

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022545Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Application Number(s) 22-545
Priority or Standard Standard

Submit Date(s) October 29, 2009
Received Date(s) October 29, 2009
PDUFA Goal Date August 29, 2010
Division / Office DCRP/ODEI/OND

Reviewer Name(s) Shen Xiao M.D, Ph.D
Review Completion Date May 24, 2010

Established Name Aliskiren/Amlodipine
(Proposed) Trade Name Tekamlo™
Therapeutic Class Antihypertensive (Renin inhibitor combined with calcium channel blocker)

Applicant Novartis

Formulation(s) Oral tablet
Dosing Regimen Aliskiren/Amlodipine: 150/5 mg, 150/10 mg, 300/5 mg, 300/10 mg
Indication(s) Treatment of hypertension
Intended Population(s) Adult patients with hypertension

Template Version: March 6, 2009

APPEARS THIS WAY ON ORIGINAL

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	11
1.1	Recommendation on Regulatory Action	11
1.2	Risk Benefit Assessment.....	12
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	12
1.4	Recommendations for Postmarket Requirements and Commitments	12
2	INTRODUCTION AND REGULATORY BACKGROUND	12
2.1	Product Information	12
2.2	Tables of Currently Available Treatments for Proposed Indications	13
2.3	Availability of Proposed Active Ingredient in the United States	14
2.4	Important Safety Issues with Consideration to Related Drugs.....	15
2.5	Summary of Presubmission Regulatory Activity Related to Submission	15
2.6	Other Relevant Background Information	16
3	ETHICS AND GOOD CLINICAL PRACTICES.....	16
3.1	Submission Quality and Integrity	16
3.2	Compliance with Good Clinical Practices	16
3.3	Financial Disclosures.....	16
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	16
4.1	Chemistry Manufacturing and Controls	16
4.2	Clinical Microbiology.....	17
4.3	Preclinical Pharmacology/Toxicology	17
4.4	Clinical Pharmacology	17
4.4.1	Mechanism of Action.....	17
4.4.2	Pharmacodynamics.....	18
4.4.3	Pharmacokinetics.....	18
5	SOURCES OF CLINICAL DATA.....	19
5.1	Tables of Studies/Clinical Trials	19
5.2	Review Strategy	20
5.3	Discussion of Individual Studies/Clinical Trials.....	21
6	REVIEW OF EFFICACY	29
6.1	Indication	30
6.1.1	Methods	31
6.1.2	Demographics.....	33
6.1.3	Subject Disposition	34
6.1.4	Analysis of Primary Endpoint(s).....	35
6.1.5	Analysis of Secondary Endpoints(s).....	36
6.1.6	Other Endpoints	44

6.1.7	Subpopulations	45
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	54
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	59
6.1.10	Additional Efficacy Issues/Analyses	60
7	REVIEW OF SAFETY	60
	Safety Summary	60
7.1	Methods.....	61
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	61
7.1.2	Categorization of Adverse Events.....	63
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	63
7.2	Adequacy of Safety Assessments	64
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	64
7.2.2	Explorations for Dose Response.....	69
7.2.3	Special Animal and/or In Vitro Testing	69
7.2.4	Routine Clinical Testing	69
7.2.5	Metabolic, Clearance, and Interaction Workup	69
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	70
7.3	Major Safety Results	70
7.3.1	Deaths.....	70
7.3.2	Nonfatal Serious Adverse Events	70
7.3.3	Dropouts and/or Discontinuations	73
7.3.4	Significant Adverse Events.....	76
7.3.5	Submission Specific Primary Safety Concerns	76
7.4	Supportive Safety Results	76
7.4.1	Common Adverse Events	76
7.4.2	Laboratory Findings	79
7.4.3	Vital Signs.....	83
7.4.4	Electrocardiograms (ECGs)	85
7.4.5	Special Safety Studies/Clinical Trials.....	85
7.4.6	Immunogenicity.....	85
7.5	Other Safety Explorations.....	86
7.5.1	Dose Dependency for Adverse Events	86
7.5.2	Time Dependency for Adverse Events.....	86
7.5.3	Drug-Demographic Interactions	86
7.5.4	Drug-Disease Interactions.....	86
7.5.5	Drug-Drug Interactions.....	87
7.6	Additional Safety Evaluations	87
7.6.1	Human Carcinogenicity	87
7.6.2	Human Reproduction and Pregnancy Data.....	87
7.6.3	Pediatrics and Assessment of Effects on Growth	87
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	87
7.7	Additional Submissions / Safety Issues	88

Clinical Review
Shen Xiao, M.D., Ph.D.
NDA 22-545; SN-000
Aliskiren/Amlodipine (Tekamlo™)

8	POSTMARKET EXPERIENCE	90
9	APPENDICES	92
9.1	Literature Review/References	92
9.2	Labeling Recommendations	92
9.3	Advisory Committee Meeting.....	92

Table of Tables

Table 1: SPA100 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg film-coated tablets (Sponsor’s table).....	13
Table 2: Commonly Used Drugs Approved for Treatment of Hypertension (from Draft of Anti-hypertensive Guidance).....	14
Table 3: Summary table of efficacy and safety studies	20
Table 4: Demographics and baseline characteristics in Study SPA2305 (Randomized patients, Sponsor’s table)	34
Table 5: Patient disposition and exposure in Study SPA2305 (Randomized population, Sponsor’s table)	35
Table 6: Statistical analysis of change from baseline in mean sitting diastolic blood pressure at endpoint (Full analysis set, reviewer’s table).....	35
Table 7: Statistical analysis of change from baseline in mean sitting systolic blood pressure at endpoint (Full analysis set, reviewer’s table).....	36
Table 8: Statistical analysis of change from baseline in mean sitting systolic blood and diastolic pressures at endpoint in Study SPA 100A 2304 (Full analysis set, reviewer’s table).....	37
Table 9: Number (%) of blood pressure response at endpoint by treatment group (Full analysis set, reviewer’s table) in pivotal study	40
Table 10: Between treatment comparison for blood pressure control rate at endpoint by treatment group (Full analysis set, reviewer’s table).....	40
Table 11: Between-treatment analysis results for change from baseline in mean 24-hour MADBP and MASBP at Endpoint, Study SPA2305 (Full analysis set, sponsor’s table).....	41
Table 12: Between treatment analysis results for change from baseline in mean daytime and nighttime ambulatory DBP at endpoint (Full analysis set, sponsor’s table)	43
Table 13: Between treatment analysis results for change from baseline in mean daytime and nighttime ambulatory SBP at endpoint (Full analysis set, Sponsor’s table).	44
Table 14: Summary statistics for change from baseline in geometric mean of PRC and PRA at Endpoint (Sponsor’s table)	45
Table 15: Change from baseline to Endpoint in msDBP and msSBP by age group (full analysis set, sponsor’s table)	46
Table 16: BP control rates (%) at Endpoint by age group (full analysis set, sponsor’s table).....	47
Table 17: Change from baseline to Endpoint in msDBP and msSBP by race of Caucasian and Black (full set analysis, Sponsor’s table)	47
Table 18: Pairwise comparison of changes from baseline to Endpoint in msDBP, msSBP and BP control rate by race of Caucasian and Black (full set analysis, reviewer’s table).....	48
Table 19: Comparison of change from baseline to endpoint in 24-hour ABPM by race of Caucasian and Black (reviewer’s table)	48

Table 20: Comparison of changes from baseline to Endpoint in msDBP, msSBP and BP control rate in African Americans (Study SPA 100A US01, full set analysis, reviewer’s table).....	49
Table 21: Change from baseline to Endpoint in msDBP and msSBP by gender in the pivotal study (full set analysis, Sponsor’s table).....	50
Table 22: Pairwise comparison of change from baseline to Endpoint in msDBP, msSBP and BP control rate by gender in the pivotal study(full set analysis, reviewer’s table).....	50
Table 23: Change from baseline to Endpoint in 24-hour ABPM by gender in the pivotal study (Reviewer’s table).....	51
Table 24: Comparison of change from baseline to Endpoint in msDBP and msSBP by gender in Study SPA 2304 (full set analysis, reviewer’s table)	51
Table 25: Change from baseline to Endpoint in msDBP and msSBP by BMI status (full set analysis, Sponsor’s table).	52
Table 26: Blood pressure control rate by BMI status (full set analysis, Sponsor’s table)	52
Table 27: Percentage of patients with aggressive BP control (less than 130/80 mmHg) at Endpoint by treatment group and baseline renal function and diabetes status (full set analysis; with BP not controlled at baseline – Sponsor’s table)	53
Table 28: Pairwise comparison of change from baseline to Endpoint in msDBP, msSBP and BP control rate in patients with Stage 2 hypertension (Full analysis, reviewer’s table).....	54
Table 29: Comparison of change from baseline to Endpoint in msDBP, msSBP, and BP control rate in patients with moderate and severe hypertension in Study SPA 2306 (Reviewer’s table)	54
Table 30: Comparison of dose-response effect after placebo subtraction (Reviewer’s table).....	55
Table 31: Change from baseline in msDBP and msSBP by treatment group in Study SPA 2303 and Study SPA 2304. (Reviewer’s table).....	55
Table 32: Patient’s exposure in Study SPA 2301 (Sponsor’s table).....	59
Table 33: Effect of combination of aliskiren and amlodipine on change of msDBP and msSBP from baseline and BP control rates at selected weeks in Study 2301 (Treated population, Reviewer’s table)	60
Table 34: Summary of clinical trials for safety evaluation in original NDA submission (reviewer’s table).....	62
Table 35: Safety data presented in the 120 day safety update (Reviewer’s table).....	62
Table 36: Clinical pharmacology and biopharmaceutical trials (Sponsor’s table).....	63
Table 37: Doses and duration of exposure to study drug after randomization in all studies (Sponsor’s table)	64
Table 38: Demographics by treatment group (randomized set), Group A, Study SPA2305: short-term, double-blind, placebo-controlled study (Sponsor’s table)	65
Table 39: Demographics by treatment group (randomized set), Group B: short-term, double blind, all controlled studies (Sponsor’s table).	66

Table 40: Demographics by treatment group (safety set), Group C: long-term, open-label study (sponsor’s table)	66
Table 41: Demographics by treatment group (randomized set), Group D: long-term, double-blind studies (Sponsor’s table)	67
Table 42: Patient participation and withdrawals, Group A, Study SPA2305: short-term, double-blind, placebo-controlled study (Sponsor’s table).....	68
Table 43: Patient participation and withdrawals, Group B: short-term, double blind, all controlled studies (Sponsor’s table)	68
Table 44: Patient participation and withdrawals, Group C: long-term, open-label Study (Sponsor’s table).....	68
Table 45: Patient participation and withdrawals, Group D: long-term study of aliskiren vs HCTZ with the open label option of amlodipine (Sponsor’s table)	68
Table 46: Brief summary of SAE in Group A (Reviewer’s table)	71
Table 47: Brief summary of SAE in Studies SPA 2303, 2304 and SPP 2305 (Reviewer’s table).....	72
Table 48: Brief summary of SAE in group C, long-term open label study (Reviewer’s table).....	72
Table 49: Summary of adverse leading study discontinuation in Group A (Reviewer’s table).....	74
Table 50: Summary of adverse leading study discontinuation in Group B (Reviewer’s table).....	74
Table 51: Summary of adverse leading study discontinuation in Group C (Reviewer’s table).....	75
Table 52: Summary of adverse leading study discontinuation in Group D (Reviewer’s table).....	75
Table 53: Number (%) of patients with most frequent AEs (at least 2% for any treatment group) in Group A, the pivotal study SPA2305 (Reviewer’s table).....	77
Table 54: Number (%) of patients with most frequent AEs in short-term, double-blind, all controlled studies (reviewer’s table).....	77
Table 55: Number (%) of patients with most frequent AEs long-term, open-label study (Reviewer’s table)	78
Table 56: Number (%) of patients with most frequent AEs (at least 2% for any treatment group) in Group D: long-term, double-blind studies (sponsor’s table).....	79
Table 57: Criteria for notable laboratory values.....	80
Table 58: Change from baseline at endpoint for hemoglobin (g/L) in Group A: short-term, double-blind, placebo controlled studies (sponsor’s table)	81
Table 59: Change from baseline at endpoint for hemoglobin (g/L) in Group B: all of short-term, controlled studies (sponsor’s table)	81
Table 60: Change from baseline at endpoint for hemoglobin (g/L) in Group C: an long-term open label study (Sponsor’s table).....	81
Table 61: Change from baseline at endpoint for hemoglobin (g/L) in Group D: long-term, double-blind studies (Sponsor’s table).....	82
Table 62: Summary of potassium, BUN, and creatinine by specified criteria in all short-term studies (Reviewer’s table).....	82

Table 63: Summary of potassium, BUN, and creatinine in long-term, open-label study (Sponsor's table).....	83
Table 64: Incidence of orthostatic blood pressure change, Group A, Study SPA2305: short-term, double-blind, placebo-controlled study (Sponsor's table)	84
Table 65: Incidence of orthostatic blood pressure change, Group B: short-term, double-blind, all controlled studies (Sponsor's table).....	84
Table 66: Incidence of orthostatic blood pressure change, Group C: long-term, open-label study (Sponsor's table).....	85
Table 67: Incidence of orthostatic blood pressure change, Group D: long-term, double-blind studies (Sponsor's table).....	85
Table 68: Comparison of incidence rate (%) of peripheral edema between genders in pivotal study (group A) and all of short-term studies (group B) (Reviewer's table).....	86
Table 69: Completed trials which contributed safety data (sponsor's table).....	88
Table 70: Summary of patients in pooled treatment groups by study (Short-term double-blind, all controlled studies, Sponsor's table)	89
Table 71: Post-marketing adverse events in the original NDA submission (sponsor's table).....	91
Table 72: Spontaneously reported adverse events with concurrent administration of aliskiren and amlodipine (Sponsor's table)	92

Table of Figures

Figure 1: Study design, Study SPA2305	33
Figure 2: Change from baseline in msDBP by week for aliskiren/amlodipine 300/10 mg vs. component monotherapies and placebo (full analysis set, sponsor's figure)	38
Figure 3: Change from baseline in msSBP by week for aliskiren/amlodipine 300/10 mg vs. component monotherapies and placebo (full analysis set, sponsor's figure)	38
Figure 4: Change from baseline in mean ambulatory DBP at endpoint by post-dosing hour for aliskiren/amlodipine 300/10mg vs. component monotherapies and placebo (Full analysis set, Sponsor's figure).....	42
Figure 5: Change from baseline in mean ambulatory SBP at endpoint by postdosing hour for aliskiren/amlodipine 300/10mg vs. component monotherapies and placebo (Full analysis set, sponsor's figure).	42
Figure 6: Dose-response surface analysis for change from baseline in msDBP at Endpoint in pivotal study (sponsor's figure)	55
Figure 7: Dose-response surface analysis for change from baseline in msSBP at Endpoint in pivotal study (sponsor's figure)	56
Figure 8: Predicted probability curves of patients with SBP control (less than 140 mmHg) versus baseline msSBP (Sponsor's figure)	57
Figure 9: Predicted probability curves of patients with DBP control (less than.....	57
Figure 10: Predicted probability curves of patients with aggressive SBP control	58
Figure 11: Predicted probability curves of patients with aggressive DBP control	58

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, I recommend that Tekamlo™, the combination of aliskiren and amlodipine, 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 based on one randomized, double-blind, placebo-controlled pivotal trial, three randomized, double-blind, active-controlled trials, and one long-term open-label trial (one year).

The antihypertensive effect of the aliskiren/amlodipine combination was largely manifested within 1 week, was near maximal at approximately 2 weeks, and was sustained throughout the study (the end of week 8). With respect to reaching BP goal (systolic BP <140 or 130 mmHg and diastolic BP <90 or 80 mmHg), a greater probability of achieving systolic or diastolic goal was seen with combination as compared to monotherapy treatment. Therefore, this combination should also be approved as first-line therapy and should be indicated for the initial treatment of hypertensive patients who are likely to need multiple drugs to achieve their blood pressure goals.

In general, the adverse event profile was similar across the aliskiren/amlodipine combination, component monotherapy and placebo treatment arms. Peripheral edema was the most common adverse event (AE) and was also the major reason for AE-related patient withdrawal. The incidence of peripheral edema seen with aliskiren/amlodipine combination at high dose was similar to amlodipine high dose monotherapy. There were higher percentage rates of peripheral edema in females than in males in both the combination and amlodipine at high dose groups. As in the short-term studies, peripheral edema was also reported for a greater percentage of female patients than male patients in the long-term open label study.

Other than peripheral edema, no dose-dependent AEs were observed in the combination studies. Hypotension was uncommon. Other common adverse events identified in aliskiren or amlodipine monotherapy, including dizziness, headache, cough, and diarrhea, occurred at a similar incidence in the combination, placebo and monotherapy treatment arms in the short-term studies. In the long-term open label study, there were no additional safety findings compared to the short-term studies.

There were no significant changes in laboratory parameters including hemoglobin, hematocrit, serum levels of potassium, BUN, creatinine, and lipids in the combination groups compared to the monotherapy groups. The incidence of hyperkalemia (defined as a serum potassium level >5.5 mmol/L at any post baseline visit) during aliskiren/amlodipine combination treatment was similar to that seen with aliskiren monotherapy. No patient was withdrawn due to a change in a laboratory parameter in the combination or monotherapy groups. Overall, the AE profile is considered to be acceptable for an antihypertensive therapy.

1.2 Risk Benefit Assessment

In the whole study program, the adverse event profile overall was generally similar for aliskiren/amlodipine combination therapy and for each component monotherapy. As observed with amlodipine monotherapy, peripheral edema is also commonly seen with the combination; it was the most common adverse event observed in the development program and it was also the major reason for AE-related patient withdrawals. There does not appear to be any unexpected adverse events in this combination compared to each monotherapy. Based on review of the submitted clinical studies and the post-marketing data available for aliskiren and amlodipine, this combination appears to have a favorable risk-benefit profile considering the long-term outcome of anti-hypertension therapy.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The sponsor provided a risk management plan for the aliskiren/amlodipine fixed combination. This plan will be the same as that planned for aliskiren monotherapy and will focus on risks including hyperkalemia, diarrhea, rash, angioedema, decreases in hemoglobin and hematocrit, hypotension, renal dysfunction, cough, 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 as shown in the aliskiren monotherapy.

The risk minimization activities for fixed combination aliskiren/amlodipine at the dose range (150 mg/5 mg, 300 mg/5 mg, 150/10mg, and 300/10mg) 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 amlodipine.

I think this plan is acceptable and don't have any recommendations for post-marketing REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

I don't have any recommendations for post market requirements and commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Tekamlo™ is aliskiren-amlodipine fixed combination tablets for the treatment of hypertension. Aliskiren is a direct renin inhibitor (DRI). It has been approved for the treatment of hypertension alone or in combination with other antihypertensive agents. Aliskiren acts by inhibiting the

renin-angiotensin-aldosterone system (RAAS) at the initial rate-limiting step, the conversion of angiotensinogen to angiotensin I (Ang I). Ang I is subsequently converted to angiotensin II (Ang II) which by interacting with its receptor exerts its effect in the pathogenesis of hypertension. Amlodipine is a long-acting dihydropyridine calcium channel blocker (CCB). It has demonstrated clinical efficacy in a wide range of the hypertensive patient populations by reducing BP. Amlodipine acts on vascular smooth muscle cells causing a reduction in peripheral vascular resistance and thus reduces BP. The combination of the DRI aliskiren and the CCB amlodipine are expected to produce stronger blood pressure lowering through the complementary mechanisms of action than the single agents while maintaining a good safety profile.

Tekamlo™ is film-coated tablets in immediate release solid dosage forms for oral administration containing fixed combinations of the drug substances aliskiren hemifumarate (SPP100) and amlodipine besylate. The four different strength tablets are described in the following table 1.

Table 1: SPA100 150/5 mg, 150/10 mg, 300/5 mg and 300/10 mg film-coated tablets (Sponsor's table)

Dosage form	Strength	Novartis reference number ¹
Light yellow, ovaloid convex shaped, film-coated tablet with a beveled edge with debossing "T2" on one side and "NVR" on the reverse side of the tablet Dimensions: Approx. 16 x 6.3 mm	150 mg aliskiren (SPP100)/ 5 mg amlodipine	6002570
Yellow, ovaloid convex shaped, film-coated tablet with a beveled edge with debossing "T7" on one side and "NVR" on the reverse side of the tablet Dimensions: Approx. 16 x 6.3 mm	150 mg aliskiren (SPP100)/ 10 mg amlodipine	6002571
Dark yellow, ovaloid convex shaped, film-coated tablet with a beveled edge with debossing "T11" on one side and "NVR" on the reverse side of the tablet Dimensions: Approx. 21 x 8.3 mm	300 mg aliskiren (SPP100)/ 5 mg amlodipine	6002572
Brown yellow, ovaloid convex shaped, film-coated tablet with a beveled edge with debossing "T12" on one side and "NVR" on the reverse side of the tablet Dimensions: Approx. 21 x 8.3 mm	300 mg aliskiren (SPP100)/ 10 mg amlodipine	6002296

¹ Novartis internal numbering system

2.2 Tables of Currently Available Treatments for Proposed Indications

A large number of drugs are currently available for reducing blood pressure. The following table 2 provides a list of the commonly used antihypertensive agents.

Regarding the combination product, there are several products of fixed combination available for the treatment of hypertension including ACEIs/CCBs, ACEIs/HCTZ, ARBs/HCTZ, Beta

blockers/HCTZ, Centrally acting drug/HCTZ, aliskiren/HCTZ, aliskiren/valsartan, ARBs/amlodipine, Amlodipine/Valsartan/HCTZ; Amlodipine/Benazepril/HCTZ etc. There is no combination product of aliskiren/CCBs on the market.

Table 2: Commonly Used Drugs Approved for Treatment of Hypertension (from Draft of Anti-hypertensive Guidance)

Pharmacologic Class	Approved Drugs
aldosterone antagonists	eplerenone, spironolactone
alpha adrenergic blockers	doxazosin , phenoxybenzamine, phentolamine, prazosin , terazosin
angiotensin converting enzyme inhibitors	benazepril, captopril , enalapril , fosinopril, lisinopril , moexipril, perindopril, quinapril, ramipril , trandolapril
angiotensin II receptor blockers	candesartan , eprosartan, irbesartan , losartan , olmesartan, telmisartan, valsartan
arteriolar vasodilators	hydralazine, minoxidil
autonomic ganglionic vasodilators	mecamylamine
beta adrenergic blockers	acebutolol , atenolol , betaxolol, bisoprolol, carvedilol , carteolol, esmolol, labetalol, metoprolol , nadolol, penbuterol, pindolol , propranolol , timolol
catecholamine-depleting sympatholytics	deserpidine, reserpine
central alpha-2 adrenergic agonists	clonidine , guanabenz, guanfacine, methyl dopa
calcium channel blockers	diltiazem, verapamil
dihydropyridine calcium channel blockers	amlodipine, felodipine, isradipine, nifedipine, nisoldipine
loop diuretics	bumetanide, ethacrynic acid, furosemide , torsemide
potassium-sparing diuretics	amiloride , triamterene
renin inhibitors	aliskiren
thiazide diuretics	chlorothiazide, hydrochlorothiazide , hydroflumethiazide, methyclothiazide, polythiazide
thiazide-like diuretics	chlorthalidone , indapamide, metolazone

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. Fixed dose combinations of aliskiren and HCTZ (Tekturna HCT[®]), aliskiren and valsartan (Valturna[™]) have been approved for the treatment of hypertension.

Amlodipine is approved for use as either monotherapy or in combination with other antihypertensive agents in once daily doses of 5 and 10 mg. Fixed dose combinations of ACEI or ARB with amlodipine including Benazepril/amlodipine (Lotrel), Azor (Amlodipine/Olmesartan), Twynsta (Amlodipine/Telmisartan) and Valsartan /amlodipine (Exforge®) have been approved for the treatment of hypertension.

2.4 Important Safety Issues with Consideration to Related Drugs

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.

Amlodipine is a long-acting dihydropyridine CCB. The primary dose-dependent adverse event (AE) induced by amlodipine, peripheral pedal edema, results from the increased capillary hydrostatic pressure from pre-capillary vasodilatation.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

At the end-of-phase 2 meeting on September 22, 2006, the Division agreed with the sponsor to conduct the fixed-dose combination study of aliskiren and amlodipine. The Division also suggested that the sponsor should test at least three doses ranges of aliskiren including 75 mg, 150mg, and 300mg. At that time, the aliskiren monotherapy had not been approved yet.

On February 8, 2008, the Division had a meeting with the Sponsor to discuss the pivotal study: Study CSPA100A2305-an 8 week double-blind, multi-center, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with amlodipine in patients with essential hypertension". The Division told the sponsor that primary analyses should be the comparisons of some dose combination or combinations with the highest doses of both monotherapies, and the combination must win on both comparisons. In addition, the Division encouraged the sponsor to use the clinical questionnaire to capture the adverse events relating to edema from spontaneous reporting by the patients in the SPA2305 study. The Division also acknowledged that rates would be higher with directed questioning.

At the pre-NDA meeting on December 17, 2008, the Division agreed that the sponsor proposed that the combination product be used when a patient's blood pressure is not adequately controlled on aliskiren or amlodipine alone, or may be substituted for the titrated components, and may also be used for initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. In addition, the Division will accept the integrated summary of clinical laboratory data in international units.

2.6 Other Relevant Background Information

N/A

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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), NDA 22-107 (Fixed combination therapy of Aliskiren/HCTZ), and NDA 22-217 (Fixed combination therapy of Aliskiren/Valsartan) where some of them have been audited by DSI, I do not think any additional audits are required.

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

3.2 Compliance with Good Clinical Practices

Based on the sponsor's claims, all studies were conducted in full compliance with Good Clinical Practice and in accordance with the ethical principles of the Declaration of Helsinki, informed patient consent and Institutional Review Board approval.

3.3 Financial Disclosures

Eight clinical studies for safety and efficacy were submitted in this NDA. The sponsor provided a detailed list of all the clinical investigators participating in these studies. The sponsor claimed that no clinical investigators were full or part-time employees with the Sponsor. There was one investigator, [REDACTED] ^{(b) (6)} has received > \$25, 000 for Speaker Honoraria. No potential conflicts of interest from other investigators have been identified.

Since only one investigator has the potential conflict of interest, it should not prejudice the results greatly even if there was overt manipulation.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dr. Soldatova suggests this NDA should be approved after the following pending issues solved:

- The drug substance DMF (b) (4) that is referenced for new process for Amlodipine Besylate, is currently inadequate
- Specification limit for sum of potentially (b) (4) in Novartis Test Specification for (b) (4) amlodipine besylate should be added
- Supportive toxicology studies should be provided to qualify specification limits for drug product impurities (b) (4) (aliskiren impurities)
- The shelf-life specification limit of (b) (4) for amlodipine-derived impurity (b) (4) (and limit for sum of the degradation products) should be tightened
- The dissolution specification limits for both, aliskiren and amlodipine, should be revised as suggested by ONDQA biopharm reviewer (Q-value = (b) (4) release of aliskiren and (b) (4) release of amlodipine at 20 minutes). Revision of the Q-time from 30 minutes to 20 minutes might cause a problem if the applicant could not provide dissolution data for drug product batches at 20 minutes
- Expiration date for drug product in different packaging configurations will depend on the resolution of the issue with revision of the dissolution specifications by Novartis

4.2 Clinical Microbiology

The submission does not include microbiology data.

4.3 Preclinical Pharmacology/Toxicology

No preclinical pharmacodynamic or pharmacokinetic studies were performed with the fixed new combination product. Toxicity studies were conducted with aliskiren and amlodipine as free combinations in the rat and included 2-week and 13-week studies. The toxicity studies were accompanied by toxicokinetic monitoring of the drugs components aliskiren and amlodipine. Based on the proposed highest therapeutic dose strengths of 300/10 mg (aliskiren/amlodipine), a ratio of approximately 30:1 was used in the preclinical safety studies. In addition, two genotoxicity assays including Ames and the chromosome aberration assays were performed on impurities.

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.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Aliskiren is a direct renin inhibitor. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Ang I is converted to the active octapeptide angiotensin II (Ang II) by angiotensin-converting enzyme (ACE) and non-ACE pathways. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and

prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Together, these effects increase blood pressure. Therefore, aliskiren will decrease plasma renin activity (PRA), inhibit the conversion of angiotensinogen to Ang I and then reduce the blood pressure.

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The effects of combined treatment of aliskiren and amlodipine arise from the actions of these two agents on different, but complementary mechanisms that regulate blood pressure, calcium channel-mediated vasoconstriction and RAAS-mediated effects on vascular tone and sodium excretion.

4.4.2 Pharmacodynamics

Two biomarkers including PRC and PRA which may represent the pharmacodynamics of aliskiren and amlodipine were evaluated in the clinical studies. PRC was performed in Studies SPA2303, SPA2304 and SPA 2305, while only PRA was evaluated in Study SPP2305. Geometric means (GM) have been applied since the biomarker values are not distributed normally.

PRC increased from baseline in all active treatment groups at Endpoint (change from baseline for placebo was minimal). A greater PRC increase was seen for aliskiren than for amlodipine while the greatest increases were observed in the fixed combination groups. The increase in PRC seen with the aliskiren/amlodipine combination is consistent with the mechanism of action of both aliskiren and amlodipine.

Consistent with the mechanism of action and pharmacodynamic effect of aliskiren, PRA decreased from baseline to Endpoint for treatment groups containing aliskiren, either as monotherapy or in combination with amlodipine. Increase of PRA was seen in the amlodipine monotherapy groups and the placebo group. These results indicate that the combination of aliskiren/amlodipine decreases PRA despite the fact that amlodipine increases PRA.

4.4.3 Pharmacokinetics

No new pharmacokinetic studies were performed with the aliskiren/amlodipine fixed combination for this submission. The drug-drug interactions potential between aliskiren and amlodipine was assessed in healthy subjects, which was conducted with free combination of aliskiren and amlodipine, and included in aliskiren monotherapy submission (NDA 21-985).

Overall, there is no clinically relevant interaction between aliskiren and amlodipine when co-administered, as compared to administration of either drug alone. Please see the clinical pharmacology review for details. Here are the brief summary of the PK data.

Following oral co-administration of aliskiren 300 mg or aliskiren 150 mg with amlodipine 10mg, peak plasma concentrations of aliskiren and amlodipine were reached in 1.5 to 3 hours and in 6 to 8 hours (median values), respectively. The mean apparent terminal elimination half-lives of aliskiren and amlodipine are about 50 to 60 hours and 45 to 50 hours, respectively. The rate and extent of absorption of both aliskiren and amlodipine from the fixed combination tablets are similar to those of aliskiren and amlodipine when administered as free combination based on the bioequivalent study. There was no clinically relevant drug-drug interaction between aliskiren 300 mg and amlodipine 10 mg at steady state. Co-administration of amlodipine increased the AUC and C_{max} of aliskiren by 29% and 18%, respectively; however, the increase in aliskiren exposure was not clinically relevant based on available information on aliskiren pharmacokinetics, and its efficacy and safety. No differences were observed between the pharmacokinetic parameters of amlodipine when dosed alone and in combination with aliskiren. No specific drug-drug interaction studies were conducted with the aliskiren/amlodipine combination and other drugs.

5 Sources of Clinical Data

The primary source of clinical data for this review was the initial NDA submission dated October 29, 2009. In addition, three new clinical studies were submitted as in the 120 days safety update after the first submission dated January 25, 2010.

5.1 Tables of Studies/Clinical Trials

The clinical studies include the biopharmaceutic studies, human pharmacokinetic and pharmacodynamic studies, and the efficacy and safety studies. The following table 3 is the summary of efficacy and safety studies only. Please see the clinical pharmacology review for the bioequivalence, pharmacokinetic and pharmacodynamic studies.

Table 3: Summary table of efficacy and safety studies

Study #	Design	Sites	Drug	Control	Outcome	Other	Review section
SPA100A2305	8-week multifactorial	Multiple sites	Aliskiren, amlodipine	placebo	Efficacy, safety	Pivotal trial	6 and 7
SPA100A2301	54-week open-label	Multiple sites	Aliskiren, amlodipine	None	Efficacy, safety	Major safety	7
SPA100A2303	8-week combo vs aliskiren	Multiple sites	Aliskiren, amlodipine	None	Efficacy, safety	Not in US	5 and 7
SPA100A2304	8-week combo vs amlodipine	Multiple sites	Aliskiren, amlodipine	None	Efficacy, safety	Not in US	5 and 7
SPA100A2306	8-week combo vs amlodipine for moderate to severe hypertension	Multiple sites	Aliskiren, amlodipine	None	Efficacy, safety	Not in US 120-day update	5, 6, and 7
SPA100A US01	8-week combo vs mono for African American	Multiple sites	Aliskiren, amlodipine	None	Efficacy, safety	120-day update	5, 6, and 7
SPP100A2305	6-week combo vs amlodipine	Multiple sites	Aliskiren, amlodipine	placebo	Efficacy, safety		7
SPP100A2323 and E1	52-week aliskiren vs HCTZ with option of amlodipine	Multiple sites	Aliskiren, amlodipine, HCTZ	None	safety		7
SAH 2302	8-week ali/aml/HCTZ vs combos of ali/aml, ali/HCTZ and aml/HCTZ	2379	8weeks	None	Efficacy/safety	120-day update	7

5.2 Review Strategy

I initially reviewed all of the eight trials as shown in table 3. I performed detailed reviews of the pivotal trial (protocol SPA100A 2305) for approval from an efficacy aspect. I have also reviewed the other 5 short-term active-controlled trials including SPA100A 2303, 2304, 2306, SPP2305 and US01 for additional information for the efficacy evaluation.

For an integrated review of safety, I relied primarily upon analyses of all of the trials from table 3. Studies SPA100A2301 is mainly for long-term safety evaluation.

As a 505b(2) combination product, I have also checked the most updated labeling and some previous clinical studies for amlodipine, and the published literatures for both aliskiren and amlodipine regarding the safety assessments.

5.3 Discussion of Individual Studies/Clinical Trials

Nine clinical efficacy and safety studies were submitted as shown above table 3. Among them, 6 studies were submitted in the original submission and three studies (SPA100A 2306, SPA 100A US01) were submitted in the 120-day safety update.

Study SPA100A2305 is the pivotal study for efficacy evaluation. It is an 8-week, double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with amlodipine in patients with essential hypertension. I will discuss this study in details in the Section 6.

Studies SPA100A2303, 2304, 2306, US01 and SPP100A 2305 are 6 to 8 weeks short-term active controlled studies for the claimed indication. The clinical findings were briefly summarized in the below. Some results from these individual studies will be discussed in the Sections 6 and 7 for the integrated reviews of efficacy and safety.

- Study SPA100A2303 was started on October 15, 2008 and completed on May 28, 2009. It is a randomized, eight-week, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren/amlodipine (300/5 mg and 300/10 mg) in comparison with aliskiren 300 mg in patients with essential hypertension not adequately responsive to aliskiren 300 mg monotherapy (msDBP \geq 90 mmHg and $<$ 110 mmHg after 4 weeks of treatment). This study was conducted in European and Asia countries including Estonia, France, Iceland, India, Italy, South Korea, Lithuania, Spain, and Venezuela. 820 patients including 496 males and 324 females at the age between 20-87 years old (average 54.6 years) were randomized in the double blind study. The race distribution included 544 Whites, 1 Black, 221 Asians, and 54 others. Patients with severe hypertension (msDBP \geq 110 mmHg and/or msSBP \geq 180 mmHg), secondary hypertension, uncontrolled diabetes, or previous or current diagnosis of heart failure were excluded. Patients with any history of hypertensive encephalopathy or cerebrovascular accident, or history of transient ischemic attack, myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention within 12 months prior to Screening were excluded as well.

The study design consisted of a 7-day washout period, a 4-week single-blind run-in treatment period in which patients received aliskiren 300 mg, and an 8-week double-blind study drug treatment period in which patients were randomly assigned to 1 of the following 3 treatment arms in a ratio of 1:1:1 aliskiren/amlodipine 300/5 mg, aliskiren/amlodipine 300/10 mg, or aliskiren 300 mg. The efficacy evaluation included changes from baseline to Endpoint in mean sitting diastolic blood pressure (msDBP) and mean sitting systolic blood pressure (msSBP), proportions of patients achieving a BP control target of $<$ 140/90 mmHg, the proportions of patients achieving a response (msDBP $<$ 90 mmHg or a \geq 10 mmHg reduction from baseline and msSBP $<$ 140 mmHg or \geq 20 mmHg reduction from baseline). The safety assessment

included adverse events, serious adverse events, evaluation of edema, hematology, blood chemistry, vital signs, physical examinations. In addition, biomarkers including Plasma renin concentration (PRC) and plasma rennin activity (PRA) were measured in a subset of patients.

Efficacy: Both doses of combination provide a statistically significant reduction in both msDBP and msSBP. The reductions from baseline in msDBP and msSBP were -13.07 mmHg and -10.54 mmHg vs. -5.84 mmHg, and -18.04 mmHg and -14.43 mmHg vs. -6.42 mmHg, in the aliskiren/amlodipine 300/10 mg and 300/5 mg groups compared to the aliskiren 300 mg group, respectively. The greater msDBP and msSBP reductions with aliskiren/amlodipine groups (300/10 mg and 300/5 mg) over the aliskiren 300 mg group were observed as early as 2 weeks after the initiation of treatment and maintained throughout the study. More patients achieved diastolic BP response (83.6% and 77.7% vs. 51.5%, $p < 0.0001$) and BP control (65.5% and 56.6% vs. 31.5%, $p < 0.0001$) in the aliskiren/amlodipine 300/10 mg and 300/5 mg groups than the aliskiren 300 mg group at Endpoint. During aliskiren run-in period, PRA was effectively reduced with aliskiren 300 mg treatment. Aliskiren/amlodipine combinations produced a reduction in PRA at the end of study from prior to the aliskiren run-in (Week -4), which may indicate that aliskiren is able to neutralize the PRA increase caused by amlodipine.

Safety: Overall, the incidences of AEs, SAEs, and AEs leading to study discontinuation were similar with both aliskiren/amlodipine 300/10 mg and 300/5 mg groups compared to the aliskiren 300 mg group with the exception of peripheral edema which was higher in the aliskiren/amlodipine 300/10 mg group. The percentages of patients experiencing any AE during the double-blind treatment period were similar in the aliskiren/amlodipine 300/10 mg (30.1%) and 300/5 mg (29.0%) groups, but slightly greater than the aliskiren 300 mg group (22.7%). Four types of AEs occurred in more than 2% of the patients in any group: peripheral edema, nasopharyngitis, dyslipidemia, and headache. Peripheral edema occurred in notably more patients in the aliskiren/amlodipine 300/10 mg group than in the aliskiren 300 mg group (9.2% and 0.4%, respectively). The aliskiren/amlodipine 300/5 mg group had a relatively lower rate of peripheral edema (2.2%) than the aliskiren/amlodipine 300/10 mg group (9.2%). These findings are consistent with the known effect of amlodipine in causing peripheral edema, especially at dose of 10 mg. Diarrhea occurred in a few patients in all treatment groups (0.4%, aliskiren/amlodipine 300/10 mg; 0.7%, aliskiren/amlodipine 300/5 mg; and 0.4%, aliskiren 300 mg). Hyperkalemia was reported as AEs in 1 patient in each of the aliskiren/amlodipine 300/10 mg and aliskiren 300 mg groups. There were no AEs of hypokalemia, syncope, hypotension, angioedema, or orthostatic hypotension reported. Few patients had serum potassium > 5.5 mmol/L post baseline in all treatment groups (0.4%, 0.7% and 1.5%, respectively, in aliskiren 300 mg, aliskiren/amlodipine 300/5 mg and aliskiren/amlodipine 300/10 mg groups, respectively).

- Study SPA100A2304 was started on October 16, 2008 and completed on June 8, 2009. It is a randomized, eight week double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren/amlodipine (150/10 mg and 300/10 mg) in comparison with amlodipine 10 mg in patients with essential hypertension (msDBP ≥ 90 mmHg and < 110 mmHg) not adequately responsive to amlodipine 10 mg monotherapy. This study was conducted in 100 centers in 7 countries including Argentina (3), Germany (46),

Norway (8), Poland (12), Slovakia (10), Sweden (9), and Turkey (12). There were no sites in the US. 847 patients including 519 males and 328 females at the age between 18-85 years old (average 54.6 years) were randomized into the double blind study. The race distribution included 842 Whites, 2 Asians, and 3 others. Patients with severe hypertension (msDBP \geq 110 mmHg and/or msSBP \geq 180 mmHg), secondary hypertension, uncontrolled diabetes, any history of hypertensive encephalopathy or cerebrovascular accident, or history of transient ischemic attack, myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention, or previous or current diagnosis of heart failure were excluded.

The study design consisted of a 7-day washout period, a 4-week single-blind run in period in which patients received amlodipine 10 mg monotherapy, and an 8-week double-blind study drug treatment period (3 periods and 9 visits) in which patients were randomly assigned to one of the following 3 treatment arms in a ratio of 1:1:1 aliskiren/amlodipine 150/10 mg, aliskiren/amlodipine 300/10 mg, or amlodipine 10mg. The efficacy evaluation included changes from baseline (Visit 5) to endpoint msDBP and msSBP, the proportions of patients achieving a blood pressure control target of msSBP/msDBP < 140/90 mmHg, and the proportions of patients achieving a diastolic blood pressure response (msDBP < 90 mmHg or a \geq 10 mmHg reduction from baseline). Biomarkers including plasma renin concentration (PRC) and plasma renin activity (PRA) in a subset of patients were also measured. Safety assessments included adverse events, serious adverse events, evaluation of edema, hematology, blood chemistry, vital signs, and physical examinations.

Efficacy: The average age was 54.6 years, 18.1% of patients were \geq 65 years; male=61.3%, female=38.7%; Caucasian=99.4%; obese=45.9% (BMI \geq 30 kg/m²); mean duration of hypertension=8.1 years; metabolic syndrome=47.8%. The combination of aliskiren/amlodipine at doses of 300/10 mg and 150/10 mg showed a statistically significant reduction in both msDBP (3.76 and 1.72 mmHg) and msSBP (6.22 and 2.81mmHg) as compared to the amlodipine 10 mg monotherapy in patients who did not show adequate blood pressure response to amlodipine 10 mg monotherapy. There is a clear incremental DBP (-10.99 vs -8.95 mmHg) and SBP (-14.42 vs -10.01 mmHg) reduction was seen with aliskiren/amlodipine 300/10 mg over 150/10 mg. The combination groups showed numerically greater msDBP and msSBP reductions over amlodipine 10 mg monotherapy as early as 2 weeks after the initiation of treatment and maintained it throughout the study duration. More patients achieved blood pressure control in the aliskiren/amlodipine 300/10 mg group as compared to amlodipine 10 mg monotherapy group. The biomarker data indicated that aliskiren reduced PRA when used in combination with amlodipine, even though amlodipine monotherapy increased PRA during the single-blind period and the aliskiren/amlodipine combination increased PRC by up to 502%.

Safety: The AE profile seen was not unexpected for this patient population and the drug classes. The most commonly reported AE, severe AE, study-drug related AE, and AE leading to discontinuation was peripheral edema and was considered to be associated with amlodipine treatment. The incidence of peripheral edema was similar in aliskiren/amlodipine 150/10 mg and amlodipine 10 mg groups while it was lower in aliskiren/amlodipine 300/10 mg group. Hypotension and related events were uncommon (in <2% patients) with the aliskiren/amlodipine treatment. Diarrhea, an AE that had been associated with high doses of

aliskiren (>300 mg/day) in previous studies, was uncommon (in <2% patients) with aliskiren/amlodipine treatment in this study. The number of patients meeting pre-specified high potassium level of >5.5 mmol/L in aliskiren/amlodipine combination groups was fewer than or similar to amlodipine monotherapy group.

- Study SPA100A 2306 was started on January 21, 2009 and completed on September 9, 2009, and was submitted in the 120-day safety update after the original submission. It is an 8-week, double-blind, randomized, parallel group, multi-center study to evaluate the efficacy and safety of the combination of aliskiren 300 mg and amlodipine 10 mg compared to amlodipine 10 mg in patients with moderate to severe hypertension. The study was conducted in a total of 59 centers in 6 countries including Germany- 22 centers; Russia- 14 centers; Spain- 9 centers; Philippines- 8 centers; Romania- 4 centers; and Singapore-2 centers. There were no sites in the US. A total of 484 patients (208 males and 276 females) at the age ≥ 18 years old (average 57 years old) were randomized and entered the double-blind treatment phase (242 to aliskiren /amlodipine combination therapy and 242 to amlodipine monotherapy). The study was composed of two periods: 1 to 4 weeks of wash-out, and 8 weeks double-blind treatment comprising 1 week of titration and 7 weeks of fixed treatment. At Visit 2, all patients who fulfilled the study entry criteria were randomized to receive the initial one week treatment with aliskiren /amlodipine 150/5 mg or amlodipine 5 mg. At Visit 3, patients treated with aliskiren /amlodipine 150/5 mg were force titrated to aliskiren /amlodipine 300/10 mg for 7 weeks and patients treated with amlodipine 5 mg were force titrated to amlodipine 10 mg for 7 weeks. The maximum duration of the study, including the maximum wash-out period, was 12 weeks. Patients with a diagnosis of moderate to severe hypertension, defined as msSBP ≥ 160 mmHg and < 200 mmHg at Visit 2. At any time during the study, patients with a msSBP ≥ 200 mmHg and/or a msDBP ≥ 120 mmHg were to be discontinued. Patients were required to taper off their previous antihypertensive medication, meet the above criteria and also completely discontinued all antihypertensive treatment prior to entering the treatment phase of the study. The efficacy evaluation included the comparison of the combination of aliskiren/amlodipine 300/10 mg versus amlodipine 10 mg monotherapy for the reduction of msSBP and msDBP from baseline, the proportion of patients achieving blood pressure control (msSBP < 140 mmHg and msDBP < 90 mmHg), , the proportion of patients achieving the systolic blood pressure response (msSBP < 140 mmHg or a reduction ≥ 20 mmHg from the baseline), and the proportion of patients achieving the diastolic blood pressure response (msDBP < 90 mmHg or a reduction ≥ 10 mmHg from the baseline), in both study arms, after 8 weeks of treatment. Biomarkers related to hypertension, hypertension-related renal dysfunction, or atherosclerosis including plasma renin activity (PRA), plasma renin concentration (PRC) and serum asymmetrical dimethylarginine (ADMA) were also measured. The safety assessment included adverse events, serious adverse events, evaluation of edema, hematology, blood chemistry, vital signs, and physical examinations.

Efficacy: The combination of aliskiren/amlodipine 300/10 mg has shown a statistically significantly greater ($p < 0.0001$) reduction in both msSBP and msDBP compared to amlodipine 10 mg monotherapy (37.72 vs 30.63 mmHg and 16.10 vs 12.27 mmHg). Significantly more patients in the aliskiren/amlodipine 300/10 mg combination group achieved BP control than in the amlodipine 10 mg monotherapy group (67% vs. 49%; $p = 0.0001$). The aliskiren/amlodipine

300/10 mg group also produced a significantly greater SBP response rate (89% vs. 79%; $p=0.0016$) and DBP response rate (93% vs. 87%; $p=0.0415$) at than the amlodipine 10 mg group. In patients with severe hypertension (baseline msSBP ≥ 180 mmHg) who were more difficult to treat, aliskiren/amlodipine 300/10 mg combination produced highly clinically significant msSBP/msDBP reductions of 47.45/18.57 mmHg, which are statistically significantly greater than amlodipine 10 mg monotherapy (37.36/14.02 mmHg). Furthermore, aliskiren/amlodipine 300/10 mg combination enabled over half (55.6%) of patients with severe hypertension to achieve BP control, which was greater than amlodipine 10 mg monotherapy (34.0%) ($p=0.0489$). Plasma renin activity (PRA) was reduced by the combination of aliskiren/amlodipine (a 61.4% decrease in the analysis of geometric mean) and increased in the amlodipine monotherapy group (a 79.6% increase in the analysis of geometric mean). In using the analysis of geometric mean, ADMA ($\mu\text{mol/L}$) was essentially unchanged in both groups (increased 0.7% in the aliskiren/amlodipine group and 1.6% in the amlodipine group).

Safety: The safety profile of the combination of aliskiren/amlodipine 300/10 mg was similar to amlodipine 10 mg monotherapy. The AE and laboratory findings are consistent with the known safety profile of the two component drugs when used alone or in combination. The overall incidence of adverse events was similar for the two treatment groups (48.6% and 48.1% in aliskiren/amlodipine group and amlodipine group, respectively). The most frequently reported AE in the study was peripheral edema which is a known side effect of amlodipine, and was reported for fewer patients in the aliskiren/amlodipine combination group than for the amlodipine monotherapy group (14.4% vs. 18.3%). No hypotension AEs were reported during the study. Dizziness was reported as an AE for comparable numbers of patients in both treatment arms (4.1% and 3.7%, respectively) and none of the episodes was severe. In both aliskiren/amlodipine combination and amlodipine monotherapy groups, the majority of reported AEs were mild (33.7% and 29.0%, respectively) or moderate in severity (12.3% and 16.2%, respectively). Severe AEs were reported for 2.5% and 2.9% of patients, respectively. There were no deaths during the study. No SAEs occurred in aliskiren/amlodipine 300/10 mg combination group, while 3 (1.2%) patients in the amlodipine monotherapy group experienced SAEs, which all led to discontinuation of study medication. Fewer patients discontinued study drug due to AEs in the aliskiren/amlodipine combination group (2.9%) than in the amlodipine monotherapy group (6.6%). Peripheral edema led to discontinuation in fewer patients in the aliskiren/amlodipine combination group (4 patients, 1.6%) than in the amlodipine group (9 patients, 3.7%). No patient discontinued for dizziness or diarrhea. The main notable laboratory finding was the percentage of patients with serum potassium <3.5 mmol/L, which was reported for few patients and at a slightly lower frequency in the aliskiren/amlodipine combination group (2.2%) than in the amlodipine monotherapy group (3.0%). No patient in the aliskiren/amlodipine group had serum potassium >5.5 mmol/L.

- Study SPA100A US01 is specifically designed for African American. This study was submitted in the 120-day safety update after the original submission. It was started on February 24, 2009 and completed on August 10, 2009. It is an 8-week Multicenter, Randomized, Double-blind, Active Control, Parallel Group Study to Evaluate the Efficacy and Safety of Aliskiren Administered in Combination with Amlodipine (150/5, 300/10 mg) versus Amlodipine alone (5, 10 mg) in African American patients with Stage 2 Hypertension. The

study was conducted in 75 centers in the United States. A total of 443 patients including 205 males and 238 females at age ≥ 18 years old (average 53 years old) were randomly assigned to 1 of the 2 treatment regimens: 220 patients to the aliskiren/amlodipine combination and 223 patients to the amlodipine regimen. A total of 147 patients were randomized to the ABPM substudy (76 patients to the aliskiren/amlodipine group and 71 patients in the amlodipine group). The study comprised 2 periods and a maximum of 8 visits. Period 1 began with a 1 to 4 week washout. Qualified patients were then randomized into Period 2 in a 1:1 ratio to 1 of the 2 treatment groups, to receive double-blind treatment with the combination of aliskiren and amlodipine 150/5 mg or amlodipine 5mg monotherapy. After 1 week of treatment, at Visit 6 (Day 7), all patients were force-titrated to elevated doses of their respective treatments to aliskiren and amlodipine 300/10 mg or amlodipine 10 mg for an additional 7 weeks of treatment. The stage 2 hypertension, defined as msSBP ≥ 160 mmHg and < 200 mmHg at Visit 5 (randomization). The efficacy evaluations included change from baseline in msSBP and msDBP, the proportion of patients achieving blood pressure control ($<140/90$ mmHg), the proportion of responders as determined by a msSBP <140 mmHg or a ≥ 20 mmHg decrease), and the proportion of patients with peripheral edema. Additionally, the plasma, serum, urine biomarker measurements were obtained in all patients at Visits 5 (Day 0) and Visit 8 (Day 56): plasma renin activity (PRA) and plasma renin concentration (PRC). Measurements of urinary albumin creatinine ratio (UACR), urinary aldosterone and urinary albumin excretion rate (UAER) were obtained for a subset of patients. Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), the regular monitoring of hematology, blood chemistry, and urine values, regular measurement of vital signs, and the performance of physical examinations.

Efficacy: The LS mean changes from the baseline for the aliskiren/amlodipine and amlodipine groups were -34.1 vs -28.9 mmHg for msSBP and -14.3 vs -10.5 mmHg for msDBP at the end of study, respectively. The combination of aliskiren/amlodipine was proven to be better to amlodipine alone ($p < 0.001$). The cumulative percentage of patients achieving BP control (msSBP/msDBP $< 140/90$ mmHg) was greater in the aliskiren/amlodipine group than the amlodipine group at Week 4 (57.7% and 45.3%, $p=0.008$) and Week 8 (71.4% and 57.4%, $p=0.002$). The cumulative percentage of responders as determined by msSBP < 140 mmHg or a ≥ 20 mmHg decrease from baseline was greater in the aliskiren/amlodipine group than in the amlodipine group at Week 4 (86.4% and 78.0%, $p=0.022$) and Week 8 (92.3% and 86.5%, $p=0.049$).

In the exploratory efficacy analysis, there was a statistically significant difference in favor of the combination group for the mean ambulatory diastolic blood pressure (MADBP, -2.9 mmHg, $p=0.032$) but no difference for the mean ambulatory systolic blood pressure (MASBP, -3.7 mmHg, $p=0.086$). There was no statistically significant between two groups for the mean ambulatory pulse pressure (MAPP). There was no statistically significant between the two groups for the mean hourly ambulatory SBP during the last 6 hours of the dosing period. However, the mean hourly ambulatory DBP during the last 6 hours of the dosing period was statistically significant between the two groups (-11.2 mmHg vs -6.7 mmHg, $p=0.018$). There was no difference between two groups for the mean daytime ambulatory BP. For the mean

nocturnal ambulatory DBP, however, there was a statistically significant difference in favor of the combination group than the monotherapy (-3.9 mmHg, $p=0.015$) but not for the SBP. In the arterial compliance measures, there were statistically significant differences in favor of the combination group for the mean central SBP, DBP, and central mean pressure. There were no statistically significant difference between two groups for the Central Augmentation Index, Normalized Augmentation Index, and central pulse pressure.

In the biomarker analysis, there was no statistically significant difference between two groups for UAER and urinary aldosterone from baseline. There was a 61.7% reduction and 50% increase in PRA from baseline in the aliskiren/amlodipine and amlodipine groups, and a 495.4% increase and 34.8% increase in PRC from baseline in the aliskiren/amlodipine and amlodipine groups, respectively; the difference between the treatment groups at Week 8 was statistically significant.

In the subgroup analysis, in patients < 55 years, < 65 years, and < 75 years, differences between treatment groups were statistically significant in favor of aliskiren/amlodipine at Week 8 for the change from baseline in msSBP and msDBP. Additionally, in patients ≥ 55 years, differences between treatment groups were statistically significant in favor of aliskiren/amlodipine at Week 8 for the change from baseline in msDBP. Subgroup analysis by gender showed that differences between treatment groups were statistically significant for both genders in favor of aliskiren/amlodipine at Week 8. Differences between treatment groups were statistically significant favoring aliskiren/amlodipine at Week 8 for msSBP and msDBP in patients with $PRA \leq 0.65$ ng/mL/hr at baseline and in patients with $PRA > 0.65$ ng/mL/hr at baseline. Reductions in PRA were similar among baseline PRA subgroups.

Safety: The AEs observed during the study were expected for this population and this class of drug and gave no indication of target organ toxicity. No patient died during the study. Two SAEs reported: 1 patient in the aliskiren/amlodipine group had severe unstable angina which resulted in the patient's discontinuation from the study and 1 patient in amlodipine group had pneumonia and did not result in the discontinuation. The AEs experienced by at least 2% of patients in the aliskiren/amlodipine group were peripheral edema, headache, fatigue, and nausea. The only AE experienced by at least 5% of patients in each treatment group was peripheral edema. Of the AEs suspected to be treatment related, most occurred in less than 2% of patients in either treatment group, except for peripheral edema, which occurred in 10 patients (4.5%) in the aliskiren/amlodipine group and 12 patients (5.4%) in the amlodipine group. The only suspected treatment-related AEs experienced by at least 1% of patients in either treatment group were fatigue, muscle spasms, joint swelling, headache, and dizziness. Adverse events that resulted in discontinuation from the study were experienced by 8 patients (3.6%) in the aliskiren/amlodipine group and 3 patients (1.3%) in the amlodipine group. Three patients (2 patients in the aliskiren/amlodipine group and 1 patient in the amlodipine group) experienced peripheral edema leading to discontinuation from the study. One patient in the aliskiren/amlodipine group and 1 patient in the amlodipine group discontinued due to a blood pressure increase. The causes of discontinuation in other 5 cases in the aliskiren/amlodipine

group including vertigo, rash, hypotension, unstable angina and chest pain. The changes from baseline in clinical laboratory tests were generally small and similar in each treatment group.

- Study SPP100A 2305 is a six-week, randomized, double-blind, parallel-group, multicenter study to evaluate the safety and efficacy of the combination of aliskiren 150 mg and amlodipine 5 mg compared to amlodipine 5 mg and 10 mg in hypertensive patients not adequately responsive to amlodipine 5 mg. This study has been reviewed by Dr. Thomas Marciniak in NDA 21-985 for aliskiren monotherapy. The conclusion is that “Aliskiren 150 mg appears to add to amlodipine 5 mg but it is not clear whether the effect of aliskiren 150/amlodipine 5 mg is greater than that of amlodipine 10 mg. The combination of aliskiren 150/amlodipine 5 mg appears to be slightly better tolerated than amlodipine 10 mg monotherapy”. Please his original review for details.

There are two long-term studies within this submission including Study SPA100A2301 and Study SPP100A2323 and 2323E1. Study SPPA100A 2301 is a 54-week, open-label, multicenter study to assess the long-term safety and tolerability of the combination of aliskiren 300mg/amlodipine 10 mg in patients with essential hypertension. I will discuss the results of this study in details in section 7. The following is a brief summary of this study regarding the study design and the summary of the efficacy and safety.

- Study SPA 100A 2301 is A 54-week, open-label, multicenter study to assess the long-term safety and tolerability of the combination of aliskiren 300 mg/ amlodipine 10 mg in patients with essential hypertension. An optional addition of HCTZ (12.5 mg with increase to 25 mg) was allowed if the patient’s blood pressure was not adequately controlled. The study was started on November 10, 2006 and completed on March 8, 2008. A total of 89 centers in eight countries including Belgium (9 centers); Switzerland (4 centers); Germany (17 centers); Denmark (8 centers); Finland (9 centers); India (3 centers); Iceland (1 enter); and USA (38 centers) enrolled patients in the study. A total of 556 patients with msDBP \geq 90 mmHg and $<$ 110 mmHg were enrolled in this study. The study was comprised of a 1-4 week washout phase, and a 54-week treatment phase. All patients received aliskiren 150 mg and amlodipine 5 mg for the first two weeks; dose was then force-titrated to aliskiren 300/amlodipine 10 mg for 52 weeks duration. On or after Day 72 (Week10; after 8 weeks of treatment with aliskiren 300 mg/amlodipine 10 mg), patients whose msSBP was \geq 140 and/ or msDBP \geq 90 mmHg for two consecutive visits may have had hydrochlorothiazide (HCTZ) 12.5 mg added. If the patient’s msSBP remained \geq 140 and/ or msDBP remained \geq 90 mmHg after adding HCTZ 12.5mg, the dose of HCTZ could be increased to 25 mg. Efficacy was a secondary objective. Efficacy variables included changes from baseline to endpoint in msDBP and 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 \geq 10 mmHg reduction from baseline). Biomarkers including hsCRP, plasma aldosterone and plasma renin activity (PRA), were determined in only those patients participating in the biomarker subset of the study. Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry, regular measurement of vital signs and the performance of physical examinations.

Efficacy and safety data are discussed in Section 6 and 7.

- Study SPP100A 2323 and 2323 E1 is a twenty six-week, randomized double-blind, parallel group, multicenter, active controlled, dose titration study to evaluate the efficacy and safety of aliskiren compared to HCTZ with the optional addition of open-label amlodipine, followed by a second twenty six weeks of blinded treatment in patients with essential hypertension. This study was completed on July 27, 2006 and has been reviewed by Dr. Thomas Marciniak in NDA 21-985. Since this study is mainly for the comparison of aliskiren to HCTZ, I do not provide the summary of the efficacy. Some safety data are discussed in the section 7.
- Study SAH 2302 is an active control study to compare the triple combination of aliskiren, amlodipine and HCTZ to the double combinations of aliskiren/amlodipine, aliskiren/HCTZ and amlodipine/HCTZ. The safety data from this study was provided in the 120-day safety update. Other data sets were not provided. Please see Section 7.7 for the safety summary.

6 Review of Efficacy

Efficacy Summary: Study SPA100A2305 is the pivotal study for the efficacy evaluation. It is an 8-week, double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy of aliskiren administered alone and in combination with amlodipine in patients with essential hypertension. Other studies including studies SPA100A2303, 2304, 2306, US01 and SPP100A2305 are 6- to 8-week short-term active controlled studies to support the claimed indication. In addition, study SPA 100A2301 is a 54-week safety study that evaluated long-term efficacy (change in BP relative to baseline) as a secondary objective.

Based on the data from the pivotal study and other supportive studies, the combination of aliskiren/amlodipine produced clinically meaningful and statistically greater reductions in msDBP (primary endpoint) compared to placebo and each respective monotherapy at the studied doses (150/5 mg, 150/10 mg, 300/5 mg, and 300/10 mg). In the pivotal study, the difference in msDBP between the combination 300/10 mg and its component monotherapies was 6.3 mmHg for aliskiren 300 mg, and 2.7 mmHg for amlodipine 10 mg, respectively. For msSBP, however, the pairwise comparisons of aliskiren/amlodipine 150/10 mg vs. amlodipine 10 mg and aliskiren/amlodipine 300/10 mg doses vs. amlodipine 10 mg have not reached statistically significant difference ($p=0.056$ and 0.143 , respectively). In Study SPA 100A 2304, a study designed to specifically evaluate the effect of the combination of aliskiren/amlodipine at doses of 150/10 mg and 300/10 mg in comparison with amlodipine 10 mg in patients with essential hypertension, the aliskiren/amlodipine combinations demonstrated statistically significantly greater reductions in both msSBP and msDBP compared to amlodipine 10mg. The difference between the combination 300/10 mg and amlodipine 10 mg alone was 3.8 mmHg for msDBP and 6.2 mmHg for SBP.

Both individual monotherapy components contributed to the antihypertensive effect of the fixed combination of aliskiren/amlodipine in the overall population. In general, the difference in the antihypertensive effect of the combination vs. aliskiren monotherapy was larger than the difference between the combination and amlodipine monotherapy. The antihypertensive effect was greater for the higher dose combinations. Regarding the duration, the antihypertensive effect of the aliskiren/amlodipine combination was largely manifested within 1 week, was near maximal at approximately 2 weeks, and was sustained throughout the study (the end of week 8). In general, the aliskiren/amlodipine fixed combinations produced clinically meaningful and statistically greater BP control (<140/90 mmHg) compared to the respective monotherapies. All fixed combination doses of aliskiren/amlodipine were statistically superior to component monotherapies and placebo in reducing mean 24-hour, daytime, and nighttime MADBP and MASBP. The greater decrease in ambulatory BP for the fixed combination over monotherapies was sustained over the full 24 hours, with no rise of BP in the morning. In the 54-week open label uncontrolled study, reductions in msDBPs and msSBPs were maintained for a treatment period of 1 year. In the biomarker analysis, the combination of aliskiren/amlodipine decreased PRA despite the fact that amlodipine increases PRA.

In the subpopulation analysis, the greater BP-lowering effect of the fixed combination of aliskiren/amlodipine compared to the component monotherapies was observed consistently across demographic subgroups of age and gender and in patients with diabetes mellitus or mild or moderate renal impairment, and in subgroups by severity of hypertension (Stage 1 and Stage 2). In the race analysis, however, the combination of aliskiren/amlodipine at the high dose level of 300/150 mg did not show a better effect than amlodipine in Black people for either msDBP or msSBP. This could be due to the variation of bioavailability of aliskiren and the small number of black patients (about 40 patients in each group) in this study. In study SPA 100A US01, a study designed specifically to test the effect of the combination versus amlodipine monotherapy on hypertension in African Americans, more than 200 African Americans in each group were evaluated. This study did show a better antihypertensive effect in the combination compared to the amlodipine monotherapy treatment arm for msDBP, msSBP, and BP control.

When used as initial therapy without titration from monotherapy, the combination of aliskiren/amlodipine produced significantly greater BP control rates compared to placebo and both aliskiren and amlodipine monotherapy in the overall population. The predicted BP control rates were greater for initial therapy with the fixed combination of aliskiren /amlodipine as compared to aliskiren or amlodipine monotherapy, regardless of baseline BP.

6.1 Indication

The indication for the proposed aliskiren/amlodipine fixed-dose combination tablets (TEKALMO^{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 amlodipine alone (or another dihydropyridine calcium channel blocker) may be switched to combination therapy with aliskiren/amlodipine.

- Replacement Therapy: Aliskiren/amlodipine may be substituted for the titrated components (aliskiren and amlodipine).
- Initial Therapy: Aliskiren/amlodipine 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

As discussed in the Section 5.3, there are total 8 studies to provide efficacy data including six short-term studies (Studies SPA 2303, 2304, 2305, 2306, US01, SPP2305) and two long-term studies (Studies SPA 2301 and SPP2323/2323E1). Study SPA 2305 is the pivotal study which provides the direct comparison of 4 doses of aliskiren/amlodipine to each of the monotherapy components. It also provides dose-response data. In addition, it serves as the basis to support the initial therapy indication, since all patients who were randomized to the aliskiren/amlodipine fixed combination groups received the fixed combination treatment as initial therapy, without titration from monotherapy.

Study SPA2303 provides efficacy data to support the use of aliskiren/amlodipine in patients not adequately responding to aliskiren 300 mg. Study SPA2304 and Study SPP2305 provide efficacy data for the use of aliskiren/amlodipine in patients not adequately responding to amlodipine monotherapy. Study SPA2306 provides efficacy data for the use of aliskiren/amlodipine vs amlodipine in patients with moderate to server hypertension. Study SPAUS01 provides efficacy data for the use of aliskiren/amlodipine vs amlodipine in African American with moderate hypertension. Study SPA2301 provides efficacy data for the long-term use of aliskiren/amlodipine, and Study SPP2323 and its extension, Study SPP2323E1, which allowed optional add-on of amlodipine to an aliskiren-based regimen, provide additional supportive efficacy data for the long-term use of the aliskiren/amlodipine combination.

The overall clinical trial data from the studies were not pooled due to the differences in study design. The efficacy of the aliskiren/amlodipine combination therapy is based upon examination of individual trial data, predominantly from Study SPA2305, with supporting evidence from the other studies. The pivotal study, Study SPA 2305 is discussed in details in the following efficacy analysis. Other studies provide additional supportive efficacy data. Individual studies other than Study SPA 2305 are discussed in Section 5.3 (discussion of individual studies) or Section 7 (discussion of safety).

Study SPA2305 was an 8-week randomized, double-blind, placebo-controlled, multifactorial study, and provides the data in this submission for the dose-response assessment as well as the rationale for the selection of aliskiren/amlodipine fixed combination doses for registration. In addition, this study evaluated the efficacy and safety of the aliskiren/amlodipine fixed combination as initial therapy for the treatment of hypertension.

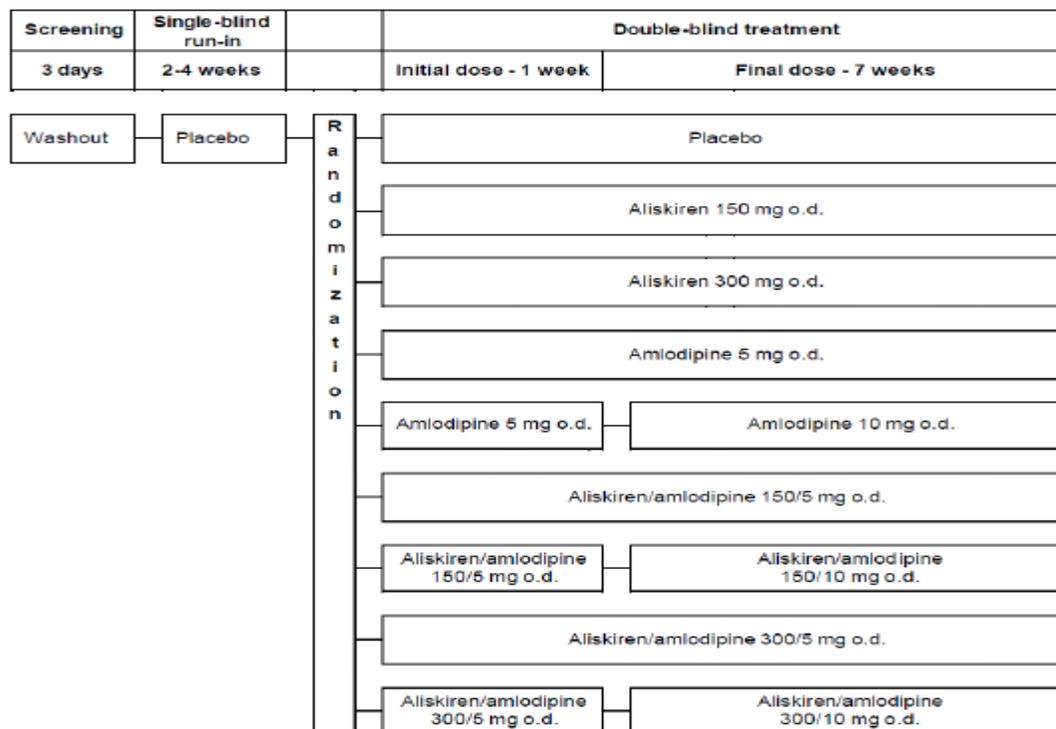
Study SPA2305 was conducted in 208 centers in 18 countries (11 in Argentina, 6 in Australia, 11 in Canada, 10 in Colombia, 14 in Denmark, 13 in Finland, 7 in Greece, 23 in Italy, 5 in Mexico, 2 in Panama, 10 in Peru, 11 in Romania, 12 in Russia, 10 in Spain, 10 in Sweden, 10 in

Taiwan, 26 in the United States, and 17 in South Africa). The first patient enrolled was on 22-Sep-2008 (first patient / first visit) and the last patient completed was on 27-May-2009 (last patient / last visit).

The planned sample size was 1611 randomized patients. A total of 2694 patients were enrolled into the study, 1688 were randomized, and 1539 completed the study. The planned sample size in an ABPM substudy was 1143 randomized patients (127 per arm) and 819 patients participated in the ABPM substudy. The study was comprised of three periods: washout; single-blind placebo run-in; and double-blind treatment. During the double-blind treatment period, eligible patients were randomized to 1 of 9 treatment groups in a ratio of 1:1:1:1:1:1:1:1:1 including aliskiren monotherapy 150 mg or 300 mg; amlodipine monotherapy 5 mg or 10 mg; the fixed combination of aliskiren/amlodipine 150/5 mg, 150/10 mg, 300/5 mg, 300/10 mg; or placebo. For patients randomized to receive amlodipine 10 mg alone or in combination with aliskiren, the initial amlodipine dose was 5 mg for 1 week. The dose was then force-titrated to 10 mg for the rest of the study.

The main inclusion and exclusion criteria included male and female patients with essential hypertension, aged 18 years and older, having msDBP ≥ 90 mmHg and < 110 mmHg at the visit prior to Visit 3. Patients must have had a msDBP ≥ 95 mmHg and < 110 mmHg at Visit 3 and must have had an absolute difference of ≤ 10 mmHg in their msDBP during the last 2 visits of the single-blind run-in period (visit prior to Visit 3 and Visit 3). Patients with severe hypertension (msDBP ≥ 110 mmHg and/or msSBP ≥ 180 mmHg), secondary hypertension, uncontrolled diabetes, any history of hypertensive encephalopathy or cerebrovascular accident, or history of transient ischemic attack, myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention, or previous or current diagnosis of heart failure were excluded. The study duration for each patient, inclusive of all periods, was approximately 10 to 12.5 weeks. The planned duration of treatment in the double-blind treatment period was 8 weeks. The study design was summarized in the following figure 1.

Figure 1: Study design, Study SPA2305



6.1.2 Demographics

In the pivotal study SPA 2305, overall, the number of males and females participating was approximately the same. The majority of patients were of Caucasian race (62.1%) and Black patients accounted for 19.9% of the total. The age-group distribution was similar in the 9 treatment groups. The majority of patients were <65 years of age with a total of 17.2% of the patients ≥ 65 years of age and 2.7% of the patients ≥ 75 years of age. Mean duration of hypertension was approximately 7.8 years in all treatment groups. Mean BMI was approximately 30.3 kg/m² in all groups. Almost half of the patient population (46.0%) was obese (BMI ≥ 30 kg/m²). Almost half (46.0%) of the patients overall suffered from metabolic syndrome with a similar incidence in the 9 treatment groups. Baseline BP values were similar in the 9 treatment groups. At baseline, 1081 (approximately 64%) patients had Stage 2 hypertension ($\geq 160/100$ mmHg). Relevant demographic and disease characteristics are shown in the following table 4.

Table 4: Demographics and baseline characteristics in Study SPA2305 (Randomized patients, Sponsor's table)

Demographic Characteristic Category/statistic	Placebo N=198	Ali 150 mg N=195	Ali 300 mg N=203	Aml 5 mg N=185	Aml 10 mg N=181	Ali/aml 150/5 mg N=181	Ali/aml 150/10 mg N=183	Ali/aml 300/5 mg N=178	Ali/aml 300/10 mg N=184	Total N=1688
Age (yrs)										
N	198	195	203	185	181	181	183	178	184	1688
mean (SD)	53.7(10.32)	54.3(11.07)	54.0(9.99)	54.2(11.61)	55.0(10.34)	53.9(10.82)	53.0(10.59)	54.8(10.29)	54.4(10.86)	54.1(10.65)
Age Group (yrs) n (%)										
<65	164 (82.8)	156 (80.0)	172 (84.7)	145 (78.4)	150 (82.9)	155 (85.6)	157 (85.8)	144 (80.9)	154 (83.7)	1397(82.8)
≥65	34 (17.2)	39 (20.0)	31 (15.3)	40 (21.6)	31 (17.1)	26 (14.4)	26 (14.2)	34 (19.1)	30 (16.3)	291(17.2)
<75	193 (97.5)	191(97.9)	196 (96.6)	178 (96.2)	176 (97.2)	176 (97.2)	181(98.9)	175 (98.3)	177(96.2)	1643(97.3)
≥75	5 (2.5)	4 (2.1)	7 (3.4)	7 (3.8)	5 (2.8)	5 (2.8)	2 (1.1)	3 (1.7)	7 (3.8)	45 (2.7)
Sex n (%)										
Female	108 (54.5)	76 (39.0)	108 (53.2)	86 (46.5)	94 (51.9)	84 (46.4)	96 (52.5)	100 (56.2)	78 (42.4)	830 (49.2)
Male	90 (45.5)	119 (61.0)	95 (46.8)	99 (53.5)	87 (48.1)	97 (53.6)	87 (47.5)	78 (43.8)	106 (57.6)	858 (50.8)
Race n (%)										
Caucasian	119 (60.1)	123 (63.1)	127 (62.6)	121 (65.4)	113 (62.4)	112 (61.9)	108 (59.0)	110 (61.8)	116 (63.0)	1049 (62.1)
Black	39 (19.7)	36 (18.5)	39 (19.2)	36 (19.5)	34 (18.8)	38 (21.0)	41 (22.4)	38 (21.3)	35 (19.0)	336 (19.9)
Asian	14 (7.1)	14 (7.2)	10 (4.9)	10 (5.4)	12 (6.6)	13 (7.2)	13 (7.1)	11 (6.2)	15 (8.2)	112(6.6)
Native American	2 (1.0)	1 (0.5)	3 (1.5)	1 (0.5)	0 (0.0)	1 (0.6)	1 (0.5)	1 (0.6)	1 (0.5)	11 (0.7)
Pacific Islander	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Other	23 (11.6)	20 (10.3)	24 (11.8)	16 (8.6)	22 (12.2)	17 (9.4)	20 (10.9)	18 (10.1)	17 (9.2)	177(10.5)
Ethnicity n (%)										
Hispanic or Latino	35 (17.7)	39 (20.0)	37 (18.2)	32 (17.3)	34 (18.8)	28 (15.5)	33 (18.0)	36 (20.2)	32 (17.4)	306 (18.1)
Chinese	11 (5.6)	11 (5.6)	9 (4.4)	9 (4.9)	11 (6.1)	10 (5.5)	12 (6.6)	10 (5.6)	13 (7.1)	96 (5.7)
Indian (Indian Subcontinent)	1 (0.5)	2 (1.0)	1 (0.5)	1 (0.5)	1 (0.6)	1 (0.6)	1 (0.5)	1 (0.6)	1 (0.5)	10 (0.6)
Japanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Mixed ethnicity	3 (1.5)	0 (0.0)	2 (1.0)	1 (0.5)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.4)
Other	148 (74.7)	143 (73.3)	154 (75.9)	142 (76.8)	135 (74.6)	140 (77.3)	137 (74.9)	131 (73.6)	138 (75.0)	1268 (75.1)
Duration of Hypertension (yrs)										
N	182	176	189	171	170	167	172	165	172	1564
mean (SD)	7.1 (6.75)	7.2 (6.50)	8.2 (7.21)	7.4 (6.60)	8.2 (7.22)	8.9 (7.91)	7.8 (7.23)	7.4 (6.25)	8.0 (8.04)	7.8 (7.10)
Naïve patients, n (%)	16 (8.1)	19 (9.7)	14 (6.9)	14 (7.6)	11 (6.1)	14 (7.7)	11 (6.0)	13 (7.3)	12 (6.5)	124 (7.3)
Body Mass Index (kg/m²)										
N	197	195	203	185	180	181	182	176	184	1683
mean (SD)	30.1 (5.44)	30.4 (5.05)	30.4 (5.22)	30.5 (5.68)	29.9 (5.47)	29.9 (5.03)	30.7 (6.27)	30.0 (5.35)	30.3 (5.26)	30.3 (5.42)
BMI status n (%)										
BMI <20 kg/m ²	2 (1.0)	0 (0.0)	0 (0.0)	2 (1.1)	3 (1.7)	2 (1.1)	1 (0.5)	1 (0.6)	1 (0.5)	12 (0.7)
20 ≤ BMI <25 kg/m ²	28 (14.1)	16 (8.2)	29 (14.3)	25 (13.5)	27 (14.9)	22 (12.2)	26 (14.2)	25 (14.0)	27 (14.7)	225 (13.3)
25 ≤ BMI <30 kg/m ²	74 (37.4)	88 (45.1)	79 (38.9)	72 (38.9)	76 (42.0)	78 (43.1)	69 (37.7)	72 (40.4)	62 (33.7)	670 (39.7)
BMI ≥ 30 kg/m ²	93 (47.0)	91 (46.7)	95 (46.8)	86 (46.5)	74 (40.9)	79 (43.6)	86 (47.0)	78 (43.8)	94 (51.1)	776 (46.0)
Baseline msDBP and msSBP (mmHg)										
N	198	195	203	185	181	181	183	178	184	1688
msDBP Mean (SD)	99.6 (3.91)	99.7 (3.55)	100.1(3.71)	99.7 (3.63)	100.1(4.10)	99.9 (3.60)	99.4 (4.24)	99.6 (3.71)	99.5 (3.78)	99.7 (3.81)
msSBP Mean (SD)	157.2 (12.07)	156.5 (12.54)	158.9 (11.06)	157.2 (10.88)	157.6 (11.85)	158.1 (11.17)	156.5 (11.79)	156.8 (11.38)	157.0 (11.72)	157.3 (11.62)
Metabolic Syndrome n (%)										
Yes	85 (42.9)	95 (48.7)	89 (43.8)	86 (46.5)	79 (43.6)	82 (45.3)	86 (47.0)	88 (49.4)	86 (46.7)	776 (46.0)
No	113 (57.1)	100 (51.3)	113 (55.7)	99 (53.5)	102 (56.4)	99 (54.7)	96 (52.5)	90 (50.6)	98 (53.3)	910 (53.9)
Diabetes- yes- n (%)	15 (7.6)	25(12.8)	24(11.8)	17(9.2)	11(6.1)	21(11.6)	30(16.4)	17(9.6)	25(13.6)	185(11.0)

Reviewer comments: This demographic distribution among the different treated groups overall is reasonable compared to other aliskiren and ACEI/ARB combination studies. .

6.1.3 Subject Disposition

The majority of the patients in Study SPA 2305 in all treatment groups completed the study (91.2%). Disposition was generally similar in all groups. Slightly more patients in the placebo group discontinued from the study prematurely, primarily due to lack of efficacy. Discontinuation due to safety was slightly higher in the amlodipine 10 mg group (4.4%) than the other individual treatment groups (0.5% to 2.2%). The mean exposure was 54.2 days. Data were summarized in the following table 5.

Table 5: Patient disposition and exposure in Study SPA2305 (Randomized population, Sponsor's table)

Treatment Group	Randomized n (%)	Treated n (%)	Completed n (%)	Discontinued n (%)				Mean exposure – Days (SD)
				Total	Safety	Lack of efficacy	Other	
Placebo	198	198 (100)	168 (84.8)	30 (15.2)	4 (2.0)	17 (8.6)	9 (4.5)	52.0 (13.91)
Ali 150 mg	195	194 (99.5)	175 (89.7)	19 (9.7)	4 (2.1)	8 (4.1)	7 (3.6)	53.4 (13.38)
Ali 300 mg	203	203 (100)	184 (90.6)	19 (9.4)	1 (0.5)	8 (3.9)	10 (4.9)	54.3 (11.69)
Mono ali	398	397 (99.7)	359 (90.2)	38 (9.5)	5 (1.3)	16 (4.0)	17 (4.3)	-----
Aml 5mg	185	185 (100)	173 (93.5)	12 (6.5)	2 (1.1)	4 (2.2)	6 (3.2)	55.6 (8.81)
Aml 10mg	181	181 (100)	162 (89.5)	19 (10.5)	8 (4.4)	2 (1.1)	9 (5.0)	54.1 (11.20)
Mono aml	366	366 (100)	335 (91.5)	31 (8.5)	10 (2.7)	6 (1.6)	15 (4.1)	-----
Ali/aml 150/5 mg	181	181 (100)	169 (93.4)	12 (6.6)	3 (1.7)	2 (1.1)	7 (3.9)	54.4 (10.83)
Ali/aml 150/10 mg	183	181 (98.9)	170 (92.9)	11 (6.0)	4 (2.2)	1 (0.5)	6 (3.3)	55.1 (9.31)
Ali/aml 300/5 mg	178	178 (100)	168 (94.4)	10 (5.6)	2 (1.1)	1 (0.6)	7 (3.9)	55.5 (9.63)
Ali/aml 300/10 mg	184	184 (100)	170 (92.4)	14 (7.6)	4 (2.2)	2 (1.1)	8 (4.3)	54.0 (10.76)
All ali/aml	726	724 (99.7)	677 (93.3)	47 (6.5)	13 (1.8)	6 (0.8)	28 (3.9)	-----
Total	1688	1685 (99.8)	1539 (91.2)	146 (8.6)	32 (1.9)	45 (2.7)	69 (4.1)	54.2 (11.26)

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.

Reviewer comments: The 10% dropout rate overall seems to be reasonable in an 8-week short-term anti-hypertensive study.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for the Study SPA2305 was the change from baseline (visit 3) in msDBP to the end of study. This is to assess whether both monotherapy treatments (aliskiren and amlodipine) contribute to the overall effect in blood pressure reduction of the combination treatment. The primary endpoint was analyzed by Hung's AVE test.

The data showed statistical significance ($p \leq 0.01$) in favor of aliskiren/amlodipine. In the pairwise comparison, both individual monotherapy components contributed to the antihypertensive effect of the combination of aliskiren/amlodipine in the overall population. All aliskiren/amlodipine fixed combination doses (150/5, 150/10, 300/5, 300/10 mg) demonstrated statistically greater reductions in msDBP than their respective component monotherapies. Data were summarized in the following table 6.

Table 6: Statistical analysis of change from baseline in mean sitting diastolic blood pressure at endpoint (Full analysis set, reviewer's table)

Treatment group	N	LSM change	Pairwise comparison	LSM difference in	P
-----------------	---	------------	---------------------	-------------------	---

		from baseline (mmHg)		change from baseline (mmHg)	value
Placebo	198	-5.4 ± 0.6	Ali/Aml 150/5 vs Ali 150	-6.0 ± 0.9	<0.001
Ali 150mg	193	-8.0 ± 0.6	Ali/Aml 150/5 vs Ami 5	-3.0 ± 0.9	<0.001
Ali 300mg	201	-10.2 ± 0.6	Ali/Aml 150/10 vs Ali 150	-8.2 ± 0.9	<0.001
Aml 5mg	184	-11.0 ± 0.7	Ali/Aml 150/10 vs Ami 10	-2.3 ± 0.9	0.01
Aml 10mg	179	-13.8 ± 0.7	Ali/Aml 300/5 vs Ali 300	-4.8 ± 0.9	<0.001
Ali/Aml 150/5 mg	179	-14.0 ± 0.7	Ali/Aml 300/5 vs Ami 5	-4.0 ± 0.9	<0.001
Ali/Aml 150/10 mg	179	-16.2 ± 0.7	Ali/Aml 300/10 vs Ali 300	-6.3 ± 0.9	<0.001
Ali/Aml 300/5 mg	175	-15.0 ± 0.7	Ali/Aml 300/10 vs Ami 10	-2.7 ± 0.9	0.004
Ali/Aml 300/10mg	183	-16.5 ± 0.7			

LSM = Least Squares Mean; Only patients with both baseline and post-baseline values are included. Least square means, 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.

Reviewer comments: The least squares mean difference in change from baseline in msDBP for the combination versus each monotherapy at the highest dose levels was about 6 mmHg for aliskiren and 3 mmHg for amlodipine. These should be considered as a clinically meaningful change. Please also note, the placebo has a -5mmHg change from baseline at the end of treatment.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints in Study SPA 2305 included 1) change from baseline (Visit 3) in mean sitting systolic blood pressure (msSBP); 2) percent of patients achieving the diastolic blood pressure response (msDBP < 90 mmHg or at least 10 mmHg reduction from baseline in msDBP); 3) percent of patients achieving the systolic blood pressure response (msSBP < 140 mmHg or at least 20 mmHg reduction from baseline in msSBP); 4) percent of patients achieving the blood pressure control (msDBP < 90 mmHg and msSBP < 140 mmHg); 5) change from baseline in 24-hour ABPM (diastolic and systolic); and 6) change from baseline in daytime and nighttime ABPM (diastolic and systolic).

Change from baseline in msSBP: The Hung's AVE test at Endpoint showed that most of the aliskiren/amlodipine combinations demonstrated statistically significantly greater reduction in msSBP than their respective monotherapies, with the exceptions of the pairwise comparisons of aliskiren/amlodipine 150/10 mg vs. amlodipine 10 mg (p = 0.056) and aliskiren/amlodipine 300/10 mg doses vs. amlodipine 10 mg (p = 0.143). Data were summarized in the following table 7.

Table 7: Statistical analysis of change from baseline in mean sitting systolic blood pressure at endpoint (Full analysis set, reviewer's table)

Treatment group	N	LSM change from baseline (mmHg)	Pairwise comparison	LSM difference in change from baseline (mmHg)	P value
Placebo	198	-6.8 ± 1.0	Ali/Aml 150/5 vs Ali 150	-10.0 ± 1.5	<0.001
Ali 150mg	193	-10.7 ± 1.0	Ali/Aml 150/5 vs Ami 5	-4.8 ± 1.5	<0.001

Ali 300mg	201	-15.4 ± 1.0	Ali/Aml 150/10 vs Ali 150	-13.2 ± 1.5	<0.001
Aml 5mg	184	-15.8 ± 1.0	Ali/Aml 150/10 vs Ami 10	-2.8 ± 1.5	0.056
Aml 10mg	179	-21.0 ± 1.1	Ali/Aml 300/5 vs Ali 300	-6.5 ± 1.5	<0.001
Ali/Aml 150/5 mg	179	-20.6 ± 1.1	Ali/Aml 300/5 vs Ami 5	-6.0 ± 1.5	<0.001
Ali/Aml 150/10 mg	179	-23.9 ± 1.1	Ali/Aml 300/10 vs Ali 300	-7.8 ± 1.4	<0.001
Ali/Aml 300/5 mg	175	-21.8 ± 1.1	Ali/Aml 300/10 vs Ami 10	-2.2 ± 1.5	0.143
Ali/Aml 300/10mg	183	-23.2 ± 1.0			

LSM = Least Squares Mean; Only patients with both baseline and post-baseline values are included. Least square means, 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.

Although the pairwise comparisons of aliskiren/amlodipine 150/10 mg vs. amlodipine 10 mg ($p = 0.056$) and aliskiren/amlodipine 300/10 mg doses vs. amlodipine 10 mg ($p = 0.143$) have not reached statistically significant difference for msSBP in Study SPA100A2035, in Study SPA 100A 2304, a study to specifically evaluate the effect of the combination of aliskiren/amlodipine at doses of 150/10 mg and 300/10 mg in comparison with amlodipine 10 mg in patients with essential hypertension, the aliskiren/amlodipine combinations demonstrated statistically significantly greater reduction in both msSBP and msDBP compared to amlodipine 10mg. Data were summarized in the following table 8.

Table 8: Statistical analysis of change from baseline in mean sitting systolic blood and diastolic pressures at endpoint in Study SPA 100A 2304 (Full analysis set, reviewer's table)

Treatment group	N	LSM change from baseline (mmHg)	Pairwise comparison	LSM difference in change from baseline (mmHg)	P value
Mean sitting diastolic blood pressure (primary endpoint)					
Aml 10mg	277	-7.2 ± 0.5	Ali/Aml 150/10 vs Ami 10	-1.7 ± 0.6	0.008
Ali/Aml 150/10 mg	281	-9.0 ± 0.5	Ali/Aml 300/10 vs Ami 10	-3.8 ± 0.6	<0.0001
Ali/Aml 300/10mg	279	-11.0 ± 0.5			
Mean sitting systolic blood pressure (secondary endpoint)					
Aml 10mg	277	-8.2 ± 0.7	Ali/Aml 150/10 vs Ami 10	-2.8 ± 1.0	0.003
Ali/Aml 150/10 mg	281	-11.0 ± 0.7	Ali/Aml 300/10 vs Ami 10	-6.2 ± 1.0	<0.0001
Ali/Aml 300/10mg	279	-14.4 ± 0.7			

LSM = Least Squares Mean; Only patients with both baseline and post-baseline values are included. Least square means, 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.

Reviewer comments: The reason of no statistically significant difference between the aliskiren/amlodipine 300/10 mg vs. amlodipine 10 mg ($p = 0.143$) in Study SPA 100A 2305 could be due to the variations of aliskiren bioavailability. As the sample size increased in Study SPA 100A 2304, the combination effect has been demonstrated. There is also a dose response effect of aliskiren in the combination in the both studies. Please see details of Study SPA 100A 2304 in Section 5.3.

The changes from baseline in msDBP and msSBP by week for aliskiren/amlodipine 300/10mg and respective monotherapies and placebo are illustrated in the following figures 2 and 3. Greater msDBP and msSBP reductions for the aliskiren/amlodipine combination group vs. each

respective monotherapy or placebo was seen at all time points beginning at Week 1, and reaching a maximum at Week 4, which was sustained throughout the study. The same trend was observed for all other doses of aliskiren/amlodipine combination (data were not present here).

Figure 2: Change from baseline in msDBP by week for aliskiren/amlodipine 300/10 mg vs. component monotherapies and placebo (full analysis set, sponsor's figure)

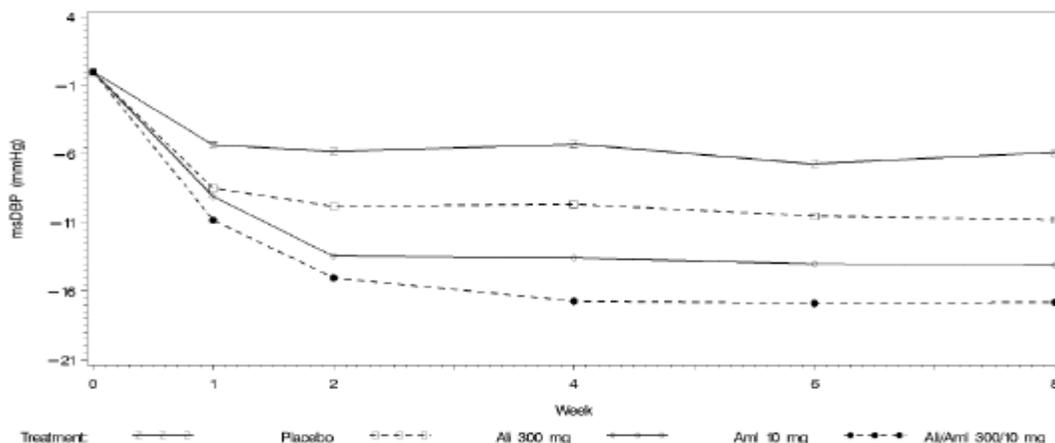
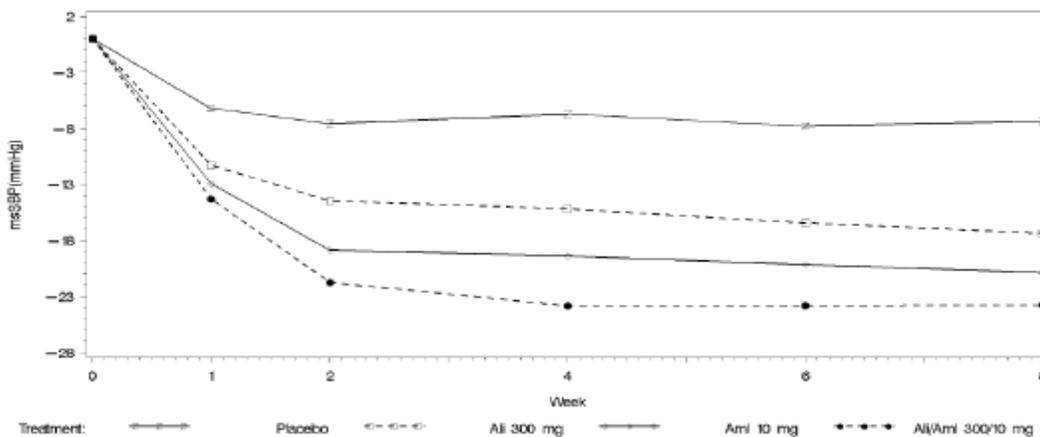


Figure 3: Change from baseline in msSBP by week for aliskiren/amlodipine 300/10 mg vs. component monotherapies and placebo (full analysis set, sponsor's figure)



Percent of patients achieving blood pressure response: The diastolic blood pressure response was defined by msDBP < 90 mmHg or at least 10 mmHg reduction from baseline in msDBP, and systolic blood pressure response was defined by msSBP < 140 mmHg or at least 20 mmHg reduction from baseline in msSBP. All combination therapy doses showed a statistically significantly higher response rate than their respective monotherapies for msDBP. The greatest msDBP response rate was seen in aliskiren/amlodipine 300/10 mg group (84.7%). For the response of msSBP, most combination aliskiren/amlodipine doses showed a statistically significantly higher response rate than their each monotherapy. The exceptions are the aliskiren/amlodipine 150/10 mg and 300/10 mg doses vs. amlodipine 10 mg, which did not reach

Clinical Review
Shen Xiao, M.D., Ph.D.
NDA 22-545; SN-000
Aliskiren/Amlodipine (Tekamlo™)

statistical significance. The greatest SBP response rate was seen in the aliskiren/amlodipine 300/10 mg group (80.3%). Data were summarized in the following table 9.

In Study SPA2304, a study to specifically evaluate the effect of the combination of aliskiren/amlodipine at doses of 150/10 mg and 300/10 mg in comparison with amlodipine 10 mg in patients with essential hypertension, the aliskiren/amlodipine 150/10 mg combination did only show a numerically greater msDBP response rate in comparison to amlodipine 10 mg that did not reach statistical significance. For msSBP response rates, a statistical superiority to amlodipine 10mg was found in both doses of aliskiren/amlodipine combination. Please see detail information in section 5.3.

Table 9: Number (%) of blood pressure response at endpoint by treatment group (Full analysis set, reviewer's table) in pivotal study

Pairwise comparison		msDBP			msSBP		
A	vs B	A n/N (%)	B n/N (%)	P value	A n/N (%)	B n/N (%)	P value
Ali 150mg	Placebo	97/193 (50)	68/198 (34)	0.002	80/193(42)	64/198(32)	0.063
Ali 300mg	Placebo	109/201(54)	68/198 (34)	<0.001	107/201(53)	64/198(32)	<0.001
Aml 5mg	Placebo	114/184(62)	68/198 (34)	<0.001	101/184(55)	64/198(32)	<0.001
Aml 10mg	Placebo	133/179(74)	68/198 (34)	<0.001	129/179(72)	64/198(32)	<0.001
Ali/Aml 150/5	Ali 150	131/179(73)	97/193(50)	<0.001	121/179(68)	80/193(42)	<0.001
Ali/Aml 150/5	Aml 5	131/179(73)	114/184(62)	0.016	121/179(68)	101/184(55)	0.009
Ali/Aml 150/10	Ali 150	150/179(84)	97/193(50)	<0.001	138/179(77)	80/193(42)	<0.001
Ali/Aml 150/10	Aml 10	150/179(84)	133/179(74)	0.030	138/179(77)	129/179(72)	0.284
Ali/Aml 300/5	Ali 300	129/175(74)	109/201(54)	<0.001	122/175(70)	107/201(53)	0.002
Ali/Aml 300/5	Aml 5	129/175(74)	114/184(62)	0.015	122/175(70)	101/184(55)	0.004
Ali/Aml 300/10	Ali 300	155/183(85)	109/201(54)	<0.001	147/183(80)	107/201(53)	<0.001
Ali/Aml 300/10	Ali 10	155/183(85)	133/179(74)	0.013	147/183(80)	129/179(72)	0.06

Only patients with both baseline and post-baseline values are included. 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 baseline and Endpoint msDBP and msSBP values.

Blood pressure control rate: The percentage of patients with BP control, defined as having msSBP <140 mmHg and msDBP <90 mmHg), was analyzed using a logistic regression model, and are summarized in the following table 10. Significantly higher percentage of patients achieved BP control in each fixed combination dose than the respective component monotherapies, with the greatest BP control rate seen in the aliskiren/amlodipine 300/10 mg fixed combination therapy group (68.3%).

Table 10: Between treatment comparison for blood pressure control rate at endpoint by treatment group (Full analysis set, reviewer's table)

Pairwise comparison		Treatment A n/N (%)	Treatment B n/N (%)	P value
A	vs B			
Ali 150mg	Placebo	52/193(26.9)	38/198(19.2)	0.054
Ali 300mg	Placebo	73/201(36.3)	38/198(19.2)	<0.001
Aml 5mg	Placebo	66/184(35.9)	38/198(19.2)	<0.001
Aml 10mg	Placebo	90/179(50.3)	38/198(19.2)	<0.001
Ali/Aml 150/5	Ali 150	88/179(49.2)	52/193(26.9)	<0.001
Ali/Aml 150/5	Aml 5	88/179(49.2)	66/184(35.9)	0.006
Ali/Aml 150/10	Ali 150	117/179(65.4)	52/193(26.9)	<0.001
Ali/Aml 150/10	Aml 10	117/179(65.4)	90/179(50.3)	0.006
Ali/Aml 300/5	Ali 300	99/175(56.6)	73/201(36.3)	<0.001
Ali/Aml 300/5	Aml 5	99/175(56.6)	66/184(35.9)	<0.001
Ali/Aml 300/10	Ali 300	125/183 (68.3)	73/201(36.3)	<0.001
Ali/Aml 300/10	Ali 10	125/183 (68.3)	90/179(50.3)	<0.001

Only patients with both baseline and post-baseline values are included. 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.
N = Number of patients with baseline and Endpoint msDBP values.

Change from baseline in 24-hour ABPM (diastolic and systolic): Twenty-four hour ambulatory blood pressure measurements (ABPM) were conducted in a subset of patients. The analyses showed that all combination therapies of aliskiren/amlodipine were statistically superior to component monotherapies in reduction of the mean 24-hour ambulatory DBP and SBP at Endpoint. Data were summarized in the following table 11.

Table 11: Between-treatment analysis results for change from baseline in mean 24-hour MADBP and MASBP at Endpoint, Study SPA2305 (Full analysis set, sponsor’s table)

Treatment Group	N	MADBP		MASBP	
		LSM change from baseline (mmHg)		LSM change from baseline (mmHg)	
Placebo	83	0.73		-0.01	
Ali 150 mg	99	-4.29		-6.65	
Ali 300 mg	94	-6.31		-9.09	
Aml 5 mg	100	-4.96		-8.86	
Aml 10 mg	91	-7.89		-12.59	
Ali/aml 150/5 mg	89	-8.86		-14.24	
Ali/aml 150/10 mg	84	-11.45		-17.28	
Ali/aml 300/5 mg	94	-10.04		-15.97	
Ali/aml 300/10 mg	85	-12.98		-19.81	
Pairwise Comparison		LSM difference in change from baseline (mmHg) / p-value			
		MADBP		MASBP	
Ali 150 mg vs. placebo		-5.02	<0.001*	-6.64	<0.001*
Ali 300 mg vs. placebo		-7.04	<0.001*	-9.08	<0.001*
Aml 5 mg vs. placebo		-5.69	<0.001*	-8.85	<0.001*
Aml 10 mg vs. placebo		-8.62	<0.001*	-12.58	<0.001*
Ali/aml 150/5 mg vs. ali 150 mg		-4.57	<0.001*	-7.59	<0.001*
Ali/aml 150/5 mg vs. aml 5 mg		-3.90	<0.001*	-5.37	<0.001*
Ali/aml 150/5 mg vs. placebo		-9.59	<0.001*	-14.23	<0.001*
Ali/aml 150/10 mg vs. ali 150 mg		-7.16	<0.001*	-10.63	<0.001*
Ali/aml 150/10 mg vs. aml 10 mg		-3.56	<0.001*	-4.68	<0.001*
Ali/aml 150/10 mg vs. placebo		-12.18	<0.001*	-17.27	<0.001*
Ali/aml 300/5 mg vs. ali 300 mg		-3.73	<0.001*	-6.88	<0.001*
Ali/aml 300/5 mg vs. aml 5 mg		-5.08	<0.001*	-7.11	<0.001*
Ali/aml 300/5 mg vs. placebo		-10.77	<0.001*	-15.96	<0.001*
Ali/aml 300/10 mg vs. ali 300 mg		-6.67	<0.001*	-10.72	<0.001*
Ali/aml 300/10 mg vs. aml 10 mg		-5.09	<0.001*	-7.21	<0.001*
Ali/aml 300/10 mg vs. placebo		-13.71	<0.001*	-19.80	<0.001*

LSM = least squares mean. P-Values and treatment comparisons were from a 2-way repeated-measures analysis-of-covariance model with treatment, region, and post-dosing hours as factors and baseline 24-hour MADBP as a covariate with treatment by post-dosing-hour interaction and autoregressive order 1 covariance structure (AR1). * Indicates statistical significance at 0.05 level

Change from baseline in hourly mean ambulatory DBP and SBP at Endpoint is shown in the following figures 4 and 5 by post-dosing hour and treatment for high-dose aliskiren/amlodipine 300/10 mg. A stable decrease in hourly mean ambulatory DBP and SBP with little fluctuation over the full 24-hour treatment period was observed. There was a greater ambulatory DBP and SBP reduction in the combination vs. both component monotherapies at every hour throughout the entire 24-hour period.

Figure 4: Change from baseline in mean ambulatory DBP at endpoint by post-dosing hour for aliskiren/amlodipine 300/10mg vs. component monotherapies and placebo (Full analysis set, Sponsor's figure)

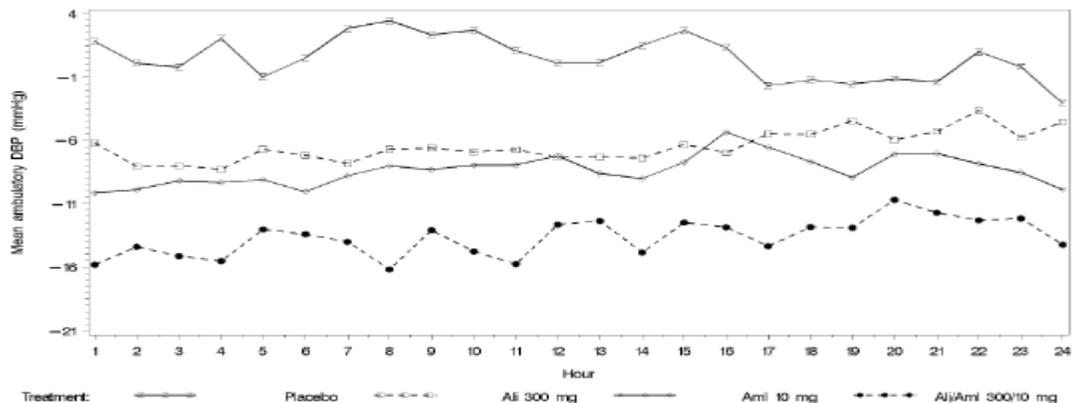
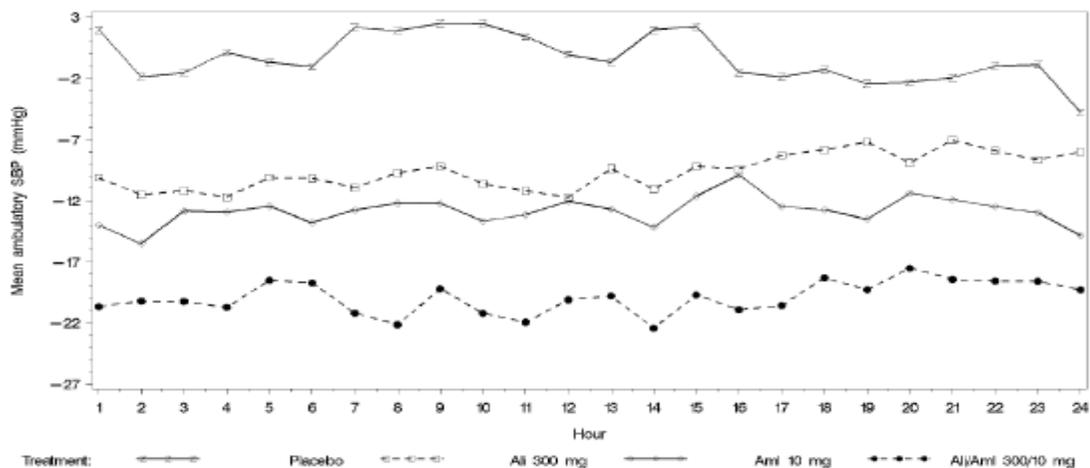


Figure 5: Change from baseline in mean ambulatory SBP at endpoint by postdosing hour for aliskiren/amlodipine 300/10mg vs. component monotherapies and placebo (Full analysis set, sponsor's figure).



Change from baseline in daytime and nighttime ABPM (diastolic and systolic): Between-treatment analysis results for change from baseline in mean daytime (6 AM to 10 PM) and nighttime (10 PM to 6 AM) ambulatory DBP and SBP at Endpoint are summarized in the following tables respectively. All fixed combination therapies of aliskiren/amlodipine were statistically superior to component monotherapies and placebo in reducing ambulatory DBP and SBP during both the daytime and the nighttime.

Table 12: Between treatment analysis results for change from baseline in mean daytime and nighttime ambulatory DBP at endpoint (Full analysis set, sponsor’s table)

Daytime									
Pairwise Comparison			N		LS Mean (SE)		Difference in LS mean (Change)		
A	vs	B	A	B	A	B	mean	95% CI	p-value
Ali 150 mg		Placebo	99	83	-4.57 (0.73)	1.22 (0.79)	-5.79 (1.06)	(-7.87, -3.71)	<.001*
Ali 300 mg		Placebo	94	83	-6.88 (0.75)	1.22 (0.79)	-8.10 (1.07)	(-10.2, -5.99)	<.001*
Aml 5 mg		Placebo	100	83	-5.37 (0.73)	1.22 (0.79)	-6.59 (1.06)	(-8.67, -4.52)	<.001*
Aml 10 mg		Placebo	91	83	-8.33 (0.75)	1.22 (0.79)	-9.55 (1.08)	(-11.7, -7.43)	<.001*
Ali/Aml 150/5 mg		Ali 150 mg	89	99	-9.23 (0.77)	-4.57 (0.73)	-4.66 (1.04)	(-6.70, -2.62)	<.001*
		Aml 5 mg	89	100	-9.23 (0.77)	-5.37 (0.73)	-3.86 (1.04)	(-5.89, -1.82)	<.001*
		Placebo	89	83	-9.23 (0.77)	1.22 (0.79)	-10.45 (1.09)	(-12.6, -8.32)	<.001*
Ali/Aml 150/10 mg		Ali 150 mg	84	99	-12.18 (0.79)	-4.57 (0.73)	-7.61 (1.06)	(-9.68, -5.53)	<.001*
		Aml 10 mg	84	91	-12.18 (0.79)	-8.33 (0.75)	-3.85 (1.08)	(-5.97, -1.73)	<.001*
		Placebo	84	83	-12.18 (0.79)	1.22 (0.79)	-13.40 (1.10)	(-15.6, -11.2)	<.001*
Ali/Aml 300/5 mg		Ali 300 mg	94	94	-10.54 (0.75)	-6.88 (0.75)	-3.66 (1.04)	(-5.70, -1.63)	<.001*
		Aml 5 mg	94	100	-10.54 (0.75)	-5.37 (0.73)	-5.17 (1.02)	(-7.17, -3.16)	<.001*
		Placebo	94	83	-10.54 (0.75)	1.22 (0.79)	-11.76 (1.07)	(-13.9, -9.65)	<.001*
Ali/Aml 300/10 mg		Ali 300 mg	85	94	-13.59 (0.79)	-6.88 (0.75)	-6.72 (1.07)	(-8.81, -4.62)	<.001*
		Aml 10 mg	85	91	-13.59 (0.79)	-8.33 (0.75)	-5.26 (1.08)	(-7.38, -3.15)	<.001*
		Placebo	85	83	-13.59 (0.79)	1.22 (0.79)	-14.81 (1.10)	(-17.0, -12.7)	<.001*

Nighttime									
Pairwise Comparison			N		LS Mean (SE)		Difference in LS mean (Change)		
A	vs	B	A	B	A	B	mean	95% CI	p-value
Ali 150 mg		Placebo	99	83	-4.02 (0.73)	0.08 (0.80)	-4.10 (1.06)	(-6.19, -2.02)	<.001*
Ali 300 mg		Placebo	94	83	-5.68 (0.75)	0.08 (0.80)	-5.77 (1.07)	(-7.87, -3.66)	<.001*
Aml 5 mg		Placebo	100	83	-4.47 (0.73)	0.08 (0.80)	-4.55 (1.06)	(-6.63, -2.47)	<.001*
Aml 10 mg		Placebo	91	83	-6.74 (0.77)	0.08 (0.80)	-6.82 (1.09)	(-8.96, -4.68)	<.001*
Ali/Aml 150/5 mg		Ali 150 mg	89	99	-8.02 (0.77)	-4.02 (0.73)	-4.00 (1.04)	(-6.04, -1.96)	<.001*
		Aml 5 mg	89	100	-8.02 (0.77)	-4.47 (0.73)	-3.55 (1.04)	(-5.59, -1.52)	<.001*
		Placebo	89	83	-8.02 (0.77)	0.08 (0.80)	-8.11 (1.09)	(-10.2, -5.97)	<.001*
Ali/Aml 150/10 mg		Ali 150 mg	84	99	-10.17 (0.79)	-4.02 (0.73)	-6.14 (1.06)	(-8.22, -4.07)	<.001*
		Aml 10 mg	84	91	-10.17 (0.79)	-6.74 (0.77)	-3.43 (1.09)	(-5.56, -1.29)	0.002*
		Placebo	84	83	-10.17 (0.79)	0.08 (0.80)	-10.25 (1.10)	(-12.4, -8.08)	<.001*
Ali/Aml 300/5 mg		Ali 300 mg	94	94	-9.30 (0.76)	-5.68 (0.75)	-3.62 (1.04)	(-5.66, -1.57)	<.001*
		Aml 5 mg	94	100	-9.30 (0.76)	-4.47 (0.73)	-4.83 (1.03)	(-6.85, -2.81)	<.001*
		Placebo	94	83	-9.30 (0.76)	0.08 (0.80)	-9.39 (1.08)	(-11.5, -7.26)	<.001*
Ali/Aml 300/10 mg		Ali 300 mg	85	94	-12.03 (0.80)	-5.68 (0.75)	-6.35 (1.08)	(-8.46, -4.24)	<.001*
		Aml 10 mg	85	91	-12.03 (0.80)	-6.74 (0.77)	-5.30 (1.09)	(-7.44, -3.15)	<.001*
		Placebo	85	83	-12.03 (0.80)	0.08 (0.80)	-12.12 (1.11)	(-14.3, -9.94)	<.001*

- 6 AM < daytime <= 10 PM; 10 PM < nighttime <= 6 AM.

- 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 time (daytime, nighttime) as factors and baseline mean 24-hour MADBP as a covariate with treatment by time interaction and compound symmetric covariance structure (CS). LS means were evaluated at the average baseline mean 24-hour MADBP.

* indicates statistical significance at 0.05 level.

Table 13: Between treatment analysis results for change from baseline in mean daytime and nighttime ambulatory SBP at endpoint (Full analysis set, Sponsor’s table).

Daytime									
Pairwise Comparison			N		LS Mean (SE)		Difference in LS mean (Change)		
A	vs	B	A	B	A	B	mean	95% CI	p-value
Ali 150 mg		Placebo	99	83	-7.17 (1.01)	0.39 (1.09)	-7.56 (1.46)	(-10.4, -4.71)	<.001*
Ali 300 mg		Placebo	94	83	-9.95 (1.03)	0.39 (1.09)	-10.34 (1.47)	(-13.2, -7.45)	<.001*
Aml 5 mg		Placebo	100	83	-9.45 (1.01)	0.39 (1.09)	-9.83 (1.45)	(-12.7, -6.98)	<.001*
Aml 10 mg		Placebo	91	83	-12.67 (1.04)	0.39 (1.09)	-13.06 (1.48)	(-16.0, -10.2)	<.001*
Ali/Aml 150/5 mg		Ali 150 mg	89	99	-14.64 (1.07)	-7.17 (1.01)	-7.46 (1.43)	(-10.3, -4.66)	<.001*
		Aml 5 mg	89	100	-14.64 (1.07)	-9.45 (1.01)	-5.19 (1.42)	(-7.99, -2.40)	<.001*
		Placebo	89	83	-14.64 (1.07)	0.39 (1.09)	-15.03 (1.49)	(-18.0, -12.1)	<.001*
Ali/Aml 150/10 mg		Ali 150 mg	84	99	-17.97 (1.09)	-7.17 (1.01)	-10.79 (1.45)	(-13.7, -7.94)	<.001*
		Aml 10 mg	84	91	-17.97 (1.09)	-12.67 (1.04)	-5.30 (1.48)	(-8.20, -2.39)	<.001*
		Placebo	84	83	-17.97 (1.09)	0.39 (1.09)	-18.35 (1.51)	(-21.3, -15.4)	<.001*
Ali/Aml 300/5 mg		Ali 300 mg	94	94	-16.77 (1.03)	-9.95 (1.03)	-6.82 (1.43)	(-9.62, -4.03)	<.001*
		Aml 5 mg	94	100	-16.77 (1.03)	-9.45 (1.01)	-7.33 (1.41)	(-10.1, -4.57)	<.001*
		Placebo	94	83	-16.77 (1.03)	0.39 (1.09)	-17.16 (1.47)	(-20.1, -14.3)	<.001*
Ali/Aml 300/10 mg		Ali 300 mg	85	94	-20.20 (1.08)	-9.95 (1.03)	-10.25 (1.47)	(-13.1, -7.37)	<.001*
		Aml 10 mg	85	91	-20.20 (1.08)	-12.67 (1.04)	-7.53 (1.48)	(-10.4, -4.63)	<.001*
		Placebo	85	83	-20.20 (1.08)	0.39 (1.09)	-20.59 (1.51)	(-23.6, -17.6)	<.001*
Nighttime									
Pairwise Comparison			N		LS Mean (SE)		Difference in LS mean (Change)		
A	vs	B	A	B	A	B	mean	95% CI	p-value
Ali 150 mg		Placebo	99	83	-6.01 (1.01)	-0.56 (1.10)	-5.45 (1.46)	(-8.31, -2.59)	<.001*
Ali 300 mg		Placebo	94	83	-7.99 (1.03)	-0.56 (1.10)	-7.43 (1.47)	(-10.3, -4.54)	<.001*
Aml 5 mg		Placebo	100	83	-8.17 (1.01)	-0.56 (1.10)	-7.61 (1.46)	(-10.5, -4.75)	<.001*
Aml 10 mg		Placebo	91	83	-11.90 (1.05)	-0.56 (1.10)	-11.35 (1.50)	(-14.3, -8.41)	<.001*
Ali/Aml 150/5 mg		Ali 150 mg	89	99	-13.54 (1.07)	-6.01 (1.01)	-7.53 (1.43)	(-10.3, -4.73)	<.001*
		Aml 5 mg	89	100	-13.54 (1.07)	-8.17 (1.01)	-5.37 (1.42)	(-8.16, -2.57)	<.001*
		Placebo	89	83	-13.54 (1.07)	-0.56 (1.10)	-12.98 (1.50)	(-15.9, -10.0)	<.001*
Ali/Aml 150/10 mg		Ali 150 mg	84	99	-16.31 (1.09)	-6.01 (1.01)	-10.30 (1.45)	(-13.2, -7.45)	<.001*
		Aml 10 mg	84	91	-16.31 (1.09)	-11.90 (1.05)	-4.40 (1.49)	(-7.33, -1.47)	0.003*
		Placebo	84	83	-16.31 (1.09)	-0.56 (1.10)	-15.75 (1.52)	(-18.7, -12.8)	<.001*
Ali/Aml 300/5 mg		Ali 300 mg	94	94	-14.93 (1.04)	-7.99 (1.03)	-6.94 (1.43)	(-9.75, -4.13)	<.001*
		Aml 5 mg	94	100	-14.93 (1.04)	-8.17 (1.01)	-6.76 (1.41)	(-9.53, -3.99)	<.001*
		Placebo	94	83	-14.93 (1.04)	-0.56 (1.10)	-14.37 (1.48)	(-17.3, -11.5)	<.001*
Ali/Aml 300/10 mg		Ali 300 mg	85	94	-19.34 (1.10)	-7.99 (1.03)	-11.35 (1.48)	(-14.2, -8.45)	<.001*
		Aml 10 mg	85	91	-19.34 (1.10)	-11.90 (1.05)	-7.43 (1.50)	(-10.4, -4.49)	<.001*
		Placebo	85	83	-19.34 (1.10)	-0.56 (1.10)	-18.78 (1.52)	(-21.8, -15.8)	<.001*

- 6 AM < daytime <= 10 PM; 10 PM < nighttime <= 6 AM.

- 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 time (daytime, nighttime) as factors and baseline mean 24-hour MADBP as a covariate with treatment by time interaction and compound symmetric covariance structure (CS). LS means were evaluated at the average baseline mean 24-hour MADBP.

* indicates statistical significance at 0.05 level.

Reviewer’s Comment: there was essentially no placebo effect on the mean 24-hour ambulatory DBP and SBP. The magnitude of the difference in 24-hour mean ambulatory BP values for the combination and respective monotherapies at the highest dose level was 6.7/10.7 for aliskiren and 5.1/7.2 mmHg for amlodipine indicating a clinically meaningful reductions.

6.1.6 Other Endpoints

Biomarkers including PRC and PRA were evaluated in a subset of 608 patients, of which 261 received aliskiren/amlodipine combination. Geometric means (GM) have been applied since the biomarker values are not distributed normally. PRC increased from baseline in all active

treatment groups at Endpoint (change from baseline for placebo was minimal). A greater PRC increase was observed for aliskiren than for amlodipine while the greatest increases were observed in the fixed combination groups.

PRA decreased from baseline to Endpoint for treatment groups containing aliskiren, either as monotherapy or in combination with amlodipine. PRA decreased in the aliskiren/amlodipine groups, with a similar decrease as the aliskiren monotherapy groups, while increase of PRA was observed in the amlodipine monotherapy groups and the placebo group. Data were summarized in the following table 14. Similar results are also observed in other short-term active controlled studies.

Table 14: Summary statistics for change from baseline in geometric mean of PRC and PRA at Endpoint (Sponsor's table)

	Placebo N=198	Ali 150 mg N=194	Ali 300 mg N=203	Aml 5 mg N=185	Aml 10 mg N=181	Ali/aml 150/5 mg N=181	Ali/aml 150/10 mg N=181	Ali/aml 300/5 mg N=178	Ali/aml 300/10 mg N=184
PRC (ng/L)									
N	66	65	75	72	68	64	69	62	66
Baseline GM	6.421	6.684	7.283	6.676	9.162	7.735	7.319	8.011	6.506
Endpoint* GM	7.064	17.143	28.374	9.297	13.275	26.965	32.973	53.963	41.715
GM in the ratio (Endpoint/baseline)	1.100	2.565	3.896	1.392	1.449	3.486	4.505	6.736	6.411
Percent change from baseline (GM)+	10.0%	156.5%	289.6%	39.2%	44.9%	248.6%	350.5%	573.6%	541.1%
PRA (ng/mL/hr)									
N	66	64	76	72	69	64	68	62	67
Baseline GM	0.617	0.541	0.475	0.579	0.703	0.701	0.541	0.536	0.556
Endpoint* GM	0.773	0.211	0.151	0.922	1.215	0.224	0.244	0.189	0.198
GM in the ratio (Endpoint /baseline)	1.253	0.390	0.317	1.593	1.729	0.319	0.451	0.353	0.356
Percent change from baseline (GM)+	25.3%	-61.0%	-68.3%	59.3%	72.9%	-68.1%	-54.9%	-64.7%	-64.4%

Reviewer's comments: The increase in PRC in the aliskiren/amlodipine combination is consistent with the mechanism of action of both aliskiren and amlodipine. The decrease in PRA is also consistent with the mechanism of action and pharmacodynamic effect of aliskiren. Although amlodipine increases PRA, the overall effect of combination of aliskiren/amlodipine is increased PRA.

Other biomarkers including urinary albumin creatinine ratio, urinary albumin excretion rate, and urinary aldosterone were measured in Study SPA 100A US01, an 8-week study of the effect of combination of aliskiren and amlodipine at doses of 150/5 mg and 300/10 mg versus amlodipine alone at doses of 5 mg and 10 mg in African American patients with Stage 2 hypertension. There were no statistically significant difference between the combinations and amlodipine monotherapy.

6.1.7 Subpopulations

Subgroups were analyzed based on age (3 groups: <65 years, ≥65 years, ≥75 years), race (Caucasian, Black, Asian, Native American, Pacific Islander, Other), BMI status (BMI <20 kg/m², 20 kg/m² ≤ BMI <25 kg/m², 25 kg/m² ≤ BMI <30 kg/m², and BMI ≥ 30 kg/m²),

gender, renal function, diabetic status, and hypertension stage. The efficacy variables include change from baseline in msSBP, change from baseline in msDBP and BP control rate (msSBP/msDBP <140/90 mmHg).

Overall, subgroup analyses indicated that the aliskiren/amlodipine combination therapies were more effective than the respective monotherapies in reduction of mean BP across all subgroups of gender, age, race, and different clinical settings. However, the number of patients in certain subgroups was too small to draw any definitive conclusions.

Age: In the pivotal study, the majority of patients (82.8%) were <65 years of age. In general, all aliskiren/amlodipine fixed combinations demonstrated greater reductions in msDBP and msSBP and a higher percentage of BP control rate than their component monotherapies for patients aged <65 and those aged ≥65 years. The magnitude of the BP reductions and BP control rate with the fixed combination treatments was similar in both age groups. The trend of greater BP reductions and BP control rate for the fixed combination treatment than respective monotherapies was also observed in patients ≥75 years old. However, the number of patients in this age category was small. Data were summarized in the following tables 15 and 16.

Table 15: Change from baseline to Endpoint in msDBP and msSBP by age group (full analysis set, sponsor's table)

Age group	Number of patients			Baseline mean			End point mean			Change from baseline					
				<65	>=65	>=75	<65	>=65	>=75	Mean			Placebo subtracted		
	<65	>=65	>=75	<65	>=65	>=75	<65	>=65	>=75	<65	>=65	>=75	<65	>=65	>=75
msDBP															
Placebo	164	34	5	99.7	99.0	97.9	95.3	90.4	91.1	-4.4	-8.7	-6.8			
Ali 150 mg	155	38	4	99.4	100.5	99.8	92.1	90.7	93.1	-7.4	-9.8	-6.7	-3.0	-1.1	0.1
Ali 300 mg	170	31	7	100.3	99.0	97.5	90.5	87.2	88.9	-9.8	-11.8	-8.6	-5.4	-3.1	-1.8
Aml 5 mg	144	40	7	99.9	98.9	100.1	89.8	85.5	82.8	-10.1	-13.4	-17.3	-5.7	-4.8	-10.5
Aml 10 mg	149	30	5	100.3	99.2	100.1	86.8	83.6	79.4	-13.5	-15.6	-20.7	-9.1	-6.9	-13.9
Ali/aml 150/5 mg	153	26	5	99.8	100.2	98.9	87.1	80.1	71.3	-12.7	-20.0	-27.6	-8.4	-11.4	-20.8
Ali/aml 150/10 mg	153	26	2	99.7	99.3	101.0	84.0	81.6	85.2	-15.7	-17.7	-15.8	-11.3	-9.0	-9.0
Ali/aml 300/5 mg	142	33	3	99.9	98.3	101.7	85.7	81.1	80.2	-14.2	-17.2	-21.4	-9.8	-8.5	-14.6
Ali/aml 300/10 mg	153	30	7	99.8	97.9	97.4	83.8	81.5	76.6	-16.1	-16.4	-20.8	-11.7	-7.7	-14.0
msSBP															
Placebo	164	34	5	156.4	161.2	157.4	150.6	152.4	153.1	-5.8	-8.8	-4.3			
Ali 150 mg	155	38	4	154.6	164.5	160.4	144.9	153.5	156.8	-9.7	-10.9	-3.7	-3.9	-2.1	0.6
Ali 300 mg	170	31	7	158.1	164.1	170.8	142.5	146.8	151.7	-15.5	-17.3	-19.1	-9.7	-8.5	-14.9
Aml 5 mg	144	40	7	156.9	158.5	154.0	141.5	143.3	146.3	-15.5	-15.2	-7.7	-9.6	-6.4	-3.4
Aml 10 mg	149	30	5	156.7	162.4	162.8	136.0	140.4	145.2	-20.7	-22.0	-17.6	-14.9	-13.2	-13.3
Ali/aml 150/5 mg	153	26	5	156.9	165.3	168.2	137.2	139.3	130.2	-19.6	-25.9	-38.0	-13.8	-17.2	-33.7
Ali/aml 150/10 mg	153	26	2	155.8	161.2	170.8	133.5	133.4	139.2	-22.3	-27.8	-31.7	-16.5	-19.0	-27.4
Ali/aml 300/5 mg	142	33	3	156.5	157.3	150.7	135.3	137.0	130.4	-21.2	-20.3	-20.2	-15.4	-11.5	-16.0
Ali/aml 300/10 mg	153	30	7	155.9	162.7	169.6	133.9	137.3	137.2	-22.0	-25.4	-32.4	-16.2	-16.7	-28.1

Table 16: BP control rates (%) at Endpoint by age group (full analysis set, sponsor’s table)

Total, N % of patients	Placebo N=198	Ali 150 mg N=195	Ali 300 mg N=203	Aml 5 mg N=185	Aml 10 mg N=181	Ali/aml 150/5 mg N=181	Ali/aml 150/10mg N=183	Ali/aml 300/5 mg N=178	Ali/aml 300/10 mg N=184
Age group*									
<65 years, N	164	155	170	144	149	153	153	142	153
n (%)	29 (17.7)	48 (31.0)	63 (37.1)	51 (35.4)	77 (51.7)	76 (49.7)	102 (66.7)	81 (57.0)	105 (68.6)
≥ 65 years, N	34	38	31	40	30	26	26	33	30
n (%)	9 (26.5)	4 (10.5)	10 (32.3)	15 (37.5)	13 (43.3)	12 (46.2)	15 (57.7)	18 (54.5)	20 (66.7)
≥ 75 years, N	5	4	7	7	5	5	2	3	7
n (%)	2 (40.0)	0 (0)	3 (42.9)	3 (42.9)	2 (40.0)	3 (60.0)	0 (0.0)	2 (66.7)	4 (57.1)

Race: Most patients were Caucasian (62.1%) in this pivotal study. Black patients accounted for 19.9% of the total study population. For Caucasian patients, the aliskiren/amlodipine fixed combination treatment groups showed a greater reduction in msDBP and msSBP, and higher percentage of BP control rate at Endpoint than the respective monotherapy groups. For Black patients, while aliskiren/amlodipine fixed combination treatment groups containing amlodipine 5 mg showed a greater reduction of msDBP and msSBP, and higher percentage of BP control rate than amlodipine 5 mg, aliskiren/amlodipine fixed combination treatment groups containing amlodipine 10 mg showed a similar or slightly lower reduction of msDBP and msSBP, and similar or lower percentage of BP control rate than amlodipine 10 mg. In the 24 hour ABPM analyses, the combination of aliskiren/amlodipine at doses of 150/5 mg and 150/10mg showed the best reduction effect in Blacks. Data were summarized in the following tables 17, 18 and 19. The number of patients in other racial subgroups was very small, making interpretation of these data difficult.

Table 17: Change from baseline to Endpoint in msDBP and msSBP by race of Caucasian and Black (full set analysis, Sponsor’s table)

Treatment Race	n		Baseline mean		Endpoint mean		Change from baseline			
							Mean		Placebo subtracted	
	C	B	C	B	C	B	C	B		
msDBP										
Placebo	119	39	99.7	99.1	94.5	95.2	-5.3	-3.9		
Ali 150 mg	121	36	99.4	101.0	90.5	95.7	-8.8	-5.3	-3.6	-1.4
Ali 300 mg	126	38	100.0	100.9	89.3	93.5	-10.7	-7.4	-5.5	-3.4
Aml 5 mg	121	35	99.5	99.9	88.3	90.5	-11.2	-9.4	-5.9	-5.5
Aml 10 mg	111	34	100.3	101.4	86.8	87.1	-13.5	-14.3	-8.3	-10.4
Ali/aml 150/5 mg	111	37	100.2	99.4	86.5	86.7	-13.8	-12.7	-8.5	-8.8
Ali/aml 150/10 mg	106	39	99.8	100.5	83.5	85.8	-16.3	-14.8	-11.0	-10.8
Ali/aml 300/5 mg	110	36	99.7	100.3	85.2	88.6	-14.5	-11.7	-9.3	-7.8
Ali/aml 300/10 mg	115	35	99.7	99.7	83.6	87.2	-16.0	-12.5	-10.8	-8.6
msSBP										
Placebo	119	39	157.8	158.1	151.0	154.0	-6.8	-4.1		
Ali 150 mg	121	36	157.1	159.3	146.3	151.6	-10.8	-7.7	-4.0	-3.6
Ali 300 mg	126	38	158.0	160.4	141.7	149.0	-16.3	-11.4	-9.6	-7.3
Aml 5 mg	121	35	156.7	162.1	142.2	143.8	-14.5	-18.3	-7.8	-14.2
Aml 10 mg	111	34	158.1	158.0	137.6	136.6	-20.5	-21.5	-13.8	-17.3
Ali/aml 150/5 mg	111	37	157.9	158.8	138.5	138.1	-19.4	-20.7	-12.7	-16.6
Ali/aml 150/10 mg	106	39	156.8	157.5	134.3	136.2	-22.5	-21.3	-15.7	-17.2
Ali/aml 300/5 mg	110	36	157.0	155.8	135.7	141.5	-21.3	-14.3	-14.5	-10.2
Ali/aml 300/10 mg	115	35	157.9	156.6	134.6	141.2	-23.4	-15.5	-16.6	-11.3

Number of patients at baseline and Endpoint.

Table 18: Pairwise comparison of changes from baseline to Endpoint in msDBP, msSBP and BP control rate by race of Caucasian and Black (full set analysis, reviewer's table)

Pairwise comparison	Mean change from baseline after monotherapy subtracted (mmHg)				BP control rate after monotherapy subtracted (%)	
	msDBP		msSBP			
	Caucasian	Black	Caucasian	Black	Caucasian	Black
Ali/Aml 150/5 vs Ali 150	-5	-7.4	-8.6	-13.0	21.4	29.2
Ali/Aml 150/5 vs Ami 5	-2.6	-3.3	-4.9	-2.4	9.0	22.2
Ali/Aml 150/10 vs Ali 150	-7.5	-9.5	-11.7	-13.6	37.0	37.1
Ali/Aml 150/10 vs Ami 10	-2.8	-0.5	-2.0	0.2	19.2	0.9
Ali/Aml 300/5 vs Ali 300	-3.8	-4.3	-5.0	-2.9	15.9	10.4
Ali/Aml 300/5 vs Ami 5	-3.3	-2.3	-6.8	4.0	28.3	19.4
Ali/Aml 300/10 vs Ali 300	-5.3	-5.1	-7.1	-4.1	27.3	25.7
Ali/Aml 300/10 vs Ami 10	-2.5	1.8	-2.9	6.0	21.9	-1.5

Table 19: Comparison of change from baseline to endpoint in 24-hour ABPM by race of Caucasian and Black (reviewer's table)

	Caucasian			Black		
	N	Mean DBP	Mean SBP	N	Mean DBP	Mean SBP
Placebo	119	0.4	-0.3	39	4.3	1.6
Ali 150mg	122	-5.0	-7.0	36	-1.2	-1.2
Ali 300mg	127	-5.9	-8.9	39	-3.6	-4.8
Aml 5mg	121	-4.8	-8.3	36	-5.1	-5.7
Aml 10mg	113	-7.7	-11.9	34	-10.1	-13.6
Ali/Aml 150/5mg	112	-7.6	-12.5	38	-13.5	-17.6
Ali/Aml 150/10mg	107	-11.6	-16.9	40	-14.1	-24.4
Ali/Aml 300/5mg	110	-10.1	-16.3	38	-6.6	-9.3
Ali/Aml 300/10mg	116	-13.8	-20.0	35	-8.5	-13.5

To further evaluate the effect of the combinations of aliskiren and amlodipine on hypertensive African Americans. Study SPA 100A US01 was conducted. It is an 8-week multicenter, randomized, double-blind, active control study to evaluate the effect of combination of aliskiren and amlodipine (300/10 mg) versus amlodipine alone (10 mg) in African American patients with Stage 2 Hypertension (defined as MSSBP \geq 160 mmHg and $<$ 200 mmHg). In this study, more than 400 African Americans with stage 2 hypertension were evaluated (please see section 5.3 for the detailed information of the study design). The results showed that the combination provided a statistically greater reduction of both msDBP and msSBP, and better BP control rate than amlodipine alone. Data were summarized in the following table 20.

Table 20: Comparison of changes from baseline to Endpoint in msDBP, msSBP and BP control rate in African Americans (Study SPA 100A US01, full set analysis, reviewer’s table)

Treatment	Number of patients	Change from baseline (mmHg)		BP control rate (%)
		msSBP	msDBP	
Aml10mg	223	-27.8±13.5	-10.4±9.1	57.4
Ali/Aml 300/10 mg	220	-33.1±14.5	-13.7±9.6	71.4
Ali/Aml 300/10 vs Aml 10	220/223	-5.2	-3.3	14.0
P value		< 0.001	<0.001	0.002

Reviewer’s comments: Although both aliskiren and amlodipine are known to be effective in lowering BP in Black patients. Just like ACEIs/ARBs, aliskiren alone is less effective in African Americans than in Caucasians. In this pivotal study, the combination at highest dose level did not show a better effect than amlodipine in African Americans. However, the small number of black patients (about 40 patients in each group) in this study may limit the interpretation of the data in this patient population. Based on the absolute values in this study, the difference between the combination and the aliskiren alone is similar in both populations.

In the Study SPA 100A US01, more than 400 African Americans with more than 200 patients in each group were evaluated. This study did show a better antihypertensive effect in the combination than the amlodipine alone. The absolute values in this study are similar to the Caucasians in the pivotal study. However, please note, these patients are in stage 2 hypertension.

Gender: Approximately 51% of patients were male. The aliskiren/amlodipine fixed combination treatment groups showed a greater reduction in msDBP and msSBP and better BP control rate for both males and females at Endpoint than the respective monotherapy groups. However, compared to the amlodipine 10mg, it seems like that the combinations have less effective in females than in males regarding the reduction of msSBP. In the 24-hour ABPM analyses, the combination showed a greater reduction in the mean DBP and SBP for both males and females compared to the respective monotherapy. Data were summarized in the following tables 21, 22, and 23.

In Study SPA 100A 2304, a study to specifically evaluate the effect of the combination of aliskiren/amlodipine at doses of 150/10 mg and 300/10 mg in comparison with amlodipine 10 mg in patients with essential hypertension, the combination showed similar effects between males and females compared to the amlodipine 10mg. Data were summarized in the following table 24.

Table 21: Change from baseline to Endpoint in msDBP and msSBP by gender in the pivotal study (full set analysis, Sponsor’s table).

Treatment/ Gender	M F		Baseline mean		Endpoint mean		Change from baseline			
							Mean		Placebo subtracted	
							M	F	M	F
msDBP										
Placebo	90	108	100.2	99.1	97.5	91.9	-2.7	-7.1		
Ali 150 mg	119	74	100.0	99.0	93.0	89.9	-7.0	-9.2	-4.3	-2.1
Ali 300 mg	93	108	100.4	99.8	91.0	89.1	-9.4	-10.6	-6.7	-3.5
Aml 5 mg	99	85	99.7	99.6	89.4	88.3	-10.4	-11.4	-7.7	-4.2
Aml 10 mg	86	93	101.1	99.2	88.0	84.7	-13.1	-14.5	-10.4	-7.4
Ali/aml 150/5 mg	96	83	100.5	99.2	88.2	83.6	-12.3	-15.5	-9.6	-8.4
Ali/aml 150/10 mg	84	95	100.1	99.2	84.7	82.7	-15.4	-16.5	-12.7	-9.4
Ali/aml 300/5 mg	78	97	99.5	99.7	85.8	84.1	-13.7	-15.6	-11.0	-8.4
Ali/aml 300/10 mg	105	78	99.8	99.2	84.0	82.6	-15.8	-16.6	-13.1	-9.4
msSBP										
Placebo	90	108	158.5	156.1	154.2	148.1	-4.3	-8.0		
Ali 150 mg	119	74	156.8	156.1	148.4	143.7	-8.4	-12.4	-4.1	-4.5
Ali 300 mg	93	108	158.7	159.2	143.7	142.8	-15.0	-16.4	-10.7	-8.5
Aml 5 mg	99	85	156.8	157.9	144.2	139.1	-12.5	-18.7	-8.2	-10.7
Aml 10 mg	86	93	158.7	156.6	141.1	132.7	-17.6	-23.9	-13.3	-15.9
Ali/aml 150/5 mg	96	83	157.4	159.0	140.9	133.7	-16.5	-25.3	-12.2	-17.3
Ali/aml 150/10 mg	84	95	158.3	155.1	136.7	130.6	-21.5	-24.6	-17.2	-16.6
Ali/aml 300/5 mg	78	97	157.8	155.8	138.3	133.5	-19.5	-22.3	-15.2	-14.3
Ali/aml 300/10 mg	105	78	157.0	156.9	135.9	132.5	-21.1	-24.4	-16.8	-16.5

Table 22: Pairwise comparison of change from baseline to Endpoint in msDBP, msSBP and BP control rate by gender in the pivotal study(full set analysis, reviewer’s table)

Pairwise comparison	Mean change from baseline after monotherapy subtracted (mmHg)				BP control rate after monotherapy subtracted (%)	
	msDBP		msSBP		Male	Female
	Male	Female	Male	Female		
Ali/Aml 150/5 vs Ali 150	-5.3	-6.3	-8.1	-12.9	15.7	27.6
Ali/Aml 150/5 vs Aml 5	-1.9	-4.1	-4.0	-6.6	7.2	20.3
Ali/Aml 150/10 vs Ali 150	-8.4	-7.3	-13.1	-12.2	36.5	36.5
Ali/Aml 150/10 vs Aml 10	-2.3	-2.0	-3.9	-0.7	16.4	13.5
Ali/Aml 300/5 vs Ali 300	-4.3	-5.0	-4.5	-5.9	22.8	17.9
Ali/Aml 300/5 vs Aml 5	-3.3	-4.2	-7.0	-3.6	13.2	15.3
Ali/Aml 300/10 vs Ali 300	-6.4	-6.0	-6.1	-8.0	32.5	33.3
Ali/Aml 300/10 vs Aml 10	-2.7	-2.1	-3.5	-0.5	21.9	15.0

Table 23: Change from baseline to Endpoint in 24-hour ABPM by gender in the pivotal study (Reviewer’s table).

	Males			Females		
	N	Mean DBP	Mean SBP	N	Mean DBP	Mean SBP
Placebo	90	1.8	0.7	108	-0.2	-0.7
Ali 150mg	119	-4.5	-5.9	75	-4.1	-6.4
Ali 300mg	95	-7.0	-9.1	108	-6.0	-10.3
Aml 5mg	99	-4.5	-7.5	86	-4.9	-8.9
Aml 10mg	87	-7.5	-10.7	94	-9.6	-15.3
Ali/Aml 150/5mg	97	-8.4	-11.8	84	-9.6	-16.7
Ali/Aml 150/10mg	85	-11.8	-16.7	96	-12.5	-19.0
Ali/Aml 300/5mg	78	-11.4	-16.3	100	-9.3	-16.7
Ali/Aml 300/10mg	106	-12.8	-17.2	78	-14.7	-24.4

Table 24: Comparison of change from baseline to Endpoint in msDBP and msSBP by gender in Study SPA 2304 (full set analysis, reviewer’s table)

	msDBP (change from baseline, mmHg)		msSBP (change from baseline, mmHg)	
	Male	Female	Male	Female
	Aml 10mg	-6.1	-9.0	-7.3
Ali/Aml 150/10 mg	-7.9	-10.4	-10.8	-12.6
Ali/Aml 300/10mg	-9.6	-12.4	-12.4	-16.3

Review comments: Please note the different changes of both msDBP and msSBP from low dose to high dose in males and females in the combination group in the pivotal study. The DBP/SBP reductions from 150/5 mg to 300/10mg are 3.5/4.6 mmHg in Males and only 1/-0.8 mmHg in females. However, in the 24-hour ABPM analyses, the DBP/SBP reductions from 150/5 mg to 300/10mg are 4.4/5.4 mmHg in Males and 5.1/7.7 mmHg in females. Therefore, even there was a higher incidence rate of peripheral edema in females at high combination dose group compared to the low dose group (please see the safety review section), there should still be benefits to females patients using high combination dose.

Body mass index: In the study, patients were divided into 4 categories based upon their baseline body mass index (BMI); BMI <20 kg/m², 20 kg/m² ≤ BMI <25 kg/m², 25 kg/m² ≤ BMI <30 kg/m², and BMI ≥ 30 kg/m². The aliskiren/amlodipine fixed combination treatment groups showed a greater reduction in msDBP and msSBP and better BP control rate for all BMI subpopulations at Endpoint than the respective monotherapy groups. There were too few patients in the <20 kg/m² category for a meaningful comparison. Data were summarized in the following tables 25 and 26.

Table 25: Change from baseline to Endpoint in msDBP and msSBP by BMI status (full set analysis, Sponsor's table).

Obesity, BMI category (kg/m ²)	Placebo		Ali 150 mg		Ali 300 mg		Aml 5 mg		Aml 10 mg		Ali/aml 150/5 mg		Ali/aml 150/10 mg		Ali/aml 300/5 mg		Ali/aml 300/10 mg	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
msDBP (mm Hg)																		
<20	2	-6.7					2	-8.8	3	-18.3	2	-11.7	1	1.0	1	-13.0	1	-14.3
20 ≤BMI<25	28	-8.5	16	-11.5	29	-13.5	24	-10.1	26	-16.1	21	-17.3	26	-17.7	23	-17.2	27	-19.0
25 ≤BMI<30	74	-4.9	88	-8.3	79	-8.9	72	-12.0	76	-15.1	77	-13.9	69	-16.7	72	-15.3	61	-15.9
BMI ≥ 30	93	-4.1	89	-6.7	93	-10.0	86	-10.1	73	-11.6	79	-12.8	83	-15.1	78	-13.6	94	-15.5
msSBP (mm Hg)																		
<20	2	-5.3					2	-19.5	3	-10.4	2	-13.7	1	14.0	1	-20.0	1	-28.7
20 ≤BMI<25	28	-9.0	16	-16.6	29	-16.7	24	-14.6	26	-25.3	21	-21.9	26	-28.1	23	-23.7	27	-29.6
25 ≤BMI<30	74	-5.5	88	-10.1	79	-14.1	72	-14.7	76	-22.1	77	-20.6	69	-23.1	72	-23.6	61	-23.2
BMI ≥ 30	93	-6.1	89	-8.6	93	-16.9	86	-16.1	73	-18.6	79	-20.3	83	-22.0	78	-17.9	94	-20.0

Table 26: Blood pressure control rate by BMI status (full set analysis, Sponsor's table)

Total, N % of patients	Placebo N=198	Ali 150 mg N=195	Ali 300 mg N=203	Aml 5 mg N=185	Aml 10 mg N=181	Ali/aml 150/5 mg N=181	Ali/aml 150/10mg N=183	Ali/aml 300/5 mg N=178	Ali/aml 300/10 mg N=184
Obesity, BMI (kg/m²)^a									
<20, N	2	0	0	2	3	2	1	1	1
n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (33.3)	1 (50.0)	0 (0.0)	1 (100)	1 (100)
20 ≤BMI<25, N	28	16	29	24	26	21	26	23	27
n (%)	9 (32.1)	8 (50.0)	13 (44.8)	9 (37.5)	15 (57.7)	11 (52.4)	20 (76.9)	14 (60.9)	21 (77.8)
25 ≤BMI<30, N	74	88	79	72	76	77	69	72	61
n (%)	14 (18.9)	24 (27.3)	24 (30.4)	26 (36.1)	42 (55.3)	39 (50.6)	43 (62.3)	42 (58.3)	41 (67.2)
BMI ≥ 30, N	93	89	93	86	73	79	83	78	94
n (%)	14 (15.1)	20 (22.5)	36 (38.7)	30 (34.9)	32 (43.8)	37 (46.8)	54 (65.1)	41 (52.6)	62 (66.0)

Reviewer's comments: It seems that the difference of the reduction of msSBP, msDBP and the BP control rate between the combination at dose of 300/10 mg and its each monotherapy is similar among the patients with different BMI.

Renal function and Diabetic status: The patients with severe renal impairment were excluded in the study and the number of patients with moderate renal impairment was small (less than 10 patients in each group). Therefore, the data are hard to be compared in this population.

In general, for both diabetic and non-diabetic patients, BP control rates were higher for the aliskiren/amlodipine combinations than for the component monotherapies or placebo at Endpoint. However, the number of patients with diabetes was small (10 to 30 in each group) and the data are to be compared.

Since patients with renal impairment or diabetes are in need of more aggressive BP control, their aggressive BP control rates (130/80 mmHg) are described in the following table 24. In general, aggressive BP control rates were higher for the combination therapies versus the component monotherapies with the highest rate seen with the aliskiren/amlodipine 300/10 mg combination. Due to the limit numbers of patients with renal impairment and diabetic patients, the data in these patients are hard to be interpreted. Data were summarized in the following table 27.

Table 27: Percentage of patients with aggressive BP control (less than 130/80 mmHg) at Endpoint by treatment group and baseline renal function and diabetes status (full set analysis; with BP not controlled at baseline – Sponsor’s table)

Parameter Statistic	Placebo N (%)	Ali 150 mg N (%)	Ali 300 mg N (%)	Aml 5 mg N (%)	Aml 10 mg N (%)	Ali/aml 150/5 mg N (%)	Ali/aml 150/10 mg N (%)	Ali/aml 300/5 mg N (%)	Ali/aml 300/10 mg N (%)
GFR ≥30 to < 60 mL/min/1.73 m²									
Total	8	8	9	12	4	6	9	6	10
n (%)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	2 (33.3)	3 (33.3)	1 (16.7)	2 (20.0)
GFR ≥ 60 to <90 mL/min/1.73m²									
Total	88	89	91	85	88	91	80	78	93
n (%)	2 (2.3)	3 (3.4)	5 (5.5)	8 (9.4)	14 (15.9)	12 (13.2)	14 (17.5)	20 (25.6)	26 (28.0)
GFR ≥ 90 mL/min/1.73 m									
Total	98	91	97	82	84	80	89	86	76
n (%)	7 (7.1)	4(4.4)	11 (11.3)	5 (6.1)	16 (19.0)	18 (22.5)	21 (23.6)	24 (27.9)	16 (21.1)
Non-diabetic									
Total	183	168	177	167	168	159	150	158	158
n (%)	9 (4.9)	7 (4.2)	17 (9.6)	9 (5.4)	28 (16.7)	27 (17.0)	32 (21.3)	41 (25.9)	40 (25.3)
Diabetic									
Total	15	25	24	17	11	20	29	17	25
n (%)	0 (0.0)	1(4.0)	0 (0.0)	4 (23.5)	2 (18.2)	6 (30.0)	6 (20.7)	5 (29.4)	5 (20.0)

Reviewer’s comments: Renal function was classified based on MDRD equation. For GFR > 60ml/min/1.73m², there will be some variations and may not reflect the renal function correctly.

Patients with Stage 2 hypertension: Combination of aliskiren/amlodipine at dose of 150/10mg compared to amlodipine 10 mg for msDBP and combination at doses of 150/10, and 300/10 mg compared to amlodipine 10mg for msSBP did not reach statistical significance in this population. Similar results were also found for the blood control rate. There was no statistically significant difference of BP control rate between the combination of aliskiren/amlodipine at dose of 150/10 mg and the amlodipine 10mg alone. Data were summarized in the following tables 28.

Study SPA 100A 2306 is an 8-week, double-blind, randomized, parallel group, multi-center study to support the efficacy of the combination of aliskiren 300 mg and amlodipine 10 mg compared to amlodipine 10 mg in patients with moderate to severe hypertension. In the study, data showed that the combination of aliskiren/amlodipine 300/10 mg demonstrated clinically meaningful and statistically significantly greater reductions in msSBP and msDBP and better BP control rate compared to amlodipine 10 mg monotherapy in patients with moderate to severe hypertension. Data were summarized in the following table 29.

Table 28: Pairwise comparison of change from baseline to Endpoint in msDBP, msSBP and BP control rate in patients with Stage 2 hypertension (Full analysis, reviewer's table)

Treatment	N	msDBP (mmHg)	msSBP (mmHg)	BP control rate (%)
Plaebo	122	-5.6	-9.0	13.9
Ali 150mg	118	-8.5	-12.7	21.2
Ali 300mg	138	-10.7	-17.6	29.0
Aml 5mg	115	-12.2	-19.2	30.4
Aml 10mg	118	-14.7	-24.6	44.1
Ali/Aml 150/5mg	126	-15.3	-25.2	49.2
Ali/Aml 150/10 mg	113	-16.7	-26.4	57.5
Ali/Aml 300/5 mg	108	-15.0	-25.0	49.1
Ali/Aml 300/10 mg	116	-17.5	-26.7	62.1

Pairwise comparison	msDBP	P value	msSBP	P value	BP control	P value
Ali/Aml 150/5 vs Ali 150	-6.7	<0.001	-12.5	<0.001	28.0	<0.001
Ali/Aml 150/5 vs Ami 5	-3.1	0.008	-6.0	0.001	27.1	0.003
Ali/Aml 150/10 vs Ali 150	-8.1	<0.001	-13.7	<0.001	36.3	<0.001
Ali/Aml 150/10 vs Ami 10	-2.0	0.093	-2.2	0.26	13.4	0.052
Ali/Aml 300/5 vs Ali 300	-4.4	<0.001	-7.4	<0.001	20.1	0.001
Ali/Aml 300/5 vs Ami 5	-2.9	0.017	-5.8	0.003	18.7	0.003
Ali/Aml 300/10 vs Ali 300	-6.9	<0.001	-9.1	<0.001	33.1	<0.001
Ali/Aml 300/10 vs Ami 10	-2.9	0.015	-2.5	0.198	18.0	0.008

Table 29: Comparison of change from baseline to Endpoint in msDBP, msSBP, and BP control rate in patients with moderate and severe hypertension in Study SPA 2306 (Reviewer's table)

Treatment	Number of patients	msDBP (mmHg)	msSBP (mmHg)	BP control (%)			
Aml 10mg	230	-12.3	-30.6	49.1			
Ali/aml 300/10mg	233	-16.1	-37.7	67.0			
Ali/Aml vs Aml	233/230	-3.8	p<0.0001	-7.1	p<0.0001	17.9	p=0.0001

Reviewer's comments: In the pivotal study, the treatment effect of the combination of aliskiren/amlodipine on patients in stage 2 hypertension is similar to the overall population. Amlodipine at dose 10 mg makes the major contribution in the blood pressure reduction, especially for the systolic blood pressure. In the additional Study SPA 2306, as sample size increased, better results were observed.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose-response effects: For the fixed combination of aliskiren/amlodipine, placebo-subtracted reductions in trough mean sitting BP and in mean 24-hour mean ambulatory BP are shown in the following table 30. Aliskiren/amlodipine combinations containing 10 mg of amlodipine showed a greater BP reduction compared to those containing amlodipine 5 mg. Aliskiren/amlodipine 300/10 mg and aliskiren/amlodipine 150/10 mg showed a similar sitting BP reduction. However,

an incrementally greater ABPM BP reduction was seen for aliskiren/amlodipine 300/10 mg over 150/10 mg.

In the other short-term active control studies, Study SPA2304 showed a clinically meaningful incremental reduction in msSBP/msDBP (3.41/2.04 mmHg) for aliskiren/amlodipine 300/10 mg over the 150/10 mg dose. Study SPA2303 and Study SPA2304 showed clinically meaningful BP reductions for aliskiren/amlodipine 300/10 mg dose compared to 300/5 mg and 150/10 mg doses with incremental msDBP reduction of >2 mmHg. Data were summarized in the following table 31.

Table 30: Comparison of dose-response effect after placebo subtraction (Reviewer’s table)

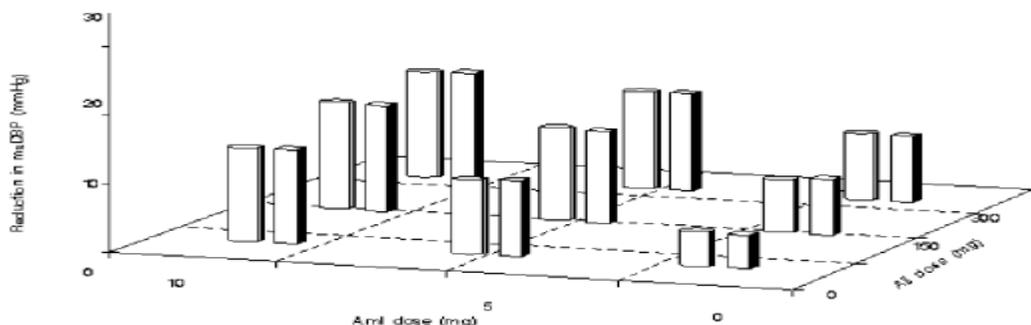
Treatment	Mean change from baseline (mmHg)		24 hours mean ABPM (mmHg)	
	msDBP	msSBP	MADBP	MASBP
Ali/Aml 150/5 mg	-8.7	-14.2	-5.7	-14.2
Ali/Aml 150/10mg	-10.9	-16.8	-12.2	-17.3
Ali/Aml 300/5 mg	-9.6	-14.8	-10.8	-16.0
Ali/Aml 300/10 mg	-11.0	-16.2	-13.7	-19.8

Table 31: Change from baseline in msDBP and msSBP by treatment group in Study SPA 2303 and Study SPA 2304. (Reviewer’s table)

Treatment	Study SPA 2303 (mmHg)		Study SPA 2304 (mmHg)	
	msDBP	msSBP	msDBP	msSBP
Ali/Aml 150/10 mg	/	/	-9.0	-11.0
Ali/Aml 300/5 mg	-10.5	-14.4	/	/
Ali/Aml 300/10	-13.1	-18.0	-11.0	-14.4

Dose-response analysis: The results of the dose-response surface analysis for msDBP and msSBP are presented graphically in the following Figures 6 and 7. The dose-response surface analyses indicated that the magnitude of reductions in msDBP and msSBP were related to the dose levels of both aliskiren and amlodipine.

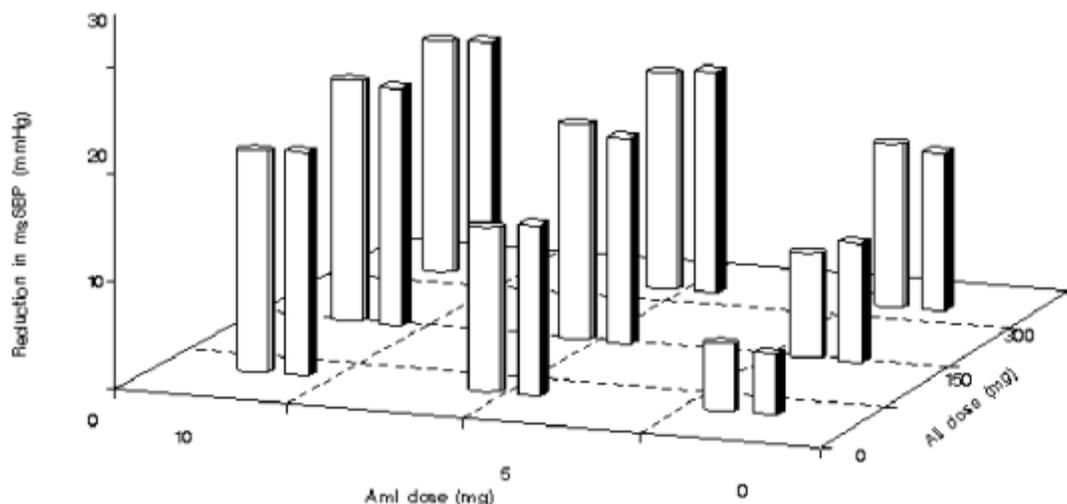
Figure 6: Dose-response surface analysis for change from baseline in msDBP at Endpoint in pivotal study (sponsor’s figure)



Pillar = raw mean

Prism = prediction in dose-response surface analysis

Figure 7: Dose-response surface analysis for change from baseline in msSBP at Endpoint in pivotal study (sponsor's figure)



Pillar = raw mean

Prism = prediction in dose-response surface analysis

Initial (first-line) therapy: Data from the pivotal study were used to support the use of the aliskiren/amlodipine fixed combination as initial therapy as all patients randomized to the aliskiren/amlodipine groups received the fixed combination treatment without the titration from the monotherapy.

To further support the first-line therapy, a supplemental analysis of SBP control (<140 or <130 mmHg) rate and DBP control (<90 or <80 mmHg) rate at Endpoint was performed using a logistic regression model with baseline msSBP and msDBP, respectively as covariate. These following figures were generated from these analyses to predict SBP and DBP control rates with the highest combination dose (aliskiren/amlodipine 300/10 mg) compared to monotherapy and placebo based on baseline BP. As expected, as baseline BP increases, 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 greater with the combination than either monotherapy.

Figure 8: Predicted probability curves of patients with SBP control (less than 140 mmHg) versus baseline msSBP (Sponsor's figure)

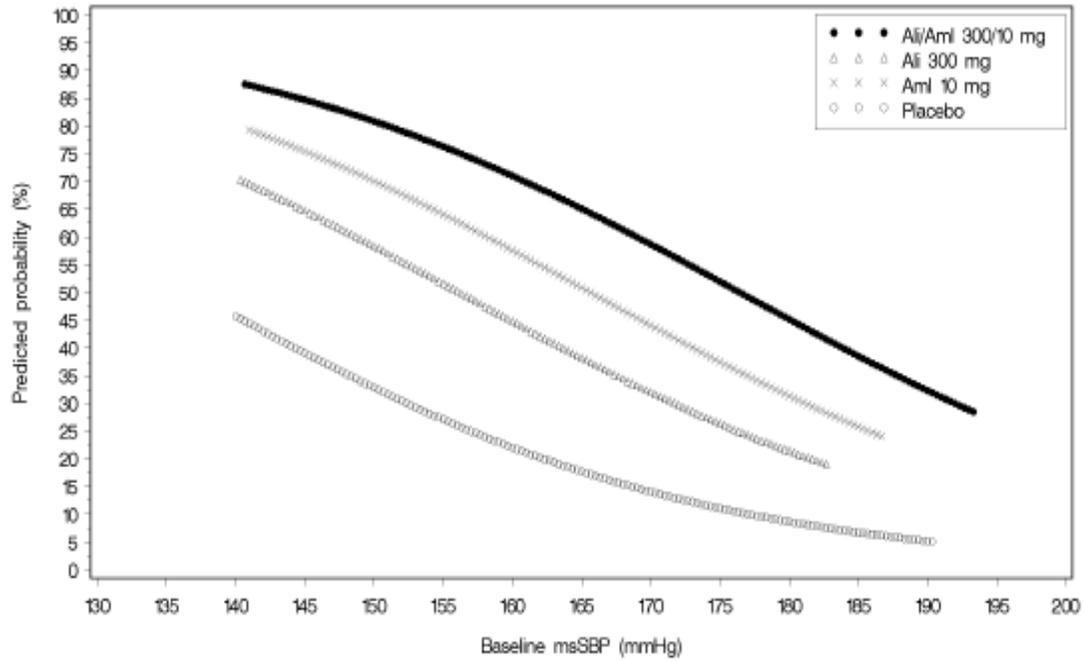


Figure 9: Predicted probability curves of patients with DBP control (less than 90 mmHg) versus baseline msDBP (Sponsor's figure)

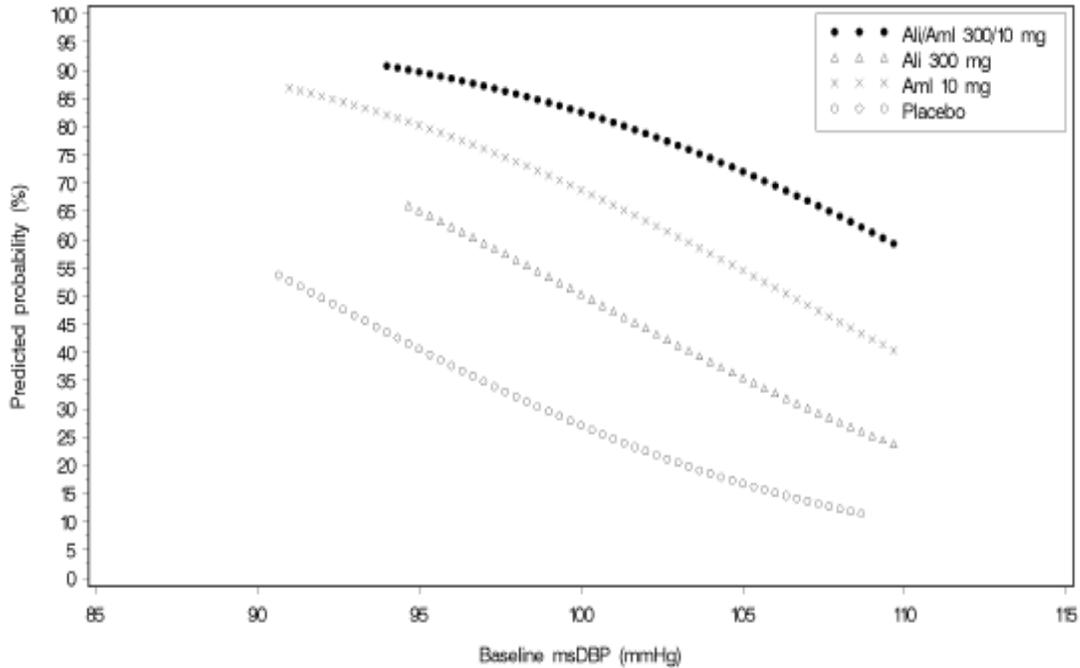


Figure 10: Predicted probability curves of patients with aggressive SBP control (less than 130 mmHg) versus baseline msSBP (Sponsor's figure)

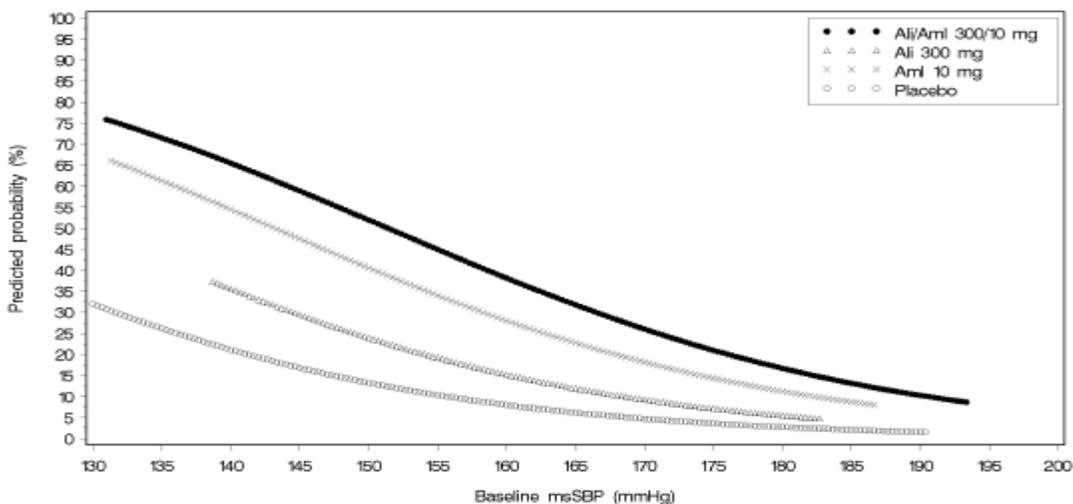
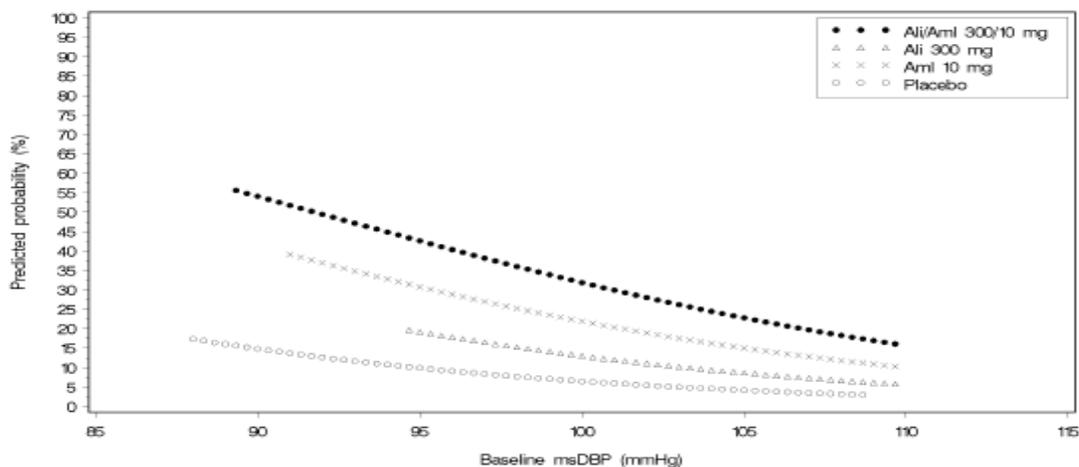


Figure 11: Predicted probability curves of patients with aggressive DBP control (less than 80 mmHg) versus baseline msDBP (Sponsor's figure)



Choice of dose and dosing interval: Both aliskiren and amlodipine have a long half-life (34 to 41 hours and 30 to 50 hours, respectively), supporting the long-lasting effect of these 2 drugs. Both aliskiren and amlodipine as monotherapy are currently approved for use with a once-daily dosing schedule. Efficacy data from office cuff BP measurement in all studies were obtained at approximately 24 hours after dosing (at trough) and thus reflect the drug's effect for the entire 24-hour period. In addition, ABPM in the pivotal study demonstrated a greater BP-lowering effect for all aliskiren/amlodipine doses over respective monotherapies at every hour throughout the entire 24 hours after dosing. Therefore, the data presented in this dossier and in the individual study reports supports the once-daily dosing of the combination of aliskiren and amlodipine.

The fixed combinations may be used as initial therapy for hypertensive patients who are likely to need multiple drugs to achieve BP control. In addition, a patient whose BP is not adequately controlled with aliskiren alone or amlodipine alone, may be switched to combination therapy with aliskiren/amlodipine. If BP remains uncontrolled after 2 to 4 weeks of therapy, the dose may be titrated up to a maximum of aliskiren 300 mg/amlodipine 10 mg. Dosing should be individualized and adjusted according to the patient’s clinical response. For convenience, patients already receiving aliskiren and amlodipine from separate tablets may be switched to a single aliskiren/amlodipine combination tablet of containing the same component doses.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy over prolonged periods was assessed by measuring changes in BP over a 54-week treatment period in Study SPA 2301, which is an open-label study to evaluate the long-term combination therapy of aliskiren and amlodipine in the target population. This study was a 54-week safety study that evaluated efficacy (change in BP relative to baseline) as a secondary objective. In this trial, hydrochlorothiazide (HCTZ) was an optional addition to therapy should a patient’s BP have remained uncontrolled. Please see section 5.3 for detailed information of the study design.

A total of 556 patients were evaluated in the 54-week long open label study. 443 patients (79.7%) exposure for at least 360 days and 480 patients (86.3%) had at least 6 months exposure to the aliskiren/amlodipine combination. Reductions in msDBPs and msSBPs were maintained for a treatment period of 1 year. The percentage of patients achieving a DBP response or BP control did not decrease over this treatment period. Data were summarized in the following tables 32 and 33.

Table 32: Patient’s exposure in Study SPA 2301 (Sponsor’s table).

Days	Aliskiren 150 mg/ Amlodipine 5 mg alone N=556	Aliskiren 300 mg/ Amlodipine 10 mg alone N=546	Aliskiren /Amlodipine alone N=556	Aliskiren 300 mg/ Amlodipine 10 mg/ HCTZ N=86	Pooled* Aliskiren 300 mg/ Amlodipine 10 mg N=546	Total N=556
≥ 1	556(100.0%)	546(100.0%)	556(100.0%)	86(100.0%)	546(100.0%)	556(100.0%)
≥ 14	445(80.0%)	542(99.3%)	551(99.1%)	83(96.5%)	542(99.3%)	551(99.1%)
≥ 30	0(0.0%)	527(96.5%)	539(96.9%)	81(94.2%)	527(96.5%)	539(96.9%)
≥ 60	0(0.0%)	473(86.6%)	522(93.9%)	78(90.7%)	518(94.9%)	524(94.2%)
≥ 90	0(0.0%)	440(80.6%)	458(82.4%)	76(88.4%)	505(92.5%)	514(92.4%)
≥ 150	0(0.0%)	416(76.2%)	419(75.4%)	72(83.7%)	483(88.5%)	486(87.4%)
≥ 180	0(0.0%)	405(74.2%)	412(74.1%)	71(82.6%)	477(87.4%)	480(86.3%)
≥ 270	0(0.0%)	391(71.6%)	394(70.9%)	57(66.3%)	463(84.8%)	465(83.6%)
≥ 330	0(0.0%)	380(69.6%)	380(68.3%)	0(0.0%)	452(82.8%)	452(81.3%)
≥ 360	0(0.0%)	292(53.5%)	372(66.9%)	0(0.0%)	350(64.1%)	443(79.7%)

* Includes Aliskiren 300 mg/Amlodipine 10 mg and Aliskiren 300 mg/Amlodipine 10 mg/HCTZ

Table 33: Effect of combination of aliskiren and amlodipine on change of msDBP and msSBP from baseline and BP control rates at selected weeks in Study 2301 (Treated population, Reviewer's table)

Time (Week)	Number of patients	msDBP (mmHg)	msSBP (mmHg)	BP control rate (%)
Week 2	467	-8.7	-14.1	165(35.3)
Week 10	440	-16.3	-25.0	387 (88.0%)
Week 28	416	-16.7	-26.4	367(88.2%)
Week 54	383	-16.3	-25.0	314 (82.0)
Endpoint ^a	467	-15.7	-24.2	361(77.3%)

a: Endpoint is the value at Week 54 or LOCF based on the availability of measurements.

Reviewer's comments: as an open label study without any control, it is hard to interpret this long-term effect and the persistence of efficacy.

The effect of treatment withdrawal was not studied specifically with aliskiren/amlodipine combination. Previous studies conducted using aliskiren monotherapy did not show any evidence for rebound or withdrawal effects (NDA 21-985, NDA 22-210). There was no evidence of rebound hypertension after abrupt cessation of aliskiren therapy. There is no mention of withdrawal or rebound effects in the prescribing information for amlodipine. Based on the existing data on both monotherapy, there is no evidence of potential rebound effects with the aliskiren/amlodipine combination treatment therapy.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

The safety analysis was based on nine clinical studies including one short-term pivotal study, four short-term active control studies and two long-term studies described in the original submission, and three short-term active control studies reported in the 120 day safety update. In addition, safety data from five completed clinical pharmacology studies, literature search from Jan-01-2000 to Jan-31-2010, and a review of post-marketing data, including spontaneous reports, reports received directly from worldwide regulatory authorities, and periodic safety updates, from over 75 countries in which aliskiren and amlodipine are registered for marketing (cut-off date: Jul-31-2009) were also evaluated.

In general, the incidence of AEs was similar across the aliskiren/amlodipine combination, component monotherapy, and placebo treatment arms. Peripheral edema, seen with amlodipine monotherapy and with the aliskiren/amlodipine combination, was the most common adverse event and was also the most common reason for AE-related patient withdrawals. The incidence of

peripheral edema with the 300/10 mg aliskiren/amlodipine combination was similar to that seen during monotherapy with amlodipine 10 mg. The combinations containing 5 mg amlodipine had a lower incidence of peripheral edema than those containing amlodipine 10 mg. In the short-term studies, peripheral edema was more common in females than in males during both combination therapy (17.9% vs 10.4%, respectively with 300/10 mg) and amlodipine monotherapy (21.3% vs 5.7%, respectively with 10 mg). As in the short-term studies, peripheral edema was also reported in a greater percentage of female (25.2%) than male (17.3%) patients in the long-term open label study.

Other than peripheral edema, no dose-dependent AEs were observed in the combination studies. Hypotension and related events were uncommon. In all of the short-term controlled studies, only 8 patients (0.4%) had an AE of hypotension reported in all treated arms. Dizziness and headache occurred in a similar number of patients in each of the combination, placebo and monotherapy groups. There was no increase in the incidence of diarrhea, an AE found to be associated with aliskiren during review of the aliskiren monotherapy development program (NDA 21-985), in the aliskiren/amlodipine treatment groups relative to the aliskiren and amlodipine monotherapy groups in the placebo-controlled pivotal study. During the long-term open label study, there were no additional safety findings compared to the short-term studies.

There were no significant changes in laboratory parameters including hemoglobin, hematocrit, serum levels of potassium, BUN, creatinine, and lipid in the combination groups compared to the each monotherapy groups. The incidence of hyperkalemia (defined as a serum potassium level >5.5 mmol/L at any post baseline visit) during aliskiren/amlodipine combination treatment was similar to that seen during aliskiren monotherapy. No patient was withdrawn due to a change in laboratory parameters in the combination or monotherapy groups.

Overall, the AE profile is considered to be acceptable for an antihypertensive therapy.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As discussed in the section 5.3, there are total nine clinical trials including seven short-term, placebo-controlled and active-controlled trials and two long-term open label trials for safety evaluation. Safety analyses and data from these studies are used to support the registration of aliskiren/ amlodipine for the treatment of hypertension.

The original NDA submission included six studies including four short-term controlled studies and two long-term open label studies as summarized in the following table 34.

Table 34: Summary of clinical trials for safety evaluation in original NDA submission (reviewer's table)

Study No	Objective	Patients treated	Duration	Daily dose (mg)	Type of trials
SPA 2305	Efficacy/safety	1685	8 weeks	9 groups: placebo; ali 150, 300; aml 5, 10; ali/aml 150/5, 150/10, 300/5, 300/10	Placebo double-blind
SPA2303	Efficacy/safety	818 not responding to ali	8 weeks	3 groups: ali/ami 300/5, 300/10; ali 300mg	Active double blind
SPA 2304	Efficacy/safety	843 not responding to aml	8 weeks	3 groups: ali/aml 150/10, 300/10; aml 10	Active double blind
SPP 2305	Efficacy/safety	544 not responding to aml	6 weeks	3 groups: ali/aml 150/5; aml 5, 10.	Active double blind
SPA 2301	Long-term safety/efficacy	556	54 weeks	Ali/Aml 150/5 for 2 weeks, then Ali/Aml 300/10 for 52 weeks (optional add-on of HCTZ 12.5 /25).	Uncontrolled, open-label
SPA 2323	Long-term efficacy/safety	1124	26 weeks	First 6 weeks: aliskiren 150, HCTZ 12.5, or placebo; Last 20 weeks: aliskiren 300 or HCTZ 25, (optional add-on of amlodipine 5/10)	Active double-blind with optional open-label amlodipine
SPA 2323 E1	Long-term efficacy/safety	965	26 weeks	Aliskiren 300, or HCTZ 25, optional add-on of amlodipine 5/10	Same as above

In the 120 days safety update, three short-term active-controlled trials were provided for the safety evaluation as summarized in the following table 35.

Table 35: Safety data presented in the 120 day safety update (Reviewer's table)

Study No	Objective	Patients treated	Duration	Daily dose (mg)	Type of trials
SPA 2306	Efficacy/safety	484	8 weeks	Two groups: aml 10; ali/aml 300/10	Active/double-blind
SPA US01	Efficacy/safety	443 African Americans	8 weeks	Two groups: aml 10; ali/aml 300/10	Active/ double-blind
SAH 2302	Efficacy/safety	2379	8weeks	Four groups: ali/aml, ali/HCTZ, aml/HCTZ, ali/aml/HCTZ	Active/ double-blind

Other source of data included in this safety evaluation include 5 completed clinical pharmacology trials as summarized in the following table 36, literature search from Jan-01-2000 to Jul-31-2009, and a review of post-marketing data, including spontaneous reports, reports received directly from worldwide regulatory authorities, and periodic safety updates, from over 75 countries in which aliskiren and amlodipine are registered for marketing (cut-off date: 31-Jul-2009).

Table 36: Clinical pharmacology and biopharmaceutical trials (Sponsor’s table)

Study No.	N	Objective	Population		Dosage form	Dose (mg)
SPA2101	60	Relative bioavailability; safety and tolerability	HS	M/F	Aliskiren/amlodipine tablet Aliskiren tablet Amlodipine tablet	300/10 300 2x5
SPA2102	120	Bioequivalence of fixed combo vs. free combo; safety and tolerability	HS	M	Aliskiren/amlodipine tablet Aliskiren tablet Amlodipine tablet	300/10 300 2x5
SPA2103	120	Bioequivalence of fixed combo vs. free combo; safety and tolerability	HS	M	Aliskiren/amlodipine tablet Aliskiren tablet Amlodipine tablet	150/10 150 2x5
SPA2104	36	Determine the effect of food on bioavailability; safety and tolerability	HS	M	Aliskiren/amlodipine tablet	300/10
SPP2218	25	Drug-drug interaction; safety and tolerability	HS	M/F	Amlodipine tablet Aliskiren tablet	10 300

7.1.2 Categorization of Adverse Events

Adverse events reported during each of the studies were classified using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs (new or worsened) was summarized by primary SOC, preferred term, and severity. In addition, the incidences of deaths, SAEs, and AEs leading to discontinuation were summarized by primary SOC and preferred term. Data from studies not included in the pooling were listed separately for the evaluation of deaths and SAEs. Data are presented as absolute numbers and frequencies in percent for appropriately defined groupings.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In the original NDA submission, studies were pooled into 4 groups, according to the type of clinical trial including:

- Group A comprised the safety population from the pivotal study-Study SPA2305;
- Group B comprised the pooled safety populations from all short-term, double-blind, placebo and active controlled studies-Study SPA2305, Study SPA2303, Study SPA2304, and Study SPP2305;
- Group C comprised the safety population from the one long-term open-label, uncontrolled Study-Study SPA2301;

- Group D comprised the safety populations from the 26 weeks, double-blind of aliskiren or HCTZ with an open-label option of amlodipine- Study SPP2323 and Study SPP2323E1.

In the 120-day safety update, two studies were pooled to provide an integrated safety profile.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the original NDA submission, the studies were pooled into 4 groups for safety valuation based on the type of clinical trials. Overall, 5549 patients were included in the safety analysis of this aliskiren/amlodipine clinical development program, with 2835 being exposed to aliskiren/amlodipine combination. There were 1396 patients exposed to the high-dose combination (300/10 mg). The overall drug exposure from all studies including all treatment, all doses, and durations for all subjects who received at least one dose of study drug were summarized in the following table 37.

Table 37: Doses and duration of exposure to study drug after randomization in all studies (Sponsor's table)

	Placebo	Mono Ali	Mono Aml	Ali/Aml 150/5 mg	Ali/Aml 150/10 mg	Ali/Aml 300/5 mg	Ali/Aml 300/10mg	All Ali/Aml	All Ali/Aml/HCTZ	Mono HCTZ	All HCTZ/Aml	Total
Exposure duration (days)	N=198 n (%)	N=1218 n (%)	N=1004 n (%)	N=924 n (%)	N=464 n (%)	N=702 n (%)	N=1396 n (%)	N=2835 n (%)	N=86 n (%)	N=554 n (%)	N=266 n (%)	N=5549 n (%)
>= 1	198 (100.0)	1218 (100.0)	1004 (100.0)	924 (100.0)	464 (100.0)	702 (100.0)	1396 (100.0)	2835 (100.0)	86 (100.0)	544 (100.0)	266 (100.0)	5549 (100.0)
>= 14	191 (96.5)	1192 (97.9)	983 (97.9)	806 (87.2)	459 (98.9)	695 (99.0)	1380 (98.9)	2801 (98.8)	83 (96.5)	538 (96.9)	262 (98.5)	5455 (98.3)
>= 28	181 (91.4)	1163 (95.5)	961 (95.7)	354 (38.3)	453 (97.6)	675 (96.2)	1345 (96.3)	2750 (97.0)	83 (96.5)	522 (96.0)	252 (94.7)	5336 (96.2)
>= 42	171 (86.4)	1135 (93.2)	864 (86.1)	307 (33.2)	441 (95.0)	656 (93.4)	1323 (94.8)	2659 (93.8)	79 (91.9)	506 (93.0)	249 (93.6)	5123 (92.3)
>= 56	129 (65.2)	990 (81.3)	477 (47.5)	136 (14.7)	343 (73.9)	534 (76.1)	1177 (84.3)	2165 (76.4)	78 (90.7)	479 (88.1)	247 (92.9)	4067 (73.3)
>= 180	0 (0.0)	302 (24.8)	0 (0.0)	0 (0.0)	0 (0.0)	113 (16.1)	478 (34.2)	612 (21.6)	71 (82.6)	256 (47.1)	203 (76.3)	1456 (26.2)
>= 270	0 (0.0)	271 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	58 (8.3)	391 (28.0)	519 (18.3)	57 (66.3)	219 (40.3)	142 (53.4)	1402 (25.3)
>= 360	0 (0.0)	196 (16.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	292 (20.9)	372 (13.1)	0 (0.0)	157 (28.9)	0 (0.0)	1140 (20.5)
Total person years	28.20	439.62	136.40	69.81	69.54	173.27	585.71	898.33	57.85	300.62	163.40	2024.43
N	198	1218	1004	924	464	702	1396	2835	86	544	266	5549
Mean	52.0	131.8	49.6	27.6	54.7	90.1	153.2	115.7	245.7	201.8	224.4	133.3
SD	13.91	124.42	10.97	17.92	8.53	75.61	136.57	118.24	93.49	133.28	83.94	135.27
Median	56.0	59.0	55.0	15.0	56.0	56.0	58.0	56.0	296.5	147.0	272.5	56.0
Minimum	3	1	1	1	1	1	3	1	12	1	2	1
Maximum	75	426	75	69	70	328	396	407	324	422	302	426

The demographics of the target populations were described in the four groups based on the type of clinical studies.

Group A: In the pivotal study SPA 2305, the mean age of patients ranged from 53.0 to 55.0 years. The majority of patients (82.8%) were less than 65 years of age. There were 17.2% of all patients ≥ 65 years of age and 2.7% of all patients were ≥ 75 years of age. The percentages of patients for each age group were similar across treatment groups. The number of male and female patients participating in the study was approximately the same. Caucasian patients accounted for the majority (approximately 62%) of the study population followed by Black patients (approximately 20%). The number of patients of other races was small. Approximately 18% of the total population was Hispanic/Latino in ethnicity. A large percentage of patients (46.0% of the total population) were obese (BMI ≥ 30 kg/m²) with mean BMI 30.3 kg/m² in the total population. A total of 11.0% of all patients had a diagnosis of diabetes (ranging from 6.1% to 16.4%). Patients with $30 \leq$ estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m² comprised 4.4% of the total population. Data were summarized in the following table 38.

Table 38: Demographics by treatment group (randomized set), Group A, Study SPA2305: short-term, double-blind, placebo-controlled study (Sponsor's table)

Treatment Group	Number of Patients	Age (yrs) Mean (SD)	Sex n (%)		Race n (%)		
			Male	Female	Caucasian	Black	Other
Placebo	198	53.7 (10.32)	90 (45.5)	108 (54.5)	119 (60.1)	39 (19.7)	23 (11.6)
Alii 150 mg	195	54.3 (11.07)	119 (61.0)	76 (39.0)	123 (63.1)	36 (18.5)	20 (10.3)
Alii 300 mg	203	54.0 (9.99)	95 (46.8)	108 (53.2)	127 (62.6)	39 (19.2)	24 (11.8)
Mono Alii	398	54.2 (10.52)	214 (53.8)	184 (46.2)	250 (62.8)	75 (18.8)	44 (11.1)
Aml 5mg	185	54.2 (11.61)	99 (53.5)	86 (46.5)	121 (65.4)	36 (19.5)	16 (8.6)
Aml 10mg	181	55.0 (10.34)	87 (48.1)	94 (51.9)	113 (62.4)	34 (18.8)	22 (12.2)
Mono Aml	366	54.6 (10.99)	186 (50.8)	180 (49.2)	234 (63.9)	70(19.1)	38 (10.4)
Alii/Aml 150/5 mg	181	53.9 (10.82)	97 (53.6)	84 (46.4)	112 (61.9)	38 (21.0)	17 (9.4)
Alii/Aml 150/10 mg	183	53.0 (10.59)	87 (47.5)	96 (52.5)	108 (59.0)	41 (22.4)	20 (10.9)
Alii/Aml 300/5 mg	178	54.8 (10.29)	78 (43.8)	100 (56.2)	110 (61.8)	38 (21.3)	18 (10.1)
Alii/Aml 300/10 mg	184	54.4 (10.86)	106 (57.6)	78 (42.4)	116 (63.0)	35 (19.0)	17 (9.2)
All Alii/Aml	726	54.0 (10.65)	368 (50.7)	358 (49.3)	446 (61.4)	152 (20.9)	72 (9.9)
Total	1688	54.1 (10.65)	858 (50.8)	830 (49.2)	1049 (62.1)	336 (19.9)	177 (10.5)

	BMI status n (%)				Diabetes n (%)		eGFR (mL/min/1.73m ²)		
	BMI < 20 kg/m ²	20 <= BMI < 25 kg/m ²	25 <= BMI < 30 kg/m ²	BMI >= 30 kg/m ²	Yes	No	30<= eGFR < 60	60 <= eGFR < 90	eGFR >= 90
Placebo	2 (1.0)	28 (14.1)	74 (37.4)	93 (47.0)	15 (7.6)	183 (92.4)	8 (4.0)	88 (44.4)	98 (49.5)
Alii 150 mg	0 (0.0)	16 (8.2)	88 (45.1)	91 (46.7)	25 (12.8)	170 (87.2)	9 (4.6)	89 (45.6)	92 (47.2)
Alii 300 mg	0 (0.0)	29 (14.3)	79 (38.9)	95 (46.8)	24 (11.8)	179 (88.2)	9 (4.4)	93 (45.8)	97 (47.8)
Mono Alii	0 (0.0)	45 (11.3)	167 (42.0)	186 (46.7)	49 (12.3)	349 (87.7)	18 (4.5)	182 (45.7)	189 (47.5)
Aml 5mg	2 (1.1)	25 (13.5)	72 (38.9)	86 (46.5)	17 (9.2)	168 (90.8)	12 (6.5)	85 (45.9)	83 (44.9)
Aml 10mg	3 (1.7)	27 (14.9)	76 (42.0)	74 (40.9)	11 (6.1)	170 (93.9)	5 (2.8)	89 (49.2)	84 (46.4)
Mono Aml	5 (1.4)	52 (14.2)	148 (40.4)	160 (43.7)	28 (7.7)	338 (92.3)	17 (4.6)	174 (47.5)	167 (45.6)
Alii/Aml 150/5 mg	2 (1.1)	22 (12.2)	78 (43.1)	79 (43.6)	21 (11.6)	160 (88.4)	6 (3.3)	91 (50.3)	82 (45.3)
Alii/Aml 150/10 mg	1 (0.5)	26 (14.2)	69 (37.7)	86 (47.0)	30 (16.4)	153 (83.6)	9 (4.9)	82 (44.8)	90 (49.2)
Alii/Aml 300/5 mg	1 (0.6)	25 (14.0)	72 (40.4)	78 (43.8)	17 (9.6)	161 (90.4)	6 (3.4)	80 (44.9)	87 (48.9)
Alii/Aml 300/10 mg	1 (0.5)	27 (14.7)	62 (33.7)	94 (51.1)	25 (13.6)	159 (86.4)	10 (5.4)	93 (50.5)	77 (41.8)
All Alii/Aml	5 (0.7)	100 (13.8)	281 (38.7)	337 (46.4)	93 (12.8)	633 (87.2)	31 (4.3)	346 (47.7)	336 (46.3)
Total	12 (0.7)	225 (13.3)	670 (39.7)	776 (46.0)	185 (11.0)	1503 (89.0)	74 (4.4)	790 (46.8)	790 (46.8)

Group B: In the short-term, double-blind, all controlled studies, the mean age of Group B patients was 54.2 years. The majority of patients (82.1%) were less than 65 years of age. There were 17.9% of all patients ≥ 65 years of age and 2.8% of all patients were ≥ 75 years of age. The

percentages of patients for each age group were similar in the placebo, Mono Ali, Mono Aml and All Ali/Aml groups. There was a greater percentage of men than women (55.5% vs. 44.5%, respectively, of total) in all except the placebo group. Caucasian patients accounted for the majority (72.1%) of the population followed by Black patients (11.1%). The number of patients of other races was small, and 10.5% of the total population was Hispanic/Latino in ethnicity. A large percentage of patients (44.1% of the total population) were obese (BMI ≥ 30 kg/m²), and 12.3% of all patients had a diagnosis of diabetes (although the percentage was lower in the placebo group (7.6%)). As in the placebo-controlled study, patients with 30 ≤ eGFR < 60 mL/min/1.73m² comprised 4.4% of the total population in all controlled studies. Data were summarized in the following 39.

Table 39: Demographics by treatment group (randomized set), Group B: short-term, double blind, all controlled studies (Sponsor’s table).

Treatment Group	Number of Patients	Age (yrs) Mean (SD)	Sex n (%)		Race n (%)		
			Male	Female	Caucasian	Black	Other
Placebo	198	53.7 (10.32)	90 (45.5)	108 (54.5)	119 (60.1)	39 (19.7)	23 (11.6)
Mono Ali	658	54.4 (10.70)	371 (56.4)	287 (43.6)	423 (64.3)	75 (11.4)	60 (9.1)
Mono Aml	1007	54.2 (10.88)	557 (55.3)	450 (44.7)	766 (76.1)	132 (13.1)	44 (4.4)
All Ali/Aml	2037	54.3 (10.73)	1147 (56.3)	890 (43.7)	1505 (73.9)	187 (9.2)	115 (5.6)
Total	3900	54.2 (10.74)	2165 (55.5)	1735 (44.5)	2813 (72.1)	433 (11.1)	242 (6.2)

Treatment Group	BMI status n (%)				Diabetes n (%)		eGFR (mL/min/1.73m ²)		
	BMI < 20 kg/m ²	20 ≤ BMI < 25 kg/m ²	25 ≤ BMI < 30 kg/m ²	BMI ≥ 30 kg/m ²	Yes	No	30 ≤ eGFR < 60	60 ≤ eGFR < 90	eGFR ≥ 90
Placebo	2 (1.0)	28 (14.1)	74 (37.4)	93 (47.0)	15 (7.6)	183 (92.4)	8 (4.0)	88 (44.4)	98 (49.5)
Mono Ali	3 (0.5)	100 (15.2)	269 (40.9)	284 (43.2)	85 (12.9)	573 (87.1)	28 (4.3)	315 (47.9)	298 (45.3)
Mono Aml	12 (1.2)	140 (13.9)	403 (40.0)	447 (44.4)	118 (11.7)	889 (88.3)	46 (4.6)	526 (52.2)	427 (42.4)
All Ali/Aml	20 (1.0)	291 (14.3)	825 (40.5)	894 (43.9)	263 (12.9)	1774 (87.1)	89 (4.4)	1044 (51.3)	883 (43.3)
Total	37 (0.9)	559 (14.3)	1571 (40.3)	1718 (44.1)	481 (12.3)	3419 (87.7)	171 (4.4)	1973 (50.6)	1706 (43.7)

Group C: In the long-term open label study SPA 2301, the mean age overall was 54.4 years. The majority of all patients (81.8%) were less than 65 years of age. There were 18.2% of all patients ≥ 65 years of age and 4.3% of all patients were ≥ 75 years of age. Overall, a higher percentage of patients were male (59.4%) than female (40.6%); and most patients (86.0%) were Caucasian. A large percentage of patients (48.7% of the total population) were obese (BMI ≥ 30 kg/m²). There were 16.0% of all patients with a diagnosis of diabetes at baseline. Patients with 30 ≤ eGFR < 60 mL/min/1.73m² comprised 4.0% of the population in this study. Data were summarized in the following table 40.

Table 40: Demographics by treatment group (safety set), Group C: long-term, open-label study (sponsor’s table).

Treatment Group	Number of Patients	Age (yrs) Mean (SD)	Sex n (%)		Race n (%)		
			Male	Female	Caucasian	Black	Other
All Ali/Aml	470	54.2 (11.66)	274 (58.3)	196 (41.7)	406 (86.4)	15 (3.2)	12 (2.6)
All Ali/Aml/HCTZ	86	55.7 (11.33)	56 (65.1)	30 (34.9)	72 (83.7)	8 (9.3)	1 (1.2)
Total	556	54.4 (11.61)	330 (59.4)	226 (40.6)	478 (86.0)	23 (4.1)	13 (2.3)

Treatment Group	BMI status n (%)				Diabetes n (%)		eGFR (mL/min/1.73m ²)		
	BMI < 20 kg/m ²	20 ≤ BMI < 25 kg/m ²	25 ≤ BMI < 30 kg/m ²	BMI ≥ 30 kg/m ²	Yes	No	30 ≤ eGFR < 60	60 ≤ eGFR < 90	eGFR ≥ 90
All Ali/Aml	7 (1.5)	83 (17.7)	163 (34.7)	216 (46.0)	73 (15.5)	397 (84.5)	16 (3.4)	234 (49.8)	220 (46.8)
All Ali/Aml/HCTZ	0 (0.0)	4 (4.7)	25 (29.1)	55 (64.0)	16 (18.6)	70 (81.4)	6 (7.0)	41 (47.7)	39 (45.3)
Total	7 (1.3)	87 (15.6)	188 (33.8)	271 (48.7)	89 (16.0)	467 (84.0)	22 (4.0)	275 (49.5)	259 (46.6)

Group D: The mean age of patients ranged from 55.0 to 57.6 years. The majority of all patients (77.2%) were <65 years of age, but there was a greater percentage of patients ≥ 65 years of age in Group D than in the short-term studies and in the open-label, long-term study. There were 22.8% of all patients ≥ 65 years of age and 3.4% of all patients were ≥ 75 years of age. Overall, a greater percentage of patients were male (55.0%) than female (45.0%); and most patients (99.0%) were Caucasian. The number of patients of other races was small. A large percentage of patients (35.2% of the total population) were obese (BMI ≥ 30 kg/m²). There were 11.0% of all patients with a diagnosis of diabetes at baseline. Patients with 30 ≤ eGFR 60 mL/min/1.73m² comprised 6.0% of the total population. Data were summarized in the following table 41.

Table 41: Demographics by treatment group (randomized set), Group D: long-term, double-blind studies (Sponsor's table)

Treatment Group	Number of Patients	Age (yrs) Mean (SD)	Sex n (%)		Race n (%)		
			Male	Female	Caucasian	Black	Other
Mono Ali	313	55.0 (11.41)	159 (50.8)	154 (49.2)	311 (99.4)	1 (0.3)	0 (0.0)
All Ali/Aml	248	57.6 (10.08)	144 (58.1)	104 (41.9)	244 (98.4)	0 (0.0)	0 (0.0)
Mono HCTZ	277	55.6 (10.55)	134 (48.4)	143 (51.6)	276 (99.6)	0 (0.0)	0 (0.0)
All HCTZ/Aml	265	55.9 (11.28)	170 (64.2)	95 (35.8)	261 (98.5)	0 (0.0)	1 (0.4)
Total	1103	55.9 (10.90)	607 (55.0)	496 (45.0)	1092 (99.0)	1 (0.1)	1 (0.1)

	BMI status n (%)				Diabetes n (%)		eGFR (mL/min/1.73m ²)		
	BMI < 20 kg/m ²	20 ≤ BMI < 25 kg/m ²	25 ≤ BMI < 30 kg/m ²	BMI ≥ 30 kg/m ²	Yes	No	30 ≤ eGFR < 60	60 ≤ eGFR < 90	eGFR ≥ 90
Mono Ali	3 (1.0)	66 (21.1)	141 (45.0)	101 (32.3)	32 (10.2)	281 (89.8)	13 (4.2)	185 (59.1)	115 (36.7)
All Ali/Aml	0 (0.0)	43 (17.3)	99 (39.9)	104 (41.9)	30 (12.1)	218 (87.9)	15 (6.0)	145 (58.5)	88 (35.5)
Mono HCTZ	3 (1.1)	65 (23.5)	122 (44.0)	87 (31.4)	30 (10.8)	247 (89.2)	17 (6.1)	171 (61.7)	89 (32.1)
All HCTZ/Aml	0 (0.0)	33 (12.5)	134 (50.6)	96 (36.2)	29 (10.9)	236 (89.1)	21 (7.9)	153 (57.7)	91 (34.3)
Total	6 (0.5)	207 (18.8)	496 (45.0)	388 (35.2)	121 (11.0)	982 (89.0)	66 (6.0)	654 (59.3)	383 (34.7)

Reviewer's comments: The total number of patients exposed to aliskiren/ amlodipine in long-term (6 month and 1 year) studies was 612 and 372, respectively. So the number of patients and the duration were reasonable based on the ICH E1 guidance for safety evaluation in patients with non-life threatening chronic disease.

In all four groups, the treatment groups were generally similar with respect to demographics and baseline characteristics, and reflected the intended target population.

The participation and withdraws in these studies were also described based on the four groups. In group A, there are more than 90% of all patients completing the study. There were more discontinuations in the placebo group due to lack of efficacy and more discontinuations for safety reasons in the amlodipine 10 mg monotherapy group. The number of discontinuations was similar or lower for the All Ali/Aml group than for either monotherapy. In group B, there are more than 90% of all patients completing the study. There were more discontinuations in the placebo group due to lack of efficacy. The percentage of patients discontinued was lower for the All Ali/Aml group than for either monotherapy group. In group C, more than 80% of all patients completed this 12 month study. Safety reasons were the most frequently reported cause for discontinuation. In group D, the study was completed by 92.3% of all patients treated with Ali/Aml and 87.9% of patients treated with HCTZ/Aml. The most frequently reported reason for discontinuation in both groups was safety. The total percentage of discontinuations and

discontinuations due to safety were greater in the HCTZ/amlodipine group (12.5% and 7.2%, respectively) than in aliskiren/amlodipine group (7.3% and 4.0%, respectively). Data were summarized in the following tables 42, 43, 44, and 45.

Table 42: Patient participation and withdrawals, Group A, Study SPA2305: short-term, double-blind, placebo-controlled study (Sponsor's table)

Treatment Group	Rand	Treated n (%)	Completed n (%)	Discontinued n (%)			
				Total	Safety	Lack of efficacy	Other
Placebo	198	198 (100)	168 (84.8)	30 (15.2)	4 (2.0)	17 (8.6)	9 (4.5)
Ali 150 mg	195	194 (99.5)	175 (89.7)	19 (9.7)	4 (2.1)	8 (4.1)	7 (3.6)
Ali 300 mg	203	203 (100)	184 (90.6)	19 (9.4)	1 (0.5)	8 (3.9)	10 (4.9)
Mono Ali	398	397 (99.7)	359 (90.2)	38 (9.5)	5 (1.3)	16 (4.0)	17 (4.3)
Aml 5mg	185	185 (100)	173 (93.5)	12 (6.5)	2 (1.1)	4 (2.2)	6 (3.2)
Aml 10mg	181	181 (100)	162 (89.5)	19 (10.5)	8 (4.4)	2 (1.1)	9 (5.0)
Mono Aml	366	366 (100)	335 (91.5)	31 (8.5)	10 (2.7)	6 (1.6)	15 (4.1)
Ali/Aml 150/5 mg	181	181 (100)	169 (93.4)	12 (6.6)	3 (1.7)	2 (1.1)	7 (3.9)
Ali/Aml 150/10 mg	183	181 (98.9)	170 (92.9)	11 (6.0)	4 (2.2)	1 (0.5)	6 (3.3)
Ali/Aml 300/5 mg	178	178 (100)	168 (94.4)	10 (5.6)	2 (1.1)	1 (0.6)	7 (3.9)
Ali/Aml 300/10 mg	184	184 (100)	170 (92.4)	14 (7.6)	4 (2.2)	2 (1.1)	8 (4.3)
All Ali/Aml	726	724 (99.7)	677 (93.3)	47 (6.5)	13 (1.8)	6 (0.8)	28 (3.9)
Total	1688	1685 (99.8)	1539 (91.2)	146 (8.6)	32 (1.9)	45 (2.7)	69 (4.1)

Table 43: Patient participation and withdrawals, Group B: short-term, double blind, all controlled studies (Sponsor's table)

Treatment Group	Randomized	Treated n (%)	Completed n (%)	Discontinued n (%)			
				Total	Safety	Lack of efficacy	Other
Placebo	198	198 (100)	168 (84.8)	30 (15.2)	4 (2.0)	17 (8.6)	9 (4.5)
Mono Ali	658	657 (99.8)	603 (91.6)	54 (8.2)	8 (1.2)	25 (3.8)	21 (3.2)
Mono Aml	1007	1004 (99.7)	931 (92.5)	74 (7.3)	36 (3.6)	7 (0.7)	31 (3.1)
All Ali/Aml	2037	2031 (99.7)	1919 (94.2)	112 (5.5)	50 (2.5)	8 (0.4)	54 (2.7)
Total	3900	3890 (99.7)	3621 (92.8)	270 (6.9)	98 (2.5)	57 (1.5)	115 (2.9)

Table 44: Patient participation and withdrawals, Group C: long-term, open-label Study (Sponsor's table)

Treatment Group	Randomized	Treated n (%)	Completed n (%)	Discontinued n (%)			
				Total	Safety	Lack of efficacy	Other
All Ali/Aml	470	470 (100)	379 (80.6)	91 (19.4)	60 (12.8)	1 (0.2)	30 (6.4)
All Ali/Aml/HCTZ	86	86 (100)	73 (84.9)	13 (15.1)	7 (8.1)	2 (2.3)	4 (4.7)
Total	556	556 (100)	452 (81.3)	104 (18.7)	67 (12.1)	3 (0.5)	34 (6.1)

Table 45: Patient participation and withdrawals, Group D: long-term study of aliskiren vs HCTZ with the open label option of amlodipine (Sponsor's table)

Treatment Group	Rand	Treated n (%)	Completed n (%)	Discontinued n (%)			
				Total	Safety	Lack of efficacy	Other
Mono Ali	313	313 (100.0)	263 (84.0)	50 (16.0)	18 (5.8)	4 (1.3)	28 (8.9)
All Ali/Aml	248	247* (99.6)	229 (92.3)	18 (7.3)	10 (4.0)	0 (0.0)	8 (3.2)
Mono HCTZ	277	277 (100.0)	206 (74.4)	71 (25.6)	20 (7.2)	8 (2.9)	43 (15.5)
All HCTZ/Aml	265	266* (100.4)	233 (87.9)	33 (12.5)	19 (7.2)	5 (1.9)	9 (3.4)
Total	1103	1103 (100.0)	931 (84.4)	172 (15.6)	67 (6.1)	17 (1.5)	88 (8.0)

7.2.2 Explorations for Dose Response

Overall, there was no clear relationship between the doses and adverse events other than the peripheral edema in Group A. In Group A, the incidence of peripheral edema was similar in the aliskiren/amlodipine 300/10 mg and amlodipine 10 mg groups (13.6% and 13.8%, respectively) while it was lower in the aliskiren/amlodipine 150/10 mg group (7.7%), aliskiren/amlodipine 150/5 mg (2.2%) and aliskiren/amlodipine 300/5 mg (1.1%). In group B: Peripheral edema was also the most common AE. Ali/Aml groups were reported for 5.9% of patients, which was lower than the percentage reported for patients treated with amlodipine monotherapy (8.4%). In group C, two patients who received Ali/Aml 300/10 mg had severe diarrhea, of which one event was an SAE. There were no other dose-related adverse event findings.

7.2.3 Special Animal and/or In Vitro Testing

Neither special animal nor in vitro testing was done.

7.2.4 Routine Clinical Testing

The routine clinical testing including adverse event data collection in both short-term and long-term studies, monitoring laboratory parameters, vital signs, and physical examinations are adequate.

Thorough QT study was not performed with the product. However, full QT study with aliskiren has been conducted and no abnormal findings were observed. Amlodipine was approved in 1987 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 amlodipine.

7.2.5 Metabolic, Clearance, and Interaction Workup

There was an open label, two-period, multiple dose trial to investigate any pharmacokinetic drug-drug interaction potential between aliskiren and amlodipine following multiple oral dose administration in healthy subjects. A total of 25 subjects between 18 and 45 years of age were enrolled. Eighteen (18) subjects (10 female and 8 male) completed the study. In Period 1 (study days 1-14), all subjects received a dose of 10 mg amlodipine once daily. Period 1 was followed by a 7 day washout period (study days 15-21). In Period 2 (study days 22-49), the subjects received a dose of 300 mg aliskiren alone once daily for 14 days (study days 22-35), followed by 300 mg aliskiren once daily co-administered with a dose of 10 mg amlodipine once daily for the last 14 days (study days 36-49). All drug administration was conducted under fasted conditions in order to have the most sensitive condition to assess potential drug-drug interaction.

Although there was a slight increase in steady-state exposure of aliskiren according to the ratio of geometric means (18% and 29% increases for C_{max} and AUC, respectively) when two drugs were co-administered as compared to aliskiren alone, given the large intra-subject pharmacokinetic variability observed in the study (intra-subject CV = 33% and 68%, respectively, for AUC and C_{max}) and the overall safety of aliskiren the changes were not found

to be statistically significant nor considered to be clinically relevant. Therefore, the impact on the pharmacokinetics is not considered clinically relevant when aliskiren and amlodipine are co-administered at steady-state as compared to administration of either drug alone.

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

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Based on the safety profiles of aliskiren and calcium blockers, the evaluation for potential adverse events was adequate

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in all of the submitted studies.

7.3.2 Nonfatal Serious Adverse Events

In group A, the Pivotal Study SPA 2305: Ten nonfatal SAEs were reported in 9 patients including 2 (0.5%) patients in amlodipine monotherapy, 5 (0.7%) patients in aliskiren/amlodipine therapy, and 2 (1.0%) patients in placebo. Data were brief summarized in the following table 46. Two possible SAEs in aliskiren/amlodipine group including cerebrovascular accident and gastroenteritis could be drug related and were described in the following:

One patient (470-3) in aliskiren/amlodipine 150/5 mg had cerebrovascular accident. This 63 year old male was diagnosed with hypertension in 1976. The patient's significant past medical history included benign hypertrophic prostrate (2004), left ventricular hypertrophy (2006), type 2 diabetes mellitus (2006), dyslipidemia (2006), hyperuricemia (2006) and dizziness (2007). On [REDACTED]^{(b) (6)} of the aliskiren/amlodipine 150/5 mg treatment, the patient experienced the adverse event of cerebrovascular accident, and was admitted to hospital. The patient experienced right arm debility and emergency room consultation showed mild right arm paresis. A brain tomography was normal. The patient was at this time admitted and diagnosed with cerebrovascular accident. An echocardiogram on the 27-Jan-09 showed mild dysfunction of left ventricle. The patient is reported to have recovered with sequelae of mild paresis in right hand and was discharged on [REDACTED]^{(b) (6)}, but did not complete the study being discontinued on 28-Jan-09 due to this event.

One patient (174-7) in aliskiren/amlodipine 300/5 mg had gastroenteritis. This 34 year old male was diagnosed with hypertension in 2008. On [REDACTED]^{(b) (6)} of the aliskiren/amlodipine

300/5 mg treatment, the patient experienced the adverse event of gastroenteritis and was hospitalized. The patient was considered to have fully recovered after 3 days and was discharged on the (b) (6). No description of the events such as amount, color or nature of the stool was provided. The event occurred on the final visit and so the patient completed the study.

Table 46: Brief summary of SAE in Group A (Reviewer’s table)

ID	SAE	Study medication	Recovery	Study	
				Interrupt ^a	Complete
42-1	Pneumonia	Aml 10mg	Yes	No	Yes
230-6	Pneumonia	Aml 5mg	Yes	No	Yes
174-7	Gastroenteritis	Ali/aml 300/5 mg	Yes	No	Yes
470-3	Cerebrovascular accident	Ali/aml 150/5mg	Yes	Yes	No
703-5	Ureter stone and hydronephrosis	Ali/aml 150/10mg	Yes	No	Yes
707-7	Acute bronchitis	Ali/aml 150/10 mg	Yes	No	Yes
745-4	left retinal detachment	Ali/aml 300/10 mg		No	
358-16	Fracture of right finger/hand	placebo	Yes	No	Yes
174-1	Lower abdominal mass	placebo	Yes	Yes	No

a: test product stopped during the SAE.

In group B, all of the short-term controlled studies: The percentage of patients with any SAE was 1.0% in the placebo group, 0.2% in the aliskiren monotherapy group, 0.5% in the amlodipine monotherapy group and 0.9% in the combined group. Other than the SAEs in Study SPA 2305 described in above, the SAEs in Studies SPA 2303 and 2304 were summarized in the following table 47.

One of SAEs, the allergy to cough syrup could be drug related and was described in the following: Patient (601-53) is a 64 year old male Asian and had a 3-month history of hypertension prior to entering the study. The patient did not have any medication allergies and had never experienced previous edematous episodes. Concomitant medications taken during the study included acetylsalicylic acid, glyceryl trinitrate, famotidine, paracetamol, fenofibrate, and atorvastatin. On the evening of (b) (6) the patient took cough syrup, which contained antimony potassium tartrate, opium tincture, papaver somniferum tincture, and terpin hydrate, and experienced lip swelling (hour unknown). The patient was hospitalized due to this event on the same evening. Symptoms included swelling of the lips but no other allergic reactions. It was reported that the patient experienced face edema. No signs of angioedema, upper body edema, GI edema, generalized or non-specified edema. The patient did not experience any of the following symptoms: shortness of breath/dyspnea, difficulty swallowing/dysphagia, difficulty speaking/dysarthria, pain on swallowing/odynophagia. The lip swelling lasted for 2 hours after the last dose of cough syrup was taken. No edema was present in any other location. The patient continued to take study medication for 3 more days without interruption. On Day 56 (27 Apr 2009), the patient withdrew consent from the trial. He completely recovered and was discharged from hospital on the same day (b) (6)

Table 47: Brief summary of SAE in Studies SPA 2303, 2304 and SPP 2305 (Reviewer's table)

ID	SAE	Study medication	Recovery	Study	
				Interrupt ^a	Complete
Study 2303					
117-8	Car accident and back pain	Ali 300mg	Yes	No	Yes
118-5	Herniated central cervical disc disorders	Ali/aml 300/10 mg	Yes	No	Yes
219-11	Vertigo	Ali/aml 300/5 mg	Yes	No	Yes
228-5	Early stage pulmonary carcinoma	Ali/aml 300/5 mg	Yes	No	No (with draw consent form)
601-1	Viral infection, fever	Ali/aml 300/5 mg	Yes	No	Yes
601-26 ^b	Left lower lobe pneumonia	Ali/aml 300/10 mg	Yes	Yes	No
601-51	Acute exacerbation of chronic obstructive pulmonary disease	Ali/aml 300/5 mg	Yes	No	Yes
601-53	Allergy to cough syrup	Ali/aml 300/10 mg	Yes	No	No (withdraw the consent form)
Study 2304					
152-23	hypertensive crisis	Ali/aml 150/10 mg	Yes	No	Yes
56-24	injury to right knee	Ali/aml 150/10 mg	Improving	No	Yes
136-6	luxation of right shoulder	Ali/aml 300/10 mg	Improving	No	Yes
153-15	tonsillar abscess	Ali/aml 300/10mg	Yes	No	No
153-69	hyperplasia lymphatic epipharynx	Ali/aml 300/10 mg	No	No	No
352-15	left arm tendon rupture	Ali/aml 300/10 mg	Yes	No	No
363-21	angiography renal artery	Ali/aml 300/10 mg	Yes	No	No

a: test product stopped during the SAE. b: Patient's blood pressure near to normal (142/80mmHg) without treatment.

In group C, the one year open label study: Sixteen patients in this study had SAEs. Data were summarized in the following table 48.

Table 48: Brief summary of SAE in group C, long-term open label study (Reviewer's table)

ID	SAE	Study medication	Recovery	Study	
				Interrupt ^a	Complete
43-6	Rotator cuff syndrome	Ali/aml 300/10 mg	Yes	No	Yes
45-5	Prostate cancer metastatic	Ali/aml 300/10 mg	No	Yes	No
82-6	Amebiasis, Gastroenteritis	Ali/aml 300/10 mg	Yes	No	Yes
91-2	Melanoma malignum	Ali/aml 300/10 mg	Yes	Yes	No
124-5	Right hip coxarthrosis	Ali/aml 300/10 mg	Yes	No	Yes
141-7	New decompensation diabetes mellitus	Ali/aml 300/10 mg	No	Yes (day 323)	No (day 323)
143-5	Fell from roof	Ali/aml 300/10 mg	Yes	No	Yes
203-8	Acute exacerbation of asthma	Ali/aml 300/10 mg	Yes	No	Yes
216-4	Prostate adenocarcinoma	Ali/aml 150/5 mg	Yes	Yes	No
506-5	Dehydration due to diarrhea	Ali/aml 300/10 mg	Yes	No	Yes

523-28	Gangrene left 4th toe, toe amputation	Ali/aml /HCTZ/ 300/10/12.5 mg	Yes	No	No
524-3	Hypotension	Ali/aml /HCTZ/ 300/10/12.5 mg	Yes	Yes	No
539-4	Ischemic colon	Ali/aml 300/10 mg	Yes	No	Yes
540-1 ^b	Atrial fibrillation	Ali/aml 300/10 mg	No	Yes	No
542-15	Attempted suicide	Ali/aml 300/10 mg	Yes	Yes	No
544-3	Pulmonary embolism	Ali/aml 300/10 mg	Yes	No	Yes

a: test product stopped during the SAE; b: blood pressure is normal without treatment

In group D, the long-term double-blind studies: SAEs were reported for 12 patients (4.8%) in the all Ali/Aml group and for 12 patients (4.5%) in the all HCTZ/Aml group. The most commonly reported SAEs in the All Ali/Aml group were neoplasms, reported for 4 (1.6%) patients. This was also the case in the aliskiren monotherapy group (4 patients; 0.7%) and the HCTZ monotherapy group (4 patients; 0.7%).

Since the two studies of Study SPP2323 and Study SPP2323E1 are mainly for the comparison of aliskiren and HCTZ. Amlodipine 5 mg or 10 mg is just an option to be added to the treatments and down-titration or discontinuation of open-label amlodipine was permitted during the extension study. The results are hard to be interpreted for either monotherapy or combination therapy. Overall, there were no drug-related findings in these studies.

Reviewer's comments: In the short-term placebo or active-controlled studies, the SAE is low just like other aliskiren studies less than 1%. The incidence rate is generally similar among the placebo, monotherapies and the combination therapies. No specific drug-related SAEs were observed either in short-term or long-term studies.

7.3.3 Dropouts and/or Discontinuations

In group A, the percentage of patients who discontinued due to an AE was low and similar in the placebo (1.5%), aliskiren monotherapy (1.0%) and all aliskiren/amlodipine (1.7%) groups while it was higher for amlodipine monotherapy (2.5%). Peripheral edema was the most common AE leading to discontinuation in patients treated with either aliskiren/amlodipine or amlodipine alone. In group B, the data were similar to the group A. The percentage of patients who discontinued due to an AE was similarly low in all groups; the highest discontinuation rate was observed in patients treated with the combination of aliskiren/amlodipine 300/10 mg (2.8%) or amlodipine monotherapy (2.9%). Peripheral edema was the most common AE leading to discontinuation in all patients treated with aliskiren/amlodipine (14 patients; 0.7%). Data were summarized in the following tables 49 and 50.

Table 49: Summary of adverse leading study discontinuation in Group A (Reviewer's table).

Treatment	N	Drop out n (%)	Adverse events
Placebo	198	3 (1.5)	tachycardia (1); abdominal mass (1); Headache (1)
Ali 150 mg	194	4(2.2)	palpitations (1); Dizziness (1); Lethargy (1); allergic dermatitis (1)
Ali 300mg	203	1(0.5)	vomiting (1)
Total Mono Ali	397	4(1.0)	
Aml 5mg	185	2(1.1)	Headache (1); allergic dermatitis (1)
Aml 10mg	181	7(3.9)	upper abdominal pain (1); peripheral edema (5) ; rash (1)
Total Mono Aml	366	9(2.5)	
Ali/aml 150/5 mg	181	3(1.7)	Sinus tachycardia (1); peripheral edema (1); Cerebrovascular accident (1)
Ali/aml 150/10 mg	181	4 (2.2)	Asthenia (1); peripheral edema (2) ; presyncope (1)
Ali/aml 300/5 mg	178	1(0.6)	Palpitations (1)
Ali/aml 300/10 mg	184	4 (2.2)	Sinus tachycardia (1); peripheral edema (1) ; headache (1); weight increased (1)
Total Combo	724	12 (1.7)	

Table 50: Summary of adverse leading study discontinuation in Group B (Reviewer's table)

Treatment	N	Drop out n (%)	Adverse events
Placebo	198	3 (1.5)	tachycardia (1); abdominal mass (1); Headache (1)
Ali	657	8 (1.2)	palpitations (1); dizziness (2) ; Lethargy (1); allergic dermatitis (1); abdominal pain (1); vomiting (1); hyperkalemia (1);
Aml	1004	29(2.9)	Palpitation (1); myocardial infarction (1); sinus tachycardia (1); vision blurred (1); Headache (2) ; allergic dermatitis (1); peripheral edema (14) ; hyperkalemia (1); arthralgia (1); dizziness (1) ; burning sensation (1); Nervousness (1); hypertension (1); angioedema (1); rash (1)
Ali/aml 150/5	368	8(2.2)	Sinus tachycardia (1); diarrhea (1); peripheral edema (1) ; Cerebrovascular accident (1); gastritis (1); diabetic hyperglycemic coma (1); hyperkalemia and acute pre-renal failure (1); erectile dysfunction (1);
Ali/aml 150/10	464	10 (2.2)	Asthenia (1); peripheral edema (6) ; presyncope (1); depressed mood (1); flushing (1)
Ali/aml 300/5	454	2(0.4)	Palpitations (1); dry mouth (1)
Ali/aml 300/10	745	21 (2.8)	Eye swelling (1); Sinus tachycardia (1); peripheral edema (7) ; headache (2) ; weight increased (1); asthenia (1); dizziness (2) ; erectile dysfunction (1); cough (1); allergic dermatitis (1); flushing (1) ; periorbital edema (1); erythema (1)
Total Ali/ami	2031	41(2.0)	

In group C, there were 10.8% of all Ali/Aml patients and 11.9% of total patients who discontinued due to an AE, with peripheral edema being the most common AE (5.9% for all

Ali/Aml; 6.5% for total patients). In group D, there were 2.4% of all Ali/Aml patients and 6.4% of all HCTZ/Aml patients with an AE that resulted in discontinuation. Discontinuation due to peripheral edema was reported for 0.4% of all Ali/Aml patients and for 1.5% of all HCTZ/Aml patients. Data were summarized in the following tables 51 and 52.

Table 51: Summary of adverse leading study discontinuation in Group C (Reviewer’s table)

Treatment	N	Drop out n (%)	Adverse events
Ali/aml 150/5 mg	556	8(1.4)	Palpitations (1); peripheral edema (1) , fatigue (2); joint swelling (1); hepatic enzyme increased (1); back pain (1); prostate cancer (1); sleep disorder (1)
Ali/aml 300/10 mg	546	52 (9.5)	Angina pectoris (1); atrial fibrillation (1); tachycardia (1); vertigo (1); abdominal pain (1); gingival hyperplasia (1); rectal hemorrhage (1); peripheral edema (32), pitting edema (3) ; joint swelling (1); arthralgia (1); compartment syndrome (1); prostate cancer (1); dizziness (1); headache (1); hypoaesthesia (1); depression (1); suicide attempt (1); nephritis (1); blister (1); erythema (1); hypertension (1)
Total Ali/aml	556	60 (10.8)	
Ali/aml/HCTZ	86	6 (7.0)	Peripheral edema (3) ; pain in extremity (1); lethargy (1); hypotension (1); peripheral vascular disorder (1).
Total	556	66 (11.9)	

Table 52: Summary of adverse leading study discontinuation in Group D (Reviewer’s table)

Treatment	N	Drop out n (%)	Adverse events
Mono Ali	561	19 (3.2)	Angina pectoris (1); vertigo (1); hyperthyroidism (1); dyspepsia (2); parotid gland enlargement (1); abdominal pain (1); generalized edema (1); malaise (1); weight increased (1); dizziness (1); erectile dysfunction (1); dyspnoea (1); rash (1); hypertension (2); hypertensive crisis (1); hypotension (1);
Ali/aml	248	6(2.4)	Ventricular extrasystoles (1); fatigue (1); peripheral edema (1) ; breast cancer (1); dysmenorrheal (1); cough (1); pruritus (1);
Mono HCTZ	544	18(3.3)	Myocardial infarction (1); abdominal pain (3); sensation of pressure (1); viral myocarditis (1); hypokalemia (1); intervertebral disc protrusion (1); muscle spasms (1); breast cancer (1); colon cancer (1); balance disorder (1); dizziness (1); headache (2); renal artery stenosis (1); urticaria (1); hypertensive crisis (1); hypotension (1)
HCTZ/aml	266	17 (6.4)	Angina pectoris (1); atrial fibrillation (1); diplopia (1); dyspepsia (1); peripheral edema (4) ; transaminases increased (1); renal cell carcinoma (1) facial palsy (1); headache (2); depression (1); erectile dysfunction (1); dyspnoea (1); pruritus (1); hypertensive crisis (1).

7.3.4 Significant Adverse Events

As discussed above, the peripheral edema is the major drug-related AE in the combination of aliskiren and amlodipine and the amlodipine alone, especially in the high dose groups. In females, there are higher incidence rate of peripheral edema than in males. It is the most common adverse event and is also the major reason for patient drop out. As expected, minor reduced hemoglobin and hematocrit were found in some subjects. These changes were not considered clinically meaningful changes. Please see the detailed discussion in the section of 7.4.2 laboratory findings.

7.3.5 Submission Specific Primary Safety Concerns

There were no primary safety concerns from these particular studies.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In group A, the incidence of total AEs was slightly higher in the aliskiren/amlodipine 300/10 mg group (44.6%) compared to the other groups (31.4 – 37.4%). The incidence of total AEs in the combined Ali/Aml group was 35.6% and was 37.4% in the placebo group. Peripheral edema was the most common AE in the amlodipine and aliskiren/amlodipine groups. The incidence of peripheral edema was similar in the aliskiren/amlodipine 300/10 mg and amlodipine 10 mg groups (13.6% and 13.8%, respectively) while it was lower in the aliskiren/amlodipine 150/10 mg group (7.7%).

The second most common AE in the All Ali/Aml group was headache (4.1%) which was reported for 10.1% of patients in the placebo group, 7.1% of patients treated with aliskiren monotherapy and 5.2% of patients treated with amlodipine monotherapy. Diarrhea, the identified adverse drug reaction during the aliskiren monotherapy program, especially notable at doses higher than 300 mg, occurred with low incidence in aliskiren/amlodipine combination groups (0 – 2.2%). Diarrhea was reported in 3.6% of patients treated with aliskiren 150 mg and 1.0% in aliskiren 300 mg group. All of the diarrhea AEs were mild or moderate in severity. None of the diarrhea events were SAEs. Dizziness was reported as an AE in 1.1% - 2.8% in aliskiren/amlodipine treatment groups, which was similar to that in the aliskiren monotherapy (2.6% - 3.0%) and amlodipine monotherapy (0.6% - 2.2%) groups. Cough was reported for a low percentage of patients (1.7%) in the All Ali/Aml group. There were no reports of angioedema. There were no new treatment-emergent AEs for aliskiren/amlodipine in addition to the AEs previously reported with the monotherapy treatments. Data were summarized in the following table 53.

Table 53: Number (%) of patients with most frequent AEs (at least 2% for any treatment group) in Group A, the pivotal study SPA2305 (Reviewer’s table)

Treatment	Number of patients	Common Adverse events: n (%)				
		Peripheral edema	Headache	Cough	Dizziness	Diarrhea
Placebo	198	2(1.0)	20(10.1)	2(1.0)	3(1.5)	1(0.5)
Ali 150mg	194	2(1.0)	13(6.7)	1(0.5)	5(2.6)	7(3.6)
Ali 300mg	203	3(1.5)	15(7.4)	1(0.5)	6(3.0)	2(1.0)
Aml 5mg	185	8(4.3)	11(5.9)	3(1.6)	4(2.2)	2(1.1)
Aml 10mg	181	25(13.8)	8(4.4)	2(1.1)	1(0.6)	2(1.1)
Ali/Aml 150/5mg	181	4 (2.2)	11(6.1)	4(2.2)	2(1.1)	1(0.6)
Ali/Aml 150/10mg	181	14(7.7)	8(4.4)	3(1.7)	2(1.1)	0(0.0)
Ali/Aml 300/5mg	178	2(1.1)	6(3.4)	1(0.6)	5(2.8)	4(2.2)
Ali/Aml 300/10mg	184	25(13.6)	5(2.7)	4(2.2)	3(1.6)	2(1.1)

In Group B for all of the short-term, all controlled studies, the incidence of total AEs was similar in the combined aliskiren/amlodipine group, the aliskiren monotherapy group and the amlodipine monotherapy group. Peripheral edema was the most common AE. The highest incidence rates occurred in patients with amlodipine 10 mg monotherapy or the combinations contained amlodipine 10mg. There were similar or low incidence rates of dizziness and headache in the combination groups compared to the placebo and monotherapies. Angioedema was reported for one patient who received amlodipine monotherapy. The event was mild in severity and was not an SAE. There were no new treatment-emergent AEs for aliskiren/amlodipine in addition to the AEs previously reported with the monotherapy treatments. Data were summarized in the following table 54. Hypotension was considered as a common adverse event in anti-hypertensive drugs. However, in these all short-term control studies, only 8 patients (0.4%) had hypotension considered as AE.

Table 54: Number (%) of patients with most frequent AEs in short-term, double-blind, all controlled studies (reviewer’s table)

	Placebo (n=198)	Mono Ali (n=657)	Mono Aml (n=1004)	Ali/Aml 150/5 mg (n=368)	Ali/Aml 150/10mg (n=464)	Ali/Aml 300/5 mg (n=454)	Ali/Aml 300/10mg (n=745)
Any AE	74(37.4)	189 (28.8)	323 (32.2)	119 (32.3)	158 (34.1)	137 (30.2)	254 (34.1)
Peripheral edema	2 (1.0)	6(0.9)	84(8.4)	8(2.2)	37(8.0)	8 (1.8)	66(8.9)
Headache	20(10.1)	38 (5.8)	36(3.6)	16(4.3)	11(2.4)	15(3.3)	11(1.5)
Dizziness	3(1.5)	14(2.1)	13(1.3)	4(1.1)	4(0.9)	8(1.8)	13(1.7)

In Group C of the long-term, open-label study: Peripheral edema was also the most common AE and was reported for 19.8% of all patients treated with Ali/Aml and for 14.0% of patients as HCTZ was added. Diarrhea was reported for 2.4% of all patients treated with Ali/Aml and for 3.5% of patients as HCTZ was added. Two patients who received Ali/Aml 300/10 mg had severe diarrhea, of which one event was an SAE. The AE profile is consistent with the short-term studies. Data were summarized in the following table 55.

Table 55: Number (%) of patients with most frequent AEs long-term, open-label study (Reviewer’s table)

Preferred term	Ali/Aml 300/10 mg, n=546 N (%)	Ali/Aml/HCTZ, n=86 N (%)
Any AE	389 (71.2)	49 (57.0)
Peripheral edema	108 (19.8)	12(14.0)
Headache	19 (3.5)	3(3.5)
Dizziness	24(4.4)	2(2.3)
Diarrhea	13(2.4)	3 (3.5)
Fatigue	6(1.1)	0 (0)
Cough	11 (2.0)	1(1.2)
Vertigo	9(1.6)	0 (0)
Gastroenteritis	11(2.0)	1 (1.2)
Tachycardia	3(0.5)	2 (2.3)

In Group D, the long-term study of comparison of aliskiren with HCTZ with the open-label option of amlodipine, peripheral edema was the most common AE reported for all patients treated with aliskiren/amlodipine (10.9%) and was reported at a similar incidence to HCTZ/amlodipine-treated patients (10.5%). The incidence of peripheral edema was much lower in aliskiren monotherapy-treated patients (0.7%) and HCTZ-monotherapy treated patients (1.1%). The next most frequent AE reported for all patients treated with aliskiren/amlodipine was headache (6.9%), which was reported for a similar percentage of patients treated with HCTZ/amlodipine (7.5%). Diarrhea and dizziness were reported with a lower incidence in aliskiren/amlodipine-treated patients (1.6% and 1.2%, respectively) than in HCTZ/amlodipine-treated patients (3.0% for each). Since this study was mainly for the comparison of aliskiren with HCTZ, amlodipine was added in an open-label and its dose could be increased, decreased, or withdrawal, results might be hard to be interpreted. Data were summarized in the following table 56.

Table 56: Number (%) of patients with most frequent AEs (at least 2% for any treatment group) in Group D: long-term, double-blind studies (sponsor's table)

Preferred term	Mono Ali N=561 n (%)	All Ali/Aml N=248 n (%)	Ali total N=562 n (%)	Mono HCTZ N=544 n (%)	All HCTZ/Aml N=266 n (%)	HCTZ total N=544 n (%)
Any AE	280 (49.9)	157 (63.3)	357 (63.5)	266 (48.9)	165 (62.0)	337 (61.9)
Edema peripheral	4 (0.7)	27 (10.9)	30 (5.3)	6 (1.1)	28 (10.5)	31 (5.7)
Headache	21 (3.7)	17 (6.9)	37 (6.6)	33 (6.1)	20 (7.5)	52 (9.6)
Back pain	17 (3.0)	11 (4.4)	28 (5.0)	16 (2.9)	10 (3.8)	25 (4.6)
Nasopharyngitis	14 (2.5)	11 (4.4)	25 (4.4)	16 (2.9)	14 (5.3)	30 (5.5)
Eczema	10 (1.8)	10 (4.0)	19 (3.4)	6 (1.1)	6 (2.3)	12 (2.2)
Respiratory tract infection	3 (0.5)	8 (3.2)	11 (2.0)	3 (0.6)	4 (1.5)	6 (1.1)
Fatigue	12 (2.1)	7 (2.8)	18 (3.2)	10 (1.8)	6 (2.3)	15 (2.8)
Pharyngitis	10 (1.8)	7 (2.8)	17 (3.0)	8 (1.5)	4 (1.5)	12 (2.2)
Abdominal pain upper	5 (0.9)	6 (2.4)	11 (2.0)	6 (1.1)	6 (2.3)	12 (2.2)
Arthralgia	11 (2.0)	6 (2.4)	17 (3.0)	13 (2.4)	6 (2.3)	18 (3.3)
Bronchitis	16 (2.9)	6 (2.4)	21 (3.7)	15 (2.8)	3 (1.1)	18 (3.3)
Myalgia	7 (1.2)	6 (2.4)	13 (2.3)	8 (1.5)	2 (0.8)	10 (1.8)
Hypercholesterolemia	13 (2.3)	5 (2.0)	18 (3.2)	14 (2.6)	1 (0.4)	15 (2.8)
Palpitations	4 (0.7)	5 (2.0)	9 (1.6)	4 (0.7)	0 (0.0)	4 (0.7)
Pruritus	5 (0.9)	5 (2.0)	10 (1.8)	1 (0.2)	4 (1.5)	5 (0.9)
Skin papilloma	2 (0.4)	5 (2.0)	7 (1.2)	0 (0.0)	3 (1.1)	3 (0.6)
Vertigo	8 (1.4)	5 (2.0)	13 (2.3)	5 (0.9)	1 (0.4)	6 (1.1)
Diarrhea	12 (2.1)	4 (1.6)	16 (2.8)	8 (1.5)	8 (3.0)	16 (2.9)
Influenza	10 (1.8)	4 (1.6)	14 (2.5)	8 (1.5)	6 (2.3)	14 (2.6)
Dizziness	15 (2.7)	3 (1.2)	18 (3.2)	19 (3.5)	8 (3.0)	27 (5.0)
Gastroenteritis	8 (1.4)	3 (1.2)	11 (2.0)	2 (0.4)	2 (0.8)	4 (0.7)
Musculoskeletal pain	4 (0.7)	3 (1.2)	6 (1.1)	9 (1.7)	2 (0.8)	11 (2.0)
Cough	14 (2.5)	2 (0.8)	16 (2.8)	14 (2.6)	8 (3.0)	22 (4.0)
Dyspepsia	9 (1.6)	2 (0.8)	11 (2.0)	4 (0.7)	2 (0.8)	6 (1.1)
Tendonitis	4 (0.7)	2 (0.8)	6 (1.1)	4 (0.7)	6 (2.3)	9 (1.7)
Hypertriglyceridaemia	11 (2.0)	1 (0.4)	12 (2.1)	5 (0.9)	2 (0.8)	7 (1.3)

Reviewer's comments: Overall, as expected, the most common drug-related AE is the peripheral edema, especially in the combination and the amlodipine groups in both and long-term studies. Headache and dizziness are also common and observed in all groups. The incidence rates of Diarrhea and cough which have been identified in aliskiren monotherapy are low. There were no additional findings in the combination compared to each monotherapies.

7.4.2 Laboratory Findings

The criteria for notable laboratory values were defined as listed in the following table 57.

Table 57: 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 blood urea nitrogen (BUN), creatinine, and potassium: BUN (>14.28 mmol/L), creatinine (>176.82 μmol/L), or potassium (<3.5 mmol/L, >5.5 mmol/L, or ≥ 6.0 mmol/L).

Hematology: In the short-term studies, the mean change from baseline in hemoglobin was a small increase in the aliskiren monotherapy (0.4 g/L in group A and 0.3 g/L in group B), small decrease in the amlodipine monotherapy group (-0.2 g/L in group A and -0.6g/L in group B). The mean change from baseline for the aliskiren/amlodipine treatment group was -1.8 g/L in the Group A study and -2.0 g/L in the Group B studies. The mean change from baseline for the placebo group was 1.4 g/L in both the Group A and Group B studies. Two patients in aliskiren/amlodipine 300/10mg group and one patient in amlodipine 5mg group had anemia and were considered as AE in the short-term studies. No patients discontinued treatment due to anemia in Group A or in Group B. Data of change from baseline at endpoint for hemoglobin in groups A and B were summarized in the following tables 58 and 59.

Table 58: Change from baseline at endpoint for hemoglobin (g/L) in Group A: short-term, double-blind, placebo controlled studies (sponsor's table)

Treatment group	n	Baseline			Endpoint			Post baseline Change from baseline		
		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=198)	188	142.7	14.70	143.0	144.1	15.07	143.5	1.4	7.94	1.0
Ali 150 mg (N=194)	185	146.3	14.23	147.0	147.0	14.51	148.0	0.7	7.39	0.0
Ali 300 mg (N=203)	193	144.3	14.83	144.0	144.4	14.62	145.0	0.1	8.03	-1.0
Mono Ali (N=297)	378	145.3	14.56	146.0	145.7	14.61	147.0	0.4	7.72	0.0
Aml 5 mg (N=185)	178	144.8	14.09	146.0	145.1	13.79	146.0	0.3	7.00	0.0
Aml 10 mg (N=181)	175	144.0	13.62	145.0	143.4	12.60	143.0	-0.6	6.99	0.0
Mono Aml (N=266)	353	144.4	13.85	146.0	144.2	13.22	145.0	-0.2	7.00	0.0
Ali/Aml 150/5 mg (N=181)	174	145.9	15.68	145.0	144.4	16.00	145.0	-1.5	7.82	-1.5
Ali/Aml 150/10 mg (N=181)	176	144.0	14.61	145.0	142.2	14.40	142.0	-1.8	7.90	-2.0
Ali/Aml 300/5 mg (N=178)	172	142.7	15.57	144.5	141.6	15.68	143.0	-1.1	9.83	-1.0
Ali/Aml 300/10 mg (N=184)	177	145.3	12.89	144.0	142.7	12.67	143.0	-2.6	7.07	-2.0
All Ali/Aml (N=724)	699	144.5	14.74	145.0	142.7	14.74	143.0	-1.8	8.21	-2.0

Table 59: Change from baseline at endpoint for hemoglobin (g/L) in Group B: all of short-term, controlled studies (sponsor's table)

Treatment group	n	Baseline			Endpoint			Post baseline Change from baseline		
		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=198)	188	142.7	14.70	143.0	144.1	15.07	143.5	1.4	7.94	1.0
Mono Ali (N=657)	632	145.1	14.56	145.5	145.4	14.53	146.0	0.3	7.96	0.0
Mono Aml (N=1004)	963	145.1	13.67	146.0	144.5	13.67	145.0	-0.6	8.01	0.0
All Ali/Aml (N=2031)	1955	145.8	13.89	147.0	143.8	13.69	145.0	-2.0	7.94	-2.0

In the long-term studies, a decrease in mean hemoglobin from baseline was observed in the aliskiren/amlodipine group (-1.9 g/L) in group C. This was comparable to the change seen in the short term studies. The mean decrease was slightly greater for the aliskiren/amlodipine/HCTZ combination therapy (-2.4 g/L). In Group D, the decrease in mean hemoglobin from baseline for the Ali/Aml group (-0.1 g/L) was less than the change seen in the short-term studies. The mean change from baseline for the HCTZ/Aml group was 2.8 g/L. Two patients (0.4%) in Ali/Aml in Group C and 3 patients (1.2%) in Ali/Aml in Group D had anemia and were considered as AE. There were no patients who discontinued treatment due to anemia in Group C or in Group D. Data of the changes from baseline at endpoint were summarized in the following tables 60 and 61.

Table 60: Change from baseline at endpoint for hemoglobin (g/L) in Group C: an long-term open label study (Sponsor's table)

Treatment group	n	Baseline			Endpoint			Post baseline Change from baseline		
		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
All Ali/Aml (N=470)	451	147.4	14.03	148.0	145.5	13.20	147.0	-1.9	8.41	-2.0
All Ali/Aml/HCTZ (N=86)	84	149.8	14.37	149.0	147.4	13.53	148.0	-2.4	9.58	-3.0
Total (N=556)	535	147.8	14.09	148.0	145.8	13.26	147.0	-2.0	8.60	-2.0

Table 61: Change from baseline at endpoint for hemoglobin (g/L) in Group D: long-term, double-blind studies (Sponsor’s table).

Treatment group	n	Baseline			Endpoint			Post baseline Change from baseline		
		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Mono Ali (N=313)	293	140.5	12.38	140.0	141.0	13.27	140.0	0.5	9.40	0.0
All Ali/Aml (N=247)	247	142.3	12.44	142.0	142.2	12.67	142.0	-0.1	8.00	0.0
Mono HCTZ (N=277)	259	139.4	11.76	140.0	142.3	12.68	143.0	2.9	8.29	3.0
All HCTZ/Aml (N=266)	266	143.0	13.62	143.0	145.8	12.28	147.0	2.8	9.06	3.0

In both the short-term and long-term studies, analyses by age, gender, race, and ethnicity, baseline renal function and BMI status showed a pattern of laboratory values not different from those in the overall population.

Clinical chemistry: In the short-term studies, there were no clinically meaningful differences across treatment groups. The incidence rate of serum potassium >5.5 mmol/L in this population was uncommon. The percentages of patients meeting the criterion of serum potassium >5.5 mmol/L at any post baseline visit were 4 patients (0.6%) in aliskiren monotherapy, 7 patients (0.7%) in amlodipine monotherapy, 19 patients (1.0%) in all aliskiren/amlodipine combination groups, and 1 patient (0.5%) in the placebo group. Data were summarized in the following table 62. A few patients had one time of potassium ≥ 6.0 mmol/L and were than became normal during the following unscheduled visit. Therefore, these may be the false positive results. The number of patients meeting the criterion of serum BUN >14.28 mmol/L or creatinine >176.8 μmol/L at any post-baseline visit was small in all groups (0 to 1 patient). There were no clinically meaningful changes in lipids or glucose, with the treatment of aliskiren/amlodipine.

Table 62: Summary of potassium, BUN, and creatinine by specified criteria in all short-term studies (Reviewer’s table)

Lab test	Placebo N=191	Mono Ali N=642	Mono Aml N=976	All Ali/Aml N=1968
Potassium > 5.5 mmol/L	1 (0.5%)	4 (0.6%)	7 (0.7%)	19 (1.0%)
BUN > 14.28 mmol/L	1 (0.5%)	0	0	3 (0.2%)
Creatinine > 176.8 μmol/L	0	0	0	0 (<0.1)

In the long-term open label study, changes from baseline to Endpoint were generally similar among the treatment groups. As expected, however, an increase of uric acid (19.5μmol/L) was observed in aliskiren/amlodipine/HCTZ treated patients although the overall mean is decreased (0.9 μmol/L). In the All Ali/Aml group, there were 10 patients (2.2%) with potassium >5.5 mmol/L and 4 patients (0.9%) with potassium ≥ 6.0 mmol/L. However, in these 4 patients with potassium ≥ 6.0mmol/L, three patients only had one time hyperkalemia and then became normal in the following unscheduled visit check. Only one patient had three times of hyperkalemia. No patients were discontinued due to the hyperkalemia. There were no patients in the All Ali/Aml/HCTZ group who met these criteria. There were 9 patients (1.9%) in the All Ali/Aml group and 10 patients (11.6%) in the All Ali/Aml/HCTZ group with serum potassium values <3.5 mmol/L. One patient (0.2%) in the All Ali/Aml/HCTZ group had a creatinine value >176.8 μmol/L. Data were summarized in the following table 63.

Table 63: Summary of potassium, BUN, and creatinine in long-term, open-label study (Sponsor's table)

Laboratory test	Criterion		All Ali/Aml (N=470) n %	All Ali/Aml/HCTZ (N=86) n %	Total (N=556) n %
Potassium	≥ 6.0 mmol/L	Total No.	463 (100)	86 (100)	549 (100)
		No. of pts meeting criterion	4 (0.9)	0 (0.0)	4 (0.7)
	> 5.5 mmol/L	Total No.	463 (100)	86 (100)	549 (100)
		No. of pts meeting criterion	10 (2.2)	0 (0.0)	10 (1.8)
	< 3.5 mmol/L	Total No.	463 (100)	86 (100)	549 (100)
		No. of pts meeting criterion	9 (1.9)	10 (11.6)	19 (3.5)
Blood Urea Nitrogen (BUN)	> 14.28 mmol/L	Total No.	463 (100)	86 (100)	549 (100)
		No. of pts meeting criterion	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine	> 176.8 μmol/L	Total No.	463 (100)	86 (100)	549 (100)
		No. of pts meeting criterion	0 (0.0)	1 (1.2)	1 (0.2)

Reviewer's comments: Although the incidence rate of reduced hemoglobin and hematocrit in the combination group was higher than in each monotherapy, the magnitude of these changes were minor and were not considered clinically meaningful changes. The incidence rate of the increase of serum level of potassium and creatinine was uncommon and similar to the aliskiren monotherapy. Therefore, there is no major safety concern about the hyperkalemia and renal impairment in this combination.

7.4.3 Vital Signs

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.

In general, orthostatic BP change was infrequent, and was seen at a higher frequency at baseline than at any individual post-baseline visit for all treatment groups. When orthostatic BP changes at any visit post-baseline were considered, the incidence with aliskiren/amlodipine (8.1%) treatment was similar to the amlodipine monotherapy (8.3%), higher than aliskiren monotherapy (5.4%), but lower than placebo (10.1%). The similar results were also found in group B. Data were summarized in the following tables 64 and 65.

Table 64: Incidence of orthostatic blood pressure change, Group A, Study SPA2305: short-term, double-blind, placebo-controlled study (Sponsor's table)

Visit	Placebo N=198 Total n (%)	Ali 150 mg N=194 Total n (%)	Ali 300 mg N=203 Total n (%)	Mono Ali N=397 Total n (%)	Aml 5 mg N=185 Total n (%)	Aml 10 mg N=181 Total n (%)
Baseline	198 11 (5.6)	192 10 (5.2)	202 9 (4.5)	394 19 (4.8)	184 8 (4.3)	181 10 (5.5)
Week 1	197 9 (4.6)	192 3 (1.6)	200 3 (1.5)	392 6 (1.5)	184 3 (1.6)	179 4 (2.2)
Week 2	189 5 (2.6)	188 2 (1.1)	198 1 (0.5)	386 3 (0.8)	182 3 (1.6)	176 3 (1.7)
Week 4	187 3 (1.6)	177 0 (0.0)	194 4 (2.1)	371 4 (1.1)	181 4 (2.2)	174 3 (1.7)
Week 6	173 2 (1.2)	174 1 (0.6)	189 1 (0.5)	363 2 (0.6)	177 4 (2.3)	170 2 (1.2)
Week 8	168 3 (1.8)	175 3 (1.7)	184 4 (2.2)	359 7 (1.9)	174 5 (2.9)	166 6 (3.6)
Endpoint	198 4 (2.0)	192 3 (1.6)	200 5 (2.5)	392 8 (2.0)	184 5 (2.7)	179 6 (3.4)
Any visit (post-baseline)	198 20 (10.1)	192 9 (4.7)	200 12 (6.0)	392 21 (5.4)	184 16 (8.7)	179 14 (7.8)

Visit	Mono Aml N=366 Total n (%)	Ali/Aml 150/5 mg N=181 Total n (%)	Ali/Aml 150/10 mg N=181 Total n (%)	Ali/Aml 300/5 mg N=178 Total n (%)	Ali/Aml 300/10 mg N=184 Total n (%)	All Ali/Aml N=724 Total n (%)
Baseline	365 18 (4.9)	180 10 (5.6)	181 4 (2.2)	177 7 (4.0)	183 12 (6.6)	721 33 (4.6)
Week 1	363 7 (1.9)	179 3 (1.7)	179 4 (2.2)	175 5 (2.9)	182 5 (2.7)	715 17 (2.4)
Week 2	358 6 (1.7)	176 6 (3.4)	178 0 (0.0)	173 2 (1.2)	177 4 (2.3)	704 12 (1.7)
Week 4	355 7 (2.0)	173 7 (4.0)	176 3 (1.7)	173 2 (1.2)	176 2 (1.1)	698 14 (2.0)
Week 6	347 6 (1.7)	170 2 (1.2)	174 2 (1.1)	172 4 (2.3)	173 3 (1.7)	689 11 (1.6)
Week 8	340 11 (3.2)	169 5 (3.0)	170 1 (0.6)	169 4 (2.4)	170 3 (1.7)	678 13 (1.9)
Endpoint	363 11 (3.0)	178 7 (3.9)	179 1 (0.6)	175 4 (2.3)	183 3 (1.6)	716 15 (2.1)
Any visit (post-baseline)	363 30 (8.3)	179 17 (9.5)	179 10 (5.6)	175 16 (9.1)	183 15 (8.2)	716 58 (8.1)

- Orthostatic BP change is defined as a decrease of at least 20 mmHg in systolic BP or a decrease of at least 10 mmHg in diastolic BP when a patient moves from a sitting to a standing position.

Table 65: Incidence of orthostatic blood pressure change, Group B: short-term, double-blind, all controlled studies (Sponsor's table)

Visit	Placebo N=198 Total, n (%)	Mono Ali N=657 Total, n (%)	Mono Aml N=1004 Total, n (%)	All Ali/Aml N=2031 Total, n (%)
Baseline	198, 11 (5.6)	654, 30 (4.6)	1003, 47 (4.7)	2024, 101 (5.0)
Week 1	197, 9 (4.6)	392, 6 (1.5)	715, 16 (2.2)	902, 18 (2.0)
Week 2	189, 5 (2.6)	645, 11 (1.7)	636, 13 (2.0)	1812, 42 (2.3)
Week 3	0, 0 (0.0)	0, 0 (0.0)	348, 7 (2.0)	186, 5 (2.7)
Week 4	187, 3 (1.6)	624, 7 (1.1)	628, 12 (1.9)	1791, 37 (2.1)
Week 6	173, 2 (1.2)	608, 9 (1.5)	952, 22 (2.3)	1946, 45 (2.3)
Week 8	168, 3 (1.8)	603, 16 (2.7)	595, 16 (2.7)	1744, 33 (1.9)
Endpoint	198, 4 (2.0)	652, 17 (2.6)	996, 28 (2.8)	2016, 39 (1.9)
Any visit (post-baseline)	198, 20 (10.1)	652, 43 (6.6)	996, 69 (6.9)	2016, 153 (7.6)

In the long-term studies, when orthostatic BP changes at any visit post-baseline were considered, the incidences was 8.6% in Ali/Aml treatment and 14.0% in Ali/Aml/HCTZ (14.0%), respectively, in the long-term open label study. In the long-term double blind study, the incidence with All

Ali/Aml (15.0%) was similar to All HCTZ/Aml therapy (12.0%). Data were summarized in the following tables 66 and 67.

Table 66: Incidence of orthostatic blood pressure change, Group C: long-term, open-label study (Sponsor's table)

Visit	All Ali/Aml (N=470)		All Ali/Aml/HCTZ (N=86)		Total N=556	
	Total	n(%)	Total	n(%)	Total	n(%)
Baseline	470	5 (1.1)	86	1 (1.2)	556	6 (1.1)
Week 14	428	4 (0.9)	85	4 (4.7)	513	8 (1.6)
Week 28	415	3 (0.7)	81	1 (1.2)	496	4 (0.8)
Week 41	395	4 (1.0)	75	2 (2.7)	470	6 (1.3)
Week 54	383	4 (1.0)	74	2 (2.7)	457	6 (1.3)
Endpoint	467	4 (0.9)	86	2 (2.3)	553	6 (1.1)
Any visit	467	40 (8.6)	86	12 (14.0)	553	52 (9.4)

Table 67: Incidence of orthostatic blood pressure change, Group D: long-term, double-blind studies (Sponsor's table)

Visit	Mono Ali (N=313)		All Ali/Aml (N=247)		Mono HCTZ (N=277)		All HCTZ/Aml (N=266)	
	Total	n(%)	Total	n(%)	Total	n(%)	Total	n(%)
Baseline	312	5 (1.6)	245	3 (1.2)	276	5 (1.8)	264	4 (1.5)
Week 12	279	4 (1.4)	244	4 (1.6)	241	5 (2.1)	266	4 (1.5)
Week 26	271	5 (1.8)	238	9 (3.8)	228	1 (0.4)	252	5 (2.0)
Week 44	261	6 (2.3)	231	4 (1.7)	214	5 (2.3)	238	4 (1.7)
Week 52	259	1 (0.4)	224	5 (2.2)	208	1 (0.5)	230	2 (0.9)
Endpoint	306	5 (1.6)	247	5 (2.0)	271	2 (0.7)	266	3 (1.1)
Any visit	306	28 (9.2)	247	37 (15.0)	271	27 (10.0)	266	32 (12.0)

7.4.4 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. Amlodipine is not known to cause adverse ECG changes.

7.4.5 Special Safety Studies/Clinical Trials

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

7.4.6 Immunogenicity

Aliskiren and amlodipine 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.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose-dependency of all AEs was counted by calculating rates for each dosage. Peripheral edema was the major finding in high dose groups of both the combination therapy (300/10mg) and amlodipine monotherapy (10mg).

7.5.2 Time Dependency for Adverse Events

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

7.5.3 Drug-Demographic Interactions

To evaluate possible effects of demographic factors on the safety of aliskiren/amlodipine combination therapy, subgroup analyses were performed by gender, age, and race for the safety parameters duration of exposure, AE incidence, laboratory parameters (hematology and clinical chemistry) evaluations, and orthostatic BP. In the AE incidence rate analysis, peripheral edema was reported for a greater percentage of females than males in the combination and amlodipine monotherapy groups. In the pivotal study, the incidence rate of peripheral edema (17.9%) seems a little bit lower compared to the amlodipine monotherapies (21.3%) in female patients. However, this change was not observed in males in this study and not in the overall short-term studies. Data were summarized in the following table 68. As in the short-term studies, peripheral edema was reported for a greater percentage of female (25.2%) patients than male (17.3%) patients in the all Ali/Aml group. There is no other clear relationship between the safety signals and the demographic factors.

Table 68: Comparison of incidence rate (%) of peripheral edema between genders in pivotal study (group A) and all of short-term studies (group B) (Reviewer's table)

Group A	Placebo	Ali 150mg	Ali 300mg	Aml 5mg	Aml 10mg	Ali/Aml 150/5 mg	Ali/Aml 150/10mg	Ali/Aml 300/5 mg	Ali/Aml 300/10mg
Males	0	2(1.7)	1(1.1)	2(2.0)	5(5.7)	2(2.1)	5(5.9)	1(1.3)	11(10.4)
Females	2 (1.9)	0	2(1.9)	6(7.0)	20 (21.3)	2 (2.4)	9 (9.4)	1(1.0)	14(17.9)
Group B	Placebo	Mono Ali		Mono Aml		Ali/Aml 150/5 mg	Ali/Aml 150/10mg	Ali/Aml 300/5 mg	Ali/Aml 300/10mg
Males	0	3(0.8)		34(6.1)		3(1.5)	19 (7.4)	4(1.6)	26(6.0)
Females	2(1.9)	3(1.0)		50 (11.1)		5(3.0)	18 (6.7)	4(2.0)	40 (12.8)

7.5.4 Drug-Disease Interactions

Adverse events were analyzed in patients with moderate renal impairment, diabetes, obesity, and stage 2 hypertension. In general, the AEs in these populations were comparable to the overall

population. For patients with moderate renal impairment, however, the results may not be conclusive due to the small sample sizes (4-6% of the total population).

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not studied in this submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

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

7.6.2 Human Reproduction and Pregnancy Data

Aliskiren was not studied during pregnancy, and is not to be used in women who are pregnant or may become pregnant. There is also no clinical experience with amlodipine in pregnancy.

There was one pregnancy reported in the pivotal study (Study SPA 2305). The patient reported the pregnancy on the completion date of the double-blind treatment period. The pregnancy was terminated. There was also one pregnancy reported in the Clinical Pharmacology study (Study SPP 2218). The subject was discontinued from the study. During follow-up of this event, the subject indicated that the pregnancy would be terminated. However, the study center was not able to contact the subject or obtain documentation of termination.

It is not known whether aliskiren or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

7.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor did not conduct pediatric studies.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reports of overdose with aliskiren/amlodipine in the clinical trials. The most likely manifestation of overdosage of aliskiren would be hypotension. The most likely manifestation of overdosage of amlodipine would be excessive peripheral vasodilation with marked hypotension.

Preclinical and clinical studies have not indicated any potential for dependence with aliskiren.

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.

Abrupt withdrawal of amlodipine has not been associated with a rapid increase in blood pressure. This has not been examined for the aliskiren/amlodipine combination.

7.7 Additional Submissions / Safety Issues

In the 120-day safety update, data from 3 completed short-term studies were provided. These studies were summarized in the following table 69. Additional sources of data provided by the sponsor in this safety update consisted of literature search to capture any investigator reports of safety aspects not included in the study reports (date of search: 01 Aug 2009 until 30 Nov 2009) and a review of the Novartis safety database (spontaneous reports) for aliskiren and amlodipine monotherapy (cut-off date: 01 Aug 2009 until 30 Nov 2009).

Table 69: Completed trials which contributed safety data (sponsor's table)

Study No.	Study objectives, population	Number of patients randomized /treated	Treatment duration	Treatment/dose (mg)	Type of control/blinding
SPA2306	Efficacy / safety in patients with moderate to severe hypertension	485/484	8 weeks	Patients were randomized to 2 treatment arms: aliskiren/amlodipine 150/5 mg for 1 week, titrated to 300/10 mg for 7 weeks -OR- amlodipine 5 mg for 1 week, titrated to 10 mg for 7 weeks.	Active/ Double-blind
SPAUS01	Efficacy / safety in Black patients with moderate to severe hypertension	443/443	8 weeks	Patients were randomized to 2 treatment arms: aliskiren/amlodipine 150/5 mg for 1 week, titrated to 300/10 mg for 7 weeks -OR- amlodipine 5 mg for 1 week, titrated to 10 mg for 7 weeks.	Active/ Double-blind
SAH2302	Efficacy / safety in patients with moderate to severe hypertension	1191/1188	8 weeks	Initially, patients were randomized to one of the following for 4 weeks: aliskiren/amlodipine 150/5 mg, aliskiren/HCTZ 150/12.5 mg, amlodipine/HCTZ 5/12.5 mg, aliskiren/HCTZ 150/12.5 mg for 3 days and then aliskiren/amlodipine/HCTZ 150/5/12.5 mg. Patients were force titrated to the following doses for another 4 weeks: aliskiren/amlodipine 300/10 mg aliskiren/HCTZ 300/25 mg amlodipine/HCTZ 10/25 mg aliskiren/amlodipine/HCTZ 300/10/25 mg	Active/ Double-blind

The safety population comprised all patients in short-term, double-blind, controlled clinical studies who received at least one dose of study drug. All 3 completed studies were pooled to provide an integrated safety profile as shown in the following table 70.

Table 70: Summary of patients in pooled treatment groups by study (Short-term double-blind, all controlled studies, Sponsor's table)

Population Study	Mono Aml n (%)	Ali/Aml n (%)	Ali/HCTZ n (%)	Aml/HCTZ n (%)	Ali/Aml/HCTZ n (%)	Total n (%)
Randomized						
SPA100A2306	241 (49.7)	244 (50.3)	0 (0.0)	0 (0.0)	0 (0.0)	485 (100)
SPA100AUS01	223 (50.3)	220 (49.7)	0 (0.0)	0 (0.0)	0 (0.0)	443 (100)
SAH100A2302	0 (0.0)	287 (24.1)	298 (25.0)	296 (24.9)	310 (26.0)	1191 (100)
Total randomized	464	751	298	296	310	2119
Safety						
SPA100A2306	241 (49.8)	243 (50.2)	0 (0.0)	0 (0.0)	0 (0.0)	484 (100)
SPA100AUS01	223 (50.3)	220 (49.7)	0 (0.0)	0 (0.0)	0 (0.0)	443 (100)
SAH100A2302	0 (0.0)	287 (24.2)	297 (25.0)	295 (24.8)	309 (26.0)	1188 (100)
Total safety	464	750	297	295	309	2115

Death: Two deaths occurred prior to randomization in Study SAH2302. This study was ongoing at the time of the original NDA submission. One patient died after discontinuing from the study during the placebo run-in period. The cause of the death was reported as "Death due to unknown street drug". The second patient died during the placebo run-in period and did not receive active study medication. The cause of death was unknown.

SAEs: In study SPA 2306, SAEs were only found in 3 patients in amlodipine monotherapy group including anemia, adenomyosis and dysfunctional uterine bleeding in one patient, myocardial infarction in a second patient and cerebral infarction in a third patient. All led to discontinuation of study medication. In study SPA US01, one patient in the aliskiren/amlodipine group experienced an SAE of severe unstable angina which led to discontinuation of study medication. One patient in the amlodipine monotherapy group experienced SAEs of moderate pneumonia and mild back pain, but completed the study. In Study SAH2302, SAEs occurred in 3 patients (1.0%) in the aliskiren/amlodipine group (ectopic pregnancy, hepatitis A and nasal septum deviation), 2 patients (0.7%) in the aliskiren/HCTZ group (stress urinary incontinence and tubo-ovarian abscess), 2 patients (0.7%) in the amlodipine/HCTZ group (cerebrovascular accident and epistaxis) and 6 patients (1.9%) in the aliskiren/amlodipine/HCTZ group (acute coronary syndrome, supraventricular arrhythmia, goiter, hypertension, psychosomatic disease and syncope). SAE discontinuations occurred in 4 patients (1.3%; worsening hypertension, psychosomatic syndrome, acute coronary syndrome, atrial cardiac arrhythmia) in the aliskiren/amlodipine/HCTZ group and in one patient each in the aliskiren/amlodipine (0.4%; hepatitis) and amlodipine/HCTZ (0.3%; cerebrovascular accident) groups.

Discontinuation: SAEs leading to discontinuation as discussed above occurred at low incidence in all groups: 3 (0.6%) patients in the amlodipine monotherapy group, 2 (0.3%) patients in the aliskiren/amlodipine group, 1 (0.3%) in the amlodipine/HCTZ group and 4 (1.3%) in aliskiren/amlodipine/HCTZ group.

The incidence of AEs leading to discontinuation was higher in amlodipine monotherapy group (4.1%) than in other groups (2.9% in the aliskiren/amlodipine group, 0.7% in the aliskiren/HCTZ group, 2.7% in the amlodipine/HCTZ group and 3.6% in the aliskiren/amlodipine/HCTZ group). The incidence of peripheral edema leading to discontinuation was higher for amlodipine monotherapy group (2.2%) compared to other groups (1.1% in the aliskiren/amlodipine group, 0% in the aliskiren/HCTZ group, 0.7% in the amlodipine/HCTZ group and 0.3% in the aliskiren/amlodipine/HCTZ group). Two patients each in the aliskiren/amlodipine group (0.3%) and amlodipine/HCTZ group (0.7%) and 1 patient in amlodipine monotherapy group (0.2%) were discontinued due to headache.

Overall, the incidence of total AEs in aliskiren/amlodipine was similar to amlodipine monotherapy (38.8% vs 40.7%). Peripheral edema was the most frequently occurring AE in the amlodipine monotherapy, aliskiren/amlodipine and aliskiren/amlodipine/HCTZ groups, and is a known dose dependent side effect of amlodipine. Peripheral edema was reported for 10.0% of patients in the aliskiren/amlodipine group and for 13.8% of patients treated with amlodipine monotherapy.

Clinical laboratory data: Overall, the clinical laboratory data were similar to the safety data in the original NDA submission.

Other updated safety information: Two pregnancies occurred in Study SAH 2302. One was an ectopic pregnancy, in the aliskiren/amlodipine group. The patient interrupted study drug for 6 days, but completed the study. The other pregnancy occurred in the amlodipine/HCTZ group and led to discontinuation from the study. No other pregnancies occurred in the completed trials that are included in this Safety Update.

Reviewer's comments: Data from 3 completed studies in patients with moderate to severe hypertension were consistent with the existing safety profile for aliskiren/amlodipine and did not reveal additional safety concern to what was already identified in the original NDA submission. The AE and laboratory findings for aliskiren/amlodipine were consistent with the known safety profile of the individual component drugs when used alone, with no additional safety concern over amlodipine monotherapy or any of the combination therapies.

The incidence of peripheral edema, a known side effect of amlodipine, was observed in aliskiren/amlodipine combination and amlodipine monotherapy.

Since a large number of Black patients were included in this safety update (Study SPA US01, exclusively enrolled Black patients) the data further support the safety of aliskiren/amlodipine in treating Black patients with hypertension.

8 Postmarket Experience

The fixed combination of aliskiren/amlodipine is not marketed in any country to date. Although both aliskiren and amlodipine are currently approved in many countries worldwide, it is not

possible to estimate accurately the exposure to the free combination of aliskiren and amlodipine worldwide. However, an estimate can be obtained of the exposure to aliskiren and amlodipine separately on the basis of the number of total Standard Units (tablets) sold according to IMS National Prescription Audit database, divided by 365 to calculate the number of patient treatment years (PTY). This helps to put spontaneously reported adverse event data into perspective. Based on the sponsor's report, the total exposure to aliskiren therapy is approximately (b)(4) PTY while for amlodipine it is approximately (b)(4) PTY.

A search was conducted in the sponsor's drug safety database for all cases with concurrent use of aliskiren and amlodipine (as single active ingredient or in combination products). The search produced 320 cases reporting 1268 events. The most frequently reported events (preferred terms reported > 10 times) are presented in the following table 71.

Table 71: Post-marketing adverse events in the original NDA submission (sponsor's table)

Preferred terms	Total	Serious cases
Edema peripheral	29	15*
Blood pressure increased	29	14
Blood creatinine increased	25	21
Blood pressure inadequately controlled	24	9
Headache	22	10#
Diarrhea	21	7*
Dizziness	21	7
Fatigue	20	10
Drug ineffective	17	2
Hypertension	16	12*
Dyspnea	15	13
Angioedema	14	14
Cough	14	8
Malaise	14	9
Hypotension	12	9
Pruritus	12	3
Asthenia	11	9
Nausea	11	3*

#, in two of the serious cases the event (headache) was reported as non-serious (event assessment)

*, in one of the serious cases the event was reported as non-serious (event assessment)

An updated search was conducted in the drug safety database for all spontaneous cases with concurrent use of aliskiren and amlodipine (as single active ingredients or in combination) received in the period from 01 Aug 2009 until 30 Nov 2009. The search produced 61 spontaneous cases reporting 134 events. The most frequently reported events (preferred terms reported > twice) were summarized in the following table 72.

Table 72: Spontaneously reported adverse events with concurrent administration of aliskiren and amlodipine (Sponsor’s table)

Preferred terms	Total	Serious*
Diarrhea	7	2
Edema peripheral	7	1
Cough	5	1
Dyspnea	4	2
Blood creatinine increased	3	0
Drug ineffective	3	0
Arthralgia	3	0
Hypertension	3	1
Hypotension	3	2
* Event level assessment		

Reviewer’s comments: These events can be either associated with the use of amlodipine and/or aliskiren or related to the underlying disease

9 Appendices

9.1 Literature Review/References

I searched the Pubmed with the key words: “amlodipine”, “aliskiren”, and “amlodipine and aliskiren”, with the “adverse events”. There were no additional safety concerns other than the described above.

9.2 Labeling Recommendations

Labeling recommendations will be discussed separately.

9.3 Advisory Committee Meeting

N/A

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22545

ORIG-1

NOVARTIS
PHARMACEUTICA
LS CORP

ALISKIREN/AMLODPINE(SPA
100A)FIXED COMBO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEN XIAO
07/07/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:Hypertension				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Shen Xiao

Reviewing Medical Officer

Date

Clinical Team Leader

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEN XIAO
12/09/2009

THOMAS A MARCINIAK
12/09/2009