8.1.5.1 Approach to eliciting adverse events in the development program
The generation of data for adverse events was from information obtained by questioning and/or examining the patient/subject. This was considered adequate for the controlled studies. Furthermore, any serious adverse experience (SAE), including a serious clinical laboratory abnormality, must be reported to Ciba immediately and the severity of an adverse experience was defined as a qualitative assessment of the degree of intensity of an adverse experience. This could be determined by the investigator or based on reports to the investigators by the patient. Assessment of severity was made irrespective of drug relationship or seriousness of the experience and should be evaluated as mild, moderate, or severe.

8.1.5.2 Appropriateness of adverse event categorization and preferred terms
Verbatim investigator terminology coded against International Medical Nomenclature (IMN) and preferred term were employed by the sponsor in reporting adverse events and experiences. The sponsor provided frequency tabulations for symptoms grouped by international medical nomenclature (IMN) term and IMN body system were made for incidence of adverse experiences delineated for all randomized patients by whether or not trial drug-related, trial drug-related or not related to trial drug as follows: by treatment group, body system, severity, sex, race and age. In addition, patient listings of adverse experiences, whether or not trial drug-related, trial drug-related and not related to trial-drug were also provided denoting action, treatment required and patient outcome to date. Protocols contained provisions for the periodic ascertainment of adverse events from all subjects through non-directive inquiries. There is no reason to suspect bias or inadequate reporting of adverse events with this methodology. Table 4 presents the frequencies of assessments during the clinical trials including the single-blind placebo run-in and washout period, and the double-blind randomization period.

Rates for common adverse events were determined solely by the sponsors categorization. Some effort was made to reduce the excessive subdivision of the preffered terms used in the adverse events by the sponsor. For example the term "dizziness" was used interchangeably with "lightheadedness". Other examples where the sponsor has listed fragmented preferred terms that may givee a misleading impression of underestimates of events included edema, allergy, dermatitis, urticaria, infections, pain, rash, skin disorder, and disorderts of cardiac conduction (See section 8.2). Categorization of events by body system and by likelihood of being related to study drug was performed by the reviewer. The resulting data by the reviewer were similar to the relatively common adverse events in other members of the class of drugs, including valsartan monotherapy. Ciba's International Medical Nomenclature Dictionary was used for coding and reviewing adverse experiences. The Treatment Emergent Signs and Symptoms (TESS) system of data management of adverse experiences was also used in this trial. With this system, pre-existing ad verse experiences were not counted as occurring during the double-blind treatment phase unless it "worsened", and/or a new onset date was recorded.

8.1.5.3 Selecting key adverse event tables for characterization and preferred terms

Table 31 summarizes the key adverse events in the controlled trials.

Table 31: Key adverse events - 19/301

	[illegible]	[illegible]	[illegible]	[illegible]
Total Patients	730 (100)	547 (100)	200 (100)	93 (100)
Total Patients+AEs	388 (53.2)	277 (50.6)	109 (54.5.)	48 (51.6)
AEs				
Headache	79 (10.8)	54 (9.87)	28 (14)	16 (17.2)
Dizziness	64 (6.02)	14 (2.56)	15 (7.5)	6 (6.5)
Fatigue	37 (5.06)	15 (2.74)	11 (5.5)	1 (1.1)
Sinusitis	23 (3.15)	12 (2.19)	6 (3.0)	3 (3.2)
Pharyngitis	22 (3.01)	10 (1.82)	3 (1.5)	1 (1.1)
Upper Respiratory Tract Infection	22 (3.01)	28 (5.11)	7 (3.5)	2 (2.2)
Coughing	21(2.87)	16 (2.92)	5 (2.5)	0 (0.0)
Pain Back	20 (2.72)	15 (2.74)	5 (2.5)	3 (3.2)
Pain Chest	18 (2.46)	11 (2.01)	2 (1.0)	1 (1.1)
Diarrhea	18 (2.46)	20 (3.66)	4 (2.0)	0 (0.0)
Infection Viral	18 (2.46)	22 (4.02)	8 (4.0)	1 (1.1)

8.1.5.4 Identifying common and drug related adverse events

Common adverse events in the placebo-controlled study are summarized in the table for key adverse events (Table 31). With the exception of headaches which was commoner in the placebo group, a comparable frequency pattern was noted for all the commonest adverse events.

8.1.5.5 Additional analyses and explorations

Additional analyses of adverse events were performed by subgroups and by protocol. The summaries and listings of patients discontinued prematurely during all the clinical studies are presented by treatment groups and protocol in Appendix Tables 3-15. The lists include groups of patients discontinued prematurely during the double-blind period and also during the open label periods (Appendix Tables 3 - 15).

8.1.6 Laboratory findings

Patients who participated in the clinical trials had laboratory safety tests performed before the first dose of trial medication (baseline), and also at periodic intervals during treatment. Laboratory tests were performed at screening in the majority of the clinical trials and on 631 and 792 completers in protocols 301 and 19, respectively (Tables 2 and 3). Clinical laboratory evaluations consisting of complete blood chemistry, hematology, and urinalysis were obtained at weeks -4, 2 and 8 following a 12-hour fast in the controlled studies. Serum pregnancy tests were also collected at weeks -4, 0, 2, 4 and 8, corresponding to Visits 1, 2, 3, 5, (and visit 6 for female patients of child-bearing potential). Specimens were sent for analyses to a central laboratory, . These laboratory safety tests were evaluated at one of six different laboratories. A single laboratory was used in each trial with the exception of Protocol 28 which used two different laboratories. Laboratory data were screened by comparison of baseline and endpoint values using tabular and graphical methods. Previously known abnormal hematological indices, chemistry function tests that are known to be adverse events in valsartan monotherapy, were selected for indepth review. Graphs of baseline and endpoint values derived from serum sodium and CPK in the

controlled trials are in Appendix 2. Graphs of this type were also produced for selected laboratory tests and used for analyses of treatment-induced outliers, or an apparent treatment effect. In some patients, CRFs were examined to fully evaluate the subjects' clinical course. The results of these analyses will be described under review of systems (Section 8.2).

8.1.6.1 Extent of Laboratory testing in the development program

The following laboratory tests were performed for the following variables:
Hematology: Hemoglobin, hematocrit, RBC, WBC, platelet count, and differential counts.
Blood chemistry: :Albumin, alkaline phosphatase, bilirubin, calcium, chloride, total cholesterol, creatinine, CPK, glucose, LDH, phosphate, potassium, sodium, SGOT, SGPT, total protein, urea (BUN), uric acid.
Urinalysis: Protein, occult blood, glucose, microscopic for RBC, WBC, bacteria, casts, epithelial cells.
For purposes of this study the absolute neutrophil count has been calculated from the differentials reported in the clinical trial reports. The count was calculated from the percentage of segmented neutrophils plus the percentage of bands.
Some of the laboratories participating in the clinical program reported values for urea instead of BUN. Therefore, the values reported for this laboratory test are reported as the measured value for BUN from some trials and a calculated value of 70% of the reported value for urea for the remaining trials.

Clinical laboratory evaluations

All laboratory data were reviewed in order to determine their acceptability in the summary statistics. Terminal Visit laboratory results were compared to the laboratory results obtained at baseline (week 2) prior to randomization. If a laboratory specimen was not obtained at baseline or if the baseline laboratory values were disrupted because of improper handling of specimens, then the laboratory test values available immediately prior to baseline were used. Erroneous values due to improper handling were not used; repeat laboratory values were also excluded from the summaries. In addition, laboratory specimens obtained more than one day after the last dose of trial medication were excluded. Limits were set for the following specific laboratory tests: WBC count, RBC count, hemoglobin, hematocrit, segmented neutrophils, platelet count, glucose, BUN, creatinine, sodium, potassium, chloride, uric acid, protein, albumin, calcium, phosphate, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, CPK, and cholesterol. Using the defined limits of percent change, a summary of the number of patients with specified percent change from baseline (week 2) for individual laboratory tests by treatment group is shown in Tables 32 -34.

Table 32: Number of patients with specific percent change from baseline for selected laboratory testsProtocol - 301

Parameter	Placebo N(%)	Valsartan 80mg N(%)	Valsartan 160 mg N(%)	HCTZ 12.5 mg N(%)	HCTZ 25 mg N(%)	V 80 HCTZ 12.5mg N(%)	V 160 HCTZ 12.5mg N(%)	V 80 HCTZ 25 mg N(%)	V 160 HCTZ 25mg N(%)
WBC Count:	89	91	91	91	93	93	93	90	91
> 50% increase	1 (1.1)	3 (3.2)	1 (1.1)	0 (0)	1 (1.0)	1 (1.1)	0 (0)	3 (3.3)	3 (3.3)
> 50% decrease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)
RBC Count:	89	94	91	91	96	93	93	90	91
> 50% increase	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
> 20% decrease	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Segmented Neutrophils	89	94	91	91	96	93	93	90	91
> 50% increase	1 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)
> 50% decrease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Platelet count	87	93	91	91	96	93	92	89	90
> 75% increase	0 (0)	1 (1.1)	1 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	1 (1.1)
> 50% decrease	1 (1.2)	0 (0)	1 (1.1)	0 (0)	0 (0)	1 (1.1)	0 (0)	1 (1.1)	0 (0)
Glucose, serum	89	90	90	87	92	90	91	87	88
>50% increase	1 (1.1)	1 (1.1)	0 (0)	2 (2.3)	1 (1.1)	0 (0)	0 (0)	1 (1.2)	1 (1.1)
> 50% decrease	0 (0)	0 (0)	2 (2.2)	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)
Continued									

Table 33: Number of patients with specific percent change from baseline for selected laboratory tests - 301

Parameter	Placebo N(%)	Valsartan 80 mg N(%)	Valsartan 160 mg N(%)	HCTZ 12.5mg N(%)	HCTZ 25 mg N(%)	V 80 HCTZ 12.5mg N(%)	V 160 HCTZ 12.5 mg N(%)	V 80 HCTZ 25mg N(%)	V 160 HCTZ 25mg N(%)
BUN	89	92	91	89	94	94	92	89	91
> 50% increase	2 (2.3)	4 (4.4)	2 (2.2)	5 (5.6)	8 (8.5)	8 (8.5)	3 (3.3)	13 (14.6)	14 (15.4)
Creatinine	89	92	91	89	94	94	92	89	91
> 50% increase	1 (1.1)	2 (2.2)	1 (1.1)	0 (0)	0 (0)	1 (1.1)	1 (1.1)	0 (0)	2 (2.2)
Sodium	91	98	96	98	99	96	94	90	92
> 7% increase	1 (1.1)	0 (0)	1 (1.0)	1 (1.0)	0 (0)	0 (0)	1 (1.1)	0 (0)	1 (1.1)
> 5% decrease	0 (0)	3 (3.1)	3 (3.1)	2 (2.0)	2 (2.0)	4 (4.2)	5 (5.3)	0 (0)	2 (2.2)
Potassium, Serum	91	98	96	97	99	96	94	90	92
> 20% increase	4 (4.4)	10 (10.2)	6 (6.3)	1 (1.0)	3 (3.0)	3 (3.1)	6 (6.4)	5 (5.6)	3 (3.3)
> 20% decrease	3 (3.3)	1 (1.0)	0 (0)	6 (6.2)	11(11.1)	1 (1.0)	2 (2.1)	8 (8.9)	4 (4.4)
Chloride	91	98	96	98	99	96	94	90	92
> 10% increase	0 (0)	1 (1.0)	2 (2.1)	1 (1.0)	0 (0)	1 (1.0)	1 (1.1)	0 (0)	0 (0)
> 10% decrease	2 (2.2)	0 (0)	0 (0)	0 (0)	4 (4.0)	1 (1.0)	0 (0)	5 (5.6)	3 (3.3)
Uric Acid	89	92	91	89	94	94	92	89	91
> 50% increase	2 (2.3)	4 (4.4)	0 (0)	0 (0)	2 (2.1)	2 (2.1)	2 (2.2)	3 (3.4)	3 (3.3)
Continued									

Table 34: Number of patients with specific percent change from baseline for selected laboratory tests - 301

Parameter	Placebo N(%)	Valsartan 80 mg N(%)	Valsartan 160 mg N(%)	HCTZ 12.5 mg N(%)	HCTZ 25 mg N(%)	V 80 HCTZ 12.5 mg N(%)	V 160 HCTZ 12.5 mg N(%)	V 80 HCTZ 25 mg N(%)	V 160 HCTZ 25 mg N(%)
Calcium	91	98	96	89	99	96	94	90	92
> 10% increase	0 (0)	1 (1.0)	1 (1.0)	2 (2.0)	3 (3.0)	1 (1.0)	2 (2.1)	4 (4.4)	0 (0)
> 10% decrease	2 (2.2)	5 (5.1)	4 (4.2)	2 (2.0)	0 (0)	2 (2.1)	2 (2.1)	1 (1.1)	2 (2.2)
Phosphate	91	98	96	97	99	96	94	90	92
> 50% increase	2 (2.2)	7 (7.1)	4 (4.2)	1 (1.0)	0 (0)	6 (6.3)	3 (3.2)	1 (1.1)	2 (2.2)
> 50% decrease	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Alkaline Phosphate	89	92	91	89	94	93	92	89	91
> 100% increase	0 (0)	0 (0)	1 (1.1)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)
SGOT	89	92	90	89	95	94	92	89	91
> 150% increase	1 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)
SGPT	89	92	90	89	95	94	92	89	91
> 150% increase	2 (2.3)	1 (1.1)	0 (0)	0 (0)	3 (3.2)	3 (3.2)	1 (1.1)	1 (1.1)	1 (1.1)
Total Bilirubin	89	92	91	89	94	94	92	89	91
> 100% increase	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2.2)	0 (0)	1 (1.1)
CPK	88	92	92	89	94	94	93	89	91
> 300% increase	2 (2.3)	0 (0)	1 (1.1)	1 (1.1)	0 (0)	0 (0)	0 (0)	2 (2.3)	1 (1.1)
Cholesterol	89	92	91	89	94	94	92	89	91
> 50% increase	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)	0 (0)
> 25% decrease	0 (0)	2 (2.2)	2 (2.2)	0 (0)	1 (1.1)	3 (3.2)	0 (0)	0 (0)	0 (0)

No patient, regardless of treatment group, had a laboratory value which exceeded the sponsor's predetermined limit for percent change from baseline for RBC count (> 50 % increase or > 20 % decrease), hemoglobin (> 50 % increase or > 20 % decrease), hematocrit (> 50 % increase or > 20 % decrease), total protein (> 50 % increase or > 25 % decrease), albumin (> 50 % increase or > 25 % decrease), LDH (> 150 % increase), and total bilirubin (> 100 % increase). The majority of patients in all four treatment groups with normal hematology, blood chemistry and urinalysis parameters at baseline did not have shifts from within the normal range post-baseline.

The treatment groups with the highest number of patients with 20% decrease from baseline were HCTZ 25mg (11%) and valsartan 80mg/HCTZ 25mg (9%), versus the remaining groups with 0-6% The treatment group with the highest number of patients with this 20% increase from baseline was valsartan 80mg (10%) versus the remaining treatment groups with 1-6%. The number and percentage of subjects with significant shifts in 6 selected laboratory tests from baseline to abnormal post baseline values were compared between placebo and treatment groups as a general measure of laboratory safety. No trends were observed for the selected variables (Table 34).

Clinical laboratory evaluations

The most significant laboratory changes from baseline were seen for serum potassium. Out of 77 patients in the combined data set who had their serum potassium values increase or decrease by 20% from baseline (as defined for this trial), fifty-five had values that were within the normal range, and twenty-one had values outside the normal range. The listing of the 21 patients with abnormal serum potassium values is in Table 35. For serum potassium, the percentage of patients who exhibited normal baseline values that decreased to values below the lower limit of normal at terminal visit was greater for the HCTZ 25mg, valsartan 80mg/HCTZ 25mg, and the valsartan 160mg/HCTZ 25mg treatment groups compared to the other treatment groups. All other treatment groups had 2-5% of patients exhibit similar

levels of decrease. In Protocol 19, the mean percent change in serum potassium from baseline to terminal visit showed statistically significant reduction inpatients on combination therapy compared to monotherapy (p=0.0001). Similarly patients on Valsartan 80mg and HCTZ 25mg showed a statistically significant reduction of the mean percent change compared to Valsartan 80mg alone. However, this difference was not observed between Valsartan 80mg and HCTZ12.5mg and valsartan 80mg alone (p=0.2928). In protocol 301, however, there was no statistically significant difference between placebo and patients on the combination therapy (Table 36). There was no statistical difference observed between the serum potassium levels of all treated groups versus placebo (Table 36). However analysis of treatment effects on serum potassium between all valsartan treated groups and all Valsartan/HCTZ treated groups in protocol 301 showed a statistically significant difference in their mean percent change (p=0.0001). This seems to suggest that the combination of Valsartan and HCTZ reduces the hypokalemic effects of HCTZ monotherapy (Table 36).

Table 35: Abnormal serum potassium changes - 19/301

Patient N=21	Treatment Group	Age	Sex	Baseline Value	Terminal Value
>20% Increase					
788/3707	Valsartan 80mg	74	M	4.4	6.4*
132/3120	Valsartan 80mg	52	M	4.4	5.7*
750/3674	Valsartan 80mg	F	F	4.1	8.0*
486/3437	Valsartan 160mg	56	M	3.9	7.6
662/3596	Valsartan 160mg	49	F	4.2	5.7*
401/3361	HCTZ 12.5mg	54	F	4.6	5.6
305/3274	Valsartan 160mg/HCTZ 12.5mg	47	M	4.3	5.4
580/3522	Valsartan 160mg/HCTZ 25mg	43	M	4.2	6.4*
494/3445	Valsartan 160mg/HCTZ 12.5mg	42	F	4.3	8.4*
>20% Decrease					
1344/4139	Placebo	48	M	4.2	2.5
812/3732	HCTZ 12.5mg	47	F	3.9	3.0*
003/3003	HCTZ 25mg	66	F	4.4	3.3
1079/3969	HCTZ 25mg	69	F	4.9	3.3
364/3328	HCTZ 25mg	51	F	4.1	3.2*
971/3857	HCTZ 25mg	46	M	4.2	3.3*
894/3921	HCTZ 25mg	70	F	4.1	3.2*
143/3128	Valsartan 80mg/HCTZ 25mg	40	M	4.6	3.4*
245/3220	Valsartan 80mg/HCTZ 25mg	46	F	4.3	3.4
127/3115	Valsartan 80mg/HCTZ 25mg	45	M	4.2	3.0*
1045/3941	Valsartan 160mg/HCTZ 25mg	56	F	3.9	3.1*
086/3077	Valsartan 160mg/HCTZ 25mg	73	M	4.4	3.3*

*Interim laboratory result, not terminal visit.

Table 36: Analysis of mean percent change in serum potassium -19/301

Protocol 301				Protocol 19			
Treatment Group	N	Mean % change	p-value versus placebo	Treatment Group	N	Mean % change	p-value for combination versus Valsartan monotherapy
Placebo	90	-1.01		Placebo			
V80	91	1.61	0.083	V80	163	0.16	
V80+HCTZ 12.5mg	196	-0.28	0.626	V80+HCTZ12.5mg	162	-1.33	0.2928
V80+HCTZ 25mg	192	-1.09	0.958	V80+HCTZ25mg	170	-5.19	0.0001
All Valsartan treated patients	182	1.25	0.084	All Valsartan treated patients	328	0.61	
HCTZ (12.5 and 25	185	-4.15	0.01				
All patients treated with Combination Valsartan + HCTZ	369	-2.48	0.218	All patients treated with Combination Valsartan + HCTZ	332	-3.31	0.0001

V=Valsartan. HCTZ= Hydrochlorothiazide. N= Number of randomized subjects

There were no discontinuations for hyperkalemia whereas there were discontinuations for hypokalemia. In protocol 301, 5 patients were discontinued for hypokalemia (Table 37 and Appendix Table 3). In the previous review of protocol 19, greater that 20% increases in serum potassium were observed in 4.4% of treated patients compared to 2.9% of placebo-treated patients (NDA 20-665).

Table 37: Discontinuations due to hypokalemia - 301

Protocol	Subject	Drug		Last Visit (wk)	History
		V	H		
301	3552	0	0	4	Discontinued for hypokalemia
301	3857	0	25	2	Discontinued for hypokalemia
301	734/3658	160	25	4	Drug discontinued for hypokalemia
301	812/3732	0	12.5	8	Discontinued for hypokalemia
301	397/3355	0	12.5	8	Discontinued for hypokalemia

A few patients with muscle cramps and fatigue that were considered to be trial drug related had either hypokalemia and or volume depletion. In the combined data base there was a total of 43 patients with myalgia and muscle weaskness. Of these 43 patients, 36 were reported to have myalgia, and 7 patients had cramps affecting muscles at different sites with or without associated muscle fatigue. There was no attempt on the part of the sponsor or the reviewer to systematically corellate this symptom of muscle cramps with hypokalemia except in one patient who were discontinued. While it is conceivable that only a fraction of patients with this symptom had hypokalemia, it is not clear whether this symptom is due to HCTZ or the combination. Muscle cramps occured in >0.2% of patients treated with valsartan monotherapy (NDA 20-665). In the combined database, 37 patients had myalgia as adverse experience. There was no corellation between this event and serum CPK changes, serum potassium alterations or dehydration.

BUN

A 50% increase was considered a clinically significant change for this trial. Fifty-five patients had this change, fifty patients remained within the normal range, and 5 patients were outside the normal range. The treatment groups with the highest number of patients with this 50% increase from baseline were the valsartan 80mg/HCTZ 25mg group (15%), and the valsartan 160mg/HCTZ 25mg (15%), HCTZ 25mg and valsartan 80mg/HCTZ 12.5mg (both 9%) versus the other treatment groups (2-6%). This could be attributed to the known effects thiazide diuretics on potassium and BUN. Two patients were considered to have clinically significant changes in their BUN (Table 38).

Table 38: Significant changes in creatinine -Protocol 301

Protocol	Patient	Treatment	Sex	Age	Baseline	Week 8
301	261/3237 Lynch	valsartan 80 mg	M	47	1.1	1.7
301	248/3224 Littlejohn	valsartan 160 mg/ HCTZ 25 mg	M	58	1.2	1.9
301	623/3560 Stafford	valsartan 160 mg/ HCTZ 25 mg	M	67	1.1	1.7

Normal range: Protocol 301 (M&F) 0.6-1.5 mg/dL.

SGOT/SGPT

There was one patient randomized to 25mg HCTZ treatment group with elevated SGOT in protocol 301. This was detected on visit 3 and the patient was discontinued on the grounds that the patient did not meet protocol requirements. It is not clear if the patient took any medication. Occasionall elevations of liver function tests were reported in patients treated with the combined drug in protocol 301 (Review of systems). In protocol 19, there were also patients with elevated liver chemistries that were considered drug related.

Uric acid

A greater than 50 % increase from baseline of uric acid was felt to represent a clinically significant change. Thiazide diuretics are known to predispose to hyperuricemia or gout. Fifteen patients on HCTZ alone or in combination with valsartan exhibited a >50% increase change in the combined database compared to 5 and 2 patients on valsartan and placebo, respectively (Table 39). Patients on combined treatment developed higher levels of serum uric acid compared to those on valsartan monotherapy. The percentage of patients with specified percent change from baseline in the controlled studies by treatment group is presented in Table 33. However four out of nine patients in protocol 301 with a > 50% change in serum uric acid levels had values that were within the normal range. The five patients that had percent changes outside the normal range were receivng combined therapy, and are listed in Table 40. Three patients had gout reported as AEs (Appendix Table 3)

Table 39: Percent of patients with changes from baseline - uric acid. 19/301

Protocols:	Valsartan/HCTZ				Valsartan		HCTZ		Placebo
	80mg/ 12.5mg N(%)	80mg/ 25mg N (%)	160mg/ 12.5mg N (%)	160mg /25mg N (%)	80mg N (%)	160 mg N %	12.5 mg N (%)	25mg N (%)	N (%)
Total Patients									
Uric Acid	260	260	92	91	257	251	89	94	89
>50% Increase	5 (1.92)	8 (3.08)	2 (2.17)	3 (3.30)	5 1.95)	0 .00)	0 (0.00)	2 (2.13)	2 (2.25)

Table 40: List of patients with >50% increase serum uric acid - 301

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]					
598/5393	Valsartan 80 mg/HCTZ 12.5 mg	67	F	5.3	8.2
20/5013	Valsartan 80 mg/HCTZ 12.5 mg	76	F	1.2	2.0
375/5250	Valsartan 80 mg/HCTZ 12.5 mg	47	M	6.0	9.3
606/5348	Valsartan 80 mg/HCTZ 25 mg	65	M	7.3	11.5
138/5095	Valsartan 80 mg/HCTZ 25 mg	48	M	7.9	11.9

Normal range=3-9mg/dL

CPK

A > 300 % increase or decrease from baseline of serum CPK was felt to represent a clinically significant change. Nine patients exhibited such a change, however 1 patient had values within the normal range. The eight patients (age range 36-67; all males) with abnormal values are listed in Table 41. The cutoff point of >300% increase in CPK level was suggested by the sponsor and had been adopted for the review of valsartan monotherapy.

Table 41: Patients with >300% Increase-serum CPK from baseline- 301

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
218/5146	Valsartan 160 mg	36	M	16	205
444/5295	Valsartan 160 mg	36	M	384	2733
133/5091	Valsartan 80 mg/HCTZ 12.5 mg	63	M	147	618
633/5446	Valsartan 80 mg/HCTZ 12.5 mg	40	M	58	323
461/5306	Valsartan 80 mg/HCTZ 25 mg	52	M	68	648
138/5095	Valsartan 80 mg/HCTZ 25 mg	48	M	167	1362
447/5302	Valsartan 80 mg/HCTZ 25 mg	49	M	140	192
799/5720	Valsartan 80 mg/HCTZ 25 mg	47	M	122	1119

Normal range= 35-120ui/L

In addition to the above listong relating to protocol 301, one patient, (Grincourt 1091), 38 year old male on Valsartan/HCTZ 80/12.5 developed increased CPK considered to be clinically significant and drug related (Protocol 20).

Hematology

White blood Cell count

A > 50 % increase or decrease from baseline of WBC count was felt to represent a clinically significant change. Neutropenia was reported in Diovan-HCT treated patients and no placebo treated patients had neutropenia. Fifteen patients exhibited a > 50% decrease. However, thirteen of these patients had values that were within the normal range. The two patients that had percent changes that were also outside the normal range had no clinical outcome (Review of systems).

Platelets

A greater than 75 % increase or > 50 % decrease from baseline platelet count was considered to represent a clinically significant change. Eight patients exhibited such a change with 4 patients in each group having an increase and a decrease in platelet count. The 5 patients with values outside the normal range are listed below in Table 42. One patient on placebo and valsartan 160mg monotherapy had a > 50% decrease in platelet count whereas 2 patients on the combined drug had this change.

Table 42: Platelet Count - Protocol 301

Patient/Protocol	Treatment Group	Age	Sex	Baseline Value	Terminal Value
75% Increase					
310/3278	Valsartan 80mg	53	F	235	421
50% Decrease					
497/3449	Placebo	64	M	372	152
307/3275	Valsartan 160mg	49	F	257	58
281/3254	Valsartan 80mg/HCTZ 12.5mg	27	M	365	152
52/3048	Valsartan 80mg/HCTZ 25mg	57	F	277	11

8.1.6.
Selection of studies and analyses for overall drug-control comparison
There was a placebo controlled and an active controlled trial in the NDA under review. The data were pooled from both studies for identification of signals that may require further investigation. Analyses of trends in laboratory data were carried out on 12 selected laboratory parameters for which there were complete data in the electronic submission including values for low and maximum high values for protocols 19 and 301.These included alk phos, Ca, CPK, creatinine, glucose, hematocrit, hemoglobin, potassium, SGOT, SGPT, sodium , total bilirubin, triglycerides, total cholesterol, uric acid, and white blood cells. For mean changes from baseline, similar results were seen among all four treatment groups for hematology and blood chemistry parameters post baseline. For all variables in all treatment groups, group mean and median values remained within the normal range during the active treatment period. No trends were observed except for serum potassium.

Standard analyses
Analyses focussed on central tendency and outliers
Laboratory data were screened and scatter plots of baseline and endpoint values were obtained. Examples of graphs generated from data on serum sodium, potassium, and CPK are in Appendix Table . Regression lines were drawn to evaluate the distribution pattern and to identify outliers. Data from the monotherapy studies were reviewed separately from data from studies in combination with HCTZ. These graphs were only reproduced in this review where neccessary to illustrate treatment effects or outliers. Treatment effects producing outliers were assessed by comparing the incidence of such outliers in placebo and controlled treatment groups. In some cases, CRFs were examined to identify any clinical correllates.

8.1.6. Dropouts for laboratory abnormalities
Withdrawals for laboratory abnormalities are listed among withdrawals for adverse events (Appendix Tables 3 -14)

8.1.7 Vital signs
Vital signs were evaluated under efficacy studies. Outliers were investigated only to the extent that they resulted in the reporting of adverse events.

Effect on pulse rate
In protocols 19 and 301, the two large trials evaluating the combination of valsartan /HCTZ, differences in mean sitting pulse rate between all the valsartan/HCTZ and placebo treatment groups were less than 2.5 bpm and were considered to be clinically insignificant. Increased pulse rate does not seem to be a clinically important safety issue with valsartan/HCTZ administration.

Safety monitoring of blood pressure
There was a similar incidence of orthostatic blood pressure changes in all treatment groups. The majority of randomized patients (≥95%) did not experience any orthostatic blood pressure changes. There were no patients who reported orthostatic hypotension, per the protocol definition of a change in blood pressure with associated symptoms. There were no clinically significant trends observed across all treatment groups on physical examination.

//////////In the combined trials, no hypotension was observed in the valsartan/HCTZ, HCTZ, or placebo treatment groups. However, hypotension occurred in 1 (0.1%) patient in the valsartan treatment group. This was considered trial drug-related. Postural hypotension occurred in 6 (0.5%) patients in the valsartan/HCTZ treatment group, 6 (0.3%) patients in the valsartan treatment group, 2 (1.8%) patients in the ACEI/HCTZ treatment group, 1 (0.4%) patient in the HCTZ treatment group, and 4 (1.3%) patients in the other treatment group. All were considered to be trial drug-related. Eight (0.6%) patients in the valsartan/HCTZ treatment group, 6 (0.3%) patients in the valsartan treatment group, 1 (0.4%) in the HCTZ treatment group, 2 (0.7%) patients in the Other treatment group reported syncope. Five (0.4%) of the reports in the valsartan/HCTZ treatment group, 3 (0.2%) in the valsartan treatment group, and 1 each in the HCTZ and Other treatment groups were considered to be trial drug-related.

8.1.8 ECGs
ECGs were only recorded once from the subjects during the single-blind placebo run in period (Table 4), and prior to the double blind period. The ECGs were not analysed in the same manner as other clinical laboratory data presumably because this was to be used to satisfy inclusion criteria prior to enrollment of subjects. The sponsor had not systemically assessed the ECG data obtained. In the absence of a second ECG record it is not possible to evaluate a systematic treatment change. There is no reason to suspect that the addition of HCTZ to valsartan will produce any clinically significant ECG changes.

8.1.9 Special studies
The sponsor carried out studies on volume depleted subjects because of the well recognized diuretic effect of HCTZ. A few subjects with chronic liver disease were enrolled in the study, and their liver function tests deteriorated, and were reported as adverse events. Patients with overt heart failure or evidence of a secondary form of hypertension were excluded from the trial. In addition, individuals with a history of either myocardial infarction, hypertensive encephalopathy, or cerebrovascular accident within the six months preceding entry into the trial; second or third degree heart block, concomitant angina pectoris; significant arrhythmias; vascular heart disease; confirmed evidence of hepatic disease or renal impairment; or insulin-dependent diabetes mellitus were excluded from the trial. The list of inclusion criteria can be found in the protocols.

8.1.10 Withdrawal phenomena and abuse potential
It is unlikely that valsartan/hydrochlorothiazide will demonstrate any potential for abuse. Other agents that affect the renin-angiotensin system have not exhibited any abuse potential. Similarly, diuretics have not exhibited any abuse potential.

8.1.11 Human reproduction data
All studies were conducted in a population at very low risk of pregnancy. The pregnancy tests were negative on all female subjects enrolled with the exception of one subject discontinued for having a positive pregnancy test.

8.1.12 Overdose experience

With valsartan monotherapy, limited data are available about overdosage in humans. Human overdosage with valsartan/hydrochlorothiazide was not reported during the clinical trials The most likely manifestations of overdosage would be hypotension, cerebral hypoperfusion, and tachycardia; bradycardia could also occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Valsartan is not removed from the plasma by dialysis.

8.2 Review of systems

General body system

The three main organs reported to be most frequently affected by adverse events were the heart, lungs and nervous system. Discontinuations due to these adverse events are presented in Appendix Table 3. The narratives of adverse events affecting the cardiovascular and cerebrovascular systems are presented in Appendix Table 2.

8.2.1. General Laboratory findings

No trends were observed.See Section 8.1.6.

8.2.1 Cardiovascular : Adequacy of assessment

In the primary safety dataset (protocols 19 and 301), cardiovascular safety was assessed at each visit through vital signs, and adverse events. ECGs were only recorded once on enrollment and only baseline data are available. This evaluation is considered to be adequate for a drug of this class, and is similar to the method used for Valsartan monotherapy.

Cardiovascular System events plausibly drug related

Cardiovascular deaths

No deaths can be attributed to have any possible relationship to the combined drug administered.

Serious cardiovascular adverse events

Serious cardiovascular events plausibly related to Valsartan monotherapy have already been discussed in NDA 20-665. Withdrawals for serious cardiovascular adverse events most of which are considered to be unrelated to the combination drug are listed in Appendix Table 2.

8.2.2 Gastrointestinal

There were no deaths due to gastrointestinal events.

Adequacy of assessment

All patients in the combined databaase were monitored for liver transaminases (AST and ALT), alkaline phosphatase, and total bilirubin as well as adverse events at each study visit. These assessments ere considered to be adequate to evaluate the possible effects on the gastrointestinal system in a drug of this class.

Adverse events at least possibly drug related

Liver injury

Examination of the mean changes from baseline to endpoint for liver function tests (SGOT/SGPT) were observed in 4 patients each from the monotherapy and the combination group in the controlled trials. Comparison of exposure adjusted rates did not reval a significantly higher rate between the groups on monotherapy and combined therapy. Among the group of volume depleted patients (protocol 28) given V80, there was only one patient with elevated level of SGOT who had to be discontinued from the trial 77 days after medication.The group on Valsartan 160mg had subjects with elevated Alk. phos., SGOT. SGPT and CPK, whereas those on Valsartan 80mg had none (Table 43).

Table 43: Liver function tests

Parameter	Valsartan 80 mg N (%)	Valsartan 160 mg N (%)	Valsartan 80 mg/ HCTZ 12.5 mg N (%)	Valsartan 80 mg/ HCTZ 25 mg N (%)
Alkaline phosphatase > 100 % increase	165 0 (0.0)	160 1 (0.6)	166 0 (0.0)	171 0 (0.0)
SGOT > 150 % increase	165 0 (0.0)	160 2 (1.3)	166 1 (0.6)	171 1 (0.6)
SGPT > 150 % increase	165 0 (0.0)	160 2 (1.3)	166 0 (0.0)	171 2 (1.2)

8.2.2 Gastrointestinal symptoms

Nausea, diarrhea, vomiting, and stomach cramps were reported as serious adverse events that required discontinuation in protocol 301 (Appendix Table 3). Out of a total of 11 events in the controlled trials, 6 were considered to be drug related, and 5 were considered not drug related. Of the 6 related events, only one event, nausea, was considered to be highly probably related to the combined drug (V80/25), whereas the others were classified as probably related. The majority of the serious adverse digestive system events were observed in patients receiving the higher dose of HCTZ (Table 44), and did not appear to be dose or time dependent. Adverse events such as abdominal pain and the relatively frequent stomach cramps reported as adverse events during the double-blind trials with the combination drug may be related to volume depletion, hypokalemia, or both. The adverse symptoms affecting the digestive system are similar in the combined and monotherapy groups, and have been reflected in the labeling.

Table 44: Discontinuations due to serious gastrointestinal adverse events

Protocol	Subject ID	Drug V	Drug H	Last visit week	Reason for discontinuation
19	5310	0	0	3	Pungent and increased flatulence
19	5305	0	0	3	Diarrhea
19	5305	0	0	3	Cramps in stomach
19	5305	0	0	3	Diarrhea
19	5305	0	0	3	Cramps in stomach
19	3844	80	25	3	Nausea
19	/5739	80	25	4	Nausea
301	3559	160	0	5	Diarrhea
301	3617	160	25	3	Vomiting
301	3617	160	25	3	Cramps in the stomach
301	998/3889	80	25	5	Nausea

8.2.2. Hematologic and Lymphatic

All patients in the combined databaase were monitored for hematologic parameters described above in Section 8.1.6.These assessments were considered to be adequate to evaluate the possible hematologic effects of the combined therapy. Five patients had serious adverse events unrelated to the trial drug for which they were discontinued (Table 45).

Safety monitoring of blood pressure
There was a similar incidence of orthostatic blood pressure changes in all treatment groups. The majority of randomized patients (≥95%) did not experience any orthostatic blood pressure changes. There were no patients who reported orthostatic hypotension, per the protocol definition of a change in blood pressure with associated symptoms. There were no clinically significant trends observed across all treatment groups on physical examination.

In the controlled studies, no hypotension was observed in the valsartan/HCTZ, HCTZ, or placebo treatment groups. However, postural hypotension occurred in 1 (0.1%) patient in the valsartan treatment group (protocol 28) after 315 days of therapy. This was considered trial drug-related. Postural hypotension occurred in 6 (0.5%) patients in the valsartan/HCTZ treatment group, 6 (0.3%) patients in the valsartan treatment group, 2 (1.8%) patients in the ACEI/HCTZ treatment group, 1 (0.4%) patient in the HCTZ treatment group, and 4 (1.3%) patients in the other treatment group. All were considered to be trial drug-related. Eight (0.6%) patients in the valsartan/HCTZ treatment group, 6 (0.3%) patients in the valsartan treatment group, 1 (0.4%) in the HCTZ treatment group, 2 (0.7%) patients in the Other treatment group reported syncope. Five (0.4%) of the reports in the valsartan/HCTZ treatment group, 3 (0.2%) in the valsartan treatment group, and 1 each in the HCTZ and Other treatment groups were considered to be trial drug-related.

8.1.8 ECGs
ECGs were only recorded once from the subjects during the single-blind placebo run in period (Table 4), and prior to the double blind period. The ECGs were not analysed in the same manner as other clinical laboratory data presumably because this was to be used to satisfy inclusion criteria prior to enrollment of subjects. The sponsor had not systemically assessed the ECG data obtained. In the absence of a second ECG record it is not possible to evaluate a systematic treatment change. There is no reason to suspect that the addition of HCTZ to valsartan will produce any clinically significant ECG changes.

8.1.9 Special studies
The sponsor carried out studies on volume depleted subjects because of the well recognized diuretic effect of HCTZ. A few subjects with chronic liver disease were enrolled in the study, and their liver function tests deteriorated, and were reported as adverse events. Patients with overt heart failure or evidence of a secondary form of hypertension were excluded from the trial. In addition, individuals with a history of either myocardial infarction, hypertensive encephalopathy, or cerebrovascular accident within the six months preceding entry into the trial; second or third degree heart block, concomitant angina pectoris; significant arrhythmias; vascular heart disease; confirmed evidence of hepatic disease or renal impairment; or insulin-dependent diabetes mellitus were excluded from the trial. The list of inclusion criteria can be found in the protocols.

8.1.10 Withdrawal phenomena and abuse potential
It is unlikely that valsartan/hydrochlorothiazide will demonstrate any potential for abuse. Other agents that affect the renin-angiotensin system have not exhibited any abuse potential. Similarly, diuretics have not exhibited any abuse potential.

8.1.11 Human reproduction data
All studies were conducted in a population at very low risk of pregnancy. The pregnancy tests were negative on all female subjects enrolled with the exception of one subject discontinued for having a positive pregnancy test.

8.1.12 Overdose experience

With valsartan monotherapy, limited data are available about overdosage in humans. Human overdosage with valsartan/hydrochlorothiazide was not reported during the clinical trials The most likely manifestations of overdosage would be hypotension, cerebral hypoperfusion, and tachycardia; bradycardia could also occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Valsartan is not removed from the plasma by dialysis.

8.2 Review of systems

General body system

The three main organs reported to be most frequently affected by adverse events were the heart, lungs and nervous system. Discontinuations due to these adverse events are presented in Appendix Table 3. The narratives of adverse events affecting the cardiovascular and cerebrovascular systems are presented in Appendix Table 2.

8.2.1. General Laboratory findings

No trends were observed.See Section 8.1.6.

8.2.1 Cardiovascular : Adequacy of assessment

In the primary safety dataset (protocols 19 and 301), cardiovascular safety was assessed at each visit through vital signs, and adverse events. ECGs were only recorded once on enrollment and only baseline data are available. This evaluation is considered to be adequate for a drug of this class, and is similar to the method used for Valsartan monotherapy.

Cardiovascular System events plausibly drug related

Cardiovascular deaths

No deaths can be attributed to have any possible relationship to the combined drug administered.

Serious cardiovascular adverse events

Serious cardiovascular events plausibly related to Valsartan monotherapy have already been discussed in NDA 20-665. Withdrawals for serious cardiovascular adverse events most of which are considered to be unrelated to the combination drug are listed in Appendix Table 2.

8.2.2 Gastrointestinal

There were no deaths due to gastrointestinal events.

Adequacy of assessment

All patients in the combined databaase were monitored for liver transaminases (AST and ALT), alkaline phosphatase, and total bilirubin as well as adverse events at each study visit. These assessments ere considered to be adequate to evaluate the possible effects on the gastrointestinal system in a drug of this class.

Adverse events at least possibly drug related

Liver injury

Examination of the mean changes from baseline to endpoint for liver function tests (SGOT/SGPT) were observed in 4 patients each from the monotherapy and the combination group in the controlled trials. Comparison of exposure adjusted rates did not reval a significantly higher rate between the groups on monotherapy and combined therapy. Among the group of volume depleted patients (protocol 28) given V80, there was only one patient with elevated level of SGOT who had to be discontinued from the trial 77 days after medication.The group on Valsartan 160mg had subjects with elevated Alk. phos., SGOT. SGPT and CPK, whereas those on Valsartan 80mg had none (Table 43).

Table 43: Liver function tests

Parameter	Valsartan 80 mg N (%)	Valsartan 160 mg N (%)	Valsartan 80 mg/ HCTZ 12.5 mg N (%)	Valsartan 80 mg/ HCTZ 25 mg N (%)
Alkaline phosphatase > 100 % increase	165 0 (0.0)	160 1 (0.6)	166 0 (0.0)	171 0 (0.0)
SGOT > 150 % increase	165 0 (0.0)	160 2 (1.3)	166 1 (0.6)	171 1 (0.6)
SGPT > 150 % increase	165 0 (0.0)	160 2 (1.3)	166 0 (0.0)	171 2 (1.2)

8.2.2 Gastrointestinal symptoms

Nausea, diarrhea, vomiting, and stomach cramps were reported as serious adverse events that required discontinuation in protocol 301 (Appendix Table 3). Out of a total of 11 events in the controlled trials, 6 were considered to be drug related, and 5 were considered not drug related. Of the 6 related events, only one event, nausea, was considered to be highly probably related to the combined drug (V80/25), whereas the others were classified as probably related. The majority of the serious adverse digestive system events were observed in patients receiving the higher dose of HCTZ (Table 44), and did not appear to be dose or time dependent. Adverse events such as abdominal pain and the relatively frequent stomach cramps reported as adverse events during the double-blind trials with the combination drug may be related to volume depletion, hypokalemia, or both. The adverse symptoms affecting the digestive system are similar in the combined and monotherapy groups, and have been reflected in the labeling.

Table 44: Discontinuations due to serious gastrointestinal adverse events

Protocol	Subject ID	Drug V	Drug H	Last Visit week	Reason for discontinuation
19	5310	0	0	3	Pungent and increased flatulence
19	5305	0	0	3	Diarrhea
19	5305	0	0	3	Cramps in stomach
19	5305	0	0	3	Diarrhea
19	5305	0	0	3	Cramps in stomach
19	3844	80	25	3	Nausea
19	/5739	80	25	4	Nausea
301	3559	160	0	5	Diarrhea
301	3617	160	25	3	Vomiting
301	3617	160	25	3	Cramps in the stomach
301	998/3889	80	25	5	Nausea

8.2.2. Hematologic and Lymphatic

All patients in the combined databaase were monitored for hematologic parameters described above in Section 8.1.6.These assessments were considered to be adequate to evaluate the possible hematologic effects of the combined therapy. Five patients had serious adverse events unrelated to the trial drug for which they were discontinued (Table 45).

Table 45: Discontinuations (DC) due to serious adverse (SAE) hematologic events

Protocol	Treatment Group	Total Daily Dose	Patient ID	Sex	Age	Visit	Adverse Experience	DC	SAE
11E1	Valsartan	80 mg	013/510	M	67	13	Leukemia	Yes	Yes
11E1	Valsartan	40 mg	009/506	M	48	12	Malignant lymphoma Splenomegaly	Yes Yes	Yes Yes
20	Valsartan	80 mg	1131	M	61	-	Microcytic anemia	Yes	Yes
11E3	Valsartan/ HCTZ	80/25 mg	008/508	M	56	-	Lymphatic leukemia	Yes	Yes

Platelets

Eleven subjects out of 25 patients with abnormal platelet counts had clinical evidence of purpura. A greater than 75 % increase or > 50 % decrease from baseline platelet count was considered to represent a clinically significant change. Eight patients exhibited such a change: 4 patients in each group with an increase or decrease in platelet count. Two patients were discontinued from the study because of low platelet count but the sponsor did not assess the relationship of the drug to this event. There was no significant relationship between drug exposure and purpura or thrombocytopenia. In the valsartan monotherapy study, (Protocol 19), a 63 year old male patient on Valsartan 80mg, was discontinued prematurely because of low platrelet count. Other hematologic adverse events observed with Valsartan monotherapy have been described in NDA20-665. Clumping of platelets was observed in a few patients in Protocol 301 following medication but the significance of this phenomenon is not clear.

Neutropenia

Neutropenia was observed in 1.9% of patients treated with valsartan monotherapy (NDA20-665), whereas it was found in 0.6% of patients treated with the combination drug (Protocol 301), and in 0.0% of placebo-treated patients. The frequency tabulation of patients with neutropenia by treatment is summarized below in Table 46. It is noteworthy that in most cases these values represented normal variability in the test or laboratory error. Interpretation of this data took variability into account.

Table 46 : Patients with absolute neutrophil values below 1.0 T/L- Protocols19/301

	Valsartan/ HCTZ N=(%)	Valsartan N=(%)	HCTZ N=(%)	Acebutolol/ HCTZ N=(%)	Other N=(%)	Placebo N=(%)
Absolute Neutrophils						
Baseline	1293 (100)	1717 (100)	240 (100)	110 (100)	289 (100)	93 (100)
< 1.0 T/L	2 (0.15)	2 (0.12)	0 (0.00)	0 (0.00)	1 (0.35)	1 (1.08)
DuringTreatment	1218 (100)	1645 (100)	192 (100)	73 (100)	251 (100)	89 (100)
< 1.0 T/L	5 (0.41)	3 (0.18)	0 (0.00)	0 (0.00)	1 (0.40)	0 (0.00)

Trials included: 11 Extension, 19, 20, 24, 28, 31 Extension, and 301.

In view of the potential importance of agranulocytosis, the narratives of the 5 patients in the valsartan/HCTZ treatment group with a value for absolute neutrophils < 1.0 T/L during treatment are documented below. Patients 291 and 50 below are in Appendix Table 16.

8.2.2. Metabolic and Endocrine

There were no deaths attributed to metabolic or endocrine adverse events in the safety datasets. All patients in the double blind trials were monitored for changes ion body weight, glucose, albumin, protein, cholesterol, and triglycerides. These assessments were considered to be adequate to evaluate the possible metabolic and endocrine effects of the combined therapy. There were only two reported adverse experiences of weight increase but this did not result in discontinuation. Out of a total of 14 patients reported as having impotence as an adverse event, 5 were discontinued. Four of the 5 discontinued patients were on Valsartan 160mg, and of these 4, three were on V160/25HCTZ (Table 47). One patient was on 160 Valsartan monotherapy. There appears to be a dose-related trend to Valsartan rather than to HCTZ because 80% of the discontinued patients were on 160 mg Valsartan compared to 1 (20%) patient on 80 mg Valsartan and 0 (0.0%) patients on placebo (Tables 47).

Table 47: Discontinuations due to Impotence

Protocol	Subject	Drug V	Drug H	Last Visit	History
301	31/3028	160	25	3	Impotence
301	36642832	160	0	5	Impotence
301	36342753	160	25	3	Impotence
301	3030	80	12.5	3	Impotence
301	31/3028	160	25	3	Impotence

8.2.2. Potassium

The shifts in serum potassium levels from baseline to post randomization values have been discussed in Section 8.1.6. Premature discontinuations due to hypokalemia in the controlled studies are in Table . Twenty one patients showed changes in serum potassium levels in the controlled and open-label extension studies (Table 36). Nine patients showed a > 20% increase, and 12 patients showed a <20% decrease. The majority (80%) of the patients with a decrease were on HCTZ alone. There were 2 patients with hyperkalemia but there were no premature discontinuations due to hyperkalemia. There were a few patients with hypokalemia in the open label extension who were not discontinued, while on the combined drug. The narratives of 2 patients discontinued because of hypokalemia are described below.

001/501/Ansari (Protocol 11E1): A 78 year old female on Valsartan 80 mg / HCTZ 12.5 mg OD was not discontinued even though she developed pneumonia considered not related, and hypokalemia possibly related to trial drug. The patient began the open-label treatment phase on 4/23/93. The patient presented in the emergency room 11 months later on 3/20/94 with left sided chest pain, which was more severe on inspiration. Her ECG was unchanged from baseline. She was in normal sinus rhythm with normal conduction. It was determined to be a pulmonary infiltrate. A venogram was negative. The patient was hypokalemic upon admission. Her potassium level was 3.1 mEq/L. The HCTZ was discontinued at that time. She was treated with IV antibiotics. Her concomitant medications were multivitamins which was ongoing at that time. No further potassium levels were available at the time. She was discharged on 3/24/94. At the time of discharge, she was given cefuroxime axetil, a cephalosporin, 250 mg bid for 5 days. In the investigator's opinion, the relationship between this adverse event, hypokalemia, and the trial treatment was possible.

734/3658/Schoenberger (Protocol 301) A 53 year old female on Valsartan 160 mg/HCTZ 25 mg was prematurely discontinued because she developed decreased potassium, muscle fatigue, decreased intravascular volume, and leg cramps.This patient had no relevant past medical history except for hypertension for three years. The initial visit

ECG revealed a first degree atrioventricular block, otherwise within normal limits, which was considered clinically insignificant by the investigator. At randomization, the patient's average sitting blood pressure was 171/109 mmHg, and weight was 138 pounds, and electrolytes were within normal limits. Five days post-randomization, the patient experienced severe leg and feet cramps for one day and took quinine sulfate and tonic water. Fourteen days post-randomization, the patient returned for a scheduled protocol visit and had a low potassium value of 3.3mEq/L (randomization potassium value was 4.0 mEq/L) and weight loss of 10 pounds (129 pounds). Fifteen days post-randomization, the patient began experiencing mild muscle fatigue; 19 days post-randomization, the patient was determined to have moderately decreased intravascular volume, and 26 days post-randomization the patient had a one day episode of moderate leg cramps. The patient was instructed to increase her potassium intake and oral hydration. On day 30 post-randomization, the patient discontinued trial medication. Final visit electrolytes were within normal limits, weight was 130 pounds, and average sitting blood pressure was 123/84 mmHg. The low potassium resolved the day after trial drug was stopped. The decreased intravascular volume and muscle fatigue resolved two weeks after trial drug was stopped. The investigator considered the leg cramps possibly related to trial drug, the muscle fatigue probably related to trial drug, and the low potassium and decreased intravascular volume highly probably related to trial drug.

Chloride:

A > 10 % increase or decrease from baseline chloride was felt to represent a clinically significant change. Fourteen patients exhibited such a change. Five of these patients had values that were within the normal range. The remaining 9 patients that had percent changes were outside the normal range. One patient had an increase and 8 patients had decreases in serum chloride levels (Tables 48 and 49).

A patient , 90/5060/Wainwright, had a decreased chloride value at a Visit 6.

The patient received no concomitant medications, nor complained of any adverse experiences during the trial. The ivestigator considered the abnormality not clinically significant, but related to trial drug.

Table 48: Patient with > 10% increase in chloride-Protocol 301

Patient	Treatment group	Age	Sex	Baseline value	Week 4 value	Terminal value
625/5440	Valsartan 80 mg/HCTZ 12.5 mg	44	M	105	120	108

Normal Range=96-106mEq/L

Table 49: Patients with >10% decrease in chloride-Protocol 301

Patient ID	Treatment group	Age	Sex	Baseline value	Visit 4 value	Terminal value
12/5757	Valsartan 80 mg	53	M	107	106	104
90/5060	Valsartan 80 mg	48	M	105	101	94
398/5265	Valsartan 80 mg/HCTZ 12.5 mg	63	M	102	90	96
38/5026	Valsartan 80 mg/HCTZ 12.5 mg	42	F	107	99	94
645/5783	Valsartan 80 mg/HCTZ 12.5 mg	54	F	105	101	93
298/5199	Valsartan 80 mg/HCTZ 12.5 mg	70	M	105	102	91
798/5719	Valsartan 80 mg/HCTZ 12.5 mg	58	M	104	93	98
849/5658	Valsartan 80 mg/HCTZ 12.5 mg	49	M	111	95	99

*Normal range= 96-106mEq/L

Table 45: Discontinuations (DC) due to serious adverse (SAE) hematologic events

Protocol	Treatment Group	Total Daily Dose	Patient ID	Sex	Age	Visit	Adverse Experience	DC	SAE
11E1	Valsartan	80 mg	013/510	M	67	13	Leukemia	Yes	Yes
11E1	Valsartan	40 mg	009/506	M	48	12	Malignant lymphoma Splenomegaly	Yes Yes	Yes Yes
20	Valsartan	80 mg	1131	M	61	-	Microcytic anemia	Yes	Yes
11E3	Valsartan/ HCTZ	80/25 mg	008/508	M	56	-	Lymphatic leukemia	Yes	Yes

Platelets

Eleven subjects out of 25 patients with abnormal platelet counts had clinical evidence of purpura. A greater than 75 % increase or > 50 % decrease from baseline platelet count was considered to represent a clinically significant change. Eight patients exhibited such a change: 4 patients in each group with an increase or decrease in platelet count. Two patients were discontinued from the study because of low platelet count but the sponsor did not assess the relationship of the drug to this event. There was no significant relationship between drug exposure and purpura or thrombocytopenia. In the valsartan monotherapy study, (Protocol 19), a 63 year old male patient on Valsartan 80mg, was discontinued prematurely because of low platrelet count. Other hematologic adverse events observed with Valsartan monotherapy have been described in NDA20-665. Clumping of platelets was observed in a few patients in Protocol 301 following medication but the significance of this phenomenon is not clear.

Neutropenia

Neutropenia was observed in 1.9% of patients treated with valsartan monotherapy (NDA20-665), whereas it was found in 0.6% of patients treated with the combination drug (Protocol 301), and in 0.0% of placebo-treated patients. The frequency tabulation of patients with neutropenia by treatment is summarized below in Table 46. It is noteworthy that in most cases these values represented normal variability in the test or laboratory error. Interpretation of this data took variability into account.

Table 46 : Patients with absolute neutrophil values below 1.0 T/L-Protocols19/301

	Valsartan/ HCTZ N (%)	Valsartan N (%)	HCTZ N (%)	ACE/ HCTZ N (%)	Other N (%)	Placebo N (%)
Absolute Neutrophils						
Baseline	1293 (100)	1717 (100)	240 (100)	110 (100)	289 (100)	93 (100)
< 1.0 T/L	2 (0.15)	2 (0.12)	0 (0.00)	0 (0.00)	1 (0.35)	1 (1.08)
DuringTreatment	1218 (100)	1645 (100)	192 (100)	73 (100)	251 (100)	89 (100)
< 1.0 T/L	5 (0.41)	3 (0.18)	0 (0.00)	0 (0.00)	1 (0.40)	0 (0.00)

Trials included: 11 Extension, 19, 20, 24, 28, 31 Extension, and 301.

In view of the potential importance of agranulocytosis, the narratives of the 5 patients in the valsartan/HCTZ treatment group with a value for absolute neutrophils < 1.0 T/L during treatment are documented below. Patients 291 and 50 below are in Appendix Table 16.

8.2.2. Metabolic and Endocrine

There were no deaths attributed to metabolic or endocrine adverse events in the safety datasets. All patients in the double blind trials were monitored for changes ion body weight, glucose, albumin, protein, cholesterol, and triglycerides. These assessments were considered to be adequate to evaluate the possible metabolic and endocrine effects of the combined therapy. There were only two reported adverse experiences of weight increase but this did not result in discontinuation. Out of a total of 14 patients reported as having impotence as an adverse event, 5 were discontinued. Four of the 5 discontinued patients were on Valsartan 160mg, and of these 4, three were on V160/25HCTZ (Table 47). One patient was on 160 Valsartan monotherapy. There appears to be a dose-related trend to Valsartan rather than to HCTZ because 80% of the discontinued patients were on 160 mg Valsartan compared to 1 (20%) patient on 80 mg Valsartan and 0 (0.0%) patients on placebo (Tables 47).

Table 47: Discontinuations due to Impotence

Protocol	Subject	Drug V	Drug H	Last Visit	History
301	31/3028	160	25	3	Impotence
301	36642832	160	0	5	Impotence
301	36342753	160	25	3	Impotence
301	3030	80	12.5	3	Impotence
301	31/3028	160	25	3	Impotence

8.2.2. Potassium

The shifts in serum potassium levels from baseline to post randomization values have been discussed in Section 8.1.6. Premature discontinuations due to hypokalemia in the controlled studies are in Table . Twenty one patients showed changes in serum potassium levels in the controlled and open-label extension studies (Table 36). Nine patients showed a > 20% increase, and 12 patients showed a <20% decrease. The majority (80%) of the patients with a decrease were on HCTZ alone. There were 2 patients with hyperkalemia but there were no premature discontinuations due to hyperkalemia. There were a few patients with hypokalemia in the open label extension who were not discontinued, while on the combined drug. The narratives of 2 patients discontinued because of hypokalemia are described below.

001/501/Ansari (Protocol 11E1): A 78 year old female on Valsartan 80 mg / HCTZ 12.5 mg OD was not discontinued even though she developed pneumonia considered not related, and hypokalemia possibly related to trial drug. The patient began the open-label treatment phase on 4/23/93. The patient presented in the emergency room 11 months later on 3/20/94 with left sided chest pain, which was more severe on inspiration. Her ECG was unchanged from baseline. She was in normal sinus rhythm with normal conduction. It was determined to be a pulmonary infiltrate. A venogram was negative. The patient was hypokalemic upon admission. Her potassium level was 3.1 mEq/L. The HCTZ was discontinued at that time. She was treated with IV antibiotics. Her concomitant medications were multivitamins which was ongoing at that time. No further potassium levels were available at the time. She was discharged on 3/24/94. At the time of discharge, she was given cefuroxime axetil, a cephalosporin, 250 mg bid for 5 days. In the investigator's opinion, the relationship between this adverse event, hypokalemia, and the trial treatment was possible.

734/3658/Schoenberger (Protocol 301) A 53 year old female on Valsartan 160 mg/HCTZ 25 mg was prematurely discontinued because she developed decreased potassium, muscle fatigue, decreased intravascular volume, and leg cramps.This patient had no relevant past medical history except for hypertension for three years. The initial visit

ECG revealed a first degree atrioventricular block, otherwise within normal limits, which was considered clinically insignificant by the investigator. At randomization, the patient's average sitting blood pressure was 171/109 mmHg, and weight was 138 pounds, and electrolytes were within normal limits. Five days post-randomization, the patient experienced severe leg and feet cramps for one day and took quinine sulfate and tonic water. Fourteen days post-randomization, the patient returned for a scheduled protocol visit and had a low potassium value of 3.3mEq/L (randomization potassium value was 4.0 mEq/L) and weight loss of 10 pounds (129 pounds). Fifteen days post-randomization, the patient began experiencing mild muscle fatigue; 19 days post-randomization, the patient was determined to have moderately decreased intravascular volume, and 26 days post-randomization the patient had a one day episode of moderate leg cramps. The patient was instructed to increase her potassium intake and oral hydration. On day 30 post-randomization, the patient discontinued trial medication. Final visit electrolytes were within normal limits, weight was 130 pounds, and average sitting blood pressure was 123/84 mmHg. The low potassium resolved the day after trial drug was stopped. The decreased intravascular volume and muscle fatigue resolved two weeks after trial drug was stopped. The investigator considered the leg cramps possibly related to trial drug, the muscle fatigue probably related to trial drug, and the low potassium and decreased intravascular volume highly probably related to trial drug.

Chloride:

A > 10 % increase or decrease from baseline chloride was felt to represent a clinically significant change. Fourteen patients exhibited such a change. Five of these patients had values that were within the normal range. The remaining 9 patients that had percent changes were outside the normal range. One patient had an increase and 8 patients had decreases in serum chloride levels (Tables 48 and 49).

A patient, 90/5060/Wainwright, had a decreased chloride value at a Visit 6.

The patient received no concomitant medications, nor complained of any adverse experiences during the trial. The ivestigator considered the abnormality not clinically significant, but related to trial drug.

Table 48: Patient with > 10% increase in chloride-Protocol 301

Patient ID	Treatment group	Age	Sex	Baseline value	Week 4 value	Terminal value
625/5440	Valsartan 80 mg/HCTZ 12.5 mg	44	M	105	120	108

Normal Range=96-106mEq/L

Table 49: Patients with >10% decrease in chloride-Protocol 301

Patient ID	Treatment group	Age	Sex	Baseline value	Visit 4 value	Termina l value
12/5757	Valsartan 80 mg	53	M	107	106	104
90/5060	Valsartan 80 mg	48	M	105	101	94
398/5265	Valsartan 80 mg/HCTZ 12.5 mg	63	M	102	90	96
38/5026	Valsartan 80 mg/HCTZ 12.5 mg	42	F	107	99	94
645/5783	Valsartan 80 mg/HCTZ 12.5 mg	54	F	105	101	93
298/5199	Valsartan 80 mg/HCTZ 12.5 mg	70	M	105	102	91
798/5719	Valsartan 80 mg/HCTZ 12.5 mg	58	M	104	93	98
849/5658	Valsartan 80 mg/HCTZ 12.5 mg	49	M	111	95	99

*Normal range= 96-106mEq/L

Sodium

For sodium , the percentage of patients who exhibited normal baseline values that decreased to values below the lower limit of normal at terminal visit was greater for the HCTZ 25mg, valsartan 80mg/HCTZ 25mg, and the valsartan 160mg/HCTZ 25mg treatment groups compared to the other treatment groups. All other treatment groups had 2-5% of patients exhibit this level of decrease. Table 50 lists 2 patients with marginal increase in serum sodium. These patients were asymptomatic. Table 51 lists 6 patients with abnormalities of serum sodium levels by visit during the trials. One patient on Valsartan 160mg and 12.5mg HCTZ was prematurely discontinued for hyponatremia (Appendix Table 10).

Table 50: Patients with > 7% increase in sodium- Protocol 19

Patient	Treatment group	Age	Sex	Baseline value	Week 4 value	Terminal value
423/5283/Alto	Valsartan 160 mg	52	F	140	150	145
1007/5383/Marzec	Valsartan 160 mg	34	M	140	132	142

Table 51: Significant changes in sodium- Protocols 19, 31 E, & 301

Protocol	Patient	Treatment	Sex	Age	Baseline	Wk 2-4	Wk 8	Wk 36	Wk 48	Wk 61
19	1007/5383 Marzec	Valsartan 160 mg	M	34	140	132	142			
31 E	007/5007/ Elinoff	Valsartan 160 mg/ HCTZ 12.5 mg	M	62	143				140	131
31 E	289/5193/ Lewis	Valsartan 160 mg/ HCTZ 12.5 mg	F	59	142			141		131
301	894/3921 Graff	HCTZ 25 mg	F	70	140	131	142			
301	1109/3999 Graff	Valsartan 80 mg/ HCTZ 12.5 mg	F	63	144		133			
301	687/3617 Thorsen	Valsartan 160 mg/ HCTZ 25 mg	F	56	141		127			

Normal range: (M&F) 135-147 mEq/L

Concomitant decrease in levels of serum sodium and potassium, or sodium and chloride were observed in a few patients.

Calcium

The sponsor did not comment on the significance of changes in serum calcium reported during the controlled trials. Eighteen subjects had >10% increase in serum calcium from baseline with the higher increases (66%) in subjects treated with the combination compared to 33 % in subjects with valsartan monotherapy . The clinical significance of this is not clear and none of the patients were symptomatic or discontinued for hypercalcemia.

Glucose

In protocol 301, examination of the meaan changes from baseline to endpoint for fasting blood glucose showed that 13 patients had more than 50% increase (Table 52).
Seven patients were in the monotherapy groups (V80 and V160), and 6 were in the combined drug group.(Table 53). The changes from baseline were considered clinically significant, but not related to trial drug by the investigators. One patient had an elevated glucose value at the terminal visit and the investigator believed that the patient was a new diabetic. And though the change was clinically significant, it was not considered to be related to trial drug. One patient was a known diabetic and another patient had a history of diabetes mellitus. The other 8 patients had no previous history of diabetes mellitus.

Table 53: Patients with > 50% increase in glucose-Protocol 301

Patient	Treatment group	Age	Sex	Baseline value	Terminal value
806/5708	Valsartan 80 mg	42	M	178	415
*601/5323	Valsartan 80 mg	42	M	95	163
751/5521	Valsartan 80 mg	63	M	94	168
1202/5816	Valsartan 80 mg	66	M	104	217
832/5570	Valsartan 80 mg	43	F	74	154
882/5594	Valsartan 160 mg	56	M	128	199
420/5926	Valsartan 160 mg	48	M	65	127
805/5707	Valsartan 80 mg/HCTZ12.5 mg	55	M	85	129
1248/5732	Valsartan 80 mg/HCTZ12.5 mg	54	M	73	142
804/5706	Valsartan 80 mg/HCTZ 25 mg	48	F	118	190
*826/5817	Valsartan 80 mg/HCTZ 25 mg	65	M	152	233
1046/5825	Valsartan 80 mg/HCTZ 25 mg	65	M	99	153
1251/5830	Valsartan 80 mg/HCTZ 25 mg	48	M	185	331

Normal ranges: (M&F) (age 0-50) 65-115 mg/dL, (age > 50) 85-125 mg/dL

**In Protocol 301, patients 601/5323/Jain and 1202/5816/Stringer were not properly fasted at the time of the terminal visit. Repeat laboratories were not performed. Neither patient had a history of diabetes mellitus. The changes from baseline were considered clinically significant, but not related to trial drug by the investigators. Patient 806/5708/Fidelholtz had an elevated glucose value at the terminal visit. The investigator believed that the patient was a new diabetic. He considered the abnormalities clinically significant and not related to trial drug.*

**Patient 26/5817/Stringer was a known diabetic. The investigator considered the abnormality clinically significant and related to trial drug. Patient 1251/5830/Lewin had a history of diabetes mellitus.*

During the open label extension study, 2 patients developed significant changes in serum glucose levels (Table 54)

Table 54: Patients with significant changes in glucose - Protocol 31

Protocol Sex/Age	Patient	Treatment	Base line	Week 2	Week 8?	Week 40	Week 52/64
31 /M/59	274/5184	valsartan 160 mg + HCTZ	132	189 (val/HCTZ 12.5)			221 (val/HCTZ 25)
31 /M/41	750/5669	valsartan 160 mg + HCTZ	129		354 (val 160)	105 (val 160)	121 (val 160)

Normal ranges: (M&F) (age 0-50) 65-115 mg/dL, (age > 50) 85-125 mg/dL

Uric acid

In the controlled studies, examination of the mean changes from baseline to endpoint for uric acid were carried out on all subjects. This is considered very important because of the effect of HCTZ on uric acid. A greater than 50 % increase from baseline of uric acid was felt to represent a clinically significant change. Nine patients exhibited such a change, however four of these patients had values that were within the normal range. The five patients that had percent changes outside the normal range were receivng combined therapy, and are listed in Table 55. All the patients were on V80/HCTZ. The values of the uric acid increased with increased dosage of HCTZ (Table 55). The sponsor reported 3 patients as having gout.

There were 33 patients with arthralgia, 26 patients with arthritis, and 14 patients with arthrosis as adverse events in the safety database (Appendix Tables 3-15).. There was no attempt to correllate uric acid levels with diseases or symptoms affecting the joints. It was not possible to exclude gout from the miscellaneous group of joint disorders. The sponsor had classified diseases of joints with the musculoskeletal system. The potential for gout will be reflected in the label for the combined drug.

Table 55: Patients with >50% increase serum Uric Acid

Patient	Treatment group	Age	Sex	Baseline value	Terminal value
>50% increase uric acid from baseline					
598/5393	Valsartan 80 mg/HCTZ 12.5 mg	67	F	5.3	8.2
20/5013	Valsartan 80 mg/HCTZ 12.5 mg	76	F	1.2	2.0
375/5250	Valsartan 80 mg/HCTZ 12.5 mg	47	M	6.0	9.3
606/5348	Valsartan 80 mg/HCTZ 25 mg	65	M	7.3	11.5
138/509	Valsartan 80 mg/HCTZ 25 mg	48	M	7.9	11.9

Normal range=3-9mg/dL

8.2.3. Musculoskeletal system

There were no deaths attributed to muscular or skeletal adverse events.

Adequacy of assessment

The assessment of musculoskeletal system was performed by monitoring spontaneously reported adverse events. Apart from the regular evaluation of serum creatine phosphokinase, which is invariably elevated in muscle diseases, no other laboratory measures were performed. This was considered adequate for safety evaluation of the musculoskeletal system. A > 300 % increase or decrease from baseline of serum CPK was felt to represent a clinically significant change. Nine patients exhibited such a change, and 1 patient had values within the normal range. Out of the 8 patients listed in Table 56 with abnormal values, 6 were on combined therapy and 2 were on high dose Valsartan monotherapy (160mg). One asymptomatic patient had a value > 6000 ui/L and was considered an outlier (Appendix Figure 2).

Table 56: Patients with >300% Increase in serum CPK

Patient	Treatment group	Age	Sex	Baseline value	Terminal value
>300% increase CPK from baseline					
218/5146/Gann	Valsartan 160 mg	36	M	16	205
444/5295/Vranian	Valsartan 160 mg	36	M	384	2733
133/5091/Montoro	Valsartan 80 mg/HCTZ 12.5 mg	63	M	147	618
633/5446/Montoro	Valsartan 80 mg/HCTZ 12.5 mg	40	M	58	323
461/5306/Koren	Valsartan 80 mg/HCTZ 25 mg	52	M	68	648
138/5095/Montoro	Valsartan 80 mg/HCTZ 25 mg	48	M	167	1362
447/5302/McInroy	Valsartan 80 mg/HCTZ 25 mg	49	M	140	192
799/5720/Williams O	Valsartan 80 mg/HCTZ 25 mg	47	M	122	1119

Normal range: 35-120ui/L

8.2.4 Nervous system

There were no deaths attributed directly to nervous system related adverse events.

Adequacy of assessment

The assessment of the nervous system was performed by monitoring spontaneously reported adverse events.

Neurological events likely to be related to combination therapy

The largest number of premature discontinuations in protocol 301 was due to headaches and dizziness regardless of race, age or sex. The incidence of headache was significantly higher in subjects receiving the combination therapy compared to placebo ($p< 0.05$). The incidence of dizziness was also significantly higher in patients receiving the combination compared to valsartan monotherapy ($p< 0.05$). The frequencies of other neurological signs and symptoms reported in the database include hypoesthesia (13), paralysis (2), hypertonia (10), paresthesia (15), depression (8), somnolence (15), insomnia (27), and tremor (1). In addition to cerebrovascular accidents and transient ischemic attacks already discussed in Table 68, there were also 7 adverse events of syncope which could be due to disturbances of glucose metabolism or be neurological in origin. In protocol 301, only one patient with a syncopal attack was discontinued (Appendix Table 2).

8.2.5 Respiratory system

There were no deaths attributed to respiratory system related adverse events.

Adequacy of assessment

The assessment of the respiratory system was performed by monitoring spontaneously reported adverse events, and chest X-rays.

Respiratory events likely to be related to combination therapy

Out of a total of 286 COSTART terms used in the data base for reporting adverse experiences in the controlled studies, the respiratory system accounted for 7 of these regardless of drug exposure. The absolute frequencies of the events out of a total of 822 reported events include sinusitis (91), rhinitis (67), pharyngitis (55), upper respiratory tract infections(86), bronchitis (24), laryngitis (4), bronchospasm (3), dyspnea (24), and coughing (72). The incidence of these adverse events affecting the respiratory system by treatment groups has been summarized above in Appendix Table 3-15.

Four patients were discontinued from the controlled studies because of respiratory symptoms (Table 61). Two of these were for dyspnea, and the other 2 for coughing.

Table 57: Discontinuations due to respiratory changes

Protocol	Patient Number	Y	HCTZ	Week	History
19	5083979	80	12.5	8	Coughing
19	5031	80	12.5	8	Coughing
19	5077	80	25	8	Shortness of breath
301	3668	160	25	8	Shortness of breath

8.2.6. Dermatological system

There were no deaths attributed to dermatological system related adverse events.

Adequacy of assessment

The assessment of the dermatological system was performed by monitoring spontaneously reported adverse events.

Events reported in combined database regardless of relationship to combination therapy

Absolute counts of adverse events affecting the skin and subcutanous tissues reported to be either highly probably or probaly relateed to drugs include skin rash (36), cellulitis (4), contact dermatitis (14), fungal dermatitis (3), Dermatitis (3) , furunculosis (3), urticaria (3), heat rash (1), hyperkeratosis (5), pruritus (5), melanosis (4), purpura (11), and other non-specific skin disorders (5).

Dermatological events likely to be related to combination therapy
Two patients were discontinued from the controlled studies because of skin rash. The time to onset of the rash was at Visit 5 (Table 58). The rash in the patient on Valsartan 160/25 HCTZ was considered to be highly probably related to the drug.

Table 62: Discontinuations due to dermatological symptoms

Protocol	Subject	Drug V	Drug H	Days Visit	History
301	3615	80	12.5	8	Rash
301	175/3158	160	12.5	8	Rash

One patient with tinea cutis infection developed abnormalities of serum creatinine, uric acid and total bilirubin. The relationship of the drug to these multiple adverse events is not known but the increaased serum creatinine was possibly related to the drug.

Patient 623/3560/Stafford had an increase in serum creatinine considered to be clinically significant and possibly related to trial drug by the investigator. This patient had developed a ***tinea cutis*** *infection 7 days prior to the Week 8 visit, which was ongoing at the time the laboratory specimen was drawn. No significant concomitant medications were taken during the trial. A follow-up laboratory test after trial completion showed the creatinine had returned to the baseline value of 1.2 mg/dL. At the Week 8 visit this patient also had abnormalities in serum uric acid and total bilirubin.*

8.2.7 Special senses

There were no deaths attributed to adverse events affecting the special senses.

Adequacy of assessment
The assessment of the special senses system was performed by monitoring spontaneously reported adverse events.

Events reported in combined database
The adverse events reported in the database include ear canal obstruction (2), ear disorder not specified (2), earache (8), otitis externa (8), otitis media (4), ototoxicity (1), tinnitus (9), vertigo (20), vestibular disorder (2) eye abnormality (1), eye 'complaints' (3), occular infection (2), ptosis (3), retinal disorder (2), conjunctival hemorrhage (5), conjunctivitis (8), eyelid disorders (1), and taste perversion (5).

Events plausibly related to combination therapy
There were no adverse events affecting the special senses alone that led to discontinuation of the trial except patients with visual disturbances (Table 59).

Table 59 : Discontinuations due to visual disturbances

Protocol	Subject ID	Age	Sex	Drug V	Drug H	Visit	History Reason for discontinuation
301	958/3844	49	M	80	25	3	"Wavy vision"
11E1	008/507	55	F	20	0	9	Blurred vision
28	1396	65	F	40	0	3	Blurred vision
11E1	009/505	44	M	40	0	10	Delayed focussing of eye
11E1	005/504	64	M	20	0	10	Burning in eyes
28	1070	65	F	40	0	3	Pan-uveitis
28	1556	83	F	80	0	3	Blurred vision
301	784/3706	65	F	0	12.5	3	Visual disturbance
19	11301	44	M	40	0	3	Blurred vision
19	1037/5693	39	F	160	0	4	III N.Palsy; Ptosis Rt upper eyelid
19	662	65	F	80	0	3	Amblyopia left eye

8.2.8 Genitourinary

There were no deaths attributed to genitourinary system related adverse events.

Adeqacy of assessment

The assessment of the genitourinary system was performed by monitoring spontaneously reported AEs..

Genitourinary adverse events reported in Protocols 19 and 301

The events reported to be either highly probably or probaly related to drugs include micturition frequency (33) hemorrhagic cystitis (1), dysuria (6), hematuria (3), hydronephrosis (2), polyuria (2), prostatic disorder (4), pyuria (1), urinary retention (1), urinary tract disorder (1); decreased libido (4), genital pruritus (2), urogenital prolapse (1), ovarian cyst (1), vaginitis (2), impotence (14), sexual problems (1), carcinoma of the bladder (1), renal cell carcinoma (1), and endometrial carcinoma (1).

Genitourinary events likely to be related to Valsartan/HCTZ

There were 3 patients with urinary frequency that led to discontinuation of the trial . All 3 patients were on high dose of HCTZ (Table 60), and there were 5 patients with drug related impotence who were discontinued. There was also one patient with proteinuria who was discontinued. This was a 45 year old female on Valsartan 80 mg.

Table 60: Discontinuations due to urinary symptoms

Protocol	Subject	Drug			History
301	3553	80	25	3	Urinary frequency
301	38571973	0	25	5	Urinary frequency
301	3857	0	25	3	Urinary frequency

8.2.9 Miscellaneous

There were no deaths and no serious adverse events attributed to any of the miscellaneous changes reported in the combined datasets. Table 61 lists 4 patients on hydrochlorothiazide with adverse events that required discontinuation of the drug. Two of these patients were prematurely discontinued because of adverse events that were trial drug related whereas the other 2 were also prematurely discontinued even though their adverse events were considered not to be related to the drug.The narratives of these events are below.

Table 61 : Miscellaneous events

Protocol	Subject	Age	Sex	Drug		Day	History
301	449/3403	51	M	0	12.5	(u)14	Cerebral lacunar infarction; stroke
301	720/3646	64	M	0	12.5	(r) 12	Orthostatic hypotension
301	784/3706	65	F	0	12.5	(r) 10	Sinus tachycardia
301	1047/3943	55	M	0	25	(u)-	Tuberculosis
301	0422/5920	65	M	0	0	(u) 17	Atrial flutter; shingles
u=unrelated; r= related (See Appendix Table).							

720/3646 Aarons Protocol 301: A 64 year old male developed dizziness and orthostatic hypotension. This patient had no significant history except for hypertension for four years. Fourteen days prior to randomization, this patient began experiencing mild dizziness and nausea. The nausea ended after four days, however, the dizziness continued post-randomization, with no change in severity. At the randomization visit, the patient's average sitting blood pressure was 139/97 mmHg and standing blood pressure was 136/90mmHg. Twelve days post-randomization, the investigator reported that the patient experienced orthostatic hypotension (according to the investigator, not the protocol

definition), and the investigator discontinued the patient from the trial. The patient's average sitting blood pressure at the final visit when the orthostatic event occurred was 156/101 mmHg, and the standing blood pressure was 142/96 mmHg. The dizziness was still continuing at the time of the orthostatic event. The dizziness and orthostatic hypotension resolved five days after trial medication was stopped. The investigator considered these events to be probably related to trial medication.

784/3706 Lee Protocol 301: A 65 year old female developed headache; darkening of peripheral vision; nausea; sinus tachycardia; numbness of right arm. This patient had a 2 year history of osteoarthritis of the neck and ankle, and an 11 year history of estrogen deficiency as well as a 5 year history of hypertension. The Visit 1 ECG finding of ventricular bigeminy was considered clinically insignificant by the investigator. Two days after the initial visit, the patient started methocarbamol 500mg four times daily for musculoskeletal pain and neck spasms. At randomization, the patient's average sitting blood pressure was 171/105 mmHg. Ten days post-randomization this patient began experiencing mild headaches, darkening of peripheral vision, nausea, sinus tachycardia, and numbness of the right arm. The patient discontinued trial medication the day of these events, and all events resolved four days later. At the final visit, the patient's average sitting blood pressure was 175/103 mmHg, and a repeat ECG revealed sinus tachycardia with premature ventricular contractions. The investigator reported that on a chronic basis this patient has had 48 multiple non-specific complaints with negative work-ups including stress tests and a negative ultrasound of her carotid arteries (performed two weeks post study). The investigator considered the events possibly related to trial medication

449/3403/Protocol 301: A 52 year old male with a past history of elevated liver function tests for ten years, and an approximate ten year history of hypertension. The Visit 1 ECG revealed clinically insignificant ST segment changes, unchanged from a previous ECG (date unknown), and the initial visit chest x-ray revealed clinically insignificant atherosclerosis of the aorta, otherwise within normal limits. At randomization the patient's average sitting blood pressure was 138/104 mmHg. Fourteen days post-randomization, the patient began experiencing moderate left-sided weakness. The following day the patient awoke with some left-sided facial paralysis and slight dysphasia. The patient reported to the local emergency room and was admitted for observation and work-up. Upon arrival at the hospital the patient was given three liters of oxygen per minute via nasal cannula and had continuous telemetry monitoring. After blood work, an ECG and a CT scan were performed, the patient was treated with nifedipine 10mg every 4 hours as needed for blood pressure greater than 150/110 mmHg, indomethacin SR 75 mg and aspirin 325 mg daily for 2 days. The hospital work-up revealed all negative results. Patient was discharged five days after admission with a diagnosis of cerebral lacunar infarction. Patient was discharged on daily doses of nifedipine 30mg, allopurinal 300 mg, aspirin 325 mg and instructed to start outpatient physical therapy. Last dose of trial medication was 14 days post-randomization when the weakness began. Dr. Surath had telephone contact with the patient two months post discharge, and the patient reported being almost back to normal and was to return to work shortly. The investigator considered this event unrelated to trial medication.

04425290/Protocol 301: A 65 year old male with a history of hypertension for 20 years, hypercholesterolemia, and hyperbilirubinemia. Seventeen days after entering the double-blind phase of the trial, the patient developed right lower quadrant pain and was admitted to the hospital for evaluation of pain. While in the hospital, the patient developed a painful rash on his buttocks and was diagnosed with shingles. Treatment with acyclovir was started and the patient's condition improved. He was discharged from the hospital after two days. The patient remained on trial drug without interruption and the investigator considered the adverse event to be unrelated to trial drug.

his patient experienced another serious adverse experience when at Visit 4, 57 days after entering the double-blind treatment phase, an ECG revealed atrial flutter. His mean sitting blood pressure (MSBP) at this visit was 150/105 mmHg. His ECG at Visit 1 had shown sinus bradycardia with first degree AV block, right bundle branch block, left anterior

fascicular block, and bifascicular block. At Visit 4, the patient was asymptomatic, however, he did state that one week prior he had experienced lightheadedness which lasted for two days. After the visit, the patient was hospitalized and on admission complained of feeling lightheaded and fatigued. An ECG showed flutter on 3:1 block with a ventricular rate of 71 beats per minute. The patient was treated with intravenous procainamide and subsequently converted to sinus rhythm with slightly prolonged intervals. The patient was discharged the same day and prescribed procainamide, triamterene/hydrochlorothiazide, lovastatin, and instructed to maintain a low salt and low fat diet. The patient completed the trial and the investigator considered the adverse experience to be unrelated to trial drug.

8.3 Summary of key adverse events and safety issues

- There were no deaths plausibly related to the combination drug-Valsartan/HCTZ.
- There was no significant evidence of hepatotoxicity based on liver enzyme evaluation.
- Valsartan/HCTZ has no greater risk of causing laboratory abnormalities than Valsartan monotherapy .
- There were no observable effects of the combined drug on serum creatinine.
- Valsartan/HCTZ was comparable to valsartan treatment group in the overall incidence of serious adverse events in the combined trials dataset.
- The addition of HCTZ to Valsartan appears to have a beneficial effect on serum potassium levels because the mean percent change in potassium in subjects treated with Valsartan monotherapy was lower compared to those on combination drug.
- There were a few withdrawals from the study drug, DIOVAN-HCT, because of, dizziness, hypokalemia, and thrombocytopenia but the observed frequencies were not greater than in subjects on placebo.
- In protocols 19 and 301, otherwise referred to as controlled trials dataset, the incidence of adverse experiences whether or not trial drug-related was unrelated to the race, gender, or age of the patients, and the incidence of specific adverse experiences in the combined trials dataset (Protocols 19, 301, 11, 20, 24, 28, 31) was similar to that observed in the controlled trials dataset.
- Six patients who received valsartan/HCTZ (0.5%) in the combined trials dataset were reported as experiencing postural hypotension. Six (0.3%) patients in the valsartan and one (0.4%) in the HCTZ treatment groups reported postural hypotension. All reports were considered trial drug-related.
- Valsartan/HCTZ was comparable to the HCTZ and placebo treatment groups and was slightly lower than the valsartan treatment group in the incidence of adverse experiences leading to premature discontinuations in the combined trials dataset.
- Drug-related angioedema and dry cough were observed in a number of subjects treated with the combination therapy.
- For protocol 301, 997 patients were enrolled into the single-blind placebo run-in phase at Visit 1. Of those enrolled, 871 were randomized to the different treatment groups, and 792 completed the trial. Of the 79 patients discontinued 41 patients were for clinical safety adverse events whereas there were no discontinuations for laboratory safety issues. For the 2 double-blind studies, (Protocols 301 and 19), a total of 166 (10.51%) patients out of 1579 randomized patients were discontinued out of which 65 (4.1%) patients were discontinued for significant adverse events and therefore did not complete the trials. The ratio of patients discontinued for adverse events to other reasons is 65:101 (about 39% versus 61%).
- The most common adverse events during the double-blind treatment and the adverse experiences that led to discontnuations during the open label periods are separately tabulated in Appendix Tables 3-15.

9.0 Labeling Review

See Appendix

10. Conclusions

10.1 Chemistry

See Chemistry review

10.2 Mechanism

Pharmacologic data show the properties of each of the components of the combined therapy. Valsartan is a potent and highly selective AT_1 angiotensin II receptor antagonist with expected antihypertensive effects in high renin models of hypertension. HCTZ is a well known and universally acclaimed diuretic with additive anti-hypertensive properties. Previous studies have shown the antihypertensive effects of these two components.

10.3 Animal toxicology

See Pharmacology review.

10.4 Pharmacokinetics

See Dr Fadiran's review. The recommended dose of 80/12.5mg valsartan/HCTZ of the combination therapy meets the bioequivalence criteria whereas the dose of 160/12.5 valsartan/HCTZ formulation does not meet the bioequivalence criteria. The latter is to be marketed formulation and was administered during the clinical trial as a formulation but the 160/25 valsartan/HCTZ formulation is not going to be marketed. The relatively higher dose of 25mg HCTZ in the combination therapy was found to be responsible for some of the adverse events observed in the controlled studies and discussed in this review.

10.5 Clinical exposure

See Dr Chun's review (Section 7).

10.6. Antihypertensive effectiveness of valsartan monotherapy

See previous review and approval of valsartan (NDA20-665).

10.7 Antihypertensive effectiveness of valsartan plus HCTZ

See Dr Chun's review of efficacy of NDA 20-818.

Risk benefit analysis of therapy

The combination therapy is intended for life long treatment of hypertension, particularly in the group of subjects identified not to be responding adequately to valsartan monotherapy. This length of exposure is several times the length of exposure obtained in the clinical development program. Considering that the expected therapeutic benefits of anti-hypertensive therapy include a reduction in fatal cardiovascular events, of the order of 1 per 1000 subject years, the available safety data would, with 95% confidence limits, exclude an undetected problem of about this magnititude.

10.8 Effectiveness in elderly and volume depleted subpopulations

See Dr Chun's review of NDA 20-818.

10.9 Safety

The valsartan and valsartan/HCTZ development programs were complementary to one another. The size of the subjects exposed was considered to be adequate and resulted in a reasonably large combined safety databases. There were no findings that distinguished the combination of valsartan/HCTZ from other combinations of this class of drugs.