(0.0)	0(0.0)
Cardiac disorders	4(2.3)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Eye disorders	5(2.8)	1(0.6)	2(1.1)	0(0.0)	0(0.0)	0(0.0)
Reproductive system and breast disorders	1(0.6)	0(0.0)	1(0.6)	0(0.0)	1(1.7)	1(1.7)
Social circumstances	2(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Primary System Organ Class	VAL 320 N=60 n (%)	ALI 75/ VAL 80 N=60 n (%)	ALI 150/ VAL 160 N=60 n (%)	ALI 300/ VAL 320 N=58 n (%)	VAL 160/ HCTZ 12.5 N=59 n (%)	Total N=1123 n (%)
-Any primary system organ class	18(30.0)	20(33.3)	16(26.7)	18(31.0)	13(22.0)	350(31.2)
Gastrointestinal disorders	2(3.3)	4(6.7)	3(5.0)	5(8.6)	3(5.1)	65(5.8)
Nervous system disorders	6(10.0)	7(11.7)	5(8.3)	6(10.3)	0(0.0)	107(9.5)
Infections and infestations	2(3.3)	4(6.7)	3(5.0)	5(8.6)	1(1.7)	68(6.1)
Musculoskeletal and connective tissue disorders	3(5.0)	5(8.3)	4(6.7)	1(1.7)	3(5.1)	57(5.1)
General disorders and administration site conditions	2(3.3)	1(1.7)	4(6.7)	5(8.6)	1(1.7)	58(5.2)
Injury, poisoning and procedural complications	0(0.0)	2(3.3)	4(6.7)	0(0.0)	0(0.0)	33(2.9)
Skin and subcutaneous tissue disorders	1(1.7)	0(0.0)	1(1.7)	1(1.7)	2(3.4)	21(1.9)

Ear and labyrinth disorders	1(1.7)	1(1.7)	0(0.0)	2(3.4)	1(1.7)	16(1.4)
Vascular disorders	0(0.0)	0(0.0)	1(1.7)	1(1.7)	0(0.0)	11(1.0)
Psychiatric disorders	2(3.3)	0(0.0)	0(0.0)	0(0.0)	1(1.7)	14(1.2)
Respiratory, thoracic and mediastinal disorders	1(1.7)	4(6.7)	1(1.7)	3(5.2)	0(0.0)	34(3.0)
Immune system disorders	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	3(0.3)
Investigations	4(6.7)	0(0.0)	0(0.0)	2(3.4)	0(0.0)	12(1.1)
Metabolism and nutrition disorders	0(0.0)	0(0.0)	1(1.7)	1(1.7)	1(1.7)	8(0.7)
Pregnancy, puerperium and perinatal conditions	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Renal and urinary disorders	1(1.7)	0(0.0)	2(3.3)	0(0.0)	1(1.7)	11(1.0)
Blood and lymphatic system disorders	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	3(0.3)
Cardiac disorders	2(3.3)	1(1.7)	0(0.0)	1(1.7)	1(1.7)	10(0.9)
Eye disorders	1(1.7)	1(1.7)	1(1.7)	1(1.7)	0(0.0)	12(1.1)
Reproductive system and breast disorders	1(1.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(0.4)
Social circumstances	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.2)

Primary system organ classes are sorted by descending frequency, as reported in the ALI 300 column.
Source: PTT 10.1-1a

Table 87: Number (%) of patients with most frequent adverse events (> or = 2.0% in any treatment group) in the double-blind randomization period, by preferred term (Safety population)

Preferred term	Placebo N=177 n (%)	ALI 75 N=179 n (%)	ALI 150 N=178 n (%)	ALI 300 N=175 n (%)	VAL 80 N=58 n (%)	VAL 160 N=59 n (%)
Headache	15(8.5)	15(8.4)	9(5.1)	7(4.0)	3(5.2)	4(6.8)
Diarrhea	3(1.7)	2(1.1)	1(0.6)	5(2.9)	1(1.7)	0(0.0)
Fatigue	4(2.3)	7(3.9)	4(2.2)	4(2.3)	0(0.0)	3(5.1)
Back pain	2(1.1)	2(1.1)	4(2.2)	3(1.7)	1(1.7)	0(0.0)
Dizziness	2(1.1)	4(2.2)	4(2.2)	3(1.7)	0(0.0)	1(1.7)
Vertigo	0(0.0)	2(1.1)	0(0.0)	3(1.7)	0(0.0)	1(1.7)
Nausea	1(0.6)	4(2.2)	0(0.0)	2(1.1)	0(0.0)	3(5.1)
Urinary tract infection	3(1.7)	1(0.6)	2(1.1)	2(1.1)	1(1.7)	1(1.7)
Cough	2(1.1)	2(1.1)	5(2.8)	1(0.6)	0(0.0)	0(0.0)
Edema peripheral	2(1.1)	1(0.6)	2(1.1)	1(0.6)	1(1.7)	0(0.0)
Bronchitis	0(0.0)	2(1.1)	1(0.6)	0(0.0)	2(3.4)	0(0.0)
Dyspnoea	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.7)
Myalgia	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	1(1.7)
Nasopharyngitis	5(2.8)	1(0.6)	1(0.6)	0(0.0)	1(1.7)	0(0.0)

Preferred term	VAL 320 N=60 n (%)	ALI 75/ VAL 80 N=60 n (%)	ALI 150/ VAL 160 N=60 n (%)	ALI 300/ VAL 320 N=58 n (%)	VAL 160/ HCTZ 12.5 N=59 n (%)	Total N=1123 n (%)
Headache	2(3.3)	3(5.0)	4(6.7)	2(3.4)	0(0.0)	64(5.7)
Diarrhea	1(1.7)	1(1.7)	3(5.0)	1(1.7)	0(0.0)	18(1.6)
Fatigue	1(1.7)	1(1.7)	4(6.7)	3(5.2)	0(0.0)	31(2.8)
Back pain	3(5.0)	2(3.3)	1(1.7)	1(1.7)	1(1.7)	20(1.8)
Dizziness	1(1.7)	1(1.7)	0(0.0)	1(1.7)	0(0.0)	17(1.5)
Vertigo	0(0.0)	1(1.7)	0(0.0)	2(3.4)	0(0.0)	9(0.8)
Nausea	0(0.0)	0(0.0)	1(1.7)	1(1.7)	0(0.0)	12(1.1)
Urinary tract infection	1(1.7)	0(0.0)	1(1.7)	2(3.4)	0(0.0)	14(1.2)
Cough	1(1.7)	1(1.7)	0(0.0)	1(1.7)	0(0.0)	13(1.2)
Edema peripheral	2(3.3)	0(0.0)	0(0.0)	1(1.7)	0(0.0)	10(0.9)
Bronchitis	1(1.7)	1(1.7)	0(0.0)	0(0.0)	0(0.0)	7(0.6)
Dyspnoea	0(0.0)	2(3.3)	0(0.0)	1(1.7)	0(0.0)	4(0.4)
Myalgia	0(0.0)	0(0.0)	2(3.3)	0(0.0)	1(1.7)	5(0.4)
Nasopharyngitis	1(1.7)	2(3.3)	1(1.7)	1(1.7)	0(0.0)	13(1.2)

Adverse event preferred terms are sorted by descending frequency, as reported in the ALI 300 column.
Source: PTT 10.1-1a

The incidence rate of deaths, serious adverse events, and other significant adverse events was summarized in the following table 88. Two patients deaths were reported, one in the placebo group and one in the valsartan 160 mg group. A 70-year-old Caucasian male patient in the placebo group was found dead with unknown reason in his home on study day 16. A 52-year-old Caucasian male patient in the valsartan 160 mg group died in an automobile accident on study day 26 after having been discontinued from the study (primary reason "lost to follow-up").

Overall, eight (0.7%) patients experienced serious adverse events during the double-blind period, 2 (1.1 %) in the placebo group, 1 (0.6 %) in the aliskiren 75 mg group, 1 (0.6 %) in the aliskiren 300 mg group, 2 (3.4%) in the valsartan 160 mg group, 1 (1.7%) in the aliskiren 75 mg/valsartan 80 mg group, and 1 (1.7 %) in the aliskiren 150 mg/valsartan l60-mg group. In the placebo group, a 65-year-old Caucasian male, was hospitalized for a myocardial infarction on study day 46. He underwent percutaneous transluminal coronary angioplasty on day 46 and again on day 50 for coronary stenting. He made a complete recovery by day 53. Study drug was discontinued. In the aliskiren 75 mg group, a 64 year-old Caucasian male, was diagnosed with coronary artery disease and was admitted to the hospital on study day 4. The last dose of study drug was taken on day 2 and the patient was discontinued from the study on day 3 due to this adverse event. The patient underwent quadruple bypass surgery two weeks after discontinuing the study and recovered with sequelae. In the aliskiren 300 mg group, a 31-year-old Black female, had a positive pregnancy test result 42 days after starting study drug. The patient discontinued study drug, with an expected delivery date of (b) (6) On (b) (6) the patient gave birth by normal vaginal delivery to a male, weight 3.8 kg and height 53.66 cm, with no abnormalities associated. No complications were associated with the patient during the delivery process. In the valsartan 160 mg group, a 57 year-old Caucasian female with a prior history of facial angioedema while receiving an ACE inhibitor, experienced angioneurotic edema on Study day 28. Study drug was stopped on day 33 and the condition resolved spontaneously without treatment three days later. The patient discontinued from the study at this time due to this event. In the aliskiren 75 mg/valsartan 80 mg group, a 49 year-old Caucasian male, was hospitalized for dyspnea and chest pressure 3 days after successfully

completing the study. Myocardial infarction was ruled out and a diagnosis of functional disorder was made. In the aliskiren 150 mg/valsartan l60-mg group, a 43 year-old Black female was hospitalized a wrist fracture due to a motor vehicle accident on day 29. The patient was discharged from the hospital and study medication was not discontinued.

An additional four patients had SAEs during the single-blind run-in period, and were discontinued from the study prior to ever receiving double-blind study drug. A 39-year-old Caucasian female, presented with a positive pregnancy test during the single-blind run-in period and was discontinued from the study due to this event. A 50-year-old Caucasian female, was hospitalized with mild melanorrhagia and gastric pain during the single-blind run-in period. Study drug was discontinued due to the gastric pain. A 44-year-old male of other race, was hospitalized for a myocardial infarction during the single blind run-in period. Study drug was discontinued and the patient withdrew consent. A 70-year-old Caucasian male, had biopsy results during the single-blind run-in period that showed squamous cell carcinoma. The patient did not qualify for randomization due to a MSDBP less than 95 mmHg.

Table 88: Number (%) of patients who died or had other serious or significant adverse events during the double-blind randomization period (Safety population)

	Placebo N=177 n (%)	ALI 75 N=179 n (%)	ALI 150 N=178 n (%)	ALI 300 N=175 n (%)	VAL 80 N=58 n (%)	VAL 160 N=59 n (%)
Deaths	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0) [1]
SAEs	2 (1.1)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	2 (3.4)
AE discontinuations	6 (3.4)	5 (2.8)	3 (1.7) [2]	3 (1.7)	0 (0.0)	2 (3.4)
Drug-related AE discontinuations	2 (1.1)	4 (2.2)	1 (0.6)	2 (1.1)	0 (0.0)	2 (3.4)
SAE discontinuations	2 (1.1)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	1 (1.7)
Discontinuations for abnormal lab values	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

	VAL 320 N=60 n (%)	ALI 75/ VAL 80 N=60 n (%)	ALI 150/ VAL 160 N=60 n (%)	ALI 300/ VAL 320 N=58 n (%)	VAL 160/ HCTZ 12.5 N=59 n (%)	Total N=1123 n (%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1) [1]
SAEs	0 (0.0)	1 (1.7)	1 (1.7)	0 (0.0)	0 (0.0)	8 (0.7)
AE discontinuations	3 (5.0)	0 (0.0)	1 (1.7)	2 (3.4)	0 (0.0)	25 (2.2) [2]
Drug-related AE discontinuations	0 (0.0)	0 (0.0)	1 (1.7)	2 (3.4)	0 (0.0)	14 (1.2)
SAE discontinuations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)
Discontinuations for abnormal lab values	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

[1] One additional patient (PID 0506-00019) in the valsartan 160 mg group died after having been discontinued from the study (primary reason "lost to follow-up").
[2] One patient's (PID 0517-00010) reason for discontinuation was "abnormal lab value".
Note: a patient can be included in more than one category of event.
Source: PTT 7.1-2, PTT 10.2-1, PTT 10.2-2 and PTT 10.2-3 and PTL 10.2-1 to PTL10.2-3

For the discontinuation due to the AEs, overall, few patients (2.2%) discontinued due to adverse events. The incidence of AEs leading to discontinuation ranged from 0% in the valsartan 80 mg, aliskiren 75 mg/valsartan 80 mg, and valsartan 160 mg/HCTZ 12.5-mg groups to 5.0% in the valsartan 320 mg group. The most frequent adverse events leading to discontinuation were fatigue (5 patients, 0.4%), headache (3 patients, 0.3%), diarrhea (2

patients, 0.2%), and peripheral edema (2 patients, 0.2%). Data were summarized in the following table 89.

Table 89: Number (%) of patients discontinued for AEs during the double-blind randomization period, by primary system organ class and preferred term (Safety population)

Primary System Organ Class Preferred term	Placebo N=177 n (%)	ALI 75 N=179 n (%)	ALI 150 N=178 n (%)	ALI 300 N=175 n (%)	VAL 80 N=58 n (%)	VAL 160 N=59 n (%)
-Any primary system organ class	6(3.4)	5(2.8)	3(1.7)	3(1.7)	0 (0.0)	2(3.4)
Cardiac disorders	2(1.1)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Arrhythmia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Coronary artery disease	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Myocardial infarction	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Palpitations	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Tachycardia	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Ear and labyrinth disorders	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
Vertigo	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
Gastrointestinal disorders	1(0.6)	2(1.1)	0(0.0)	0(0.0)	0(0.0)	1(1.7)
Abdominal pain	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Diarrhoea	1(0.6)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Nausea	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.7)
General disorders and administration site conditions	3(1.7)	1(0.6)	1(0.6)	1(0.6)	0(0.0)	1(1.7)
Influenza like illness	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
Fatigue	1(0.6)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	1(1.7)
Oedema	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Oedema peripheral	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Sudden death	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Investigations	0(0.0)	0(0.0)	2(1.1)	0(0.0)	0 (0.0)	0(0.0)
Blood creatine phosphokinase increased	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Pulse pressure increased	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Weight increased	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	0(0.0)
Musculoskeletal and connective tissue disorders	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0 (0.0)	0(0.0)
Flank pain	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0 (0.0)	0(0.0)
Back pain	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	0(0.0)
Nervous system disorders	1(0.6)	2(1.1)	1(0.6)	0(0.0)	0 (0.0)	1(1.7)
Dizziness	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1(1.7)
Headache	1(0.6)	1(0.6)	0(0.0)	0(0.0)	0 (0.0)	1(1.7)
Lethargy	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	0(0.0)
Migraine	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0 (0.0)	0(0.0)
Syncope	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0 (0.0)	0(0.0)
Pregnancy, puerperium and perinatal conditions	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0 (0.0)	0(0.0)
Pregnancy	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0 (0.0)	0(0.0)
Skin and subcutaneous tissue disorders	0(0.0)	1(0.6)	1(0.6)	0(0.0)	0 (0.0)	1(1.7)
Angioneurotic oedema	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1(1.7)
Cold sweat	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0 (0.0)	0(0.0)

Dermatitis bullous	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0 (0.0)	0(0.0)
Eczema	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0 (0.0)	0(0.0)

Primary System Organ Class	VAL 320 N=60 n (%)	ALI 75/ VAL 80 N=60 n (%)	ALI 150/ VAL 160 N=60 n (%)	ALI 300/ VAL 320 N=58 n (%)	VAL 160/ HCTZ 12.5 N=59 n (%)	Total N=1123 n (%)
-Any primary system organ class	3(5.0)	0 (0.0)	1(1.7)	2(3.4)	0 (0.0)	25(2.2)
Cardiac disorders	2(3.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(0.4)
Arrhythmia	1(1.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Coronary artery disease	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Myocardial infarction	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Palpitations	1(1.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Tachycardia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Ear and labyrinth disorders	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Vertigo	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Gastrointestinal disorders	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(0.4)
Abdominal pain	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Diarrhoea	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.2)
Nausea	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
General disorders and administration site conditions	0(0.0)	0(0.0)	1(1.7)	2(3.4)	0(0.0)	10(0.9)
Influenza like illness	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Fatigue	0(0.0)	0(0.0)	1(1.7)	1(1.7)	0(0.0)	5(0.4)
Oedema	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Oedema peripheral	0(0.0)	0(0.0)	0(0.0)	1(1.7)	0(0.0)	2(0.2)
Sudden death	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Investigations	0(0.0)	0 (0.0)	0(0.0)	1(1.7)	0 (0.0)	3(0.3)
Blood creatine phosphokinase increased	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Pulse pressure increased	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Weight increased	0(0.0)	0 (0.0)	0(0.0)	1(1.7)	0 (0.0)	1(0.1)
Musculoskeletal and connective tissue disorders	1(1.7)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	2(0.2)
Flank pain	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.1)
Back pain	1(1.7)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.1)
Nervous system disorders	0(0.0)	0 (0.0)	0(0.0)	1(1.7)	0 (0.0)	6(0.5)
Dizziness	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.1)
Headache	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	3(0.3)
Lethargy	0(0.0)	0 (0.0)	0(0.0)	1(1.7)	0 (0.0)	1(0.1)
Migraine	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.1)
Syncope	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.1)
Pregnancy, puerperium and perinatal conditions	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.1)
Pregnancy	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.1)
Skin and subcutaneous tissue disorders	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	3(0.3)
Angioneurotic oedema	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.1)
Cold sweat	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.1)
Dermatitis bullous	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.1)
Eczema	0(0.0)	0 (0.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.1)

Source: PTT 10.2-3

There were no clinically meaningful changes of hematology parameters and no adverse events related to a hematology abnormality. There were one patient had an adverse event related to a biochemistry abnormality. This patient was in the aliskiren 150 mg group and was discontinued for the primary reason of abnormal laboratory value (elevated creatinine kinase, also reported as an AE leading to discontinuation). The frequency of patients with specified abnormal values for selected biochemistry parameters (BUN > 40 mg/dL, creatinine > 2

mg/dL, potassium > 5.5 mEq/L, and potassium < 3.5 mEq/L) was summarized in the following table 90. The most frequent abnormality was potassium < 3.5 mEq/L, reported in 2.5% of patients in the placebo group. Potassium values > 5.5 mEq/L were observed in one (0.6%) patient each in the placebo, aliskiren 75 mg, and aliskiren 300 mg groups, one (1.9%) patient in the aliskiren 150 mg/ valsartan 160 mg group, and one (1.8%) patient in the aliskiren 300 mg/valsartan 320 mg group. None of the potassium values > 5.5 mEq/L met the criteria for a clinically notable increase from baseline and none of the five patients had any adverse events.

Table 90: Number (%) of patients with specified abnormal values for selected biochemistry parameters: BUN > 40 mg/dL, creatinine > 2 mg/dL, potassium > 5.5 mEq/L, and potassium < 3.5 mEq/L (Safety population)

Laboratory test Criterion	Placebo (N=177) n (%)	ALI 75 (N=179) n (%)	ALI 150 (N=178) n (%)	ALI 300 (N=175) n (%)	VAL 80 (N=58) n (%)	VAL 160 (N=59) n (%)
Blood Urea Nitrogen (BUN)						
Total no. of patients	176 (100)	173 (100)	176 (100)	171 (100)	58 (100)	57 (100)
>40 mg/dL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine						
Total no. of patients	176 (100)	173 (100)	176 (100)	171 (100)	58 (100)	57 (100)
>2 mg/dL	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
High (#)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Potassium						
Total no. of patients	161 (100)	167 (100)	168 (100)	161 (100)	56 (100)	52 (100)
>5.5 mEq/L	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
High (#)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 0.0
Total no. of patients	161 (100)	167 (100)	168 (100)	161 (100)	56 (100)	52 (100)
<3.5 mEq/L	4 (2.5)	2 (1.2)	1 (0.6)	1 (0.6)	1 (1.8)	0 (0.0)
Low (#)	4 (2.5)	2 (1.2)	1 (0.6)	1 (0.6)	1 (1.8)	0 (0.0)

Laboratory test	VAL 320 (N=60) n (%)	ALI 75/ VAL 80 (N=60) n (%)	ALI 150/ VAL 160 (N=60) n (%)	ALI 300/ VAL 320 (N=58) n (%)	VAL 160/ HCTZ 12.5 (N=59) n (%)
Blood Urea Nitrogen (BUN)					
Total no. of patients	60 (100)	57 (100)	58 (100)	58 (100)	58 (100)
>40 mg/dL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine					
Total no. of patients	60 (100)	57 (100)	58 (100)	58 (100)	58 (100)
>2 mg/dL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
High (#)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Potassium					
Total no. of patients	56 (100)	55 (100)	54 (100)	55 (100)	54 (100)
>5.5 mEq/L	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.8)	0 (0.0)
High (#)	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.8)	0 (0.0)
Total no. of patients	56 (100)	55 (100)	54 (100)	55 (100)	54 (100)
<3.5 mEq/L	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Low (#)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)

A patient must have both baseline and post-baseline values to be included.
A further classification of patients who meet the specified criterion with respect to laboratory normal ranges. It indicates that the most extreme (highest/lowest) post-baseline test value is either above, below or within the normal range.
Baseline is the week 0 value, or the previous screening value (week -4 to week -2) if the week 0 value was not available.
Source: PTT 10.3-6

In the analysis of the vital signs, a 54-year-old Caucasian male in the aliskiren 150 mg group, was discontinued on study day 8 for adverse events of increased pulse pressure (reported term "intermittent bounding heart rate"), cold sweat (reported term "intermittent clamminess"), and intermittent fatigue beginning on study day 1. A 53-year-old Caucasian male in the valsartan 320 mg group, discontinued on study day 31 for an adverse event of palpitations (reported term "heart pounding") beginning on study day 29. An 80-year-old Caucasian male in the placebo group with a history of paroxysmal tachycardia, discontinued on study day 3 for an adverse event of tachycardia (reported term "worsening of tachycardia") beginning on that day. No information was given as to what the heart rate was or if the patient was symptomatic. Electrocardiograms performed on day 1 and on day 7 were normal. The incidence of orthostatic blood pressure changes was generally low and comparable across treatment groups as shown in the following table 91.

Table 91: Number (%) of patients with orthostatic blood pressure changes* (Safety population)

	Placebo N=177		ALI 75 N=179		ALI 150 N=178		ALI 300 N=175		VAL 80 N=58		VAL 160 N=59	
Visit	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Baseline	177	1 (0.6)	179	5 (2.8)	178	2 (1.1)	175	3 (1.7)	58	0 (0.0)	59	0 (0.0)
Week 1	176	2 (1.1)	177	2 (1.1)	176	9 (5.1)	175	1 (0.6)	58	1 (1.7)	57	1 (1.8)
Week 2	171	3 (1.8)	176	5 (2.8)	173	3 (1.7)	173	6 (3.5)	58	2 (3.4)	56	1 (1.8)
Week 4	168	2 (1.2)	168	3 (1.8)	171	9 (5.3)	173	2 (1.2)	57	2 (3.5)	56	1 (1.8)
Week 6	166	3 (1.8)	162	3 (1.9)	168	3 (1.8)	169	4 (2.4)	56	1 (1.8)	53	1 (1.9)
Week 8	163	3 (1.8)	158	0 (0.0)	165	9 (5.5)	165	1 (0.6)	54	1 (1.9)	52	0 (0.0)
Endpoint	176	4 (2.3)	177	0 (0.0)	177	9 (5.1)	175	1 (0.6)	58	1 (1.7)	58	0 (0.0)
Any visit**	176	12 (6.8)	177	12 (6.8)	177	24 (13.6)	175	9 (5.1)	58	4 (6.9)	58	4 (6.9)

	VAL 320 N=60		ALI 75/VAL 80 N=60		ALI 150/VAL 160 N=60		ALI 300 VAL 320 N=58		VAL 160/HCTZ 12.5 N=59	
Visit	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Baseline	60	3 (5.0)	60	1 (1.7)	60	1 (1.7)	58	0 (0.0)	59	0 (0.0)
Week 1	60	1 (1.7)	60	3 (5.0)	60	0 (0.0)	58	0 (0.0)	58	1 (1.7)
Week 2	59	0 (0.0)	57	3 (5.3)	59	2 (3.4)	57	0 (0.0)	58	1 (1.7)
Week 4	59	2 (3.4)	56	2 (3.6)	59	2 (3.4)	57	0 (0.0)	58	0 (0.0)
Week 6	57	0 (0.0)	56	2 (3.6)	58	2 (3.4)	55	2 (3.6)	57	0 (0.0)
Week 8	56	1 (1.8)	55	2 (3.6)	57	3 (5.3)	55	4 (7.3)	56	2 (3.6)
Endpoint	60	1 (1.7)	60	2 (3.3)	60	3 (5.0)	58	4 (6.9)	58	2 (3.4)
Any visit**	60	4 (6.7)	60	7 (11.7)	60	6 (10.0)	58	5 (8.6)	58	4 (6.9)

* Orthostatic blood pressure change is defined as a decrease of at least 20 mmHg in systolic blood pressure or a decrease of at least 10 mmHg in mean diastolic blood pressure when a patient moves from a sitting position to a standing position.
**Any post-baseline visit
Source: PTT 10.4-4

10.1.2.12. Summary and conclusion

In this study as other aliskiren monotherapy studies, aliskiren monotherapy was significantly superior to placebo in blood pressure reduction. Comparison of the combination therapies with each monotherapy, however, there no statistically significant difference between the combination and each monotherapies. In evaluating these results, it should be noted that a large placebo response occurred in this study, and it increased over time. This large placebo response could partly explain the failure of these differences to reach statistical significance. The

interpretation of the comparisons between the combinations and their component monotherapies is limited by the wide confidence intervals observed.

The number of patients discontinuing therapy due to AEs was similar in all groups, ranging from 0% in the valsartan 80 mg, aliskiren 75 mg/valsartan-80 mg, and valsartan 160/HCTZ 12.5 mg groups to 5.0% in the valsartan 320 mg group. The laboratory results showed no evidence of hyperkalemia or renal toxicity and no patients were discontinued due to hypotension. The safety and tolerability of the combination of aliskiren and valsartan were similar compared with their component monotherapies administered for 8 weeks. There do not appear to be any adverse effects that are increased with combination therapy.

10.1.3. SPV100A2301. A 54-week, open-label, multicenter study to assess the long-term safety and tolerability of the combination of aliskiren 300 mg / valsartan 320 mg in patients with essential hypertension

10.1.3.1. Study objectives

The primary objective of this study was to assess (from the 12 month core study) the long-term (6 month and 12 month) safety of the combination of aliskiren 300 mg / valsartan 320 mg in patients with essential hypertension (msDBP ≥ 90 mmHg and < 110 mmHg).

The secondary objectives were:
• To assess the long-term blood pressure lowering efficacy of the combination of aliskiren/ valsartan in patients with essential hypertension (msDBP ≥ 90 mmHg and <110 mmHg) at the end of the 12 month core study.
• To evaluate the proportion of patients achieving the blood pressure control target of < 140/90 mmHg at the end of 12 month core study.

The exploratory objective was to explore the effect of long-term treatment with the combination of aliskiren 300 mg / valsartan 320 mg on plasma renin activity (PRA), plasma aldosterone and plasma renin concentration (PRC).

10.1.3.2 Design

This was a 54 week, open-label, multicenter study evaluating the safety of the combination of aliskiren 300 mg / valsartan 320 mg in patients with essential hypertension. This study was comprised of two periods and 13 visits. The study design was consisted of a 1-4 week washout period, a 54 week, open-label, multicenter study (two periods and 13 visits). The design was described in the following table 92 and figure 12.

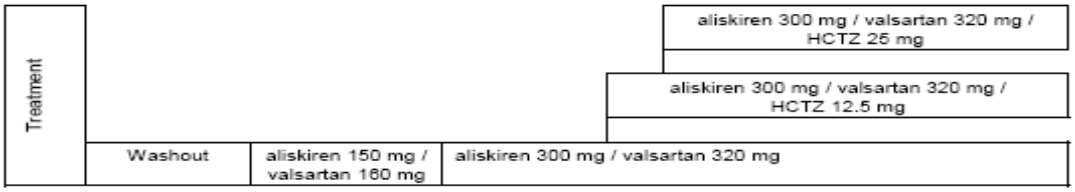
Table 92: Study outline

Phase	Washout			Study drug treatment									
Period	Washout			Low dose	High dose								
Duration	1 week	1 week	2 weeks	2 weeks	52 weeks								
Visit	1	2 [1]	3 [2]	4	5	6	7	8	9	10	11	12	13
Day	-7	n/a	n/a	1	14	28	42	72	102	132	196	287	378
	-28 / -14	-21 / -7	-14										

[1] Visit 1 and Visit 2 were combined for all untreated patients.

[2] Visit 3 and Visit 4 were combined for previously untreated patients that met all entry criteria at Visit 3. If an additional two weeks of washout was required, then Visit 1 became Day -28, Visit 2 became Day -21, and Visit 3 became Day -14. Newly diagnosed patients and untreated patients skipped Visit 3 and went directly to Visit 4.

Figure 12: Study outline



Valsartan 320 mg taken as two 160 mg capsules daily

It was planned that approximately 834 patients with essential hypertension (msDBP ≥ 90 and < 110 mmHg at Visit 4) would be screened in order to enroll approximately 500 patients in 100 centers worldwide.

GCP non-compliance issues were identified and confirmed at one study site (Site 38) by the study sponsor (Novartis), that render the safety and efficacy data unreliable for this center's patients (Washout period N=42; treatment phase N=40). These patients were, therefore, excluded from the analyses presented in this report; data including these patients are available in the data listings.

Efficacy was a secondary objective in this study. Efficacy variables included changes from baseline to endpoint in mean sitting diastolic blood pressure (msDBP) and mean sitting systolic blood pressure (msSBP), and the proportions of patients achieving the blood pressure control target (msSBP/msDBP < 140/90 mmHg) post-baseline and response rate (msDBP < 90 mmHg or a ≥10 mmHg reduction from baseline).

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), the regular monitoring of hematology and blood chemistry, regular measurement of vital signs and the performance of physical examinations. Biomarker measurements, including plasma renin concentration (PRC), plasma renin activity (PRA) and plasma aldosterone, were obtained in the subset of participating patients.

Efficacy and safety measurements were summarized in the following table 93.

Table 93: Evaluation and visit schedule

	Cat. [1]	Washout [2]			Treatment									
Visit		1	2	3[4]	4	5	6	7	8[5]	9[5]	10[5]	11[5]	12	13
Day		-28 /-14 [3]	-21 /-7	-14	1	14	28	42	72	102	132	196	287	378
Informed consent, taper / discontinue antihypertensive medications, screening physical exam	S	X												
Inclusion/exclusion Criteria	S	X	X	X	X									
Screening log, demography and history (medical, hypertension, smoking), ECG, urine dipstick	D	X												
Height, waist circumference	D				X									
Weight	D				X									X [9]
Blood pressure, pulse, prior/concomitant/antihypertensive meds	D	X	X	X	X	X	X	X	X	X	X	X	X	X [9]
Complete physical exam	S				X									X [9]
Complete laboratory evaluation [6,7]	D	X			X							X		X [9]
Electrolytes: BUN & creatinine	D						X	X		X			X	
Serum / urine pregnancy test [8]	D	X			X									X [9]
Biomarkers (patient subset)	D				X									X [9]
Adverse events	D					X	X	X	X	X	X	X	X	X [9]
Dispense study medication	S				X	X		X	X	X	X	X	X	
Drug accountability	S					X		X	X	X	X	X	X	X [9]
Study completion form	D													X [9]

[1] Cat. = Category: indicates if data were entered into the database (D) or in source documents only (S).
[2] Washout - Patients discontinued or started tapering antihypertensive medications according to the manufacture's recommendations at Visit 1.
[3] For patients newly diagnosed with uncomplicated hypertension or without any hypertensive mediation for 4 weeks prior to Visit 1, Visit 1 and Visit 2 combined. If study criteria at Visit 4 were met, the patient was enrolled into the treatment period of the study. If entry criteria at Visit 4 were not met, the patient was discontinued from study.
[4] Visit 3 required for previously treated patients if randomization blood pressure criteria not met at Visit 4: Visit 1 (Day -28), Visit 2 (Day -21), Visit 3 (Day -14).
[5] Visits occurred on the same day of the next calendar month (e.g. V7 = 15-MAR-07, V8 = 15-APR-07).
[6] Electrolytes, blood urea, creatinine are included in the complete laboratory assessments.
[7] Lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C, VLDL-C) performed at Visit 4, Visit 11 & Visit 13.
[8] Women of childbearing potential only. Serum samples by central laboratory at Visit 1 and Visit 13. A negative urine pregnancy test (by on-site study staff) at Visit 4 prior to the first dose of study medication.
[9] These assessments also performed for patients who discontinued study drug.

10.1.3.3 Patients deposition, demographic and other baseline characteristics

Including Site 38, a total of 734 patients were enrolled into the washout phase. Of the 641 patients (87.3%) who continued into the study drug treatment phase, 428 received aliskiren/valsartan only and 213 received aliskiren/valsartan with at least one dose of HCTZ. Data were summarized in the following table 94.

Table 94: Patient disposition by treatment group (study drug treatment phase enrolled population, excluding site 38)

Disposition in study drug treatment phase	Aliskiren/ valsartan * N=404 n (%)		Aliskiren/ valsartan/HCTZ * N=197 n (%)		Total N=601 n (%)	
Enrolled	404	(100.0)	197	(100.0)	601	(100.0)
Completed	320	(79.2)	166	(84.3)	486	(80.9)
Discontinued	84	(20.8)	31	(15.7)	115	(19.1)
Reason for discontinuation						
Adverse events	35	(8.7)	5	(2.5)	40	(6.7)
Abnormal laboratory values	2	(0.5)	1	(0.5)	3	(0.5)
Unsatisfactory therapeutic effect	15	(3.7)	8	(4.1)	23	(3.8)
Condition no longer requires study drug	3	(0.7)	1	(0.5)	4	(0.7)
Patient withdrew consent	10	(2.5)	5	(2.5)	15	(2.5)
Lost to follow-up	13	(3.2)	10	(5.1)	23	(3.8)
Administrative problems	1	(0.2)	0	(0.0)	1	(0.2)
Protocol deviation	5	(1.2)	1	(0.5)	6	(1.0)

* Aliskiren/valsartan group is defined as patients who received only aliskiren/valsartan (without HCTZ) in the study. 'Aliskiren/valsartan/HCTZ' group is defined as patients who received HCTZ in addition to aliskiren/valsartan at any time during the study.
Percentage (%) is calculated using the study drug treatment phase enrolled population as the denominator.
Results are presented for the study population excluding site 38.

Demographic and other baseline disease characteristics were generally comparable across the

treatment groups. Overall, the majority of patients were Caucasian (84.5%) or Black (12.6%), and greater proportion of study patients were males (54.9%). The mean BMI was 31.5 kg/m^2. Half the population was obese (BMI ≥ 30 kg/m^2). About 42.6% of patients fulfilled the criteria for metabolic syndrome. The mean age was 55 years and ranged from 23 to 85 years. Most patients were younger than 65 years old (80%) and 3.5% of patients were over 75 years of age. The mean duration of hypertension was 7.7 years. The aliskiren/valsartan/HCTZ group had a greater proportion of patients who were Black (21.8% vs. 8.2% aliskiren/valsartan) and who were obese (BMI > 30 kg/m2; 58.4% vs. 46.8% aliskiren/valsartan). Further the mean duration of hypertension was slightly longer in the aliskiren/valsartan/HCTZ group (8.4 years vs. 7.3 years aliskiren/valsartan. Data were summarized in the following table 95.

Table 95: Patient background characteristics (treated population, excluding site 38)

Demographic variable		Aliskiren/ valsartan * N=404	Aliskiren/ valsartan/HCTZ * N=197	Total N=601
Age (years)	n	404	197	601
	mean (SD)	55.0 (11.59)	55.1 (10.39)	55.0 (11.20)
	median	56.0	54.0	55.0
	range (min – max)	23.0 – 85.0	32.0 – 80.0	23.0 – 85.0
Age group – n (%)	< 65 years	319 (79.0%)	162 (82.2%)	481 (80.0%)
	≥ 65 years	85 (21.0%)	35 (17.8%)	120 (20.0%)
	< 75 years	391 (96.8%)	189 (95.9%)	580 (96.5%)
	≥ 75 years	13 (3.2%)	8 (4.1%)	21 (3.5%)
Gender – n (%)	Male	223 (55.2%)	107 (54.3%)	330 (54.9%)
	Female	181 (44.8%)	90 (45.7%)	271 (45.1%)
Race – n (%)	Caucasian	357 (88.4%)	151 (76.6%)	508 (84.5%)
	Black	33 (8.2%)	43 (21.8%)	76 (12.6%)
	Asian	6 (1.5%)	2 (1.0%)	8 (1.3%)
	Native American	2 (0.5%)	0 (0.0%)	2 (0.3%)
	Pacific Islander	2 (0.5%)	0 (0.0%)	2 (0.3%)
	Other	4 (1.0%)	1 (0.5%)	5 (0.8%)
Ethnicity – n (%)	Chinese	1 (0.2%)	1 (0.5%)	2 (0.3%)
	Hispanic or Latino	13 (3.2%)	4 (2.0%)	17 (2.8%)
	Indian (Ind. subcont.)	3 (0.7%)	0 (0.0%)	3 (0.5%)
	Mixed ethnicity	6 (1.5%)	2 (1.0%)	8 (1.3%)
	Other	381 (94.3%)	190 (96.4%)	571 (95.0%)
Duration of hypertension (years)	n	404	197	601
	mean (SD)	7.3 (7.10)	8.4 (6.97)	7.7 (7.07)
	median	5.0	7.0	6.0
	range (min – max)	1.0 – 51.0	1.0 – 45.0	1.0 – 51.0
Body mass index (kg/m^2)	n	402	197	599
	mean (SD)	31.1 (6.50)	32.2 (6.35)	31.5 (6.47)
	median	29.4	31.6	30.1
	range (min – max)	19.6 – 71.1	17.5 – 52.7	17.5 – 71.1
Obesity – n (%)	BMI ≥ 30 kg/m^2	189 (46.8%)	115 (58.4%)	304 (50.6%)
	BMI < 30 kg/m^2	213 (52.7%)	82 (41.6%)	295 (49.1%)
Diabetes – n (%)	Yes	45 (11.1%)	25 (12.7%)	70 (11.6%)
	No	359 (88.9%)	172 (87.3%)	531 (88.4%)
Metabolic syndrome – n (%)	Yes	174 (43.1%)	82 (41.6%)	256 (42.6%)
	No	230 (56.9%)	115 (58.4%)	345 (57.4%)

SD = standard deviation min - max = minimum and maximum values for the parameter
* Aliskiren/valsartan group is defined as patients who received only aliskiren/valsartan (without HCTZ) in the study. 'Aliskiren/valsartan/HCTZ' group is defined as patients who received HCTZ in addition to aliskiren/valsartan at any time during the study.
Metabolic syndrome present if any 3 of the following 5 statements are true: 1. Waist circumference > 102 cm (40 in) for men, or > 88 cm (35 in) for women; 2. Triglycerides ≥ 150 mg/dL (1.69 mmol/L); 3. HDL cholesterol < 40 mg/dL (1.04 mmol/L) for men, or < 50 mg/dL (1.29 mmol/L) for women; 4. SBP ≥ 130 or DBP ≥ 85 mmHg; 5. Fasting glucose ≥ 110 mg/dL (6.1 mmol/L).
Results are presented for the study population excluding site 38.
Source: PT-table 14.1-3.1

10.1.3.4. Efficacy summary

For the mean sitting diastolic blood pressure in the overall population, a clinically significant mean reduction from baseline in msDBP was observed as early as Week 2 (7.9 mmHg) and a mean reduction of 13.4 mmHg was seen at endpoint, indicating that the blood pressure reductions were sustained for the one year duration of the study. Similar to the mean sitting diastolic blood pressure, a clinically significant mean reduction from baseline in msSBP was also observed as early as Week 2 (11.0 mmHg) and a mean reduction of 20.5 mmHg was seen at the endpoint. Data were summarized in the following tables 96 and 97.

Table 96: Summary statistics for change from baseline in mean sitting diastolic blood pressure (mmHg) by visit and treatment group .

	Aliskiren /valsartan *		Aliskiren /valsartan/HCTZ *		Total	
Week (Visit)	n **	mean change (SD) mmHg	n **	mean change (SD) mmHg	n **	mean change (SD) mmHg
Week 2 (Visit 5)	398	-9.1 (7.13)	197	-5.6 (6.60)	595	-7.9 (7.14)
Week 4 (Visit 6)	386	-12.2 (7.74)	196	-8.1 (7.32)	582	-10.8 (7.83)
Week 6 (Visit 7)	370	-14.0 (7.39)	197	-7.7 (7.73)	567	-11.8 (8.09)
Week 10 (Visit 8)	357	-15.6 (6.84)	197	-8.9 (7.62)	554	-12.5 (8.26)
Week 14 (Visit 9)	346	-15.7 (7.10)	197	-10.1 (7.92)	543	-13.7 (7.87)
Week 18 (Visit 10)	339	-16.4 (7.22)	194	-12.7 (8.75)	533	-15.0 (8.00)
Week 28 (Visit 11)	335	-16.1 (6.96)	189	-13.7 (7.50)	524	-15.2 (7.24)
Week 41 (Visit 12)	327	-15.9 (7.30)	178	-13.9 (7.98)	505	-15.2 (7.60)
Week 54 (Visit 13)	322	-14.5 (7.86)	169	-13.6 (8.15)	491	-14.2 (7.96)
Endpoint ***	398	-13.6 (8.96)	197	-13.1 (8.32)	595	-13.4 (8.75)

* Aliskiren/valsartan group is defined as patients who received only aliskiren/valsartan (without HCTZ) in the study. 'Aliskiren/valsartan/HCTZ' group is defined as patients who received HCTZ in addition to aliskiren/valsartan at any time during the study.

** n is the number of patients with observations at both baseline and the post-baseline visit.

*** Endpoint is the value at Week 54 (Visit 13 or the last observation carried forward (LOCF)) based on the availability of measurements.

Results are presented for the study population excluding site 38.

Source: PT-table 14.2-1.1

Table 97: Summary statistics for change from baseline in mean sitting systolic blood pressure (mmHg) by visit and treatment group.

	Aliskiren/ valsartan *		Aliskiren/ valsartan/HCTZ *		Total	
Week (Visit)	n **	mean change (SD) mmHg	n **	mean change (SD) mmHg	n **	mean change (SD) mmHg
Week 2 (Visit 5)	398	-12.5 (12.36)	197	-8.1 (12.05)	595	-11.0 (12.42)
Week 4 (Visit 6)	386	-16.9 (13.66)	196	-11.0 (13.94)	582	-15.0 (14.03)
Week 6 (Visit 7)	370	-20.5 (13.74)	197	-12.2 (13.16)	567	-17.6 (14.10)
Week 10 (Visit 8)	357	-23.1 (12.76)	197	-10.0 (13.23)	554	-18.4 (14.37)
Week 14 (Visit 9)	346	-23.0 (12.05)	197	-16.7 (14.74)	543	-20.7 (13.42)
Week 18 (Visit 10)	339	-24.1 (12.91)	194	-19.9 (15.42)	533	-22.6 (14.01)
Week 28 (Visit 11)	335	-24.8 (12.85)	189	-23.5 (15.09)	524	-24.3 (13.70)
Week 41 (Visit 12)	327	-24.7 (12.55)	178	-23.5 (14.50)	505	-24.3 (13.27)
Week 54 (Visit 13)	322	-21.8 (13.49)	169	-23.1 (16.30)	491	-22.3 (14.51)
Endpoint ***	398	-19.7 (16.26)	197	-22.1 (16.60)	595	-20.5 (16.40)

* Aliskiren/valsartan group is defined as patients who received only aliskiren/valsartan (without HCTZ) in the study. 'Aliskiren/valsartan/HCTZ' group is defined as patients who received HCTZ in addition to aliskiren/valsartan at any time during the study.

** n is the number of patients with observations at both baseline and the post-baseline visit.

*** Endpoint is the value at Week 54 (Visit 13 or the last observation carried forward (LOCF)) based on the availability of measurements.

Results are presented for the study population excluding site 38.

Source: PT-table 14.2-1.2

The proportion of patients with controlled blood pressure (msDBP < 90 mmHg and msSBP < 140 mmHg) at endpoint is summarized by visit in table 98. About more 30% patients achieved blood pressure control after two weeks of treatment. The proportion generally rose throughout the one year treatment period, with 67% of patients achieving blood pressure control at endpoint. By study design, patients who received add-on HCTZ were those whose blood pressure was more difficult to control. As expected, the blood pressure (BP) control rate was lower in the aliskiren/valsartan/HCTZ group than in the aliskiren/valsartan group. A larger increase in BP control rate was seen in the aliskiren/valsartan/HCTZ group after Week 10 in comparison to previous visits (37.1% at Week 14 compared to 14.7% at Week 10), indicating that the addition of HCTZ to aliskiren/valsartan is effective in patients who did not show adequate response to aliskiren/valsartan treatment. At endpoint, the BP control rate was nearly 60% in the aliskiren/ valsartan/HCTZ treated patients.

Table 98: Frequency of patients for blood pressure control by visit and treatment group (treated population, excluding site 38)

	Aliskiren/ valsartan * N=404			Aliskiren/ valsartan/HCTZ * N=197			Total N=601		
Week (Visit)	Total	n	(%)	Total	n	(%)	Total	n	(%)
Week 2 (Visit 5)	398	166	(41.7)	197	29	(14.7)	595	195	(32.8)
Week 4 (Visit 6)	386	226	(58.5)	196	41	(20.9)	582	267	(45.9)
Week 6 (Visit 7)	370	259	(70.0)	197	38	(19.3)	567	297	(52.4)
Week 10 (Visit 8)	357	308	(86.3)	197	29	(14.7)	554	337	(60.8)
Week 14 (Visit 9)	346	300	(86.7)	197	73	(37.1)	543	373	(68.7)
Week 18 (Visit 10)	339	302	(89.1)	194	105	(54.1)	533	407	(76.4)
Week 28 (Visit 11)	335	297	(88.7)	189	111	(58.7)	524	408	(77.9)
Week 41 (Visit 12)	327	284	(86.9)	178	111	(62.4)	505	395	(78.2)
Week 54 (Visit 13)	322	248	(77.0)	169	104	(61.5)	491	352	(71.7)
Endpoint **	398	284	(71.4)	197	114	(57.9)	595	398	(66.9)

Blood pressure control defined as a msDBP < 90 mmHg and msSBP < 140 mmHg.

N = total number of patients in the treatment group.
Total is the number of patients with observations at both baseline and the post-baseline visit.
n is the number of patients meeting the criteria for blood pressure control.
Proportions are calculated from the number of patients meeting the criteria for blood pressure control divided by the number of patients with observations at both baseline and the post-baseline visit (n/Total).

* Aliskiren/valsartan group is defined as patients who received only aliskiren/valsartan (without HCTZ) in the study. 'Aliskiren/valsartan/HCTZ' group is defined as patients who received HCTZ in addition to aliskiren/valsartan at any time during the study.

** Endpoint is the value at Week 54 (Visit 13 or the last observation carried forward (LOCF)) based on the availability of measurements.

Results are presented for the study population excluding site 38.

Source: PT-table 14.2-1.15

Patients with blood pressure response in msDBP (msDBP < 90 mmHg or a ≥10 mmHg reduction from baseline) by visit and treatment group is summarized in table 99. About 82.5% of patients achieved the blood pressure response at the endpoint.

Table 99: Frequency of patients with blood pressure response in msDBP by visit and treatment group (treated population)

	Aliskiren/ valsartan * N=404			Aliskiren/ valsartan/HCTZ * N=197			Total N=601		
Week (Visit)	Total	n	(%)	Total	n	(%)	Total	n	(%)
Week 2 (Visit 5)	398	257	(64.6)	197	80	(40.6)	595	337	(56.6)
Week 4 (Visit 6)	386	312	(80.8)	196	106	(54.1)	582	418	(71.8)
Week 6 (Visit 7)	370	329	(88.9)	197	99	(50.3)	567	428	(75.5)
Week 10 (Visit 8)	357	343	(96.1)	197	90	(45.7)	554	433	(78.2)
Week 14 (Visit 9)	346	330	(95.4)	197	128	(65.0)	543	458	(84.3)
Week 18 (Visit 10)	339	326	(96.2)	194	146	(75.3)	533	472	(88.6)
Week 28 (Visit 11)	335	318	(94.9)	189	156	(82.5)	524	474	(90.5)
Week 41 (Visit 12)	327	311	(95.1)	178	145	(81.5)	505	456	(90.3)
Week 54 (Visit 13)	322	289	(89.8)	169	137	(81.1)	491	426	(86.8)
Endpoint **	398	336	(84.4)	197	155	(78.7)	595	491	(82.5)

Blood pressure response defined as a msDBP < 90 mmHg or a ≥ 10 mmHg reduction from baseline (Visit 4) value

N = total number of patients in the treatment group.
Total is the number of patients with observations at both baseline and the post-baseline visit.
n is the number of patients meeting the criteria for blood pressure control.
Proportions are calculated from the number of patients meeting the criteria for blood pressure control divided by the number of patients with observations at both baseline and the post-baseline visit (n/Total).

* Aliskiren/valsartan group is defined as patients who received only aliskiren/valsartan (without HCTZ) in the study. 'Aliskiren/valsartan/HCTZ' group is defined as patients who received HCTZ in addition to aliskiren/valsartan at any time during the study.

** Endpoint is the value at Week 54 (Visit 13 or the last observation carried forward (LOCF)) based on the availability of measurements.

Results are presented for the study population excluding site 38.

Source: PT-table 14.2-1.16

10.1.3.5. Safety summary

No study medications were taken during the washout period. After the washout period, at Visit 4, all study patients received aliskiren 150 mg/valsartan 160 mg daily for 2 weeks, then the doses were force-titrated to aliskiren 300 mg / valsartan 320 mg for 52 weeks. Starting after Week 10 and continuing through the remainder of the 52 week high dose treatment period, patients whose msSBP was ≥ 140 mmHg and/or msDBP ≥ 90 mmHg for two consecutive visits had HCTZ 12.5 mg daily added. The dose of HCTZ was increased to 25 mg daily for patients whose msSBP remained ≥ 140 mmHg and/or msDBP remained ≥ 90 mmHg. The mean duration of exposure to study medication was 327.6 days. For the 601 patients entering the 2 week low dose period, the mean duration of exposure to aliskiren 150 mg /valsartan 160 mg was 14.1 days. The mean duration of treatment for the 585 pooled patients who continued into the 52 week high dose treatment period was 322 days, indicating an adequate exposure to study medication. Most patients (80.0%) in the study population received at least 360 days of treatment. Three hundred and forty five patients were treated with aliskiren 300 mg/valsartan 320 mg for at least 6 months (180 days) and 270 patients were treated for at least 12 months (360 days) without the need for the addition of HCTZ. Of the 197 patients who received add-on HCTZ, 164 were treated with aliskiren/valsartan/HCTZ for at least 6 months. Data were summarized in the following tables 100 and 101.

Approximately 96% of patients had at least one concomitant medication or significant non-drug therapy. The types of the concomitant medications are expected in this patient population. The most frequently reported (≥20.0% of patients) medication classes were anti-inflammatory preparations, non-steroids for topical use (24.8%), non-drug therapies and procedures (22.8%), HMG CoA reductase inhibitors (21.8%), and anilides (21.1%). The most commonly used medications were acetylsalicylic acid (16.0%), ibuprofen (13.5%), and paracetamol (12.5%). The vast majority of patients (96.7%) did not take antihypertensive medication (other than study drug) after Visit 4 (Day 1).

Table 100: Duration of exposure (days).

	Aliskiren 150 mg/ valsartan 160 mg alone N = 601	Aliskiren 300 mg/ valsartan 320 mg alone N = 585	Aliskiren/ valsartan/HCTZ N = 197	Pooled * aliskiren 300 mg/ valsartan 320 mg N = 585	Total N = 601
Mean	14.1	236.8	253.1	322.0	327.6
SD	2.15	146.52	85.04	102.58	113.89
Median	14.0	357.0	300.0	364.0	378.0
Min - max	1 – 25	1 – 386	2 – 333	1 – 390	1 – 405

SD = standard deviation min - max = minimum and maximum values for the parameter

* Includes aliskiren 300 mg / valsartan 320 mg and aliskiren / valsartan / HCTZ groups.

Results are presented for the study population excluding site 38.

Source: PT-table 14.3-1.1

Table 101: Duration of exposure (days) by interval.

Days	Aliskiren 150 mg/ valsartan 160 mg alone N = 601 n (%)	Aliskiren 300 mg/ valsartan 320 mg alone N = 585 n (%)	Aliskiren/ valsartan/HCTZ N = 197 n (%)	Pooled * aliskiren 300 mg/ valsartan 320 mg N = 585 n (%)	Total N = 601 n (%)
≥ 1	601 (100.0)	585 (100.0)	197 (100.0)	585 (100.0)	601 (100.0)
≥ 14	493 (82.0)	570 (97.4)	196 (99.5)	570 (97.4)	591 (98.3)
≥ 30	0 (0.0)	553 (94.5)	193 (98.0)	553 (94.5)	568 (94.5)
≥ 60	0 (0.0)	461 (78.8)	184 (93.4)	544 (93.0)	546 (90.8)
≥ 90	0 (0.0)	386 (66.0)	179 (90.9)	538 (92.0)	540 (89.9)
≥ 150	0 (0.0)	351 (60.0)	168 (85.3)	520 (88.9)	522 (86.9)
≥ 180	0 (0.0)	345 (59.0)	164 (83.2)	511 (87.4)	517 (86.0)
≥ 270	0 (0.0)	332 (56.8)	130 (66.0)	500 (85.5)	502 (83.5)
≥ 330	0 (0.0)	321 (54.9)	1 (0.5)	487 (83.2)	489 (81.4)
≥ 360	0 (0.0)	270 (46.2)	0 (0.0)	411 (70.3)	481 (80.0)

* Includes aliskiren 300 mg / valsartan 320 mg and aliskiren / valsartan / HCTZ groups.
Results are presented for the study population excluding site 38.

Source: PT-table 14.3-1.1

The most frequently affected system organ classes were infections and infestations (37.3%), musculoskeletal and connective tissue disorders (22.6%), nervous system disorders (22.0%) and gastrointestinal disorders (21.1%). The most frequently reported AEs in the treated population were dizziness (9.3%), nasopharyngitis (8.8%), headache (8.0%) and diarrhea (7.0%). Dizziness was reported in 56 (9.3%) patients. Dizziness was most often mild (43 patients, 7.2%) or moderate (12 patients, 2.0%) and transient in nature. One patient had severe dizziness, which lasted for one day and resolved without treatment. Further, syncope was reported in three patients at different severities (1 mild, 1 moderate, and 1 severe). The majority of patients with dizziness (49 of 56 patients) were less than 65 years of age. Two of

the three patients with syncope were ≥ 65 years of age at baseline. Diarrhea was reported as an AE in 42 patients (7.0%) during the study. None of these AEs were serious. Twenty-eight patients had events that were mild in nature, thirteen had events that were moderate, and one had a severe event. Two patients (0.3%) discontinued due to diarrhea while receiving aliskiren 300 mg / valsartan 320 mg. For these two patients, the events were moderate in nature. At discontinuation, diarrhea had resolved in one of the two patients. The one severe case of diarrhea in aliskiren 300 mg / valsartan 320 mg resolved after three days without requiring treatment. This patient had an active history of gastro-esophageal reflux disease and diverticulitis. The patient continued in the study until completion. There were no cases of colorectal neoplasms observed in this 12-month long-term study. Data were summarized in the following tables 102 and 103.

Table 102: Number (%) of patients with AEs by system organ class, treatment group.

Primary system organ class	Aliskiren 150 mg/ valsartan 160 mg alone N = 601 n (%)	Aliskiren 300 mg/ valsartan 320 mg alone N = 585 n (%)	Aliskiren/ valsartan N=601 n (%)	Aliskiren/ valsartan/HCTZ N = 197 n (%)	Total N = 601 n (%)
Any system organ class	124 (20.6)	381 (65.1)	423 (70.4)	120 (60.9)	458 (76.2)
Infections and infestations	29 (4.8)	174 (29.7)	187 (31.1)	50 (25.4)	224 (37.3)
Nervous system disorders	32 (5.3)	97 (16.6)	117 (19.5)	20 (10.2)	132 (22.0)
Musculoskeletal and connective tissue disorders	17 (2.8)	92 (15.7)	105 (17.5)	38 (19.3)	136 (22.6)
Gastrointestinal disorders	28 (4.7)	89 (15.2)	109 (18.1)	21 (10.7)	127 (21.1)
Respiratory, thoracic and mediastinal disorders	4 (0.7)	52 (8.9)	54 (9.0)	15 (7.6)	66 (11.0)
Skin and subcutaneous tissue disorders	5 (0.8)	44 (7.5)	49 (8.2)	22 (11.2)	68 (11.3)
General disorders and administration site conditions	8 (1.3)	43 (7.4)	51 (8.5)	16 (8.1)	64 (10.6)
Injury, poisoning and procedural complications	2 (0.3)	41 (7.0)	43 (7.2)	15 (7.6)	57 (9.5)
Metabolism and nutrition disorders	13 (2.2)	27 (4.6)	40 (6.7)	13 (6.6)	52 (8.7)
Psychiatric disorders	4 (0.7)	26 (4.4)	29 (4.8)	2 (1.0)	31 (5.2)
Vascular disorders	2 (0.3)	19 (3.2)	21 (3.5)	10 (5.1)	30 (5.0)
Eye disorders	4 (0.7)	15 (2.6)	19 (3.2)	9 (4.6)	28 (4.7)
Cardiac disorders	4 (0.7)	11 (1.9)	15 (2.5)	5 (2.5)	20 (3.3)
Reproductive system and breast disorders	0 (0.0)	9 (1.5)	9 (1.5)	3 (1.5)	11 (1.8)
Investigations	6 (1.0)	8 (1.4)	14 (2.3)	3 (1.5)	17 (2.8)
Ear and labyrinth disorders	2 (0.3)	7 (1.2)	9 (1.5)	4 (2.0)	13 (2.2)
Renal and urinary disorders	5 (0.8)	7 (1.2)	11 (1.8)	1 (0.5)	12 (2.0)
Blood and lymphatic system disorders	0 (0.0)	6 (1.0)	6 (1.0)	1 (0.5)	7 (1.2)
Neoplasms benign, malign., unspec. (incl cysts and polyps)	1 (0.2)	6 (1.0)	7 (1.2)	4 (2.0)	11 (1.8)
Immune system disorders	0 (0.0)	4 (0.7)	4 (0.7)	2 (1.0)	6 (1.0)
Surgical and medical procedures	0 (0.0)	4 (0.7)	4 (0.7)	0 (0.0)	4 (0.7)
Hepatobiliary disorders	0 (0.0)	2 (0.3)	2 (0.3)	0 (0.0)	2 (0.3)

System organ classes are sorted in descending frequency, as reported in the aliskiren 300 mg / valsartan 320 mg alone column.
A patient with multiple adverse events within a primary system organ class is counted only once.
Results are presented for the study population excluding site 38.

Source: PT-table 14.3.1-1.1

Table 103: Number (%) of patients with common AEs (> = 2.0% in any group).

Primary system organ class	Aliskiren 150 mg /valsartan 160 mg alone N = 601 n (%)	Aliskiren 300 mg / valsartan 320 mg alone N = 585 n (%)	Aliskiren/ valsartan N=601 n (%)	Aliskiren/ valsartan/ HCTZ N = 197 n (%)	Total N = 601 n (%)
Dizziness	16 (2.7)	39 (6.7)	50 (8.3)	6 (3.0)	56 (9.3)
Nasopharyngitis	6 (1.0)	39 (6.7)	43 (7.2)	11 (5.6)	53 (8.8)
Headache	16 (2.7)	33 (5.6)	45 (7.5)	4 (2.0)	48 (8.0)
Diarrhea	8 (1.3)	27 (4.6)	34 (5.7)	10 (5.1)	42 (7.0)
Upper respiratory tract infection	2 (0.3)	25 (4.3)	27 (4.5)	6 (3.0)	32 (5.3)
Bronchitis	3 (0.5)	24 (4.1)	27 (4.5)	4 (2.0)	31 (5.2)
Cough	1 (0.2)	23 (3.9)	24 (4.0)	7 (3.6)	29 (4.8)
Back pain	4 (0.7)	19 (3.2)	22 (3.7)	8 (4.1)	30 (5.0)
Arthralgia	3 (0.5)	18 (3.1)	20 (3.3)	4 (2.0)	24 (4.0)
Sinusitis	2 (0.3)	18 (3.1)	20 (3.3)	6 (3.0)	25 (4.2)
Urinary tract infection	2 (0.3)	17 (2.9)	18 (3.0)	1 (0.5)	19 (3.2)
Nausea	3 (0.5)	15 (2.6)	18 (3.0)	3 (1.5)	21 (3.5)
Fatigue	4 (0.7)	13 (2.2)	17 (2.8)	6 (3.0)	23 (3.8)
Influenza	1 (0.2)	12 (2.1)	13 (2.2)	1 (0.5)	14 (2.3)
Vomiting	1 (0.2)	12 (2.1)	13 (2.2)	2 (1.0)	15 (2.5)
Pharyngolaryngeal pain	1 (0.2)	11 (1.9)	12 (2.0)	1 (0.5)	13 (2.2)
Myalgia	3 (0.5)	10 (1.7)	13 (2.2)	1 (0.5)	14 (2.3)
Pain in extremity	3 (0.5)	10 (1.7)	13 (2.2)	4 (2.0)	17 (2.8)
Constipation	4 (0.7)	8 (1.4)	12 (2.0)	2 (1.0)	14 (2.3)
Dyspepsia	2 (0.3)	7 (1.2)	9 (1.5)	4 (2.0)	13 (2.2)
Osteoarthritis	1 (0.2)	7 (1.2)	8 (1.3)	5 (2.5)	13 (2.2)
Muscle spasms	0 (0.0)	6 (1.0)	6 (1.0)	5 (2.5)	11 (1.8)
Hypercholesterolemia *	9 (1.5)	5 (0.9)	14 (2.3)	0 (0.0)	14 (2.3)
Rash	1 (0.2)	5 (0.9)	6 (1.0)	6 (3.0)	12 (2.0)

Edema peripheral – There were 12 patients (1.997%) in the Total column. Due to rounding conventions, it is listed in the PT-table as 2.0%. It has been excluded from the above table.

Preferred terms are sorted in descending frequency, as reported in the aliskiren 300 mg / valsartan 320 mg alone column.
A patient with multiple episodes of an adverse event is counted only once.

*For 13 out of the 14 cases, the AE of hypercholesterolemia was reported based on the lab results at Visit 4 (baseline) which occurred prior to the initiation of the study drug.
Results are presented for the study population excluding site 38.

Source: PT-table 14.3.1-1.1

There were no deaths. The incidence of SAEs was 3.7% (22 patients). The most frequently affected primary system organ classes were cardiac and vascular disorders, in five patients (0.8%) and 4 patients (0.7%), respectively. One patient had 6 of the SAEs listed: cardiac failure, with ventricular hypokinesia, pulmonary congestion, ascites, generalized edema, and tachycardia; each resolving after 17-23 days. The events were moderate to severe in nature and not suspected as related to study medication by the investigator. This patient was hospitalized and discontinued due to these events. One patient was hospitalized with SAEs of subdural hematoma,intracerebral bleeding and syncope, which were continuing at the time of study discontinuation. One patient had severe hypotension required hospitalization, resolved after 2 days and required discontinuation from study medication. Eight patients discontinued study treatment due to SAEs. In addition to the events in the two patients discussed above, angina pectoris and retinal vascular thrombosis (occurring under low dose treatment) and acute MI

(occurring under aliskiren 300 mg /valsartan 320 mg treatment), each resulted in discontinuation.

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In the treated population, 6.7% of patients had an AE leading to discontinuation and the most frequently affected system organ classes were nervous system disorders (13 patients, 2.2%) and gastrointestinal disorders (8 patients, 1.3%). The most frequently reported AEs leading to discontinuation were dizziness (n=6, 1.0%), and headache, and hypotension (4 patients each, 0.7%). The nature and frequency of AEs was not unusual for this population and drug class.

One patient in the group of aliskiren/valsartan/HCTZ discontinued at day 296 due to low potassium results, which developed during study treatment period, and elevated creatinine kinase, glucose and triglycerides, which were present prior to study treatment. This patient had a potassium level of 4.3 mmol/L at entry and ranging from 3.0 to 3.9 mmol/L during study participation. Adverse events of hypokalemia, hyperglycemia and hypertriglyceridemia were noted at Day 117 and continued through discontinuation.

Data of patients with deaths, SAEs, and discontinuation of study drugs due to AEs were summarized in the following tables 104, 105, and 106.

Table 104: Number (%) of patients with deaths, SAEs, adverse events and abnormal laboratory values leading to permanent discontinuation of study drugs.

Category	Aliskiren 150 mg /valsartan 160 mg alone N = 601 n (%)	Aliskiren 300 mg /valsartan 320 mg alone N = 585 n (%)	Aliskiren /valsartan N=601 n (%)	Aliskiren /valsartan/HCTZ N = 197 n (%)	Total N = 601 n (%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	3 (0.5)	14 (2.4)	17 (2.8)	5 (2.5)	22 (3.7)
AE discontinuations	10 (1.7)	27 (4.6)	36 (6.0) [3]	4 (2.0)	40 (6.7)
Drug-related AE discontinuations	5 (0.8)	19 (3.2)	24 (4.0)	2 (1.0)	26 (4.3)
SAE discontinuations	3 (0.5)	5 (0.9)	8 (1.3)	0 (0.0)	8 (1.3)
Abn. laboratory result discontinuations	1 (0.2) [1]	1 (0.2) [1]	2 (0.3) [1]	1 (0.5) [2]	3 (0.5)

SAE = Serious adverse events AE = adverse events Abn. = Abnormal
A patient with multiple episodes of an adverse event is counted only once or categories for discontinuations are not mutually exclusive.
Results are presented for the study population excluding site 38.
[1] Abnormal lab result present at baseline; however result was not available until after the patient had entered treatment period
[2] Patient 0511/00012 with hypokalemia
[3] Patient 0524/00005 had two AEs leading to study drug discontinuation, one which started while the patient was receiving aliskiren/valsartan 150/160 mg alone and the second while receiving aliskiren/valsartan 300/320 mg alone. Therefore, the sum of AE discontinuations across the three treatment groups does not match the number of patients in the Total column.

Table 105: Number (%) of patients with any SAEs by preferred term.

Preferred term	Aliskiren 150 mg /valsartan 160 mg alone N = 601 n (%)	Aliskiren 300 mg /valsartan 320 mg alone N = 585 n (%)	Aliskiren /valsartan N=601 n (%)	Aliskiren /valsartan/HCTZ N = 197 n (%)	Total N = 601 n (%)
Any SAE - total	3 (0.5)	14 (2.4)	17 (2.8)	5 (2.5)	22 (3.7)
Accidental overdose	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Aortic aneurysm	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Appendicitis	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Arthralgia	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Ascites	0 (0.0)	1 (0.2) [1]	1 (0.2)	0 (0.0)	1 (0.2)
Breast cancer	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Cardiac failure	0 (0.0)	1 (0.2) [1]	1 (0.2)	0 (0.0)	1 (0.2)
Cerebral hemorrhage	0 (0.0)	1 (0.2) [2]	1 (0.2)	0 (0.0)	1 (0.2)
Gallbladder disorder	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Generalized edema	0 (0.0)	1 (0.2) [1]	1 (0.2)	0 (0.0)	1 (0.2)
Hypertension	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Hypotension	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Myocardial infarct.	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Osteoarthritis	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.5) [3]	2 (0.3)
Pulmonary congestion	0 (0.0)	1 (0.2) [1]	1 (0.2)	0 (0.0)	1 (0.2)
Subdural hematoma	0 (0.0)	1 (0.2) [2]	1 (0.2)	0 (0.0)	1 (0.2)
Substance abuse	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Syncope	0 (0.0)	1 (0.2) [2]	1 (0.2)	0 (0.0)	1 (0.2)
Tachycardia	0 (0.0)	1 (0.2) [1]	1 (0.2)	0 (0.0)	1 (0.2)
Therapeutic agent toxicity	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Ventricular hypokinesia	0 (0.0)	1 (0.2) [1]	1 (0.2)	0 (0.0)	1 (0.2)
Acute myocardial infarct.	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Angina pectoris	1 (0.2) [4]	0 (0.0)	1 (0.2)	1 (0.5)	2 (0.3)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5) [3]	1 (0.2)
Dizziness	1 (0.2) [4]	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Hypoglycemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5) [5]	1 (0.2)
Malignant melanoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Peritoneal abscess	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5) [5]	1 (0.2)
Retinal vascular thromb.	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)

infarct. = infarction thromb. = thrombosis
Preferred terms are sorted in descending frequency, as reported in aliskiren 300 mg / valsartan 320 mg alone.
A patient with multiple episodes of an adverse event is counted only once.
Results are presented for the study population excluding site 38.
[1]Patient 0036/00005 [2]Patient 0084/00004 [3]Patient 0036/00001 [4]Patient 0517/00007 [5]Patient 0049/00002

Source: PT-table 14.3.1-1.5 and PT-listing 14.3.2-1.2

Table 106: Number (%) of patients with AEs leading to discontinuation by preferred term.

Preferred term	Aliskiren 150 mg /valsartan 160 mg alone N = 601 n (%)	Aliskiren 300 mg /valsartan 320 mg alone N = 585 n (%)	Aliskiren /Valsartan N=601 n (%)	Aliskiren /valsartan/HCTZ N = 197 n (%)	Total N = 601 n (%)
Any AE leading to discontinuation - total	10 (1.7)	27 (4.6)	36 (6.0)	4 (2.0)	40 (6.7)
Dizziness	2 (0.3)	4 (0.7)	6 (1.0)	0 (0.0)	6 (1.0)
Hypotension	1 (0.2)	3 (0.5)	4 (0.7)	0 (0.0)	4 (0.7)
Diarrhea	0 (0.0)	2 (0.3)	2 (0.3)	0 (0.0)	2 (0.3)
Fatigue	1 (0.2)	2 (0.3)	3 (0.5)	0 (0.0)	3 (0.5)
Hyperkalemia	0 (0.0)	2 (0.3)	2 (0.3)	0 (0.0)	2 (0.3)
Headache	2 (0.3)	2 (0.3)	4 (0.7)	0 (0.0)	4 (0.7)
Syncope	0 (0.0)	2 (0.3)	2 (0.3)	0 (0.0)	2 (0.3)
Cardiac failure	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Myocardial infarct.	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Tachycardia	1 (0.2)	1 (0.2)	2 (0.3)	0 (0.0)	2 (0.3)
Ventricular hypokinesia	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Ascites	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Gastrointestinal disorder	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Nausea	1 (0.2)	1 (0.2)	2 (0.3)	0 (0.0)	2 (0.3)
Chest discomfort	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Generalized edema	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Sinusitis	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Accidental overdose	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Subdural hematoma	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
ECG T wave abnormal	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Heart rate irregular	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Myalgia	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Cerebral hemorrhage	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Lethargy	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Transient ischemic attack	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Dyspnea	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Pulmonary congestion	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Dermatitis	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Urticaria	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Acute myocardial infarct.	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Angina pectoris	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Tinnitus	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Retinal vascular thrombosis	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Abdominal distension	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Dyspepsia	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Weight increased	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Muscle spasms	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Polymyalgia rheumatica	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Depression suicidal	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Insomnia	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Skin irritation	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)

infarct. = infarction
Preferred terms are sorted in descending frequency, as reported in aliskiren 300 mg / valsartan 320 mg alone.
A patient with multiple episodes of an adverse event is counted only once.
Results are presented for the study population excluding site 38.
Source: PT-table 14.3.1-1.6 and PT-listing 14.3.2-1.3

The AEs had an incidence of < 2% but may be of special interest for this combination treatment based on the pharmacologic effect of the drugs in the regimen including hyperkalemia and hypotension. During the 54-week study treatment, there were 6 patients (1.0%) with hyperkalemia patients. The incidents occurred in five patients treated with aliskiren 300 mg / valsartan 320 mg and one patient while treated with aliskiren/valsartan/HCTZ. Two of the patients discontinued due to hyperkalemia: one event lasted for 38 days, and one event was continuing at discontinuation. The remaining four patients with hyperkalemia had events that did not require additional treatment or study drug

interruption. Two of these patients completed the study, and two discontinued participation for reasons unrelated to hyperkalemia.

There were six patients (1.0%) who experienced hypotension during the study. Five patients had non-serious AEs of hypotension, which were moderate in severity. The duration for these five cases was four days for two patients, 20 days for one patient, and ongoing at the time of discontinuation for two patients. Patient 0503/00007 (aliskiren 300 mg / valsartan 320 mg) had severe hypotension lasted for 2 days and required hospitalization and treatment with i.v. fluids with electrolytes. The event was reported as a SAE. Four of the six patients were discontinued due to the hypotension. In the remaining two patients, one was treated by temporarily stopping HCTZ for about 2.5 weeks, and one required no treatment. A total of four patients (0.7%) experienced mild, non-serious orthostatic hypotension. None of the events were considered SAEs or required study drug discontinuation. Patient 0003/00014 had mild orthostatic hypotension, which resolved without treatment after 16 days. Approximately two months later, this patient had onset of moderate dizziness that resulted in discontinuation from the study. Patient 0083/00001 had orthostatic hypotension that resolved without treatment after 22 days, and had a concomitant AE of hyperkalemia and a history of chronic obstructive pulmonary disease (COPD). The two remaining cases had mild orthostatic hypotension, which required no treatment. None of the patients with orthostatic hypotension also reported hypotension.

A few patients had notable changes from baseline in hematology tests including:
• Hemoglobin > 20% decrease: 8 patients (1.4%) met the criteria; 1 patient was within the normal range (0.1%).
• WBC > 50% increase: 19 patients (3.3%) met the criteria; 8 patients (1.4%) were within the normal range.
• Platelets > 75% increase: 9 patients (1.6%) met the criteria; 3 patients (< 0.1%) were within the normal range.
For the clinical chemistry, a low proportion of patients had shifts from normal biochemistry values at baseline to values outside the normal range including:
• BUN > 50% increase: 197 patients (33.5%) met the criteria; 131 patients (22.3%) were within the normal range.
• Uric acid > 50% increase: 22 patients (3.8%) met the criteria; 16 patients (2.8%) were within the normal range.
• Creatinine > 50% increase: 21 patients (3.6 %) met the criteria; 3 patients (0.5%) were within the normal range.
• Potassium > 20% increase: 74 patients (12.6%) met the criteria; 62 patients (10.5%) were within the normal range.

Overall, 20 patients (3.4%) had potassium > 5.5 mmol/L with more patients not receiving HCTZ add-on. Among the 20 patients whose potassium values exceeded 5.5 mmol/L, 16 had transient elevations that returned to normal at subsequent or final visits. At final visits, potassium levels remained high in three patients in the aliskiren/valsartan group (ranging from 5.5 – 8.5 mmol/L) and one in the aliskiren/valsartan/HCTZ group (ranging from 5.9 mmol/L). In one of these patients (0042/00011; aliskiren/valsartan, Potassium = 8.1 mmol/L), the laboratory blood sample was obtained after the patient had discontinued study medication for

three days. The AEs related to increased potassium or hyperkalemia were reported in a total of six patients, and resulted in discontinuation in two patients.

Twenty three patients (3.9%) had potassium < 3.5 mmol/L with the majority of them (17 patients) receiving HCTZ add-on. Overall, 78% (18 of the 23 patients) of the patients with potassium value < 3.5 mmol/L had transient decreases that returned to normal at subsequent or final visits. Seventeen of the 23 patients completed the study. Of the six patients who did not complete study, one discontinued due to an AE of hypokalemia and the remaining were lost-to follow up or withdrew consent. Three patients had low potassium at final visit. Of the two patients with creatinine values > 176.8 umol/L, one had associated clinically notable increases in BUN; however, both laboratory test values returned to within normal range at subsequent visits and at the end of study, and the other patient was lost to follow up. Data of laboratory parameters were summarized in the following table 107. There were total 13 patients who had creatinine values >132.6 µmol/L (1.5 mg/dl) and >30% from baseline during the study and 3 patients remaining the abnormal values at the end of study.

Table 107: Percentage of patients with specified criteria in selected labs by laboratory parameter.

Laboratory test	Aliskiren/valsartan* N = 404 n (%)		Aliskiren/valsartan/HCTZ * N = 197 n (%)		Total N = 601 n (%)	
Potassium < 3.5 mmol/L						
Total No. – n (%)	391	(100)	197	(100)	588	(100)
Low (#)	6	(1.5)	17	(8.6)	23	(3.9)
Potassium > 5.5 mmol/L						
Total No. – n (%)	391	(100)	197	(100)	588	(100)
High (#)	16	(4.1)	4	(2.0)	20	(3.4)
Potassium ≥ 6.0 mmol/L						
Total No. – n (%)	391	(100)	197	(100)	588	(100)
High (#)	3	(0.8)	0	(0.0)	3	(0.5)
Creatinine > 176.8 umol/L						
Total No. – n (%)	391	(100)	197	(100)	588	(100)
High (#)	1	(0.3)	1	(0.5)	2	(0.3)
Blood urea nitrogen > 14.28 mmol/L						
Total No. – n (%)	391	(100)	197	(100)	588	(100)
High (#)	2	(0.5)	3	(1.5)	5	(0.9)

* Aliskiren/valsartan group is defined as patients who received only aliskiren/valsartan (without HCTZ) in the study. 'Aliskiren/valsartan/HCTZ' group is defined as patients who received HCTZ in addition to aliskiren/valsartan at any time during the study.

A further classification of patients who meet the specified criterion with respect to laboratory normal ranges. It indicates that the extreme (highest/lowest) post-baseline test value is either above or below the normal range.

Percentages based on the number of patients with laboratory results.

Results are presented for the study population excluding site 38.

Source: PT- table 14.3-2.3

Changes of vital signs, physical findings, and other observations related to safety from baseline to endpoint and at each time point, including endpoint, were generally small and clinically insignificant. The incidence of orthostatic blood pressure change (defined as a decrease of ≥ 20 mmHg in systolic blood pressure or a decrease of ≥ 10 mmHg in diastolic blood pressure when a patient moves from a sitting position to a standing position) at each visit was summarized in

the following table 108. When orthostatic blood pressure changes at any visit post-baseline were counted, the incidence was 11.3%.

Table 108: Number (%) of patients with orthostatic blood pressure change.

	Aliskiren/ valsartan * N=404			Aliskiren/ valsartan/HCTZ * N=197			Total N=601		
Week (Visit)	Total	n	(%)	Total	n	(%)	Total	n	(%)
Baseline (Visit 4)	404	4	(1.0)	197	3	(1.5)	601	7	(1.2)
Week 2 (Visit 5)	396	6	(1.5)	197	5	(2.5)	593	11	(1.9)
Week 4 (Visit 6)	386	6	(1.6)	194	2	(1.0)	580	8	(1.4)
Week 6 (Visit 7)	370	8	(2.2)	197	4	(2.0)	567	12	(2.1)
Week 10 (Visit 8)	356	5	(1.4)	196	3	(1.5)	552	8	(1.4)
Week 14 (Visit 9)	346	5	(1.4)	197	6	(3.0)	543	11	(2.0)
Week 18 (Visit 10)	336	6	(1.8)	193	4	(2.1)	529	10	(1.9)
Week 28 (Visit 11)	335	1	(0.3)	188	1	(0.5)	523	2	(0.4)
Week 41 (Visit 12)	327	7	(2.1)	177	2	(1.1)	504	9	(1.8)
Week 54 (Visit 13)	322	8	(2.5)	169	3	(1.8)	491	11	(2.2)
Endpoint **	397	9	(2.3)	197	3	(1.5)	594	12	(2.0)
Any visit (post-baseline)	397	41	(10.3)	197	26	(13.2)	594	67	(11.3)

* Aliskiren/valsartan group is defined as patients who received only aliskiren/valsartan (without HCTZ) in the study. 'Aliskiren/valsartan/HCTZ' group is defined as patients who received HCTZ in addition to aliskiren/valsartan at any time during the study.

Orthostatic blood pressure change is defined as a decrease of ≥ 20 mmHg in systolic blood pressure or a decrease of ≥ 10 mmHg in diastolic blood pressure when a patient moves from a sitting position to a standing position.

** Endpoint is the value at Week 54 (Visit 13 or the last observation carried forward (LOCF)) based on the availability of measurements.

A patient is only counted once if the patient has orthostatic blood pressure change at any time from baseline (Visit 4).

Results are presented for the study population excluding site 38.

Source: PT- table 14.3-3.4

10.1.3.6. Summary and Conclusions

The study was conducted to support the registration of the combination of aliskiren/valsartan for the treatment of essential hypertension in long–term. In this open-labeled and uncontrolled study, the data summarized here demonstrated that the combination of aliskiren/valsartan is effective as a long-term treatment for patients with hypertension.

From safety aspect, this study demonstrated that the combination of aliskiren/valsartan with or without the addition of HCTZ is well-tolerated when used as a long term treatment in patients with hypertension. The AE profile seen is expected for this patient population and drug class. Diarrhea is an AE that has been associated with the aliskiren treatment, especially at the high dose (> 300 mg). The incidence of diarrhea was 7.0%, which is slightly higher than that seen in previous short term studies with aliskiren. The majority of the diarrhea cases resolved while patients continued on the treatment. There were no patient deaths and the number of patients with SAEs is acceptable. The incidences of AEs of hypotension and orthostatic hypotension reported as AEs were 1.0% and 0.7%, respectively. The proportion of patients with orthostatic blood pressure changes at any time during the study (11.3%) was not unexpected.

The lab analyses showed no noteworthy findings in hematology. Agents that block the RAS are known to have potential to increase serum potassium. In this study the incidence of hyperkalemia defined as serum potassium > 5.5 mmol/L was 3.4% and there were three

patients (0.5%) with a potassium level over 6.0 mmol/L. There three patients (0.5%) with serum level of creatinine> 132.6 (1.5 mg/dl) and >30% from baseline at the end of study.

Overall, the safety profile of the combination regimen, aliskiren 300 mg / valsartan 320 mg with or without the addition of HCTZ was acceptable.

10.1.4. Study No: SPP100A 2331. An eight week, randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren/valsartan / HCTZ (300/320/25 mg), compared to the combinations of aliskiren/HCTZ (300/25 mg) and valsartan/HCTZ (320/25 mg) in patients with essential hypertension not adequately responsive to HCTZ 25 mg

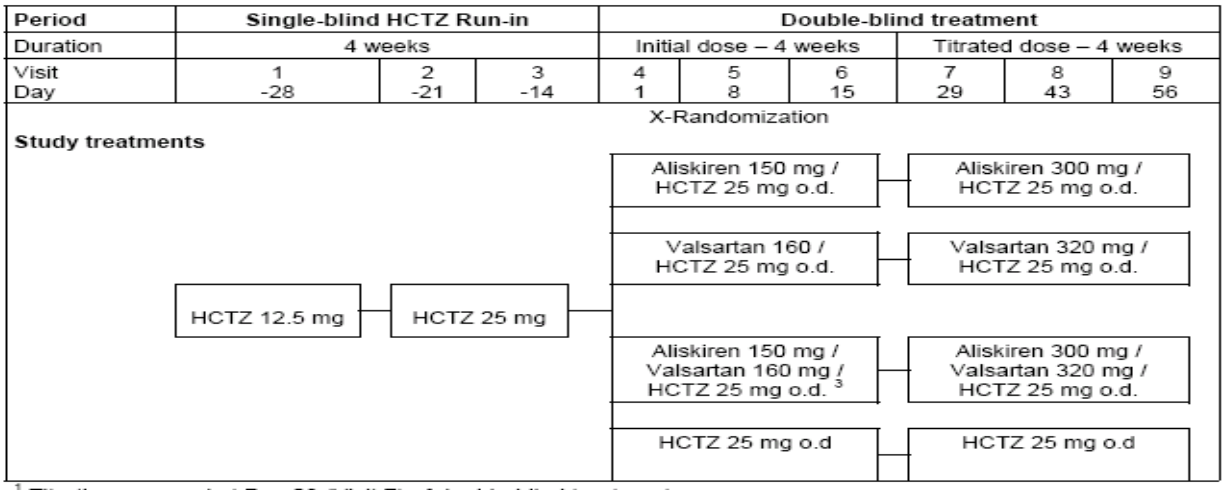
10.1.4.1. Objectives

The primary objective of this study was to demonstrate that the combination of aliskiren /valsartan/HCTZ (300/320/25 mg) has superior efficacy compared to the combinations of aliskiren/HCTZ (300/25 mg) and valsartan / HCTZ (320/25 mg) in reducing mean sitting diastolic blood pressure (msDBP) from baseline to the end of 8 weeks of treatment in patients with hypertension not adequately responsive to HCTZ 25 mg. In addition, the safety and tolerability profile of all treatment groups were evaluated.

10.1.4.2. Study design

This was a randomized, double-blind, parallel group, multicenter, active-control, dose escalation study primarily comparing the efficacy and safety of the combination of aliskiren/valsartan/ HCTZ (300/320/25 mg) to the combinations of aliskiren/HCTZ (300/25 mg) and valsartan / HCTZ (320/25 mg) in hypertensive patients who were not adequately responsive to HCTZ monotherapy. The total duration of study participation for each patient, inclusive of all phases, was approximately 12 weeks, and consisted of two periods, as shown in the following figure 13. Approximately 1540 patients from approximately 100 centers were planned for screening so that approximately 624 adult patients with essential hypertension who did not demonstrate adequate blood pressure response after 4 weeks of treatment with HCTZ could be randomized (156 in each of the four treatment groups). The assessment schedule was summarized in the following table 109.

Figure 13: Study design



[1] Titration occurred at Day 29 (Visit 7) of double-blind treatment.
[2] Duration refers to the time between the current visits.
[3] Aliskiren/valsartan/HCTZ (150/160/25 mg) treatment arm was treated with valsartan/HCTZ (160/25 mg) for the first week followed by aliskiren/valsartan/HCTZ (150/160/25 mg) for 3 weeks.

Table 109: Assessment schedule

Period	Category[1]	Single-blind HCTZ Run-in			Double-blind treatment					
Visit		1	2	3	4	5	6	7	8	9
Day		-28	-21	-14	1	8	15	29	43	56
Duration (weeks)[2]		4			8					
Informed consent	S	X								
Inclusion/exclusion criteria	S	X	X	X	X					
Demography and histories: medical, hypertension, smoking	DS	X								
Taper / discontinue antihypertensive medications	S	X								
Height, waist circumference	DS				X					
Weight	DS				X					X*
Blood Pressure and Pulse	DS	X	X	X	X	X	X	X	X	X*
Complete physical exam	S	X								X*
ECG	DS	X								X*
Complete laboratory evaluations[2]	DS	X			X					X*
Electrolytes / BUN and creatinine[2]	DS						X		X	
Hba_{1c}	DS	X								
Serum/urine pregnancy test[3]	DS	X			X					X*
Biomarkers ("established" and/or optional) in a subset of patients)	DS				X					X
Beneficial side effects	DS		X	X	X	X	X	X	X	X
Adverse events	DS		X	X	X	X	X	X	X	X*
Prior/concomitant meds (incl. antihypertensives)[4]	DS	X	X	X	X	X	X	X	X	X*
Randomization	DS				X					
Call IVRS	S	X	X		X	X		X		X
Dispense study drugs	S	X	X		X	X		X		
Drug accountability[5]	S		X		X	X		X		X*
End of Study Phase Information	DS				X					
End of Study Information	DS									X*
Screening log	DS	X								

[1] Category: indicates if data are entered into the database (DS) or in source documents only (S).
[2] Laboratory samples obtained with patient in a fasting state, lipid profile was completed at Visits 4 and 9.
[3] Women of childbearing potential only. Visits 1 and 9 serum samples tested by central laboratory; Visit 4 urine pregnancy tests by site study staff prior to the first dose of study drug.
[4] Antihypertensive medication and prior/concomitant medications were collected at Visit 1. After Visit 1, any medication taken other than the study drug was considered a concomitant medication.
[5] Visits 3, 6 and 8 compliance was discussed with patient to confirm sufficient study drug remained for next visit. At Visits 2, 4, 5, 7 and 9 drug was collected, counted, and recorded in the Drug Accountability Log.
* Assessments were required for patients who discontinued double-blind study drug

10.1.4.3. Efficacy summary

The demographic and other baseline characteristics were summarized in the following tables 110 and 111. The treatment groups were generally comparable with respect to demographics and baseline characteristics. The majority of patients were Caucasian (86%); more than half of the patients (57%) were male. The mean age of patients was 53.2 years with a mean duration of hypertension of 8.4 years. Approximately 15% of patients were 65 years of age or older, and 3% were 75 years of age or older. The valsartan/HCTZ group had a slightly greater mean age (55 years) and a greater proportion of patients ≥ 65 years old (21%) compared to the other three treatment groups. Approximately half (53%) of patients were obese (BMI ≥ 30 kg/m2), while 12% of patients were diabetic and 53% fulfilled the criteria for metabolic syndrome.

Table 110: Analysis population for each treatment group (randomized patients)

Population	HCTZ n (%)	Aliskiren / HCTZ n (%)	Valsartan / HCTZ n (%)	Aliskiren / Valsartan / HCTZ n (%)	Total n (%)
Randomized population	152 (100)	166 (100)	155 (100)	168 (100)	641 (100)
Intent-to-treat population (ITT)	151 (99.3)	164 (98.8)	154 (99.4)	168 (100)	637 (99.4)
Safety population (SAF)	152 (100)	165 (99.4)	154 (99.4)	168 (100)	639 (99.7)
Per Protocol population (PP)	118 (77.6)	131 (78.9)	129 (83.2)	155 (92.3)	533 (83.2)

Percentage (%) is calculated using the randomized population as the denominator.
Source: PT-table 14.1-2.1

Table 111: Patient background characteristics by treatment group (randomized population)

Demographic variable		HCTZ N = 152	Aliskiren / HCTZ N = 166	Valsartan / HCTZ N = 155	Aliskiren / Valsartan / HCTZ N = 168	Total N = 641
Sex – n (%)	Female	58 (38.2)	74 (44.6)	67 (43.2)	77 (45.8)	276 (43.1)
	Male	94 (61.8)	92 (55.4)	88 (56.8)	91 (54.2)	365 (56.9)
Race – n (%)	Caucasian	131 (86.2)	141 (84.9)	135 (87.1)	147 (87.5)	554 (86.4)
	Black	13 (8.6)	16 (9.6)	14 (9.0)	15 (8.9)	58 (9.0)
	Asian	3 (2.0)	5 (3.0)	4 (2.6)	1 (0.6)	13 (2.0)
	Native American	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
	Other	5 (3.3)	4 (2.4)	2 (1.3)	4 (2.4)	15 (2.3)
Ethnicity – n (%)	Hispanic/Latino	28 (18.4)	20 (12.0)	26 (16.8)	31 (18.5)	105 (16.4)
	Indian (Indian subcont.)	1 (0.7)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.3)
	Mixed ethnicity	0 (0.0)	4 (2.4)	0 (0.0)	1 (0.6)	5 (0.8)
	Other	123 (80.9)	142 (85.5)	128 (82.6)	136 (81.0)	529 (82.5)
Age Group – n (%)	<65	136 (89.5)	143 (86.1)	123 (79.4)	141 (83.9)	543 (84.7)
	≥ 65	16 (10.5)	23 (13.9)	32 (20.6)	27 (16.1)	98 (15.3)
	≥ 75	3 (2.0)	4 (2.4)	6 (3.9)	4 (2.4)	17 (2.7)
Age (yrs)	n	152	166	155	168	641
	Mean (SD)	52.6 (9.93)	52.3 (10.90)	55.0 (11.40)	52.9 (10.83)	53.2 (10.81)
Duration of hypertension (yrs)	n	149	161	151	162	623
	Mean (SD)	8.0 (7.42)	7.8 (7.38)	9.2 (8.96)	8.6 (8.06)	8.4 (7.98)
Body mass index (BMI) (kg/m^2)	n	152	166	154	166	638
	Mean (SD)	31.8 (6.13)	31.3 (6.28)	31.3 (5.85)	31.9 (6.21)	31.6 (6.12)
Obesity* – n (%)	Yes	80 (52.6)	84 (50.6)	78 (50.3)	96 (57.1)	338 (52.7)
	No	72 (47.4)	82 (49.4)	76 (49.0)	70 (41.7)	300 (46.8)
Metabolic syndrome# – n (%)	Yes	80 (52.6)	87 (52.4)	76 (49.0)	96 (57.1)	339 (52.9)
	No	72 (47.4)	79 (47.6)	78 (50.3)	72 (42.9)	301 (47.0)
	Not available	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Diabetes – n (%)	Yes	21 (13.8)	20 (12.0)	19 (12.3)	18 (10.7)	78 (12.2)
	No	131 (86.2)	146 (88.0)	136 (87.7)	150 (89.3)	563 (87.8)

SD = standard deviation.
* Obesity = yes if BMI ≥ 30 kg/m^2.
# Metabolic Syndrome=Yes, if any 3 of the following are true:
1. Waist circumference >102 cm (40 in) for men, or > 88 cm (35 in) for women;
2. Triglycerides ≥ 150 mg/dL (1.69 mmol/L);
3. HDL cholesterol <40 mg/dL (1.04 mmol/L) for men, or <50 mg/dL (1.29 mmol/L) for women;
4. SBP ≥ 130 / or DBP ≥ 85 mmHg;
5. Fasting glucose ≥ 110 mg/dL (6.1 mmol/L).
Source: PT-table 14.1-3.1a

The primary efficacy evaluation was the change from baseline in msDBP at the Week 8 Endpoint. The aliskiren/valsartan/HCTZ (300/320/25 mg) group had statistically greater mean

reductions in msDBP at the Week 8 Endpoint, with further reductions of 5.4 mmHg (compared to the aliskiren/HCTZ 300/25 mg group) and 2.4 mmHg (compared to the valsartan/HCTZ 320/25 mg group). All four treatment groups demonstrated statistically significant changes ($p<0.0001$) in msDBP from baseline at Week 8 Endpoint. Both the aliskiren/HCTZ (300/25 mg) and valsartan/HCTZ (320/25 mg) groups had statistically greater mean reductions in msDBP (4.1 mmHg and 7.1 mmHg, respectively) over the HCTZ 25 mg group at the Week 8 Endpoint. Data were summarized in the following table 112.

Table 112: Statistical analysis of change from baseline in mean sitting diastolic blood pressure at Week 8 Endpoint (ITT population)

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

SE = Standard Error; LSM = Least Square Mean; CI = Confidence Interval
Least square mean, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
[1] p-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).
Source: PT-table 14.2-1.1.

For the changes of systolic pressure, the aliskiren/valsartan/HCTZ (300/320/25 mg) group had also statistically greater mean reductions in msSBP at the Week 8 Endpoint, with further reductions of 6.5 mmHg and 3.3 mmHg (aliskiren/HCTZ 300/25 mg and valsartan/HCTZ 320/25 mg groups, respectively). Aliskiren/HCTZ versus HCTZ monotherapy: Greater and statistically significant mean reductions in msSBP were observed in the aliskiren/HCTZ 300/25 mg group when compared to the HCTZ monotherapy group at the Week 8 Endpoint. The aliskiren/HCTZ 300/25 mg group had further reductions in msSBP of 8.7 mmHg at the Week 8 Endpoint. Data were summarized in the following table 113.

Table 113: Statistical analysis of change from baseline in mean sitting systolic blood pressure at Week 8 Endpoint (ITT population)

Treatment group		N	LSM change from baseline (SE)	
HCTZ		151	-6.3 (1.12)	
Aliskiren/HCTZ		164	-15.0 (1.08)	
Valsartan/HCTZ		154	-18.3 (1.12)	
Aliskiren/valsartan/HCTZ		168	-21.6 (1.07)	
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value[1]**
Aliskiren/valsartan/HCTZ	vs. Aliskiren/HCTZ	-6.5 (1.51)	(-9.51, -3.57)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. Valsartan/HCTZ	-3.3 (1.55)	(-6.31, -0.23)	0.0350*
Aliskiren/HCTZ	vs. HCTZ	-8.7 (1.55)	(-11.79, -5.68)	<0.0001*
Valsartan/HCTZ	vs. HCTZ	-12.0 (1.58)	(-15.11, -8.90)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. HCTZ	-15.3 (1.55)	(-18.31, -12.2)	<0.0001*

SE = Standard Error; LSM = Least Square Mean; CI = Confidence Interval.
Least square mean, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
[1] p-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).
Source: PT-table 14.2-2.1.

At Week 4 Endpoint with patients at lower doses of each of the study medications, the aliskiren/ valsartan/HCTZ (150/160/25 mg) had greater and statistically significant reductions in msDBP and msSBP from baseline when compared to the double combination groups of aliskiren /HCTZ (150/25 mg) and valsartan/HCTZ (160/25 mg).

In the aliskiren/valsartan/HCTZ (300/320/25 mg) regimen 66.7% of patients met the criterion for blood pressure control (target of < 140/90 mm Hg). When compared to the control rates in the aliskiren/HCTZ (300/25 mg) (40.9%) and valsartan/HCTZ (320/25 mg) (48.7%) regimens, a statistically significant difference in favor of the aliskiren/valsartan/HCTZ (300/320/25 mg) regimen was observed. The control rate in the aliskiren/HCTZ (300/25 mg) regimen was also found to be significantly higher than that found in the HCTZ monotherapy (20.5%). Similar results were achieved at the Week 4 Endpoint.

For response rate (msDBP < 90 mmHg, and/or a ≥ 10 mmHg reduction from baseline), at Week 8 Endpoint, the aliskiren/valsartan/HCTZ (300/320/25 mg) group had a greater and statistically significant proportion (81.6%) of patients that met the responder criteria (when compared to the aliskiren/HCTZ (300/25 mg) group (64.0%; p=0.0004). The difference in the proportions for the aliskiren/valsartan/HCTZ (300/320/25 mg) group and valsartan/HCTZ (320/25 mg) group (74.0%) did not achieve statistical significance. In comparison to HCTZ monotherapy (39.1%), the aliskiren/HCTZ (300/25 mg) group had a greater and statistically significant proportion of patients (64.0%; p<0.0001) meeting the responder criteria. Similar results were achieved at the Week 4 Endpoint.

10.1.4.4. Safety summary

The patient exposure was summarized in the table 114. In all treatment groups, the mean and median duration of exposure reflected the planned 8 weeks (56 days) of study treatment, considering patients who prematurely discontinued.

Table 114: Duration of exposure (Days) to double-blind study medication (safety population)

	HCTZ N = 152 n (%)	Aliskiren / HCTZ N = 165 n (%)	Valsartan / HCTZ N = 154 n (%)	Aliskiren / Valsartan / HCTZ N = 168 n (%)
N	152	165	154	168
Mean (SD)	52.4 (11.66)	52.5 (11.03)	53.3 (9.62)	54.5 (7.15)
Median	56.0	56.0	56.0	56.0
Min - Max	2 - 63	1 - 61	7 - 67	1 - 64

SD = standard deviation
Source: PT-table 14.3-1.1b

The most frequently affected primary system organ classes overall were nervous system disorders (9.7%, with 7% of the overall population reporting headaches), gastrointestinal disorders (6.4%), and infections and infestations (5.5%). Low blood pressure was reported in one patient, dizziness was reported in 29 (1.9%) of patients, diarrhea was reported in 11 (0.9%) of patients, and vertigo was reported in 6 (0.5%) of patients. Hypokalemia was reported in three patients (0.2%). No clinically important increases in the overall rate of AEs within specific system organ classes were observed in the aliskiren/valsartan/HCTZ group when compared to the rates in the two double combination treatment groups. In both the aliskiren/valsartan/HCTZ and the aliskiren/HCTZ groups, the common AEs (occurring in at

least 2% of patients) were reported at rates that were generally similar or less than found in the other treatment groups, with the exception of pollakiuria (frequent urination) that was more frequently reported in the aliskiren/HCTZ group when compared to the other treatment groups, vertigo and back pain that were reported more frequently in the aliskiren/valsartan/HCTZ group. Data were summarized in the following tables 115 and 116.

Table 115: Number (%) of patients with overall AEs in double-blind period by treatment group and body system (safety population)

Primary system organ class	HCTZ N = 152 n (%)	Aliskiren / HCTZ N = 165 n (%)	Valsartan / HCTZ N = 154 n (%)	Aliskiren / Valsartan / HCTZ N = 168 n (%)
Any body system	64 (42.1)	60 (36.4)	72 (46.8)	62 (36.9)
Nervous system disorders	13 (8.6)	8 (4.8)	28 (18.2)	21 (12.5)
Infections and infestations	24 (15.8)	16 (9.7)	15 (9.7)	17 (10.1)
Gastrointestinal disorders	10 (6.6)	9 (5.5)	16 (10.4)	10 (6.0)
Musculoskeletal and connective tissue disorders	11 (7.2)	7 (4.2)	7 (4.5)	10 (6.0)
General disorders and administration site conditions	8 (5.3)	5 (3.0)	7 (4.5)	8 (4.8)
Metabolism and nutrition disorders	6 (3.9)	6 (3.6)	6 (3.9)	7 (4.2)
Respiratory, thoracic and mediastinal disorders	6 (3.9)	4 (2.4)	8 (5.2)	7 (4.2)
Investigations	4 (2.6)	1 (0.6)	0 (0.0)	6 (3.6)
Ear and labyrinth disorders	1 (0.7)	3 (1.8)	2 (1.3)	5 (3.0)
Injury, poisoning and procedural complications	6 (3.9)	0 (0.0)	2 (1.3)	3 (1.8)
Skin and subcutaneous tissue disorders	5 (3.3)	6 (3.6)	7 (4.5)	3 (1.8)
Vascular disorders	0 (0.0)	4 (2.4)	4 (2.6)	3 (1.8)
Renal and urinary disorders	2 (1.3)	6 (3.6)	4 (2.6)	2 (1.2)
Reproductive system and breast disorders	0 (0.0)	1 (0.6)	4 (2.6)	2 (1.2)
Eye disorders	2 (1.3)	1 (0.6)	1 (0.6)	1 (0.6)
Psychiatric disorders	2 (1.3)	0 (0.0)	2 (1.3)	1 (0.6)
Blood and lymphatic system disorders	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Cardiac disorders	2 (1.3)	2 (1.2)	2 (1.3)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Immune system disorders	1 (0.7)	1 (0.6)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Social circumstances	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)

Organ systems are sorted in descending frequency, as reported in the Aliskiren/Valsartan/HCTZ column. A patient with multiple adverse events within a primary system organ class is counted only once.

Source: PT-table 14.3.1-1.1b

Table 116: Number (%) of patients with adverse events (> or = 2.0%) starting in double-blind period in any treatment group (safety population)

Preferred term	HCTZ N = 152 n (%)	Aliskiren / HCTZ N = 165 n (%)	Valsartan / HCTZ N = 154 n (%)	Aliskiren / Valsartan / HCTZ N = 168 n (%)
Any adverse event	64 (42.1)	60 (36.4)	72 (46.8)	62 (36.9)
Dizziness	3 (2.0)	3 (1.8)	13 (8.4)	10 (6.0)
Headache	8 (5.3)	4 (2.4)	9 (5.8)	5 (3.0)
Fatigue	4 (2.6)	2 (1.2)	3 (1.9)	4 (2.4)
Back pain	1 (0.7)	2 (1.2)	2 (1.3)	4 (2.4)
Vertigo	0 (0.0)	2 (1.2)	1 (0.6)	4 (2.4)
Nasopharyngitis	10 (6.6)	5 (3.0)	4 (2.6)	3 (1.8)
Cough	2 (1.3)	2 (1.2)	4 (2.6)	3 (1.8)
Hyperlipidemia	3 (2.0)	2 (1.2)	3 (1.9)	3 (1.8)
Diarrhea	4 (2.6)	2 (1.2)	3 (1.9)	2 (1.2)
Bronchitis	3 (2.0)	0 (0.0)	2 (1.3)	2 (1.2)
Upper respiratory tract infection	3 (2.0)	3 (1.8)	2 (1.3)	1 (0.6)
Eczema	3 (2.0)	1 (0.6)	1 (0.6)	1 (0.6)
Edema peripheral	3 (2.0)	0 (0.0)	1 (0.6)	1 (0.6)
Pollakiuria	0 (0.0)	4 (2.4)	2 (1.3)	0 (0.0)

Preferred terms are sorted in descending frequency, as reported in the Aliskiren/Valsartan/HCTZ column.
A patient with multiple occurrences of any adverse events within a preferred term is counted only once.
Source: PT-table 14.3.1-1.1b

There were no deaths reported during the single-blind period, and one death during the double-blind period. One patient in the valsartan/HCTZ group, a 46 year old Black female died on Day 43. The principal cause of death was sudden cardiac death. During the single-blind period, eight patients reported SAEs. During the double-blind period, SAEs were reported for a total of 7 patients, five in the valsartan/HCTZ group, and one each in the HCTZ and the aliskiren/HCTZ group. These SAEs are summarized in the following:

Aliskiren/HCTZ treatment group:
• Patient (PID A2331-0036-00004), a 70 year old Caucasian female was hospitalized due to severe episodes of nausea, electrolyte depletion and vertigo, which began on Day 48. The nausea resolved after 2 days, and the electrolyte depletion and vertigo resolved after 8 days. Study medication was permanently discontinued due to these events.
Valsartan/HCTZ treatment group:
• Patient (PID A2331-0018-00023), a 61 year old Caucasian female was hospitalized due to a severe hypertensive crisis, which began on Day 38, and resolved on Day 39. Study medication was permanently discontinued.
• Patient (PID A2331-0529-00001), a 66 year old Caucasian male had moderate syncope, which began on Day 29, and resolved on Day 31. The patient was treated with a concomitant medication, and continued participation in the study.
• Patient (PID A2331-0025-00012), a 84 year old Caucasian female had chronic pancreatitis and islet cell hyperplasia, and further developed hydrocholecystis, biliary dilatation and

jaundice and was hospitalized on Day 47. On Day 50 the patient was diagnosed with a pancreatic neoplasm. Study medication was permanently discontinued due to these events.
• Patient (PID A2331-0051-00002), a 58 year old Caucasian female was diagnosed with breast cancer of moderate severity on Day 1 of the study. Study medication was permanently discontinued due to this event.
• Patient (PID A2331-0505-00005), previously described as a death occurring during the study.
HCTZ treatment group:
• Patient (PID A2331-0505-00007), a 52 year old Black male was hospitalized for cocaine abuse on Day 9. This event was continuing at study discontinuation.

The incidence rate of deaths, SAEs, and other significant AEs were summarized in the following tables 117 and 118.

Table 117: Number (%) of patients with deaths, serious adverse events, and discontinuation due to adverse events or abnormal laboratory values during double-blind period (safety population).

	HCTZ N = 152 n (%)	Aliskiren / HCTZ N = 165 n (%)	Valsartan / HCTZ N = 154 n (%)	Aliskiren / Valsartan / HCTZ N = 168 n (%)	Total N = 639 n (%)
Deaths	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
SAEs	1 (0.7)	1 (0.6)	5 (3.3)	0 (0.0)	7 (1.1)
AE discontinuation	4 (2.6)	5 [a] (3.0)	5 [a] (3.2)	4 (2.4)	18 (2.8)
Drug-related AE discontinuation	0 (0.0)	4 (2.4)	1 (0.7)	3 (1.8)	8 (1.3)
SAE discontinuation	1 (0.7)	1 (0.6)	3 (2.0)	0 (0.0)	5 (0.8)

[a] During the double-blind period, patients PID A2331-0537-00010 (valsartan/HCTZ) and PID A2331-0506-00001 (aliskiren/HCTZ) discontinued due to AEs that began during the single-blind period. These patients are not included in this table since the AEs did not worsen in severity during the double-blind period but are counted as discontinuing due to AEs in Table 10-1.

Source: PT-table 14.1-1.2, PT-table 14.3.1-1.4b, PT-table 14.3.1-1.5b, and PT table14.3.1-1.6; and PT-listing 14.3.2-1.1b, PT-listing 14.3.2-1.2b and PT-listing 14.3.2-1.3

Table 118: Number (%) of patients with any SAEs (including death) by preferred term and treatment group during the double-blind period (safety population)

Preferred term	HCTZ N = 152 n (%)	Aliskiren / HCTZ N = 165 n (%)	Valsartan / HCTZ N = 154 n (%)
Any SAE	1 (0.7)	1 (0.6)	5 (3.2)
Biliary dilatation	0 (0.0)	0 (0.0)	1 (0.6)
Breast cancer	0 (0.0)	0 (0.0)	1 (0.6)
Hydrocholecystis	0 (0.0)	0 (0.0)	1 (0.6)
Hypertensive crisis	0 (0.0)	0 (0.0)	1 (0.6)
Jaundice	0 (0.0)	0 (0.0)	1 (0.6)
Pancreatic islets hyperplasia	0 (0.0)	0 (0.0)	1 [a] (0.6)
Pancreatic neoplasm	0 (0.0)	0 (0.0)	1 [a] (0.6)
Pancreatitis chronic	0 (0.0)	0 (0.0)	1 [a] (0.6)
Sudden death	0 (0.0)	0 (0.0)	1 [a] (0.6)
Syncope	0 (0.0)	0 (0.0)	1 [a] (0.6)
Electrolyte depletion	0 (0.0)	1 (0.6)	0 (0.0)
Nausea	0 (0.0)	1 (0.6)	0 (0.0)
Vertigo	0 (0.0)	1 (0.6)	0 (0.0)
Drug abuser	1 (0.6)	0 (0.0)	0 (0.0)

No patient in the aliskiren/valsartan/HCTZ group experienced any SAE.
A patient with multiple occurrences of any adverse events within a preferred term is counted only once.
[a] Chronic pancreatitis, islet cell hyperplasia, hydrocholecystis, biliary dilatation, jaundice and pancreatic neoplasm occurred in the same patient.

Source: PT-table 14.3.1-1.5b and PT-listing 14.3.2-1.2b

AEs leading to discontinuation of study medication are summarized in the following table 119. Approximately 3% of patients in any treatment group discontinued from the study due to AEs. Dizziness resulted in the discontinuation of three patients (one patient in the aliskiren/valsartan /HCTZ group and two patients in the aliskiren/HCTZ). Each of these events was moderate in severity. Two events were transient, lasting 1-4 days, and the remaining was continuing at study discontinuation. Syncope and positional vertigo (both reported in the same patient in the valsartan/HCTZ group), and vertigo (one patient in the aliskiren/HCTZ group) were observed in two patients. Hypotension resulted in the discontinuation of three patients (two patients in the aliskiren/valsartan/HCTZ group and 1 patient in the valsartan/HCTZ group). Each of these events was moderate in severity. Two events were transient, lasting 5-13 days, and the remaining was continuing at study discontinuation. None of the patients were discontinued primarily due to laboratory abnormalities. However, 2 patients discontinued for AEs that involved laboratory abnormalities: Mild increase in serum creatinine (HCTZ) lasting 13 days, and severe, non-specified electrolyte deficiency (aliskiren/HCTZ) lasting 8 days. There were two patients with AEs that started in run-in and subsequently led to discontinuation during the double-blind period: Patient PID A2331-0537-00010 (valsartan/HCTZ) with onset of moderate nausea on Day -27 that persisted until Day 26, and patient (PID A2331-0506-00001) (aliskiren/HCTZ) with onset of moderate to severe events of fatigue, asthenia, exertional dyspnea, myalgia and arthralgia at Day -4 that was continuing at study discontinuation.

Table 119: Number (%) of patients with adverse events leading to discontinuation by preferred term and treatment group (safety population).

Preferred term	HCTZ N = 152 n (%)	Aliskiren / HCTZ N = 165 n (%)	Valsartan / HCTZ N = 154 n (%)	Aliskiren / Valsartan / HCTZ N = 168 n (%)
Any primary system organ class	4 (2.6)	5 (3.0)	5 (3.2)	4 (2.4)
Angle closure glaucoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Biliary dilatation	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Blood creatinine increased	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cancer	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Dizziness	0 (0.0)	2 (1.2)	0 (0.0)	1 (0.6)
Drug abuser	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Electrolyte depletion	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Gout	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Hydrocholecystis	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Hyperhidrosis	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertensive crisis	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.2)
Jaundice	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Nausea	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Neck pain	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Edema peripheral	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.6)
Pancreatic islets hyperplasia	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pancreatitis chronic	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Rash	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Sudden death	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Vertigo	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Vertigo positional	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)

Note: During the double-blind period, patient (PID A-2331-0537-00010) (valsartan/HCTZ with nausea) and patient (PID A2331-0506-00001) (aliskiren/HCTZ with fatigue, arthralgia, myalgia, and exertional dyspnea) discontinued due to AEs that began during the single-blind period. These patients are not included in this table since the AEs did not worsen in severity during the double-blind period but are counted as discontinuing due to AEs in Table 10-1.

Source: PT-table 14.3.1-1.6 and PT-listing 14.3.2-1.3

A slightly greater proportion of patients in the aliskiren/valsartan/HCTZ group went from normal baseline levels to low hemoglobin levels (n=5, 3.1%) or low RBC levels (n=10, 6.3%) during the study. However; none of them met the criteria for notable changes (> 20% decrease from baseline). The aliskiren/valsartan/HCTZ combination group had higher proportions of patients with changes from normal at baseline to high at any time point during the study in creatinine and BUN (20.2% and 16.6%, respectively) than in the other combination groups and more patients (25.2%) in aliskiren/valsartan/HCTZ group had BUN increase meeting the criterion of notable change (>50% increase) than other groups. However, the majority of them (17.2%) had the BUN value within the normal range and none of them had the pre-specified significant value of 14.28 mmol/L. The percentage of patients meeting the notable change (>50% increase) in serum creatinine was low (<2%) in all groups. Only one patient (PID A2331-0530-00008 in valsartan/ HCTZ group) had BUN value which exceeded 14.28 mmol/L. The patient's BUN was elevated at baseline and remained high throughout study participation (ranging from 10.7 to 15.7). None of the patients had an increase in creatinine above 176.8 µmol/L.

The number of patients meeting the notable decrease in potassium (>20% decrease) was slightly higher in aliskiren/HCTZ group (4.4%) and HCTZ group (2.7%) compared to other groups (<2%). However, only one of these patients (0.6%) in aliskiren/HCTZ group had the potassium value below the normal range. Serum potassium levels below 3.5 mmol/L were reported at comparable rates in the two treatment groups receiving combination treatments containing aliskiren (5% and 6% in the aliskiren/HCTZ and aliskiren/valsartan/HCTZ groups, respectively). In comparison, approximately 9% of patients in the HCTZ and valsartan/HCTZ groups had serum potassium values below 3.5 mmol/L. Serum potassium elevation above normal range was rare, and reported in one patient in the aliskiren/valsartan/HCTZ group. This patient (PID A2331-0537-00016) had a value of 6.8 mmol/L at Visit 6, approximately 14 days after the start of study medication. The patient's potassium was within the normal range when repeated approximately 14 days later, and remained normal at all subsequent visits. Data were summarized in the following table 120.

Table 120: Percentage of patients exceeding pre-specified lab criteria by laboratory parameter and treatment group (safety population).

		HCTZ N = 152		Aliskiren / HCTZ N = 165		Valsartan / HCTZ N = 154		Aliskiren / Valsartan / HCTZ N = 168	
Biochemistry variable		N	n (%)	N	n (%)	N	n (%)	N	n (%)
Potassium	≥ 6.0 mmol/L	150	0 (0.0)	160	0 (0.0)	153	0 (0.0)	167	1 (0.6) [a]
	> 5.5 mmol/L	150	0 (0.0)	160	0 (0.0)	153	0 (0.0)	167	1 (0.6) [a]
	< 3.5 mmol/L	150	14 (9.3)	160	8 (5.0)	153	13 (8.5)	167	10 (6.0)
Blood urea nitrogen	> 14.28 mmol/L	150	0 (0.0)	161	0 (0.0)	153	1 (0.7)	167	0 (0.0)

[a] One patient with elevated potassium of 6.8 mmol/L.
Source: PT-table 14.3-2.

Notable changes in vital signs occurred at isolated time points, and were observed only in pulse measurements. No obvious trends were observed in changes from baseline in sitting or

standing pulse or weight. Approximately 4-7% of patients had orthostatic blood pressure changes at baseline (Week 0, the end of the 4-week HCTZ run-in period). The incidence of orthostatic BP changes at each subsequent visit was similar to or less than that at the baseline in all groups. When the orthostatic BP changes at any post baseline visit were used to calculate the incidence rate, the incidence was slightly higher in the aliskiren/HCTZ group (15%) when compared to the other treatment groups (10-11%). None of the patients with orthostatic blood pressure changes discontinued due to hypotension. Patients with orthostatic blood pressure changes are summarized in the following table 121.

Table 121: Number (%) of patients with orthostatic blood pressure change during the double-blind period (safety population)

Timepoint	HCTZ N = 152 n/N (%)	Aliskiren / HCTZ N = 165 n/N (%)	Valsartan / HCTZ N = 154 n/N (%)	Aliskiren / Valsartan / HCTZ N = 168 n/N (%)
Week 0	10 / 152 (6.6)	9 / 165 (5.5)	7 / 154 (4.5)	7 / 168 (4.2)
Week 1	4 / 150 (2.7)	3 / 164 (1.8)	2 / 154 (1.3)	3 / 167 (1.8)
Week 2	2 / 147 (1.4)	5 / 158 (3.2)	6 / 151 (4.0)	3 / 165 (1.8)
Week 4	4 / 142 (2.8)	8 / 157 (5.1)	7 / 148 (4.7)	6 / 165 (3.6)
Week 6	4 / 138 (2.9)	8 / 155 (5.2)	2 / 146 (1.4)	7 / 164 (4.3)
Week 8	2 / 134 (1.5)	6 / 153 (3.9)	2 / 141 (1.4)	3 / 161 (1.9)
Week 8 (Endpoint)				
	3 / 151 (2.0)	6 / 164 (3.7)	2 / 154 (1.3)	3 / 168 (1.8)
Any post-baseline visit				
	15 / 151 (9.9)	25 / 164 (15.2)	16 / 154 (10.4)	19 / 168 (11.3)

Orthostatic blood pressure change - a decrease of ≥ 20 mmHg in systolic blood pressure or a decrease of ≥ 10 mmHg in diastolic blood pressure when a patient moves from a sitting position to a standing position.
Source: PT-table 14.3-3.4

10.1.4.5. Summary and Conclusion.

The study results demonstrated the additional blood pressure lowering effect of this triple combination over the component double combinations while maintaining a similar safety profile.

There was no excess of AEs, SAEs, or AEs leading to discontinuation with the combination treatment of aliskiren/valsartan/HCTZ. The laboratory results showed no evidence of renal toxicity in any of the treatment groups.

10.2. Labeling review

The labeling review will be discussed in the upcoming labeling meetings.

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/s/

Shen Xiao
7/10/2009 12:36:20 PM
MEDICAL OFFICER

Ququan Liu
7/10/2009 12:42:53 PM
BIOMETRICS

James Hung
7/10/2009 01:51:06 PM
BIOMETRICS