reported in: 0.5% of patients receiving placebo, 0.7% of patients receiving aliskiren monotherapy, 0.7% of patients receiving HCTZ monotherapy, and 1.3% of patients receiving aliskiren/HCTZ. Similarly, in the short term controlled studies cough was reported in 0.5% of patients receiving placebo, 0.7% of patients receiving aliskiren monotherapy, 0.9% of patients receiving HCTZ monotherapy, and 1.1% of patients receiving aliskiren/HCTZ. In the long-term open-label studies, the incidence of cough was 1.5% for aliskiren monotherapy and 2.2% for aliskiren/HCTZ combination therapy. In the long-term double-blind studies, the incidence of cough was 3.3% for aliskiren monotherapy and 1.6% for aliskiren in combination with HCTZ compared to 4.3 % in ramipril/HCTZ. Data were summarized in the following table 44.

Table 44: Incidence rate of cough in different studies

Study		Placebo	Aliskiren	HCTZ	Aliskiren /HCTZ	Amlodipine /HCTZ	Irbesartan /HCTZ	Lisinopril /HCTZ
Placebo-controlled	Patients	193	550	555	1464	-	-	-
	n (%)	1 (0.5)	4 (0.7)	4 (0.7)	19 (1.3)	-	-	-
Short-term controlled	Patients	193	675	678	1654	127	120	26
	n (%)	1 (0.5)	5 (0.7)	6 (0.9)	18 (1.1)	3 (2.4)	1 (0.8)	0 (0.0)
Long-term open-label	Patients	-	1955	-	871	-	-	-
	n (%)	-	30 (1.5)	-	19 (2.2)	-	-	-
Long-term Double-blind	Patients	-	421	-	193	210 (HCTZ combined with Ramipril)		
	n (%)	-	14 (3.3)	-	3 (1.6)	9 (4.3)		

7.1.3.3.4 Anemia

A slight decrease in mean hemoglobin was observed in the aliskiren monotherapy and aliskiren/HCTZ combination treatment groups as shown in the following table 45. These changes are very minor and are not considered to have any clinical significance. There is no change in mean hematorcit from baseline in aliskiren/HCTZ-treated patients. Small decreases in hemoglobin and hematocrit are also seen with other agents acting on the rennin angiotensin system, such as ACEIs and ARBs.

Table 45: Changes of hemoglobin and hematocirt from baseline in short-term active controlled studies.

Hematology: Haemoglobin (g/L)

		Baseline			Post baseline Endpoint			Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=193)	184	145.3	12.23	146.0	146.5	12.13	146.0	1.2	5.81	1.0
Mono Ali (N=608)	578	145.3	13.13	146.0	145.1	13.10	145.0	-0.2	6.66	0.0
Mono HCTZ (N=678)	657	144.5	14.35	145.0	145.4	14.67	146.0	0.9	7.98	1.0
All Ali/HCTZ (N=1654)	1602	145.1	13.61	145.0	144.8	13.32	145.0	-0.3	7.16	0.0
Amlodipine/HCTZ (N=127)	123	141.7	12.02	142.0	141.3	13.08	142.0	-0.5	9.09	0.0
Irbesartan/HCTZ (N=120)	117	142.1	13.11	142.0	141.0	11.88	138.0	-1.1	9.29	-2.0
Lisinopril (N=32)	31	141.1	10.86	143.0	140.7	11.40	140.0	-0.4	8.43	0.0
Lisinopril/HCTZ (N=26)	26	140.9	11.74	143.0	143.3	10.73	142.5	2.4	8.01	2.5

Hematology: Haematocrit (1)

		Baseline			Post baseline Endpoint			Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=193)	184	0.4415	0.04021	0.4300	0.4482	0.03965	0.4400	0.0067	0.02033	0.0100
Mono Ali (N=608)	578	0.4421	0.04213	0.4400	0.4447	0.04262	0.4400	0.0026	0.02423	0.0000
Mono HCTZ (N=678)	656	0.4394	0.04237	0.4400	0.4425	0.04454	0.4400	0.0031	0.02638	0.0000
All Ali/HCTZ (N=1654)	1601	0.4402	0.04222	0.4400	0.4410	0.04097	0.4400	0.0008	0.02714	0.0000
Amlodipine/HCTZ (N=127)	123	0.4309	0.03569	0.4300	0.4228	0.03833	0.4200	-0.0081	0.03225	-0.0100
Irbesartan/HCTZ (N=120)	117	0.4345	0.03852	0.4300	0.4227	0.03453	0.4200	-0.0118	0.03393	-0.0100
Lisinopril (N=32)	31	0.4374	0.03151	0.4400	0.4384	0.03465	0.4400	0.0010	0.02427	0.0000
Lisinopril/HCTZ (N=26)	26	0.4358	0.03765	0.4300	0.4496	0.03767	0.4450	0.0138	0.02531	0.0150

7.1.3.3.5 Hyperuricemia, gout, and renal stones

Aliskiren monotherapy produced small median increases in serum uric acid levels (5 µmoL) while HCTZ produced larger increases (22 µmol/L). The combination of aliskiren with HCTZ appears to be additive (34 µmol/L increase). Although the changes of uric acid were not measured in the long-term studies, the increases in uric acid do appear to lead to slight increase in uric acid related to AE of gout (0.1% vs 0.5% in aliskiren monotherapy vs the combination therapy), but not closely related to the renal stone as shown in the following table 46.

Table 46: Summary of incidence rates of gout, nephroliathiasis and changes of uric acid from baseline

Study		Placebo	Mono Ali	Mono HCTZ	Ali /HCTZ	Amlo /HCTZ	Irb /HCTZ	Lis /HCTZ
Short-term controlled	Patients	193	608	678	1654	127	120	26
	Uric acid (µmol/L)	0.7	5.0	22.4	33.9	-8.5	-19.1	81.9
	Gout, n (%)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Stone, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Long-term open-label	Patients	-	1955	-	871	-	-	-
	Uric acid (µmol/L)	-	-	-	-	-	-	-
	Gout, n (%)	-	**1 (0.1)**	-	**4 (0.5)**	-	-	-
	Stone, n (%)	-	1 (0.1)	-	1 (0.1)			
Long-term Double-blind	Patients	-	421	-	193	-	-	-
	Uric acid (µmol/L)	-	-	-	-	-	-	-
	Gout, n (%)	-	0 (0.0)	-	0 (0.0)	-	-	-
	Stone, n (%)	-	1 (0.2)	-	0 (0.0)	-	-	-

7.1.3.3.6 Angioedema

Angioedema is a known serious side effect of ACEIs. It has also been reported in patients who were treated with ARBs but the causality relationship between the event and ARB treatment has not been clearly established. There were 5 cases of angioedema reported in the whole aliskiren clinical program . One occurred in a patient who received aliskiren, one in a patient who received aliskiren/HCTZ, one in a patient who received valsartan, one in a patient treated with single-blind placebo, and one non-serious case of angioedema was reported in a patient treated with ramipril. In addition, there were total 26 patients with eyelid, face, hands, or whole body edema in the aliskiren treated groups and two patients in HCTZ treated groups. There were two cases treated with the combination of aliskiren with HCTZ among the 26 patients.

7.1.4 Other Search Strategies

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

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

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

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

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

7.1.5.3 Incidence of common adverse events

For common adverse events the sponsor tabulated event rates in four pooled studies including the placebo-controlled studies, short-term active controlled studies, the long-term open-label studies, and the long-term double-blind studies as shown in the previous tables 22 and 23. This approach for estimating the incidence of common adverse events is preferred.

7.1.5.4 Common adverse event tables

The common adverse events in the placebo-controlled studies are presented by treatment group in table 47. Headache and nasopharyngitis were the most frequent AEs overall. The incidence of headache ranged from 4.6% in the aliskiren/HCTZ 150/6.25 mg group to 13.5% in the placebo group. The incidence of nasopharyngitis ranged from 1.6% in the aliskiren/HCTZ 150/12.5 mg group to 5.4% in the aliskiren/HCTZ 75/25 mg group, and was 5.2% in the placebo group. Dizziness was one of the more prevalent AEs in the HCTZ 25 mg, aliskiren/HCTZ 150/12.5 mg, and 300/12.5 mg groups. Diarrhea was reported in rates > 2% in the aliskiren/HCTZ 300/12.5

mg, aliskiren/HCTZ 150/25 mg, HCTZ 12.5 mg, and aliskiren 300 mg groups (3.3%, 3.2%, 2.7%, and 2.2%, respectively). The rate of diarrhea in the placebo group was 0.5 %.

Table 47: Number (%) of patients with common AEs (> = 2% for any treatment group) in short-term placebo-controlled studies (safety population)

Preferred term	Placebo N=193 n (%)	Ali 75 mg N=184 n (%)	Ali 150 mg N=185 n (%)	Ali 300 mg N=181 n (%)	Mono Ali N=550 n (%)	HCTZ 6.25 mg N=194 n (%)	HCTZ 12.5 mg N=188 n (%)	HCTZ 25 mg N=173 n (%)	Mono HCTZ N=555 n (%)
Any Adverse Experience	85(44.0)	69(37.5)	69(37.3)	71(39.2)	209(38.0)	75(38.7)	79(42.0)	72(41.6)	226(40.7)
Headache	26(13.5)	13 (7.1)	13 (7.0)	10 (5.5)	36 (6.5)	12 (6.2)	15 (8.0)	12 (6.9)	39 (7.0)
Nasopharyngitis	10 (5.2)	9 (4.9)	5 (2.7)	3 (1.7)	17 (3.1)	6 (3.1)	9 (4.8)	6 (3.5)	21 (3.8)
Dizziness	2 (1.0)	1 (0.5)	1 (0.5)	3 (1.7)	5 (0.9)	4 (2.1)	3 (1.6)	6 (3.5)	13 (2.3)
Influenza	3 (1.6)	1 (0.5)	7 (3.8)	3 (1.7)	11 (2.0)	0 (0.0)	3 (1.6)	3 (1.7)	6 (1.1)
Diarrhoea	1 (0.5)	3 (1.6)	3 (1.6)	4 (2.2)	10 (1.8)	3 (1.5)	5 (2.7)	3 (1.7)	11 (2.0)
Back pain	5 (2.6)	3 (1.6)	4 (2.2)	1 (0.6)	8 (1.5)	1 (0.5)	1 (0.5)	4 (2.3)	6 (1.1)
Cough	1 (0.5)	1 (0.5)	2 (1.1)	1 (0.6)	4 (0.7)	1 (0.5)	1 (0.5)	2 (1.2)	4 (0.7)
Asthenia	0 (0.0)	3 (1.6)	2 (1.1)	1 (0.6)	6 (1.1)	3 (1.5)	2 (1.1)	1 (0.6)	6 (1.1)
Nausea	4 (2.1)	1 (0.5)	1 (0.5)	2 (1.1)	4 (0.7)	3 (1.5)	3 (1.6)	1 (0.6)	7 (1.3)
Vertigo	1 (0.5)	2 (1.1)	0 (0.0)	1 (0.6)	3 (0.5)	1 (0.5)	4 (2.1)	1 (0.6)	6 (1.1)
Upper respiratory tract infection	2 (1.0)	2 (1.1)	0 (0.0)	5 (2.8)	7 (1.3)	0 (0.0)	2 (1.1)	2 (1.2)	4 (0.7)
Palpitations	3 (1.6)	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.4)	2 (1.0)	4 (2.1)	0 (0.0)	6 (1.1)
Arthralgia	1 (0.5)	4 (2.2)	0 (0.0)	0 (0.0)	4 (0.7)	0 (0.0)	2 (1.1)	1 (0.6)	3 (0.5)
Abdominal pain upper	1 (0.5)	1 (0.5)	1 (0.5)	3 (1.7)	5 (0.9)	3 (1.5)	3 (1.6)	2 (1.2)	8 (1.4)
Oedema peripheral	1 (0.5)	4 (2.2)	3 (1.6)	2 (1.1)	9 (1.6)	2 (1.0)	3 (1.6)	1 (0.6)	6 (1.1)
Constipation	3 (1.6)	4 (2.2)	0 (0.0)	3 (1.7)	7 (1.3)	1 (0.5)	1 (0.5)	1 (0.6)	3 (0.5)
Bronchitis	1 (0.5)	0 (0.0)	3 (1.6)	5 (2.8)	8 (1.5)	2 (1.0)	1 (0.5)	1 (0.6)	4 (0.7)
Muscle spasms	1 (0.5)	4 (2.2)	3 (1.6)	3 (1.7)	10 (1.8)	0 (0.0)	2 (1.1)	3 (1.7)	5 (0.9)
Urinary tract infection	3 (1.6)	2 (1.1)	2 (1.1)	1 (0.6)	5 (0.9)	2 (1.0)	1 (0.5)	2 (1.2)	5 (0.9)
Flatulence	1 (0.5)	1 (0.5)	0 (0.0)	2 (1.1)	3 (0.5)	0 (0.0)	2 (1.1)	1 (0.6)	3 (0.5)
Vomiting	4 (2.1)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)	2 (1.0)	0 (0.0)	1 (0.6)	3 (0.5)
Rhinitis	0 (0.0)	1 (0.5)	1 (0.5)	2 (1.1)	4 (0.7)	0 (0.0)	2 (1.1)	4 (2.3)	6 (1.1)

Preferred term	Ali/HCTZ 75/6.25 mg N=188 n (%)	Ali/HCTZ 75/12.5 mg N=190 n (%)	Ali/HCTZ 75/25 mg N=186 n (%)	Ali/HCTZ 150/6.25 mg N=174 n (%)	Ali/HCTZ 150/12.5 mg N=184 n (%)	Ali/HCTZ 150/25 mg N=188 n (%)	Ali/HCTZ 300/12.5 mg N=181 n (%)	Ali/HCTZ 300/25 mg N=173 n (%)	Ali/HCTZ N=1464 n (%)
Any Adverse Experience	65(34.6)	75(39.5)	77(41.4)	66(37.9)	72(39.1)	83(44.1)	82(45.3)	71(41.0)	591(40.4)
Headache	11 (5.9)	14 (7.4)	11 (5.9)	8 (4.6)	15 (8.2)	9 (4.8)	16 (8.8)	14 (8.1)	98 (6.7)
Nasopharyngitis	9 (4.8)	6 (3.2)	10 (5.4)	5 (2.9)	3 (1.6)	7 (3.7)	7 (3.9)	9 (5.2)	56 (3.8)
Dizziness	1 (0.5)	5 (2.6)	5 (2.7)	2 (1.1)	6 (3.3)	3 (1.6)	9 (5.0)	3 (1.7)	34 (2.3)
Influenza	5 (2.7)	5 (2.6)	4 (2.2)	3 (1.7)	1 (0.5)	6 (3.2)	2 (1.1)	7 (4.0)	33 (2.3)
Diarrhoea	0 (0.0)	2 (1.1)	3 (1.6)	3 (1.7)	1 (0.5)	6 (3.2)	6 (3.3)	3 (1.7)	24 (1.6)
Back pain	2 (1.1)	7 (3.7)	1 (0.5)	1 (0.6)	2 (1.1)	3 (1.6)	3 (1.7)	2 (1.2)	21 (1.4)
Cough	3 (1.6)	3 (1.6)	2 (1.1)	2 (1.1)	2 (1.1)	4 (2.1)	2 (1.1)	1 (0.6)	19 (1.3)
Asthenia	1 (0.5)	2 (1.1)	4 (2.2)	2 (1.1)	1 (0.5)	3 (1.6)	2 (1.1)	2 (1.2)	17 (1.2)
Nausea	2 (1.1)	5 (2.6)	0 (0.0)	1 (0.6)	2 (1.1)	4 (2.1)	2 (1.1)	1 (0.6)	17 (1.2)
Vertigo	2 (1.1)	2 (1.1)	1 (0.5)	0 (0.0)	1 (0.5)	3 (1.6)	3 (1.7)	5 (2.9)	17 (1.2)
Upper respiratory tract infection	2 (1.1)	0 (0.0)	2 (1.1)	3 (1.7)	3 (1.6)	2 (1.1)	2 (1.1)	2 (1.2)	16 (1.1)
Palpitations	1 (0.5)	2 (1.1)	1 (0.5)	1 (0.6)	2 (1.1)	5 (2.7)	2 (1.1)	1 (0.6)	15 (1.0)
Arthralgia	2 (1.1)	2 (1.1)	6 (3.2)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	2 (1.2)	14 (1.0)
Abdominal pain upper	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	3 (1.6)	4 (2.1)	1 (0.6)	2 (1.2)	13 (0.9)
Oedema peripheral	1 (0.5)	3 (1.6)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.5)	3 (1.7)	3 (1.7)	13 (0.9)
Constipation	3 (1.6)	2 (1.1)	2 (1.1)	0 (0.0)	1 (0.5)	2 (1.1)	2 (1.1)	0 (0.0)	12 (0.8)
Bronchitis	1 (0.5)	2 (1.1)	0 (0.0)	4 (2.3)	2 (1.1)	1 (0.5)	1 (0.6)	0 (0.0)	11 (0.8)
Muscle spasms	3 (1.6)	1 (0.5)	3 (1.6)	1 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.2)	11 (0.8)
Urinary tract infection	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.1)	3 (1.6)	0 (0.0)	5 (2.8)	0 (0.0)	11 (0.8)
Flatulence	1 (0.5)	0 (0.0)	4 (2.2)	1 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	8 (0.5)
Vomiting	0 (0.0)	1 (0.5)	2 (1.1)	0 (0.0)	3 (1.6)	2 (1.1)	0 (0.0)	0 (0.0)	8 (0.5)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.1)	2 (1.1)	2 (1.2)	7 (0.5)

The common AEs in the short-term controlled studies are presented by treatment group in table 48. Results were consistent with those in the placebo-controlled studies. AEs experienced by ≥1% of patients taking aliskiren/HCTZ and were more frequent than in patients taking placebo were dizziness (2.3% vs 1.0%), influenza (2.3% vs 1.6%), diarrhea (1.6% vs 0.5%), cough (1.3% vs 0.5%), vertigo (1.2% vs 0.5%), asthenia (1.2% vs 0.0%), upper respiratory tract infection (1.1% vs. 1.0%), and arthralgia (1.0% vs. 0.5%). The only AEs that were experienced by ≥2% of

patients taking aliskiren/HCTZ and were more frequent than in patients taking placebo were dizziness and influenza. There was an increase of peripheral edema in amlodipine/HCTZ group (11%) compared to other groups (< 2%), which is in consistent with the known effect of amlodipine.

Table 48: Number (%) of patients with most frequent AEs (> = 2% for any group) in short term, controlled studies (safety population)

Preferred term	Placebo N=193 n (%)	Mono Ali N=675 n (%)	Mono HCTZ N=678 n (%)	Ali/HCTZ 75/6.25 mg N=188 n (%)	Ali/HCTZ 75/12.5 mg N=190 n (%)	Ali/HCTZ 75/25 mg N=186 n (%)	Ali/HCTZ 150/6.25 mg N=174 n (%)	Ali/HCTZ 150/12.5 mg N=184 n (%)
Any adverse experience	85 (44.0)	241 (35.7)	270 (39.8)	65 (34.6)	75 (39.5)	77 (41.4)	66 (37.9)	72 (39.1)
Headache	26 (13.5)	46 (6.8)	43 (6.3)	11 (5.9)	14 (7.4)	11 (5.9)	8 (4.6)	15 (8.2)
Nasopharyngitis	10 (5.2)	19 (2.8)	26 (3.8)	9 (4.8)	6 (3.2)	10 (5.4)	5 (2.9)	3 (1.6)
Dizziness	2 (1.0)	5 (0.7)	15 (2.2)	1 (0.5)	5 (2.6)	5 (2.7)	2 (1.1)	6 (3.3)
Influenza	3 (1.6)	11 (1.6)	6 (0.9)	5 (2.7)	5 (2.6)	4 (2.2)	3 (1.7)	1 (0.5)
Diarrhoea	1 (0.5)	10 (1.5)	14 (2.1)	0 (0.0)	2 (1.1)	3 (1.6)	3 (1.7)	1 (0.5)
Back pain	5 (2.6)	9 (1.3)	11 (1.6)	2 (1.1)	7 (3.7)	1 (0.5)	1 (0.6)	2 (1.1)
Cough	1 (0.5)	5 (0.7)	6 (0.9)	3 (1.6)	3 (1.6)	2 (1.1)	2 (1.1)	2 (1.1)
Nausea	4 (2.1)	4 (0.6)	9 (1.3)	2 (1.1)	5 (2.6)	0 (0.0)	1 (0.6)	2 (1.1)
Asthenia	0 (0.0)	6 (0.9)	6 (0.9)	1 (0.5)	2 (1.1)	4 (2.2)	2 (1.1)	1 (0.5)
Arthralgia	1 (0.5)	4 (0.6)	7 (1.0)	2 (1.1)	2 (1.1)	6 (3.2)	0 (0.0)	1 (0.5)
Oedema peripheral	1 (0.5)	11 (1.6)	8 (1.2)	1 (0.5)	3 (1.6)	0 (0.0)	0 (0.0)	2 (1.1)
Fatigue	2 (1.0)	6 (0.9)	6 (0.9)	1 (0.5)	3 (1.6)	1 (0.5)	2 (1.1)	1 (0.5)
Urinary tract infection	3 (1.6)	5 (0.7)	7 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.1)	3 (1.6)
Bronchitis	1 (0.5)	8 (1.2)	5 (0.7)	1 (0.5)	2 (1.1)	0 (0.0)	4 (2.3)	2 (1.1)
Flatulence	1 (0.5)	4 (0.6)	3 (0.4)	1 (0.5)	0 (0.0)	4 (2.2)	1 (0.6)	0 (0.0)
Vomiting	4 (2.1)	1 (0.1)	3 (0.4)	0 (0.0)	1 (0.5)	2 (1.1)	0 (0.0)	3 (1.6)
Sinusitis	1 (0.5)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	1 (0.5)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Tendonitis	0 (0.0)	2 (0.3)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

Preferred term	Ali/HCTZ 150/25 mg N=311 n (%)	Ali/HCTZ 300/12.5 mg N=181 n (%)	Ali/HCTZ 300/25 mg N=354 n (%)	Ali/HCTZ N=1654 n (%)	Amlodipine/ HCTZ N=127 n (%)	Irbesartan/ HCTZ N=120 n (%)	Lisinopril N=58 n (%)	Lisinopril/ HCTZ N=26 n (%)
Any adverse experience	103 (33.1)	82 (45.3)	112 (31.6)	645 (39.0)	55 (43.3)	41 (34.2)	14 (24.1)	3 (11.5)
Headache	12 (3.9)	16 (8.8)	18 (5.1)	104 (6.3)	9 (7.1)	3 (2.5)	5 (8.6)	0 (0.0)
Nasopharyngitis	11 (3.5)	7 (3.9)	16 (4.5)	67 (4.1)	7 (5.5)	6 (5.0)	2 (3.4)	0 (0.0)
Dizziness	6 (1.9)	9 (5.0)	5 (1.4)	38 (2.4)	1 (0.8)	3 (2.5)	1 (1.7)	1 (3.8)
Influenza	7 (2.3)	2 (1.1)	7 (2.0)	34 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	6 (1.9)	6 (3.3)	3 (0.8)	24 (1.5)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	3 (1.0)	3 (1.7)	3 (0.8)	22 (1.3)	5 (3.9)	2 (1.7)	1 (1.7)	0 (0.0)
Cough	4 (1.3)	2 (1.1)	3 (0.8)	21 (1.3)	3 (2.4)	1 (0.8)	1 (1.7)	0 (0.0)
Nausea	4 (1.3)	2 (1.1)	2 (0.6)	18 (1.1)	1 (0.8)	2 (1.7)	1 (1.7)	0 (0.0)
Asthenia	3 (1.0)	2 (1.1)	2 (0.6)	17 (1.0)	2 (1.6)	1 (0.8)	0 (0.0)	0 (0.0)
Arthralgia	0 (0.0)	1 (0.6)	3 (0.8)	15 (0.9)	1 (0.8)	2 (1.7)	0 (0.0)	0 (0.0)
Oedema peripheral	1 (0.3)	3 (1.7)	4 (1.1)	14 (0.8)	14 (11.0)	1 (0.8)	0 (0.0)	0 (0.0)
Fatigue	1 (0.3)	2 (1.1)	2 (0.6)	13 (0.8)	1 (0.8)	2 (1.7)	2 (3.4)	0 (0.0)
Urinary tract infection	0 (0.0)	5 (2.8)	1 (0.3)	12 (0.7)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Bronchitis	1 (0.3)	1 (0.6)	0 (0.0)	11 (0.7)	1 (0.8)	3 (2.5)	0 (0.0)	0 (0.0)
Flatulence	1 (0.3)	0 (0.0)	1 (0.3)	8 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	2 (0.6)	0 (0.0)	0 (0.0)	8 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	3 (1.7)	1 (0.3)	7 (0.4)	3 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Angina pectoris	0 (0.0)	0 (0.0)	2 (0.6)	3 (0.2)	1 (0.8)	0 (0.0)	0 (0.0)	1 (3.8)
Tendonitis	0 (0.0)	0 (0.0)	3 (0.8)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
Myocardial infarction	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)

The common AEs in the long-term open-label studies are summarized in table 49. The most frequently reported AE with aliskiren/HCTZ and aliskiren monotherapy was nasopharyngitis (6.1% and 6.9%, respectively). There was no increase in AE rates with the addition of HCTZ to aliskiren treatment. In fact, the rates of headache, diarrhea, fatigue, and nausea were lower in the aliskiren/HCTZ group compared with aliskiren monotherapy.

Table 49: Number (%) of patients with most frequent AEs (> = 2% for any treatment group) in long-term open-label studies (safety population)

Preferred term	Mono Ali N=1955 n (%)	Ali/HCTZ 300/12.5 mg N=843 n (%)	Ali/HCTZ 300/25 mg N=454 n (%)	Ali/HCTZ N=871 n (%)
Any Adverse Experience	1050 (53.7)	314 (37.2)	197 (43.4)	464 (53.3)
Nasopharyngitis	135 (6.9)	38 (4.5)	15 (3.3)	53 (6.1)
Dizziness	75 (3.8)	21 (2.5)	11 (2.4)	31 (3.6)
Bronchitis	63 (3.2)	13 (1.5)	17 (3.7)	29 (3.3)
Back pain	68 (3.5)	22 (2.6)	5 (1.1)	26 (3.2)
Influenza	50 (2.6)	16 (1.9)	10 (2.2)	26 (3.0)
Headache	153 (7.8)	12 (1.4)	10 (2.2)	22 (2.5)
Arthralgia	36 (1.8)	8 (0.9)	11 (2.4)	19 (2.2)
Cough	30 (1.5)	15 (1.8)	4 (0.9)	19 (2.2)
Diarrhoea	69 (3.5)	12 (1.4)	6 (1.3)	18 (2.1)
Upper respiratory tract infection	42 (2.1)	12 (1.4)	4 (0.9)	16 (1.8)
Fatigue	41 (2.1)	10 (1.2)	2 (0.4)	12 (1.4)
Nausea	42 (2.1)	0 (0.0)	5 (1.1)	5 (0.6)

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

The common AEs during the long-term double-blind studies are summarized in table 50. The most frequently reported AEs during long-term double-blind treatment with aliskiren/HCTZ were dizziness, nasopharyngitis, fatigue, and headache. Gastrointestinal events overall and the rate of diarrhea in particular were not increased with aliskiren/HCTZ combination treatment. Headache and peripheral edema were less frequent in the aliskiren/HCTZ group compared with aliskiren and ramipril monotherapy. Dizziness was slightly more frequent with aliskiren/HCTZ than ramipril/HCTZ. The incidence of cough was highest in the ramipril monotherapy group. An increased rate of cough was observed in ramipril group (8.1 %) and ramipril/HCTZ group (4.3 %) compared with aliskiren (3.3 %) and aliskiren/HCTZ (1.6 %).

Table 50: Number (%) of patients with most frequent AEs (> = 2% for any treatment group) in long-term double-blind studies (safety population)

Preferred term	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 (%)	Ramipril/ HCTZ/ N=210 n (%)
Any adverse experience	237 (56.3)	64 (33.2)	35 (38.0)	85 (44.0)	234 (55.5)	98 (46.7)
Dizziness	16 (3.8)	7 (3.6)	1 (1.1)	8 (4.1)	16 (3.8)	5 (2.4)
Nasopharyngitis	19 (4.5)	5 (2.6)	3 (3.3)	8 (4.1)	24 (5.7)	9 (4.3)
Fatigue	13 (3.1)	3 (1.6)	3 (3.3)	6 (3.1)	16 (3.8)	1 (0.5)
Headache	45 (10.7)	6 (3.1)	1 (1.1)	6 (3.1)	33 (7.8)	8 (3.8)
Bronchitis	9 (2.1)	5 (2.6)	0 (0.0)	5 (2.6)	5 (1.2)	2 (1.0)
Diarrhoea	13 (3.1)	2 (1.0)	3 (3.3)	5 (2.6)	8 (1.9)	1 (0.5)
Sinusitis	4 (1.0)	4 (2.1)	2 (2.2)	5 (2.6)	8 (1.9)	4 (1.9)
Upper respiratory tract infection	11 (2.6)	3 (1.6)	2 (2.2)	5 (2.6)	11 (2.6)	13 (6.2)
Cough	14 (3.3)	3 (1.6)	0 (0.0)	3 (1.6)	34 (8.1)	9 (4.3)
Pain in extremity	13 (3.1)	2 (1.0)	1 (1.1)	3 (1.6)	5 (1.2)	3 (1.4)
Back pain	13 (3.1)	1 (0.5)	1 (1.1)	2 (1.0)	7 (1.7)	8 (3.8)
Blood glucose increased	0 (0.0)	0 (0.0)	2 (2.2)	2 (1.0)	1 (0.2)	1 (0.5)
Nausea	10 (2.4)	1 (0.5)	1 (1.1)	2 (1.0)	5 (1.2)	3 (1.4)
Oedema peripheral	14 (3.3)	1 (0.5)	1 (1.1)	2 (1.0)	13 (3.1)	2 (1.0)
Dyspepsia	11 (2.6)	0 (0.0)	1 (1.1)	1 (0.5)	4 (0.9)	0 (0.0)

7.1.5.5 Identifying common and drug-related adverse events

Like the aliskiren and HCTZ monotherapy, the common drug-related adverse events in the combination study of aliskiren/HCTZ included diarrhea, cough, and dizziness. Based on both the short term and long term study data, the incidence rates of these AEs were comparable to the individual monotherapy. These AEs were also analyzed in Sections 7.1.3.2 and 7.1.3.3.

7.1.5.6 Additional analyses and explorations

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

7.1.6 Less Common Adverse Events

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

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

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

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

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

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Lab tests that showed changes in measures of central tendency in the aliskiren groups were hemoglobin, creatinine and urea, potassium, and uric acid.

For hemoglobin, a slight decrease in mean hemoglobin from baseline was observed in the aliskiren monotherapy and aliskiren/HCTZ combination treatment groups in the short-term placebo-controlled studies and short-term controlled studies. In the long-term studies, however, the decreased hemoglobin was not observed. Data were summarized in the following table 51. There is no correlated decrease of hematocrit and red blood cells in all above studies.

Table 51: Changes from Baseline in Hemoglobin (g/L) in short-term placebo-controlled, short-term active controlled, long-term open labeled, and long-term double-blind studies

(Group A: short term, double-blind, placebo controlled studies)

Hematology: Haemoglobin (g/L)

		Baseline			Post baseline: Endpoint			Post baseline: Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=193)	184	145.3	12.23	146.0	146.5	12.13	146.0	1.2	5.81	1.0
Ali 75 mg (N=184)	176	145.2	12.44	146.0	145.3	12.98	146.0	0.1	6.20	0.0
Ali 150 mg (N=185)	177	145.5	13.21	146.0	145.5	12.69	145.0	-0.0	6.54	0.0
Ali 300 mg (N=181)	173	146.0	13.46	148.0	145.4	13.84	145.0	-0.6	7.21	0.0
Mono Ali (N=550)	526	145.6	13.02	146.0	145.4	13.15	145.0	-0.2	6.65	0.0
HCTZ 6.25 mg (N=194)	187	144.7	14.23	146.0	145.5	14.42	145.0	0.8	7.57	1.0
HCTZ 12.5 mg (N=188)	183	144.8	15.25	146.0	145.8	15.58	148.0	1.0	5.89	1.0
HCTZ 25 mg (N=173)	170	145.2	13.25	145.0	145.4	13.92	145.0	0.2	8.57	1.0
Mono HCTZ (N=555)	540	144.9	14.26	146.0	145.6	14.65	146.0	0.7	7.39	1.0
Ali/HCTZ 75/6.25 mg (N=188)	185	146.1	13.12	146.0	145.7	13.06	145.0	-0.4	6.58	0.0
Ali/HCTZ 75/12.5 mg (N=190)	179	145.5	12.01	146.0	145.0	13.05	144.0	-0.5	6.09	0.0
Ali/HCTZ 75/25 mg (N=186)	183	144.2	14.92	145.0	144.6	13.59	146.0	0.4	8.50	0.0
Ali/HCTZ 150/6.25 mg (N=174)	167	146.2	13.59	146.0	145.5	13.10	145.0	-0.7	6.54	-1.0
Ali/HCTZ 150/12.5 mg (N=184)	180	145.2	12.60	144.5	144.6	12.24	144.0	-0.7	6.10	-1.0
Ali/HCTZ 150/25 mg (N=188)	180	145.9	15.06	147.0	145.4	14.29	146.5	-0.5	7.37	-0.5
Ali/HCTZ 300/12.5 mg (N=181)	176	144.0	13.52	145.0	143.3	13.68	144.0	-0.6	6.79	-1.0
Ali/HCTZ 300/25 mg (N=173)	172	144.6	12.92	145.0	144.2	12.64	143.0	-0.4	6.78	-1.0
All Ali/HCTZ (N=1464)	1422	145.2	13.50	145.5	144.8	13.21	145.0	-0.4	6.88	-1.0

(Group B: short term, double-blind, all controlled studies)

Hematology: Haemoglobin (g/L)

		Baseline			Post baseline: Endpoint			Post baseline: Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=193)	184	145.3	12.23	146.0	146.5	12.13	146.0	1.2	5.81	1.0
Mono Ali (N=608)	578	145.3	13.13	146.0	145.1	13.10	145.0	-0.2	6.66	0.0
Mono HCTZ (N=678)	657	144.5	14.35	145.0	145.4	14.67	146.0	0.9	7.98	1.0
All Ali/HCTZ (N=1654)	1602	145.1	13.61	145.0	144.8	13.32	145.0	-0.3	7.16	0.0
Amlodipine/HCTZ (N=127)	123	141.7	12.02	142.0	141.3	13.08	142.0	-0.5	9.09	0.0
Irbesartan/HCTZ (N=120)	117	142.1	13.11	142.0	141.0	11.88	138.0	-1.1	9.29	-2.0
Lisinopril (N=32)	31	141.1	10.86	143.0	140.7	11.40	140.0	-0.4	8.43	0.0
Lisinopril/HCTZ (N=26)	26	140.9	11.74	143.0	143.3	10.73	142.5	2.4	8.01	2.5

(Group C: long term open-label studies)

Hematology: Haemoglobin (g/L)

		Baseline			Post baseline: Endpoint			Post baseline: Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Mono Ali (N=1084)	1001	143.4	13.47	144.0	143.2	13.59	143.0	-0.2	8.33	0.0
All Ali/HCTZ* (N=871)	854	144.3	12.94	144.5	145.0	12.93	145.0	0.8	8.50	1.0

(Group D: long term, double-blind studies)

Hematology: Haemoglobin (g/L)

		Baseline			Post baseline: Endpoint			Post baseline: Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Mono Ali (N=226)	191	143.6	15.16	143.0	145.7	14.62	146.0	2.1	7.36	2.0
Ali/HCTZ* (N=193)	188	143.2	14.91	144.0	144.2	16.38	146.0	1.0	9.77	1.0
Ramipril (N=212)	186	145.5	13.50	147.0	148.3	13.71	150.0	2.8	6.77	3.0
HCTZ/Ramipril* (N=210)	200	144.7	14.83	146.0	147.3	15.48	148.0	2.6	8.61	3.0

For clinical chemistry parameters, in short-term studies, a mean increase in BUN was seen in the aliskiren/HCTZ group (0.45 mmol/L) compared with HCTZ group (0.28 mmol/L), but comparable to irbesartan/HCTZ (0.51 mmol/L) and lisinopril/HCTZ (0.52 mmol/L) groups. The majority of these increases were not outside the laboratory normal range for BUN. Mean increases in creatinine were seen in the HCTZ (1.7 mmol/L), aliskiren/HCTZ (2.2 mmol/L) and irbesartan/HCTZ (3.0 mmol/L) groups compared with placebo and aliskiren monotherapy (0.5 mmol/L for each). Mean changes from baseline in potassium values showed small mean increases for placebo (0.03 mmol/L) and aliskiren monotherapy (0.08 mmol/L) and small mean decreases for aliskiren/HCTZ (-0.07) and HCTZ (-0.10). A mean increase in uric acid was seen with aliskiren/HCTZ (33.9 µmol/L) compared with HCTZ group (22.4 µmol/L), but less than lisinopril/HCTZ (81.9 µmol/L). For the other biochemistry parameters, no major differences were observed between the aliskiren treatment groups vs. the controls. Data were summarized in the following table 52.

Table 52: Summary of changes in potassium, sodium, calcium, uric acid, BUN, and creatinine for placebo, aliskiren and HCTZ monotherapy, and combination therapy in short-term controlled studies (safety population)

	Placebo (N=193)	Mono Ali (N=608)	Ali HCTZ (N=678)	Ali/HCTZ (N=1654)	Amlo/HCTZ (N=127)	Irb/HCTZ (N=120)	Lis/HCTZ (N=26)
Potassium (mmol/L)							
N	155	486	565	1357	126	120	26
Baseline	4.35 (0.397)	4.37 (0.400)	4.34 (0.400)	4.35 (0.398)	4.19 (0.369)	4.14 (0.417)	4.28 (0.393)
Mean (SD) change	0.03 (0.380)	0.08 (0.387)	-0.10 (0.406)	-0.07 (0.422)	-0.05 (0.485)	0.13 (0.485)	-0.06 (0.483)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
> 20% decrease	1 (0.6)	6 (1.2)	20 (3.5)	40 (2.9)	3 (2.4)	3 (2.5)	2 (7.7)
> 20% increase	6 (3.9)	20 (4.1)	18 (3.2)	48 (3.5)	10 (7.9)	21 (17.5)	3 (11.5)
Sodium (mmol/L)							
N	187	595	669	1623	126	120	26
Baseline	141.5 (2.89)	141.4 (2.75)	141.2 (2.74)	141.5 (2.72)	140.9 (2.35)	140.8 (2.07)	139.9 (2.00)
Mean (SD) change	0.3 (2.86)	0.1 (2.44)	0.4 (2.49)	-0.1 (2.58)	-0.1 (2.27)	-0.7 (2.31)	0.1 (2.31)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
> 5% decrease	3 (1.6)	2 (0.3)	5 (0.7)	16 (1.0)	2 (1.6)	5 (4.2)	0 (0.0)
Calcium (mmol/L)							
N	187	592	666	1621	124	118	26
Baseline	2.389 (0.1296)	2.384 (0.1416)	2.388 (0.1276)	2.391 (0.1232)	2.352 (0.0812)	2.377 (0.0909)	2.386 (0.1049)
Mean (SD) change	-0.001 (0.1614)	0.005 (0.1192)	0.010 (0.1000)	0.015 (0.0947)	-0.002 (0.0948)	-0.022 (0.0968)	-0.017 (0.0815)
	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)	n (%)
>10% increase	4 (2.1)	18 (3.0)	17 (2.6)	46 (2.8)	0 (0.0)	2 (1.7)	0 (0.0)
>10% decrease	1 (0.5)	3 (0.5)	6 (0.9)	10 (0.6)	2 (1.6)	2 (1.7)	0 (0.0)
Uric Acid (umol/L)							
N	184	581	658	1608	124	118	26
Baseline	337.9 (86.49)	339.7 (85.13)	344.1 (90.87)	340.0 (83.76)	363.6 (87.38)	382.9 (101.21)	343.1 (80.29)
Mean (SD) change	0.7 (45.33)	5.0 (51.97)	22.4 (62.86)	33.9 (57.15)	-8.5 (65.74)	-19.1 (71.00)	81.9 (58.86)
	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)	n (%)
> 50% increase	0 (0.0)	6 (1.0)	20 (3.0)	35 (2.2)	1 (0.8)	5 (4.2)	1 (3.8)
BUN (mmol/L)							
N	187	595	669	1623	126	120	26
Baseline	5.42 (1.262)	5.44 (1.474)	5.50 (1.430)	5.45 (1.396)	5.70 (1.649)	5.44 (1.327)	6.07 (2.476)
Mean (SD) change	-0.03 (1.095)	0.18 (1.351)	0.28 (1.249)	0.45 (1.291)	0.12 (1.542)	0.51 (1.677)	0.52 (2.521)
	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)	n (%)
> 50% increase	13 (7.0)	50 (8.4)	63 (9.4)	192 (11.8)	14 (11.1)	17 (14.2)	3 (11.5)
Creatinine (umol/L)							
N	187	595	669	1623	126	120	26
Baseline	79.9 (15.15)	78.6 (16.46)	78.5 (16.41)	79.0 (16.30)	77.5 (13.81)	77.4 (15.68)	88.3 (44.29)
Mean (SD) change	0.5 (8.06)	0.5 (8.93)	1.7 (9.57)	2.2 (9.69)	0.8 (11.06)	3.0 (11.86)	-3.5 (45.36)
	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)	n (%)
> 50% increase	2 (1.1)	3 (0.5)	9 (1.3)	14 (0.9)	5 (4.0)	7 (5.8)	0 (0.0)

In the pooled analysis of the long-term open-label studies, mean increases from baseline at endpoint were seen for ALT/SGPT, creatinine, and uric acid. Patients on combination therapy in

the open-label period had greater mean increases in uric acid than those on monotherapy. They also had greater mean increases in BUN, creatinine and low potassium. These findings are all consistent with the expected effects of HCTZ. Otherwise, the results were similar with monotherapy and combination therapy during the open-label period. Changes from baseline for the other blood chemistry variables were minor and not indicative of a safety issue.

Table 53: Changes of clinical chemistry parameters in long-term open-label studies

(Group C: long term open-label studies)

Biochemistry: SGPT (ALT) (U/L)

		Baseline			Post baseline Endpoint			Post baseline Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Mono Ali (N-1084)	1003	25.6	13.27	22.0	26.7	15.02	23.0	1.1	13.17	0.0
All Ali/HCTZ* (N-871)	855	26.8	14.98	23.0	29.8	17.35	26.0	3.0	15.89	2.0

Biochemistry: Creatinine (umol/L)

		Baseline			Post baseline Endpoint			Post baseline Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Mono Ali (N-1084)	1036	77.9	16.58	78.0	79.9	16.50	80.0	2.0	10.46	1.0
All Ali/HCTZ* (N-871)	867	79.6	16.46	80.0	84.1	17.60	81.0	4.5	11.87	4.0

Biochemistry: Blood Urea Nitrogen (BUN) (mmol/L)

		Baseline			Post baseline Endpoint			Post baseline Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Mono Ali (N-1084)	1036	5.54	1.544	5.40	5.55	1.514	5.40	0.01	1.388	0.00
All Ali/HCTZ* (N-871)	867	5.65	1.500	5.50	5.96	1.664	5.70	0.32	1.522	0.30

Biochemistry: 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
Mono Ali (N-1084)	1003	341.5	86.24	340.0	345.0	83.03	340.0	3.5	61.85	10.0
All Ali/HCTZ* (N-871)	854	352.1	81.44	350.0	381.9	89.42	380.0	29.8	65.17	30.0

Biochemistry: Potassium (mmol/L)

		Baseline			Post baseline Endpoint			Post baseline Change from baseline		
Treatment group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Mono Ali (N-1084)	871	4.32	0.362	4.30	4.38	0.376	4.40	0.06	0.383	0.00
All Ali/HCTZ* (N-871)	776	4.27	0.386	4.20	4.23	0.405	4.20	-0.04	0.409	0.00

In long-term double blind studies, as would be expected, larger mean increases from baseline in uric acid occurred with the aliskiren/HCTZ and ACEI/HCTZ groups compared with aliskiren and ACEI monotherapy. Other changes are consistent with those observed in the long-term open-label studies.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The criteria for notable laboratory values were defined as in the following table 54.

Table 54: Criteria for notable laboratory values

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

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

A summary of potassium, BUN, and creatinine by specified criteria that were considered clinically significant for placebo-controlled studies is presented in table 55; similar data are summarized for the short-term controlled trials in table 56. Hypokalemia with K<3.5 mmol/L was more common in the HCTZ monotherapy (3.4%) and HCTZ-containing combination groups (2.2%) than in placebo (1.3%) and aliskiren monotherapy groups (0.4%). Hyperkalemia with K>5.5 mmol/L were infrequent (0 to 1.3%) in patients treated with various doses of aliskiren/HCTZ in the placebo-controlled trials . Only one patient (<0.1%) treated with aliskiren/HCTZ had hyperkalemia with K≥ 6.0 mmol/L. In the short-term controlled studies, the incidence of hyperkalemia with K>5.5 mmol/L in patients treated with aliskiren/HCTZ (0.8%) was similar to patients treated with CCB/HCTZ (0.8%) and lower than patients treated with ARB/HCTZ (2.5%) or aliskiren monotherapy (2.3%). No cases of elevated BUN and creatinine

meeting clinically significant criteria were observed in patients treated with aliskiren/HCTZ in placebo-controlled and short term active-controlled studies.

Table 55: Summary of potassium, BUN and creatinine by specified criteria –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=560)		HCTZ 6.25 mg (N=194)		HCTZ 12.5 mg (N=188)		HCTZ 25 mg (N=173)		Mono HCTZ (N=565)	
	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)

N'=number of patients with lab measurement, n=number of patients meeting the criteria, %=(n/N')*100.

Table 56: Summary of potassium, BUN and creatinine by specified criteria –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)

N'=number of patients with lab measurement, n=number of patients meeting the criteria, %=(n/N')*100.

A summary of potassium, BUN, and creatinine by specified criteria that were considered clinically significant in long-term studies is presented in the following tables 57 (long-term open-label studies) and 58 (long-term double-blind studies). As expected, more patients receiving aliskiren/HCTZ combination therapy than monotherapy patients had potassium values < 3.5 mmol/L in the long-term open-label studies. The incidence of hyperkalemia was low and similar between the monotherapy and the combination therapy patients. No patients discontinued due to abnormal potassium values, either reported as AEs or identified as such on the end of study

eCRF page. More patients in aliskiren/HCTZ and ramipril/HCTZ combination therapies had potassium values < 3.5 mmol/L than monotherapies of aliskiren and ramipril. The specified increases in BUN and creatinine occurred for too few patients to show any meaningful differences between treatment groups. Two patients (1 %) in the ramipril/HCTZ regimen had creatinine > 176.8 umol/L versus none in the aliskiren/HCTZ regimen.

Table 57: Summary of potassium, BUN, and creatinine by specified criteria 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)

N'=number of patients with lab measurement, n=number of patients meeting the criteria, %=(n/N')*100.

Table 58: Summary of potassium, BUN, and creatinine by specified criteria 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)

N'=number of patients with lab measurement, n=number of patients meeting the criteria, %=(n/N')*100.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

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

7.1.7.4 Additional analyses and explorations

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

7.1.7.5 Special assessments

Special assessments for renal function and potassium are addressed in Section 7.1.7.3.1. I did not identify any other laboratory value concerns for which special assessment are needed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Blood pressure and pulse were routinely measured at most visits for the efficacy evaluations. Weight was typically measured during baseline and at the end. Temperature and respirations were not routinely recorded. The main discussion is the orthostatic pressure.

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

Like at the beginning of the safety review, all data set included short-term placebo controlled study, short-term controlled, long-term open label study, and long-term double blind study.

7.1.8.3 Standard analyses and explorations of vital signs data

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

Orthostatic pressure was analyzed in all of four data sets as shown in the following tables 59-62. Orthostatic blood pressure changes were defined as a decrease of at least 20 mm Hg in systolic blood pressure or a decrease of at least 10 mm Hg in diastolic blood pressure when a patient moves from a sitting position to a standing position. In short-term studies, overall, orthostatic BP change was infrequent and similar between the combination therapy and monotherapies.

Table 59: Incidence of orthostatic blood pressure change in short-term placebo-controlled studies (safety population)

	Placebo (N= 193)		Ali75 mg (N=184)		Ali150 mg (N= 185)		Ali300 mg (N=181)		Mono Ali (N= 550)		HCTZ6.25 mg (N=194)	
Visit	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
Baseline	191	6 (3.1)	183	5 (2.7)	184	4 (2.2)	181	6 (3.3)	548	15 (2.7)	192	4 (2.1)
Endpoint	192	4 (2.1)	183	5 (2.7)	182	3 (1.6)	180	4 (2.2)	545	12 (2.2)	194	2 (1.0)
Any visit	192	17 (8.9)	183	15 (8.2)	182	26 (14.3)	180	23 (12.8)	545	64 (11.7)	194	15 (7.7)

	HCTZ 12.5 mg (N=188)		HCTZ25 mg (N=173)		Mono HCTZ (N=555)		Ali/HCTZ 75/6.25 mg (N=188)		Ali/HCTZ 75/12.5 mg (N=190)		Ali/HCTZ 75/25 mg (N=186)	
Visit	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
Baseline	187	3 (1.6)	172	6 (3.5)	551	13 (2.4)	188	7 (3.7)	190	7 (3.7)	186	5 (2.7)
Endpoint	188	3 (1.6)	173	4 (2.3)	555	9 (1.6)	187	6 (3.2)	189	4 (2.1)	186	8 (4.3)
Any visit	188	16 (8.5)	173	23 (13.3)	555	54 (9.7)	187	22 (11.8)	189	20 (10.6)	186	29 (15.6)

	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)	
Visit	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
Baseline	173	3 (1.7)	183	5 (2.7)	188	8 (4.3)	181	5 (2.8)	173	5 (2.9)	1462	45 (3.1)
Endpoint	173	3 (1.7)	184	2 (1.1)	187	7 (3.7)	180	3 (1.7)	173	8 (4.6)	1459	41 (2.8)
Any visit	173	17 (9.8)	184	17 (9.2)	187	15 (8.0)	180	18 (10.0)	173	22 (12.7)	1459	160 (11.0)

Table 60: Incidence of orthostatic blood pressure change in short-term controlled studies (safety population)

	Placebo (N=193)		Mono Ali (N=608)		Mono HCTZ (N=678)		ALI/HCTZ (N=1654)		Amlo/HCTZ (N=127)		Irb/HCTZ (N=120)		Lisinopril (N=32)		Lisinopril/HCTZ (N=26)		Total (N=3438)	
Visit	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
Baseline	191	6 (3.1)	606	15 (2.5)	674	14 (2.1)	1652	49 (3.0)	127	2 (1.6)	120	4 (3.3)	32	0 (0.0)	26	1 (3.8)	3428	91 (2.7)
Endpoint	192	4 (2.1)	602	12 (2.0)	676	12 (1.8)	1649	45 (2.7)	127	4 (3.1)	120	6 (5.0)	32	0 (0.0)	26	1 (3.8)	3424	84 (2.5)
Any visit	192	17 (8.9)	602	65 (10.8)	676	60 (8.9)	1649	181 (11.0)	127	9 (7.1)	120	10 (8.3)	32	2 (6.3)	26	2 (7.7)	3424	346 (10.1)

Amlo=amlodipine; Irb=irbesartan

In the long-term studies, The incidence of patients with orthostatic changes at any visit was slightly higher in the combination therapy group than in the monotherapy group in both the open-label studies (12.4% vs 8.3%) and double blind studies (11.9% vs 7.7%) as shown in the following tables. No patient was discontinued due to orthostatic hypotension reported as an AE.

Table 61: Number (%) of patients with orthostatic blood pressure changes in long-term open-label studies (safety population)

	Mono Ali (N=1084)		ALI/HCTZ (N= 871)		Total (N=1955)	
Visit	Total	n (%)	Total	n (%)	Total	n (%)
Baseline	1082	19(1.8)	869	23(2.6)	1951	42(2.2)
Endpoint	1060	15(1.4)	871	28(3.2)	1931	43(2.2)
Any visit	1060	88(8.3)	871	108(12.4)	1931	196(10.2)

Table 62: Number (%) of patients with orthostatic blood pressure changes in long-term double-blind studies (safety population)

	Mono Ali (N=226)		ALI /HCTZ (N=193)		Mono Ramipril (N=212)		HCTZ/Ramipril (N=210)		Total (N= 841)	
Visit	Total	n(%)	Total	n(%)	Total	n(%)	Total	n(%)	Total	n(%)
Baseline	226	5 (2.2)	192	1 (0.5)	212	6 (2.8)	210	3 (1.4)	840	15 (1.8)
Endpoint	220	4 (1.8)	193	2 (1.0)	208	4 (1.9)	210	6 (2.9)	831	16 (1.9)
Any visit	220	17 (7.7)	193	23 (11.9)	208	16 (7.7)	210	24(11.4)	831	80 (9.6)

7.1.8.4 Additional analyses and explorations

I did not perform any additional analyses of vital signs.

7.1.9 Electrocardiograms (ECGs)

No post-baseline ECGs were performed in studies included in this submission. In the previous NDA review (NDA 21, 985), aliskiren monotherapy does not appear to have an appreciable effect on QT interval. HCTZ is not known to cause ECG changes. However, in the case of electrolyte abnormalities secondary to the use of HCTZ, relevant ECG changes may occur.

7.1.10 Immunogenicity

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

7.1.11 Human Carcinogenicity

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

7.1.12 Special Safety Studies

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

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No withdrawal or rebound effects on efficacy of aliskiren monotherapy have been observed. There is no mention of withdrawal and rebound effects in the prescribing information for HCTZ. In one study (Study 2206), there was a 4-week, double-blind, placebo-controlled, randomized withdrawal period at the end of the 26-week active treatment. The withdrawal period included patients who were on monotherapy as well as patients who received HCTZ add-on to aliskiren or ramipril. Among patients who were treated with aliskiren with or without HCTZ and then randomized to placebo in the withdrawal period, a gradual BP increase (3-4 weeks) towards baseline was observed with no evidence of a rebound effect. Among patients who were treated with ramipril with or without HCTZ and then randomized to placebo, most of the treatment effect was lost at 1 week. Withdraw study with combination of aliskiren/HCTZ was not performed.

There is no reason to suspect this combination that has the potential for abuse in humans.

7.1.14 Human Reproduction and Pregnancy Data

Studies of either aliskiren monotherapy or the combination of aliskiren with HCTZ were not conducted in pregnant women. The sponsor is proposing a black box warning in the label regarding use in pregnancy as is currently included in the labels for ACEIs and ARBs. There are three pregnant cases in the studies as summarized in the following:

1. A 26-year-old Caucasian female subject who received one dose of aliskiren/HCTZ 300/12.5 mg had a positive β -hCG test result at the exit (early termination) visit. The subject had been dropped from the study prior to Period 2 dosing due to a protocol violation. A final report was submitted to Novartis Clinical Safety and Epidemiology, stating that the subject was lost to follow up.
2. A 40 year old female Caucasian patient in Study 100A 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)
3. A 29 year old Black female patient in Study 100A 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.

7.1.15 Assessment of Effect on Growth

The product has not been studied in children

7.1.16 Overdose Experience

There were no reports of overdose in the clinical trials.

7.1.17 Post-marketing Experience

Aliskiren/HCTZ has not yet marketed anywhere in the world.

7.2 Adequacy of Patient Exposure and Safety Assessments

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

The primary clinical data sources were summarized in tables 23 and 24 in section 7.1.

7.2.1.1 Study type and design/patient enumeration

There are four data sets in this application for the safety analysis including 1) Short-term placebo-controlled study (Study 2204); 2) short-term active-controlled studies (Studies 2303 and 2309); 3) long-term open-label studies (studies 2302 and 2302E1); and 4) long-term double blind study (Study 2306).

7.2.1.2 Demographics

The demographics of patients were summarized in the following tables 63-66. In these studies, blacks comprised only less than 7% in the key study. Considering that other RAAS inhibitors have shown reduced activity and in which adverse effects such as angioedema are more common in black people, a higher representation of blacks is desirable to define better aliskiren/HCTZ activity in this subgroup.

Table 63: Demographics in the short-term placebo-controlled study (Study 2204, 8-week study)

	Monotherapy	Placebo N = 195	ALI75 N = 184	ALI150 N = 185	ALI300 N = 183	HCTZ6.25 N = 194	HCTZ12.5 N = 188	HCTZ25 N = 176
Sex–n (%)	Male	109 (55.9)	103 (56.0)	112 (60.5)	99 (54.1)	109 (56.2)	103 (54.8)	92 (52.3)
	Female	86 (44.1)	81 (44.0)	73 (39.5)	84 (45.9)	85 (43.8)	85 (45.2)	84 (47.7)
Age (years)	n	195	184	185	183	194	188	176
	Mean (SD)	54.4 (11.80)	55.0 (11.81)	53.5 (12.34)	54.2 (12.19)	55.2 (12.77)	55.4 (11.99)	55.1 (11.98)
Age group –n (%)	< 65	157 (80.5)	138 (75.0)	150 (81.1)	144 (78.7)	140 (72.2)	138 (73.4)	139 (79.0)
	≥ 65	38 (19.5)	46 (25.0)	35 (18.9)	39 (21.3)	54 (27.8)	50 (26.6)	37 (21.0)
	≥ 75	10 (5.1)	5 (2.7)	8 (4.3)	10 (5.5)	9 (4.6)	7 (3.7)	6 (3.4)
Race–n (%)	Caucasian	164 (84.1)	153 (83.2)	157 (84.9)	155 (84.7)	161 (83.0)	160 (85.1)	155 (88.1)
	Black	7 (3.6)	9 (4.9)	11 (5.9)	7 (3.8)	13 (6.7)	9 (4.8)	9 (5.1)
	Asian	5 (2.6)	6 (3.3)	4 (2.2)	3 (1.6)	5 (2.6)	3 (1.6)	4 (2.3)
	Nat. American	3 (1.5)	4 (2.2)	3 (1.6)	5 (2.7)	6 (3.1)	4 (2.1)	2 (1.1)
	Pacific Islander	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)
	Other	16 (8.2)	11 (6.0)	9 (4.9)	13 (7.1)	8 (4.1)	11 (5.9)	6 (3.4)

Combination therapy		ALI75 / HCTZ6.25 N = 188	ALI75 / HCTZ12.5 N = 193	ALI75 / HCTZ25 N = 186	ALI150 / HCTZ6.25 N = 176	ALI150 / HCTZ12.5 N = 186	ALI150 / HCTZ25 N = 188	ALI300 / HCTZ12.5 N = 181	ALI300 / HCTZ25 N = 173	Total N =2776
Sex–n (%)	Male	108 (57.4)	101 (52.3)	101 (54.3)	96 (54.5)	98 (52.7)	104 (55.3)	89 (49.2)	98 (56.6)	1522 (54.8)
	Female	80 (42.6)	92 (47.7)	85 (45.7)	80 (45.5)	88 (47.3)	84 (44.7)	92 (50.8)	75 (43.4)	1254 (45.2)
Age (years)	n	188	193	186	176	186	188	181	173	2776
	Mean (SD)	55.1 (10.63)	54.4 (10.11)	54.7 (12.17)	53.9 (11.12)	54.7 (11.35)	53.7 (11.58)	55.5 (11.67)	54.8 (10.86)	54.6 (11.63)
Age group –n (%)	< 65	153 (81.4)	166 (86.0)	147 (79.0)	148 (84.1)	148 (79.6)	151 (80.3)	133 (73.5)	138 (79.8)	2190 (78.9)
	≥ 65	35 (18.6)	27 (14.0)	39 (21.0)	28 (15.9)	38 (20.4)	37 (19.7)	48 (26.5)	35 (20.2)	586 (21.1)
	≥ 75	6 (3.2)	3 (1.6)	9 (4.8)	5 (2.8)	6 (3.2)	7 (3.7)	6 (3.3)	2 (1.2)	99 (3.6)
Race–n (%)	Caucasian	165 (87.8)	165 (85.5)	165 (88.7)	149 (84.7)	158 (84.9)	163 (86.7)	153 (84.5)	149 (86.1)	2372 (85.4)
	Black	5 (2.7)	12 (6.2)	5 (2.7)	8 (4.5)	10 (5.4)	5 (2.7)	10 (5.5)	7 (4.0)	127 (4.6)
	Asian	7 (3.7)	4 (2.1)	4 (2.2)	5 (2.8)	5 (2.7)	4 (2.1)	5 (2.8)	5 (2.9)	69 (2.5)
	Nat. American	3 (1.6)	3 (1.6)	3 (1.6)	4 (2.3)	3 (1.6)	3 (1.6)	3 (1.7)	1 (0.6)	50 (1.8)
	Pacific Islander	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	7 (0.3)
	Other	7 (3.7)	8 (4.1)	9 (4.8)	10 (5.7)	10 (5.4)	12 (6.4)	10 (5.5)	11 (6.4)	151 (5.4)

Table 64: Demographics in active-controlled studies (Studies 2303 and 2309, 8-week and 12-week studies)

Demographic characteristic	Aliskiren N=125	Lisinopril N=58	Total N=183
Sex – n (%)			
Female	55 (44.0)	24 (41.4)	79 (43.2)
Male	70 (56.0)	34 (58.6)	104 (56.8)
Race – n (%)			
Caucasian	124 (99.2)	58 (100)	182 (99.5)
Other	1 (0.8)	0 (0.0)	1 (0.5)
Ethnicity – n (%)			
Hispanic or Latino	29 (23.2)	12 (20.7)	41 (22.4)
Other	96 (76.8)	46 (79.3)	142 (77.6)
Age groups – n (%)			
< 65 years	97 (77.6)	46 (79.3)	143 (78.1)
≥ 65 years	28 (22.4)	12 (20.7)	40 (21.9)

Demographic Variable	Aliskiren 300mg HCTZ 25mg N=122	Irbesartan 300mg HCTZ 25mg N=119	Amlodipine 10mg HCTZ 25mg N=126	HCTZ 25mg N=122	Total N=489
Sex n (%)					
Female	62 (50.8)	71 (59.7)	73 (57.9)	70 (57.4)	276 (56.4)
Male	60 (49.2)	48 (40.3)	53 (42.1)	52 (42.6)	213 (43.6)
Race n (%)					
Caucasian	122 (100.0)	118 (99.2)	126 (100.0)	121 (99.2)	487 (99.6)
Other	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)	2 (0.4)
Ethnicity n (%)					
Hispanic/Latino	24 (19.7)	20 (16.8)	25 (19.8)	23 (18.9)	92 (18.8)
Other	98 (80.3)	99 (83.2)	101 (80.2)	99 (81.1)	397 (81.2)
Age (years)					
n	122	119	126	122	489
Mean	53.1	53.0	55.2	55.2	54.1
SD	11.94	11.01	11.88	12.32	11.82
< 65 n (%)	101 (82.8)	99 (83.2)	98 (77.8)	90 (73.8)	388 (79.3)
≥ 65 n (%)	21 (17.2)	20 (16.8)	28 (22.2)	32 (26.2)	101 (20.7)
≥ 75 n (%)	4 (3.3)	1 (0.8)	6 (4.8)	8 (6.6)	19 (3.9)

Table 65: Demographics in long-term open-label studies (Studies 2302 and 2302E1, 12-month study)

Demographic variable	Statistic/category	Aliskiren 150 mg (R) N=1179	Aliskiren 300 mg (R) N=776	Mono*** N = 1085	Combo*** N = 870
Age (years)	Mean (SD)	55.7 (11.30)	55.9 (11.48)	54.8 (11.55)	57.0 (11.03)
	Range	19.0 - 88.0	22.0 - 86.0	19.0 - 88.0	22.0 - 86.0
Age group n (%)	< 65 years	912 (77.4)	604 (77.8)	862 (79.4)	654 (75.2)
	≥ 65 years	267 (22.6)	172 (22.2)	223 (20.6)	216 (24.8)
	< 75 years	1126 (95.5)	739 (95.2)	1041 (95.9)	824 (94.7)
	≥ 75 years	53 (4.5)	37 (4.8)	44 (4.1)	46 (5.3)
Sex n (%)	Male	613 (52.0)	414 (53.4)	546 (50.3)	481 (55.3)
	Female	566 (48.0)	362 (46.6)	539 (49.7)	389 (44.7)
Race n (%)	Caucasian	1020 (86.5)	667 (86.0)	921 (84.9)	766 (88.0)
	Black	69 (5.9)	46 (5.9)	59 (5.4)	56 (6.4)
	Asian	5 (0.4)	10 (1.3)	11 (1.0)	4 (0.5)
	Native American	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
	Pacific Islander	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
	Other	83 (7.0)	53 (6.8)	93 (8.6)	43 (4.9)

Demographic variable	Statistic	Aliskiren + HCTZ 300/25 mg N=198
Age (years)	Mean	57.2 (9.98)
	Range	30.0 - 82.0
Age group (years)	<65	154 (77.8%)
	≥ 65	44 (22.2%)
Age group (years)	<75	192 (97.0%)
	≥ 75	6 (3.0%)
Sex	Male	98 (49.5%)
	Female	100 (50.5%)
Race	Caucasian	186 (93.9%)
	Black	9 (4.5%)
	Asian	1 (0.5%)
	Other	2 (1.0%)

***Monotherapy patients are those who never took HCTZ. Combo = combination therapy (patients who took HCTZ at least once).

Table 66: Demographics in long-term double-blind study (Study 2306, 26-week study)

Demographic Characteristic Category/Statistic	Aliskiren Regimen N=420	Ramipril Regimen N=422	Total N=842
Sex n (%)			
Male	224 (53.3%)	256 (60.7%)	480 (57.0%)
Female	196 (46.7%)	166 (39.3%)	362 (43.0%)
Race n (%)			
Caucasian	312 (74.3%)	326 (77.3%)	638 (75.8%)
Black	84 (20.0%)	67 (15.9%)	151 (17.9%)
Asian	14 (3.3%)	13 (3.1%)	27 (3.2%)
Native American	0 (0.0%)	2 (0.5%)	2 (0.2%)
Other	10 (2.4%)	14 (3.3%)	24 (2.9%)
Ethnicity n (%)			
Hispanic or Latino	63 (15.0%)	63 (14.9%)	126 (15.0%)
Chinese	7 (1.7%)	7 (1.7%)	14 (1.7%)
Indian (India Subcontinent)	11 (2.6%)	10 (2.4%)	21 (2.5%)
Other	339 (80.7%)	342 (81.0%)	681 (80.9%)
Age (years)			
N	420	422	842
Mean (SD)	53.4 (10.78)	53.1 (11.21)	53.3 (10.99)
Age group n (%)			
< 65	356 (84.8%)	359 (85.1%)	715 (84.9%)
>=65	64 (15.2%)	63 (14.9%)	127 (15.1%)
>=75	13 (3.1%)	12 (2.8%)	25 (3.0%)

7.2.1.3 Extent of exposure (dose/duration)

- The key study of this combination of aliskiren with HCTZ is study 2204. In this study, a total of 1471 patients received the aliskiren/HCTZ for a planned 8 weeks in the placebo-controlled studies.
- A total of 1725 patients received aliskiren/HCTZ in all other studies. The duration of treatment is from 8 weeks to 12 months.
- The tested doses included aliskiren/HCTZ 75/6.25, 75/12.5, 75/25, 150/6.25, 150/12.5, 150/25, 300/12.5 and 300/25 mg as shown previous tables 63-66.
- The sponsor's analysis of the duration of exposure by aliskiren monotherapy and with HCTZ combination therapy are shown in Tables 67 and 68.

Table 67: Patient disposition and exposure in short-term controlled Study 2204, Study 2309, and Study 2303 (randomized populations)

Study Treatment / dose		N	Discontinuations – n (%)				Mean (SD) exposure (days)
			Total	Safety	Lack of efficacy	Other	
2204							
Placebo		195	22 (11.3)	8 (4.1)	8 (4.1)	6 (3.1)	52.5 (13.21)
Aliskiren	75 mg	184	15 (8.2)	2 (1.1)	7 (3.8)	6 (3.3)	53.9 (10.45)
	150 mg	185	16 (8.6)	2 (1.1)	5 (2.7)	9 (4.9)	53.7 (10.73)
	300 mg	183	17 (9.3)	8 (4.4)	4 (2.2)	5 (2.7)	54.0 (10.55)
Aliskiren/HCTZ	75 / 6.25 mg	188	9 (4.8)	3 (1.6)	2 (1.1)	4 (2.1)	54.7 (10.30)
	75 / 12.5 mg	193	15 (7.8)	7 (3.6)	4 (2.1)	4 (2.1)	53.5 (11.47)
	75 / 25 mg	186	13 (7.0)	5 (2.7)	4 (2.2)	4 (2.2)	53.9 (10.33)
	150 / 6.25 mg	176	17 (9.7)	8 (4.5)	5 (2.8)	4 (2.3)	53.7 (12.48)
	150 / 12.5 mg	186	7 (3.8)	4 (2.2)	0 (0.0)	3 (1.6)	55.8 (7.91)
	150 / 25 mg	188	18 (9.6)	8 (4.3)	1 (0.5)	9 (4.8)	53.6 (12.96)
	300 / 12.5 mg	181	11 (6.1)	3 (1.7)	2 (1.1)	6 (3.3)	54.4 (9.27)
	300 / 25 mg	173	7 (4.0)	5 (2.9)	2 (1.2)	0 (0.0)	55.3 (8.14)
HCTZ	6.25 mg	184	13 (6.7)	2 (1.0)	7 (3.6)	4 (2.1)	54.0 (9.91)
	12.5 mg	188	10 (5.3)	1 (0.5)	4 (2.1)	5 (2.7)	55.1 (7.55)
	25 mg	176	14 (8.0)	5 (2.8)	1 (0.6)	8 (4.5)	54.0 (10.75)
2309							
Aliskiren/HCTZ	300 mg / 25 mg	122	10 (8.2)	3 (2.5)	1 (0.8)	6 (4.9)	79.0 (18.46)
IRB/HCTZ	300 mg / 25 mg	119	7 (5.9)	4 (3.4)	1 (0.8)	2 (1.7)	82.4 (10.40)
AMLO/HCTZ	10 mg / 25 mg	126	11 (8.7)	8 (6.3)	1 (0.8)	2 (1.6)	80.3 (14.84)
HCTZ	25 mg	122	13 (10.7)	5 (4.1)	5 (4.1)	3 (2.5)	80.2 (16.16)
2303							
Aliskiren regimen	150 mg or 300 mg or 300 mg+ HCTZ 25 mg	125	14 (11.2)	4 (3.2)	2 (1.6)	8 (6.4)	52.2 (12.04)
Lisinopril regimen	20 mg or 40 mg or 20 mg + HCTZ 25 mg	58	4 (6.9)	2 (3.4)	1 (1.7)	1 (1.7)	53.9 (8.12)

HCTZ = hydrochlorothiazide; AMLO = amlodipine; IRB = irbesartan

Safety=Adverse event, death, abnormal laboratory values, abnormal test procedure result(s)
Lack of efficacy=Unsatisfactory therapeutic effect
Other=Administrative problems, subject's condition no longer requires study drug, lost to follow up, subject withdrew consent, protocol violation

Table 68: Patient disposition and exposure in open-label long-term Study 2302 and Study 2302E1 (open-label population) and active-controlled long-term Study 2306 (randomized population)

Study treatment / dose	N	Discontinuations – n (%)				Mean (SD) duration of exposure
		Total	Safety	Lack of efficacy	Other	
2302 and 2302E1						
Monotherapy*	1084	224 (20.7)	87 (8.0)	27 (2.5)	110 (10.2)	209.3 (140.83)[1]
Combo*	871	120 (13.8)	32 (3.7)	37 (4.3)	51 (5.9)	275.2 (103.90)
Total	1955	344 (17.6)	119 (6.1)	64 (3.3)	161 (8.3)	318.5 (100.4)
2302E1						
Ali 300/HCTZ 25 mg						
Total	198	9 (4.5)	2 (1.0)	0 (0.0)	7 (3.5)	374.6 (45.13)
2306						
Active controlled period						
Aliskiren regimen	420	79 (18.8)	28 (6.7)	12 (2.9)	39 (9.3)	159.2 (51.48)[2]
Ramipril regimen	422	71 (16.8)	21 (5.0)	14 (3.3)	36 (8.5)	162.9 (47.13)
Randomized withdrawal period						
Aliskiren regimen						
Aliskiren	170	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	28.6 (2.6)
Placebo	163	16 (9.8)	7 (4.3)	7 (4.3)	2 (1.2)	27.3 (5.06)
Total	333	17 (5.1)	7 (2.1)	8 (2.4)	2 (0.6)	28.0 (4.05)
Ramipril regimen						
Ramipril	165	7 (4.2)	1 (0.6)	3 (1.8)	3 (1.8)	28.3 (4.57)
Placebo	177	7 (4.0)	6 (3.4)	1 (0.6)	0 (0.0)	28.1 (4.32)
Total	342	14 (4.1)	7 (2.1)	4 (1.2)	3 (0.9)	28.2 (4.44)

Safety=Adverse event, death, abnormal laboratory values, abnormal test procedure result(s)
Lack of efficacy=Unsatisfactory therapeutic effect
Other=Administrative problems, subject's condition no longer requires study drug, lost to follow up, subject withdrew consent, protocol violation

*Monotherapy patients are those who never took HCTZ. Combo = combination therapy (patients who took HCTZ at least once).

[1] Exposure is based on a total of 1955 patients exposed to Mono-ali

[2] Exposure is based on total of 421 subjects

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Not available

7.2.2.2 Postmarketing experience

Tekturna HCT® (aliskiren/HCTZ combination) has not been marketed.

7.2.2.3 Literature

No new additional safety issues related to the combination of aliskiren and HCTZ were found in the public literature search.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience appears to have been adequate to evaluate the product safety.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The reviewer does not consider that the pre-clinical testing is needed.

7.2.5 Adequacy of Routine Clinical Testing

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

Thorough QT study was not performed with the product. However, neither aliskiren nor HCTZ has shown any effects on QT interval. The reviewer does not think there is a potential QT impact with the combination of aliskiren and HCTZ based on the conducted trials.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Based on the reviewer of NDA 21, 985 for aliskiren monotherapy, the metabolic, clearance, and interaction workup were considered to be adequate.

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

The evaluation for potential adverse events was adequate.

7.2.8 Assessment of Quality and Completeness of Data

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

7.2.9 Additional Submissions, Including Safety Update

In the additional submission, sponsor submitted a 120-day safety update. In the 120-day safety update, sponsor submitted a Study 2331: An eight week, randomized, double-blind, parallel-group, multi-center 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.

In this study, 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.

Data from the 120-day safety update were incorporated into my discussions of specific adverse events.

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

The adverse events in the combination of aliskiren and HCTZ were generally comparable with each of monotherapy.

Since both of them can increase the serum level of uric acid. This combination product may increase rates of gout and renal stones. There was no difference of incidence rates of gout and kidney stone in short-term studies. In the long-term open label study, however, the incidence rate of gout was 0.5% (4 cases) in the combination therapy and 0.1% (1 case) in the aliskiren monotherapy. Overall, AE profile is considered to be acceptable for antihypertensive therapy.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1Pooled data vs. individual study data

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

7.4.1.2 Combining data

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

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

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

7.4.2.2 Explorations for time dependency for adverse findings

Time-dependency for adverse findings was followed in the short-term studies and long-term studies.

7.4.2.3 Explorations for drug-demographic interactions

Subgroup specific rates were analyzed when sufficient events were available in subgroups, by age, race, and gender.

7.4.2.4 Explorations for drug-disease interactions

Drug-disease interactions were not studied.

7.4.2.5 Explorations for drug-drug interactions

In addition to this combined product of aliskiren with HCTZ, the AE rates were also analyzed in aliskiren with ACEIs, ARBs and calcium blockers in the long-term studies.

7.4.3 Causality Determination

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

8 Additional Clinical Issues

8.1 Dosing Regimen and Administration

The combination of aliskiren/HCTZ generally produced clinically and statistically significant reductions in both diastolic and systolic blood pressure compared to placebo and each respective monotherapy in the studied dose ranges of 150 mg or 300 mg of aliskiren in combination with HCTZ 12.5 mg or 25 mg. Therefore, the sponsor proposed clinical doses of aliskiren/HCTZ including 150/12.5, 150/25, 300/12.5, and 300/25 are acceptable.

8.2 Drug-Drug Interactions

The sponsor did not conducted any drug-drug interactions.

8.3 Special Populations

Aliskiren/HCTZ was effective regardless of gender, age, and disease factor of obesity. Regarding the race/ethnicity, however, due to the paucity of non-Caucasian patients in the studies, the subgroup analysis for race/ethnicity (Caucasian, Black, Asian, Native American, Pacific Islander, and Other) was not performed.

8.4 Pediatrics

The sponsor did not conduct pediatric studies. The Division granted the sponsor a pediatric deferral.