10.1.2.22. Summary and conclusion

The combination of aliskiren with HCTZ has shown an added effect in reduction of in both msDBP and msSBP as compared to each of the monotherapies. Please see details for the efficacy discussion in Section 6.

The adverse events and event rates in this study are similar to those reported in the monotherapy of aliskiren or HCTZ. The most significant event in this combination study compared to the monotherapy of each study is the addition of increased serum level of uric acid. The overall toxicity in this study appears to be acceptable.

10.1.3. Study 2302: 12 month, randomized, open-label, multicenter, study to assess the long term safety of aliskiren 150 mg alone and 300 mg alone or with the optional addition of hydrochlorothiazide (12.5 mg or 25 mg) in patients with essential hypertension.

10.1.3.1. Study objectives

- The primary objective of this study was to assess the long-term safety and tolerability of aliskiren 150 mg and aliskiren 300 mg, with the optional addition of HCTZ 12.5 mg or 25 mg to aliskiren 300 mg, in patients with essential hypertension (mean sitting diastolic blood pressure (msDBP) $\geq$ 90 mmHg and < 110 mmHg).
- The secondary objectives were to:
  - Assess the long-term blood pressure efficacy of aliskiren 150 mg and 300 mg with the optional addition of HCTZ 12.5 mg or 25 mg to aliskiren 300 mg, in patients with essential hypertension.
  - Explore the effect of long-term treatment with aliskiren 150 mg and 300 mg on plasma rennin activity and active renin (plasma renin concentration) (only in patients enrolled in U.S. centers).
  - Provide evidence of long-term efficacy of aliskiren monotherapy by comparing the change in msDBP and msSBP from Month 11, following a one month, double-blind, placebo-controlled, randomized withdrawal period.
  - Evaluate the potential for rebound hypertension following abrupt withdrawal of aliskiren treatment on blood pressure and symptoms at one week and two weeks in those patients who were randomized to placebo and completed 11 months of treatment.
  - Evaluate the effect of treatment and treatment withdrawal on plasma renin concentration (active renin) and plasma renin activity in a subset of patients.
  - Evaluate the 24-hour blood pressure profile of patients treated with aliskiren monotherapy versus placebo by utilizing 24 hour ambulatory blood pressure monitoring (ABPM) in a subset of patients during the double-blind, placebo-controlled randomized drug withdrawal period.

10.1.3.2 Design

This study provides longer term safety data for aliskiren with and without HCTZ in hypertensives. This was a randomized (to starting dose), open-label, titrated, international, multi-

center study of aliskiren 150 and 300 mg with titrated-to-effect addition of hydrochlorothiazide (HCTZ) 12.5 or 25 mg. At months 2 and 3 investigators could increase aliskiren 150 to 300 or, for patients receiving 300, add HCTZ 12.5 mg or increase HCTZ to 25 mg to reach a target BP of <140/90. HCTZ could be down-titrated but aliskiren could not. At month 11 the first 320 patients on aliskiren alone were to undergo a randomized (current dosage or placebo), double-blind, placebo-controlled, one-month withdrawal. A 50% of these withdrawal patients were also to undergo ABPM at months 11 and 12. The primary evaluation for the whole study was regarding safety; the withdrawal was intended to show long-term efficacy. A sample size of 1500 was planned.

In the end 1955 patients were treated (1951 randomized) at 185 centers in 12 countries (50 centers in the US, 48 in Germany, 18 in Italy, 12 in Switzerland, 11 in Belgium 10 in Peru, 9 in the UK, 8 in Russia, 8 in Denmark, 5 in the Netherlands, 4 in Canada, and 2 in Iceland) from June 15, 2004, through October 13, 2005. Among all randomized patients 1624 (83%) completed the open-label period and 261 started and 250 patients finished the randomized withdrawal period. A slight majority of the patients were male (52.5%), predominantly white (86%). The median age was 56. Many patients were obese (about 38% BMI ≥ 30). Mean sitting BP at baseline was 153/97. These baseline characteristics were reasonably well balanced between the two baseline randomization groups. The mean exposure was 318.5 days, or about 1705 person-exposure years (PEYs) in total.

10.1.3.3 Efficacy summary

Examination of the demographics and background characteristics of the patients who remained on monotherapy throughout the study and the patients who were titrated to combination therapy patients in the open-label period showed a few important differences. Combination therapy patients were slightly older than monotherapy patients (mean age of 57.0 vs. 54.8 years), had a longer duration of hypertension (8.2 vs. 6.5 years), and included more males (55.3% vs. 50.3%), obese patients (41.6% vs. 34.3%) and those with metabolic syndrome (47.7% vs. 41.7%). The baseline blood pressures were slightly higher in the combination therapy group than in the monotherapy group (msDBP: 98.4 mmHg vs 96.7 mmHg; msSBP: 156.1 mmHg vs 150.5 mmHg). During the randomized withdrawal period, the demographic and baseline characteristics for patients randomized to remain on aliskiren were similar to those randomized to placebo. In both treatment groups, the majority of the patients were Caucasian (97.7%). Males and females were evenly distributed. The overall mean age was 55.0 years, with most patients younger than 65 years of age (77.4%). There were few diabetics, and less than half of the patients met the criteria for metabolic syndrome. Approximately one third were obese (BMI ≥ 30 kg/m2). The mean duration of hypertension was 6.4 years.

Efficacy results in the open-label period: During the open-label period, clinically meaningful reductions from baseline in sitting blood pressures were achieved with both doses of aliskiren as monotherapy and also combination therapy. The reductions were similar in both aliskiren randomization groups. The responder rates and control rates were slightly greater in the aliskiren 300 mg randomization group than in the aliskiren 150 mg randomization group during the first 4 months of the open-label period. The highest response and control rates were achieved at Month 9 (Visit 9), at which time all patients could have been titrated to the maximum dose of aliskiren

300 mg plus HCTZ 25 mg. At Visit 10 of the open-label period, the responder rates and control rates were nearly identical at 85.6% and 86.2%, and 65.9% and 66% for the aliskiren 150 and 300 mg randomization groups, respectively. Data were summarized in the following table 89.

Table 89: Summary of blood pressure results at Visit 10 (final visit, Month 11/12) of the open label period in Study 2302

	Monotherapy		Combo therapy		Aliskiren 150 mg(R)		Aliskiren 300 mg(R)	
	Mean change from BL (mmHg)	BP at Visit 10 (mmHg)	Mean change from BL (mmHg)	BP at Visit 10 (mmHg)	Mean change from BL (mmHg)	BP at Visit 10 (mmHg)	Mean change from BL (mmHg)	BP at Visit 10 (mmHg)
msDBP	-14.7	81.7	-12.8	85.6	-13.5	83.6	-14.2	83.4
msSBP	-19.5	130.5	-19.8	136.2	-19.3	133.2	-20.2	133.0

BL = baseline Monotherapy patients were those who never took HCTZ; Combo patients were those who took HCTZ at least once during the open label period. (R) = Randomized aliskiren treatment group.

Randomized withdrawal period: During the randomized withdrawal period, the blood pressure reductions achieved during the open-label period were generally maintained in patients who continued taking aliskiren, but increases were observed in patients who switched to placebo. At Endpoint of the randomized withdrawal period, msDBP was 83.0 mmHg for All Aliskiren and 86.7 mmHg for All Placebo; msSBP was 134.2 mmHg for All Aliskiren and 140.2 mmHg for All Placebo. The between-treatment analysis demonstrated that aliskiren was statistically superior to placebo at Month 12 and at Endpoint. Data were summarized in the following table 90.

Table 90: Comparison between treatment groups for change from Month 11 (Visit 10) in msDBP and msSBP at Endpoint of the randomized withdrawal period in study 2302

	Pairwise Comparison (A vs. B)		LS Mean difference		
	A	B	A – B (SE)	95% CI	p-value
msDBP at Endpoint	Aliskiren mono	Placebo	-3.87 (0.88)	(-5.61,-2.13)	< .0001*
msSBP at Endpoint	Aliskiren mono	Placebo	-5.99 (1.34)	(-8.63,-3.34)	< .0001*

Least squares mean, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, strata as factors, msDBP at Month 11 (Visit 10) as a covariate.
[1] Nominal P-values and treatment comparisons were evaluated at the average msDBP at Month 11 (Visit 10).
* indicates statistical significance at 0.05 level.

There was no evidence of rebound effect for either msDBP or msSBP during the drug withdrawal period.

10.1.3.4. Safety summary

Overall AEs were reported in about 65% of patients with similar rates in both initial dosage groups and with or without the addition of HCTZ. The common AEs and AEs by organ class were not substantially different among the groups, e.g., nasopharyngitis, headache, dizziness, back pain, and bronchitis were the five most common AEs. Diarrhea, the sixth most common AE, was more frequent in the 300 mg group, but the differences in the rates for diarrhea were

similar to the differences in rates of other AEs, some more frequent in the 150 mg group. Deaths, SAEs, and discontinuations may be more revealing than the overall AEs. The rates of these serious events were summarized in the following table 91.

Table 91: Rates of Death, SAEs, and AE Discontinuations in study 2302

	Aliskiren 150 mg N=1174 n (%)	Aliskiren 300 mg N=1443 n (%)	Ali/HCTZ 300/12.5 mg N=843 n (%)	Ali/HCTZ 300/25 mg N=453 n (%)	Total N=1955 n (%)
Death	1 (0.1)	3 (0.2)	0 (0.0)	1 (0.2)	5 (0.3)
SAEs	33 (2.8)	35 (2.4)	10 (1.2)	16 (3.5)	93 (4.8)
AE discontinuations	46 (3.9)	41 (2.8)	9 (1.1)	16 (3.5)	111 (5.7)
SAE discontinuations	10 (0.9)	13 (0.9)	1 (0.1)	7 (1.5)	31 (1.6)
Discontinuations for abnormal lab value(s)	7 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	8 (0.4)

Brief descriptions of the deaths are as follows:

- The aliskiren 150 mg death was a 74-year-old Hispanic white male who died on day 27 of a ruptured aortic aneurysm. The patient's baseline BP (last recorded) was 159/96.
- The three aliskiren 300 mg deaths were the following:
  - A 79-year-old white female with a history of hyperlipidemia and also taking diclofenac who died on day 296 of a MI. Her last BP on day 260 was 130/83.
  - A 61-year-old female (150 mg group initially) without significant other comorbidities who was found dead in bed on day 71. No autopsy was preformed and death was attributed to "natural causes". Her baseline BP was 170/106, 160/96 on day 28 and 150/93 on day 56, at which time aliskiren was increased from 150 to 300.
  - A 77-year-old Hispanic male (150 mg group initially) with a 27 year history of hypertension but no other significant comorbidities who died on day 102 of a stroke. His baseline BP was 173/93 and his last recorded BP on day 91 was 158/91, so aliskiren was increased from 150 to 300. He presented on day 92 with dizziness, confusion, headache, and hypertension but no BPs are reported. The next day a CAT scan showed an intracerebral hemorrhage in the posterior fossa for which he underwent surgery. He became comatose post-op.
- The aliskiren 300/HCTZ 25 death was a 56-year-old white male with a history of tobacco abuse, coronary disease, and peripheral vascular disease who died suddenly at home on day 308. An autopsy showed severe coronary atherosclerosis with calcification, three vessel disease with acute plaque erosion and non-occlusive thrombus in mid left anterior descending artery and occlusion of right coronary artery. The investigator reported this event as a MI. His last recorded BP was 171/91 on day 279.

Noteworthy among the discontinuations were four discontinuations for MI in the 150 group and five in the 300 mg group and four discontinuations for stroke in the 150 group and one in the 300 mg group. The MIs, other than the two diagnosed fatal ones described above, were the following:

- A 52-year-old female in the 300 mg group presented with chest pain on day 180 and was diagnosed as having a non-Q wave MI. An ECG showed lateral ischemia. Angiography

showed a systolic reduction of the LAD due to myocardial bridging. Echo showed an ejection fraction of 59%. Her BP two months earlier was 129/77.

- A 50-year-old white male in the 300 mg group was hospitalized with dyspnea on day 161. His blood pressure was 110/80. His ejection fraction was 30% with hypokinesis of the left ventricular. The SAE report lists a CK of 452 and a CK-MB of 32.1 with dates of eight days after the event.

The strokes other than the fatal one described above were the following:

- A 67-year-old white female in the 150 mg group also treated with HCTZ was hospitalized with dysarthria and leftward deviation of the tongue on day 304. She also had hypokalemia. Her BP was 150/100. Echo and cranial imaging did not demonstrate occlusion or an ischemic lesion. She was rehospitalized with recurrent symptoms on day 334 and recovered by day 340.
- A 68-year-old white male in the 150 mg group fell and became unconscious for a short while on day 302. He had facial nerve paralysis and a head wound and was hospitalized with a stroke. He was reported as completely recovered nine days later. At day 274 his BP was 140/73. No additional details are provided.
- A 42-year-old Peruvian ("other" race and ethnicity) male in the 150 mg group with recent onset hypertension developed a right faciobrachial hemiparesis on day 77 and was hospitalized. Tomography revealed an infarct in the left thalamic region. MRI showed signs of recent ischemic infarction affecting the lenticular nucleus with extension to the corona radiata of the left cerebral hemisphere. There was a lacunar infarction in the pons. There were no visible signs of vascular malformation. Two weeks prior to the stroke his BP was 121/85. On the day of the stroke his BP was 150/105. Pulse was 78-84 with no mention of arrhythmias. He had undergone a hemorrhoidectomy one week prior to the stroke and on the night before he strained for a bowel movement with subsequent headache and weakness.
- A 65-year-old diabetic black male in the 300 mg group also receiving HCTZ suffered stroke (loss of balance and one-sided weakness) on day 157. He was hospitalized with an initial BP of 185/113. An ECG showed sinus rhythm, LVH, and LAH. The diagnosis was an acute left pontine CVA. His BP on day 92 was 160/189 and on day 120 was 159/99.
- A 48-year-old white female in the 150 mg group experienced left-sided weakness and paresthesias intermittently and was hospitalized on day 69. Her BP the next day was 151/109 and pulse 76, while her BP on day 29 was 139/88 and pulse 84. Because she had intermittent tachycardia, 24-hour Holter monitoring was done that recorded normal sinus rhythm or sinus tachycardia. A CT scan showed a small, 1 cm, hypodense focus in the right frontal subcortical white matter. A MRI showed a showed a small area of acute infarct involving the posterior right frontal region and a small area of abnormality involving the lenticular striate distribution and external capsule on the right side.

A SAE of angioneurotic edema was reported for a patient receiving aliskiren 300 mg/HCTZ 25 mg. After being on open-label study medication for 372 days, this patient (a 47 year old Caucasian female) experienced itching and edema of the left ear which quickly spread to the lips and eyes. Inspiratory stridor was also present. The investigator diagnosed angioneurotic edema and prescribed prednisolone and an antihistamine. On the following day, the facial edema had become more symmetric and her chin was red. No rash was present. Bronchial stridor had decreased but rhonchi were present. The patient completed the study (4 more days) without

interruption of study drug. She was seen one day after study completion and had made a full recovery.

A 74-year-old white male in the 150 mg group experienced a tonic/clonic convulsion for ten minutes followed by unconsciousness for 30 minutes on day 124, eleven days after being uptitrated to 300 mg. He had no prior history of seizures. A CAT scan five days later and an EEG 22 days later were normal. Another patient in the aliskiren 150 mg group, a 52-year-old male with a history of epilepsy, had an epileptic fit on day 187. He was not discontinued and completed the study through one year.

There were reportedly eight discontinuations for lab value increases. However, many of these patients had baseline abnormalities.

10.1.3.5. Conclusions

This study mainly focuses on the longer term safety data for aliskiren with and without HCTZ in hypertension treatment. The blood pressure results during the withdrawal period confirm that aliskiren has an antihypertensive effect sustained for at least one year. There is no direct comparison of the efficacy between the monotherapy and combined treatment. The incidence rates of adverse events in combined therapy are comparable to the monotherapy.

10.1.4. Study 2302 E1: A 4 month extension to a 12 month, randomized, open label, multicenter, study to assess the long term safety of aliskiren 150 mg alone and 300 mg alone or with the optional addition of hydrochlorothiazide (12.5 mg or 25 mg) in patients with essential hypertension

10.1.4.1. Objectives

The objective of this extension study (also stated as a secondary objective in the core protocol of CSPP100A2302) was to assess the long-term (12 months) safety of aliskiren 300 mg in combination with HCTZ 25 mg in patients with essential hypertension (MSDBP $\geq$90 mmHg and < 110 mmHg).

10.1.4.2. Study design

This was an open-label, uncontrolled study. Patients who completed at least eight months of treatment with aliskiren 300 mg and HCTZ 25 mg in Study 2302 were eligible. Of 250 patients planned, 198 were eventually enrolled. Patients took two aliskiren 150 mg tablets and one HCTZ 25 mg capsule at the same time each morning without regard to food intake for the four month treatment period. BP and safety labs were evaluated at the end of the treatment period. About 96% (189) of the patients completed the study. They were predominantly white (94%) and evenly distributed between the genders (50% male) with a mean age of 57. About 49% were obese (BMI $\geq$ 30) and 47% met criteria for the metabolic syndrome.

10.1.4.3. Efficacy summary

The mean BP at the original baseline (not the start of this extension) was 159/99; the mean BP at the end of this extension was 142/89. The mean BP in this group was similar through the original study period and the extension. Because of the lack of a control and the fact that this study population is a group selected for having completed at least eight months of therapy, the BP results are difficult to interpret.

10.1.4.4. Safety summary

About 49% of the patients experienced at least one AE during the study. The common non-serious AEs were typical of a study population with similar age and comorbidity and not clearly drug-related, e.g., bronchitis, nasopharyngitis, and headache were the most frequent AEs. Data were summarized in the following table 92.

Table 92: Incidence rate of common adverse events (>= 1%) in order of frequency during high dose combination therapy Aliskiren/HCTZ 300/25 mg (All extension population) in Study 2302 E1

	Aliskiren + HCTZ 300/25 mg N=198
Preferred term	n (%)
-Any primary system organ class	97 (49.0)
Bronchitis	12 (6.1)
Nasopharyngitis	10 (5.1)
Headache	7 (3.5)
Arthralgia	5 (2.5)
Dizziness	5 (2.5)
Epicondylitis	5 (2.5)
Nausea	5 (2.5)
Back pain	4 (2.0)
Influenza	4 (2.0)
Contusion	3 (1.5)
Diabetes mellitus	3 (1.5)
Diarrhea	3 (1.5)
Hypercholesterolemia	3 (1.5)
Osteoarthritis	3 (1.5)
Sinusitis	3 (1.5)
Spinal osteoarthritis	3 (1.5)
Upper respiratory tract infection	3 (1.5)
Bone pain	2 (1.0)
Bursitis	2 (1.0)
Cataract	2 (1.0)
Conjunctivitis	2 (1.0)
Depression	2 (1.0)
Dyspepsia	2 (1.0)
Febrile infection	2 (1.0)
Gastro-esophageal reflux disease	2 (1.0)
Hyperlipidemia	2 (1.0)
Hypertriglyceridemia	2 (1.0)
Hypokalemia	2 (1.0)
Joint sprain	2 (1.0)
Muscle spasms	2 (1.0)
Myalgia	2 (1.0)
Sciatica	2 (1.0)
Shoulder pain	2 (1.0)
Spinal muscular atrophy	2 (1.0)
Supraventricular extrasystoles	2 (1.0)
Tinnitus	2 (1.0)
Vertigo positional	2 (1.0)

No deaths occurred during the extension period. Six patients (3.0%) experienced SAEs throughout the entire study with 2 SAEs during the extension period. Four SAEs led to hospitalization, but none led to discontinuation, and none were suspected to be study drug related. Data were summarized in the following table 93.

Table 93: Incidence of serious adverse events including death by primary system organ class and preferred term during the high dose combination therapy Aliskiren/HCTZ 300/25 mg (All extension population) in study 2302 E1

Primary System Organ Class Preferred term	Aliskiren + HCTZ 300/25 mg N=198 n (%)
All SAEs	6 (3.0)
Gastrointestinal disorders	
Umbilical hernia	1 (0.5)
Nervous system disorders	
Cerebrovascular accident	1 (0.5)
Polyneuropathy	1 (0.5)
Musculoskeletal and connective tissue disorders	
Arthralgia	1 (0.5)
Injury, poisoning and procedural complications	
Meniscus lesion	1 (0.5)
Muscle rupture	1 (0.5)

Noteworthy among changes in lab values were increases in uric acid. An increase in mean uric acid of 31.4 µmol/L from baseline to the end of study was observed as was the shift from normal to high value in a portion of the patients (41% in any post-baseline visit and 22% at the endpoint). Gout or exacerbation of gout was reported in five patients. Data were summarized in the following table 94.

Table 94: Change of uric acid from baseline in the extension of study

Uric Acid (umol/L)

		Baseline			Post baseline: Endpoint			Post baseline: Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Aliskiren + HCTZ 300/25 mg (N=198)	198	351.5	85.4	350.0	382.9	92.4	370.0	31.4	65.5	30.0

		Baseline		Extreme value: Low		Normal		High	
Treatment		n	(%)	n	(%)	n	(%)	n	(%)
Aliskiren + HCTZ 300/25 mg (N=198)	Low	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Normal	139	(70.2)	0	(0.0)	58	(29.3)	81	(40.9)
	High	59	(29.8)	0	(0.0)	4	(2.0)	55	(27.8)
	Total	198	(100)	0	(0.0)	62	(31.3)	136	(68.7)

		Baseline		Final value: Low		Normal		High	
Treatment		n	(%)	n	(%)	n	(%)	n	(%)
Aliskiren + HCTZ 300/25 mg (N=198)	Low	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Normal	139	(70.2)	0	(0.0)	96	(48.5)	43	(21.7)
	High	59	(29.8)	0	(0.0)	12	(6.1)	47	(23.7)
	Total	198	(100)	0	(0.0)	108	(54.5)	90	(45.5)

10.1.4.5 Conclusion

This study mainly focuses on the longer term safety data for aliskiren at the highest dose of 300 mg with HCTZ at dose of 25 mg. It provides little useful information regarding efficacy. In the safety analysis, no new significant safety issues were identified in this extension study except that gout may be a potential problem with the combination of aliskiren and HCTZ.

10.1.5. Study 2303: An eight-week, randomized, double-blind, multi-center, active controlled, parallel group study to evaluate the safety and efficacy of an aliskiren based regimen compared to a lisinopril based regimen in patients with uncomplicated severe hypertension

10.1.5.1 Objectives

The primary objective of this study is to evaluate the overall safety of a regimen of aliskiren 150 mg potentially titrated to 300 mg with the potential addition of hydrochlorothiazide (HCTZ) compared to a regimen of lisinopril 20 mg potentially titrated to 40 mg with the potential addition of HCTZ in patients with uncomplicated severe hypertension (msDBP $\geq$ 105 mmHg and < 120 mmHg). This study was designed to meet European Union regulatory requirements.

10.1.5.2 Study design

This was a multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group study of aliskiren compared to lisinopril with the potential addition of hydrochlorothiazide in adult patients with uncomplicated moderately severe hypertension (DBP 105-119). Eligible patients were randomized to receive aliskiren 150 mg or lisinopril 20 mg in a 2:1 ratio. Patients were titrated to goal BP (BP < 140/90) following these three steps:
Step 1: aliskiren 150 mg or lisinopril 20 mg.
Step 2: aliskiren 300 mg or lisinopril 40 mg.
Step 3: aliskiren 300 mg + HCTZ 25 mg or lisinopril 40 mg + HCTZ 25 mg.

Visits occurred at week 1, 2, 4, 6, and 8 with BP measured by cuff approximately 24 hours after the last dose. A sample size of 180 was planned, 183 patients were randomized, and 165 (90%) complete including 11% with aliskiren and 7% with lisinopril. All but one patient were white, a little more than half were male (57%), and the mean age was 55 years. The mean baseline BP was 163/108.

10.1.5.3 Efficacy summary

Both of the treatment regimens produced clinically significant reductions in msDBP and msSBP at all time points. The mean decrease at 8 weeks (LOCF) was slightly lower with aliskiren (-20.0/-18.5) than with lisinopril (-22.3/-20.1). A slightly higher percentage of aliskiren patients had HCTZ added (54%) than lisinopril patients (45%) while the percentage on the high dose alone was similar in both groups (about 20%).

There is no different comparison of the efficacy between the monotherapy of aliskiren and the combination of aliskiren with HCTZ.

10.1.5.4. Safety summary

Extent of exposure: Of the 125 patients in the aliskiren treatment regimen, most titrated from 150 mg to 300 mg (92 patients, or 73.6 %), and a little more than half (67 patients, or 53.6 %) added on 25 mg HCTZ. Of the 58 patients in the lisinopril treatment regimen, most titrated from 20 mg to 40 mg (38 patients, or 65.5%), and almost half (26 patients, or 44.8%) added on 25 mg HCTZ. Data were summarized in the following table 95.

Table 95: Number of patients who received the actual treatment dose regimen during the double-blind period (randomized population) in study 2303

Aliskiren 150 mg	Aliskiren 300 mg	Aliskiren / HCTZ 300/25 mg	Lisinopril 20 mg	Lisinopril 40 mg	Lisinopril / HCTZ 40/25 mg
N	N	N	N	N	N
125	92	67	58	38	26

The proportion of patients who experienced AEs during the double-blind period was comparable for the two treatment regimens, occurring for 32.8% of patients in the aliskiren regimen and 29.3% of patients in the lisinopril regimen. Organ systems with more AEs in the aliskiren group was skin and subcutaneous disorders (4.8% vs. 0%) and respiratory and thoracic (3.2% vs. 1%), with neither organ system showing a clear pattern of AEs for aliskiren. Data were summarized in the following table 96. The direct comparison between the monotherapy and the combination therapy were shown in the integrated safety review (Section 7).

Table 96:Number (%) of patients with AEs (at least 2% in total) by primary system organ class during the double-blind period (Safety population) in study 2303

Primary System Organ Class	Aliskiren N=125 n(%)	Lisinopril N=58 n(%)	Total N=183 n(%)
Total	41 (32.8)	17 (29.3)	58 (31.7)
Gastrointestinal disorders	5 (4.0)	2 (3.4)	7 (3.8)
General disorders and administration site conditions	4 (3.2)	3 (5.2)	7 (3.8)
Infections and infestations	6 (4.8)	3 (5.2)	9 (4.9)
Musculoskeletal and connective tissue disorders	3 (2.4)	4 (6.9)	7 (3.8)
Nervous system disorders	13 (10.4)	6 (10.3)	19 (10.4)
Respiratory, thoracic and mediastinal disorders	4 (3.2)	1 (1.7)	5 (2.7)
Skin and subcutaneous tissue disorders	6 (4.8)	0 (0.0)	6 (3.3)

The most frequent adverse events (at least 3 patients overall) were headache, nasopharyngitis, dizziness, and fatigue. Other adverse events occurred for fewer patients and did not show marked differences between treatment groups. Data were summarized in the following table 97.

Table 97: Number (%) of patients with common AEs (at least 1% in total) by preferred term during the double-blind period (Safety population) in study 2303.

Preferred term	Aliskiren N=125 n(%)	Lisinopril N=58 n(%)	Total N=183 n(%)
Headache	11 (8.8)	5 (8.6)	16 (8.7)
Nasopharyngitis	3 (2.4)	2 (3.4)	5 (2.7)
Dizziness	1 (0.8)	2 (3.4)	3 (1.6)
Fatigue	1 (0.8)	2 (3.4)	3 (1.6)
Edema peripheral	2 (1.6)	0 (0.0)	2 (1.1)
Vertigo	2 (1.6)	0 (0.0)	2 (1.1)
Back pain	1 (0.8)	1 (1.7)	2 (1.1)
Cough	1 (0.8)	1 (1.7)	2 (1.1)
Neck pain	1 (0.8)	1 (1.7)	2 (1.1)

There were no deaths reported, and about 3% of patients in each group discontinued for an AE. The discontinuations for aliskiren were for headache, hypotension, dysesthesia, and pruritus. One patient in the lisinopril group discontinued for an MI. AEs leading to discontinuation from the study were summarized in the following table 98.

Table 98: Number (%) of patients with adverse events leading to discontinuation during the double-blind period by preferred term and randomized treatment group (Safety population) in study 2303

Preferred term	Aliskiren N=125 n(%)	Lisinopril N=58 n(%)	Total N=183 n(%)
Total no. of patients with AEs leading to discontinuation	4 (3.2)	2 (3.4)	6 (3.3)
Appendicitis	0 (0.0)	1 (1.7)	1 (0.5)
Dysesthesia	1 (0.8)	0 (0.0)	1 (0.5)
Headache	1 (0.8)	0 (0.0)	1 (0.5)
Hypotension	1 (0.8)	0 (0.0)	1 (0.5)
Myocardial infarction	0 (0.0)	1 (1.7)	1 (0.5)
Pruritus generalized	1 (0.8)	0 (0.0)	1 (0.5)

10.1.5. Conclusion

In patients with severe hypertension, an aliskiren-based treatment regimen (aliskiren 150 mg potentially titrated to 300 mg O.D. with the potential addition of HCTZ) seems to produce a more reduction in both systolic and diastolic blood pressure compared to the lisinopril-based treatment regimen (lisinopril 20 mg potentially titrated to 40 mg O.D. with the potential addition of HCTZ). Aliskiren may have slightly more minor AEs, while differences in SAEs are too small to evaluate.

The AEs between the aliskiren monotherapy and the combination of aliskiren with HCT are comparable as shown in the integrated safety review (Section 7) .

10.1.6. Study 2306: A 26 week, double-blind, randomized, multicenter, parallel group, active-controlled study comparing aliskiren to ramipril with optional addition of hydrochlorothiazide, followed by a 4 week double-blind, randomized, placebo-controlled withdrawal in patients with essential hypertension.

10.1.6.1 Objectives

The primary objective of this study is to evaluate the efficacy of an aliskiren-based antihypertensive regimen (aliskiren 150 mg, aliskiren 300 mg, aliskiren 300 mg with HCTZ 12.5 mg/25 mg) when compared to a ramipril-based antihypertensive regimen (ramipril 5 mg, ramipril 10 mg, ramipril 10 mg with HCTZ 12.5 mg/25 mg) by testing: (i) the hypothesis of non-inferiority for the aliskiren regimen versus the ramipril regimen on reduction in mean sitting diastolic blood pressure (msDBP) from baseline to Week 26 and (ii) the hypothesis of superiority for the aliskiren regimen versus the ramipril regimen on reduction in msDBP from baseline, if the hypothesis of non-inferiority was achieved. It will also evaluate the efficacy of an aliskiren-based antihypertensive regimen by testing the hypothesis of superiority on the change (i.e. smaller change for the aliskiren regimen when compared to placebo) in msDBP and msSBP from Week 26, after a 4-week randomized, double-blind, placebo-controlled withdrawal period when compared to placebo.

Regarding the current application for the combined therapy, this study could provide a long term safety and tolerability of the combination of aliskiren with HCTZ.

10.1.6.2 Study design

A randomized, double-blind, parallel group, active-controlled multicenter study in patients with uncomplicated essential hypertension (msDBP $\geq$ 95 mmHg and < 110 mmHg) with four periods: a 2-week washout period, 2- to 4-week single-blind placebo run-in period, 26-week double blind active-controlled treatment period, and 4-week double-blind placebo-controlled withdrawal period.

The double-blind active-controlled treatment was initiated with either aliskiren 150 mg or ramipril 5 mg; after 6 weeks, there was optional up-titration to high-dose monotherapy, optional addition of low-dose HCTZ (12.5 mg), and optional up-titration of HCTZ to 25 mg, which occurred in 3 sequential steps at 6-week intervals, based on blood pressure response [i.e. achieving of target blood pressure of < 140/90 mmHg (msSBP/msDBP)]. After 26 weeks of double-blind treatment, patients were re-randomized to either continue on their existing dosing regimen at the end of the double-blind active-controlled treatment period or to placebo, in the assignment ratio of 1:1 for a 4-week double blind withdrawal period.

In total, 842 patients were randomized to the double-blind active-controlled treatment period (420 patients to the aliskiren regimen and 422 patients to the ramipril regimen). Of the 842 randomized patients, 687 (81.6%) completed the active-controlled treatment period and 150 (17.8%) discontinued.

10.1.6.3 Efficacy summary

The least-squares mean reduction in msDBP and msSBP at the Week 26 endpoint in an aliskiren-based regimen versus a ramipril-based regimen were -13.17 mm Hg versus -11.96 mm Hg, and -17.88 mm Hg versus -15.24 mmHg, respectively. it demonstrated superiority of the aliskiren-based regimen versus the ramipril-based one in the intent-to-treat population.

The proportion of patients controlled to a target blood pressure of < 140/90 mm Hg on the aliskiren based antihypertensive regimen was statistically greater than that on the ramipril-based regimen at the Week 26 endpoint (61.4% vs. 53.1%) (p=0.0205).

In the aliskiren regimen, more patients remained on monotherapy until Week 26 and considerably fewer patients required the addition of HCTZ compared with the ramipril regimen. Overall, 209 patients required the addition of HCTZ 12.5 mg in the ramipril group, compared with 193 in the aliskiren group. Only 92 patients in the aliskiren regimen were titrated from 12.5 to 25 mg HCTZ compared with 132 patients in the ramipril regimen

In the group of patients who received placebo in the treatment withdrawal period, those who had been treated with aliskiren in the active-controlled treatment period had a more gradual return toward baseline (3-4 weeks) compared with patients who had received ramipril in the active-controlled treatment period, where most of the treatment effect was lost at 1 week.

10.1.6.4 Safety summary

Patient exposure: Duration of exposure to study drug in active-controlled treatment was summarized in the following table 99.

Table 99: Duration of exposure to study drug in active-controlled treatment period by dose level (Randomized population) in study 2306

Duration (days) Statistics	Ali 150 mg n (%)	Ali 300 mg n (%)	Ali/HCTZ 300/12.5 mg n (%)	Ali/HCTZ 300/25 mg n (%)	Aliskiren Regimen n (%)
N	421	285	193	92	421
Mean	83.3	61.1	51.4	50.3	159.2
SD	58.09	36.19	25.04	10.45	51.48
Median	44	43	42	56	182
Min	1	1	1	27	1
Max	200	146	105	68	200
>= 1	421 (100)	285 (100)	193 (100)	92 (100)	421 (100)
>= 42	331 (78.6)	214 (75.1)	124 (64.2)	65 (70.7)	392 (93.1)
>= 84	161 (38.2)	72 (25.3)	35 (18.1)	0 (0.0)	366 (86.9)
>= 126	114 (27.1)	34 (11.9)	0 (0.0)	0 (0.0)	349 (82.9)
>= 182	63 (15.0)	0 (0.0)	0 (0.0)	0 (0.0)	261 (62.0)
Duration (days) Statistics	Ramipril 5 mg n (%)	Ramipril 10 mg n (%)	Ramipril/HCTZ 10/12.5 mg n (%)	Ramipril/HCTZ 10/25 mg n (%)	Ramipril Regimen n (%)
N	422	300	209	132	422
Mean	82.2	56.6	50.1	49.8	162.9
SD	57.5	33.22	23.44	10.82	47.13
Median	44	42	42	55	182
Min	3	1	7	1	3
Max	193	150	109	69	197
>= 1	422 (100)	300 (100)	209 (100)	132 (100)	422 (100)
>= 42	343 (81.3)	211 (70.3)	145 (69.4)	95 (72.0)	400 (94.8)
>= 84	159 (37.7)	65 (21.7)	32 (15.3)	0 (0.0)	370 (87.7)
>= 126	110 (26.1)	27 (9.0)	0 (0.0)	0 (0.0)	362 (85.8)
>= 182	57 (13.5)	0 (0.0)	0 (0.0)	0 (0.0)	252 (59.7)

- Duration of exposure (days) is defined as follows:
If last study drug date is known: Last study drug date - Day study drug administered + 1
If last study drug date is unknown: Last visit date on or before Week 28 - Day study drug administered + 1.
The percentages were calculated using the denominator of total number of patients in each regimen of aliskiren or ramipril.

There were two deaths in the double-blind active treatment period, one in each treatment regimen. One patient in the aliskiren regimen died during the placebo-controlled treatment withdrawal period and one patient in the ramipril regimen died during the 30-day follow up period after the trial.

One patient is a 57 year-old Caucasian male with a significant medical history including ischemic heart disease with coronary bypass surgery in 1981 and a smoking history of 34 years. He collapsed and was unable to breathe on Day 18 of the placebo-controlled treatment withdrawal period and Day 198 of the double-blind treatment phase. The patient had completed the active-controlled treatment period with aliskiren 300 mg/day and had been re-randomized to placebo. The investigator subsequently informed that the cause of death was either a massive pulmonary embolism or myocardial infarction

One patient is a 53- year-old Caucasian male in the ramipril regimen with a 21-year history of essential hypertension and relevant medical history and risk factors including dyslipidemia and a smoking history of 30 years. He experienced a stroke and was hospitalized on Day 186 of the double-blind active-control period. Study drug treatment with ramipril 10 mg + HCTZ 25 mg/day was subsequently discontinued due to this event. Three days later the patient experienced abdominal pain and nausea and was transferred to intensive care due to suspected septicemia. An exploratory laparotomy was performed, which revealed mesenteric thrombosis with massive necrosis of the small intestine and colon. The patient died 3 days later due to mesenteric thrombosis.

Aliskiren or ramipril-based regimens experienced SAEs were 1.9% and 1.4%, respectively, in the active-controlled treatment period; 0.9% of patients in the aliskiren regimen during the placebo-controlled treatment withdrawal period. The SAEs were not clustered in any particular primary system organ class and the only SAE suspected to be study drug related was angioneurotic edema reported in one patient in the aliskiren regimen.

This is a 57 year old female Caucasian patient with a 11 year history of essential hypertension. Her prior medication included Coversyl Plus (perindopril erbumine with indapamide). On Day 23 (31-Jul-2005) of the double-blind active-controlled study period, the patient experienced worsening shortness of breath and throat tightness. She was diagnosed with angioedema, instructed to stop study medication and had medical treatment initiated with prednisolone and loratadine. The investigator reported that the patient's clinical examination on the day of the event showed facial skin flushing and itching without any signs of rash or skin eruptions, that her lips and tongue were slightly swollen and pharynges were congested and that there was no wheezing or other signs of respiratory difficulty. The study medication dose at the time of the adverse experience was aliskiren 150 mg per day. The study medication was permanently discontinued on 10-Aug-2005 due to this adverse event. The patient recovered completely from the adverse event in 11 days.

The rate of discontinued treatment due to AEs in the aliskiren or ramipril regimen were 5.7% and 4.7%, respectively, during the active-controlled treatment period; 1.2% and 0.9%, respectively in the placebo-controlled treatment withdrawal period. The most common AE leading to discontinuation in both regimens was cough, reported in 2.1% of patients in the ramipril regimen

and less than half that number (1.0% of patients) in the aliskiren regimen. Data were summarized in the following tables 100 and 101.

Table 100: Adverse events leading to discontinuation in active-controlled treatment period by preferred term and treatment group (safety population) in study 2306

	Aliskiren Regimen	Ramipril Regimen*
	N=419 n (%)	N=422 n (%)
Any Adverse Events leading to discontinuation	24 (5.7)	20 (4.7)
Preferred term		
Cough	4 (1.0)	9 (2.1)
Dizziness	3 (0.7)	2 (0.5)
Headache	3 (0.7)	4 (0.9)
Angina pectoris	2 (0.5)	0 (0.0)
Abdominal pain	1 (0.2)	0 (0.0)
Acute coronary syndrome	1 (0.2)	0 (0.0)
Angioneurotic oedema	1 (0.2)	1 (0.2)
Back pain	1 (0.2)	0 (0.0)
Diarrhoea	1 (0.2)	0 (0.0)
Endometriosis	1 (0.2)	0 (0.0)
Hallucination, auditory	1 (0.2)	0 (0.0)
Hypercholesterolaemia	1 (0.2)	0 (0.0)
Hypokalaemia	1 (0.2)	0 (0.0)
Hypotension	1 (0.2)	0 (0.0)
Insomnia	1 (0.2)	0 (0.0)
Laryngeal cancer	1 (0.2)	0 (0.0)
Malaise	1 (0.2)	0 (0.0)
Nausea	1 (0.2)	0 (0.0)
Neoplasm prostate	1 (0.2)	0 (0.0)
Oedema peripheral	1 (0.2)	0 (0.0)
Orthostatic hypotension	1 (0.2)	0 (0.0)
Pain in extremity	1 (0.2)	0 (0.0)
Staphylococcal infection	1 (0.2)	0 (0.0)
Vertigo	1 (0.2)	0 (0.0)
Cerebrovascular accident	0 (0.0)	1 (0.2)
Eczema	0 (0.0)	1 (0.2)
Fatigue	0 (0.0)	1 (0.2)
Hyperhidrosis	0 (0.0)	1 (0.2)
Hyperthyroidism	0 (0.0)	1 (0.2)
Hypoaesthesia facial	0 (0.0)	1 (0.2)
Migraine	0 (0.0)	1 (0.2)
Muscle spasms	0 (0.0)	1 (0.2)
Syncope	0 (0.0)	1 (0.2)

Preferred terms are sorted by descending frequency, as reported in the Aliskiren Regimen column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Table 101: Adverse events leading to discontinuation in placebo-controlled treatment withdrawal period by preferred term and treatment group (withdrawal safety population) in study 2306

	Aliskiren Regimen			Ramipril Regimen		
	Aliskiren N=170 n (%)	Placebo N=163 n (%)	Total N=333 n (%)	Ramipril N=165 n (%)	Placebo N=177 n (%)	Total N=342 n (%)
Any Adverse Events leading to discontinuation	0 (0.0)	4 (2.5)	4 (1.2)	0 (0.0)	3 (1.7)	3 (0.9)
Preferred term						
Anaemia	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	2 (1.1)	2 (0.6)
Pulmonary embolism	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)

Preferred terms are sorted by descending frequency, as reported in the Aliskiren Total column.

The overall incidence of AEs in the active-controlled treatment period was comparable in both

treatment regimens (61.3% in the aliskiren regimen versus 60.4% in the ramipril regimen). The most common AEs in the aliskiren regimen during the active controlled treatment period were headache (11.2%), nasopharyngitis (6.0%), and dizziness (5.5%) and the most common AEs in the ramipril regimen were cough (9.5%), headache (8.3%), and nasopharyngitis (6.2%). The incidence of diarrhea was higher in the aliskiren regimen (3.8%) compared to the ramipril regimen (1.7%). Cough was more common in the ramipril regimen. Data were summarized in the following tables 102.

Table 102: Number (%) of patients with common adverse events (> or = 2% in any treatment group) in active-controlled treatment period by the order of the frequency (safety population) in study 2306

	Aliskiren Regimen	Ramipril Regimen
	N=419	N=422
	n (%)	n (%)
Any Adverse Events	257 (61.3)	255 (60.4)
Preferred term		
Headache	47 (11.2)	35 (8.3)
Nasopharyngitis	25 (6.0)	26 (6.2)
Dizziness	23 (5.5)	20 (4.7)
Fatigue	18 (4.3)	15 (3.6)
Cough	17 (4.1)	40 (9.5)
Diarrhoea	16 (3.8)	7 (1.7)
Oedema peripheral	16 (3.8)	13 (3.1)
Back pain	15 (3.6)	13 (3.1)
Pain in extremity	15 (3.6)	8 (1.9)
Bronchitis	13 (3.1)	4 (0.9)
Upper respiratory tract infection	12 (2.9)	17 (4.0)
Nausea	11 (2.6)	8 (1.9)
Dyspepsia	10 (2.4)	4 (0.9)
Sinusitis	8 (1.9)	10 (2.4)
Influenza	6 (1.4)	11 (2.6)

Laboratory findings were consistent with previous studies of aliskiren and the known characteristics of ramipril and HCTZ.

AEs in the placebo-controlled treatment withdrawal period were more frequent in the ramipril regimen (29.5%) than in the aliskiren regimen (20.7%), however the incidence of AEs was greater in the group of patients re-randomized to placebo for each regimen. The most common AEs in both the aliskiren and ramipril regimens during the placebo-controlled treatment withdrawal period were headache, upper respiratory tract infection, and nasopharyngitis. Data were summarized in the following table 103.

Table 103: Number (%) of patients with common adverse events (> or = 2% in any treatment group) in placebo-controlled treatment withdrawal period (withdrawal safety population) in study 2306

	Aliskiren Regimen			Ramipril Regimen		
	Aliskiren	Placebo	Total	Ramipril	Placebo	Total
	N=170	N=163	N=333	N=165	N=177	N=342
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any Adverse Events	38 (22.4)	31 (19.0)	69 (20.7)	49 (29.7)	52 (29.4)	101 (29.5)
Preferred term						
Headache	3 (1.8)	7 (4.3)	10 (3.0)	3 (1.8)	14 (7.9)	17 (5.0)
Upper respiratory tract infection	3 (1.8)	2 (1.2)	5 (1.5)	7 (4.2)	2 (1.1)	9 (2.6)
Nasopharyngitis	2 (1.2)	1 (0.6)	3 (0.9)	8 (4.8)	9 (5.1)	17 (5.0)

The direct comparison between the aliskiren or Ramipril monotherapy and its combination therapy with the addition of HCTZ were discussed in the integrated safety review (section 7). Overall, the safety profiles were comparable between the monotherapies and the combination treatments.

10.1.6.5 Conclusion

From the efficacy aspect, the aliskiren-based regimen produced statistically superior reductions in msDBP and msSBP at Week 26 endpoint when compared to the ramipril-based regimen. The aliskiren-based regimen also showed continued efficacy after 26 weeks of treatment as assessed by a 4-week randomized, double-blind placebo-controlled withdrawal.

No significant adverse events in the combined product vs the monotherapy in this 26 week study were observed.

10.1.7. Study 2309: A 12-week randomized double-blind parallel group study to evaluate the efficacy and safety of the combination of aliskiren with HCTZ compared to irbesartan or amlodipine with HCTZ or HCTZ alone in hypertensive patients with BMI $\geq$ 30 kg/m^2 not adequately responsive to HCTZ 25 mg

10.1.7.1 Objectives

The primary objective is to evaluate the blood pressure lowering effects of the combination of aliskiren 300 mg and HCTZ 25 mg in obese patients with essential hypertension inadequately treated with HCTZ 25 mg by testing the hypothesis of superior reduction from baseline in mean sitting diastolic blood pressure (MSDBP) with aliskiren-HCTZ treatment compared to HCTZ alone at Week 8. This study is also to compare the change in msDBP and msSBP of the aliskiren with HCTZ combination to irbesartan-HCTZ combination and amlodipine-HCTZ combination treatments from baseline to Week 4 and to the end of study; compare the change in msDBP and msSBP from baseline to week 4 of aliskiren 150 mg with HCTZ 25 mg combination versus HCTZ 25 mg treatment alone; and to evaluate the safety and tolerability of aliskiren in combination with HCTZ versus HCTZ alone, irbesartan-HCTZ and amlodipine-HCTZ in patients with essential hypertension inadequately treated with HCTZ alone.

10.1.7.2 Study design

This is a international multiple center study including Belgium (3 centers), France (8 centers), Germany (28 centers), Israel (3 centers), Norway (7 centers), Russia (10 centers), and Spain (10 centers). A total of 489 patients were randomized to the double-blind treatment period (122 patients to aliskiren/HCTZ, 119 to irbesartan/HCTZ, 126 to amlodipine/HCTZ, and 122 to HCTZ alone). The study had three periods: a 2- to 4-week washout period, a 4-week, single-blind, HCTZ treatment period, and a 12-week, randomized, double-blind treatment period. Double-blind treatment was initiated with one of the following 4 treatment arms assigned in a ratio of 1:1:1:1: aliskiren 150 mg, irbesartan 150 mg, amlodipine 5 mg, or placebo. At the end of Week 4 (Visit 6), patients were titrated to the next dose strength within each treatment arm they

were assigned: aliskiren 300 mg, irbesartan 300 mg, amlodipine 10 mg or placebo, respectively, for the remaining 8 weeks. All patients continued on HCTZ 25 mg for the entire 12-week double-blind treatment period.

10.1.7.3 Efficacy summary

Of the 489 randomized patients, 448 (91.6%) completed the double-blind treatment period and 41 (8.4%) discontinued. 13 (10.7%) from the HCTZ group, 11 (8.7%) from the amlodipine/HCTZ group, 10 (8.2%) from the aliskiren/HCTZ group, and 7 (5.9%) from the irbesartan/HCTZ group. The most frequent reason for discontinuation overall was adverse events (3.5%), ranging from 5.6% in the amlodipine/HCTZ group to 1.6% in the aliskiren/HCTZ group. The most frequent reason for discontinuation in the aliskiren/HCTZ group was withdrawal of consent, reported in 4.1% of patients.

Aliskiren 300 mg added to HCTZ 25 mg produced statistically significant reductions in both msDBP and msSBP compared to HCTZ 25 mg alone at Week 8 endpoint. The reductions from baseline to Week 8 endpoint in msDBP and msSBP with aliskiren/HCTZ were numerically greater than but not statistically different from irbesartan/HCTZ or amlodipine/HCTZ. Data were summarized in the following tables 104 and 105.

Table 104: Between-treatment analysis for change from baseline in msDBP at Week 8 endpoint (intent-to-treat population) in study 2309

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

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

Table 105: Between-treatment analysis for change from baseline in msSBP at Week 8 endpoint (intent-to-treat population)

Treatment Group	N	LSM change from baseline (SE)	
Aliskiren 300 mg / HCTZ 25 mg	113	-15.79 (1.01)	
Irbesartan 300 mg / HCTZ 25 mg	117	-15.44 (1.00)	
Amlodipine 10 mg / HCTZ 25 mg	122	-13.55 (0.98)	
HCTZ 25 mg	117	-8.62 (1.00)	
Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
Aliskiren 300 mg / HCTZ 25 mg vs. HCTZ 25 mg	-7.17 (1.40)	(-9.93, -4.41)	<.0001*
Aliskiren 300 mg / HCTZ 25 mg vs. Irbesartan 300 mg / HCTZ 25 mg	-0.35 (1.40)	(-3.11, 2.40)	0.8006
Aliskiren 300 mg / HCTZ 25 mg vs. Amlodipine 10 mg / HCTZ 25 mg	-2.24 (1.39)	(-4.97, 0.49)	0.1071

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

The addition of aliskiren 150 mg to HCTZ 25 mg also significantly reduced msDBP and msSBP at the Week 4 endpoint as did the regimen after 12 weeks of treatment. Aliskiren 300 mg/HCTZ 25 mg produced a statistically significant superior responder rate compared with HCTZ 25 mg alone at Week 8 endpoint and Week 12. The response rate to aliskiren 300 mg/HCTZ 25 mg was not statistically different from irbesartan 300mg/HCTZ 25mg or amlodipine/HCTZ at the Week 8 endpoint or Week 12. Significantly more patients in the aliskiren/HCTZ group achieved blood pressure control compared with HCTZ 25 mg alone at Week 8 endpoint and Week 12. The number of patients in the aliskiren/HCTZ group who achieved blood pressure control at Week 8 endpoint and Week 12 was not statistically different from irbesartan/HCTZ or amlodipine/HCTZ.

10.1.7.4 Safety summary

Patient exposure: Duration of exposure to double-blind medication was similar across treatment groups in the double-blind treatment period as shown in the following table 106.

Table 106: Duration of exposure to study medication during the double-blind treatment period by treatment group in study 2309

Duration of Exposure (Days)	Aliskiren 300mg HCTZ 25mg N=122	Irbesartan 300mg HCTZ 25mg N=119	Amlodipine 10mg HCTZ 25mg N=126	HCTZ 25mg N=122
Mean	79.0	82.4	80.3	80.2
SD	18.46	10.40	14.84	16.16
Median	84.0	84.0	84.0	84.0
Min	1	9	3	2
Max	91	90	92	93

Duration of exposure in days; if last study drug date is known then last study drug date – day study drug administered + 1 day, if last study drug date is not known then last visit date – day study drug administered + 1

Overall, 195 (39.9%) of 489 patients had an adverse event during the double-blind treatment period. The incidence of AEs ranged from 45.2% in the amlodipine/HCTZ group to 38.5% in the HCTZ group, 39.3% in the aliskiren/HCTZ group, and 36.1% in the irbesartan/HCTZ group. the most common AEs in the aliskiren/HCTZ group and the irbesartan/HCTZ group during the double-blind treatment period were nasopharyngitis, headache, and dizziness. As expected, peripheral edema was the most frequent AE in the amlodipine/HCTZ group and was much more frequent than in any of the other treatment groups. The most common AEs in the HCTZ regimen were nasopharyngitis, back pain, and headache. Headache was relatively frequent across treatment groups, as is common in patients with hypertension. Data were summarized in the following table 107.

Table 107: Number (%) of patients with common adverse events (>= 2.0%) starting in double-blind period in any treatment group by the order of frequency (safety double-blind population) in study 2309

Any Adverse Events	Aliskiren 300mg HCTZ 25mg N=122 n (%)	Irbesartan 300mg HCTZ 25mg N=119 n (%)	Amlodipine 10mg HCTZ 25mg N=126 n (%)	HCTZ 25mg N=122 n (%)	Total N=489 n (%)
Nasopharyngitis	10 (8.2)	6 (5.0)	7 (5.6)	5 (4.1)	28 (5.7)
Headache	5 (4.1)	3 (2.5)	9 (7.1)	4 (3.3)	21 (4.3)
Dizziness	4 (3.3)	3 (2.5)	1 (0.8)	2 (1.6)	10 (2.0)
Oedema peripheral	1 (0.8)	1 (0.8)	14 (11.1)	2 (1.6)	18 (3.7)
Back pain	1 (0.8)	2 (1.7)	5 (4.0)	5 (4.1)	13 (2.7)

Primary system organ classes are sorted by descending frequency, as reported in the aliskiren/HCTZ column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

There were no patient deaths during the single- or double-blind treatment periods in this study. The incidence of SAE was lowest in the aliskiren/HCTZ group (1.6%), followed by the irbesartan/HCTZ group (2.5%), and the amlodipine/HCTZ (3.2%) and HCTZ group (3.3%). The only SAE considered possibly related to study drug was a case of peripheral edema reported in the amlodipine/HCTZ group; study drug was discontinued due to this SAE and the event resolved. The one SAE of myocardial infarction in the aliskiren/HCTZ group occurred in a 58 year old Caucasian male patient diagnosed with an anterior myocardial infarction without clinical symptoms (no pain) on Day 67 of double blind treatment. The patient had a normal ECG result at the time of randomization. Study medication was temporarily interrupted and the patient completed the study. The number of SAE was summarized in the following table 108.

Table 108: Number (%) of patients with SAEs during double-blind treatment period by preferred term and treatment group (safety double-blind population) in study 2309

Primary system organ class Preferred term	Aliskiren 300mg HCTZ 25mg N=122 n (%)	Irbesartan 300mg HCTZ 25mg N=119 n (%)	Amlodipine 10mg HCTZ 25mg N=126 n (%)	HCTZ 25mg N=122 n (%)
Any primary system organ class/preferred term	2 (1.6)	3 (2.5)	4 (3.2)	4 (3.3)
Cardiac disorders	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Edema peripheral	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Infections and infestations	1 (0.8)	1 (0.8)	0 (0.0)	1 (0.8)
Hepatitis A	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Urinary tract infection	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Viral infection	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Forearm fracture	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Cerebrovascular disorder	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Confusional state	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Renal and urinary disorders	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)
Renal failure acute	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Urinary retention	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Epistaxis	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)

The overall incidence of AEs beginning in the double-blind treatment period and leading to discontinuation was lowest in the aliskiren/HCTZ group (1.6%), followed by the HCTZ group (3.3%), the irbesartan/HCTZ group (3.4%), and the amlodipine/HCTZ group (4.8%). All AEs leading to discontinuation occurred in a single patient each with the exception of peripheral edema, reported in 4 (3.2%) patients in the amlodipine/HCTZ group and nausea, reported in 2 (1.7%) patients in the irbesartan/HCTZ group. Data were summarized in the following table 109.

Table 109: Adverse events starting in double-blind treatment period and leading to study drug discontinuation by system organ class and treatment group (safety double-blind population)

Preferred term	Aliskiren 300mg HCTZ 25mg N=122 n (%)	Irbesartan 300mg HCTZ 25mg N=119 n (%)	Amlodipine 10mg HCTZ 25mg N=126 n (%)	HCTZ 25mg N=122 n (%)
Any Adverse Events	2 (1.6)	4 (3.4)	6 (4.8)	4 (3.3)
Abdominal pain upper	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Cerebrovascular disorder	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Confusional state	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Cystitis	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Diabetes mellitus non- insulin-dependent	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Drug hypersensitivity	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Erythema	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)
Facial palsy	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Hypoaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Myocardial infarction	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Oedema peripheral	0 (0.0)	0 (0.0)	4 (3.2)	0 (0.0)
Palpitations	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Renal failure acute	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Swelling face	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Urinary tract infection	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Vertigo	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)

Adverse event preferred terms are sorted alphabetically

In contrast to prior studies with aliskiren alone, diarrhea was not reported as an AE in aliskiren/HCTZ group in this study. The expected laboratory findings including the increase of uric acid, BUN and creatinine were not observed in the aliskiren/HCTZ group compared to HCTZ alone and other combination treatments.

In the vital signs, physical findings, and other observations related to safety analysis, the total incidence rate of orthostatic blood pressure was a little bit higher in the aliskiren/HCTZ group compared to HCTZ alone and other combination treat groups. Data were summarized in the following table 110.

Table 110: Number (%) of patients with orthostatic blood pressure during the double-blind treatment period (safety double-blind population) in study 2309

	Aliskiren 300mg HCTZ 25mg N = 122 N n (%)	Irbesartan 300mg HCTZ 25mg N = 119 N n (%)	Amlodipine 10mg HCTZ 25mg N = 126 N n (%)	HCTZ 25mg N = 122 N n (%)	Total N = 489 N n (%)
Baseline	122 2 (1.6)	119 4 (3.4)	126 2 (1.6)	122 1 (0.8)	489 9 (1.8)
Week 2	121 4 (3.3)	119 3 (2.5)	125 1 (0.8)	120 0 (0.0)	485 8 (1.6)
Week 4	116 2 (1.7)	118 3 (2.5)	124 1 (0.8)	117 3 (2.6)	475 9 (1.9)
Week 6	113 6 (5.3)	117 3 (2.6)	122 3 (2.5)	116 0 (0.0)	468 12 (2.6)
Week 8	113 4 (3.5)	116 0 (0.0)	120 0 (0.0)	116 1 (0.9)	465 5 (1.1)
Week 10	113 1 (0.9)	116 3 (2.6)	118 1 (0.8)	113 1 (0.9)	460 6 (1.3)
Week 12	113 2 (1.8)	115 6 (5.2)	115 3 (2.6)	111 3 (2.7)	454 14 (3.1)
Any visit post-baseline	122 15 (12.3)	119 10 (8.4)	126 9 (7.1)	120 6 (5.0)	487 40 (8.2)

10.1.7.5 Conclusion

This is a add on study to compare the addition of aliskiren, irbesartan, or amlodipine to HCTZ 25 mg with the HCTZ 25 mg alone in obese patients with essential hypertension. The results indicated that the combination treatments produced higher reductions in both msDBP and msSBP than the HCTZ treatment alone at weeks 4, 8, and 12. The reductions from baseline to Week 4 endpoint and Week 8 endpoint in msDBP and msSBP with aliskiren/HCTZ were not statistically different from irbesartan/HCTZ or amlodipine/HCTZ.

In the safety analysis, there were no new safety findings in the combination of aliskiren with HCTZ in this 12-week study compared with the previous studies. There is no direct comparison of either efficacy or safety between the aliskiren monotherapy and aliskiren/HCTZ.

10.1.8 Study 1202: Long-term study with SPP100 (aliskiren) in patients with essential hypertension

10.1.8.1 Objectives

The objectives in this study is to assess the long-term safety, tolerability, and efficacy of aliskiren alone or with a diuretic or a calcium channel blocker in patients with essential hypertension.

10.1.8.2 Study design

This study is followed the study 1201 (please see the NDA 21-985 review for study 1201). This is a multicenter, open parallel-group study conducted in Japan. The study was comprised of two periods: titration period (8 weeks) and fixed-dose/optional concomitant therapy period (44 weeks).

In the titration period, Patients began taking the prescribed SPP100 75 mg dose once daily. At Visits 2, 3 and 4, investigators could adjust individual SPP100 dose in order to achieve a goal mean sitting diastolic blood pressure (msDBP) < 90 mmHg. At these visits, SPP100 75 mg could be increased stepwise to 150 mg and to 300 mg. However, if the SPP100 daily dose at Visit 3 was 300 mg, this dose level was maintained through Visit 4 even though msDBP exceeded 90 mmHg. In the fixed-dose/optional concomitant therapy period, the SPP100 daily dose was fixed at the visit 4 dose level. If msDBP had exceeded 90 mmHg at the last two consecutive visits, a diuretic or a Ca-blocker could be added to the therapy regimen. The diuretics will be limited to thiazide diuretics and thiazide congeners. The dosage and administration were shown in the following table 111.

Table 111: Study design in study 1202

	1. Dose titration period				2. Fixed-dose/optional concomitant therapy period		
Visit	1*	2	3	4	5	6	16
Week	0	2	4	6	8	12	52
Dosage	↓				Diuretic or Ca blocker		
			SPP100 300 mg				
		SPP100 150 mg					
	SPP100 75 mg						

* Visit 1 date for this long-term treatment study falls on Visit 8 date for the dose finding study.
1. Dose titration period: Raise the daily dose level stepwise to 150 mg and to 300 mg as long as the msDBP exceeds 90 mmHg.
2. Fixed-dose/optional concomitant therapy period: Fix the Visit 4 dose level of SPP100 and further maintain it. If the msDBP exceeds 90 mmHg at two consecutive visits, then add a diuretic or a Ca blocker to the regimen, increasing dosage of the added agent as required.

A total of 345 patients who completed the previous dose-finding study (CSPP100A1201) participated in the titration phase in this study. All but one patient (344 patients) received the study drug at least one after the baseline (Visit 1), and 45 who discontinued. Data were shown in the following table 112.

Table 112: Patient disposition and analysis set in study 1202

	All patients	All treated patients	Aliskiren monotherapy	Aliskiren + Ca blocker	Aliskiren + diuretic
	n (%)	n (%)	n (%)	n (%)	n (%)
Patients (total N=345)					
Enrolled	345(100.0)	344(100.0)	175(100.0)	90(100.0)	79(100.0)
Received study medication	344(99.7)	344(100.0)	175(100.0)	90(100.0)	79(100.0)
Completed	299(86.7)	299(86.9)	149(85.1)	81(90.0)	69(87.3)
Discontinued	46(13.3)	45(13.1)	26(14.9)	9(10.0)	10(12.7)
Safety analysis set	344(99.7)	344(99.7)	175(50.7)	90(26.1)	79(22.9)
Full analysis set (FAS)	344(99.7)	344(99.7)	175(50.7)	90(26.1)	79(22.9)

Percentages based on the number of enrolled patients

10.1.8.3 Efficacy summary

During the study period, when the baseline value of the study CSPP100 1201 was used as the baseline, clinically meaningful reductions from baseline in msDBP and msSBP were achieved in all patients exposed to SPP100 regardless of the dose or treatments received. As expected, when the start of the study CSPP100 1202 was used as the baseline, smaller reductions in msDBP and msSBP were seen than those when the baseline value of the study CSPP100 1201 was used as the baseline, although 1-week washout period was set between the studies. Data were summarized in the following table 113.

Table 113: Summary of mean sitting blood pressure results at end of treatment (Visit 16 or last observation carried forward) in all treated patients in study 1202

Baseline	Study CSPP100 1201		Study CSPP100 1202	
	n*	Mean (SD)	n*	Mean (SD)
msDBP	344	-12.8(8.25)	344	-7.5(9.85)
msSBP	344	-17.6(14.42)	344	-11.9(14.92)

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

10.1.8.4 Safety summary

Patient exposure: As shown in the following table 114. Only limited number of patients were exposed to the combination therapy for more than 6 months.

Table 114: Exposure to actual therapy by interval during the entire study in study 1202

Exposure duration	Aliskiren monotherapy n (%)	Aliskiren + Ca blocker n (%)	Aliskiren + diuretic n (%)	Aliskiren + Ca blocker + diuretic n (%)
Exposure				
0 days (no drug)	1(0.3)	226(65.5)	254(73.6)	304(88.1)
> 0 days	344(99.7)	119(34.5)	91(26.4)	41(11.9)
> 14 days	342(99.1)	117(33.9)	91(26.4)	41(11.9)
> 28 days	341(98.8)	113(32.8)	87(25.2)	38(11.0)
> 42 days	339(98.3)	113(32.8)	85(24.6)	37(10.7)
> 56 days	280(81.2)	108(31.3)	82(23.8)	36(10.4)
> 70 days	262(75.9)	107(31.0)	81(23.5)	35(10.1)
> 84 days	239(69.3)	103(29.9)	73(21.2)	29(8.4)
> 98 days	234(67.8)	102(29.6)	72(20.9)	28(8.1)
> 112 days	217(62.9)	98(28.4)	70(20.3)	25(7.2)
> 126 days	211(61.2)	97(28.1)	69(20.0)	25(7.2)
> 140 days	201(58.3)	93(27.0)	62(18.0)	21(6.1)
> 154 days	198(57.4)	92(26.7)	60(17.4)	18(5.2)
> 168 days	189(54.8)	87(25.2)	55(15.9)	15(4.3)
> 182 days	187(54.2)	86(24.9)	53(15.4)	14(4.1)
> 196 days	182(52.8)	80(23.2)	47(13.6)	12(3.5)
> 210 days	180(52.2)	79(22.9)	46(13.3)	12(3.5)
> 224 days	175(50.7)	67(19.4)	42(12.2)	8(2.3)
> 238 days	174(50.4)	63(18.3)	41(11.9)	7(2.0)
> 252 days	169(49.0)	49(14.2)	33(9.6)	2(0.6)
> 266 days	167(48.4)	43(12.5)	31(9.0)	0(0.0)
> 280 days	163(47.2)	34(9.9)	26(7.5)	0(0.0)
> 294 days	161(46.7)	30(8.7)	24(7.0)	0(0.0)
> 308 days	158(45.8)	9(2.6)	8(2.3)	0(0.0)
> 322 days	153(44.3)	0(0.0)	0(0.0)	0(0.0)
> 336 days	151(43.8)	0(0.0)	0(0.0)	0(0.0)

Source: PT-Table 14.3-1.2

% calculation formula: number of patients / number of enrolled patients (345) x 100

The most frequently reported AEs overall regardless of causality were nasopharyngitis, blood triglycerides increased, back pain , gamma-glutamyltransferase increased, alanine aminotransferase increased, and blood uric acid increased. Data were summarized in the following table 115.

Table 115: Common AEs (>= 2% in all treated patients) by actual therapy received- n (%) of patients (Safety population) in study 1202

Preferred term	Aliskiren monotherapy N=344 n (%)	Aliskiren + Ca blocker N=119 n (%)	Aliskiren + Diuretic N=91 n (%)
Nasopharyngitis	118 (34.3)	40 (33.6)	23 (25.3)
Blood triglycerides increased	14 (4.1)	5 (4.2)	5 (5.5)
Back pain	12 (3.5)	3 (2.5)	3 (3.3)
Gamma-glutamyltransferase increased	8 (2.3)	6 (5.0)	5 (5.5)
Alanine aminotransferase increased	6 (1.7)	8 (6.7)	6 (6.6)
Blood uric acid increased	5 (1.5)	3 (2.5)	10 (11.0)
Seasonal allergy	11 (3.2)	0 (0.0)	3 (3.3)
Blood creatine phosphokinase increased	9 (2.6)	3 (2.5)	2 (2.2)
Aspartate aminotransferase increased	4 (1.2)	6 (5.0)	4 (4.4)
Hyperuricaemia	5 (1.5)	0 (0.0)	6 (6.6)
Musculoskeletal stiffness	6 (1.7)	3 (2.5)	2 (2.2)
Diarrhoea	9 (2.6)	0 (0.0)	1 (1.1)
Headache	8 (2.3)	2 (1.7)	1 (1.1)
Laryngopharyngitis	8 (2.3)	1 (0.8)	4 (4.4)
Influenza	9 (2.6)	0 (0.0)	0 (0.0)
Rhinitis allergic	8 (2.3)	0 (0.0)	0 (0.0)
Gastritis	4 (1.2)	2 (1.7)	2 (2.2)

No patient was died. A total of 13 patients experienced SAEs including those captured outside the study period. Nine of which were captured during the pre-defined period for reporting and only 3 were suspected to be related to study drug (brain stem infarction, acute myocardial infarction, neoplasm malignant). These 3 patients were in aliskiren monotherapy. Data were summarized in the following table 116.

Table 116: Serious adverse events in the actual therapy group (Safety population) in study 1202

Preferred term	Aliskiren monotherapy N=344	Aliskiren + Ca blocker N=119	Aliskiren + Diuretic N=91
Any primary system organ class	0 (0.0)	1 (0.8)	1 (1.1)
Acute myocardial infarction	1 (0.3)	0 (0.0)	0 (0.0)
Herpes zoster	0 (0.0)	0 (0.0)	1 (1.1)
Joint dislocation	1 (0.3)	0 (0.0)	0 (0.0)
Blood pressure increased	0 (0.0)	1 (0.8)	0 (0.0)
Intervertebral disc protrusion	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasm malignant *	1 (0.3)	0 (0.0)	1 (1.1)
Rectal cancer**	1 (0.3)	0 (0.0)	0 (0.0)
Brain stem infarction	1 (0.3)	0 (0.0)	0 (0.0)
Calculus ureteric	0 (0.0)	1 (0.8)	1 (1.1)

Source: PT-Table 14.3.1-1.4

* As the start date of this event was unknown, actual treatment group at the onset was not defined.

**One patient who had this event had the other SAE (neoplasm malignant)

Seven out of 9 patients with SAEs were discontinued from the study and 7 were hospitalized. Discontinuations due to AEs occurred at 7.0% of all treated patients. The most frequently reported AEs leading to discontinuation was blood pressure increased. Data were summarized in the following table 117.

Table 117: Adverse events leading to discontinuation in actually therapy (Safety population) in study 1202

Preferred term	Aliskiren monotherapy N=344 n (%)	Aliskiren + Ca blocker N=119 n (%)	Aliskiren + Diuretic N=91 n (%)
Blood pressure increased	2 (0.6)	0 (0.0)	1 (1.1)
Atrial fibrillation	2 (0.6)	0 (0.0)	0 (0.0)
Rectal cancer	1 (0.3)	0 (0.0)	1 (1.1)
Acute myocardial infarction	0 (0.0)	1 (0.8)	1 (1.1)
Brain stem infarction	1 (0.3)	0 (0.0)	0 (0.0)
Cardiac disorder	0 (0.0)	1 (0.8)	0 (0.0)
Chest discomfort	1 (0.3)	0 (0.0)	0 (0.0)
Diarrhea	1 (0.3)	0 (0.0)	0 (0.0)
Hemorrhoids	1 (0.3)	0 (0.0)	0 (0.0)
Herpes zoster	1 (0.3)	0 (0.0)	0 (0.0)
Hypertension	1 (0.3)	0 (0.0)	0 (0.0)
Hyperuricaemia	0 (0.0)	0 (0.0)	1 (1.1)
Hypotension	1 (0.3)	0 (0.0)	0 (0.0)
Intervertebral disc protrusion	0 (0.0)	1 (0.8)	0 (0.0)
Meniere's disease	1 (0.3)	0 (0.0)	0 (0.0)
Muscular weakness	0 (0.0)	1 (0.8)	0 (0.0)
Neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)
Nephrosclerosis	0 (0.0)	1 (0.8)	0 (0.0)
Ovarian cyst	0 (0.0)	0 (0.0)	1 (1.1)
Rash	1 (0.3)	0 (0.0)	0 (0.0)
Urticaria	0 (0.0)	1 (0.8)	0 (0.0)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	1 (1.1)

The mean change from baseline in both hematology and biochemistry parameters for all treated patients were generally small during the study period. More combination therapy of SPP100 + diuretic than that of SPP100 + Ca blocker and monotherapy patients exhibited notably abnormal changes in bilirubine (increase), potassium (decrease), and uric acid (increase). Data were summarized in the following tables 118.

Table 118: Biochemistry notable change from baseline by therapeutic group– n (%) of patients (safety population) in study 1202.

		All treated patients N=344	Aliskiren monotherapy N=175	Aliskiren + Ca blocker N=90	Aliskiren + Diuretic N=79
Notable abnormality		n (%)	n (%)	n (%)	n (%)
Abnormal liver parameters:					
Bilirubin	High	52 (15.1)	28 (16.0)	9 (10.0)	15 (19.0)
AST (GOT)	High	6 (1.7)	3 (1.7)	1 (1.1)	2 (2.5)
ALT (GPT)	High	19 (5.5)	10 (5.7)	5 (5.6)	4 (5.1)
ALP	High	1 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)
Abnormal kidney parameters:					
BUN	High	38 (11.0)	17 (9.7)	11 (12.2)	10 (12.7)
Creatinine	High	2 (0.6)	0 (0.0)	0 (0.0)	2 (2.5)
CPK	High	8 (2.3)	3 (1.7)	1 (1.1)	4 (5.1)
Abnormal fluid / electrolyte parameters:					
Sodium	Low	2 (0.6)	0 (0.0)	0 (0.0)	2 (2.5)
Potassium	Low	13 (3.8)	2 (1.1)	3 (3.3)	8 (10.1)
	High	15 (4.4)	9 (5.1)	3 (3.3)	3 (3.8)
Chloride	Low	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.3)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Calcium	Low	7 (2.0)	4 (2.3)	0 (0.0)	3 (3.8)
	High	5 (1.5)	4 (2.3)	0 (0.0)	1 (1.3)
Abnormal metabolic parameters:					
Uric acid	High	5 (1.5)	3 (1.7)	0 (0.0)	2 (2.5)

10.1.8.5 Conclusion

There is no direct comparison of the efficacy between the aliskiren monotherapy and the combined treatment of aliskiren with diuretics and/or calcium channel blockers.

The objective of this study was mainly to evaluate the safety of aliskiren alone or with the addition of diuretics and calcium channel blocker used over a long period. There were no new significant findings in Japanese population compared to other studies with Western population. Since this is a non-randomized and open labeled study without placebo control, it is difficult to interpret the incidence rates of the safety data. However, in the treatment group with the combination of aliskiren and diuretics, the higher incidence rate of increased serum level of bilirubin, uric acid and decreased potassium were observed than in the aliskiren monotherapy and the combination of aliskiren and calcium channel blocker.

10.1.9 Study 2331: An eight week, randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren/valsartan/HCTZ (300/320/25 mg), compared to the combinations of aliskiren/HCTZ (300/25 mg) and valsartan/HCTZ (320/25 mg) in patients with essential hypertension not adequately responsive to HCTZ 25 mg

10.1.9.1 Objectives

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

Since the overall application is for the approval of combination of aliskiren and HCTZ in the treatment of hypertension, the objective of this submission is a 120-day safety update to evaluate the safety and tolerability profile of the combination of aliskiren and HCTZ compared to all other treatment groups.

10.1.9.2 Study design

This is a randomized, double-blind, parallel-group, multi-center, active control, dose-escalation study in hypertensive patients who were not adequately responsive to HCTZ monotherapy. The study included two periods: the first period of 4 week single-blind run-in with HCTZ (12.5 mg for one week and 25 mg for three weeks) and the second period of 8 week double-blind treatment with HCTZ 25 mg, aliskiren/HCTZ (150/25 mg for four weeks and 300/25 mg for another four weeks), valsartan/HCTZ (160/25 mg for four weeks and 320/25 mg for another four weeks), or aliskiren/valsartan/HCTZ (150/160/25 mg for four weeks and 300/320/25 mg for another four weeks).

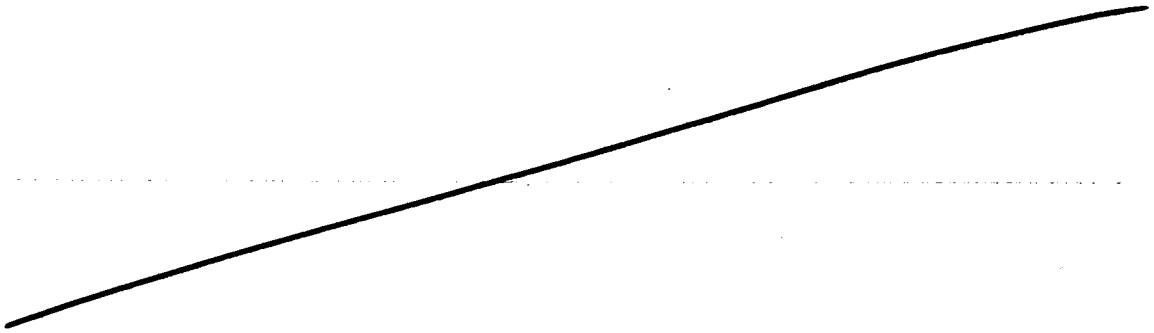

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Table 119: Patient disposition and analysis populations in study 2331

	HCTZ n (%)		Aliskiren / HCTZ n (%)		Valsartan / HCTZ n (%)		Aliskiren/ Valsartan / HCTZ n (%)		Total n (%)	
Double-blind period (plan)	156		156		156		156		624	
Randomized	152		166		155		168		641	
Completed	133	(87.5)	149	(89.8)	140	(90.3)	161	(95.8)	583	(91.0)
Discontinued	19	(12.5)	17	(10.2)	15	(9.7)	7	(4.2)	58	(9.0)
Intent-to-treat (ITT)	151	(99.3)	164	(98.8)	154	(99.4)	168	(100)	637	(99.4)
Safety (SAF)	152	(100)	165	(99.4)	154	(99.4)	168	(100)	639	(99.7)
Per-protocol (PP)	118	(77.6)	131	(78.9)	129	(83.2)	155	(92.3)	533	(83.2)

Percentage (%) is calculated using the randomized population as the denominator.
[a] Source is study documentation

10.1.9.3 Efficacy summary

The treatment groups were generally comparable with respect to demographics, baseline characteristics, and the average baseline mean sitting and standing diastolic pressures.

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Both of the combinations of aliskiren/HCTZ and valsartan/HCTZ provided significantly reductions in msDBP and msSBP at Week 8 (high doses) and Week 4 endpoints (low doses) when compared to HCTZ 25mg monotherapy. At both the Week 4 Endpoint (lower doses) and Week 8 Endpoint (higher doses) combination therapy with aliskiren/HCTZ produced a significantly greater proportion of patients achieving a blood pressure control target of < 140/90 mm Hg compared with HCTZ monotherapy.

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10.1.9.4 Safety summary

Overall, adverse events during the double-blind period were reported in fewer patients treated with aliskiren/valsartan/HCTZ and aliskiren/HCTZ (37% and 36%, respectively) compared to patients treated with HCTZ and valsartan/HCTZ groups (42% and 47% respectively). The aliskiren/HCTZ group had similar or lesser incidences of patient events in most system organ classes than was found in the HCTZ group, with the exception of higher incidences of vascular disorders (n=4 versus HCTZ n=0), and renal and urinary disorders (n=6 versus HCTZ n=2). In both the aliskiren/valsartan/HCTZ and the aliskiren/HCTZ groups, the common AEs (occurring in at least 2% of patients) were reported at rates that were generally similar or less than found in the other treatment groups, with the exception of pollakiuria that was more frequently reported in the aliskiren/HCTZ group when compared to the other treatment groups, vertigo and back pain that were reported more frequently in the aliskiren/valsartan/HCTZ group. Diarrhea, the AE that was identified to be dose dependent with aliskiren especially at doses higher than 300 mg during the earlier clinical programs, was reported in only 1.2% of patients treated with aliskiren/valsartan/HCTZ and aliskiren/HCTZ, numerically lower than in HCTZ (2.6%) and valsartan/HCTZ (1.9%) groups. Data were summarized in the following table 120.

Table 120: Number (%) of patients with adverse events (> or = 2.0%) starting in double-blind period in any treatment group (safety population) in study 2331

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

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

During the double-blind period, Severe AEs were reported in 17 patients (2.7%) in the total study. Aliskiren/valsartan/HCTZ group had the fewest patients (n=2) including increased triglycerides and angle closure glaucoma. Neither event was suspected to be related to study Medication. The latter, however, resulted in patient discontinuation. Aliskiren/HCTZ group had 4 SAEs including nausea, vertigo, and electrolyte deficiency in one patient who discontinued due to these events, arthralgia, gout, and diarrhea (each in one patient). Gout was suspected to be

related to study medication, and resulted in discontinuation. Valsartan/HCTZ group had 6 SAEs including severe events of pancreatic islets hyperplasia, chronic pancreatitis, biliary dilatation, hydrochlecystits, jaundice, and pancreatic neoplasm in one patient, sudden death in another patient, neuralgia, toothache, irritability, and gout. HCTZ monotherapy group had 5 SAEs including drug abuse and neck pain, which resulted in patient discontinuation, and reflux esophagitis, facial injury and musculoskeletal pain. These were not considered as drug-related.

The most frequently reported AEs suspected to be study drug related during the overall double-blind period were dizziness (n=15 patients), headache (n=9 patients) and fatigue (n=7 patients). For these events suspected to be related to study medication, the rates were slightly higher in the valsartan/HCTZ groups than in the other treatment groups. Dizziness and vertigo (including positional or postural) were suspected to have a relationship to study medication in 8 patients receiving aliskiren/valsartan/HCTZ, 3 patients receiving aliskiren/HCTZ, 7 patients receiving valsartan/HCTZ, and 2 patients receiving HCTZ monotherapy. None of these events were considered severe; however, 3 patients discontinued, and one patient temporarily discontinued study medication due to these events.

Pollakiuria and/or polyuria were suspected as related to study medication in 7 patients, including 4 patients in the aliskiren/HCTZ group. All events were mild and required no treatment or action.

In 3 patients in the valsartan/HCTZ group, diarrhea was suspected to have a relationship to study medication. All events were mild, transient, untreated, and did not require study medication discontinuation. No diarrhea cases in aliskiren/valsartan/HCTZ and aliskiren/HCTZ groups were suspected to be related to the study drugs.

AEs leading to discontinuation of study medication are summarized in the following table 121. Approximately 3% of patients in any treatment group discontinued from the study due to AEs.

Table 121 : Number (%) of patients with adverse events leading to discontinuation by preferred term and treatment group (safety population) in study 2331

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

Clinical Laboratory data generally did not show meaningful differences between treatment groups except that the proportion of patients with hypokalemia in aliskiren/valsartan/HCTZ group (6.0%) was lower than both valsartan/HCTZ (8.5%) and HCTZ (9.3%) groups, and similar to aliskiren/HCTZ group (5.0%).

In the analysis of vital sign, physical findings and other observation related to safety during the double-blind period, approximately 4-7% of patients had orthostatic blood pressure changes at baseline (Week 0, the end of the 4-week HCTZ run-in period). The incidence of orthostatic BP changes at each subsequent visit was similar to or less than that at the baseline in all groups. When the orthostatic BP changes at any post baseline visit were used to calculate the incidence rate, the incidence was slightly higher in the aliskiren/HCTZ group (15%) when compared to the other treatment groups (10-11%). None of the patients with orthostatic blood pressure changes discontinued due to hypotension

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Aliskiren/valsartan/HCTZ demonstrated a safety profile similar to the component double combinations. Aliskiren/valsartan/HCTZ and aliskiren/HCTZ did not cause clinically meaningful abnormal laboratory changes, including BUN, creatinine and serum potassium. Gout is the concern of the combination of aliskiren with HCTZ.

10.2 Labeling Review

A detailed line-by-line review of labeling will be provided in a separated documents after the labeling meeting.

11 References

NDA 21-985 reviewed by Dr. Thomas Marciniak.

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/s/

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