Table 30: Serious adverse events in long-term, open-label studies by primary system organ class (safety population)

Primary system organ class	Mono Ali N=1955 n (%)	Ali/HCTZ 300/12.5 mg N=843 n (%)	Ali/HCTZ 300/25 mg N=454 n (%)	Ali Ali/HCTZ N=871 n (%)
-Any primary system organ class	66(3.4)	10(1.2)	18(4.0)	30(3.4)
Cardiac disorders	7(0.4)	1(0.1)	4(0.9)	5(0.6)
Endocrine disorders	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Gastrointestinal disorders	4(0.2)	0(0.0)	1(0.2)	1(0.1)
General disorders and administration site conditions	4(0.2)	1(0.1)	0(0.0)	1(0.1)
Hepatobiliary disorders	3(0.2)	1(0.1)	1(0.2)	2(0.2)
Infections and infestations	9(0.5)	2(0.2)	0(0.0)	2(0.2)
Injury, poisoning and procedural complications	8(0.4)	4(0.5)	3(0.7)	7(0.8)
Metabolism and nutrition disorders	0(0.0)	0(0.0)	0(0.0)	1(0.1)
Musculoskeletal and connective tissue disorders	4(0.2)	0(0.0)	2(0.4)	2(0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9(0.5)	0(0.0)	0(0.0)	1(0.1)
Nervous system disorders	9(0.5)	0(0.0)	4(0.9)	5(0.6)
Psychiatric disorders	1(0.1)	1(0.1)	0(0.0)	1(0.1)
Renal and urinary disorders	2(0.1)	0(0.0)	0(0.0)	0(0.0)
Reproductive system and breast disorders	3(0.2)	1(0.1)	0(0.0)	1(0.1)
Respiratory, thoracic and mediastinal disorders	3(0.2)	0(0.0)	0(0.0)	0(0.0)
Skin and subcutaneous tissue disorders	0(0.0)	0(0.0)	1(0.2)	1(0.1)
Vascular disorders	8(0.4)	0(0.0)	2(0.4)	2(0.2)

Twenty-eight patients received aliskiren/HCTZ combination treatment other than aliskiren/HCTZ 300/12.5 mg (first titrated combination dose).

Table 31: Serious adverse events in long-term, double-blind studies by primary system organ class (safety population)

Primary system organ class	Mono Ali N=421 n (%)	Ali/HCTZ 300/12.5 mg N=193 n (%)	Ali/HCTZ 300/25 mg N=92 n (%)	Ali/HCTZ N=193 n (%)	Ramipril N=422 n (%)	HCTZ/ Ramipril N=210 n (%)
-Any system organ class	5 (1.2)	3 (1.6)	1 (1.1)	4 (2.1)	5 (1.2)	1 (0.5)
Blood and lymphatic system disorders	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Cardiac disorders	2 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Infections and infestations	1 (0.2)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.5)	2 (0.5)	0 (0.0)
Investigations	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.2)	1 (0.5)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SAE in other studies: Two patients in Study 0014 (both treated with aliskiren/HCTZ) had SAEs during active treatment: patient 321 experienced a head injury, and patient 328 experienced paraesthesia, diverticulitis NOS, dysuria, and mental disorder NOS. In biopharmaceutic study (Study 2103), Subject No. 5157, who received one dose of aliskiren/HCTZ 300/25 mg, had an episode of acute cholecystitis which required hospitalization. These are not considered to be drug-related SAE.

Overall there was no significant difference of SAE between the aliskiren mono-therapy and the combination of aliskiren/HCTZ therapy. A brief narratives of SAE in patients who were treated with the combination of aliskiren/HCTZ were in the following:

Study 2204:

1. Psychotic symptoms: A 59 year old female Caucasian patient in Study 2204 was diagnosed with hypertension 8 months prior to entering the study. On Day 13 (06 Apr 2005) of the double-blind study period, the patient experienced feeling "different" than normal, had unmotivated crying and some movement difficulties of her right hand (including inability to write). The study medication dose at the time of the adverse experience was Aliskiren 75 mg / HCTZ 12.5 mg po OD. Diagnosis was a severe mood organic disorder associated to psychotic symptoms (delirium).

2. Deep vein thrombosis: A 46 year old male Caucasian patient in Study 2204 was diagnosed with hypertension 8 years prior to entering the study. On Day 23 (18 Nov 2004) of the treatment with double-blind study medication Aliskiren 75 mg / HCTZ 12.5 mg, the patient experienced phlebitis and severe pain of the right calf. Diagnosis of deep vein thrombosis was confirmed by an echo-Doppler.

3. Syncope: A 57 year old male Caucasian patient in Study 2204 was diagnosed with hypertension 10 months prior to entering the study. On Day 60 (———) of the double-blind study period, the patient experienced syncope which resulted in hospitalization. No other signs or symptoms of cardiac diseases or ischemic brain disorders were reported. No treatment was dispensed. ECG, tomography scan, carotid ultrasonography, and echocardiography were all normal. Blood pressure at the time of the event was unknown. His blood pressures were 147.3/91.3 (10 Jan 2005), 155.3/96 at baseline (31 Jan 2005), 130.6/88 (7 Feb 2005), 142/92.7 (14 Feb 2005), 134/88 (28 Feb 2005), 136.6/87.3 (14 March 2005), and 149.3/98 (31 March 2005). The patient was discharged on ——— without a definite diagnosis and a reported condition of "improving". The study medication Aliskiren 75 mg / HCTZ 12.5 mg/day was not interrupted and the patient completed the study as planned on 31 March 2005. b(6)

4. Suspected oculomotor palsy: A 51 year old male Caucasian patient in Study 2204 was diagnosed with hypertension 2.5 years prior to entering the study. The patient's significant medical history included dyslipidemia, diabetes mellitus and a family history of cardiovascular disease. On Day 26 (12 Apr 2005) of double-blind study medication, the patient presented with dizziness and double vision. His sitting blood pressures on 14 April 2005 were 169/97, 166/102, and 159/100. Sitting pulse was 90. The study medication was Aliskiren 75 mg / HCTZ 12.5 mg.

5. Small intestinal obstruction: A 56 year old male Caucasian patient was diagnosed with hypertension 15 years prior to entering the study. The patient's significant medical history included hyperlipidemia, abdominal hernia repair, upper respiratory infection, right arm sprain and headache. Concomitant medications taken at the time of the adverse experience included azithromycin and guaifenesin, ibuprofen and atorvastatin. On Day 10 (———) of the double-blind study period, the patient experienced vomiting which resulted in hospitalization. A diagnosis of a small intestinal obstruction was confirmed by a computerized tomography. The study medication Aliskiren 75 mg / HCTZ 12.5 mg was not interrupted throughout the study. b(6)

6. Syncope: A 57 year old male Caucasian patient was diagnosed with hypertension 10 years prior to entering the study. The patient's significant medical history included syncope, headache, smoking, reflux disease, and back pain. Concomitant medications taken at the time of the adverse experience included buproprion hydrochloride, pantoprazole sodium, and diclofenac sodium for back pain. On Day 40 (3 Dec 2004) of the double-blind study period, the patient experienced vomiting and syncope which resulted in hospitalization on ——— A computerized tomography scan of the head was negative. His blood pressure readings were 125/80 on 4 Dec 2004, 148.6/92.7 on 5 Dec 2004, and unknown on 3 Dec 2004. The final diagnosis was dehydration and a vasovagal episode. The study medication Aliskiren 75 mg / HCTZ 12.5 mg/day was interrupted on 4 Dec 2004 and restarted on 5 Dec 2004. The patient completed the study as planned on 17 Dec 2004. b(6)

7. Myocardial infarction: This 45 year old male Caucasian patient was diagnosed with hypertension one year prior to entering the study. The patient's significant medical history included hypercholesterolemia and elevation of creatine kinase (CK) since Nov 15 2004, obesity since 1994, smoking for 20 years, chronic bronchitis and sleep apnea. On ——— (day 41 of the double blind study period), the patient was hospitalized due to a probable inferior myocardial infarction. ECG showed ST segment elevation of 1mm in V2-V3-V4 and negative T waves in II-III-aVF. A diagnosis of myocardial infarction with occlusion of first and second marginal branch was made on 12 Jan 2005. The study medication Aliskiren 75 mg / HCTZ 25 mg/day was discontinued on 11 Jan 2004. The patient was withdrawn from the study on 24 Jan 2005 due to this adverse event A complete recovery was achieved on 14 March 2005. b(6)

8. Ureterolithiasis, renal colic: A 34 year old male Caucasian patient in Study 2204 was diagnosed with hypertension 3.5 years prior to entering the study. On Day 38 (———) of the double-blind study period, the patient experienced renal colic and pelvic pain which resulted in hospitalization. He was diagnosed with ureterolithiasis. A full recovery was made on 9 April 2005. The study medication Aliskiren 75 mg/ HCTZ 25 mg was temporarily interrupted. The patient completed the study as planned on 27 April 2005. b(6)

9. Cerebral infarction: A 61 year old male Caucasian patient in Study 2204 was diagnosed with hypertension one year prior to entering the study. The patient's other significant medical history included smoking. On Day 2 (10 March 2005) of the double-blind study period, the patient experienced dysarthria. He was hospitalized on ——— due to a disability in moving the right hand. A diagnosis of cerebral infarction was confirmed by magnetic resonance on ——— His blood pressure readings were 172/102 (23 Feb 2005), 165/97 (9 March 2005), and b(6)

unknown at the time of the adverse event. The study medication Aliskiren 75 mg / HCTZ 25 mg/day was discontinued on 10 March 2005. The patient was withdrawn from the study due to this event on 22 March 2005.

10. Pregnancy: A 40 year old female Caucasian patient in Study 2204 was diagnosed with hypertension 1 month prior to entering the study. On Day 1 (22 Feb 2005) of the double-blind study period, the patient discovered she was pregnant. She underwent a planned abortion on [redacted] The study medication Aliskiren 75 mg / HCTZ 25 mg/day was not interrupted throughout the study. b(6)

11. Idiopathic ulcerative colitis: A 54 year old male Caucasian patient in Study 2204 was diagnosed with hypertension 5 years prior to entering the study. On Day 24 (21 Feb 2005) of the double-blind treatment phase, the patient experienced abdominal pain and one incident of rectal bleeding. Videocolonoscopy revealed diffuse inflammatory colitis. A diagnosis of idiopathic ulcerative colitis was confirmed by the biopsy report. The dose of the study medication at the time of the adverse event was Aliskiren 150 mg / HCTZ 6.25 mg/day. The patient was withdrawn from the study due to this adverse event.

12. Angina: A 49 year old Black male patient in Study 2204 was diagnosed with hypertension 5 years prior to entering the study. The patient's other significant medical history included headache, past smoking, sinusitis, bronchitis, hemoptysis, gastric esophageal reflux disease, erectile dysfunction and urinary frequency. On Day 62 [redacted] of the double-blind study period, the patient experienced angina which resulted in hospitalization. The study mediation Aliskiren 300 mg / HCTZ 25 mg/day was discontinued on 6 March 2005. The patient was withdrawn from the study on 15 March 2005 due to this adverse event. b(6)

13. Pneumonia: A 56 year old female Caucasian patient in Study 2204 was diagnosed with hypertension 5 years prior to entering the study. On Day 3 ([redacted] of the double-blind study period, the patient was diagnosed with upper respiratory infection and was hospitalized with a diagnosis of bronchitis and pneumonia. The study medication Aliskiren 150 mg / HCTZ 6.25 mg/day was not interrupted throughout the study. b(6)

14. Chest pain: A 60 year old male Caucasian patient in Study 2204 was diagnosed with hypertension 1.5 years prior to entering the study. The patient's other significant medical history included depression, nephrolithiasis and knee ligament disorder. Concomitant medications taken at the time of the adverse experience included paroxetine hydrochloride, diazepam, and Citodon (acetaminophen/codeine phosphate). On Day 41 [redacted] of the double-blind study period, the patient experienced chest pain which radiated towards the back. No ECG or other test results were reported. He was discharged from the hospital on the same day. He was diagnosed with hiatus hernia and treated with omeprazole and oxygen. The study medication Aliskiren 150 mg / HCTZ 12.5 mg/day was discontinued. b(6)

15. Pregnancy: A 29 year old Black female patient in Study 2204 was diagnosed with hypertension 5 years prior to entering the study. On Day 38 (17 Dec 2004) of the double-blind study period, the patient was found to be pregnant due to inability to follow the instruction on the

usage of condoms and spermicide. The study medication Aliskiren 150 mg / HCTZ 12.5 mg/day was discontinued.

16. Lung tumor: A 65 year old male Caucasian patient in Study 2204 was diagnosed with hypertension 1.5 years prior to entering the study. The patient's significant medical history included cigarette smoking for 40 years, lung tumor shown by X-ray on [redacted] and Crohn's disease. On Day 6 (26 March 2005) of the double-blind study period, the patient fell and hurt his chest. Chest X-rays was taken and revealed two lung tumors. The study medication Aliskiren 150 mg / HCTZ 25 mg/day was not interrupted. The patient completed the study as planned. b(6)

17. Severe type II diabetes mellitus: A 56 year old male Caucasian patient in Study 2204 was diagnosed with hypertension one year prior to entering the study. The patient's significant medical history included obesity, rectal carcinoma with subsequent resection, esophagitis, chronic diarrhea, steatosis hepatica and venous insufficiency. Baseline fasting blood glucose was 6.33 mmol/L (reference range: 3.33-5.55 mmol/L), HbA1c was not performed. On day 1 (6 Jan 2005) of the double blind study period, his fasting blood glucose level was 8.38 mmol/L. HbA1c was not performed. On Day 51 (3 March 2005, study visit 8), his fasting blood glucose was 16.32 mmol/L. A diagnosis of severe type II diabetes mellitus was made. The study medication Aliskiren 300 mg / HCTZ 12.5 mg/day was not interrupted throughout the study.

18. Dyspnea: A 66 year old female Caucasian in Study 2204 was diagnosed with hypertension 15 years prior to entering the study. The patient's other significant medical history included venous insufficiency and gastroesophageal reflux. On Day 22 [redacted] of the double-blind study period, the patient was hospitalized due to a sudden breathlessness which led to the diagnosis of suspected pulmonary embolism. All tests including echography, scan and scintigraphy were normal. Pulmonary embolism was ruled-out. No diagnosis was made. The study medication Aliskiren 300mg / HCTZ 12.5 mg/day was not interrupted.

19. Ischemic stroke in the follow up period: A 67year old male Caucasian in Study 2204 was diagnosed with hypertension 13 years prior to entering the study. The patient's significant medical history included head trauma with loss of consciousness in at traffic accident, left anterior hemi-block, non-insulin dependent diabetes, hypertriglyceridemia, lower limbs arteriopathy, pseudo-angina pectoris crisis and being overweight. The patient completed the study of Aliskiren 150 mg / HCTZ 6.25 mg without incident. On Day 19 of the follow-up study period, the patient suddenly experienced a partial deficit of the right part of the body with elocution disorders. A cerebral scan performed in the emergency room did not reveal any evidence of any recent parenchymatous lesion. The patient's BP was 170/90 mmHg. Cardiovascular examination did not reveal any abnormalities.

20. Malignant mammary tumor in the follow up period: A 57 year old female Caucasian patient in Study 2204 was diagnosed with hypertension 1.25 years prior to entering the study. On day 61 [redacted] of the double blind study period, the patient completed the study of Aliskiren 150 mg / HCTZ 6.25 mg. In the morning, and subsequently had a prescheduled routine mammography which revealed a mammary tumor. b(6)

21. Thyroid nodule in the follow up period: A 43 year old Black female patient in Study 2204 was diagnosed with hypertension 4 months prior to entering the study. The patient's significant medical history included enlarged thyroid diagnosed during the study screening physical examination. The patient completed the study of Aliskiren 150 mg / HCTZ 6.25 mg as planned without incident. On 18 days after completing the study, the patient was hospitalized for thyroidectomy. No further information available on the pathology report.

Study 2302 and 2302 E1:

1. Brain stem ischemia: This 67 year old female Caucasian patient was diagnosed with hypertension 7 years prior to entering the study. The patient was randomized into the open label phase of the study and began medication (Aliskiren 150 mg) on 26 August 2004. HCTZ 12.5 mg was mistakenly added to Aliskiren 150 mg on 21 October 2004 in violation of the protocol. On [redacted] the patient was admitted to the hospital due to a suspicion of transient ischemic attack. A diagnosis of brain stem ischemia was assumed, but could not be demonstrated by cranial imaging. [redacted] the patient presented with renewed brain stem ischemia and required hospitalization. The study medication was permanently discontinued on the same day. b(6)

2. Prostate cancer: This 52 year old male Black patient was diagnosed with hypertension 9 years prior to entering the study. The patient's other significant medical history included vertebral fracture, nausea and smoking. The patient was randomized into the open label phase of the study and began medication (Aliskiren 150 mg) on 24 August 2004. HCTZ 12.5 mg was mistakenly added to Aliskiren 150 mg on 23 November 2004. On [redacted] the patient was diagnosed with cancer of the prostate. The study medication was permanently discontinued on 23 May 2005. b(6)

3. Chest pain, dyspnea, asthenia, tachycardia: This 61 year old female Native American patient, was diagnosed with hypertension 3 years prior to entering the study. The patient's other significant medical history included hyperlipidemia, chronic obstructive lung disease, cervical polyps, degenerative disc disease, menopause, mild insomnia, osteoarthritis, pressure and decreased hearing in the right ear, impaired fasting glucose, and a laparoscopic tubal occlusion. The patient was randomized into the open label phase of the study and began study medication (Aliskiren 150 mg) on 10 August 2004. The patient's medication was up titrated to Aliskiren 300 mg on 12 October 2004. On 12 November 2004, HCTZ 12.5 mg was added to Aliskiren 300 mg. On [redacted] the patient was admitted to the hospital due to pain in her chest. The study medication was temporarily interrupted for seven days and then resumed. b(6)

4. Diverticulitis: This 68 year old male Caucasian patient was diagnosed with hypertension 7 years prior to entering the study. The patient was randomized into the open label phase of the study and began medication (Aliskiren 150 mg) on 02 September 2004. He was subsequently uptitrated to Aliskiren 300 mg on 03 November 2004. HCTZ 12.5 mg was added to Aliskiren 300 mg on 01 December 2004. On Day 246 (05 May 2005) the patient had diverticulitis. The study medication was permanently discontinued on 14 August 2005.

5. Unstable angina pectoris: This 58 year old male Caucasian patient was diagnosed with hypertension 4 years prior to entering the study. The patient's other significant medical history

included ischemic heart disease, Hodgkin's lymphoma, hypercholesterolemia, and coronary artery bypass graft surgery. The patient was randomized into the open label phase of the study and began medication (Aliskiren 300 mg) on 29 September 2004. HCTZ 12.5 mg was added to Aliskiren 300 mg on 22 October 2004. On [redacted] the patient presented with increasing symptoms of unstable angina pectoris, which resulted in hospitalization. T he patient left the hospital on [redacted] and went on to complete the study. b(6)

6. Polyneuropathy: (unknown duration), polyneuropathy, hyperuricemia, hyperlipidemia, and left foot talus necrosis and lymphedema. This 53 year old male Caucasian patient had a significant medical history of hypertension of unknown duration. The patient's other significant medical history included polyneuropathy, hyperuricemia, hyperlipidemia, and left foot talus necrosis and lymphedema. The patient was randomized into the open label phase of the study and began medication (Aliskiren 300 mg) on 29 June 2004. Subsequently HCTZ 12.5 mg was added to Aliskiren 300 mg on 01 September 2004. The HCTZ was increased to 25 mg on 29 September 2004. On [redacted] the patient was admitted to the hospital for polyneuropathy. b(6)

7. Arteriosclerosis right popliteal artery and superficial femoral artery, pain right leg: This 71 year old female Caucasian patient was diagnosed with hypertension prior to entering the study. The patient's other significant medical history included hyperlipidmia and hyperuricemia. The patient was randomized into the open label phase of the study and began medication (Aliskiren 150 mg) on 11 August 2004. She was subsequently up titrated to aliskiren 300 mg on 06 October 2004. HCTZ 12.5 mg was added to Aliskiren 300 mg on 09 November 2004. The HCTZ was increased to 25 mg on 10 December 2004. On Day 127 (15 December 2004) the patient experienced pain in her right leg and was diagnosed with arteriosclerosis the same day. She went on to complete the study.

8. Muscle rupture, pain, swelling: This 60 year old male Caucasian patient was diagnosed with hypertension 4 years prior to entering the study. The patient's other significant medical history included lumbar disc degeneration, spondylarthrosis of lumbar spine, protrusion of intervertebral disc (L5/S1), hyperlipidemia, Type II diabetes mellitus, radicular syndrome (right), obesity, stomach ulcer, recurrent gastritis, arthritis uricase, hyperuricemia, and hepatic steatosis. Concomitant medications taken during the study included allopurinol, simvastatin, tramadol hydrochloride, ibuprofen, influenza vaccine and pantoprazole. This patient was randomized into the open label phase of the study, and began study medication (Aliskiren 300 mg) on 19 August 2004. He was subsequently up-titrated to the maximum study dose Aliskiren 300 mg plus HCTZ 12.5 mg on 19 October 2004. The HCTZ was increased to 25 mg on 23 November 2004. [redacted] the patient experienced sudden pain and a small swelling in the right thigh without any trauma or redness. He was diagnosed with a muscle fiber rupture and hospitalized. No study drug was adjusted or interrupted during this event. The patient went on to complete the study. b(6)

9. Cerebral vascular accident: This 64 year old male Caucasian patient was diagnosed with hypertension 6 years prior to entering the study. The patient's other significant medical history included gout and diabetes. The patient was randomized into the open label phase of the study and began medication (Aliskiren 150 mg) on 14 September 2004. He was subsequently up titrated to aliskiren 300 mg on 09 November 2004. HCTZ 12.5 mg was added to Aliskiren 300

mg on 11 January 2005. The HCTZ was increased to 25 mg on 14 June 2005. On [redacted] b(6)
[redacted] the patient fell because of unconsciousness for a short moment. He had paralysis of the nervus facialis and a wound at his head. He was diagnosed with a stroke which resulted in a hospitalization. Study medication was permanently discontinued on 11 July 2005.

10. Myocardial infarction: This 61 year old male Caucasian patient was diagnosed with hypertension 7 months prior to entering the study. The patient's other significant medical history included smoking. The patient was randomized into the open label phase of the study and began medication (Aliskiren 150 mg) on 13 October 2004. He was uptitrated to Aliskiren 300 mg on 09 December 2004. HCTZ 12.5 mg was added to Aliskiren 300 mg on 10 January 2005. The HCTZ was increased to 25 mg on 09 February 2005. On Day 268 (07 July 2005), He was diagnosed with a myocardial infarction. The patient did complete the study.

11. Arthralgia in right ankle: This 59 year old female patient was diagnosed with hypertension 11 years prior to entering the study. The patient's other significant medical history included multiple cesareans, bronchitis, postmenopause, dyslipidemia and cough related to captopril. The patient was randomized into the open label phase of the study and began medication (Aliskiren 300 mg) on 01 September 2004. HCTZ 12.5 mg was added to Aliskiren 300 mg on 02 November 2004. On 01 December 2004, HCTZ was increased to 25 mg. On Day 108 (17 December 2004) following start of the open label study period, the patient presented with arthralgia in right ankle of moderate intensity with functional ambulatory limitation. The patient went on to complete the study.

12. Hypertensive crisis: entering the study. The patient was randomized into the open label phase of the study and began medication (Aliskiren 150 mg) on 24 September 2004. He was subsequently uptitrated to Alikiren 300 mg on 22 November 2004. HCTZ 12.5 mg was added to Aliskiren 300 mg on 27 December 2004. The HCTZ was increased to 25 mg on 17 January 2005. On [redacted] the patient presented with hypertensive crisis (blood pressure 200/130 mmHg), which resulted in hospitalization. The study medication was permanently stopped on the same date. b(6)

13. Angina pectoris: This 58 year old male Caucasian patient was diagnosed with hypertension 3 years prior to entering the study. The patient's other significant medical history included mild hyperlipidemia. The patient was randomized into the open label phase of the study and began medication (Aliskiren 150 mg) on 13 September 2004. He was subsequently uptitrated to Aliskiren 300 mg on 12 November 2004. HCTZ 12.5 mg was added to Aliskiren 300 mg on 13 December 2004. The HCTZ was increased to 25 mg on 12 January 2005. On [redacted] the patient presented with angina pectoris which resulted in hospitalization. The patient discontinued the study medication on 27 June 2005. b(6)

14. Cerebrovascular accident: This 65 year old Black male patient was diagnosed with hypertension 39 years prior to entering the study. The patient's other significant medical history included right inguinal hernia, status post repair, diabetes mellitus II, constipation, cerebrovascualar accident (2004), peripheral vascular insufficiency, cataract, status post extraction, hyperopia, and cataract right eye. The patient was randomized into the open label phase of the study, and began study medication (Aliskiren 300 mg) on 11 October 2004. HCTZ

12.5 mg was added to Aliskiren 300 mg on 06 December 2004. He was subsequently up titrated to the maximum study medication dose of aliskiren 300 mg plus HCTZ 25 mg on 10 January 005. On [redacted], the patient experienced a sudden loss of balance and weakness on one side of his body. He was taken to hospital and treated for a possible cerebrovascular accident with grenox (aspirin/dipyridamole), pravastatin, and atenolol. On 16 March 2005 the study was permanently discontinued. b(6)

15. Acute myocardial infarction: This 55 year old male Caucasian patient was diagnosed with hypertension 9 years prior to entering the study. The patient's other significant medical history included surgical repair of medial cartilage damage bilateral knees, knee pain, dry skin, hyperlipidemia and obesity. The patient was randomized into the open label phase of the study and began medication (Aliskiren 300 mg) on 05 October 2004. HCTZ 12.5 mg was added to Aliskiren 300 mg on 01 December 2004. He was subsequently up titrated to the highest dose of Aliskiren 300 mg and HCTZ 25 mg on 06 January 2005. On Day 135 (16 February 2005) the patient was diagnosed with an acute myocardial infarction. The study medication was discontinued on the 15th of February.

16. Ischemic stroke: This 61 year old female Caucasian was diagnosed with hypertension 15 years prior to entering the study. The patient's other significant medical history included atherosclerosis of the cerebral vessels, dyslipidemia, menopause and myoma. The patient participated in Study CSPP100A2302 and began medication (Aliskiren 150 mg) on 3 August 2004. The study medication was subsequently up-titrated and the patient began taking the high dose combination (Aliskiren 300 mg / HCTZ 25 mg) on 2 December 2004. The patient completed the core portion of the study and entered the four month extension on 2 August 2005. On [redacted] of the core study [redacted] day [redacted] of the four month open-label extension period of the trial (CSPP100A2302E1), the patient experienced a stroke and was admitted to the hospital two days later on [redacted] The study medication was interrupted on 15 September 2005 and re-started on [redacted] when the patient was discharged from the hospital. The final diagnosis of this event was an ischemic stroke of the left middle cerebral artery. The patient completed the study on 30 November 2005. b(6)

17. Hospitalization (umbilical hernia): This 52 year old female Caucasian was diagnosed with hypertension 16 years prior to entering the study. The patient's other significant medical history included vascular encephalopathy, osteosclerosis and retino-angiopathia-Grade II. The patient participated in Study CSPP100A2302 and began medication (Aliskiren 150 mg) on 2 August 2004. The study medication was subsequently up-titrated and the patient began taking the high dose combination (Aliskiren 300 mg / HCTZ 25 mg) on 25 November 2004. The patient completed the core portion of the study and entered the four month extension on 27 July 2005. On [redacted] of the core study [redacted], day [redacted] of the four month open-label extension period of the trial (CSPP100A2302E1), the patient presented with an umbilical hernia which resulted in hospitalization. No study drug was adjusted or interrupted during this event. The patient completed the study on 18 December 2005. b(6)

Study 2306

1. Lung infection: This 63 year old female Caucasian patient had a 2 year history of essential hypertension. Her medical history included hysterectomy, dyspepsia, fibromyalgia, urinary

incontinence, migraine, and chronic obstructive lung disease. On Day 176 (16-Jan-2006) of the double-blind active-controlled period, the patient presented with lung infection. The study medication dose at the time of the start of the adverse experience was aliskiren 300 mg and hydrochlorothiazide 12.5 mg per day.

2. Cerebrovascular accident, cerebral disorder, cerebral infarct: This 66 year old female Caucasian patient was diagnosed with essential hypertension approximately a month prior to receiving double-blind medication. Her significant medical history and risk factors included dyslipidemia and a smoking history of 47 years with 10 cigarettes smoked on an average per day in the past 6 months. On Day 110 [redacted] of the double-blind active-controlled study period, the patient presented with signs and symptoms of cerebrovascular accident and was hospitalized. A computerized tomography scan showed leucomalacia with small infarcts in the left side of the brain. The study medication dose at the time of the adverse experience was aliskiren 300 mg and hydrochlorothiazide 12.5 mg per day. b(6)

3. Blue toe syndrome: This 75 year old male Caucasian patient had a 2 year history of essential hypertension. Patient's significant medical history included atrial fibrillation, pleurisy and gastroduodenal ulcer. On Day 196 [redacted] of the double-blind study phase and day 19 of the double-blind placebo-controlled withdrawal period, the patient experienced arteriothrombosis of a distal artery which resulted in hospitalization. The study medication dose at the time of the adverse experience was aliskiren 300 mg and hydrochlorothiazide 25 mg. b(6)

4. Acute coronary syndrome, angina pectoris: This 51 year old male Caucasian patient had a 1 year history of essential hypertension. His significant medical history included right bundle branch block and anterior hemi-block. On Day 171 [redacted] of the double-blind active-controlled treatment period, the patient was admitted to the hospital with acute coronary syndrome. The study medication dose at the time of this adverse event was aliskiren 300 mg and hydrochlorothiazide 12.5 mg. The study medication was permanently discontinued following this adverse event. b(6)

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1. Myocardial infarction: This 58 year old male Caucasian patient was diagnosed with hypertension 3 years prior to entering the study. The patient's significant medical history included hyperuricemia and asthma. On 25 Oct 2005, the patient entered the single-blind hydrochlorothiazide run-in phase and was randomized to the active double-blind phase on 22 Nov 2005 with Aliskiren 150 mg and 300 mg + HCTZ 25 mg. On Day 67 (27 Jan 2006) of the double blind study period, the patient was diagnosed with an anterior myocardial infarction without clinical symptoms (no pain). The study medication was temporarily discontinued on 28 Jan 2006 and re-started. The patient completed the study as planned.

2. Viral infection, pyrexia, myalgia, headache and dizziness: This 54 year old female Caucasian patient was diagnosed with hypertension 2 years prior to entering the study. The patient's significant medical history included gingivitis, back pain and headaches. On 30 Jun 2005, the patient entered the single-blind hydrochlorothiazide run-in phase and was randomized to the active double-blind phase on 16 Aug 2005 with Aliskiren 150 mg and 300 mg + HCTZ 25 mg

. On Day [redacted] of the double blind study period, the patient experienced a fever (up to 39°C), muscular and articular pain, headaches and dizziness which resulted in hospitalization. He was diagnosed with a non-specified viral infection. The study drug was not interrupted and the patient completed the study as planned. b(6)

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The overall profile of dropouts from the conducted clinical trials were summarized in the following tables 32-35. Patients on aliskiren/HCTZ combination therapy had discontinuation rates that were generally comparable to the monotherapy components (6.6% vs 6.6% and 8.7%, respectively, in short-term studies and 13.8% vs 20.7% in long-term studies). More patients in the placebo group discontinued treatment early compared with the other groups (11.3% vs 6.6 and 8.7%), mostly due to a higher rate of withdrawal for unsatisfactory therapeutic effect.

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

				Discontinued n (%)			
Treatment Group	Ran-domized	Treated n (%)	Completed n (%)	Total	Safety	Lack of efficacy	Other
Placebo	195	193 (99.0)	171 (87.7)	22 (11.3)	8 (4.1)	8 (4.1)	6 (3.1)
Ali 75 mg	184	184 (100)	169 (91.8)	15 (8.2)	2 (1.1)	7 (3.8)	6 (3.3)
Ali 150 mg	185	185 (100)	169 (91.4)	16 (8.6)	2 (1.1)	5 (2.7)	9 (4.9)
Ali 300 mg	183	181 (98.9)	164 (89.6)	17 (9.3)	8 (4.4)	4 (2.2)	5 (2.7)
Mono Ali	552	550 (99.6)	502 (90.9)	48 (8.7)	12 (2.2)	16 (2.9)	20 (3.6)
HCTZ 6.25 mg	194	194 (100)	181 (93.3)	13 (6.7)	2 (1.0)	7 (3.6)	4 (2.1)
HCTZ 12.5 mg	188	188 (100)	178 (94.7)	10 (5.3)	1 (0.5)	4 (2.1)	5 (2.7)
HCTZ 25 mg	176	173 (98.3)	159 (90.3)	14 (8.0)	5 (2.8)	1 (0.6)	8 (4.5)
Mono HCTZ	558	555 (99.5)	518 (92.8)	37 (6.6)	8 (1.4)	12 (2.2)	17 (3.0)
Ali/HCTZ 75/6.25 mg	188	188 (100)	179 (95.2)	9 (4.8)	3 (1.6)	2 (1.1)	4 (2.1)
Ali/HCTZ 75/12.5 mg	193	190 (98.4)	175 (90.7)	15 (7.8)	7 (3.6)	4 (2.1)	4 (2.1)
Ali/HCTZ 75/25 mg	186	186 (100)	173 (93.0)	13 (7.0)	5 (2.7)	4 (2.2)	4 (2.2)
Ali/HCTZ 150/6.25 mg	176	174 (98.9)	157 (89.2)	17 (9.7)	8 (4.5)	5 (2.8)	4 (2.3)
Ali/HCTZ 150/12.5 mg	186	184 (98.9)	177 (95.2)	7 (3.8)	4 (2.2)	0 (0.0)	3 (1.6)
Ali/HCTZ 150/25 mg	188	188 (100)	170 (90.4)	18 (9.6)	8 (4.3)	1 (0.5)	9 (4.8)
Ali/HCTZ 300/12.5 mg	181	181 (100)	170 (93.9)	11 (6.1)	3 (1.7)	2 (1.1)	6 (3.3)
Ali/HCTZ 300/25 mg	173	173 (100)	166 (96.0)	7 (4.0)	5 (2.9)	2 (1.2)	0 (0.0)
Ali/HCTZ	1471	1464 (99.5)	1367 (92.9)	97 (6.6)	43 (2.9)	20 (1.4)	34 (2.3)

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.

Table 33: Overall profile of dropout rates in short-term active controlled studies

Treatment Group	Randomized	Treated n (%)	Completed n (%)	Discontinued n (%)			
				Total	Safety	Lack of efficacy	Other
Placebo	195	193 (99.0)	171 (87.7)	22 (11.3)	8 (4.1)	8 (4.1)	6 (3.1)
Mono Ali	610	608 (99.7)	548 (89.8)	60 (9.8)	15 (2.5)	18 (3.0)	27 (4.4)
Mono HCTZ	681	678 (99.6)	627 (92.1)	51 (7.5)	13 (1.9)	17 (2.5)	21 (3.1)
Ali/HCTZ	1661	1654 (99.6)	1545 (93.0)	109 (6.6)	47 (2.8)	21 (1.3)	41 (2.5)
Amlodipine/HCTZ	127	127 (100)	116 (91.3)	11 (8.7)	8 (6.3)	1 (0.8)	2 (1.6)
Irbesartan/HCTZ	120	120 (100)	113 (94.2)	7 (5.8)	4 (3.3)	1 (0.8)	2 (1.7)
Lisinopril	32	32 (100)	30 (93.8)	2 (6.3)	1 (3.1)	1 (3.1)	0 (0.0)
Lisinopril/HCTZ	26	26 (100)	24 (92.3)	2 (7.7)	1 (3.8)	0 (0.0)	1 (3.8)
Total	3452	3438 (99.6)	3174 (91.9)	264 (7.6)	97 (2.8)	67 (1.9)	100 (2.9)

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.

Table 34: Overall profile of dropout rates in long-term open labeled studies

Treatment Group	Randomized	Treated n (%)	Completed n (%)	Discontinued n (%)			
				Total	Safety	Lack of efficacy	Other
Mono Ali	1082	1084 (100)	860 (79.5)	224 (20.7)	87 (8.0)	27 (2.5)	110 (10.2)
Ali/HCTZ	869	871 (100)	751 (86.4)	120 (13.8)	32 (3.7)	37 (4.3)	51 (5.9)
Total	1951	1955 (100)	1611 (82.6)	344 (17.6)	119 (6.1)	64 (3.3)	161 (8.3)

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.
The number of treated patients was greater than the number of randomized patients because four patients in Study CSPP100A 2302 received treatment but did not receive a randomization number: PID 0205/00021 (aliskiren 300 mg; discontinued due to protocol violation), PID 0205/00022 (aliskiren 150 mg titrated to aliskiren 300 mg then aliskiren/HCTZ 300/12.5mg; completed the study), PID 0125/00016 (aliskiren 300 mg; discontinued due to protocol violation) and PID 0540/00019 (aliskiren 300 mg titrated to aliskiren/HCTZ 300/12.5 mg then aliskiren/HCTZ 300/25 mg; completed the study).

Table 35: Overall profile of dropout rates in long-term double blind studies

Treatment Group	Randomized	Treated n (%)	Completed n (%)	Discontinued n (%)			
				Total	Safety	Lack of efficacy	Other
Mono Ali	227	226 (99.6)	158 (69.6)	66 (29.1)	23 (10.1)	12 (5.3)	31 (13.7)
Ali/HCTZ*	193	193 (100)	178 (92.2)	15 (7.8)	5 (2.6)	1 (0.5)	9 (4.7)
Ramipril	212	212 (100)	149 (70.3)	61 (28.8)	19 (9.0)	15 (7.1)	27 (12.7)
Ramipril/HCTZ*	210	210 (100)	193 (91.9)	17 (8.1)	3 (1.4)	2 (1.0)	12 (5.7)
Total	842	841 (99.9)	678 (80.5)	159 (18.9)	50 (5.9)	30 (3.6)	79 (9.4)

* Patients started with aliskiren or ramipril monotherapy and were later titrated to Ali/HCTZ or Ramipril/HCTZ combination.
Safety = Adverse event(s), death, abnormal laboratory values, abnormal test procedure result(s).
Other = Administrative problems, subject's condition no longer requires study drug, lost to follow up, subject withdrawal consent, protocol violation, or other.

7.1.3.2 Adverse events associated with dropouts

The incidence of AEs leading to discontinuation in the placebo-controlled studies was 3.6% in patients treated with placebo, 1.6% in patients treated with aliskiren monotherapy, 1.3% in patients treated with HCTZ monotherapy, and 2.7% of patients treated with aliskiren/HCTZ

combination treatment. Headache was the most frequent AE leading to discontinuation, reported in 3 (1.6%) patients receiving placebo, 1 (0.2%) patient receiving aliskiren monotherapy, no patient receiving HCTZ monotherapy, and 8 (0.5%) patients receiving aliskiren/HCTZ combination treatment. The remaining AEs leading to discontinuation occurred in only one or two patients each. Diarrhea led to discontinuation in only one (0.1%) patient overall, in the aliskiren/HCTZ group. In the short-term controlled studies, 2.5% of all patients treated with aliskiren/HCTZ had AEs leading to study discontinuation compared with 1.3% in the aliskiren monotherapy group, 1.6% in the HCTZ monotherapy group, and 3.6% in the placebo group. The pattern of events was similar to that seen in the placebo-controlled studies. Data were summarized in the following tables 36 and 37. There were no dose-related adverse events in either monotherapy or combined therapy. Therefore, the tables only summarized the adverse events in each treatment but not the each individual dose.

Table 36: Summary of adverse events associated with dropouts in short-term, placebo-controlled studies

Primary system organ class/preferred term		Placebo N=193 n(%)	HCTZ N=555 n(%)	Aliskiren N=550 n(%)	Aliskiren/HCTZ N=1464 n(%)
Total		7 (3.6)	7 (1.3)	9 (1.6)	39 (2.7)
Cardiac disorders	Total	0 (0.0)	1(0.2)	1(0.2)	3 (0.2)
	Angina pectoris	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)
	Atrioventricular block third degree	0(0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Coronary artery disease	0(0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Myocardial infarction	0(0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Palpitations	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Sinus tachycardia	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	Total	1 (0.5)	0 (0.0)	0 (0.0)	3 (0.2)
	Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
	Tinnitus	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	Total	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
	Conjuntivitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Eye pruritus	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Lacrimation increased	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	Total	1 (0.5)	3 (0.5)	1 (0.2)	7 (0.5)
	Nausea	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)
	Abdominal pain	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.1)
	Colitis Ulceative	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Inflammatory bowel disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Proctitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Rectal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Abdominal distension	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
	Gastritis	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	Total	0 (0.0)	2 (0.4)	3 (0.5)	4 (0.3)
	Fatigue	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
	Malaise	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Non-cardiac chest pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Sense of oppression	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Asthenia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
	Chest discomfort	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

	Edema, peripheral	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
Injury, poisoning and procedure complications	Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Road traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Investigations	Total	1 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
	Blood pressure increased	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Transaminases increased	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Musculoskeletal and connective disorders	Total	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
	Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Muscular weakness	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Nervous system disorders	Total	4 (2.1)	0 (0.0)	3 (0.5)	12 (0.8)
	Headache	3 (1.6)	0 (0.0)	1 (0.2)	8 (0.5)
	Cerebral infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Dizziness	1 (0.5)	0 (0.0)	2 (0.4)	1 (0.1)
	Dysarthria	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Presyncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Tremor	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pregnancy, puerperium and perinatal conditions	Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Psychiatric disorders	Total	2 (1.0)	0 (0.0)	1 (0.2)	4 (0.3)
	Depression	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.1)
	Confusion state	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Mood disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Nervousness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Psychotic disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Emotional disorder	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
	Insomnia	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Total	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.2)
	Cough	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)
	Dyspnoea exertional	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Skin and subcutaneous tissue disorders	Total	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)
	Rash	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
	Photo sensitivity reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Rash pruritic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Social circumstances	Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Physical disability	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vascular disorders	Total	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
	Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Orthostatic hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Venous thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Table 37: Summary of adverse events associated with dropouts in short-term, controlled studies

Primary system organ class/preferred term		Placebo N=193 n(%)	Aliskiren N=675 n(%)	HCTZ N=678 n(%)	Aliskiren /HCTZ N=1654 n(%)	Amlodipine /HCTZ N=127 n(%)	Irbesartn /HCTZ N=120 n(%)	Isinopril /HCTZ N=26 n(%)
Total		7 (3.6)	9 (1.3)	11(1.6)	41 (2.5)	4 (3.1)	3 (2.5)	1 (3.8)
Cardiac disorders	Total	0 (0.0)	0 (0.0)	2 (0.3)	3 (0.2)	0 (0.0)	1 (0.8)	1 (3.8)
	Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	1 (3.8)
	Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Palpatations	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Sinus tachycardia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	Total	1 (0.5)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	1 (0.8)	0 (0.0)
	Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	1 (0.8)	0 (0.0)
	Tinnitus	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	Total	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Eye pruritus	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Lacrimation increased	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GI disorders	Total	1 (0.5)	0 (0.0)	3 (0.4)	6 (0.4)	0 (0.0)	2 (1.7)	0 (0.0)
	Nausea	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (1.7)	0 (0.0)
	Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Abdominal pain, upper	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.1)	0 (0.0)	1 (0.8)	0 (0.0)
	Ulcerative colitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Inflammatory bowel disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Proctitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Rectal hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Abdominal distension	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	Total	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
	Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cystitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Injury	Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	Total	1 (0.5)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Increased blood pressure	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Increased transaminases	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutritional disorders	Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Non-insulin diabetes mellitus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective disorders	Total	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Muscular weakness	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	Total	4 (2.1)	4 (0.6)	1 (0.1)	12 (0.7)	1 (0.8)	0 (0.0)	0 (0.0)
	Headache	3 (1.6)	2 (0.3)	0 (0.0)	8 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Cerebral infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Dizziness	1 (0.5)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Dysarthria	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Presyncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Tremor	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

	Cerebrovascular disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
	Dysaesthesia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Hypoaesthesia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	Total	2 (1.0)	1 (0.1)	1 (0.1)	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Depression	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Confusion	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Mood disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Nervousness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Psychotic disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Emotional disorder	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Insomnia	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Total	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cough	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Obstructive pulmonary disease	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	Total	0 (0.0)	1 (0.1)	1 (0.1)	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Rash	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Photo sensitivity	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Pruritic rash	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Erythema	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Generalized pruritus	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Swelling face	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Social circumstance	Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Disability	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	Total	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Orthostatic hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Venous thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

In long-term studies, the most frequently reported AEs leading to discontinuation in the long-term open-label studies were headache, 14 patients (0.7%) in aliskiren monotherapy and 1 patient (0.1%) in aliskiren/HCTZ, and dizziness, 13 patients (0.7%) in aliskiren monotherapy, and no patient in aliskiren/HCTZ. In the long-term double-blind studies, the overall rates of AEs leading to discontinuation were lower in the combination groups than in the component monotherapy groups. In both open-label and double-blind long term studies, there was no increase in AEs leading to discontinuation with the addition of HCTZ to aliskiren. The pattern of events was similar to that seen in the placebo-controlled studies. Data were summarized in the following tables 38 and 39. There were no dose-related adverse events in either monotherapy or combined therapy. Therefore, the tables only summarized the adverse events in each treatment but not the each individual dose.

Table 38: Summary of adverse events associated with dropouts in long-term, open-label studies

Primary system organ class/preferred term		Aliskiren N=1955 (%)	Aliskiren/HCTZ N=871 (%)
Total		87 (4.5)	26 (3.0)
Cardiac disorders	Total	12 (0.6)	8 (0.9)
	Acute myocardial infarction	2 (0.1)	2 (0.2)
	Cardiac failure	1 (0.1)	2 (0.2)
	Angina pectoris	1 (0.1)	1 (0.1)
	Aortic valve stenosis	0 (0.0)	1 (0.1)
	Myocardial infarction	1 (0.1)	1 (0.1)
	Palpitations	2 (0.1)	1 (0.1)
	Atrial fibrillation	2 (0.1)	0 (0.0)
	Atrioventricular block first degree	1 (0.1)	0 (0.0)
	Cardiovascular disorder	1 (0.1)	0 (0.0)
	Coronary artery stenosis	1 (0.1)	0 (0.0)
	Tachycardia	1 (0.1)	0 (0.0)
Ear and labyrinth disorders	Total	3 (0.2)	2 (0.2)
	Vertigo	3 (0.2)	2 (0.2)
Eye disorders	Total	1 (0.1)	1 (0.1)
	Visual acuity reduced	0 (0.0)	1 (0.1)
	Retinopathy, hypertensive	1 (0.1)	0 (0.0)
Gastrointestinal disorders	Total	10 (0.5)	1 (0.1)
	Diarrhea	1 (0.1)	1 (0.1)
	Abdominal pain	2 (0.1)	0 (0.0)
	Abdominal pain upper	1 (0.1)	0 (0.0)
	Constipation	1 (0.1)	0 (0.0)
	Dyspepsia	1 (0.1)	0 (0.0)
	Flatulence	1 (0.1)	0 (0.0)
	Nausea	3 (0.2)	0 (0.0)
	Pancreatitis	1 (0.1)	0 (0.0)
	Vomiting	2 (0.1)	0 (0.0)
General disorders and administration site conditions	Total	12 (0.6)	2 (0.2)
	Asthenia	3 (0.2)	1 (0.1)
	Fatigue	3 (0.2)	1 (0.1)
	Chest discomfort	2 (0.1)	0 (0.0)
	Death	1 (0.1)	0 (0.0)
	Feeling hot	1 (0.1)	0 (0.0)
	Generalized edema	1 (0.1)	0 (0.0)
	Peripheral edema	2 (0.1)	0 (0.0)
Injury, poisoning and procedural complications	Total	1 (0.1)	1 (0.1)
	Scrotal hematoma	0 (0.0)	1 (0.1)
	Road traffic accident	1 (0.1)	0 (0.0)
Investigations	Total	4 (0.2)	1 (0.1)
	Blood glucose increased	0 (0.0)	1 (0.1)
	Blood creatine phosphokinase increased	1 (0.1)	0 (0.0)
	Blood potassium decreased	1 (0.1)	0 (0.0)
	Transaminases increased	1 (0.1)	0 (0.0)
	Weight decreased	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders	Total	0 (0.0)	1 (0.1)
	Gout	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue	Total	4 (0.2)	0 (0.0)
	Arthralgia	1 (0.1)	0 (0.0)

disorders	Muscle spasma	1 (0.1)	0 (0.0)
	Neck pain	1 (0.1)	0 (0.0)
	Pain in extremity	1 (0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Total	3 (0.2)	0 (0.0)
	Breast cancer	1 (0.1)	0 (0.0)
	Lung neoplasm malignant	1 (0.1)	0 (0.0)
	Metastases to liver	1 (0.1)	0 (0.0)
Nervous system disorders	Total	33 (1.7)	7 (0.8)
	Cerebrovascular accident	3 (0.2)	2 (0.2)
	Brain stem ischemia	0 (0.0)	1 (0.1)
	Dizziness postural	0 (0.0)	1 (0.1)
	Dizziness postural, Dysaesthesia	0 (0.0)	1 (0.1)
	Headache	14 (0.7)	1 (0.1)
	Somnolence	1 (0.1)	1 (0.1)
	Cerebral hemorrhage	1 (0.1)	0 (0.0)
	Convulsion	1 (0.1)	0 (0.0)
	Dizziness	13 (0.7)	0 (0.0)
	Hypoaesthesia	1 (0.1)	0 (0.0)
	Hypotonia	1 (0.1)	0 (0.0)
	Multiple sclerosis	1 (0.1)	0 (0.0)
	Myelitis transverse	1 (0.1)	0 (0.0)
	Paraesthesia	1 (0.1)	0 (0.0)
	Syncope	1 (0.1)	0 (0.0)
	Tremor	2 (0.1)	0 (0.0)
Psychiatric disorders	Total	3 (0.2)	2 (0.2)
	Anxiety	2 (0.1)	1 (0.1)
	Depression	1 (0.1)	1 (0.1)
Renal and urinary disorders	Total	0 (0.0)	1 (0.1)
	Proteinuria	0 (0.0)	1 (0.1)
Reproductive system and breast disorders	Total	3 (0.2)	0 (0.0)
	Erectile dysfunction	2 (0.1)	0 (0.0)
	Gynecomastia	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Total	8 (0.4)	0 (0.0)
	Chronic obstructive pulmonary disease	2 (0.1)	0 (0.0)
	Dry throat	1 (0.1)	0 (0.0)
	Dyspnoea	2 (0.1)	0 (0.0)
	Dyspnoea exertional	1 (0.1)	0 (0.0)
	Epistaxis	1 (0.1)	0 (0.0)
	Pulmonary embolism	1 (0.1)	0 (0.0)
	Respiratory disorder	1 (0.1)	0 (0.0)
Skin and subcutaneous tissue disorders	Total	7 (0.4)	2 (0.2)
	Psoriasis	0 (0.0)	1 (0.1)
	Skin lesion	0 (0.0)	1 (0.1)
	Eczema	1 (0.1)	0 (0.0)
	Erythema	1 (0.1)	0 (0.0)
	Rash	3 (0.2)	0 (0.0)
	Rash erythematous	1 (0.1)	0 (0.0)
	Urticaria	1 (0.1)	0 (0.0)
Vascular disorders	Total	6 (0.3)	1 (0.1)
	Hypertensive crisis	2 (0.1)	1 (0.1)
	Aortic aneurysm rupture	1 (0.1)	0 (0.0)
	Circulatory collapse	1 (0.1)	0 (0.0)
	Hypertension	1 (0.1)	0 (0.0)

	Hypotension	1 (0.1)	0 (0.0)

Table 39: Summary of adverse events associated with dropouts in long-term, double-blinded studies

Primary system organ class/preferred term		Aliskiren	Aliskire/ HCTZ N=193 n (%)	Ramipril N=422 n (%)	Ramipri/ HCTZ N=210 n (%)
Total		21 (5.0)	3 (1.6)	18 (4.3)	3 (1.4)
Cardiac disorders	Total	2 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
	Acute coronary syndrome	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
	Angina pectoris	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	Total	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Vertigo	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	Total	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
	Hyperthyroidism	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Gastrointestinal Disorders	Total	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Abdominal pain	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Diarrhea	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Nausea	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	Total	2 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
	Fatigue	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
	Malaise	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Edema, pheripheral	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	Total	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Staphylococcal infection	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders nutrition disorders	Total	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Hypercholesterolemia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Hypokalemia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	Total	2 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
	Back pain	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Muscle spasms	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
	Pain in extremity	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Total	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Laryngeal cancer	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Neoplasm prostate	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	Total	5 (1.2)	1 (0.5)	8 (1.9)	1 (0.5)
	Dizziness	2 (0.5)	1 (0.5)	2 (0.5)	0 (0.0)
	Cerebrovascular	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
	Headache	3 (0.7)	0(0.0)	5 (1.2)	0 (0.0)
	Migraine	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
	Syncope	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Psychiatric disorders	Total	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Hallucination, auditory	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Insomnia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	Total	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Endometriosis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Total	3 (0.7)	1 (0.5)	8 (1.9)	1 (0.5)
	Cough	3 (0.7)	1 (0.5)	8 (1.9)	1 (0.5)
Skin and subcutaneous tissue disorders	Total	1 (0.2)	0 (0.0)	2 (0.5)	1 (0.5)
	Angioneurotic edema	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
	Eczema	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
	Hyperhidrosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
	Hypoaesthesia facial	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Vascular disorders	Total	1 (0.2)	1 (0.5)	0 (0.0)	0 (0.0)
	Hypotension	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
	Orthostatic hypotension	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

7.1.3.3 Other significant adverse events

7.1.3.3.1 Renal function

Like the other ACE inhibitors, drugs that inhibit the renin-angiotensin-aldosterone system may be associated with changes in renal function in susceptible individuals. There were no cases of elevated BUN (> 14.28 mmol/L equal to 40 mg/dl) or creatinine (> 176.8 µmmol/L equal to 2 mg/dl) meeting clinically significant criteria in patients treated with aliskiren/HCTZ in the placebo-controlled and short term active controlled studies. There was a very low incidence of BUN elevation (0.5%) and no case of creatinine elevation meeting clinically significant criteria reported in patients treated with aliskiren/HCTZ in both long term open-label and active controlled studies. The incidence of hyperkalemia was similar to HCTZ and lower than that seen with aliskiren monotherapy. Data were summarized in the following tables 40-43.

Table 40: Summary of potassium, BUN and creatinine in short-term placebo-controlled studies (safety population)

Parameter	Placebo (N=193)		Ali 75 mg (N=184)		Ali 150 mg (N=185)		Ali 300 mg (N=181)		Mono Ali (N=550)		HCTZ 6.25 mg (N=194)		HCTZ 12.5 mg (N=188)		HCTZ 25 mg (N=173)		Mono HCTZ (N=555)	
	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)
Potassium (mmol/L)																		
< 3.5	155	2 (1.3)	148	0 (0.0)	145	0 (0.0)	137	2 (1.5)	430	2 (0.5)	157	1 (0.6)	153	6 (3.9)	135	7 (5.2)	445	14 (3.1)
> 5.5	155	1 (0.6)	148	2 (1.4)	145	3 (2.1)	137	5 (3.6)	430	10 (2.3)	157	3 (1.8)	153	0 (0.0)	135	1 (0.7)	445	4 (0.9)
≥ 6.0	155	0 (0.0)	148	0 (0.0)	145	1 (0.7)	137	0 (0.0)	430	1 (0.2)	157	1 (0.6)	153	0 (0.0)	135	0 (0.0)	445	1 (0.2)
Blood Urea Nitrogen (mmol/L)																		
> 14.28	187	0 (0.0)	180	0 (0.0)	181	0 (0.0)	178	1 (0.6)	539	1 (0.2)	191	0 (0.0)	186	0 (0.0)	172	0 (0.0)	549	0 (0.0)
Creatinine (umol/L)																		
> 176.8	187	0 (0.0)	180	0 (0.0)	181	0 (0.0)	178	0 (0.0)	539	0 (0.0)	191	0 (0.0)	186	0 (0.0)	172	0 (0.0)	549	0 (0.0)

Parameter	Ali/HCTZ 75/6.25 mg (N=188)		Ali/HCTZ 75/12.5 mg (N=190)		Ali/HCTZ 75/25 mg (N=186)		Ali/HCTZ 150/6.25 mg (N=174)		Ali/HCTZ 150/12.5 mg (N=184)		Ali/HCTZ 150/25 mg (N=188)		Ali/HCTZ 300/12.5 mg (N=181)		Ali/HCTZ 300/25 mg (N=173)		Ali/HCTZ (N=1464)	
	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)
Potassium (mmol/L)																		
< 3.5	158	2 (1.3)	151	2 (1.3)	148	4 (2.7)	135	1 (0.7)	147	1 (0.7)	145	5 (3.4)	149	3 (2.0)	138	3 (2.2)	1171	21 (1.8)
> 5.5	158	2 (1.3)	151	1 (0.7)	148	0 (0.0)	135	0 (0.0)	147	0 (0.0)	145	2 (1.4)	149	1 (0.7)	138	0 (0.0)	1171	6 (0.5)
≥ 6.0	158	0 (0.0)	151	0 (0.0)	148	0 (0.0)	135	0 (0.0)	147	0 (0.0)	145	1 (0.7)	149	0 (0.0)	138	0 (0.0)	1171	1 (<0.1)
Blood Urea Nitrogen (mmol/L)																		
> 14.28	186	0 (0.0)	184	0 (0.0)	185	0 (0.0)	169	0 (0.0)	182	0 (0.0)	182	0 (0.0)	177	0 (0.0)	172	0 (0.0)	1437	0 (0.0)
Creatinine (umol/L)																		
> 176.8	186	0 (0.0)	184	0 (0.0)	185	0 (0.0)	169	0 (0.0)	182	0 (0.0)	182	0 (0.0)	177	0 (0.0)	172	0 (0.0)	1437	0 (0.0)

Table 41: Summary of potassium, BUN and creatinine in short-term controlled studies (safety population)

Parameter	Placebo (N=193)		Mono Ali (N=608)		Mono HCTZ (N=678)		Ali/HCTZ (N=1654)		Amlodipine/ HCTZ (N=127)		Irbesartan/ HCTZ (N=120)		Lisinopril (N=32)		Lisinopril/ HCTZ (N=26)	
	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)
Potassium (mmol/L)																
< 3.5	155	2 (1.3)	486	2 (0.4)	565	19 (3.4)	1357	30 (2.2)	126	13 (10.3)	120	3 (2.5)	32	2 (6.3)	26	1 (3.8)
> 5.5	155	1 (0.6)	486	11 (2.3)	565	7 (1.2)	1357	11 (0.8)	126	1 (0.8)	120	3 (2.5)	32	0 (0.0)	26	0 (0.0)
≥ 6.0	155	0 (0.0)	486	1 (0.2)	565	2 (0.4)	1357	3 (0.2)	126	1 (0.8)	120	0 (0.0)	32	0 (0.0)	26	0 (0.0)
Blood Urea Nitrogen (mmol/L)																
> 14.28	187	0 (0.0)	595	2 (0.3)	669	1 (0.1)	1623	0 (0.0)	126	0 (0.0)	120	3 (2.5)	32	0 (0.0)	26	0 (0.0)
Creatinine (umol/L)																
> 176.8	187	0 (0.0)	595	0 (0.0)	669	2 (0.3)	1623	0 (0.0)	126	0 (0.0)	120	0 (0.0)	32	0 (0.0)	26	0 (0.0)

Table 42: Summary of potassium, BUN, and creatinine in long-term open-label studies (safety population)

Parameter	Mono Ali N=1084		Ali/HCTZ N=871	
	N'	n (%)	N'	n (%)
Potassium (mmol/L)				
< 3.5	871	8 (0.9)	776	38 (4.9)
> 5.5	871	18 (2.1)	776	16 (2.1)
≥ 6.0	871	3 (0.3)	776	3 (0.4)
Blood Urea Nitrogen (mmol/L)				
> 14.28	1036	1 (<0.1)	867	4 (0.5)
Creatinine (umol/L)				
> 176.8	1036	1 (<0.1)	867	0 (0.0)

Table 43: Summary of potassium, BUN, and creatinine in long-term double-blind studies (safety population)

Parameter	Mono Ali (N=226)		Ali/HCTZ (N=193)		Ramipril (N=212)		Ramipril/HCTZ (N=210)	
	N'	n (%)	N'	n (%)	N'	n (%)	N'	n (%)
Potassium (mmol/L)								
< 3.5	219	5 (2.3)	193	21 (10.9)	207	6 (2.9)	210	19 (9.0)
> 5.5	219	4 (1.8)	193	4 (2.1)	207	2 (1.0)	210	5 (2.4)
≥ 6.0	219	1 (0.5)	193	1 (0.5)	207	1 (0.5)	210	1 (0.5)
Blood Urea Nitrogen (mmol/L)								
> 14.28	219	0 (0.0)	193	1 (0.5)	208	0 (0.0)	210	1 (0.5)
Creatinine (umol/L)								
> 176.8	219	0 (0.0)	193	0 (0.0)	208	1 (0.5)	210	2 (1.0)

7.1.3.3.2 GI toxicity

Dose-related diarrhea was observed in aliskiren monotherapy (original review of NDA 21-985). The incidence of diarrhea seen with patients treated with aliskiren/HCTZ in placebo controlled and active-controlled studies in this submission was low and generally comparable to the individual monotherapy components.

7.1.3.3.3 Cough

Cough was common in ACE inhibitors. It seems that the incidence rate of cough was slightly lower in aliskiren monotherapy than in the ACE inhibitors (NDA 21, 985). In this NDA, cough occurred in ≤ 2.1% of patients in any treatment group in the placebo-controlled studies; it was